National Institute on Drug Abuse

Research 20

MONOGRAPH SERIES

Self-Administration of Abused Substances: Methods for Study

U.S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
Public Health Service Alcohol, Drug Abuse, and Mental Health Administration

Self-Administration of Abused Substances: Methods for Study

Editor:

Norman A. Krasnegor, Ph.D.

NIDA Research Monograph 20
July 1978

DEPARTMENT OF HEALTH. EDUCATION, AND WELFARE
Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration

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5600 Fishers Lane
Rockville, Maryland 20857

For sale by the Superintendent of Documents
U.S. Government Printing Office, Washington, D.C. 20402
Stock No. 017-024-00794-3

The NIDA Research Monograph series is prepared by the Division of Research of the National Institute on Drug Abuse. Its primary objective is to provide critical reviews of research problem areas and techniques, the content of state-of-the-art conferences, integrative research reviews and significant original research. Its dual publication emphasis is rapid and targeted dissemination to the scientific and professional community.

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Self-Administration of Abused Substances: Methods for Study

ACKNOWLEDGMENTS

This monograph is based on papers presented at a technical review conducted by Plog Research, Inc., Reseda, California, under NIDA Contract No. 271-77-3413.
The conference took place on February 14 and 15, 1978, in Reston, Virginia.

Library of Congress catalog card number 78-63094

NIDA Research Monographs are indexed in the *Index Medicus.* They are selectively included in the coverage of *BioSciences Information Service, Chemical Abstracts, Psychological Abstracts,* and *Psychopharmacological Abstracts.*

DHEW Publication No. (ADM) 80-727
Formerly DHEW Publication No. (ADM) 78-727
Printed 1978 Reprinted 1979

Foreword

In July of 1975, the National Institute on Drug Abuse held a conference on the possible commonalities inherent in four substance use patterns : cigarette smoking, alcohol drinking, excessive caloric intake, and illicit drug use. The consensus of the conferees was that there may be a set of basic processes which underlie these four behaviors and that the scientific evidence may be available and accessible if the data on each of these patterns are assessed within a broad framework. By widening the perspective, it is hoped that features common to substance abuse behavior can be discovered from the gestalt of this generic approach.

While it is clear that there are numerous ways to conceptualize and study substance abuse behavior (e.g., psychodynamics, personality theory, etc.), the papers in this volume focus upon methodological approaches used to study self-administration of abused substances by humans under controlled laboratory conditions. This unique monograph illustrates the convergence of techniques used by behavioral scientists working in this area of inquiry and can serve as a point of reference for others who wish to conduct similar research.

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II. FOOD AND TOBACCO

Chapter 1

Introduction and Implications

Norman A. Krasnegor, Ph.D.

This monograph is the first in a series of related volumes which will address different aspects of an area of research which has been termed "substance abuse." For the purposes of this exposition, the definition has been restricted to include only four behavioral categories, namely: excessive caloric intake, and use of ethanol, illicit drugs, and tobacco. These behaviors in their extreme form have generally been labelled as addictions (for example, to drugs and alcohol) or forms of dependency (cigarette smoking and over-eating). Thus, the focus of the definition is upon the pattern of excessive habitual use of these substances by individuals who exhibit such behaviors chronically over a period of years.

Of particular interest is the question, are these four separate behavioral patterns, or conversely, can they be understood as manifestations of the same more basic processes? The papers that follow address one aspect of a quest to determine empirically whether there are commonalties among the several substance abuse behaviors. Specifically, this monograph was organized to provide the reader with an appreciation of the methods used by behavioral scientists to observe and study the self-administration of cigarettes, alcohol, food and illicit drugs by humans under controlled laboratory conditions.

It is necessary to point out that many of the techniques employed have been adapted from paradigms originally designed to study the self-administration of these same substances in laboratory animals. This application of methodology represents a significant and important step in the field of substance abuse research. Thus, the rigor of the preclinical laboratory is being brought to bear in an applied problem area, thereby helping to upgrade the scientific quality of the observations made. In addition, the data derived from using such methods with human subjects has the salutary effect of confirming the validity of animal models of, self-administration.

During the course of the two-day conference which led to the publication of this monograph, a number of creative ideas and suggestions were presented concerning new directions for the study of

substance self-administration in humans. It was suggested, for example, that behavioral measurement techniques ought to be combined with those of the pharmacokineticist to correlate a substance's fate and distribution in the body with its behavioral effect. Another useful direction concerns the investigation of substance abuse patterns and the resultant interaction phenomena that accrue when two or more substances are used concurrently or sequentially. For instance, data now available indicate that use of alcohol increases the probability and amount of cigarette smoking. Whether this observation relates to behavioral, pharmacological, or both types of interactions is not yet known; however, research on these questions would appear to be essential to elucidate commonalities and determine mechanisms which may underlie such usage patterns.

"Binges" appear to occur in people who abuse substances from the categories germane to this monograph. Such behavioral excesses often have been reported in connection with the start of treatment designed to alter the self-administration frequency of food, alcohol, illicit drugs, and cigarettes. Is this behavior pattern a commonality that can be studied systematically, and can it enlighten us about some of the variables which control substance use? Similarly, one might conduct experiments to determine what are the necessary and sufficient conditions to maintain substance use behaviors once such patterns are established. Answers *to* these questions would help immeasurably to target and tailor our treatment efforts.

Further studies aimed at elucidating historical determinants of substance use behavior should be initiated to help us understand and characterize substance abuse patterns in groups at risk. Finally, an important area to explore is the relationship between subjective state and self-administration of various substances. The mapping of affect and mood on a baseline of self-administration behavior can provide a rich and comprehensive analysis of the total organism and insights into the motivational factors involved in substance abuse.

The additional reason for our interest in this research domain is that substance abuse has major implications for the public health. That is, the continual and substantial use of these four categories of substances has been linked etiologically and causally to the onset of major chronic illnesses: cardiovascular; hepatic, pulmonary, and neoplastic diseases. An understanding of substance abuse behavior, therefore, has a potential for impacting significantly upon health care and the health delivery system.

I am extremely pleased that the National Institute on Drug Abuse is in the forefront of developing the knowledge base in this emerging field, and I look forward to a continued and broadened interest in substance abuse research by the scientific community. Hopefully, this volume will provide a stimulus toward this goal.

I. Drugs and Ethanol

Chapter 2

Drug Seeking: A Behavioral Analysis in Animals and Humans

Marian W. Fischman, Ph.D., and
Charles R. Schuster, Ph.D.

Although data have been available for at least 20 years indicating that nonhuman organisms will self-administer morphine and ethanol. (Richter and Campbell 1940; Headlee, Coppock, and Nichols 1955; Reach 1957), the bulk of the data on drug-taking behavior has been collected during the past decade and has formed the basis for the development of an animal model of drug abuse. As has been indicated in several comprehensive reviews on the subject (Schuster and Thompson 1969; Schuster and Johanson 1974; Goldberg 1976; Johanson 1978; Woods 1978) this research has shown that drugs can serve as reinforcers for laboratory animals, and are therefore capable of controlling behavior in the same manner as other more extensively studied reinforcers such as food and water. The establishment of the fact that drug-taking is an operant, maintained and controlled by its consequences, has provided the basis for its investigation within the framework of behavior analysis. Viewing human drug taking as a class of responses within the conceptual context of behavior analysis makes possible a functional evaluation of a broad range of variables that may influence that behavior. There is a large body of data available from the analysis of other reinforcers which can be applied to the study of the variables important in influencing drug-taking. Studied in this light, the illicit use of drugs is a behavior problem comparable to other repetitive behaviors maintained by certain schedules of food or water reinforcement. The factors which affect it are the same as those which modify all behavior and much can be gained from examining sources of control utilizing nondrug reinforcers.

A major advantage of investigating the behavioral aspects of human drug abuse within the conceptual context of behavior analysis is the way in which the abuser is evaluated. Traditional approaches to the problems of drug taking in humans view that behavior as pathological and the abuser as abnormal. With the development of an animal model of human drug abuse, what has perhaps been most surprising is the universality of drug-taking behavior. Given the opportunity, a wide range of laboratory animals including rats, cats, dogs, monkeys and apes will self-administer most of the drugs

that are used by man for non-medical purposes. As has recently been pointed out by Goldstein (1976) discussing opiate use, in the absence of "countervailing influences in human society," drug use might well be the normal rather than the aberrant response. The best that we can hope to do with the problem of drug abuse, given the presence of drugs in our society, is to offer help to those who need it and limit the dimensions of the problem. The amazing frequency of heroin use in Viet Nam by U.S. soldiers who were not involved with heroin before or after their tour of duty offers strong support for the contention that drug abuse is not an aberrant pattern of behavior but instead, a response under the control of a variety of environmental stimuli (Robins, Helzer and Davis 1975).

This paper is concerned with addressing some of the issues involved in proceeding from an animal model of drug-taking behavior to a human model in which drug self-administration by humans is studied under controlled laboratory conditions. Of specific interest are the kinds of generalization that can be made from these studies to the actual abuse of drugs in society.

As was pointed out earlier, this model utilizes the concept that drugs, under appropriate conditions, can maintain or suppress behavior in much the same way as other more traditionally studied reinforcing stimuli. In order to take advantage of the generality of reinforcers, there is a need to systematically investigate their similarities and differences. Some of these studies have been done, and we will give examples of areas in which the commonality of effect has been demonstrated as well as point out specific areas where drugs, because of their diverse pharmacological properties, may differ from other reinforcers. In addition to their reinforcing properties, drugs have other effects. There may, for example, be substantial differences in the toxicity produced by drugs with equal reinforcing effects. Thus, another important aspect of drug abuse to be described in this paper involves the biological and behavioral consequences produced by the self-administered drug. The concept of drug use as pathological behavior will be discussed, and an alternative way of evaluating the same behavior will be described. Applications of the principles derived from utilization of this model will be suggested and, lastly, the advantages and disadvantages of collecting subjective measures of drug effects will be examined.

his discussion is not meant to be a comprehensive review of the literature in these areas. Rather, specific examples will be taken from research reports in order to provide illustrations for our discussion of some considerations in the extrapolation of animal laboratory data to research on human drug taking.

DRUGS AS REINFORCERS

he presentation of a stimulus event known to be a reinforcer under one set of conditions may not have the same effect under other

conditions. The most obvious example of this is the fact that food presentation will not always control responding in a non-food-deprived animal. In the same way, a variety of variables can modify the ability of drug presentation to serve as a reinforcer. Drugs maintain behavior only under certain conditions; rates and patterns of responding for drug presentation depend on variables such as drug history of the organism, schedule of drug injection and dose of drug injected. A number of different studies have shown that the same variables which affect behavior maintained by traditional reinforcers like food also modify behavior maintained by drug reinforcers. Goldberg (1973), for example, demonstrated the similarity of effect of varying the amount of food or dose of drug on behavior. Increasing the dose of cocaine or the amount of food presented resulted first in an increase and then a decrease in the average response rate under 10- or 30- response fixed ratio (FR) schedules. The pattern of responding, high at the beginning of the session and lower at the end of the session, was similar for both reinforcers. Further, when a second-order fixed interval (FI) schedule of FR components was introduced, response rate remained constant as drug dose or amount of food was varied. The effect of changing the parameter value of the reinforcer was the same regardless of the reinforcer, although different from that seen under simple FR schedules. Thus the schedule of reinforcement under these conditions was more important in the control of behavior than the nature of the reinforcer.

The similarity of drugs to more traditional reinforcing stimuli is shown by the fact that the same drug can serve to either maintain or suppress the behavior it follows. Thus, it is well known that under some circumstances animals will respond vigorously to receive electric shocks which, under other conditions, they will vigorously respond to avoid (Kelleher and Morse 1968; McKearney 1968). In the same way, certain drugs have been shown to have functionally different stimulus properties depending on the schedule parameters being used. For example, physically dependent rhesus monkeys will respond either to postpone or terminate the injection of naloxone or nalorphine (Goldberg, Hoffmeister, Schlichting and Wuttke 1971; Holz and Gill 1975; Kandel and Schuster 1977). On the other hand, Woods, Downs and Carney (1975) have reported responding maintained by comparable doses of naloxone in morphine-dependent monkeys. The similarity of shock and drug in their ability to control behavior in a variety of ways is impressive. Clearly, in these cases, it is not the stimulus controlling the behavior, but the scheduling of that stimulus that modifies the behavior.

An impressive example of the ability of scheduled stimulus events to control behavior is seen with second order schedules of food or drug presentation. These schedules maintain long orderly sequences of responding but limit the frequency of reinforcer presentations which may decrease responding. In these schedules a brief stimulus is presented at the end of each unit schedule and paired with the reinforcer which is only presented according to a schedule of the unit schedules (Gollub 1977). A number of

studies have indicated that high rates of responding over prolonged periods of time can be maintained with minimal presentations of the reinforcing stimulus. The implication for drug-maintained behavior in humans is obvious. Drug-taking generally involves a chain of behaviors including obtaining the money, looking for a source of drug, buying and preparing it, and only then taking it and experiencing its effects. All the parts of this sequence have stimulus properties which can be conditioned because of their association, albeit occasional, with the drug. These conditioned reinforcers can then serve to maintain drug-taking or even to re-initiate it after some period of abstinence.

Further evidence for the similarity of drugs to other reinforcers has been accumulated through manipulation of deprivation conditions. Such manipulations have been shown to alter responding maintained by food, water and sex in a lawful and predictable fashion (Ferster and Skinner 1957). Similarly, responding maintained by opiate injections has been shown to vary as a function of these parameters. Just as food satiation can be accomplished by giving the animal graded amounts of food prior to an experimental session, so drug satiation has been studied by administering a range of doses of the reinforcer just prior to the experimental session. Under these circumstances, as with other reinforcing stimuli, responding maintained by morphine (other drugs have rarely been studied in this way) is decreased with opiate pretreatment (Thompson and Schuster 1964; Thompson 1968). This concept forms the basis for the use of methadone maintenance therapy with heroin addicts (Dole and *Nys*-wander 1965). The effects of opiate deprivation in physically dependent animals are opposite to those of satiation; increasing the deprivation of morphine-dependent monkeys from 6-24 hours causes an increase in response rate (Thompson and Schuster 1964). There also seems to be a comparability of the effects of deprivation when discrimination behavior is examined. In a series of studies investigating the effects of food deprivation on responding maintained by food presentation under variable interval extinction (VI EXT) in pigeons, Powell (1971, 1973) reported that the increase in responding during the extinction stimulus was four times as great when food deprivation was increased from 24-72 hours as when deprivation was increased from 24-48 hours. Similarly, a loss of stimulus control has been shown when opiate deprivation is increased in opiate dependent animals. Woods and Schuster (1968) showed, that physically dependent monkeys responding under a multiple variable interval extinction (mult VI EXT) schedule for morphine showed an increase in responding during the extinction portion of the schedule as morphine deprivation was increased. In general, the data showing a relationship between deprivation level and stimulus control have not been collected for non-opiate drug reinforcers. There is, however, some preliminary evidence from our laboratory indicating that the same relationship does not hold for drugs in the stimulant class. Preliminary data have been reported by Johanson (1978) indicating that there is no breakdown in stimulus control when the

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time between 3-hour sessions is varied from 1-45 hours for monkeys responding under a fixed-ratio or fixed-interval 5-min schedule of 0.2 mg/kg cocaine delivery. Similar data were found with pentobarbital in nondependent animals.

Because drugs have pharmacological as well as reinforcing effects, there are limitations in their functional similarity to nondrug reinforcers. With repeated intake of a drug, metabolic as well as behavioral changes occur which modify the organism and its relationship to the environment. Thus, the physical dependence caused by long term opiate intake or the flashbacks reported after LSD ingestion may indicate changes in the organism which permanently alter the pattern of its interaction with its environment. It is possible that, at least for drug reinforcers, we have to differentiate between variables responsible for initiation of responding and those responsible for its long term maintenance. This may also be true for nondrug reinforcers; the data are simply not available.

It should be clear from the above examples that both drug and other reinforcer-maintained responding can be affected similarly by a number of different variables. As previously mentioned, this enables us to study drug taking using procedures developed for research in the area of behavior analysis. This methodological approach allows us to precisely quantify the behavior in question as well as to utilize the principles derived from the study of behavior maintained by other stimulus events in developing a model of human drug abuse.

CONSEQUENCES OF DRUG SELF-ADMINISTRATION

The concept of drug abuse involves more than the statement that an organism is self-administering a drug for nonmedical purposes. Implicit in the word abuse is the idea that there are toxic behavioral and physiological consequences associated with this drug self-administration. As has been argued elsewhere (Renault and Schuster 1972), society is not primarily concerned with whether a drug is self-administered, but rather whether or not a drug produces physiological and/or behavioral effects which are deleterious to the individual or society. Clearly, there is no moral outrage concerning the many people who self-administer large doses of caffeine in coffee every day despite the fact that this is a drug with clear-cut CNS stimulant properties. In examining the problem of human drug taking, there has been minimal research on differentiating use and abuse.

It is frequently difficult to measure behavioral consequences of drug taking in people involved in the activities of their daily lives. Procedures most commonly used for evaluation of drug effects in humans have relied heavily on personal subjective reports (Fraser et al. 1961; Hollister et al. 1968; Teasdale and Hinkson 1971) as well as short term structured performance tests (Mirsky and Kornetsky 1964). There have been few attempts to collect data in more naturalistic environments using a range of

reinforcers and evaluating interactions of reinforcers and behaviors. To this end, Brady and his colleagues have built a unique programmed residential environment in which drug-behavior interactions can be assessed in a reasonably naturalistic setting over extended periods of time. They have designed a system which allows a substantial amount of experimental control including the manipulation, measurement and recording of pharmacological and environmental variables relevant to the analysis of antecedents and consequences of drug-taking (Emurian, Emurian, Bigelow and Brady 1976). The high level of experimental control possible in their studies allows for a systematic manipulation of appropriate variables and careful analysis of any change in behavior. Such research can be invaluable in validating hypotheses derived from less complex laboratory models and should be encouraged.

When the consequences of drug-taking are evaluated, clearly the amount and pattern of intake are both very relevant. Compulsive repetitive drug self-administration is very different in its effects from the well regulated intake of a drug. The concept of controlled drug use is important in the assessment of toxic consequences. Data collected in the animal laboratory indicate that when animals are given limited access to a wide range of drugs, they will self-administer them in similar amounts with similar patterns of intake across a number of different species and drugs (e.g., Johanson 1978). Clearly, this intake of drug has not resulted in a loss of schedule or stimulus control. In fact, under conditions of limited access there do not appear to be irreversible toxic effects produced by drugs. However, there are substantial data indicating that unlimited access to drug reinforcement can lead very rapidly to irreversible toxic consequences (Johanson, Balster and Bonese 1976). The implications of this for societal regulation of recreational drugs is quite apparent. The common phenomenon of not having an alcoholic drink before 5 p.m. is a self-control procedure designed to provide only limited access to alcohol in order to avoid toxic consequences. Unfortunately, little cultural regulation exists in relation to the recreational use of other drugs.

DRUG SELF-ADMINISTRATION: NORMAL OR ABNORMAL?

It has been suggested by a number of different investigators that drug dependence is a disease, characterized by a readily recognizable set of symptoms (Martin, Haertzen and Hewett 1978; Lindesmith 1937). Thus, Martin et al. (1978) have called this syndrome hypophoria and define it as a "negative feeling state" similar to, but not the same as, depression, since these drug abusing patients with negative self-image view their rejection as a failure of others to appreciate them. Drugs reverse their feelings of inadequacy by producing feelings of wellbeing and reducing need states. Senay and his colleagues (personal communication) have collected a substantial amount of data showing that chronic drug users are likely to be diagnosable as depressed. More than 60 percent of a 600 subject sample requesting treatment at drug abuse treatment centers in

Chicago were diagnosed as severely depressed based on their responses on a series of pencil and paper measuring instruments including the Hopkins Symptom Checklist and the Beck Depression Scale. After nine months of treatment 20 percent of that sample still scored in the severely depressed range.

A possible alternative, but not necessarily opposite, way of looking at the drug user is as an organism who lacks other available reinforcers, or the repertoire to obtain other reinforcers. Thus, both the depression and the drug-seeking behavior may be the product of inadequate reinforcement schedules. As has been pointed out by Renault and Schuster (1972), the strength and immediacy of drug reinforcement make it likely that drug taking, particularly when it is intravenous, will be able to override other behaviors which depend on long chains of conditioned reinforcers and a final payoff which is frequently remote. The frequently noted communality of drug users may reflect the fact that the more traditional reinforcers in human society are not available or not as potent as for non-drug-users. It has been hypothesized that the depressed patient is someone who is not responsive to the contingencies of reinforcement but shows more responsivity to contingencies as the depression is alleviated (Ferster 1966). In the same way, the drug abuser may be responding to this lack of reinforcers by self-administering an immediate-acting potent reinforcer. Similarly, the observation by Martin et al. (1978) that "drug-abusers feel unpopular, inept and not respected or appreciated" may he another way of saying that these people lack either the repertoire to obtain the traditional reinforcers of our society or the conditioning history to utilize those reinforcers. The depressed symptomatology measured by Senay and his colleagues may also be interpreted in this light.

APPLICATIONS OF THE SELF-ADMINISTRATION MODEL

One application of an animal model of human drug abuse is the preclinical assessment of the abuse liability of new drugs. As we stated earlier in this paper, it has been found that animals self-administer the same drugs which humans take for nonmedical purposes. These include opiates, barbiturates, alcohol and stimulants (Schuster and Thompson 1969; Schuster and Johanson 1974). Further, the patterns of intake in the animals are similar to those seen in humans illicitly abusing them. Thus, the cycles of high stimulant intake alternating with days of low intake are reminiscent of the pattern reported for humans (Johanson, Balster and Bonese 1976; Kramer, Fischman and Littlefield 1967). Finally, the behavioral and physiological consequences of repetitive drug self-administration are similar in animals and humans. It is for these reasons that the assumption is made that if animals readily self-administer a specific drug, it is likely that humans will abuse it with the same toxic consequences as are observed in animals.

There is no difficulty in choosing appropriate animals for the preclinical assessment of the abuse liability of new compounds. A number of different species have been used in the development of the model, and since they are all laboratory animals their past drug and conditioning histories are known and can be controlled. This is clearly not the case when we do drug abuse research using human subjects . The use of human research subjects in the study of drug self-administration is ethically limited to those people who have previously abused the drug being studied. The fact that we use a subject population with a prior drug-taking history means that our subjects are selected according to certain characteristics which may not be typical of the population at large. The observation that morphine has different subjective effects in the opiate abuser as opposed to the non-opiate abuser (Lasagna et al. 1955; Smith and Beecher 1959) lends credence to this statement. There is also evidence from the animal laboratory indicating that drug-taking behavior is modifiable by the subject's prior history (Goldberg 1973; Schlichting, Goldberg, Wuttke and Hoffmeister 1971) although the way in which these variables interact has not been systematically investigated. If, in fact, the non-drug abusing population does not respond to drugs in the same way as the abuser population, we must take care when doing studies on the prediction of abuse liability as well as the assessment of toxic consequences of drugs. It may well be, for example, that in normals the only performance effects that we can expect to see are deficits (Pillard and Fisher 1978). The true "normal," by definition, is probably functioning at or near optimal performance levels and therefore there would be a ceiling effect on any possible performance facilitation. In contrast the drug users' performance may be enhanced because they start at a different performance baseline.

The view of the drug user as a self-medicator fits into this analysis. Teasdale and Hinkson (1971) presented data suggesting that stimulant abusers viewed themselves as deficient in certain personality traits and that these deficits disappeared, as measured by a series of pencil and paper checklist instruments, after stimulant ingestion. In the same way, there is more objective evidence from the animal laboratory indicating that specific abused drugs may function to aid the organism in adapting to some potentially toxic effects of aversive environmental stimulation. Hutchinson (personal communication) has found that certain stressful stimuli can cause an increase in blood pressure in squirrel monkeys. If these animals are maintained on nicotine, those same stimuli have little effect on blood pressure.

A second application of the animal model of drug abuse is in the development of therapeutic treatment programs for human drug abusers. The self-administration model assumes that those variables which modify drug-taking behavior are the same in animals and in humans. In order to determine the validity of this assumption, and thereby make this information available for use in treatment programs we must test some of the principles with human research

subjects . A substantial amount of research has been carried out in the animal laboratory isolating the variables that maintain drug-taking, a necessary first step in developing procedures for reducing drug abuse in humans. We must, however, move on from the isolation of variables to a consideration of ways in which these can be therapeutically applied.

Contingent time out from positive reinforcement has been shown to be effective in the animal laboratory in suppressing behavior maintained by more traditional reinforcers such as food (Ferster 1958; Holz, Azrin, Ayllon 1963). Recently, a systematic series of studies addressing this topic of contingent time out from positive reinforcement after a drinking response by alcoholic subjects has been reported (Bigelow, Liebson and Griffiths 1974; Griffiths, Bigelow and Liebson 1974, 1977). Initially, it was demonstrated that when 10 or 15 minutes of physical and social isolation was the immediate consequence of each drink, alcoholics given access to substantial amounts of alcohol in a residential hospital research ward suppressed their drinking behavior to approximately one-half of baseline levels. Secondly, the procedure was adapted to determine which aspect of the isolation was controlling the drinking. It was found that contingent restriction of either social interactions or of physical activity was successful in suppressing drinking. In fact, contingent time out suppressed the drinking response as a function of the number of other available privileges; the greater the number of restrictions, the greater the effect of the time out. These data demonstrate the control of drug-taking behavior by more than one variable and indicate the need to study effects of manipulating a range of variables in developing any successful drug abuse treatment program.

A recent operant approach, using the principles just described, to the development of therapeutic procedures for maintaining drug abstinence, was reported by Hunt and Azrin (1973) for use with alcoholics. The theoretical basis for their methodology was also the concept of time out from reinforcement contingent on the ingestion of alcohol. In order to maximize the effects of the time out, the reinforcers assumed to be maintaining nondrinking behavior in the alcoholics were grouped closely in time and increased in magnitude. Thus, community reinforcers such as jobs, family and social relations were rearranged such that each research subject had a job, intensive family counseling, a place to socialize and legal help if necessary, all contingent on abstention from drinking alcohol. Alcoholics on this program drank less, worked more and spent more time with their families and out of institutions than a matched control group of alcoholics. It is clear that the manipulation of a wide range of contingencies was effective in suppressing the drinking behavior. This is an excellent example of the way in which principles from the animal and human laboratory were utilized to design a successful drug abuse treatment program. Data collected using the methodology of behavior analysis suggested the relevant manipulations.

Another possible therapeutic manipulation is the reduction of drug-taking through pretreatment with other less toxic substances. Thus, it has been reported that pretreatment with etonitazine, codeine and meperidine decreases the rate of responding by rats maintained by morphine while dexoxadrol and dextromethorphan do not (Weeks and Collins 1964). This procedure has been extended to humans who were given the opportunity to ride an exercise bicycle for saline or 4 mg i.v. hydromorphone several times per week before and during a period of daily maintenance on 100 mg of oral methadone (Jones and Prada 1975). Measures of pupillary change and reports of "liking" in response to the hydromorphone dropped to saline control levels during the methadone maintenance period and bicycle riding for the hydromorphone dropped substantially, occurring only intermittently in two of the six subjects. Studies such as this one can be useful in designing treatment programs which utilize principles of drug substitution such as methadone maintenance.

Since morphine pretreatment decreases the rate of morphine self-administration (Thompson and Schuster 1964) it is tempting to predict that this principle will hold for other classes of drugs. For example, Lucchesi, Schuster and Emley (1967) studying cigarette.. smoking in humans found that the intravenous infusion of 22 mg of nicotine over 6 hours caused a 27 percent decrease in the number of cigarettes smoked (as well as a significant decrease in the amount of each cigarette smoked) compared with a 6-hour period when saline was administered intravenously. That this was not simply a toxic effect is suggested by the fact that subjects were not able to correctly discriminate whether they were receiving nicotine or saline. A further extrapolation from the opiate data might be the prediction that other drugs in the same class as nicotine (i.e., stimulants) should also cause a decrease in the rate of nicotine (or cigarette) self-administration. In an unpublished study by Schuster and Emley (personal communication) three volunteer research subjects, who were unaware of the purpose of the study, were observed during a series of 6-hour experimental sessions while they were engaged in a number of simple behavioral tasks. Subjects were pretreated with a range of doses of d-amphetamine or meprobamate as well as placebo at the beginning of each 6-hour session. In addition, they received 2.5 mg of lobeline (a naturally occurring alkaloid similar in action to nicotine but less potent [Volle and Koelle 1975]) three times a day for 4 days and were tested each day. During each daily session the number of cigarettes smoked and the weight of all remaining butts were recorded. Table 1 presents the mean number of cigarettes smoked and the mean butt weight during each pretreatment condition. Perhaps the most striking finding in this study is the degree of regulation shown by each subject during the placebo pretreatment condition. The number of cigarettes smoked by each subject during each day of this condition was: (S-1) 8, 8, 8, 9, 8; (S-2) 9, 9, 10, 9, 9; (S-3) 10, 11, 11, 11, 13, 13, 13, 10. Given the fact that each session was 6 hours in length, the stability of intake is impressive. d-Amphetamine caused an increase in the number of cigarettes smoked in 2 of the 3 subjects tested and had no effect in one subject (S-1).

TABLE 1

THE EFFECTS OF DRUG PRETREATMENT ON CIGARETTE SMOKING IN HUMANS, DURING 6-HOUR EXPERIMENTAL SESSION*

Pretreatment Condition	Mean # Cigarettes Smoked ± S. D.	Mean Butt Weight ± S.D.
Placebo	9.6 ± 1.2**	.505 ± 0.11**
d-Amphetamine		
5.0 mg	12.25 ± 3.1	.463 ± .026
7.5 mg	12.3 ± 4.5.	.456 ± .012
Meprobamate		
400 mg (n=2)	10.0 ± 1.4	.504 ± .002
600 mg	10.0 ± 1.7	.475 ± .039
800 mg (n=2)	11.0 ± 2.8	.472 ± .006
Lobeline***		
2.5 mg day 1	11.6 ± 3.2	.471 ± .029
day 2 (n=2)	10.0 ± 0	.514 ± .Oll
day 3	10.7 ± 2.5	.505 ± .015
day 4	11.3 ± 3.0	.489 ± .015

* N=3 unless otherwise noted
** Standard error of the mean of all three means
*** Administered t.i.d. and tested daily for four days

This does not simply reflect an increase in the number of cigarettes lit but not smoked since butt size showed a small decrease (i.e., more of each cigarette was smoked). Meprobamate had no effect in any of the subjects at any of the doses tested. Lobeline was administered in a dose of 2.5mg three times each day so that plasma levels would be relatively constant. It was hypothesized that if nicotine infusions could cause a decrease in cigarette smoking, lobeline, a compound with similar actions on the body, should also have the same effect. This, however, was not the case. No change in cigarette consumption was recorded in any of the 3 subjects tested, an indication that attempting to substitute this dose regimen of lobeline for nicotine in the treatment of cigarette smokers would ‘probably be unsuccessful. Thus, cigarette smoking is a complex phenomenon, and the use of a substance with physiological actions similar to nicotine is insufficient to cause a change in cigarette consumption.

SUBJECTIVE MEASURES

The pertinence of laboratory studies of drug reinforcement using nonhuman subjects to the design of experiments using human subjects. cannot be overestimated. Clearly, the development of an animal model of drug dependence has created a factual and conceptual basis for the design of investigations of drug-taking behavior in humans. Operant research has traditionally taken advantage of the existing behavioral repertoire of the organism. Thus, the already present discrete pecking behavior of the pigeon has been used by experimenters as a key-peck response, and the exploratory behavior of rats has been utilized in the shaping of a lever-press response. In a similar fashion, humans are capable of verbal behavior and it would be a mistake to ignore this unique behavioral repertoire.

Behavioral pharmacology and psychopharmacology, both studying drug-behavior interactions, have developed along parallel lines; the former within an operant framework and the latter utilizing the more traditional methodology of psychology. One of the most useful psychopharmacological tools in the assessment of drug effects in humans has been the subjective report of a drug's effect, usually assessed with a standard drug effects questionnaire such as the Addiction Research Center Inventory. Operant psychologists have tended to shy away from the utilization of verbal reports as an indication of drug effects because of its historical association with inner mental processes. Verbal behavior is, however, an operant in and of itself, which may be divided into response classes for investigative purposes (Skinner 1957). Initial research by Greenspoon (1951, 1955) in the area of the behavioral analysis of verbal behavior has been corroborated and extended by a substantial number of other investigators (see Holz and Azrin 1966 for a review of this literature). They have shown that verbal behavior, when the response is well defined and the reinforcer consistently applied, comes under the control of reinforcement contingencies in the same manner as other behaviors.

In evaluating the abuse potential of psychotropic drugs in humans, a recently described approach (Fischman 1977; Jasinski 1977) is to establish a profile of the effects of a standard known drug of abuse and use that profile as a template against which the abuse liability of other drugs in the same class can be assessed. Subjective effects are clearly important in this evaluation of a drug's effects in humans. These are valid measures which, when taken under relatively standard conditions? have been shown to vary lawfully with the dose and drug administered (Martin and Fraser 1961; Martin, Sloan, Sapira et al. 1971; Fischman, Schuster Resnekov et al. 1976; Fischman 1977; Jasinski 1977).

Holtzman and his colleagues (Shannon and Holtzman 1977, Schaefer and Holtzman 1977) have recently reported a procedure for use in the animal laboratory which, they speculate, measures behavior in rats or squirrel monkeys that is under the stimulus control of specific drugs in much the same way as subjective

effect reports of humans. Animals were trained in a two-choice, discrete trial avoidance paradigm to discriminate morphine from saline. Similarity to morphine was then evaluated for representative narcotic analgesics, analgesics with mixed agonist and antagonist properties, and nonopioid psychoactive drugs by determining their dose-response characteristics. Discriminative effects equivalent to those of morphine were found for the narcotic analgesics and narcotic antagonists which produce morphine-like subjective effects in humans. Thus, the functional similarity between the lever-press response in rats or monkeys and the humans' verbal reports has been shown. Both of these responses can be brought under stimulus control of drugs.

Implicit in the use of subjective effects questionnaires is the acceptance of verbal behavior as a reliable response class, and the understanding that the report of a drug's effects is verbal behavior under the stimulus control of the specific drug being tested. In the same way that we accept the data collected in the animal laboratory with a rat or monkey lever-pressing, we must remember that verbal behavior is under the control of a range of contingencies, some of which may be as important or more important than the stimulus control exerted by the physiological effects of the drug being studied. Thus, a study by Schachter and Singer (1962) indicates the potent effects of external stimuli in the assessment of a drug's effect. Subjects, ignorant of what they were receiving, were injected with epinephrine and then allowed to interact with a second "subject" (really someone trained by the experimenter) who behaved either in a highly euphoric or very angry fashion. They were then asked to rate how angry and how happy they felt. They all reported heart palpitations and tremors of the hands and legs. Those exposed to the euphoric second subject reported being more happy than angry; the opposite was true for those exposed to the angry second subject. In the same way, it is stated that the lower the dose and the less potent the drug, the more likely it is that environmental stimuli will play a part in determining a specific drug response. Anecdotal reports by recreational marihuana users indicate that an abrupt change in mood by one of a group who have smoked together will often be the stimulus for mood change in everyone else in the group. This does not mean that subjective drug effects data are too variable to be useful. It simply indicates that we must exert great care to administer our questionnaires under standard conditions, controlling the drug-taking environment and contingencies as much as possible.

A second area of concern in the utilization of subjective measures of drug effects is the tendency by some investigators to ascribe causality to what is simply a response. Thus, the equating of "reinforcing" with "euphorogenic" (Mello 1977). This has nothing to do with the verbal behavior being measured - only with the inappropriateness of the experimenter's verbal behavior. The danger lies in generalizing from the response to the cause. We do not assume that the presentation of a food pellet maintains

lever pressing in the rat because of its euphoric effect, and, by analogy, we have no reason to assume that drugs are self-administered because of their euphoric effects. The stimulus properties of the drug being self-administered are maintaining the drug-taking; the subjective effects are simply one of the behavioral measures being taken. Further, at this point we have no data to indicate that these variables even co-vary. In fact, another paper in this monograph discusses research designed to investigate this question. Johanson and Uhlenhuth (1978) gave human research subjects the opportunity to choose between d-amphetamine (5 or 10 mg) or diethylpropion (25 or 50 mg) and placebo as well as between doses of the two drugs. At the same time, mood change was assessed using the Profile of Mood States (POMS). Their results suggest that there is no simple relationship between the reinforcing properties of these two drugs, as measured by the frequency that subjects chose to self-administer them, and their mood changes, as measured by their Arousal score on the Profile of Mood States. In fact, there appear to be more dysphoric effects reported after ingestion of the more highly preferred drug and dose of drug. Clearly more research must be done in this area.

A drug's profile of action in humans should also include some basic physiological and behavioral measures. In animal self-administration studies we have the luxury of studying a wide range of doses of a specific drug in order to be sure that we are presenting appropriate doses to the animal. Because human research subjects are more limited in number we should obtain as many measures as possible in each subject to determine that the dose range in question is both safe and effective. In addition, it is obvious that when we maintain human subjects in a hospital facility for some period of time we should collect as much information as possible on many different measures. Just as animal laboratory studies are frequently designed to assess the behavioral effects of the drug being self-administered using, for example, multiple schedules (Johanson 1978), so the human studies should do the same.

CONCLUSION

This paper has attempted to discuss some of the issues involved in proceeding from an animal to a human model of drug-taking behavior. As was pointed out, we use animal models because the phenomenon under study is complex and demands vigorous control over both past conditioning and drug histories as well as the current behavioral contingencies. Further, for ethical, medical and legal considerations, it is impossible to make the appropriate manipulations necessary for an analysis of the phenomenon under study using human subjects. It should be emphasized that although research with humans is necessary, the majority of the systematic studies carried out in this area must be implemented in the animal laboratory. Carefully selected studies should then be done with humans to establish the generality of our model across species. Given the fact of evolution, coupled with the generality of the data already collected across infra-human species using drugs as

reinforcers; we have every reason to expect that this generality will continue to prevail when human subjects are tested. Since we do not have the luxury of running a large number of human studies, each subject that we test is a precious commodity and we must look systematically for similarities and differences in effects of drug reinforcers on behavior, carefully based on an analysis of the currently available data from the animal laboratory. Such validation of an animal model of drug abuse may be one of the most important reasons for conducting human drug self-administration studies.

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ACKNOWLEDGMENT

This research was supported by grants from the National Institute on Drug Abuse DA-00024 and DA-01491, Charles R. Schuster, Principal Investigator.

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Chapter 3

Experimental Drug Self-Administration: Generality Across Species and Type of Drug

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Abstract. Human drug self-administration methods in residential settings have been developed, and research has examined a range of variables which systematically influence the drug taking behavior. Confidence in the results with these methods is increased by the demonstration of two types of generality: across species and across drug. Across species generality is demonstrated by the fact that similar effects on drug taking are obtained in human and infrahuman experiments when the same variables are manipulated (including: type of drug; dose of drug; response requirement to obtain drug; punishment of drug self-administration; and drug preloads). Across drug generality is demonstrated in human research by the fact that manipulation of major variables (including dose of drug; response requirement to obtain drug; and minimum interingestion interval) produces similar effects on the self-administration of different drugs (e.g., ethanol, diazepam and pentobarbital). Across drug generality is also demonstrated by the finding that the self-administration of different drugs produces similar effects on the social behavior of the drug user. Demonstration of across species and across drug generality suggests that common processes may underlie various aspects of drug self-administration, and supports the supposition of a generalized behavioral phenomenon of substance self-administration.

INTRODUCTION

Human research characterizing the effects of chronic administration of various drugs began more than 40 years ago at the Addiction Research Center (cf. Jasinski 1973 and Wikler 1977 for reviews of this early research). In 1964 Mendelson reported a classic set of studies involving chronic administration of ethanol to alcoholics. In 1965 Mello and Mendelson published their first of many subsequent studies which involved free choice ethanol self-administration by alcoholics in a hospital ward setting (cf. Mello 1972 for a review of this early work).

Over the last 15 years, the technology for studying self-administration of drugs in residential ward settings has been developed and refined. Bigelow, Griffiths, and Liebson (1975a, b) have reviewed the historical development of these procedures for analyzing human drug self-administration and have commented upon the importance of some of the major methodological characteristics which have evolved. Typically drugs are made available for ingestion to volunteers with histories of drug abuse under conditions which permit the gathering of empirical information concerning the patterns and effects of drug self-administration. The experiment is usually conducted over the course of several weeks, and the subject is sequentially exposed to different experimental conditions using a within subject methodology. These experimental procedures involving controlled laboratory environments were originally developed in the analysis of ethanol self-administration and they have subsequently been extended to the analysis of other drugs of abuse. Research has been reported on the self-administration of marihuana (Miles, Congreave, Gibbins, Marshman, Devenyi, and Hicks 1974; Mendelson, Rossi, and Meyer 1974), opiates (Jones and Prada 1975; Meyer, Mirin, Altman, and McNamee 1976; Angle and Parwatikar 1973), sedatives (Griffiths, Bigelow, and Liebson 1976b; Pickens, Cunningham, Heston, Eckert, and Gustafson 1977) and nicotine (Mello and Mendelson 1971; Griffiths, Bigelow and Liebson 1976a). Presently, a considerable literature exists concerning the behavioral pharmacological relationships observed in studies of human drug self-administration, and this methodology appears to provide a fruitful context within which to study an experimental model of the phenomenon of substance abuse.

Confidence in the results of research utilizing experimental human drug self-administration methods is increased to the extent that they can be replicated across a range of conditions. Such generalizability of results is important for establishing that the results are not merely artifacts of the experimental situation. The present paper will review the evidence that has established two major types of generality of drug self-administration results: across species and across drug generality.

ACROSS SPECIES GENERALITY

Across species generality has been established by comparing the results of human drug self-administration studies with similar studies done with infrahuman subjects. In infrahuman drug self-administration research animals are given access to an operandum, and responding on the operandum results in delivery of drug. This model has been established using a variety of animal species (e.g., rat, dog, cat, monkey, baboon), types of operandum (e.g., lever press, panel press) and routes of drug administration (e.g., intravenous, oral, intragastric, inhalation). As with the human drug self-administration procedures, these animal techniques have been developed over the last 15 years (cf. Schuster and Thompson 1969 and Spealman and Goldberg 1978 for reviews).

In spite of vast methodological differences between the human and infrahuman drug self-administration research, some convergence of results is apparent. The present section will review the major classes of experimental manipulations that have been undertaken in drug self-administration research and emphasize those instances in which there is a good correspondence in results of the human and infrahuman research.

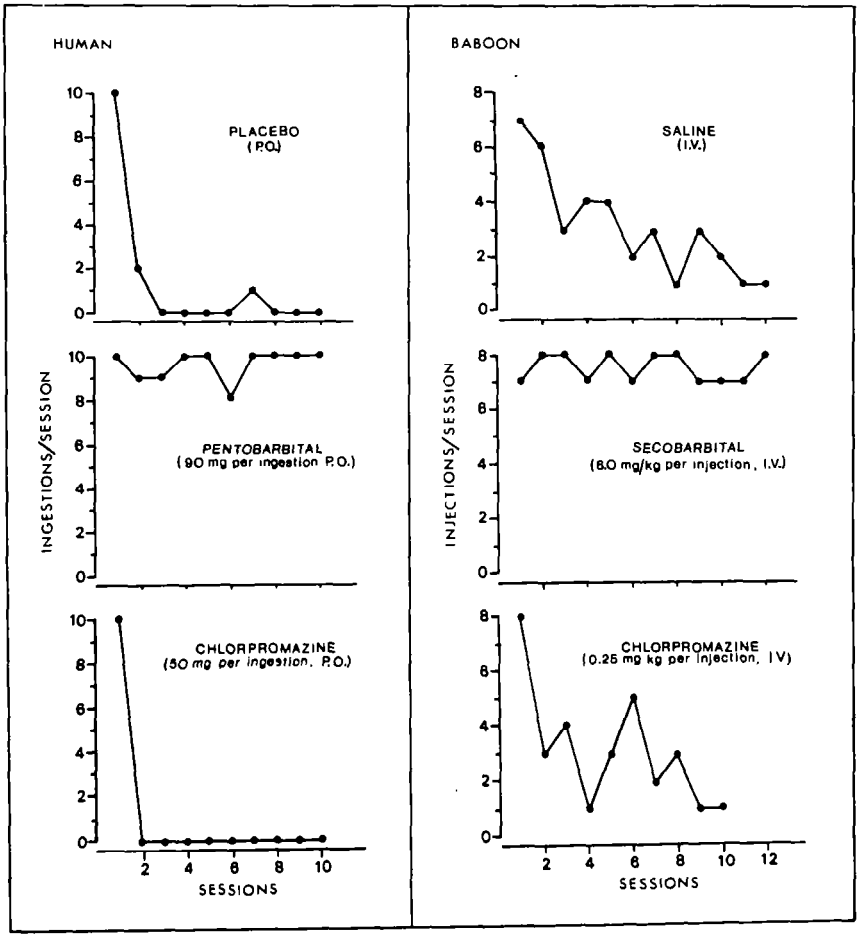
Type of Drug The type of drug available is perhaps the most basic druq variable that has been shown to be a determinant of druq self-administration in humans and infrahumans. For example, Fig. 1 presents representative individual subject drug self-administration data showing that selected doses of pentobarbital or secobarbital maintain regular daily self-administration in both humans and baboons. In contrast, the drug vehicle (placebo or saline) and chlorpromazine failed to maintain self-administration. These data show that drugs differ with respect to their capacity to maintain self-administration behavior in both animals and man. Other research has shown that there is a good relationship between those drugs self-administered by laboratory animals and those abused by man (e.g., Deneau, Yanagita, and Seevers 1969; Griffiths, Brady, and Snell 1978a,b). For instance, with a standard drug substitution procedure, baboons will self-administer the opiate drugs heroin, morphine and codeine, the sedative compounds pentobarbital, secobarbital and methaqualone, as well as the stimulant compounds cocaine, amphetamine and methylphenidate. All of these compounds have been associated with numerous reports describing their abuse. In contrast, the baboon will not self-administer the opiate antagonists naloxone and nalorphine, the sedative phenobarbital, the major tranquilizer chlorpromazine and the anorectic drugs phenylpropanolamine and fenfluramine. These data correspond well to the fact that human abuse of these drugs is relatively rare (cf. Griffiths, Brady, and Bradford 1978 for a comprehensive review of this literature with stimulant compounds).

Drug Dose Drug dose is a variable that influences virtually all pharmacological responses, and therefore it is not surprising to find that it directly affects human and infrahuman drug self-administration. Fig. 2 shows that under some conditions in both humans and baboons, increasing doses of a reinforcing drug (in this case ethanol or cocaine) are associated with increasing levels of drug self-administration. Other animal drug self-administration studies have shown that when a wide range of doses is examined, the total number of infusions varies as an inverted U-shaped function when dose per infusion is varied. In the data shown in Fig. 2 it is probable that further increases in drug doses would have eventually produced toxic or debilitating drug effects and produced decreases in drug intake, thus resulting in an inverted U-shaped function.

Response Requirement Fig. 3 illustrates the commonality of effect upon both human and animal drug self-administration of variations in the response cost (amount of behavior) required to obtain single

FIGURE 1

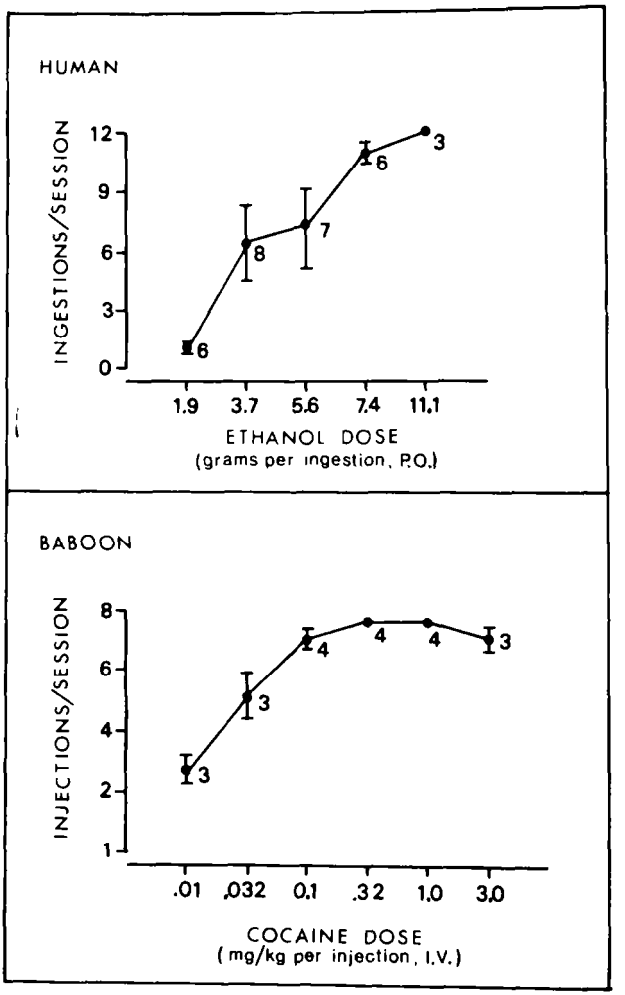
ACROSS SPECIES GENERALITY:
Effect of Type of Drug on Self-Administration



Effect of type of drug on drug self-administration in humans and baboons. Each graph shows the amount of drug self-administered by one representative subject over consecutive daily sessions. The drug, dose, and route of administration are indicated. The human experiment (Griffiths, Bigelow, and Liebson, unpublished data) utilized general methods described previously (Griffiths, Bigelow, and Liebson 1976b) to study the effect of various drugs at several doses under double blind conditions. The baboon experiment (Griffiths, unpublished data) also utilized general methods described previously (Griffiths, Winger, Brady, and Snell 1976).

FIGURE 2

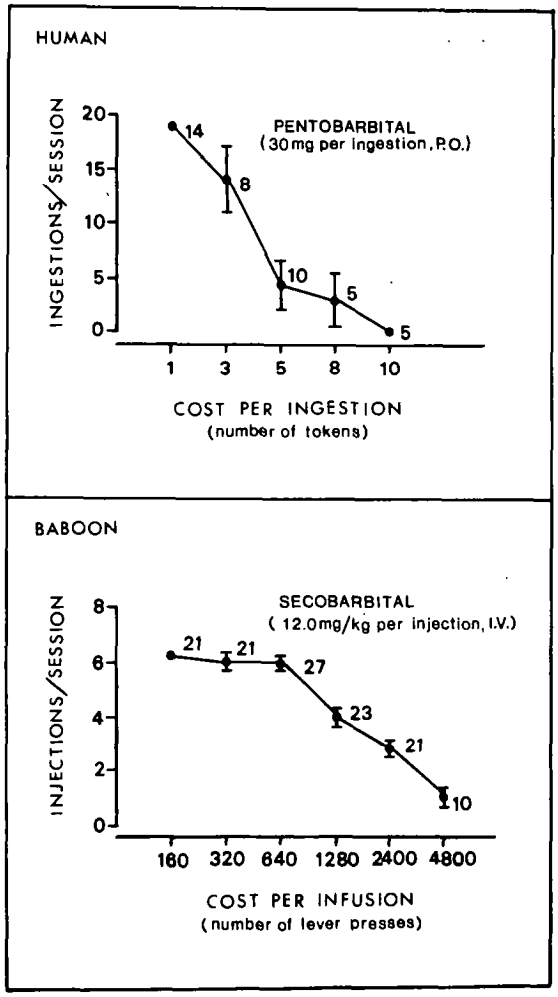
ACROSS SPECIES GENERALITY:
Effect of Drug Dose on Self-Administration



Effect of drug dose on self-administration. The human data are replotted from an experiment involving two alcoholic subjects (Griffiths, Bigelow, and Liebson 1976b). Data points indicate means, brackets indicate ± one standard error of the mean, and numerals indicate total number of observations at each dose. The baboon experiment (Griffiths, unpublished) utilized general procedures described previously (Griffiths, Winger, Brady, and Snell 1976) with four baboon subjects. Data points show mean number of injections per day on days 8 through 12 of drug exposure. Brackets indicate ± one standard error of the mean and numerals indicate total number of observations at each dose.

FIGURE 3

ACROSS SPECIES GENERALITY:
Effect of Work Requirement on Drug Self-Administration



Effect of work requirement on drug self-administration. Human data are replotted from an experiment involving oral drug self-administration in three volunteer sedative abuser subjects (Bigelow, Griffiths, and Liebson 1976). Data points indicate means, brackets indicate ± one standard error of the mean, and numerals indicate total number of observations at each cost level. Baboon data are derived from an experiment involving intravenous drug maintained progressive ratio performance in two baboons (Griffiths, Findley, Brady, Gutcher, and Robinson 1975). Data points indicate means, brackets indicate ± one standard error of the mean, and numerals indicate total number of observations at each cost level.

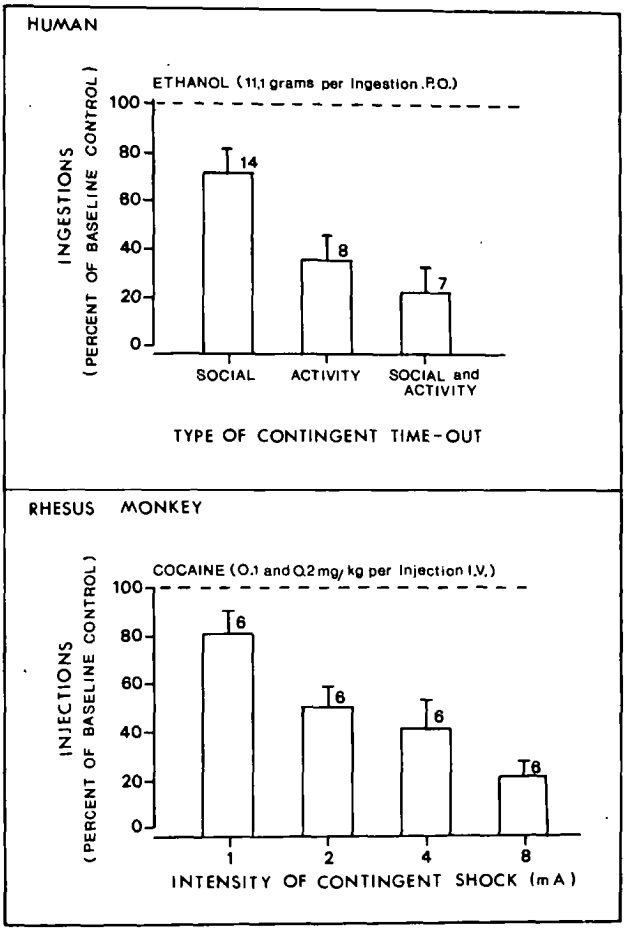
doses of drug. In the human experiment (Bigelow, Griffiths, and Liebson 1976) volunteer sedative abusers were permitted to self-administer orally up to twenty 30 mg sodium pentobarbital doses daily. Each dose was purchased with tokens earned by riding a stationary exercise bicycle. The number of tokens (and, therefore, the amount of exercise) required to obtain drug doses was varied in a mixed order across days. In the animal experiment (Griffiths, Findley, Brady, Gutcher, and Robinson 1975) baboons could self-administer intravenously up to eight 12.0 mg/kg sodium secobarbital doses daily. Each injection was consequent upon a fixed number of responses on a lever. The number of lever presses required to obtain drug doses was progressively increased across days. Similar effects of response cost variations are observed in both animals and humans: as the response requirement increases, drug self-administration decreases. This relationship has been observed repeatedly in both animal and human studies and has been observed across a variety of drug classes.

Punishment Another variable that has been shown to affect drug self-administration in human and infrahuman subjects is punishment. Punishment refers to the reduction of the future probability of a behavior as a result of the occurrence of some event contingent on the behavior. Fig. 4 shows the suppression of drug self-administration by contingent punishment manipulations in both humans and rhesus monkeys. In the human experiment (Griffiths, Bigelow, and Liebson 1977) ethanol self-administration by volunteer alcoholic subjects was suppressed by several different contingent' time out procedures which differed in suppressive potency. Time out periods were scheduled as an immediate consequence to each instance of ethanol self-administration and involved restriction of the subject's social interactions, physical and recreational activities, or both of these simultaneously. In the animal experiment (Grove and Schuster 1974) various intensities of contingent electric shock were superimposed upon a cocaine self-administration baseline.

Conditioned Stimuli The importance of antecedent environmental stimuli has been emphasized in a major current theory concerning the etiology of relapse to drug abuse. It is speculated that environmental stimuli previously paired with either opiate drug use or drug withdrawal can come to elicit the symptoms of drug withdrawal which are subjectively perceived as craving (Wikler 1965). Both animal and human studies have confirmed that such conditioned withdrawal can be established under controlled conditions (Goldberg 1970; O'Brien, Testa, O'Brien, Brady, and Wells 1977). The degree to which this conditioning phenomenon is relevant to the relapse to drug self-administration remains to be empirically determined. Similarly, the relevance of this stimulus elicited conditioned withdrawal/craving phenomenon to drugs other than narcotics has yet to be determined.

FIGURE 4

ACROSS SPECIES GENERALITY:
Effect of Punishment on Drug Self-Administration



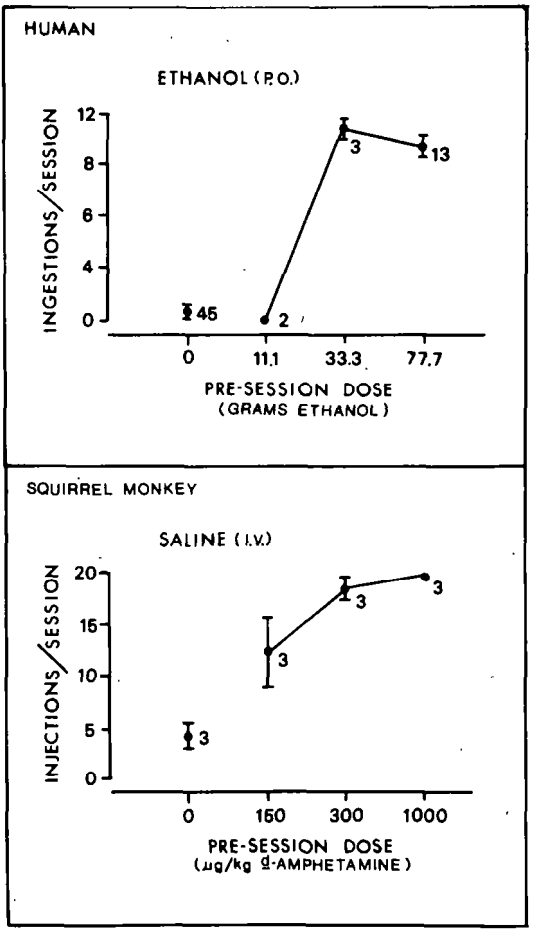
Effect of punishment on drug self-administration. Human data are replotted from an experiment which compared three contingent time out procedures in suppressing oral ethanol self-administration in fourteen alcoholic subjects (Griffiths, Bigelow, and Liebson 1977). Heights of bars indicate means, brackets indicate one standard error of the mean and numerals indicate total number of observations at each time out condition. Monkey data are replotted from an experiment demonstrating the suppression of intravenous cocaine self-administration by contingent electric shock in three rhesus monkeys (Grove and Schuster 1974). Heights of bars indicate means, brackets indicate one standard error of the mean and numerals indicate total number of observations at each shock intensity.

Drug Preload: Preload doses of drugs represent one type of antecedent stimulus which has clearly been shown to influence drug self-administration behavior in both animals and man. Fig. 5 shows that under some conditions priming doses of drug can increase subsequent drug self-administration behavior. In the human experiment (Bigelow, Griffiths, and Liebson 1977) volunteer alcoholics were permitted to self-administer ethanol orallywhile occasionally receiving various presession doses of ethanol. In the animal experiment (Gerber and Stretch 1975) squirrel monkeys with prior histories of cocaine self-administration were studied under extinction conditions (saline self-administration) while occasionally receiving various presession doses of d-amphetamine. These data illustrate that in both animals and humans presession drug doses can result in increases in drug seeking behavior. It should be noted that the relationship of drug preload to drug self-administration is complex, since other studies in humans (Jones and Prada 1975) and animals (Griffiths, Wurster, and Brady 1975) have shown that under other conditions preloads with drugs that are pharmacologically similar to the self-administered drug can result in reductions of subsequent drug self-administration behavior.

Historical Variables A wide range of historical influences modulate drug self-administration in animals and humans. It should: be recognized that many of the variables described in this paper require a history before they can exert an influence on drug self-administration (e.g., stimuli which elicit conditioned withdrawal effects). There are numerous other historical influences which probably influence drug self-administration, including the pharmacological and behavioral history of a subject. Finally, further exploration of historical variables may ultimately explain some paradoxical forms of drug self-administration. For instance, a number of animal studies have shown that under certain conditions electric shock can maintain responding when shock is delivered as a consequence of responding (Morse and Kelleher 1970). A subsequent study has extended this work by demonstrating that morphine dependent monkeys with certain histories will self-administer the opiate antagonist naloxone (Woods, Downs, and Carney 1975). These results are interesting because electric shock, for virtually all animals, and naloxone, for morphine dependent animals are usually considered to be "noxious" stimuli which animals will readily learn to avoid. Although more research is necessary to determine all the conditions under which such seemingly aberrant behavior can be established, the phenomenon can cautiously be interpreted as indicating an important role for the organism's history. Some data from an ongoing experiment suggest that analogous phenomena may occur with human drug self-administration. The experiment involves a double blind comparison of self-administration of various doses of placebo, pentobarbital, diazepam or chlorpromazine in volunteer subjects with histories of sedative drug abuse (Griffiths, Bigelow, and Liebson, unpublished). Of the fourteen subjects exposed to several doses of chlorpromazine, most stopped self-administering

FIGURE 5

ACROSS SPECIES GENERALITY:
Effect of Drug Preload on Self-Administration



Effect of drug preload on self-administration. Human data are replotted from an experiment in which the effects of oral ethanol preloads were studied on subsequent ethanol self-administration in four volunteer alcoholic subjects (Bigelow, Griffiths, and Liebson 1977). Data points indicate means, brackets indicate + one standard error of the mean, and numerals indicate total number of observations at each preload dose. Monkey data are replotted from an experiment in which the effects of intravenous d-amphetamine were studied on saline self-administration in three squirrel monkeys which had histories of cocaine self-administration (Gerber and Stretch 1975). Data points indicate means, brackets indicate + one standard error of the mean, and numerals indicate total number of observations at each preload dose.

the drug after several initial days of drug availability. Fig. 1, for example, shows the data for a representative subject. However, one of the subjects reliably self-administered chlorpromazine (approximately 250 mg/day) at rates above placebo. The subject had no history of psychosis, and therefore it is not likely that the drug was self-administered because of the antipsychotic properties. The subject reported that he thought the drug was probably a barbiturate, and that he felt it helped him sleep at night. It is possible that future research will indicate that such idiosyncratic instances of drug self-administration are somewhat analogous to responding maintained by shock, and that these phenomena will be shown to be dependent upon the subject's history.

ACROSS DRUG GENERALITY

A second area in which significant generality of human experimental drug self-administration results has been demonstrated is across different classes of drugs. Across drug generality is demonstrated by the fact that manipulation of major variables produces similar effects on self-administration of different drugs. The discussion here will focus upon data from human studies only. As in the preceding section, the discussion will be organized under the types of manipulations which have shown across drug generality.

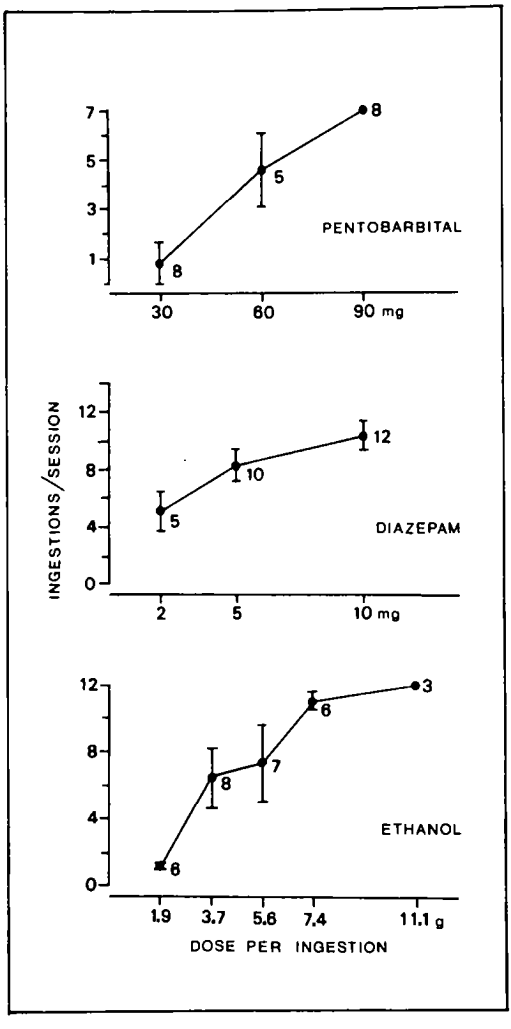
Dose of Drug Several studies have examined the effects of manipulatinq dose of drug on human self-administration of nicotine (see Jaffe and Jarvik 1978 for review) and various sedative drugs (Griffiths, Bigelow, and Liebson 1976b; Pickens, Cunningham, Heston, Eckert, and Gustafson 1977). Since very different methods were utilized in each of these studies, it is difficult to compare results between experiments. However, in one of the studies (Griffiths, Bigelow, and Liebson 1976b) similar experimental conditions were used to examine the effects of drug dose on self-administration of pentobarbital, diazepam and ethanol in drug abuser and alcoholic subjects. As shown in Fig. 6, with all three drugs increasing doses were associated with increasing levels of drug self-administration. As mentioned earlier, it is likely that higher doses of drug would have produced severe drug effects that would be associated with a descending limb to this dose effect function.

Response Requirement Several studies have demonstrated that increasing the response requirement or response cost to obtain alcohol decreases the total amount of alcohol consumed by alcoholic subjects (Mello, McNamee, and Mendelson 1968; Bigelow and Liebson 1972; Babor, Greenberg, Mendelson, and Kuehnle 1977). These findings have recently been extended to two additional sedative drugs, pentobarbital and diazepam (Bigelow, Griffiths, and Liebson 1976). Fig. 7 shows the results of two of these studies (Bigelow and Liebson 1972; Bigelow, Griffiths, and Liebson 1976) in which drug abuser or alcoholic subjects could obtain drug by either riding an

FIGURE 6

ACROSS DRUG GENERALITY:

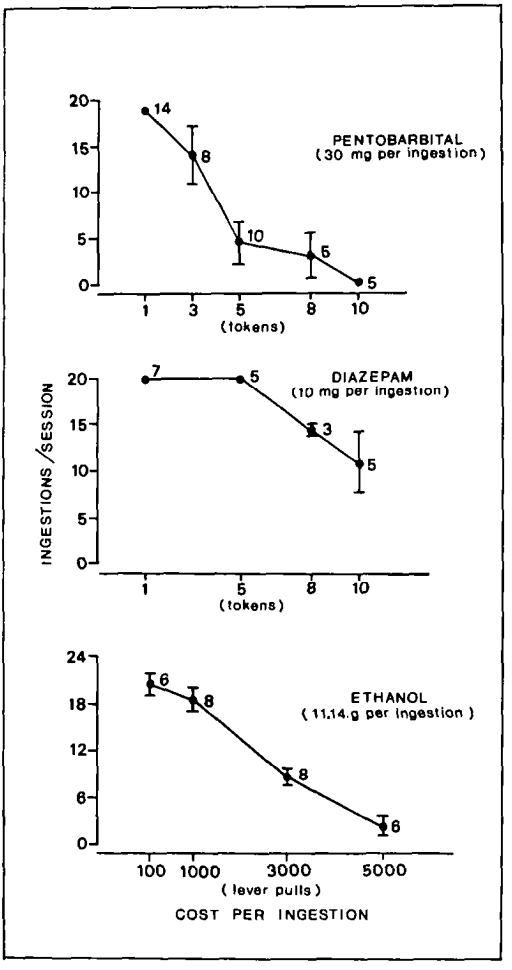
Effect of Drug Dose on Human Drug Self-Administration



Effect of drug dose on human self-administration of pentobarbital, diazepam and ethanol. Data are replotted from an experiment involving oral drug self-administration by volunteer sedative abuser or alcoholic subjects (Griffiths, Bigelow, and Liebson 1976b). Two subjects were exposed to each of the three drugs. Data points indicate means, brackets indicate ± one standard error of the mean and numerals indicate total number of observations at each interingestion interval.

FIGURE 7

ACROSS DRUG GENERALITY:
Effect of Work Requirement on Human
Drug Self-Administration



Effect of work requirement on human self-administration of pentobarbital, diazepam and ethanol. Data are replotted from experiments involving oral drug self-administration by volunteer sedative abusers (Bigelow,Griffllths, and Liebson 1976) and alcoholics (Bigelow and Liebson 1972). Two subjects were exposed to diazepam and ethanol and three subjects were exposed to pentobarbital. Data points indicate means, brackets indicate ± one standard error of the mean, and numerals indicate total number of observations at each cost level.

exercycle or pulling a lever. With all three drugs, increasing the response requirement was associated with systematic decreases in the amount of drug self-administered.

Interingestion Interval Another variable which produces similar effects across different drugs is the minimum interval which is experimentally imposed between successive drug ingestions. Fig. 8 presents the results from several studies (Bigelow, Griffiths, and Liebson 1975a; Griffiths, Bigelow, and Liebson 1976b) which examined the effects of interingestion interval manipulation on self-administration of pentobarbital, diazepam and ethanol in sedative abuser or alcoholic subjects. Procedures were similar to those utilized in the other human drug self-administration studies, except that the minimum interval subjects were required to wait between successive doses of drug was varied from day to day. Under these conditions increases in the minimum interingestion interval uniformly reduced the number of ingestions (as well as percent of available ingestions) consumed.

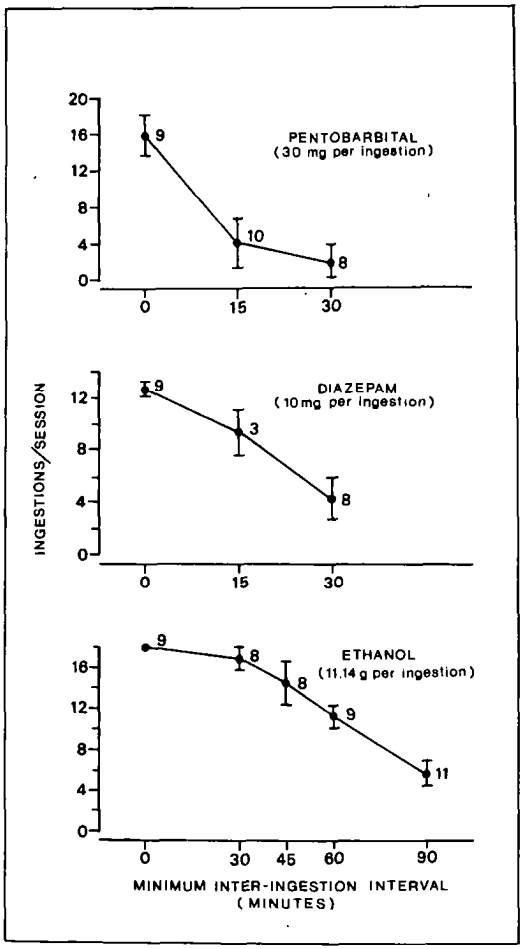
Effects of Drug Self-Administration on Social Behavior A final area where there appears to be some across drug generality is the acute effects of moderate doses of self-administered drugs on the social behavior of experienced users. Most relevant research in this area has been done with ethanol's effects on the social behavior of alcoholics, and it has been clearly demonstrated in a variety of situations (e.g., Mendelson 1964; Griffiths, Bigelow, and Liebson 1974; 1975) that the acute effects of moderate ethanol doses uniformly increase social behavior of alcoholics (see Griffiths, Bigelow, and Liebson 1978 for review). This general finding has been extended to three other drugs of abuse: heroin, d-amphetamine and marihuana. Babor, Meyer, Mirin, McNamee, and Davies (1976) showed that although increasing doses of intravenous heroin were associated with decreases in the overall rates of social interactions among hospitalized drug abuser subjects over a ten day period, the acute effects of heroin were associated with increases in social interactions immediately after injection. Griffiths, Stitzer, Corker, Bigelow, and Liebson (1977) have shown that d-amphetamine also produces dose related increases in social behavior of drug abusers and normals under several different experimental conditions. For marihuana, the evidence for drug facilitated socializing is both more complex and tenuous. Babor, Rossi, Sagotsky, and Meyer (1974a, b) have noted that free choice marihuana smoking in a hospital ward situation is a social activity around which verbal interaction and other types of social behavior are invariably centered; however, these investigators have also noted that marihuana smoking may decrease subsequent verbal interaction in a structured group situation.

DISCUSSION

The preceding sections have provided a partial review of human drug self-administration studies in residential settings with

FIGURE 8

ACROSS DRUG GENERALITY:
Effect of Minimum Interingestion Interval on Human Drug Self-Administration



Effect of minimum interingestion interval on human self-administration of pentobarbital, diazepam and ethanol. Data are replotted from experiments involving oral drug self-administration by volunteer sedative abuser (Griffiths, Bigelow, and Liebson 1976b) and alcoholic (Bigelow, Griffiths, and Liebson 1975a) subjects. Two subjects were exposed to pentobarbital and diazepam and four subjects were exposed to ethanol. Data points indicate means, brackets indicate ± one standard error of the mean, and numerals indicate total number of observations at each interingestion interval.

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emphasis on those results which have shown across species and across drug generality. Such replication of results across major aspects of the experimental situation is important to establishing the reliability of the procedures. The systematic replication of some of the human results in an animal drug self-administration model is particularly dramatic because besides species differences, there are numerous additional experimental and methodological differences. The demonstration of across species generality suggests that the experimental findings are robust, reflect basic underlying processes of drug self-administration, and are not artifacts of the human or animal experimental models. The replication of human drug self-administration results across different types of pharmacological agents also suggests that similar behavioral pharmacological processes underlie the self-administration of various drugs. It should be noted, however, that the demonstration of across drug generality does not imply that there are not important differences in the self-administration of different drugs.

An important area of generality which has not been addressed in the current paper is the generality of results from the residential laboratory to clinical phenomena observed in the "natural environment." The establishment of such generality will require objective clinical observation in combination with sociological and epidemiological studies.

The demonstration of across species and across drug generality suggests that common processes underlie these various forms of drug self-administration, and supports the supposition of a generalized behavioral phenomenon of substance self-administration. It is likely that further characterization of these common processes will be valuable to understanding the etiology of, and to developing treatment strategies for various forms of substance abuse.

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ACKNOWLEDGMENTS

Preparation of this manuscript was supported in part by National Institute on Drug Abuse grants DA-01147, DA-01022, and National Institute on Drug Abuse Research Scientist Development Award DA-00050. The discussion of across species generality is based on a previous paper by Griffiths and Bigelow (1978).

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Chapter 4

Therapeutic Self-Medication as a Context for Drug Abuse Research

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Julia Kaliszak, and Roland R. Griffiths, Ph.D.

The majority of our laboratory's research on substance self administration has been conducted with chronic substance abusers to whom drugs or alcohol have been made available specifically for research purposes. Elsewhere we have described the experimental methodology which has been developed and utilized in these residential laboratory drug self administration studies (Bigelow, Griffiths, and Liebson 1975a; 1975b), and recent reviews have summarized many of the behavioral relationships observed (Griffiths, Bigelow, and Liebson in press; Griffiths and Bigelow in press). Among the purposes of these basic human laboratory studies is to identify relationships which may be relevant to the prevention or treatment of drug abuse. Thus, at times the implicit assumption is made that behavioral relationships observed among abusers in nontherapeutic situations will generalize to nonabusers and/or to therapeutic situations. However, the extent of such generalizability has yet to be determined.

This paper will describe and present preliminary data from two experimental contexts currently being developed for the study of drug self administration. It is hoped that these contexts will extend the experimental analysis of drug self administration and help to reveal the determinants of drug self administration by nonabusers and within therapeutic situations. Both of the studies to be described examine drug self administration within the context of therapeutic self medication. The first examines the self administration by nonabusers of anorectic medications prescribed as an aid to weight loss. The second examines the self administration of methadone by dependent patients during voluntary self regulated detoxification.

SELF-ADMINISTRATION OF THERAPEUTICALLY PRESCRIBED MEDICATIONS BY NON-DRUG-ABUSERS

Many abused substances also have therapeutic indications and are frequently prescribed to and self-administered by non-drug-abuser patients. This self-administration of legitimate prescription medications can provide a valuable context for the experimental study of drug self-administration. This context can permit analysis of influences upon self-administration of abused drugs in the absence of the phenomenon of drug abuse and with patients who are not habitual drug abusers.

We will describe here preliminary results obtained in a comparative double blind evaluation of self-administration of anorectic medications by overweight women enrolled in an outpatient weight control program. The study compared two chemically related anorectic medications of presumably differing reinforcing efficacy. d-Amphetamine is a reinforcing drug which is readily self-administered by animals and has been widely abused by humans. Fenfluramine is not a reinforcer; it has dysphoriant properties (Griffith, Nutt, and Jasinski 1975); it is not readily self administered by animals (Woods and Tessel 1974); and it is rarely abused by humans (Griffiths, Brady, and Snell, in press). In the present study drug self-administration was compared for placebo, fenfluramine and d-amphetamine in weight control patients who were given substantial self control over the extent of their drug taking. The study was intended to assess the relevance of the concepts of reinforcing efficacy or abuse liability to the control of drug self-administration by non-drug-abuser patients being prescribed these drugs as part of a medical treatment regimen.

Method

Participants. Volunteer participants were solicited from among employees at Baltimore City Hospitals by placing a notice in the employee newsletter announcing an experimental weight control program involving medications. Criteria for acceptance into the program included being female, employed at the Hospital, at least 20 percent overweight, without any medical contraindications such as hypertension, and with a history of failure at previous weight control efforts. Volunteers received medical and psychiatric screening and provided their written informed consent prior to participation.

Characteristics of the forty-eight participants are summarized in Table 1. They appear to be typical of the general weight control treatment population. Their age averaged 38, and they were an average of 41.6 percent overweight. All had failed at previous weight control attempts; the table shows the percent of patients who had previously tried various types of weight loss procedures.

TABLE 1

SUMMARY OF PARTICIPANTS CHARACTERISTICS (N=48)

Sex:	Female
Age (mean and range):	38 (20-54)
% Overweight (mean and range):	41.6 (20-111)
Prior Weight Loss Attempts (% of patients, and type):	93.7% Personal Attempts 54.2% Organized Program 60.4% Prescribed Medications 39.6% OTC Medications

Procedure. The study was conducted within the context of a behavioral self-management treatment program for overweight in which patients were asked to self-record and self-evaluate their eating and exercise habits throughout each day, and were provided weekly individual counseling sessions to discuss their eating and exercise habits. Patients enrolled in a five week treatment program, with medications being prescribed only during the last four weeks. They were informed that the purpose of this study was to compare several different medications which were already in clinical use for the treatment of overweight. The specific drugs to be used were not identified. Volunteers were informed of a variety of side effects which they might experience, and they were informed that they would not necessarily receive active drug. Patients were also informed that they would be paid $15.00 at the end of the five weeks if they reported to their weekly counseling sessions for weighin; it was clear that payment was not contingent upon taking medications.

The first week of the study was a baseline self-recording period without medication and without structured self-evaluation, during which patients were instructed to observe and record their eating and exercise habits but not to attempt weight loss.

At the beginning of the four week drug period patients were randomly assigned to one of three medications -- placebo (N=18), fenfluramine (N=17), or &amphetamine (N=13). All medications were dispensed double blind and were prepared in identically appearing opaque capsules. Doses of the active drugs in each capsule were 5 mg d-amphetamine, and 20 mg fenfluramine. These are the standard recommended therapeutic doses of each drug, and these doses have previously been shown to be equipotent in facilitating weight loss in a controlled outpatient clinical evaluation (Stunkard, Rickels, and Hesbacher 1973). Patients were informed that the average proper dose was three capsules per day -- one capsule three times per day about one hour before meals (this corresponds to the normal

therapeutic recommendation for both d-amphetamine and fenfluramine). However, patients were told that since individuals differ in their sensitivity to the drugs' effects and side effects they should self-regulate their own medication intake in the range of 0 to 6 capsules per day.

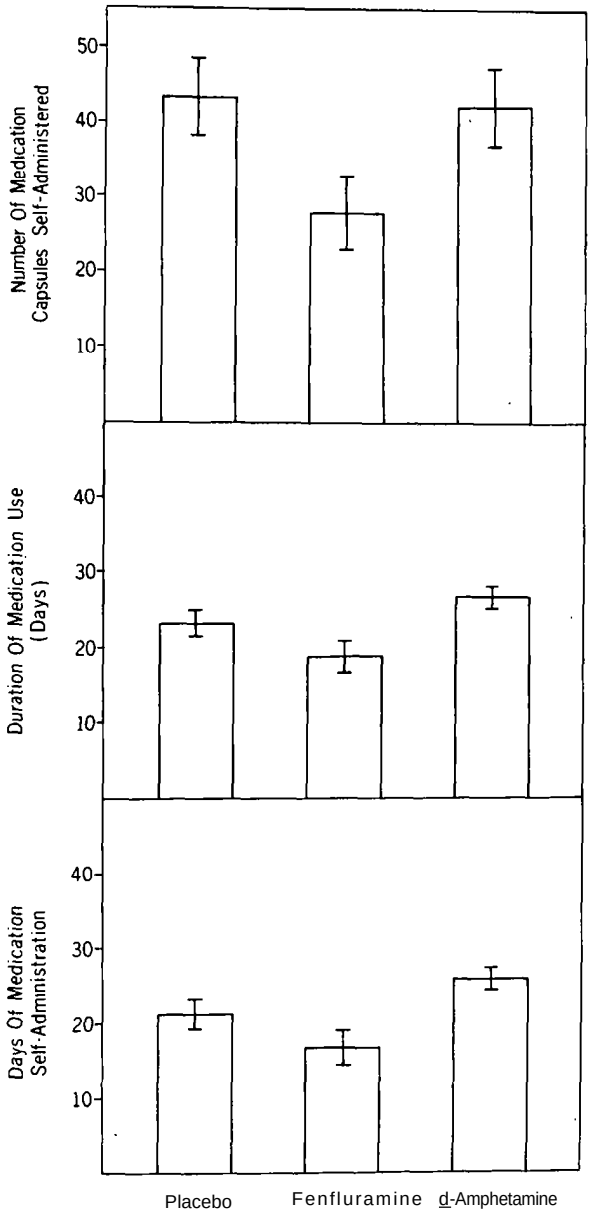
Only a small amount of medication was dispensed to each patient at any one time; on day one of the drug period each patient was given 12 medication capsules. Patients were told to report back to the clinic to pick up additional medication whenever they needed it; on these subsequent visits patients were given enough capsules to bring the number in their possession up to 18 capsules. Patients were told to bring their medication bottle with them at each visit so the remaining capsules could be counted. The clinic dispensary was open sixteen hours per day, seven days per week, to facilitate medication pickups regardless of patients' work shifts.

Results

Figure 1 presents three related measures of the maintenance of self-administration of the three medications. The top panel shows the mean number of medication capsules self-administered in each of the three medication groups: placebo, 43.3; fenfluramine, 27.8; and d-amphetamine, 42.2. Pairwise t tests revealed that the number of capsules self-administered of fenfluramine was significantly less than that of placebo ($p<0.025$, one tailed) and significantly less than that of d-amphetamine ($p<0.05$, one tailed). The number of capsules self-administered of placebo and d-amphetamine did not differ significantly.

The above measures of the amount of drug self-administered may reflect differences in the effective potencies of the different medications. Therefore, the remaining two panels of Figure 1 present data concerning the temporal persistence of drug self-administration, which should be uninfluenced by variations in the acute effective dose. The middle panel shows, for each drug group, the mean duration of medication use. This duration measure is the number of days from the beginning of the drug period until the last capsule was taken; medication was not necessarily taken on every day during this period. The mean durations of medication use were: placebo, 23.2 days; fenfluramine, 18.9 days; and d-amphetamine, 26.7 days. The bottom panel shows the mean number of days medication was actually taken; this is the duration of use minus any gaps of nonuse of greater than 2 day duration (shorter gaps may have gone undetected). The resulting mean numbers of days of medication self-administration were: placebo, 21.2; fenfluramine, 16.7; and d-amphetamine, 25.7. Pairwise t tests revealed the same results for both the duration and the number of days measures: self-administration of d-amphetamine was better maintained than that of fenfluramine ($p<0.005$, one tailed), but the differences between placebo and fenfluramine and between placebo and

FIGURE 1



Three measures of the maintenance of drug self-adninistration are shown for each medication group; the number of medication capsules self-administered, the duration of medication use, and the number of days of medication self-administration. Heights of bars indicate means; brackets indicate ± one standard error of the mean.

d-amphetamine were borderline insignificant in all cases ($0.05 < p < 0.10$, one tailed).

Another way of assessing the persistence of drug self administration is to examine the pattern of dropout from medication use over time. This is done in Figure 2, which shows over consecutive days the percent of patients in each drug group who continued to use their assigned medication. Patients were considered as continuing medication use through the day they took their last dose, even if they had temporarily suspended use prior to that time. As can be seen, there is no overlap in the data for the three medication groups, except during the early days when all patients were continuing their medication use. Fenfluramine use falls off most rapidly; placebo use falls off next most rapidly; and d-amphetamine use is most strongly maintained. The percentages of patients continuing medication use through day 28 were: fenfluramine, 29.4 percent; placebo, 38.9 percent; and d-amphetamine, 76.9 percent. Pair-wise z tests for differences between these proportions revealed that &amphetamine use was significantly better maintained on day 28 than either placebo ($p<0.02$, one tailed) or fenfluramine ($p<0.005$, one tailed), but that placebo and fenfluramine did not differ significantly from one another.

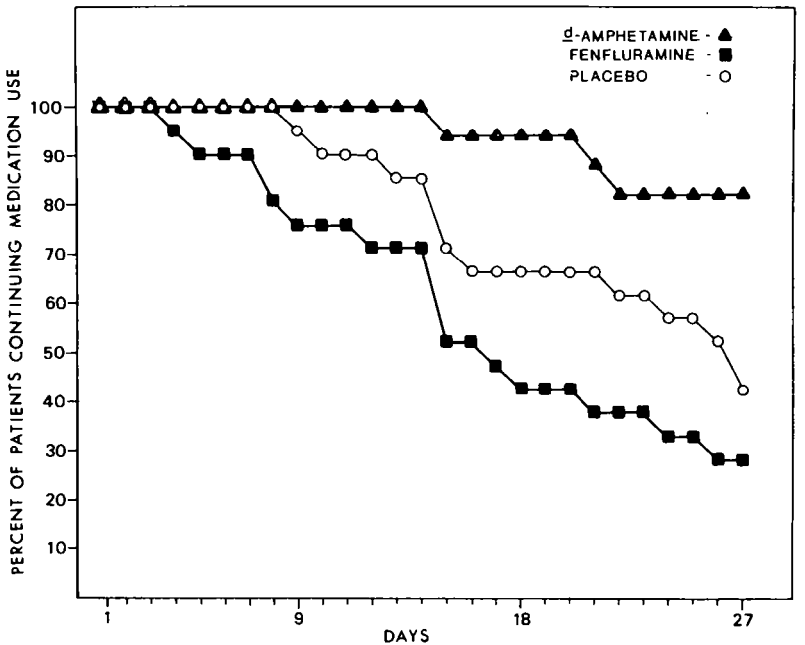
Weight change during the 4 week drug study was quite variable between patients, and there were no significant differences between the three medication groups. On the average patients lost weight at the rate of approximately three-quarter pounds per week; this rate is modest, but is within the appropriate range to be sought in a gradual weight loss program.

Discussion

Overall, these data show that self-administration of d-amphetamine is most well maintained, that self-administration of fenfluramine is least well maintained, and that self-administration of placebo is intermediate. Two main points should be noted in these data. First, these results show that the concept of drug reinforcement appears to be a relevant influence upon the medication-taking behavior of normal non-drug-abuser patients who have received prescription medications as part of a medical treatment regimen. Second, the potency of this drug reinforcement is not so great that it produces any significant deviation from the appropriate pattern of medication intake.

The rank ordering of these compounds with respect to the maintenance of self-administration corresponds to the ranking one would expect if medication taking were controlled by drug reinforcement. It differs from the ranking one would expect if medication taking were controlled by therapeutic efficacy (i.e., both d-amphetamine and fenfluramine self-administration would be better-maintained than that of placebo), and it differs from the ranking one would

FIGURE 2



For each of the three medication groups the percent of patients continuing to use the medication is shown over consecutive days.

expect if medication taking were controlled by the physicians' instructions and/or by the patients' expectations (i.e., self-administration of all three medications would be equally well maintained). Thus, this study demonstrates that one of the major variables which influences drug self-administration by drug abusers (drug reinforcement) has generalized applicability as a determinant of nonabusive drug self-administration by non-drug-abuser patients. Perhaps most importantly, these data demonstrate that the context of therapeutic self-medication can serve as a sensitive experimental setting for investigating behavioral pharmacological factors involved in drug self-administration and drug abuse.

The fact that the phenomenon of drug reinforcement can reveal its influence without leading to deviation from the prescribed appropriate pattern of drug intake is especially interesting. Thus, the data from this study indicate that &amphetamine was not an especially potent reinforcer in this context. While it maintained greater persistence of drug self-administration over time it did not lead to increases in total medication intake or increases in drug seeking behavior (as assessed by frequency of clinic visits to pick up additional medication). Except in very rare instances patients picked up medications only at the time of their scheduled weekly weighin and counseling sessions. Thus, the limited amount of medication (18 doses) dispensed to patients at each pickup may have functioned as a ceiling on the extent of their self-administration. It is possible that d-amphetamine self-administration would be less restrained if larger numbers of capsules were dispensed at any one time. Still, d-amphetamine was not sufficiently reinforcing to maintain additional visits to the clinic to pick up medication. Overall, the lack of any strong reinforcing effect of amphetamine is impressive. No patient self-administered even as much as half of the available medication, patients tended to drop out of medication use as time passed, and no patient showed a pattern of progressively increasing drug intake.

Despite the fact that d-amphetamine's reinforcing effect influenced patients' medication intake, the extent of their drug use was conservative. When given the opportunity to self-regulate their drug intake patients self-administered less medication than if they had followed the usual prescription directive for these drugs of 'one capsule three times per day. Other investigators have also reported this finding of conservative self-medication by patients permitted to self-regulate their intake of prescription medications generally thought to possess reinforcing properties. For example, Sechzer (1971) has permitted patients during the immediate post-surgical recovery period to self-administer narcotic analgesics via intravenous infusion in a manner quite similar to that used in infrahuman laboratory studies and has found that, on the average, patients self-administer less medication than would be given according to the usual physician-determined regimens. In two

separate studies Winstead and colleagues have permitted unselected psychiatric inpatients to self-medicate on request with either diazepam (Winstead et al. 1974) or propoxyphene (Winstead, Parker, and Willi 1977). In both cases it was noted that self-medication was quite conservative; diazepam was self-administered at an average rate of one dose (10 mg) per three patient days, and propoxyphene at an average rate of one dose (100 mg) per fourteen patient days. Despite these low rates Winstead and colleagues have been able to identify significant demographic, psychometric and situational correlates of drug self-administration. These data support the thesis of this paper that the self-administration of prescribed medications by non-drug-abusers can provide a valuable research context for identifying and studying influences upon drug self-administration.

The data from the present study and the other data reviewed indicate both that prescription drug self-administration provides a sensitive and orderly dependent measure and that studies in this context can be conducted without significant risk of overmedication. Since the vast majority of drugs possessing significant abuse potential are dispensed by legitimate medical order or prescription, there exists a great potential for study of drug self-administration which has been in the past largely ignored. Because studies in this context can be conducted with non-drug-abusers, the relationships discovered may be of particular relevance to prevention of drug abuse.

SELF-REGULATED DETOXIFICATION BY DRUG DEPENDENT PATIENTS

The previous section has dealt with prescription self-medication situations in which one can examine influences upon the drug self-administration of relatively drug naive non-drug-abusers who are being exposed to a drug of potential abuse liability. In this section we describe a situation in which one can examine influences upon the process of discontinuing chronic drug use by drug abusers.

A major goal of drug abuse treatment is the termination of drug self-administration. Human laboratory drug self-administration research is, however, typically conducted with patients who have volunteered to take, rather than to stop taking, drugs. Conducting drug self-administration with chronic drug users who are attempting to discontinue their drug use may yield unique information about factors which can enhance the transition from being drug dependent to being drug abstinent.

Method

Participants. Participants have been 8 methadone maintenance patients who expressed a desire to detoxify and who volunteered to do so in our residential hospital research unit. Age averaged 26.5 years (range 20-37). Patients averaged over 8 years since their first narcotics addiction (range 4-16) and over 2 years of

prior methadone maintenance (range ¼-6). Six patients were white and two black. None were currently living with a spouse; all were unemployed; three were under legal supervision (parole, probation, or pretrial).

Procedure. Following several days on the residential research ward at their stable daily methadone dose patients were given self control of their methadone intake and instructed that they would be responsible for decreasing their dose to zero and that they could do this in whatever pattern or schedule they wished, but should plan to complete the detoxification within six weeks. During the self-regulation period patients could obtain small doses of methadone (ranging, between patients, from 2 mg to 5 mg) any time between 11:30 a.m. and 9:30 p.m.; each dose was dispensed contingent upon 5 minutes of exercise on a stationary exercise bicycle. The total daily methadone allowable ranged, between patients, from 120 percent to 150 percent of the patient's prior stable dose. At the beginning of dose self-regulation patients were informed of their prior stable dose and of the number and magnitude of the doses available for self-administration. Staff provided no instructions, suggestions, or feedback to patients concerning what might be an "appropriate" sequence of dosages; patients were told they were free to choose whatever they wished. Within the thirty minutes preceding each daily session patients completed a 59 item symptom checklist describing how they felt during the preceding 24 hours. The checklist included item clusters concerning symptoms of overdose, withdrawal, psychological distress, sleep disturbance, and libido disturbance. Patients indicated the severity of each symptom on a four point scale ranging from 0 (not at all) to 3 (severe).

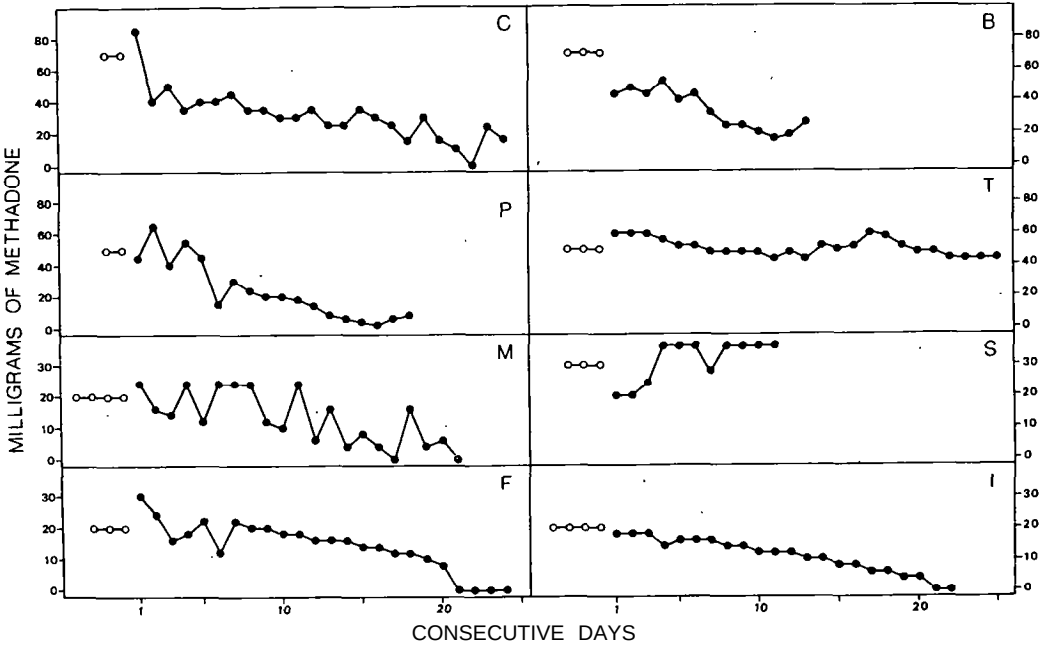
Results

Figure 3 shows the total daily dose of methadone self-administered over consecutive days for each patient enrolled in the self-regulated methadone detoxification procedure. Six of these patients progressively decreased their methadone dose, and five at some point achieved a zero or near zero dose level. Also, six of the eight patients at some time self-administered a daily dose greater than that at which they began self-regulation. Three patients chose to be discharged into continued methadone maintenance (patients B, T, S); one of these (T) had failed ever to make any significant dose reduction below his initial maintenance level.

Figure 4 shows for two patients their self-report symptomatology scores and their total daily methadone dose over consecutive days. Symptomatology scores increased dramatically during the latter portions of the detoxification. Patients did not regulate their dose so as to minimize symptomatology, but continued to decrease their dose despite increasing symptomatology.

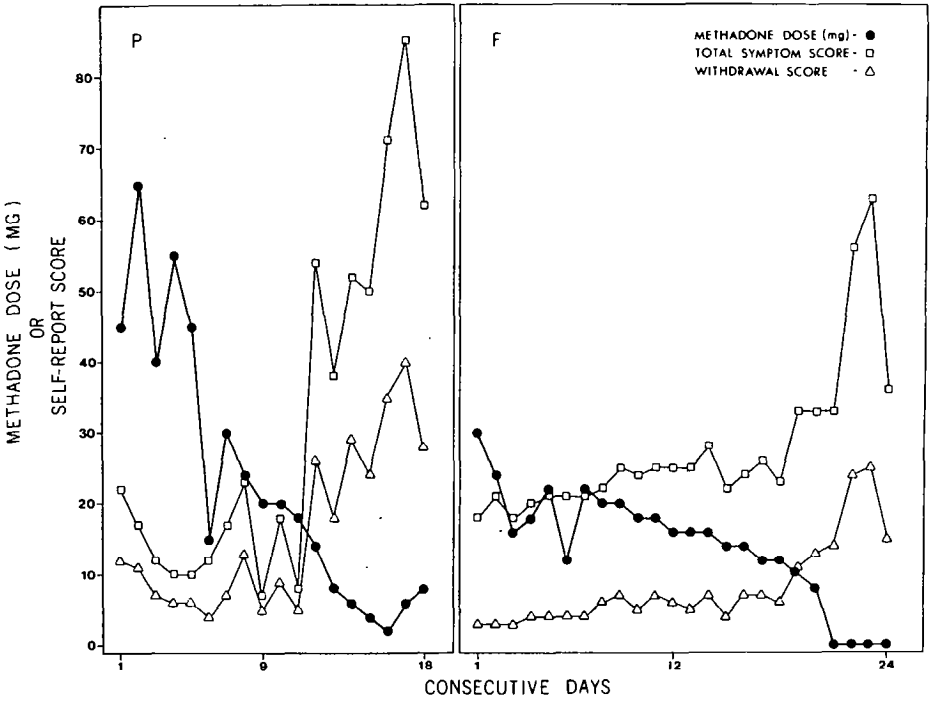
FIGURE 3

SELF-REGULATED METHADONE DETOXIFICATION



Total daily methadone intake over consecutive days is shown for each of eight patients participating in self-regulated methadone detoxification; Open circles indicate the stable maintenance dose prior to self-regulation. Filled circles indicate the period of dose self-regulation.

FIGURE 4



For two patients the daily self-administered methadone dose is shown along with two daily symptom checklist scores.

Discussion

These data are descriptive of the phenomenon of voluntary self-regulated detoxification. They are presented to demonstrate that the process of self-regulated detoxification is orderly and amenable to laboratory study. Our laboratory is now in the process of developing this self-regulated detoxification procedure as a context for experimental studies of influences upon methadone self-administration.

Self-regulated detoxification has previously been reported and recommended as an improved detoxification treatment procedure for narcotics addicts (Raynes and Patch 1973; Razani et al. 1975). In both of those reports the focus was upon achieving detoxification rather than upon examining patterns of or influences upon methadone self-administration; consequently patients were not permitted complete freedom to increase and decrease their doses as they wished.

Angle and Parwatikar (1973) have reported a self-regulated detoxification study in which the focus was upon analysis of the behavior of methadone self-administration. They noted that scheduling a 24 hour leave from the hospital appeared to trigger a relapse to maximal methadone self-administration. However, the phenomenon did not replicate when a second 24 hour leave was scheduled later in the study.

The possibility of studying influences upon relapse may be a desirable outgrowth of studies of self-regulated detoxification. The procedure of self-regulation can permit relapse to occur under experimentally controlled conditions. As is known from followup studies the occurrence of relapse is highly probable shortly after detoxification. The present data indicate that a phenomenon analogous to relapse can be observed prior to completion of detoxification.

Finally, it should be noted that because the joint phenomena of detoxification and relapse are so widespread with all of the addictive or substance abuse disorders, comparative studies of self-regulated detoxification and relapse may provide an especially interesting dimension upon which to look for commonalities and differences among different varieties of substance self-administration.

COMMENT

The intent of this paper is advocacy of the increased use of therapeutic self-medication contexts for studies of drug abuse related phenomena. There are several bases for this advocacy. One is that self-medication contexts can provide unique opportunities to study phenomena of special interest to the drug abuse field. For example, if we wish to develop behavioral pharmacological

principles relevant to prevention and treatment, it is necessary to analyze how drug self-administration is influenced in non-drug-abusers (the prevention analogue), and in patients attempting to terminate chronic drug use (the treatment analogue). The present studies indicate that in the self-medication context these situations can be studied under sufficiently rigorous conditions of objective measurement and experimental control to permit analysis of influences upon drug self-administration. A second major basis for advocating self-medication as a research context is the accessibility of drug self-administration to study in this context. Self-medication is widespread and occurs for therapeutic reasons. Research in such a therapeutic context can be conducted relatively nonintrusively compared to techniques involving introduction of drugs purely for research purposes. Thus. therapeutic self-medication would appear to offer considerable-potential for drug abuse related research. The actual yield of this research context has yet to be determined.

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ACKNOWLEDGMENTS

This research was supported by United States Public Health Service research grants DA-01022, DA-01472, and DA-01943, and by Research Scientist Development Award DA-00050.

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Chapter 5

Drug Abuse Research in Outpatient Clinics

Maxine Stitzer, Ph.D., and George E. Bigelow, Ph.D.

Drug abuse research ultimately seeks to understand the pharmacological, environmental and historical determinants of drug ingestion in humans. Significant advances have been made recently in developing methodologies for studying determinants of drug abuse in human addict populations. These methodologies are characterized by direct observation and objective quantification of the behavior of primary interest in drug abuse research, namely, drug ingestion itself. Drug self-administration experiments seek to identify variables which, when manipulated, will lead to orderly changes in observable drug ingestion behavior. Human self-administration studies are characteristically conducted in hospital ward settings with inpatient participants. In these settings, experimental control can be exerted over many significant variables which influence drug ingestion so that the variables of interest can be isolated and studied. In particular, daily routine, nutrition, availability of drugs, and the social and environmental context of drug use are controlled in inpatient settings. Specific methodologies have been developed for studying self-administration in hospital ward settings of a variety of drugs including ethanol (Bigelow, Griffiths and Liebson 1975; Mello 1972; Nathan and O'Brian 1970), sedatives (Bigelow, Griffiths and Liebson 1976; Pickens et al. 1977), narcotics (Angle and Parwatikar 1973; Jones and Prada 1975; Meyer et al. 1976), nicotine (Griffiths, Bigelow and Liebson 1976), and marihuana (Mendelson et al. 1976).

Inpatient settings, however, are not always necessary or ideal for conducting drug abuse research, and in fact may have certain disadvantages. First, inpatient research is limited to a population of drug abusers who are willing and able to give up several weeks of their time in order to live on a hospital ward while participating. Secondly, inpatient research, while controlling environmental context of drug ingestion, at the same time creates an atypical or artificial context for the occurrence of this behavior. Outpatient clinics can also provide a setting for drug self-administration research. Methadone maintenance clinics and other drug abuse treatment facilities constitute a naturalistic setting for conducting research with readily available and appropriate subject

populations. The present paper will describe drug self-administration research that has been conducted in outpatient settings. The paper will review some of the experimental questions that have been explored in these settings and discuss methodologies that have been developed for self-administration research in outpatient settings, primarily methadone maintenance clinics. We will focus on two broad research areas that have been explored in outpatient settings. The first concerns evaluation of the abuse liability of compounds whose reinforcing potential for human drug addicts is unknown. The second concerns identifying treatment interventions which will influence the quantity and pattern of drug ingestion in human addicts.

Two basic approaches are possible for' studying drug self-administration in outpatient settings. In one approach, the drug self-administration of interest to the investigator is that which takes place outside the clinic, while the independent variable is some intervention which takes place at the clinic. Drug ingestion outside the clinic can be assessed by client self-report or, more objectively, by urinalysis results. This is not entirely satisfactory, however, since urinalysis results yield little information about quantitative or temporal aspects of drug ingestion. A second approach is to study ingestion of abused drug directly by offering a limited quantity of these drugs at the outpatient clinic. This latter approach has the advantage of achieving direct experimental control over a portion of drug use. This paper will focus primarily on research which has utilized drug ingestion at the clinic as a primary dependent variable.

Outpatient Studies of Reinforcing Efficacy

One question that has been explored in outpatient drug self-administration research concerns the reinforcing efficacy of drugs. A drug acts as a reinforcer if it maintains self-administration behavior, and drugs which maintain self-administration presumably have abuse potential for the populations studied. Self-administration studies may evaluate the reinforcing efficacy of a compound whose abuse potential is unknown by comparing self-administration of the unknown with that of a nonreinforcing placebo and with that of a drug which is known or presumed to be reinforcing. Schuster, Smith and Jaffe (1971) conducted such a study designed to evaluate the reinforcing efficacy of pentazocine, a mixed narcotic agonist and antagonist with unknown abuse potential in humans. Self-administration of pentazocine was compared with self-administration of placebo as well as with self-administration of codeine and methadone, both of which were presumed to be reinforcers for narcotics-dependent individuals. Participants were eligible for methadone maintenance and were on a waiting list for maintenance treatment. During the waiting period they were offered the chance to come to the clinic daily for ten days to pick up bottles of medication which might help them with their addiction problem. Medication bottles for each participant contained either 400 mg pentazocine, 400 mg codeine, 40 mg methadone or 400 mg dextrose placebo. The study showed that clients assigned to methadone or codeine picked up more drug than did those assigned to pentazocine or placebo.

However, drug pickup dropped off dramatically for all compounds, including methadone and codeine. The results indicated that pentazocine may have less reinforcing efficacy and abuse potential than either methadone or codeine, but the results were also somewhat equivocal as they failed to demonstrate the presumed high reinforcing efficacy of methadone and codeine. A second study (Schuster 1975) replicated the results for methadone and placebo under conditions where clients were required to swallow medication at the clinic.. This procedure ensured that drug pickup behavior was maintained by the drug ingestion consequence rather than by some other consequence such as the opportunity to sell the medication. Again, there was a high attrition rate for subjects in the methadone group with more than 60% of the group lost from participation by the end of ten days. The finding that methadone failed to maintain high rates of drug pickup was surprising, since methadone regularly maintains daily clinic attendance in the context of drug treatment programs, and suggests that the procedures employed may not have been optimal for assessing abuse liability in the outpatient setting.

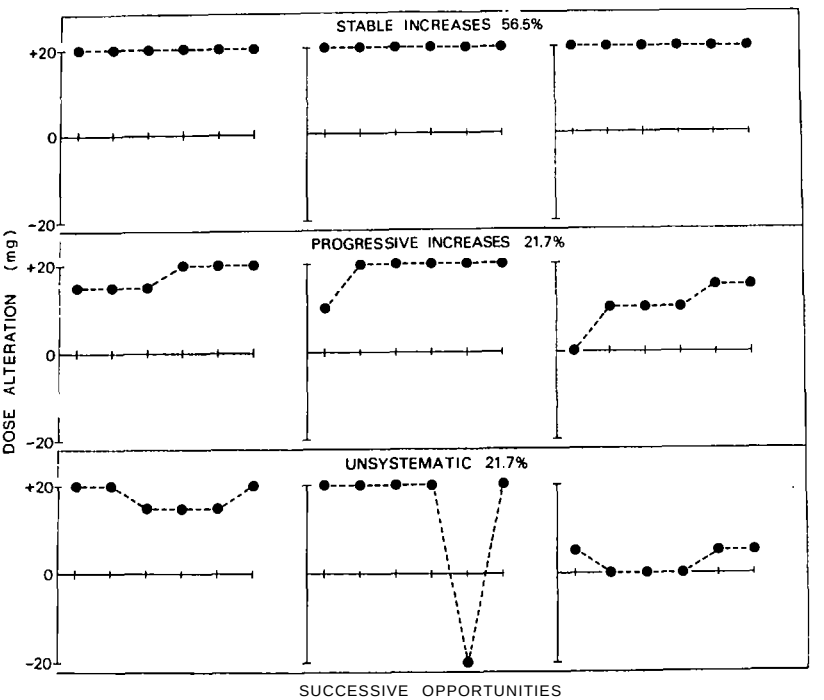
As Schuster (1975) points out, many other factors are involved in maintenance of self-administration besides the pharmacological properties of the drug. Of utmost importance may be the response cost for obtaining the drug and the availability of alternative drug sources. The problems engendered by a high response cost for drug pickup may be circumvented by studying self-administration of drugs which are offered to individuals who are already attending a drug treatment clinic regularly. Studies which have examined reinforcing efficacy of altered methadone dose are illustrative of this approach. In one study (Goldstein et al. 1974) methadone maintenance clients were allowed to alter their own methadone dose by ± 5mg each week in order to determine whether large dose increments would be self-selected by clients. However, requests for increases in methadone which resulted in doses above 50 mg also resulted in loss of medication take-home privileges. Under these conditions, 62.7% of the 59 clients studied raised their dose by at least 10 mg at some point during the study, but median dosage of the clinic population increased by only 10 mg during 25 study weeks. Thus, increases in stable methadone dose did not appear to be highly reinforcing. In Goldstein's study, however, many clients were essentially faced with a choice between higher methadone doses or continuing their take-home privileges. In addition, the size of each dose increase allowed was quite small. These factors could account for the lack of clear reinforcing effects of methadone dose increases.

Self-Regulation of Methadone Doses

A recent study conducted at Baltimore City Hospitals has shown more clearly that methadone dose increases can act as reinforcers for clients maintained on stable doses of methadone. In this study 23 clients enrolled at a maintenance clinic were given an opportunity to regulate their own dose for a single day on 6 separate occasions. Doses could be altered up or down by as much as 20 mg or 50% of the stable dose, whichever was smaller. The dose self-regulation opportunity was offered twice a week for three consecutive weeks. Clients chose to alter their dose on 97.1% of opportunities and chose dose

increases on 94.3% of opportunities. Of the dose increases selected, 81.2% were the maximum allowable size. Figure 1 shows typical patterns of dose self-regulation which were observed over successive self-regulation opportunities. The majority of clients (56.5%) always took maximum allowable dose increments. A smaller percentage (21.7%) took gradually larger dose increments on successive opportunities, while an additional 21.7% of clients showed unsystematic patterns of dose adjustment. This study showed that acute methadone dose increases act as a reinforcer for methadone maintained clients, since these clients will reliably self-administer acute dose increases in the choice situation.

FIGURE 1



Acute (single day) methadone dosage alterations selected by nine individuals clients on six successive opportunities. Doses could be altered by as much as ± 20 mg on each occasion. Three patterns of dosage alteration emerged: stable increases, progressive increases and unsystematic alterations. Percent of clients studied Who showed each type of pattern is indicated. Examples of dosage alterations selected by three representative clients are shown for each pattern.

The studies reviewed, using several specific experimental designs and methodologies, have shown that it is feasible to study drug self-administration in outpatient settings when a portion of drug ingestion which is under direct experimental observation constitutes the behavior of interest. Using drug self-administration methodologies, it has been possible to differentiate some drugs according to their relative abuse liability and to demonstrate reliable self-administration of methadone dose increases in narcotics dependent individuals.

Self-administration methodologies have also been used in outpatient settings to study the influence of treatment interventions on drug ingestion. Liebson et al. (1973), for example, took advantage of the reinforcing properties of methadone to reduce excessive use of ethanol in a group of narcotics dependent individuals with concurrent alcoholism. To accomplish this, a contingent arrangement was designed which encouraged ingestion of disulfiram at the clinic. Participants were methadone maintained clients who had a substantial drinking problem in addition to their narcotics dependence. These clients were initially assigned randomly to contingent or noncontingent conditions. The noncontingent group were offered disulfiram (Antabuse (^{R})) and encouraged to take it at home. The contingent group were required to ingest disulfiram daily at the clinic in order to receive their full dose of methadone. Because methadone was a reinforcer for these clients, the contingent arrangement maintained high rates of disulfiram ingestion. The study revealed striking differences in the amount of ethanol intake (as measured via self-reports and regular breath alcohol tests) of clients under the two conditions. Clients who were required to ingest disulfiram as a condition of receiving their methadone drank ethanol less frequently than those who were simply instructed to take disulfiram at home. In this experiment, ingestion of disulfiram at the clinic was encouraged by contingencies which took advantage of the reinforcing properties of methadone, and this in turn had a large impact on self-administration of ethanol in the natural environment.

Control of Benzodiazepine Use by Methadone Clinics

Abuse of benzodiazepine tranquilizers is also common among narcotics dependent individuals maintained on methadone. In a group of 57 clients, for example, enrolled in a methadone maintenance clinic at Baltimore City Hospitals during January, February, and March of 1975, 40% showed benzodiazepine positives on 80% or more of urines tested for this drug class, while only 20% of clients were entirely benzodiazepine free. Similarly, out of 50 new admissions to methadone maintenance from September, 1976 to November, 1977, 40% showed consistent benzodiazepine positives over the first three months of enrollment. Consequently, a study was designed whose purpose was two-fold: first, to gain experimental control over a portion of benzodiazepine use among these abusers; and second, to influence this observable portion of drug self-administration by offering incentives contingent upon discontinuation of benzodiazepine use.

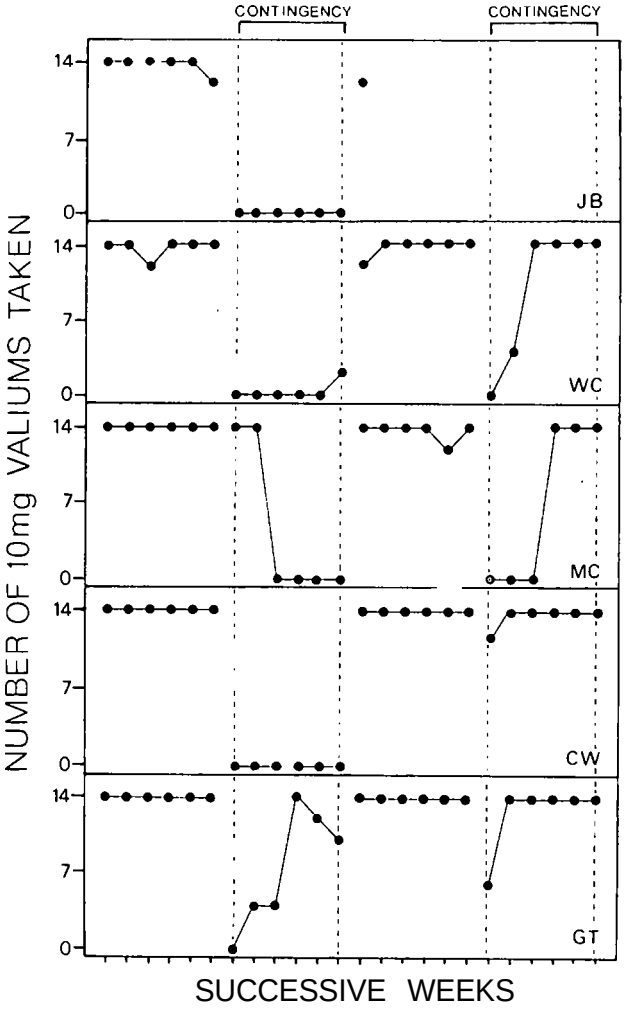
Five clients have participated in this ongoing experiment. These clients were selected on the basis of benzodiazepine use as revealed

in clinical interviews and confirmed by urinalysis results. The clients received prescriptions for diazepam (Valium), 20 mg per day, which they were free to request or refuse at the dispensary window throughout the course of the study. If Valium was requested the client was required to swallow one 10 mg tablet at the dispensary under nursing supervision and was given the second 10 mg tablet *to* ingest away from the clinic later in the day. Following a six week baseline period during which Valium was available, clients were offered a choice between continuing Valium ingestion at the clinic or receiving a clinic privilege: Clients could obtain a single methadone take home day by refusing Valium at the clinic window on four consecutive days. By refusing Valium every day of the week, a maximum of two nonconsecutive take home days could be earned each week. The incentive period lasted six weeks and was followed by a return to baseline. After six weeks of baseline a second choice was offered between Valium ingestion and a different clinic privilege. This time four consecutive days of Valium refusal resulted in the opportunity to self-regulate methadone dose for a single day by as much as ± 20 mg. Again, a maximum of two dose self-regulation opportunities-could be earned each week by refusing all available Valium.

Figure 2 shows results for individual clients participating in this study. During the six week baseline periods, 99.0% of available Valiums were requested at the dispensary. When take home privileges could be earned by Valium refusal, only 17.6% of available Valiums were requested by five clients, while 77.4% of available Valiums were requested by four clients during the period when dosage self-regulation could be obtained by Valium refusal. The opportunity to obtain methadone take home medication resulted in dramatic reduction of Valium ingestion at the clinic while the dosage self-regulation opportunity was much less potent in influencing Valium self-administration. The relative effectiveness of methadone take home and dosage self-control privileges were not fully assessed in this study, however. It is likely, for example, that the effectiveness of limited dosage self-control as a contingent reinforcer may be related to the size of the allowable dose alteration, with larger allowable dose increases having better reinforcing efficacy. Nevertheless, this study has demonstrated that a portion of the drug use of drug abusers can be brought under experimental observation and control and that this observable portion of drug use can be influenced by contingent privileges which are available in the context of a drug treatment clinic.

Outpatient clinics thus provide a useful natural setting in which drug abuse research can be conducted. Sufficient experimental control can be gained to generate orderly data without unduly restricting the environmental context of experiments or the activities of the subject population. A variety of research areas can be explored with a readily available population of appropriate subjects. Information can be obtained which has direct relevance for improved treatment of drug abusers. Hopefully the potential of outpatient clinics for drug self-administration research will continue to be expanded.

FIGURE 2



Number of 10 mg Valiums requested by five individual clients during 24 successive weeks of a contingency study. Two 10 mg Valiums were available daily to each client throughout the study. The first and third six week blocks were baseline periods. During the first contingency period (second column from left) methadone take home privileges could be earned by Valium refusal. During the second contingency period (fourth column from left), limited methadone dosage self-control could be earned by Valium refusal.

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Chapter 6

Drug Self-Administration in Humans

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Over the last 25 years, there have been increasing research efforts to understand the basis of illicit psychotropic drug use in humans. A major portion of this effort includes studies investigating pharmacological and environmental variables affecting the self-administration of psychotropic drugs using an animal model of human drug abuse (Schuster and Thompson 1969; Schuster and Johanson 1974). Such studies have not only been useful in delineating factors which contribute to the initiation and maintenance of drug use, but have also provided a methodology for predicting the abuse potential of new compounds before they are introduced to the marketplace (Johanson and Schuster 1977b; Thompson and Unna 1977). Obviously, there are a number of practical and ethical advantages of using animals in studies where potentially harmful drugs are administered. Both the range of manipulations and the degree of experimental rigor can be greater. On the other hand, it is essential to validate the findings of animal studies if we are to have any confidence in the predictive utility of our animal model for human drug abuse problems.

Studies have found that the major classes of drugs serving as positive reinforcers in infra-human organisms are those commonly used illicitly by humans (Schuster and Johanson 1974). Further, the patterns of intake (cyclical vs. continuous) of various classes of drugs are similar in animals and humans (Deneau, Yanagita, and Seevers 1969; Johanson, Balster, and Bonese 1976; Kramer, Fischman and Littlefield 1967; Schuster 1970). There are functional similarities as well. Altering availability, dose, pharmacological and environmental history, or pretreatment with other drugs has similar effects across a variety of species including humans (Johanson 1978). Likewise, the effects of repeated drug administration, including tolerance, physical dependence, and toxicity are remarkably similar between animals and humans (Jaffe 1975).

As previously mentioned, one important use of animal drug self-administration studies is to provide a methodology for predicting the abuse potential of new compounds. It is assumed that psychotropic drugs have as an inherent pharmacological property the capacity to serve as positive reinforcers and that this capacity is directly related to their abuse potential. It is also assumed that this capacity is relative, so that it is possible to rank drugs in their ability to function as positive reinforcers along a continuum. Therefore, it might be possible to discover drugs with similar therapeutic efficacy but with different potentials for abuse (Griffiths, Brady, and Snell 1978; Thompson 1977).

In developing a methodology for predicting abuse potential using animals, it would be ideal to first determine whether the procedures being tested rank drugs known to be abused by humans correctly, i.e., according to their relative frequency of abuse (Martin 1977). Unfortunately, obtaining valid, reliable estimates of a drug's actual abuse in society is an enormous methodological problem, since the pharmacological effect of the drug alone does not determine drug use. It would seem useful, therefore, to attempt to replicate certain animal studies, using humans, to determine whether similar results are found. However, in recent years, there has been an increased concern with the ethics of human drug research. These ethical considerations limit the participation of humans in self-administration studies. Nevertheless, the replication of a few carefully selected experiments in humans could help to determine the validity and hence predictive utility of an animal model of drug abuse. Ultimately such an animal model might serve to decrease the necessity for human subjects in drug abuse research.

Although drug abuse and considerations of abuse potential have been studied extensively in humans, the direct approach of studying actual drug-taking behavior is relatively new. Generally, the assessment of abuse potential has been based upon a comparison of the profile of action of a new drug with one of known abuse potential. One of the principal measures in such comparisons is the subjective judgment of institutionalized, ex-addict subjects; these subjects are given a drug and asked whether they like it or whether it resembles any drug they have ever used (Haertzen 1966, 1974; Martin and Fraser 1961). In some instances, mood scales purporting to measure a drug's ability to produce euphoria are used, on the assumption that a drug's euphorigenic properties are the basis of its abuse. Clearly, the results of this type of study are difficult to compare with animal studies where the frequency of drug-seeking or drug-taking behavior is the measure used to assess abuse potential. The present study was an outgrowth of years of laboratory studies using infra-human research subjects. An attempt has been made to adapt the methods

used in animals for human subjects in order to determine the comparability of results. In addition, however, changes in mood were measured to determine whether self-administration behavior is related to alterations in mood as is often assumed. If such relations are found, they would validate the use of such mood changes as predictors of actual drug use and suggest mechanisms which contribute to drug abuse.

A procedure which has proven effective in differentiating drugs in terms of their reinforcing properties in animals involves giving an organism a choice between compounds (Findley, Robinson, and Peregrino 1972; Johanson 1975; Johanson and Schuster 1975, 1977a). Choice in this case is considered a measure of preference. This research has shown that animals prefer many drugs over saline, high doses of a drug over low doses, and certain drugs over others. For example, cocaine is generally preferred to diethylpropion even when there is a 10-20 fold difference in dose (Johanson and Schuster 1977a). This potency difference is larger than that seen when comparing other behavioral properties of these two drugs (Johanson 1978). The finding that diethylpropion is not as reinforcing as cocaine corresponds well with reports of the relative incidence of abuse of diethylpropion (Jasinski, Nutt, and Griffith 1974) and suggests the possible usefulness of the choice procedure in predicting the relative abuse liability of drugs.

The first study using human subjects was designed to be methodologically similar to the previously conducted animal studies. Human subjects were given a choice between two psychomotor stimulant drugs, d-amphetamine and diethylpropion. Since the results of this study indicated the usefulness of this method, a second study was done where humans were given a choice between diazepam and placebo. Diazepam was tested because of the increasing concern over its purported abuse as well as our desire to determine the utility of this method with a drug from another pharmacological class.

Study 1: Self-Administration of d-Amphetamine (AMP) and Diethylpropion (DEP)

METHODS

Subjects: Three female and seven male subjects between the ages of 21 and 37 participated. All subjects were volunteers I recruited by placing advertisements in a student newspaper. All subjects were considered normal on the basis of extensive psychological screening, physical examination, ECG, complete blood chemistries, blood count, differential and routine urinalysis. Subjects signed a consent form prior to participation which outlined the study in detail and indicated all possible side effects of any drug they would be given. They were specifically informed that they would not be told what drug they ingested at the time, except that it would be either a psychomotor stimulant, minor tranquilizer or placebo, and the dose would be within the daily therapeutic range. Except for the actual drug ingested, subjects

were completely informed of all other procedural details as outlined below.

Procedure: Each subject participated in three to six different choice experiments involving d-amphetamine (5 and 10 mg), diethylpropion (25 and 50 mg) and placebo (dextrose) given in capsules for oral ingestion.. During each of these experiments, subjects were given a choice either between one of the two drugs and placebo or between AMP and DEP. For each subject, the procedure was identical across all experiments except for the drug choices available. The procedure was similar for all 10 subjects except as noted below.

Each experiment consisted of 9 sessions, three per week. During the initial (sampling) sessions, the subjects were given an opportunity to experience the effects of each of the two choice drugs before being asked *to* choose between them *in* later (choice) sessions. The first 5 subjects had 6 sampling and 3 choice sessions, and the last 5 subjects had 4 sampling and 5 choice sessions. Subjects were unaware of the actual drug dispensed but each drug and dose was associated with a different colored capsule. The capsule colors associated with the different doses of the two drugs were assigned randomly across subjects to partially avoid problems of color preference.

Subjects reported to the laboratory any 3 mornings each week between 9 and 11 a.m. During the sampling sessions, they ingested a capsule and filled out a mood scale form (see below). The color of the capsule alternated every session so that each of the two possible choices was ingested either 2 or 3 times. Subjects were told to note the color of the capsule and try to associate it with its effects, whatever they might be. They were informed that they would be asked to choose between the 2 colors in later sessions. The subjects then were free to leave the laboratory but were asked to remain within the university complex for the next six hours. In addition, they took 3 additional mood forms with them to fill out 1, 3 and 6 hours after drug ingestion.

During the subsequent choice sessions, the procedure was identical except *that* the subjects were asked *to* choose which of the 2 colored capsules they would like to ingest, 'The number of choices for each color was the dependent variable used for assessing preference.

The initial experiments were designed to determine whether subjects preferred d-amphetamine or diethylpropion over placebo. If both drugs at either dose were preferred, they were compared to each other in additional experiments. Table 1 shows the number of subjects given each of the 8 possible combinations as a choice. Subjects participated in a maximum of 6 experiments. The decision as to which experiments each subject participated in were based on the following considerations. In the first two experiments, the lowest dose of each drug was compared to placebo. If either

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TABLE 1

Number of Subjects Participating in Each Experiment in Study 1.1

	Placebo	5 mg AMP	10 mg AMP
25 mg DEP	10	8	3
50 mg DEP	1	7	4
5 mg AMP	10		
10 mg AMP	2		

[1]The column and row headings for each box indicate the two possible choices.

TABLE 2

Subscales for Each Form of the Profile of Mood States

Subscale	65-Item Scale	72-Item Scale
1	Anxiety	Anxiety
2	Depression	Depression
3	Anger	Anger
4	Vigor	Vigor
5	Fatigue	Fatigue
6	Confusion	Confusion
7*	Arousal	Arousal
8		Friendliness
9		Elation

*Subscale (1 + 4) - (5 + 6)

5 mg AMP or 25 mg DEP was not preferred to placebo, the higher dose of that drug (10 mg AMP or 50 mg DEP) was compared to placebo. If a dose of each drug was found which was preferred to placebo, they were compared to each other in additional experiments. The dose of the drug NOT preferred in this comparison was increased *to* the limits of the dose range (10 mg AMP or 50 mg DEP). If subjects participated in additional experiments, a comparison was made between other possible combinations of AMP and DEP.

Profile of Mood States (POMS): The scale used to assess changes in mood was the POMS (McNair, Lorr, and Doppleman 1971). With the first five subjects a form of the P0MS using 65 adjectives was used. Subsequently a revised version having 72 adjectives became available and this was used with the remaining five subjects. The adjectives in the POMS are those used commonly to describe momentary mood states, Subjects were asked to check how they felt AT THAT MOMENT in relation to that adjective on a 4 (the 65-item scale) or 5 point scale (the 72-item scale) from not at all (0) to very (3 or 4). Table 2 shows the different subscales for each version of the POMS. Except for Arousal, these subscales have been determined empirically using factor analysis. The names are given for convenience. The measure of Arousal is derived by combining four of the subscales as noted in the table.

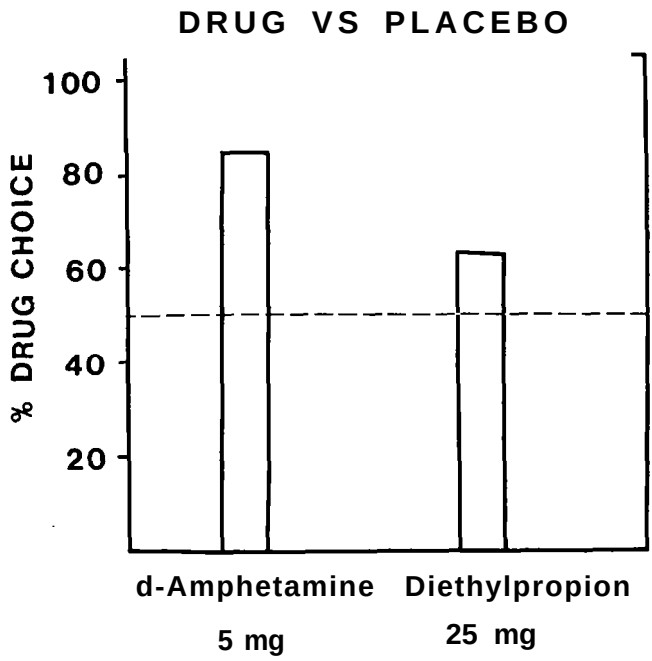
Changes in mood for each subscale were determined for each hour following drug ingestion (1, 3 and 6) as the difference from hour 0. It is these difference scores which were used in all data analyses.

RESULTS

Drug vs. Placebo: All 10 subjects initially were given a choice between 5 mg AMP and placebo and between 25 mg DEP and placebo. Since the number of choices possible differed among subjects (3 or 5), the results were expressed as a mean of the percent drug choices for each subject who participated in each experiment. As Figure 1 shows, both drugs were preferred to placebo with the preference being greater for 5 mg AMP (85%) than for 25 mg DEP (63%). While not all subjects chose drug consistently, only one subject out of 10 chose placebo over 50% of the time for both 5 mg of AMP and 25 mg of DEP. When given a choice between 10 mg AMP and placebo, he chose drug on all sessions. However, given a choice between 50 mg DEP and placebo, he still chose placebo consistently. A second subject also preferred placebo to both doses of DEP on every choice. With these exceptions, all subjects preferred the psychomotor stimulant drugs to placebo on the majority of trials.

AMP vs. DEP: Since not all subjects were in each experiment and the number of choices varied among subjects, the results are expressed as the mean of the percent of AMP choices of each subject. The two subjects who did not prefer either dose of DEP to placebo were not used in any further analyses. As shown in Figure 2, both doses of AMP were preferred to 25 mg DEP. The higher dose

FIGURE 1

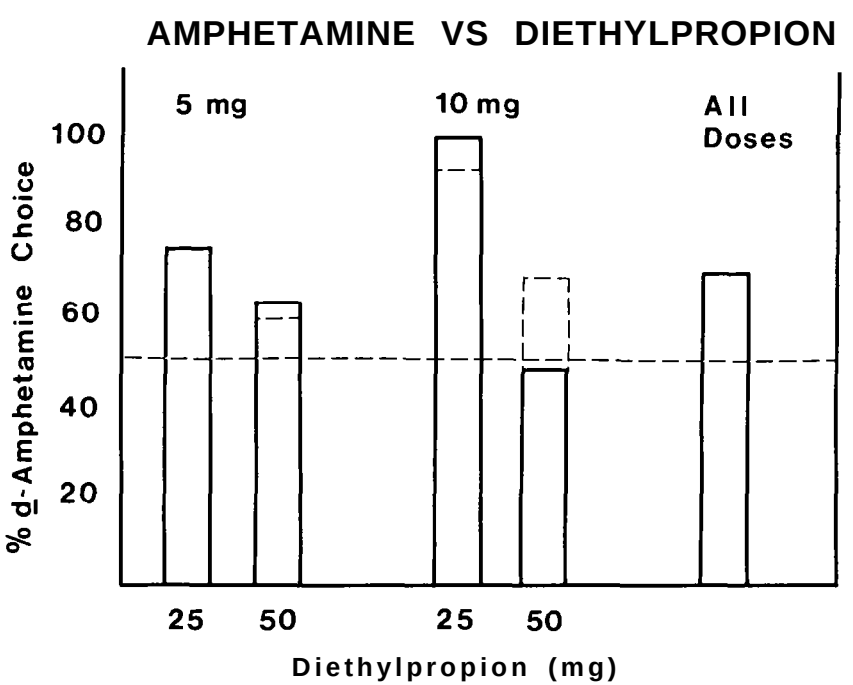


The percent choice of 5 mg d-amphetamine and 25 mg diethylpropion over placebo. The percent is a mean of individual percent drug choices for 10 subjects in Study 1. Only 1 subject chose 5 mg d-amphetamine less than 50% and 2 subjects chose 25 mg diethylpropion less than 50%.

of AMP was chosen on every possible occasion over the low dose of DEP. Increasing the dose of DEP to 50 mg decreased this preference. In the comparison between 5 mg AMP and 50 mg DEP, there was still an overall preference for AMP. On the other hand, 10 mg AMP and 50 mg DEP were chosen approximately the same number of trials. This was true both within subjects as well as across subjects.

This equal preference seems surprising and may largely be an artifact as a result of the design of the study. Subjects who preferred 5 AMP over 50 mg DEP were not tested in the comparison between 10 mg AMP and 50 mg DEP on the assumption that if 5 mg AMP was preferred, 10 mg AMP also would be. If we assume that these subjects would have chosen 10 mg AMP over 50 mg DEP, the

FIGURE 2



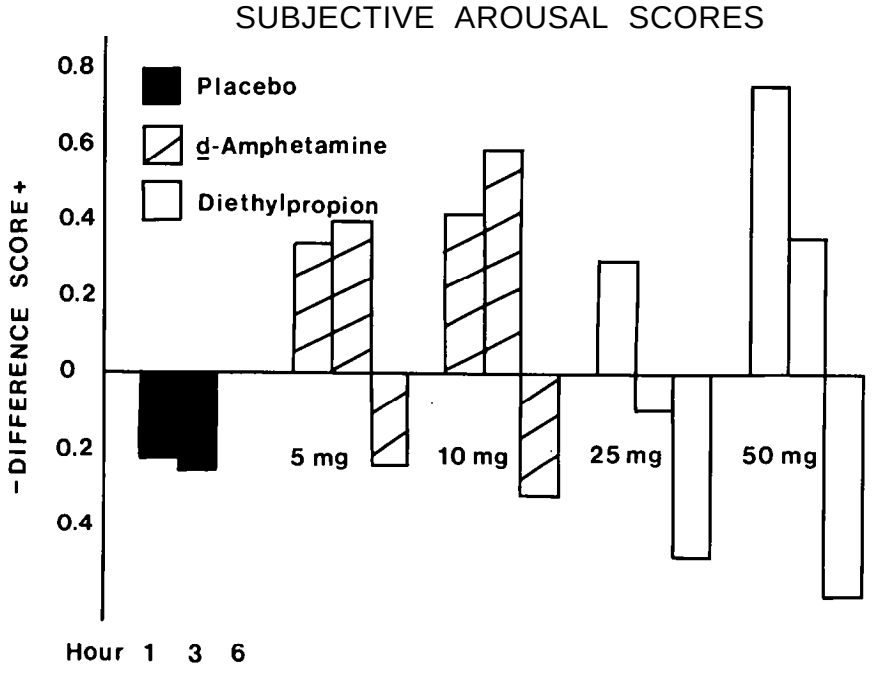
The percent choice of 5 mg (left bars) and 10 mg d-amphetamine (middle bars) compared to 2 doses of diethylpropion in study 1. The solid lines are the means of individual percent choices for subjects participating in each experiment (see Table 1). The dotted lines are the same means assuming that all 8 subjects Were in every comparison. For instance, if a subject chose 5 mg d-amphetamine rather than 25 mg diethylpropion on 4 of the 5 choice, it would be assumed that he would choose 10 mg d-amphetamine compared to 25 mg diethylpropion the same number of times. The bar on the right is the percent choice of amphetamine rather than diethylpropion regardless of dose.

percent choice of 10 mg AMP over 50 mg DEP would be 69% (see Fig. 2). In addition, if all comparisons between AMP and DEP are averaged together, regardless of dose, AMP is preferred to DEP 70% of the time. If it is assumed that the 2 subjects who did not prefer either dose of DEP to placebo would have always preferred AMP to DEP, this overall percentage would have been even higher. In general, therefore, AMP is preferred to DEP. It is important to note, however, that it appears that this preference

declines as the dose of DEP increases. It is possible that higher doses of DEP would have been preferred to AMP. We can only conclude that, in the range of doses commonly used for therapeutic purposes, AMP is preferred to DEP.

POMS: Although the POMS data could be analyzed a variety of ways, this preliminary analysis will include only the Arousal score since it has been shown in other studies in our laboratory to be sensitive to the effects of psychomotor stimulants. Data are included only from the 5 subjects who filled out the 65-item checklist. Fig. 3 shows the difference scores for each drug at both doses for 1, 3 and 6 hours after drug ingestion. Comparable scores for placebo are also shown. In general, both AMP and DEP

FIGURE 3



The Arousal scores derived from the Profile of Mood States for hours 1, 3, and 6 expressed as a difference from the score for hour 0 shown separately for placebo, 5 and 10 mg d-amphetamine and 25 and 50 mg diethylpropion in Study 1. The scores are the means of 5 subjects who fitted out the 65-item version. The Arousal score is the sum of factors 5 and 6 subtracted from the sum of factors 1 and 4.

increased Arousal relative to placebo. The effect for DEP peaked at hour 1 while AMP's effect peaked at hour 3. The order of increase was 50 mg DEP>l0 mg AMP>5 mg AMP>25 mg DEP which is certainly compatible with the choice data. On the other hand, at hour 6 Arousal was considerably decreased by all drugs, particularly DEP, relative to placebo. How these 2 effects might combine and affect preference is difficult to predict. Preliminary analysis of changes in individual POMS scores failed to reveal any differences in the effects of the drugs on Arousal that reflect differences in preference. This was as well true for all the individual subscales of the POMS (Johanson and Uhlenhuth 1977). It seems, therefore, that while the POMS Arousal scale *is* sensitive to the effects of both AMP and DEP, the change produced is not related to preference in a straightforward manner. Further analysis of the POMS data is currently being conducted which may reveal subtler systematic differences related to drug preference.

Study 2: Self-Administration of Diazepam (DZ).

METHODS

Subjects: Three female and eight male normal volunteer subjects participated. They were screened and prepared in exactly the same manner as subjects in Study 1.

Procedure: The subjects participated in 4 or 5 different choice experiments involving diazepam (2, 5 and 10 mg) vs. placebo, 5 mg d-amphetamine vs. placebo or d-amphetamine vs. diazepam (DZ) . The procedure was identical to Study 1 except that in each experiment all subjects had 4 initial sampling sessions designed to provide experience with the effects of each of the 2 choice drugs followed by 5 choice sessions.

In the initial experiments, an attempt was made to determine whether 5 mg AMP and 2 or 3 doses of DZ (2, 5 or 10 mg) were preferred to placebo. In additional experiments, DZ and AMP were compared to each other. Table 3 shows the number of subjects given each of the possible combinations as a choice.

The strategy was first to determine whether one or more doses of DZ were preferred to placebo. If so, the lowest preferred dose was compared to AMP. If, regardless of dose, DZ was not preferred and the subject was scheduled to participate in additional experiments, 2 mg DZ was compared to 5 mg AMP.

RESULTS

Although all subjects had 5 choice opportunities, the results are expressed as a mean of the percent drug choices for each subject who participated in each experiment in order to permit comparison of the results to Study 1. Figure 4 shows the results of the experiments comparing the 3 doses of DZ (2, 5 and 10 mg) and 5 mg AMP to placebo. As in the first study, AMP was preferred to placebo

TABLE 3

Number of Subjects Participating in Each

Experiment in Study 2.1

	2 mg DZ	5 mg DZ	10 mg DZ
Placebo	10	11	10
5 mg AMP	8	2	
10 mg AMP		1	

[1]The column and row headings for each box indicate the two possible choices.

The lowest dose of DZ (2 mg) was chosen on approximately half the trials. Preference varied considerably among subjects, with 4 subjects choosing DZ less than 2 times, 4 subjects choosing DZ 4 or 5 times and the other 3 choosing the drug 2 or 3 times. However, the higher doses of DZ were seldom chosen by any subjects. Similarly, in the comparison between 2 mg DZ and 5 mg AMP, DZ was only preferred on 25% of the choices. Figure 5 (top panel) shows the results from a typical subject. Compared to placebo this subject only preferred the lowest dose of D&which in turn was not preferred to 5 mg AMP.

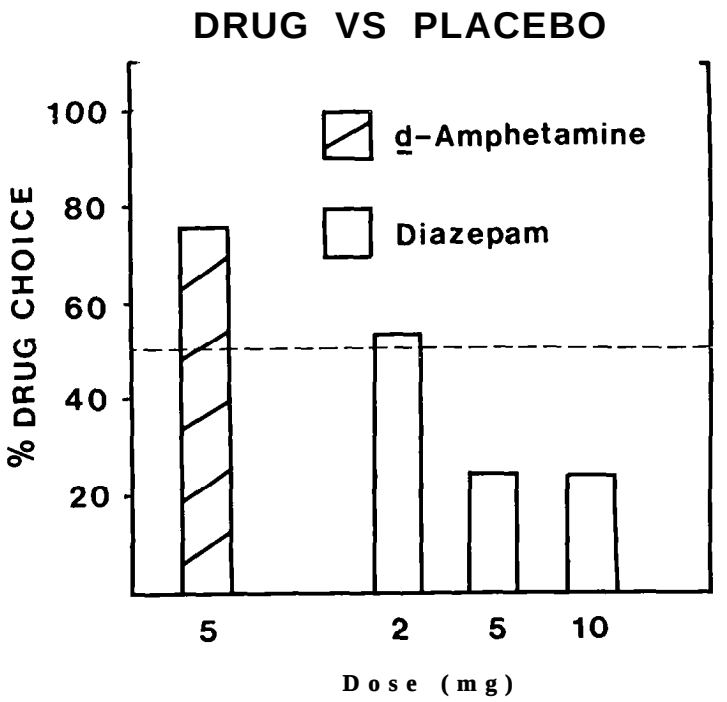
As mentioned above, the higher doses of DZ were seldom chosen over placebo. However, 2 subjects did prefer 5 mg DZ on the majority of choice sessions. Therefore, this dose of DZ was compared to 5 mg AMP. In that comparison one of the subjects preferred DZ, and in a subsequent experiment even preferred 5 mg DZ to 10 mg AMP (Fig. 5). The second subject, however, preferred 5 mg AMP to the DZ. In general, therefore, DZ was seldom preferred either to placebo or to AMP.

The analyses of the POMS data are incomplete at this time, as this study is still in progress.

DISCUSSION

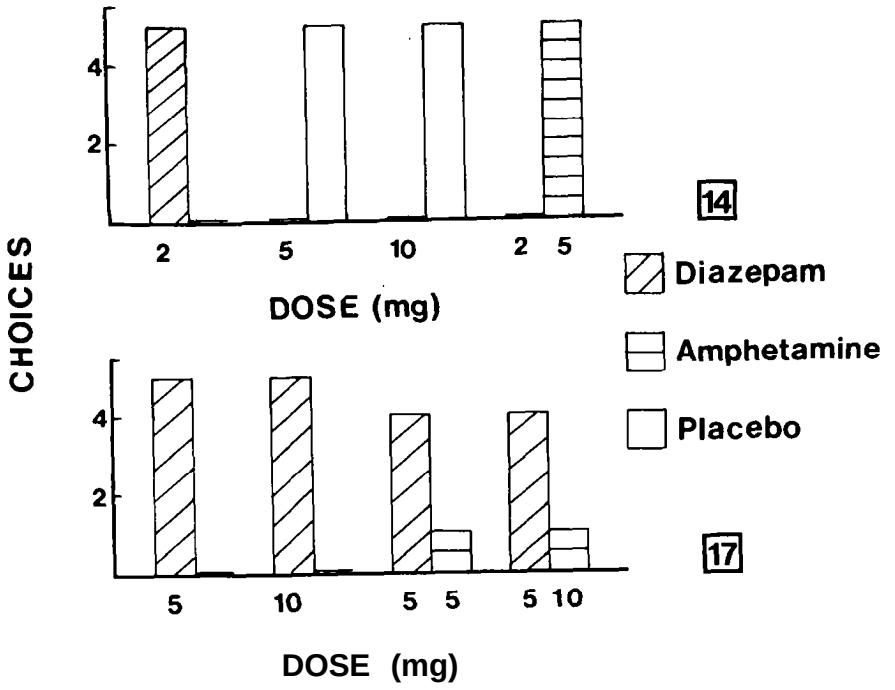
The present studies are important in two respects. The first concerns the design of methodologies for the prediction of the abuse potential of new compounds. Over the last 15-20 years, attempts have been made using an animal model of drug abuse to develop ways of determining, prior to the introduction of new drugs on the market, whether they might be abused. The strategy is to find procedures which measure the reinforcing properties of drugs along a continuum of increasing strength or efficacy. The assumption

FIGURE 4



The percent choice of 5 mg d-amphetamine (left bar) and-three doses of diazepam over placebo. The percent is a mean of individual percent drug choices for subjects in study 2 (see Table 3).

FIGURE 5



The number of choices for each alternative in 4 experiments for 2 subjects in study 2. The drug is indicated by the hatching of the bar and dose is shown below each bar.

has been that the reinforcing properties of drugs in animals are correlated with their abuse potential in humans.

One of the problems faced in this endeavor has been the validation of results. Investigators have studied drugs, such as heroin and amphetamine, whose frequency of abuse is presumably known. However, there are enormous methodological problems in making estimates of actual abuse, and it is not at all clear whether these estimates are adequate for validating an animal model. Therefore, the initial study was similar to a previous animal experiment where the reinforcing properties of intravenous cocaine and diethylpropion were compared. In this animal experiment both drugs were preferred to saline over a large dose range (Johanson and Schuster 1975, 1977a). In addition, although cocaine was generally preferred to diethylpropion, there was some indication that increasing the dose of diethylpropion decreased this preference. The dose required was 10 to 20 times that of cocaine. In other animal studies comparing these two drugs behaviorally, the potency difference was only 4- to 6-fold (Johanson 1978). It seems, therefore, that in addition to a potency difference between these two drugs, this study indicates that cocaine is more efficacious as a positive reinforcer. Similar results have been found in other animal studies (Griffiths, Brady, and Snell 1977). Certainly, the reports of their relative abuse, however inaccurate they may be, agree with this rank order.

Although the results of the present *study* using humans may indicate that diethylpropion is a weaker reinforcer, they are not conclusive. Despite the use of low oral doses, the subjects generally preferred both d-amphetamine and diethylpropion over placebo. This result corresponds to the fact that animals self-administer both of these drugs at a greater frequency than saline (placebo) (Griffiths, Brady, and Snell 1977; Johanson and Schuster 1975, 1977a).

In comparisons between these two drugs, d-amphetamine was generally preferred. However, as the dose of diethylpropion was increased, preference for d-amphetamine decreased much as was found in the animal study. In the comparison between 10 mg d-amphetamine and 50 mg diethylpropion, both were equally preferred., but by projecting data of all the subjects (see Fig. 3), amphetamine appears to be preferred. Since higher doses of diethylpropion were not tested, it is difficult to assign a potency ratio for the two drugs. However, the estimated potency difference (1:5) is certainly similar to that recognized therapeutically and found in other behavioral studies using both animals and humans (Griffiths, Brady, and Snell 1978; Jasinski, Nutt, and Griffith 1974; Jonsson 1969). These other studies, regardless of species, do not conclude that d-amphetamine and diethylpropion differ in abuse potential. Clearly additional research in both animals and humans is necessary to determine whether there is any significant difference in the abuse potential of these two drugs. What is significant, however, is that the results from both animal and human studies are similar.

This is also true in the second study. Except at the lowest dose of 2 mg, few subjects chose diazepam over placebo. Even at the 2 mg dose, preference was just over 50%, which may only indicate that subjects could not discriminate this drug from placebo. In addition, with one exception, doses of diazepam which were preferred over placebo were not preferred to 5 mg d-amphetamine. Unfortunately, these results cannot be compared-directly to animal studies. Perhaps due to its insolubility in water, there is only one published report of diazepam self-administration in animals (Yanagita and Takahashi 1973). This experiment involved very high doses of drug under conditions of unlimited access. Although 3 of the 4 monkeys self-administered the drug at rates above saline, the authors state that this drug was not as potent a reinforcer as many other drugs tested under similar conditions (Yanagita and Takahashi 1973). Furthermore, in other animal experiments where chlordiazepoxide has been made available, rates of self-administration have been relatively low, similar to those for saline (Johanson and Balster 1978). Although, in another animal study using a choice procedure, chlordiazepoxide was preferred to saline, secobarbital was overwhelming preferred to chlordiazepoxide (Findley, Robinson, and Peregrino 1972). Therefore, while the benzodiazepines may be capable of maintaining some responding, other drugs are readily preferred in animal studies as well as the present one with humans.

The second aspect of these studies concerns the relationship between the self-administration of drugs and their effects on subjective rating scales. It has been assumed that particular changes in mood states, such as increased euphoria, are good predictors of the abuse potential of a drug (Haertzen 1966, 1974). If an unknown drug produces a profile of action on a variety of subjective and perhaps physiological measures similar to a drug known to be abused, then their abuse potentials are considered similar.

A study by Jasinski, Nutt, and Griffith (1974) is an excellent example of research making this assumption. They compared orally administered d-amphetamine and diethylpropion in humans by assessing their relative profiles of action on a variety of subjective and physiological measures. The effects of both drugs were qualitatively similar, although diethylpropion was 1:6 to 1:11 as potent as d-amphetamine.

In the present study, subjective effects were measured using a derived measure (Arousal) from the Profile of Mood States. While all doses of both d-amphetamine and diethylpropion increased Arousal, the potency difference was not as great as in the Jasinski, Nutt, and Griffith (1974) study. In addition, the changes in Arousal were seen at much lower doses. On the other hand, there is some indication that increases in Arousal were not predictive of preference. Clearly, these results should only be considered preliminary, as it is possible to do additional analyses of the POMS involving other combinations of subscales.

Although these results are not conclusive, they do cast doubt on the assumption that mood changes and drug self-administration are related in a straightforward predictive matter.

The results of the present studies indicate that it is possible to develop methodologies of drug self-administration in humans which are sensitive to different drugs. The comparability of results with animal studies helps validate an animal model of human drug abuse. In addition, human studies of drug self-administration can provide important information on the relationship between a drug's reinforcing efficacy and its mood altering properties. Application of this combination of methodologies can provide new insights into the motivational basis for drug abuse.

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ACKNOWLEDGMENT

This work was supported in part by Research Scientist Award number MH-18, 611 from the National Institute of Mental Health.

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Chapter 7

Experimental Studies of Sedative Self-Administration by Humans

Roy W. Pickens, Ph.D., and Leonard L. Heston, M.D.

Recently we reported an experimental study of pentobarbital self-administration by humans (Pickens et al. 1977). In that study, relations were determined between daily drug intake and blood serum levels during self-administration and measures of metabolic and CNS tolerance to pentobarbital. We also used a self-administration choice procedure to determine relative preference for various doses of pentobarbital. In this paper we will review our findings and discuss implications of the results. Additional details of the study can be found in the original published report.

Our subjects were eleven adults with confirmed histories of sedative drug abuse. Ten of the eleven had a prior history of treatment for drug abuse and four of the eleven had a prior history of seizures related to sedative withdrawal. Almost all were women, with only one male included to assess generality of the results. The subjects ranged in age from 26 to 63 years and weighed between 44 and 93 kg.

All subjects were self-administering sedative drugs on hospital admission when they were informed of the project and invited to participate as research subjects. Written consent was obtained in all cases prior to testing. Subjects were maintained on sedative drugs for the duration of the research project, after which they were gradually withdrawn and given appropriate treatment for drug dependence .

In the first part of the study, subjects were tested to determine degree of central nervous system (CNS) tolerance and metabolic tolerance to pentobarbital. This was accomplished by measuring the degree of sedation and drug metabolic half-life following 200 mg pentobarbital administration. Subjects were examined hourly at 1, 2, and 3 hours postdrug for slurred speech, ataxia, and sleep. CNS tolerance was considered minimal if a subject slept and showed slurred speech or ataxia during this time, moderate if only slurred speech or ataxia was seen and marked if none of the above signs was seen. Blood samples were also obtained at 2-4 hr intervals for 18 hrs postdrug and analyzed by gas chromatography for quantitative pentobarbital content. Drug metabolic half-life was determined from rate of decline in drug serum levels over the postdrug period.

Although all subjects were self-administering sedative drugs on hospital admission, a wide range of metabolic and CNS tolerance was seen (see Table 1). Three subjects showed pentobarbital half-lives within the normal range (21-42 hours), four subjects showed mo-moderate increases in metabolic rate (t½ = 13-21 hours) and four subjects showed marked increases in metabolic rate (t½ = 5-12 hours). Four subjects were minimally tolerant, two subjects were moderately tolerant, and five subjects were markedly tolerant to the CNS effects of pentobarbital. As might be expected, subjects who showed metabolic tolerance to pentobarbital also showed CNS tolerance as well, with the correlation between the two measures being r_b = +0.73 ($p < .05$).

Following metabolic half-life and CNS tolerance determination, subjects were allowed to self-administer pentobarbital for four days to determine relations between tolerance and drug taking behavior. During drug self-administration, subjects were given a 50 mg dose of pentobarbital upon each request to the nursing staff, who then verified the oral drug consumption. Drug was available 24 hrs/day for self-administration except that a 30-min minimal interval was imposed between successive drug requests to minimize intoxication. Amount of drug taken was determined each day, and pentobarbital blood serum level was obtained on the morning after each self--administration day. These results were then correlated with measures of CNS tolerance and metabolic tolerance to pentobarbital.

For all subjects, drug intake ranged between 312.5 and 675.0 mg pentobarbital per day and blood serum levels ranged between 2.0 and 3.9 μg/ml (Table 1) . The correlation between drug intake and blood serum level of pentobarbital on the morning after each self-administration day was r = +0.49, which was not significant statistically ($p > .05$) . However, factors other than drug intake also influence drug serum level. One of these is drug metabolic rate, which controls the rate of elimination of drug from the body. Higher metabolic rates would result in more drug being eliminated from the body overnight, producing lower drug serum levels on the following morning. When differences in metabolic rate were controlled by a partial correlation test, the relationship between drug intake and drug serum level increased to $r_{12.3}$ = +0.64, which was statistically significant at $p < .01$ ($t = 3.77$, $df = 8$).

The correlation between drug intake and metabolic tolerance was r = +0.33, while that between drug intake and CNS tolerance was r-b = +0.47. Neither of these correlations was statistically signif icant. The failure to obtain significant correlations between drug intake and degree of CNS or metabolic tolerance was surprising, as these factors are frequently reported together in case studies of human sedative abuse. While the direction of the correlations indicated that more drug was self-administered each day by subjects showing shorter drug half-lives and greater degrees of CNS tolerance, the failure to find statistically significant relationships may be due to the present experimental design (only 11 subjects, relatively imprecise measures of CNS and metabolic tolerance, etc.). Alter-

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TABLE 1

Pentobarbital CNS tolerance, half-life and self-administration characteristics (mean ± S.E.M.) for individual subjects

Subject	Initial Testing		Self-Administration	
	CNS tolerance[a]	Half-life	Drug intake	Serum level
		hr	*mg/day*	*μg/ml*
F1	+	6.6	525.0 ± 47.8	3.0 ± 0.3
F2	0	14.5	473.5 ± 62.5	2.8 ± 0.5
F3	++	13.5	337.5 ± 47.3	2.0 ± 0.3
F4	0	17.5	420.0 ± 30.0	3.9 ± 0.2
F5	0	22.4	312.5 ± 42.7	2.7 ± 0.5
F6	0	31.7	362.5 ± 31.5	3.0 ± 0.2
F7	++	6.6	360.0 ± 29.1	2.3 ± 0.3
F8	++	24.2	600.0 ± 35.0	3.6 ± 0.4
F9	++	16.2	400.0 ± 47.4	3.6 ± 0.7
F10	++	9.1	460.0 ± 40.0	2.9 ± 0.3
M1	+	5.5	675.0 ± 47.8	3.3 ± 0.9

[a] 0, *minimal or absent; +, moderate; ++, marked.*

natively, since significant relationships were obtained between metabolic and CNS tolerance to pentobarbital and between drug intake and blood serum level during self-administration, the results may indicate that CNS and metabolic tolerance are not the sole determinants of daily drug intake in fixed-dose pentobarbital self-administration.

In the second part of the study we determined relative preference for various doses of pentobaribtal using a self-administration choice procedure. Drug dispensing was from an automatic vending machine. Subjects were allowed to obtain their daily drug supply by selecting between two identically-appearing drug capsules available in adjoining channels of the machine. Each day, one machine channel always contained 50 mg pentobarbital (standard compound), whereas the other channel contained either 30, 50, 100, 150, or 200 mg pentobarital (test compound) . Subjects were instructed to start each morning by alternately selecting capsules from the two channels until a preference developed, and then to take capsules from the preferred channel for the remainder of the day. If no preference developed, subjects were to alternate between channels for the entire day. Standard and test compounds were assigned to channels on a random basis daily. Every second day was a control day, in which 50 mg pentobarbital (standard compound) appeared in both vending channels. The machine was programmed to record drug selections and to require a 30-min minimum interval between successive drug deliveries. All testing was double blind.

Dose preference was expressed as a preference ratio, the ratio of test capsule selections to total capsule selections (standard + test) for a given day. Ratio values of 0.5 indicated no preference between test and standard compound, whereas ratio values greater than 0.5 indicated a preference for the test over the standard compound, and ratio values less than 0.5 indicated a preference for the standard over the test compound.

All of the subjects showed highest preference ratios for intermediate capsule doses (50-150 mg). The most preferred pentobarbital dose was 50 mg for two subjects (F8 and M1), 100 mg for one subject (F6) and 150 mg for three subjects (F7, F9, and F10). No subject most preferred the 30 mg or 200 mg test doses (Figure 1).

From individual data, two types of preference profiles were seen. Four of the subjects (F6, F8, F10, and Ml) showed curvilinear relations between preference ratio and capsule dose. As. pentobarbital dose increased, preference ratio initially increased and then declined. Low preference ratios (<0.5) were obtained at both the lowest and highest test doses, indicating a preference for the standard over the test compound. Highest preference ratios were obtained at the intermediate test doses (50-150 mg/capsule), indicating a preference for the test over standard.

The remaining two subjects (F7 and F9) showed a preference for only a single dose of pentobarbital. Both subjects preferred the 150 mg test dose to the 50 mg standard. At all other test doses these two subjects alternated between channel selections, indicating no preference between test and standard compound. While preference for a single intermediate dose of pentobarbital also produced a curvilinear dose preference function, these subjects differed from the four

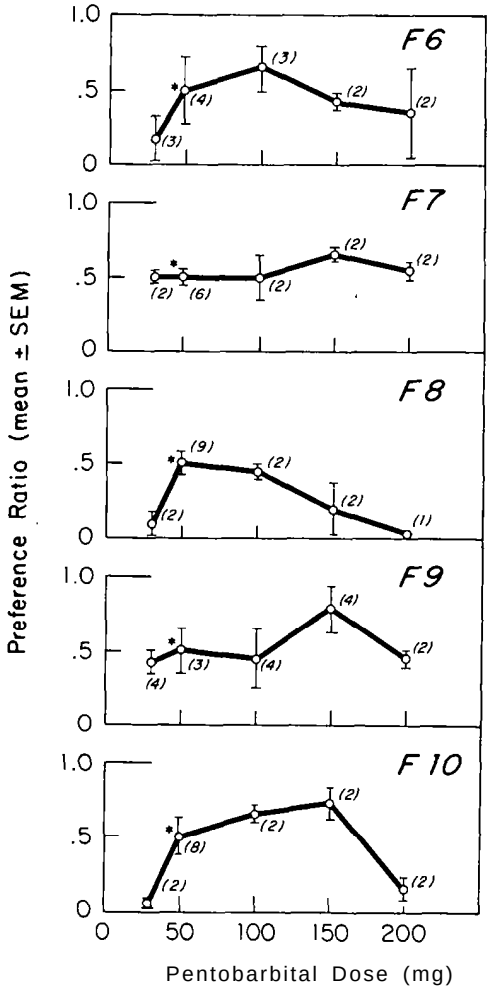

FIGURE 1 *Preference ratios for 30, 50, 100, 150, and 200 mg/capsule pentobarbital, using 50 mg pentobarbital as the comparison standard. Replications are shown in parenthesis beside each test dose. Vertical lines are + S.E.M. * are control days when 50 mg pentobarbital was available in-both vending channels. Vertical lines for this data point indicate range of differences in frequency of channel selection. Data shown are for 5 female subjects (F6-F10). Data for male subject (Ml) are not presented, as additional procedures involving this subject were not described in the present report.*

subjects reported above in not showing a preference for the standard over the test compound at any dose tested.

For all subjects, daily pentobarbital intake increased with increases in dose available for self-administration. While theoretically the same total amount of drug could be taken each day at all test doses, there was approximately a 2-fold increase in intake over a 6-fold range of test doses. However, there was no effect of the increased drug intake on measures of the subject's grooming, self-maintenance, or social behaviors. In fact, throughout the study the subjects rarely appeared overtly intoxicated, although this may be more a function of the type of subject employed (middle-aged females) than a characteristic of pentobarbital abusers in general. More recent work with young male sedative abusers has supported this observation.

Our research has produced a number of interesting findings. As might be expected, statistically significant correlations were found between degree of CNS tolerance and metabolic tolerance to pentobarbital in human sedative abusers. However, neither could be reliably used to predict drug intake in pentobarbital self-administration. While blood serum levels of pentobarbital were not significantly related to the preceding day's drug intake, when the subject's degree of metabolic tolerance to pentobarbital was taken into account, a significant relationship was found between serum level and drug intake. Intermediate pentobarbital doses (50-150 mg) were preferred to both lower (30 mg) and higher (200 mg) doses during oral self-administration. Total daily drug intake was influenced by capsule dose, and possibly by subject characteristics as well.

Human studies of drug self-administration provide data relevant to many aspects of drug dependence. However, these studies contain two major sources of subject variability that affect outcome results. One of these is past drug history, which includes the various pharmacological and behavioral aspects of previous drug use. Even when subject characteristics are well-defined, differences may still exist among subjects in terms of past history of drug use. For example, while the subjects in the present study were primarily middle-aged women with sedative abuse problems, they nevertheless differed considerably in terms of types of drugs used, the dosage, duration, and conditions of drug use, etc. Unfortunately, in conducting studies of this type such information cannot always accurately be obtained. Past drug history factors may be expected to increase data variability and thereby possibly obscure significant results. This occurred in the present study, for example, when a significant correlation between drug intake and drug serum level was obtained only after the subjects' differences in metabolic rate were taken into account. Drug history factors are not typically involved to the same extent in experimental studies of self-administration by rats and monkeys.

In addition to drug history, genetic factors also would be expected to influence results of human drug self-administration studies. Genetic differences may be expected to occur at any point from absorption to excretion where drug interacts with tissue. The pharmacologic action of most drugs probably depends on events at the cell membrane

where drugs interact with receptor glycoproteins: individual variation in the affinity of receptors for drug, in most cases genetically controlled, would, of course, be associated with variation in whatever intercellular events are induced by the affected receptors. Some of the intracellular events would be temporary and depend on continued presence of drug at the receptor site, but others could be quite persistent, as would be needed to account for cellular tolerance. Mechanisms producing persistent change are known to exist, although an example linking such change to drug action through specific steps has not been demonstrated so far as we know. Interactions between drug and events occurring before and after drug-membrane interactions would change the concentration of drug or possibly the concentration of active metabolites at receptor sites, and thus account for individual differences in drug response. Variation due to genes, though still unexplored, could well be of central importance in liability to drug abuse.

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ACKNOWLEDGMENT

This work was supported by Grant DA 00939 from the National Institute on Drug Abuse, and by Special Appropriation in Psychiatry, State of Minnesota.

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Chapter 8

Marihuana, Alcohol, and Polydrug Use: Human Self-Administration Studies

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Although the examination of patterns of drug self-administration in human subjects is a relatively recent development, the value of this approach for the study of substance abuse has now been amply demonstrated in many laboratories. Advances in techniques for the analysis of behavior have been paralleled by an expansion of and refinement in the types of questions asked. This review will discuss some dependent variables that can be studied in a human drug self-administration paradigm. These issues will be considered in the context of a quasi-historical review of some operant procedures we have developed and their advantages and limitations. Finally, some data obtained on patterns of alcohol, marihuana and multiple-drug self-administration will be described.

DEPENDENT VARIABLES IN HUMAN DRUG SELF-ADMINISTRATION

Over the past fourteen years, our clinical research program has studied the self-administration of a number of abused drugs in human volunteers with a history of drug use or addiction. Multi-disciplinary studies have been conducted on an inpatient research ward and each individual has been observed before, during, and after a period of self-regulated drug intoxication. This approach permits study of an encapsulated sequence of the basic behavioral disorder, drug abuse, under clinical research ward conditions.

Our objective has been to study natural or relatively unconstrained drug use patterns, and to correlate these with a number of biological and behavioral variables. We have attempted to devise situations where the pattern of drug self-administration would simulate, as closely as possible, drug use patterns in the natural environment. Two general categories of dependent variables can be examined in such studies: drug-effect variables and patterns of drug self-administration.

Drug Effect Variables

The pharmacological actions of drugs are defined by effects on many aspects of behavioral and biological function. Studies of physiological responses to drugs may include examination of many systems such as neuroendocrine hormones, plasma lipid levels and sleep EEG (Mendelson 1970; Mendelson and Mello 1976; Mendelson et al. 1978). Behavioral studies may explore drug-related changes in subjective states, perceptual and cognitive function, social interaction and objective measures of performance. Another drug-effect variable is the fine-grain analysis of operant responding, including inter-response time analysis. Many other examples of drug-effect variables could be listed. However, the main point is to distinguish drug-effect variables and patterns of drug self-administration.

Patterns of Drug Self-Administration

The pattern of drug self-administration is itself an important dependent variable which may be central to our understanding of human substance abuse. Basic and human behavioral pharmacology have repeatedly shown that the schedule of drug reinforcement, i.e., the dose and frequency of drug availability, influences the effects of drugs on behavior (Kelleher, Goldberg, and Krasnegor 1976). By observing an individual's drug self-administration pattern, we can study the self-imposed schedule of reinforcement. However, this is only possible if the individual determines his own pattern of drug use.

Examination of the self-imposed pattern of drug use may assist in the identification of factors which contribute to the maintenance of drug abuse. The diversity of individuals with drug abuse problems, and the fact that no single psychological, social or biological factor appears to predict drug abuse, suggest that it may be more productive to try to determine how drug abuse is maintained than to focus exclusively on etiological factors. Moreover, as we study the self-administration of different drugs under similar conditions. we house to be able to compare use patterns across drugs. Eventually, this type of analysis should help to identify some commonalities and differences in the determinants' of patterns of heroin abuse, alcohol abuse, marihuana and tobacco use, stimulant and hallucinogen abuse, etc. If an analysis of drug use patterns can reveal commonalities which transcend particular drug effects, such information might be generalizable to future forms of drug abuse as well. Although we cannot now predict the specific types of future drug abuse problems, some type of substance abuse seems almost inevitable. Clarification of factors which maintain drug self-administration should facilitate development of more effective intervention procedures.

The pattern of drug self-administration can be operationally defined by the following measures:

(1) Number of drug self-administration occasions (per hour; per day; per week)

(2) Drug dose per occasion

(3) Interval between drug self-administration occasions, i.e., the distribution of drug doses over a 24-hour period.

Although it could be argued that drug use also affects the subsequent pattern of drug self-administration, and that this also should be classed as a drug effect variable, we feel the distinction between drug use patterns and drug effects has both conceptual and methodological advantages.

This approach to the study of human drug self-administration and the questions posed are different from studies which attempt to manipulate human drug use patterns by variation of the conditions necessary for drug acquisition. It has been demonstrated that manipulation of conditions such as response-cost, the time of drug availability, the dose of drug available, can change both the amount and frequency of drug use (Griffiths, Bigelow, and Liebson 1976a; Bigelow, Griffiths, and Liebson 1976; Mello et al. 1968; Pickens et al. 1977; Babor et al. 1978). Factors such as drug dose and response-cost also effect drug self-administration in animal models in a similar way (Griffiths and Bigelow 1978).

Since the use patterns of several drugs have been shown to be modified by manipulation of acquisition variables, these studies may have implications for social controls of drug use, i.e., hours of drug availability, taxation and price, etc. (Popham, Schmidt and deLint 1975). However, the identification of common controlling variables cannot be interpreted to suggest that the use patterns of different drugs are identical. Rather, use patterns appear to be quite different depending upon the pharmacological action and rate of absorption and disposition of the particular drug.

Limitations of Drug Self-Administration Studies

One disadvantage of the study of spontaneous drug self-administration patterns is that precise time-dose-response relationships between the various drug-effect variables cannot be established since drug dose, frequency, and inter-dose intervals will vary on an unpredictable basis. Yet, this variability constitutes the drug self-administration pattern which is our primary dependent variable.

One alternative is to ignore drug self-administration patterns and to focus instead on drug-effect variables. The most efficient way to do this is to use a programmed drug administration regimen in which fixed doses are administered every 4 to 6 hours. This permits precise dose-time correlations with whatever drug-effect variable has been selected for study.

Programmed drug administration is the traditional method used to examine the basic pharmacological effects of drugs. The pioneering studies of drug effects conducted at the Lexington Addiction Research Center employed programmed drug administration with only one exception (Wikler 1952). The first studies of the effects of alcohol intoxication in alcoholics were conducted in a programmed administration paradigm (Mendelson 1964).

It is evident that programmed dose paradigms are useful for asking different types of questions than self-administration paradigms. However, there are also other factors which may limit the utility of a programmed dosage paradigm, even for the study of drug-effect variables. When the effects of programmed alcohol administration and spontaneous self-regulated alcohol consumption were compared in eight alcoholic subjects, it was found that biological drug-effect variables varied markedly between the two alcohol administration conditions (Mello and Mendelson 1970). Each subject served as his own control during a 20-day programmed alcohol administration regimen and during a 20-day spontaneous alcohol self-administration paradigm. Programmed alcohol administration was associated with greater toxicity (gastritis, vomiting) during intoxication than spontaneous drinking. Subjects were able to tolerate higher doses of alcohol during the spontaneous self-administration paradigm and distributed alcohol consumption to achieve higher peak blood alcohol levels than were measured during programmed administration. The severity of alcohol withdrawal signs and symptoms after cessation of drinking was markedly greater after spontaneous drinking than after programmed alcohol administration, even in those subjects that drank equivalent quantities of alcohol in each condition.

It was concluded that the pattern of drinking was more critical than duration of drinking as a determinant of biological reactions to alcohol intoxication and withdrawal. These data seemed to justify our pursuit of self-determined patterns of drug self-administration, both as a primary dependent variable, and as the most sensitive and reality-concordant baseline against which to correlate biological as well as behavioral drug effect variables.

TECHNIQUES TO STUDY HUMAN DRUG SELF-ADMINISTRATION

Operant techniques to study human drug self-administration have developed in parallel with those used in basic behavioral pharmacology, and are derived from concepts and procedures for the experimental analysis of behavior (Skinner 1938, 1953). Operant procedures have been shown to produce orderly sequences of responding which provide an objective index of the relative reinforcing consequences of various drugs (or competing reinforcers such as money) at any point in time. It is possible to directly observe the amount and frequency of drug self-administration, and the behavioral consequences of drug use intoxication, without reliance upon retrospective self-reports.

Drug acquisition in real life involves engaging in a variety of behaviors, since drugs are not available without some expenditure of effort or money. Consequently, it seems realistic to require performance on an operant task to obtain drugs in a clinical research setting. The nature of the task can vary from performance on a relatively simple schedule of reinforcement, to complex procedures which concurrently assess variables such as timing behavior or memory function. When we designed our first operant paradigm to study alcohol self-administration by alcoholics, we thought it necessary to use a very simple task so that subjects could perform, and earn alcohol, irrespective of their intoxication level (Mello and Mendelson 1965). We anticipated that if alcohol reinforcement was made contingent upon successful performance of a complex discrimination task, the subject would not be able to sustain his initial performance as he became progressively more inebriated. Of course, this would preclude examination of behavior to acquire alcohol, and would only yield data on the effects of alcohol on some aspect of perceptual or cognitive function, which was not the primary goal. Subsequently, we learned that this concern about task complexity was unrealistic, since the behavioral tolerance of alcohol addicts for alcohol permits them to perform very complex tasks with accuracy, even when blood alcohol levels exceed 250 mg/100 ml (Mello 1973).

Study of drug acquisition using operant techniques permits examination of a wide range of behavioral variables: e.g., time, duration, and pattern of operant work for the drug; the rate of operant work [assessed by both analog (cumulative recorder) measures and quantitative inter-response time measures]; the time and number of drug purchases; the effects of each successive drug use occasion on both rate and duration of operant responding. The effects of drug use on operant response patterns. and choices between alternative reinforcers, for example, marihuana vs. money; alcohol vs. marihuana; can also be examined. Such data provide direct measures of performance capacity and permit inferences about intervening variables such as “motivation," sometimes postulated to affect performance.

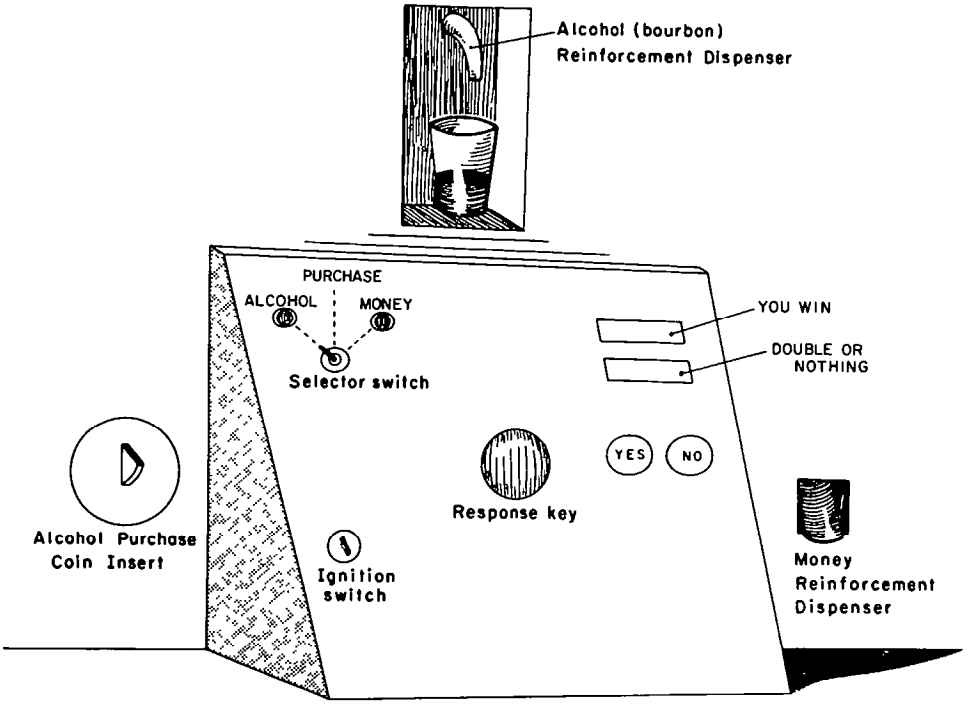
There are a variety of ways to examine human drug self-administration. Since the technical aspects of the behavioral procedures define and limit the type of data acquired, some discussion of procedures is necessary. It may be of some historical interest to review the types of operant procedures we have developed and comment on their advantages and limitations. The first machine designed for the study of alcohol self-administration in alcoholic subjects is shown in Figure 1 (Mello and Mendelson 1965) . The subject could work at the system at any time by turning on the ignition switch and could select whether to work for alcohol or money reinforcement.

The subjects' task was to press the center response key which was transluminated with a number of colored stimulus lights associated with a series of simple schedules of reinforcement. These schedules occurred in an irregular sequence and included Fixed Ratios of 360, 240, 120, and 60; Fixed Intervals of 1, 2, and 3 minutes; Extinction of one minute; and Differential Reinforcement of No Responding. Subjects were told to press the translucent response key in order to make the key color change as often as possible, since reinforcement occurred only when the colors changed. Upon completion of the response requirement, ten ml of bourbon or 3 nickels were directly dispensed, and the key color and schedule changed. The value of a single alcohol or money reinforcement was equated and subjects could use money earned to buy alcohol. In an effort to make the task more interesting, a gambling contingency was added. When reinforcement became available, subjects could choose to take that reinforcement or try for double-or-nothing by pressing the yes or no key at the right of the operant panel.

Subjects worked at the operant task for a 14-day period of alcohol availability. After seven days, when subjects' response behavior failed to come under control of the various schedules of reinforcement, explicit verbal descriptions of the schedule requirements associated with the various colored lights were provided. Subjects still failed to respond under schedule control, except for one component: differential reinforcement of no responding. When that particular stimulus light appeared on the response key, subjects usually left the room. This behavior was adventitiously reinforced since the light associated with another schedule came on during their absence.

Rates of operant responding and time spent at the machine were unimpaired by alcohol intoxication. Subjects maintained relatively high blood alcohol levels (200 to 300 mg/100 ml) throughout the period of alcohol access. Subjects usually worked for 1.5 to 2 oz of alcohol before removing the glass. Each glass removal shut off the machine for a period of 10 minutes. An immediate alcohol reinforcement was consistently preferred to money reinforcement, even though money could be used to buy an equivalent amount of alcohol at any time.

FIGURE 1



Operant Manipulation Used to study alcohol self-administration by alcoholic subjects (Mello 1972). Reprinted with permission of Plenum Publishing Corporation, © 1972. From The Biology of Alcoholism, Vol. II, Physiology and Behavior, *Kissin and Begleiter, eds.*

Despite the ease and simplicity of the operant task, subjects complained continually about the machine. They were bored, and they did not gamble (double-or-nothing) except on rare occasions. Distaste for the machine was illustrated by the fact that one subject incorporated distorted thoughts and perceptions about the operant instrument in his hallucinatory experiences and delusional ideations during alcohol withdrawal.

Negative reactions to the task did not prevent subjects from working for alcohol. However, since response behavior did not come under control of any of the operant schedules of reinforcement provided, these data suggested that analysis of drug effects on schedule control, in the usual sense, would be very difficult in alcoholic subjects. Subsequently, we have used a simple fixed ratio or fixed interval schedule rather than multiple schedules for drug acquisition studies.

An additional fourteen subjects were studied under comparable experimental conditions over a 7-day period of alcohol availability (Mello et al. 1968). The machine shown in Figure 1 was modified so that the subjects task was to press the response key whenever a light of 500 msec duration appeared, i.e., an observing response. The light onset occurred at irregular intervals which ranged between 2.5 and 10 seconds. Errors of omission or of commission resulted in the loss of all accumulated points. Alcohol and money acquisition were contingent upon completion of a Fixed Ratio of 16 or 32 consecutive responses to the signal light.

Although differences in response-cost did not change the amount of alcohol earned per session (as defined by removal of the receptacle glass), the average blood alcohol levels maintained by the FR 16 group were almost twice as high as in the FR 32 group. Subjects required to work twice as hard for alcohol tended to drink half as much, Individual blood alcohol levels were highly variable within and between days and no subject earned all the alcohol potentially available.

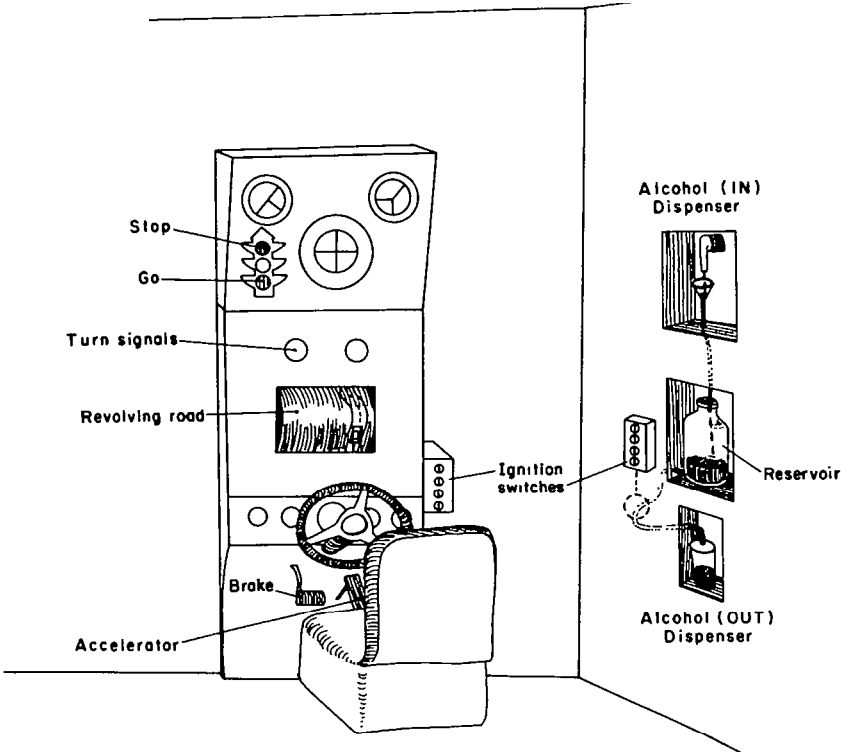
Subjects complained about the demands of the operant task, and pounded the machine in frustration after an omission or commission error. However they were able to perform at all levels of intoxication and the accuracy of performance was unrelated to blood alcohol levels. Most subjects did not work for money, and only five subjects gambled (double-or-nothing) with any consistency. The occurrence of gambling was also unrelated to blood alcohol levels. These data suggest that risk taking as defined by this task cannot be predicted on the basis of intoxication. The accuracy of performance at blood alcohol levels which averaged 200 mg/100 ml testifies to the behavioral tolerance for alcohol developed by alcohol addicts.

Figure 2 shows a machine that was developed to study group drinking behavior (Mendelson, Mello and Solomon 1968). The subjects' task was to steer a model automobile and keep it on the moving road on a revolving drum. Each time the auto touched a metal contact on the road, a point was registered. After 120 points were earned, 10 ml of bourbon was the automatically dispensed into a common reservoir.
subject could earn about 60 points per minute or 3600 points per hour, the maximum amount of alcohol that could be earned each hour was about 300 ml or 10 oz. Each subject had an ignition key and could work at the machine at any time. Each subject could also withdraw as much alcohol from the reservoir as he wished at any time by activating the ignition switch. The total time each subject worked, the number of 10 ml alcohol reinforcements earned, and the amount of alcohol each subject withdrew were automatically recorded. Subjects were permitted to work at the driving machine to earn alcohol for a period of 30 days.

Subjects took turns working at the driving machine and their ability to perform was not discernibly impaired, even at blood alcohol levels over 200 mg/100 ml. No subject drank continuously throughout the 30-day period and no subject drank as much alcohol as was available. Subjects spontaneously terminated drinking episodes on several occasions, four of which were correlated with an obvious stress situation on the ward. There were seldom clearly definable events which accompanied resumption of drinking by these subjects. All subjects showed discernible increases in anxiety and agitation during intoxication and appeared far more depressed and anxious when they terminated drinking than when they initiated a subsequent drinking episode. Two subjects drank more than one fifth of bourbon per day on an average and maintained blood alcohol levels that fluctuated between 50 and 250 mg/100 ml. A third subject drank during three separate episodes of 8, 6, and 7 days respectively. A fourth subject became agitated, depressed, and assaultive and left the study after 3 days of drinking.

These subjects evolved a stable pattern of group interaction and maintained their mutually defined roles in relation to alcohol acquisition. One subject consistently removed more from the group alcohol reservoir than he contributed and another consistently contributed more than he removed, The free-loader appeared to be the leader of the group. Another subject contributed an amount of alcohol to the group reservoir approximately equivalent to the amount that he withdrew. This machine was considerably more acceptable to the subjects than the machine shown in Figure 1. Subjects perceived the driving machine as more of a game than a performance task.

FIGURE 2



Driving machine used to study group alcohol acquisition patterns (Mendelson, Mello, and Solomon 1968). Reprinted with permission of Williams and Wilkins Co., Baltimore, © 1968, from The Addictive States, *A. Wikler, ed.*.

Relocation of our laboratory to Washington prevented further studies with these instruments and necessitated the development of a non-automated, portable instrument shown in Figure 3 (Mello and Mendelson 1972). While new automated instruments were being constructed, these simple hand-held manipulanda permitted study of operant work-contingent drinking patterns in alcoholic individuals. Subjects could work for alcohol or for cigarettes by depressing a button which in turn activated a mechanical counter inside the box. Subjects could earn one ounce of alcohol or one cigarette by approximately five minutes of performance on a Fixed Ratio of 1000 schedule of reinforcement. Points earned were exchanged for color-coded tokens each day.

Tokens could be used to buy alcohol or cigarettes directly dispensed from an apparatus shown in Figure 4. To activate the dispenser, the subject turned on an ignition switch with a coded ignition key which indicated to the circuitry who was activating the dispenser and when. After the subject set a glass receptacle over the photocell, a signal came on indicating that the dispenser would receive tokens. One oz of alcohol was dispensed into the glass for each token deposited, The circuitry recorded the time of purchase, the number of purchases, and the subjects' identification number. Subjects could also buy alternative reinforcers such as 15 minutes of television time.

The major disadvantage of the portable manipulandum was that no analysis of time, duration or rate of operant work was possible since responses could not be recorded by the programming circuitry. However the manipulanda proved to be tamper proof and yielded reliable data on drinking patterns to be described in a later section of this review. The manipulandum was also used to study marihuana self-administration patterns (Mendelson, Rossi, and Meyer 1974).

The behavioral tolerance for alcohol shown by alcoholics throughout these several studies persuaded us that it was possible to couple work-contingent alcohol acquisition with the assessment of behavioral drug-effect variables in addition to operant performance. Consequently, we designed and constructed an operant system which could be used to evaluate various aspects of perceptual or cognitive function. Each response panel was located in a separate operant booth,and six subjects could work at their machines in relative privacy.

There was considerable debate about whether alcohol directly affected short term memory function. The machine was first programmed to evaluate this question using a titrated delayed matching-to-sample procedure. The operant response panel is shown in Figure 5 (Mello 1973).

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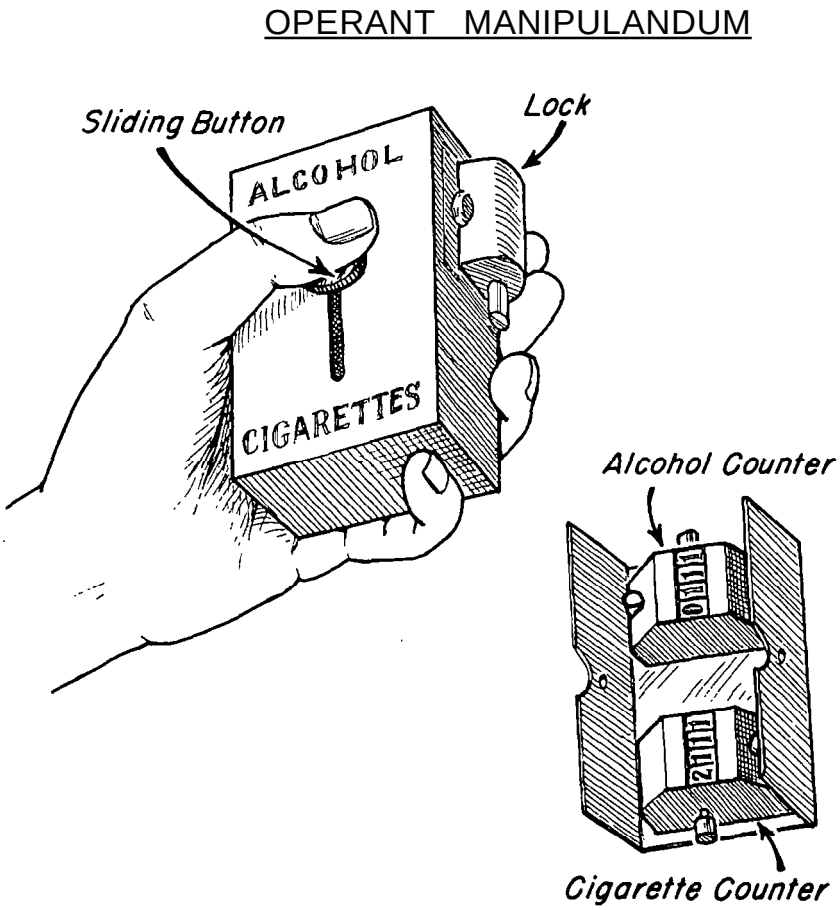
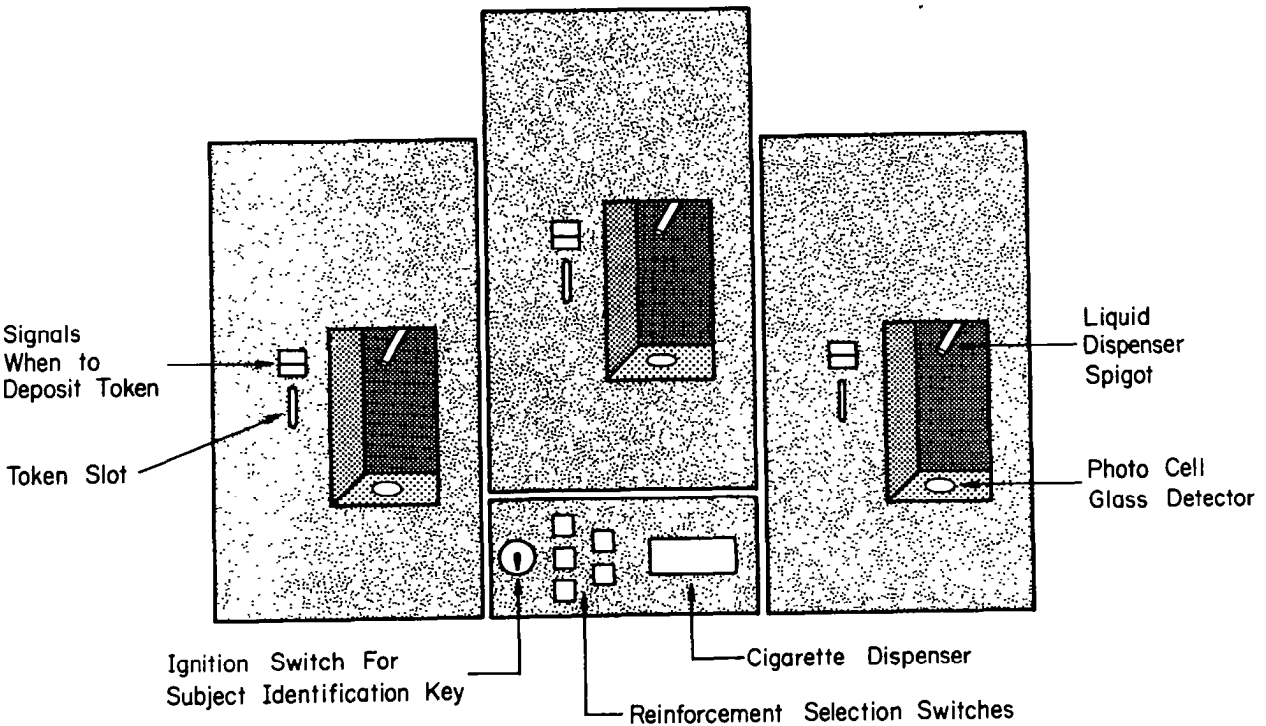
FIGURE 3



Mechanical device used to study alcohol self-administration patterns in alcoholic subjects (Mello and Mendelson 1972). Reprinted with permission of the publisher, American Psychosomatic Society, © 1972, from Psychosomatic Medicine, Vol. 34, No. 2.

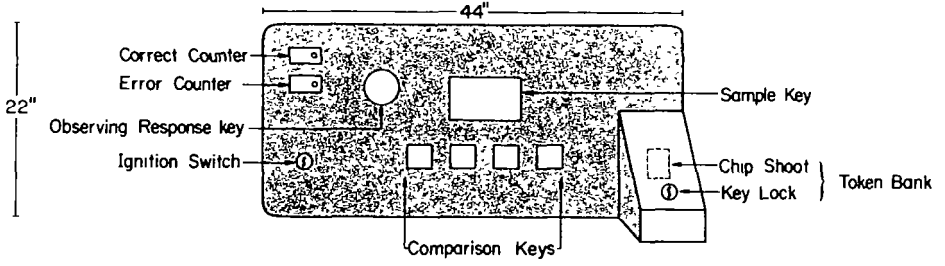
FIGURE 4



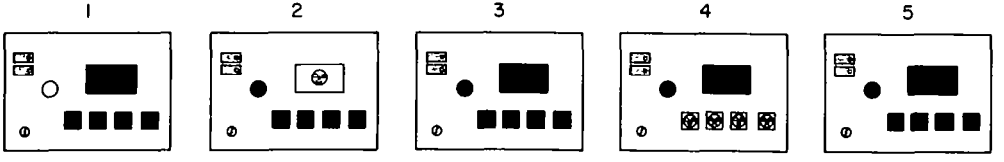
SCHEMATIC DIAGRAM OF ALCOHOL AND CIGARETTE DISPENSER PANEL

FIGURE 5

SCHEMATIC DIAGRAM OF RESPONSE PANEL



SEQUENCE OF EVENTS IN A MATCHING TO SAMPLE TRIAL



Procedure used to study alcohol self-administration and the effects of alcohol on short term memory function in alcoholic subjects (Mello 1973). Reprinted with permission of Plenum Publishing Corporation, New York, © 1973, from Alcohol Intoxication and Withdrawal: Experimental Studies, *M. Gross, ed.*

subjects' task was to select the comparison key which contained a picture identical to that which had previously appeared on the sample key. Short term memory was defined as the interval between the offset of a picture on sample key and the onset of pictures on four comparison keys. Attention to the sample stimulus was ensured by requiring the subject to make an observing response (FR 10) to turn on the sample stimulus. The subject then pressed the sample key until the picture projected on it went off. After a delay interval elapsed, four pictures were projected on the comparison keys. Selection of one of the comparison keys ended the trial. The length of the delay interval increased with each correct match trial and decreased with each incorrect trial in 4 second increments. The possible delay 'intervals ranged from 0 to six minutes. The matching-to-sample stimuli included pictures of the ward staff? movie stars and political figures, household objects, liquor and cigarette labels, nude figures, trigrams and abstract geometric designs - a total of 120 stimulus sets in several different sequences.

In order to encourage the subject to perform as well as possible, completion of four correct trials was required to earn a single token. Correct trials were indicated - in the correct counter at the upper left of the panel. How - ever, if 4 error trials occurred before completion of 4 correct trials, each counter reset to 0 and the subject was required to begin accumulating correct trials again in order to earn tokens to buy alcohol. After completion of four correct trials, a single token was directly dispensed into the token bank shown on the right of the operant panel. The bank was clear plastic, and the subject could see the number of tokens he had earned at any time, Each subject had the only key to his token bank and could remove tokens to purchase alcohol from the dispen- ser (Fig, 4) whenever he wished.

All subjects maintained high blood alcohol levels and perfor- mance for alcohol was sustained throughout a twelve day period of alcohol access. Alcohol had no discernible effect on “short term memory” defined operationally by the interval between sample stimulus offset and comparison stimulus onset. Subjects were able to match correctly at the longest delay intervals even when blood alcohol levels exceeded 300 mg/100 ml. Subjects with a history of alcoholic “blackouts” performed as well as subjects who had never experienced blackouts during intoxication. The conclusion that alcohol does not impair “short term memory” and that the alcoholic “blackout” probably cannot be accounted for by an alcohol-specific disruption of memory (Mello 1973) has been confirmed in other laboratories (cf. Mello and Mendel- son 1978 for review),

This machine was probably the most powerful tool for assessing both alcohol acquisition behavior and the effects of alcohol on cognitive function that we have developed. Perhaps because a continuously changing array of visual stimuli was provided, subjects found the task challenging and interesting. Since subjects were highly motivated to acquire alcohol, they appeared to perform at the limit of their capacity. Unfortunately, a de emphasis on intramural research by the National Institute on Alcohol Abuse and Alcoholism during the early 1970's prevented further studies with this instrument. However, this study demonstrated the feasibility of asking questions related to drug-effects in combination with questions about drug self-administration patterns.

After return of the laboratory to Boston, we again developed a simple hand-held operant manipulandum for the study of drug acquisition patterns. The manipulandum was about the size of a pack of cigarettes and weighed about 198 grams. Initially, the manipulandum was attached to a movable cable which could be connected to coded terminals permitting subjects to work at the operant task either in their individual bedrooms or in a central day room. Subsequently, the manipulandum was modified to be completely portable. Each response transmits a radio frequency signal on a discrete band which activates the programming and recording circuitry in an adjacent room. Points earned are registered on a central panel and subjects always have a record of their earnings. Unlike the portable manipulandum shown in Figure 3, this manipulandum permits analysis of automatically recorded operant response patterns. Each manipulandum is color coded and labeled with the subject's number to permit easy identification by the ward staff and to discourage subjects from exchanging manipulanda.

Subjects are required to press the button on the manipulandum on a fixed interval one-second schedule of reinforcement (FI 1 sec). Only the first response after one second elapsed was recorded as a point by the programming circuitry. Subjects can earn one point for 300 effective responses or five minutes of sustained operant work. The prices of different drugs or. money reinforcers are assigned a certain point cost which can be easily translated into time required at the operant task. The price of drugs or money can be adjusted to reflect the current price prevailing in the Boston area. Whenever a subject elects to purchase a drug, the points spent are immediately deducted from his reinforcement point accumulation. Subjects are allowed to work on the operant task at any time and a record of their point accumulation is continuously available.

We have used this simple procedure to study alcohol, marihuana, and heroin self-administration. The manipulanda and the task are well tolerated by subjects, and subjects have not been able to tamper with or destroy the device. Subjects are able to perform the task while talking, reading, watching television, eating. Although the manipulandum can be used with virtually any schedule of reinforcement, we have continued to employ an FI l-second schedule to permit comparisons across successive studies with different samples of drug users.

In summary our experience with these several operant drug-acquisition procedures suggest the following general conclusions. Subjects will accept complicated and challenging procedures which maintain their interest (e.g. Fig. 5). If acquisition of a meaningful reinforcer (drugs or money) is contingent upon accurate performance, subjects will usually perform to the limit of their capacity. Severe intoxication produces surprisingly little performance impairment in alcohol addicts because of behavioral tolerance. The generality of this degree of behavioral tolerance to other categories of drug abuse remains to be determined. However it appears feasible to study drug self-administration patterns with a task that simultaneously assesses some drug-effect variable.

A task which requires minimal attention or effort to perform, such as our current simple schedule procedure, is also accepted by subjects and yields reliable data on drug self-administration patterns as well as operant responding. The relative ease of construction and maintenance of a portable manipulandum must be balanced against the complexities of construction and maintenance of a device which involves coded filmstrips, special recording procedures, and continual adjustment as did the machine shown in Figure 5. The most realistic compromise is probably to use a simple procedure to study drug self-administration patterns, and to assess cognitive and perceptual variables separately in a situation where relatively larger volumes of drug are provided as a reinforcer for accurate performance. A common failure to reinforce accurate performance with a consequence that is significant for the subject has contributed to the numerous inconsistencies in data on the behavioral effects of alcohol (Mello and Mendelson 1978).

The importance of a mechanical dispenser for drug and money reinforcers cannot be over-emphasized. The machine is consistently neutral and cannot encourage or discourage drug purchase. Although staff can be trained to dispense drugs without comment, some attitude about further drug use by an intoxicated individual is inevitably conveyed. It is impossible to evaluate the extent to which the attitude of a staff drug-dispenser may have influenced the basic datum, drug self-administration patterns.

PATTERNS OF ALCOHOL, MARIHUANA, AND POLYDRUG SELF-ADMINISTRATION

This section will summarize selected data on alcohol, marihuana and polydrug self-administration and illustrate the application of several of the techniques previously described. In each of the studies to be described, volunteer subjects lived on a clinical research ward for several weeks. Behavioral studies were conducted simultaneously with physiological, biochemical and neuroendocrine studies designed to examine the biological effects of chronic drug use. Subjects were observed during a drug free baseline, a period of drug self-administration and a post-drug baseline period. An own-control design is essential for human drug self-administration studies, since the use of normal control groups in the conventional sense is precluded by medical and ethical considerations. Moreover, occasional drug users are not sufficiently drug tolerant to permit meaningful comparisons with heavy users or addicts.

ALCOHOL SELF-ADMINISTRATION

A number of stereotypes and beliefs about alcoholism often appear in the clinical literature, despite accumulating evidence to the contrary. One persistent belief is that the alcohol addict has a predictable and invariant drinking pattern, i.e., to drink as much as possible. This stereotype is linked to the concept of "craving," usually defined as a loss of control over drinking, with the implication that each time an alcoholic starts to drink he is compelled to continue until he reaches a state of severe intoxication. The circularity inherent in this reasoning is evident, i.e., craving is defined by the behavior it is invoked to explain. Empirical observations of alcoholics allowed to self-administer alcohol have not supported this view (cf. Mello 1975 for review).

Two groups of four subjects were allowed to work for alcohol and cigarettes for periods of 30 and 62 consecutive days respectively (Mello and Mendelson 1972). The operant manipulandum shown in Figure 3 was used and a fixed ratio of 1,000 responses was required to earn a single token which could be used to buy one cigarette or one oz of bourbon from an automated dispenser (Fig. 4) . Subjects were able to earn one token in about 5 minutes of rapid performance, or about 12 oz of alcohol per hour. The task could easily be performed while watching television, eating, drinking, or talking. Each subject had a color-coded manipulandum and an identical colored token to prevent exchanges between subjects. The volume of alcohol and the number of cigarettes purchased by each subject were recorded by the programming circuitry and checked against the number of colored tokens in the dispenser. Blood alcohol levels were measured daily at 8 am, 4 pm and 12 midnight.

The earning and spending pattem of a typical subject during the pre-alcohol baseline, the alcohol availability and alcohol withdrawal periods is shown in Figure 6. The pattern of earning and spending for cigarettes is shown in the top row. The pattern of earning and spending for alcohol is shown in the middle row. Daily mean blood alcohol levels are shown in the bottom row. Partial withdrawal signs (tremor and gastritis) are indicated as asterisks. The type and duration of alcohol withdrawal signs and symptoms are shown at the right of the middle row.

Each subject could work for points for alcohol during the last day of the pre-alcohol baseline period. The number of points earned that day was sufficient to sustain a period of drinking of 3 to 6 days. Throughout the remainder of the drinking period, there was a clear dissociation between periods of earning and spending. Subjects alternated between working to earn points for alcohol and spending points earned for a work-free drinking spree. This pattern persisted throughout the 30 and 62 alcohol available periods and was strikingly similar in all subjects. Fluctuations in the average blood alcohol levels correlated roughly with the pattern of spending for alcohol. Subjects sustained relatively high blood alcohol levels averaging between 130 and 200 mg/100 ml for periods up to 62 days. No subject drank all the alcohol available and all subjects tolerated the discomfort of withdrawal symptoms during the intermittent periods of self-imposed abstinence. These abstinent periods were unexpected in view of the relatively trivial performance requirement involved. Ability to perform was not impaired by intoxication.

Although all subjects showed a dissociation between working and drinking, subjects worked and drank at different times. Some member of the group was always working; while others were drinking. It is unlikely that the observed behavior represented satiation for alcohol, since other subjects given alcohol with no operant work requirement sustained blood alcohol levels which averaged above 200 mg/100 ml for periods of 14 to 20 days (Mello and Mendelson 1972). Similarly, the decrease in operant work for cigarettes does not reflect decreased interest in smoking since subjects attempted to acquire cigarettes from staff throughout the study.

These subjects described themselves as periodic spree drinkers. The observed pattern of discordant working and drinking is probably more comparable to their real world experience than a stable alcohol intake permitted by an unlimited supply. Since the subjects determined their pattern of alcohol self-administration, it is reasonable to assume that this was their preferred or accustomed pattern. This technique appeared to result in an adequate simulation of normal

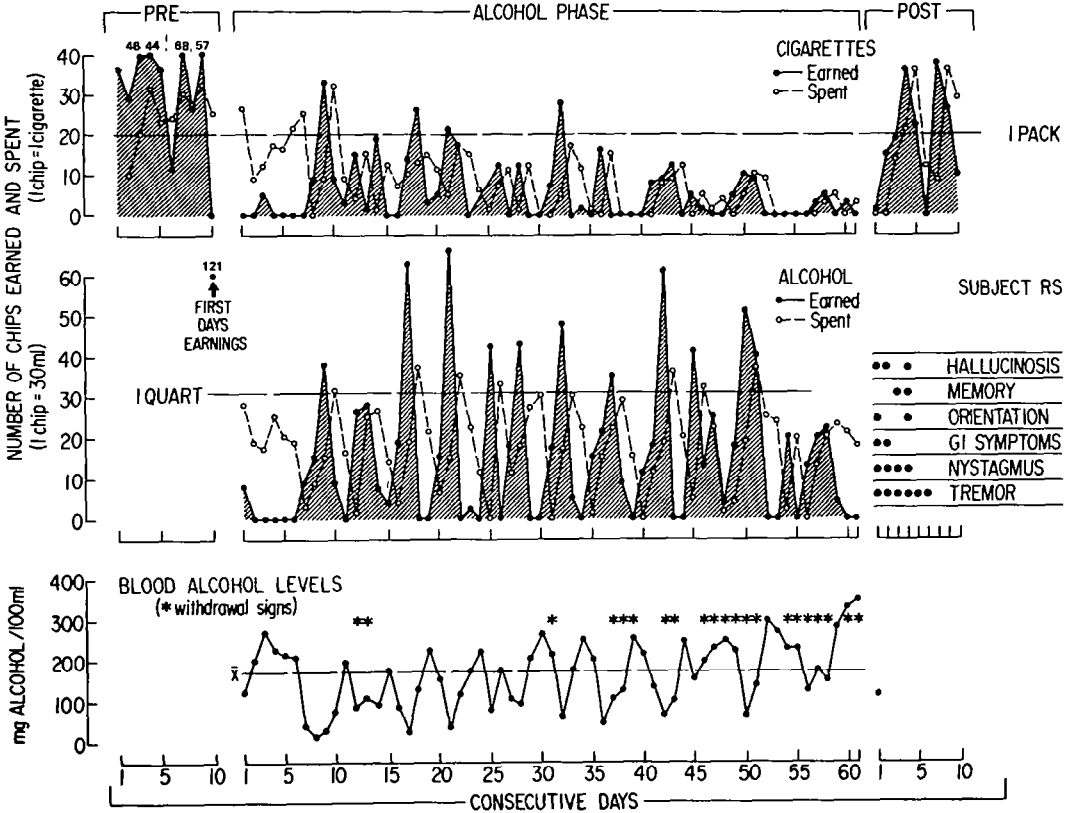


FIGURE 6. *From Mello and Mendelson (1972). Reprinted with permission of American Psychosomatic Society, © 1972, from* Psychosomatic Medicine, *Vol. 34, NO. 2.*

drinking patterns by chronic alcoholic individuals in a clinical research ward context. A similar alternation between working and drinking has also been reported by Nathan and co-workers in alcoholics who worked at a comparably simple task (photo cell interruption) for points that could be converted into alcohol (Nathan et al. 1970; Nathan, O'Brien, and Lowenstein 1971).

MARIHUANA SELF-ADMINISTRATION

Recently a number of multidisciplinary studies of marihuana self-administration have been conducted in our laboratory (Mendelson, Rossi, and Meyer 1974; Mendelson et al. 1976a). Biological studies of marihuana effects examined in a self-administration paradigm have been included- studies of the effects of marihuana: on CNS structure (Kuehnle et al. 1977); on pituitary gonadal hormones (Mendelson et al. 1974, 1978); and on cardiac and pulmonary function (Bernstein, Kuehnle and Mendelson 1976). Behavioral studies have examined the effects of marihuana on mood, memory and social interactions (Mendelson et al. 1976a). In addition to studies of the pattern of marihuana self-administration, the hypothesis that marihuana induces an "amotivational" syndrome was also examined (Mendelson et al. 1976b). Among the effects often ascribed to marihuana are apathy, lethargy, diminished "drive" and ambition, decreased productivity and goal directedness, and indolence.

Marihuana self-administration patterns were examined in 12 casual and 15 heavy users, allowed to work for marihuana for 21 consecutive days. "Motivation" was inferred from time spent at the operant task working for marihuana and for money. Subjects worked at the portable operant manipulandum previously described on an FI 1 sec schedule. One marihuana cigarette cost 6 points or 30 minutes of sustained operant work. Each marihuana cigarette contained approximately 1 gm of marihuana (1.8 to 2.3 percent THC) . Subjects could also work for money at the cost of 50 cents per 6 points or 30 minutes of sustained operant work.

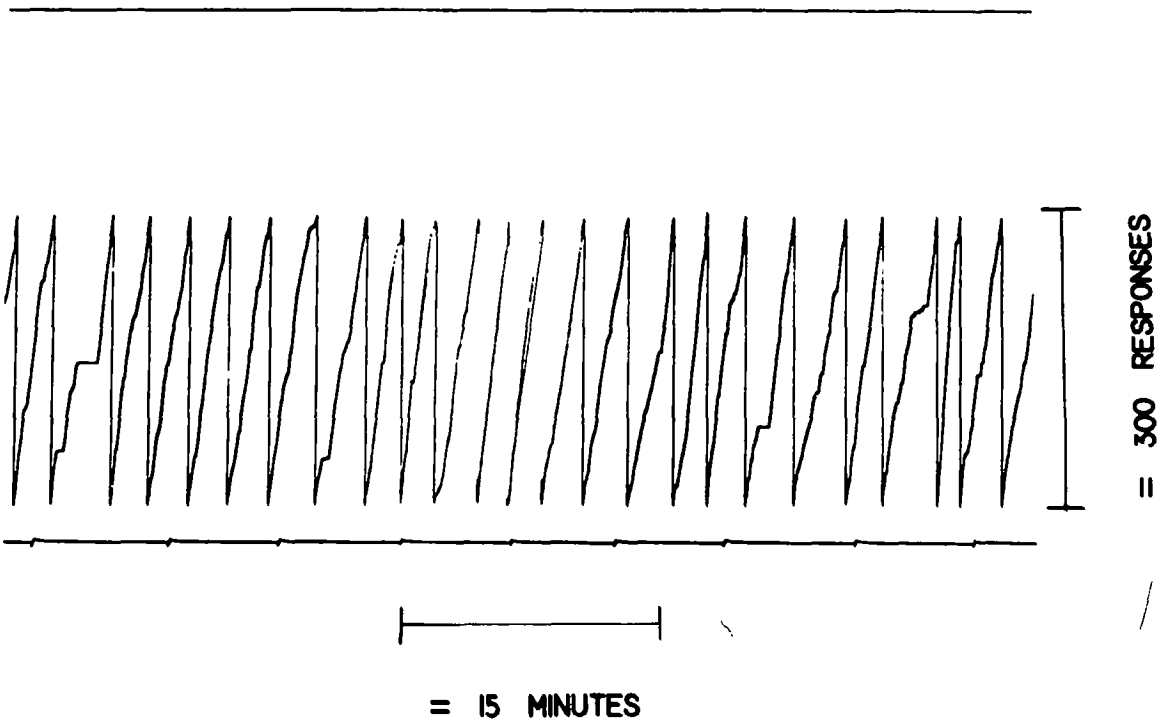
All subjects smoked some marihuana every day. Casual marihuana smokers smoked an average of 2.6 cigarettes per day and heavy marihuana users smoked an average of 5.7 cigarettes per day. However, both groups showed a linear increase in marihuana smoking over the 21 day period of marihuana availability. On the final day of marihuana availability, the casual users smoked an average of 5.8 cigarettes and the heavy users smoked an average of 14.3 cigarettes.

All subjects worked longer at the operant task and earned far more points than were required to buy the quantity of marihuana they actually smoked. The heavy user group worked between 6.7 and 14.4 hours per day even though 2.2 to 3 hours of work were required for the 4.3 to 6 cigarettes usually smoked per day. Throughout the period of marihuana use, heavy users worked up to an average of 10 hours each day. The casual marihuana users worked between 5 and 11.1 hours each day, even though the number of cigarettes smoked (2-3 per day) required only 1 to 1.5 hours of operant work. No subject stopped operant work even when he smoked ten or more marihuana cigarettes per day. Moreover, periods of maximal operant work coincided with periods of maximal marihuana smoking, i.e., between 4 pm and 12 midnight each day.

Subjects worked more for money than for marihuana, and the dollars saved far exceeded dollars spent on marihuana by both the casual and the heavy marihuana users. At the conclusion of the study, the heavy user group had saved an average of $242.38 (+ $19.22 S.E.) and the casual users had saved an average of $233.17 (+ $26.31 S.E.). These earnings reflected sustained operant work and saving during the period of marihuana availability. Since both casual and heavy marihuana users sustained operant work for both money and marihuana reinforcement during a period of unrestricted marihuana smoking, these data appear to argue strongly against simplistic descriptions of marihuana effects and amotivation (Mendelson et al. 1976b).

A typical cumulative record of response on a FI 1 second schedule of reinforcement during the period of active marihuana use is shown in Figure 7. Although only the first response after an interval of one second had elapsed was counted as an effective response by the programming circuitry, subjects typically responded at a much higher rate than required. The response requirements were carefully explained to the subjects but most reported they preferred to respond at a comfortable rate. In most instances, this resulted in the emission of approximately 600 responses for each point earned, when 300 responses distributed over 5 minutes would have sufficed. A rate of 120 responses per minute or 2 responses per second was typically seen. Sustained high rates of operant responding by casual and heavy marihuana users during the period of active marihuana smoking are also inconsistent with the notion that marihuana induces an “amotivational” syndrome.

FIGURE 7



Cumlative record of responses for marihuana on an FI 1 sec sechedule of reinforcement.

POLYDRUG USE: MARIHUANA, ALCOHOL AND TOBACCO

Operant procedures for the examination of single drug self-administration patterns can also be extended to study the concurrent self-administration of two or more drugs. Polydrug use appears to be an increasingly frequent drug use pattern, according to clinical and epidemiological studies (Bourne 1975; Benvenuto, Lau, and Cohen 1975). The possible combinations of drugs abused simultaneously appear almost infinite and defy any effort at simple categorization. However, survey data suggest that marihuana is often used in combination with alcohol (Goode 1969; Grupp 1972; Carlin and Post 1971; Tec 1973) and alcohol is perhaps the most commonly used and abused recreational drug available today. Tobacco use frequently accompanies alcohol use and it has recently been shown that alcohol facilitates cigarette smoking in alcoholics (Griffiths, Bigelow and Liebson 1976b).

The way in which alcohol and marihuana interact and influence concurrent use patterns has long been a subject of speculation. However, there is a prevailing impression that the combined use of mariiuana and alcohol leads to a subjective enhancement of the positive or euphorigenic properties of marihuana (Hollister 1976; Manno et al. 1974). Since the combined effects of alcohol and marihuana are thought to be facilitatory, we were interested in exploring the effects of concurrent access to marihuana and alcohol on use patterns and subjective effects. We were interested in learning whether concurrent access to marihuana and alcohol led to an increase, a decrease, or no change in use patterns of these drugs. On the basis of data demonstrating that alcohol induced an enhancement of tobacco use, we postulated that marihuana and alcohol use would be increased under concurrent access conditions (Mello, Mendelson, and Kuehnle 1978).

Sixteen adult male volunteers with a history of concurrent alcohol and marihuana use were studied in groups of four on a clinical research ward. Patterns of drug use during 10 days of concurrent access to marihuana and alcohol were compared with successive five day periods when only alcohol or only marihuana was available.. Two groups were studied in the alcohol-first sequence and two groups were studied in the marihuana -first sequence. A drug free control period preceded and followed the 20-day period of spontaneous drug self-administration.

Drug use patterns were assessed by performance on the simple operant task used in studies of marihuana self-administration described previously. Subjects could earn money (50 cents) or marihuana (a 1 gm cigarette containing 1.8 to 2.3 percent

THC) by working at the operant task on a Fixed Interval one-second schedule of reinforcement for 30 minutes. Alcohol (1 oz) was available as wine, beer, or distilled spirits for 15 minutes of operant work.

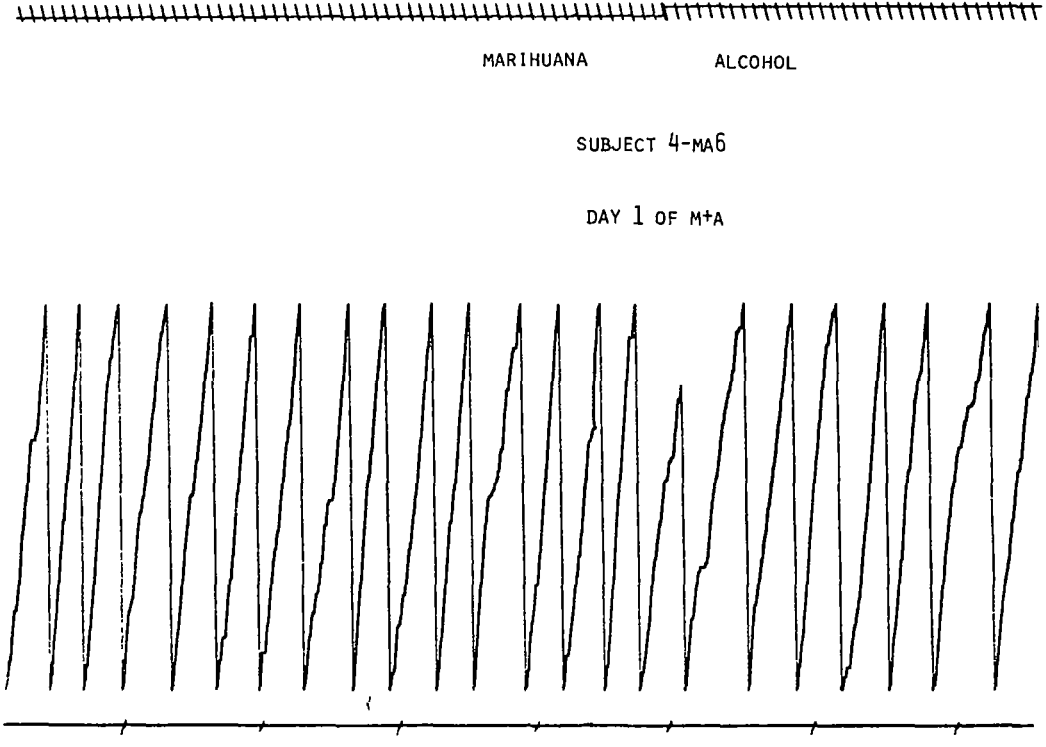
Typical cumulative records of performance for concurrent access to marihuana and alcohol are shown in Figures 8 and 9. Subjects tended to work at a high sustained rate for drug or money reinforcements. Subjects usually emitted appropriately twice the number of responses required to earn a single point. These data are comparable to operant responding for marihuana (Mendelson et al. 1976c) and for heroin (Mendelson and Mello 1978, this volume). Examination of drug effects on inter-response distributions is currently in progress.

The major finding of this study was that concurrent access to alcohol and marihuana resulted in a significant decrease in alcohol consumption, in comparison to the five-day baseline period of only alcohol availability. Fourteen of the sixteen subjects studied decreased alcohol use when marihuana was also available ($p < .01$) and the magnitude of the decrease in drinking was significant for seven subjects ($p < .05$).

During the ten-day period of alcohol and marihuana access, subjects gradually increased marihuana smoking and this increase was significant ($p < .001$) as evaluated by a trend analysis. However, this increase cannot be attributed to the concurrent availability of alcohol, since a similar trend was seen in our previous study of casual and heavy marihuana use under comparable experimental conditions (Mendelson et al. 1976 b & c). Although twelve subjects increased marihuana smoking when alcohol was also available ($p < .05$), the magnitude of this increase was statistically significant in only two instances.

Figure 10 illustrates the most common drug use pattern observed, i.e., an increase in marihuana use and decrease in alcohol during the period of concurrent marihuana and alcohol availability. This subject was a heavy marihuana user who smoked an average of 9 cigarettes per day during the baseline period of marihuana availability. He was also a heavy drinker and consumed an average of 12 drinks per day during the baseline period of alcohol availability. Peak blood alcohol levels ranged between 50 and 150 mg/100 ml during the hours of maximum drinking. When both alcohol and marihuana were concurrently available, marihuana smoking increased slightly to an average of 10 cigarettes per day. Alcohol consumption decreased to a mean of 5 drinks per day. Peak blood alcohol levels never exceeded 65 mg/1000 ml during the period of concurrent marihuana and alcohol access.

FIGURE 8



Cumulative records of responding. The step pen reset after 300 responses and deflections of the baseline pen indicate completion of 300 effective responses on an FI 1 sec schedule.

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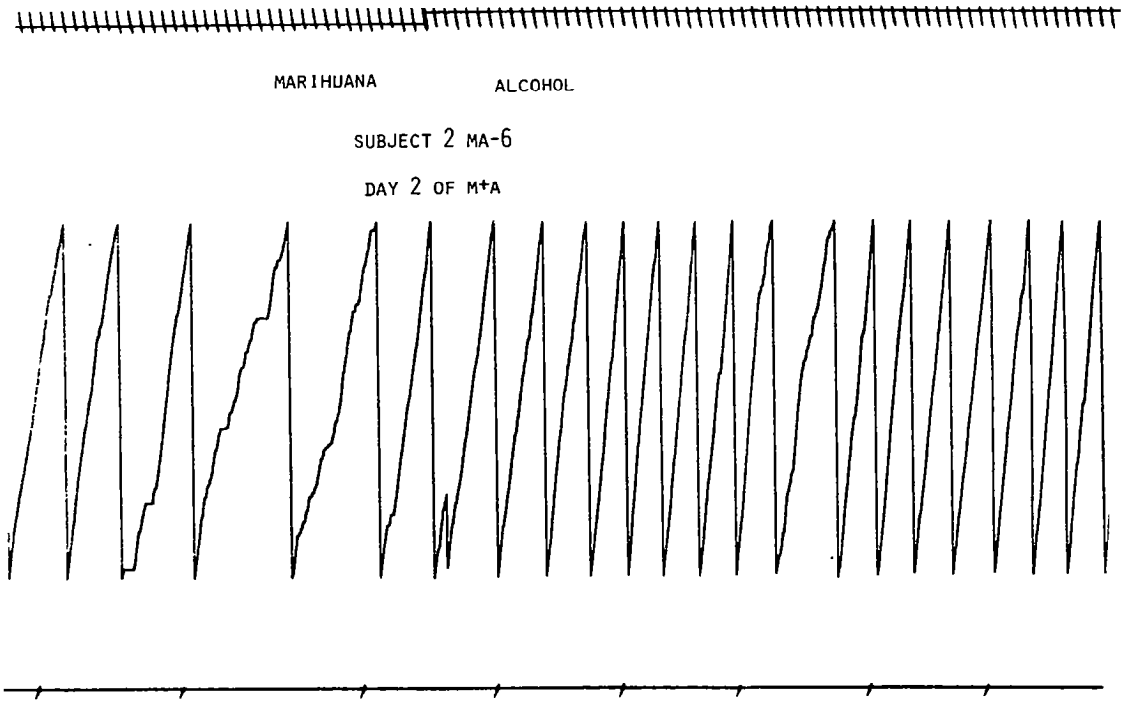
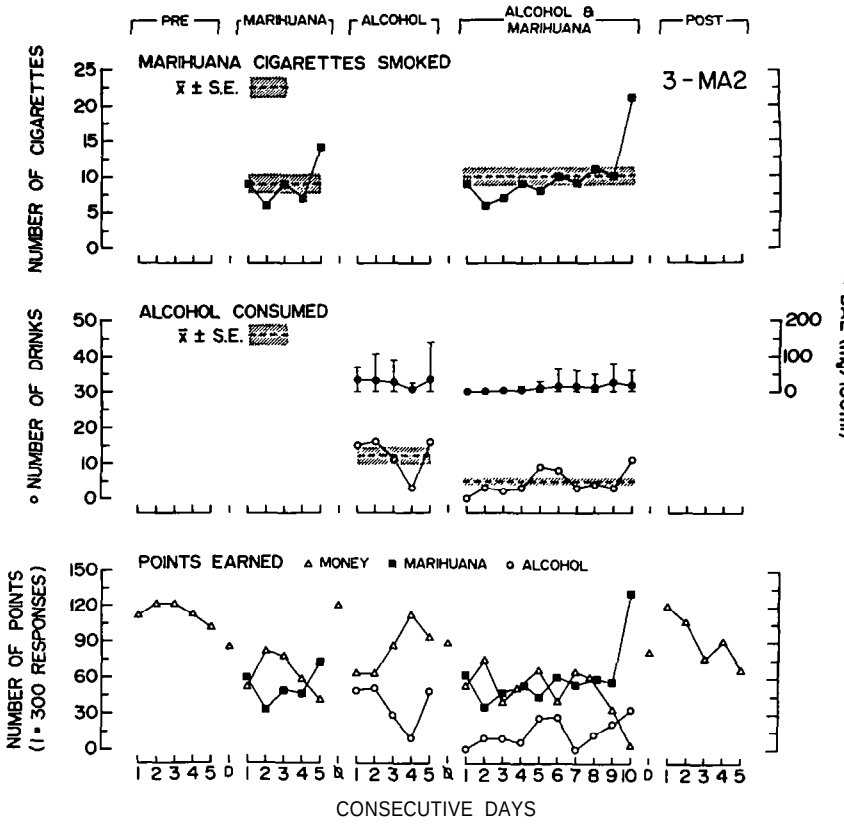
FIGURE 9



Cumulative records of responding. The step pen reset after 300 responses and deflections of the baseline pen indicate completion of 300 effective responses on an FI 1 sec schedule.

FIGURE 10


PRE
MARIHUANA
ALCOHOL
ALCOHOL & MARIHUANA
POST
MARIHUANA CIGARETTES SMOKED
X̄ ± S.E.
3-MA2
NUMBER OF CIGARETTES
ALCOHOL CONSUMED
X̄ ± S.E.
NUMBER OF DRINKS
BAL (mg/100ml)
POINTS EARNED
MONEY
MARIHUANA
ALCOHOL
NUMBER OF POINTS (1 = 300 RESPONSES)
CONSECUTIVE DAYS

Subjects usually used alcohol and marihuana together during the period of concurrent availability. Despite the temporal concordance of marihuana and alcohol use there were no instances of adverse reactions or other evidence of toxic drug interactions as has been reported by others following low acute doses of alcohol and marihuana (Sulkowski and Vachon 1977).

Only six of the sixteen subjects studied were consistent tobacco users who smoked an average of 15.9 cigarettes per day. Tobacco use was significantly correlated ($p < .05$) with both alcohol and marihuana use. Tobacco use also accompanied alcohol use and marihuana use during the single drug availability period. These data are consistent with previous reports of alcohol-induced increases in tobacco use (Griffiths, Bigelow, and Liebson 1976b) and survey reports of a high correlation between marihuana and tobacco use (O'Donnell 1976).

Data obtained are not consistent with the hypothesis that the simultaneous availability of marihuana and alcohol will lead to a significant increase in the use of both drugs. Only two of the sixteen subjects increased consumption of both alcohol and marihuana during the simultaneous access conditions, even though alcohol and marihuana were usually used together. These data suggest the importance of defining conditions under which multiple drug access will result in a depression of the use of one or more drugs; an increase in the use of one or both drugs; or no change in drug use as a function of single or multiple drug access. It will be important to attempt to identify the interacting pharmacological and behavioral variables which control patterns of multiple drug use. It will also be necessary to determine the generality of these findings with other groups of heavy drinkers and alcoholic individuals. Analysis of the subjective consequences of single and concurrent drug use is in progress.

SUMMARY AND CONCLUSIONS

Data have been presented to illustrate some ways in which operant procedures can be used to study self-administration patterns of a variety of substances. Operant procedures for drug self-administration studies have also been shown to be useful for concurrent examination of a variety of drug-effect variables, especially the effects of drugs on biological function. Behavioral data were selected to illustrate some clinical research findings which are contrary to conventional wisdom and common expectation. We have seen that alcohol addicts do not maintain a constant pattern of alcohol intake and do not drink all the alcohol available when

given unrestricted access to alcohol in a self-administration paradigm. Rather, alcohol addicts tend to alternate periods of alcohol intoxication and operant work, even though periods of abstinence working are accompanied by partial withdrawal symptoms. These data are inconsistent with the notion that alcohol abuse is maintained by either the avoidance of withdrawal signs and symptoms or an uncontrollable "craving" for alcohol (Mello and Mendelson 1972; Mello 1975). Studies of marihuana self-administration are not consistent with the notion that marihuana induces an "amotivational" syndrome (Mendelson et al. 1976 b & c). Studies of polydrug use involving alcohol and marihuana indicate that concurrent access to these drugs is not necessarily associated with increased use of alcohol and marihuana as would be predicted from data on alcohol and tobacco (Griffiths, Bigelow, and Liebson 1976b). Rather, the simultaneous availability of marihuana and alcohol was associated with a significant decrease in alcohol consumption in comparison to a baseline period when only alcohol was available (Mello, Mendelson, and Kuehnle 1978).

There is no substitute for direct clinical observation of drug use patterns and the effects of drugs on behavioral and biological variables under controlled conditions. The direct observation of patterns of drug use and assessments of the subjective and objective consequences of drug intoxication have challenged many prevalent assumptions derived from retrospective reports by drug abusers during sobriety (Mello and Mendelson 1978). It is our contention that direct clinical observation of drug use patterns and associated drug effects in the same individual over time is essential to an improved understanding of the behavioral bases of drug abuse. The experimental analysis of drug use patterns is one way to examine factors which maintain and perpetuate drug abuse. The periodicity of drug use and the rate and duration of operant behavior involved in drug acquisition are data which can be measured directly without reliance on alleged intervening variables such as "drug hunger." On the basis of such information, certain inferences can be made concerning broader questions about the phenomenology of drug abuse. It is of interest to determine if there are consistencies in drug use patterns within the behavior of a single individual, or between individuals with comparable drug use histories. Comparisons of drug use patterns across addictive disorders may eventually permit identification of some reliable commonalities and differences, that in turn will help to clarify the nature of drug-related reinforcers.

An examination of factors which initiate and maintain periodic substance abuse episodes may prove more productive than a search for origins, given the diversity of individuals with substance abuse problems. A better understanding of

how drug self-administration is maintained should permit more effective manipulation of critical maintenance variables and lead to the development of more effective forms of intervention. Both the conceptual and technical aspects of an operant analysis of drug self-administration behavior appear to be optimally designed to facilitate our understanding of how substance abuse is maintained.

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ACKNOWLEDGMENT

Preparation of this review was supported by grants DA 01676 and DA 4RG010 from the National Institute of Drug Abuse, ADAMHA.

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Chapter 9

Heroin Self-Administration: An Operant Analysis

Jack H. Mendelson, M.D., and Nancy K. Mello, Ph.D.

Over the past fifteen years, many investigators have studied opiate self-administration patterns using animal models (Schuster and Johanson 1974). Canparable studies of human opiate self-administration and its consequences are a relatively recent development. In this review, some data on heroin self-administration by heroin addicts will be described and compared with studies of primate models.

PRIMATE MODELS OF OPIATE SELF-ADMINISTRATION

A brief and selective review of some data obtained with primate models illustrates that opiate self-administration is lawful and orderly behavior, subject to control by schedules of reinforcement, discriminative stimuli, conditions of deprivation and satiation, and a variety of other environmental factors. It has been repeatedly shown that rhesus monkeys will self-administer opiates and many other psychoactive drugs, to the point of inducing physical dependence (Deneau 1969; Deneau, Yanagita and Seevers 1969; Findley, Robinson and Peregrino 1972; Thompson 1968; Woods and Schuster 1970; Yanagita and Takahashi 1970). The extent to which physical dependence is necessary for a drug to remain "reinforcing" has been studied by several groups. Three lines of evidence now indicate that physical dependence is not a necessary or sufficient condition for drug self-administration. It has been shown that opiate drug self-administration will occur at unit doses too low to induce physical dependence (Woods and Schuster 1970). Moreover, naive monkeys will self-administer opiates and barbiturates even if physical dependence does not develop (Deneau, Yanagita and Seevers 1969; Winger, Stitzer and Woods 1975). Finally, stimulants such as cocaine which have not been shown to produce physical dependence are readily self-administered by monkeys (Balster and Schuster 1973; Goldberg and Kelleher 1976; Johanson, Balster and Bonese 1976).

It is well established that drug self-administration behavior can come under the control of discriminative stimuli. Discriminative stimuli are an experimental analogue of the complex external-situational stimuli alleged to contribute to the maintenance and relapse of drug abuse in man (Wikler 1973a).

The secondary reinforcing properties of visual stimuli, previously associated with drug reinforcement, can come to control behavior leading to the presentation of the stimulus itself, even in the absence of drug reinforcement (Goldberg 1976; Goldberg, Morse and Goldberg 1976; Kelleher 1976).

Stimulus control of drug reinforced behavior has also been demonstrated in association with conditions of narcotic antagonist-induced drug withdrawal (Goldberg 1976). If a visual stimulus is paired with narcotic antagonist administration in morphine-dependent animals, that stimulus can subsequently elicit withdrawal signs in the absence of antagonist administration (Goldberg and Schuster 1967) and presentation of the stimulus is associated with increased responding for morphine reinforcement (Goldberg, Woods and Schuster 1969). Stimulus control of withdrawal signs was found to persist for 60 to 120 days after monkeys had been abstinent from morphine (Goldberg and Schuster 1970). This observation of protracted abstinence phenomena in abstinent monkeys, elicited by a discriminative stimulus previously paired with narcotic antagonist administration, is a provocative parallel to observations of protracted abstinence in man (Martin and Jasinski 1969).

It has been repeatedly shown that relative conditions of deprivation or satiation influence responding for drug reinforcement, just as is the case for food and water reinforcement (Thompson 1968; Thompson and Schuster 1968). Although opiate reinforcement will maintain responding in nondependent monkeys, conditions of drug withdrawal are most effective in enhancing the reinforcing properties of opiates in dependent monkeys (Schuster 1968; Schuster and Thompson 1969; Woods and Schuster 1968). The effect of antagonist-induced withdrawal on morphine-maintained responding is a function of the antagonist dose, the order of antagonist dose administration (ascending or descending) and the conditions of morphine access (limited or unlimited) (cf. Goldberg, Woods and Schuster 1971; Schuster 1968; Schuster and Johanson 1974; Woods, Downs and Villarreal 1973). Following acute administration of the antagonist naltrexone (0.005 to 0.020 mg/kg), an initial increase in morphine-maintained responding did not result in an overall increase in morphine intake, but rather was sufficient only to maintain each animal's usual morphine intake. In contrast to the stability of morphine self-administration following naltrexone-precipitated withdrawal, food-maintained responding was profoundly disrupted for at least 24 hours (Mello and Mendelson 1977).

The behavioral pharmacology of antagonist drugs is poorly understood (Mello 1977). It has been repeatedly observed that morphine-dependent monkeys will work to avoid and escape from injections of antagonists (Goldberg et al. 1971; Hoffmeister and Wuttke 1973a; Hoffmeister and Wuttke 1973b.

However, comfortable commonsense assumptions about the behavioral effects of these compounds in opiate-dependent monkeys have recently been challenged by the provocative findings of Woods and co-workers (Woods, Downs and Carney 1975).

Monkeys trained to avoid antagonist infusions will work to produce antagonist infusion at the same dose per injection, after an unavoidable antagonist infusion has been superimposed upon the avoidance-escape schedule. Monkeys worked for an injection of naloxone on a second-order schedule FR 10 (FR 30:S) in which completion of each ratio of 30 responses was followed by a brief visual signal, and completion of 10 successive fixed ratios of 30 responses produced a single injection of naloxone (0.002 mg/kg/inj) followed by a one minute time out. The occasional delivery of noncontingent naloxone injections further increased rates of responding maintained by naloxone infusion and removal of naloxone decreased responding (Woods, Downs and Carney 1975).

These data extend observations that presentation of an electric shock can maintain response behavior to opiate antagonists. Kelleher and co-workers (Kelleher, Riddle and Cook 1963), were the first to observe that response behavior of squirrel monkeys can be maintained by the same electric shock that animals previously worked to avoid. This finding has been repeatedly reconfirmed (Kelleher and Morse 1968%; McKearney 1969; McKearney 1972) and the contributing factors in the behavioral history and the schedule of reinforcement have been clarified and specified (cf. Morse and Kelleher 1970 for review).

These seemingly anomalous findings that monkeys will work to produce the same event they previously worked to avoid question our traditional assumptions about what constitutes positive and negative reinforcement. The view that events do not have inherently reinforcing or punishing properties, but rather should be defined in terms of the way they influence behavior, has been most fully developed by Morse and Kelleher (Kelleher and Morse 1968b; Morse and Kelleher 1970; Morse and Kelleher 1977). There is now considerable evidence that both the experimental history and the ongoing schedule performance are critical determinants of how any event (food, shock or drugs) will affect operant behavior. A variety of seemingly “aversive” events extending from electric shock to opiate antagonists can maintain operant response behavior which leads to the administration of these events, under certain conditions. It is the schedule on which these events are presented, rather than the apparent properties of the events themselves, which determines if responding is maintained to produce, avoid, or escape from a particular consequence. The

extent to which these basic behavioral findings in primates are generalizable to man remains to be determined. Certainly data from basic behavioral studies and from behavioral pharmacology suggest numerous hypotheses concerning the maintenance of opiate abuse in man which can be subject to experimental test (cf. Mello 1977,' 1978).

OPIATE SELF-ADMINISTRATION IN MAN

Unfortunately, there is no comparable reservoir of behavioral data on patterns of opiate self-administration in humans. Most studies of the effects of opiates in addicts have employed a fixed-dosage opiate administration regimen consistent with the traditional paradigms used in pharmacology (e.g. Fraser et al. 1963; Haertzen and Hooks 1969; Himmelsbach 1942; Martin and Fraser 1961). Wikler was one of the first to examine the effects of self-determined patterns of morphine administration in a single addict subject in 1952 (Wikler 1952).

Antagonist Effects on Heroin Self-Administration

Meyer and Mirin (1978) have examined the therapeutic potential of narcotic antagonist drugs in heroin addicts who were allowed self-regulated access to increasing doses of intravenous heroin on a variable dose, variable interval schedule of their own choosing. Some of the major findings from these studies are summarized as follows:

Naltrexone (50 mg) produces a total blockade of narcotic effects for a period of 24 hours. These findings are consistent with the observations of Martin and co-workers (Martin, Jasinski and Mansky 1973). Narcotic addicts report no subjective effects when they self-administer heroin under antagonist blockade. In the majority of addicts studied, there was no objective evidence (miosis, changes in vital signs, etc.) that heroin produced physiologic effects during naltrexone blockade. However, six of the eleven subjects who sampled heroin frequently during naltrexone blockade, did show respiratory depression and pupillary constriction after the first several heroin doses. Meyer and Mirin (1978) suggest that these autonomic effects were not due to inadequate antagonist blockade, but rather were classically conditioned responses which extinguished after repeated blocked heroin injections. The importance of conditioning effects associated with the ritual of heroin self-injection has been clearly demonstrated by O'Brien (1976).

When naltrexone is administered to informed subjects, there is little experimentation with heroin: e.g., 7 of 9 subjects sampled heroin an average of 13 times (range 2 - 46) over a 10 day period of heroin availability while maintained on naltrexone blockade (75 mg/day P.O.). When naltrexone was administered under double-blind conditions, each of 22 subjects sampled heroin occasionally. Over a 10 day period of heroin access, 11 subjects took heroin on an average of 15.9 occasions, whereas the other 11 took heroin on an average of 4.3 occasions.

Both social and experiential factors appeared to influence heroin self-administration on the research ward. Addicts with a long history of heroin addiction persisted longer in heroin self-administration under conditions of naltrexone blockade (Meyer et al. 1978) and parallel findings have been reported in an animal model (Meyer et al. 1976b). However, all subjects self-administered significantly more heroin under placebo conditions than under naltrexone blockade. Frequency of heroin self-administration among the other members of the group appeared to be the best predictor of self-administration frequency in any individual. The relative contribution of these factors to the patterns of heroin self-administration observed remains to be clarified.

Subjective Consequences of Heroin Self-Administration

In contrast to retrospective accounts by addicts, chronic opiate use appears to be accompanied by an increase in dysphoria, hypochondriasis and irritability as well as increased psychopathology, belligerence, negativism, motor retardation and social isolation. These findings confirm and extend previous observations of Wikler (1952) and Haertzen and Hooks (1969). Subjects maintained on naltrexone throughout this period did not evidence a comparable increase in psychopathology or dysphoria. Although it appeared that each heroin injection was associated with a transient elevation in mood, even this transient mood change diminished as a function of chronic drug intoxication (Meyer and Mirin 1978; Mirin, McNamee and Meyer 1976). These data attesting to the dysphoric consequences of chronic heroin use are concordant with data on chronic alcohol intoxication and challenge the notion that drugs are used solely for their rewarding or euphorigenic properties (Mello 1977, 1978).

Narcotic antagonist blockade not only reduced the frequency of heroin self-administration but was also associated with subjective reports of a diminution of “craving” for heroin. Meyer and Mirin suggest that once subjects become aware of the naltrexone blockade, they redefine the situation as one

of drug unavailability, even though heroin remains freely available. In subjects who continued to self-administer heroin during naltrexone blockade, "craving" scores remained high (Meyer and Mirin 1978).

Initially, most patients did not continue antagonist medication on an outpatient basis for longer than one month after they left the research ward. However, compliance was significantly enhanced by providing small but apparently powerful monetary reinforcements for naltrexone use outside the hospital. The 10 to 20 percent of patients who are able to find steady employment and are gradually able to change their life styles, tend to maintain stable abstinence assisted by naltrexone.

Although Meyer and Mirin (1978) attempted to obtain information about operant patterns of heroin acquisition, this effort was frustrated by several factors. These studies were conducted using mechanical hand counters similar to those which had previously been used in studies with alcohol addicts (Mello and Mendelson 1972). Unfortunately, the heroin addict subjects repeatedly tampered with and occasionally destroyed these manipulanda with the result that it was not possible to relate heroin purchase patterns to operant acquisition. Moreover, the mechanical hand counter did not permit measures of operant response rate, response persistence (hours of work), inter-response times, or temporal patterns of operant responding. Finally, the frequency of heroin self-administration was limited both in terms of dosage and inter-dose interval; (a limitation which is shared by our recent studies). Consequently, behavioral data obtained described the presence or absence of heroin purchase at the prescribed intervals and does not provide information about the operant patterns or the effects of drug use on heroin acquisition (cf. Meyer et al. 1976a; Meyer et al. 1976c; Meyer and Mirin 1978; Meyer et al. 1978).

OPERANT ANALYSIS OF HEROIN SELF-ADMINISTRATION

We have reexamined the effects of naltrexone and naltrexone placebo (under double-blind conditions) on heroin self-administration patterns in a situation which permits a detailed analysis of operant acquisition. These studies of operant acquisition patterns for heroin are not a replication of previous studies by Meyer and Mirin (1978), but rather, represent a significant departure from those studies in terms of the experimental goals, the rationale, and most importantly, the technology applied. Previous studies (Meyer et al. 1976a; Meyer et al. 1976b; Meyer et al. 1978) were primarily concerned with determining if

"extinction" of heroin self-administration occurs under conditions of antagonist blockade, as has been postulated by Wikler Wikler 1973a and b). Meyer, Mirin and co-workers have now concluded that "extinction" is not a useful formulation for narcotic antagonist treatment since: (a) many subjects did not administer heroin in the presence of naltrexone and therefore "extinction" could not occur; (b) suppression of heroin self-administration did not predict compliance with outpatient naltrexone therapy (Meyer and Mirin 1978).

In order to evaluate the effects of heroin acquisition and use, it is important to have an objective and quantifiable measure of drug seeking behavior. Operant techniques for the experimental analysis of behavior yield objective and quantifiable data. Moreover, drug acquisition patterns can be compared with acquisition of an alternative reinforcer, money. Since drugs are not available to most users without some expenditure of effort or money, it seems realistic to require that an addict subject perform a simple operant task to obtain drugs or money within the clinical research setting. Comparison of drug acquisition patterns of subjects maintained on placebo or naltrexone under double-blind conditions provides another index of the effectiveness of these compounds in modifying heroin acquisition and subjective drug reactions.

During the past year, twelve heroin addict volunteers have participated in multidisciplinary clinical studies. Analysis of these data is currently in progress. Some major behavioral findings are summarized in the following sections.

Heroin Self-Administration Procedures

Adult male heroin addicts provided informed consent for participation in a 34 day inpatient clinical study. Subjects were studied in groups of four. A nine day drug-free baseline was followed by a ten day period of heroin availability when either naltrexone (50 mg P.O.) or naltrexone placebo was administered. The post-heroin baseline period included a five day period of methadone detoxification, a 7 day drug-free period and a final 3 day period when all subjects were given naltrexone each day (50 mg. P.O.). Subjects maintained on active naltrexone continued to receive naltrexone throughout the remainder of the study.

Subjects worked for heroin or for money on a simple operant task. Subjects were required to choose whether to work for money or heroin each time they activated their operant instrument. They could work at any time. A portable

manipulandum transmits a signal to recording and programming apparatus after each response. Only the first response after a fixed interval of one second had elapsed was counted as an "effective" response, by the circuitry (an FI 1 sec schedule of reinforcement). Approximately ninety minutes of sustained performance on an FI 1 sec schedule earned 18 purchase points which could be used to buy one 10 mg dose of heroin or exchanged for $1.50 in cash upon completion of the study. Points earned for money could not be exchanged for points earned for heroin. A record of points earned was continuously available.

Subjects self-administered heroin intravenously under supervision of a physician. The total amount of heroin available each day was 40 mg. Four ten mg doses were available each day at 8:00 am, 2:00 pm, 8:00 pm and 2:00 am. Subjects could omit any dose but could not receive a larger or smaller dose than 10 mg. Medical considerations precluded unlimited heroin access.

Representative behavioral data for one subject maintained on naltrexone blockade and one subject maintained on naltrexone placebo are shown in Figures 1 and 2. Statistical evaluation of these data has not been completed, but these graphs illustrate some clear trends in heroin and money acquisition and use.

Effects of Naltrexone Blockade

The number of doses of heroin taken, the number of hours worked for money and for heroin, and the number of purchase points earned for money and heroin over consecutive days of the study are shown in Figure 1 for a subject (1-HA1) maintained on active naltrexone throughout the period of heroin availability.

On days 8 and 9 of the pre-heroin baseline period, the subject worked most of the time for heroin points and earned enough to self-administer the maximum amount of heroin available for the first two days of heroin availability. This subject administered only two doses of heroin. He immediately perceived the absence of heroin effects and concluded that he received active naltrexone. This subject did not work for, or attempt to self-administer heroin throughout the remainder of the study. At the conclusion of the study, this subject was allowed to convert unused heroin points earned on baseline days 8 and 9 into points for money so he was not penalized for working in anticipation of unblocked heroin.

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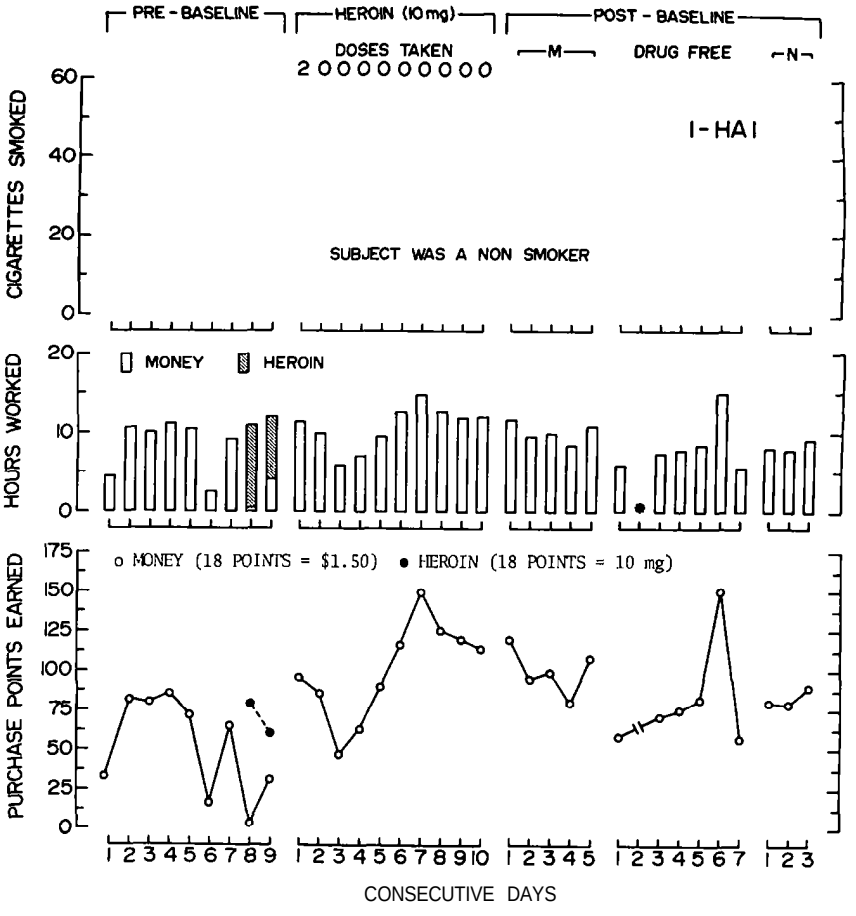
FIGURE 1


PRE - BASELINE
HEROIN (10 mg)
POST - BASELINE
DOSES TAKEN
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M
DRUG FREE
N
I - HA I
SUBJECT WAS A NON SMOKER
CIGARETTES SMOKED
HOURS WORKED
MONEY
HEROIN
o MONEY (18 POINTS = $1.50) • HEROIN (18 POINTS = 10 mg)
PURCHASE POINTS EARNED
CONSECUTIVE DAYS

The findings obtained with subjects under naltrexone blockade confirm previous reports of the effectiveness of the naltrexone (Martin, Jasinski and Mansky 1973) but are not consistent with previous reports of intermittent heroin sampling during naltrexone administration (Meyer and Mirin 1978; Meyer et al. 1978). Subject 1-HA1 reported a seven year history of heroin addiction.

This subject earned an equivalent or greater number of points for money during the first 15 days of naltrexone blockade than during the drug-free baseline. Naltrexone was administered daily throughout the remainder of the study. The fact that this subject remained in the study and continued to work for money when his peers were self-administering heroin is of interest. Although it might be assumed that a subject would become despondent and not work for anything in the presence of active heroin use by others, this was clearly not the case. Rather naltrexone maintenance appeared to be associated with increased operant work for money, even in an environment of active heroin use.

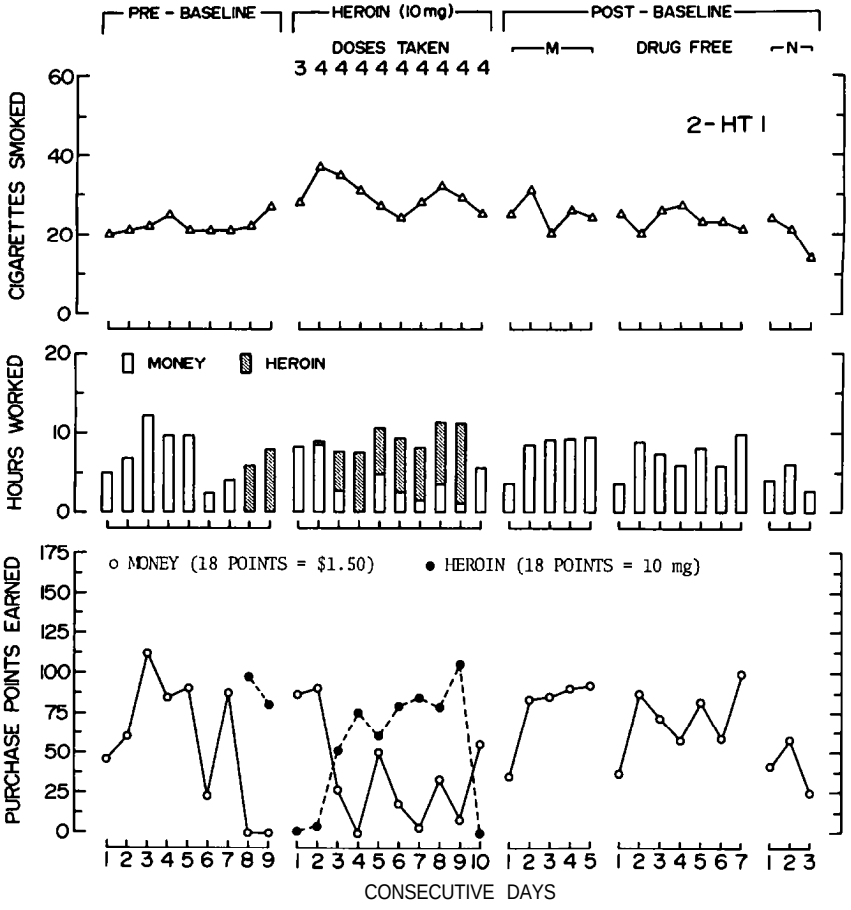
Effects of Naltrexone Placebo

Figure 2 presents heroin self-administration and earning data for a subject maintained on naltrexone placebo during the ten day period of heroin availability. A maximum of four 10 mg doses of intravenous heroin was available each day, once every six hours. Accumulation of 72 points per day (6 hours of work) was required to purchase all four heroin doses.

Figure 2 shows a subject who took all the available heroin doses except one on the first day of heroin availability. Most subjects earned enough heroin points during days 8 and 9 of the pre-heroin baseline period to support about two days of heroin use. One subject earned just enough for two doses of heroin. Since subjects had already accumulated enough heroin points to support one or two days of use, heroin earnings were usually somewhat depressed during the first two days of heroin availability as is shown in Figure 2.

Only three subjects took all the heroin doses available throughout the ten day heroin period. Other subjects occasionally missed one or two heroin doses and one subject only took two doses per day during the ten day period of heroin availability. One subject often slept through the 2:00 am heroin dose, even though he had earned enough points to buy heroin. Although heroin is a powerful reinforcer which allegedly exerts strong control over self-administration

FIGURE 2


PRE - BASELINE
HEROIN (10 mg)
POST - BASELINE
DOSES TAKEN
3 4 4 4 4 4 4 4 4 4
M
DRUG FREE
N
2-HT I
CIGARETTES SMOKED
60
40
20
0
HOURS WORKED
20
10
0
MONEY
HEROIN
PURCHASE POINTS EARNED
175
150
125
100
75
50
25
0
o MONEY (18 POINTS = $1.50)
• HEROIN (18 POINTS = 10 mg)
1 2 3 4 5 6 7 8 9
1 2 3 4 5 6 7 8 9 10
1 2 3 4 5
1 2 3 4 5 6 7
1 2 3
CONSECUTIVE DAYS

behavior, these data suggest this control is not invariant and may be modulated by a desire to sleep or to acquire money.

During the period of heroin self-administration, subjects tended to earn just enough heroin points to insure heroin administration. On day 9, subjects often increased earning of heroin points so that the final day of heroin availability was almost heroin work-free (Figure 2). Since excess points earned for heroin could not be converted into money, subjects carefully monitored their earned-spent ratios to avoid accumulation of unusable points. Subjects adjusted their earning rates so precisely that there was a surplus of only one or two purchase points following the period of heroin availability.

In terms of total time spent at the operant task, subjects tended to work an equivalent or a greater number of hours during the period of heroin availability than during the baseline period. However, it is evident that points earned for money were greatly suppressed in comparison to baseline during period of heroin availability (Figure 2). The degree of suppression is particularly dramatic when these heroin users are compared to subjects on active naltrexone during the same period (Figure 1).

During the five days of methadone detoxification, time spent in operant work and points earned were equivalent to or greater than during the drug free baseline period. Work to acquire money was not impaired during methadone detoxification and was initially sustained during the subsequent drug-free period.

Although naltrexone administration was associated with a decrease in earnings and tine spent in operant work, this effect cannot be attributed to naltrexone. During this three day period, subjects spent more time off the ward, arranging job interviews and planning for their transition back into the community. Subject 2-HA1 continued to earn money at a higher rate than during drug-free baseline periods when naltrexone was administered. The sustained performance of the subjects maintained on naltrexone blockade is another indication that naltrexone does not impair operant performance or motivation to acquire money.

Operant Response Patterns

A typical cumulative record of responding for points for heroin under an FI 1 sec schedule of reinforcement is shown

in Figure 3. This record is from day five of the period of heroin availability during late afternoon, about 90 minutes after the 2:00 pm heroin dose.

The cumulative record provides a direct analogue read-out of rate of response.' Each response advances a pen l/4 mm and the paper moves at approximately 11 inches per hour. The response pen reset after 300 responses. Each deflection of the baseline pen indicates that 300 effective responses have been emitted. Each response after a fixed interval. of one second has elapsed is defined as an effective response. Deflections of the pen above the response record indicate the reinforcement condition, upward deflections indicate a subject is working for heroin and no deflections indicate that a subject is working for money.

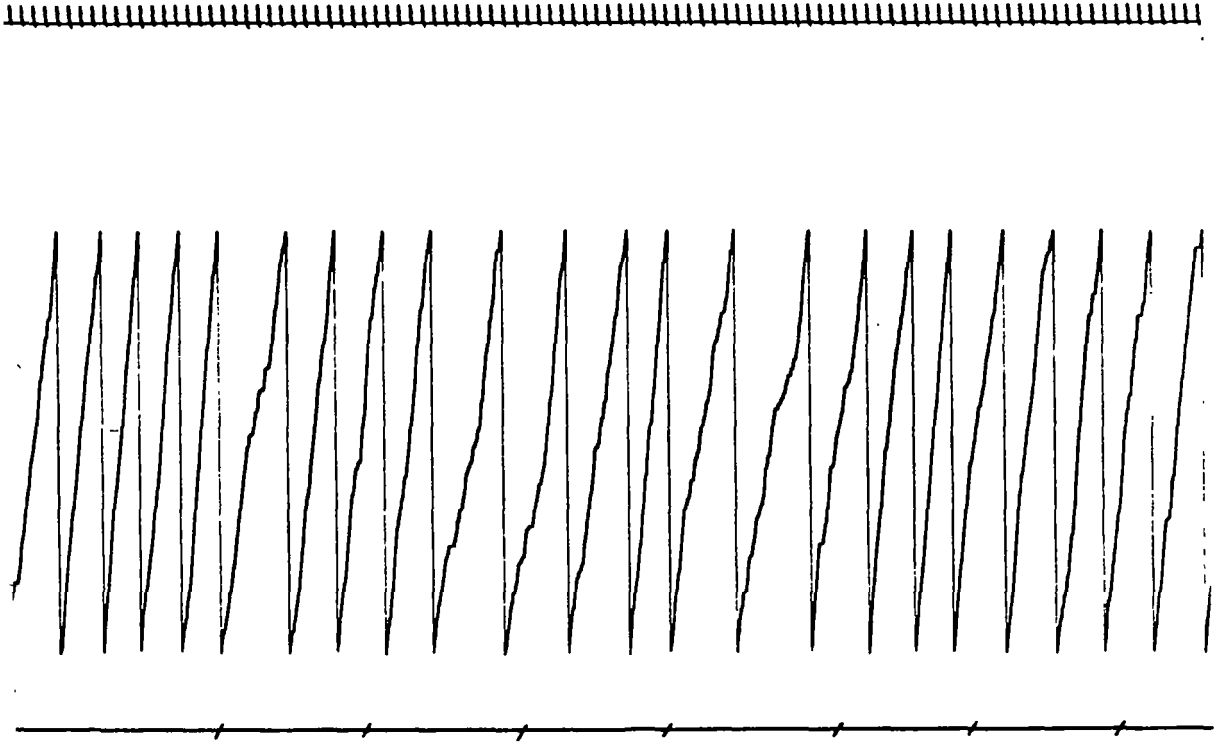
Figure 4 shows a typical cumulative record of responses for money by the same subject on Day 5 of the period of heroin availability. All other features of the record are identical to those described for Figure 3.

These records are typical of operant response patterns by heroin addicts for heroin or money under an FI 1 sec schedule of reinforcement. Subjects consistently responded at very high running rates, punctuated by brief pauses. Subjects consistently responded at rates faster than once per second, even though faster responses had no programmed consequence. Subjects reported that they preferred to respond at a rate that was comfortable, and this was invariably faster than required by the schedule of reinforcement.

Cumulative records of operant responding for heroin are very similar to cumulative records of responding for marihuana and alcohol under an FI 1 sec schedule of reinforcement (Mello and Mendelson 1978, this volume). Qualitative examination of cumulative records did not reveal major changes in response patterns following an acute 10 mg dose of heroin. An analysis of inter-response times prior to and following heroin self-administration is currently in progress.

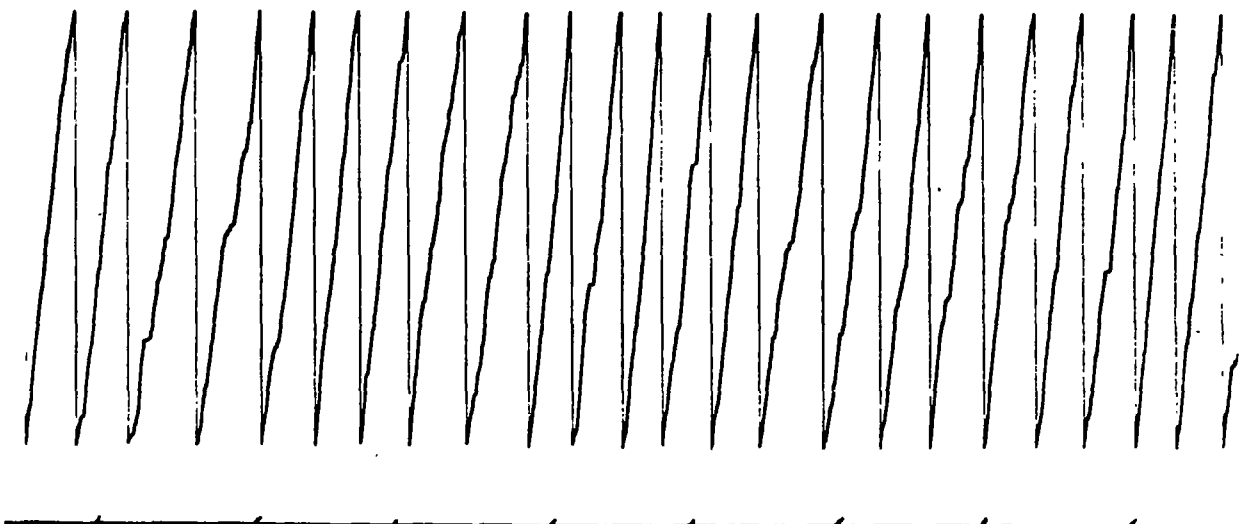
The response cost for heroin, defined in terms of sustained work required for a single dose of heroin (90 minutes), was considerably greater than in our previous studies of marihuana, alcohol and multiple drug self-administration (15 or 30 minutes) (Mello and Mendelson 1978). Operant work for heroin acquisition was also more stable and consistent than we have seen previously. Subjects carefully monitored their point accumulation and adjusted their work output to earn just enough for the heroin available. The accumulation of points during baseline to support two days of work-free heroin and the increase in heroin points earned on the ninth day of heroin availability, are reminiscent of the alternate

FIGURE 3



Cumulative record of responses for heroin on a FI 1 sec schedule of reinforcement.

FIGURE 4



Cumulative record of responses for money on an FI 1 sec schedule of reinforcement.

working and drinking pattern shown by alcohol addicts (Mello and Mendelson 1972). However, heroin addicts did not elect to remain abstinent for several days and precipitate withdrawal signs and symptoms as the alcohol addicts did (Mello and Mendelson 1972). Despite occasional missed doses, heroin use was sustained throughout the period of availability. Individual variability in heroin self-administration is also seen in primate models of opiate self-administration.

These studies illustrate the feasibility of applying procedures for the experimental analysis of behavior to the study of heroin self-administration in man. Patterns of heroin acquisition and the consequences of chronic heroin use can be examined in a clinical research ward setting. Further interpretation of these findings will require completion of data analyses now in progress.

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ACKNOWLEDGMENT

This research and preparation of this review were supported by grants DA01676 and DA 4RG010 from the National Institute of Drug Abuse, ADAMHA.

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Chapter 10

Studying Social Reactions to Drug Self-Administration

Thomas F. Babor, Ph.D.

Behavioral scientists have become increasingly aware of the social context of drug taking behavior (Goode 1969; Kandel 1974) and of the mediating role that, the social environment exerts in the manifestation of drug effects (Schachter and Singer 1962; Nowlis 1958). In spite of this recognition, little research attention has been given to the group dynamics surrounding the act of drug self-administration, and even less to the social effects of repetitive drug use. In part, this can be attributed to inadequacies inherent in current methodological approaches which rely almost entirely on retrospective surveys of drug users or laboratory experiments of acute drug intoxication (Sadava 1975).

Not until almost 30 years after publication of the classic LaGuardia study on the effects of marihuana (Mayor's Committee on Marihuana 1945) did a small number of collaborative research groups begin to develop procedures for the experimental analysis of repeated drug self-administration (Mendelson 1964). The major characteristics of this approach came to include subject participation in a controlled residential laboratory; free access to a limited range of social, recreational and instrumental (operant) stimuli; repeated assessments during successive periods of drug availability and drug nonavailability; and optional drug self-administration as both an independent and dependent variable (see Bigelow, Griffiths, and Liebson 1975, 1976; and Mello 1972 for reviews of procedural developments and representative research). In the present paper we will review those studies in which the effects of optional drug self-administration on social behavior were investigated. Because the major thrust of much research on drug self-administration has been behavioral and biomedical, few studies have been designed explicitly to investigate social effects. Nevertheless, social assessments have been incorporated into a sufficient number of studies of marihuana, heroin and alcohol to generate a significant body of literature. What follows will summarize some of the representative studies, discuss their methodological limitations, and evaluate their contributions to the understanding of both drug effects and social behavior.

By way of introduction it would seem important to address two issues concerning the pursuit of knowledge on the social effects of drugs. The first can be phrased in this manner: Why should social reactions be an important focus of drug self-administration research? One of the most obvious reasons to focus on social reactions is that this is the kind of behavior that policy makers, public health officials and the general public are interested in knowing about. There is a general belief that some of the most complex and meaningful components of social functioning are altered by drugs. Inadequate role performance, antisocial behavior, faulty communication, distorted social perceptions, sexual inadequacy, deteriorated social relations, and lack of conventional motivation have all been attributed to the negative consequences of drug use. Ironically, an equally impressive array of behavioral changes has been attributed to the positive consequences of drugs: facilitated communication, sexual arousal, enhanced self-esteem, insightful social perceptions, feelings of intimacy and closer identification with others. It is often these molar units of social behavior which intrigue the psychologist in all of us, but to date not enough has been derived from either survey studies or laboratory investigations to provide a scientific basis for our often contradictory notions about drug effects.

Another reason to focus on the social effects of drugs is theoretical. It has been proposed, for example, that the reinforcing properties of drugs are in part related to the personality functions altered during drug intoxication (Teasdale and Hinkson 1971). By providing an empirical basis for these generalizations, self-administration research can play an important role in theory development.

And for those less interested in drugs than in more fundamental questions about social processes, self-administration research offers a means of studying how complex behaviors are mediated by biochemical, physiological and affective changes (Russell 1960; Nowlis 1958). The interdisciplinary nature of self-administration research has great potential for integrating data from different levels of analysis. By viewing drugs as tools for systematically varying the biological substrate of behavior, drug research need no longer be considered an illegitimate offspring of pure science.

The second issue relevant to the study of social behavior in drug self-administration research is this: How can self-administration studies facilitate an understanding of the social effects of drugs? Although drug effects on humans have been studied intensively in the experimental laboratory, the dosage, setting and conditions of administration are often unrepresentative of self-determined usage in the natural environment (Jones 1971). By allowing subjects to choose the timing and context of drug use in naturalistic settings, the self-administration paradigm permits a more realistic analysis of the relation between the pattern of consumption and the consequences of drug use. As Mello and Mendelson (1970) have shown, it is often the pattern of consumption, and not absolute dosage, which determines the individual's reaction to a drug.

Another advantage of the self-administration paradigm is that it simulates the natural social context of drug use. One of the more universal aspects of drug use is that it takes place in face to face. social settings. There is compelling evidence that this social context exerts

a powerful influence on the labeling of and reaction to internal changes induced by drugs (Schachter and Singer 1962; Nowlis 1958; Pliner and Cappell 1974; Sice et al. 1975). Although the group nature of much self-administration research has been dictated more by the economy of batch processing than by an appreciation of social context, self-administration research can provide valuable data on the influence of the prevailing social environment.

Further justification for using the self-administration paradigm derives from the fact that it allows the rare luxury of studying social reactions within a time frame adequate for the assessment of a full range of social reactions. As much as questionnaire and other retrospective methods seek to give substance to drug use patterns, nothing provides a better alternative to selective recall than empirical observation. Drug effects are influenced by tolerance, dependence, and by a variety of nonpharmacological factors, and the contributions of these factors change over time. By providing an opportunity to observe the consequences of both acute and chronic intoxication, self-administration research makes it possible to describe drug effects in their true complexity, a fact which will become apparent as we review those self-administration studies which have treated social variables as consequences of drug self-administration. Marihuana, heroin and alcohol, the three drugs which have received most of the research attention, will be discussed in succession. Because our research group at McLean Hospital has struggled with many of the methodological problems in this area, our own research efforts will be reviewed in some detail.

MARIHUANA

In 1938 Fiorello H. LaGuardia, then mayor of New York, commissioned the first comprehensive scientific study of marihuana. Responding to the same kind of public pressure which was to give impetus to future drug research (Mendelson, Rossi, and Meyer 1974) Laguardia requested that the New York Academy of Medicine investigate the social, as well as the physical, implications of marihuana use. Although the mayor's scientific committee focused primarily on the acute and chronic effects of fixed doses of marihuana, their clinical studies of volunteer prisoners also included observations of informal social interaction following self-selected doses (Mayor's Committee on Marihuana 1945). This procedure was motivated in part by a desire to observe global reactions to marihuana under conditions approximating the natural environment.

Recognizing the possible contributions of contextual factors in mediating social reactions to drugs, the researchers simulated the setting of the "tea pad party" during two informal group smoking sessions. It was reported that laughter, joking, restlessness and conversation, observed soon after the initiation of smoking, gradually gave way to general relaxation. While marihuana had a "convivial" effect on group members, "a mental state characterized by a sense of well-being, relaxation and unawareness of surroundings, followed by drowsiness, was present in most instances when the subject was left undisturbed" (Mayor's Committee on Marihuana 1945, p. 215).

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One year after the publication of the Laguardia report, the results of a second clinical study were published by Williams et al. (1946). Six prisoner volunteers were allowed to self-administer marihuana cigarettes (of undetermined dosage) during a 39-day period of confinement on a hospital ward. The subjects smoked an average of 17 cigarettes a day. Clinical observation suggested that subjects became more talkative, carefree, and physically active during the first few days of marihuana smoking, but this was followed by a longer period of decreased activity and lack of motivation. While lacking methodological controls and empirical observations, these early studies demonstrated the feasibility of investigating drug effects on complex social behavior.

It was not until the renewal of interest in clinical self-administration studies in the early 1970's that it became possible to investigate social reactions in a systematic way. Miles and his colleagues (1974) studied six male volunteers, all regular marihuana users, during a 70-day period which included 42 days of free access to 1 g (.09% THC) marihuana cigarettes, and beverage alcohol. Drug self-administration and concomitant activities were observed at half hour intervals 24 hours per day. During the initial period of marihuana availability, a slight suppression in mean daily conversation was noted, but with continued smoking there was a progressive increase in social interaction. During the drug period subjects were found to make significantly greater use of passive entertainment facilities such as television, radio and phonograph. Although the authors concluded that no changes in social behavior could be attributed to the introduction or removal of the drug, their methodology, like those of previous studies, contains limitations which preclude such unequivocal statements. Little is said of the possible confounding influence of concomitant alcohol use and tolerance development, and there is no attempt to distinguish acute effects from the more general measure of average daily conversation.

The powerful and often interacting contributions of such variables as dosage, tolerance, individual differences, expectancy, setting and social influence became evident to the McLean Hospital research group during a series of clinical studies on marihuana self-administration begun in 1971. The initial investigation of 20 marihuana users was performed at the request of the National Commission on Marihuana and Drug Abuse (Mendelson et al. 1972; Mendelson, Rossi, and Meyer 1974). Since that time an additional 75 subjects have been studied in related investigations of marihuana self-administration. While the primary focus of these studies has been on biological and behavioral concomitants, the interdisciplinary nature of the research program gave ample opportunity for the systematic study of interpersonal behavior.

In the National Commission study separate groups of 10 casual and 10 heavy marihuana users lived on a closed research ward for 31 days. A S-day drug-free period preceded and followed 21 days of work-contingent access to 1 g (2% THC) marihuana cigarettes. Special attention was devoted to the observation of marihuana smoking patterns? informal affiliation networks, and verbal interaction in formal discussion groups (Babor et al. 1974a,b). The data indicated very strongly that marihuana smoking, in addition to being a subjective drug experience, is also a social activity around which communication and other types

of social behavior are organized. Specifically, the subjects rarely chose to smoke alone. More than 94% of all marihuana consumed by either type of user was smoked in a place where other subjects were present. In addition to observing marihuana smoking patterns in informal social settings, subjects were also studied in task-oriented discussion groups each afternoon during the three phases of the investigation. Each discussion was tape recorded and later coded according to Bales' Interaction Process Analysis (Bales 1950). Both casual and heavy users showed a marked decrement in verbal interaction during groups occurring in the first quarter of the marihuana smoking period (Babor et al. 1974b. While the heavy users tended to exceed pre-drug levels of interaction after the first quarter of the drug period, total interaction among the casual users continued to diminish. The results suggested that the heavy users accommodated themselves better to the long-term effects of marihuana. The results also indicated that while the quality of interaction shifted away from task-oriented responses, there was no general disruption of verbal interaction.

These findings were supported by correlational analyses in which individual levels of intoxication (as determined by self-reports) were correlated with amount and quality of output. Total interaction decreased at higher levels of intoxication, and this relationship was found most consistently in the category of attempted answers. In general, interaction tended to be more positive and less task-oriented during intoxication.

The fruitfulness of studying marihuana effects in both formal and informal social settings led to a major refinement in observational methods which were next applied to an investigation of 10 four-person groups of moderate and heavy marihuana users (Babor, Mendelson, and Kuehnle 1976; Mendelson et al. 1976). Twenty-six of the male volunteers were systematically observed before, during and after a 21-day period of self-determined marihuana use. The subjects were free to choose from a variety of activities, including sleep, work and recreation, those which they preferred during and after intoxication. Because previous studies had lacked control groups, 11 additional subjects not having access to marihuana were studied under identical experimental conditions to determine the effects, if any; of the experimental procedures, institutionalization, group development and other extraneous factors. Additional data were obtained by means of the Behavior Inventory (BI) Checklist, a computerized observational system designed to obtain a representative sample of each subject's daily activity. Trained research aides observed each subject once every hour during fifteen-second time intervals. The time at which hourly observations were initiated varied randomly from day to day. Immediately following observation, the subject ' s primary (predominant) and secondary (nonpredominant) activities were coded according to a list of 20 possible behaviors. The list included sleep, watching television, listening to music, watching others, reading, testing, vital signs, talking, stationary play (games), active play (sports), operant work, "no apparent activity ," and several miscellaneous cate-
. In addition, social affiliation patterns were coded on a grid representing subjects and staff in the immediate proximity of the smoker. Reliability and validity of the procedure were checked and found to be uniformly high (Babor, Mendelson, and Kuehnle 1976).

Changes in interpersonal behavior were analyzed by combining selected BI categories reflecting three levels of social interaction. Social isolation refers to situations where the subject was alone or in presence of others but neither interacting nor coacting. Social interaction refers to situations where the subject's primary or secondary activity was a stimulus or response to the behavior of another (e.g., conversation, ping pong) . Social coaction applies to situations where the subject engages with others in some mutual task or activity (e.g., watching television, listening to music) but without direct communication or interaction.

During the 21-day smoking period moderate users consumed an average of 2.6 cigarettes per day while heavy users smoked more than twice this number daily (5.7) . Smokers in both groups gradually increased consumption during the period of availability, a pattern suggestive of physiological and/or psychological tolerance. As in our previous study, marihuana smoking typically occurred within a social context. More than 80 percent of each subject's marihuana was consumed in the presence of at least one other subject.

Immediate changes* in social behavior were analyzed by comparing percent time observed in each level of interaction during the hour immediately preceding and immediately following marihuana smoking. Figure 1 shows that one hour after intoxication moderate users were interacting significantly less and coacting significantly more than during the hour preceding smoking. Daily changes in social behavior were evaluated by correlating the number of marihuana cigarettes smoked each day with the percent daily waking time observed in each level of interaction. The correlation coefficients, averaged across subjects 'and shown in table 1, gave no evidence of a marihuana-related change in daily amounts of isolation, coaction or interaction. These

TABLE 1. Average Pearson Correlation Coefficients: Number of Marihuana Cigarettes Consumed per Day Correlated With Measures of Three Categories of Social Interaction

Interaction Category	Same Day		Next Day[1]	
	Moderate	Heavy	Moderate	- Heavy
Isolation	-.08	-.17*	-.06	.08
Coaction	.06	-.08	.19*	-.03
Interaction	.02	.26*	-. 15**	-.02

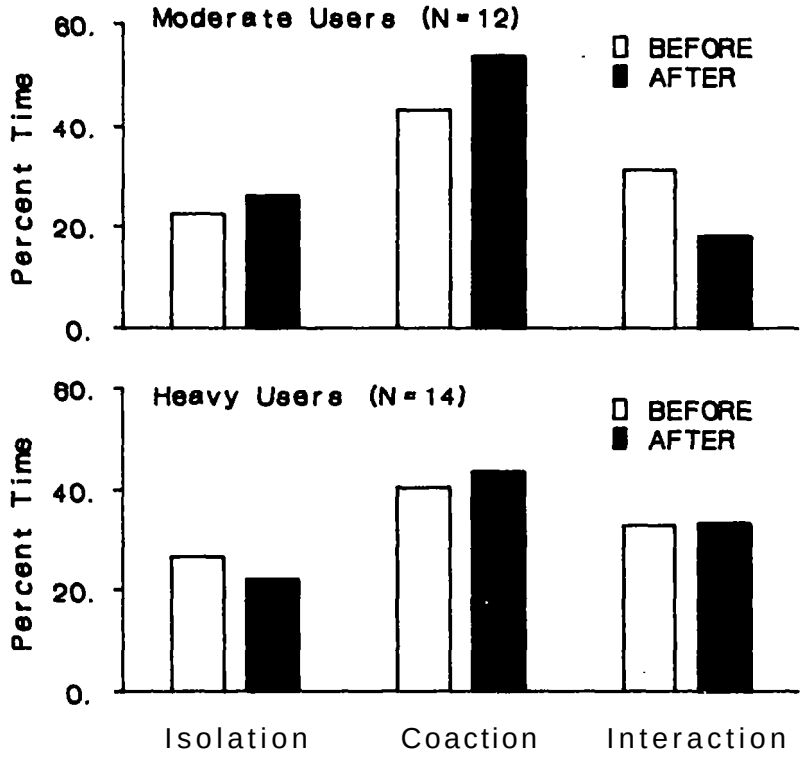
'Average Pearson Correlation coefficients, next day, are means of partial correlations. The effect of the number of marihuana cigarettes smoked on the next day has been partialed out of the relationship.

* p< .05
** p< .01

*NOTE: In this discussion the words "change" and "reaction" are used advisedly. Because of methodological limitations, to be discussed later, it cannot be assumed that behavioral changes following single and daily drug doses are determined solely by the pharmacological action of the drug. The term "drug effect" therefore has been avoided.

FIGURE 1

Interaction, Coaction and Isolation Before and After Marihuana Smoking



findings suggest that the acute reactions to marihuana by moderate users are transitory and are more than compensated by the greater opportunity for interaction afforded by the social context before marihuana smoking.

Individual correlations between the three indexes and amount smoked daily were next computed using a one day time lag. These statistics were used to estimate delayed reactions resulting from variations in daily marihuana intake. Averages of the moderate users' correlation coefficients (table 1) showed that the more a subject smoked on the preceding day the less he tended to interact on the following day. The cumulative effect of these delayed reactions was evident in the analysis of persistent and chronic changes in social behavior. These were evaluated by comparing baseline averages with those measured

during successive five day blocks of the smoking period. Moderate users engaged in less interaction and more coaction during the entire drug period (persistent reaction), but interaction returned to its initial baseline level during the final drug-free period. Control subjects, on the other hand, showed no consistent variations in social behavior over the course of the experiment.

In contrast to the moderate users, heavy users showed relatively mild alterations in social behavior (cf. fig. 1, table 1). Of the five dependent measures, only the correlations with daily amount smoked showed significant variations. On days of heavier consumption heavy users were found to be less isolated and to engage in more interaction than on days of lighter consumption. In the absence of acute reactions, the daily changes suggest that heavy users were interacting more in response to the social circumstances of marihuana use than to the pharmacological action of the drug.

In order to obtain a more refined picture of the social reactions to marihuana, and to determine whether the immediate changes observed in the moderate users were trans-situational, all subjects were observed daily in a task-oriented group discussion situation similar to that employed in our previous research (Babor et al. 1974b). The discussion task was chosen because of its simplicity and comparability from one topic to another. No verbal or intellectual skills are required, and performance is affected minimally by repetition. Further, the task resembles many employment situations where individuals meet to discuss practical, theoretical, or "human relations" problems.

Ongoing interaction (who speaks to whom) and role behavior were observed according to Robert Bales' procedures. Developed out of a long tradition of small group research, Bales' (1970) methods were used to quantify the amount of verbal interaction given and received, as well as the social role of each participant in terms of the following bipolar dimensions: dominant-submissive, friendly-unfriendly, task oriented-nontask oriented. The results indicated that during intoxication, moderate users were less task-oriented and participated less in group discussion. No significant changes on any of the dependent measures were noted for the heavy users, although there was a trend toward less task-orientation during intoxication (Babor et al. 1978).

The findings emerging from our research on the social reactions to marihuana can be summarized as follows: (1) While marihuana may be a "sociogenic" drug (i.e., it brings people together by serving as a focus of interaction) in the sociological sense proposed by Goode (1969), following intoxication there is a shift from a social, verbal, external focus of attention to a more internal, detached, contemplative orientation. (2) In formal discussion situations, there is also a reduction in task orientation which is reflected both in the content of the interaction and the role of the communicator. (3) The general lack of social reactions in heavy users suggests that social effects are mitigated by behavioral tolerance which may develop after continued marihuana use. (4) When combined with systematic observational procedures, the drug self-administration paradigm provides a fruitful means of describing acute and chronic social reactions in both formal and informal settings.

HEROIN

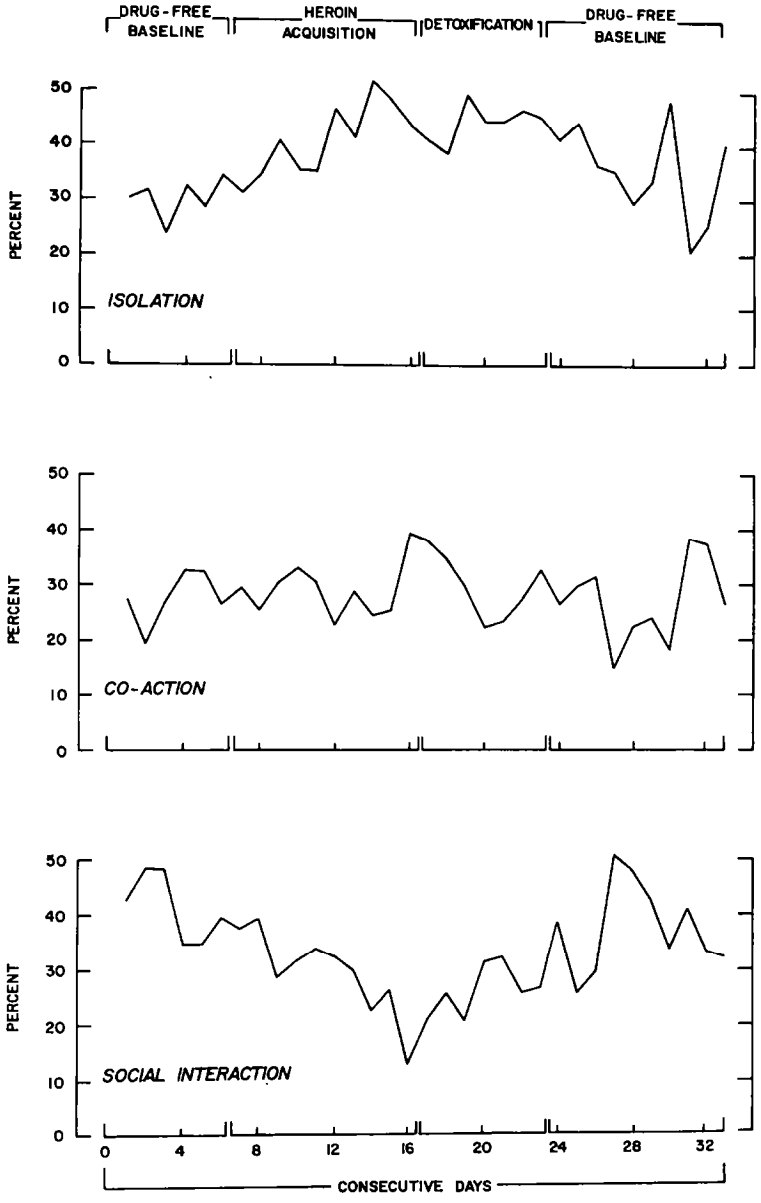
The literature of drug abuse is replete with descriptions of the social effects of acute and chronic heroin intoxication. Ausubel (1958), for example, describes the opiate effect as primarily depressant, consisting of analgesia, sedation, drowsiness, decreased motor activity, and lethargy. Habitual users surveyed by Chein and his colleagues (1964) reported loss of vitality during addiction as well as a general deterioration in social relations and leisure pursuits. Because of the confounding influence of the addict's lifestyle and social environment, it was not possible to obtain a clear estimate of the social effects of heroin until the initiation of clinical studies in controlled settings.

The first of these studies consisted of programmed heroin administration in doses increasing from 10 mg to 95 mg over a 60-day period. Under these conditions Fraser et al. (1963) observed five prisoner addicts during a three-month period of gradual addiction and withdrawal. Compared with placebo, heroin was found to increase physical activity and sociability after the first dose. But during a period of chronic intoxication activity became depressed and social affiliation was reduced. Self-report ratings, obtained from these and nine additional subjects by Haertzen and Hooks (1969) revealed less motivation for social and sexual activity, neglect of social affairs, and greater irritation in social situations. These findings suggest that chronic heroin intoxication induces persistent changes in subjective feeling states, social perceptions and interpersonal behavior. However, they leave unanswered many questions about the underlying dynamics of these reactions. Partially in an attempt to address these issues our collaborative group at McLean Hospital undertook an exploration of the heroin addiction cycle as part of a larger interdisciplinary investigation of the efficacy of narcotic antagonists (Meyer et al. 1976).

In the first of a series of three studies, groups of four addict volunteers lived on an experimental research ward for 60 days. During this time heroin was made available for self-administration under blocked (heroin antagonist) and unblocked conditions. The unblocked heroin condition lasted 10 days, during which time the available dose increased from 6 to 60 mg/day. All subjects chose to self-administer the maximum available daily dose, although the frequency of administration varied from group to group. Procedures identical to those used in our research on marihuana self-administration were employed to measure variations in social behavior during the cycle of addiction and withdrawal (Babor et al. 1976b). In addition, psychiatric interviews and semantic differential rating scales were used to evaluate concomitant changes in social adjustment and subjective feeling states (Mirin et al. 1976).

The results of the hourly observations are shown in figure 2. Reactions to heroin self-administration were most pronounced in the categories of isolation and social interaction, which varied inversely during the periods of addiction and detoxification. Time spent in social interaction decreased from a drug-free level of 47% to a low of 12% late in the heroin phase.

FIGURE 2



Average percent daily waking time spent in isolation, coaction, and interaction. Babor et al. 1976b. Copyright 1976, American Medical Association. Reprinted, with permission, from Arch Gen Psychiatry, 33:363-367, 1976.

Although the results suggest strongly that social interaction is directly affected by heroin self-administration and withdrawal, it is conceivable that certain extraneous nonpharmacologic factors also influenced the results. One such factor could have been expectancy. Since patients were fully cognizant that they were receiving heroin and later methadone, they may have been reacting to expected rather than actual drug effects. Another possible extraneous factor is behavioral contagion. This refers to the spread of drug reactions from one group member to another through a process of modeling and imitation. In a subsequent series of studies using a modified design, an attempt was made to distinguish between these sources of variance by controlling for expentancy (through double blind administration of naltrexone and placebo) and by manipulating the numbers of blocked and unblocked members within successive groups. Observations identical to those employed on the first 12 subjects were repeated on 37 additional subjects. The findings were very consistent with the results of our first study. Unblocked subjects interacted least and were most isolated in the late stages of heroin acquisition and in this respect they differed significantly from blocked subjects.

The identification of significant modifications in social interaction during the addiction cycle raised additional questions about the underlying dynamics of these effects. Do chronic reactions represent the accumulation of acute effects, or are they related more to the development of abstinence symptoms? Is there evidence that acute positive effects compensate for the chronic negative effects, thereby suggesting a possible reinforcing mechanism of heroin? Finally, do the immediate effects of heroin satisfy specific personality needs, for example, by increasing dominance, reducing hostility or facilitating interaction?

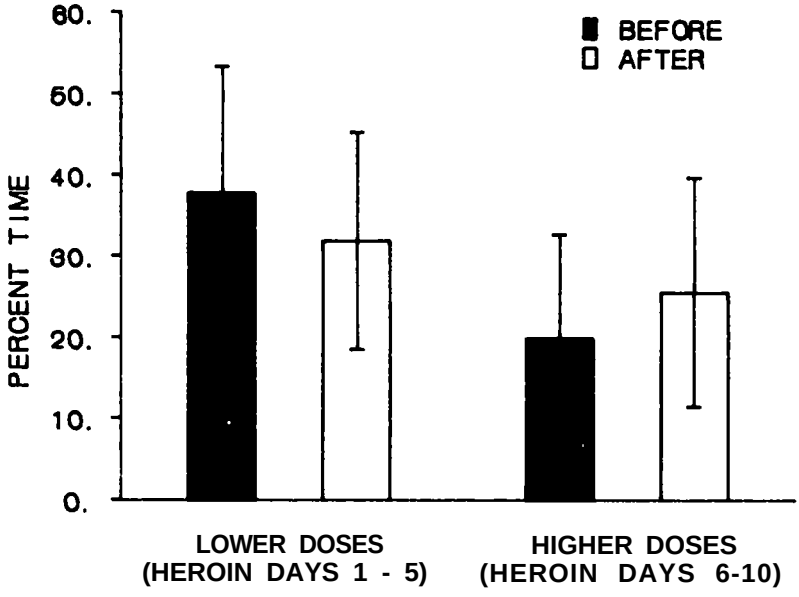
To identify acute behavioral and social changes taking place after heroin administration on the research ward, all observations that preceded and followed each drug administration were analyzed. Because heroin doses were escalating gradually, the data were summarized at both lower (first five days of heroin) and higher (second five days) dose levels. As shown in figure 3, subjects indicated somewhat less interaction following lower doses and significantly more interaction following higher doses. Even though subjects were interacting more after higher doses than before, the absolute level of interaction was significantly less than that seen at lower doses. This means that while interaction was generally declining during the heroin phase, the effect of higher doses was to reverse this effect temporarily.

In addition to the hourly observations conducted on the research ward, subjects were also studied while participating in a 45 minute therapy group (Babor et al. 1976a). Ongoing interaction (who speaks to whom) and role behavior were observed according to procedures used in the marihuana research described previously (Babor et al. 1978). In addition, a five-point interpersonal hostility scale was used to assess verbal and nonverbal hostility. These observations made it possible to determine whether the immediate changes observed in the ward setting generalize to the more socially demanding group therapy situation.

The results showed no significant changes in group participation or role behavior. However, hostility differed significantly among phases,

FIGURE 3

Social Interaction Before and After Lower and Higher Doses of Heroin



reaching its highest level during the latter part of the heroin period. The increase in hostility correlated positively with dosage level. In related findings, subjects reported increasingly dysphoric mood states, while independent psychiatric observations revealed greater somatic concern and belligerance (Mirin et al. 1976).

Considered in their totality, the results suggest a complicated relationship between acute and chronic reactions to heroin and their cumulative effects on physiological functioning, subjective states and social behavior. Although single doses of heroin apparently provide a brief respite from dysphoric mood states, it is likely that negative affect is intensified by physical dependency and the development of tolerance. Tolerance develops rapidly to the analgesic and euphoric effects of opiates, thereby requiring the addict to increase his dose to attain previous degrees of euphoria. As physical dependence develops, abstinence symptoms become more intense between doses. These factors undoubtedly reduce the addict's interest in social contact, which often involves frustration, competition and conflict in the street environment. Aggression and social withdrawal may be two means of coping with the internal changes being experienced during the addiction cycle. Aggression would be more likely to occur in those interpersonal situations perceived as threatening or frustrating. Since hostile behavior is often punished or negatively reinforced, a

more functional way of dealing with inner hostility would be to reduce the possibility of interpersonal conflict by withdrawing from social situations. Thus social withdrawal may be an avoidance response intended to cope with negative feeling states and sources of frustration in the environment.

In summary, this research illustrates the importance of using an interdisciplinary approach to study drug effects. Without the use of multiple measures to monitor underlying changes at different levels of analysis, factors mediating social reactions may only be inferred.

ALCOHOL

Despite the abundance of folklore attributing prosocial as well as antisocial behavior to the effect of alcohol, social variables have been considered in only a few self-administration studies of drinking.

McNamee, Mello and Mendelson (1968) report the results of nonsystematic clinical observations of 12 alcoholics during a seven day period of free access to 86 proof bourbon. Although subjects maintained a high degree of social interaction, they tended to withdraw from social contact during periods of maximum intoxication. Nine subjects demonstrated a progressive increase in anxiety and depression which correlated with amount of alcohol consumed. The emergence of assertiveness, hostility and belligerence during chronic intoxication was also noted in many of the subjects.

Using self-report behavioral assessments, Tamerin, Weiner and Mendelson (1970) obtained similar results in a study of 13 male alcoholics. Subjects' expectancies prior to drinking were compared to self-reports obtained during the experimental period of ethanol self-administration. Subjects reported significantly more dysphoria, sexuality and aggression during intoxication than they had predicted during sobriety. The findings suggested that alcoholics drink in order "to regress, rebel and more comfortably act out (p. 1703)," and not, as many have assumed from alcoholics' retrospective accounts, to be more sociable or to feel better.

In contrast to those self-administration studies where subjects are studied concurrently in homogeneous groups, Griffiths, Bigelow and Liebson (1974) employed a design where five male alcoholics participated consecutively. In the initial phase of each subject's program a maximum daily dose of 12 oz of 95 proof ethanol was available on randomly selected days. In the second phase the same amount of ethanol was available during successive days on a nonrandom schedule. Social interaction, defined as behavior which required the presence of or involved another person, was observed on a random schedule. Social interaction was found to be significantly greater on ethanol days than on nonethanol days in both random and successive scheduling conditions. Although it is suggested that increased social interaction may be one of the reinforcing effects of drinking, the authors avoid implicating alcohol, qua pharmacological agent, directly with this effect. Their methodology, as well as their interpretation, leaves open the possibility that the subject's expectancy or other factors in the ward environment contributed to the increased socialization.

Two recent studies manipulated psychological "trait" variables to observe their interaction with alcohol self-administration and social behavior. Martorano (1974) used observational and self-report procedures to study the effects of alcohol and assertion training on social perception in one group of four alcoholics. Observers' ratings indicated decreased cooperation and communication during alcohol intoxication, a pattern which tended to be exacerbated following assertion training. Thornton et al. (1976) investigated the relation between socialization, drinking behavior and the introversion-extroversion personality factor in 98 alcoholics participating in a six-week treatment and research program. Socializing increased significantly in the early stages of drinking. Drinking alcoholics maintained a higher rate of socializing than a control group of nondrinking alcoholics. Although extroverted alcoholics socialized at a significantly higher rate than introverted alcoholics, the personality factor did not interact with drinking.

In a series of related investigations, Nathan and his colleagues (Nathan et al. 1970; Nathan, O'Brien, and Norton 1971; Tracey and Nathan 1976) studied alcoholic and nonalcoholic drinkers during alternating periods of isolation (confinement to bedroom) and socialization (free access to all ward areas). Points earned on a simple operant device could be used to purchase alcohol and/or relief from isolation. In one study (Nathan et al. 1970) 11 alcoholic subjects participated in three separate groups for periods ranging from 30 to 42 days. A nondrinking phase of six days preceded and followed an interim period of alcohol availability. Several observational procedures were employed to obtain time samples of social behavior but no statistics are reported. According to the authors, the "average" subject , when drinking, attempted more often to initiate communication, was more aggressive verbally, and failed more often to respond to another person's initiation of communication. No consistent preference for drinking was demonstrated during either isolation or socialization periods. In another report (Nathan, O'Brien, and Norton 1971), one four-person group of alcoholics was compared to a matched group of nonalcoholic drinkers. Each group was observed during a 33-day study having alternating three day periods of isolation and socialization. Although the alcoholic subjects were demonstrably more isolated than the nonalcoholics, neither group showed social changes which could be attributed to either the experimental condition (isolation vs. socialization) or the availability of alcohol. Finally, in yet another. study (Tracey and Nathan 1976), a single group of four female alcoholics was observed over a period of 22 days, 12 of which provided access to alcohol. As in the previous studies, attendance at the ward bar was not affected by the isolation/socialization condition. Compared to the results of previous studies, the authors suggest that socialization patterns of female alcoholics were more like those of the male nonalcoholics than the male alcoholics.

In our own research at McLean Hospital ten four-person groups of nonalcoholic drinkers were observed during a 30-day investigation of the effects of purchase price on alcohol self-administration (Babor, Mendelson, Greenberg and Kuehnle, in press) . Frequency of alcohol consumption (number of drinks per day) over a 20-day period was correlated with the three daily measures of social behavior derived from

the Behavior Inventory. Data from 11 heavy drinkers, shown in table 2, indicates that the more subjects drank on a given day the more they engaged in social interaction. On the day after alcohol consumption, however, subjects interacted less in direct proportion to the amount they drank on the previous day.

TABLE 2. Average Pearson Correlation Coefficients: Number of Alcoholic Drinks Consumed per Day Correlated With Measures of Three Categories of Social Interaction

Interaction Category	Same Day	Next Day[1]
Isolation	-.01	.09
Coaction	-.20**	.16*
Interaction	.17*	-.26**

[1]Average Pearson Correlation coefficients, next day, are means of partial correlations. The effect of the number of drinks consumed on the next day has been partialed out of the relationship.

* $p < .05$
** $p < .01$

To date research relating alcohol self-administration to changes in social interaction has not generated a consistent set of findings. Findings from a number of studies suggest that socializing increases among alcoholics during alcohol self-administration, particularly at low and moderate doses and during the initial period of an experimental drinking period (McNamee, Mello and Mendelson 1968; Griffiths, Bigelow and Liebson 1974; Thornton et al. 1976). Studies by Nathan and his colleagues (Nathan et al. 1970; Nathan, O'Brien and Norton 1971; Tracey and Nathan 1976), however, have yielded findings which are somewhat equivocal on this question. Because studies differ markedly in the nature and sophistication of methodology, it is extremely important to weigh methodological issues when seeking to integrate inconsistent findings.

METHODOLOGICAL ISSUES

Having reviewed some of the major studies of social reactions to drug self-administration, and having presented in some detail methods and findings emerging from our own research, it is fitting that a more critical evaluation of methodological issues be presented. In what follows drug self-administration studies will be discussed in terms of sampling and group composition, specification of the independent variable, dependent variables and assessment procedures, and problems related to research design.

Sampling and Group Composition

The procedure used to choose a representative subset of the population to which the researcher wishes to generalize results is commonly called sampling. Ideally, subjects should be sampled randomly from the population of interest. The absence of any allusion to random sampling procedures in the studies reviewed above attests to the relative

difficulty of employing this precaution in drug self-administration research. Because of cost, effort and ethical considerations, random sampling is rarely attempted, even from the more restricted populations of interest such as addicts or alcoholics. Another reason for the lack of random sampling is that the boundaries of the addict and alcoholic populations are unknown, so appropriate sampling frames and probabilistic methods cannot be applied. Thus nonprobabilistic procedures are the rule rather than the exception in all self-administration research conducted to date. As a consequence, inferences from such samples are risky since subjects may not accurately reflect the population itself.

In general the sampling procedures employed in these studies can be classified as either accidental or purposive. In accidental or haphazard sampling the researcher includes any cases that happen to be available from the general population of interest. This is mostly the case in studies where subjects are drawn from institutions with so-called "captive" populations. Thus prisoner volunteers have been a convenient source of recruiting marihuana users (Williams et al. 1946), and alcoholics (Nathan et al. 1970; McNamee, Mello and Mendelson 1968). Hospitalized patients undergoing detoxification or treatment have been another pool of alcoholic subjects (Griffiths, Bigelow and Liebson 1974; Thornton et al. 1976; Nathan, O'Brien and Norton 1971) and narcotic addicts (Babor et al. 1976). In two reports no information is given on methods of recruitment (Martorano 1974; Tamerin, Weiner and Mendelson 1970).

Purposive sampling involves some use of judgment by the researcher who attempts to select a representative cross section of the population. One method is to select subjects from a large pool of volunteers solicited through newspaper advertisements (Babor et al. 1974a,b; Babor et al. 1978; Tracey and Nathan 1976). These subjects are usually screened to fit into some predetermined drug use category such as casual marihuana user (Babor et al. 1974a,b) or female alcoholic (Tracey and Nathan 1976). One limitation of this procedure is that the requirements of volunteering often exclude large segments of the population who, for whatever reasons, have neither the time nor the inclination to volunteer. In the absence of statements clarifying the limits of generalizability, there is an implicit assmuption in many of these studies that the subjects sampled are representative of the group sharing their primary designation. Because of the predominance of nonprobabilistic sampling procedures, inferences from such samples should be cautious, qualified and conservative.

An issue related to representativeness is that of sample size. The studies reviewed here are based on samples ranging from four (Tracey and Nathan 1976; Martorano 1974) to 98 subjects (Thornton et al. 1976). To the extent that small sample size increases the risk of sampling bias and statistical error, this factor should be taken into account in evaluating the results. This is particularly true when the problem of group composition is considered.

With the exception of one study (Griffiths, Bigelow, and Liebson 1974), research subjects in all of these investigations were studied in groups living together in a controlled setting. Despite some rather compelling evidence (Hare 1976) that social, personality and demographic

characteristics affect, group development and functioning, researchers have generally failed to consider individual differences, either as mediating variables or as a source of statistical error variance. Reiss and Salzman (1973) define the "compositional effect" as the influence on a group of the individuals who compose the group. In much drug self-administration research it is generally assumed either that group members are equivalent on various personal, social or demographic characteristics, or that homogeneity on some factors (e.g., sex, drug use history, age) sufficiently restricts intersubject variance.

Age may be one of the most important compositional factors since differences in tolerance, dependence and value orientations tend to be age-related. Variations in age among subjects are greatest in those studies relying on accidental sampling procedures. The difference between oldest and youngest subjects exceeds 20 years in some studies (Tamer-in, Weiner and Mendelson 1970; Nathan, O'Brien and Norton 1971; Martorano 1974; Thornton et al. 1976). Personality factors may also be important since traits such as dominance, sociability and neuroticism will affect rates of interaction, interpersonal compatibility and group cohesiveness . In the only study relevant to the contribution of personality variables (Thornton et al. 1976) , it was found that the introversion-extroversion dimension did not differentiate alcoholics' social response to alcohol. However, it was reported that extroverted alcoholics socialized at significantly higher rates than introverted subjects. Conceivably, failure to match subjects or otherwise control for personality factors could lead to erroneous inferences from data comparing groups of drinkers on their social response to alcohol.

The issue of group composition becomes particularly acute when considering those studies where the results of a single group were considered alone (Williams et al. 1946; Tracey and Nathan 1976; Martorano 1974) or in comparison to another group having a different drug use history (Nathan, O'Brien, and Norton 1971). Without replications across groups of comparable drug users, it is impossible to ascertain the degree to which drug reactions interact with differences in group composition.

Independent Variables

Although optional drug self-administration is common to all of the studies reviewed, the method in which this variable is operationalized differs from one study to another. The most common procedure is to treat drug use over a period of days as a dichotamous variable. Thus comparisons are most often made between blocks of drug days and blocks of nondrug days (Martorano 1974; Tamer-in, Weiner and Mendelson 1970; Griffiths, Bigelow and Liebson 1974). This method presents some problems when there is large variability among subjects. It is also a rather gross variable which is susceptible to sequence effects when drug and nondrug blocks are not randomized or counterbalanced.

In research at the McLean Hospital an effort has been made to consider different aspects of drug self-administration as independent variables. Immediate intoxication was defined in one study (Babor et al. 1974b) by ratings on a subjective intoxication scale which correlated significantly with physiological parameters. Number of self-administrations

per day has also been used (Babor et al. in press). These measures have same advantage over the more diffuse measure of drug use because (1) they constitute continuous variables; (2) they allow a more accurate assessment of within subject variability on the dependent variable; and (3) they are more sensitive to the subject's individual pattern of drug use.

One important distinction when discussing the definition of the independent variable in these studies is that between drugs versus drug self-administration. When the subject determines the frequency, timing, dosage and social circumstances of drug administration, a number of nonpharmacological variables are introduced into the determination of drug effects. Since most of these studies fail to specify or define what they consider to be the independent variable, there is a tendency for the terms drug and drug self-administration to be used interchangeably. The importance of this distinction will become evident in discussing research design issues and the problems of interpretation and generalizability.

Dependent Variables and Assessment Procedures

The dimensions of social behavior investigated as dependent variables in these studies can be classified in five categories. While these categories by no means exhaust the social behaviors affected by drugs, they do cover some of the major variables worthy of attention. The first and most frequently investigated category is aimed at providing a gross description of interpersonal activity. Described variously as social interaction (McNamee, Mello and Mendelson 1968; Thornton et al. 1976; Griffiths, Bigelow and Liebson 1974; Babor et al. 1976b, socialization (Nathan et al. 1970; Nathan, O'Brien and Norton 1971) and social contact (Martorano 1974), this variable is often considered in contrast to the total absence of interpersonal activity. The latter condition has been defined variously as social isolation (Nathan et al. 1970; Babor et al. 1976b), no interaction (Griffiths, Bigelow and Liebson 1974) or solitary activity (Miles et al. 1974). An intermediate level of sociability, called coaction, has been employed in our research to describe parallel activity which is neither interactive nor isolated (Babor et al. 1976b; Babor et al. in press). One advantage of this latter differentiation is suggested by comparing the social reactions of heroin addicts and moderate marihuana smokers. Although both groups demonstrated less interaction during periods of chronic intoxication, the heroin addicts became more isolated while the marihuana smokers favored coaction (Babor et al. 1976b; Babor et al. in press) . As suggested previously in the discussion of heroin research, voluntary isolation may represent a social avoidance response, while coaction may merely imply greater attention to the subjective experience.

A second dependent variable investigated in these studies deals with sane of the more qualitative dimensions of interpersonal behavior. In our group interaction studies (Babor et al. 1976a; 1978) Bales' (1970) procedures were used to measure what some social psychologists consider to be the major dimensions of social behavior, namely, dominance vs. submissiveness, positive vs. negative, task orientation vs. nontask orientation. Variants of these dimensions, such as assertiveness (McNamee, Mello and Mendelson 1968), hostility (Babor et. al. 1976a)

and cooperation (Martorano 1974) have been investigated in other self-administration studies.

Subjective feelings states indicative of certain social orientations is the fourth category investigated as a dependent variable. In one study (Martorano 1974) an adjective check list was administered twice daily to measure phenomenological aspects of friendliness, warmth and abrasiveness. In another study (Tamerin, Weiner and Mendelson 1970) a modified Q-sort test was administered on five occasions to measure feelings of aggression and sexuality before, during and after a period of alcohol self-administration.

Nonverbal behavior is the fifth category of social behavior investigated. To the extent that voluntary or concious control of nonverbal behavior is minimal, it is likely to provide an even more sensitive measure of drug effects than verbal behavior. To date nonverbal behavior has not been investigated extensively in drug self-administration research, although several measures were included in the Behavior Inventory used by Babor et al. (1976b). Body orientation and eye contact were used to classify subjects as affiliating or isolated, and ratings were also made of posture and head position. As expected, the latter measures were sensitive to the acute effects of heroin. With the ready availability of video tape technology future researchers may find it fruitful to concentrate on one or several of the following nonverbal behaviors: eye contact, postural relaxation, body lean, speech intonation, touching, facial activity, hand movements and physical distance.

The procedures used in these studies are so diverse that it would be difficult to compare findings from one study to another, even when the same dependent variable, such as "social interaction," is under investigation. For those interested in conducting further research on social reactions to drug self-administration, several points should be considered when choosing dependent variables and assessment procedures. In several studies an attempt has been made to apply the measurement procedure at different times after the ingestion of the drug and during the course of repeated drug self-administration (Babor et al. 1976b; Babor et al. in press). Because the effects of drug self-administration are often cumulative, and are modified over time by tolerance and dependence, it would seem important to monitor acute as well as chronic effects. In studying social reactions to heroin self-administration, for example, it was found that a daily trend toward reduced interaction was temporarily reversed by single doses of heroin late in the addiction cycle (cf. figure 3). Similarly, changes in social interaction following single doses of marihuana were different from those observed when an entire day of drug use was monitored (cf. figure 1, table 1). As Nash (1960) has pointed out: "acute effects of a single dose of a drug may differ qualitatively as well as quantitatively from the chronic effects of repeated doses" (p. 146).

Another consideration is the use of reactive vs. nonreactive measures. Nonreactive measures are those which do not require direct participation by the subject. Structured observation, particularly when conducted at random time intervals in an unobtrusive manner, is the most commonly employed nonreactive procedure. Its main advantage is

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that the subject is less likely to modify his or her behavior as a function of the measurement procedure itself. Reactive measures, on the other hand, require some response on the part of the subject, either through performance on some task or reports of psychological processes. A disadvantage of reactive measures is that the process of measurement may generate expectancies, heighten arousal, or increase motivation, all factors which could temporarily suppress an otherwise prominent drug effect. Evidence for such an effect can be found in a study of subjective reactions to marihuana conducted by Rossi et al. (1974). Subjects who believed their mood reports would be used to assess the acute effects of marihuana gave a different pattern of response than those who believed their responses would be used to assess mood at that time of day regardless of drug ingestion.

A procedure which combines the naturalness of nonreactive measures with the greater control afforded by reactive tests is the "situational" test (Fiske 1960). Designed to evoke behavioral reactions to realistic problems, the situational test consists of a contrived situation occurring in a natural setting which requires an adaptive rather than a test response. The "human relations" discussion task used in our group interaction studies (Babor et al. 1974b; 1976a; 1978) is an example. The situation generates verbal interaction similar to that occurring in natural settings and the subjects are unaware of the purpose or nature of the observations.

A major consideration in the evaluation and selection of any measurement procedure is the extent to which it is reliable and valid. With few exceptions the procedures employed in these studies were developed by the researchers themselves or adopted and modified from the work of other researchers. Given the pervasive use of nonstandardized instruments, it is unfortunate that reliability data is lacking in all but a few (Griffiths, Bigelow and Liebson 1974; Babor et al. 1974b; 1976a; 1978) of the research reports. Similarly, there is almost total neglect in these studies of the crucial question of external and/or internal validity. In our research the validity of at least one of our behavioral categories was checked by correlating the daily frequency of "operant responding" observations with the actual output recorded on an automated counter (Babor, Mendelson, and Kuehnle 1976). Convergent validity was examined by comparing the consistency of social reactions in both formal and informal situations (Babor et al. 1976a,b; 1978, in press).

One final consideration concerning the choice and measurement of dependent variables relates to the unit of analysis. In addition to the social reactions of the individual ingesting the drug, Lennard, Epstein and Katzung (1967) have suggested the following parameters as worthy of inquiry: (1) changes in the behavior of other persons interacting with the intoxicated person; (2) changes in the structure and process of the group; (3) the extent to which characteristics of the group mediate the behavior of the subject; and (4) the extent to which changes in the subject's behavior are perceived by other group members.

Research Design

The ostensible purpose of research design is to control or minimize the effects of extraneous variables so that changes in the dependent

variable can be clearly observed and causal inferences can be made unambiguously. The design feature common to all of the drug self-administration studies reviewed here is repeated measurement of social behavior over an extended period of time. With one exception (Thornton et al. 1976) each study attempts to compare the subject's behavior during drug self-administration to that same subject's behavior during periods when the drug is not available. Although repeated measurements and within-subjects comparisons are acceptable procedures, they contain certain inherent limitations. If these problems are not controlled or eliminated by use of commonly accepted experimental precautions, they can introduce needless error variance and experimental bias into the results, and seriously compromise the validity and generalizability of the findings. The major design problems which plague many drug self-administration studies, particularly those focusing on social behavior, will be discussed in terms of control group comparisons, sequence effects, social system phenomena, sample size and placebo effects.

An elementary if not essential feature of good scientific research is the use of a control group or control condition as a standard of comparison for the experimental treatment. While all of the reviewed studies have made some provision for comparing behavior under conditions of drug availability (experimental) and drug unavailability (control), many of the designs are compromised by problems related to the sequential order in which conditions are presented. The sequence common to many self-administration studies consists of a predrug or baseline phase, a drug availability or drug self-administration phase, and a postdrug or drug withdrawal phase. The rationale for this abstinence-drug-abstinence design is not clearly explained by most researchers but two considerations appear to be paramount.

The first is that the sequence of conditions resembles the standard ABA design in which an experimental treatment (B) is interspersed between one or more control conditions (A). This design permits the researcher to logically detect linear effects caused by extraneous factors such as learning, maturation, habituation, order of presentation, repeated testing, the mere passage of time, or familiarity with the experimental procedures. Examples of linear trends resulting from extraneous factors can be found in the results of several studies (cf. Miles et al. 1974; Babor et al. 1974b; Nathan, O'Brien and Norton 1971; Tracey and Nathan 1976). In the study by Nathan, O'Brien and Norton (1971) attendance at the ward bar, a dependent measure of socialization, increased progressively during the study regardless of phase (predrinking, drinking, postdrinking) or condition (isolation vs socialization). Similarly, the four subjects in the Tracey and Nathan (1976) study progressively increased spending to purchase time spent out of their rooms, possibly because confinement became more aversive during the course of the 33-day study period. Although the inclusion of predrug and postdrug control conditions can assist with the detection of linear trends, only a crossover or randomized blocks design can completely control for this source of bias. This was achieved in the design used by Griffiths, Bigelow and Liebson (1974), who randomly distributed days of ethanol availability with an equal number of ethanol nonavailability days.

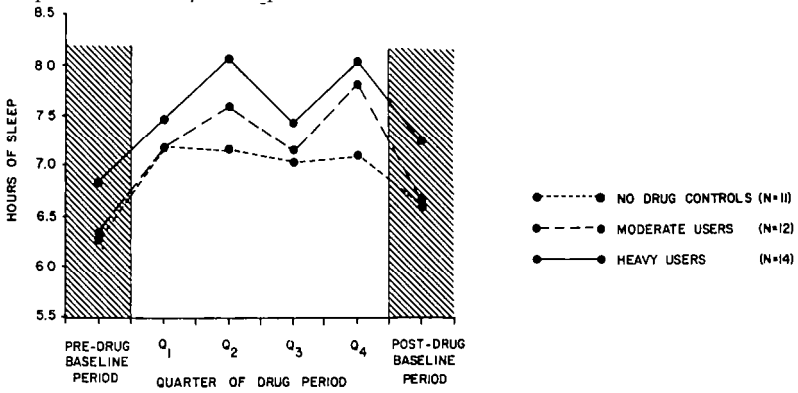
The second ostensible rationale for the pervasive use of the abstinence-drug-abstinence design is that in many ways it simulates the actual conditions of drug self-administration and withdrawal resulting from use of dependence-producing drugs like alcohol and heroin. With experimental induction of the addiction cycle, however, the researcher is left with three distinct conditions (abstinence, drug, and withdrawal), and the problem of sorting out the effects of order and sequence again becomes a serious methodological issue. This problem can be overcome to some extent by the addition of another abstinence period following the cessation of withdrawal symptoms (cf. Babor et al. 1976a,b).

Another design feature which provides a better estimate of extraneous sources of experimental bias is the inclusion of a no-drug control group. Ideally the control subjects should be studied under conditions identical to those of the experimental subjects, including optional access to drug self-administration. This was accomplished to a major extent in only two studies (Thornton et al. 1976; Babor et al. in press) . In the Thornton et al. (1976) study subjects who did not avail themselves of the opportunity to drink served as a control group. One problem with this method of selecting control subjects, however, lies in the very fact that these subjects voluntarily refused alcohol. This in itself (and not the absence of alcohol per se) may have constituted the characteristic distinguishing them from those who chose to drink, and may have contributed in part to the observed differences in socialization. This problem was overcome in a study of moderate and heavy marihuana smokers (Babor et al. in press) where both control subjects and control conditions were employed. Control subjects were selected from participants in an ethanol self-administration study. These subjects, comparable in background characteristics to the moderate marihuana smokers, also were exposed to an identical sequence of control and experimental conditions (predrug, drug, postdrug). To control further for the minimal amount of alcohol ingested by these subjects, observations occurring within an hour after drinking were eliminated from the analysis. An unquestionable advantage of this procedure is illustrated in Figure 4 which shows five-day means of daily sleep time for control subjects and marihuana subjects. Had only the marihuana smokers been included in the analysis, the data might have suggested that chronic marihuana smoking, rather than confinement on a clinical research ward, is associated with increased sleep during the middle period.

One design feature sorely lacking in these studies is the use of either a placebo control group or placebo control condition. The use of a placebo is essential if the researcher is interested in differentiating between reactions mediated by the pharmacological action of the drug, on the one hand, and that deriving from such nonpharmacological factors as suggestion and expectancy on the other. Because researchers have been interested in rather gross social reactions, they have perhaps not felt the need to examine the extent to which acute doses precipitate placebo reactions. Further, it can be argued that the utility of placebos in such research would be vitiated by the possibility that experienced drinkers and drug users would quickly detect the absence of pharmacological effect during repeated self-administration trials. This indeed proved to be the case in double blind studies of heroin self-administration under either

FIGURE 4

Averages of daily sleep time for successive 5-day blocks (excluding day 26) of 31-day marihuana self-administration study. Sleep data obtained by means of hourly observations. Mendelson and Kuehnle, in Psychopharmacology, 50:11-19, 1976. Copyright 1976. Reprinted with permission of the publisher.



blocked (naltrexone) or unblocked conditions conducted at McLean Hospital. It did not take many heroin challenges before subjects receiving naltrexone realized that they were, in effect, the unfortunate members of the placebo control group. A more feasible alternative to the placebo control group would therefore be the placebo control condition. Placebo doses of marihuana, alcohol or heroin could easily have been distributed randomly among the actual doses available to research subjects. By carefully observing or measuring the responses to these doses, researchers would be in a better position to estimate the contribution of nonpharmacological factors to both acute and chronic reactions. Major problems of interpretation could also be avoided. as exemplified-in the data presented in figures 1 and 3, and tables 1 and 2. While acute and daily doses of heroin. marihuana and alcohol were found to be associated with systematic changes in social behavior, it was impossible to ascertain how much subjects were responding to psychological expectancies, social rituals, and other factors related to recreational drug use. The pervasive tendency for interaction to coalesce around drug self-administration, and for recreational activity to coincide with the period of maximum intoxication, constitutes a major interpretational problem.

Without the benefit of a placebo condition researchers risk confounding drug effects with the psychosocial factors surrounding the act of drug self-administration. A growing body of evidence suggests that such factors can exert a profound influence on the manifestation of both drug effects and placebo reactions. One of the first psychologists to identify these sources of confounding is Vincent Nowlis (Nowlis and Nowlis 1956; Nowlis 1958; 1960). In studies of subjective and behavioral reactions to various drugs Nowlis often observed a contagion of mood and behavior among subjects undergoing testing in a group setting. The influence of the group on drug effects has also been noted

by others. Fiske (1960) has observed that "the group tone or atmosphere exercises a major constraint on the subject's dispositions" (p. 317), while Nash (1960) points out that this "special form of suggestion may give rise to error when subjects are examined in groups" (p. 141). Nowlis and Nowlis (1956) argue that since this source of error cannot be controlled in group settings the group itself must be considered the unit of analysis. In the McLean Hospital studies of marihuana, heroin and alcohol self-administration various statistical procedures have been employed to analyze this phenomenon. When cluster analysis was applied to daily measures of operant work output, physical activity, mood state, hours of sleep and the three levels of social behavior, it was found that marihuana smokers clustered uniformly according to the groups they were studied in. The tendency for individual behavior to covary in group settings has received little research attention, but it is likely the result of a social influence process which includes behavioral contagion, social facilitation and conformity pressures. Of all the self-administration studies reviewed, only one attempted to control for this factor by running subjects consecutively rather than concurrently (Griffiths, Bigelow and Liebson 1974). In drug self-administration studies conducted at the McLean Hospital analysis of variance is applied routinely to test for differences across groups exposed to similar treatment conditions. If drug effects are more consistent within than between groups it is likely that social factors are mediating the manifestation of drug effects. In one study (Babor et al. in press) significant drug X groups interaction effects were noted in analyses of each of the three indices of social behavior (isolation, coaction, interaction). Only in the case of interaction was there a consistent directional variation across all study groups. Although percent daily interaction decreased in each of three moderate user groups during the drug period, the greatest decrements occurred in groups which interacted most during the predrug baseline. Among heavy users, some groups showed significant increases while other groups, paradoxically, showed significant decreases.

The potential sources of experimental error and confounding associated with group composition, group development and behavioral contagion pose a serious challenge to those who would investigate social reactions to drug self-administration. In those studies where these factors were neither acknowledged nor controlled the validity and generalizability of the findings can be seriously questioned. This is particularly true of studies reporting the results of only one group of subjects (Williams et al. 1946; Miles et al. 1974; Tracey and Nathan 1976; Martorano 1974), since there is no way of replicating findings across groups. It should be emphasized that while repeated measures on the same subjects increase the reliability of measurement, this in no way affects the degree to which the results are generalizable to the broader population of interest. As Nash (1960, p. 137) points out: "The fewer subjects selected from a given population, the smaller the likelihood of a given drug effect being detected, and the less precise is the estimate of that effect . . . the investigator's energies are more richly rewarded by an increase in the number of subjects selected than by a corresponding increase in the number of observations collected per subject."

Failure to control for extraneous sources of variance can render the dependent measure relatively insensitive. For example, three studies by Nathan and his associates (Nathan et al. 1970; Nathan, O'Brien and Norton 1971; Tracey and Nathan 1976) failed to establish any consistent relationship between ethanol self -administration and preference for socialization, as measured by time spent working on an operant work device. A recent review of this research (Griffiths, Bigelow and Liebson, in press) pointed to a number of extraneous factors which could have interfered both directly and indirectly with the subject's preference for socialization while under the influence of alcohol. These include locating the operant task in the subject's private room, permitting subjects to allocate point earnings for the purchase of both ethanol and time out of social isolation, the sharing of drinks among subjects, and the effects of accumulating surplus points on subsequent socializing. To the extent that these design limitations constitute sources of error variance, it is not surprising that the researchers failed to find a relationship between ethanol and socialization.

To some extent inefficient design features and small sample size can be compensated by the judicious use of established statistical procedures in conjunction with accessory information. For example, differences in baseline (predrug) measures of social behavior or personality can be corrected by means of analysis of covariance or by use of difference scores. Analysis of variance can be used to partition the variance associated with drug self-administration from that associated with differences between study groups. Trend analysis can be applied to detect systematic variations associated with the passage of time (e.g., linear trends) and with the introduction of the experimental condition (e.g., curvilinear trend). One alternative to merely aggregating data across subjects and conditions is to use correlational procedures to relate each subject's drug self-administration pattern to his or her dependent measures (cf. tables 1 and 2). Partial correlations can be used to control for known sources of bias, and coefficients can be summed across subjects to determine the magnitude and consistency of the effect. Another correlational procedure which could be applied to the analysis of equally spaced repeated measurements in drug self-administration research is autocorrelation (Huba et al. 1976). By providing knowledge of the serial dependency structure of the time series, autocorrelation can quantify longitudinal stability and help to detect cyclical fluctuations. To date these statistical procedures have been used sparingly, if at all. Several studies failed to report statistical analyses of social measures even when quantitative data was collected (Nathan et al. 1970; Nathan, O'Brien and Norton 1971; Tracey and Nathan 1976).

CONCLUSION

In this paper an attempt has been made to deal with the pitfalls as well as the potential benefits of studying social reactions to drug self-administration. Having reviewed some 30 years of drug self-administration research, the scientific purist might be tempted to conclude that not much has been learned beyond how to confound drug effects with error variance. In a discussion of basic principles of research design, Nash (1960) distinguishes between <u>essential</u> features which must be incorporated into a scientific experiment, and <u>economic</u>

design features which merely increase the efficiency of experimentation. Cited as essential design features are elimination or segregation of any factors which introduce bias into the experiment; comparison of drug-related observations-with those obtained under control or standard conditions; representative sampling; random assignment to treatment conditions; fulfillment of the assumptions underlying the analysis of variance. Applying these criteria, few of the studies reviewed would seem to qualify as scientific experiments. While a number of interesting findings have emerged from these studies, there has been a tendency to confuse covariation with causal relations, if not by the researchers themselves, then by those who cite the findings in support of some hypothesis. Before definitive statements can be made about the relation between drugs and social behavior, researchers will have to provide a sufficient demonstration of the nonspuriousness of these covariations.

There is no doubt that mundane realism is accomplished at the cost of experimental efficiency, but all too often researchers have used the self-administration paradigm as a license to dispense with some of the most conventional precautions of good social research. In part, this state of affairs can be attributed to the fact that the social assessments included in many of these studies were ancillary to the major purpose of the research, which was typically focused on detecting the biomedical concomitants of chronic drug self-administration. Nevertheless, there is no intrinsic reason why interdisciplinary research could not be designed so as to satisfy the criteria of "good science" at each level of analysis.

All this is not to say that the studies we have reviewed have been done in vain. Considering the descriptive nature of much of this research, it can be said that its value lies in providing an elementary comprehension of the relation between drug self-administration and social behavior. It appears that single and repeated doses of marihuana and heroin result in a general suppression of social interaction. Interestingly, unlike marihuana, chronic heroin intoxication is associated with almost total withdrawal from the social environment. In the case of alcohol self-administration by alcoholics, the evidence suggests that socializing increases during the early stages of drinking but at higher doses or with prolonged drinking social withdrawal may occur. These studies have also been instructive in suggesting the possible mediating role of affective states, physiological mechanisms, biochemical alterations, personality variables and the prevailing social environment.

Unfortunately, there has been little attempt to go beyond descriptive statements to the level of integration and analysis. Furthermore, the hypothesis generating value of this research has not been generally exploited. One notable exception to this statement is the work of the Baltimore City Hospital group. Following their study demonstrating an association between ethanol self-administration and increased social interaction (Griffiths, Bigelow and Liebson 1974), it was hypothesized that the reinforcing social consequences of drinking may be one of the factors maintaining drinking behavior. A subsequent series of related experimental studies resulted in a confirmation and elaboration of this hypothesis (Griffiths, Bigelow and Liebson 1975; 1977). By moving from the descriptive, hypothesis-generating stage to a more

experimental, hypothesis-testing approach, this research illustrates the potential contributions of self-administration research. But until researchers begin to demonstrate greater interdisciplinary coordination, experimental sophistication and sensitivity to the complexity of factors affecting human social behavior, the potential contributions of drug self-administration research will not be realized.

ACKNOWLEDGMENT

The writing of this paper was supported in part by Research Scientist Development grant 1 K01 AA 00025-01

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II. Food and Tobacco

Chapter 11

Defective Long-Term Caloric Regulation in Obesity

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INTRODUCTION

Our methods for the study of overeating were first devised for investigations of ingestive behavior in animals but have been applied now to the study of humans.

We began our work in an attempt to test the assumption that the ventromedial hypothalamus is a "satiety center" (McHugh, et al. , 1975; McHugh, Moran, and Balston, 1975; McHugh and Moran, 1977; and in press). This commonly held idea derives from the observed change in feeding behavior that follows destruction of the ventromedial hypothalamus. Animals with such neural lesions overeat and grow fat. The seemingly logical assumption that the overeating was a result of a disturbance in satiation is susceptible to direct testing. If satiety is viewed as an inhibition on feeding produced by food itself, then a graded inhibition of feeding should follow the intake of nutrients. If there is a disorder of satiety then the inhibition produced by a given nutrient quantity should be less than normal. To study this question, we installed chronic intragastric cannulae through which nutrients can be infused directly into the gastrointestinal tract in normal and hypothalamic hyperphagia monkeys.

ANIMAL EXPERIMENTS

These rhesus Monkeys weighing from 4 to 8 kgms were trained to take all of their food in the form of Purina Monkey Chow in a 4-hour period. Prior to the feeding period we infused a nonnutrient solution (saline) or 135, 270, or 540 ccs of a nutrient (Carnation Instant Breakfast in milk) containing 1.1 kilocalories per cc. The reduction in food intake produced by the nutrient was graded in a dose response fashion. The crucial observation, however, was that no differences between normal and hypothalamically lesioned monkeys were found. Both groups showed an identical reduction in feeding for each nutrient infusion. Thus the overeating with hypothalamic lesions cannot be attributed to a loss of satiety as we defined it. However, when chow and infusions were converted to calories, we

found that the overeating animals were consuming 850 + 25 kilocalories of Purina Monkey Chow per day. Infusing Carnation Instant Breakfast into their stomachs reduced the chow they ate in a quite precise way. Specifically, we found that the total calories (chow eaten plus calories infused) did not change significantly from 850 ± 25 kilocalories. This result indicated that the total calories taken each day was quite precisely regulated and that feeding was controlled by a graded satiety signal to maintain this regulation.

By employing the same paradigm of intragastric infusions prior to meals, we demonstrated this capacity for the precise regulation of caloric intake in normal monkeys. The precision could be demonstrated in a range of caloric infusions from 0 to 300 Kcal. This relationship was sustained whether the infusions were given 0-20 hours before meals and whether the infusions were of fat, protein, or carbohydrate.

These results in the normal and the overeating, hypothalamically lesioned monkey demonstrate that both appear to be regulating a caloric intake and maintain that intake over a range of preloads. The level maintained need not be physiologically appropriate, since the overeating animal is rapidly gaining weight. However, the precision of behavior is impressive and suggests the search for similar precision in the feeding behaviors of humans.

HUMAN EXPERIMENTS

The literature on human feeding is contradictory. Some investigators report that humans can, and others that they cannot, compensate for extra calories given as preloads (Wooley 1971; Wooley et al. 1972; Nisbett 1972; Spiegel 1973; Schacter and Rodin 1974; Hunt et al. 1975; Booth et al. 1976; Hibscher and Herman 1977). We decided to carry out our own investigation in subjects who had applied for a weight reduction program but had not lost more than 5 pounds of weight. Subjects were all at least 20 percent overweight; average weight was 250 pounds. The average age was 42. Subjects were volunteers for this research program and were provided with full informed consent. (For further information on the subjects, see table 1.) A normal control group was taken from the community and was matched for age, sex, and social class.

TABLE 1

Sample Short-Term Regulation

Dx	N	Age	Wt.	Ht.	Hours Fasting
Obese	34	42	231	65	6
Controls	15	42	146	65	5

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All the subjects were asked to fast for 5 hours before the test, which was conducted in the evening at the weight reduction class. The subjects were asked to participate for two sessions on successive weeks. On both weeks, self-rating visual analog scales for hunger and fullness were filled out before and after the test meals (Robinson, McHugh and Folstein 1975; Folstein et al. 1977). During the first session, the subjects were required to ingest 400 ccs of Carnation Instant Breakfast and whole milk with a caloric value of 540 calories. During the second session, they were asked to take 400 ccs of Carnation Instant Breakfast and milk containing a total caloric value of 270 calories. Fifteen minutes after these mandator-y meals, the subjects were given the opportunity to approach a table on which were cups containing 200 ccs of the same Carnation Instant Breakfast solution that they had ingested in the mandatory meal. Subjects were instructed that they could ingest as much or as little from these cups as they wished. A comparison was drawn between their caloric intake of the concentrated and of the dilute nutrient.

This method was similar to that employed in our monkeys study where we also investigated feeding after a standard known preload, and where the total calories taken were estimated. There are some important differences between the two experiments, however. The nutrient used as the preload and that ingested in the "meal" were the same in the human experiment rather than different as in the monkey study. The human subjects ate in a group setting. There was no attempt to estimate the calories taken before the test, although the subjects were asked to fast for 5 to 6 hours prior to the start of the study. Also, both the preload and the feedings were orally ingested rather than one being infused intragastrically.

Despite these differences in design, the results obtained were similar. Both normal and obese individuals control their caloric intake in response to the calories ingested in the preload. In an effort to observe the accuracy of this reduction, we devised a method to estimate the individual's error in caloric regulation. If there were a perfect control, subjects should take as many calories in dilute form as in concentrated form. Accordingly, we established the following ratio: Calories taken in concentrated form minus those taken in the dilute form divided by the calories in the concentrated form. This ratio provides an error rate (multiplying this by 100 would give a percentage) which can be applied to both individuals and groups.

The error rate for the normal individuals was less than 1 percent. That for obese individuals was 4 percent. Also, we noted that there was no statistical difference in the obese group between the calories taken with the concentrated or the dilute preload (table 2).

TABLE 2

Normal Subjects Regulate Calories

Preload Concentration	Calories Ingested	Volume Ingested	Error
1.1 Kcal/cc	649 ± 61	590 ± 55 cc	
.78 Kcal/cc	651 ± 54	838 ± 69 cc	-.3%

Normal subject ingested the same number of calories of each concentration. But more volume of the dilute nutrient was ingested.

Obese Subjects Regulate Calories

Preload Concentration	Calories Ingested	Volume Ingested	Error
1.1 Kcal/cc	723 ± 41	657 ± 50 cc	4%
.78 Kcal/cc	752 ± 39	965 ± 35 cc	

Similarly obese subjects ingested the same number of calories of each concentration and thus ingested a greater volume of the dilute nutrient. However obese subjects ingested more calories than normal subjects 723 vs. 649.

The analog scales for hunger and fullness for both the normal and obese reflected the accuracy of the regulation. Whether the preloads were in the concentrated or dilute form, both the normal and the obese individuals reported that similar calories had similar effects on their hunger and fullness (table 3).

Next we observed the effects of increasing the delay between preload and feeding upon caloric regulation. In this "long- term" experiment the subjects were asked to eat only Carnation Instant Breakfast for 3 days and return to us the empty packages to determine how much they had eaten (table 4). At the end of day 1, when they ingested as much as they wanted, normal and obese subjects were asked to ingest an extra 1000-2000 calories of the mixture of Carnation Instant Breakfast and milk before going to bed. On the days following, their caloric intake of Carnation Instant Breakfast was documented. Prior to each meal subjects were instructed to fill out analog scales of subjective hunger. Ratings were made each day during the 3-day course of the experiment.

The results of the chronic experiment were different from those seen in the acute study. Normal individuals again reduced their ingestion on the days after the excess of calories was given. Obese subjects, on the other hand, ate just as much on the days after the excess calories. This finding demonstrates that there was no effect

TABLE 3

Analog Scale Rating of Hunger and Fullness

Preload Concentration	Normal Weight Change in Hunger	Normal Weight Change in Fullness	Obese Change in Hunger	Obese Change in Fullness
1.1 Kcal/cc	58	51	28	35
.78 Kcal/cc	57	57	32	37

TABLE 4

Sample Long-Term Regulation

Dx	N.	Age	Weight	Height
Obese	35	37	231 ± 9	65 ± 6
Normals	16	43	153 ± 4	66 ± 7

TABLE 5

Calories Ingested

	Day 1	Evening Preload	Day 2	Day 3
7 Normals	2501	1000	1927	1927
9 Normals	1886	2000	1107	1558
23 Obese	2839	1000	2788	2710
12 Obese	3485	2000	3998	4100

TABLE 6

Morning Hunger

	Day 1		Day 2	Day 3
Obese	64	-ns-	55	66
Normals	90	-.001-	42	80

of the extra calories on ingestion (table 5). Furthermore, the obese individuals did not show a significant change in their hunger reports on the days after the excess, as did the normal weight controls (table 6).

In summary: Whereas precise caloric intake occurs in normal and obese individuals on an acute basis, obese subjects do not maintain caloric regulation when there is a long overnight delay between the preload and the subsequent meals.

DISCUSSION

These studies demonstrate a potential for accurate caloric regulation in human beings similar to that observed in our monkey experiments. We cannot say anything at present concerning the physiological importance of this regulation. However, a difference emerges between normal and obese subjects. Obese subjects showed a small short-term error. More important. however, they exhibit a large long- term error. Preloads of up to 2000 calories given the night before were shown to have no effect on ingestion on the next day.

These differences between short-and long-term control may in part explain some of the difficulties in interpreting the literature on obesity. The time intervals between preloads and feeding behavior and sleep may be critical variables.

It is possible, however, to demonstrate a major difference in the feeding controls of normal and obese individuals. This difference may or may not be a causal factor in obesity. Further studies of both thin and obese individuals are needed to determine the significance of caloric regulation in onset and maintenance of obesity.

ACKNOWLEDGMENTS

The work reported in this paper was supported by National Institute of Health grants 14327-01 and Rol AM 19302-03.
We acknowledge the tireless work of M. Simonson and T. Moran, who collected the data.

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Chapter 12

Methods and Findings in Study of Food Regulation in Obesity

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OBESITY AND SUBSTANCE ABUSE

The classification of obesity as a form of substance abuse poses an immediate problem regarding the definition of abuse. Presumably, somewhat different problems occur with respect to the definition of abuse of alcohol, tobacco, and drugs, since, if increased risk to physical or mental health is taken as a criterion, virtually any use of these substances is undesirable. Cultural definitions of abuse show an imperfect and often delayed relationship to medical Knowledge of associated health risks. In practice, however, it is not difficult to isolate cases of drug, alcohol, or tobacco abuse which clearly merit investigation or intervention, and the problem of arriving at a precise definition of the degree of substance use which should constitute a therapeutic target can be postponed.

In the case of obesity, the problems surrounding definition of substance abuse are absolutely fundamental. If increased actuarial health risk is taken as the criterion, virtually all overweight people are classified as abusers. However, in contrast to the cases of smoking, drinking, or drug use, it frequently proves impossible to detect anything unusual in the substance consumption patterns of a group selected under this definition. Decades of investigation have failed to show that, on the average, the obese eat any more than people of normal weight or have a distinctive pattern of food consumption.

Much interest was generated in the configuration of meal eating patterns by the report that restriction of access to food to a single time interval per day preceeded weight gain in the rat without increased caloric intake. (Tepperman and Tepperman 1964; Cohn and Joseph 1959; Cohn 1961). Early surveys of eating patterns of the obese had called attention to patterns of meal skipping, concentration of eating in evening hours and irregular timing of meals (Schachter and Gross 1968; Mayer, Monello, and Seltzer 1965). When scrutiny of eating patterns in behavior modification programs revealed these features, as well as rapid eating, eating in the absence of hunger, frequent snacking, etc., it was assumed that eating patterns would be "normalized" by teaching patients to eat slowly three regular meals a

day. However, further study has shown that eating patterns of the lean are as varied and erratic as those of the obese. Statistical comparisons on a multitude of dimensions, measured both in naturalistic observations and taken from food diaries, have failed to isolate any reproducible differences in eating styles of the obese and nonobese (Kissileff, Jordan, and Levitz 1977; Player, Stunkard, and Co11 1977) It is clearly possible that subtle but important variables have been overlooked or that the important obese-normal differences occur over longer time spans than typically studied, but until such discoveries are made, obesity must be regarded as a deviant consequence for which no deviant antecedent behavior is known.

Social definitions of food abuse are particularly arbitrary. Consumption of most ordinary foods by the overweight is socially disapproved, while exceedingly high intake in the absence of overweight is not judged inappropriate. Indeed, overeating is at the heart of many of our social customs. Interestingly, the numerous forms of malnutrition and dietary imbalance in adults created by weight consciousness and food faddism in our culture also escape social disapproval, although these patterns probably carry significant health risks and are a subject of immediate concern when observed in children and, to a lesser extent, adolescents.

Finally, one could define abuse of food in terms of behavioral departures from population averages. It can be inferred that application of a quantitative criterion would result in the isolation of a group containing lean and overweight people roughly in proportion to their numbers in the general population (Garrow 1974; Johnson, Burke, and Mayer 1956; Hampton et al. 1967; Stefanik et al. 1961; Kissileff, Jordan, and Levitz 1977). A criterion of qualitative abnormality would lead to the detection of peculiarities of eating behavior, some associated with obesity, and some which lead to no maladjustment other than the potential for being regarded as eccentric in addition to the clinically defined “eating disorders” which are associated with emotional distress (usually on the part of the patient, though occasionally only by those around him). Extreme binge eating, waking to eat during the night, refusing food, and regurgitating after eating are some of these. The latter is of special interest because it appears to be on the increase. It is possible that publicity has merely increased the detection rate, but recent studies have reported very high incidence rates in college females (Boskind-Lodahl 1976). Clearly this is abuse of food in the most literal sense of the word, but is a behavior adopted primarily to achieve social conformity by controlling weight. Eating disorders are of great intrinsic interest and their careful study may be useful in understanding normal regulation and more subtle regulatory defects. With the exception of the bulimarexic syndrome, however, they are relatively rare and do not have the priority of importance of obesity. Indeed, in many instances, eating disorders seem to be the outcome of attempts to control or prevent obesity and may be counted among the unfortunate results of our ignorance about obesity itself.

OBESITY AS AN ERROR IN REGULATION

The difficulty with which researchers must contend is that obesity represents an error in regulation which may be quite small - too small to be detected by many of the methods of measurement which have been developed. Periods of imbalance leading to weight gain may be restricted to a relatively short time period in an individual's life span, with normalization during static obesity. Finally, it is unclear what form most regulatory errors take, and there may be several subtypes which cause obesity.

The first type of error, which is usually assumed to be the main cause of obesity, is an increase in food intake above normal levels while energy expenditure remains constant. It should be noted that increased food intake does not automatically lead to weight gain. Studies of overfeeding have shown that lean volunteers nearly always fail to gain at expected rates and a few gain nothing at all on dietary increases as high as 1,500 calories a day given for periods of many weeks (Miller and Mumford 1966; Miller, Mumford, and Stock 1967; Sims et al. 1968; Ashworth et al. 1962). It has not been possible to account for differences in rate of weight gain by variations in spontaneous motor activity. Individual differences in thermogenic responses to food are considered the most likely explanation, i.e., diet-induced waste of calories through production of excess heat.

Thus, increased food intake within a particular range will lead to weight gain only in predisposed individuals. In searching for the causes of increased food intake which lead to weight gain, a tentative distinction should be made between an initial gain to a given level of obesity and regain of weight lost after cessation of diets. While the processes may be similar, there are reasons to suggest that they may not be. Initial gains may involve proliferation of fat cells, while later gains involve only increases in cell size. The process of weight loss may have effects on subsequent behavior and physiologic responses to food. Since dieting by definition requires that the person ignore internal signals of hunger and satiety, important conditioning processes may be affected. Meal patterns and food preferences may be permanently altered. The effort of dieting may produce an obsessive preoccupation with food or an intention to self-starve which leads to binge eating. Naturally, not all gains occurring after weight loss are due to unusually high food intake, since severe caloric restriction may lead to decreases as high as 20 to 30 percent in basal metabolic rate (Wiley and Newburgh 1931; Howard et al. 1977) which are not reversed immediately with refeeding. Thus, weight is often regained during periods of relative hypophagia. For these and other reasons, prospective studies of the development of obesity are to be much preferred to studies of static obesity or weight regain. They are, of course, exceedingly hard to do.

The second major type of regulatory error is a decrease in energy expenditure while food intake is held constant or at "average" levels. Decreased physical activity in middle age is widely held to be a significant cause of obesity. As Warwick, Toft, and Garrow

(1977) note, individual differences in metabolic rate within the "normal" range may account for differences as great as 700 calories per day in individuals, without measurable differences in gross motor activity or food intake. Finally, the fact that obese and nonobese groups are found to have equal caloric intake is not incompatible with obesity, even if the groups are assumed to have identical levels of physical activity, since any group of obese subjects will contain a sizable proportion of individuals who have recently been or are on low calorie reducing diets at the time of the study. These individuals will have diet-induced reductions in resting metabolic rate, so that the energy expenditure of the obese sample is almost of necessity lower than that of the lean control group. What remains to be explained is why intake is not adjusted to lower levels of expenditure, as evidently occurs in people who maintain a stable weight despite presumed fluctuations in activity.

Finally, there is a third kind of regulatory error in which neither activity level or food intake differs from average, but there is a bias in the metabolic system toward increased fat storage. It has been shown, for example, that genetically obese Zucker rats deposit more fat in the first week of life without accompanying hyperphagia (Boulange, Planche, and de Gasquet 1977). Presumably there is the potential for considerable variation in how much energy is wasted and how much is conserved. Obesity of this type may have no behavioral antecedents.

METHODS OF MEASUREMENT

Methods for studying energy expenditure are obviously of great importance, but fall outside the scope of this paper. It is worth noting, however, that simple measures of resting metabolic rate show important relationships to changes in diet and should probably be included in more studies. Adequate measurement of energy output during normal activity is exceedingly difficult. The best systems are too cumbersome and obtrusive for extensive use, while the more practical continuous monitoring of heart rate has been reported by Dauncey and James (1977) to have very large measurement errors when used in relatively sedentary individuals. Experience in using activity diaries in patients suggest that compliance is quite good, and such diaries should perhaps at least be used in research designs in which subjects serve as their own controls. A convenient system is found in the Jordan-Levitz manual for analysis of food intake and energy expenditure.

Development of methodology for study of eating behavior in humans has met with many problems which have made it difficult to test the generalizability of results of animal experiments. In addition to the obvious limitations on the kinds of manipulations which can be performed on humans, simple measurement of hunger and food intake has proved complex. Humans have rather definite expectations about how much of what kinds of foods should be eaten at what times, and, in addition, typically think about of the meaning of their behavior in experimental settings. Thus, in the series of experiments by Schachter and his colleagues, reduction in subsequent intake following experimental meals was taken as evidence of sensitivity to internal

cues on the part of nonoverweight subjects (Schachter 1968). However, using essentially the same experimental design but with the caloric content of the preloads disguised, it was found that neither obese nor lean subjects adjusted intake to the actual calories of 200 versus 600 calorie preloads (Wooley 1972). Instead, both responded to the apparent calories, manipulated by appearance and mode of presentation. Speigel (1973) obtained the same results using disguised liquid preloads varying in caloric density from .25 cal/ml to 1.8 cal/ml; Wooley, Wooley and Dunham (1972a) found cyclamate and glucose solutions to have indistinguishable effects on hunger ratings and liking for sweet solutions, both producing greater subjective satiety at higher concentrations. These results strongly suggest that in this experimental paradigm short term adjustments to undisguised food preloads by lean subjects are attributable to cognitive and sensory factors.

The failure of obese subjects to reduce intake following preloads requires another kind of explanation. Given the knowledge or belief that they have already consumed a substantial quantity of food, why don't obese subjects respond by a reduction in additional food intake as do lean subjects? A probable answer to this question lies in the findings of Herman and Polivy (1975) on disinhibition of dietary restraint. These investigators found that subjects who were selected for a history of chronic dieting ate more, not less, following preloading with rich foods such as milkshakes. Consumption of a forbidden food made them feel that they had already violated their planned control and had nothing to lose by eating more. Obese samples selected without regard to this variable usually contain high proportions of restrained eaters. Statistical averaging of their tendency to eat more after experimental preloads with the more normal responses of unrestrained obese subjects usually leads to a finding that the preloads have either no effect or a statistically insignificant increase.

To determine whether subjects could perceive differences in caloric values of foods eaten when this was made the explicit experimental task, Wooley, Wooley, and Dunham (19724) asked subjects to guess whether they had eaten a high or low calorie liquid meal given on a random schedule over twenty successive days. Hunger ratings and guesses were made at fixed intervals during the twenty-four -hours following each experimental meal. At no point in time were subjects' guesses better than chance. Hunger ratings were related to guesses about the caloric content of the meals, whether correct or incorrect, and showed a cyclic relationship to mealtimes, the latter possibly also influenced by expectations.

Do these findings mean that there-is no short term regulation in humans? Not necessarily. There are two reported studies in which short term effects of disguised preloads on subsequent intake have been observed demonstrating that such regulation can occur and will be observed, when the experimental conditions are right (Booth, Campbell, and Chase 1970; Booth, Chase, and Campbell 1970). Unfortunately, comparison of described procedures provides no clue as to what was done differently in these experiments than in those with negative outcomes. One can only conclude that intake of an experimental meal

in a laboratory is a rather unstable dependent variable, susceptible to extraneous influences which are not easily controlled. The same criticism can be made of hunger ratings; but, beyond this, even the logic of hunger ratings is open to question, since there is an implicit assumption that hunger exists as a continuous subjective experience which is correlated with hours of deprivation and unrelated to external stimuli. Common sense suggests this is not true. For example, a few additional minutes of food deprivation cannot account for the increase in hunger experienced as one puts down a difficult piece of work and prepares to leave for lunch. Indeed the thought and sight of food produce marked physiologic changes. These conditioned responses anticipatory to food ingestion are logically viewed as a component of hunger but are clearly situational. l-lunger is perhaps best defined as the probability of having an appetitive response in the presence of food stimuli. The sensitivity of hunger ratings would doubtless be improved if they were obtained under conditions standardized with respect to imagined or actual food cues, preferably with reference to hunger for a particular food or set of foods. Booth (1976) has found subjects' ratings of how much they would like to eat of each item on a list of foods to be a sensitive measure of hunger and satiety.

New Approaches to Study of Appetite Regulation

To avoid the problems inherent in use of subjective ratings and intake of conventional foods in laboratory settings, three new approaches to the study of appetite regulation have been developed. The first retains experimental observation of food intake as a measure, while seeking to change the nature of the feeding experience so that stereotyped or cognitively controlled behaviors are minimized and dependence on internal cues maximized. An example of such an approach is the use of all liquid diets delivered from concealed reservoirs or pump operated feeding machines (Hashim and Van Itallie 1965; Jordan 1969). In these instances? the nature of the food is changed and the normal behaviors involved in food ingestion replaced by such behaviors as lever pressing. In some instances, food has been delivered directly to the stomach to remove oropharyngeal sensations. In these paradigms the subjects' ability to cognitively monitor his intake is obviously impaired. Finally, when used as a substitute for regular eating for long periods of time, it seems reasonable to assume that biologic hunger signals will eventually override extraneous influences in determining intake. The major disadvantage is that the artificiality of the procedures leads to results which may not generalize to other situations. In particular, the low palatability of liquid diets may have a distorting influence on observed intake patterns and subjects may never experience the normal appetitive responses which precede meal eating. Nevertheless, this model has permitted study of responses to diet dilution and enrichment, an important model in animal experimentation. A number of such experiments have now been done. In contrast to the findings of prompt compensation in animals, humans have usually shown sluggish responses, often failing to adjust the volume of intake until the second week after the caloric density is changed (Wooley 1971; Spiegel 1973; Leitzmann et al. 1977).

A second new approach to hunger measurement has been the use of conditioned salivary responses to the sight of food. The potential advantage of this technique which led to its development was the fact that salivation was an involuntary behavior which was not subject to the same cognitive controls as food intake measures. In an initial study (Wooley and Wooley 1973), it was found that salivation rate (measured by obtaining pre and postexperimental weights of cotton dental rolls inserted in the mouth for three two minute collection intervals) increased with hours since last meal and was related to palatability of the food stimuli. During collection periods subjects were instructed to attend to actual foods placed directly in front of them. These values were compared to baseline levels obtained while subjects read. It has since been found that the sensitivity of the measure is increased by the use of only one dental roll, placed under the tongue, and one two-minute collection is sufficient (Wooley, Wooley, and Williams 1977a). The method is, therefore, quite simple to use and well tolerated by subjects. The chief methodologic requirement is that the testing situation sufficiently approximate prior ones in which the conditioned response was acquired. Thus the setting should be a familiar one in which subjects have eaten at least once, the foods should be familiar ones liked by the subject, and they should expect to eat the food immediately after the tests are completed. However, we have found that even thinking of food produces salivary increases if the subject has a specific food in mind. Use of imagined stimuli (Wooley, Wooley, and Williams 1977b), which permits repeated measures and which subjects can carry out anywhere with a timer, increases the flexibility of the method. Responses to imagined food stimuli are greater with images of highly preferred vs. neutral. foods and increase with hours of deprivation. Conditioned salivation has been found to be reliably affected by differences in caloric levels of preloads, even when these are disguised. Preload differences as small as 150 calories (of carbohydrate) influence salivation rate to palatable food viewed one hour later. To test the assumption that salivation rate reflects hypothalamic activity, the effects of amphetamine and fenfluramine were studied. Amphetamine was found to suppress salivation to the sight of food, an effect measurable for up to two days after a dose of 10 mg. Fenfluramine, which is believed to act through different neural pathways and which has the effect of reduced meal size rather than delayed meal onset in rats, was found to have no effect on salivary responses to food in humans (Wooley et al. 1977).

Comparison of obese and lean subjects showed that a preload sufficient to entirely suppress responses to the sight of food one hour later in lean subjects (900 calories) did not suppress salivation in the obese (Wooley, Wooley, and Woods 1975). In a subsequent study, caloric value of preloads was held constant while protein content was varied. obese and lean subjects showed satiety following high protein meals, with no obese-nonobese differences apparent (Wooley and Wooley 1977).

This finding is interesting because it is one of several recent studies suggesting that regulation of protein intake is independent of caloric regulation and takes place through a separate mechanism. Wurtman and Wurtman (1977) reported that anoretic doses of fenfluramine suppressed

caloric intake but not protein intake in the rat, whereas d-amphetamine suppressed both proportionately. This tends to suggest protein regulation is mediated by hypothalamic centers, since it is disturbed by amphetamine, whose site of action is in the hypothalamus and since protein content of diet influences salivary responses. On the other hand, Anderson, Leprohon and Coscina (1977) report that the hyperphagia and weight gain produced in MH lesioned rats occur while protein intake is maintained at control levels. Finally, increases in protein density of the diet have been reported to produce decreased ad lib intake in both children (Ditschuneit, Jung, and Ditschuneit 1977) and rats (Hershberger, Jenkins, and Martin 1977). Whatever the mechanisms involved, these findings underscore the importance of keeping separate manipulations of protein and calories in studies of regulatory processes,

The finding of sustained appetitive responses to food in the obese even after substantial preloading is consistent with one of the most frequently replicated findings of the work by Schachter, Rodin and associates regarding eating behavior and obesity. This is the observation that the obese show an exaggerated response to palatable food stimuli (see Wooley, Tennenbaum, and Wooley 1978). This finding has been obtained using such diverse measures as intake of test foods, food selections at cafeterias varying in palatability of offerings, salivary responses to food, and insulin secretion to the sight of food. Taken together these measures suggest a strong physiologic as well as behavioral response to food stimuli which is characteristic of high levels of hunger. However, a caution needs to be introduced in interpreting these findings. In order to separately assess the effects of high body weight per se and a pattern of chronic dieting, Wooley, Wooley, and Williams (1977c) selected a group of nonobese subjects who scored high on the Herman-Polivy (1975) measure of dietary restraint. Measurements of appetitive salivary response following preloads of disguised caloric value in restrained eaters showed the same failure of calories to inhibit appetite as was observed in previous obese samples. This was not true of a matched control group of nonobese unrestrained eaters. The correlation of dietary restraint and overweight is so high that one must admit there is a very serious confounding of obesity and restraint in virtually all cross sectional studies. Much of this work needs to be redone, and it is strongly recommended that restraint scores be controlled or at least recorded in subjects of any study of eating behavior.

Finally, a third new approach to the study of feeding has been the observation of food choices, food intake, and parameters of eating style in natural settings. In most such studies, raters record the data and rate weight unobserved by the subjects or in such a way that the observation process cannot influence the behavior (e.g., recording choices as people exit a cafeteria line). The obvious advantage to this procedure is that it dispenses with the problems of demand characteristics which pervade laboratory studies and allows access to large sample sizes, sometimes numbering in the thousands. As such, it is an excellent means of testing simple hypotheses which require only single observations of overt behaviors. The disadvantages are that the same subject cannot be studied under varying conditions, and,

although sometimes subjects are approached for questioning as they leave the site of the study, the amount of information which can reasonably be obtained from a sufficient percent of the sample to avoid selection bias is quite limited. However, institutional settings in which the same individuals can bc observed over time and in which some experimental manipulations can be carried out, offer a promising modification of this approach. Rodin (personal communication) has 'begun a longitudinal study in a dormitory setting in which observations extend over a period of years and in which there is access to additional subject information. It might be noted that high school students, college students, and pregnant women constitute particularly important populations for study, since they are likely to contain a larger than average number of people who become overweight for the first time.

Researchers of alcoholism and drug abuse have made wide use of the model of relatively long term observation of subjects in inpatient settings with ad lib access to substances of interest. Such an experimental model might profitably be employed in studies of food Two problems would arise, however. First, confinement of subjects would alter activity patterns. The advantage of being able to measure energy expenditure, therefore, would be somewhat offset by the limitations placed on spontaneous variation in activity. Secondly, the chronic motivation of most overweight people to lose weight often causes them to use any interruption of normal stresses and responsibilities as an opportunity to go on a reducing diet. Careful subject selection could counteract this problem to some extent. Eating behavior, like other important forms of substance consumption, is firmly rooted in social customs, personal habits, and variation in psychological states. Thus, while much is lost in laboratory study, much might be gained in the form of better understanding of physiologic variables governing eating patterns in humans which have, to this day, largely eluded discovery.

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Chapter 13

Tobacco Smoking and Nicotine Tolerance

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Nicotine and tetrahydrocannabinol are commonly self-administered. A puff on a tobacco cigarette can be considered one dose of the fairly potent drug, (or substance, if you will), nicotine. By that measure, tobacco smokers consume about 3 x $1O^{13}$ doses of nicotine annually. The numbers regarding cannabis self-administration are less precise, but if each cannabis cigarette provides 5 to 10 doses of tetrahydro~ cannabinol (THC) taken as deep inhalations, then large number of THC doses are taken each year. Yet animals will not self-administer either cannabis or tobacco. We wondered what it is about the smoking process or the pharmacology of cannabis or tobacco or nicotine and THC that makes for such behavior.

Our laboratory has been concerned with the phenomenon of tolerance anddependence, both as to characteristics and mechanisms. We are particularly interested in how self-administration of a drug might change as tolerance and dependence to the drug or to related drugs develops. Much of our work has focused on cannabis; thus an interest in tobacco consumption seems to be a logical progression because of the many similarities in the two substances. This report makes some comparisons between cannabis and tobacco and describes the results of some preliminary studies in humans given intravenous doses of nicotine.

Some readers might be skeptical about the utility of any comparisons between cannabis and tobacco. Tobacco is probably used more often, by more people in the world, than any other psychoactive drug. Cannabis, although receiving much attention in recent years, is still not used as intensively or extensively. Thus, the current pattern of cannabis and tobacco drug seeking behavior appears quite different. However, if one considers some of the important general factorsin any drug seeking behavior, perhaps differences in current level of use maybe partially understood, at least to the extent that useful predictions can be made about future patterns of self-administration as the factors change.

Drug seeking and self-administration are modified by such variables as:

1. Availability
2. Rewards- both psychosocial and pharmalogic
3. State of the organism - including degree of tolerance and dependence
4. Setting- including peer influences and contingencies
5. Set- learning and expectation.

Despite similarities that will be described in a moment, there are still obvious differences in the availability of cannabis and tobacco. Cannabis is still not readily and continuously available to the older potential user. Although many young adults are in the right setting and have developed correct Expectations to enhance cannabis seeking behavior, the majority of people have not. 'The importance of such factors as the state of the organism is still unclear regarding both tobacco and cannabis self-administration. Tolerance and dependence develop to both drugs. Both drugs can offer an array of psychosocial and pharmacologic rewards, though some of the rewards may be changing rapidly as society's attitudes change regarding both tobacco and cannabis smoking.

If tobacco users are asked why they smoke, the answers are similar to those given by cannabis users when they are asked why they smoke cannabis. Tobacco smokers give the following reasons *for smoking* (Ikard et al. 1969):

1. Stimulation - increased energy and arousal
2. Relaxation and to enhance social interactions
3. Manipulation and handling of things (the cigarettes or pipe)
4. Habit
5. To decrease unpleasant affect-- tension, anxiety, anger
6. Because it's "addictive" - to decrease craving

Not all tobacco smokers give all the reasons. There appear to be subgroups of smokers who think they smoke for one or more of the above. The same list of reasons can be culled from the responses of cannabis smokers in various studies when they were asked why they smoke (O'Donnell et al. 1976). Some might question reason number six as not in keeping with usual experience. The high level of dependence that develops to tobacco has been described in detail in recent reviews (Jarvik et al. 1977; Russell 1977). Cannabis users in countries where very frequent use of potent materials possible occasionally include reason number six to explain self-administration.

For reasons too complicated to go into here, our society is troubled when drug users cite (or are assumed to have) reason number six to explain self-administration of a drug. Russell (1977) discusses why a high level of dependence on tobacco should be expected. These reasons include:

1. Rapid and numerous reinforcements from the inhalation of tobacco smoke (about 10 per cigarette).
2. The rapid clearance and metabolism of nicotine
   a. Allows frequent and repeated use,
      Makes for the rapid onset of withdrawal symptoms.
3. Complex pharmacologic effects, both central and peripheral, perhaps satisfying a variety of needs.

4. Psychologic and social rewards from use, especially in youth.
5. Pattern of use allows generalization and conditioning to other activities.
6. Combined pharmacologic effects and ritual.
7. No marked performance impairment - perhaps enhances some performance .
8. Great social acceptability.
9. High availability - inexpensive relative too other psychoactive drugs.

The psychology of tetrahydrocannabinol (THC) and cannabis smoking is such that reasons one through six could well apply to THC, nicotine, cannabis and tobacco. The performance impairments after cannabis are often subtle, as judged by the user, when compared to other central nervous system intoxicants. Reasons eight and nine may be changing for both substances. Thus, as judged by experience with tobacco, perhaps cannabis could be a substance with a high dependence liability if only a few factors change.

The abstinence symptoms following cessation of prolonged tobacco or prolongedcannabis intoxication have many similarities (Jarvik 1977; Jones, Benowitz, and Bachman 1976; Nowlan and Cohen 1977). The rapidly appearing tobacco abstinence symptoms include irritability, restlessness, sleep disturbances, gastrointestinal disturbances, headache, anxiety and decreased concentration, judgment, psychomotor performance, dullness and drowsiness. Except for the drowsiness and dullness, all the other symptoms appear with similar intensity during cannabiswithdrawal and follow a similar time course. Of course, the relationship between drug seeking behavior and such dysphoric withdrawal symptoms is not a simple one, but is certainly worthy of consideration. Could differences in expectations andavailability account for different self-administration patterns? Perhaps the fact that animals won't self administer either tobacco or cannabis not only makes the study of drug seeking behavior and its relationship to dependence difficult, but also points out yet another similarity between cannabis and tobacco.

For all the above reasons, we thought it interesting to attempt to investigate tobacco seeking behavior in tobacco dependent individuals using a research strategy similar to that used in our cannabis studies. As have other investigators, we thought it important to focus on the role of nicotine in maintaining and altering such behavior. The study of the role of THC concerning cannabis self-administration would be analogous study. As Jarvik points out (Jarvik et al. 1977), we found that the relationship between nicotine ingestion, at least when administered in the peripheral circulation, and snaking behavior may well be a complicated one because of the rapid tolerance that develops to many nicotine effects.

Nicotine alone has been administered to man in relatively few studies (Lucchesi, Schuster, and Emley 1967; Jarvik 1977; Kumar et al. 1977). The intravenous infusion either had no effect on con current smoking behavior or minimal effects. Prior to doing a study where we wanted to measure smoking behavior, we investigated the physiologic and subjective effects of repeated, rapid injections of nicotine to abstinent cigarette smokers and noncigarette smokers. The 700 microgram

nicotine doses given to the smokers were slightly less than those likely to be delivered by moderate potency cigarettes (Russell 1976). The 300 microgram dosage given to nonsmokers was determined in pilot studies as representing an average acceptable dose. An attempt was made to mimic the rapid administration of a dose of nicotine produced by the inhalationof tobacco smoked during a typical puff.

The eight smokers regularly consumed 20 to 50 cigarettes daily, with an average of 30. The nonsmokers had enough past experience with tobacco to understand the symptoms of nicotine toxicity. None had ever been regular smokers. All were young adults. The subjects arrived in the laboratory at about 8 a.m., having not smoked for the previous eight to ten hours. During the four hour experimental session, the subjects lay quietly in bed with an intravenous catheter in a forearm vein. Under single blind conditions in an alternatingorder, eitherplacebo (saline) or nicotine was injected into the catheter rapidly over a three second interval, with the injections spacedabout to 30 minutes apart. Thus, the interval between nicotine injections was approximately one hour. The injections always were given at the beginning of a three minute period when the subjects lay quietly with their right arm extended for the measurement of finger tremor, thus providing a quiet recording period with minimal activity. Subjects were asked to report mood and symptoms before and after each injection and were asked periodically about craving for a tobacco cigarette. A battery of physiologic measures were taken continually during the experiment. These included heart rate as measured by electrocardiogram, skin temperature, finger tremor as measured by power spectral analysis of an accelerometer taped to the index finger, and blood pressure, measured with a cuff on the right arm.

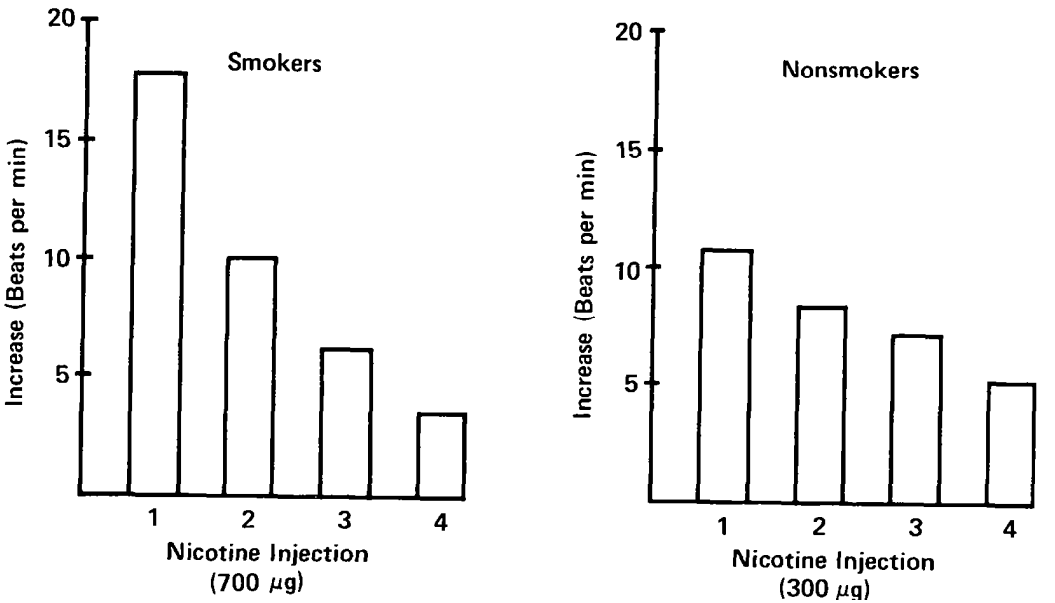
The heart rate changes are illustrated in Figure 1. All subjects had a significant increase in heart rate after the nicotine injections ($p < .0001$). The smokers had a significant increase in heart rate after the first three nicotine injections but no significant change after the fourth. Then nonsmokers had a significant heart rate increase after all four injections. The average latency from beginning of injections for the peak heart rate change was 97 seconds with a standard deviation of 3.7 seconds and did not differ for the smokers and nonsmokers. The placebo injections produced no change in heart rate.

Blood pressure or finger tremor did not change after nicotine injection. The finger skin temperature gradually decreased through the course of the experiment, probably reflecting a cumulative vasoconstrictive effect of nicotine.

Seven of the eight smokers reported the nicotine injections to be rapidly followed by a pleasurable, stimulant-like sensation that many of them termed a "rush". Four of the nonsmokers reported similar effects. Four of the smokers so enjoyed this feeling that they requested substantially higher doses. The smokers did not report a consistent decrease in their desire to smoke tobacco during the experiment. All subjects experienced feelings of skin flushing and warmth,

FIGURE 1

PEAK HEART RATE CHANGE AFTER IV NICOTINE



lightheadedness, cool extremities, increased heart rate and some dizziness. The effects were short lived and disappeared three to four minutes post injection. All subjects were able to discriminate the placebo injections from the nicotine. All subjects reported the subjective effects at the fourth nicotine injection to be much less than those experienced after the initial injection. Thus, in the smokers rapid tolerance to the nicotine, cardiac and subjective effects occurred during the experiment. A similar trend was evident in the non smoker subjects. The smoker group was more tolerant to nicotine effects than the nonsmokers. Both groups had a similar time of occurrence of peak heart rate change. The peak heart rate occurs at about 97 seconds after nicotine injection into the forearm, a tine at which one would expect rapidly rising brain concentrations. This is consistent with the notion that many nicotine effects are centrally mediated.

It may well be that single bolus injections of nicotine have a quite different pharmacology than nicotine administered in a sequence of eight to ten boli, as would occur after puffing on a tobacco cigarette. However, the relatively rapid development of tolerance to some effects of nicotine suggests that the pharmacologic effects of nicotine are not major determinants of smoking behavior throughout the smoking day. Eight hours without tobacco appears to be time enough to lose some degree of tolerance, since our subjects gave some evidence of having lost a degree of their acquired nicotine tolerance during the night of abstinence. If a similar pattern of tolerance acquisition and loss occurs with smoked material, it may well be that in the two pack a day smoker it is only the first few inhalations in the morning or the first few cigarettes that are of positive reinforcement value, at least in terms of nicotine related effects. The self-administration of tobacco that occurs for the rest of the day may well be mainly to avoid the dysphoria associated with abstinence.

Tolerance or dependence are quite often thought of as relatively slowyly developing phenomena. The pharmacokinetics and pharmacodynamics of both nicotine and tetrahydrocannabinol are such that things happen relatively rapidly. The development or relative loss of tolerance throughout the 24 hour cycle may be such that the reinforcing properties of such druqs vary at differing times of the day. Experiments should be designed to take such temporal criteria into account. The measurement of rate or amount of self-administered drugs without independent manipulation of tolerance levels can be misleading, at least in terms of providing explanations or reasons for drug self-administration.

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Chapter 14

Tobacco and Nicotine Self-Administration in Humans: The Evolution of a Methodology

Jerome H. Jaffe, M.D., and Maureen B. Kanzler, Ph.D.

The role of response cost in tobacco smoking behavior and the development of productive methods for its study have interested my coworkers and me for a good many years. Our work was stimulated in part by the observations of Lucchesi, Schuster, and Emley (1967). These investigators found that when human cigarette smokers are given intravenous infusions of nicotine under laboratory conditions, they continue to smoke, although their consumption of cigarettes is reduced.

Some scientists hypothesize that people smoke primarily for the effects of nicotine. Thus one might assume that these subjects continued to smoke because the dose of intravenous nicotine was inadequate. We made quite a different assumption, namely, the behavior was related to response cost.

To draw some parallels from observations on self-administration of food, people tend to eat at a sumptuous buffet long after they are no longer hungry. The marginal cost of eating more of the food is zero. If dessert is included in the price of a restaurant meal, most people will eat it, no matter how filling the preceding dishes; otherwise, they are likely to forego dessert. People who are hungry often will wait several hours for food in order to get it at considerably lower cost. In short, it appears that response cost is more important over a certain range than the biological drives of hunger and satiation.

In the experiments of Lucchesi and coworkers, cigarettes had been simply and casually available; the response cost for smoking a cigarette approached zero. On the basis of such a characterization one might logically ask next: In a similar experiment, how would smokers behave if the response cost of the cigarettes was systematically varied?

By 1973, when our group returned to work on the role of response cost in smoking, much additional work had been done. It had been found that when nicotine levels in cigarettes are varied, smokers

attempt to titrate body levels of nicotine by altering the number or depth of puffs or the number of cigarettes smoked (Ashton and Watson 1970; Frith 1971). In other studies, smokers were given preloads of oral nicotine or nicotine antagonists, and the number of cigarettes smoked was the dependent variable (Jarvik, Glick, and Nakamura 1970; Kozlowski, Jarvik, and Gritz 1975). No one, however, had undertaken a study in which nicotine levels and response cost for tobacco were both systematically varied.

Preliminary Experiments

First we wanted to find the most effective methods to investigate how cigarette smoking varies as a function of response cost. We also wanted to work toward an acceptable definition of that concept. In collaboration with Dr. Miriam Cohen, Dr. Maureen Kanzler and I first took an approach used in many laboratory experiments involving self-administration of alcohol or other drugs. Subjects perform some simple work (button pressing, bicycle riding, etc.) which is directly rewarded with a unit of the drug or paid for by tokens or credits which can be exchanged for the drug. Dr. Murray Jarvik lent us a device that dispensed a cigarette after the subject turned a handle an arbitrary number of times. The turning generated an electrical current, and the experimenter could vary the total energy required to produce a reinforcement. This procedure was abandoned, chiefly because it was difficult to make the machine tamper-proof. We also considered using bicycles, but a personal trial made it clear that, without energy output calibrations, pushing the pedals simply amounted to spending time sitting on a seat.

Next we instituted a procedure in which we viewed response cost as the total effort required to obtain a cigarette. Normally, once a smoker has bought a pack or carton of cigarettes, the response cost is as low as reaching into a shirt pocket. To observe the effect of increasing that cost, we recruited three hospitalized, detoxified male drug abusers on a research ward. They were paid a small fee to participate in an B-day experiment in which they were required to walk to the nurses' station to obtain free cigarettes. These were of a brand delivering more than 1.0 mg nicotine, but the cigarettes could be smoked only to a line drawn at the halfway point. Subjects were cooperative when each trip produced eight of these half cigarettes. There was little complaint at four cigarettes per trip, but dissatisfaction mounted sharply when each trip produced only one or two.

Data were orderly for the more stable subjects: consumption went down as response cost went up and then rose again, but not to the starting point, as response cost was lowered. The experiment was repeated for another 8 days, with response cost varied from one trip per half cigarette to one per 20 half cigarettes. Although there was a very crude orderliness in the data, the "noise" caused by medical and psychiatric complications among the subjects motivated us to reassess our own cost/benefit ratio for this kind of

research. Me also wanted to find a procedure that would provide a finer measure of tobacco consumption. Thus, in this preliminary work, we did not even reach the stage of using preloading of nicotine.

We then tried working with paid subjects who were not hospitalized and not obviously psychologically impaired, so that we could control their periods of abstinence and observe their intake with greater precision. These volunteers were observed in the laboratory for S-hour periods during which they were permitted to smoke and were charged $.00 to $.50 for each puff in some cases, for each quarter cigarette. Under these conditions we were able to vary either cost per puff (or quarter cigarette) or the nicotine content per puff (or quarter cigarette) by selecting from various commercial brands. By direct observation, we noted the number of puffs (or quarters), inter-puff interval and puff duration. This arrangement did not permit a precise measure of actual nicotine intake, but it did yield orderly data. For example, as the price per quarter of a cigarette increased, the inter-puff interval decreased, the tobacco became a more valuable commodity, and the subjects did not wish to see it bum unpuffed (See figure 1).

The major problem with this procedure was that our informed consent requirements made the nature of the dependent variables quite obvious and introduced a number of variables related to subject attitudes. For example, one subject informed us in advance that it would not make much difference whether we charged $.005 or $.0l per puff but that under no circumstances would he smoke when the price reached $.02 per puff. He correctly predicted his own behavior. However, he lit a cigarette immediately when the session was over. Other subjects did not predict their behavior, but showed changes in smoking style (changes in puff duration and inter-puff interval) as the price went up. The subject in figure 1 smoked quarter cigarettes over a wide price range, $.005 to $.35 per quarter cigarette! but the number smoked decreased, and smoking finally stopped entirely at $. 50 per quarter.

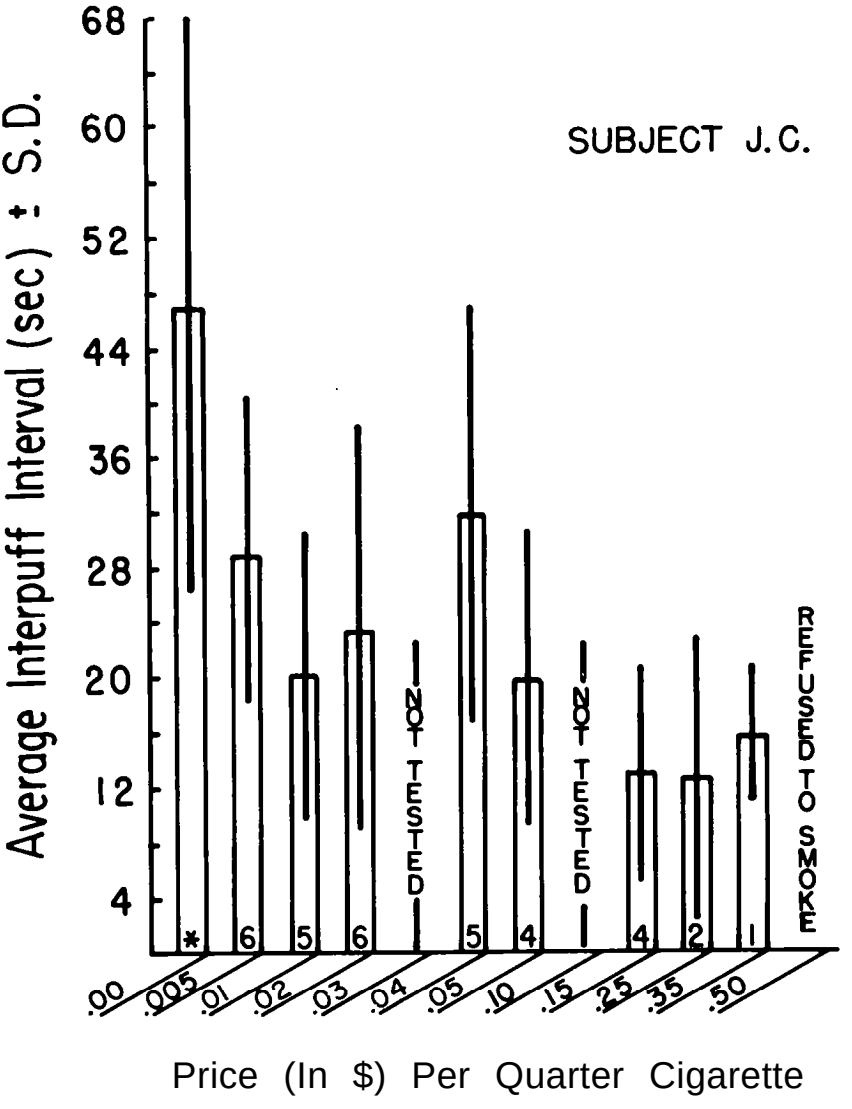
It became apparent, however, that while this approach would yield some orderly relationships with some subjects, it would not provide answers to certain questions we had come to believe were of greater practical importance.

A New Approach to Cost and Nicotine Content

With the advent of low tar/low nicotine cigarettes, our group began to wonder less about the role of nicotine plasma levels in short term regulation of smoking and more about the relationship between response cost (or economic cost) and the nicotine content of cigarettes that subjects in the real world would consume over the long run.

Findings from most laboratory experiments in which animals are able to self-administer drugs show that, other factors being equal, they will make more responses for larger doses than for smaller ones. Humans might reasonably be expected to do the same. Yet many people

FIGURE 1



Average interpuff interval during baseline (whole cigarettes) and during smoking of quarter cigarettes at different prices. Number at base of bars shows number of quarter cigarettes smoked during the experimental session. Four whole cigarettes were smoked under ad lib conditions (*).

buy low tar/low nicotine cigarettes, even though the cost of the less potent cigarettes is the same as those delivering several times the nicotine per puff. It seems apparent that these people are concerned about their health. They are trying simultaneously to obtain nicotine and to avoid a future aversive consequence, the brand selection being a resultant of the interaction of the two sets of reinforcers. We wondered what would happen if the reinforcers were arranged to be summative rather than tending to cancel each other.

Method for the Pilot Study

We devised a method to explore this question with ambulatory smokers going about their usual daily activities. Our primary interest was to study the relationship between overall response cost and nicotine content of cigarettes purchased. We recognized, however, that cognitive factors were also operative. Our subjects might perceive that as medical researchers we believed low nicotine/low tar cigarettes were less hazardous than, other brands, and these perceptions might affect their behavior.

We began the pilot study by identifying through questionnaire a group of smokers at our own institution who met the following criteria:

1. They smoked cigarettes of at least 1.0 mg nicotine per cigarette as determined by the FTC method.
2. They smoked at least 20 cigarettes per day.
3. They were willing to participate in a study of "Safer Smoking."

We offered 23 smokers who met these criteria, 16 women and 7 men, an opportunity to obtain cigarettes from us at $4.50 per carton, while the usual cost in local stores ranged from $4.65 to $6.00. We also offered to pay subjects each time they provided us with a set of smoked butts. We asked for butts both during a two-week baseline observation period and each time a subject changed brands.

After baseline information was obtained on the brand and number of cigarettes smoked, we weighed the butts collected. The proportion of the cigarette each subject usually smoked was determined by subtracting average butt weight (minus filter) from the whole cigarette weight (minus filter). Then we developed an estimate of daily nicotine intake. This was based on nicotine delivered according to published FTC figures, number of cigarettes smoked per day, and the proportion of each cigarette smoked. We used these values to develop two experimental groups matched for nicotine intake. After matching, the groups were assigned to one of two programs by a flip of a coin. A third group served as controls. This consisted of seven women who met the original criteria but were not contacted until the study had been underway for three months.

After the baseline period, cigarettes were made available for purchase for about three hours per day, three times per week, at the

office of one of the researchers. Subjects could purchase any brand. At the time of each purchase, for most subjects approximately once a week, subjects were asked to estimate the number of cigarettes smoked each day, the number given away or purchased elsewhere, "bummed," etc. Subjects also filled out a check list designed to measure withdrawal symptoms.

All cigarettes were sold at $4.50 per carton, but subjects were given refunds for each empty pack returned. Those in Group A were offered $.10/pack rebate regardless of the brand purchased. Subjects in Group B were given a progressive incentive rebate for returned packs: $.05 for brands delivering 1.0 mg or more nicotine per cigarette; $.10 for "lights" (0.9-0.6 mg nicotine); $.20 for "lows" (0.5-0.4 mg nicotine), and $.30 for "very lows" (0.1- 0.2 mg nicotine per cigarette). Thus, in Group B, the net cost of a pack of very low nicotine cigarettes would be $.15 if all empty packs were returned. At the time of the study cigarettes were selling at between $4.50-$6.00, depending on place of purchase.

Because we were concerned that some subjects might inhale more deeply when smoking the lower nicotine cigarettes and thus develop higher carboxy hemoglobin levels, we wanted to monitor carbon monoxide in exhaled breath. A delay in obtaining equipment postponed this monitoring until the study had been underway for several weeks. Thereafter, a breath sample was obtained at each purchase.

For any given subject, the study extended over a 3-month period. Then both groups were again given an opportunity to purchase any brand at $4.50 per carton, with a $.05/pack rebate for returned empty packs. At the 3-month point, we obtained a sample of butts, a breath sample for CO, and some additional data from the control group of women who had been identified earlier. We continued to obtain followup data once a month for two to four months on both the subjects who completed the 12-week experiment and the control group.

Results and Interpretation

There were important behavioral differences between the men and the women in this study. Fewer men (7) volunteered to participate and a higher proportion dropped out. In addition, the behavior of the men who remained in the study tended toward erratic compliance with study requirements. Four of the seven completed the 12 weeks, and these four showed substantial reductions in nicotine and tar consumption. Because of the small N, however, we will focus on the results from the women.

Twelve of the 16 women who started completed 12 weeks; 13 completed at least 8 weeks. The dropout rate was similar for Groups A and B. The most striking finding was that all of the women who remained for more than a few weeks changed to lower nicotine brands. For both groups the estimated mean nicotine intake level dropped relatively rapidly over the first 6 weeks and then continued to decline more gradually. For both groups the differences from baseline to the 6th week were statistically significant ($p < .01$) and remained so through

the 12th week. We believe these differences were also biologically significant (see figure 2). The mean daily tar intake at baseline for the combined experimental groups was 492 mg (±163) as compared to 401 mg (±126) for the controls. At 12 weeks the intake for the experimental group was 126 mg (±162) compared to 393 mg (±260) for controls. The difference is significant at the .01 level.

There was no significant difference between the two experimental groups in terms of tar and nicotine intake. Although the subjects in Group 3 switched more rapidly to lower nicotine cigarettes, within a week or two those in Group A, without the special economic incentive, followed suit. Under the experimental conditions, the degree of economic incentive offered did not increase the tendency to change brands. We need to point out, however, that the cost of cigarettes for our subjects is ordinarily so low that our capacity to lower the cost of the low tar/low nicotine cigarettes was limited. We might also note that under most circumstances it is a rise in price of the commodity regularly purchased that changes behavior rather than a decrease in an alternative commodity.

Furthermore, because we were our own "salespeople," and because we were trying to measure CO and nicotine withdrawal, each encounter at the purchasing site sharply raised the subjects' awareness of the medical implications of smoking.

While in this experiment extra monetary incentives for change did not cause a greater rate of change in the brand of cigarettes purchased, payment apparently was sufficient to motivate most of our subjects to buy cigarettes from us. This situation (purchasing from us) increased the subjects' awareness of the disparity between the health risks of their behavior and their perception of themselves as rational beings. We believe that the results of this pilot project support the view that health concerns rather than different cost of low tar brands motivated the switching behavior. But the economic incentives did play a role in that they brought our subjects into a situation in which they experienced cognitive dissonance (an uncomfortable disparity between their health concerns and their use of high tar cigarettes) -- a dissonance they reduced by changing to lower tar/lower nicotine cigarettes.

Several other methodological issues arose during this study. One concerned the validity of subjects' reports. While we could look at actual purchases, subjects could give away or save the cigarettes they purchased from us or buy additional cigarettes elsewhere. At each visit, therefore, we questioned them, in a nonjudgmental manner, implying that it was all right to buy supplementary cigarettes as long as they told us.

Additional methods were introduced to crosscheck the subjects' self-reports. For instance, every tenth pack was marked with a label on which the subject was to record the dates and times the first and last cigarettes in that pack were smoked. If the subject slept before completing a pack, hours of sleep were recorded. These labels should have provided a measure of waking time required to smoke 20 cigarettes.

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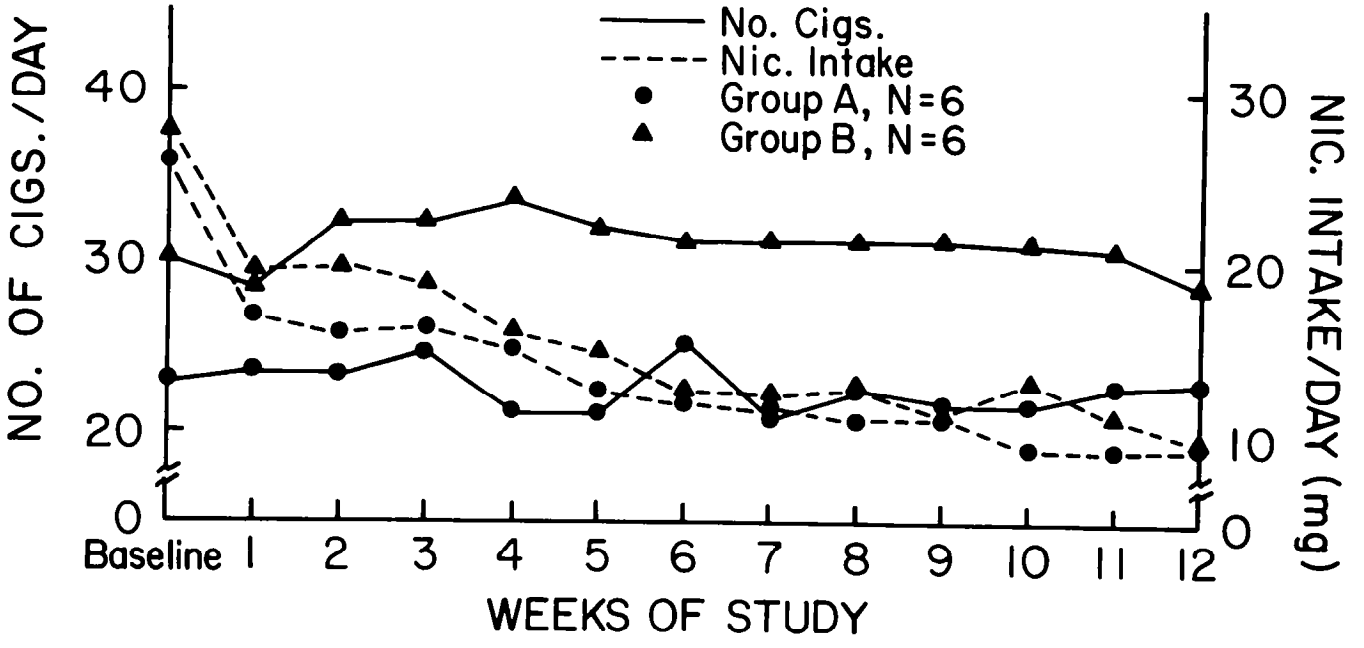
FIGURE 2



Cigarette and nicotine intake per day for two groups over twelve weeks.

The subjects admitted, however, that every time they came to the labelled pack they took pride in slowing down their smoking rate. Thus, while subject reports of number of cigarettes smoked per day correlated quite well (r=.82) with actual purchases? both estimates of consumption correlated less well with values derived from the data on hours to smoke one pack.

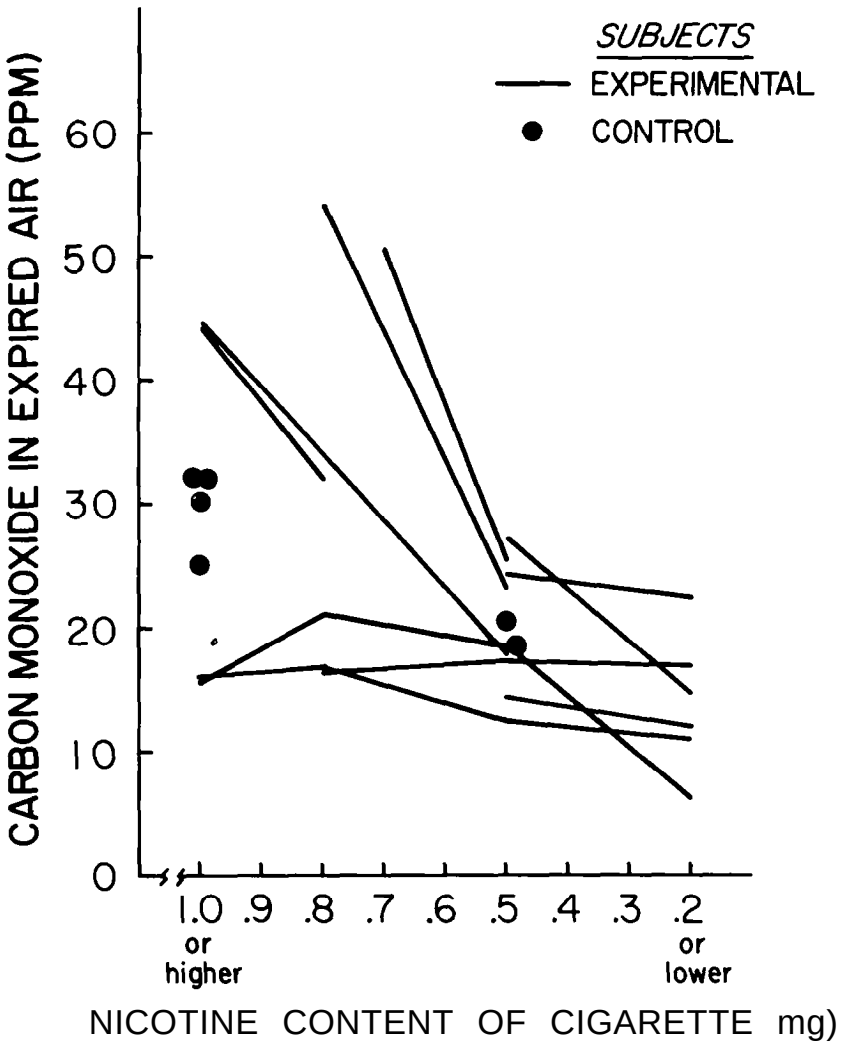
Whether one is interested in the titration hypothesis or in the public health implications of less hazardous cigarettes, it is worth noting that over the long run our subjects as a group showed no significant increase in the number of cigarettes smoked. Most reported concern about smoking more as they changed to lower tar and nicotine brands. We told them that the drop in tar and nicotine would more than compensate for any increase in smoking that might occur. Some subjects did show increases in number of cigarettes smoked per day as they changed brands, but these increases tended to be transient and modest in magnitude.

Our subjects did tend to consume more of each cigarette as the nicotine content decreased. For eight female subjects who switched from high nicotine (at least 1.0 mg nicotine per cigarette) to very low nicotine (0.2 mg or less) cigarettes, the proportion smoked changed from 76 percent to 83 percent. Despite this tendency to smoke a larger proportion of each cigarette and perhaps to inhale more deeply, however, we did not observe any increase in CO levels in exhaled breath. Indeed, although the number of observations were limited, we observed some tendency toward decrease in these levels (see figure 3). However we should note that participation in the project may have inhibited an increase in the number of cigarettes that might have occurred under more natural conditions. If the number of cigarettes had gone up we might have seen increases in CO levels.

We conclude that factors other than nicotine content, probably social factors, health concerns and long standing associations between smoking and other behaviors (e.g., drinking coffee, drinking alcohol), play a role in determining the number of cigarettes smoked per day.

In this pilot study, our estimate of each smoker's daily nicotine and tar intake was based on the self-reported number of cigarettes smoked and the total tobacco smoked per cigarette, estimated from butts returned. The weight of tobacco smoked was compared to the weight consumed when the cigarette was smoked by the FTC method. FTC figures for nicotine and tar yields were then used to derive the figure for each subject's daily intake. This approach is admittedly not as sophisticated as actually measuring the nicotine depositied in filters, as was done by Turner, Sillett, and Ball (1974). Even that measurement, however, provides only an indirect estimate. For those whose primary interest is titration of body nicotine levels, more invasive techniques such as the measure of plasma nicotine or cotinine may be required.

FIGURE 3



Carbon monoxide in expired air of subjects smoking cigarettes delivering decreasing amounts of nicotine.

Changes in Tolerance to Nicotine

In the work with human subjects described here we encountered some problems that are more easily controlled when working with animals. For one thing, in a typical animal experiment measuring work an animal will do for differing doses of a reinforcer or for different reinforcers (e.g., using a progressive ratio design), access *to* drugs is controlled so that tolerance and physical dependence do not develop. In our work, subjects were assumed to be in some ways dependent on tobacco when they began the study. Based on a number of studies (see Larson and Silvette 1975), we believed them to be tolerant to nicotine. We also believed that as they changed to lower nicotine cigarette brands they would lose some of this tolerance. In examining the relationship between cost and nicotine content in brand selection? therefore, we were looking at a situation that we believe was changing over time.

If our experiment is viewed as exploring factors that determine a subject's self-selection of cigarettes that are delivering varying doses of nicotine per puff, we should recognize that the difference in response cost or price necessary to induce a change to a brand delivering a lower nicotine dose per puff be greater than the difference required to maintain self-selection of that dose. Once subjects adjust to the new nicotine dose, the new brand of *cigarettes* may be more reinforcing than it was when the change first occurred.

Two findings in our pilot work are consistent with the view that subjects do lose tolerance to nicotine after shifting to low nicotine cigarettes. First, while many subjects initially complained that the lower nicotine brands were unsatisfying, most adapted to them. As the study progressed, some subjects reported that cigarettes delivering only half as much nicotine as their original brands were quite satisfactory.

The second observation is that during the 2- to 4-month followup period, only 1 of 12 female subjects who remained in the study for 12 weeks returned to purchasing cigarettes delivering 1.0 mg of more nicotine. One other has been smoking lights (0.8 mg per cigarette). The remaining ten are smoking either low (0.5 mg) or very low (0.1-0.2 mg) brands. We cannot be certain what factors are maintaining the behavior (i.e., paying the same price for very little nicotine that could purchase two to ten times as much). Neither can we be certain how long it will last.

Conclusion

We feel that we have begun to develop a model for studying self-administration of tobacco which falls somewhere between laboratory and marketing models. We believe that further use of this model may help to tell us more about why people smoke and about the kinds of price changes that might lead to less hazardous smoking for the population as a whole.

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Chapter 15

Patterns of Puffing in Cigarette Smokers

Ellen R. Gritz. Ph.D.

Cigarette smoking is an integral part of the life of 30 percent of the adult females and 40 percent of the adult males in this country (USDHEW, 1976). Its prevalence and tenacity in the behavioral repertoire of so many people must be explained in terms of powerful reinforcing value. As psychopharmacologists, we have a strong conviction that nicotine, a potent drug with multiple central and peripheral nervous system effects (Volle and Koelle 1975; Russell 1976) is the primary reinforcer in cigarette tobacco.

A growing literature has been devoted to establishing nicotine seeking as a basic mechanism in smoking. Titration, the self-regulation of smoking and presumably nicotine intake, has been demonstrated both behaviorally and physiologically using variables such as number of cigarettes and puffs, butt nicotine residue, and the quantity of nicotine found in various body fluids (Ashton and Watson 1970; Frith 1971; Russell et al. 1975; Lucchesi, Schuster, and Emley 1967; Goldfarb et al. 1976; Gritz, Baer-Weiss, and Jarvik 1976).

It is perplexing to investigators in this field that nicotine titration has been only moderately demonstrated; people seem to smoke for reasons other than *to* self-administer nicotine. Some of these reasons may be inherent in the secondary reinforcing value acquired by components of the behavior. In the first place, secondary reinforcers such as the sight, smell, and handling of a cigarette are capable of developing great strength through association with a primary reinforcer which, in this case, is delivered at the rate of once per puff. For the "average" pack-a-day smoker, this amounts to 73,000 reinforcements per year. It is very possible that overlearning and stereotypy of motor behavior may mask or prevent titration of nicotine intake. Secondly, when smoking is studied in a laboratory situation and experimental cigarettes are used, results may be confounded by taste aversions and changes in the burning and filtration properties of the cigarettes.

Two experiments performed in naturalistic situations with commercial cigarettes also indicate that smokers do titrate intake by changing the way in which they smoke their cigarettes. Russell et al. (1975)

gave smokers cigarette: of high, medium, and low nicotine content in their work environment. The number of high nicotine cigarettes smoked was reduced 38% and the number of low nicotine cigarettes increased an average of two cigarettes compared to the medium nicotine cigarettes. Plasma nicotine levels were more similar in the high and medium nicotine conditions than in the medium and low nicotine conditions. Russell concluded that the plasma nicotine levels obtained after smoking depended more on how the cigarette was smoked than on the nicotine content of the cigarette, since the low nicotine cigarettes had tight filters and were very aversive in drawing quality.

In the second experiment, Vogt, Selvin, and Billings (submitted for publication) demonstrated a similar effect with smokers enrolled in a disease prevention program. The general aim of the study was to help participants reduce their levels of smoking, serum cholesterol, and blood pressure. Measures of expired air carbon monoxide (CO) and serum thiocyanate (SCN) were taken at the beginning and up to a year following treatment to correlate with smoking. SCN and CO values correlated with change in the number of cigarettes smoked? but opposite to the predicted direction. Those who failed to quit smoking and only cut down on the number of cigarettes smoked actually increased their exposure per cigarette. Presumably they compensated for smoking fewer cigarettes by smoking them more thoroughly.

Both studies demonstrate that smokers changed their puffing pattern when their cigarette or nicotine intake was varied. Furthermore, relatively little attention has been paid to the “finer grain” behaviors in smoking: the parameters of puffing, which include number of puffs, duration, volume, inter-puff interval and depth of inhalation. Fredericksen, Miller, and Peterson (1977) observed changes in the topographical components of smoking behavior (i.e., cigarette duration, puff frequency, puff volume, and inter-puff interval) during an experimental session after subjects were instructed to alter one or more components. They reported a strong interrelationship between components, such that changes in one produced compensatory adjustment in others.

The series of studies reported in this paper represents an initial attempt to assess some of the parameters of puffing. In the first study, the rate at which cigarettes were presented to smokers was increased to twice and four times baseline (ad lib) rates. In a subsequent pilot study, the role of visual variables in the stimulus control of smoking was evaluated by comparing a baseline smoking condition to conditions in which subjects smoked through transparent (lucite) and opaque (wooden) “smoke screens.” Finally, some observations will be offered from an exploratory study in which puffing parameters were analyzed when subjects smoked their own cigarettes and specially prepared nicotine-free tobacco cigarettes under conditions of smoking deprivation and no deprivation.

EXPERIMENT 1

Subjects

Eleven paid volunteers from the Veterans Administration Hospital Brentwood gave informed consent to participate in the experiment. Subjects were drug-free male patients who ranged in age from 26 to 56 years (mean = 40.6) and who smoked an average of one pack of cigarettes per day.

Apparatus

All subjects smoked each cigarette through a modified plastic holder. The holder contained a sensing device, a thermistor, which was activated whenever air passed over it. The cigarette holder was attached to a freely extending lead that could be either held in the hand or affixed to an opaque panel. The cigarette holder apparatus was interfaced with a Vetter 8-channel magnetic tape recorder which recorded the occurrence and duration of each puff, and starting time of each cigarette. The tapes were played back into an IBM 360/91 computer at the University of California, Los Angeles, Health Sciences Computing Facility via a Sykes floppy disc system.

Procedure

Each subject served in four conditions in a repeated measures design: baseline (ad lib smoking), two and four times baseline rate, and opaque smoke screen. The baseline condition always occurred first; the order of the remaining three conditions was randomized. In the two and four times baseline conditions, cigarettes were presented at timed intervals and subjects were required only to light each cigarette. In the smoke screen condition, the opaque screen was positioned so that subjects could remain seated and merely turn their heads to take a puff on a cigarette. Cigarettes were kept constantly lit from the opposite side of the panel and out of view of the subject. Subjects were free to smoke or take puffs on an ad lib basis in all conditions. Television and reading material were available during the two-hour session.

EXPERIMENT 2

Subjects

Four paid volunteers from the Veterans Administration Hospital Brentwood gave informed consent to participate in the experiment. Subjects were drug-free male patients who ranged in age from 40 to 60 years (mean = 51) and who smoked an average of 47.5 cigarettes per day.

Apparatus

The cigarette holder and opaque screen were identical to those used in Experiment 1. In addition, a clear lucite screen of identical dimensions was used.

Procedure

Each subject served in three conditions in a repeated measures design: baseline (ad lib smoking), opaque screen, lucite screen. The order of conditions was randomized for each subject. As in the previous experiment, sessions were two hours in length and subjects were free to smoke or take puffs on an ad lib basis in all conditions. Television and reading material were available. During the two smoke screen conditions, the cigarette holder was affixed to the panels as described in Experiment 1. When the lucite screen was used subjects could see the lighting and burning of each cigarette on the opposite side of the panel.

EXPERIMENT 3

Subjects

Nine paid male volunteers who were either UCLA staff or students, or outpatients from the Veterans Administration Hospital Brentwood participated in the experiment. Subjects ranged in age from 21 to 40 (mean = 29) and smoked an average of one pack of cigarettes per day.

Apparatus

The cigarette was affixed in a Fleisch flow meter which was connected in series with a Statham strain gauge and a magnetic tape drive. The air flow produced by puffing (puff volume) created a differential pressure, which was converted into a variable resistance; i.e., a constant current of 10 mamp was passed through the Statham strain gauge, and the voltage across it was measured. The voltage was recorded as an analog signal on magnetic tape, to be later digitized and analyzed on an IBM 360/91 computer at the Health Sciences Computing Facility, UCLA.

Nicotine-free tobacco, genetically bred at the University of Kentucky, was processed into unfiltered cigarettes and donated by International Flavors and Fragrances, Inc.

Procedures

Each subject reported to the laboratory on two separate occasions, once having been deprived of smoking since the previous evening, and once in a non-deprived state. Subjects smoked two cigarettes through the apparatus, one of their own brand, and one which was nicotine free. The order of cigarettes was balanced across subjects and cigarettes were smoked 45 minutes apart.

RESULTS

Experiment 1

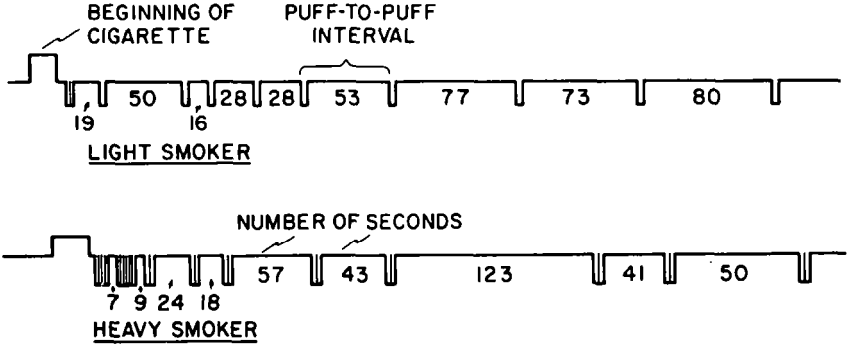
Data was calculated on all puff-to-puff intervals excluding the interval between completing one cigarette and lighting the next. Short

puffs following the first puff of each cigarette were also eliminated from the analyses, as they represent an artifact of inhaling to light up.

Subjects smoked an average of 5.5 cigarettes (range = 4-7) in two hours of ad lib smoking. Nine of eleven subjects smoked either five or six cigarettes. Subjects lit a cigarette approximately every 20 minutes in baseline, every 10 minutes in the doubled rate, and every five minutes in the quadrupled rate condition.

The puff-to-puff (P-P) interval is defined as the time lapsed from the onset of one puff to the onset of the following puff (Figure 1).

FIGURE 1

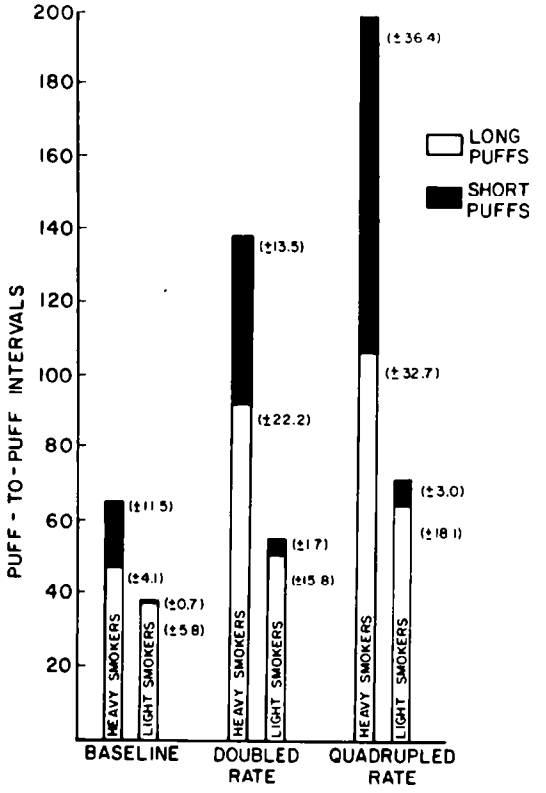


Polygraph record of a typical baseline cigarette: heavy and light smoker

When visual records of the pattern of puffing were examined, the presence of two distinct types of smokers was revealed: a group (n = 5) who had a mixture of long (5 seconds or greater) and short (less than 5 seconds) P-P intervals, and a group (n = 6) who had almost exclusively long P-P intervals. The former were, on the average, heavy smokers (mean = 30 cigarettes/day) and were older (mean = 54 years), compared to the latter group who were, on the average, lighter smokers (mean = 18 cigarettes/ day) and younger (mean = 30 years). Therefore, comparisons between these two subgroups were made on a post hoc basis.

Figure 2 presents the number of long and short P-P intervals for light and heavy smokers across conditions. It can be seen that the light smokers do not markedly increase the number of P-P intervals even when given quadruple the baseline number of cigarettes. On the other hand, the heavy smokers continue to increase the number of both long and short P-P intervals across conditions.

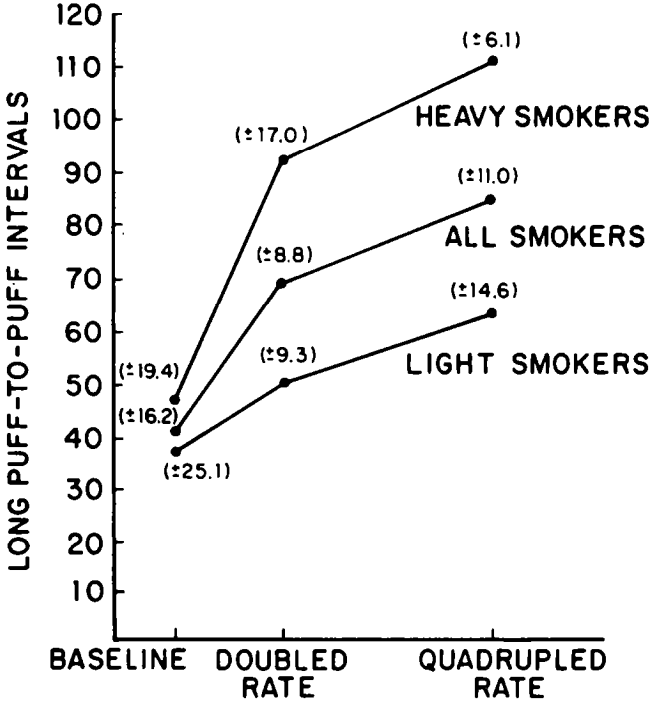
FIGURE 2



Number of long and short puff-to-puff intervals for heavy and light smokers in baseline, doubled rate and quadrupled rate conditions (mean and s. e.)

Figure 3 depicts the number of long P-P intervals across conditions for the entire group and for the light and heavy smoker subgroups.

FIGURE 3

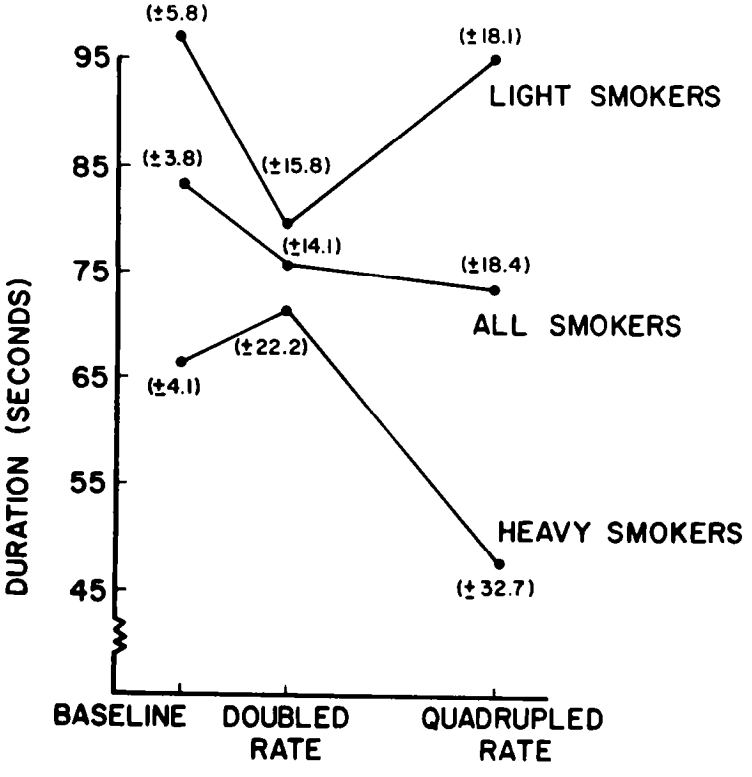


Number of long puff-to-puff intervals for heavy and light smokers in baseline, doubled rate and quadrupled rate conditions (mean and s.e.)

The between condition effect was significant ($F = 4.55$, $df = 2,20$, $p<0.05$) for all subjects, but does not reach significance for either subgroup.

There was no significant change in the duration of the long P-P interval across conditions. The mean duration ranged from 73.4 to 83.4 seconds across conditions. Light smokers spaced their puffs farther apart than heavy smokers (Figure 4).

FIGURE 4

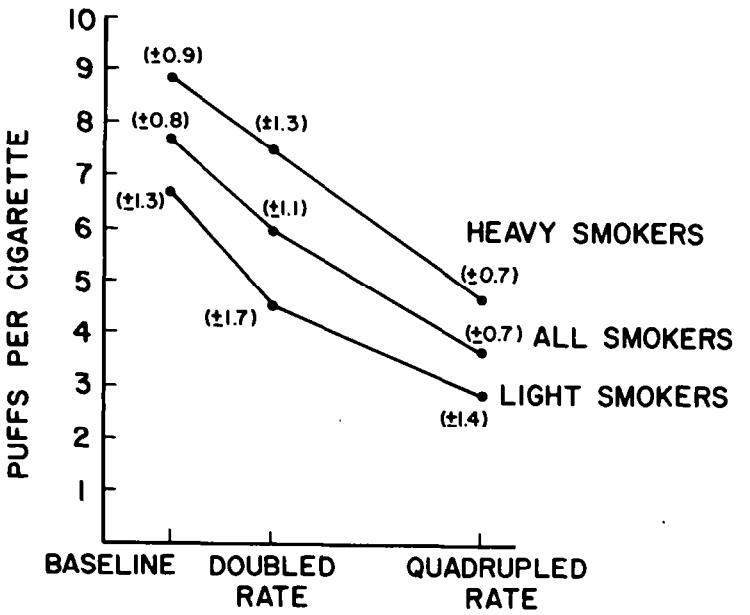


Duration of Long puff-to-puff intervals for heavy and Light smokers in baseline, doubled rate and quadrupled rate conditions (mean and s.e.)

Heavy smokers attempted to maintain a constant number of puffs per cigarette in the double-rate condition, decreasing only 1.5 puffs,

(n.s.), while light smokers decreased approximately three puffs per cigarette ($F = 3.81$, $df = 2,15$, $p<0.05$) (Figure 5).

FIGURE 5

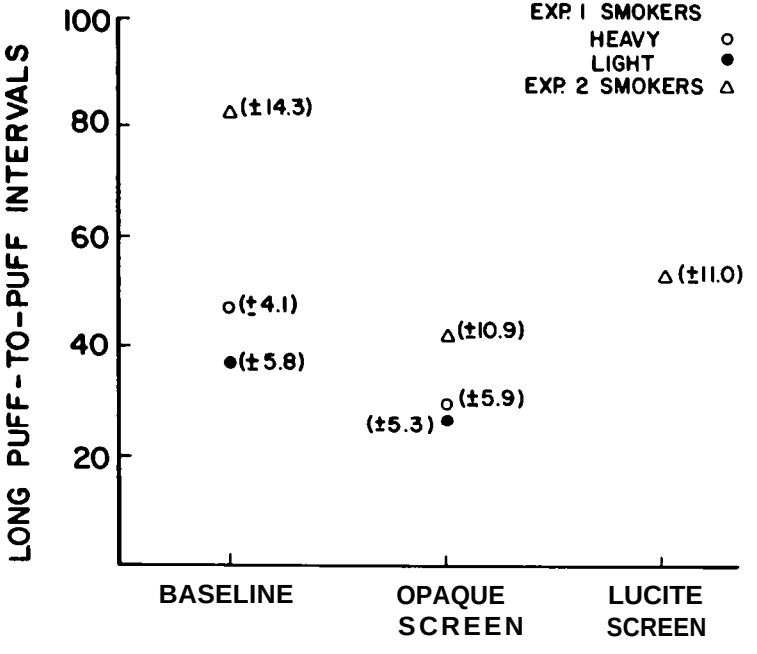


Number of puffs per cigarette for heavy and light smokers in baseline, doubled rate and quadrupled rate conditions (mean and s. e.)

For all subjects, the decrease in puffs/cigarette across conditions was also significant ($F = 4.91$, $df = 2,30$, $p<0.01$). The rate of lighting cigarettes in the quadrupled-rate condition was confounded by the fact that subjects were often interrupted while smoking one cigarette *to* light the next.

Smoking was depressed in the opaque screen condition for all subjects ($t = 2.81$, $df = 10$, $p<0.02$) (Figure 6).

FIGURE 6



Number of long puff-to-puff intervals for heavy and light smokers and smokers from Exp. 2 across baseline, opaque and lucite screen conditions (mean and s.e.)

The number of long P-P intervals dropped markedly for both heavy and light smokers compared to baseline values.. This figure also presents data from Exp. 2.

Experiment 2

Subjects in Exp. 2, referred to in the figure as Exp. 2 smokers, were heavier smokers than those in Exp. 1. This is evidenced by the fact that the mean number of long P-P intervals in baseline was approximately double that of subjects in Exp. 1 (Figure 6). However, although subjects in Exp. 2 smoked a mean of 9.5 cigarettes in baseline, their average number of puffs per cigarette (8.7) was similar to that of the heavy smokers in Exp. 1.

Puffing was more depressed on the opaque smoke screen (51 percent of baseline) than on the lucite smoke screen (63.6 percent of baseline), although the overall difference among conditions was only marginally significant ($F = 3.02$, $df = 2,9$, $p<0.09$).

Experiment 3

In this study, the four variables selected for analysis were puff duration, puff volume, maximum rate of inhalation and location of the maximum (Figure 7).

FIGURE 7

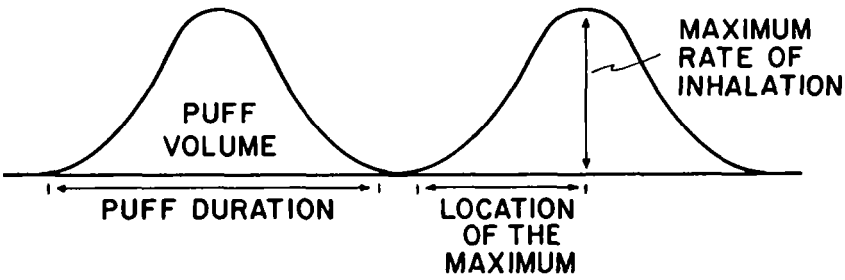


Diagram of *variables used* in puff *pattern analyses, Exp. 3.*

The first seven puffs on each cigarette were analyzed. Different burning properties of the experimental nicotine free and commercial cigarettes precluded use of number of puffs as a variable. Puff volume and maximum rate of inhalation are expressed in arbitrary units because of mechanical difficulties with calibration.

Puff duration was significantly shorter when subjects had abstained from smoking than when they had not, regardless of cigarette nicotine content ($F = 14.4$, $df = 1,8$, $p<0.005$) (Table 1). Deprivation also affected puff volume. Puffs were marginally greater in volume in the nondeprived condition ($F = 4.65$, $df = 1,8$, $p<0.063$).

TABLE 1

Condition	Puff Duration (sec)		Puff Volume		Maximum Rate of Inhalation	
	Cigarette type		Cigarette type		Cigarette type	
	Commercial	Nicotine-free	Commercial	Nicotine-free	Commercial	Nicotine-free
Deprived	2.6	2.5	1.17	1.59	171.4	186.7
Non-Deprived	2.8	3.0	1.58	1.73	185.9	197.0

Exp. 3: Summary of puff duration, puff volume and maximum rate of *inhalation*

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Nicotine content of the cigarette significantly affected only maximum rate of inhalation, or peakedness of the puff: the nicotine-free cigarettes were inhaled more sharply ($F = 17.78$, $df = 1,8$, $p<0.003$). When subjects were deprived, the maximum rate of inhalation was differentially greater on the nicotine-free than on the nicotine cigarettes (significant deprivation x nicotine content interaction) ($F = 26.05$, $df = 1,8$, $p<0.001$).

The variables reflecting skewness of the puff showed no differences between conditions on either variable.

DISCUSSION

The studies described in this paper were undertaken to further elucidate the manner in which smokers self-regulate nicotine intake. This was done by examining some of the parameters of smoking behavior not routinely measured.

Although the number of cigarettes smoked per day was not included as a variable in the design of these experiments, it was discovered that there were differences in the way cigarettes were smoked by light and heavy smokers. The small sample size of these two subgroups most likely accounted for the lack of statistically significant differences in the variables discussed in the paper. In Exp. 1, the light smokers, who averaged 18 cigarettes per day, took discrete, well-spaced puffs, while the heavy smokers, who averaged 30 cigarettes per day, often took rapid successive puffs. It is likely that the short puff-to-puff intervals represent deep inhalations, an attempt by heavier smokers to maximize nicotine intake.

The light smokers attempted to titrate their smoking, that is, to maintain a constant rate of puffing across all two-hour sessions, even when lighting two and four times the number of cigarettes smoked ad lib (Figure 2). On the other hand, the heavy smokers demonstrated stereotypy of motor behavior; this is most clearly seen by looking at the number of puffs per cigarette (Figure 5). Heavy smokers took almost as many puffs/cigarette when smoking at double their ad lib rate, while light smokers decreased the number of puffs/cigarette by 33 percent. Puffs/cigarette were automatically decreased in the quadrupled rate condition since subjects smoking one cigarette were often interrupted to light the next.

Spacing of puffs (duration of P-P interval) did not change significantly across conditions, and so does not seem to be a mechanism in titration. We have as yet to examine sequential duration effects, either within a cigarette or over a two-hour session.

From the results of Exp. 1, it is clear that light smokers titrate by regulating the total number of puffs and not by spacing of puffs. Depth of inhalation and puff volume were not measured in this study, but we can hypothesize from the pattern of “short” puff-to-puff intervals in heavy smokers that depth of inhalation is important in regulating nicotine intake. The study of Vogt

and his colleagues (submitted for publication) and other reports (Schachter 1978) of smokers switching to low-nicotine cigarettes suggest adaptations in inhalation do occur.

Some clues to the mechanisms operative in titration are provided by Exp. 3. In this pilot exploration, there were significant changes in puff duration and volume related to smoking deprivation, but not to cigarette nicotine content (Table 1). Non-deprived smokers may take longer, deeper (greater volume) puffs than deprived smokers because. acute tolerance diminishes the effects of nicotine. The maximum rate of inhalation changed significantly as a function of cigarette nicotine content; however, this finding may have been confounded by the differential burning and filtration properties of the cigarette used. We are beginning a replication of this study in which light and heavy smokers will be compared, and cigarettes used will be identical in burning properties and filtration.

Another dimension to the regulation of puffing was added by the use of opaque and transparent "smoke screens" (Figure 6). The number of puff-to-puff intervals radically decreased (approximately 50 percent) when ad lib smoking was compared to opaque screen condition. The clear screen depressed smoking somewhat less than the opaque screen, although subjects still took 36 percent fewer puffs. The depression of puffing may be due to a loss of stimulus control, of the secondary reinforcing value of lighting, handling factors, and visual factors (in the opaque condition), or to the generally aversive nature of puffing at a cigarette stuck in a board.

We may conclude from these studies of puffing behavior that there are differences among subjects in the way cigarettes are smoked, that these differences are very likely a function of the overall rate at which subjects smoke, and that lighter smokers do try to titrate their smoking behavior, while heavier smokers show stereotypy in the puffing variables measured. Heavy smokers may have greater tolerance to nicotine than light smokers. They may thus be able to increase their intake up to some limit without experiencing the toxic effects to which light smokers may be more sensitive. Then again, heavy smokers may be like the obese individual who will eat whenever food is presented, ignoring satiety mechanisms. The parallels have yet to be explored.

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Chapter 16

Self-Administration of Cigarettes With Varying Tobacco' and Nicotine Content

Murray E. Jarvik, M.D., Ph.D.

Of all the self-administered substances discussed in this volume, alcohol, heroin, and food, none is self-administered at a higher rate than cigarette smoke. A chain smoker can light a cigarette every five to ten minutes, and puffing occurs once every twenty or thirty seconds. Of course, the average pack-a-day smoker only uses twenty cigarettes per day, but even so, with nine or ten puffs per cigarette this amounts to more than 70,000 puffs per year. We want to know what factors maintain such high rates of responding in a habit so apparently meaningless as the sucking in of smoke from burning vegetable matter. We surmise that smoking is really drug seeking behavior, and that smokers attempt to regulate their levels of nicotine intake. Probably the nicotine is sought because it produces some pleasurable sensation by an action on the brain or it reduces unpleasant sensations also by acting upon the brain.

If a smoker is attempting to keep the level of nicotine constant, say in the blood, and if we lower the amount of nicotine available in a cigarette, then he should compensate by smoking more. One indirect way to test this hypothesis is to give shortened cigarettes to smokers and measure the smoking response. Each cigarette will deliver not only less nicotine but all other components of the cigarette which have been burned and converted into smoke. We can test the nicotine hypothesis directly by lowering or raising the nicotine content of cigarettes and seeing whether subjects will smoke more or less in accordance with the content.

There have been a few other attempts to vary nicotine levels in cigarettes and see whether compensatory behavior resulted. One of the reasons why such studies have been few is that cigarettes varying in nicotine content simply have not been available. The first published experiment in which nicotine was varied by comparing low nicotine cigarettes with the same type of cigarettes to which nicotine had been added was by Finnegan, Larson, and Haag (1945). They found that some smokers smoked the same number of cigarettes whether the nicotine content was low or normal. These subjects expressed great dissatisfaction with the cigarettes. On the other hand smokers who tended to increase their consumption of low nico-

tine cigarettes tended not to miss the nicotine. Thus, they provided evidence that some smokers will compensate for the lack of nicotine by smoking more. More recently Russell et al. (1975) found that smokers did attempt to compensate for low nicotine levels in experimental cigarettes by smoking more, but not nearly enough to compensate for the diminution in nicotine. Correspondingly, the blood levels of nicotine fell in these subjects who were unable to compensate. Subject satisfaction with these low nicotine cigarettes was low.

Goldfarb, Jarvik, and Glick (1970) in our laboratory found that lettuce cigarettes were disliked by smokers. When nothing else was available they did smoke them, but to a lesser extent than their own cigarettes. Adding nicotine to these cigarettes did not increase their acceptability even though subjects were able to accept the change in strength. One explanation is that the aversiveness of the burning lettuce swamped all other effects. However, another possibility is that nicotine in regular cigarettes interacts in some way with other components, perhaps the tar, to produce the effects desired by the smoker. Gritz, Baer-Weiss, and Jarvik (1976) gave smokers full length cigarettes and instructed them to smoke in their usual way on some days, and on other days only half way down, to a red mark. On a different day, subjects were given cigarettes cut in half. When 24-hour urinary contents were measured it was found that the nicotine excreted was highest for the whole cigarettes, lower for the proximally smoked cigarettes and lowest for the distally smoked cigarettes. The amount extracted from half cigarettes was more than half the amount extracted from the full cigarettes, so apparently some compensation occurred, perhaps in the way the cigarettes were smoked.

Nicotine can also be taken by routes other than inhalation. Chewing tobacco and snuffing snuff used to be fairly popular ways of using tobacco and presumably of absorbing nicotine. Johnston (1942) administered nicotine hypodermically and felt that it substituted for smoking, but his studies were uncontrolled. Lucchesi, Schuster, and Emley (1967) found that intravenous nicotine produced some diminution in smoking, but Kumar et al. (1977) could not produce any effect on rate of smoking with intravenous nicotine. The Lucchesi experiment was probably a more valid estimate of intravenous nicotine action because the Kumar study undoubtedly used inadequate amounts of nicotine. Kumar et al. (1977), however, found that preloading with high nicotine but not low nicotine cigarettes did diminish subsequent smoking and one would have to ascribe this effect to the nicotine alone since all other factors were held constant. Nicotine chewing gum (Russel, Feyerabend, and Cole 1976; Kozlowski, Jarvik, and Gritz 1975) or even nicotine swallowed in orally administered capsules (Jarvik et al, 1970) produced decreases in smoking. One possible explanation is that the subject attempted to titrate his nicotine levels by smoking less in the face of increased levels produced by these other types of administration.

Another approach used in our laboratory was to block nicotine with mecamylamine, a drug that crosses the blood brain barrier. This produced an increase in smoking. Pentolinium, a peripheral blocking agent, produced no such effect (Stolerman et al. 1973).

The existence of some attempt to titrate nicotine intake shows that nicotine seeking plays at least some role in smoking. The lack of perfect titration indicates that other factors, presumably secondary reinforcers, play a role in maintaining the smoking behavior. It is possible or even likely that a smoker's need or desire for nicotine may fluctuate with time and with the effect that he desires from the nicotine. Until we can identify these factors we assume that his nicotine need is constant over time and of course assumption probably is an added source of variance. At any rate if we assume that the smoker attempts to keep his nicotine intake constant within limits, then the way he can control the nicotine intake is to vary the rate at which he lights cigarettes, to modify his puffing rate, and to change the topography of each puff. The present experiment examined the first two variables.

In Experiment 1 nine paid volunteers from the Veterans Administration Hospital Brentwood participated. Their ages ranged from 25 to 50 years and they reported smoking an average of 18.5 cigarettes per day.

Subjects were tested in an air-conditioned room where they sat for two hours watching television. They were instructed to insert the cigarette into a special cigarette holder containing a thermistor which was activated whenever air passed over it. This device was connected through appropriate circuitry to a Vetter 8-channel physiological magnetic tape recorder which recorded the puffs against time. Puffs were later analyzed with special counting apparatus.

Each subject was tested in four different conditions. On the first day they smoked their own brand of cigarettes and on successive occasions these same brands were given in whole, half, quarter and one-eighth lengths with random orders. Subjective evaluations of satisfaction with cigarettes were made at the end of each session and a seven-point semantic differential scale was used.

The results can be seen in Table 1. As the cigarette length decreased the number of cigarettes smoked increased ($F=14.85$, $p<0.001$) with a linear trend ($F=18.30$, $p<0.03$). T-tests performed between all possible pairs of means for number of cigarettes were significant at the .01 level except between half and quarter lengths.

The number of puffs was greater for shorter cigarettes and the differences were significant ($F=3.91$, $p<0.02$) and linear ($F=6.38$, $p<0.03$). Differences between whole and quarter, half and quarter, and half and eighth, were significant by t-tests. The average number of puffs per cigarette, of course, decreased with decreasing length. Satisfaction was inversely proportional to length, i.e., shorter cigarettes were less satisfying. These changes were also highly significant.

The second experiment was designed to examine the effects of varying both nicotine content and length of cigarettes. Twenty-eight male and one female volunteers from the Veterans Administration Hospital Brentwood participated in this study. They were 23 to 54 years of age

TABLE 1

Condition		Size of Cigarette			
		1/8	1/4	1/2	1
Number of cigarettes	Mean	15.2	10.3	8.2	5.4
	s.d.	(6.4)	(3.5)	(2.3)	(1.8)
Number of Puffs	Mean	43.7	3 . 8	53.7	54.0
	s.d.	(19.9)	(15.4)	(14.6)	(11.5)
Puffs per cigarette		2.9	4.2	6.5	9.7
Satisfaction Ratings	Mean	2.7	3.6	4.9	5.2
	s.d.	(1.4)	(1.1)	(1.4)	(1.2)

Number of Cigarettes, Puffs, and Satisfaction Ratings
In Z-Hour Sessions
As a Function of Cigarette Size

and smoked at least a pack a day. Experimental cigarettes were used and these were supplied by Dr. Gio Gori of the National Cancer Institute. The cigarettes were made from the same tobacco, but the low nicotine cigarettes delivered 0.2 mg nicotine per cigarette and the high had nicotine added so that they delivered 2.0 mg nicotine per cigarette.

A 2x2 factorial design with repeated measures was used; all subjects served in all four conditions. Again sessions took place in the same experimental rooms, subjects were allowed to smoke ad lib but always through the holder that counted their puffs. After each session strength and satisfaction ratings were made of the cigarettes smoked in that session. It can be seen in Table 2 that subjects smoked more low nicotine cigarettes and also puffed more on low nicotine cigarettes than on high nicotine cigarettes. Similarly subjects smoked more quarter length than full length cigarettes. All of these differences were highly significant. Although they puffed more on the long than on the short cigarettes, they puffed proportionately more on the short cigarettes when the factor of length is taken into account. The number of puffs per cigarette remained constant in the face of changing nicotine content. This indicates that number of cigarettes smoked and not puffing rate was used to compensate for change in nicotine content.

The satisfaction ratings were low and approximately equal for both nicotine content and length. There is a suggestion that subjects disliked all of these experimental cigarettes since their satisfaction rating ranged around 4.0 or lower, whereas subjects rated their own cigarettes in the previous experiment about 5.2. It is very likely that the nicotine deliveries were either too high or too low, certainly not the middle range of 1.0 to 1.5 that they were used to. Strength was accurately judged by the subjects.

In the first study it was clear that the subjects did not smoke eight times as many of the one-eighth cigarettes but only three times as many. The lack of perfect titration was not unexpected. First of all, a small cigarette is much stronger than a long one, because it has less filtering capacity. Lighting the small cigarette is more difficult and it takes more effort to smoke the additional number of small cigarettes to equal the tobacco or smoke content of the longer ones. The satisfaction ratings show a linear trend with longest cigarettes being liked most. This meant that subjects preferred the length they were used to. Familiarity probably plays an important role in satisfaction rating of all sorts of things. As a general rule one probably prefers a familiar form of stimulation to a new one particularly if one has had an opportunity to seek out an optimal level of that type of stimulation in the past. Since cigarettes varying pretty widely in nicotine content are available on the market, one can assume that the subjects already selected their favorite brands on the basis of a desirable level of nicotine delivery and any deviation would be less preferred.

The number of puffs per cigarette decreased monotonically with the length of the cigarette. But subjects took proportionately more puffs on the shorter cigarettes. It may take more puffs to light one of

TABLE 2

		Cigarettes		Puffs		Puffs/Cigarette	
		Low	High	Low	High	Low	High
Long							
	Mean	7.0	5.7	58.8	50.7	8.4	8.9
	s.d.	(2.8)	(2.7)	(29.6)	(32.4)		
Quarter							
	Mean	14.0	11.7	49.9	40.3	3.6	3.4
	s.d.	(10.4)	(10.2)	(48.1)	(33.9)		

Number of Cigarettes and Puffs in 2-Hour Sessions As a Function of Cigarette Size and Nicotine Content

the shortest cigarettes than to smoke it, and this tends to give a disproportionate weighting of this measure to the shorter cigarettes. Also subjects tended to smoke the shorter cigarettes right down to the end, whereas they stopped smoking or even put out the longer cigarettes before they burned down to the end.

In the second experiment, although there was a significant effect of nicotine content in the expected direction, the subjects fell short of perfect titration. There was less than a 20 percent change in the smoking rate related to nicotine, and one might have expected a tenfold change since there was a tenfold difference in nicotine delivery. Similarly, although the long cigarette was four times the length of the short, there was only about a 50 percent change in the number of short cigarettes smoked. Such factors as behavioral stereotypy, inertia, and a change in puffing parameters may have contributed to these results.

In summary, it is clear that subjects do regulate their nicotine intake and attempt to keep it within optimal limits. We assume that we were measuring smoking under basal conditions where titration should be optimal. Since people smoke more under conditions of stress or boredom (Fuller and Forrest, 1973) they may adjust their nicotine intake to maintain a comfortable level. In future studies we will vary stress and measure nicotine in blood and possibly spinal fluid.

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U.S. GOVERNMENT PRINTING OFFICE : 1979-0-304-494

DHEW Publication No. (ADM) 80-727
Formerly DHEW Publication No. (ADM) 78-727
Printed 1977 Reprinted 1979