# Behavioral Pharmacology of Human Drug Dependence

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A review of the contributions of research on behavioral mechanisms of drug dependence, to interpret the relation of animal and human behavioral pharmacology findings to prevention of human drug dependence. The monograph brings together concepts from clinical and behavioral pharmacology and seeks the common processes underlying various forms of substance abuse. It describes effects of personality and the individual's history of drug exposure upon drug self-administration and discusses control of drug-related behavior by external and internal stimuli. Other sections deal with commonalities and differences among reinforcers and the maintenance of drug dependence by complex second-order schedules, in which drug-using behavior is maintained by environmental stimuli only remotely linked with drug administration. Intended readership includes clinicians, researchers, pharmacologists, and others interested in behavioral analysis and treatment of drug dependence.

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# Behavioral Pharmacology of Human Drug Dependence

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Drs. Travis Thompson and Chris E. Johanson served on the staff of the Clinical/Behavioral Branch, NIDA Division of Research, during the 1979-1980 academic year by agreement under the Intergovernmental Personnel Act of 1970 (IPA). Dr. John Grabowski has been serving in a similar capacity since October 1980.

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# Foreword

The behavioral description of drug dependence which began with anecdotal accounts has now progressed to the sophisticated behavioral analysis so well summarized in this monograph. The result of a technical review held by the National Institute on Drug Abuse (NIDA), this book describes a growing body of systematically derived data on the behavioral mechanisms involved in the use of drugs and their all too frequent abuse. By emphasizing human use, it provides a valuable link between the neatly arrayed drug use paradigms of the animal laboratory and those governing street drug use.

By describing some of the remarkable parallels in many forms of substance abuse--from smoking cigarettes to mainlining heroin--we hope that this monograph will be both a useful compendium of what is presently known about the behavioral pharmacology of drug dependence and a spur to additional research.

Many difficult issues inherent in this increasingly sophisticated research area have been addressed by an impressive diversity of researchers. As our understanding of these behavioral mechanisms is enhanced, so is the possibility of more effective prevention and treatment. It is that goal--ultimately minimizing the extent and cost of dysfunctional drug use--to which NIDA dedicates its research efforts. We hope that this book will help to provide the scientifically based foundation upon which better intervention techniques must be built.

Robert C. Petersen, Ph.D.
Editor-in-Chief
NIDA Research Monograph Series

# Preface

The National Institute on Drug Abuse (NIDA) has published in its Research Monograph series several volumes focusing on the discipline of behavioral pharmacology. These monographs represent only a sampling of the extensive data base which has developed over the past two decades. Their content closely parallels the history of the field, reflecting its foibles as well as its evolution toward greater sophistication. Clearly, many important questions remain, and investigators will not find it difficult to identify areas requiring further research, as is well documented in the pages of this volume.

Many investigators have been involved in the expansion of our knowledge and understanding of the orderly relationships between drugs and behavior; a few have made particularly notable contributions in the field of drug abuse research. Dr. Joseph Brady, for example, has contributed substantially to the shaping of the discipline itself and to the careers of several of the investigators represented in this volume. Drs. Norman Krasnegor and Pierre Renault, while serving at NIDA, devoted persistent and energetic efforts toward development of an integrated program in behavioral pharmacology of drug dependence. Their work and that of many other individuals has been reflected in this monograph series and in the philosophical and technological evolution of the field.

Behavioral pharmacology has evolved into a mature discipline. Drs. Thompson and Johanson have provided us with a monograph indicative of the field's vitality, which both delineates and goes well beyond efforts of the past.

Progress in behavioral pharmacology as represented in microcosm in this volume is not a chimera. It is evidenced in two ways. First, "steps beyond" are evident in the hard data. For example, additional important data on aspects of drug self-administration are presented. Drug actions and interactions under a greater variety of circumstances are considered and explicit factors modulating drug effects are more clearly delineated. Specific data based and data bound advances such as these are, and should be, the foundation of science.

It is from expansion and integration of the data that a second category of "steps beyond" emanates. In the present volume, the fields and subfields of psychology, psychiatry, pharmacology, and neurology are all represented. Thus it is fair to say that the interdisciplinary nature of behavioral pharmacology is now well established. Rapprochement is clearly increasing. A joining of the conceptual, methodological, and technological approaches of traditional pharmacological and psychopharmacological perspectives with those of behavioral pharmacology is evident. Each of the disciplines stands to gain from interdisciplinary activity, the sharing of traditional wisdom, and by utilizing innovative techniques--all trends clearly manifested in this monograph. From this vantage point the volume presents an integrated conceptual framework for delineating behavioral mechanisms of drug dependence across a range of levels of analysis.

Within the psychological viewpoints represented, the need for reconciliation of classical and operant psychological perspectives in analyzing drug use and drug effects has become apparent and has emerged herein. Similarly the need to account for and measure human behavioral idiosyncracies such as verbal behavior, an area in which animal models are limited, is also addressed. It is also evident that better understanding of the limitations of animal models has enhanced their usefulness. As a result data from the animal laboratory has increased our understanding of aspects of drug use and has most certainly disproved Sir William Osler's comment that "the desire to take medicine is perhaps the greatest feature which distinguishes man from animals." Overall, robust and significant linkages have emerged between basic and applied, and laboratory and clinical, research.

The efforts to develop statements concerning substance abuse which are of greater scope and generality are direct consequences of this coming together of diverse perspectives. However, a word of caution must prevail. While "seeing the forest" of general statements and unifying concepts is important, it should be remembered that this has resulted from inspecting the individual trees. Careful experimental analysis and precise atheoretical data-seeking (couched in creativity) have, after all, been the methods by which our revelation of the forest has occurred.

The present volume emphasizes "commonalities" in data, descriptions, and explanations for diverse habitual patterns of behavior. In this sense behavioral analysis has come full circle. Initially the findings of early nondrug studies were used to shore up our basis for understanding substance use and abuse. At this juncture, techniques and conceptual vantage points derived from the study of interrelationships of pharmacological, behavioral, and environmental variables in drug abuse have been turned to advantage in better understanding parallel nondrug phenomena. This evidence best represents the progress and promise of behavioral pharmacology as a discipline and points to the need to maintain and nurture its development.

As with earlier volumes in this series, answers are presented while further questions are raised. This volume certainly reflects

advances in the science of behavioral pharmacology and points to the ultimate goals of a better understanding of human behavior, alleviation of disorders characterized by dysfunctional and maladaptive substance use, and improved treatment with behaviorally active drugs.

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STIMULUS CONTROL AND DRUG DEPENDENCE



COMMONALITIES AND DIFFERENCES AMONG REINFORCERS



COMPLEX SCHEDULES AND MAINTENANCE OF DRUG DEPENDENCE

# Introduction and Overview

# Behavioral Mechanisms and Loci of Drug Dependence: An Overview

Travis Thompson, Ph.D.

The search for a more thorough understanding of the basic common processes underlying drug dependence has been thwarted by the lack of a conceptual map of the terrain. Investigators have been in the position of the crew in Lewis Carroll's The Hunting of the Snark. The Bellman brought a map purporting to show the elusive Snark's location: once the voyage was underway, however, the crew discovered the map was completely blank. All too often those of us in the field of drug dependence find ourselves floating on an uncharted conceptual sea, zigging and zagging in search of a common causal process. It would be as naive to suppose that all forms of heart disease have a common cause. Instead, it is more reasonable to suppose that, just as there are similarities in the symptoms in various forms of heart disease, there are also similarities in the symptoms in various forms of drug dependence. However, in both cases one cannot expect the normal controlling mechanisms to have gone awry in precisely the same ways. It must be assumed that a relatively limited number of variables, whose weightings differ among forms of substance abuse, interact to produce the various states of dependence (see Levison's discussion, this volume).

A second problem facing the field has been the absence of a unit of analysis and a metric for assessing the control drugs exercise over the behavior of the user. It wasn't until the mid 1960's that control over objectively measurable behavior was suggested as a criterion for assessing dependence-producing properties of drugs.

Finally, we have struggled to develop more objective ways of assessing behavioral consequences of the drugs which are self-administered, and to provide a consistent framework within which to interpret those effects. Thus, like Janus's two faces, two opposite-facing problems of drug dependence have oriented investigators in opposite directions. Behavioral pharmacologists have treated drug self-administration and the study of other behavioral effects of drugs as only nominally related. People in the drug treatment community have focused primarily on the adverse consequences of drug dependence, with little interest in drug self-administration, per se. Now the two have finally come face to face (see chapters by Brady and Lasagna).

Drug dependence involves a cluster of processes in which a state is produced by repeated self-administration of the drug, such that the drug user will engage in substantial amounts of behavior leading specifically to further administration of the drug, which will continue even when this requires the sacrifice of other important reinforcers and sources of satisfaction (Kalant et al. 1978). An understanding of drug dependence requires knowledge of the factors responsible for development, maintenance, and elimination of drug self-administration, and of the effects of the self-administered drug on other ongoing biobehavioral processes. We are interested, therefore, not only in how a drug comes to serve as a potent reward exercising extensive behavioral control, but how the drug influences the subject's ability to meet environmental demands. The aspects of an animal's or person's behavioral functioning which are altered by a drug are the drug's locus of action. The processes which account for the drug's behavioral effects are the mechanisms of action.

## BEHAVIORAL MECHANISMS OF DRUG ACTION

In the natural sciences, there is broad agreement concerning what the term "mechanism" means. For example, the mechanism by which oxygen is transferred from the atmosphere into the blood stream involves the differing gradients of partial pressure of oxygen and carbon dioxide in the alveoli of the lungs and in the bloodstream. The degree to which oxygen and carbon dioxide are exchanged has to do with differential pressure gradients. Therefore, in this case we refer to a general principle of gradients of partial pressure of gases across a membrance in specifying the mechanism.

In pharmacology, the concept of mechanism of action is intertwined with that of locus of action. Claude Bernard (1856) conducted several experiments elucidating these two concepts. In one study, he examined the site of the paralytic action of curare. Using a nerve-muscle preparation, Bernard showed that if a muscle was stimulated directly, the muscle would contract. However, if the nerve itself was stimulated, even though the nerve continued to conduct along its axons, the muscle would not contract. Therefore, Bernard concluded that the site of action of curare must be at the myoneural junction. In a related experiment, Bernard studied the mechanism by which carbon monoxide causes asphyxiation. He knew it was necessary for oxygen to be carried to the tissues by the bloodstream. Moreover, he knew that when an animal was placed under a bell jar filled with carbon monoxide, the animal was asphyxiated. In a series of elegant experiments, he demonstrated carbon monoxide has a differential and selective affinity for hemoglobin, the active element responsible for distribution of oxygen to the tissues. Bernard's experiment was critically important for the development of the concept of mechanism of action, because he demonstrated that carbon monoxide altered a normal function of hemoglobin which was responsible for oxygenation of tissues. Thus, the term "mechanism" in pharmacology, as in other areas of natural sciences, refers to a description of a phenomenon in terms of a more general set of scientific principles.

In pharmacology, most of the mechanisms to which we have customarily referred have been reductionistic. To a degree, this has been a fortuitous historical development which has become entangled with unwarranted tenacity in our theoretical fabric. In attempting to specify the mechanism responsible for the effects of mescaline on the behavior of certain native Indian tribes who use the drug as part of religious rites, it is not especially helpful to specify the receptor sites in the central nervous system activated by the drug. The mechanisms which account for the drug's effect have to do with psychological, social, and cultural factors rather than specific neurochemical factors.

It becomes evident that the choice of level of analysis is dictated by the system under study and by the degree to which the mechanisms prooosed fit into an established set of lawful relationships. The existence of a substantial knowledge base with a rich network of lawful relationships makes it profitable to explore behavioral mechanisms of drug action. By behavioral mechanism of drug action, we refer to a description of a drug's effect on a given behavioral system (locus) expressed in terms of some more general set of environmental principles regulating behavior.

Specifying the behavioral mechanism(s) responsible for an observed effect involves: a) identifying the environmental variables which typically regulate the behavior in question, and b) characterizing the manner in which the influence of those variables is altered by the drug. In some instances, the drug assumes the status of a behavioral variable, per se, rather than modulating an existing environmental variable. The search for environmental controlling variables which can be modulated by drugs is aided by a systematic exploration of antecedent factors, current environmental variables, and response consequence factors which are known to regulate behavior. Thus, the three terms in the statement of a behavioral mechanism are: 1) the drug; 2) the behavioral phenomenon; and 3) a qualitative statement of the relation between the two. The papers in the present volume are, therefore, organized around these three classes of mechanisms.

## ANTECEDENT VARIABLES

Behavioral mechanisms of drug dependence can involve three classes of antecedent variables regulating behavior. The subject's history provides the first class of variables. Environmental history can modulate the behavioral locus of a drug's action: for example, whether punished responding is increased or decreased by amphetamine, or whether response rates increase under fixed interval schedules following amphetamine administration. Figure 1 illustrates such a reinforcement history effect (see chapter by Weiner). Environmental history as well as genetic factors can control the reinforcing efficacy of drugs. Pharmacological history can determine the magnitude of a drug's effect (e.g., tolerance) and the disruptive effect of discontinuing administration of certain drugs (withdrawal) (see chapter by Young et al.). In humans, the confluence of historical and genetic dispositional variables is usually

Figure 1

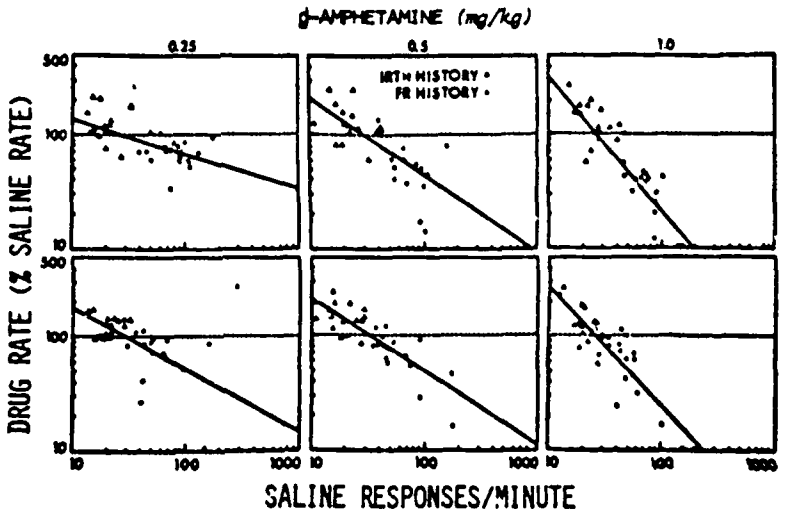


*Fig. 1. Effects of d-amphetamine on lever-pressing performance of rats maintained by a FI 15 sec. food reinforcement schedule. Half of the rats had histories of exposure to Fixed Ration 40 reinforcement schedules (triang'es) and half had comparable exposure to a DRL 11 sec. reinforcement schedule. Each data point represents the response rate of an individual subject during a single drug session graphed as a percent of the saline control rate maintained in the session preceding drug injection. (From: Urbain, Poling, Millam, and Thompson. d-Amphetamine and fixed-interval performance: Effects of operant history. Journal of the Experimental Analysis of Behavior, 29:385-392, 1978. © 1978, Society for Experimental Analysis of Behavior. Reprinted by permission.*

called personality or psychopathological mechanisms (see chapters by Pickens and Heston, and Woody et al.).

A second class of antecedent behavioral mechanisms includes various deprivation conditions. The efficacy of a drug reinforcer depends in part on the time since last drug administration. Drug deprivation that increases the efficacy of *nondrug reinforcers* (e.g., *food*) can also alter the efficacy of drug reinforcers.

A third class of antecedent behavioral mechanisms involves modulation of behavior by aversive stimulation. The efficacy of some drug reinforcers derives from the diminution of aversive stimulation the subject brings to the situation.

It may be expected that in the drug user these factors interact in a complex fashion. However, appropriately designed experiments provide the opportunity to delineate the relative contribution of these antecedent conditions and thus identify the behavioral mechanisms of action.

## DRUGS MAY BE INVOLVED IN THE PROCESS OF STIMULUS CONTROL

Behavioral mechanisms involving stimulus control include the stimulus properties of drugs and modulation of discriminative control over behavior by drugs. Stereotyped movements and locomotor activity (e.g., circling) can be elicited by drugs. Drugs administered to animals and people can also serve as discriminative stimuli, setting the occasion for responding maintained by other reinforcers. Such discriminative stimulus properties of drugs are the basis for classifying drugs by animals and people (usually termed subjective effects) (see chapter by Schuster et al.). Drugs can selectively modulate control by certain environmental cues. For example, $\Delta$ 9 THC has marked effects on a temporal discrimination while methadone has little or no effect on the same performance (figure 2). Whether a drug's effects are evident may depend critically on stimulus complexity. Thus, for example, many simple visual discriminations are minimally affected, but certain complex discriminations are significantly altered by the same dose of drug.

The role of social stimulus variables in drug effects has been the subject of considerable speculation and, more recently, careful objective analysis (see Stitzer et al.). That such complex and subtle stimulus events can serve multiple functions is attested to by the fact that one and the same stimulus can serve as an unconditioned stimulus for classical conditioning (see chapter by O'Brien et al.) and as an unconditioned reinforcer for operant behavior (see chapter by Henningfield et al. and discussion by Jasinski).

## BEHAVIORAL LOCUS OF DRUG ACTION

Behaviorally active drugs may alter some behaviors which are topographically distinguishable from others. In understanding effects of drugs people and animals self-administer, it is useful to know which behaviors are changed and which are relatively unaffected. Some effects may be readily apparent. A drug may, in a direct and

Figure 2

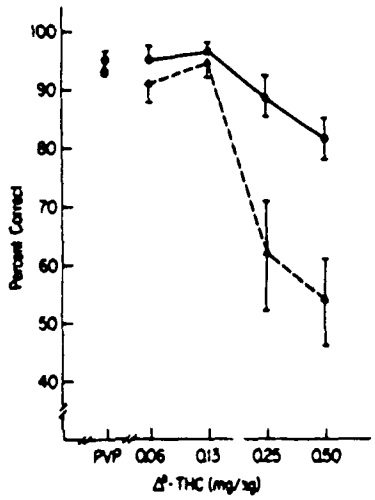


*Fig. 2. Effects of vehicle control (PVP) 0.06 - 0.50 mg/kg of Δ 9 THC on percent of correct choices in a temporal discrimination task (4-second vs. 8-second stimuli). The solid line shows percent of correct choices after a 4-second duration stimulus has been presented, and the dashed line shows percent correct choices on trials after a long duration stimulus has been presented. (From: Daniel, S.A., and Thompson, T. Methadone-induced attenuation of the effects of Δ 9 THC on temporal discrimination in pigeons. Journal of Pharmacology and Experimental Therapeutics, 213(2):247-253, 1980.* 

obvious fashion, alter the pattern of self-administration. Alternatively the effects may be subtle. Although performance may seem unaffected across classes of responses, fine grained analysis within a given response class may reveal some components are affected more than others. The locus of some effects may be the pattern of intervals between successive responses. Several drugs under an array of conditions modify the overall rate of responding which is specifically observed as decreases in long inter-response times and increases in short ones. In this case, the generality of the phenomenon, rate dependency or rate constancy, depends in part on the nature of different controlling consequences.

DRUGS MAY ALTER THE WAY CONSEQUENCES REGULATE BEHAVIOR

The type of motivating event can be a significant determinant of the effects of a wide variety of drugs on behavior maintained under a broad range of conditions. This fact does not negate the importance of other determinants of drug action, nor should it revive notions that hypothetical underlying states determine a drug's effects. The differences in drug effects depend on maintaining motivating events under some conditions. They do not under others, even when the same events are studied. Performances controlled by dissimilar events under one schedule can be affected differently by a drug, whereas under a different schedule with the same maintaining events, these performances can be affected uniformly (see figure 3 and chapter by Barrett). These findings argue against the specificity of the effects of drugs on behavior controlled by a single event.

It appears behavioral mechanisms of drug action involving schedules can reflect direct and indirect schedule mechanisms. These mechanisms may modulate contiguity of the response-reinforcer relation, may alter the number of responses per reinforcer, the reinforcement density, or reinforcer availability at critical times when responding weakens. Any of the above mechanisms can be responsible for systematic changes in schedule-controlled behavior.

DRUGS MAY SERVE AS CONTROLLING CONSEQUENCES REGULATING BEHAVIOR

Two aspects of drug dependence were discussed in our opening remarks: 1) The effects of self-administered drugs on the ability of the subject to meet normal environmental demands (behavioral mechanisms and toxic effects involving antecedent factors, stimulus control variables, and the behavioral locus of drug action have already been mentioned); and 2) Variables which determine when and to what extent various drugs can serve as controlling consequences.

Over the past two decades an experimental model of this latter aspect of drug dependence has developed, using laboratory animals. Animals are given access to a manipulandum which when operated results in delivery of a drug. A variety of species have been studied (e.g., rat, dog, cat, monkey, baboon) using several types of responses (e.g., lever press, chain pull, panel press) and routes of administration (e.g., intravenous, oral, intragastric, inhalation).

Figure 3

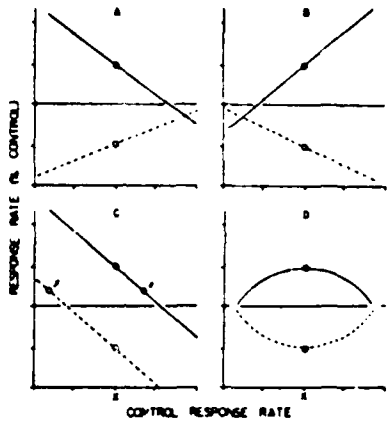


*Fig. 3. Hypothetical functions depicting possible relationships between the control rate of responding maintained by different events (open and closed circles) and the effects of certain drugs. On the basis of experimental data, it is assumed here that the drug produces differential effects on comparable response rates at point X and that this represents an intermediate rate value. The dashed line at 100% represents control, or nondrug, rates of responding; points above and below this line represent increases and decreases, respectively, produced by a drug. None of the relationships shown reflects an invariant relationship (i.e., have no slope) between response rate and drug effects. Although an outcome of this type is possible, it appears to be characteristic of low doses that are not typically behaviorally active. Similar drug effects are obtained when control rates are high (graph A), low (Graph B), or at both high and low values (graph D); in graph C similar effects are obtained when response rates maintained by one event are low (y) and those maintained by a different event (x) are high. (From: Barrett, J.E., and Katz, J.L. Drug effects on behaviors maintained by different events. In: Thompson, T., and Dews, P.B., eds. Advances in Behavioral Pharmacology, Vol. I.*

From the beginnings of these studies, animals appeared to self-administer the same drugs as those abused by humans (see chapter by Griffiths et al. and discussion by Johanson). Subsequent research has investigated pharmacological and environmental variables determining the degree to which and circumstances uner which a given compound would serve as a reinforcing consequence for the behavior leading to drug administration (see the Meisch and Carroll chapter as an illustration).

Most broadly, the behavioral mechanism responsible for compulsive drug-seeking is the principle of reinforcement. It seems unlikely that a useful single common reductionistic mechanism can be identified accounting for the reinforcing property of such diverse drugs as toluene, heroin, ethanol, phencyclidine, tobacco, and cocaine. No common reductionistic mechanism has ever been found to account for the efficacy of other reinforcers (e.g., food, water, sexual stimulation, visual stimulation, opportunity for aggression, presentation of painful shock). It therefore seems improbable that we will be more successful with drug reinforcers. Thus, we are led to explicate the concept of drug reinforcement at its own level of analysis, i.e., to specify as fully as possible the environmental and pharmacological conditions determining the reinforcing efficacy of a drug.

A description of the mechanisms responsible for the reinforcing efficacy of a drug takes the form: The reinforcing efficacy of X is a function of A, B, C, . . . Z, where A through Z are qualitative variables. The independent variables determining the ability of a drug to maintain behavior producing drug administration must be explicated in detail, specifying the quantitative nature of those relationships. Variables A and B, etc., include such factors as drug dose, hours of deprivation, and schedule of drug presentation.

## THE RELATION OF ANIMAL MODELS TO HUMAN DRUG DEPENDENCE

There is a growing appreciation of the importance of behavioral factors in controlling drug self-administration (Henningfield and et al chapter). Drug-maintained responding is controlled in the same manner as responding regulated by a variety of other reinforcers. The illicit use of drugs is a behavioral problem, and the variables controlling it appear to be the same as those controlling any behavior. By viewing drugs as reinforcers, it is possible to profit from previous studies of the variables affecting the rate, pattern, and persistence of behavior maintained by other stimulus events such as food and water presentation (Thompson and Pickens 1969, Schuster and Thompson 1969). Persistent drug-seeking can be produced by the same reinforcement schedules generating persistent food-seeking. The persistence of these behaviors is often as attributable to the schedule of drug reinforcement as it is to inherent properties of the agent (see Goldberg and Gardner chapter). Though excessive and persistent drug-seeking is regarded as abnormal, these qualities are generated by the same variables producing excessive and persistent behaviors lauded by society (see chapter by Falk and discussions by Barrett and Mello).

The specific papers and discussions contained in this volume are intended to be an illustrative guide, not an exhaustive literature review. Collectively, they supply a conceptual map of a very difficult empirical terrain. We trust the reader will find the volume prescriptively useful.

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# Common Mechanisms in Substance Abuse

Joseph V. Brady, Ph.D.

Among the many perplexing aspects of the substance abuse domain, the topic which provides the title for this essay appears to present some of the more challenging methodological and conceptual problems. In recent years, this field of inquiry has been cultivated assiduously, and the current lively interest in common factors determining patterns of substance use and abuse is generously reflected in an expanding literature of multi-disciplinary origins (e.g., Maloff and Levison 1980, Krasnegor 1980, Levison, 1977, Griffiths and Bigelow 1978). It is unfortunately true, however, that dedication and industry, even of the most intense sort, do not guarantee authentic scientific achievement. In biology and the social sciences, wide gaps frequently separate experimental operations and interpretive formulations. Progress in developing systematic and coherent conceptualizations which serve to integrate and unify interactive levels of discourse can be painfully slow. Even at the most basic level, there appear to be no generally acceptable theoretical formulations which can bring conceptual order to the rapidly expanding frontiers of inquiry and application in the extended domain of substance abuse. It seems clear, nonetheless, that the development of a unifying conceptual framework for encompassing the commonalities in substance abuse must appeal in the first instance to an analysis of the data base which focuses upon the behavioral interactions between organism and environment, both intrapersonal and social.

Within this behavioral context, the most obvious commonality which unites the range of phenomena falling within the compass of substance abuse is the involvement of a self-administration performance. More traditional views of this process have tended to emphasize what appeared to be its reactive features with substance use and/or abuse viewed as a response to some particular set of conditions or circumstances (e.g., the "you-drove-me-to-drink" model of alcohol abuse). In addition, the biochemical dimensions of the problem focusing upon the structure of the molecule and function of the receptor have dominated the search for mechanisms,

common and otherwise. Since the discovery, some two decades ago, that animals implanted with intravenous catheters would repeatedly self-inject drugs, however, it has been convincingly shown that there is a good correspondence between the range of chemical compounds self-administered by animals and those abused by humans. Moreover, the variables of which such drug self-administration are a function (e.g., dose, response cost, schedule of availability, environmental conditions, past history) have been found to exert their influence in a similar fashion independently of the type of substance maintaining the performance or the species of organism involved (Griffiths, Bigelow, and Henningfield 1980). The recognition of these cross-species and cross-drug generalities has radically changed conceptualizations of substance abuse from a reactive to a more active process, and has encouraged the kind of functional analysis of drug-seeking and drug-taking which has proven productive and useful in other behavioral interactions.

The pursuit of this latter course in search of substance abuse commonalities would seem to have at least two clear advantages. First, it meets the literal requirements for a "mechanism" in the sense of a collective arrangement of, or relationship between, parts or components to produce an effect (i.e., adaptation and adjustment of the living system in a changing environment). Secondly, it makes contact with an expanding body of knowledge, based upon observation and experiment, focusing on the interactive process between organism and environment which defines the unique domain of behavioral science. Under such circumstances, the search for common mechanisms in substance abuse within the context of this existing data base takes on an investigative focus, and is advantaged by the strong empirical influence of the experimental laboratory.

Conceptually, the roots of such behavior-laboratory initiatives can of course be identified with the fundamentals of environmentalism which has two main features. The first of these is the conviction that knowledge comes from experience rather than from innate ideas, divine revelation, or any of those other obscure sources. And the second holds that action is governed by consequences rather than by instinct, reason, will, cognitions, beliefs, attitudes, or any of those myriad explanatory fictions which appear to have been created out of the whole cloth by the magic of human language. Taken together, these two constructs about human nature define a philosophy of social optimism which says that if you want persons to be a certain way or to do certain things, circumstances can be arranged. The coalescence of these two ideas appears to have taken place in 19th century England - the names of Locke and Darwin come to mind - and can be seen to date the emergence of modern behaviorism. Their influence upon medicine in general and the problems of substance abuse in particular appears to have developed much more slowly amidst dominant biochemical and physiological orientations, but their impact is now beginning to find expression in the somewhat explosive emergence of Behavioral Medicine as a field of scientific and professional endeavor encompassing virtually all aspects of health and disease (Pomerleau and Brady 1979).

The important influence of the experimental laboratory in establishing the data base which now provides the empirical foundations for such assertions can be traced to the contributions of I. P. Pavlov focusing upon the role of environmental circumstances and behavioral activities in the biochemical and physiological adaptations and adjustments of the milieu interieur. Among the many "firsts" with which Pavlov has been credited, his probable role as the father of behavioral pharmacology has been acknowledged in a recent historical note by Laties (1979). But of at least equal importance was the foundation Pavlov's work provided for conceptualizing behavioral interactions within the framework of an orderly and systematic body of scientific knowledge based upon observation and experiment. The contrast between this objective approach to the analysis of behavior and more traditional (and lamentably, to some considerable extent, contemporary) appeals to unobserved and unobservable "mental" processes (in whatever "cognitive" guise they may appear) is worth emphasizing.

The lessons learned about behavior under such controlled experimental conditions with individual organisms seem to have been lost, in large part, on the "psycho" disciplines so long preoccupied with the average behavior of groups, and the insights which emerged from the animal behavior laboratory have seldom been warmly embraced at the clinical level for reasons which appear somewhat unique to the human condition. Unlike other aspects of biology (e.g., biochemistry, anatomy, physiology, etc.), where behavior is concerned, we bipeds at the head of the line harbor strong chauvinistic dispositions which have nothing to do with gender, skin pigmentation, or other personal characteristics of the species. Acceptance of the notion that experimentally analyzing the behavior of so-called "lower organisms" can meaningfully reveal anything about our own exalted performance repertoires has been modest and hard-won in the face of considerable "higher order" resistance.

But polemics aside, what, in fact, have we learned on the basis of observations and experiments in the laboratory about the mechanisms involved in behavioral interactions, and to what extent do they provide insights with regard to substance abuse commonalities? Such analysis has revealed two basic modes of organism-environment interactions. The first appears to be a very fundamental reactive process rooted in the biochemical and physiological adaptations of the organism to environmental influences (i.e., the environment acts upon the organism and the organism reacts). The major contributions to our understanding of the regularities and orderliness of the process whereby the influences of such eliciting environmental stimulus events are broadened through reflex conditioning are of course associated with Pavlov and are too well-known to require extensive review. They have, in fact, been so widely disseminated in popular parlance and quasi-technical language that this reactive form of "conditioning" has been somewhat overburdened in well-meaning but misguided attempts to operationalize the analysis of behavioral interactions in general, and substance abuse in particular. To the extent, however, that

substance-oriented behavioral interactions can be demonstrated to involve salient eliciting functions and discriminable environmental stimulus events temporally ordered in associative relationship to reactive biochemical and/or physiological changes, such Pavlovian or classical conditioning processes can be presumed operative, and to that same extent must be considered prime "suspects" in the search for common mechanisms in substance abuse.

In this regard of course, the early work of Wikler (1965) and the more contemporary contributions of Siegel (1976), and of course O'Brien and his colleagues (1977), to be reviewed in a later section of this volume, firmly establish the potent influence of such common mechanisms in at least several aspects of conditioned drug tolerance and withdrawal. And this classical associative process appears to be as ubiquitous as environmental stimulus events and their effects upon the milieu interieur, both substance related and otherwise.

The second basic and generally more active mode characterizing behavioral transactions focuses on the operations performed by organisms upon their environments (both internal and external) rather than on their reflex reactions to such environmental influences. Technically, this operant mode has been explicated within the framework of a 3-term contingency analysis which delineates the temporal ordering of organismic performances (R), reinforcing consequences ($S^R$), and the environmental context ($S^D$) in which the $R \rightarrow S^R$ relationship occurs. The major contributions to the experimental analysis of such operant behavior interactions have been identified with the work of B. F. Skinner, his students and colleagues (not to mention his disciples!). The dominant relationship between these component terms emphasizes the governance of action (i.e., the likelihood of a response) by the contingently occurring effects of that action (i.e., its reinforcing "consequences"). Emergent relations between $S^D$ (i.e., environmental context) and R (i.e., response) components are also specified to the extent that "response-consequence" contingency relations are dependent upon contextual occasioning (i.e., environmental stimulus) events. More complex interrelationships between these terms have of course been elaborated (e.g., rule or schedule relations), and along with historical variables, must necessarily enter into a precise definitional account of such behavioral contingencies. Within the framework of these empirical referents, however, the likelihood, strength, and persistence of behavior can be more readily understood than by any other means.

What has all this to do with common mechanisms in substance abuse? To the extent that the substances of concern can serve a reinforcing function (i.e., consequate a self-administration performance and increase the probability of its reoccurrence), a common operant behavior mechanism can be presumed operative in substance-seeking and substance-taking. Moreover, to the extent that such performances occur in a given environmental context and in accordance with the ubiquitous rule governance of virtually all behavioral interactions, the common functional mechanisms of

stimulus control and reinforcement scheduling (along with the history of the behavioral interactions in these regards) will exert a powerful influence upon the likelyhood, strength, and persistence of substance abuse, regardless of its specific topography or formal characteristics.

I would beg your indulgence to entertain at least a few striking (and I believe relevant) illustrations of the limits to which control by these common behavioral mechanisms can be extended. In citing these admittedly atypical cases, I have chosen to focus upon the demonstrably potent influence of schedule and stimulus control upon the strength and persistence of behavior because these properties frequently appear as the most baffling and recalcitrant aspects of the substance abuse scene. Moreover, the explanations frequently offered to account for such phenomena in the form of appeals which range from biochemical defects to personality variables and other creative constructs like "associative bonds" and "opponent processes" tend to violate the law of parsimony—Lloyd Morgan's canon. The field of substance abuse is ill-served by explanatory fictions which, at the very least, fail to take account first and foremost, of those operationally defined behavioral relationships which emerge on the basis of observation and experiment in laboratory settings.

Of particular relevance in this regard would seem to be the experimentally (and clinically) documented effects of scheduling conditions which determine under what circumstances and in accordance with what behavioral requirements a valued commodity or substance, be it food, drug, money, social interaction or whatever, can be obtained. All such consequating events are subject to this kind of rule governance, some of which is very complex, as those of you know who have suffered through the Ferster and Skinner "catalogue" (1957). But they all appear to be variations and/or combinations of a few basic types, and a great deal has been learned about their properties and effects, both in the experimental laboratory and in the natural ecology. The two major classes into which such effects can be categorized appear to be those which are schedule-maintained, on the one hand, and those which are schedule-induced on the other. Both of these areas have been generously covered by experts in the succeeding pages of this volume. The curious side effects of reward-enhancing intermittent schedules and complex historical circumstances (e.g., maintenance of shock-producing performances and great strengthening of adjunctive or ancillary behaviors) certainly provide ample grist for the "commonalities" discussion mill (Falk 1971, Kelleher and Morse 1968). But it is to the power of the kind of environmental constraints imposed by such scheduling to entrain performances of remarkable persistence that I would like to call particular attention in the context of the search for common mechanisms in substance abuse.

Figure 1 illustrates a typical segment of a cumulative record from an experiment in which a chimpanzee sustained performance on a ratio-schedule which required 120,000 responses on a heavy

push-button manipulandum for access to food (Findley and Brady 1965). After each 4,000 responses toward the total requirement, a brief flash of light was presented - the same light that was illuminated continuously during food access once the total ratio was completed. Of particular interest is the pause which follows each flash of light after a block of 4,000 responses illustrating the control acquired by this conditioned reinforcing stimulus event. Subsequent extension to a 250,000 response ratio and manipulations involving removal and reintroduction of the light flash after each 10,000 responses documented the critical interactions between rule-goverance and stimulus control in the establishment and maintenance of such remarkably persistent performance repertoires. It seems important to recognize that while such unusual and extreme examples of schedule and stimulus conditions may appear to push the limits of adaptive functions, they are not tricks or circus acts. They do in fact represent the orderly and lawful operation of general relationships which are common to all behavioral interactions, including substance seeking and substance taking, and appear to be of particular relevance to the excessive or abusive aspects of such performances.

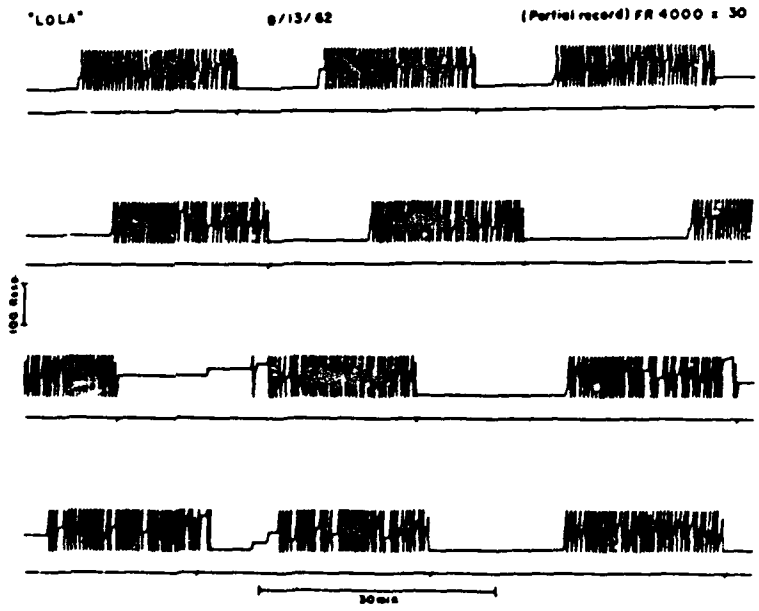


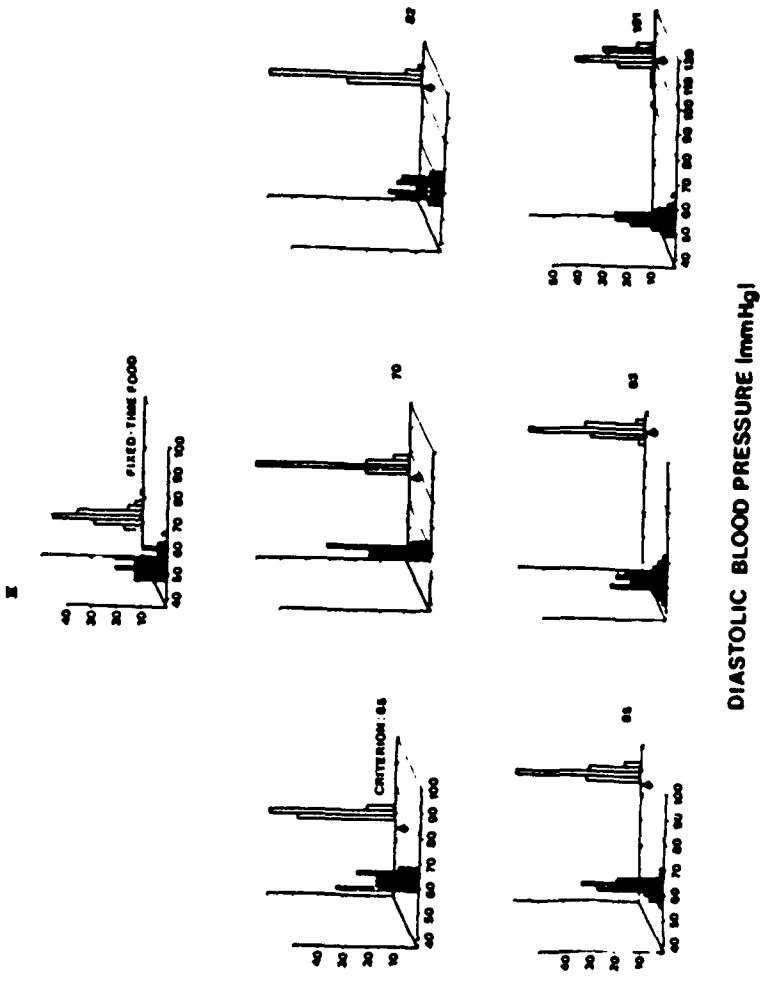

FIGURE 1

One final point, I believe, bears on the relationship of the "common behavioral mechanisms" argument to substance abuse. While the thrust of this obviously provincial commentary may suggest an empty-organism denial of relevance with respect to anything going on inside the skin, the ubiquity with which a host of substances, and particularly a variety of drugs, can maintain common behavior patterns leading to their self-administration in both animals and man clearly attests to the fact that some basic biochemistry must be involved. By the same token, there would seem to be little need to appeal to special pathophysiological conditions to account for the excesses which define continued abuse. That at least some of the more basic behavioral mechanisms represented as common in this abbreviated essay can be demonstrated operative with respect to events and processes uniquely confined within the skin is illustrated in Figure 2.

This figure shows the relative frequency distributions of diastolic blood pressure from an experiment in which a baboon learned to increase and maintain blood pressure elevations in order to obtain food and avoid shock (Turkkan and Harris, 1980). The shaping procedure illustrated in Figure 2 involved delivery of food pellets for accumulation of 600 sec of time above the diastolic pressure criterion level and delivery of a single electric shock to the tail for accumulation of 240 sec of time below that criterion level. When the pressure level was above criterion, a white light appeared on the animal's work panel, and when pressure was below criterion, a red light, accompanied by a 1000 Hz tone, was presented. Experimental sessions began at noon each day, and ended at midnight. Criterion levels beginning at 65 mm Hg (i.e., pre-experimental baseline average diastolic pressure level) were progressively elevated at a rate approximating 2-3 mm Hg per week. The systematic shaping of diastolic pressure elevations over a 10-12 week conditioning period is illustrated in Figure 2 which compares the diastolic pressure levels recorded during sessions (open bars) with the levels recorded during the 12-hour intervals between sessions (filled bars) under baseline conditions (top segment) and during successive stages of conditioning. At the highest criterion (lower right segment), diastolic pressures were elevated above 100 mm Hg in order to maintain a food-abundant environment throughout the 12-hour experimental session during which less than one shock per hour was delivered. And remarkably, there was absolutely no overlap between the distributions of pressure levels recorded at this highest criterion and those recorded during the baseline period. The operation of a common behavioral mechanism is clearly reflected in the development and maintenance of this completely new physiological response pattern.

This appeal to the participation of operant mechanisms in the regulation of physiological processes traditionally considered under more reactive control does not, of course, imply any claim to exclusivity. It seems self-evident that multiple mechanisms, both behavioral and physiological, must be concurrently operative in the mediation of such complex psychophysiological interactions. Certainly, in so far as the environmental stimulus events (both

FIGURE 2


FIXED-TIME FOOD
CRITERION: 85
DIASTOLIC BLOOD PRESSURE [mmHg]
RELATIVE FREQUENCY (%)

internal and external' involved in these processes have common functional properties (e.g., eliciting, reinforcing, etc.), both operant and respondent conditioning mechanisms, at the very least, can be presumed operative and coextensive. Considering the magnitude of our ignorance in the substance abuse domain, however, we can hardly afford to neglect any field of inquiry which promises enlightenment with respect to mechanisms, common or otherwise, particularly those so obviously related to the behavioral interactions between organism and environment.

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# Towards a Rapprochement Between Clinical Pharmacology and Behavioral Pharmacology

Louis Lasagna, M.D.

Every scientist is a prisoner of his own background, training, and interests, and I am no exception. My experience is largely limited to human experimentation, involving healthy volunteers, patients, or addicts, and I therefore read the literature on behavioral pharmacology as a sort of scientific voyeur. But it may be helpful for those who are expert in operant conditioning research to hear the benighted remarks of an amateur who at least has a dilettante's acquaintance with the field. I can assure you that most clinical pharmacologists are almost virginal with regard to classical behaviorism and its experimental consequences. (I know that wearing a tie in a nudist colony doesn't make one a fashion plate in the world at large.)

Let me begin by stating that my attitude is really a very positive one, so that the reservations that I shall begin with should not be taken as an index of my overall position.

Let me start, then, with some difficulties that plagued behavioral pharmacology in its early days. One trouble was a tendency to overpromise. Many people were led to believe that the discovery of new drugs, for example, would be revolutionized by the use of operant techniques. This proved to be a foolish hope, and the result was an unfortunate overswing of the pendulum. For some, the pendulum fell clear off its hook, and the potential contributions of behavioral pharmacology were cruelly denigrated.

There was also at one time an excessive preoccupation with schedules qua schedules. At times one sensed almost a perverse pride in trumpeting the merits of FI, VI, FR, DRL, etc. schedules for their own sake. If someone asked for a translation of these data into terms that had more meaning for non-Skinnerians, one met with either scorn or abuse.

I must stress that this is not a problem unique to behaviorists. I have the same feeling about a lot of biochemical or pharmacokinetic research, for example, where no biological correlates are provided to allow one to incorporate the data into ones gestalt.

This is not to say that bits of data cannot eventually prove of considerable use -- that would be silly. But it is unrealistic to ignore the aversive effects on non-behaviorists of data and conclusions which cannot be readily integrated into a biologic framework. If I am told that morphine has differential effects on visual and food reinforcers, I appreciate some insight into whether this might be due to something like pupillary effects, and whether this has been studied. To be told that it is important just to know that the reinforcers perform differently is off-putting.

I believe that this problem affects science a great deal these days, in part because it reflects our specialization and the increasing difficulty of studying in an expert fashion two very different kinds of data. To make correlations, one has to have behavioral and other sorts of data (pharmacokinetic, for example) that are both measured in expert fashion. They don't necessarily have to be gathered by the same people, but the data have to be of high quality.

It is also a pity that in the past one sensed often a preoccupation with what could be easily (or automatically) measured, rather than with other sorts of behavior that might also be of interest. Again, this is not a sin of the Skinnerians alone. We are all guilty at times of ignoring those things that we didn't set out to measure, or that are difficult to measure. But to make a good out of this constitutes a kind of hubris.

Residuals of these problems remain. There is still a reluctance to deal with subjective reports, despite abundant evidence that subjective responses can be quantified in a reproducible way that satisfies all the requirements of good science. Reports of pain and analgesia have been useful in this way for years, and in my own experience have provided occasional important insights. Some years ago, for example, I noticed that an occasional patient who received a narcotic antagonist complained of "pain all over." This was seen again when we studied naloxone, another antagonist, some years later. Now, I can appreciate that this was probably a blocking of endogenous opiate-like materials, but even at the time it was obvious that <u>something</u> important was going on. Similarly, I think it important to know when addicts "like" drug effects. I admit that this doesn't tell us a lot about what they <u>mean</u> by the word "like" or <u>why</u> they "like" a drug, but they don't often abuse drugs whose effects they don't enjoy in some sense.

The traditional interests of the clinical pharmacologist concerned with substance abuse are not, I believe, generally different from those of the behavioral pharmacologist, with some exceptions. Both types of researchers are interested in the factors that initiate substance use and abuse, those that maintain it, the somatic consequences, and the conditions that may act to stop or decrease substance abuse. The fact that the <u>nature</u> of the factors may vary considerably from the street to the <u>laboratory</u> does not mitigate what I have just said. Peer pressure, the mystique surrounding drugs, the desire to flout authority or gain social status by "hustling" may not be readily studied in the lab, but "price" certainly can. So can the effects of withdrawal after induction of physical dependence. So can tolerance.

The big differences, to me at least, lie in the economic and legal aspects of substance abuse, and those drug effects or co-factors whose appreciation requires the ability of our research subjects to talk to us. Some verbalized experiences (like hallucinations) can only be guessed at in non-human subjects. (The same is true for painting or poetry or philosophical insights that may follow as a consequence of drug experience. It is not the fault of a rat or a pigeon -- or even of the researcher studying them -- that the subhuman repertoire is importantly different from that of humans.)

Differences between experiment and "naturally" occurring events are also a problem. When one tries, e.g., to correlate "drug abusability" in animals and humans, one is hampered by the confounding factors at play in the street. "Popularity" will show better correlations between humans and animals in the lab, I'm sure, than if one tries to equate "addiction potential" in the lab with street abuse. The latter is affected to a large degree by availability and price of drug. What is being "pushed" is an important determinant of quantity of usage. Supply affects demand at least as much as demand affects supply. Some years ago, when morphine and heroin were both trafficked illegally to a considerable degree in the U.S., heroin would be the illegal drug of choice in one big city, whereas morphine would be in another. Such patterns illustrate the danger in equating abuse figures quantitatively with addiction liability, yet we continue to play this game -- as if availability, mystique, and media coverage were trivial determinants of drug abuse.

The field of substance abuse has, in my view, provided perhaps the most impressive opportunity for BP to help those scientific colleagues who perform other kinds of research. The remarkable correlations between effects in ex-addicts and animal self-administration data (Griffiths and Balster 1979), e.g., cannot be ignored. The fact that dextromethorphan and a few other drugs don't fit neatly into the correlation is hardly cause for despair.

Nor is the fact that hallucinogens are not successfully predicted by self-administration techniques (Griffiths et al. 1979), for a lot of reasons (von Felsinger et al. 1956). The ability to predict abuse liability for stimulant drugs (Griffiths et al. 1979) is also reasonably impressive, although my own guess is that diethylpropion looks more "abusable" in BP studies than in fact it has proven to be in man. This might be due, however, to pharmacokinetic or other differences between species. We know that in human beings diethylpropion undergoes a rapid but limited first pass effect, metabolically speaking. Oral doses are more potent than subcutaneous in man, and the possibility exists that the activity of diethylpropion depends on the formation of active N-deethylated metabolites. If so, this might explain a tendency for diethylpropion to be less attractive by the intravenous route than other stimulants that don't require conversion to active metabolites, and also allows the possibility of greater abuse potential appearing in animals that are more "active" metabolically and are therefore able to produce greater amounts of the active metabolites. This may not be the correct explanation, but I pose it as a scenario that might explain differences of this sort when they occur.

The "negative" evidence is also helpful, i.e., the knowledge that some drugs that have little or no abuse liability in humans also have little appeal to animals. And it is very impressive that animals will actually "self-destroy" if allowed to self-administer certain drugs without restraint. This, too, is similar to the human situation.

Behavioral pharmacology offers certain advantages over clinical pharmacology, in part because it allows true experimentation rather than simply description of "natural" events. I realize that true experiments can be done (and have been) in humans, but there are serious legal and ethical restrictions on what one can do in people (such as full exploration of dosage effects).

But equally import is the heuristic value of animal experiments that mimic human situations. Self-administration experiments with animals somehow underscore human behavior in a remarkable -- they contribute a type of "legitimacy" in the minds of many, to say nothing of generalizability. Also, it is often possible to define quantitative and even qualitative differences more reliably in the animal lab than in the human lab or clinic.

Another advantage of behavioral pharmacology is that its proponents often have reminded us to be careful not to be trapped by inference or theory that goes far beyond the fact. I believe that pharmacologists have, for example, been trapped by the orientation of the field of drug abuse for many years around the opiate model. This model has dominated the field for decades, and for good reason. Human abuse of heroin, other opium derivatives, or synthetic morphine-like substances has been a social problem for centuries; and one can defend this widespread research interest in opiates, especially since morphine was the first alkaloid ever isolated in pure form (in 1803). But we have paid a price for this, in that models of physical dependence, tolerance, and withdrawal effects tended to be set up in the image of morphine. I believe that this largely explains the long delay in appreciating the existence and nature of physical dependence to alcohol and barbiturates, which is so different in kind, severity, and risk from that seen with opiates.

I believe, further, that this preoccupation plagues us with respect to the amphetamine class of drugs, for which one continues to read and hear that no physical dependence exists. What should we demand of a drug before we decide on its ability to produce physical dependence? I submit that all that is needed is a predictable pattern of behavior that occurs over a certain time frame after discontinuance of drug and which can be relieved or abolished by reinstituting the drug.

I suggest that amphetamine's withdrawal effects fit the bill. After significant and prolonged use of amphetamine, stopping the drug is followed by severe somnolence and then hyperphagia. Emotional depression is not uncommon. Reinstituting amphetamine reverses this picture. Note that (as with other drug classes) the withdrawal syndrome is in many respects the mirror image of the "primary" effects of the drug. All of this adds up to physical dependence, in my view. The fact that it is unlike opiate withdrawal is no more relevant than

the fact that barbiturate and alcohol withdrawal effects are different from those induced by heroin.

There are many important questions begging to be answered:

1. Why do some people, with ready access to illicit drugs, never experiment with them? Why do some try, but never get "hooked"? Is the same true for animals? I know that behaviorists have often been most interested in phenomena that seem very "orderly," and go across not only individuals but species. I should like to make a plea for interest in "disorderly" behavior, not behavior that is chaotic, but that is predictably different from one individual of the species to another. Amphetamine given to human beings doesn't make everybody alert, stimulated, and euphoric. Some people are made sleepy and dysphoric, and predictably so.

2. What underlies the relationship between food deprivation and certain forms of habitual behavior and substance abuse?

3. What underlies "compensatory" behavior in cigarette smokers who switch to low tar, low nicotine cigarettes? What substance or substances are they "tracking"? What subjective effects? (Since nicotine doesn't seem to be an impressive reinforcer in animals, these studies may need to be done in humans.)

4. What is the basis for abuse of oral analgesic combinations? Is it really due to the phenacetin component, which clearly has behavioral effects in humans (Eade and Lasagna 1967)?

5. How different are the various anorexigenic agents in their effects on the behavioral repertoire of animals and humans (Garattini et al. 1974)? Are differential effects, e.g., on appetite and satiety (defined as initiation and cessation of eating), present? Are they important in achieving weight loss? Do any of the drugs facilitate fundamental changes in eating behavior (perhaps achieved by concomitant behavior modification therapy) that will outlast the taking of the drug?

I find myself fascinated by experimental obesity models and excessive food consumption in humans. We now have a variety of ways of producing obesity in animals, ranging from the genetic to repeated tail pinching. These models are of interest to a pharmacologist at least in that drugs may affect the obesity differentially.

The work of Rogers and Blundell (1979) is also provocative. In their studies of healthy volunteers, a detailed analysis of the microstructure of eating behavior was abstracted from videotaped recordings of the test meal. When one studies latency to initiation of eating, the rate of food ingestion, the change in rate of feeding across the course of the meal, etc., it appears that drugs like amphetamine and fenfluramine differ importantly in their effects. Such studies may be enormously important not only in understanding how these drugs work, but in planning more effective interventions for the future in the management of human obesity.

I believe that we have long since passed from the period of scientific hostility or isolation to an era where behavioral pharmacology and other types of pharmacology research are ready, willing, and able to work together to combine the best of what each approch has to offer. Clearly, looking at drugs to the exclusion of other variables is as silly as ignoring drugs as a major component in substance abuse. No one can pretend any longer that human substantiation of animal experiments is unimportant, or vice versa.

We will, I believe, make the most rapid progress by integrating and comparing the empiric data obtained by different techniques and different populations. Both commonalities and exceptions have the capability of providing new insights as well as better general theories. The exciting work reported at this meeting shows the wisdom of the NIDA program for support of behavioral pharmacology. Research funds allocated by NIDA have obviously been put to good use, and I can only pray that this kind of work receives full support in the future as in the past.

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# Discussion

## An Analysis of Commonalities in Substance Abuse and Habitual Behavior

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### INTRODUCTION

What is the problem? Societies have long been concerned about ingestion of nonnutritive substances that, used in excess, have unacceptable effects and may lead to states of dependence. Concerns have centered on the health, welfare, and significant social relationships of heavy users, and on the physical, psychological, and social consequences that even episodic use may produce. Moral judgments about substances and their users weigh heavily in the policies, practices, and legal categories with which societies attempt to contain excessive use. There have been strong efforts to treat or incarcerate the afflicted, to control production and markets, and to discover through research how these substances gain such a terrible hold on heavy users. Policies are further complicated by the many occasional and moderate users who regard temperate consumption of some substances under appropriate circumstances as desirable. More recently, there has been concern that some, perhaps many, activities other than intake of substances may share important attributes with the classic pharmacological dependencies.

Given the variety of factors operating, no single theory or set of principles can be expected to organize all or even most features of the disparate set of phenomena we refer to as substance abuse and related habitual behaviors. However, some characteristics may be common to most of these patterns, especially when the focus is on very heavy use. The purpose of this paper is to consider the possible common features, weigh their importance, and suggest how research on common factors may increase our understanding and control of addictive-like phenomena.

### On Commonalities

The popularity of the idea of "commonalities" in discussions of the self-administration of psychoactive substances for recreational

purposes is relatively new, especially the extension of this idea to cover, e.g., binge eating and heavily involving activities such as gambling, TV watching, or exercise, in which no substance is ingested. This readiness to think of such phenomena as having common properties, which hardly existed ten years ago, has scientific, clinical, and political implications. The term "substance abuse" has gained wide currency, including as the title of a broad section of the influential DSM-III (1980). New symposia, books and articles, including some written for a general audience (e.g., Peele and Brodsky 1975) feature cross-substance discussions of basic principles and treatment applications. There also appears to be a greater willingness for the major treatment constituencies--notably "drug addiction" and "alcoholism"--to acknowledge their similarities rather than insist upon their differences.

"Commonality" is defined by Webster's Third New International Dictionary (1976) as "possession with another of a certain attribute." This definition places a strong requirement on the attributes being compared to be alike at some fundamental level. It is easy to point out some descriptive similarities in excessive substance use and other habitual behaviors; "commonalities," however, implies that at some deeper level a common set of mechanisms organizes and energizes the variety of patterns we call compulsive habitual behaviors. Similarities in the excessive use of opiates, alcohol, tobacco, opportunities to gamble, etc., have been pointed out many times. But the task becomes different if one posits that the similarities reflect powerful underlying mechanisms, still to be discovered, which give rise to socially intrusive phenomena.

## The Task

The general task is to discern frameworks to organize knowledge about common properties of different addictions. Identification of commonalities can provide better understanding of the addictions and greater potential for preventing or bringing them under control.

The first step is to characterize the common phenomena. Second, the characterizations are to be refined on the basis of understanding their important features, and new instances of commonalities may be included while some initially included may be discarded. The tentative subject matter, then, consists of phenomena which are commonly labeled addictions: dependencies on such drugs as opiates, alcohol, tobacco, barbiturates, and stimulants; and compulsive pursuit of activities such as gambling, TV viewing, or long-distance-running. The task is to find the attributes these phenomena have in common, and to rule out from a commonalities analysis attributes that are specific to a small subset.

A useful starting point is to compare addictive phenomena with other strongly motivated behavior patterns that have a clear

biological basis and are not considered to be addictions, such as the search for food, sex, warmth, pain avoidance, etc. Although some features of a starving person seeking food in a famine-struck environment (total involvement, craving) may resemble addictive behavior, the biological necessity of food-seeking for survival excludes it from the category of addiction. Addictions are induced by repeated but in general biologically superfluous contact with certain substances or environmental conditions; people not exposed do not become addicted or suffer from being "deprived" of them. The starving person's actions can resemble an addictive pattern, but starvation-related behaviors are themselves excluded by definition from the addictions.

## COMMONALITIES

The following discussion covers a number of major commonalities which have received attention, describes them briefly, and points out their limitations.

### Loss of Self-Control

Loss of "self-control" is the preeminent criterion for addiction: when stimuli in the environment indicate availability to the addict, steps to taking a substance or engaging in an activity appear to be inexorable. The victim loses "self-control," and perhaps while concurrently expressing severe self-criticism, despite the best intentions at other moments, engages in the addictive behavior. Loss of control is not absolute, however. "Availability" does not totally determine use. Under threat of detection or punishment, the addict may refrain. It might be better to describe addiction as an extreme loss of personal flexibility (Jaffe 1980).

"Self-control" usually describes motivational conflicts in which strong tendencies are pitted against strong personal efforts to contain them. The basis for containment has usually been learned as part of a socialization process; i.e., the person's attempts not to use or behave in some habitual way result from a history of moral training. Self-control issues are attributed only when such a conflict is recognized. For cigarette smokers to describe themselves as addicted has become common only since smoking was recognized as health threatening and large numbers of smokers attempted to quit. Decisionmaking conflicts between positive alternatives do not involve self-control, e.g., should I go to a movie or to a concert; should I order steak or chicken from the menu?

"Loss of self-control" is a common and often vivid subjective experience, and is also frequently reported by others, often as an apology to explain their own unwanted actions. Hence, there is a high degree of intersubjective agreement that loss of self-control

is a valid mechanism to explain a part of the addictive process. However, the concept of self-control is difficult to specify objectively in a behavioral analysis, and its place in any biological inquiry at present is highly questionable. Moreover, because self-control conflicts are private events they may for many reasons be distorted in public self-reports. The addict may report loss of control because punishment for undesirable behavior is tempered when a person is judged "not responsible" by others, and addiction is commonly regarded as a state that includes loss of control. The term "compulsive" in "compulsive habitual behavior" or "compulsive substance use" also implies loss of self-control. If one is "compelled" to act, then responsibility lies elsewhere--for example, with "society," for providing the temptations, or with heredity, for determining an innate vulnerability. Hence, the addict can be partially forgiven for irresponsible acts.

Personal conflicts between strong urges and attempts at self-control can be construed in normative terms which bring a moral quality to issues in addictions. This quality is central in any psychosocial or political consideration of addictive behaviors. Whatever its difficulties for a scientific analysis, self-control is likely to persist as a main concept in public discussions of the addictions.

## Involvement

Jaffe's (1980) definition of addiction is a "behavioral pattern of drug use characterized by overwhelming involvement with the use of the drug (compulsive use), securing of its supply, and a high tendency to relapse after withdrawal." "Involvement" may also include shared social rituals, emphasis in discussions and planning, and self-acceptance of a label such as "addict."

Seeking the substance or activity. The degree of involvement with securing a supply depends upon a drug or activity's price, the proximity of a market, and its legal status. Heroin is illegal, expensive, and sometimes scarce at any price. A heroin user may be required by the conditions of the drug's availability to be heavily "involved" much of the time in obtaining it. In contrast, the heavy smoker may pay virtually no attention to cigarette supply, except on the unusual occasions when they are difficult to obtain.

Involvement may be most pronounced in states of extreme deprivation; the individual can hardly think of anything or do anything which does not relate to the addictive substance or activity--the starving person analogy applies. The subjects in the Minnesota starvation experiments during World War II had imagery, conversations, and pastimes which were completely dominated by food (e.g., Keys et al. 1950). In considering involvement, it is important to distinguish the addict in a satisfied state from a deprived one. Otherwise, as in cigarette use, the dependency will

be unobtrusive when the substance (or activity) can be easily obtained. The behaviors involved in obtaining addictive substances may not be compatible with (incapable of concurrent occurrence) and therefore displace normatively more desirable behaviors. The uninvolved observer may consider the addict's disregard for personal health or social obligations to be totally irrational, and the effect of some disease-like process. Indeed, it is a hallmark of the classic addictions that these patterns are personally and socially destructive, largely because they displace socially desirable ones.

The effects of altered states. Involvement which competes with normal activities may occur not only during substance or activity seeking, but during the main phase of the drug effect, e.g., intoxication. The distinction is clearest in the initial stages of a cycle of excessive heroin or alcohol use. (The case is less clear for other drugs such as tobacco, and for nondrug habitual behaviors.) Substances and activities regarded as addictive generally may produce strong alterations in many of the following traditional categories: mood, social behavior, psychomotor skills, problem-solving and attentional and perceptual processes. There are elaborate experiential reports of drug effects, some of which try to account for repeated use by the quality of the psychological effect. However, complex psychological effects presumably unique to the human species are not necessary for drug dependencies. All the species of animals that have been studied in behavioral pharmacology laboratories repeatedly self-administer most of the same substances taken by humans (Griffiths et al. 1980).

There are psychological effects of drugs and habitual behaviors which appear to be essential for persistent involvement with use. These effects have been described both in behavioral and in experiential frameworks; i.e., as reinforcement or as hedonic effects: heroin is a powerful reinforcer, or it produces euphoria. Both views posit a strong positive effect as an important commonality in the development of addictive patterns; however, reinforcement can be more directly specified than experiential states and so has become preferred for experimental research with living organisms. "Powerful" suggests that given the opportunity to choose among an array of familiar reinforcers, the organism (human or not) will tend to select the addicting drug or activity. "Euphoria" has been difficult to describe, in part because it is a private event. It has been suggested that "euphoria" as a drug response was invented to fill the need for an exceptionally powerful, hedonic effect to explain how something as bad as drug addiction could persist so stoutly in the face of treatment, punishment, and personal resolve.

Positive reinforcement is not, of course, an exclusive feature of behaviors generally described as addictions. Reinforcers not generally considered to be involved in addictions may also be strong competitors for control of behavior, and may maintain long chains of behavior which are frequently repeated; e.g., sex, food, money, or praise. Excessive involvement with one of these

reinforcers may earn an individual a label which implies that he or she is obsessed in a way tantamount to what is meant by "addiction," such as "nymphomaniac," "compulsive" or "binge" eater, "scrooge," or "exhibitionist," respectively. Considered from this perspective, one finds insufficient reasons why "excessive" behavior patterns reinforced by opiates, alcohol, tobacco, or high-stakes gambling may be regarded as addictions, while those maintained by sex, food, money, or praise are not. An adequate definition of addictive behavior patterns cannot be based alone on a taxonomy of reinforcers.

Habit and frequency. The term "habitual behavior" in the context of addictions means a repetition of a pattern, or in Jaffe's terms, involvement in use. Habit has a number of connotations: the sense that repeated behavior wears a groove in daily life and thus persists; chronicity--implying repeated relapses after abstemious periods; or an activity in which the person engages much of the time. Habit also implies a learning process; in some learning theory frameworks, a habit is a relatively stable state of the learned behavior. Habits may vary in strength, depending in part on reinforced repetitions and motivating conditions; also, the greater the variety of settings in which a behavior pattern occurs and is reinforced, the more tenacious the habit. Thus, it is not surprising that many Americans who used heroin in Vietnam gave it up readily on returning home to the United States where they had never obtained or used it (Robins 1978).

Frequent occurrence is a necessary feature of behavior which is regarded as an addiction, but not a sufficient one. There are no absolute frequencies which define addictive use; rather, to be a candidate for the label "addict," an individual must use a substance at a higher rate (frequency over some time base) than most others in the appropriate comparison population. Frequencies of use for individuals who comprise the treatment population for a substance also are used to characterize "typical" addictive patterns. However, rate of an event does not by itself define an addiction. Some activities required for work or family care roles, for example, occur very often, such as writing for a writer, operating a punch press for an assembly line worker, or picking up a small child for a parent. How many single instances form a pattern? How can "normal," "light," or "moderate" use be characterized and distinguished from patterns which shade into addiction? Simple counting is insufficient.

Substance use per se is excluded as an addiction, although the term "abuse" is often used very loosely to include either patterns of excessive use of legally available substances or any use of illegal ones. A one-time user of heroin may be defined as a substance abuser, but a single trial has little in common socially, economically, psychologically, and biologically with regular patterns of opiate use, except in popular beliefs about substance use, or where a narrow legality is the exclusive interest.

## Tolerance and Withdrawal

It can be clearly demonstrated that repeated administration of some drugs results in progressive decreases in some of the effects. For example, the socially important properties of the opiates--analgesic and pleasurable effects--show this kind of change, called tolerance. Tolerance was once believed to be a requisite to addiction. Classic studies of addicts showed that increasing dose was necessary to produce the same effects--leading to more exposure to the drug and perhaps to greater frequency of administration. Tolerance was closely linked to another phenomenon, withdrawal or abstinence effects. Disuse of the drug resulted in marked physiological reactions and psychologically unpleasant experiences. It was assumed that eventually the addict could not get enough drug to continue the early "euphoric" experiences because of tolerance, but would desperately seek the drug to prevent withdrawal effects. It was postulated that through repeated administration the drug brought about a novel biological requirement analogous to nutrition. Absence of the drug or its metabolites resulted in a strong biological drive which could only be satisfied by more drug and a restoration of the balance.

Although the biological mechanisms are not understood, some drugs, including alcohol, result in directly observable physiological withdrawal effects which can be extremely unpleasant or even life threatening. However, the contribution of withdrawal effects to maintaining addictive behavior patterns is far from clear. From clinical and observational evidence, there appears to be a strong short-term effect. Addicts report that they become desperate to obtain the drug to avoid or escape the dreadful abstinence reactions. But in a longer time frame, relapse frequently occurs long after withdrawal symptoms have ceased.

The discussion of tolerance and withdrawal has so far been restricted to the "classic" addictive substances. The problems in satisfactory resolution of the role of these processes in compulsive habitual behaviors are intensified when the analysis turns to other drugs, and especially to nondrug habitual behaviors. Even before the popularity of suggesting that a host of strongly motivated, unwanted behaviors are addictions, pharmacologists and other specialists argued over reports of tolerance without withdrawal, withdrawal without tolerance, and dependence without either, all within the context of drugs alone.

What problems are raised when these concepts are extended to nondrug habitual behaviors? Interruption of some high frequency activity suspected of having addictive properties is reported to be accompanied by a variety of unpleasant effects. Compulsive gamblers in "withdrawal" are said to resemble opiate addicts or alcoholics. The restlessness, irritability, and reported craving of cigarette smokers in abstinence is familiar. The dysphoria of hobbled joggers is reported. The anguish of compulsive eaters under dietary control is well known. However, it has often been observed that initially withdrawing any reinforcer is accompanied

by emotional reactions. Are all unpleasant reactions to abstinence withdrawal phenomena? Or should that concept be restricted to highly specific patterns including specifiable physiological events?

In sum, those who would extend the concept of addiction to a far larger set of everyday occurrences must at least be aware of the conceptual problems engendered by using emotional disturbance, when strongly motivated behavior is blocked, as the sole criterion of "addictive-like." Where do we go from there? One way points to research to specify more carefully the events which occur when a reinforcer is withdrawn, and to map out a set of categories which would be useful in organizing other purported properties of addictions. Another approach is to retreat, at least temporarily, to the classic substances--opiates, alcohol, barbiturates, etc.--that more clearly satisfy criteria setting their use apart as a special class of behaviors.

## Addictions as Adaptations

Coping strategies. It is commonly held, although difficult to demonstrate, that addictions are symptoms of "underlying" personal problems. The addiction is said to be a psychological mechanism for temporarily reducing the personal anguish caused by a personal conflict. Although in its initial stages the habitual behavior may provide relief, ultimately the addiction creates secondary problems and the addict's emotional balance sheet totals up to suffering, not relief. In one of the major clinical views of addiction, addicts require psychological treatment, and the problem is staked out in terms compatible with psychotherapeutic strategies. In this view, the general commonality in addictions is a maladaptive attempt to solve personal problems and avoid/escape psychological pain; while clinical strategies based upon other conceptions of the problem, e.g., current methadone maintenance systems, place greater emphasis on biologically based vulnerabilities.

In a simplified statement of the coping strategy viewpoint, an addictive behavior may relieve some intolerable emotional state by distracting the person from the generative conflict, allowing the attendant anxiety to be "bound" rather than consciously experienced. Substance effects--intoxication is a major one--may dampen one's response to danger signals, i.e., "tranquilize." Even occasional users benefit in this fashion. When such relief is sought repeatedly, an addiction may be attributed. In this clinical framework, addicts are defined as individuals who habitually adapt to conflicts they cannot face by a pattern of substance use; in this pattern, the power of the substance or activity to grip the person is multiplied. In addition to its positive reinforcing properties--similar to those which engage laboratory animals--the habit is reinforced by providing functional avoidance or escape from aversive stimulation.

It is difficult to untangle the web of motives in an addict's often disordered life to be confident whether the addictive behavior is

mostly cause or effect. The case for the symptomatic nature of addictive behavior patterns has not been made, although the experience of temporary relief by using substances is common enough. Finally, there is the puzzle of the control cases: why some troubled individuals have ample contact with potential addictions but resist acquiring an addictive habit.

The addictive personality. One line of addiction research seeks to discover relatively stable psychological characteristics that provide unique vulnerability to some addictions. In the early decades of substance abuse research, personality configurations were considered substance-specific; alcoholics and drug addicts were supposedly different. Increased awareness of drug substitution and the perception of a polydrug abuse subgroup in the population has been responsible for a view more oriented toward commonalities. The evidence for the addictive personality conception is not compelling. Identified groups of addicts in treatment can be shown to deviate markedly from the general population on personality scale scores. However, these studies mostly lack sufficient controls, and differential prediction of who will become addicted from personality-scale scores in the general population has not been demonstrated. This caveat notwithstanding, there are no doubt personality configurations or perhaps specific traits which change the likelihood of the person's acquiring some addictive habit. This is a far cry from "the addictive personality," however.

For almost all substances and habitual activities, many more individuals have experienced the effects and not developed addictive patterns than have become habitual users. Scarcely more than a generation ago, it was widely believed that a single administration of heroin was virtually certain to lead to an addiction; similar beliefs about marijuana, which is not now regarded as addicting, are evident in the documentary film classic, Reefer Madness. In fact, many people who experiment with drugs discontinue their use after an initial experience.

The development of addictive patterns. This process appears to follow known principles of behavior acquisition. Both operant and Pavlovian conditioning are entailed. Are there common features in the establishment of addictive patterns which are distinct from well-maintained, nonaddictive habits? One strategy is to look for new phenomena which emerge from the study of excessive habitual behaviors. Two of these are adjunctive behaviors, repetitive patterns associated with specific conditions under which reinforcement is scheduled, but not attributable to the reinforcement contingencies per se (Falk 1971); and behavior maintained by the delivery of stimuli which in all other known contexts are aversive (e.g., Morse and Kelleher 1970).

Normative Behavior and Deviance

Characterizing deviant behaviors as addictions. "Normal" activities such as TV viewing, gambling, or taking exercise, may be regarded as addictive phenomena when the frequency and involvement is very high for some, relative to most other participants. People "explain" the intense involvement of others in activities that they themselves find uninteresting as addictions. An "otherwise reasonable" person who has a passion for running which is not shared by acquaintances may be considered "addicted" by them. This attribution perhaps reflects a growing tendency in modern American society to judge deviant behaviors in medical or psychological frameworks rather than moral ones.

Activities suspected of addictive qualities are usually regarded as recreational, not necessary for a "successful" life, or for "personal survival." "Recreational" in this sense means activities which are time-outs from "work" and other serious business of living. Despite the frequently discussed pleasure-seeking bent of modern Americans, excessive or intrusive activities are considered a distortion of acceptable pleasure-seeking, and pathological explanations are sought.

Illicit drugs are a special case which illustrates the operation of normative standards in forming judgments about addictive phenomena. For example, hallucinogens such as LSD are not usually classified as addictive in technical treatises on drugs. However, the general public has strong beliefs in the biological and psychosocial harmfulness of "drugs"; i.e., illicit substances used for recreational purposes. Anyone who would voluntarily risk his or her physical and mental health must be misled about the consequences or in the grip of some powerful force in the substance, i.e., addicted. Therefore, hallucinogen use is popularly regarded as addictive behavior.

Substance use practices in some population subgroups, e.g., heroin with inner city black youth, and marijuana with the 1960's "counterculture," have been regarded by many Americans as uniformly destructive and dangerous. The attribution of addiction is easily made when the practice is deviant, when the deviance is institutionally affirmed by control policies such as law enforcement, and when the deviant group is remote from those making value judgments. Belief in the harmful properties of illicit drugs is buttressed by concerns that other deviant behaviors, e.g., crime and dangerous political views, are associated with use.

Reputations. Popular conceptions about drugs determine informal and formal response to substance use. Reputation is a major commonality which aligns the fates of otherwise quite different activities (Becker, forthcoming). A commonality is established, for example, when a drug is declared illicit and its use takes on the features of a forbidden activity. To keep such use private, common social practices are developed which minimize detection. A

reputation influences the effects a user experiences; it may, for example, enhance the user's belief that he or she is "hooked"; reputation also partially governs the social response of others to a user. In the extreme case, e.g., heroin, the drug's reputation among nonusers is very firm although they have no direct contact with users, let alone personal experience with its effects.

Intrusiveness. Phenomena which are candidates for the label "addiction" have the property that they are in some way considered socially intrusive by those who are abstinent or engage in the activity "moderately." Intrusiveness is multidimensional and difficult to characterize; in some fashion the activities disrupt the preferred routine of others, offending them concretely or symbolically. In some cases, the threat of danger, e.g., heroin leads to crime, drunks may be physically abusive, gamblers may lose the family fortune, etc., is a basic feature of the intrusion, but the sight of "falling-down drunks" in public may also offend the values of observers.

Because of the complexity of social relations and symbolic responses to intrusive activities, producing a clear analysis of intrusiveness in addictive phenomena is difficult; but it is an important task. Intrusiveness is a determinant of a substance's reputation, norms about its use, and relevant control practices. Intrusiveness may be determined either by effects on users or on those nonusers in the environment when use occurs. An account of intrusiveness must include historical analysis; e.g., a commonality in a drug's reputation as dangerous is its introduction into society by a disapproved minority, such as use of marijuana by Mexicans in the 1930's (Musto 1973); but introduction of a drug as a legitimate medicine may buttress its reputation as safe even when widespread misuse occurs; e.g., minor tranquilizers. Similarly, familiarity as a food or a major economic staple, e.g., coffee and tobacco, may prevent application of sanctions although less dangerous activities are forbidden.

## Social Group Factors

Social pathways and gates to addiction. What are the common social chracteristics of an environment which selectively shapes some individuals so that the likelihood of their addiction is enhanced? There are two kinds of influences: (1) social factors which can be regarded as selective gates, blocking most from becoming addicted but letting some through; these factors chiefly apply to illicit drugs like heroin; and (2) social enhancers--the most discussed is peer influence--which can initiate use or push a moderate habit to excessive levels. As with many extreme, undesirable fates, we want to know why this person, not some other from the same environment, "went bad." Often biological or psychological uniqueness is attributed, and proper attention is not given to social commonalities.

Symbolism in use. Behavior can have a symbolic, ritual meaning for a group, whether it be the members of an organized religion, a group of political activists, or the patrons of a neighborhood bar. What common, special properties do substances have that make them useful for group cohesion and identification? Not using may be also a distinct group value and contribute to group strength, e.g., temperance groups.

Addictive subcultures. The use of some illicit substances, or the excessive use of licit ones, may be differentially characteristic of some nationalities, ethnic groups, or socioeconomic classes. Irish and Finnish drinking practices, and heroin use in lower class black neighborhoods are well-known examples. Eating patterns of some groups, certainly of some families, likely engender such food disorders as binge eating. Although some stereotyping is no doubt involved in common social conceptions of these relationships, there is a substantiating literature for many cultural differences (e.g., Blane 1976). Membership in an ethnic group or social class, however, cannot carry a commonalities analysis very far. It needs to focus on the opportunities and social structuring in environments which enhance the likelihood of problematic use. Prohibition of use at home and among the young is a well-discussed example. Group membership also provides the setting for transmission of cultural recipes for substance use.

## Genetic Commonalities

Every measurable behavioral trait can be shown to vary in degree among individuals; usually the data are normally distributed in a randomly selected, genetically heterogeneous population. It is not unreasonable to assume that genotypic differences are in part responsible for the distributions. A single gene cannot account for differences in such complex sociobehavioral patterns as addictions, but combinations of genes, along with environmental opportunities, may contribute to differences in use patterns. The nature of the contribution may not be immediately obvious; e.g., reduced sensitivity to specific toxic side effects of a drug.

## Neurobehavioral Commonalities

Common neural subsystems mediating addictive behaviors. Addictions are patterns exhibited by behaving individuals. No piece of behavior occurs in the absence of some corresponding action of the nervous system. The assertion that there are biological commonalities "underlying" the addictions is in that trivial sense true. The important issue is whether relatively discrete (and related) brain systems organize and control the impetus, direction, and operation of patterns we characterize as addictions. The hypothetical addictive system might be anatomically discrete, but is more likely a functional identity, possibly with a common

neurotransmitter. The large question is: does such a system(s) exist? If so, how is it arranged so that the classic addictive substances are immediately "recognized" by it, and how do more complex, nonsubstance addictions like gambling become subsumed by it?

Opiate receptor-endorphin system. The discoveries of the opiate receptor and the family of neuropeptides known as endorphins lend powerful impetus to the idea of a discrete addictive system. Reasonable speculations about the functions of such a system can be provided: To maximize survival, an organism must be reactive to dangerous stimulation, and monitor damage to itself, but not be so swamped by these signals that it is immobilized. The findings on the endogenous opiate system were a precursor to the discovery of analog biochemical systems subserving other psychoactive drugs, e.g., the benzodiazapines. With the demonstrable explanatory power of the receptor concept, it is not surprising to find that there are specific sites where known active compounds have their effects chemically. How nondrug addictive behaviors would fit this model is difficult to imagine, however.

The concept of pain is often extended to include various forms of psychological distress. It is not unreasonable that the relief of a broad class of physical and psychological pains might be neurochemically mediated by opiate receptor-endorphin systems. If this hypothetical function is combined with the chemical-coping-with-life interpretation of the function of addiction, then the grand commonality could be located at that intersection. Unfortunately for this reasonable theory, research on biochemical activity of the putative system in animals given opiates does not yet provide support for the theory applied to opiates, let alone a broader class of addictive behaviors.

## SUMMARY

The foregoing discussion attempts to accomplish two objectives: (1) to present criteria which are commonly employed to characterize "addictions"; (2) to discuss the usefulness of such criteria as a first step toward a more sophisticated analysis. It should be obvious that no single criterion is sufficient to define an addiction. Also, not all are necessary. These criteria, growing out of common usage, are imprecise, but they offer a basis for assessing common properties in more highly refined ways.

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# Historical and Personality Factors

 

# Personality Factors in Human Drug Self-Administration

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For several years we have been conducting experimental studies of human sedative dependence. The studies are conducted in a controlled hospital environment, employing adult volunteers with established histories of sedative abuse as subjects. The aim of the research is to identify factors controlling human oral drug-taking behavior and to determine drug and dose preference for prototypic sedative drugs. To date, a total of 40 subjects have been involved in the research, self-administering a wide range of sedative compounds including pentobarbital, secobarbital, phenobarbital, diazepam, clorazepate, and methaqualone.

In the studies, subjects are given ad lib 24 hr/day drug access, with only a 30-minute minimum interval being required between successive drug doses. Drugs are available in standard unmarked capsules from an automatic vending machine, which dispenses capsules in small envelopes, controls the minimum interval between successive drug self-administrations, and records the time and dosage amount of each capsule dispensed. In this manner, drug-taking behavior is brought under experimental control, allowing factors that control both rate and pattern of drug-taking behavior to be studied objectively (Pickens and Heston 1978).

As research subjects, humans show considerable individual variability in drug-taking behavior. For example, some subjects self-administer as little as 100-200 mg of pentobarbital per day, while others self-administer as much as several thousand mg of pentobarbital per day. In an attempt to identify sources of this variability, we assessed metabolism rate and CNS sensitivity (tolerance) of subjects to pentobarbital and then related such measures to their daily rate of pentobarbital intake. We found mean daily pentobarbital intake was higher for individuals with faster metabolic rates and lower CNS sensitivity to pentobarbital. This indicated that metabolic rate and CNS sensitivity to pentobarbital may be factors controlling pentobarbital self-administration in humans (Pickens et al. 1977).

In the present report we describe relations between personality measures and drug-taking behavior. Subjects were administered the Minnesota Multiphasic Personality Inventory (MMPI) while engaged in ad lib pentobarbital self-administration. Scores on the various scales that comprise the personality inventory were correlated with both amount and pattern of daily pentobarbital intake.

## THE MMPI

The MMPI is the most widely used personality inventory in the world today. It was developed in the late 1930s and early 1940s by Starke Hathaway and Charnley McKinley at the University of Minnesota. The test consists of 550 items, each written in a first-person self-report format. Examples of items include "I believe people are plotting to get me," and "I sometimes think about things that are best kept to myself." Subjects are asked to answer each item either "True" or "False," depending on whether the statement accurately describes their behavior, thinking, or mood. Items appearing on the test were validated empirically, by comparing differences in endorsement frequency in psychiatric and normative populations (Butcher and Owen 1978).

In constructing the MMPI, individual items were selected to form scales. For example, if 90% of paranoids answered affirmatively to a given item while only 10% of the normal population did so, then the item became part of the paranoid cluster. Any subject answering the item affirmatively has a point added to the raw score on the paranoia scale. For each scale, raw scores are converted to T-scores, with a T-score of 50 being the average score for the reference group. In general, the higher the scale score, the more psychopathology is evidenct. T-scores above 70 are typically taken to be clinically significant (Dahlstrom, Welsh, and Dahlstrom 1972).

Both validity scales and clinical scales are derived from scoring the MMPI. Validity scales are measures of test-taking attitude, while clinical scales are measures of subject deviation from the normal reference group. Brief descriptions of validity and clinical scales on the MMPI are given in Table 1.

## SUBJECT CHARACTERISTICS

Characteristics of subjects employed in the research are shown in Table 2. There were 8 male and 14 female subjects. All were adults, referred to the ward for treatment of sedative dependence. All subjects volunteered for the research prior to drug withdrawal and start of treatment. Their mean age was 43.2 years and their mean body weight was 68.8 kg. The majority used only sedative drugs (predominantly barbiturates and benzodiazepines), several used combinations of sedatives and stimulants or sedatives and analgesics, while only one subject could be classified as a polydrug abuser. All subjects indicated sedatives as their preferred drugs.

TABLE 1

Personality Characteristics Associated with Elevations on the Basic MMPI Scales

| Scale | Characteristics of High Scores |
|---|---|
| L (Lie) | Tendency to present oneself in an overly favorable light |
| F (Validity) | Carelessness, confusion, or claiming an inordinate amount of symptoms |
| K (Correction) | Subtle measure of defensiveness |
| 1 (Hypochondriasis) | Cynical, defeatist, preoccupied with self, complaining, hostile, presenting numerous physical complaints |
| 2 (Depression) | Moody, shy, despondent, pessimistic, distressed |
| 3 (Hysteria) | Repressed, dependent, naive, outgoing, multiple physical complaints |
| 4 (Psychopathic Deviate) | Rebellious, impulsive, hedonistic, antisocial |
| 5 (Masculinity Femininity) | Males: sensitive, aesthetic, passive<br>Females: aggressive, rebellious, unrealistic |
| 6 (Paranoia) | Suspicious, aloof, shrewd, guarded, worrisome, overly sensitive |
| 7 (Psychasthenia) | Tense, anxious, ruminative, preoccupied, obsessional, phobic, rigid |
| 8 (Schizophrenia) | Withdrawn, shy, unusual, strange, having peculiar thoughts or ideas |
| 9 (Hypomania) | Sociable, outgoing, impulsive, overly energetic, optimistic |
| 0 (Social Introversion) | Modest, shy, withdrawn, self-effacing, inhibited |

Adapted from Butcher, J. Objective Personality Assessment. © 1971. Silver Burdett Co.

TABLE 2

Subject Characteristics

| | |
|---|---|
| Total | N = 22 |
| Sex | |
| Males | N = 8 |
| Females | N = 14 |
| Age (years) | |
| Mean ± SEM | 43.2 ± 2.7 |
| Range | 24 - 67 |
| Body Weight (kg) | |
| Mean ± SEM | 68.8 ± 3.9 |
| Range | 41 - 100 |
| Drug History | |
| Sedatives only | N = 14 |
| Sedatives/Stimulants | N = 3 |
| Sedatives/Analgesics | N = 4 |
| Sedatives/Multiple | N = 1 |

Self-administration data for the subjects are shown in Table 3. While several drugs were self-administered by some subjects as part of the research design, only data on single-dose pentobarbital self-administration are included in the present report. The selection of unit dose of pentobarbital for self-administration was based on sensitivity of subjects to the sedative effects of the drug. This was assessed by determining the magnitude of subject's response to a single challenge dose of 200 mg pentobarbital administered (typically) on the second hospital day. Subjects showing moderate sedation from the challenge dose were allowed to self-administer 30/mg capsule of pentobarbital; subjects showing minimal effects were allowed to self-administer 50 mg/capsule of pentobarbital; and subjects showing no effect from the challenge dose were allowed to self-administer 100 mg/capsule of pentobarbital. More details on this testing are presented elsewhere (Pickens et al. 1977). Thus, an attempt was made to adjust capsule dose to achieve approximately equivalent unit-dose effects in the various subjects.

The subjects were tested for a mean of 5.5 days (only one subject was tested for 1 day, with the majority for 4-6 days). Their mean drug intake was 491.2 mg, an amount sufficient to produce abstinence symptoms if drug administration were abruptly discon-

tinued. Their pentobarbital metabolism rate was determined by calculating the rate of decline of blood serum levels of pentobarbital following administration of the 200 mg challenge dose described earlier. Drug half-lives were determined individually for each subject by exponential curve fit. The mean metabolic rate for the subjects was 15.1 hrs (metabolic rate for pentobarbital in normals is 22-40 hrs). One subject showed an unusually long half-life (67.1 hrs); all other half-lives were under 22.4 hrs. Mean blood serum level of drug maintained by subjects was 2.8 ug/ml.

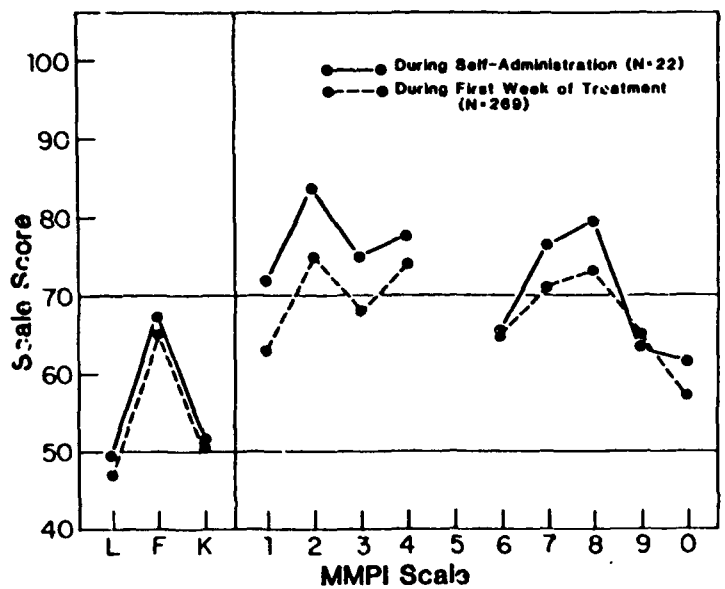
PROFILES OF SEDATIVE ABUSERS

Figure 1 shows the mean MMPI profile of the 22 subjects in our sample (solid line). The profiles were obtained during the subjects' first week on the research ward, with pentobarbital available on an ad lib basis for oral self-administration. Also shown is the mean MMPI profile of 269 sedative-dependent patients from another, larger treatment center (dashed line). These profiles were also obtained during the patients' first week at the treatment center, but while they were drug-free (i.e., with no drug self-administration allowed). Both groups were composed of patients from the same geographical region and referred to treatment by similar types of referral agencies. The mean age of subjects in our sample was 43.2 years, while that from the other treatment center was 40.2 years.

In the figure, combined scores for males and females in both samples were plotted for all scales except Scale 5 (Masculinity-Femininity), where the scores of males and females are scored differently. Both samples showed almost identical scores on the validity scales, indicating similar attitudes regarding test-taking. A similar clinical profile pattern was also seen for both groups, with highest elevations on Scale 2 (Depression), Scale 8 (Schizophrenia), Scale 4 (Psychopathic Deviate), and Scale 7 (Psychasthenia). Elevation on these scales is not unusual for drug-dependent individuals. Gilbert and Lombardi (1967) found this profile to be the mean MMPI profile in their study of male heroin addicts. Elevation on the same scales has also been frequently reported with alcoholics (Owen and Butcher 1979).

The most significant difference between the two profiles is the considerably higher scores obtained by subjects during pentobarbital self-administration than by comparable subjects during drug abstinence. Since higher scores indicate greater deviation from the population norm, more psychopathology and personal distress are being exhibited by subjects during pentobarbital self-administration than by similar subjects during drug abstinence. Clinically, both groups would be described as depressed, tense, irritable, and immature (Marks and Seeman 1963). However, the characteristics were more exaggerated in subjects during drug self-administration than in subjects during drug abstinence.

FIGURE 1




*Mean MMPI profile of sedative dependent subjects during pentobarbital self-administration (solid line) and during drug abstinence (dashed line). See Table 1 for names of scales. Score on Scale 5 (Masculinity-Femininity) not plotted, since scale is scored differently for males and females.*

TABLE 3

Drug Self-Administration Characteristics

| Drug | Pentobarbital, p.o. |
|---|---|
| Dose | |
| 30 mg/capsule | N = 4 |
| 50 mg/capsule | N = 13 |
| 100 mg/capsule | N = 5 |
| Days Tested | |
| Mean ± SEM | 5.5 ± .6 |
| Range | 1 - 12 |
| Daily Intake (mg) | |
| Mean ± SEM | 491.2 ± 62.1 |
| Range | 105 - 1300 |
| Metabolic Rate ($t_{\frac{1}{2}}$) | |
| Mean ± SEM | 15.1 ± 3.6 |
| Range | 4.2 - 67.1 |
| Blood Serum Level (ug/ml) | |
| Mean ± SEM | 2.8 ± .3 |
| Range | .9 - 4.9 |

The finding that pentobarbital self-administration increases depression, irritability, etc., in sedative-dependent subjects should not be surprising. Several investigators have experimentally administered ethanol to alcoholics and measured the resulting personality changes. In most cases, ethanol increased both depression and anxiety scores in the subjects (McNamee, Mello, and Mendelson 1968). The present findings suggest that when sedative-dependent subjects are allowed to regulate the amount and temporal pattern of pentobarbital administrations, drug-related increases in depression and irritability are also seen. For a more detailed discussion of this issue, see Mello (1978).

MMPI CORRELATES OF SEDATIVE SELF-ADMINISTRATION

Table 4 shows MMPI correlates of drug-taking behavior. The relationship was determined by correlating scores on each MMPI scale with mean mg/day pentobarbital intake. While the 2, 8, 4, and 7 scales had been previously found to be significantly elevated in profiles of sedative subjects, none of these scale scores was

significantly correlated with amount of daily pentobarbital intake. However, a significant correlation ($4 = +.45$, $p < .01$) was found between daily pentobarbital intake and score on Scale 9 (Hypomania) of the MMPI. In general, the higher the score on this scale, the greater was the amount of daily pentobarbital intake.

TABLE 4

Correlation Between MMPI Scale Scores and Mean Daily Pentobarbital Intake

| MMPI Scale | Pearson r |
|---|---|
| L (Lie) | -.03 |
| F (Validity) | +.02 |
| K (Correction) | +.20 |
| 1 (Hypochondriasis) | +.12 |
| 2 (Depression) | +.03 |
| 3 (Hysteria) | +.04 |
| 4 (Psychopathic Deviate) | -.09 |
| 6 (Paranoia) | +.14 |
| 7 (Psychasthenia) | +.29 |
| 8 (Schizophrenia) | +.19 |
| 9 (Hypomania) | +.45* |
| 0 (Social Introversion) | -.06 |

* $p < .01$

On the MMPI, the Hypomania scales is a measure of the individual's energy level. As the score on this scale increases, individuals tend to become increasingly involved in activities. While individuals with low scores show low energy levels, those with moderately elevated scores are active, exuberant, and energetic. With T scores above 70, hyperactivity, irritability, and grandiosity characterize the individual's behavior (Marks and Seeman 1963).

Unfortunately, correlation coefficients indicate strength, not causal directions of relationships. The finding of a significant correlation between Hypomania score and drug intake can be taken to indicate either that subjects who are hyperactive, irritable, and grandiose tend to take higher daily amounts of drug, or that as daily drug intake increases, subjects tend to become more hyperactive, irritable, and grandious. Both of the above could also be true, or both could be determined by a third factor as yet unknown. Since pentobarbital is classified as a sedative drug, one might expect hyperactivity to decrease rather than increase with increases in daily pentobarbital intake. That this does not occur is suggested by our previous research, where no

effect of daily pentobarbital intake was found on behavioral measures of subject performance on the research ward (Pickens et al. 1977). If drug intake were responsible for the personality scores obtained, the effect of pentobarbital must be primarily on irritability and grandiosity, rather than hyperactivity.

These findings also indicate that the elevated profiles found in subjects during pentobarbital self-administration were not due simply to the effect of the drug on behavior, since as Table 4 shows, elevations on the various scales were not directly related to pentobarbital intake.

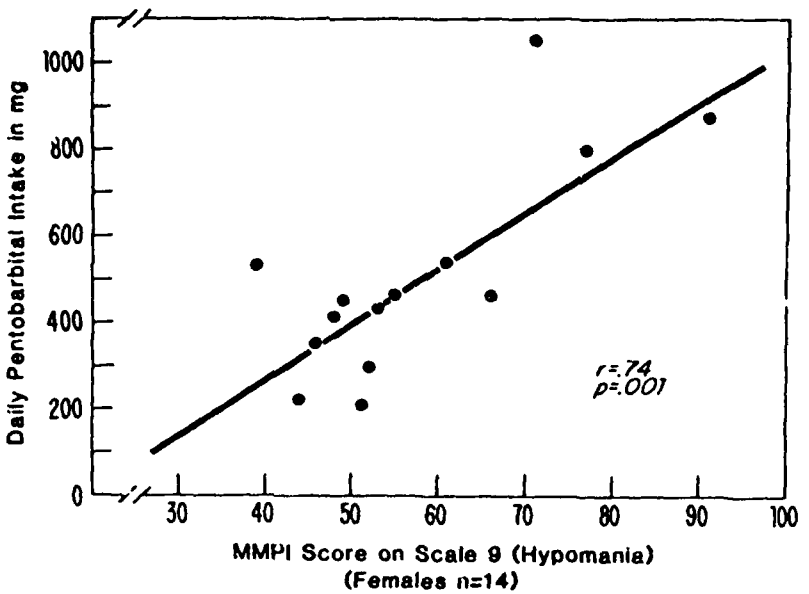
When these results were analyzed separately by sex of subject, the relationship between drug intake and Hypomania score was found to be localized primarily in female subjects (see Table 5). The correlation between drug intake and Hypomania score was +.74 for females ($p < .001$), while only +.25 for males (n.s.). This difference in relationship for males and females cannot be explained by sex differences in body weight producing differential drug effects. When variability in body weight was controlled for by partial correlation, a statistically significant correlation between drug intake and Hypomania score still remained ($r = +.46$, $p < .05$). Except for the Hypomania scale, no other clinical scale was significantly correlated with drug intake for either sex.

There was a significant effect of sex on the correlation between drug intake and K-scale score for males ($r = +.64$). This can be taken to indicate either that males tend to become more defensive and guarded as their drug intake increases, or that the more defensive and guarded the male, the higher will be his level of drug intake.

Concerning the relationship between drug intake and Hypomania score for females, a scatterplot of each individual's drug intake and Hypomania score was constructed to determine the validity of the obtained correlation coefficient. The scatterplot is presented in Figure 2. Daily drug intake is plotted along the vertical axis and Hypomania score is plotted along the horizontal axis. A line of best fit, calculated by the least-squares method, is also shown. As can be seen, most data points fall along this line. From these data, the correlation coefficient appears to accurately reflect the relationship between the two variables. Low scores on the Hypomania scale are associated with low daily amounts of drug intake, and high scores are associated with high daily amounts of drug intake.

That the relationship between Hypomania score and daily drug intake holds primarily for females was unexpected. While one might expect a sex difference in sedative self-administration based on the fact that women are more likely to be sedative abusers than men, this difference is apparently related to the fact that women are more likely to be prescribed sedative drugs than men, with the incidence of abuse relative to use being about the same for the two sexes (Cooperstock 1976).

FIGURE 2




*Scatterplot of daily drug intake and score on Hypomania scale for female subjects during ad lib pentobarbital self-administration.*

TABLE 5

Correlation Between MMPI Scale Scores and Mean Daily Pentobarbital Intake for Male and Female Subjects

| MMPI Scale | Males (N=8) | Females (N=14) |
|---|---|---|
| L (Lie) | +.29 | -.30 |
| F (Validity) | -.08 | +.20 |
| K (Correction) | +.64* | -.03 |
| 1 (Hypochondriasis) | +.55 | -.14 |
| 2 (Depression) | +.22 | -.23 |
| 3 (Hysteria) | +.48 | -.16 |
| 4 (Psychopathic Deviate) | -.18 | .00 |
| 6 (Paranoia) | +.07 | +.21 |
| 7 (Psychasthenia) | +.47 | +.19 |
| 8 (Schizophrenia) | +.06 | +.40 |
| 9 (Hypomania) | +.25 | +.74** |
| 0 (Social Introversion) | +.19 | -.32 |

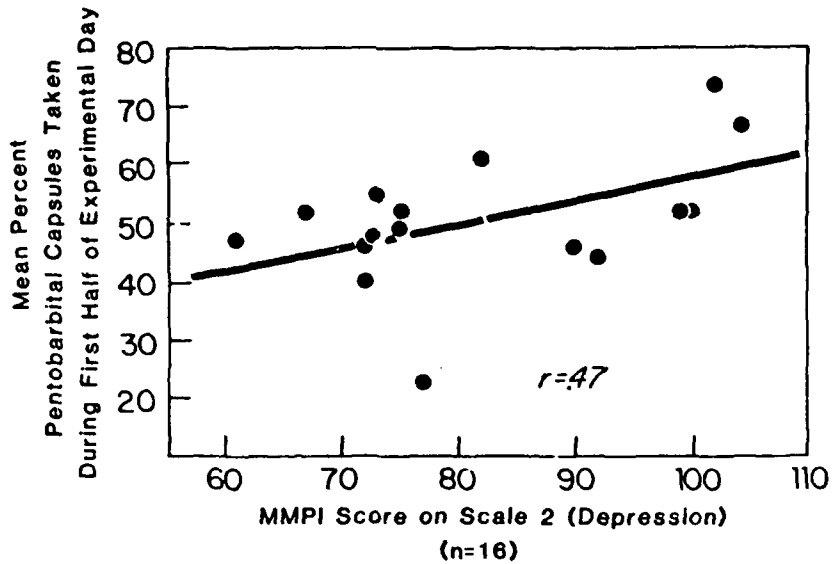
* $p < .05$
** $p < .001$

## DEPRESSION AND SEDATIVE SELF-ADMINISTRATION

Depression is a disorder frequently associated with both alcoholism and drug dependence (Cadoret and Winokur 1974; Schuster, Renault, and Blaine 1979). However, in the present research no significant relationship between daily drug intake and score on Scale 2 (Depression) was found, either for men or women (see Tables 4 and 5). One reason for this could be that all subjects tended to score high on the Depression scale and therefore between-subject variability was insufficient to yield significant correlation coefficients. However, when the patterning of drug responding was examined, a significant relationship was found between Depression score and pattern of drug-taking behavior. This relationship is shown in Figure 3.

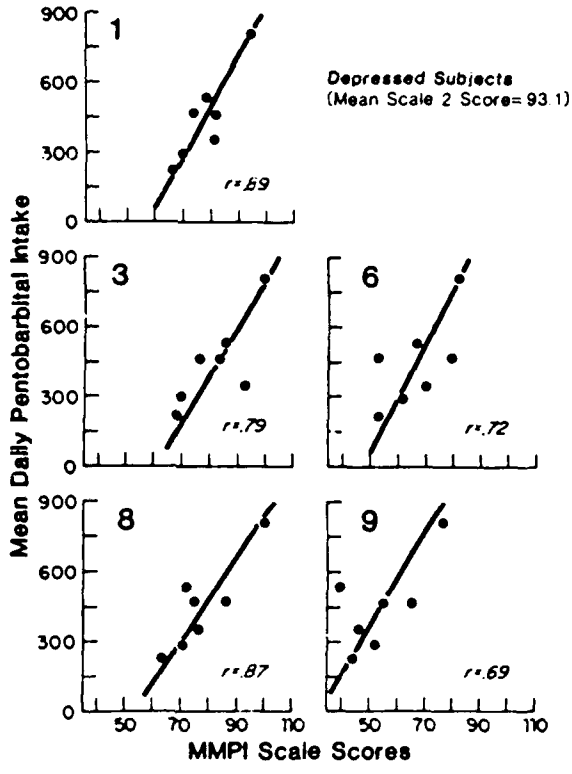
For this analysis, the experimental day was divided into two halves. While drugs were available to subjects 24 hr/day, 6 AM to midnight was considered to be the experimental day, excluding midnight to 6 AM as the sleep period. The first half of the experimental day was from 6 AM to 3 PM, and the second half was from 3 PM to midnight. If drug-taking behavior were evenly spaced throughout the day, then equal numbers of drug responses would be expected during the first half and second half of the

FIGURE 3




*Scatterplot of percent of total capsules taken during first half of experimental day and score on Depression scale for subjects during ad lib pentobarbital self-administration.*

FIGURE 4




*Scatterplots of daily drug intake and score on Hypochondriasis (1), Hysteria (3), Paranoia (6), Schizophrenia (8), and Hypomania (9) scales for clinically depressed subjects during ad lib pentobarbital self-administration.*

day. Only subjects with event records showing daily pattern of drug intake for three or more days of pentobarbital self-administration were employed in the study. Correlation coefficients were computed between mean percent of drug capsules taken during the first half of the day and score on each MMPI scale. Only scores on the Depression scale were found to be significantly related to pattern of drug intake ($r = +.47$, $p = .03$). As is evident from the line of best fit through the individual data points, a greater proportion of drug capsules was taken during the first half of the day by subjects with high scores on the Depression scale than by subjects with lower scores on the scale.

On the MMPI, Depression scale scores reflect the degree of pessimism and depression felt by the individual at the time the MMPI is administered. Individuals with low scores tend to be optimistic, alert, and g[illegible]s, while those with moderate elevations tend to be dissatisfied and prone to worry. Marked elevations on the Depression scale are associated with depression, pessimism, and social withdrawal (Marks and Seeman 1963).

The relationship found between Depression score and pattern of drug-taking behavior may reflect altered sleep patterns in depressed individuals. Depressed subjects may awaken earlier or go to sleep at night earlier than other individuals, thus altering the distribution of their daily drug responses. However, since patients on the ward are routinely awakened at 7 AM and ward activities typically continue until approximately 10 PM, the ward schedule insured that all patients were awake throughout most of the experimental day. Alternatively, the pattern of drug taking may be related to depression in yet another way. Depressed patients typically report most distress in the early morning, with progessively less distress as the day continues. Taking more drug in the morning may be an attempt at self-medication to lessen the increased distress they feel at that time of day. However, the results may equally indicate that depression is worsened in individuals who tend to take most of their drugs in the morning, an interpretation which is more consistent with other findings that show sedative drugs tend to exacerbate depression in drug-dependent individuals (McLellan, Woody, and O'Brien 1980).

In another attempt to examine the relationship between depression and sedative self-administration, subjects were divided into two groups depending upon whether or not their discharge summary included a psychiatric diagnosis of depression in addition to sedative dependence. The diagnosis of depression was made after the subjects had been treated for sedative dependence (i.e., were drug abstinent). The diagnosis was made by experienced psychiatrists who were blind to the eventual use of the information.

Differences between clinically depressed and non-depressed subjects are shown in Table 6. For both groups of subjects, corre-

lations between mean daily pentobarbital intake and score on each MMPI scale are shown. No significant correlation was found between drug intake and any MMPI scale for clinically non-depressed subjects. However, very strong relationships between drug intake and MMPI scores were found on several scales for clinically depressed subjects. These scales were 1 (Hypochondriasis), 3 (Hysteria), 6 (Paranoia), 8 (Schizophrenia), and 9 (Hypomania). Except for Scale 9 (Hypomania), none of these scales approached statistical significance for non-depressed subjects.

TABLE 6

Correlation Between MMPI Scale Scores and Mean Daily Pentobarbital Intake for Depressed and Non-Depressed Subjects

| MMPI Scale | Depressed (N=7) | All Other (N=15) |
|---|---|---|
| L (Lie) | -.07 | .00 |
| F (Validity) | +.15 | -.01 |
| K (Correction) | +.36 | +.21 |
| 1 (Hypochondriasis) | +.89** | +.06 |
| 2 (Depression) | +.01 | +.03 |
| 3 (Hysteria) | +.79* | -.12 |
| 4 (Psychopathic Deviate) | +.60 | -.35 |
| 6 (Paranoia) | +.72* | .00 |
| 7 (Psychasthenia) | +.63 | +.28 |
| 8 (Schizophrenia) | +.87** | +.06 |
| 9 (Hypomania) | +.69* | +.41 |
| 0 (Social Introversion) | -.46 | -.02 |

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

Because only seven subjects comprised the depressed group, scatterplots were constructed for each scale that significantly correlated with drug intake. These scatterplots are shown in Figure 4. The data points are homoscedastically distributed along the lines of best fit, indicating the correlation coefficients were accurately reflecting the relationship between the measures. The findings indicate that for clinically depressed subjects, increases in drug intake are associated with increases in distress as measured by several scales of the MMPI. Alternatively, however, the findings could also indicate tnat higher levels of distress are associated with higher rates of drug intake. Regardless of the direction of the association, the

same relationship does not hold for clinically non-depressed sedative-dependent subjects.

These results do not appear to be a statistical artifact. While varying degrees of inter-correlations are found among the various scales of the MMPI, none of these scales (including the depression scale) was previously found to be significantly correlated with drug intake. Perhaps clinically depressed individuals simply represent a different biological substrate upon which drugs act.

In clinically depressed subjects, if personal distress increases with increases in pentobarbital intake, this finding may be related to the individual's relative preference for different doses of the drug. Earlier we reported a curvilinear relationship between capsule dose and dose preference (Pickens et al. 1977). Preference tended to increase for doses up to about 100-150 mg/capsule, and then to decline. Several of our original subjects were included in the present report. Five of these seven are included in the group of clinically depressed subjects. Perhaps for these subjects, higher capsule doses of pentobarbital produced increased levels of distress, which was responsible for the decrease in mean preference scores found across all subjects at the higher capsule doses.

## SUMMARY

By comparing MMPI profiles of sedative-dependent subjects during pentobarbital self-administration with comparable subjects during drug abstinence, the present study has found that self-administration tends to increase rather than decrease indicators of personal distress (MMPI scale scores). This finding agrees fully with other studies of drug effects on mood of drug-dependent subjects. (This finding should disturb only those who equate reinforcement with euphoria and other pleasurable states. Those familiar with the concept of reinforcement understand that reinforcement deals only with behavior and implies nothing about corresponding subjective states). Only scores on the Hypomania scale of the MMPI were found to correlate significantly with amount of daily drug intake, and this relationship occurred primarily in females. Scores on the Depression scale were correlated significantly with the daily pattern of drug-taking behavior. However, in neither case is it known whether the relationship reflects influences of personality factors on drug-taking behavior, or influences of drug-taking behavior on the obtained personality measures. Other research will be needed to answer this question. Clinically depressed individuals may constitute a special sub-group of subjects in which scores on many MMPI scales are related to daily amount of drug intake. Studies of human drug self-administration provide an excellent opportunity for more detailed research into these and other clinical research questions.

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# Personality Factors in Methadone Self-Administration by Heroin Addicts

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## INTRODUCTION

Causes for the pattern of compulsive, repetitive self-administration of psychoactive drugs by humans that is known clinically as drug addiction are poorly understood. What differentiates the person who receives narcotics for post-operative pain and never develops drug-seeking behavior, from the individual who has the same experience but goes on to become a narcotic addict? As we look for answers to this question, several areas come to mind: the individual's socio-cultural experiences, both past and current; biological variables that may influence one's vulnerability; and psychiatric illnesses.

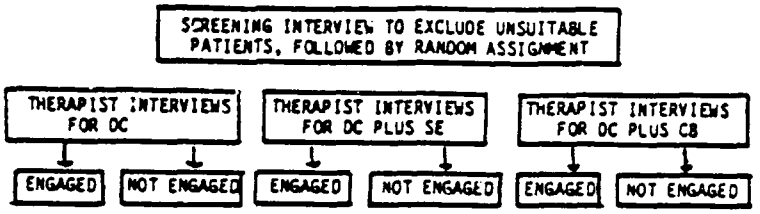
This paper presents data which explores relationships between personality and addiction that are found in the last of these areas, namely those existing between psychiatric illness and substance abuse. The data to be presented comes from a study aimed to measure what benefits may be obtained by adding professionally trained psychotherapists to routine counseling services in a methadone treatment program. Preliminary analyses of general treatment effects have shown superior results for patients receiving psychotherapy. However, because there is great variability among patients in the treatment groups, these general effects can be examined for the purpose of studying important treatment-patient interactions. The specific interaction we have examined for this paper is the effect of psychiatric symptoms, and of psychotherapy, on drug use and other measures of treatment outcome. The hypotheses tested are that (1) psychiatric symptoms act as internal stimuli that can set the stage for drug-taking behavior and that (2) psychotherapy done by trained professionals can reduce drug self-administration by diminishing the intensity of psychiatric symptoms.

## METHOD

Subjects and Design - The subjects are opiate addicts who are starting a new treatment episode with methadone maintenance. Patients eligible for this study must be between 18 and 55 years of age, cannot be

psychotic, and must not have subnormal intelligence or a persistent and clinically significant organic brain syndrome. They must also have some interest in psychotherapy and give informed consent to participate. After initial screening for eligibility, patients complete an intake evaluation and are randomly assigned to one of three treatment conditions: drug counseling (DC), counseling plus supportive-expressive therapy (SE) and counseling plus cognitive-behavioral therapy (CB). Each therapy is described in a treatment manual. An outline of the design is seen in Figure 1. All sessions are taped and 15-minute segments of each recording are rated by independent observers to determine their fit with the specifications in the manuals. Evaluations are done at 1, 7, and 12 months post-intake. An outline of these evaluations is presented in Table 1.

Figure 1
INTAKE




TREATMENTS

Drug Counseling - Drug counseling is a treatment that focuses on identifying specific needs and delivering concrete services. Its major emphasis is on providing external services rather than dealing with intrapsychic processes. Counselors monitor patient progress by reviewing urinalysis reports, personal, vocational, and legal situations. They provide liaison services with physicians, courts, and social agencies. A typical counseling session might begin when a counselor meets with his patient, reviews the clinic chart and observes that the urine tests show opiates. He questions the patient regarding what has been happening and how he is feeling. The patient says his methadone dose is not high enough, that he is having withdrawal symptoms beginning about 16 hours after he takes his methadone and that he has been using heroin. The counselor then arranges for the patient to meet with the program physician to be evaluated for an increase in the methadone dose. At the same time, the patient mentions that he has a court appearance in 2 weeks and requests a note for the judge saying that he is participating in a treatment program. The counselor has the patient sign a release of information statement, prepares a note and gives it to the patient to take to his lawyer. Counselors sometimes also intervene directly in emergencies such as loss of a place to live, family crises, or management of intense affects, such as anxiety or anger. In these situations, they meet with the patient, form an opinion regarding the cause of the problem and often arrange for a meeting with a program physician for a brief session which may include ventilation of affect, tranquilization or encouraging the patient to take positive action.

Table I
PSYCHOTHERAPY STUDY
SCHEDULE OF TESTING

| | INTAKE | 1 MONTH | 7 MONTH | 12 MONTH |
|---|---|---|---|---|
| CONSENT FORM | X | | | |
| MAUDSLEY PERSONALITY INVENTORY | X | X | X | X |
| BECK DEPRESSION INVENTORY | X | X | X | X |
| SOCIAL ADJUSTMENT SCALE (WEISSMAN) | X | X | X | X |
| SCL 90 | X | X | X | X |
| SHIPLEY | X | | | |
| RELATIONSHIP INVENTORY- COUNSELOR | | X | | |
| RELATIONSHIP INVENTORY - THERAPIST | | X | | |
| HELPING RELATIONSHIP - COUNSELOR | | X | | |
| HELPING RELATIONSHIP - THERAPIST | | X | | |
| PATIENT TERMINATION | | | X | |
| SCHEDULE FOR AFFECTIVE DISORDERS & SCHIZOPHRENIA -LIFE TIME VERSION (SADS-L) | X | | | |
| RESEARCH DIAGNOSTIC CRITERIA | X | | | |
| DSM III | X | | | |
| PREVIOUS TREATMENT FORM | X | | | |
| SCHEDULE FOR AFFECTIVE DISORDERS- CHANGE VERSION (SADS-C) | X | X | X | X |
| ADDICTION SEVERITY INDEX (ASI) | X | X | X | X |
| BACKGROUND DATA INTERVIEW (BLAINE) | X | | | |
| SOCIAL INFORMATION FORM (LUBORSKY) | X | | | X |
| FOLLOW-UP FORM | | X | | |
| THERAPIST FACILITATIVE BEHAVIOR | | X | | |
| GOALS OF THERAPY - THERAPIST | | | X | |
| TERMINATION FORM - THERAPIST | | X | | |
| COUNSELOR FACILITATIVE BEHAVIOR | | | X | |
| TERMINATION FORM - COUNSELOR | | | | |

Supportive-Expressive Therapy - Supportive-expressive therapy is an analytically oriented, focal psychotherapy modeled after that described by Sifneos (1972) and Malan (1963). It aims to help the patient identify and work through problematic relationship themes. The therapist identifies these themes via the relationship with the patient (transference), or according to what the patient says about other important relationships such as those with wife or other family members. Special attention is paid to the meaning that the patient attaches to the drug dependence. For example, a therapist might have a patient who denies having any problems. He keeps appointments out of "curiosity" or because he thinks he "ought to," but he maintains that things are going well in spite of being unemployed and having an unstable living situation. When he has a problem with his girlfriend, he refuses to discuss it, misses several sessions, and uses drugs, then asks his counselor to have his methadone increased. In this case, the therapist identifies the patient's denial as it appears in the transference, in the relationship with his girlfriend and in his drug use. The therapist works with the patient, aiming to diminish

the denial. If the therapist is successful, treatment should help the patient address his problems more directly, and thus increase the likelihood of finding better solutions to life problems than using drugs.

Cognitive-behavioral Therapy. Cognitive-behavioral therapy is a treatment that aims to identify and change false beliefs, unhealthy moods and problematic behavior. It is a treatment that has been developed by Dr. Aaron T.Beck and has been shown to be effective for treating certain types of depression (1976). Dr. Beck and his colleagues have found that depressed patients often have false and negative beliefs such as seeing themselves as helpless or worthless and that these beliefs can have a profound influence on mood. Reversing these false beliefs can significantly improve mood. For example, a person is withdrawn, depressed and feels that he is worthless and cannot succeed at anything. A CB therapist, having identified these false beliefs, attacks them actively and directly, aiming to show the patient how and why they are untrue. If the therapist succeeds in reversing them, the patient's mood brightens and the associated social withdrawal decreases. During CB therapy, the patient may be required to do "homework" such as recording daily activities and thoughts or deliberately altering certain behaviors. Some false beliefs commonly seen in narcotic addicts are, "I'm a junkie, I'll never get better," or "I can't possibly feel good without drugs." The CB Therapist identifies these beliefs and works actively with the addict to change them.

Initiating Treatment

After being randomly assigned to one of these three treatment conditions, the patient is given a brief explanation of the kind of treatment he will receive. The importance of keeping regular appointments is emphasized at this time. All patients are then required to have at least three meetings with their counselor and their therapist (if they are assigned a therapist) within the first 4 weeks. These mandatory sessions are required to make sure that all patients have an opportunity to gain some familiarity with the treatment conditions. After these three sessions are completed, patients are encouraged but not required to keep appointments. Patients who do not complete the initial sessions are not counted as part of the study, though data is collected on their progress. Those patients who are assigned a therapist have an opportunity to continue with that person for 6 months.

DATA ANALYSIS

To examine our hypotheses, we examined data on the first 62 patients to complete therapy and divided them into four groups based on ratings of psychiatric symptoms that were obtained at intake, and upon their treatment assignment. The measures used to make these subdivisions were the Beck Depression Inventory, the Maudsley Neuroticism Scale, and the psychological scale of the Addiction Severity Index. The Addiction Severity Index is a structured 20-30 minute, clinical research interview designed to assess problem severity in six areas

commonly affected by addiction. These problem areas include: medical, legal, substance abuse, employment, family and psychological status. In each of the problem areas, objective data on the number, extent and duration of problem symptoms in the patient's lifetime is collected, along with the recent (prior 30 days) subjective report of the severity and importance of the treatment problem from his perspective. The interviewer assimilates the two types of information to produce a rating (0-9) of the subject's need for treatment. These 10-point ratings have been shown to provide reliable and valid general estimates of problem severity for both alcoholics and drug addicts (McLellan et al. 1980).

We felt that these pre-treatment measures provided a valid estimate of general psychological status and on this basis we selected two extreme groups: those showing high levels of symptoms and clear, if presumptive, evidence of psychological problems (N=21), and those showing low levels of psychiatric symptoms (N=21) A total of 42 patients were included in these four groups, leaving 20 patients who were in the midrange and who were not included. We selected only the extremes since we felt that this method would give us the best chance to test our hypotheses.

We then subdivided these groups on the basis of their treatment assignment into high severity counseling (N=10), high severity therapy (N=11), low severity counseling (N=11), and low severity therapy (N=10). No distinction was made between the two psychotherapy groups because preliminary analyses showed no significant differences in outcome between them. A summary of the psychological test results for these four groups is presented in Table II. As seen, the groups are distinctly different in terms of the amount of psychopathology. The number of DSM III diagnoses (other than drug dependence) for these groups is seen in Table III. About 76 percent (7 of 10; 9 of 11) patients in the high severity groups had a DSM III Axis I diagnosis while only about 28 percent (2 of 10; 4 of 11) of the low severity patients were given DSM III diagnoses other than drug dependence. Axis II diagnoses were equal between the groups and were almost always antisocial personality disorder.

TABLE II
PSYCHOLOGICAL STATUS OF THE FOUR GROUPS AT THE START OF THE SURVEY

| | HIGH-SEV COUNS. | LOW-SEV. COUNS. | HIGH-SEV. THER. | LOW-SEV. THER. |
|---|---|---|---|---|
| N | 10 | 11 | 11 | 10 |
| Beck | 18 | 10 | 21 | 9 |
| Maudsley-N | 41 | 24 | 37 | 20 |
| Shipley IQ | 100 | 102 | 96 | 104 |
| Shipley CQ | 80 | 87 | 80 | 94 |
| ASI Psych. Sev. | 5.1 | 2.7 | 5.6 | 2.3 |

TABLE III

DSM III DIAGNOSES

| | HIGH SEV.-COUNS. | LOW SEV.-COUNS. | HIGH SEV.-THER. | LOW SEV.-THER. |
|---|---|---|---|---|
| # Patients w/Axis I Diagnosis | 7/10 | 2/10 | 7/11 | 4/11 |
| EXAMPLES | Bipolar Affective<br>General Anxiety<br>Chronic Affective | Bipolar Affective<br>Single Depressive | Bipolar Affective<br>Chronic Depressive<br>General Anxiety | Bipolar Affective<br>Manic Disorder<br>General Anxiety |
| # Patients w/Axis II Diagnosis | 7/10 | 5/10 | 9/11 | 7/11 |
| Ave. Axis IV (Stress Severity) | 4 | 3 | 4 | 1 |
| Ave. Axis V (Highest Function) | 4 | 4 | 4 | 2 |

## Pre-to Post-treatment Improvement

We examined pre-to post-therapy improvement for patients in each group using the ASI. The ASI severity scores and other related items are presented in Table IV. As seen, the high severity counseling group shows improvement only in areas clearly related to drug use. One might expect this since the patients were on methadone. The low severity counseling group demonstrated significant improvement in several areas, indicating the counselors are having a distinctly greater impact on this group than on the high severity patients. Conversely, the high severity therapy group demonstrated significant improvement in several areas, equal to that seen in the low severity counseling group. The low severity therapy group is also making considerable improvement, perhaps of greater magnitude than the low severity counseling group.

TABLE IV
PRE TO POST THERAPY (7-MONTHS) IMPROVEMENT

| | HIGH-SEV. COUNS. | | LOW-SEV. COUNS. | | HIGH-SEV. THER. | | LOW-SEV. THER. | |
|---|---|---|---|---|---|---|---|---|
| N | 10 | | 11 | | 11 | | 10 | |
| Medical Sev. | 3.1 | 2.4 | 1.7 | 3.2 | 2.5 | 3.5 | 1.8 | 0.7 |
| Days Med. Probs. | 4 | 2 | 2 | 4 | 3 | 3 | 1 | 1 |
| Employment Sev. | 4.5 | 4.6 | 5.1 + | 3.2 | 3.8 | 3.0 | 3.9 + | 2.7 |
| Days worked | 9 | 11 | 10 | 13 | 7 | 10 | 9 | 13 |
| Money earned | 272 | 306 | 242 + | 380 | 309 + | 482 | 318 * | 523 |
| Abuse Sev. | 5.7 + | 3.8 | 3.8 * | 1.4 | 4.9 + | 3.0 | 4.0 * | 1.4 |
| Days drunk | 4 | 2 | 2 | 1 | 3 | 2 | 2 | 0 |
| Days opiate | 6 | 3 | 10 * | 2 | 5 | 2 | 8 + | 3 |
| Days non opiate | 10 | 8 | 4 | 2 | 7 + | 3 | 3 | 1 |
| Money for drugs | 430 * | 190 | 164 * | 47 | 344 * | 65 | 188 * | 8 |
| Legal Sev. | 3.1 | 3.0 | 4.5 + | 3.1 | 2.8 + | 0.7 | 2.0 + | 0.8 |
| Days crime | 6 | 3 | 10 + | 4 | 5 + | 0.8 | 1 | 0.4 |
| Illegal income | 216 | 181 | 506 + | 300 | 186 * | 43 | 166 * | 10 |
| Psychological Sev. | 5.1 | 4.8 | 2.7 | 1.8 | 5.6 + | 3.0 | 2.5 + | 1.0 |
| Days psych. prob. | 17 | 13 | 8 | 3 | 15 + | 8 | 4 + | 1 |

* = $p < .01$
+ = $p < .05$

## During Treatment Results

The mean methadone doses for each group are seen in figure 2. There was a significantly ($p < .01$) higher mean methadone dose for the high severity counseling than for any of the other three groups. The low severity therapy group received a significantly ($p < .05$) lower dose than any of the other three groups, and the high severity therapy and

low severity counseling groups received comparable intermediate dosages. The mean dosage of the high severity counseling group is significantly greater than the other groups in both a statistical and clinical sense. In addition to methadone we often prescribe ancillary psychotropic medications for temporary symptomatic complaints of depression, anxiety or insomnia. These medications include doxepin, oxazepam, flurazepam or chloral hydrate. The percentage of subjects who were prescribed ancillary psychotropic medication is seen in figure 3, and the data show a pattern identical to the methadone doses. We feel these data indicate fewer symptoms and a corresponding reduction in need for medication among both groups of therapy patients and also among the low severity counseling patients. Urine drug screening results are seen in figure 4. The high severity counseling group has significantly ($p < .05$) more "dirty" urines than either of the other three groups, who have about the same frequency of positive urines. Nonprescribed benzodiazepines were counted as a positive urine in this category which may mask slight differences between groups because one dose of a benzodiazepine can be detected in the urine for 3-5 days.

## COMMENT

These data tend to confirm our hypotheses. Patients with high levels of psychiatric symptoms use more drugs (both prescribed and illicit) than patients with low levels of symptoms. This finding is especially clear in Figures 2,3, and 4, where high severity therapy patients have higher methadone doses, use more ancillary medications and have more drugs in their urine than low severity therapy patients. These same relationships are seen in the high and low severity counseling groups.

Similarly, the psychotherapy patients appear to be doing better than patients receiving only counseling. This is particularly evident when we examine the high severity groups. In these very difficult patients, the counselors seem to be having little impact, whereas the therapists are having an impact in several areas, including the ASI rating of psychological severity.

In terms of behavioral pharmacology, psychiatric symptoms appear to act as internal stimuli that set the stage for drug-taking behavior. Thus, psychiatric symptoms appear to increase one's vulnerability to self-administration of non-prescribed drugs.

We did not look at the relationships between specific symptoms and specific drugs, such as the one which may exist between depression and amphetamine use, or between anxiety and benzodiazepine use. These and further analyses of the relationships between psychiatric symptoms and drug self-administration appear to us to be areas that should be explored with the hope of finding practical solutions to the problem of drug addiction.

FIGURE 2

MEAN METHADONE DOSAGE BY GROUP

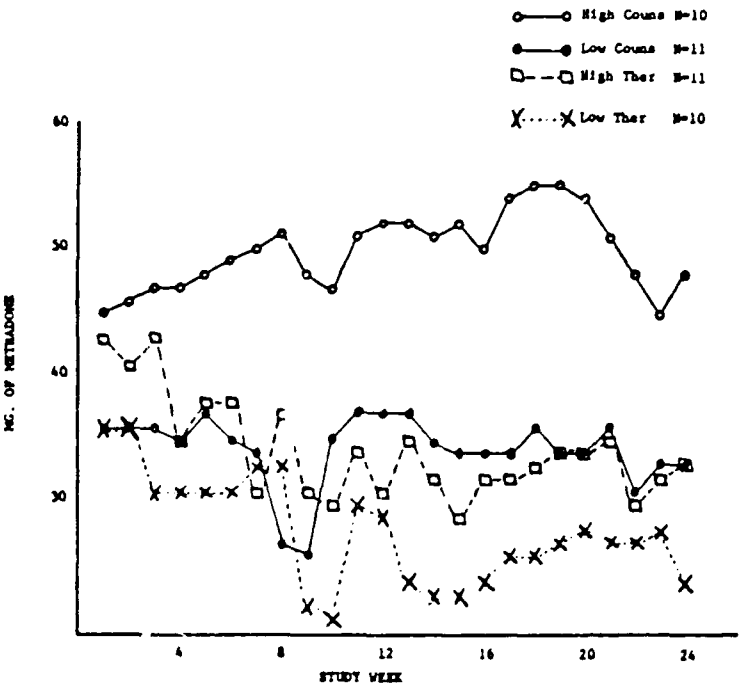


FIGURE 3

PATIENTS RECEIVING ANCILLARY MEDICATION BY GROUP

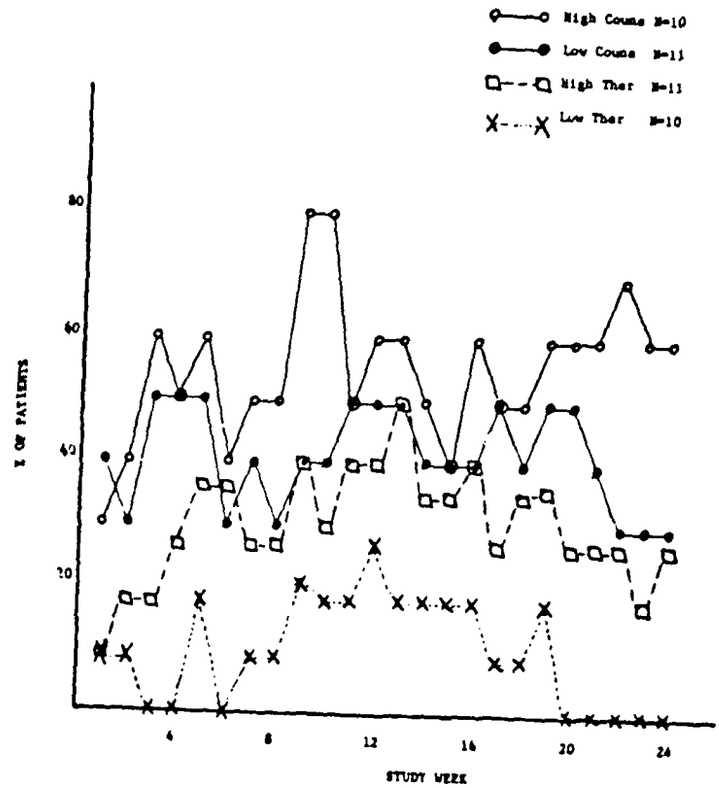
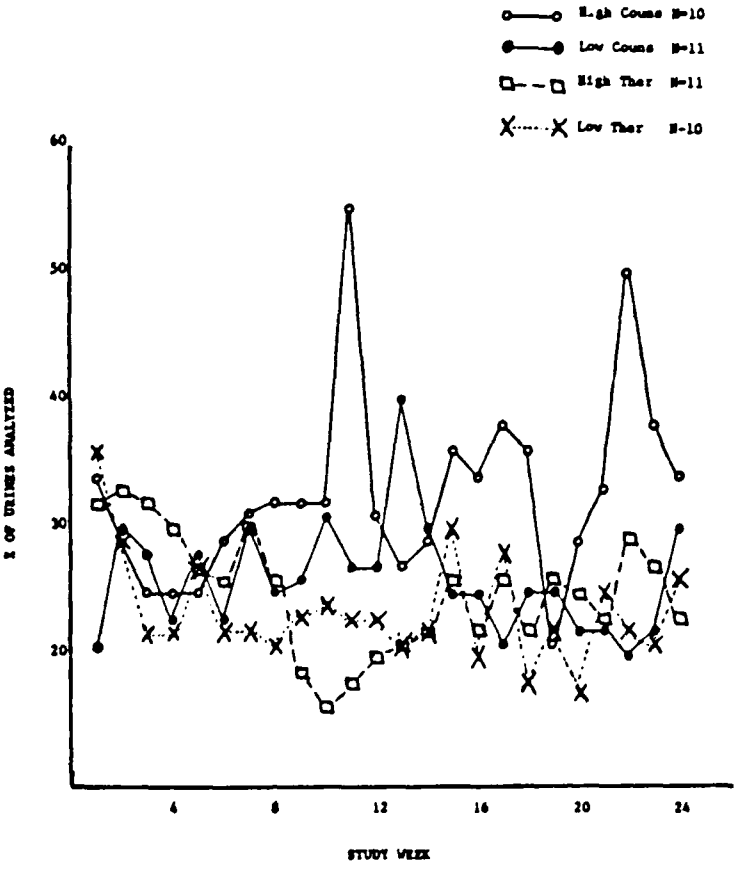


FIGURE 4

POSITIVE URINES BY GROUP



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# History of Drug Exposure as a Determinant of Drug Self-Administration

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The purpose of this paper is to review how a drug's effectiveness in initiating and maintaining self-administration can be influenced by a subject's past experience with drugs. Drug self-administration by humans and laboratory animals is considered an instance of operant behavior (e.g., Schuster and Thompson, 1969; Goldberg, 1976), controlled by the subject's genetic constitution, past history, and the current circumstances of drug availability (of Skinner, 1938). The influence of history of drug exposure on current drug-maintained behavior may be controlled, in turn, by the particular drugs and doses employed and the conditions under which the drug is administered. This discussion will focus on the ways in which a history of drug exposure can control later drug self-administration in laboratory animals.

## EFFECTS OF HISTORY OF DRUG EXPOSURE ON INITIATION OF DRUG SELF-ADMINISTRATION

In order to study drug self-administration by laboratory animals, an experimenter must set up a situation in which subjects are exposed to some contingency between the occurrence of a specific response and delivery of a particular drug. For many drugs, no explicit behavioral or pharmacological history is necessary for the drug to maintain behavior. In one initial study, for example, Deneau et al. (1969) surgically prepared drug-naive rhesus monkeys with indwelling venous catheters and presented the monkeys with a response lever. Presses on the lever delivered an intravenous injection of a drug. If a monkey did not press the lever at all during the experimental periods, a raisin or bit of candy was taped to the lever so that the monkey would depress the lever when grabbing for the food. Under these conditions, for the majority of monkeys tested, lever pressing was initiated and maintained by injection of appropriate doses of morphine, codeine, cocaine, d-amphetamine, pentobarbital, or ethanol. On the other hand, lever pressing was not maintained by injections of nalorphine, chlorpromazine, mescaline, or saline. These initial results have been amply replicated and extended to other drugs by numerous

investigators (see reviews by Pickens et al., 1978; Schuster and Balster, 1973; Woods, 1978). Thus, for many drugs, a history of drug exposure is not necessary for the drugs to function as reinforcers. Exposure to the contingency between a specific behavior and drug delivery is sufficient for the drugs to function as reinforcers and maintain subsequent behavior.

While prior drug administration is not necessary for the initiation and maintenance of self-administration of many drugs, it can hasten the development of asymptotic performance at a particular drug dose and schedule parameter. For example, if a monkey whose behavior has been maintained by intravenous injection of codeine loses its catheter and does not self-administer the drug for some period of time, replacement of the catheter is quickly followed by a return to the previous response rates. Additionally, exposure to schedule contingencies for the delivery of other drugs or other events such as food can increase rates of behavior that may be initially low when maintained by a drug such as ethanol. Winger and Woods (1973) reported that for certain rhesus monkeys, intravenous delivery of ethanol under a FR 1 schedule maintained few responses when available 24 hr per day. When injections of cocaine or methohexital replaced the ethanol, responding was initiated and maintained during 3 hr access periods. When ethanol was then reintroduced, responding continued at the higher levels. Moreover, the intake of ethanol for these subjects under the 3 hr access conditions did not differ from that for subjects that initiated ethanol self-administration without exposure to cocaine or methohexital.

Under certain conditions, the availability of a drug is not sufficient for it to function as a reinforcer. In a well-studied example, behavior often is not readily maintained by the oral delivery of drugs. However, a history of drug exposure that ensures that an organism will readily ingest an effective dose of a drug can increase the likelihood that certain drugs will serve as oral reinforcers. A good example of this effect of history of drug exposure is provided by the procedures developed by Meisch and colleagues (see review by Meisch, 1977) to establish ethanol as an oral reinforcer in rhesus monkeys. When ethanol is presented to monkeys, they do not readily drink large quantities, and, above small concentrations (5%), they may drink water to the exclusion of ethanol (Mello, 1973). Under certain schedules of food delivery (e.g., Falk, 1971), however, monkeys will adjunctively drink large quantities of ethanol (Meisch et al., 1975). After a history of adjunctive or schedule-induced drinking of gradually increasing concentrations of ethanol, high concentrations of ethanol can maintain responding in the absence of the original inducing schedule (Henningfield and Meisch, 1978). Subsequent work (e.g., Carroll and Meisch, 1978, 1980) has shown that a variety of inducing schedules are also effective in establishing drugs such as etonitazene and phencyclidine as oral reinforcers in rhesus monkeys. These compounds do not maintain behavior initially, but after gradually increasing concentrations have been consumed under an inducing procedure, each will maintain

behavior in the absence of the original inducing condition. To date, the particular history used to establish a drug as a reinforcer has not been shown to control the later behavior maintained by the drug. The behavior maintained by oral ethanol after exposure to an inducing schedule, for example, varies as a function of the current schedule conditions in the same way as does behavior maintained by the intravenously delivered drugs that do not require prior exposure to inducing schedules to function as reinforcers (Meisch, 1977).

## IMPORTANCE OF PHYSIOLOGICAL DEPENDENCE

For those drugs that have been extensively studied, it appears that prior physiological dependence is not necessary for a drug to function as a reinforcer (e.g., Woods and Schuster, 1971). The conditions under which such dependence is maintained, however, can influence the later probability of drug self-administration. In the case of physiological dependence on morphine, the likelihood that a post-dependent subject will self-administer morphine is controlled, in part, by the conditions under which the dependence was maintained. Rats that have maintained their physiological dependence on morphine by oral or intravenous self-administration will self-administer more morphine following a withdrawal period than will subjects that received the same maintenance doses of morphine noncontingently (Nichols et al., 1956; Weeks and Collins, 1968).

Current physiological dependence can alter the likelihood that certain drugs will serve as positive reinforcers. In particular, narcotic dependence can alter the reinforcing properties of a variety of narcotic mixed agonist-antagonists. While morphine-like agonists such as morphine, heroin, and the systemically active met-enkephalin analogue FK 33-824 maintain behavior in both nondependent and morphine-dependent rhesus monkeys (e.g., Hoffmeister, 1979; Mello and Mendelson, 1978; Roemer et al., 1977; Thompson and Schuster, 1964), mixed agonist-antagonists such as profadol, propiram, and pentazocine maintain behavior only in nondependent monkeys (see review by Hoffmeister, 1979). A second group of mixed agonist-antagonists, including nalorphine and cyclazocine, and the narcotic antagonist naloxone generally do not maintain responding by either nondependent or morphine-dependent monkeys (Downs and Woods, 1976; Hoffmeister, 1979). Morphine dependence can also alter the negative reinforcing properties of the mixed agonist-antagonists and antagonists. The mixed agonist-antagonist profadol maintains responses leading to the termination or postponement of its injection in morphine-dependent monkeys, but not in nondependent monkeys. The mixed agonist-antagonists nalorphine and cyclazocine and the antagonist naloxone, on the other hand, maintain responding leading to termination or postponement of their injection in both dependent and nondependent monkeys (Downs and Woods, 1976; Hoffmeister, 1979). The doses of these drugs required to maintain such behavior, however, are up to 1000 fold lower in dependent than in nondependent monkeys.

The reinforcing properties of narcotic antagonists can be altered dramatically under certain conditions (e.g., Downs and Woods, 1976; Goldberg et al., 1971b). As described above, the narcotic antagonist naloxone will readily function as a negative reinforcer, maintaining behavior leading to the postponement or termination of its injection in both dependent and nondependent monkeys (Downs and Woods, 1976). In morphine-dependent monkeys with an appropriate behavioral history, however, the same naloxone doses that maintain behavior leading to postponement or termination of their injection will also maintain behavior leading to the presentation of an injection. Downs and Woods (1976) conditioned morphine-dependent monkeys to terminate and/or postpone injections of 2 microgram/kg naloxone. Characteristic fixed-ratio performance was maintained by termination and postponement of naloxone injections. Then, the schedule contingencies were changed so that completion of each ratio produced a brief light flash; completion of every fifth or tenth ratio produced the light flash and an injection of naloxone. Behavior was maintained by the injection of naloxone in these morphine-dependent monkeys for as many as fifteen sessions. This apparently disparate effect of a presumably noxious pharmacological stimulus underlines the importance of the behavioral contingencies under which a subject is exposed to a drug in determining the later likelihood that the drug will maintain behavior leading to its administration.

## EFFECTS OF SELF-ADMINISTRATION HISTORY

A history of drug self-administration can influence the dose of a drug that will subsequently maintain behavior. In general, behavior is maintained by lower doses of drug in subjects with an extensive self-administration history than in subjects with a more limited history. For example, Goldberg (1973) showed that a low cocaine injection dose (12 microgram/kg) initially failed to maintain fixed-ratio responding in monkeys with a limited history of cocaine-maintained behavior, but maintained high response rates in the same subjects after a period during which responding was maintained by higher cocaine doses. The actual response rates maintained by certain doses of a drug can also be altered by a history of drug-maintained behavior. For example, Downs and Woods (1974) reported that the response rates maintained by injections of low doses of cocaine (3 and 10 microgram/kg) in rhesus monkeys increased dramatically when these doses were retested after exposure to other cocaine doses. Similarly, Carney et al. (1976) showed that the response rates maintained by several doses of ethanol increased when monkeys had a history of behavior maintained by higher ethanol doses.

The rate and pattern of behavior maintained by one drug can also influence both the initial pattern of intake of a substituted drug and the dose of that drug that will maintain behavior. For example, Schlichting et al. (1971) reported that when amphetamine was substituted for cocaine, codeine, or pentobarbital under a

fixed-ratio schedule in rhesus monkeys, the pattern of behavior initially maintained by amphetamine varied with the drug used to engender responding. Initially, the spacing of amphetamine injections was similar to that maintained by the maintenance drug. Cocaine maintained responses at regular intervals throughout experimental sessions, and all substituted amphetamine doses (0.005 to 0.05 mg/kg) maintained response rates above those maintained by saline, with responses spaced at regular intervals. The maintenance drugs codeine and pentobarbital, on the other hand, maintained frequent injections at the beginning of the session, followed by long pauses interspersed with bursts of injections over the remainder of the session. When substituted for these drugs, low amphetamine doses (0.005 and 0.01 mg/kg) maintained patterns of responding similar to those maintained by codeine or pentobarbital. When the high dose of amphetamine (0.05 mg/kg) was substituted for these drugs, however, several injections were taken rapidly, followed by no responding until the end of the experimental session. Thus, as a result of the pattern of injections engendered by the maintenance drug, higher doses of amphetamine maintained more behavior when substituted for cocaine than when substituted for codeine or pentobarbital.

The drug used to maintain behavior in the monkey can also alter the behavior maintained by substitutions of narcotic agonists and mixed agonist-antagonists. Hoffmeister and Schlichting (1972) reported that codeine, morphine, d- propoxyphene, pentazocine, and propiram will maintain behavior at lower doses when substituted for codeine than when substituted for cocaine. In addition, although the doses of each narcotic that maintained the maximal number of injections did not vary with the drug used to engender responding, the maximally effective doses of all the narcotics except morphine maintained more injections when substituted for codeine than when substituted for cocaine. As was the case for amphetamine, such differences in behavior may have resulted from the different patterns of drug injections engendered by the maintenance drugs. Thus, under similar behavioral schedules, the asymptotic pattern of drug intake can vary markedly among drugs from different pharmacological classes. When behavior is initially established with a particular drug, however, the pattern of intake maintained by that drug can control the initial pattern of intake of quite different drugs.

Under certain conditions, a monkey's self-administration history can alter not only the dose of a substituted drug that will maintain responding and the initial pattern of such responding, but also the likelihood that any dose of the new drug will maintain behavior. For example, self-administration of the antitussive dextrorphan is controlled, in part, by the subject's self-administration history. Dextrorphan does not maintain behavior following one type of self-administration history, but readily maintains behavior following certain other histories. When dextrorphan is substituted for codeine under a FR 30 TO 10 min schedule of intravenous injection in rhesus monkeys, no dose maintains response rates higher than those maintained by saline

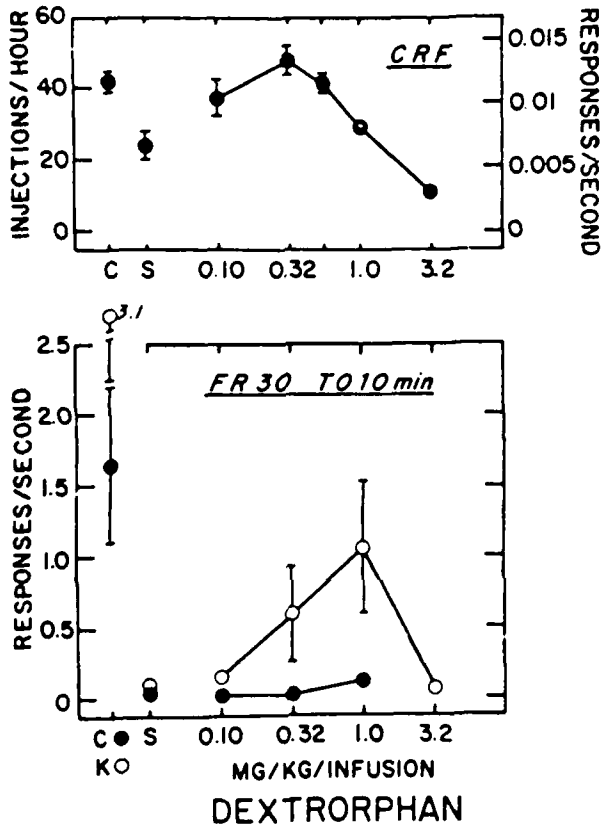
(Young et al., 1981). However, when dextrorphan is substituted for codeine under a FR 1 schedule, it maintains response and injection rates similar to those maintained by codeine. Figure 1 compares the behavior maintained by dextrorphan when substituted for codeine under these two conditions. The upper panel shows the response rates and injections per hour maintained under the FR 1 (or CRF) schedule by codeine (C), saline (S), and various doses of dextrorphan. Dextrorphan injection doses of 0.32 and 0.56 mg/kg maintained response rates similar to those maintained by 0.1 mg/kg codeine. However, as shown by the closed circles in the lower panel, the same doses of dextrorphan did not maintain responding when substituted for 0.32 mg/kg codeine under a different schedule, FR 30 TO 10 min.

These differences in the ability of dextrorphan to maintain behavior when substituted for codeine may be due to several factors. Dextrorphan may be relatively ineffective in maintaining behavior at high ratio requirements (cf Goldberg et al., 1971a). Alternatively, the monkeys' behavioral histories may have contributed to the differences in dextrorphan self-administration. The monkeys performing under the FR 1 schedule continued to respond for an average of 20 injections per session when saline replaced codeine, while the monkeys performing under the FR 30 TO 10 min schedule rarely completed the ratio requirement to deliver more than 4 or 5 injections. The maintenance of behavior under the FR 1 contingencies may have resulted in the monkeys' self-administering sufficient dextrorphan for it to acquire a reinforcing function.

The importance of self-administration history in controlling the ability of dextrorphan to maintain behavior under FR schedules was given added weight by the results of an additional experiment (Young et al., 1981). In this study, other monkeys self-administered the dissociative anesthetic ketamine under the FR 30 TO 10 min schedule of intravenous injection. During selected sessions, various doses of dextrorphan were substituted for the ketamine maintenance dose. As shown by the open circles in the lower panel of Figure 1, dextrorphan readily maintained behavior when substituted for ketamine under the FR 30 TO 10 min schedule. Thus, under the FR 30 TO 10 min schedule, dextrorphan maintained response rates higher than those maintained by saline when substituted for ketamine but not when substituted for codeine. Two other compounds, the dissociative anesthetic phencyclidine and the analgesic dexoxadrol, also maintained behavior under the FR 30 TO 10 min schedule when substituted for ketamine but did not maintain behavior when substituted for codeine (Young et al., 1981).

These differences in the ability of dextrorphan, dexoxadrol, and phencyclidine to maintain behavior when substituted for ketamine or for codeine may be controlled in part by the similarities in the behavioral properties of these compounds and ketamine. These drugs that maintained behavior only when substituted for ketamine share discriminative stimulus effects with ketamine, but not with

Figure 1




*Behavior maintained by intravenous injection of various doses of dextrorphan tartrate under different conditions. Upper panel: Injections per hr and responses per s maintained by dextrorphan under a CRF schedule when substituted for 0.1 mg/kg injections of codeine (C) for 10 consecutive 1 hr sessions. Each point represents the mean ± SEM for three monkeys. Lower panel: Responses per s maintained by dextrorphan under a FR 30 TO 10 min schedule when substituted for 0.32 mg/kg codeine (C: closed cirles) or 1.0 mg/kg ketamine (K: open circles) during single experimental sessions. Each point represents the mean ± SEM for two observations in each of three monkeys. In both panels, saline substitutions are indicated at S.*

codeine, in the rhesus monkey (Young et al., 1981; unpublished observations). Common discriminative effects among ketamine, phencyclidine, dextrorphan, and dexoxadrol have also been reported in rats, pigeons, and squirrel monkeys (Brady and Balster, 1980; Herling et al., 1981; Holtzman, 1980). Similarities among the discriminative stimulus properties of ketamine and those of phencyclidine, dexoxadrol, and dextrorphan may increase the reinforcing effectiveness of the latter three compounds when substituted for ketamine as compared to their effectiveness when substituted for codeine.

The control of the reinforcing effectiveness of a substitution drug by the maintenance drug itself is modulated by several factors. The maintenance drug is not a primary determinant of the ability of certain drugs to maintain behavior. For example, codeine, cocaine, and ketamine each maintain behavior when substituted for the other, while certain other drugs, such as cyclazocine and SKF-10,047 (N-allyl-normetazocine), do not maintain behavior when substituted for either codeine or ketamine (e.g., Hoffmeister, 1979; Young and Woods, 1980; Young et al., 1981). The duration of exposure to a substitution drug and the prevailing schedule contingencies may also modulate the effects of the original maintenance drug. For example, with repeated exposure to phencyclidine or dextrorphan these compounds will maintain behavior in monkeys whose behavior is initially maintained by codeine or cocaine (Figure 1; Balster et al., 1973; Pickens et al., 1973). Furthermore, drug-naive monkeys will initiate and continue responding leading to phencyclidine injection under FR 1 schedules during repeated daily sessions (Balster et al., 1973; Balster and Woolverton, 1980). Thus, control of the self-administration of a new drug by a subject's self-administration history varies with the particular drug under study, the drug with which the subject is experienced, and the behavioral conditions under which the new drug and the maintenance drug are available.

## EFFECTS OF PRIOR PAIRING BETWEEN ENVIRONMENTAL STIMULI AND DRUG ADMINISTRATION ON SELF-ADMINISTRATION BEHAVIOR

The general environmental context in which prior drug administration has occurred can be an important determinant of drug self-administration. For example, environmental stimuli paired with morphine self-administration can control the degree of self-administration by subjects previously dependent on morphine. If subjects self-administer sufficient morphine to develop physiological dependence in one environment and are subsequently withdrawn and then reexposed to morphine, the probability that they will later self-administer morphine varies as a function of the similarity of the environments in which the initial self-administration and reacquisition occur (Thompson and Ostlund, 1965). Rats exposed to the same environment in which self-administration originally occurred drink much more morphine after withdrawal than do rats reexposed to morphine in a different environment after withdrawal. Thus, the environmental stimuli

associated with previous narcotic self-administration can control the likelihood that morphine self-administration will be reestablished in post-dependent subjects.

Under appropriate circumstances, environmental stimuli paired with the scheduled delivery of a drug can powerfully control the rate and pattern of ongoing drug-reinforced behavior (see review by Goldberg, 1976). Following exposure to certain behavioral schedules, stimuli paired with the administration of drugs such as cocaine and morphine can control behavior in the same way as do injections of the drug themselves. Moreover, the environmental stimuli associated with prior noncontingent administration of one drug can control the later self-administration of a second drug. For example, under appropriate conditions, stimuli associated with narcotic antagonists can produce conditioned changes in the rate of morphine self-administration by morphine-dependent subjects. In morphine-dependent monkeys, administration of the antagonist nalorphine increases the rate of responding maintained by morphine (e.g., Thompson and Schuster, 1964). With a history of repeated exposure to nalorphine, these increases occur with a much shorter latency and can be elicited by environmental stimuli paired with nalorphine (Goldberg et al. 1969). Such conditioned stimuli can produce large but transitory increases in morphine self-administration in morphine-dependent subjects. These conditioned stimuli are also capable of eliciting certain of the signs of morphine withdrawal, including emesis, salivation, changes in heart rate, and disruption of the rate of food-maintained operants (Goldberg and Schuster, 1967; 1970). These latter conditioned stimulus effects, in contrast to the effects on morphine self-administration, are remarkably resistant to extinction and persist after monkeys have been withdrawn from morphine for two to four months.

A history of exposure to nalorphine can also control its potency in altering rates of morphine self-administration. Goldberg et al. (1971a) assessed the effects of nalorphine on the rate of responding maintained by morphine injections in morphine-dependent monkeys. In monkeys with a limited history of nalorphine injections, high nalorphine doses (1 to 3 mg/kg) suppressed the rate of morphine-maintained responding. In contrast, in monkeys that had received ascending doses of nalorphine and so had several sessions' experience with lower nalorphine doses, 1 and 3 mg/kg nalorphine slightly increased the rate of morphine self-administration. Likewise, in monkeys repeatedly exposed to 0.1 mg/kg nalorphine injections, the first injection of 1 mg/kg nalorphine increased the rate of morphine self-administration in two of four monkeys. This increase was transitory, however; the second injection of 1 mg/kg nalorphine did not increase morphine self-administration, and all succeeding 1 mg/kg nalorphine injections markedly suppressed morphine-maintained responding. It is likely that, with repeated exposure to low doses of nalorphine, interoceptive stimuli associated with the injection procedure became conditioned stimuli for increases in morphine self-administration. The initial effect of the higher nalorphine dose was then a conditioned increase in responses maintained by morphine.

With repeated exposure to high nalorphine doses, this response rapidly extinguished.

Recently, Herling (1981; unpublished observations) has presented evidence that a history of exposure to the narcotic antagonist naltrexone may also produce conditioned changes in the rate of narcotic-maintained behavior in nondependent monkeys. In these experiments, responding was maintained by codeine or food in alternate components of a multiple reinforcement schedule. Low doses of naltrexone antagonized the actions of codeine, increasing the injection dose of codeine required to maintain behavior and the cumulative dose necessary to decrease rates of food-maintained behavior. Higher doses of naltrexone suppressed responding maintained by all doses of codeine. In certain monkeys, some doses of naltrexone initially increased the rates of behavior maintained by codeine but suppressed behavior following repeated exposure. This suppression of codeine-maintained behavior by naltrexone was often greater than the effect produced by substituting saline in the session; i.e., extinction (Carney, 1976; Herling, 1981; Woods and Schuster, 1971). Herling and others (Harrigan and Downs, 1978; Woods et al., 1975) have suggested that such decreases in narcotic-maintained behavior may reflect a punishing effect of agonist-antagonist combinations, an effect that may be exacerbated by a history of repeated exposure to such combinations.

## SUMMARY

Drug self-administration is controlled, in part, by the subject's history of drug exposure. Although a history of drug administration is not necessary for many drugs to function as reinforcers, prior exposure can increase the likelihood that certain drugs, such as ethanol, will maintain behavior. While it has been demonstrated that physiological dependence is not necessary for a drug to function as a reinforcer, the conditions under which such dependence is maintained can control the later self-administration of the drug. Once drug-maintained behaviors are established, the particular drug that maintains behavior can influence the initial pattern of intake of a new drug and thus the dose of that drug that will maintain behavior. Additionally, under certain conditions, similarity between the discriminative stimulus effects of the drug that previously maintained behavior and those of a new drug can increase the likelihood that the new drug will function as a reinforcer. Finally, stimuli that have been paired with drug administration can powerfully control later drug-maintained behavior, the direction of such control being determined by the conditions under which such pairing occurred. In summary, both the type of drug with which a subject has experience as well as the contingencies governing that experience contribute to subsequent drug self-administration.

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# Contributions of Reinforcement Schedule Histories to Our Understanding of Drug Effects in Human Subjects

Harold Weiner, Ph.D.

ABSTRACT

Like other reinforcing stimuli, drug effects may vary with the reinforcement history of an individual. Data are presented which demonstrate that histories contribute to individual differences in response to reinforcement contingencies and modification of maladaptive behavioral persistence. Possible relevance of these findings to an understanding of drug effects in humans is discussed.

INTRODUCTION

Drug-seeking is a form of operant behavior under the control of schedules of reinforcement (Schuster and Thompson, 1969; Kelleher, Goldberg, and Krasnegor, 1976). Usually, the schedules are complex, involving chains of behavior under the control of discriminative stimuli and conditioned reinforcers unique to a particular drug-related environment. The precise nature of behavior related to drugs is determined by a number of antecedent factors as they interact with current environmental circumstances.

Antecedent factors may contribute to the development of a drug as a reinforcer, may determine the rate and form of drug-controlled performances, and may account for idiosyncratic and sometimes paradoxical drug effects (Griffiths, Bigelow, and Henningfield, in press). Among the more prepotent antecedent variables found to affect drug-related behaviors are prior exposure to the drug in question or related types of drugs (McMillan, Harris, Frankenheim, and Kennedy, 1970; McMillan, Dewey, and Harris, 1971); conditioned effects produced by past pairings of stimuli or activities with drug administrations (Pickens and Crowder, 1967; Goldberg, Woods, and Schuster, 1969); the state of drug deprivation (Woods, Downs, and Villarreal, 1973) and its interaction with the amount of previous reinforcement (Surgh and Manocha, 1966); and the nature of the acquisition of the performances under investigation (Terrace, 1963).

One of the more important current environmental variables affecting drug-seeking behavior is the formally defined

reinforcement contingencies. Another factor is the likelihood that drug-maintained performance will be punished (Thompson, Pickens, and Griffiths, 1973).

The behavior maintained by a given drug reinforcer is determined by a dynamic interplay between current schedules of drug reinforcement and performances brought to the current situation as a result of reinforcement schedule histories. Features of performance which we often portray as arising from personality or other dispositional states can be characterized as the product of the interaction between reinforcement schedule histories and contingencies in the current environment. Thus, some people are "perseverant" and others are "impetuous," referring to the degree of schedule-controlled persistence. Individual differences in such features, though seemingly bewildering, may actually be subject to analysis if we begin to look at historical variables in a more systematic way.

Although the effects of prior experience have always been regarded as important in a number of fields of psychology, in the early period of the growth of operant conditioning there was a strong emphasis on the power of current schedule contingencies to control behavior. There was a tendency to ignore prior experience. Indeed, it was common practice to use the same subjects, particularly pigeons, repeatedly from one experiment to the next, because it was assumed that the effects of the earlier histories were erased by the powerful current conditions. However, we find that a satisfactory account of operant behavior in all but the simplest and most powerfully controlled schedule conditions requires taking into account both histories and current conditions.

This is particularly true when one works with human subjects in operant research. A major problem encountered in the laboratory with humans under schedules of reinforcement is inter-subject variability. Experimental situations may look strange to humans at first, but are not unfamiliar to them as categories of experience. Generalization from other situations (e.g., problem solving in work or school) is more likely with humans than with infrahuman (animal) subjects. This is especially true of the task component of the situation. Inter-subject variability commonly exhibited by humans in free operant experiments is largely due to the variety of their behavioral histories.

Inter-subject variability implies lack of control by the current schedule of reinforcement. When the behavior of an individual is so inappropriate to its current schedule conditions that the person loses reinforcement or suffers unnecessary punishment, we sometimes label the behavior as pathological or maladaptive. This is true both in "real life" and in the laboratory (Weiner, 1965). The label remains even when we can attribute the behavior to persisting effects of earlier conditions which are no longer appropriate for current reinforcement requirements.

In most non-laboratory settings, we are not able directly to observe, manipulate, and systematically analyze the effects of histories on human operant behaviors such as drug-seeking. Like clinicians concerned with psychopathology, we often have to infer the nature of these histories from the individual's current verbal, motor, and/or physiological responses.

The experimentalist in an operant laboratory is in a somewhat better position. While acknowledging the simplicity of the laboratory situation, the relatively short temporal duration of a laboratory experiment, and the open question concerning the relation between experimentally induced behavior and behavior in more natural contexts, the investigator can, nevertheless, deliberately program and manipulate a variety of historical experiences and systematically examine the effects of such experiences upon the subsequent development and maintenance of operant behavior (Sidman, 1960, p. 300).

For a number of years, I have been conducting research with humans on the effects of reinforcement histories in conjunction with a number of other procedures (e.g., response cost, biofeedback) in individual and social operant contexts, with both normal and psychiatric subject populations (e.g., Weiner, 1969, 1970a, 1970b, 1977, 1981). In this paper, I will present samples from this research and its implications for understanding drug effects in humans. These examples involved normal adult humans and employed conditioned reinforcers. The findings which have emerged have been replicated with a wide variety of reinforcers and have also been replicated in drug studies with animals (Urbain, Poling, Millam, and Thompson, 1978). Their relevance to human drug-seeking is further suggested by considerable research which has demonstrated that drug reinforcers regulate operant performances of animals in ways similar to other reinforcers (Johanson, 1978) and that drug-maintained behavior in animals bears striking resemblance to drug-seeking in humans (Griffiths, Bigelow, and Henningfield, in press).

RESEARCH FINDINGS

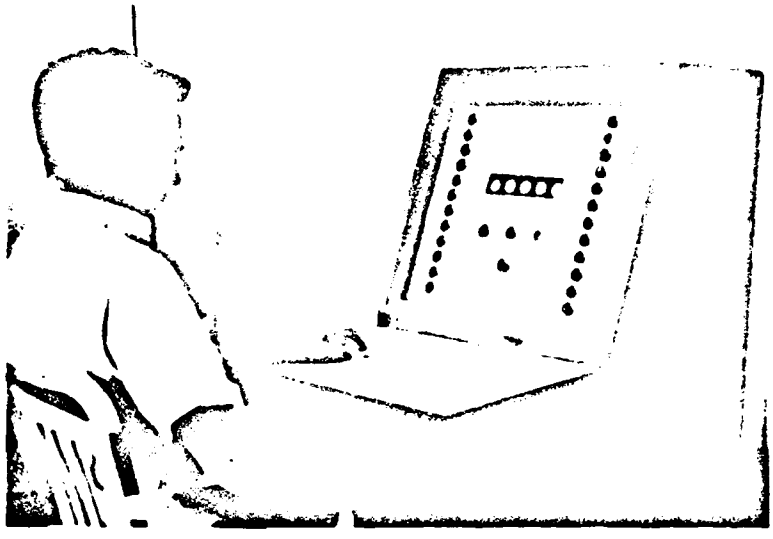

Figure 1. Subject and experimental apparatus.

Consider the following experimental situation depicted in Figure 1. A normal adult human sits in front of a console and is instructed to either press or not press a key in order to maximize his/her point score on a counter. Various schedules of reinforcement (100-point additions to the counter score) are programmed, each for 10 one-hour sessions. The subject is told nothing about the purpose of the experiment, the nature of the point reinforcement schedules, or at what rate to press the key. Rates and patterns of responding under the different point reinforcement schedules are recorded continuously over time using standard cumulative recorders.

Early operant research with humans in this experimental context produced surprising results in my own laboratory and in others. Our data showed that all schedules were not equal in terms of producing orderly and predictable performances from humans without resorting to special procedures not required with animal subjects. Good control with humans was obtained using schedules which one might refer to colloquially as "authoritarian." These schedules reduced behavioral degrees of freedom by making reinforcement frequency directly contingent upon particular rates and patterns of responding. Two examples of authoritarian schedules are fixed-ratio (FR) and differential-reinforcement-of-low-rates (DRL) schedules. FR schedules provide reinforcement whenever a fixed number of responses is emitted, while DRL schedules provide reinforcement only when two successive responses are spaced by a minimum period of time.

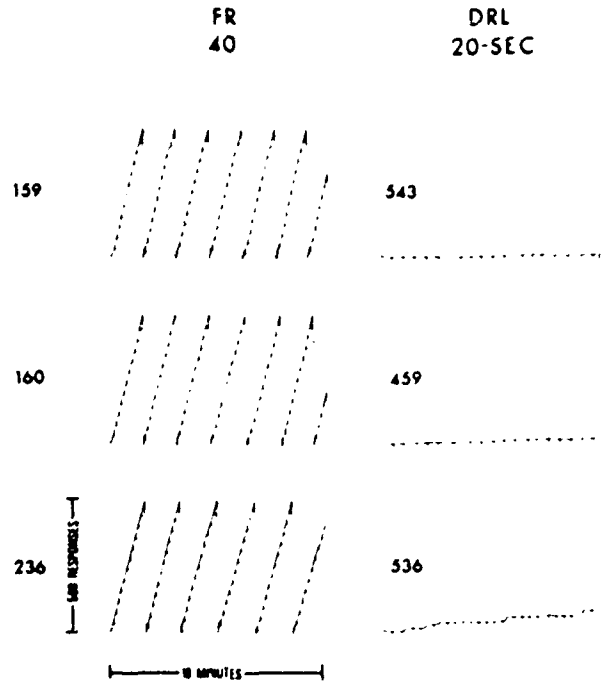


Figure 2. Final FR 40 and DRL 20-sec performances. Vertical marks on the records indicate the occurrence of 100-point reinforcements.

Figure 2 shows cumulative records of final performances obtained from human subjects under a 40 response fixed-ratio (FR 40) schedule and under a 20-second differential-reinforcement-of-low-rates (DRL 20-sec) schedule. High constant rates of responding are typically emitted under FR 40. Low rates of temporally spaced responding commonly occur under a DRL 20-sec schedule. Human performances under FR 40 and DRL 20-sec schedules resemble those obtained from animals under these schedules.

Rates and patterns of human responding under FR 40 and DRL 20-sec schedules tend to show minimal individual differences. This is because reinforcement rate under these schedules is contingent upon a narrow band of response rates and patterns. Any deviation from this narrow band would produce adverse reinforcement consequences, i.e., loss of opportunities for reinforcement.

Other schedules, more "democratic" in nature, permit individuals to "do their own thing" and still get reinforced. Inter-subject variability (poor schedule control) tends to increase and human

performances deviate from those of animals under democratic schedules, where a variety of response rates and patterns can result in the same rate of reinforcement. A fixed-interval (FI) schedule is a democratic schedule which provides reinforcement for a single response if sufficient time has passed from a previous reinforcement. Unlike DRL, an FI schedule does not require a minimum interresponse time for reinforcement. Responses emitted before enough time has elapsed from a previous FI reinforcement do not affect the frequency of reinforcement (i.e., they are unnecessary). Under an FI schedule, humans tend to exhibit a variety of rates and patterns of responding. High rates of unnecessary responding are not uncommon under an FI schedule with humans whereas low rates of positively accelerating responding (i.e., scalloping) are commonly obtained from animals under FI schedules.

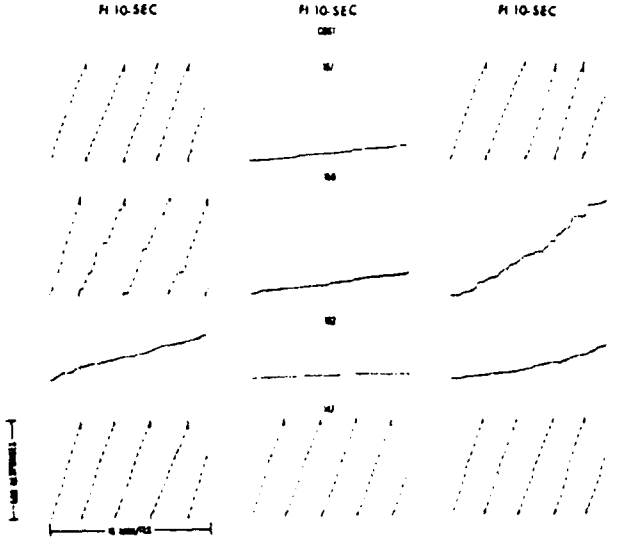


Figure 3. Final FI 10-sec to FI 10-sec cost to FI 10-sec performances. Other details as in Figure 2.

The cumulative records on the left side of Figure 3 show typical stable FI 10-sec performances obtained from humans. Under an FI 10-sec schedule, reinforcement depends upon a single response after at least 10 sec have elapsed from a previous reinforcement. All other responses are unnecessary.

Two general types of FI 10-sec responding can be distinguished: high and relatively constant response rates without post-reinforcement pauses (hereafter referred to as high-rate responding) and lower response rates with post-reinforcement pauses (hereafter referred to as low-rate responding). From an

efficiency point of view, low-rate FI 10-sec responding is, of course, more desirable because it consists of fewer unnecessary responses between reinforcements. It is also more desirable for inter-species comparisons because a wide variety of animals tend to produce low-rate responding under an FI 10-sec schedule.

Much of my research and that of others in the human operant laboratory has been directed toward identifying and manipulating conditions that could suppress high-rate FI responding to reduce inter-subject variability and produce human performances in concert with those obtained from animals. Studies have shown that high-rate FI responding can be suppressed by increasing the effort required to emit a response, by providing schedule information, by adding discriminative stimuli of a temporal nature, and by disrupting responding either by introducing an incompatible response or by adding punishment contingencies (cf., Weiner, 1969; Matthews, Shimoff, Catania, and Sagvolden, 1977).

My own research focused upon schedule conditions which might contribute to high-rate FI responding. Initially, I attempted to reduce high-rate FI 10-sec responding by introducing a type of punishment procedure called response cost. This procedure consisted of the subtraction of one point from the score on the reinforcement counter for each response between reinforcements. As can be seen from the data in the middle of Figure 3, cost suppressed the unnecessary FI 10-sec responding of most of the subjects. The degree of responding following the removal of cost (relapse) varied as a function of the amount of low-rate responding under FI 10-sec prior to the introduction of cost.

Cost punishment had no effect on one of the subjects. He maintained similar high-rate responding under FI 10-sec and FI 10-sec cost. Under the latter, his high-rate responding produced unnecessary (avoidable) punishment because reinforcement was possible without cost.

Thus, although cost produced more low-rate FI 10-sec performances, it did not entirely remove inter-subject variability. Since the two patterns of FI 10-sec responding produced by humans bore some resemblance to responding under FR and DRL schedules, I wondered whether histories under these schedules could account for the different FI 10-sec and FI 10-sec cost performances shown in Figure 3. If this was the case, I could control individual differences in FI 10-sec performances and produce systematic effects by arranging various FR and DRL reinforcement histories.

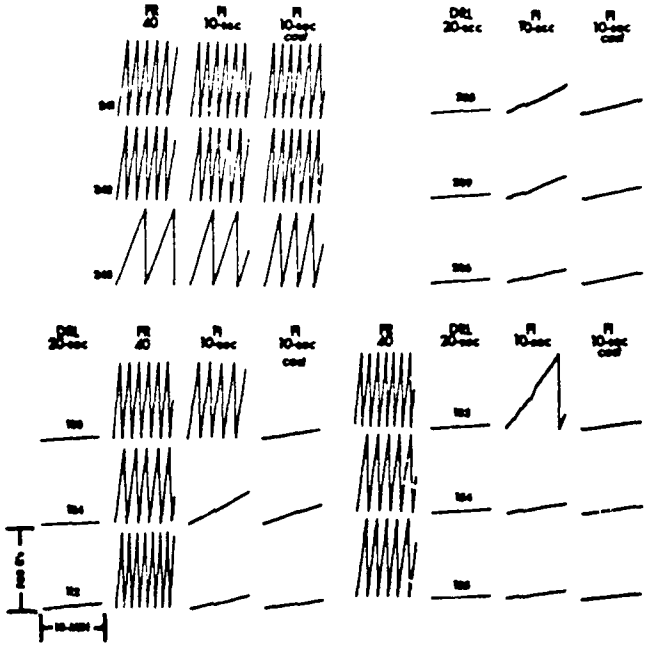

Figure 4. Final performances obtained under FR 40 to FI 10-sec to FI 10-sec cost; DRL 20-sec to FI 10-sec to FI 10-sec cost; DRL 20-sec to FR 40 to FI 10-sec to FI 10-sec cost; and FR 40 to DRL 20-sec to FI 10-sec to FI 10-sec cost. Other details as in Figure 2.

The effects of FR 40 and DRL 20-sec histories upon FI 10-sec performances are summarized in Figure 4. Final FI 10-sec and FI 10-sec cost responding of four groups of subjects with different reinforcement schedule histories is presented. One group had an FR 40 history, another group had a DRL 20-sec history, a third group had a DRL 20-sec to FR 40 history sequence, and a fourth group had an FR 40 to DRL 20-sec history sequence. It can be seen that subjects with an FR 40 history emitted high-rate responding under FI 10-sec with and without cost. Subjects with a DRL 20-sec history produced low-rate responding under FI 10-sec and FI 10-sec cost. Subjects with both histories, i.e., either a DRL 20-sec to FR 40 or FR 40 to DRL 20-sec history sequence, emitted either high-rate or low-rate responding (mostly low-rate responding) under FI 10-sec without cost. When cost was introduced under FI 10-sec, all of these history subjects produced low-rate responding. In other words, cost consistently suppressed responding whenever subjects had a DRL 20-sec history, i.e., there was an interactive effect between cost and reinforcement schedule histories.

It should be noted that FR 40 and DRL 20-sec responding persisted under FI 10-sec, whereas FR 40 responding did not persist under DRL 20-sec or vice-versa. Under FI 10-sec, high-rate or low-rate responding can persist without adversely affecting reinforcement frequency. High-rate FR 40 responding cannot persist under DRL 20-sec nor can low-rate DRL 20-sec responding persist under FR 40 without reducing the frequency of reinforcement.

It should also be noted that ongoing behavior immediately prior to FI was not always predictive of FI performances. Thus, different FI 10-sec and FI 10-sec cost performances were obtained from the FR 40 history and DRL 20-sec to FR 40 history subjects even though their FR 40 responding just prior to FI 10-sec was similar. These FI performances were affected by the presence or absence of a DRL 20-sec history which occurred prior to FR 40 and which was not reflected in the rates and patterns of final FR 40 responding.

The persistence of FR responding (without a DRL history) under FI and FI cost has been subjected to considerable experimental analyses (Weiner, 1969, 1970a, 1970b). Two important findings should be mentioned. First, in moving from FR to FI, subjects may occasionally emit low-rate responding. Despite differential reinforcement for such low-rate responding, subjects who only have an FR history do not produce low-rate FI performances. Said another way, unless histories have established needed repertoires (e.g., DRL), merely making contact with differential current contingencies of reinforcement may not be sufficient to produce adaptive changes in behavior.

A second finding of importance is that high-rate FI performances are obtained even when FR responding is extinguished prior to FI. History effects cannot be removed by simply extinguishing behavior. Said another way, organisms whose behavior has been extinguished are not necessarily organisms who have been returned to their pre-history state.

The data in Figure 4 provide information on the etiology and prevention of maladaptive excessive responding, i.e., they show how one can produce it or prevent its occurrence by arranging reinforcement schedule histories. Can we treat such behavior successfully after it has occurred? The answer is yes. The method of treatment is the same as the method of prevention shown in Figure 4, i.e., it requires providing subjects with a repertoire of DRL responding.

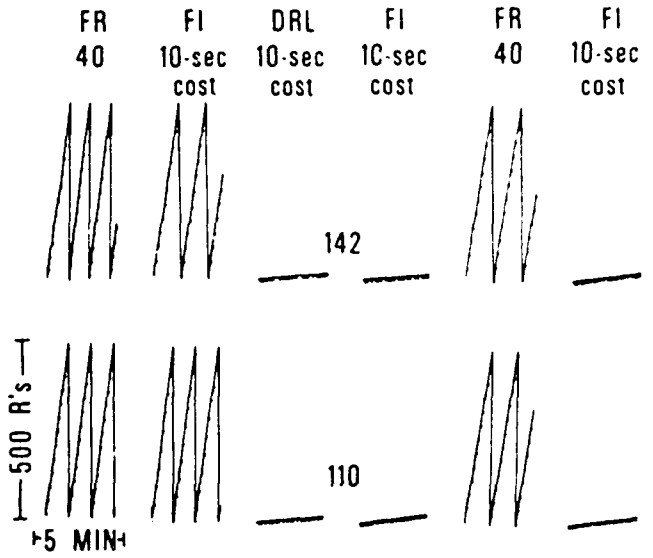


Figure 5. Final performances obtained under the following sequence of schedules: FR 40 to FI 10-sec cost to DRL 10-sec cost to FI 10-sec cost to FR 40 to FI 10-sec. Other details as in Figure 2.

Figure 5 presents the data of two FR 40 history subjects who persisted in their high-rate responding under FI 10-sec cost. This persistence represents not just response induction but contingency induction as well. These FR 40 history subjects were responding under FI 10-sec cost "as if" an FR contingency was in effect. If an FR schedule was in effect, high constant rates would have been produced despite cost, unless the cost was equal to or greater than the reinforcement, whereupon responding would have ceased (Weiner, 1964). Rates of responding under FI 10-sec cost were such that the cost of responding was less than the reinforcement.

The FR 40 history subjects were therefore acting appropriately under FI 10-sec cost in terms of their history but not in terms of the reality of current contingencies. Given that they were under FR rather than FI control, increasing cost punishment would not have been a successful treatment because it would have produced response cessation rather than low-rate FI 10-sec cost responding. What these high-rate FI 10-sec cost responders needed was not more punishment, but a new behavioral repertoire (i.e., DRL responding) in order to produce low-rate FI 10-sec cost responding.

As you can see from Figure 5, whereas high-rate responding persisted under FI 10-sec cost, low-rate responding was produced

under DRL 10-sec cost. As mentioned previously, under FI 10-sec cost, these FR 40 history subjects could maintain high-rate responding and still obtain a net gain of reinforcement. A net gain was possible because they were emitting less than 100 responses between reinforcements. Reinforcement was 100 points while cost was only one point per response. Under DRL 10-sec cost, however, high-rate responding following FR 40 produced reinforcement loss rather than net gains of reinforcement because the DRL reinforcements were contingent upon low-rate responding. As a result, high-rate responding changed to low-rate responding under DRL 10-sec cost.

After acquiring a history of DRL 10-sec cost responding, low-rate responding was produced under FI 10-sec cost. This was true even after reconditioning under FR 40. It may be said, therefore, that high-rate FI cost responding can be treated successfully by making all net gains of reinforcement contingent upon its cessation, thereby enabling the acquisition of a DRL repertoire. Exposure to the original condition responsible for the high-rate FI cost responding will not produce relapse when individuals are armed with this repertoire.

## FINAL COMMENTS

The data presented in this paper have shown that individuals may differ in their operant behavior under a schedule of conditioned reinforcement (e.g., FI 10-sec) and that such inter-subject differences may result from their reinforcement histories. In addition, it was shown that history-related differences in response rates and patterns may persist despite extended exposure to new contingencies and despite the fact that such persistence is maladaptive, i.e., produces avoidable punishment or net loss of reinforcement.

To the extent that point reinforcers and drug reinforcers have similar properties, these findings have significant implications for analyses of drug effects with humans. Different, persistent, and sometimes maladaptive drug-seeking behaviors by two or more individuals, though the current environmental conditions appear identical, may be related to distinctively different reinforcement histories.

Support for the notion that drugs may have different effects as a function of different reinforcement histories has been obtained from laboratory research with animals. Barrett (1977) found that the effects of d-amphetamine on punished and unpunished responding differed, depending on whether the animals had a prior history of Sidman avoidance. Animals with avoidance histories showed rate increases with d-amphetamine, while animals without the avoidance histories showed rate decrements during punishment. Urbain, Poling, Millam, and Thompson (1978) replicated some of the human data presented in this paper with rats. Further, they investigated the effects of d-amphetamine upon terminal FI lever-pressing. Rats with a history of DRL showed dose-dependent rate increases when administered d-amphetamine, whereas rats

having FR reinforcement histories exhibited rate decreases following d-amphetamine administration. Such sensitivity to reinforcement history-drug manipulations suggests that analyses of reinforcement history factors in drug-maintained performances may be fruitful.

In the present study, cost punishment was shown to be effective in reducing point-maintained FI responding for subjects with certain reinforcement histories. The use of punishment procedures to regulate drug-maintained responding has not been explored extensively, but our data suggest that under certain conditions, punishment may be effective in this regard. Research with animals using ethanol and cocaine as reinforcers and with human alcoholics using ethanol as the reinforcer has demonstrated that drug-related performances can be controlled by a variety of punishment procedures. Well-established principles and effects of punishment, generally similar to those reported for cost punishment in this paper, were obtained in these studies (Griffiths, Bigelow, and Henningfield, in press).

I have presented a set of laboratory methods for systematic evaluation of history effects with human subjects and have tried to demonstrate that histories can be manipulated to provide a wide variety of rates and patterns of responding with a high degree of reliability. Such experimental control might be important for the behavior pharmacologist in attempts to pinpoint the behavioral mechanisms of drug effects.

I have also attempted to show that histories can be manipulated to enable the experimental production of persistent human behavior which is costly to the individual. In this respect, this work could provide models of addictive behavior. It could be carried out in conjunction with other types of experimental analyses in which addicted humans are brought into the laboratory and studied when access to their addictive substance is controlled.

Finally, my data suggest that histories can be introduced in the laboratory and studied in terms of their effects upon maladaptive human operant behavior, either in terms of precluding its occurrence or of modifying it after it has occurred. This suggests the possibility that the operant laboratory may be able to provide interesting analogs to the prevention and treatment of undesirable drug-related operant behaviors.

Assuming that the findings I have presented pertain to drug reinforcement as well as point reinforcement, a number of tentative hypotheses may be offered:

First, it may be suggested that drug effects with humans depend upon reinforcement schedule histories as they interact with current contingencies of reinforcement;

Second, histories may make two or more individuals behave differently in relation to drugs even when current contingencies of reinforcement are the same for each individual;

Third, consistent drug effects may be produced by controlling the reinforcement schedule histories of individuals;

Fourth, histories may induce the persistence of undesirable human behavior which is unaffected by conditions of drug reinforcement;

Fifth, this persistence may be prevented and/or modified (treated) without relapse by arranging reinforcement schedule histories which enable an individual to acquire behavioral repertoires critically needed for change when drug reinforcers are introduced.

It seems clear that powerful laboratory procedures now exist to test these hypotheses. Hopefully, such testing will occur. There is a critical need for more research on the contribution of historical influences to drug effects in humans (Griffiths, Bigelow, and Henningfield, in press).

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# Stimulus Control and Drug Dependence

# Classically Conditioned Phenomena in Human Opiate Addiction

Charles P. O'Brien, M.D., Ph.D., Joseph W. Ternes, Ph.D., John Grabowski, Ph.D., and Ronald Ehrman

## INTRODUCTION

Classical and operant conditioning factors are both potentially significant in the maintenance of opiate use. Analysis from the perspective of the operant conditioning paradigm emphasizes the importance of discriminative stimulus control and the efficacy of opiates as reinforcers (e.g., Griffiths, Bigelow, and Henningfield 1980). In the context of the classical conditioning paradigm, emphasis is placed on environmental correlates of drug effects and withdrawal symptoms as elicitors of overt behavioral and physiological responses. Concurrently it must be recognized that a model based on integration of both paradigms probably reflects most accurately the reality of human opiate dependence (Grabowski and O'Brien 1981).

In the context of either the operant or classical conditioning paradigms, seemingly contradictory and diverse effects of stimuli and events may be identified. However, careful analysis leads to the conclusion that systematic results prevail and that findings parallel those involving other behaviors and reinforcers. As has been discussed in a recent review (Grabowski and O'Brien 1981), the primary problems appear to arise in delineating the phase of opiate action (e.g., onset, termination, withdrawal) with which stimulus events are associated. A secondary problem arises in differentiating patterns of use and determining presence or absence of dependence and the withdrawal syndrome. That is, certain behavioral features, development of conditioned correlates, and hence the nature of explanatory concepts are related to certain aspects of drug effects or sequelae.

Two major categories of events are associated with chronic administration of opiates. One is drug onset, with its diverse physiological effects. The second is characterized by the myriad physiological and behavioral responses in the physically dependent organism following termination of a regimen of opiate administration.

The first major category was the object of early investigations of conditioning phenomena in relation to drug effects. These involved the classical conditioning paradigm and focused on conditioned

responses correlated with the drug effects. A neutral stimulus was presented in temporal contiguity with an injection of morphine. After repeated pairings the formerly neutral stimulus became clearly established as a conditioned stimulus (CS) as indicated by physiological or behavioral changes elicited when it was presented without the morphine injection. This response or group of responses, termed the conditioned response (CR), typically reflected, but was not necessarily identical to, the unconditioned effects of morphine. The seminal work of Pavlov entailed analysis of this aspect of conditioning in relation to drug effects. Much of the operant self-administration research likewise involves examination of aspects of conditioning in relation to drug onset effects.

The second major category of experiments entails analysis of two aspects of phenomena generally associated with physical dependence. One class of experiments involves analysis of conditioned stimuli established in relation to the opiate withdrawal syndrome which reliably emerges at some point following administration of the last opiate dose in the physically dependent subject. In these experiments the environmental stimulus previously paired with either antagonist- or metabolism-induced withdrawal symptoms elicits similar symptoms. That is, the conditioned response resembles the unconditioned responses of the abstinence syndrome. In a second class of experiments for which the observed response is similar to withdrawal syndrome, the phenomenon under study is "conditioned tolerance." The experimental design is similar to that in which conditioned drug effects are examined. The resultant CR, however, is abstinence-like and is termed a "counteradaptive" (Wikler 1973) or "conditioned tolerance" response (Siegel 1975). Although this second class of withdrawal phenomena remains controversial, it continues to be of considerable scientific interest (e.g., Eikelboom and Stewart 1979, Sherman 1979). While these phenomena have been demonstrated in the laboratory to be robust, the extent to which they obtain in the natural environment of opiate-using patients is unclear; further, the extent to which they may contribute to persistence of opiate use is yet to be objectively determined.

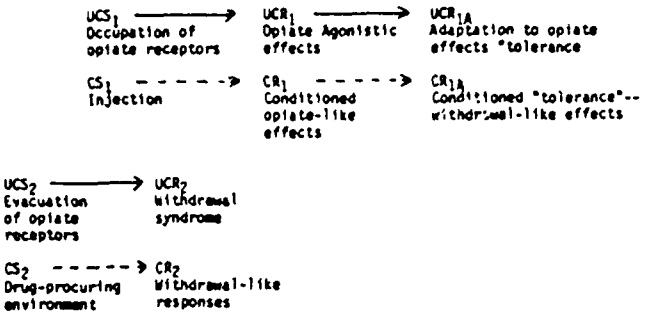
A series of investigations directed at the analysis of conditioned responses in opiate-dependent or postdependent human sujects has been implemented at our University of Pennsylvania/Veterans Administration Medical Center laboratory. Analysis has involved responses which have been established either naturally or experimentally. That is, in some cases the circumstances for development of classically conditioned responses have been established in the laboratory, and exposure to these situations has elicited appropriate responses. In other cases the investigations have involved analysis of the behaviors established in the subjects' natural environment which are elicited through various experimental manipulations and evaluated in the laboratory setting. Evidence has emerged for both conditioned drug effects and conditioned withdrawal effects. The focus of the current discussion will be elicitation of withdrawal-like responses and description of the circumstances under which these responses evolve.

## OPIATE-LIKE CONDITIONED RESPONSES

There have been several clinical reports of what may be identified as "conditioned drug responses" associated with the behavior of self-injection (Blachly 1971, Levine 1974, O'Brien 1975). This so-called "needle-freak" phenomenon, which also represents a clear "placebo response," is characterized by pleasurable subjective effects during and following self-administration of saline or other pharmacologically inert solutions. Presumably conditioned physiological changes also occur, and the analysis of these responses is of considerable interest since it clearly indicates the potential importance of drug-use-correlated behaviors serving as conditioned reinforcers. Although this phenomenon has not been studied systematically, it has been observed that some subjects exhibited morphine-like subjective and physiological effects when saline was self-injected (O'Brien 1975, O'Brien et al. 1980). Typically, these opiate-like effects follow self-injection rather than occurring during the preinjection period. Meyer and Mirin (1979) have also reported opiate-like postinjection autonomic changes in 11 of 22 patients who self-injected heroin while opiate agonist effects were blocked by naltrexone. As shown in figure 1, the injection ritual ($CS_1$) may act as a complex conditioned stimulus which, after repeated pairing with opiate agonistic effects ($UCS_1$), attains the ability to evoke weak agonistic effects ($CR_1$).

FIGURE 1

Dependent Subject




The foregoing reports and observations parallel studies with animals in which environmental stimuli previously associated with drug effects can serve as conditioned reinforcers or classically conditioned elicitors of behavior. Thus, for example, Woods and

Schuster (1967) noted that a stimulus previously associated with drug self-administration in monkeys can, for a period of time, maintain responding for saline infusions. Similarly, but in the context of the classical conditioning paradigm, Lal and coworkers (1976) reported that a stimulus previously paired with drug effects can attenuate a component of the opiate withdrawal syndrome. Therefore, it is clear that mechanisms associated with either operant or classical conditioning may directly or indirectly contribute to persistence in responses associated with drug-correlated stimuli. In turn, it can be argued that conditioned drug effects may contribute to the general pattern of persistence observed in human drug-seeking behavior.

## OPIATE WITHDRAWAL-LIKE CONDITIONED RESPONSES

Since one phase of opiate action (i.e., onset) can serve as the basis for a conditioned response and can generate behaviors associated with opiate self-administration, conditioned responses may also be expected to emerge in relation to the other major physiological/behavioral event associated with opiate use--that is, the withdrawal syndrome. Wikler's early observations led to the proposal that conditioned responses might serve to generate drug-seeking behavior. Thus, for example, conditioned withdrawal has been presumed to underlie case reports involving drug-free postdependent patients who exhibit physical and subjective evidence of opiate withdrawal when they return to the environment in which drugs were used (Wikler 1965, O'Brien 1975). In the laboratory the conditioned withdrawal phenomenon has been established in patient volunteers maintained on a methadone regimen by pairing naloxone-precipitated withdrawal (unconditioned response, UCR) with a novel stimulus (CS). The resultant CR resembles the UCR (opiate withdrawal) (O'Brien et al. 1975, 1977). Similar physiologic, behavioral, and subjective responses have been observed when methadone-maintained patients were exposed to videotaped sequences of themselves using drugs in the laboratory (O'Brien et al. 1975) and when stimuli such as drug-related videotapes, slides, or objects were shown to drug-free or methadone-maintained patients (Ternes et al. 1980). Sideroff and Jarvik (1980) also reported that both physiologic and subjective withdrawal effects occur in patients undergoing detoxification after viewing a videotape of drug use by other individuals.

Analysis of the above-described phenomena is of course difficult and complex, and unresolved questions exist despite numerous and repeated observations of dependent and postdependent patients in the laboratory setting. For example, it appears that typically when patient subjects perform the preinjection rituals, i.e., "cook up" (drug preparation) and "tie off" (tourniquet application), their physiologic, subjective, and behavioral responses resemble opiate withdrawal (O'Brien et al. 1980). Only rarely have drug-like responses been observed. Several factors may contribute to the observed preponderance of "withdrawal-like" responses. First, it should be noted that the physiological concomitants of opiate withdrawal are similar to those of nonspecific autonomic arousal

reactions evidenced when individuals with no drug use history view drug-related stimuli, including videotapes of individuals injecting drugs.

Second, it is at times difficult to identify separately the physiological correlates of drug-like and withdrawal-like phenomena since some of the physiological responses (but presumably not mechanisms) are similar. One direct effect of opiates is nausea; indeed, this is sometimes used as an indicant of "street drug" quality and is termed a "good sick" by opiate users (Stolerman and Kumar 1972). Yet, nausea is also one of the clearly observable responses during opiate withdrawal. This is just one example of possible problems in analysis. It should be noted that the physiological response changes correlated with stimulus presentations for patients tend to be more durable and robust than in drug-naive subjects.

A third consideration is the possibility that responses elicited by preinjection stimuli differ from those immediately post injection. That is, withdrawal-like responses may precede injection, while conditioned drug-like responses may follow placebo self-administration. This issue too requires further analysis, and the data of Eikelboom and Stewart (1979) suggest that more refined analyses may permit differentiation of these phenomena.

It was noted that withdrawal-like responses may emerge via a second mechanism reflected by "conditioned tolerance" (Siegel 1976, 1978), although this explanation is at present tenuous. Figure 1 shows conditioning paradigms which could be expected to produce withdrawal-like CR's in dependent subjects. One procedure involves opiate withdrawal occurring as the opiate is metabolized and opiate receptors are evacuated ($UCS_2$). Since $UCS_2$ is directly paired with drug procurement or preinjection stimuli ($CS_2$), the preinjection stimuli acquire the ability to evoke conditioned withdrawal ($CR_2$).

The other procedure leading to withdrawal-like responses involves an adaptive or homeostatic response ($UCR_{1A}$) to the occupation of the opiate receptors. This adaptive response may be partially responsible for tolerance phenomena because it tends to oppose or diminish the agonistic action of the opiate. The tolerance response $UCR_{1A}$, reliably follows $UCS_1$ (receptor occupation), so that an adaptive conditioned response ($CR_{1A}$) may also be conditioned to preinjection stimuli ($CS_1$).

Since the drug procurement ($CS_2$) and preinjection rituals ($CS_1$) are usually paired with both receptor evacuation (the UCS for the withdrawal UCR) and subsequently with receptor occupation (the UCS for the compensatory UCR), these stimuli may elicit either adaptive reactions or the withdrawal reactions as conditioned responses. However, in terms of physiological variables, both types of conditioned response resemble opiate withdrawal ($UCR_2$). Thus, what appear as withdrawal responses in a drug procurement area actually may be the result of two different conditioning processes, conditioned tolerance and conditioned withdrawal. Because both may be

operative, a redundancy occurs which may increase the apparent strength of the conditioned response observed.

## EXTINCTION OF CONDITIONED OPIATE EFFECTS IN HUMANS

If, as has been suggested, drug-like and drug withdrawal-like effects can be established via operant and classical conditioning, it should be expected that they can similarly be extinguished. That is, if the unconditioned stimulus eliciting classically conditioned responses is no longer paired with the conditioned stimulus or if the operant behavior is no longer reinforced, a decrease in response strength should be expected. Goldberg and Schuster (1970) reported that conditioned withdrawal in morphine-dependent monkeys was quite resistant to extinction. With humans, the laboratory investigations have produced variable results in resistance to extinction. Thus, for example, in the analysis of experimentally conditioned withdrawal in humans using a novel conditioned stimulus and a small number of training trials, O'Brien and coworkers (1975, 1977) reported that conditioned withdrawal symptoms diminished rapidly during repeated unreinforced (test) trials. In contrast to these studies of laboratory conditioned withdrawal responses, studies of withdrawal CR's in response to naturalistic conditioned stimuli ("cook-up" and "shoot-up" rituals) indicate great resistance to extinction. Presumably, these naturally conditioned CR's are established during an extensive history of opiate use involving a large number of "training" trials in the user's natural environment. In addition, a schedule of intermittent reinforcement in the natural environment may evolve with respect to some features of operant behaviors, thereby adding to the complexity of factors contributing to behavioral persistence. These differences between the laboratory and natural environment may contribute to the apparent disparity of resistance to extinction (Grabowski and O'Brien 1981).

In a double-blind experimental design, the effects of systematic repetition of drug-associated rituals under circumstances in which opiate reinforcement was either absent or blocked by an antagonist have been further examined. Opiate-free postdependent subjects were permitted, in the laboratory setting, to engage in the preinjection and self-injection rituals (using opiate or saline) while being maintained on the opiate antagonist naltrexone (O'Brien et al. 1980). Typically, withdrawal-like autonomic responses were observed during the preinjection ritual. Initially opiate-like subjective and physiological effects occurred after injection regardless of the contents of the syringe. Subsequently, the opiate-like subjective effects disappeared (extinguished) after a few unreinforced trials. Interestingly, on later trials, when opiate-like effects no longer occurred, the injection ritual was followed by an increase in the autonomic withdrawal-like responses (O'Brien et al. 1980).

In another study (Ternes et al., in preparation) it was found that detoxified patients who were allowed to self-inject either opiate or saline showed compensatory (i.e., withdrawal-like) autonomic changes prior to self-injection and opiate-like autonomic changes after the injection. In contrast, the same subjects given an unsignalled

infusion of an opiate showed only the opiate-like changes and these effects only occurred after the infusion. These findings are strikingly similar to those of Eikelboom and Stewart (1979), who reported differing response patterns to the two stimulus conditions previously paired with preinjection withdrawal responses and postinjection drug effects. Thus in both human subjects (postdependent patients) and a nonhuman species, the preinjection stimuli elicited withdrawal-like responses and the postinjection stimuli elicited opiate-like changes. Whether or not these differential responses reflect conditioned tolerance or conditioned compensatory responses prior to injection is, of course, unclear. Both patterns of responses can be observed in experimental paradigms designed to reflect a sequence of events which prevails in the natural environment for some opiate users. Efforts to eliminate both patterns of responding using extinction procedures in the laboratory thus far suggest that the conditioned positive reinforcing effects diminish more rapidly than the conditioned withdrawal responses. In addition it appears that elements of both response patterns may persist in some human subjects (Grabowski et al. 1980). The difficulties in experimental analysis of these phenomena are considerable, and it is clear that further research is required.

## CONCLUSIONS

Laboratory investigations with postdependent and dependent human subjects, as well as studies with rodents and primates, have demonstrated that behavioral and physiological correlates of drug and withdrawal responses can be conditioned using operant and/or classical procedures. In addition it appears that the behaviors and physiological responses of the several phenomena may coexist and be evident concurrently or sequentially in the same subject. Presumably when the more complex patterns emerge, as is typical with human subjects who are former opiate users, the results reflect the complexities of an extensive and variable past history. Many factors potentially may influence the relative strengths of both operant and respondent behaviors. For example, opiate users who are not physically dependent because they use insufficiently high daily drug doses may experience unconditioned withdrawal rarely or not at all. These subjects could be expected to show mainly opiate-like CR's; theoretically, however, some compensatory CR's should also occur, albeit less intensely. On the other hand, for subjects who are physically dependent, two mechanisms for withdrawal-like conditioned responses (figure 1) exist: compensatory CR's and withdrawal CR's. This redundancy may explain why, in investigations with some human opiate users, withdrawal-like CR's dominate and are difficult to extinguish.

While it is apparent that conditioning in opiate users is complex and incompletely understood, the effects appear strong enough to have clinical implications. Studies involving opiate-using patients or postdependent individuals present special problems because of their variable "training" histories. Perhaps further research with both humans and animals will elucidate the conditions under which the different types of conditioned responses are most likely to develop.

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# Internal Stimulus Control and Subjective Effects of Drugs

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For many years psychotropic drugs have been characterized and classified using methods designed to measure their subjective effects in humans (Beecher 1959). This research approach has two principal purposes: 1) to investigate the efficacy of a drug in attenuating unwanted subjective states in patients (e.g., pain, anxiety, depression), 2) to investigate the abuse potential of new drugs by comparing their subjective effects in experienced drug abusers to those produced by known drugs of abuse. In regard to the latter, such methods have been used to determine whether there are any common subjective states produced by all drugs of abuse (e.g., euphoria).

Systematic studies of subjective methods for drug classification have been conducted at the Addiction Research Center (ARC) in Lexington, Kentucky, now part of the National Institute on Drug Abuse. A major mission of the ARC has been to evaluate new analgesic compounds to determine whether they produced morphine-like effects. The subjective effects of morphine and related compounds were an important aspect of this evaluation. The research demonstrated that morphine and related narcotic analgesics produced a unique spectrum of subjective effects that can be reliably discriminated from subjective effects produced by other psychotropic drugs in experienced narcotic addicts (Hill et al. 1963). Even within the analgesic class, mixed agonist-antagonists (e.g., cyclazocine) can be readily discriminated from morphine in terms of their subjective effects (Haertzen 1974). Other studies have also shown that the methods for measuring the subjective effects of drugs are useful for characterizing and differentiating other classes of abused drugs (e.g., psychomotor stimulants: Martin et al. 1971; sedative-hypnotics: Martin et al. 1974, Jasinski, 1977; hallucinogens: Martin 1973). Thus, it is possible to determine whether an unknown drug belongs to the opiate, psychomotor stimulant, sedative-hypnotic, or hallucinogenic drug class on the basis of its subjective effects.

Until recently, measurement of drug-induced changes in subjective effects was possible only with humans, since only this species has the necessary verbal skills to describe how a drug makes them feel. However, behavioral methods have been developed over the past decade which

allow animals to report on discriminations between psychotropic drugs (Schuster and Balster 1977). There is a striking concordance between drug classes based on similarities in the subjective effects produced in humans and on similarities as discriminative stimuli in animals (Schaefer and Holtzman 1977, Shannon and Holtzman 1976,1977). This has led many researchers in behavioral pharmacology to make the working assumption that the components of drug action responsible for the discrimination among various classes of psychotropic drugs by animals are the same as those responsible for the differences in the subjective effects of these drugs in humans. In part, the purpose of the present paper is to show that this concordance across species is not surprising, since the same learning processes are involved in both species. The fact that humans learn to apply a topographically unique response (verbal) to drug-induced discriminative stimuli should not mask the fact that the same fundamental processes are involved. A second major purpose of this paper is to examine the hypothesis that although each class produces certain distinctive subjective effects, all drugs of abuse produce certain common subjective effects (e.g., euphoria) and it is these effects which are responsible for their abuse.

## BEHAVIOR ANALYSIS OF DRUG-INDUCED CHANGES IN SELF-REPORTS

An analysis of the processes involved in measuring drug-induced changes in subjective states requires a review of precisely what subjects are asked to do in these experiments. The most common instruments used to measure subjective states are paper and pencil inventories. Some of these instruments are composed of a list of adjectives commonly used to describe mood (e.g., happy, angry) and the subject is asked to rate how he/she feels in relation to that mood (e.g., the Profile of Mood States: POMS). Other instruments consist of statements related to sensations and perceptions about which subjects are asked to indicate their agreement or disagreement (e.g., the Addiction Research Center Inventory developed at the ARC). In some procedures, greater quantification is obtained by having subjects indicate the strength of their mood or agreement with each adjective or statement on an ordinal scale. Instructions to the subjects indicate that they should respond in a manner which best reflects how they feel at that moment. The responses before and after drug or under drug and placebo conditions are compared to determine whether the drug has produced a significant change. It is usually assumed that the verbal behavior accurately represents a matching between the subject's feelings and the statements or adjectives checked. Since the individual's feelings are a private event, there is no way for the investigator to determine the degree of accuracy of the subject's verbal report, i.e., how precisely it reflects a feeling state. For most purposes, such as drug classification, this problem can be ignored as long as the data produced are lawful (i.e., show comparable dose-related changes across individuals).

The self-reporting response is operant behavior controlled by its consequences and thus susceptible to change by a variety of influences

besides the drug administered. It is well established for example, that verbal behavior can be markedly altered by social contingencies. The Greenspoon phenomenon (1955) has amply demonstrated that powerful control can be exerted over the verbal behavior of subjects who were unaware that their behavior was being manipulated by subtle responses of the experimenter. In the Greenspoon study, human subjects were instructed to "say words" during a 50-minute experimental session. When the experimenter made a specific verbal response ("mmm-hmm") following every plural noun uttered by the subject, there was a significant increase in that class of verbal responses (plural nouns). The existence of such influences make one less comfortable in assuming the accuracy of the reporting of private events.

Therefore, one approach in dealing with self-report data is to treat the verbal response as devoid of a referent. Thus, if after being given a sedative drug, subjects say "I feel sleepy," one can record this as a change in verbal behavior induced by the drug, without any inference about changes in subjective state. Thus, a positive answer to that statement conceived of in this way would have no value in predicting other behavior of the individual, such as the likelihood of reclining on a bed, or of exhibiting a sleep-appropriate EEG. However, this "black box" approach is inadequate to account for the subjective drug effects data. If drug-induced changes in verbal responses are treated as devoid of a referent the meaning of the verbal response should be irrelevant. Subjects could be asked to check off boxes labeled with color names or numbers rather than mood descriptors. Since we usually have no discriminative training for applying such color names or numbers to internal states, we would probably get little consistency in drug effects. On the other hand, as we will illustrate, when we allow subjects to respond using common adjective or simple descriptive statements of mood words, we see a fair degree of agreement in responses across individuals who are given certain psychotropic drugs. This agreement is based on a common conditioning history in which certain adjectives or mood descriptions have been associated with certain internal states. Whether or not one chooses to ignore the internal cues, we are taking advantage of a conditioning history based on these internal cues when self-report methods are used for investigating drug effects.

How do humans learn to apply verbal labels to private events? It is clear how children can be differentially reinforced for correctly labeling colors, sounds, and other publicly observable stimulus events. Internal stimuli represent a special problem for such differential conditioning since the mediator of reinforcement cannot observe the private event to determine the accuracy of the labeling. Under these conditions, the trainer uses a combination of observing the external environment for significant cues and collateral responses as an indication of the veracity of the verbal label. For example, we would agree with (i.e., reinforce) a child who says she is sad when found sitting hunch-shouldered in her bedroom with tears streaming down her face if we also saw that her favorite toy had been ruined by the family dog. Conversely, if she comes bounding in the door, whistling and swinging her lunch pail with a smile on her face to show us her good report card, we would reinforce

her for saying she is happy. As a child matures, some of the more observable parts of these behavior patterns (e.g., crying, whistling) may diminish, but the label is still accurately associated with the internal stimulus events. It is this type of conditioning history which we utilize when subjects are asked to match their internal state with a list of adjectives or statements. It is most remarkable that such conditioning histories are consistent enough across individuals so that drugs induce a fairly close agreement in self-reports of internal states. Although some radical behaviorists may still choose to deal with such self-reports as simply verbal behavior and ignore the internal cues setting the occasion for the responses, it is obvious that the subjects do not ignore them.

## DRUG DISCRIMINATION STUDIES IN ANIMALS

It is well established that animals can be trained to discriminate between the internal cues associated with food and water deprivation (Hull 1933, Leeper 1935). For example, we could arrange conditions so that following 24 hrs of food deprivation an animal would be reinforced with the termination of electric shock for turning right in a T-maze. Turning left would not be reinforced under these stimulus conditions but would be reinforced when the animal was not food deprived. After several trials, the animal's behavior would become appropriate to the deprivation conditions. The animal is correctly identifying an internal state in the same way that a human subject might check the adjective "hungry" under similar food deprivation conditions. In the case of the animal, we have controlled the conditioning history, whereas in the human we usually assume that such discriminative training has already occurred.

In the same manner, animals can be taught to discriminate between various drugs (Schuster and Balster 1977). Holtzman and his colleagues have developed a method using a discrete-trial avoidance-escape paradigm in which animals (rats and monkeys) can prevent the onset of or terminate an electric shock by pressing one of two choice levers (Schaefer and Holtzman 1977, Shannon and Holtzman 1976, 1977). The animals were trained to press one lever after drug injection (morphine or cyclazocine) and the other lever after placebo administration. Specifically, rats were injected 30 minutes prior to each daily 20-trial session. During the session, a light was illuminated for 5 seconds prior to the onset of electric shock. Depression of the correct choice lever terminated the light (an avoidance response) or both the light and shock (escape response). On days when a rat had received morphine, one of the choice levers was correct; on days when saline was administered, the other choice lever was correct. Rats were trained until they completed at least 18 trials on the appropriate choice lever (90% correct). After this criterion for discrimination between drug and placebo was reached, drug test sessions were periodically conducted with a new drug or new dose. During training trials only one of the two choice levers was operable and could terminate a trial. Thus, after the first trial was completed, the reinforcement, i.e., the shock and/or warning stimulus termination, might then serve as the cue to the correct choice lever for the remainder of the session. To deal with this problem, on test

days depression of either lever satisfied the avoidance-escape contingency. Thus, the effectiveness of the response could not function as a cue to signal the animal which choice lever was correct. Amazingly, when drug pretreatment times were arranged so that the onset of drug effect occurred half way through the session, animals switched from responding on the saline-appropriate lever to the drug-appropriate lever. Clearly, the drug cues are a more effective discriminative stimulus than even the reinforcer (i.e., light and/or shock terminations).

Following establishment of such stimulus control, it is of interest to determine to what degree such control will generalize to other drug stimuli. There are two ways in which discriminative stimuli may be varied for generalization testing--quantitatively and qualitatively. When a drug is used as the discriminative stimulus, quantitative generalization tests are accomplished by varying the dose. When this is done in animals trained to discriminate 3.0 mg/kg of morphine from saline, lowering the morphine dose results in dose-related decrements in responding on the morphine-appropriate choice lever with a concomitant increase in responding on the saline-appropriate choice lever. Doses higher than that used in training produce similar or even greater discriminative stimulus control (i.e., responding on the morphine-appropriate lever) until behaviorally toxic doses are reached. This relation between morphine dose and response choice is similar to that observed when exteroceptive discriminative stimuli (e.g., light) are varied along a quantitative dimension (e.g., intensity). It is also the same relationship as that shown between dose and the intensity of the subjective effects produced by a drug in humans (Fischman et al. 1976).

When conducting generalization studies in which the discriminative stimulus is varied qualitatively, the situation is more complex. With an auditory discriminative stimulus, the unidimensional continuum of frequency can be manipulated. For a visual stimulus the continuum is wavelength. When using drug states as discriminative stimuli, however, we do not know the relevant continua along which changes might show a lawful relationship to behavior. This deficit is not unique to drugs, however, as the same problem exists with olfactory stimuli. Nevertheless, it is possible to do generalization tests from training drugs to other drugs with different structures and pharmacologic properties. For example, after approximately 8 to 10 weeks of training in the Holtzman experiments, most animals responded almost exclusively on the appropriate lever when given either morphine or saline. Subsequently, a variety of psychotropic drugs were investigated to determine which produced "morphine-like" discriminative effects (i.e., animals responding on the morphine-appropriate choice lever 18 out of 20 trials). For the following reasons, the results of these generalization tests indicate that the discriminative control exerted by morphine is a specific narcotic effect:

(1) all narcotic drugs tested showed morphine-like discriminative control in a dose-related manner;

(2) these narcotics showed a ranking in potencies highly correlated with their potencies in producing morphine-like subjective effects in humans;

(3) the stimulus control exerted was stereospecific with only analgesically active isomers exerting morphine-like effects;
(4) naloxone administration produced a pronounced shift in the dose response curve relating dose of morphine to its discriminative control;
(5) tolerance to the discriminative effects of morphine developed after repeated administration and there was cross tolerance to methadone; and finally
(6) d-amphetamine, chlorpromazine, ketamine, mescaline, pentobarbital, physostigmine, and scopolamine failed to exert morphine-like discriminative stimulus control.

The results of studies in which monkeys were trained to discriminate between cyclazocine and saline were comparable to those described for the rat with morphine. Naloxone diminished the stimulus control exerted by cyclazocine, i.e., on days when the animals were given both drugs, most of their responses were made on the choice lever associated with saline administration. Studies in humans have shown that cyclazocine produces subjective effects distinctly different from morphine. Accordingly, in the monkey experiments, morphine did not substitute for cyclazocine as a discriminative stimulus. These results indicate that cyclazocine and morphine produce distinctive stimulus effects in animals and humans. In contrast, in monkeys trained to discriminate cyclazocine, there was generalization to drugs such as nalorphine, levallorphan, and ketocyclazocine, all of which produce a common set of dysphoric subjective reactions in humans (Haertzen 1974).

This series of experiments conducted by Holtzman and his colleagues has convincingly demonstrated that generalization tests in animals can be used to classify drugs in the opiate class as well as those with mixed opiate agonist-antagonist properties. Further, the classification derived from animal experiments is in concordance with that based upon the subjective effects of these drugs in humans (Jasinski 1972, Haertzen 1974). Similarly, animals can be trained to discriminate prototypic agents from other classes of abused drugs (e.g., cocaine as a prototypic stimulant) and then generalization tests can be conducted by testing other psychotropic drugs (e.g., amphetamines, barbiturates, etc.). Again the drug classes based upon discriminative effects in animals and upon subjective effects in humans are in striking concordance.

## THE RELATIONSHIP OF SUBJECTIVE AND REINFORCING EFFECTS OF PSYCHOTROPIC DRUGS

Although the classes of abused drugs can be differentiated on the basis of their spectrum of subjective effects, certain effects in common are produced by all such drugs. When hospitalized exaddicts are tested with the Addiction Research Center Inventory (ARCI), scores on the Morphine-Benzedrine Group Scale (MBG) show dose-related increases when subjects are administered narcotic analgesics (Jasinski 1973a,b, Jasinski et al. 1974; Martin et al. 1971) barbiturates (McClane and Martin 1976) or amphetamine-like drugs (Martin et al. 1971, Fischman et al. 1976).

William Martin, Director of the ARC for several years, believes that LSD-like hallucinogens, alcohol, and marijuana would also produce similar results on the MBG Scale if tested in an appropriate subject population (Martin et al. 1978). The items in the MBG Scale are related to feelings of popularity, efficiency, social effectiveness, pleasant feelings, absence of worry, good self-image, and feelings of insight and satisfaction. This scale is designed to measure a drug's ability to produce a subjective state of "euphoria" (Martin et al. 1978). It is the opinion of many researchers that drugs are abused by humans because they produce this state of "euphoria" (Isbell 1958, Martin et al. 1978, Jasinski 1977).

Another approach used to study factors contributing to drug abuse in humans has been to develop an animal drug self-administration model (see Griffiths et al., this volume). In these studies animals are given an opportunity to emit a response which is followed by the drug delivery. If responding is maintained by a drug it is said to possess positive reinforcing properties, i.e., the drug is a positive reinforcer.

Previously we discussed the similarity in drug classifications formed on the basis of subjective effects in humans and discriminative stimulus effects in animals. If animals and humans have similar "subjective" responses to drugs one might predict that drugs which serve as reinforcing stimuli in animals should produce "euphoria" in humans. If we operationally define "euphoria" as the state measured by the MBG Scale of the ARCI, this relationship can easily be determined. Table 1 shows that there is a good correlation between these two procedures. Drugs in the opiate agonist, psychomotor stimulant, and barbiturate classes generally serve as reinforcers in animal studies and, as well, produce dose-related increases in MBG Scale scores (i.e., "euphoria"). Further, both opiate agonist/antagonists, such as nalorphine and cyclazocine, and neuroleptics produce "dysphoria" and are generally not self-administered by animals. These results are also in accord with actual street abuse of these various drugs. That is, commonly abused drugs serve as reinforcers in animals and produce "euphoria," whereas drugs producing "dysphoria" are neither abused nor do they generally serve as reinforcers in animals. It remains to be determined whether this pattern generalizes to alcohol, marijuana, and LSD-like hallucinogens. The data available suggest that both drug self-administration experiments in animals and investigations of the subjective effects of drugs in humans can be used to predict whether a new drug has significant abuse potential. This has led, in our opinion, to the incorrect use of the term "reinforcing" as synonymous with "euphorigenic," and has produced both theoretical and practical problems.

Since it would be difficult to measure "euphoria" in animals, animal self-administration studies cannot shed light on whether the reinforcing effects of drugs are based upon their ability to produce "euphoria." In order to answer this question, human experimentation is required in which measures of both a drug's reinforcing properties and its subjective effects are obtained. Only if the concordance between the two measures is invariant can a causal hypothesis be tenable.

TABLE 1

Changes in "Euphoria" Rating on the ARCI (MBG Scale) Correlated with Animal Drug Self-Administration[1]

| Drug | Effect on MBG Score Increase (+) No increase (-) | Self-Administration Yes (+) No (-) |
|---|---|---|
| Morphine | + Jasinski, 1973b | + Thompson & Schuster, 1964 |
| | - (chronic) Haertzen & Hooks, 1969 | |
| Profadol | + Jasinski et al., 1971 | + Woods, 1977 |
| Propiram | + Jasinski et al., 1971 | + Hoffmeister & Schlichting, 1972 |
| Methadone | + Martin et al., 1971 | + Woods, 1977 |
| Pentazocine | + (weak) Jasinski et al., 1970 | + Hoffmeister & Schlichting, 1972 |
| Heroin | + Jasinski & Nutt, 1972 | + Hoffmeister & Wuttke, 1974 |
| Propoxyphene | + Jasinski et al., 1974 | + Hoffmeister & Schlichting, 1972 |
| Codeine | + Jasinski et al., 1974 | - Hoffmeister & Schlichting, 1972 |
| Etorphine | + Jasinski et al., 1974 | + Woods, 1977 |
| Cyclazocine | + Jasinski et al., 1968 (at some doses) | - Hoffmeister & Wuttke, 1974 |
| Butorphanol | + Jasinski et al., 1975 | + Woods, 1977 |
| Buprenorphine | + Jasinski et al., 1976 | + Woods, 1977 |
| Naloxone | - Jasinski, 1972 | - Balster et al., 1977 |
| Nalorphine | - Jasinski, 1973a | - Hoffmeister & Schlichting, 1972 |
| Pentobarbital | + McClane & Martin, 1976 | + Goldberg et al., 1971 |
| Cocaine | + Fischman et al., 1976 | + Wilson et al., 1971 |
| d-Amphetamine | + Fischman et al., 1976 | + Balster & Schuster, 1973 |
| Methamphetamine | + Martin et al., 1971 | + Balster & Schuster, 1973 |
| Ephedrine | + Martin et al, 1971 | + Woods (unpublished) |
| Phenmetrazine | + Martin et al., 1971 | + Wilson et al., 1971 |
| Methylphenidate | + Martin et al., 1971 | + Wilson et al., 1971 |
| Diethylpropion | + Jasinski et al., 1974 | + Johanson & Schuster, 1977 |
| Phentermine | + Jasinski et al., 1976 | + Griffiths et al., 1976 |
| Fenfluramine | - Griffith et al., 1975 | - Woods & Tessel, 1974 |

[1]The self-administration studies were arbitrarily restricted to those using monkeys.

The administration of single (or a limited number of) doses of drugs in the opiate, psychomotor stimulant, and sedative-hypnotic class produces "euphoria" in "appropriate" subjects. To demonstrate that a drug serves as a reinforcer, however, it is necessary to show that the drug increases the response rate on which its administration is contingent. When this is done, a dissociation between the reinforcing effects and mood effects appears. Clinical data indicate that the continued use of alcohol and opiates is associated with progressive dysphoria, anxiety, irritability, and aggressiveness (see review by Mello 1977). Unfortunately, most studies have not used the MBC Scale from the ARCI as their measure of euphoria. Nonetheless the measures of "euphoria" show a progressive decline although the drug continues to maintain self-administration and is by definition a reinforcer. Furthermore, Johanson and Uhlenhuth (1980, 1981) have shown that when normal human subjects are allowed to choose between self-administering d-amphetamine (5 mg orally) or a placebo they initially prefer the drug. This preference is associated with a spectrum of subjective changes on the Profile of Mood States (McNair et al. 1971) indicative of "euphoria." With repeated opportunities to choose, however, the number of drug choices declines despite the fact that when the drug is taken (during forced "sampling" administrations), it still produces the same changes on the POMS. Thus, a drug can continue to serve as a reinforcer despite the development of progressive "dysphoria," and, moreover, a drug can continue to produce "euphoria" but not continue to serve as a reinforcer. Thus, mood changes do not necessarily covary with changes in the reinforcing efficacy of drugs. This weakens the hypothesis that drugs serve as reinforcers because of their ability to produce "euphoria."

Another line of evidence bearing on the issue of concordance between a drug's "euphorigenic" and reinforcing actions is based on individual differences in response to drugs. In the preceding section we have qualified the description of drug-induced mood changes by saying that these occurred in "appropriate" subjects. This implies that mood changes should differentiate those individuals for whom drugs serve as reinforcers and those for whom they do not. There is very little acceptable evidence on this point. Drug-induced mood changes often differ between humans who abuse drugs and those that do not. Beecher (1959) demonstrated that morphine generally produced "dysphoria" and aversion in normal subjects whereas it produced "euphoria" and a desire to repeat the drug experience in ex-heroin addicts. In contrast, amphetamines produced "euphoria" in normals but not in the ex-heroin addicts. Unfortunately, since the reinforcing actions of these drugs were not determined with the same subjects, we cannot state they would have covaried with the mood measures.

It is commonly assumed by many clinicians that patients who experience a "euphoric" response to medically prescribed drugs are at greater risk for iatrogenic addiction. In one recent study (Johanson and Uhlenhuth 1980), the mood changes induced by d-amphetamine or placebo were compared in normal human subjects. POMS scores revealed that d-amphetamine produced an increase in Arousal, Positive Mood, and Elation. After this experience subjects were given repeated opportunities to

choose between ingesting d-amphetamine or placebo. Though most preferred d-amphetamine, some did not self-administer it at every opportunity despite the fact that the drug produced comparable mood changes in all subjects. Thus one could not predict on the basis of similarities in drug-induced mood changes whether the drug would serve as a reinforcer. On the other hand, it was demonstrated that there was a subset of individuals who chose d-amphetamine on every opportunity and these individuals did not differ in their subjective response to the drug. They did, however, show significant differences in mood prior to ingestion of the drug. Subjects who showed this decided preference for d-amphetamine were more anxious and depressed as measured by the POMS (Uhlenhuth et al. 1981). It is important to stress that despite these differences in pre-drug mood, their subjective responses to drug were no different from those of the other subjects.

It is clear that we need a great deal more informaton on how individuals differ in their subjective responses to drugs and the importance of these differences as a determinant of whether the drug serves as a reinforcer. Ideally these studies should be done in drug-naive subjects, but there are limitations on the types of drugs, range of doses, and duration of exposure which must be imposed for ethical and practical reasons. With therapeutic drugs such studies are, however, of extreme importance in order to define populations which may be at greater risk for dependence when exposed to the drug during treatment.

The evidence reviewed suggests that drug-induced changes in the subjective state called "euphoria" are produced by many drugs which readily serve as reinforcers in both animals and humans. There are circumstances, however, in which these two measures of drug effect do not covary. Thus one effect cannot be caused by the other; rather both are produced by the interaction of the drug with the organism (with a unique genetic behavioral and pharmacologic history) under a particular set of environmental conditions. Both organismic and environmental variables may modify the reinforcing and subjective drug effects differentially. It would not be unexpected then, using appropriate subjects under appropriate environmental circumstances (e.g., exaddicts in a controlled hospital setting), that one could predict the reinforcing effects of all drugs from their subjective effects. Clearly, the ARC has isolated effective procedures for selecting subjects and an environmental situation for predicting a drug's reinforcing actions from measures of its subjective effects. This has had predictive utility for preventing the unwitting introduction of drugs with high reinforcing efficacy into medical practice. However, the close correlation between these two drug effects in these carefully selected subjects under highly controlled environmental conditions should not lead to the conclusion that the drug's "euphorigenic" actions produce its reinforcing actions. These two aspects of drug action dissociate under a wide variety of conditions. Such dissociation can only lead to the conclusion that subjective and reinforcing effects are correlated but that neither is causal of the other.

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# Social Stimulus Factors in Drug Effects in Human Subjects

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## INTRODUCTION

Effects of drugs on human behavior are frequently studied in the laboratory under conditions in which a single isolated subject is the focus of analysis. Much of human drug use, however, appears to occur in social rather than isolated contexts (e.g., Babor 1978). A complete understanding of drug effects in humans must ultimately take into account the effects of drugs on behavior in social contexts and the modulating influence that social stimuli may exert upon the expression of drug effects. The present paper is concerned with the interaction between drugs and social stimuli in humans. Three general categories of interaction will be discussed: First, modulation of human social behavior by drugs; second, modulation of the behavioral and subjective effects of drugs by social stimuli; third, modulation of drug self-administration by social stimuli. In this paper, existing data will be reviewed which support each of these categories of interaction between drugs and social stimuli, and the implications of these interactions for the understanding of the behavioral pharmacology of drugs of abuse will be discussed.

## DRUG EFFECTS ON HUMAN SOCIAL INTERACTION

It is widely believed that people behave differently within a social context when under the influence of drugs than when sober. Evidence is now available from behavioral pharmacology research which supports the observation that drugs from a variety of pharmacological classes can modulate human social behavior.

Studies of drug effects on human social behavior have differed markedly in their approach to the problem and in the specific experimental methods employed. However, two general classes of studies can be distinguished which differ primarily in the subject population studied and the methodologies employed. One type of study has its origins in drug abuse research. Subjects employed have histories of chronic use or abuse of the drug to be investigated, and experiments are generally conducted while subjects reside in an inpatient research unit. During

the study, subjects are typically allowed to self-administer the drugs of interest up to a maximum allowable limit of daily ingestion. Self-administration is typically permitted over a prolonged period of time, so that drug ingestion is chronic rather than acute, and the dose and pattern of ingestion is controlled by the subject. Categories of behaviors including social interaction are defined in advance and scored observationally by nursing and research staff. Levels of social interaction observed during drug self-administration may then be compared to levels observed when drug is not available, typically before and after the period of programmed drug availability. This research design allows for correlational analyses of social behavior as a function of drug availability or amount of drug consumed, but does not allow experimental control of the independent variable, drug intake. Occasionally (e.g., Griffiths et al. 1974a) investigators have experimentally varied drug availability or administered known quantities of drug as experimental manipulations within the context of inpatient research with chronic drug abusers.

The second type of study which has examined drug effects on social behavior has its origin in clinical psychopharmacology, that is, in research concerned with behavioral or psychiatric effects of drugs. These studies have typically examined effects of acute drug doses and employed normal volunteers or psychiatric patients as research subjects. Although specific procedures have varied widely from study to study, subjects are typically studied in groups of two, three, or four individuals seated together in the experimental situation. Active drug may be given to a single member or to multiple members of the group simultaneously. Dosing is generally acute, and drug dose may be manipulated as an independent variable. Social interaction in these studies has typically been examined by using verbal behavior as the dependent variable. Verbal behavior may occur in the context of social conversation, in response to interview questions, or in response to a problem-solving or group discussion task imposed by the experimenter. Observational techniques have typically been used to score both quantitative and qualitative aspects of verbal output of study participants, while more recently, automated equipment involving voice-operated relays has been used to collect quantitative information on talking.

Several classes of drugs have been examined for their effects on human social or verbal behavior using the two approaches described above. Virtually every drug which has been studied has produced observable alterations in social or verbal behavior. These drugs include ethanol (Griffiths et al. 1974a; Mendelson 1964; Stitzer et al. in press; Thornton et al. 1976), barbiturate sedatives (Reiss and Salzman 1973; Stitzer et al. in press), stimulants (Griffiths et al. 1977b), opiates (Fraser et al. 1963; Babor et al. 1976), phenothiazine tranquilizers (Lennard et al. 1967; Stitzer et al. in press), benzodiazepine tranquilizers (Salzman et al. 1974; Kochansky et al. 1977), marijuana (Babor et al. 1974a 1974b 1978b; Janowsky et al. 1979), and hallucinogens (Cheek and Holstein 1971).

In the present paper, these relationships will be illustrated by discussing the effects of four drugs on human social behavior: ethanol, secobarbital, chlorpromazine and d-amphetamine. These particular drugs were chosen for discussion because their effects have recently been studied systematically after acute administration to normal volunteer subjects. Such a systematic comparison across several drug classes using a single methodology has not been available previously for acute dosing studies. Where appropriate, effects of acute drug doses on social behavior of nonabuser volunteers will be compared with effects which have been observed in drug abusers who are chronically self-administering the drug.

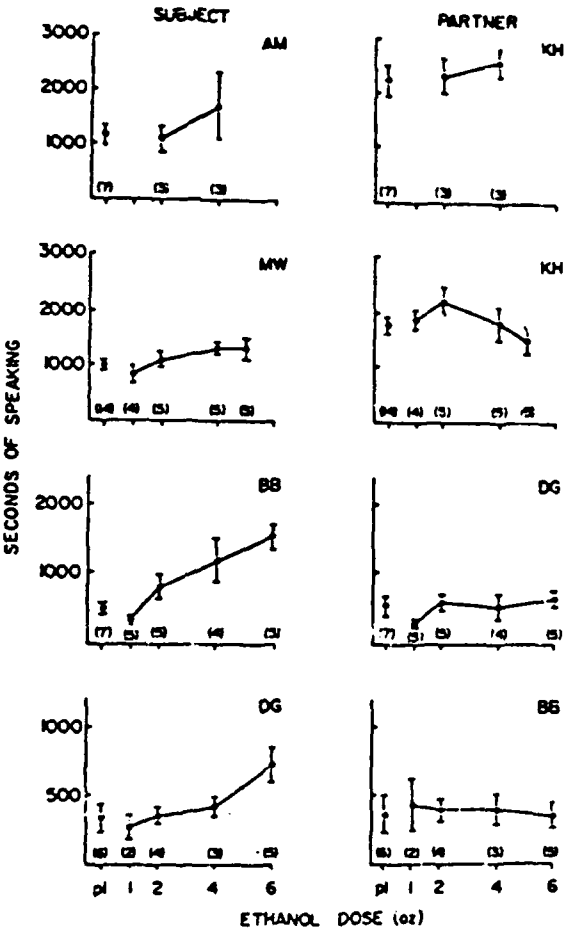
Ethanol

Ethanol has been studied more than any other type of drug for its effects on human social and verbal behavior. Two previous studies suggested that ethanol may enhance social conversation when administered in acute doses to nonalcoholic subjects (Smith et al. 1975; Pliner and Cappell 1974). Smith et al. (1975) studied effects of acute doses of ethanol (about 1 ml/kg absolute) given to both members of a dyadic social pair, and observed small increases after ethanol in amount of speech as well as increases in speech initiations and overlapping speech. Pliner and Cappell (1974) studied effects of ethanol (0.5 gm/kg) in groups of three normal volunteers. Observational ratings on an "amusement index" revealed higher scores for groups of subjects who received ethanol than for placebo controls. Thus, ethanol enhanced socializing and specifically the amount of smiling, laughing, and joking observed in the social situation.

Facilitation of social conversation by ethanol in nonalcoholic subjects has recently been confirmed in a study conducted at Baltimore City Hospitals which employed quantitative methods to investigate effects of acute drug doses on vocalization of dyadic interaction pairs (Stitzer et al. in press). In this study, amount of vocalization was monitored automatically and independently for each pair member by microphones strapped around the throat and connected to voice-operated relays. Same sexed subject pairs participated in daily one-hour sessions scheduled five days a week, and multiple observations were obtained of the effects of placebo and several doses of ethanol within the same subject. Test doses were given to only one member of each pair, referred to as the subject, while the other pair member, referred to as the partner, received placebo drinks (fruit juice) throughout the study. Figure 1 shows that ethanol (1-6 oz 95 proof) ingested one-half hour prior to the sessions enhanced the amount of vocalization recorded in the pair member who received active drug, while talking by the partner was relatively unaffected. The drug effect was dose-related and was observed in all four pairs who were studied.

Available evidence supports the conclusion that acute doses of ethanol enhance or facilitate social conversation in nonalcoholic normal volunteers. Consistent findings have not emerged, however,

FIGURE 1




*Effect of oral ethanol on seconds of speaking in a dyadic social interaction pair. Data are shown in the lefthand column for four individual subjects who received placebo (pl) and several doses of ethanol. Shown in the righthand column are data for partners, who received placebo only, on days when subjects received active drug. Seconds of speaking were cumulated during sessions of 3600 sec duration. Data points indicate means, brackets indicate ± 1 S.E.M. Shown in parentheses are number of observations included in each data point. From Stitzer et al. in press.*

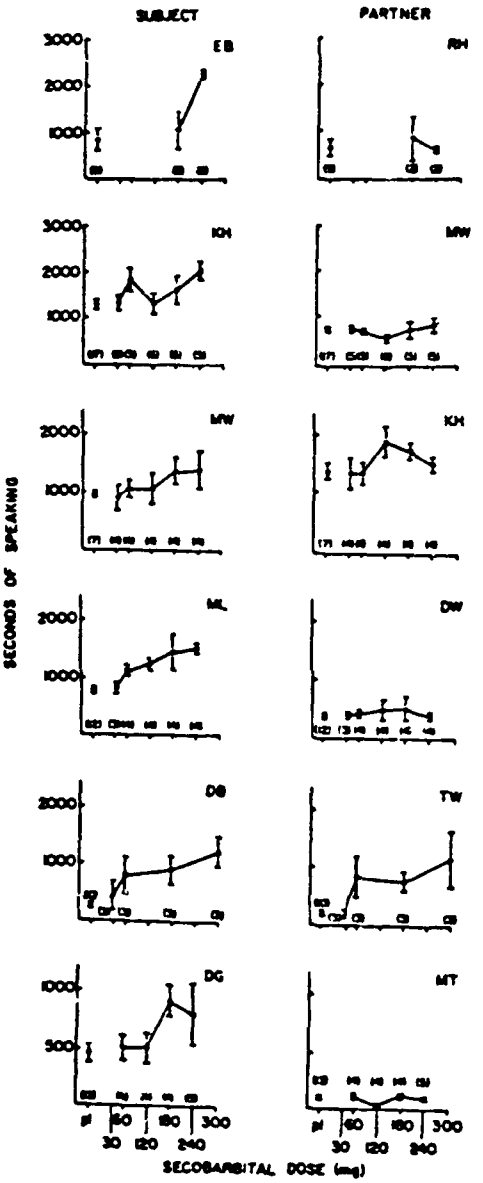
when ethanol has been studied in nonalcoholic volunteers who are allowed to self-administer the drug chronically. McGuire et al. (1966) noted increases in socializing (at unspecified doses) in three members of a four-man group of nonalcoholic subjects given access to ethanol during research participation in an inpatient unit. However, other investigators using similar methodologies (Babor et al. 1978a; Nathan and O'Brien 1971) failed to note any significant differences in amount of socializing during periods of drinking versus nondrinking or significant correlations between amount of drinking and amount of socializing.

Most inpatient research involving chronic self-administration of ethanol by alcoholic subjects has revealed a drug-related facilitation of social behavior. In the pioneering studies of ethanol self-administration conducted by Mendelson and colleagues (Mendelson 1964; McNamee et al. 1968), it was noted that social behavior remained intact during periods of heavy drinking by chronic alcoholic subjects and dropped out only after consumption of very high doses of ethanol (McNamee et al. 1968). Subsequent correlational observations have indicated that social behavior in chronic alcoholics is actually enhanced during periods of ethanol self-administration (Docter and Bernal 1964; McGuire et al. 1966; Thornton et al. 1976). The relationship between drinking and socializing was demonstrated in one study by Griffiths and coworkers (1974a) by manipulating the availability of ethanol. Amount of social interaction observed within individual subjects was consistently higher on days when ethanol drinking occurred (12 oz 95 proof ethanol) than on days when ethanol was not available. Another study by this group (Griffiths et al. 1975), using a choice procedure, demonstrated that ethanol enhances the desirability of socializing as compared to receiving money. Thus, a considerable body of data supports the conclusion that ethanol facilitates social behavior in chronic alcoholic subjects, while the few studies which have failed to show this positive correlation (e.g., Nathan and O'Brien 1971; Mortanero 1974) used procedures which tended to suppress the occurrence of socializing altogether (see also Griffiths et al. 1978). Comparison of studies with chronic alcoholics and nonalcoholic volunteers suggests that the effects of ethanol on social behavior may be similar for these two groups, but that chronicity of ingestion is a factor which may influence drug effects on social behavior in nonalcoholic subjects.

### Secobarbital

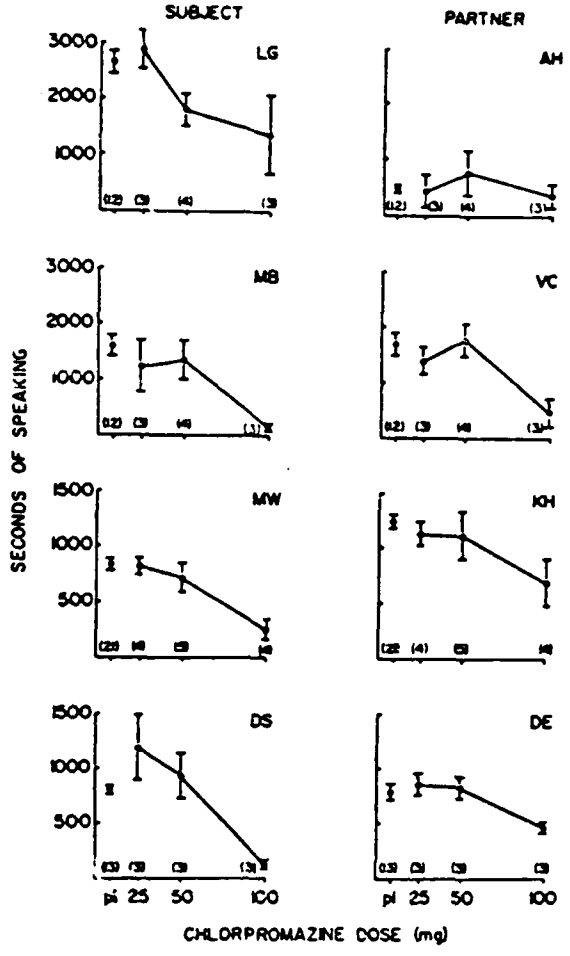
Only one previous study is available in which the effects of barbiturate sedatives have been examined on human social behavior (Reiss and Salzman 1973). This study showed marginal facilitation of verbal interaction when secobarbital (175 ml) was administered to the adolescent member of a three-member family group during a group problem-solving task. Secobarbital has recently been studied in dyadic social interaction pairs using procedures developed at Baltimore City Hospitals, as previously described for studies of

FIGURE 2




*Effect of oral secobarbital on seconds of speaking in a dyadic social interaction pair. Data are shown in the lefthand column for six individual subjects who received placebo (pl) and several doses of secobarbital. Shown in the righthand column are data for partners, who received placebo only on days when subjects received active drug. See Figure 1 legend for other features of data presentation. From Stitzer et al. in press.* © *AMRHO International, Inc. Reprinted with permission.*

FIGURE 3




*Effect of oral chlorpromazine on seconds of speaking in a dyadic social interaction pair. Data are shown in the lefthand column for four individual subjects who received placebo (pl) and three doses of chlorpromazine. Shown in the righthand column are data for partners, who received placebo only, on days when subjects received active drug. See Figure 1 legend for other features of data presentation. From Stitzer et al. in press.* 

ethanol (Stitzer et al. in press). The results of this study are presented in Figure 2. It can be seen that secobarbital in doses of 30-300 mg produced dose-related increases in vocalization in all six of the pair members who received active drug, while having no consistent effect on speaking by the partners who received placebo only. The appearance of behavioral facilitation following administration of a barbiturate drug is noteworthy since these drugs frequently produce only sedation and performance decrements (Epstein and Lasagna 1968; Idestrom and Cadenius 1963; Frankenhaeuser et al. 1964; Loomis and West 1958). Furthermore, although subject history and expectations of drug actions (e.g., Lang et al. 1975) are frequently involved in interpretation of behavioral effects of ethanol, such history and expectation variables should not be significant determinants of barbiturate effects in subjects who are relatively inexperienced with the drug. Thus, the similar behavioral effects of secobarbital and ethanol suggest that facilitation of social conversation represents a behavioral pharmacological effect of these drugs which is relatively independent of subject history or expectations.

Chlorpromazine

One previous study, which examined effects of 50 mg chlorpromazine on social conversation in normal volunteers (Lennard et al. 1967), reported that the drugged subject in a three-person group initiated less communication and had less communication directed toward him. Chlorpromazine has also been studied recently at Baltimore City Hospitals in the dyadic social interaction situation previously described for studies of ethanol and secobarbital (Stitzer et al. in press). Doses of 25-100 mg were administered to a single member of the interaction pair three hours prior to the social session. Figure 3 shows that the amount of vocalization was reduced in a dose-related manner for pair members who received active drug, and, in this case, talking by the partner who received placebo only was also generally reduced on days when the subject received active drug. These results are consistent with previous observations of a depressant effect of chlorpromazine on social conversation in normal volunteer subjects (Lennard et al. 1967). Chlorpromazine serves as a negative control in the social interaction studies conducted at Baltimore City Hospitals by demonstrating that social conversation does not invariably increase after drug administration, but rather that pharmacological specificity exists with regard to drug effects on social conversation in the dyadic interaction situation.

d-Amphetamine

Clinical case reports and survey studies suggest that normal social behavior is markedly disrupted during periods of chronic high dose use of amphetamines, while repetitive stereotyped actions which do not involve other people are typically observed during periods of chronic use (Schiørring 1977). In contrast, acute administration of modest doses of stimulants such as d-amphetamine can produce dramatic

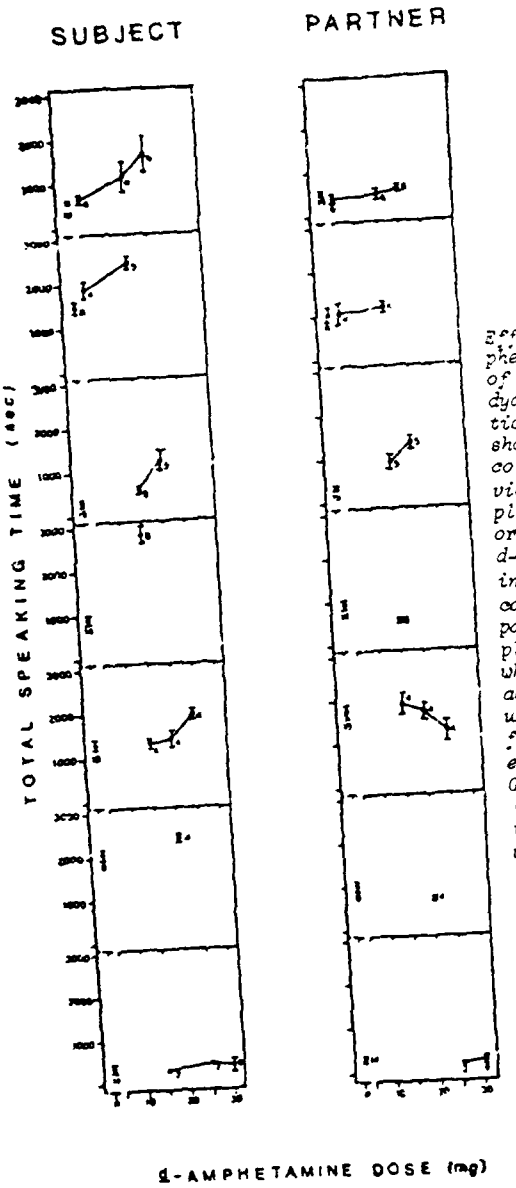
increases in verbal and social behavior. One study by Griffiths et al. (1977b) used behavioral observation to assess amounts of socializing in which study participants engaged. The study, which was conducted in an inpatient research unit with subjects who had histories of alcoholism, showed reliable dose-related increases in amounts of socializing after acute oral doses of d-amphetamine. Effects of d-amphetamine have also been studied in the dyadic social interaction situation using procedures developed at Baltimore City Hospitals, as previously described (Griffiths et al. 1977b). Acute doses of 5 to 30 mg were administered two hours prior to the daily social session to a single member of the interaction pair. Figure 4 shows that the drug produced a dose-related increase in vocalization in five of seven pair members who received active drug, while talking by the partner who received placebo only was generally unaffected. While there are apparently individual differences in response to d-amphetamine, with a certain portion of subjects showing no effect, facilitation of social conversation after acute doses of d-amphetamine is very dramatic and consistent for most subjects.

Overall, the studies described in this section have shown that drugs can influence the amount of social conversation and social interaction observed in human subjects. The ability of drugs to modify social behavior appears to have considerable generality across drug classes, having been observed for stimulants (Griffiths et al. 1977b), sedatives, major tranquilizers and ethanol (Stitzer et al. in press), as well as opiates (Babor et al. 1976) and marijuana (Babor et al. 1974a 1974b 1978b). Drug effects on social behavior also have considerable generality across subject populations, having been observed in both chronic users of the drugs under study and volunteer nonabuser subjects; furthermore, these effects have been observed across a wide range of doses in both acute dosing studies and chronic drug self-administration paradigms. It seems clear that the ability to modulate human social behavior is an important behavioral property of a wide variety of psychoactive drugs.

## MODULATION OF DRUG EFFECTS BY SOCIAL STIMULI

As discussed in the previous section, evidence has now accumulated that drugs from several pharmacological classes modulate human behavior in social contexts. The question addressed in this section is whether the reciprocal relationship can also be demonstrated--that is, whether there is any evidence that social context can modulate other physiological, behavioral, or subjective effects of drugs. Although only a limited amount of research has addressed this question, results of available studies suggest that some of the subjective effects attributed to drugs can differ markedly depending on the social context in which the drug is administered. Pliner and Cappell (1974) studied subjective effects of ethanol 0.5 gm/kg (3-4 oz 80 proof) in normal volunteer subjects who were either alone or in a three-person group. In both situations, subjects worked during 20 min sessions on a "creative" task, which involved

FIGURE 4




*Effect of oral d-amphetamine on seconds of speaking in a dyadic social interaction pair. Data are shown in the lefthand column for four individuals who received placebo (pl) and one or more doses of d-amphetamine. Shown in the righthand column are data for partners, who received placebo only on days when subjects received active drug. See Figure 1 legend for other features of data presentation. From Griffiths et al. 1977b. © ANKHO International, Inc. Reprinted with permission.*

composing cartoon captions. Mood reports completed after the session (Clyde Mood Scale) showed that subjects who experienced the drug effect in an isolated situation reported feeling less clear thinking, more dizzy and more sleepy as a result of the drug, while subjects who experienced drug effects in the group situation became less bored and more elated as a result of drug. Estimates by the subjects of their degree of intoxication, on the other hand, did not differ in the social and nonsocial conditions. Thus, there was a distinction in this study between qualitative aspects of the subjective drug effect which were modulated by social context, and quantitative estimates of intoxication which were not modulated by social context.

Results remarkably similar to those reported by Pliner and Cappell (1974) were also obtained in a study of marijuana effects conducted by Jones (1971). In this study, subjects smoked marijuana cigarettes containing 9 mg THC during two experimental sessions spaced one week apart. In one session, subjects smoked alone; in the other session they were in a four-person group. While smoking alone, subjects generally reported feeling relaxed and drowsy. In the group situation, however, subjective reports indicated elated mood and a lack of sedation. Global ratings of the degree of intoxication, however, were similar across the two situations. This study therefore confirms the observation made by Pliner and Cappell that qualitative aspects of the subjective reports after drug were modulated by social setting, while quantitative estimates of degree of intoxication were unaffected by setting.

In a final study of this type by Warren and Raynes (1972), the direction and magnitude of mood change as revealed by subjective report did not differ significantly during social and nonsocial conditions, but there was a tendency for mood effects to be more extreme in the social setting.

Studies by Jones (1971) and Pliner and Cappell (1974) demonstrate nicely that social context may alter the qualitative nature of subjective effects reported after drug ingestion. This finding is supported by less systematic observations of other investigators who have noted that subjective reports of drug effects can depend to a large extent upon the specific social and affective context in which the effects are experienced (Schachter and Singer 1962; Nowlis and Nowlis 1956; Sicé et al. 1975). Since subjective effects attributed to drugs can differ qualitatively in different social contexts, we may assume that these subjective effects are not immutable properties of the drug but rather effects which can be determined or modulated by social context and other environmental variables.

## MODULATION OF DRUG SELF-ADMINISTRATION BY SOCIAL STIMULI

Since social stimuli can modulate certain subjective effects of drugs, as discussed in the previous section, these stimuli may also

modulate the propensity to ingest drugs. For example, social stimuli could function as discriminative stimuli which control drug ingestion, in which case, presence of social cues would increase the likelihood of drug ingestion. Alternatively, social stimuli could actually alter the reinforcing properties of drugs, making it either more or less likely that drugs would be ingested in social situations. Finally, access to social stimuli could act as a reinforcer or punisher to enhance or suppress drug self-administration. Irrespective of the possible mechanisms involved, it is of interest to determine the extent to which social stimuli modulate rates and patterns of drug self-administration by humans.

The studies which will be reviewed in this section have in common a behavioral measure of drug ingestion as the primary dependent variable. Social conditions are then manipulated to determine the effect on amount and pattern of drug self-administration. In fact, information about social modulators of drug self-administration has all been derived from studies which employ ethanol as the drug to be self-administered. This is not too surprising in view of the relative ease with which this drug can be studied in a variety of settings. Although ethanol can be considered a prototypic drug for studies of the influence of social variables, the generality of results obtained with ethanol remains to be determined.

Social versus Nonsocial Context

The few studies which directly compared ethanol self administration in social and nonsocial contexts have not found consistent differences in drug self-administration in these two contexts. One study by Nathan and coworkers (Nathan et al. 1970) examined ethanol self-administration in chronic alcoholic subjects under conditions of free socialization or enforced isolation. Although most subjects claimed that they enjoyed drinking more during the social condition than during the isolation condition, there were no consistent differences in amount of drinking during socialization and isolation. In subsequent studies conducted by these investigators (e.g., Nathan and O'Brien 1971), subjects were allowed to determine the social context of drinking by buying their way out of isolation using the same points which purchased ethanol. This procedure clouded the distinction between social and isolated conditions and precluded an analysis of drinking rate as a function of social context.

Fox and Simon (1978) studied drinking topography as a function of solitary versus social context. Chronic alcoholic subjects participated in 30 min sessions during which they drank their preferred beverage either alone or in a three-person group. In this study, the alcoholic subjects tended to consume all available ethanol, and drinking patterns in the social setting did not differ significantly from drinking patterns in the solitary setting.

The fact that chronic alcoholics will tend to drink all available ethanol in experimental situations poses a methodological barrier

to demonstrating environmental influences that increase drinking. It is possible that longer sessions (e.g., Caudill and Lipscomb 1980) or other methodological refinements which suppress baseline drinking rates (Bigelow et al. 1975) would enhance sensitivity to effects of social cues. It is also possible, however, that social context per se may play an insignificant role in drinking by alcoholics. This might be predicted if the reinforcing properties of the drug itself were so prominent in these individuals that they overwhelm the influence of relatively subtle environmental modulators such as social context. Social modulation of ethanol self-administration might be more easily demonstrated in nonalcoholic social drinkers or in situations in which baseline drinking is suppressed below maximal levels.

One recent study (Tomaszewski et al. 1980) examined the influence of social cues on ethanol consumption in college student beer drinkers. During experimental sessions subjects were randomly assigned to drink beer with a partner who had soft drinks but no ethanol available (social setting), with a partner who also drank beer (social drinking), or alone (control). Paired subjects were matched for rate and amount of beer drinking as determined during a baseline session. Subjects in the social setting condition but not those in the social drinking condition consumed more beer than control subjects who drank in isolation. This study, while providing some evidence for enhanced drinking in a social context, failed to demonstrate a robust and reliable effect of social cues on drinking. It should be noted that the college student beer drinkers in the Tomaszewski et al. study, as well as alcoholic subjects in other studies (e.g., Nathan and O'Brien 1971), consumed substantial amounts of ethanol under isolated conditions. It is clear therefore that social cues are not necessary for the maintenance of drinking in these situations. While social cues may, under some conditions, modulate the amount of ethanol consumed, a clear demonstration of this effect remains elusive at the present time.

## Modeling

Although there is no strong evidence at present that social context per se has a marked impact on the self-administration of drugs or ethanol, compelling evidence has accumulated that modeling can play an important role in modulating rates and amounts of ethanol consumption. The initial demonstration of a modeling effect was made by Caudill and Marlatt (1975). The college student volunteers in this study were told that they would be taking part in a wine tasting test in which they would sample and rate two decanters of wine on various subjective dimensions. The real dependent variable of interest, however, was the amount of ethanol consumed during a 15 min taste test. Subjects were randomly assigned to complete the taste test with a high consumption model (700 ml consumption), a low consumption model (100 ml consumption), or no model. While there was no difference in the average amount of wine consumed by subjects who drank alone and by subjects exposed to the low consumption

model, subjects exposed to the high consumption model consumed significantly more wine than those in either of the other groups.

Garlington and Dericco (1977) have demonstrated the modelirg effect using a within-subject experimental design. Subjects dranl. beer during a one-hour session in the company of a confederate model. Models were trained to match their drinking rate to that of the subject, or to drink at rates one-third higher or one-third lower than the ongoing rates of the subject. Each condition (baseline-matched drinking, high rate drinking, low rate drinking) was in effect during successive sessions and each continued until a criterion of stability had been achieved. Figure 5 shows stable drinking rates of subjects and confederates as recorded by independent observers present in the experimental room. It is clear that subjects' drinking rates tracked those of the confederate model with a high degree of accuracy.

The generality of modeling effects has been extended to female subjects and to subjects with higher drinking histories (Lied and Marlatt 1979). Finally, modeling effects have recently been demonstrated in alcoholic subjects during both taste test and free drinking procedures (Caudill and Lipscomb 1980).

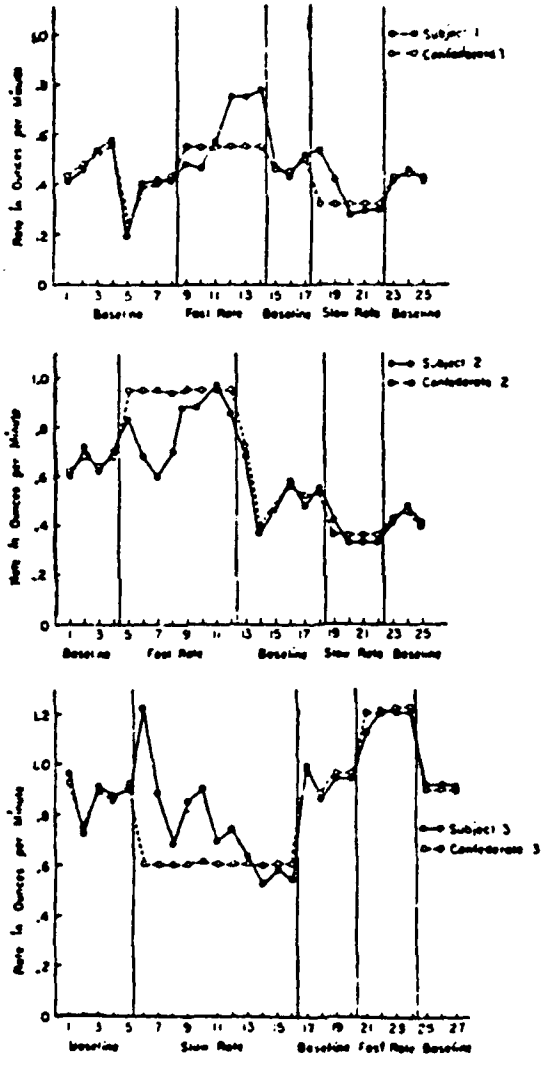
A series of studies has demonstrated that modeling can exert a powerful and systematic influence on rates and patterns of drinking within an experimental social drinking setting and that the influence of modeling is apparent in both social drinkers and chronic alcoholics. Modeling could clearly be an important regulatory mechanism controlling drug intake in naturally occurring social situations. It will be of interest in future studies to determine the generality of modeling effects across a variety of drugs and to delineate the conditions under which modeling factors operate (e.g., Dericco and Garlington 1977; Dericco and Niemann 1980; Hendricks et al. 1978).

Contingent Access to Social Interaction

Positive social reinforcement is presumed to operate in the etiology of drug use since such use is typically associated with peer models and friendship groups (Hughes and Crawford 1972; Kandel et al. 1978). Facilitation of drug ingestion through contingent access to social stimuli has never been demonstrated in laboratory situations. On the other hand, studies conducted at Baltimore City Hospitals by Griffiths, Bigelow, and colleagues have clearly demonstrated that contingent access to social stimuli can be used to suppress ethanol self-administration in chronic alcoholics.

A case study reported in a review by Griffiths et al. (1978) illustrates the potentially powerful impact of contingent access to social stimuli on alcoholic drinking. The subject, a chronic alcoholic, had 12 drinks (1 oz 95 proof ethanol) available daily during his participation in an inpatient research unit. Under base-

FIGURE 5



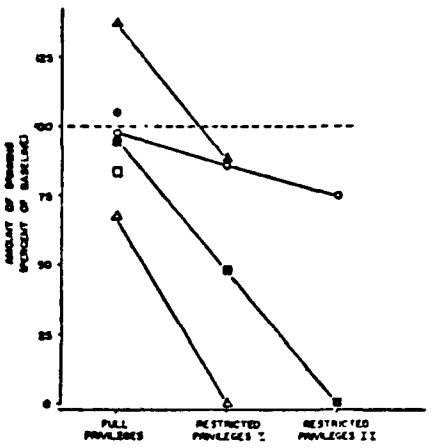
*Drinking rates in ounces per minute of subjects and confederates during successive one-hour experimental sessions. From Carlington and Dericco 1977. © Journal of Applied Behavior Analysis. Reprinted with permission.*

line conditions, he consumed all available ethanol. Subsequently, he could earn visiting privileges for his girlfriend by restricting his drinking to a moderate amount (no more than 5 drinks in a day). The subject fulfilled the moderate drinking requirements on five of six days during which the contingency was in effect. During another study phase, the subject could receive an overnight pass to visit his girlfriend by restricting his drinking to 5 drinks per day or less for 10 consecutive days. He was successful in doing so, and earned the pass. This case study illustrates that drinking by an alcoholic subject can be precisely modulated by reinforcement techniques which involve contingent access to social stimuli.

A series of studies was subsequently undertaken by this group of investigators to examine contingent access to social stimuli as a modulator of ethanol self administration in chronic alcoholic subjects. In the first study of this type (Bigelow et al. 1974), ten chronic alcoholic subjects had access to one oz (95 proof) drinks during daily 16 hr sessions. The number of drinks available varied from 12 to 24 for individual subjects. Following a baseline assessment period during which subjects consumed all available ethanol, subjects were required to sit for 10 or 15 min in a small isolation booth each time they chose to take a drink. This contingent isolation procedure resulted in marked suppression of drinking (to an average of 50 percent of baseline) in 7 of the 10 subjects.

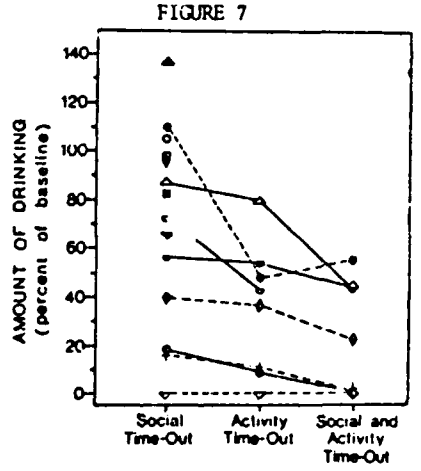
Physical isolation in a booth removes subjects from social stimuli as well as social interaction and also greatly restricts activity levels. A study by Griffiths et al. (1974b) was undertaken to separate the influence of some of these factors. In this study, six chronic alcoholic volunteers had access to seventeen 1 oz (95 proof) drinks daily during an 11-hr session. Under baseline conditions of availability subjects did not generally consume all available drinks, although they typically consumed at least nine drinks and as many as 16 drinks. During the contingent time-out intervention, subjects were required to spend 40 min in a time-out from social interactions each time they chose to drink. During social isolation subjects could remain in the dayroom of the research unit but could not talk to other ward residents. They could engage in activities (TV, reading, cards, pool) as long as these did not involve participation by another person. Figure 6 summarizes results of this experiment, and shows that contingent social isolation under these conditions initially did not result in a consistent suppression of drinking. The experiment was repeated in some of the subjects under slightly different conditions. During these replications, certain ward privileges were restricted during the entire experimental session whether or not the subject chose to drink. During restricted privileges I, subjects were not allowed to watch television; during restricted privileges II, subjects were not allowed to read or to watch television. It is clear from Figure 8 that the contingent social isolation procedure became more effective as alternative activities were more severely restricted.

FIGURE 6



*Effect of contingent timeout from social interactions on amount of drinking in six individual study participants during three conditions of available privileges: Full Privileges; Restricted Privileges I (no television); Restricted Privileges II (no television, no reading). From Griffiths et al. 1974b. © Pergamon Press. Reprinted with permission.*

FIGURE 7




*Effects of three different timeout procedures on drinking of 14 chronic alcoholic subjects. Different symbols represent different study participants. See text for explanation of social and activity timeout procedures. From Griffiths et al. 1977a. © Pergamon Press. Reprinted with permission.*

A final study by Griffiths et al. (1977a) compared the efficacy of contingent social time-out and contingent activity time-out in suppressing drinking of alcoholics. Throughout the study, 17 drinks (1 oz 95 proof) were available to alcoholic subjects in the research unit during daily 11-hr sessions. Eight subjects were exposed to three different time-out conditions presented either on several consecutive days or under a procedure in which conditions changed on a daily basis. During social time-out, subjects could stay in the dayroom and engage in activities as previously described, but could not talk or interact with other ward residents. During activity time-out subjects had to spend 40 min following each drink sitting in a specified chair located near the nursing station. They could not participate in ward activities, but could talk and socialize with ward residents and staff. A third procedure examined was a combination of the social and activity time-outs. Figure 7 presents a summary of results for this experiment. Overall, the response of individual subjects to the social time-out contingency was highly variable: social time-out alone suppressed drinking in about half of the subjects exposed to this condition. In subjects exposed to both social and activity time-out conditions, the two procedures were frequently about equivalent in suppressing drinking, although the activity time-out was more effective in some subjects. The combined social and activity time-outs, on the other hand, were generally more effective than either one alone, and about equally as effective as contingent time-out in the isolation booth had been in a previous study (Bigelow et al. 1974).

It can be concluded from these studies that while contingent time-out from social interaction may produce variable effects in individual subjects, the procedure was generally quite effective in suppressing drinking of many alcoholic subjects. Furthermore, the efficacy of contingent time-out from social interaction was improved by restricting the other activities which were available to the subject. Finally, other types of contingent restrictions such as activity time-out were also effective in suppressing drinking, so that contingencies which employed time-out from social interaction were not unique in their ability to suppress drinking.

Experiments reviewed in this section have shown that social stimuli play important roles in modulating ethanol self-administration under some conditions but not under other conditions. On the basis of limited data available, social context per se does not appear to modify amounts or patterns of ethanol self-administration. Rather, drinking may occur at high rates under both social and isolated conditions. Modeling influences within a social context, on the other hand, are potent and reliable determinants of amounts and patterns of ethanol self-administration in both alcoholic and nonalcoholic subjects. Contingent time-out from social interaction is also a potent modulator of ethanol self-administration, acting to suppress drinking in chronic alcoholics. Since the presence of social stimuli and the opportunity to interact socially do not appear to be critical for maintenance of ethanol self-administration, it is likely that the efficacy of contingent social time-out repre-

sents a direct suppression of drinking by contingent application of an aversive event rather than a unique interaction between ethanol and social stimuli.

## SUMMARY AND CONCLUSIONS

It is clear that the relationships between drugs and social stimuli are myriad and complex. Furthermore, the state of our current knowledge about these relationships is quite rudimentary. Nevertheless, studies of social factors in drug effects have revealed several potent and intriguing relationships. These include facilitation of social behavior by drugs of abuse, modulation of subjective and behavioral drug effects by social context, modeling effects on rates and patterns of consumption and suppression of ethanol self-administration by contingent access to social stimuli.

Studies of social factors in drug effects may ultimately contribute greatly to our understanding of the relationship between reinforcing properties of drugs and their other behavioral actions. For example, many drugs which are abused by humans have been shown to enhance or facilitate human social interaction (Drug Effects on Human Social Interactions section). It is possible that drug-produced facilitation of social behavior may constitute one component of the reinforcing properties of drugs of abuse. If this were the case, drugs should be better reinforcers and hence more readily self-administered in social as opposed to isolated contexts. To date, there is no clear demonstration that social cues or social context per se facilitate drug self-administration. However, very little research has been focused on this particular question, and more self-administration studies which manipulate social cues would be desirable. Another type of study which would bear on this issue is one in which subjects self-administer drugs in a social context but instructions or other interventions are used to prevent the normal drug-produced increases in social behavior. If this manipulation were to reduce drug self-administration, this result would suggest that the behavioral drug effect was contributing to the maintenance of self-administration and hence contributing to the reinforcing properties of the drug.

It has long been supposed that subjective effects of drugs are an integral part of their reinforcing properties (Jasinski 1973, 1977; WHO 1975). More recent studies, on the other hand, have suggested that subjective and reinforcing properties of drugs may be relatively independent (Johanson and Uhlenhuth 1978). The fact that social context may alter qualitative subjective drug effects poses intriguing possibilities for distinguishing the contribution of specific subjective effects to the reinforcing properties of drugs. For example, self-administration could be compared in social situations which produce different affective states and hence different qualitative reports of subjective drug effect. If the quality of subjective effects attributed to drugs is important in determining reinforcing properties (e.g., elation versus depression), then self-administration should differ in these situations. If degree of intoxication

is a primary determinant, on the other hand, the specific context or affective milieu may have little impact on rates and patterns of self-administration. An illustration of this approach is found in a recent study by Pihl and Yankofsky (1979). In this study subjects were given contrived feedback about their performance on an "intelligence test." The feedback indicated that they had performed either very well or very poorly on the task. Demonstrable changes in affect occurred as a result of these manipulations. In an alcohol taste test which followed, subjects exposed to the positive feedback drank significantly more than subjects who had been exposed to the negative feedback. In the case of chronic alcoholic subjects, on the other hand, a change in affective state from elation to depression, which is commonly observed during periods of chronic ethanol self-administration, does not appear to influence rates and patterns of drinking (Mendelson 1964; McNamee et al. 1968; Nathan et al. 1970; Tamerin and Mendelson 1969). Further research along these lines would be desirable to clarify the interaction between affective states, subjective drug effects, and the reinforcing properties of drugs.

Other powerful social modulators of drug self-administration, such as modeling and contingent access to social stimuli, may operate relatively independently of the reinforcing properties of drugs. These factors are clearly important, however, for our understanding of etiology and maintenance of drug consumption in both abusive and nonabusive patterns. We might speculate, for example, that initial exposure to drugs within a social context facilitates drug use via explicit social reinforcement of drug ingestion combined with modeling. Once consumption is established, modeling and reinforcement influences would continue to operate in determining rates and patterns of ingestion and ultimately in determining social versus abusive patterns of ingestion. The demonstrated potent influence of social factors on drug consumption is also relevant for developing rational treatment strategies for drug abusers. The use of modeling as a treatment procedure has received little attention, while the potential utility of arranging contingent access to social stimuli is generally recognized (Hunt and Azrin 1973) but infrequently implemented within treatment programs.

We are just beginning to understand the interactive relationships between drug effects and social factors. A complete understanding of the behavioral pharmacology of drugs, as well as an understanding of the factors which maintain drug self-administration in humans, will depend upon an eventual unravelling of these interactive relationships. The study of social factors in drug effects promises to make an exciting and worthwhile contribution to behavioral pharmacology.

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# Discussion

## Stimulus Control and Drug Dependence

Donald R. Jasinski, M.D.

The administration or termination of narcotics and other substances of abuse to drug-dependent patients alters physiologic functioning and behavior, as well as feelings, thinking, perception, and mood (subjective effects) (Martin and Sloan 1977, Jasinski 1977). For the most part, these alterations are reproducible as to character and time course and are distinct for classes of drugs (Jasinski 1977). The study of these phenomena in man in conjunction with operant studies in man and animals has created a "psychology" of drug abuse. (This is evidenced by the fact that explanations of the addictive process derive from the study of these phenomena and that a unique set of psychopharmacologic instruments and techniques exists for drug abuse.) In my opinion, the most critical of these phenomena is the alteration of subjective effects. It seems appropriate, therefore, to summarize the concepts explaining the role of subjective effects in psychopharmacologic studies of abused drugs.

The first set of concepts relates to the opiate withdrawl syndrome. In initial studies of addiction to morphine, it was recognized that characteristic and stereotyped physiologic subjective and behavioral changes followed termination of morphine-like drugs (Kolb and Himmelsbach 1938). Among the behavioral phenomena was drug seeking to relieve the discomfort. An initial and understandable assumption was that in withdrawl syndrome the physiologic changes, the subjective effects, and the behavior covaried. Consequently, the more easily measured physiologic and behavioral changes were utilized to measure the intensity and time course of the withdrawl syndrome. The concepts of physical dependence, subjective distress, and behavior as they related to the addictive process were considered interchangeable to such a degree that physiologic changes were felt to be indications of subjective discomfort and drug-seeking behavior (Jasinski 1977).

Studies of the drug cyclazocine changed this concept (Martin et al. 1965). It was observed that the withdrawl syndrome of cyclazocine consisted of physiologic changes similiar to opiate withdrawl but without subjective distress or drug-seeking behavior. This observation led to the conclusion that the critical consequences of physical dependence could be best measured by subjective effects.

The second set of concepts relates to the alterations in subjective effects (apart from relief of withdrawal) following drug administration. Addict subjects given opioids, sedative hypnotics, and centra stimulants discriminate among these drugs and between these drugs and placebo even when observers cannot discriminate among the drugs on the basis of behavioral changes (Jasinski 1977). Alterations in feelings, perceptions, and thinking produced by the drugs have differences and commonalities. The most important commonality relates to elevation of mood reflected in feeling of well-being, relaxation, enhanced self-image, and loss of anxiety. These effects are usually labeled euphoria and are felt to be responsible for the reinforcing effects of the drug. (This discriminability among drugs and the measurement of euphoria have been utilized to classify drugs and measure their reinforcing properties for the purpose of assessing abuse potential.) In summary, some 40 years of clinical research at the Addiction Research Center in drug-dependent patients has led to the conclusion that subjective alterations induced by the administration or withdrawal of drugs of abuse are among the most sensitive and specific psychopharmacologic measures.

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# Commonalities and Differences Among Reinforcers

# Differential Drug Effects as a Function of the Controlling Consequences

James E. Barrett, Ph.D.

One of the central themes during the initial period in the development of behavioral pharmacology was the issue of whether motivational factors influence the effects drugs have on behavior. Though seemingly a straightforward question, the translation of this problem into an experimentally addressable form was, and continues to be, somewhat difficult. Motivational concepts almost inevitably pose formidable experimental problems, and studies designed to resolve those problems have often yielded equivocal results. Typically, however, the question has been approached experimentally by comparing the effects of various drugs on behavior controlled by different types of events, e.g., food presentation and escape from electric shock. Presumably, different events and the behavioral consequences associated with them engendered different motivational states. The influence of motivational factors as determinants of drug action should then be reflected by differential changes in overt behavior when the organism is given certain drugs.

This approach had one rather substantial problem that was not always recognized. Behavioral consequences are important in several different ways, not only when they differ on some hedonic dimension, but also depending precisely on how they are arranged or scheduled with regard to behavior. Characteristics of behavior such as the rate, duration, intensity, and temporal distribution of responding are typically quite distinctive under different schedules even when only a single consequence is arranged. Further, it has been shown repeatedly that one of these characteristics, the rate and pattern of responding, can contribute significantly to the effects many drugs have on behavior (Dews and DeWeese 1977, Kelleher and Morse 1968a, McKearney and Barrett 1978). It remains possible that other less intensively studied factors, quite apart from the type of consequence, also play an important role in determining the behavioral effects of drugs.

Because it has been shown that the effects of various drugs on behaviors maintained by only one type of event can depend at least on the schedule-controlled rate and pattern of responding, experimental efforts directed towards understanding whether the nature of the event maintaining responding affects drug action cannot be conducted arbitrarily (Dews and Morse 1961; Kelleher and Morse 1964, 1968a). For example, if one is interested in comparing drug effects on behaviors maintained by food and shock, it would be less meaningful to compare performances under a continuous shock-postponement (avoidance)

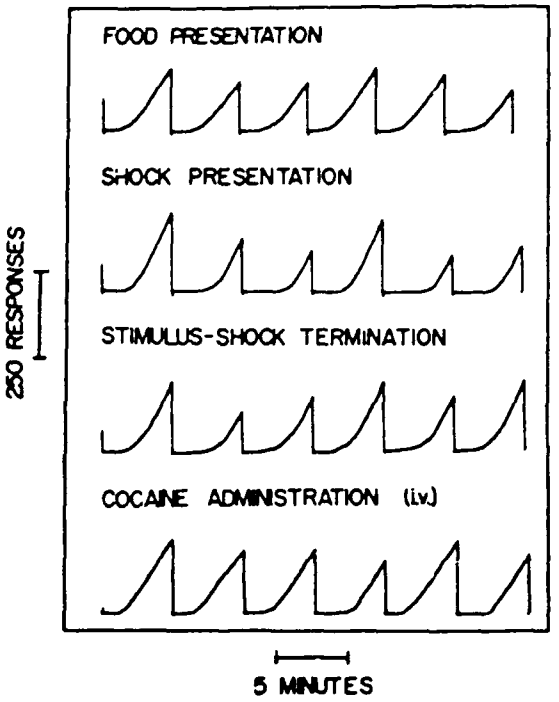
schedule with those under a fixed-interval food-presentation schedule than it would be to compare drug effects under comparable fixed-interval schedules of food or termination of a stimulus correlated with shock. In the first comparison, even if overall rates of responding were similar, it is almost certain that the temporal distribution or the patterning of responding would be quite different. Consequently, most individuals that have recently examined drug effects on behaviors maintained by different events have consistently emphasized the importance of making such comparisons under conditions as comparable as possible (see reviews by Barrett and Katz 1981, McKearney and Barrett 1978, Morse et al. 1977).

Figure 1 shows similarities in performances maintained by different events under comparable schedules of reinforcement. These records depict responding of squirrel monkeys maintained under 5-minute fixed-interval schedules of food presentation, shock presentation, stimulus-shock termination, or intravenous cocaine self-administration. Despite the marked differences in the nature of these consequent events, the schedule-controlled rate and pattern of responding maintained by each was remarkably similar. Comparisons of drug effects under conditions such as these minimize the influence of other variables and permit reasonably straightforward analyses.

This approach was taken in experiments by Kelleher and Morse (1964) and by Cook and Catania (1964). These investigators studied the effects of several different drugs (e.g., chlorpromazine, d-amphetamine, chlordiazepoxide, and imipramine) on behavior maintained under similar schedules of food presentation, escape from continuous electric shock, or termination of a stimulus associated with electric shock. Although Cook and Catania (1964) studied only fixed-interval schedules, Kelleher and Morse (1964) compared drug effects under both fixed-interval and fixed-ratio schedules of either food presentation or stimulus-shock termination. None of the drugs in these experiments had behavioral effects that depended on the type of event maintaining behavior. However, in the Kelleher and Morse (1964) study, the effects of d-amphetamine and chlorpromazine were related to whether responding was maintained under the fixed-interval or fixed-ratio schedules. These findings were of considerable significance because they suggested that the nature of the event controlling behavior was less important than the schedule under which that event occurred. Motivational factors, at least as assessed in this manner, appeared superfluous in attempting to account for the behavioral effects of drugs.

Until recently, there have been very few additional experiments that focused on comparisons of the effects of drugs on behaviors maintained by different events. Tremendous progress has occurred recently because of the development and refinement of certain procedures that have permitted an examination of more diverse events under conditions where the behavioral performances are often nearly identical. Experimental efforts addressing the question of differential drug effects as a function of the controlling consequences have incorporated many of the fundamental principles in behavioral pharmacology. The results of these studies, therefore, have general implications for principles

FIGURE 1




*Comparable performances of squirrel monkeys responding under 5-minute fixed-interval schedules with different maintaining events. The pens reset to baseline at reinforcement. Each component was separated by a one-minute timeout period during which all illumination in the chamber was extinguished. Food presentation consisted of the delivery of a 300 mg Noyes banana-flavored pellet; shock presentation was a 200 msec 9 mA electric shock delivered to the shaved portion of the monkey's tail which was held motionless by a small stock. Under the stimulus-shock termination schedule, 9 mA shocks were scheduled to occur beginning one second after the elapse of the 5-minute fixed interval; a response after the 5-minute interval had elapsed terminated the prevailing stimuli and shock schedule and produced the timeout period. Cocaine hydrochloride was injected via an indwelling intravenous catheter connected to a motor-driven syringe; a response after the 5-minute fixed interval produced a 50 µg/kg infusion of cocaine. Note that performances maintained by the different events are quite similar despite their various characteristics and means of administration. (From Barrett and Katz 1981.© 1981, Academic Press)*

in this field. In addition, these experiments have also helped clarify and delineate other important environmental determinants of the behavioral effects of drugs. Continued research, therefore, should yield valuable information for developing a broad perspective and better understanding of drugs of abuse.

## BEHAVIOR MAINTAINED BY DIFFERENT EVENTS

Recent studies comparing drug effects on behavioral performances controlled by different events have incorporated a number of developments in the experimental analysis of behavior maintained under various schedules of reinforcement. These advances have extended the range of useful consequent events and the specific conditions under which they can be studied.

Several experiments, to be described below, compared the effects of various drugs on responding maintained either by the presentation of food or electric shock. Figure 1 showed that performances maintained by response-produced shock were indistinguishable from those maintained under similar schedules by food, i.v. cocaine administration, or by the termination of a stimulus in the presence of which shock occurred. Although a great deal has already been written about the maintenance of behavior by shock presentation (McKearney and Barrett 1978; Morse and Kelleher 1970, 1977), a few brief summary points are necessary for much of the material that is to follow in this chapter.

Noxious events, such as shock, have typically been used either as punishing stimuli that, when presented, suppress responding or as stimuli that maintain responding by their termination or postponement. However, several studies now indicate that response-produced shock presentation can also maintain responding and that both reinforcing and punishing effects of shock presentation can be obtained in the same organism at the same time (Barrett 1977a, Barrett and Glowa 1977, Kelleher and Morse 1968b, McKearney 1972). Recent experiments have also demonstrated that behavior can be maintained simultaneously under concurrent schedules when one schedule programs response-produced shock and the second consists either of stimulus-shock termination (Barrett and Spealman 1978) or shock avoidance (Barrett and Stanley 1980a). In these studies responses on one lever produced shock; at the same time, responses on a second device, either a lever or chain, were maintained by the postponement of shock or by the termination of the stimulus-shock schedule. Thus, animals were responding to produce a shock that, at the same time, they were also responding to terminate or postpone. Performances maintained under each concurrent schedule were comparable to those obtained when these schedules have been arranged individually.

Taken together, these several findings indicate that the reinforcing or punishing properties of behavioral consequences are not invariant features of an event, but depend on other factors such as the schedule under which that event is presented and the history of the organism. Significantly, these factors not only determine the effects that consequent events have on behavior, but also appear to influence the effects of a variety of drugs. For example, the effects of

amphetamine are different depending on whether responding is suppressed or maintained by shock delivery. Punished behavior is typically decreased by amphetamine, whereas behavior maintained by shock is increased (Barrett 1977b, Hanson et al. 1967, McKearney 1974, McKearney and Barrett 1975). These results reaffirm the view that the schedule can be a critical aspect in determining the effects both of events and of drugs on behavior.

The finding that animals respond to produce shock by no means implies that the physical properties of the shock have changed. The same intensity of shock that increases responding under one condition will continue to suppress performance of the same animal under another condition. It is also apparent that this is not a feat obtained only by means of experimental deceit and that the organisms in these studies are insensitive to the prevailing contingencies. Performances simultaneously maintained under concurrent schedules of shock avoidance and fixed-interval shock presentation, for example, are characteristic of those maintained when these behaviors are studied in isolation, thereby indicating precise differential control by the two schedules in effect.

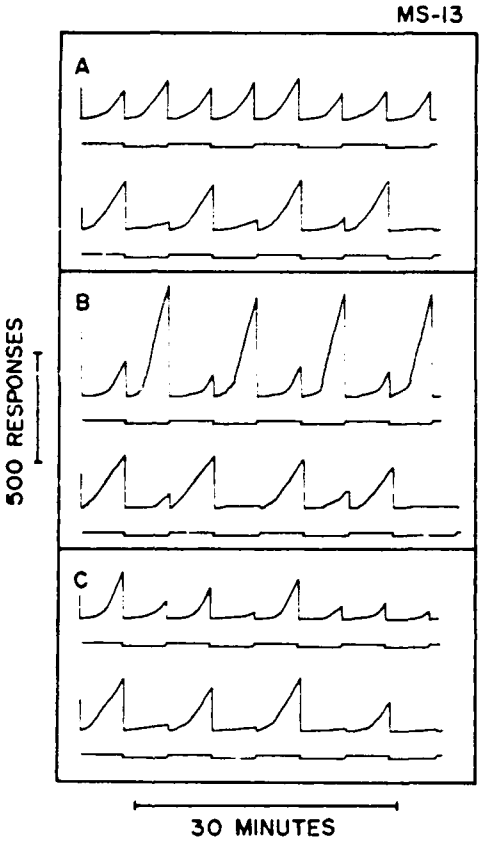
Dual behavioral effects have been found with stimuli other than shock (Spealman 1979, Wise et al. 1976, Woods et al. 1975), indicating that a variety of other consequent events do not have static, immutable behavioral effects. Stimuli have multiple effects on behavior. More extensive investigation of the generality of these effects and an exploration of their implications will undoubtedly provide a more meaningful understanding of processes controlling behavior. Eventually, such efforts may help in clarifying some of the problems involved in apparently anomalous habitual behaviors such as substance abuse.

## DRUG EFFECTS ON BEHAVIOR MAINTAINED BY FOOD, ELECTRIC-SHOCK PRESENTATION AND STIMULUS-SHOCK TERMINATION

Although early experiments did not find differences in drug effects depending on the type of event, more recent studies have reported several instances in which the maintaining event appeared to influence the effects of several drugs on behavior. For example, morphine, methadone, and the narcotic antagonists naloxone and nalorphine decreased responding maintained under 5-minute fixed-interval food-presentation schedules at doses that increased responding comparably maintained by the presentation of an electric shock (McKearney 1974, 1975). Under similar schedule conditions, both amphetamine (McKearney 1974) and cocaine (Barrett 1976) increased responding maintained by these two events. However, appropriate doses of pentobarbital, ethanol, and chlordiazepoxide increased responding maintained by food, while only decreasing responding under shock-presentation schedules (Barrett 1976).

These findings suggested that there were several conditions under which certain drugs appeared to affect similar performances maintained under comparable schedules in an event-dependent manner. Further, as shown in Figure 2, at least the differential effects of

FIGURE 2




*Effects of chlordiazepoxide on different control rates of responding under 5-minute fixed-interval schedules of food or shock presentation. The event pen was deflected downward during the shock-presentation component. The top record of each pair represents control performance and the lower record the effects of chlordiazepoxide. Panel A: top record: comparable rates of responding maintained by food and shock; lower record: effects of 5.6 mg/kg chlordiazepoxide. Panel B: top record: substantially higher control rates of shock-maintained responding; lower record: effects of 17.0 mg/kg chlordiazepoxide. Shock intensity was 4 mA in panels A and B. Panel C: control response rates maintained by food were higher than those maintained by 1 mA shock; lower record shows changes in performance with 17.0 mg/kg chlordiazepoxide. Although control rates of responding maintained by shock differed widely, chlordiazepoxide consistently decreased shock-maintained responding, while responding maintained by food was only increased. (From Barrett 1976. © 1976, American Society for Pharmacology and Experimental Therapeutics)*

chlordiazepoxide appeared to be relatively independent of the control rate of responding maintained by the presentation of food and shock (Barrett 1976).

In subsequent research the effects of several different drugs were studied on comparable rates and patterns of responding of squirrel monkeys maintained under 5-minute fixed-interval schedules by food presentation or by the termination of a stimulus associated with shock (Barrett et al. 1977). Responding under both consequent events was decreased with promazine and increased by d-amphetamine. However, chlordiazepoxide produced effects that depended on the type of event: food-maintained responding was increased at doses that decreased responding under the stimulus-shock termination schedule.

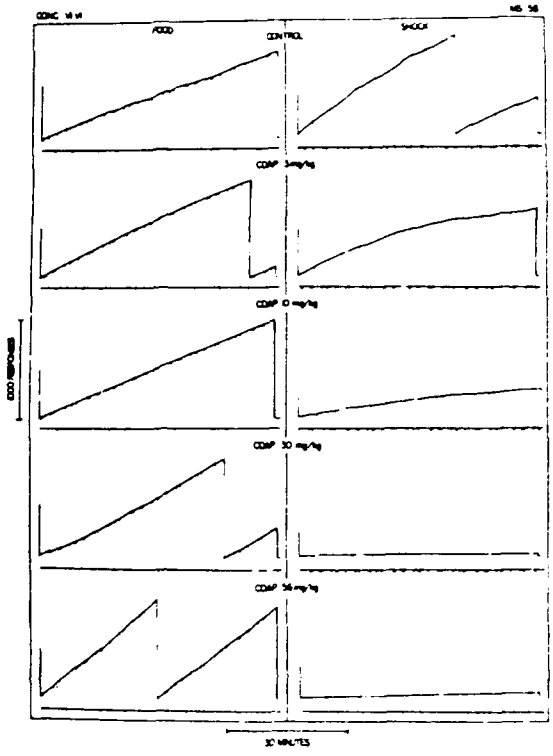
Chlordiazepoxide also differentially affected responding maintained under concurrent variable-interval and concurrent fixed-interval food- and shock-presentation schedules. In these experiments responses on one lever produced shock while responses on a second lever produced food. Despite the fact that these performances were occurring simultaneously, chlordiazepoxide selectively increased responding maintained by food while decreasing that maintained by shock (Barrett et al. 1981c). Figure 3 illustrates this effect under the concurrent variable-interval schedule. Finally, in a recent study with rats, where comparable rates and patterns of responding were maintained under variable-interval food-presentation and shock-cancellation schedules, chlordiazepoxide increased responding maintained by food but decreased responding under the shock-cancellation schedule (Ator 1979).

Evidence indicating that the nature of the event could be a factor determining the effects of certain drugs under interval schedules prompted additional work in which responding was maintained by different events under fixed-ratio schedules. In one experiment similar rates and patterns of responding of squirrel monkeys were maintained under a multiple fixed-ratio 100-response schedule of food presentation or stimulus-shock termination. In contrast to the differential effects found under fixed-interval schedules with these different consequent events, chlordiazepoxide, pentobarbital, and ethanol decreased responding under both fixed-ratio schedules regardless of whether food or stimulus-shock termination maintained responding (Katz and Barrett 1978a).

The finding that the different behavioral effects of drugs are related to the maintaining event under one schedule but not another reaffirmed the importance of schedule factors. In addition, the result that differential drug effects occur under one schedule but not another, implies that unitary motivational accounts of the effects of drugs based simply on the type of consequent event are implausible.

Although only decreases in responding were obtained under the fixed-ratio schedules with pentobarbital, chlordiazepoxide, and ethanol, other experiments have reported increases in responding maintained under fixed-ratio stimulus-shock termination schedules with

FIGURE 3




*Control performances and effects of chlordiazepoxide under concurrent variable-interval schedules of food (1.5 minute) or shock (6 minute) presentation (MS-58). Abscissae: time; ordinates: cumulative responses. Recordings of food-maintained (left panels) and shock-maintained (right panels) responding were made simultaneously. On the records showing food-maintained responding diagonal marks on the upper tracing denote food delivery and the marks on the lower line represent shock delivery. On the records showing shock-maintained responding diagonal marks on the upper tracing denote shock delivery and marks on the lower line represent food delivery. Pens reset to base after 1100 responses. Note that chlordiazepoxide increased responding maintained by food but only decreased responding maintained by shock. (From Barrett et al. 1981c (in press).*

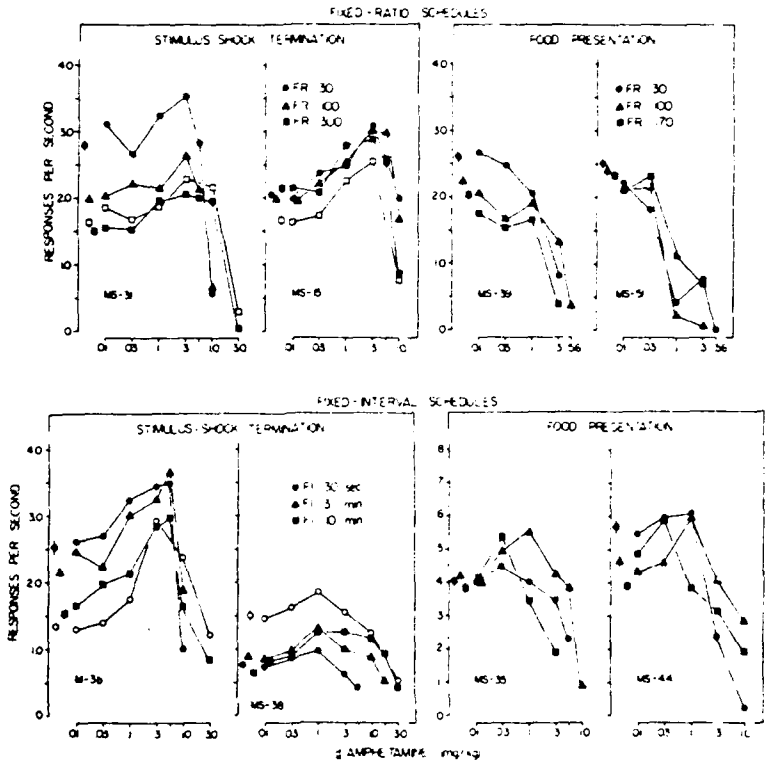
d-amphetamine (Barrett et al. 1981a, Johanson 1978, Katz and Barrett 1978b). Increases in responding maintained by food did not occur with d-amphetamine, however, in those studies that examined these effects under comparable schedules. Since these results differed from those reported earlier by Kelleher and Morse (1964), several other experiments were conducted in which the effects of d-amphetamine were examined under a broad range of fixed-interval and fixed-ratio parameter values, as well as under multiple fixed-ratio fixed-interval schedules (Barrett et al. 1981a). Over a range of fixed-ratio values, from 30 to 300 (30 to 170 for food-maintained monkeys) and a range of response rates from approximately 1.5 to 3.0 responses per second, most doses of d-amphetamine consistently increased responding maintained by stimulus-shock termination, but only decreased responding under the food schedule (figure 4).

Under fixed-interval schedules, however, that were varied from 30 seconds to 10 minutes, and over a range of response rates, d-amphetamine usually increased responding maintained by both food and stimulus-shock termination (figure 4). The differential effects of d-amphetamine on responding under fixed-ratio schedules with different events, but not under the fixed interval, were also found when these schedules were studied together as components of a multiple schedule (figure 5).

These studies suggest quite convincingly that d-amphetamine differentially affects responding maintained by food and stimulus-shock termination under fixed-ratio schedules. Under fixed-interval schedules, however, the effects of d-amphetamine are largely independent of the event that maintains responding. Significantly, the different effects of amphetamine on responding maintained by food and stimulus-shock termination occur over a wide range of parameter values and response rates. The results, therefore, cannot be regarded as being of limited generality; the type of event can play a more significant role than was apparent in early studies.

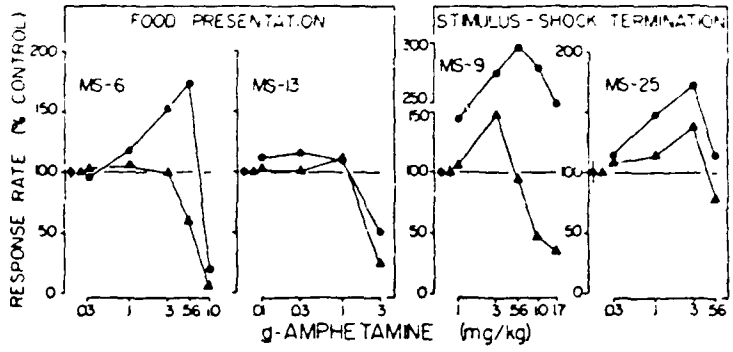
Sweeping generalizations about the relative independence of drug effects and consequent behavioral events are not possible. A number of different drugs have shown effects that depend on the event; the specific outcome, however, depends on the drug, the schedule, and the event. Under some conditions drug effects may also depend on the parameter value of the schedule. For example, figure 6 shows that pentobarbital increased responding under 40-response fixed-ratio schedules of food presentation but not under comparable schedules of stimulus-shock termination (Barrett et al. 1981a); in the study described above (Katz and Barrett 1978a), pentobarbital decreased responding maintained by both events under higher-valued fixed-ratio schedules. Other studies have indicated that drug effects under one component of a multiple schedule can be dramatically modified by changing the parameter value in another component, even when performance in the unchanged component is not affected (Barrett and Stanley 1980b). The conclusion that the event can play an important function in determining the behavioral effects of many drugs is inescapable; the conclusion that such effects are exclusively dependent on the type of event, independent of other factors, however, is clearly

FIGURE 4



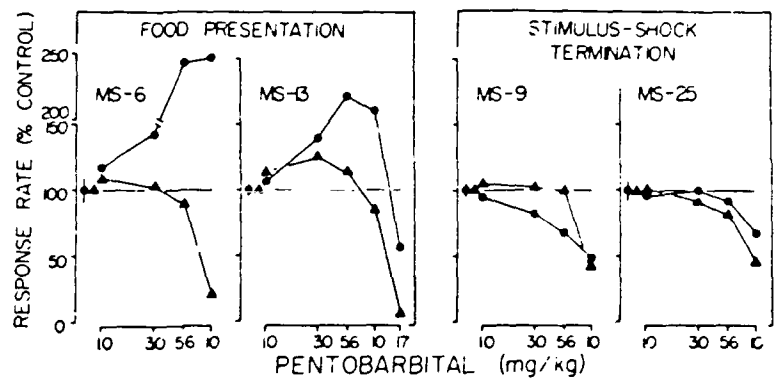

*Effects of d-amphetamine on responding under different parameter values of fixed-ratio (top) or fixed-interval (bottom) schedules of food presentation or stimulus-shock termination. Each point represents the mean usually of at least two determinations. The points on the left represent the mean of control observations ± 1 S.E. Note that at all of the fixed-ratio parameter values studied, d-amphetamine decreased responding maintained by food but markedly increased responding under the stimulus-shock termination schedule. Under the fixed-interval schedules, a broad range of doses of d-amphetamine increased responding under all parameter values of the fixed-interval stimulus-shock termination schedule. Increases in response rate were slightly less or did not occur under the food-presentation schedule at the 30-second value, whereas at the 3- and 10-minute values rates were markedly increased. Note the different ordinates for the two graphs in the lower figure. (Figure from Barrett et al. 1981a)*

FIGURE 5




*Effects of d-amphetamine on responding under a multiple 40-response fixed-ratio 3-minute fixed-interval schedule of food presentation or stimulus-shock termination. Figures shown are percent changes in control rates of responding. Circles denote responding under the fixed-interval schedules, triangles responding under the fixed-ratio schedules. Points with vertical lines on the extreme left of each curve represent control observations ± 1 S.E.; where there are no vertical lines, this measure of variability fell within the area encompassed by the point. Average control rates under the fixed-interval food-presentation schedule were 0.412 and 0.606 responses per second for MS-6 and MS-13, respectively; under the fixed-ratio schedule these rates were 3.799 (MS-6) and 3.651 (MS-13) responses per second. When responding was maintained by stimulus-shock termination schedules, rates under the fixed-interval were 0.651 (MS-9) and 1.605 (MS-25); under the fixed-ratio schedule these rates were 2.303 (MS-9) and 2.339 (MS-25) responses per second. (Figure from Barrett et al. 1981a)*

FIGURE 6




*Effects of pentobarbital on responding under a multiple 40-response fixed-ratio 3-minute fixed-interval schedule of food presentation or stimulus-shock termination. Details are the same as in figure 5. Note that pentobarbital increased responding under both fixed-interval and fixed-ratio schedules of food presentation, but only decreased responding under these schedules when the maintaining event was stimulus-shock termination. (Figure from Barrett et al. 1981a)*

wrong. The same drug will produce similar effects on responding maintained by different events under one schedule, but dissimilar effects under another schedule. Although the findings described in this section suggest that certain modifications are necessary in existing views of the role of the event, they also reaffirm the fundamental importance of schedule-controlled responding in determining the behavioral effects of drugs.

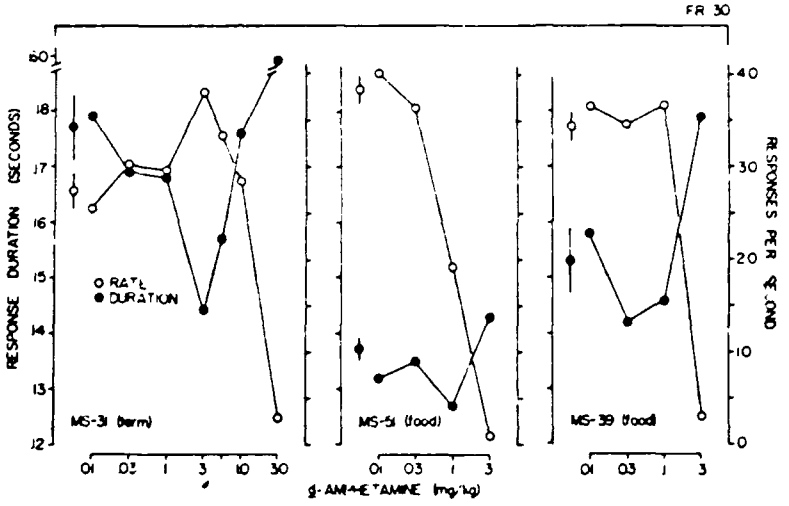
Response Duration and the Effects of d-Amphetamine

The effects with d-amphetamine were unexpected and somewhat difficult to reconcile with earlier work. As reproducible results accumulated and response rate appeared to play a less important role in determining some of these effects (see figures 4 and 5), it seemed reasonable to examine a dimension of the response other than rate. Recordings were made, therefore, of response duration under the 30-response fixed-ratio schedules of food presentation or stimulus-shock termination with squirrel monkeys. Subsequently, the effects of d-amphetamine on both response rate and response duration measures were examined. Figure 7 shows data from these experiments. Average response duration was considerably longer under the stimulus-shock termination (MS-31) schedule than under that maintained by food (MS-51 and MS-39); response rates maintained by food were slightly higher than those maintained by termination of the stimulus associated with shock.

Even though there were initial differences in response duration, the effects of d-amphetamine on this measure under the two schedules were similar: duration decreased at low to intermediate doses (.01-0.1 mg/kg) and increased at the higher doses (0.3-1.0 mg/kg). As in the work described above, however, response rates were affected differentially; sizeable increases in rates occurred under the termination schedule at doses that did not affect or decreased food-maintained responding. Thus, whether differential or comparable effects of d-amphetamine are obtained under fixed-ratio schedules utilizing different consequent events depends on whether the experimental focus is on response rate or response duration. Different conclusions would be drawn depending on which response characteristic was examined. Although response rate has been the traditional measure used in behavioral studies and in behavioral pharmacology, other dimensions may also provide beneficial information. As has been the case with response rate, however, further research would necessarily have to examine conditions where response duration maintained by the different events was comparable or was manipulated over a wide range.

Although these several findings are somewhat difficult to summarize, it clearly appears that the type of maintaining event can influence the specific effects a drug will have on behavior. At the present time it is not possible to provide a general framework within which these several different findings can be easily placed and evaluated. Such problems are often true initially when newer findings do not confirm earlier results. Different events can unquestionably produce different behavioral effects. At the present time it is difficult to determine which, if any, of these multiple effects contribute to

FIGURE 7




*Effects of d-amphetamine on response rate and response duration under fixed-ratio 30-response schedules of stimulus-shock termination (MS-31) or food presentation (MS-51 and MS-33). Note that response duration was longer under the termination schedule than under the food schedules but that at low to intermediate doses this measure decreased for all animals regardless of the maintaining event. Response rates were higher under the food schedules and were not increased with d-amphetamine; responding under the stimulus-shock termination schedule, however, was increased substantially with d-amphetamine. (Figure from Barrett et al. 1981a)*

the differential behavioral effects of drugs. Further experiments addressed to this issue, which may eventually help in formulating general principles, are summarized below.

Second-Order Schedules

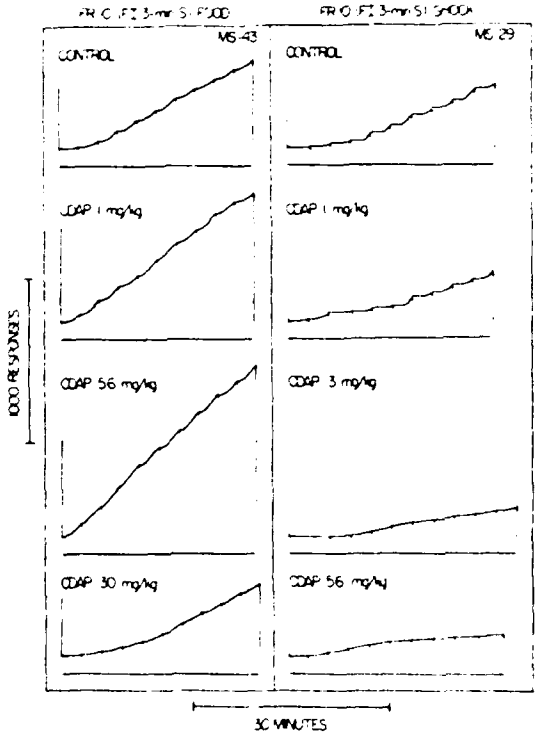
In the experiments described thus far, all of the procedures involved schedules where the completion of each schedule requirement produced the consequent-maintaining event. Within the past ten years several experiments have been conducted in which responding has been maintained by stimuli paired with consequent events such as food or drug administration (Goldberg 1975, Kelleher 1975). Formally termed second-order schedules (Kelleher 1966), such procedures arrange for responding to produce a brief, usually visual, stimulus according to a particular schedule; responding under that schedule is then treated as a unitary response that is then also reinforced according to a specific schedule.

The control performances in figure 8 illustrate characteris rates and patterns of responding of squirrel monkeys under second-order schedules of food or shock presentation [fixed-ratio 10 (fixed-interval 3-minute:S)]. Under these schedules the first response after 3 minutes produced a 3-second change in the color of the visual stimulus illuminating the experimental chamber; after completion of ten fixed intervals, the brief stimulus was followed by the delivery of ten food pellets (MS-43) or ten 8 mA shocks (MS-29). The presentation of food or shock occurred only once, at the end of the complete session. This aspect of arranging the consequent events to occur at the end of the entire session may be particularly advantageous in experiments where one is interested in examining the effects of presession drug administration on drug-maintained responding. It has not always been possible to prevent interactions between the drug given prior to the session and the maintaining drug because of the occurrence of repeated injections throughout the session which were required to maintain performance. Second-order schedules, where responding is maintained by brief stimuli only eventually paired with drug injection at the end of the session, eliminate most direct interactions with the presession drug and provide a convenient means for assessing several experimental issues (see below).

Similar interactions between presession drugs and consequent events could also exist when events other than drugs maintain responding and are presented intermittently throughout the session. For example, during an experimental session in which a drug is given as a pretreatment, the recurrence of shock or food could produce changes in behavior and in drug effects which may differ from those obtained when the maintaining event is presented only once at the end of the session.

Several studies conducted over the past few years have examined these possibilities using second-order schedules of food or shock presentation, stimulus-shock termination, or intramuscular cocaine administration as maintaining events. Figure 8, for example, in addition to depicting performances under second-order schedules of food or shock

FIGURE 8




*Control performances and effects of chlordiazepoxide on responding maintained under second-order schedules of brief stimuli paired with either food or electric shock when those events occurred only at the completion of each daily session. Abscissae: time; ordinates: cumulative responses. The diagonal marks on each record denote the occurrence of the 3-second visual stimulus. The recording pen was reset with the presentation of either food (MS-43, left) or shock (MS-29, right) at the end of the session. Note that chlordiazepoxide increased responding maintained by food but only decreased responding maintained by shock. (From Barrett et al. 1981c (in press). © 1981, American Society for Pharmacology and Experimental Therapeutics)*

presentation, also shows that chlordiazepoxide increased responding maintained under second-order food-presentation schedules but only decreased comparable responding maintained under similar schedules by the presentation of shock (see also dose-effect curves in figure 9). These differential effects are similar to those found under single-component fixed-interval schedules described earlier and suggest that those effects are not influenced substantially by the recurring delivery of food or shock. Together with the effects of chlordiazepoxide on responding maintained under the concurrent variable-interval schedules (figure 3) and under stimulus-shock termination schedules, these several experiments provide rather compelling evidence for the event-dependent effects of chlordiazepoxide on responding maintained under interval schedules of reinforcement.

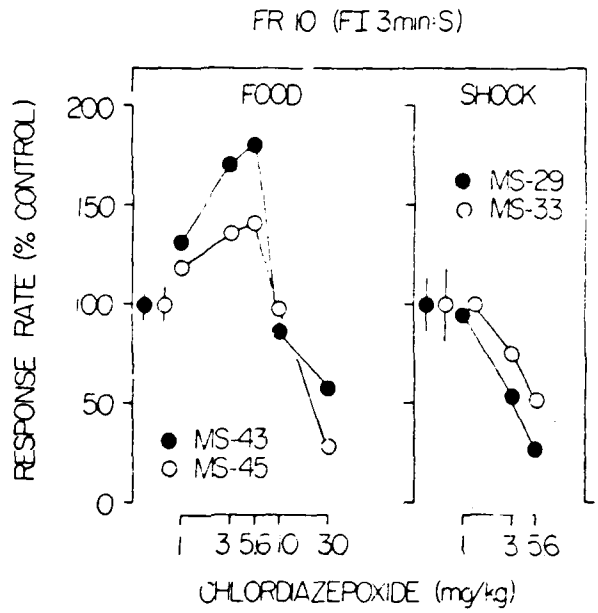
In the studies using basic schedules summarized previously the effects of d-amphetamine under fixed-interval schedules were largely independent of the type of maintaining event. d-Amphetamine also produced similar effects under second-order schedules of food or shock presentation, stimulus-shock termination or intramuscular cocaine administration (Barrett et al. 1981b, Katz 1980). Both promazine (Katz 1980) and chlorpromazine (Valentine et al. 1981) decreased responding under second-order schedules where responding was maintained by food or by intramuscular cocaine administration. Other experiments comparing the effects of drugs on performances maintained by food and drug administration under similar second-order schedules have not typically found differential effects with pentobarbital, cocaine or chlordiazepoxide (Herling et al. 1979; Valentine et al 1981).

These several experiments indicate that, at least thus far, the effects of drugs or behaviors under basic schedules are similar to those obtained when those same events occur under second-order schedules. It is interesting that drugs such as pentobarbital and chlordiazepoxide which produce different effects on responding maintained by food and shock, appear to affect responding maintained by food and cocaine administration in a similar manner. Further experiments that examine a wider variety of different maintaining and pretreatment drugs, as well as different experimental procedures (e.g., termination of a stimulus associated with naloxone administration in morphine-dependent monkeys), will undoubtedly help clarify these issues.

## SUMMARY AND CONCLUSIONS

This chapter has reviewed much of the recent experimental information pertaining to our current understanding of the role of the consequent event as a determinant of the behavioral effects of drugs. Although it appeared at one time that the nature of the consequences controlling behavior were less important than other factors, such as the schedule-controlled rate and pattern of responding, this conclusion no longer seems true. Several experiments described in the preceding sections provide overwhelming evidence that the type of event controlling behavior can be an important aspect of the environment contributing to the behavioral effects of a number of drugs.

FIGURE 9




*Effects of chlordiazepoxide on responding maintained under the FR 10 (FI 3-minute:S) second-order schedules of food (left panels) or shock (right panels) presentation. Abscissae: chlordiazepoxide dose; ordinates: response rate, percent of control. Unconnected points on the left of each panel are means (± 1 S.E.) of at least five control observations. Connected points are means of at least two observations per dose. Note that across the range of doses that increased food-maintained responding, responding maintained by shock was only decreased. (From Barrett et al. 1981c (in press). © 1981, American Society for Pharmacology and Experimental Therapeutics)*

Despite the fact that the event can be an important factor, other features of the behavioral situation such as the schedule under which the event is presented can also play a role. This was clearly seen with d-amphetamine which increased responding maintained by food or stimulus-shock termination under fixed-interval schedules; when these same events controlled responding under fixed-ratio schedules, however, d-amphetamine decreased food-maintained responding but increased responding maintained under the termination schedule. Differential effects were also obtained with chlordiazepoxide under fixed-interval but not fixed-ratio schedules. These findings point to the increasing level of complexity involved in behavioral pharmacology as progress is made in attempting to characterize determinants of the behavioral effects of drugs.

It has been clear for some time that environmental factors can play an exceedingly influential role in determining the effects of a wide variety of abused drugs. Environmental factors also exert tremendous control over behavior and unquestionably influence its distinctive nature. Many of the factors that are responsible for the subtle idiosyncratic characteristics of behavior, as well as its more global features, can be traced directly to the interaction of behavior with the environment. Ongoing and newly emerging behavior has inevitable consequences which not only affect that behavior directly and immediately, but also that of future behavior as well.

Drugs of abuse also produce extremely powerful effects on behavior. It is significant that many of the variables that control behavior also determine the behavioral effects of drugs. This natural reciprocity between the study of behavior and the behavioral effects of abused drugs is beneficial because research on drug abuse advances knowledge in both fields. Despite the fact that the effects of drugs on ongoing behavior represent a vast integration of changes occurring at several different levels, many of the principal determinants of the behavioral effects of abused drugs can be attributed directly to specific aspects of the environmental conditions under which that behavior has occurred or is occurring. It has been shown repeatedly that the same drug can have completely opposite effects on behavior depending on any of several influential environmental variables.

An emphasis on the clarification and significance of environmental variables, such as the role of the maintaining event, in attempting to understand the behavioral effects of abused drugs is not meant to deny or negate the importance of other factors. Changes in behavior produced by drugs, however, are often most conspicuous because of the excessive nature, intensity,and disruption that typically occurs. Drugs of abuse produce a variety of pharmacological effects that are usually physiologically consistent. Yet, at the level of behavior, there are often noteworthy discrepancies, particularly in what seems to be a drug's abuse potential. Many abused drugs, for example, produce marked uniform effects on psychomotor activity, physiological and sensory processes that are reasonably consistent from individual to individual. However, many of these drugs are not ubiquitously abused nor do they produce entirely uniform behavioral effects. This suggests that perhaps many of the changes in

behavior produced by drugs of abuse, as well as a drug's abuse liability, may be related more directly to environmental than to pharmacological variables. Future research will hopefully identify and provide a balanced account of the importance and generality of both environmental and pharmacological determinants of the behavioral effects of abused drugs.

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# Predicting the Dependence Liability of Stimulant Drugs

Roland R. Griffiths, Ph.D., Joseph V. Brady, Ph.D., and George E. Bigelow, Ph.D.

Over the last 15-20 years, methods have been developed and refined for examining the self-administration of drugs by animals (e.g., Spealman and Goldberg 1978, Griffiths et al. 1980). One interesting issue which can be addressed with these methods involves differentiating between drugs with respect to their relative efficacy in maintaining self-administration. Initial interest in this scientific pursuit was stimulated when it was recognized that there is a good correspondence between those drugs self-administered by laboratory animals and those abused by man. In 1970, interest was further augmented when Congress passed the Controlled Substances Act which required that drugs be classified under a five-tier schedule system which differentiated between drugs on the basis of several criteria, including their actual or relative potential for abuse.

This paper will review animal drug self-administration methods and describe their usefulness in providing information about the dependence liability of psychomotor stimulant drugs. Specifically, animal self-administration results with a wide range of psychomotor stimulants will be reviewed (section I), and approaches for measuring the relative reinforcing efficacy of different drugs in animals will be described (section II). A third section will discuss the relationship between the reinforcing and anorectic properties of appetite suppressant drugs. The final section will discuss the correspondence of the animal drug self-administration results to clinical information relevant to human drug abuse.

## I. SELF-ADMINISTRATION OF PSYCHOMOTOR STIMULANTS BY ANIMALS

The most common and reliable procedure for determining whether a drug will maintain self-administration is the substitution procedure (Johanson and Balster 1978). The procedure involves establishing self-administration using a dose of a standard drug which is known to maintain reliable self-administration behavior. After this behavior baseline has stabilized, a dose of the test drug is substituted for the standard compounds to determine whether the test drug will maintain self-administration.

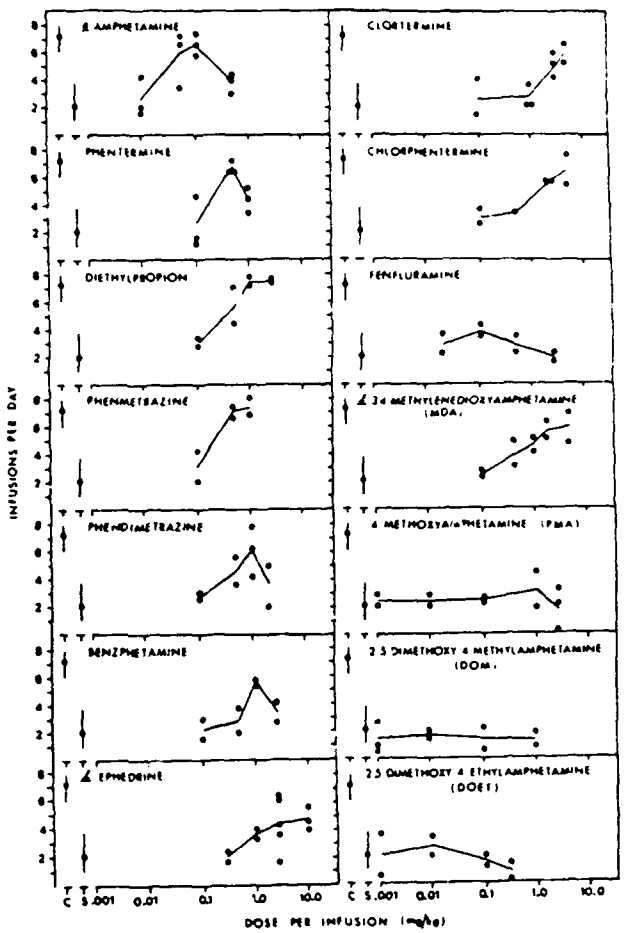
Using this basic approach, our laboratory has examined the intravenous self-administration of a range of psychomotor stimulants and structurally related compounds (Griffiths et al. 1976, Griffiths et al. 1979b). These studies were conducted with male baboons weighing 15-24 kg and having histories involving self-infusion of a variety of drugs.

The availability of an intravenous infusion was indicated by a 5-sec tone and illumination of a light directly over a lever on the intelligence panel. When the light was illuminated, each response produced a brief feedback tone. Upon completion of a 160-response fixed-ratio schedule requirement (FR 160), the light over the lever was extinguished and the drug infusion began. Also at this time a light was illuminated in the upper left-hand corner of the intelligence panel for a 1-hr period. A time-out period of 3 hrs followed each infusion, permitting a maximum of eight infusions per day.

Self-infusion performance was first established with cocaine at a dose of 0.4 mg/kg per infusion. After a minimum of 3 consecutive days of cocaine availability during which six or more infusions were taken each day a specified dose of a test drug or saline was substituted for the cocaine. Self-administration testing involved access to the test drug for at least 12 days. After exposure to each dose of test drug, cocaine was reinstated, and when the criterion of a minimum of 3 consecutive days of six or more infusions per day had been met, another dose or drug was again substituted. This procedure of replacing cocaine with a test drug was continued throughout the experiment. The order of exposure to drugs, saline, and different doses was mixed.

Figure 1 presents mean levels of self-infusion for the 14 phenylethylamines. Of 11 the drugs examined, d-amphetamine was the most potent, maintaining levels of self-administration above saline at doses of 0.05 and 0.1 mg/kg. Phentermine, diethylpropion, phenmetrazine, phendimetrazine, benzphetamine, and MDA all maintained levels of self-administration above saline at doses of 0.5 or 1.0 mg/kg. ℓ-Ephedrine, clortermine, and chlorphentermine were the least potent of the drugs which maintained performance, supporting self-infusion rates above saline control levels at doses of 3.0 and 10.0 mg/kg (ℓ-ephedrine), 3.0 and 5.0 mg/kg (clortermine), and 2.5 and 5.0 mg/kg (chlorphentermine). In contrast to most of the other phenylethylamines which maintained self-infusion behavior, the pattern of self-administration with ℓ-ephedrine was particularly unstable, characterized by either an erratic or cyclic pattern over days. Finally, in contrast to all of the other phenylethylamines tested, fenfluramine, PMA, DOM, and DOET were not self-administered at a level greater than saline at any of the doses studied (means of the determinations at each dose did not exceed the range of saline values). Three animals exposed to 1.0 mg/kg per infusion of DOET died within the first three days.

FIGURE 1




Average number of infusions per day with 14 phenylethylamines. Intravenous infusions were delivered upon completion of 160 lever presses; a 3-hr time-out followed each infusion, permitting a maximum of eight infusions per day. C indicates mean of all the 3-day periods with cocaine which immediately preceded every substitution of a phenylethylamine or saline. S indicates mean of days 8-12 after substitution of saline (two saline substitutions in each of 15 animals). Brackets indicate ranges of individual animals' means. Drug data points indicate mean of days 8-12 after substitution of a drug for individual animals. Lines connect means at indicated doses of drug. (From R.R. Griffiths, J.V. Brady and L.D. Bradford. In: Thompson, T. and Dews, P.B., eds. Advances in Behavioral Pharmacology. Vol. 2. New York: Academic Press, 1979. pp. 163-208. Reprinted by permission.)

Figure 2 shows mean levels of self-infusion for three additional central nervous system stimulant compounds which are not phenylethylamines: cocaine, caffeine, and nicotine. Cocaine maintained high levels of self-infusion performance through a broader range of doses than any of the 16 other drugs tested (0.032-3.2 mg/kg). Figure 2 shows that mean levels of self-infusion of both nicotine and caffeine were within the saline control range. Inspection of the day-to-day data revealed that the caffeine dose of 3.2 mg/kg was sometimes associated with variable daily patterns of self-administration.

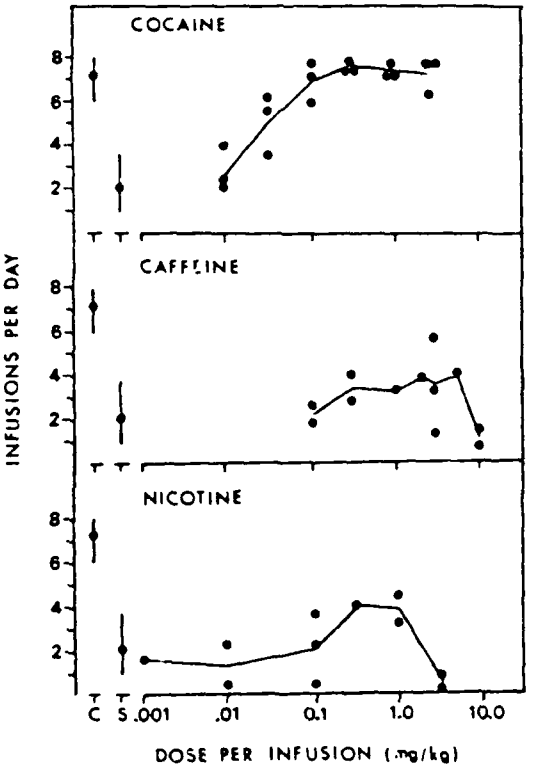
The preceding findings are derived from one specific drug substitution procedure. Obviously in such self-administration testing, many methodological variations are possible. The overall reliability of animal drug self-administration testing is indicated by the replicability of results across a range of methodological and procedural variations. Assessments of drug self-administration have been conducted using different species, routes of administration, response requirements, durations of availability, behavioral or pharmacological histories, etc. with remarkably consistent results. For example, a comprehensive review of published studies with psychomotor stimulants (Griffiths et al. 1979b) indicated there were 36 published experiments across five different species and three different routes of administration, in which d-amphetamine maintained self-administration, whereas there was only one published report which described a failure to obtain self-administration. This same replicability across published studies holds true for drugs which do not maintain self-administration. For instance, with fenfluramine, eight different studies in three different species uniformly failed to demonstrate self-administration.

Data from drug self-administration testing provide information for making the relatively dichotomous discrimination about whether or not a drug maintains self-administration. Table 1 summarizes the results of a large number of studies of psychomotor stimulant drug self-administration in animals (Griffiths et al. 1980). Drugs were selected for inclusion in the table if they had been available through licit or illicit channels for human use or abuse. Maintenance of self-administration by each drug in the table was rated as "yes," "no," or "equivocal," based on the conclusions of the published reports. Drugs were also rated as maintaining "equivocal" self-administration if different studies reported conflicting results.

## II. ASSESSING THE RELATIVE REINFORCING EFFICACY OF DRUGS IN ANIMALS

Data from substitution procedures such as that described above for the phenylethylamines permit a relatively gross discrimination about whether or not a drug will serve as a reinforcer. In recent years increasing experimental attention has been directed toward developing more sensitive drug self-administration procedures to make more refined and graded discriminations of the relative reinforcing efficacy of different drugs. Behavioral procedures for

FIGURE 2




Average number of infusions per day with cocaine, caffeine, and nicotine. Details of figure identical to Figure 1. (From R.R. Griffiths, J.V. Brady and L.D. Bradford. In: Thompson, T. and Dews, P.B., eds. Advances in Behavioral Pharmacology. Vol. 2. New York: Academic Press, 1979b. pp. 163-208. Reprinted by permission.)

TABLE 1

Summary of Results from Animal Drug Self-Administration Studies

| | Drug Self-Administration | | |
|---|---|---|---|
| | NO | EQUIVOCAL | YES |
| Psychomotor Stimulants (and structurally related compounds) | | | |
| amphetamine | | | X |
| benzphetamine | | | X |
| clortermine | | | X |
| cocaine | | | X |
| diethylpropion | | | X |
| ephedrine | | | X |
| mazindol | | | X |
| methylamphetamine | | | X |
| methylphenidate | | | X |
| phendimetrazine | | | X |
| phenmetrazine | | | X |
| phentermine | | | X |
| caffeine | | X | |
| chlorphentermine | | X | |
| nicotine | | X | |
| fenfluramine | X | | |
| pemoline | X | | |
| phenylpropanolamine | X | | |

assessing the relative reinforcing efficacy of drugs are derived from procedures which have been used for evaluating the behavior-maintenance properties (i.e., reinforcing properties) of a variety of environmental stimuli (e.g., food, water, drugs, etc.). Observed variation in this performance-maintenance property has been assumed to reflect the "strength," "efficacy," or "value" of stimuli as reinforcers, although the hypothetical status of such intervening processes requires interpretative caution (as discussed in detail by Griffiths et al. 1979b).

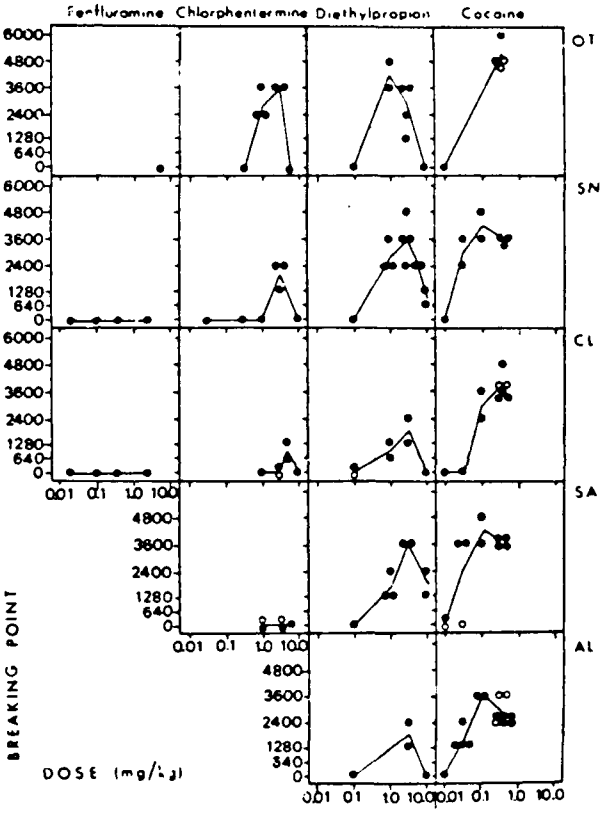
Comparison of Different Cocaine Doses: In a variety of studies, methods that may assess relative reinforcing efficacy have been used to examine the effects of a range of cocaine doses. In spite of wide procedural differences, a clear generalization has emerged from this research: higher doses of cocaine are associated with higher measures of reinforcing efficacy than lower doses, except that doses exceeding 0.1 or 0.5 mg/kg are usually shown to be equally reinforcing. This relationship has been demonstrated with discrete-trial choice procedures (Johanson and Schuster 1975, Brady and Griffiths 1977), concurrent schedules (Iglauer and Woods 1974, Llewellyn et al. 1976), fixed-interval schedules (Balster and Schuster 1973, Goldberg and Kelleher 1976, Bradford and Griffiths 1980), second-order schedules (Kelleher and Goldberg 1977), progressive-ratio schedules (Yanagita 1973, Bedford et al. 1978, Griffiths et al. 1978a, 1979a), and fixed-ratio schedules (Griffiths et al. 1979a).

Comparison of Different Drugs: Fewer studies have attempted to compare the reinforcing efficacy of different stimulant drugs (Yanagita 1973, Griffiths et al. 1975, Griffiths et al. 1978a, Johanson and Schuster 1975, 1977). One study (Griffiths et al. 1978a) used a progressive-ratio schedule for comparing performance maintained by cocaine and three amphetamine derivatives (diethylpropion, chlorphentermine, and fenfluramine) over a substantial range of doses. Infusions of drug were contingent upon completion of a FR response requirement, with a 3-hr time-out period following each infusion. Prior to testing each dose of drug, stable self-infusion performance was first established with cocaine when the FR requirement was 160. Subsequently, a test dose of drug was substituted for the standard dose of cocaine. If the dose of drug maintained a criterion level of self-infusion performance, the ratio requirement was systematically increased every day until the "breaking point" at which the self-infusion performance fell below a criterion level (one or zero infusions per day). A breaking point was defined as the ratio value at which criterion performance disruption occurred.

Figure 3 shows the results in five baboons. Within-animal comparison of the maximum breaking points maintained by the different drugs indicates that cocaine maintained the highest breaking points, followed in order by diethylpropion, chlorphentermine, and fenfluramine. More specifically, within-animal comparison of the data presented in Fig. 3 reveals doses of cocaine that maintained higher average breaking points than all the doses of diethylpropion,

chlorphentermine, and fenfluramine tested. Similarly, there were doses of diethylpropion that maintained higher average breaking points than all doses of chlorphentermine and fenfluramine; and finally, there were doses of chlorphentermine that maintained higher average breaking points than all doses of fenfluramine.

FIGURE 3




Breaking point values for doses of fenfluramine, chlorphentermine, diethylpropion, and cocaine in 5 baboons. Each point represents a single breaking point observation. Lines connect the means of the breaking point observations at different doses of drug. Closed circles indicate data obtained during the first exposure to a drug dose. Open circles indicate data obtained during a second exposure to a drug dose. (From: R.R. Griffiths, J.V. Brady and J.D. Snell. Psychopharm. 56:5-13, 1978a. Reprinted by permission. © Springer-Verlag New York, Inc.)

Johanson and Schuster (1977) provided additional information about several of these same compounds in a study which examined drug choice performance in rhesus monkeys. Using a two-lever discrete trial choice procedure, these investigators compared cocaine (0.1 and 0.5 mg/kg) and diethylpropion (0.5 and 1.0 mg/kg), and showed that cocaine was generally preferred to diethylpropion. These results are compatible with the previously cited progressive-ratio study, and suggest that, under these conditions, cocaine is a more efficacious reinforcer than diethylpropion.

## III. ASSESSMENT OF THE RELATIONSHIP BETWEEN ANORECTIC AND REINFORCING PROPERTIES OF APPETITE SUPPRESSANT DRUGS

The previous sections have focused on the reinforcing properties of stimulant drugs. It has been argued that a balanced assessment of dependence liability should not consider the reinforcing properties of a drug independently of the therapeutic properties; rather, it is important to consider the relationship between the reinforcing properties and therapeutic properties. Knowledge about this relationship provides information about the extent to which therapeutic applications of a drug will necessarily involve exposure to the drug's reinforcing effects (Griffiths et al. 1979b).

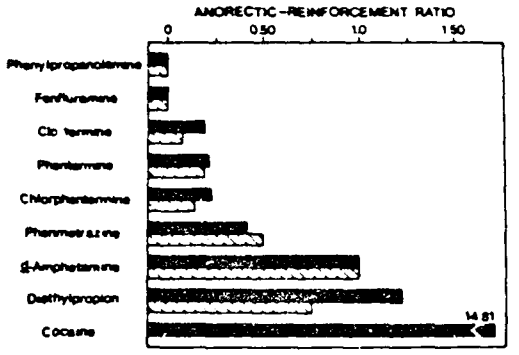
Using baboon drug self-administration data Griffiths et al. (1978b) developed a quantitative measure of this relationship between the reinforcing and therapeutic properties of a series of anorectic compounds. It was reasoned that, in terms of minimizing dependence liability, the most desirable anorectic drug would be more potent as an anorectic than as a reinforcer; while an undersirable anorectic drug would be more potent as a reinforcer than as an anorectic. Existing anorectic drugs may fall anywhere on the continuum defined by these parameters. A quantitative measure of this continuum is provided by the anorectic-reinforcement ratio which compares the relative potency of a drug as an anorectic with its relative potency as a reinforcer (Griffiths et al. 1978b).

A standardized drug self-administration substitution procedure with baboons (Griffiths et al. 1976) similar to that described in an earlier section of this chapter was used to determine the lowest drug dose which maintained intravenous self-administration above saline control levels. This dose provided the denominator for calculation of the anorectic-reinforcement ratio. A measure of anorectic effects in the baboon was also obtained by determining the dose of drug which suppressed daily food intake to 50% of control levels. This dose provided the numerator for calculation of the anorectic-reinforcement ratio.

The filled bars of Figure 4 show the resulting anorectic-reinforcement ratios (based upon adjustment to an arbitrarily assigned d-amphetamine value of 1.0) derived from the relationship between food suppression dose (numerator) and lowest reinforcing dose (denominator) for each of nine drugs. The ratio values range from a low of zero for fenfluramine and phenylpropanolamine to a a high of 14.81 for cocaine, and reflect the fact that compounds

with high ratio values are more potent reinforcers (relative to their anorectic potency) than compounds with lower ratio values.

FIGURE 4




*Anorectic-reinforcement ratios for cocaine and eight anorectic drugs. Filled bars show data derived entirely from baboon experiments. Striped bars show data derived from both human clinical information and baboon experiments. Compounds with high ratio values are more potent reinforcers (relative to their anorectic potency) than compounds with lower ratio values. (From: R.R. Griffiths, J.V. Brady, and L.D. Bradford. In: Thompson, T., and Dews, P.B., eds. Advances in Behavioral Pharmacology. Vol. 2. New York: © Academic Press, 1979b. pp. 163-208. Reprinted by permission.)*

Since the measure of anorectic potency as determined with the baboon could be confounded by nonspecific psychopharmacological effects such as drug-induced sensory or motor decrements, an alternative set of values was derived by utilizing as the ratio's numerator the lowest recommended daily human anorectic doses. This alternative method of calculation provided a comparative set of ratio values. Comparison of the striped bars vs. the filled bars in Figure 4 shows the correspondence between the ratios based upon these two independent measures of anorectic potency. Since cocaine is not used clinically as an anorectic, no striped bar appears in the figure for cocaine.

## IV. CORRESPONDENCE OF ANIMAL DRUG SELF-ADMINISTRATION RESULTS TO CLINICAL INFORMATION

Relationship Between Animal Data and Human Drug Abuse: In general, there is a good correspondence between those drugs self-administered by laboratory animals and those abused by man. This section will involve a discussion of self-administration results summarized in Table 1 in relation to subjective-effect information obtained in clinical studies, and in relation to the incidence of clinical

case reports describing abuse obtained from thorough reviews of the literature (Griffiths et al. 1979b; Griffiths et al. 1980).

Amphetamine, diethylpropion, cocaine, methylamphetamine, methylphenidate, and phenmetrazine are all associated with numerous clinical case reports involving abuse. Furthermore, all of these drugs plus benzphetamine and *l*-ephedrine have been evaluated on subjective-effect questionnaires (Addiction Research Center Inventory, ARCI) in drug abuser subjects and have been shown to produce a similar constellation of "euphoric" effects presumed to reflect abuse potential. This information concerning the abuse and subjective effects of these drugs corresponds with the fact that all of these drugs maintain self-administration in animals, as shown in Table 1.

In contrast, Table 1 shows that neither phenylpropanolamine nor fenfluramine maintained self-administration in animals. This corresponds well to the available clinical information about these anorectic phenylethylamines. Both of these drugs are associated with a relatively low incidence of abuse. There are no reports of human abuse of phenylpropanolamine in spite of its wide availability as a nonprescription anorectic sold on an over-the-counter basis. There have been only two reports describing the nonmedical misuse of fenfluramine, and in both instances, the drug was apparently used for its hallucinogenic effects. As discussed elsewhere (Griffiths et al. 1979b), animal drug self-administration does not provide accurate predictive information about hallucinogens. Furthermore, fenfluramine was evaluated on questionnaire ratings and the ARCI, and produced a subjective-effect profile which was unlike that produced by amphetamine and which has been interpreted to indicate dysphoria.

Table 1 shows that chlorphentermine is associated with equivocal self-administration in animals which indicates that chlorphentermine is a less robust reinforcer than drugs such as cocaine, amphetamine, and phenmetrazine. Available information about chlorphentermine provides no basis for differentiating this drug from fenfluramine or phenylpropanolamine: the incidence of case reports involving abuse is extremely low, and evaluation of subjective and objective effects indicated that the drug was dissimilar to amphetamine.

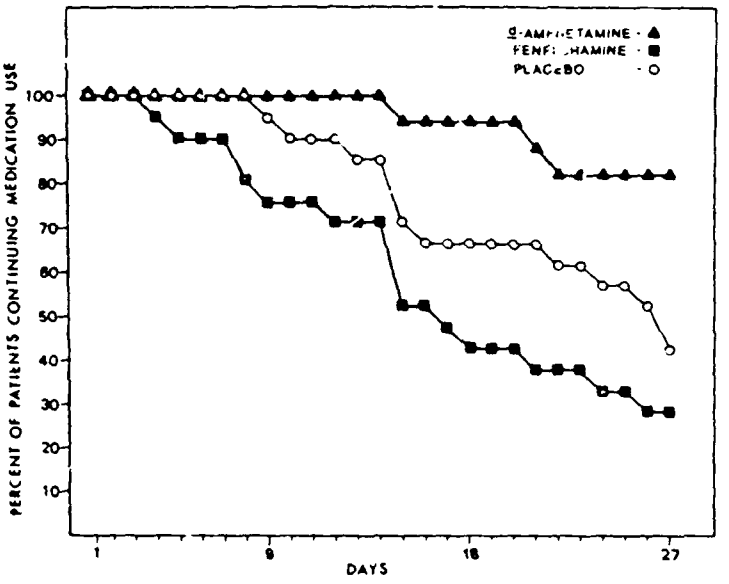
Table 1 also indicates that both caffeine and nicotine produce only equivocal self-administration in animals, indicating that these drugs are less robust reinforcers than some of the other drugs listed. This finding does not adequately predict the fact that human self-administration and dependence on these compounds are ubiquitous. It seems probable that wide social acceptance and availability of these compounds are responsible for greatly potentiating their use and abuse.

Finally, Table 1 shows that pemoline is not self-administered by laboratory animals. This information corresponds to the fact that

there are relatively few clinical case reports describing its abuse as a psychomotor stimulant.

Relationship Between Animal and Human Drug Self-Administration Data: The preceding discussion describes the relationship between the animal self-administration results and existing clinical and experimental information about the abuse and subjective effects of the psychomotor stimulants. There have been several recent experimental reports which have directly examined the human self-administration of several psychomotor stimulants. In a study by Bigelow et al. (1980), human self-administration of d-amphetamine, fenfluramine, and placebo were compared under double-blind conditions in the context of an outpatient weight-control program. Overweight women were randomly assigned to a medication group and given substantial self-control over the amount of anorectic medication they could take over a four-week period while enrolled in a behavioral self-management treatment program for overweight. The medication groups differed in the persistence of drug self-administration. Figure 5 shows the percentage of patients in each drug group who continued to use their assigned medications over consecutive days.

FIGURE 5




Human self-administration of d-amphetamine, fenfluramine and placebo over consecutive days. Subjects were overweight women enrolled in an outpatient weight-control program and randomly assigned to a medication group: d-amphetamine (N = 17), fenfluramine (N = 21), placebo (N = 21). Use of d-amphetamine was significantly better maintained than use of fenfluramine. (From: R.R. Griffiths, L.E. Bigelow and J.E. Henningfield. In: Mello, N.K. ed. Advances in Substance Abuse. Greenwich, Conn.: JAI Press, Inc., 1980. pp. 1-90. Reprinted by permission.)

Patients were considered to have continued medication use through the day they took their last dose, even if they had temporarily suspended use prior to that time. Fenfluramine use fell off most rapidly; placebo use fell off next most rapidly; and d-amphetamine use was most strongly maintained. Statistical comparison revealed that the mean duration of d-amphetamine use was significantly longer than that for placebo, and that the mean duration of fenfluramine was significantly less than that for placebo. Other recent studies by Johanson and Uhlenhuth (1978, 1980) have described human self-administration of the psychomotor stimulants d-amphetamine and diethylpropion. On three days each week, normal volunteers, who were blind to the type of drug available, were permitted to choose between differently colored capsules containing placebo or various doses of drug. The results showed that subjects generally preferred the psychomotor stimulant drugs to placebo on the majority of trials. As with the other clinical and experimental information about abuse and subjective effects, the results of these three human drug self-administration studies correspond to the animal drug self-administration results by demonstrating that both d-amphetamine and diethylpropion maintain higher levels of self-administration than placebo in contrast to fenfluramine which does not maintain self-administration above placebo levels.

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# Establishment of Orally Delivered Drugs as Reinforcers for Rhesus Monkeys: Some Relations to Human Drug Dependence

Richard A. Meisch, M.D., Ph.D., and Marilyn E. Carroll, Ph.D.

The study of drug-seeking behavior in laboratory animals was made possible by the development of techniques that permit an animal to intravenously self-administer drugs (Deneau et al. 1969, Thompson and Schuster 1964, Weeks 1961). These intravenous techniques have been used in many subsequent studies; on the other hand, the oral route has not often been used. Over the last 10 years, procedures have been devised that result in orally delivered drugs serving as reinforcers (Meisch 1975; Samson and Falk 1974).

A major problem in studies of oral drug intake is that animals reject most drug solutions, probably because they have an aversive taste. One way to overcome this problem has been to induce the drinking of large volumes of water and then to substitute drug solutions at low concentrations for the water. Specifically, in the initial studies water drinking was induced by intermittent delivery of food pellets to food-deprived rats. When water was replaced by ethanol solutions, the rats drank large amounts of ethanol (Falk et al. 1972; Freed et al. 1970; Holman and Myers 1968; Meisch and Thompson 1971; Senter and Sinclair 1967). When deliveries of food pellets were discontinued, water drinking diminished, whereas ethanol drinking persisted at rates that far exceeded water drinking (Freed et al. 1970; Meisch and Thompson 1971). Thus, ethanol was functioning as a reinforcer. Results of subsequent studies demonstrated that several different procedures could be used to establish ethanol as a reinforcer (Meisch 1975). This research has been extended to rhesus monkeys (Meisch et al. 1975) and to other drugs (Carroll and Meisch 1978, 1979a,b, 1980b; Meisch and Stark 1977).

In the last three years orally delivered etonitazene, pentobarbital, and phencyclidine have been established as reinforcers for rhesus monkeys (Carroll 1981; Carroll and Meisch 1978, 1980b; Meisch et al. 1981). The procedures used in these studies were derived from procedures used in the earlier studies.

This paper concerns features common to the procedures used to establish orally delivered drugs as reinforcers and variables that control drug-reinforced behavior. Some implications of these results for an analysis of human drug dependence are mentioned.

## METHODS

### Animals

Male adult rhesus monkeys (Macaca mulatta) are housed in individual experimental chambers. The monkeys are reduced to and maintained at 70 to 85 percent of their free-feeding weights.

### Apparatus

Stainless steel primate cages (Labco #ME 1305 or Hoeltge #HB-108) with three solid walls and one barred wall serve as the experimental chambers. A response lever for food, a drinking spout, and corresponding stimulus lights are mounted on one solid wall. A red stimulus light, 14 cm above the food lever, is illuminated when food is available. One-g Noyes banana-flavored pellets are delivered to a small tray recessed in the wall beneath the food lever. The drinking spout is electrically nonconductive, 1 cm in diameter, and protrudes 2.7 cm into the cage. A small brass contact plate (0.5 cm in diameter) is recessed 1 cm from the tip of the spout and is wired to a lip-sensitive drinkometer. A lip contact activates a solenoid for a maximum duration of 0.25 sec, thereby delivering approximately 0.5 ml of liquid through the spout. A break in lip contact during liquid delivery immediately terminates solenoid operation; this arrangement prevents spillage. Lip contact with the brass plate on the spout results in illumination of one of two pairs of stimulus lights. The lights are mounted at the 2, 4, 8, and 10 o'clock positions on a 3.2 cm radius measured from the center of the drinking spout. Each light within a pair is 180 degrees from the other light. The white pair of lights is illuminated for the duration of each lip contact response when water is present; the green pair of lights is illuminated for the duration of a response when the drug is present. In addition to the two pairs of feedback lights, a larger yellow light is 9 cm above the drinking spout. This light is illuminated when water is available during sessions and intersessions, and it blinks at a rate of 10 Hz when drug is available. Liquids are contained in covered stainless steel reservoirs. There is no measurable evaporation. Solid state equipment or computers for scheduling and recording events are located in an adjacent room. Details concerning the apparatus, control equipment and drinking devices have been presented elsewhere (Carroll et al., 1981b; Henningfield and Meisch 1976a; Meisch and Henningfield 1977).

## Procedure

Food-induced drinking of water. Daily sessions are 3 hours in length and are preceded and followed by a 1-hour stimulus blackout so that data can be recorded and liquids changed. Water is continuously available via the drinking spout during the remaining 19 hours.

Water deliveries occur under a fixed-ratio 1 schedule (FR 1); that is, each lip-contact response produces one delivery of approximately 0.5 ml of water. Initially, water intake during the sessions is measured in the absence of within-session food availability; the daily food ration is given during the 19-hour intersession period. Subsequently, access to food is shifted to the beginning of the second hour of the 3-hour session. Food availability is signaled by illumination of a light above the food lever. In the presence of the food light, lever presses produce food pellets according to various schedules. An FR 1 schedule was used with pentobarbital and a DRL (Differential Reinforcement of Low Rates) 30 sec was used with etonitazene and phencyclidine. After the fixed number of pellets is obtained, the food light is turned off.

During the 3-hour session, each lip-contact response results in water delivery. After water drinking is stable for five consecutive sessions, water is replaced by a low drug concentration (e.g., 0.0078 mg/ml of sodium pentobarbital). In all experiments behavior is judged stable when visual inspection of the data reveals no systematic trends in either the rate or pattern of responding over five consecutive sessions.

Increases in drug concentration are made by doubling the concentration. Each concentration is presented until five sessions of stable behavior are obtained.

Termination of access to food within sessions. Access to food within sessions is permanently terminated either when drinking becomes dissociated from eating (e.g., drinking during the first hour of the session) or when drinking results in pronounced effects (e.g., severe ataxia). When access to food within sessions is stopped, the maintenance feedings of food are given at least 1 hour after the session.

Increases in fixed-ratio size. After drug intake is stable in the absence of inducing conditions (i.e., food available during the session) the fixed-ratio size is gradually increased. Fixed ratios are increased in the sequence FR 1, 2, 4, 8, ....

Comparisons of drug- and water-maintained behavior. Rates of drug responding are compared with rates of vehicle (water) responding either by substituting water for drug solutions or by making water concurrently available via a second drinking spout. When water is concurrently available, the locations of the drug and water are reversed from session to session to control for possible side preference.

Effects of drug concentration. Drug concentrations are presented in either an increasing (e.g., ethanol) or decreasing (e.g., etonitazene, pentobarbital) series of concentrations. Each concentration is present until five sessions of stable behavior are obtained.

Effects of food deprivation and satiation. Drug and water sessions occur on alternate days. After 10 sessions of stable behavior (5 drug and 5 water sessions), the food-deprived monkeys are satiated by rapidly increasing the amount of food available between sessions until not all available food is consumed. This phase lasts for 30 sessions. The monkeys are again food deprived.

RESULTS

Acquisition

Water drinking. During 3-hour sessions in which only water is available, food-deprived rhesus monkeys usually drink less than 150 ml. The water drinking occurs in an irregular pattern.

In the next phase, the daily food allotment is made available within the session either intermittently or in a single meal. Both ways of presenting food generate substantial water drinking that ranges among monkeys from 300 to 1000 ml per session. When food pellets are presented intermittently, a pattern of schedule-induced drinking develops; and when food is given in a single meal, a high rate of drinking occurs for about 30 minutes after the meal (see figure 1).

Induced drug intake. In the next phase a low drug concentration (e.g., 0.0078 mg/ml of sodium pentobarbital) replaces water during the session. Between sessions water is freely available. After five sessions the concentration is doubled. However, if a trend emerges over a block of five sessions, the concentration is held constant until behavior is stable.

Drug intake (mg/kg of body wt/session) generally increases with increases in drug concentration (figure 2). Figure 3 shows that higher drug concentrations and under intermittent schedules of food reinforcement, the pattern of food-reinforced lever pressing is disrupted (Carroll and Meisch 1980b). Thus, the animals consume quantities of the drug sufficient to alter ongoing behavior.

Removal of food. Access to food is shifted from within the session to after the session either when drug intake becomes dissociated from food intake or when drug intake produces marked behavioral effects such as anesthesia. In the absence of food, drug intake persists but usually at a lower level than in the presence of food (figure 2).

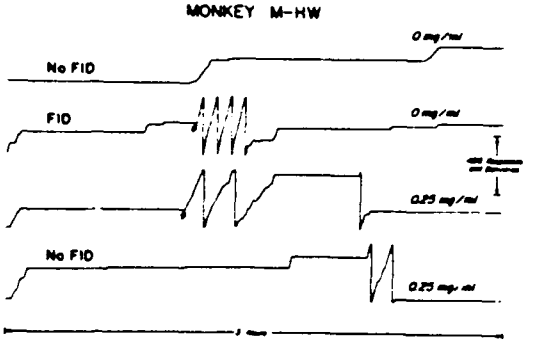
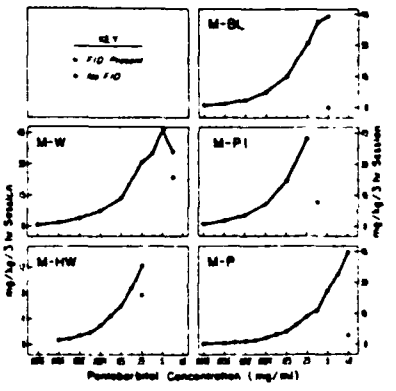



*Figure 1. Cumulative records for monkey M-HW showing representative performances under several conditions. Since the monkey was responding under an FR 1 schedule, vertical increments in the records represent both liquid responses and deliveries. The records labeled "No FID" are from sessions when only water (0 mg/ml) or pentobarbital (0.25 mg/ml) was present. Records labeled "FID" are from sessions when the daily food ration was given to the monkeys one hour after the start of the session. All food was generally consumed within 10 minutes, and this point is indicated by the arrows. Note the high rate of drinking after eating. Also, note that in the absence of food, pentobarbital deliveries maintained higher response rates than did water deliveries (from Henningfield et al. 1978).*

*Figure 2. Pentobarbital intake (mg/kg/3-hour session) as a function of pentobarbital concentration. Each point is a mean of the last five sessions at each concentration. Not illustrated is monkey P1's food-induced intake at .35 mg/ml; at this concentration his intake was considered dangerously high and food-induced drinking was discontinued after two sessions at this concentration (from Henningfield et al. 1978).*



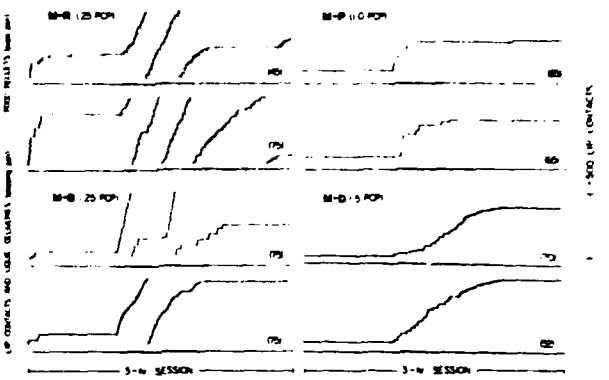


*Figure 3. Cumulative records are presented for four rhesus monkeys during 3-hour sessions. Phencyclidine (PCP) was available on an FR 1 schedule throughout the 3 hours and food (1g banana pellets) was available during the last 2 hours of the session according to a DRL 30 sec schedule. A maximum of 75 pellets was available, and the numbers in parentheses refer to the actual number of pellets obtained. The upper record for each monkey was taken from the first session at a particular PCP concentration. The lower record was taken five sessions later. Food pellet deliveries were marked by the event pen at the lower edge of each record. Lip contact responses were recorded by the stepping pen which stepped once with each lip contact response. Downward deflections of the stepping pen represent deliveries of 0.5 ml of drug solution. In three of the four monkeys (M-R, M-B, M-P) the food maintained behavior was less disrupted five sessions after the inital exposure to the PCP concentration, suggesting the development of tolerance, (Carroll, unpublished data).*

Maintenance

Increases in fixed-ratio size. To determine if the drug is functioning as a reinforcer, comparisons are made between rates of drug deliveries and water deliveries. Before these comparisons are made, the size of the fixed-ratio schedule is increased in order to amplify differences in drug- and water-maintained behavior. Earlier work with rhesus monkeys showed that occasionally ethanol drinking did not exceed water drinking at low fixed-ratio values (Henningfield and Meisch 1976b). At low fixed-ratio values, increases in the ratio usually produce

increases in response rates and no changes in the number of liquid deliveries (figure 4).

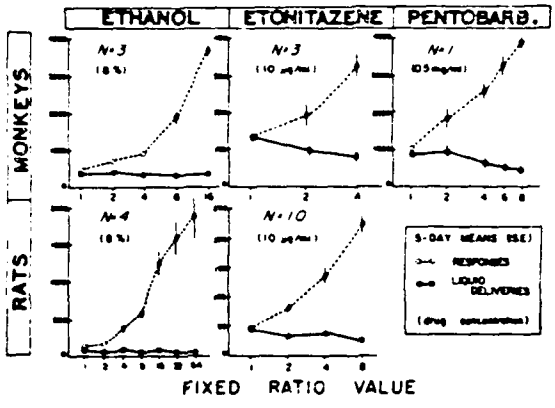



*Figure 4. Responses and liquid deliveries as a function of fixed-ratio value. Note the increases in response rate with increases in the fixed-ratio value (from Carroll et al. 1978).*

Comparisons of drug- and water-maintained response rates. If a drug is serving as a reinforcer, it should be possible to obtain rates of drug-reinforced behavior that exceed rates of water-reinforced behavior. Three ways of comparing rates have been used. One is to compare blocks of water sessions with blocks of drug sessions. Figure 5 shows that the number of liquid deliveries decreases when water is introduced and that the number of liquid deliveries increases when the drug is reintroduced. A second way to compare drug and water response rates is to alternate drug and water sessions. With this procedure, drug-maintained behavior exceeds water-maintained behavior. A third procedure consists of providing concurrent access to both drug and water and alternating the side positions of the liquids. Under these conditions monkeys reliably choose drug over water (Carroll 1981; Henningfield and Meisch 1979).

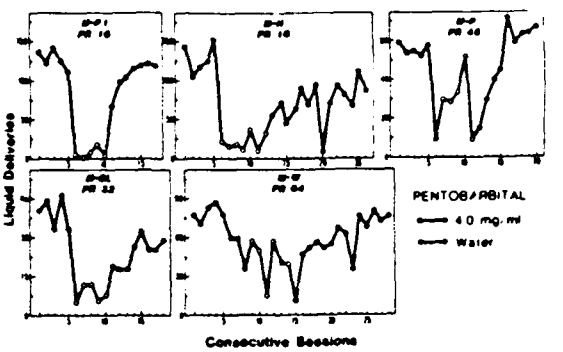



*Figure 5. Liquid deliveries per 3-hour session as a function of liquid delivered: 4.0 mg/ml pentobarbital or water. Note that the ordinate scales and fixed-ratio values differed among the monkeys (from Henningfield et al. 1981).*

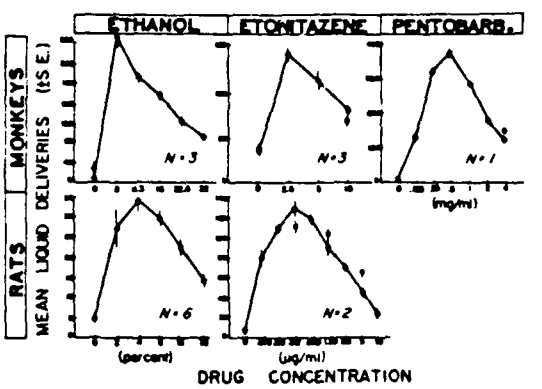



*Figure 6. Liquid deliveries as a function of drug concentration. "N" specifies the number of animals in each group. Values for each animal are from the last five sessions at each concentration. Closed circles refer to the initial concentration series; open circles are retest points obtained after the initial series, in the opposite sequence of the initial series. Ethanol was presented in an ascending series for both rats and monkeys. The other drugs were given in a descending sequence for both rats and monkeys (from Carroll et al. 1978).*

Effects of drug concentration. Figure 6 shows an inverted U-shaped function relating drug concentration to number of liquid deliveries. Initially, as drug concentration is increased, the number of liquid deliveries also increases. Further increases in concentration result in decreases in the number of deliveries. However, total drug intake per session (mg of drug per unit of body weight) generally increases directly with drug concentration.

Effects of food deprivation and satiation. Another variable that affects drug-maintained behavior is food intake. Figure 7 shows that food satiation decreases pentobarbital deliveries whereas food deprivation increases drug deliveries. Similar findings have been reported with phencyclidine (Carroll 1981; Carroll and Meisch 1980b). Also, food deprivation increases oral and intravenous drug intake in rats (Carroll and Meisch 1979b, 1980a, 1981; Carroll et al. 1979, 1981a; Meisch and Kliner 1979). With ethanol it is generally known that food deprivation increases intake (for a review see Meisch 1977); however, the increases in ethanol drinking with food deprivation have usually been attributed to the caloric value of ethanol.

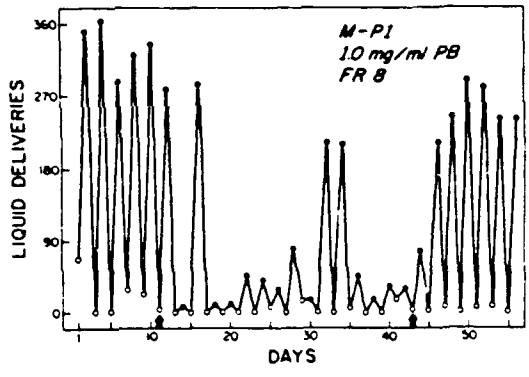



*Figure 7. Liquid deliveries of pentobarbital (1.0 mg/ml; closed circles) or water (0 mg/ml; open circles) across consecutive daily 3-hour sessions for monkey P1. The arrows along the abscissa mark where changes occurred in the food conditions. The first arrow shows the change from limited food access (food deprivation) to unlimited food access (food satiation) during the 18-hour intersession period. The second arrow shows the change from unlimited food access (food satiation) to limited food access (food deprivation) during the intersession period (Kliner and Meisch, unpublished data).*

## DISCUSSION

Orally delivered ethanol, etonitazene, pentobarbital, and phencyclidine have been established as reinforcers for rhesus monkeys (Carroll 1981; Carroll and Meisch 1978, 1980b; Meisch et al. 1981; Henningfield and Meisch 1978). The procedures used with each drug have certain features in common. The monkeys were food deprived, usually to 80 percent of their free feeding weight and in some cases to 70 percent. During daily 3-hour sessions water drinking was induced by feeding the monkeys. Once high rates of water drinking occurred, a low drug concentration replaced the water. The drug concentration was gradually increased across sessions. When high levels of drug intake were reached, the time of feeding was shifted from within the session to after the session. In the absence of inducing conditions, rates of drug-maintained responding consistently exceeded rates of water-maintained responding.

The establishment of orally delivered drugs as reinforcers is one facet of a more general program to analyze drug-reinforced behavior. Variables affecting behavior maintained by drug drinking have just begun to be examined. Results obtained so far appear consistent with results of intravenous drug studies. It is now apparent that high rates of responding can be sustained in rhesus monkeys with drugs such as ethanol, pentobarbital, and phencyclidine. In experienced organisms the taste of drug solutions may function as both discriminative and conditioned reinforcing stimuli in maintaining extended sequences of drug-reinforced behavior (Carroll and Meisch 1979a).

Although there is a substantial delay between drinking a drug solution and onset of the effects that occur once the drug is absorbed, learning occurs in spite of the delay, for the drugs come to serve as reinforcers. In taste-aversion conditioning there is also learning over long temporal delays. Both situations have in common the drinking of chemical solutions with subsequent onset of drug-produced interoceptive effects.

In medicine, progress has been made in analyzing disease states by producing them in animals. Thus, when drugs function as reinforcers for animals, one has an experimental preparation that reproduces the most critical feature of human drug dependence; namely, that for drug-dependent humans a drug serves as a reinforcer. Since the oral route is a common mode of human drug abuse, it is desirable to have an animal oral self-administration preparation. As in other areas of medicine, experimental studies with a valid animal model should ultimately result in improved clinical treatment.

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# Human Dependence on Tobacco and Opioids: Common Factors

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Recent years have seen increasing acceptance of the notion that tobacco is an addictive or dependence-producing substance, particularly as it is used in cigarette smoking. This idea is supported by the observations that tobacco serves as a reinforcer (i.e., it maintains behavior leading to its use) and that most people who smoke cigarettes would like to quit but cannot, even in the face of well documented health risks and economic sacrifices (Surgeon General's Report 1979). The term "drug dependence" suggests that (1) the drug serves as a reinforcer, (2) behavior occurs which is maintained by the opportunity to take the drug, and/or (3) other reinforcers are sacrificed as a consequence of taking the drug (Kalant et al. 1978). Many cigarette smokers in some degree satisfy these criteria for drug dependence (Russell 1976; Jaffe and Kanzler 1979).

Since cigarette smoking has only recently been conceptualized as an instance of drug dependence, it should be useful to systematically compare cigarette smoking with another more thoroughly studied dependence process such as opioid dependence or narcotic addiction. At first blush, cigarette smoke and opioid drugs appear to produce vastly differing pharmacological and behavioral effects: large doses of opioids can produce a debilitating sedation that is not produced by heavy cigarette smoking. However, these differing direct drug effects may be only marginally relevant to the ongoing dependence processes per se, and certain functional similarities in the two forms of dependence suggest that opioid dependence may, in fact, provide a useful and valid conceptual model to which cigarette smoking may be compared.

The purpose of this chapter is to compare the functional similarities between tobacco and opioid dependence. Relevant experimental data, clinical observations, and epidemiological findings will be discussed under the organizational framework shown in table 1.

TABLE 1

| |
|---|
| Patterns of Use |
| Personality Characteristics and Social Factors |
| Physiologic Dependence |
| Deprivation Effects |
| Tolerance |
| Dose Effects on Drug Intake |
| Reinforcing Efficacy and Dependence Liability |
| Response Requirement |
| Conditioning Factors |
| Antagonist Administration Effects |
| Preloading Effects |
| Relapse Patterns Following Abstinence Treatment |
| Feeding Behavior Effects |

## PATTERNS OF USE

In both cigarette smoking and opioid dependence, use of the respective drug occurs on a regular daily basis and, given adequate supplies, self-imposed abstinence is infrequent. This overall pattern of use is distinct from that of many other drugs of abuse (e.g., the sporadic use of the hallucinogens or the use of psychomotor stimulants in which periods of self-administration are broken by periods of abstinence, cf. Jaffe 1975). With both tobacco and opioids, simple exposure to the drugs ("experimentation") frequently leads to chronic use (Bejerot and Bejerot 1978). In fact, while exact figures vary, it has been estimated that 85% of adolescents who smoke one or more cigarettes become compulsive smokers (Russell 1971). Similarly, with opioids, it has been found that a high percentage of experimental users become dependent users, e.g., 97 percent in a study by Robins and Murphy (1967). From this perspective, both drugs have a high "dependence liability" or "addictive potential." A difference in this regard is that most cigarette smokers are compulsive daily users (about 95%, Russell 1971) whereas current data suggest that a substantial portion of the total population of opioid users are not compulsive daily users (that is, they are "chippers," Zinberg 1979). With both tobacco and opioids, certain routes of administration are preferred (smoking and injecting, respectively) but other routes or forms of the drug will be substituted if the preferred one is precluded. For example, most tobacco users are cigarette smokers (Surgeon General's Report 1979) but some smokers will change to chewing tobacco or snuff if their occupation does not permit smoking (Russell 1971). With individual opioid users for whom the intravenous route is preferred, other routes and drug forms also will suffice (e.g., oral methadone, Jaffe 1975, and smoking of opioids, Way 1968).

Finally, when asked to give reasons for their smoking behavior, the answers obtained from most cigarette smokers may be categorized as follows: (1) smoking for the "pleasurable-relaxing" effects is the most common reason; (2) smoking for the stimulating effects is next most common; (3) smoking to "reduce negative feelings" or to "relieve anxiety" is the third most common (Green 1977). This constellation is more similar to that reported by opioid users (cf. Dr. Charles Haertzen, personal communication) than it is, for instance, to that reported by amphetamine users, in which stimulation is the foremost reason for drug-taking behavior.

## PERSONALITY CHARACTERISTICS AND SOCIAL FACTORS

Social pressure from both peers and family members is critical in initiating and terminating the process of dependence to both tobacco and opioids. Specifically, there is a high probability that friends and family users will share the same pattern of drug use (cf. Reeder 1977; Evans et al. 1978; Kozlowski 1979; Nurco 1979). Additionally, a prime indicator of treatment success for both cigarette smoking and opioid dependence is the presence of friends and/or peers who have been successfully treated for their dependency (Levitt 1971; Kozlowski 1979; Nurco 1979). That there are commonalities in the personalities of tobacco and opioid users is suggested by the fact that most opioid users (about 95 percent) are also cigarette smokers (O'Donnell 1979). As groups, users of different drugs may be characterized by particular constellations of social and personality variables, and these constellations show greater overlap across certain drug classes than others. In this respect, psychological characteristics of opioid users (Kissin 1972) show considerable overlap with those of cigarette smokers (Eysenck 1973; Kozlowski 1979). Particular points of similarity include an increased prevelence of antisocial and psychopathic tendencies, rebelliousness, anxiety, repressed hostility, and extroversion. Additionally, in both cigarette smokers and opioid users, there is evidence that experimentally elicited aggressive responses are attenuated by use of cigarettes in cigarette smokers (Hutchinson and Emley 1973; Jaffe and Jarvik 1978) and opioids in opioid users (Wallace 1979).

## PHYSIOLOGIC DEPENDENCE

Physiologic dependence is a factor of significance in opioid dependence and of suspected significance in cigarette smoking. There are three primary aspects of physiologic dependence. The first is important in the maintenance of opioid-taking behavior, in which the emergence of the withdrawal syndrome is correlated with increasingly intense craving scores (Wikler 1961). Some analogous findings in animal studies are that the onset of the opioid withdrawal syndrome is correlated with increased rates of drug-taking behavior (Wikler et al. 1963) and increases in the reinforcing

efficacy of opioid drugs (Thompson and Schuster 1964). The second aspect of physiologic dependence to opioids is the increasing propensity of a person in withdrawal to become anxious and to emit aggressive and antisocial acts (Kissin 1972; Brill and Laskowitz 1972). The third aspect of physiologic dependence is the phenomenon of protracted abstinence (cf. Martin et al. 1978), which, in the most rigorous use of the term, refers to physiologic withdrawal signs that are present for more than six months following the onset of opioid abstinence (Himmelsbach 1941; Martin 1978). Protracted abstinence to opioids has also been well documented in animal studies (Martin et. al. 1978). With regard to cigarette smoking, it has been recently postulated that withdrawal phenomena occur and are similar in certain respects to those which characterize opioid dependence (e.g., Schachter 1979; Fagerstrom 1980). Specifically (1) the onset of withdrawal increases desire to smoke and also increases the probability of smoking, thus helping maintain patterns of smoking (e.g., Schachter et al. 1977; Jaffe 1978); (2) the emergence of withdrawal is associated with an increase in levels of anxiety (Nesbitt 1973) and an increase in the propensity of the person to emit aggressive or antisocial acts (Heimstra 1973; Perlick 1977); (3) there is a protracted withdrawal syndrome whose main characteristic is a long-term recurrent craving (cf. Eisinger 1971; Shiffman 1979).

While it is becoming more widely accepted that a withdrawal syndrome can emerge during tobacco abstinence, there has been relatively little systematic study or quantification of such a syndrome (Surgeon General's Report 1979). Available data suggest that measurable physiological changes such as decreased heart rate and blood pressure, and decreased excretion of catecholamines occur within hours after smoking is terminated and last up to 30 days; symptoms such as sleep disturbance, headache, and gastrointestinal discomfort occur and may persist for several days after abstinence ensues; weight gain is a frequent concomitant to abstinence; finally, the most prevalent symptom, desire to smoke, occurs and may recur for many years (cf. review by Shiffman 1979). Such a synopsis of possible withdrawal signs and symptoms is somewhat misleading, however, since the kinds of symptoms which have been reported and the temporal patterns of the emergence of these symptoms are not consistent across studies or even across individuals within studies. An important series of human studies would be one similar to those done by the Addiction Research Center on opioids, sedatives, and ethanol, in which the hypothesized withdrawal syndrome is characterized and quantified. If a quantifiable syndrome is verified, then factors could be studied which are of known importance in determining the magnitude of other kinds of drug withdrawal syndromes (e.g., factors such as the preabstinence dosing regimen). Classic substitution procedures could also be done to identify which specific factors attenuate or block the syndrome (e.g., a preliminary study by Fagerstrom, 1980, suggests that nicotine-containing chewing gum is partially effective in blocking cigarette withdrawal symptoms, cf. also Johnston 1942).

Another line of research that must be pursued is abstinence studies using animals. Animal studies would be of particular interest since, to date, there have been no demonstrations of either nicotine or tobacco withdrawal in animals, even following prolonged exposure to nicotine (e.g., Stolerman, Fink and Jarvik 1973) or tobacco (Jarvik 1967). However preliminary studies have revealed some physiological rebound effects which occur when chronic nicotine administration is terminated in rats (e.g., Wenzel and Azmeh 1970), suggesting the possibility that a withdrawal syndrome may be produced.

## DEPRIVATION EFFECTS

Deprivation of opioids and tobacco increases the tendency of humans and animals to self-administer opioids and of humans to smoke cigarettes. While deprivation of opioids in an opioid user, and possibly deprivation of tobacco in a cigarette smoker usually results in the onset of a withdrawal syndrome, deprivation is, operationally, a temporal manipulation which may increase the reinforcing efficacy of a substance regardless of whether or not a withdrawal syndrome also happens to occur. In clinical studies, a sensitive measure of the deprivation effect is the probability that the drug will be self-administered. With cigarettes this effect was demonstrated in our laboratory when cigarette smokers were deprived 0, 1, or 3 hours and then given access to cigarettes (Henningfield and Griffiths 1979). Figure 1 shows that latency to the first puff following access to cigarettes was inversely related to the duration of the deprivation period. Curiously, a subsequent study showed that "anticipated deprivation" did not produce measurable changes in the smoking of a single cigarette when subjects were given a cigarette and were informed that after smoking that cigarette they would be required to abstain for 0, 1, or 3 hours (Griffiths and Henningfield 1981a). One measure of deprivation is desire to smoke, and several cigarette smoking studies have shown (as noted in the Physiologic Dependence section) that strength of the desire to smoke is a direct function of the deprivation period (e.g., Shiffman 1979; Shiffman and Jarvik 1981). With the opioid drugs it is well known clinically that the probability of self-administration is a direct function of the deprivation period, though this effect is usually considered to reflect the onset of physiologic withdrawal symptoms (Wikler 1952; Jaffe 1975). Similarly, several human studies on opioid withdrawal effects have shown that self-reported craving strength is a direct function of the deprivation period (Wikler 1978).

## TOLERANCE

Tolerance to toxic or aversive effects of both tobacco and opioids is thought to be important in the ontogeny of dependence. Tolerance may also be a determinant of levels of drug intake. When tolerance is suspected to have occurred at the cellular level it is

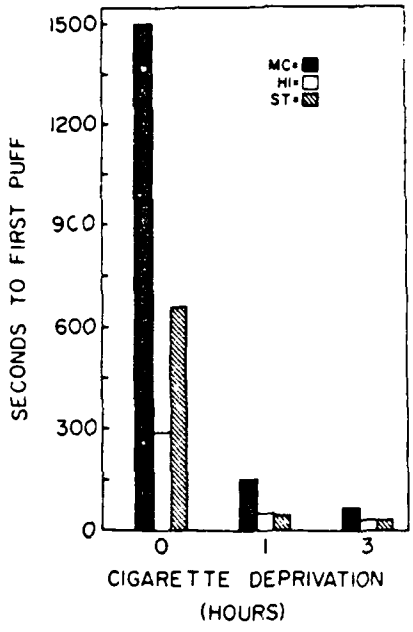


*Figure 1. For each of three subjects the mean number of seconds from the start of the session until the first puff occurred is shown as a function of hours of deprivation of cigarette smoking.* [© *The Psychonomic Society. From Behavior Research Methods and Instrumentation, Vol. 11, No. 6, 1979. Reprinted with permission.*]

of additional significance since it may be part of the phenomenon of physical dependence (cf. Kalant et al. 1971), and hence share a role in the maintenance of the self-administration behavior (cf. Physiologic Dependence section). Tolerance to the various effects of opioids has been extensively studied in both animals and humans (cf. Way and Glasgow 1978). Tolerance to the effects of nicotine, and to a lesser extent, cigarette smoke, have also been studied in both humans and animals (cf. Goodman et al. 1980; Domino 1973; Jarvik 1979). The extent to which there are similarities and differences in the development of tolerance to tobacco as compared to the opioids must await further studies. However, it is possible that tolerance to certain effects of smoking may occur more rapidly than opioid tolerance. For example, it is known that tolerance to cardiovascular effects of nicotine can develop within a few hours when nicotine is injected intravenously every 20-30 minutes and that the development of this tolerance is more pronounced in smokers than in nonsmokers (Jones et al. 1978). In our laboratory

at the Addiction Research Center, preliminary data indicate that tolerance to certain effects of cigarette smoking, (e.g., attenuation of the patellar reflex and subjective responses) may be lost overnight and gained after a few hours of smoking, while tolerance to other effects may be more slowly acquired and more slowly lost. Interestingly, while tolerance to the initial nausea and dysphoria are thought to be important in the acquisition of smoking, even chronic cigarette smokers whom we have tested usually show these symptoms when they are given a high nicotine cigarette to smoke as their first cigarette of the day and only to a lesser extent when given an identical cigarette to smoke after several hours of normal smoking.

## DOSE EFFECTS ON DRUG INTAKE

Drug dose is an important pharmacologic variable that can determine rate of self-administration and quantity of drug obtained. If the rate of drug self-administration is an inverse function of the unit dose, and total drug intake remains constant across doses, then the organism is "regulating" its drug intake and "titration" or "compensation" is said to have occurred. In animal studies of both intravenous opioid self-administration (e.g., Stretch and Gerber 1977) and intravenous nicotine self-administration (Hanson et al. 1979), drug intake is a direct function of drug dose. That is, except at high doses which have "rate-limiting" effects, drug intake regulation is poor at best. This relationship is distinct from that obtained in studies of intravenous psychomotor stimulant self-administration (e.g., amphetamine or cocaine) where dose regulation is more precise (e.g., Yokel and Pickens, 1974).

In clinical studies on the effects of drug dose, findings with tobacco are mixed. When nicotine content of cigarettes is varied, findings are similar to those obtained in the animal studies described. That is, nicotine intake increases as a direct function of nicotine dose except at the highest doses, at which rate of self-administration declines sharply (cf. Schachter 1979; Russell 1976, 1979; Gritz 1980). Dose compensation is much more striking when amount of cigarette smoke is manipulated as may be accomplished by varying cigarette size (Gritz et al. 1976; Jarvik et al. 1978) or the concentration of the cigarette smoke is varied (Sutton et al. 1978; Henningfield and Griffiths 1980). Figure 2 shows that when tobacco product concentration was decreased across sessions, from 100% (no. 0) to 10% (no. 4), number of puffs taken per 3-hour session doubled in 3 subjects tested. Expired air carbon monoxide levels confirmed that measured changes in puff parameters plus unmeasured but likely changes in inhalation parameters resulted in good tobacco smoke dose compensation by these subjects. Thus, while manipulations of cigarette dose may produce good titration, manipulations of nicotine content do not produce reliable changes in rate of self-administration and hence titration (cf. Gritz 1980). Comparable studies of the effects of dose manip-

ulations on rate of opioid self-administration in humans have not been conducted. However, clinical studies in which humans are permitted to self-regulate their analgesic drug (opioid) intake indicate that humans are sensitive to drug dose manipulations and suggest that moderate intake compensation occurs (Keats et al. 1969; Sechzer 1971).

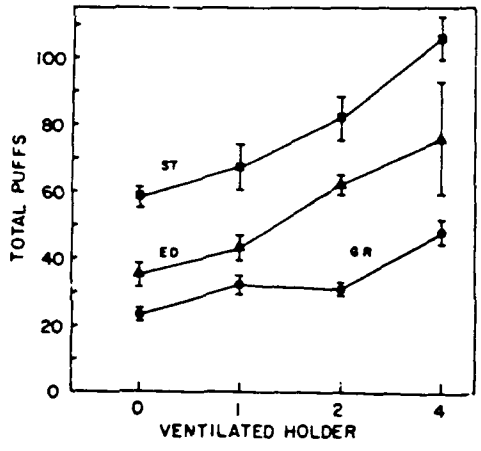


*Figure 2. Mean total puffs per session (N=4) and standard error values obtained during daily 3-h sessions are shown for each of three subjects as a function of cigarette holder number. The approximate concentrations of delivered tobacco product are indicated by the holder number in which 0=100%, 1=75%, 2=50%, and 4=10%.* [© *Springer-Verlag, from* Psychopharmacology, *Vol. 68, 1980. Reprinted by permission.*]

## REINFORCING EFFICACY AND DEPENDENCE LIABILITY

Retrospective analyses suggest that cigarettes and opioids have high dependence liability; that is, a single exposure to either cigarettes or opioids is often followed by the development of a pattern of compulsive use (a notable exception being therapeutic administration of opioids in clinical settings). Furthermore, once compulsive use develops, users of both opioids and tobacco emit large amounts of work, spend considerable sums of money, and endure sacrifices in health and other areas to maintain their self-administration behaviors. A historical perspective illustrates a similarity with regard to the abuse potential of tobacco and opioids: Cocteau's dictum regarding opium smoking, that "he who has smoked will smoke" is equally true with regard to tobacco (Russell 1976).

One approach to providing information about the relative dependence liability of drugs is to examine their efficacy in maintaining drug self-administration behavior in laboratory animals. Studies to date suggest that both opioids and nicotine (as well as cigarette smoke) do maintain self-administration in animals; however, opioids appear to be more efficacious reinforcers than nicotine or tobacco smoke. Specifically, while many studies have shown that opioids, delivered intravenously, intramuscularly, and orally, serve as effective reinforcers for animals (cf. Johanson 1978; Carroll and Meisch 1979), studies involving intravenous self-administration in rats, monkeys, and baboons suggest nicotine to be an equivocal reinforcer when compared to other drugs of abuse, including opioids (Griffiths et al. 1979). However, it would be premature to pass final judgement on the results of the animal studies of nicotine and/or tobacco smoke self-administration, firstly, because the route of administration that is preferred by humans (inhalation) has not been extensively used with animals. Just as it required many years to develop a preparation in which orally delivered ethanol served as a potent reinforcer for animals (cf. Meisch 1977), it may take a long time to develop the appropriate procedures for studying tobacco use in animal preparations (cf. Ando and Yanagita, 1981, for a promising development in tobacco smoke self-administration by monkeys). Secondly, the animal nicotine self-administration data are of questionable relevance to the reinforcing efficacy of cigarettes since it is clear that nicotine is not the sole determinant of smoking rates (Russell 1979; Gritz 1980) and that noninhalation routes of nicotine administration are not equivalent to nicotine administration via cigarette smoking (Russell and Feyerabend 1978). Finally, there have been no clear demonstrations that intravenously delivered nicotine is an effective reinforcer for humans (see below).

Another approach to providing information about the dependence liability of drugs is to conduct human studies and systematically evaluate self-reports of subjective "liking" or "drug satisfaction" (Jasinski 1977). The validity of this approach is suggested by the similarities in the human findings, animal self-administration findings, and in the epidemiological reports of drug abuse (Griffiths and Balster 1979; Griffiths et al., this volume; Yanagita 1980). Intravenous injections of opioids in most addict subjects (Jasinski 1977), or of nicotine in cigarette smokers (Johnston 1942; Jones et al. 1978) are reported to be pleasurable. With both opioids and tobacco, studies have demonstrated an additional similar relationship: as dose of opioids, intravenous nicotine or cigarettes is increased, subjective reporting indicates that satisfaction also increases (e.g., Kay et al. 1967; Goldfarb et al. 1976; McClane and Martin 1976; Jarvik et al. 1978; Griffiths and Henningfield 1981b).

## RESPONSE REQUIREMENT

Response requirement, also referred to as "response cost," may be defined as the amount of behavior required to obtain a reinforcer. With regard to drug self-administration by humans, response cost can be defined as the amount of effort required to obtain the drug, or as the monetary value of the drug when monetary earning is proportional to work output. Economic theory uses the concept of "elasticity" to describe the extent to which consumption of a commodity varies with the price of that commodity. From a common perspective of drug addiction, opioids and cigarettes might be viewed as relatively inelastic commodities in dependent persons, i.e., that as price increases, consumption would remain relatively constant. In fact, however, both opioid demand and cigarette consumption have proved to be relatively elastic in that consumption decreases when price increases (cf. Peto 1974; Nurco 1979). This is not to say that increasing the price or response requirement for cigarettes and opioids does not result in an increase in net expenditure or response output. Response output does increase --it just does not keep pace with the requirements for maintaining a constant level of intake.

A clear experimental demonstration of the interactions between response requirement and intake of methadone or cigarettes was shown in preliminary studies by Bigelow and his co-workers. In these studies, response requirement was defined as the number of lever pulls per delivery of a methadone dose (Bigelow 1978) or a cigarette (Griffiths et al. 1980). As response requirement increased, for either cigarettes or methadone doses, response rate was an increasing or inverted U-shaped function, and the number of cigarettes or methadone doses obtained decreased. These findings are consistent with epidemiological findings which showed that for both opioids and cigarettes, increased prices result in increased spending but decreased intake (Peto 1974; Nurco 1979). Analogous results have been obtained in animal drug self-administration studies using opioids (cf. Griffiths et al. 1980), but these procedures have not been applied in animal studies of cigarette smoking or intravenously delivered nicotine.

## CONDITIONING FACTORS

Conditioning of both the operant type and the respondent (or Pavlovian) type is thought to occur as an integral part of the dependence process with both cigarette smoking and opioid dependence. Specifically, the development of conditioned stimuli, discriminative stimuli, and conditioned responses may contribute to maintenance of the pattern of compulsive use and facilitate relapse following a period of abstinence. For instance, clinical lore suggests that environmental stimuli previously associated with smoking are likely to evoke craving responses and increase the probability of smoking when these stimuli recur (cf. Pomerleau and Pomerleau

1977; Danaher and Lichtenstein 1978; Pomerleau 1979). Therefore, in most smoking treatment programs it is recommended that the abstaining smoker try to avoid environmental stimuli which are highly associated with smoking, e.g., having visual access to cigarettes, social and drinking situations, etc (cf. Danaher and Lichtenstein 1978; Pomerleau and Pomerleau 1977; USDHEW 1978). Systematic studies are needed to determine if these environmental stimuli elicit withdrawal type responses in a manner similar to the elicited opioid withdrawal described below. It is known that desire to smoke cigarettes may persist for several years after smoking was terminated and that formerly high probability smoking situations are particularly effective at evoking the craving responses (Shiffman 1979). Finally, a preliminary study by Gritz (1977) has shown that sight and smell of tobacco smoke are important determinants of smoking rate, demonstrating that tobacco self-administration, like opioid self-administration, may be influenced by external stimulus factors.

With regard to opioid dependence, the evidence that conditioning factors play a critical role has grown since the notion was first postulated by Wikler (1952, 1965, 1978). Recent studies by O'Brien and his colleagues have demonstrated that opioid withdrawal can occur as a conditioned response to administration of placebo in patients who have previously received naloxone injections (O'Brien et al. 1980; O'Brien et al., this volume). In another study from the same laboratory, it was demonstrated that subjective and physiologic responses which are normally elicited by opioid administration could also be elicited by presentation of heroin-related stimuli or by the self-administration of placebo in patients with histories of hydromorphone injections (Ternes et al. 1980; Sideroff and Jarvik 1980). Analogous findings have been obtained in animal studies (cf. Thompson and Schuster 1964; Schuster and Woods 1968; Davis and Smith 1976; Wikler 1978). These studies are important in that they demonstrate that stimuli previously associated with drug administration or drug withdrawal may attain functional roles in the dependence process via conditioning (learning) mechanisms. While further experimental data are required for a more definitive conclusion, it is clear that conditioning factors may be important controlling variables which are common to both opioid and cigarette dependence.

## ANTAGONIST ADMINISTRATION EFFECTS

One factor that distinguishes cigarette smoke from substances such as alcohol, barbiturates, and food is that the primary pharmacologically active constituent (nicotine) has a specific cellular site of action (viz., nicotinic receptors). It is well known that opioids are also receptor-specific. Self-administration of both opioids and cigarette smoke may be influenced by administration of pharmacologic antagonists. Clinical administration of opioid antagonists (e.g., naltrexone) to human opioid users decreases opioid

self-administration (Mello and Mendelson 1978; Meyer and Mirin 1979). The limited available data regarding nicotine antagonist administration showed that mecamylamine (a centrally acting nicotinic blocker) administration to human cigarette smokers produced increases in smoking during weekly 2-hour sessions: it was not determined whether or not continuous antagonist administration ultimately would have reduced smoking rates (Stolerman, Goldfarb, Fink and Jarvick 1973). Pentolinium (a peripherally acting nicotinic blocker) did not affect smoking rates. In a study of cigarette smoking by monkeys, mecamylamine (but not the peripherally acting hexamethonium) reduced overall levels of smoking over the course of several weeks (Glick et al. 1970). A caveat with regard to the interpretation of results of antagonist administration in cigarette smoking studies is that, strictly speaking, there is not a tobacco antagonist; rather, there are nicotine antagonist drugs. Administration of nicotine antagonists (e.g., Goldberg and Spealman 1981) or of opioid antagonists (Moreton et al. 1975; Davis and Smith 1976) to animals which are intravenously self-administering nicotine or intravenous opioids, respectively, decreases the self-administration behaviors.

The effects of opioid antagonists in blocking or reversing the responses produced by opioids have been extensively studied and reviewed for both humans (e.g., Jasinski 1978) and animals (e.g., Way and Glasgow 1978). Preliminary studies of antagonism of the effects of nicotine in animals (cf. Domino 1973) and the effects of smoking in humans (Jarvik 1973) indicate similar antagonist blockade and reversal of effects. A noteworthy difference is that opioid antagonists may precipitate withdrawal in opioid-dependent organisms, while no similar phenomenon has been demonstrated in organisms chronically exposed to tobacco smoke or nicotine.

## PRELOADING EFFECTS

In human research, acute preload administration of opioid drugs or tobacco products (e.g., nicotine or cigarette smoke) decreases subsequent administration of opioids or cigarettes, respectively. A good clinical example of this opioid preload effect is the use of methadone to treat illicit opioid dependence (cf. Kreek 1979). Jones and Prada (1975) showed that methadone administration to patients who were given the opportunity to obtain intravenous hydromorphone (Dilaudid) produced decreases in self-administration of the opioid. Of six subjects tested, 3 completely stopped working for hydromorphone while the other 3 worked intermittently for hydromorphone. These findings are compatible with those obtained in studies of cigarette smoking in which preloading subjects with cigarette smoke produces a decrease in subsequent smoking (e.g., Kozlowski et al. 1975; Kumar et al. 1977). Nicotine preloading given either orally (Jarvik et al. 1970) or intravenously (Lucchesi et al. 1967) also may produce decreases in smoking, although these kinds of preloading manipulations produce

weaker and less consistent decrements in smoking than when cigarette smoke preloading is done (cf. Kumar et al. 1977). These results show that nicotine is not the sole determinant of cigarette smoking. Consistent with these experimental findings are the modest rates of therapeutic success of preload types of treatment for cigarette smoking (e.g., nicotine-containing chewing gum) which are similar to the modest rates of success of methadone programs for opioid dependence when methadone is dispensed to a heterogeneous population of opioid users.

These drug preloading effects have also been studied in animals where it has been demonstrated that opioid preloads usually (e.g., Wurster et al. 1977; Jones and Prada 1975) but not invariably (Jones and Prada 1977), reduce subsequent opioid self-administration by animals -- these opioid findings are consistent with those obtained in human studies. Similarly, one study has demonstrated decreases in cigarette smoking rates in monkeys which occurred when nicotine was added in the monkeys' drinking water (Jarvik 1973).

## RELAPSE PATTERNS FOLLOWING ABSTINENCE TREATMENT

Hunt and his co-workers have shown that patterns of relapse to drug use following abstinence are similar for cigarette smoking, opioid dependence, and alcoholism (Hunt et al. 1971; Hunt and General 1973; Hunt and Bespalec 1974). During the first few months, roughly 70% of patients relapse. Subsequently, the rates of relapse approach asymptotically a level at which about 75% have relapsed, and the rest are still abstaining. These findings suggest an important commonality, but one whose mechanisms are not clear. Perhaps the protracted abstinence syndrome (Physiologic Dependence section), conditioned craving (Conditioning Factors section), or social and personality variables (Personality Characteristics and Social Factors section) are significant.

## FEEDING BEHAVIOR EFFECTS

Both opioids and tobacco can reduce feeding behavior and produce weight loss, and intake of both opioids and tobacco may be increased by food deprivation. The effects of food intake on opioid and nicotine self-administration have been experimently studied using animals. Meisch and his co-workers (e.g., Meisch and Stark 1977; Carroll et al. 1979; Meisch and Kliner 1979) showed that oral or intravenous etonitazine intake by rats was inversely related to body weight when body weight was manipulated by varying size of the daily food ration. A similar finding was obtained in rats which drank morphine solutions (Nichols 1972). In a study of intravenous nicotine self-administration, nicotine was self-injected at significant levels when the animals were at 80 percent of their normal weights but not when the animals were at 100 percent body weight and allowed free access to food (Lang et al. 1977).

In a clinical study of the effects of severe food deprivation, it was found that cigarette smokers smoked much more and that non-smokers learned to smoke. A similar finding was obtained with regard to coffee drinking (Keys et al. 1950). Similarly, addicts sometimes report that when they are hungry (for food) they have a stronger craving for opioids and cigarettes and that they smoke more. Clinically, it has been observed that opioid dependence is frequently accompanied by nutritional deficiency, though it is not clear whether this effect is mediated pharmacologically or sociologically (Kreek 1979). With regard to cigarette smoking, epidemiological data have shown that cessation of cigarette smoking is frequently accompanied by a gain (often excessive) in weight (Garvey et al. 1974; Heyden 1976; Schacter 1979). The possibility of a direct interaction between nicotine obtained by cigarette smoking and appetite has been experimentally demonstrated by Perlick (1977) who showed that subjects who were given low- or no-nicotine cigarettes to smoke ate twice as many jelly beans as subjects who were given high nicotine cigarettes to smoke.

## DISCUSSION AND CONCLUSIONS

The behavior of cigarette smoking, as it occurs in many cigarette smokers, may be properly regarded as an instance of drug dependence or as an addiction. As a form of drug dependence, cigarette smoking bears striking similarities in its functional characteristics to the prototypic form of drug dependence--opioid dependence or narcotic addiction. The extent to which similar controlling variables pervade tobacco and opioid dependence may not be readily apparent when only the commonly described features of cigarette smoking and opioid dependence are considered. However, the idea that these two seemingly diverse kinds of drug dependence share some common features is not a new one: commonalities between tobacco smoking, opioid use (e.g., opium smoking), and alcoholism have been noted for several hundred years (Jaffe 1978; Austin 1978). The present paper has extended these observations by systematically comparing functional relationships found in cigarette smoking and opioid dependence which are empirically based on laboratory and clinical data. The research reviewed shows that many fundamental commonalities exist between tobacco and opioid dependence, adding further support to the notion that cigarette smoking is an instance of drug dependence.

Some of the common functional relationships reviewed in this paper are not uniquely shared by cigarette smoking and opioid dependence. For instance, most forms of drug and substance abuse can probably be reduced by increasing the response requirement necessary to maintain the dependence (Griffiths et al. 1980). Other commonalities are less widely shared: the similarities in cigarette smoking and opioid dependence noted in the pattern of chronic daily use, receptor specificity, and the role of physical dependence do not appear to be shared with most other forms of drug or substance abuse.

In this paper we have explicitly avoided equating cigarette smoking with nicotine dependence or nicotine self-administration. This approach is consistent with a conservative evaluation of the available data which show that, while nicotine accounts for many of the effects produced by cigarette smoking, clinical and experimental manipulations of nicotine administration do not affect cigarette smoking to the degree that would be predicted if nicotine were the only factor controlling cigarette smoking.

The comparison of the functional similarities between tobacco and opioid dependence has been made possible largely by the application of the methodology of behavioral pharmacology to the analysis of drug dependence. Future basic science research will undoubtably point out further functional similarities and dissimilarities between cigarette smoking and other forms of drug and substance abuse. Such research will ultimately provide a thorough analysis of the dependence process, per se, and will have important implications for the treatment of drug dependence.

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# Discussion

## Commonalities and Differences Among Reinforcers

Chris E. Johanson, Ph.D.

Since I entered the field of behavioral pharmacology, there has been an enormous increase in the number of studies in the area of drug self-administration and a utilization of these techniques in the development of an animal model for the assessment of abuse potential of drugs. I often forget that although there were some isolated self-administration studies before 1960, the field really began in 1962 with a publication by Weeks (1962) and later in 1964 with a publication by Thompson and Schuster (1964). Since I entered the area in 1970, it is not surprising that I have the feeling that there has been a logarithmic increase in the number of studies in the field because this 10-year period makes up well over 50% of its total life. I make this comment not to show you that I, too, am a pioneer in the field but that the field is very young and that we should be very encouraged by the enormous progress that we've made in assessing the determinants of drug self-administration in animals and now humans during a relatively short period of time. The present conference could not illustrate this progress more clearly. I fully appreciated this enormous increase in knowledge when Bob Schuster and I were asked last year to write a review article; the fact that it was completed 6 months late indicates that we had a great deal of trouble trying to summarize the vast amount of research on drug self-administration in animals. We concentrated in the review on studies of maintenance variables, i.e., determinants of drug self-administration. We noted in our review that early research was concerned primarily with the type of drug that would maintain responding and the investigators simply marched through the pharmacopeia using the same simple behavioral preparations (e.g., low fixed ratio schedules) for every drug. This perseveration was most likely the consequence of the researchers being continually impressed, even amazed, that animals would self-administer the same drugs that humans abused without any clever coercion. Unfortunately, this led some investigators to the premature conclusion that drug abuse was a totally pharmacological problem. In recent years, there has been a shift in emphasis to environmental determinants of the reinforcing properties of drugs. In my opinion this shift has led some investigators to the equally inappropriate conclusion that the pharmacological properties of the drug itself have little to do with its behavioral effects. Clearly, as this conference has shown, drug self-administration is determined by a complex interaction between both pharmacological and behavioral variables. In addition, the variables

which control responding maintained by drugs operate in a similar manner to variables that control other types of behavior. This similarity has led researchers and clinicians to conclude that it is appropriate to search for commonalities in the determinants of substance abuse or excessive behavior.

Although the primary application of drug self-administration studies is the understanding of the determinants of drug abuse in humans, the procedures and techniques which have been developed are also useful for a variety of other purposes. First of all, there is a special set of manipulations which decreese rate of drug self-administration and therefore have relevance for treatment approaches. These variables are both behavioral, such as punishment, and pharmacological (e.g., drug treatments such as methadone maintenance). Self-administration studies can also be useful for understanding certain problems encountered in the treatment of drug abuse patients. For instance, an understanding of conditioned drug effects, such as those described by O'Brien, incorporated within the context of actual drug self-administration studies, can help us elucidate mechanisms of relapse in exdrug users. Studies of drugs as negative reinforcers may help us understand that essential medications are often not taken by patients because they have aversive properties. However, as with positive reinforcers, the aversive properties of a drug are not immutable and can be affected by the context of their administration.

There are also studies that use drug self-administration methodologies to elucidate biochemical mechanisms of action of a specific drug. While this approach has great appeal, investigators should exercise caution in interpreting their findings and should be especially careful in recognizing the multiple determinants of responding. Self-administration studies can also be used to study drug toxicity. It is far more important in the determination of a drug's abuse potential to study this toxicity within the range of doses that are self-administered rather than at some arbitrarily chosen dose range.

Finally, but first in some sense, drug self-administration methods are useful for screening new compounds for abuse potential. In this application, it may appear that we are retreating to an emphasis on the pharmacological properties of drugs. During our break, a member of this audience pointed out to me that outsiders (I have to include as outsiders people from funding agencies who are here to learn how drug self-administration techniques can be used ) might view this field as schizophrenic. We believe that any event can function as a reinforcer under some environmental condition. On the other hand, the mission of screening to predict the abuse liability of a compound implies that drugs differ in their ability to serve as reinforcers. In my opinion, both of these views are correct. Clearly psychologists are clever and can produce conditions under which any drug might serve as a reinforcer. So then what is the mission of screening for abuse potential? I believe it is to determine at a pre-clinical level those drugs for which there is a high probability that the drug will serve as a reinforcer in a variety of people under a variety of environmental circumstances. In order to accomplish this mission, therefore, drugs must be evaluated under a range of conditions. The abuse liability of a drug simply corresponds

to the extent of the conditions under which this drug maintains responding. Drugs which are positive reinforcers under only a very limited number of conditions are less likely to be abused to a serious extent by humans than drugs that are self-administered no matter what the environmental situation. The assessment of the abuse liability is a drug is a complex question, and while researchers are often prone to promise simple answers, it is clear that if we are to make progress in decreasing the abuse of drugs, our efforts must continue.

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# Complex Schedules and Maintenance of Drug Dependence

# Second-Order Schedules: Extended Sequences of Behavior Controlled by Brief Environmental Stimuli Associated with Drug Self-Administration

Steven R. Goldberg, Ph.D., and Michael L. Gardner, Ph.D.

## INTRODUCTION

A factor common to all conceptualizations of drug dependence is the persistent maintenance of behavior that leads to drug self-administration. Vivid descriptions of the complex, often protracted, sequences of activities involved in obtaining and administering various drugs are contained in both the lay and scientific literatures on human drug abuse. Such a sequence might, for example, consist of breaking into a home, stealing property, converting the property to money, and finally purchasing, preparing, and administering a drug--the effects of which are often short-lived. Although the terminal event, administration of the drug, is ultimately responsible for those behaviors, the environmental stimuli occurring in specific temporal relations throughout the sequence must also contribute heavily to the maintenance of both the individual components of the sequence and the overall pattern of behavior (Wikler, 1965, 1973; Goldberg, 1970, 1975; O'Brien, 1975). An experimental analysis of the functions of environmental stimuli in the maintenance of extended sequences of behavior terminating in drug injection is of obvious interest.

Over the last 20 years this kind of analysis has been pursued in the laboratory using the preparation, techniques, and theoretical framework developed by Skinner (1938) and Ferster and Skinner (1957) in the study of operant conditioning. Requirements for the basic preparation consist of an experimental subject, response manipulandum, method of drug delivery, and means of presenting exteroceptive stimulus changes within a controlled environment. Studies of drug self-administration usually employ rats or monkeys as subjects and a lever press as the response. Drug solutions are typically infused through chronically implanted venous catheters and can be delivered

automatically according to specified relations between responding and environmental events (i.e., according to given schedules). Lights and tones most often are used as exteroceptive stimuli in addition to drug injections.

Generally, responding by laboratory animals has been maintained under relatively simple schedules of drug injection. Drugs have most often been injected following a fixed number of responses, an arrangement designated a fixed-ratio (FR) schedule. Although occasional experiments have used FR schedules requiring 100 or more responses per injection (FR 100), most have not exceeded FR 30, and by far the most common schedule has been FR 1. Fixed-interval (FI) and variable-interval (VI) schedules also have been used. Under an FI schedule, the first response after a fixed period of time produces an injection; under a VI schedule the period of time before a response can produce an injection is not fixed but varies from one injection to the next. These simple schedules have been used with many drugs to determine if responding that results in the injection of a drug will be initiated, and, if so, to study the effects on rate of responding and drug intake of variations in dose of the drug and parameter value of the schedule. Results of these studies have provided useful parametric information and have demonstrated the validity of applying a behavioral analysis to the problem of human drug abuse (see Goldberg, 1976; Johanson, 1978; Spealman and Goldberg, 1978 for reviews). Under appropriate conditions, injections of drugs from diverse pharmacological classes have been shown to control rates and patterns of responding in much the same manner as more frequently studied maintaining events such as food or water presentation.

Although laboratory experiments on responding maintained under simple schedules of drug injection have contributed much to an analysis of the ways in which different drugs interact with ongoing behavior to produce a given effect, a more complete understanding of the complex patterns of behavior involved in human drug self-administration necessarily requires the use of correspondingly complex laboratory preparations. It is up to laboratory investigators to develop experimental procedures for the generation of response sequences that closely resemble, in terms of complexity and persistence, the patterns of behavior characteristic of human endeavors. To the extent that we can do so, our confidence in the relevance of those procedures as components of animal models of human drug self-administration will be increased. In recent years a growing number of studies have employed second-order scheduling procedures to gain experimental control over long and orderly sequences of behavior terminating in drug injection.

## SECOND-ORDER SCHEDULES OF DRUG INJECTION

Under second-order schedules, completion of an individual component (or unit) schedule, rather than an individual response, produces the terminal event according to another overall

schedule. Thus, they are appropriately considered "schedules of schedules" (cf., Kelleher, 1966a, b). Second-order schedules have been used extensively in behavioral preparations to study the unitary properties of complex patterns of behavior, the generality of schedule processes, and stimulus functions in extended behavior sequences. The rates and patterns of responding maintained under second-order schedules are of wide generality with respect to the species of subject, type of response, and type of maintaining event (cf., Findley, 1962; Kelleher, 1966a; Goldberg et al., 1975; Marr, 1979).

Figure 1 serves to illustrate some of the terminology, procedures, and results common to studies of second-order schedules of drug self-administration. Cumulative records of lever pressing by squirrel monkeys under two second-order schedules of intravenous cocaine injection are shown. In the top panels, lever presses produced a 2-sec illumination of amber stimulus lights (S) according to a 30-response fixed-ratio component schedule (FR 30: S); and, component completion produced the amber lights and an injection of 100 µg/kg of cocaine according to an overall 5-min fixed-interval schedule (FI 5-min). The entire second-order schedule is abbreviated: FI 5-min (FR 30: S), and is read: "a fixed-interval 5-min schedule of fixed-ratio 30 components." Diagonal marks of the response pen in each record indicate brief-stimulus presentations; resetting of the response pen to baseline indicates cocaine injection. In the bottom panels, the component schedule remained FR 30, but the overall schedule was lengthened to FI 15-min. With S-254 and S-60, the response pen now occasionally reset automatically after 1100 responses as well as with cocaine injection. Overall rates of responding in excess of one response per second were maintained under both schedules. The inserts (a and b to the right of the figure) show that patterns of responding typical of FR schedules were maintained within individual components that terminated only with brief stimulus presentations (see also, Goldberg, 1973a, b; Goldberg et al., 1975). In further experiments, discussed below, the functions of stimuli paired with response-produced injections of morphine or cocaine under second-order schedules have been examined. Results of these studies provide important information on the role of drug-paired stimuli in the acquisition, maintenance, and extinction of long and orderly sequences of behavior terminating in drug self-administration.

## EFFECTS OF DRUG-PAIRED STIMULI DURING ACQUISITION

Two experiments have demonstrated enhanced control over responding as the result of presenting brief drug-paired stimuli during acquisition (Kelleher, 1975; Goldberg and Tang, 1976). In the first experiment, lever presses by a rhesus monkey (R-529) produced intravenous injections of 30 µg/kg of cocaine under an FI 10-min schedule; each injection was preceded by a 2-sec illumination of amber stimulus lights. The top panel in figure 2 shows a cumulative record of responding under this schedule from early in the animal's history. Rate of responding was low, and

FIGURE 1

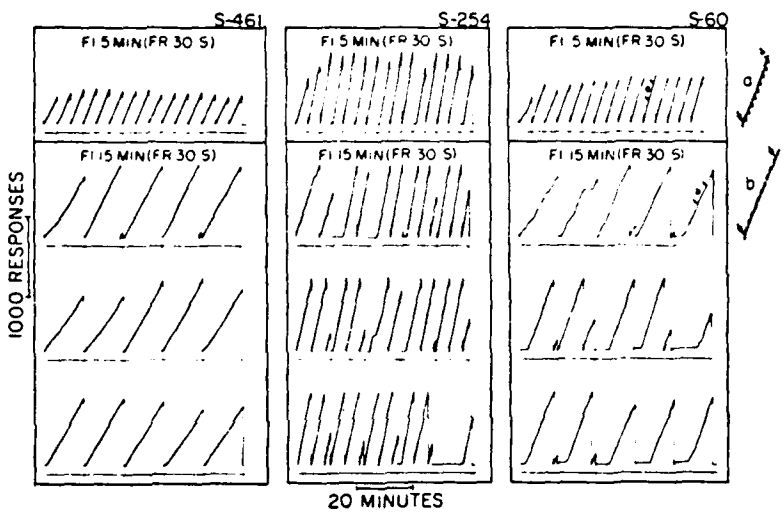


FIG. 1. High rates of responding maintained in squirrel monkeys (S-461, S-254 and S-60) under two second-order schedules of cocaine injection. Completion of each 30-response fixed-ratio component schedule produced a 2-sec presentation of amber stimulus lights (FR 30: S); the first FR 30 component completed after 5 min elapsed [top records; FI 5-min (FR 30: S)] or 15 min elapsed [lower records; FI 15-min (FR 30: S)] produced both the amber lights and an intravenous injection of 100 µg of cocaine hydrochloride per kg. Abscissae: time. Ordinates: cumulative number of lever-pressing responses. Short diagonal deflections of the response pen indicate brief stimulus presentations. The response pen reset to the bottom of the record whenever 1100 responses cumulated and when cocaine was injected; downward deflections on the horizontal event lines also indicate injection of cocaine. After each injection there was a 1-min timeout period during which the recorder was stopped. Each session ended after the 15th timeout period. A complete experimental session at the 5-min fixed-interval condition is shown for each monkey in the top panel; a complete experimental session for each monkey at the 15-min fixed-interval condition is shown in the lower panel (from top to bottom). (S. R. Goldberg, unpublished observations).

FIGURE 2

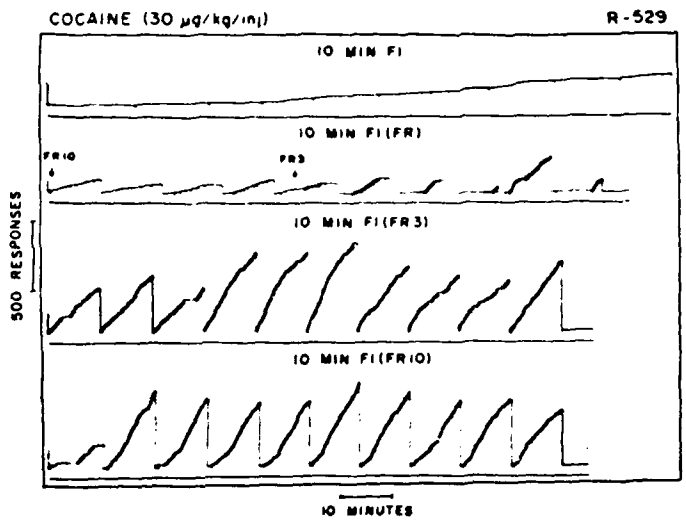


FIG. 2. Increases in responding after the transition from a 10-min fixed-interval schedule of cocaine injection to a second-order schedule of cocaine injection with fixed-ratio components (rhesus monkey R-529). Abscissae: time. Ordinates: cumulative number of lever-pressing responses. First panel: performance under a 10-min fixed-interval schedule of cocaine injection. Each short diagonal stroke on the record indicates 2-sec presentation of amber lights accompanied by an intravenous injection of 30 µg/kg of cocaine hydrochloride. Second panel: first session under a second-order schedule. Completion of each 10-response (FR 10) or 3-response (FR 3) fixed-ratio schedule component produced a 2-sec illumination of amber stimulus lights, indicated by a short deflection of the response pen. The first FR component completed after a fixed interval of 10 min elapsed produced the amber lights and an injection of 30 µg/kg of cocaine, indicated by the resetting of the pen to the bottom of the record. Third panel: Second session under a second-order schedule with FR 3 components; recording as in second panel. Fourth panel: subsequent performance under a second-order schedule with FR 10 components: [FI 10-min (FR 10: S)]; recording as in second panel.
(From Kelleher, R. T. Characteristics of behavior controlled by scheduled injections of drugs. Pharmacological Reviews, 27: 307-323. © 1975, American Society for Pharmacology and Experimental Therapeutics.)

no clear indication of the temporal patterning characteristic of FI schedules was yet evident. The second panel shows the effects of changing from the simple FI 10-min schedule to a second-order FI 10-min schedule of FR components. Initially every tenth response, and later every third response, produced the brief amber lights; the first FR component completion after 10 min had elapsed produced both the amber lights and cocaine injection. Rate of responding increased slightly when the ratio requirement under the second-order schedule was 10 responses and increased markedly when the requirement was reduced to three responses. Subsequently, rates of responding in excess of one response per sec were maintained with either FR 3 or FR 10 components. Although these second-order schedules did not alter the maximum frequency of cocaine injection, rate of responding increased greatly within a very short period of time.

A second experiment (Goldberg and Tang, 1976) also showed that high rates of responding could be rapidly engendered when brief presentations of drug-paired stimuli were scheduled during acquisition. Another rhesus monkey (AX) was initially exposed to experimental conditions under which each lever press produced an intravenous injection of 0.2 mg/kg of morphine accompanied by a 2-sec illumination of red stimulus lights. Record A in figure 3 shows responding from the first session under this FR 1 schedule of morphine injection. Two or three injections were produced early in the session; then, approximately midway through the session, rate of responding increased and over 40 injections were produced within the next 15 min. In the third session a fixed ratio of 10 responses was required for every injection. Only low rates of responding were maintained during the eight sessions that this FR 10 schedule of morphine injection remained in effect (Record B). The experimental conditions then were changed to a second-order FI 60-min (FR 10: S) schedule: every tenth response produced the 2-sec red lights and the first FR 10 component completion after 60 min produced both the red lights and intravenous injection of 5 mg/kg of morphine. Under this schedule, injection of drug was restricted to the end of each session, and 23 hr or more elapsed before the start of the next session. Rate of responding increased dramatically during the first session under this second-order schedule (Record C). After 40 sessions, the within-component patterns of responding were characteristic of those maintained by simple FR schedules and responding over the 60-min interval showed the gradual positive acceleration typical of simple FI schedules. Overall rate of responding remained at a substantial level (Record D).

The final performance of monkey AX illustrates an important characteristic of second-order brief-stimulus schedules of drug injection. Long and orderly sequences of behavior can be maintained when the direct effects of the drug are minimal or absent. This characteristic can be particularly useful when studying drugs with pronounced suppressant effects on behavior, such as morphine.

FIGURE 3

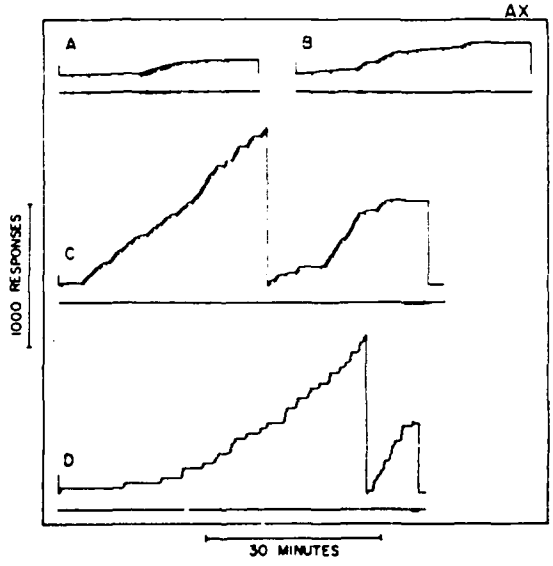


FIG. 3. Increases in responding after transition from a simple fixed-ratio (FR) schedule of intravenous morphine injection to a second-order schedule with FR units (rhesus monkey AX). Abscissae: time. Ordinates: cumulative number of lever-pressing reponses. Top records: the first session (A; session 1) when each response produced a 0.2 mg/kg injection of morphine sulfate and the third session (B; session 3) when every tenth response produced a 0.2 mg/kg injection of morphine sulfate. Each injection was accompanied by a 2-sec presentation of red stimulus lights. A short diagonal deflection of the response pen and the event pen indicates presentation of the red lights accompanied by a morphine injection. The session ended after 47 injections (A) or 19 injections (B). Middle and bottom records: the first session (C; session 5) and 37th session (D; session 40) under a second-order schedule, in which completion of every 10-response (C) or 30-response (D) FR schedule component during a 60-min interval of time produced only the 2-sec red lights; the first FR component completed after 60 min elapsed produced the red lights which remained on until 25 injections of 0.2 mg/kg morphine sulfate were delivered (total dose of 5 mg/kg). Diagonal deflections of the response pen indicate presentations of the red lights and downward deflections on the horizontal event line indicate injections of morphine spaced 10 sec (C) or 2 sec (D) apart. The response pen reset to the bottom of the cumulative record whenever 1100 responses cumulated and when the session ended. (From Goldberg and Tang 1976).

## EFFECTS OF DRUG-PAIRED STIMULI DURING EXTINCTION

The effects of presenting brief stimuli during periods in which saline is substituted for drug (extinction) have been shown to depend on the interaction between the animal's history of stimulus presentations before and during extinction and the ongoing rates and patterns of behavior (Kelleher and Goldberg, 1977; Goldberg et al., 1981). When previously drug-paired stimuli were presented regularly during the time that extinction was occurring, responding declined rapidly and little evidence for any effect of the stimulus presentations was found. Figure 4 shows the effects of substituting saline for cocaine on responding by a squirrel monkey (S-461) under a second-order FI 5-min (FR 30: S) schedule. Responding was maintained at the high rate typical of this monkey during the early intervals of the first saline-substitution session, but declined rapidly towards the end of this session and remained low in subsequent saline-substitution sessions. These results indicate that the brief light presentations that were so important in the rapid acquisition of high rates of responding rapidly lost their efficacy when drug was no longer injected.

Under slightly different conditions, however, presentations of previously drug-paired stimuli can markedly enhance behavior undergoing extinction (Kelleher and Goldberg, 1977; Goldberg et al., 1981). With one squirrel monkey (S-416) that had shown high overall rates of responding under a second-order schedule of cocaine injection identical to the one shown in figure 4 with S-461, the schedule was first modified by increasing the overall FI length to 180 min (i.e., 10,800 sec) before extinction of behavior was studied (Goldberg et al., 1981). Every 30th response during the overall 180-min interval produced a brief illumination of amber stimulus lights; cocaine was injected in association with the lights only once each day at the end of the 3-hr session (figure 5). Despite the extended session length and very low frequency of drug injection, high overall rates continued to be maintained throughout each session. When injections of saline were substituted for cocaine and the brief light presentations were omitted, rate of responding fell and the within-component fixed-ratio patterns of responding were absent. Saline substitution without brief stimulus presentations was continued for eight sessions. In the ninth session, brief stimulus presentations were reinstated under the component FR 30 schedule, but saline continued to be injected at the end of the overall FI 180-min schedule. The original high rate and fixed-ratio patterns of responding were almost totally restored. Over the next nine sessions of saline substitution with the brief stimulus presentations, rate of responding gradually decreased to the level maintained previously without the stimuli. At this point, cocaine was again injected at the end of the overall FI 180-min schedule, and responding was quickly restored to pre-extinction levels.

FIGURE 4

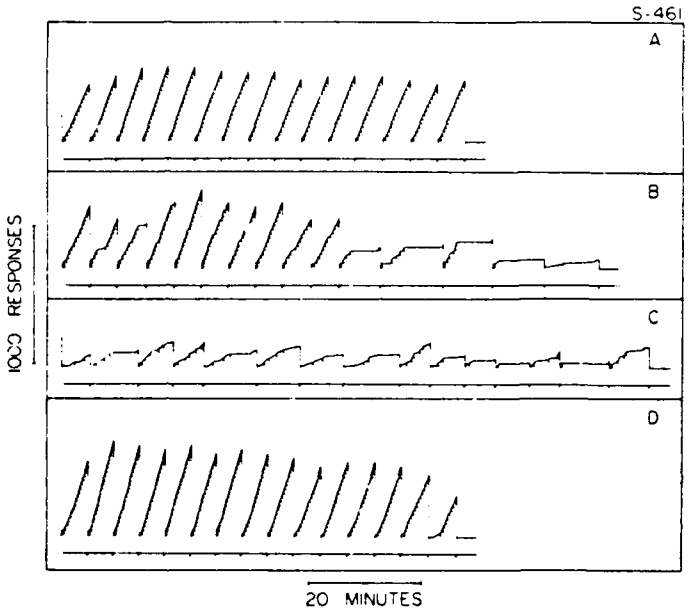


FIG. 4. Effects of substituting saline injections for cocaine injections with squirrel monkey S-461. Completion of each 30-response fixed-ratio (FR 30) component produced a 2-sec presentation of amber lights; the first FR 30 component completed after 5 min elapsed produced both the lights and intravenous injection of either 100 μ/kg cocaine hydrochloride or saline. Recordings as in figure 1 except that the recorder was stopped during both the timeout periods and 2-sec presentations of the amber lights. Panel A shows the last session with cocaine injections before substituting saline; Panels B and C show the first and fourth sessions of saline substitution, respectively; and Panel D shows a subsequent session with cocaine injections reinstated. (S. R. Goldberg, unpublished observations).

FIGURE 5

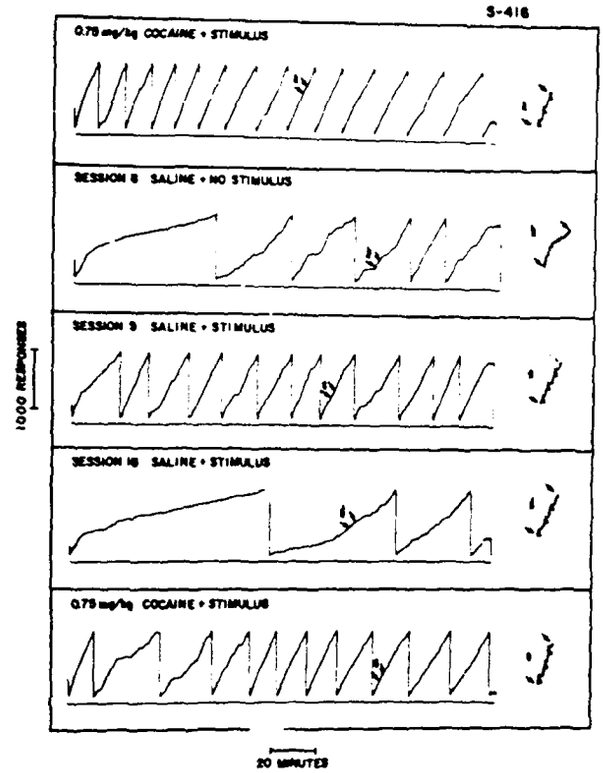


FIG. 5. Effects of reinstating brief stimulus presentations during saline substitution after an intervening number of sessions of saline substitution in which the stimuli were not presented (squirrel monkey S-416). Abscissae: time. Ordinates: cumulative responses. Diagonal deflections of the response pen indicate brief stimulus presentations. The response pen reset to the bottom of the record after 1100 responses and at the end of the session. The event pen was displaced downward during the period of time in which repeated injections of cocaine hydrochloride (total dose of 0.75 mg/kg) or injections of saline were associated with amber lights. Components were 30-response fixed-ratio schedules; the overall schedule was a 10,800-sec (i.e., 180-min) fixed-interval schedule. Component completions produced 2-sec presentations of the amber lights in all records except the one shown in the second panel in which no brief stimuli were presented. The top panel shows responding under the second-order FI 10,800-sec (FR 30: S) schedule of cocaine injection. Saline was then substituted for cocaine and the brief stimuli were omitted for the next eight sessions; the eighth session is shown in the second panel. Next, the brief stimuli were reinstated, but saline continued to be injected; the first (session 9) and last (session 18) sessions under these conditions are shown in the next two panels. The last panel shows reinstatement of cocaine injections. Note the immediate restoration of high rates and fixed-ratio patterns of responding when the brief stimuli were first reinstated during saline substitution (session 9).
(From Goldberg, S.R., Kelleher, R.T., and Goldberg, D.M. Fixed-ratio responding under second-order schedules of food presentation or cocaine injection. J Pharmacol Exp Ther, 218(1):271-281, 1981. © 1981, American Society for Pharmacology and Experimental Therapeutics.)

Very similar results were obtained in a related study with squirrel monkeys in which completion of 10 consecutive FI 5-min components resulted in injection of 300 µg/kg of cocaine (Kelleher and Goldberg, 1977). When saline was substituted for cocaine and brief light presentations at the completion of each FI component were omitted, rate of responding fell and the within-component fixed-interval patterns of responding were absent. Reinstating brief presentations of previously drug-paired stimuli at completion of the fixed-interval components, while saline substitution continued, increased the overall rate of responding and engendered within-component patterns of responding characteristic of simple FI schedules.

These experiments indicate that an animal's history with respect to brief stimulus presentations during extinction is an important factor in determining the effects of those stimuli on ongoing behavior. When the stimuli were presented throughout the course of extinction, response rate decreased rapidly and patterns of responding were disrupted. If, however, responding was allowed to decline during an initial extinction period in which the stimuli were not presented, subsequent reintroduction of the stimuli temporarily restored rates and patterns of responding to pre-extinction levels.

## EFFECTS OF DRUG-PAIRED STIMULI DURING MAINTENANCE

Comparisons of Presence Versus Absence of Drug-Paired Stimuli. Just as brief presentations of drug-paired stimuli can enhance performance during both acquisition and extinction of behavior, brief stimulus presentations during long-term maintenance of responding by consequent drug injections also have pronounced effects (Kelleher and Goldberg, 1977; Goldberg et al., 1981). Figure 6 shows the effects of omitting the brief stimulus presentations on responding by monkey S-254 under a second-order FI 15-min (FR 30: S) schedule of intravenous cocaine administration. When every 30th response produced brief illumination of amber stimulus lights, and the first component FR 30 schedule completed after 15 min produced both the lights and 100 µg/kg of cocaine, responding was maintained at a high rate throughout the overall FI 15-min schedule (panel A). Omitting the brief stimuli, while leaving all other conditions the same, greatly decreased the overall rate of responding and engendered long pauses at the beginning of many of the intervals (panels B and C). Reinstating the brief stimulus presentations returned responding to previous levels (panel D).

Figure 7 summarizes these data on the effects of omitting the brief stimulus presentations under the FI 15-min (FR 30: S) schedule, and shows the effects of varying the dose per injection on quarterlife and overall rate of responding. Quarterlife is a measure frequently used to assess the amount of positive acceleration in responding under FI schedules, and is defined as the percentage of the interval during which 25 percent of the responses are made. Thus, a linear rate of responding produces

FIGURE 6

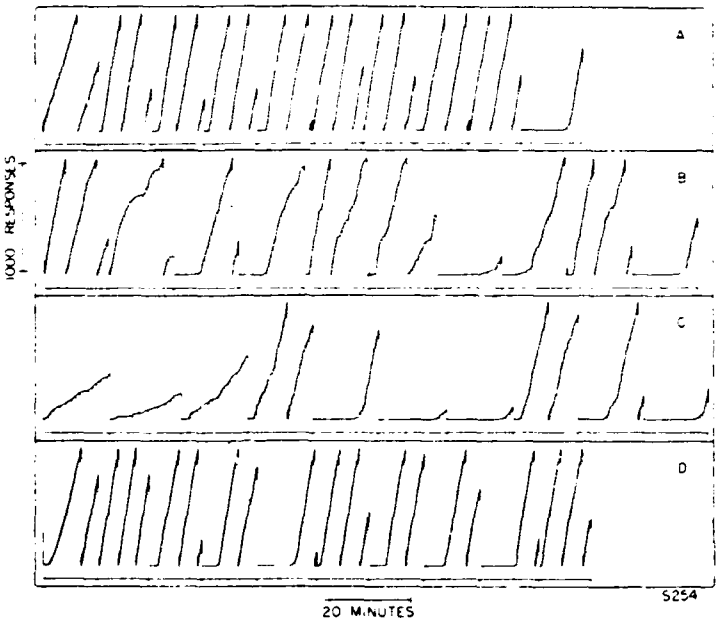


FIG. 6. Effects of omitting brief stimulus presentations under a second-order schedule of cocaine injection in squirrel monkey S-254. The first 30-response fixed-ratio component completed after 15 min elapsed produced a 2-sec presentation of the amber stimulus lights and intravenous injection of 100 µg/kg of cocaine hydrochloride [FI 15-min (FR 30: S)]. Recordings as in figure 1 except that the recorder was stopped during 2-sec presentations of the amber lights in records A and D (indicated by downward deflections of the response pen). When the brief stimulus presentations were omitted (records B and C), 2-sec presentations of the amber lights occurred only in association with the injection of cocaine at the end of each interval (downward deflections of the response pen indicate FR component completions). Cumulative records are shown from the last session before omitting the brief stimulus presentations (A), the first session (B) and the third session (C) in which brief stimuli were not presented during the intervals, and the second session (D) after reinstating the brief stimuli. (S. R. Goldberg, unpublished observations).

FIGURE 7

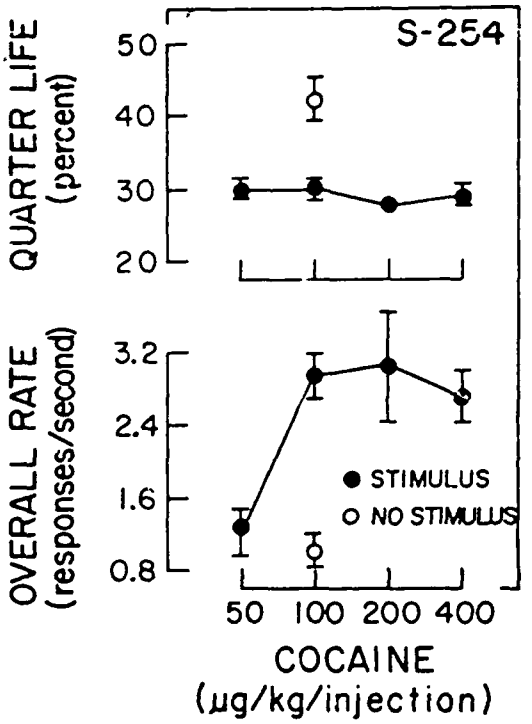


FIG. 7. Quarterlife values and overall response rates for a squirrel monkey (S-254) as a function of the dose of cocaine hydrochloride per injection. Components were 30-response fixed-ratio schedules; the overall schedule was a 15-min fixed-interval schedule. Component completions produced either a brief presentation of drug-paired stimulus lights (filled circles) or no stimulus change (open circles). Abscissae: dose, log scale. Ordinates: quarterlife values (top) and overall response rates (bottom). Circles represent the mean of the last three sessions (stimulus) or two sessions (no stimulus) at a dose; bracketed vertical lines show the range. Each dose of cocaine was studied for at least four sessions, and the no stimulus condition was studied for three sessions. Note the marked decrease in overall response rate and increase in quarterlife when the brief stimuli were omitted. (S. R. Goldberg, unpublished observations).

a quarterlife value of approximately 25 percent; progressively higher quarterlife values indicate progressively more positive acceleration (i.e., lower rates at the beginning of the interval and higher rates at the end of the interval). With monkey S-254, quarterlife values remained at approximately 30 percent across a range of cocaine doses from 50 to 400 µg/kg/injection, indicating a relatively constant rate of responding throughout the overall interval. Omitting the brief stimulus presentations at the 100 µg/kg/injection dose (open circle) increased the quarterlife to over 40 percent, indicating relatively less responding at the beginning of the interval and more responding at the end of the interval. Overall rate of responding was lowest at the 50 µg/kg/injection dose, approximately tripled at the 100 µg/kg/injection dose, and then remained high at the last two doses. As previously seen in figure 6, omitting the brief stimulus presentations greatly decreased the overall rate of responding. These findings have been replicated in additional squirrel monkeys with variations in the type and parameter value of the second-order schedule of cocaine injection (Kelleher and Goldberg, 1977; Goldberg et al., 1981).

The effects of omitting brief stimulus presentations during maintenance of responding also have been replicated using both rhesus and squirrel monkeys responding under second-order schedules of morphine injection (Goldberg and Tang, 1976, 1977). In the Goldberg and Tang studies, the schedules were of the general form FI 60-min (FR 30). Every 30th response produced either a brief illumination of stimulus lights or no stimulus change; the first component completion after 60 min produced repeated morphine injections paired with the stimulus lights. Figure 8 shows the effects on overall response rates of varying the dose of morphine at the end of the 60-min interval. Rates of responding were lowest at the 0 mg/kg dose (saline) and either increased steadily or increased to asymptotic levels as the dose of morphine was increased.

Figure 9 shows the effects of omitting and reinstating the brief stimulus presentations on overall rates of responding with two squirrel monkeys (S-369 and S-405). When the morphine-paired brief stimuli were no longer presented, rate of responding declined over several sessions to approximately half the level maintained before the stimuli were omitted; responding quickly recovered to the higher rate when the brief stimulus presentations were reinstated. A comparable effect is shown in figure 10 with a rhesus monkey (AT) responding at two different doses of morphine (0.5 and 5.0 mg/kg). Although the 5.0 mg/kg dose maintained higher rates under both stimulus and no stimulus conditions than did the 0.5 mg/kg dose under comparable conditons, omitting the stimuli at either dose produced large decreases in rates of responding.

Comparison of Drug-Paired and Nonpaired Stimuli. The experiments up to this point have all investigated the effects of presence versus absence of brief stimulus presentations. A

FIGURE 8

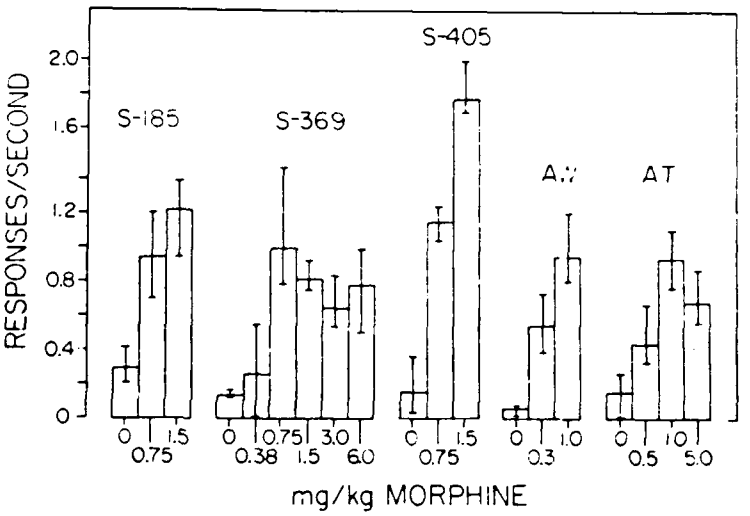


FIG. 8. Overall response rates of three squirrel monkeys (S-185, S-369 and S-405) and of two rhesus monkeys (AW and AT) under a second-order schedule of intravenous morphine injection as a function of the total dose of morphine sulfate injected at the end of the session. Abscissae: dose. Ordinates: mean response rate. Each bar represents the mean and the brackets the range of the last five sessions at each dose of morphine and of the last three (squirrel monkeys) or two (rhesus monkeys) sessions of saline (0 mg/kg) substitution. Doses of morphine were studied for eight to sixteen sessions, saline for at least four sessions. (Based on data from Goldberg and Tang, 1976, 1977).

FIGURE 9

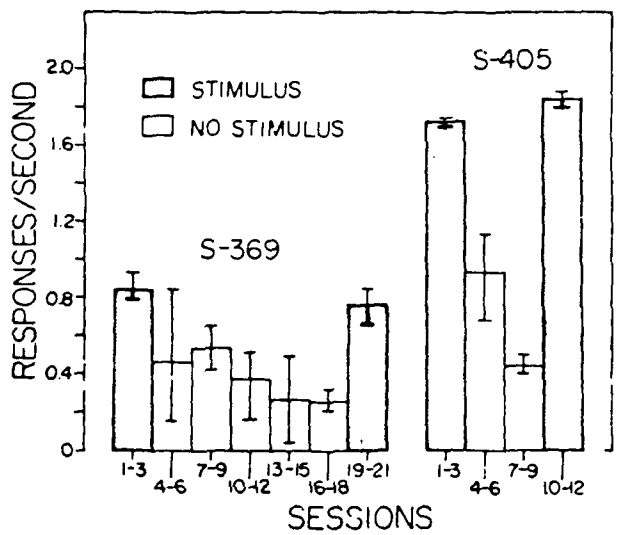


FIG. 9. Overall response rates of two squirrel monkeys (S-369 and S-405) under the second-order schedule of intravenous morphine injection as a function of presenting or not presenting 2-sec amber stimulus lights at completion of each 30-response fixed-ratio (FR 30) component. Abscissae: consecutive sessions. Ordinates: mean response rate. Each bar represents the mean and the brackets the range of three sessions. Each session ended with intravenous injection of a total dose of 1.5 mg/kg morphine sulfate. Shaded bars represent sessions when the 2-sec stimulus occurred at completion of each FR 30 component; open bars represent sessions when no stimulus change occurred at completion of each FR 30 component (the amber lights occurred only in association with injection of morphine at the end of the session). Note the marked decrease in responding when the brief stimuli were omitted. (Based on data from Goldberg and Tang, 1976, 1977).

FIGURE 10

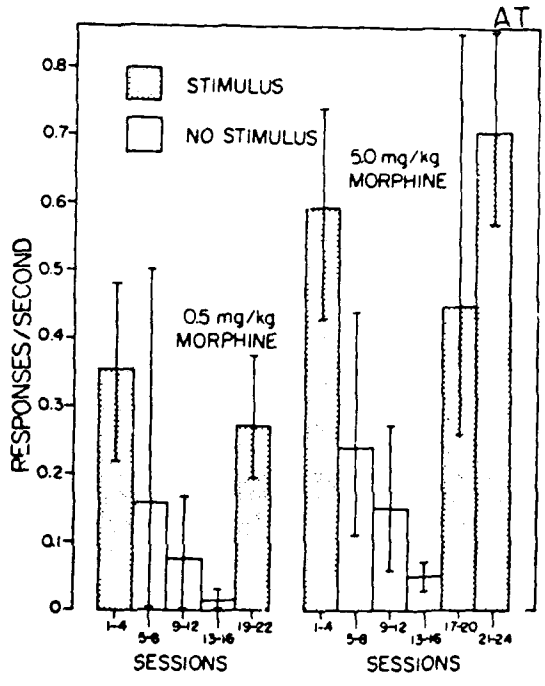


FIG. 10. Overall response rates of rhesus monkey AT under the second-order schedule of intravenous morphine injection as a function of presenting or not presenting 2-sec red lights (brief stimulus) at completion of each 30-response fixed-ratio (FR 30) component. Abscissae: consecutive sessions. Ordinates: mean response rate. Each bar represents the mean and the brackets the range of four sessions. Each session ended with intravenous injection of a total dose of 0.5 mg/kg or 5.0 mg/kg morphine sulfate. Shaded bars represent sessions when the 2-sec stimulus occurred at completion of each FR 30 component and open bars represent sessions when no stimulus change occurred at completion of each FR 30 component. When the brief stimuli were omitted at the 0.5 mg/kg morphine dose, mean response rate dropped to such a low rate (session 16), that when the brief stimuli were reinstated the FR response requirement was initially reduced to one and three (sessions 17 and 18, respectively; not shown in this figure) and subsequently returned to 30 (FR 30; sessions 19 to 22). (From Goldberg and Tang, 1976).

recent study (Goldberg et al., 1979) examined the extent to which the pairing of a stimulus with drug injection was responsible for the enhanced performance when brief presentations of the stimulus were scheduled. Squirrel monkeys responded under second-order schedules in which completion of component fixed-ratio schedules produced either morphine or cocaine injection according to overall fixed-interval schedules. With the group of monkeys for which morphine injection was the terminal event (S-667, S-388, S-369 and S-405), the parameter value of the overall FI schedule was 60 min; with the group for which cocaine injection was the terminal event (S-334, S-333 and S-411), the parameter value of the overall FI schedule was 10 min. Components consisted of FR 30 schedules for all monkeys in the morphine group and for one monkey (S-334) in the cocaine group; components were FR 100 schedules for the other two monkeys in the cocaine group. With all animals, injections at the end of the interval were accompanied by illumination of amber stimulus lights. Completions of component FR schedules produced, in separate experimental phases: 1) brief illumination of amber lights; 2) brief illumination of blue lights; or 3) no stimulus change. Thus, comparisons were made between 1) paired stimulus, 2) nonpaired stimulus, and 3) no stimulus changes at completion of components.

Figure 11 shows cumulative records of responding by monkeys from each group under the three conditions. High rates of responding were engendered by the second-order schedules with paired brief stimuli. Additionally, within-component patterns of responding characteristic of simple FR schedules were maintained. When nonpaired stimuli were presented, overall rates of responding decreased, and component FR patterns of responding were disrupted. These changes were even more pronounced when the stimuli were omitted altogether.

Figure 12 summarizes the effects of the different methods of presenting stimulus changes at component completion on local and overall rates of responding for all monkeys in both groups. Local rates of responding in figure 12 were calculated as the average rate from the first to last response in each FR component (i.e., pause time before the first response in each fixed ratio was not included in the computations). Overall rates of responding were calculated by dividing the total number of responses by the total time, excluding responses and time in the presence of the amber or blue lights. Paired brief stimulus presentations clearly maintained higher local and overall rates of responding than either nonpaired stimulus presentations or no stimulus presentations; with monkeys for which the comparison can be made, nonpaired stimuli maintained higher rates than no stimuli. Thus, the discriminative control exerted by brief stimuli occurring regularly throughout sequences of behavior terminating in drug injection is sufficient to enhance responding somewhat, but pairing the stimuli with drug injection increases their efficacy.

FIGURE 11

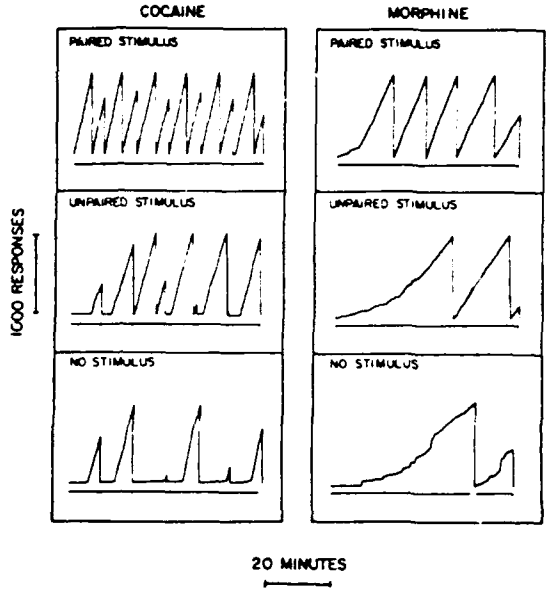


FIG. 11. Representative cumulative records showing responding under the second-order schedules of intravenous cocaine or morphine injection when the completion of every fixed-ratio component during the fixed interval produced either a paired (amber light) or a nonpaired (blue light) brief stimulus or when the brief stimuli were omitted. Abscissae: time. Ordinates: cumulative responses. Short diagonal deflections of the response pen indicate brief stimulus presentations; downward deflections on the horizontal event lines indicate injection of drug. Left panels show responding during portions of the session under the secondorder schedule of cocaine injection (monkey S-411); recordings as in figure 1. Right panels show responding during the entire session under the second-order schedule of morphine injection (monkey S-388, paired and nonpaired stimuli; monkey S-405, no stimulus); recordings as in figure 2.
(From Goldberg, S.R., Spealman, R.D., and Kelleher, R.T. Enhancement of drug-seeking behavior by environmental stimuli associated with cocaine or morphine injections. Neuropharmacology, 18:1015-1017, 1979. © 1979, Pergamon Press, Ltd.)

FIGURE 12

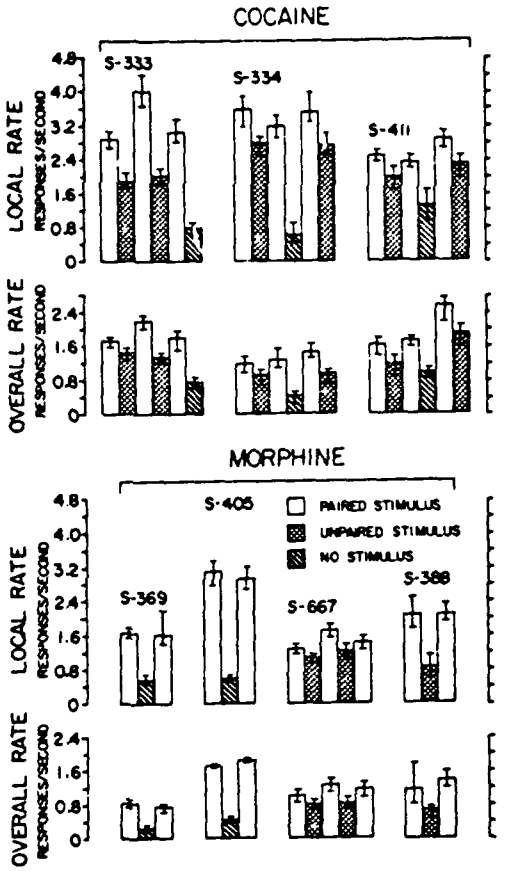


FIG. 12. Local and overall rates of responding (responses/sec) under the second-order schedules of intravenous cocaine or morphine injection when the completion of every fixed-ratio component during the fixed interval produced either a paired or a nonpaired brief stimulus or when the brief stimuli were omitted. Bars show average rates of responding during the last three sessions of each successive condition for individual monkeys; brackets show ranges. Each condition was studied for 5 to 20 consecutive sessions.

(From Goldberg, S.R., Spealman, R.D., and Kelleher, R.T. Enhancement of drug-seeking behavior by environmental stimuli associated with cocaine or morphine injections. Neuropharmacology, 18:1015-1017, 1979. © 1979, Pergamon Press, Ltd.)

Second-Order Schedules of Nicotine Injection. In addition to providing useful procedures for the study of stimulus functions in extended behavior sequences, second-order schedules have enabled other phenomena to be studied under laboratory conditions that might otherwise have been difficult to control experimentally. For example, a number of investigators have noted that nicotine maintains very low rates of responding leading to its injection by laboratory animals under conditions in which presentation of other drugs maintains high rates of responding (e.g., Deneau and Inoki, 1967; Yanagita, 1972, 1977; Griffiths et al., 1979). Indeed, it has been suggested that nicotine may have aversive properties that limit human smoking behavior (Russell, 1976, 1979). However, in a recent laboratory study, high rates of responding by squirrel monkeys were maintained under second-order brief-stimulus schedules of nicotine injection (Goldberg et al., 1981; Goldberg and Spealman, 1981a).

The procedures involved were similar to those employed in previous studies with cocaine and morphine. Squirrel monkeys responded under second-order schedules in which every tenth response produced brief illumination of amber stimulus lights; the first component FR 10 schedule completed after an overall FI schedule of 1 or 2 min had elapsed produced both the brief lights and intravenous injection of 30 µg/kg of nicotine. Each injection was followed by a 3-min timeout period during which the chamber was dark and responses had no programmed consequences.

Representative cumulative records of responding by each of three squirrel monkeys (S-151, S-200 and S-156) under these schedules are shown in figure 13. Responding was well maintained by 30 µg/kg injections of nicotine at overall rates of approximately one response per sec. Characteristic fixed-ratio patterns of responding were controlled by the brief stimuli: responding during each ratio unit was usually characterized by an initial pause, followed by an abrupt transition to a high steady rate of responding that terminated with presentation of the brief stimulus or drug. The average local rate of responding was about four responses per sec.

These results are especially interesting in view of the fact that the same doses of nicotine that functioned to maintain responding under the second-order schedule also can function effectively to suppress responding maintained under an FR schedule of food presentation (Goldberg and Spealman, 1981b). Thus, nicotine can have pronounced actions in either maintaining or suppressing behavior, depending on the environmental context within which it is studied. Current studies of second-order performances maintained by nicotine injection are being conducted to determine the range of conditions resulting in rapid acquisition, prolonged maintenance, and subsequent extinction of the behavior.

FIGURE 13

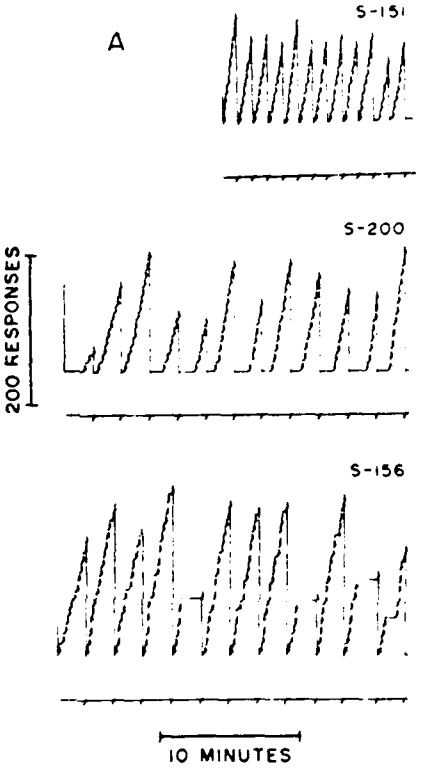


FIG. 13. Representative performance of three squirrel monkeys (S-151, S-200 and S-156) under a second-order schedule of intravenous nicotine injection. Every 10th lever pressing response (FR 10) during a 1-min (S-151) or 2-min interval (S-200 and S-156) produced a 2-sec illumination of amber stimulus lights; the first FR 10 component completed after 2 min elapsed produced the 2-sec amber light and a 30 µg/kg injection of nicotine tartrate [FI 2-min (FR 10: S)]. Recordings as in figure 1. (S. R. Goldberg, unpublished observations).

Second-Order Schedules of Intramuscular Drug Injection. Using second-order schedules, it has also been possible to maintain long, reproducible sequences of behavior terminating in intramuscular drug injections (e.g., Goldberg and Morse, 1973; Goldberg et al., 1976; Katz, 1979). Figure 14 shows representative cumulative records of responding by a squirrel monkey (S-667) under a second-order schedule of intramuscular cocaine injection. The experimental conditions, and resulting performance, are very similar to those described previously except that injections of cocaine were given intramuscularly rather than intravenously. The second-order schedule used in this study was a 30-min fixed-interval schedule of 30-response fixed-ratio components. Completion of the first FR 30 component after 30 min had elapsed illuminated amber stimulus lights for 2 min. While the amber lights were on, the door of the experimental chamber was opened and 3.0 mg/kg of cocaine was injected into the monkey's calf muscle.

Figure 14 shows the effects of substituting saline for cocaine, and of removing and reinstating brief presentations of the amber lights at completion of the FR 30 components. The effects of these manipulations were similar to the effects of comparable manipulations when drugs were injected intravenously: rate of responding decreased when saline was substituted for cocaine (left panel), and rate of responding decreased and component FR patterns of responding were absent when the brief stimuli were omitted (right panel). The demonstration that responding can be maintained under second-order schedules terminating in intramuscular injections of drugs provides a potentially important technical contribution to the laboratory analysis of drug self-administration. It may be possible, using these techniques, to study drugs that are difficult to administer intravenously because of low solubility or other factors. Also, longer studies may be attempted since the need to implant and maintain chronic venous catheters is eliminated.

## SUMMARY AND CONCLUSIONS

The present results, and those of other studies of responding under second-order schedules of drug injection (e.g., Goldberg et al., 1975, 1976, 1981; Kelleher and Goldberg, 1977; Katz, 1979), were generally similar to results of studies that have used food as the maintaining event (for reviews see Gollub, 1977; Kelleher, 1966a; Marr, 1969, 1979). Rates and patterns of responding under second-order schedules have been shown to be controlled by interactions among: 1) the type and parameter value of the component schedule; 2) the type and parameter value of the overall schedule; and 3) the manner of presenting exteroceptive stimulus changes at completion of components. When brief stimuli paired with cocaine, morphine, or nicotine injections were presented at completion of fixed-ratio component schedules, rates and patterns of responding typical of simple fixed-ratio schedules were obtained. Presentation of the drug-paired stimuli controlled high rates and characteristic fixed-

FIGURE 14

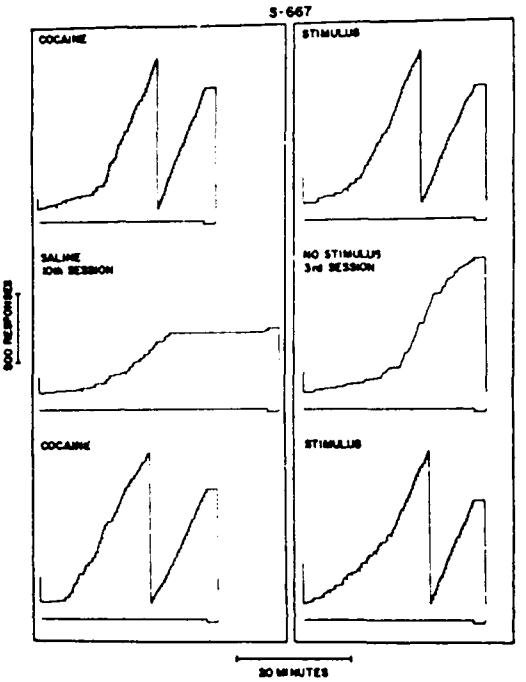


FIG. 14. Representative performance maintained under a second-order schedule of intramuscular cocaine injection in squirrel monkey S-667. Abscissae: time. Ordinates: cumulative lever-pressing responses. Short diagonal deflections of the response pen indicate brief stimulus presentations. The response pen reset to the bottom of the cumulative record whenever 1100 responses cumulated and at the end of the session. Completion of each 30-response fixed-ratio (FR 30) component during a 30-min interval produced a 2-sec presentation of amber stimulus lights (all records except the one at the middle right in which no brief stimuli were presented). The first FR 30 component completed after 30 min elapsed illuminated the amber lights for 2 min during which time the chamber was opened and the monkey given an intramuscular injection of 3 mg/kg of cocaine hydrochloride in the calf muscle. The event pen was displaced downward during this 2-min period of time. The effects of substituting saline injections for cocaine injections for 10 sessions (middle left record) and of omitting the brief stimulus presentations for three sessions (middle right record) are shown. Upper and lower records show control performance before and after saline substitution or omission of brief stimuli. (S. R. Goldberg, unpublished observations).

ratio patterns of responding in much the same manner as other frequently studied consequent events, such as food presentation. When the stimuli were omitted, rates of responding were lower and component fixed-ratio patterns were absent. Presenting stimuli that were not paired with drug injection produced intermediate rates of responding and patterns of responding that were less distinct than those obtained with paired stimuli. Previous studies that have used fixed-interval rather than fixed-ratio schedules as components of second-order schedules of drug injection have found similar effects of presenting or omitting drug-paired stimuli (e.g., Kelleher and Goldberg, 1977; Katz, 1979).

The experiments reviewed in this paper all used overall fixed-interval schedules under which fixed-ratio component completions produced drug injections only after fixed periods of time elapsed. Results of these experiments were generally consistent with those of previous experiments that have used food presentation as the maintaining event; responding either was maintained at a high rate throughout the overall interval or consisted of an initial pause followed by positive acceleration to a high rate that terminated with drug injection. However, studies of comparable second-order brief-stimulus schedules of food presentation have sometimes reported more pausing at the beginning of overall fixed-interval schedules than those reported here under the second-order schedules of cocaine or nicotine injection (e.g., Gonzalez and Goldberg, 1977; Goldberg et al., 1981; Kelleher, 1966b). The relatively higher rates early in the interval when cocaine or nicotine was used as a maintaining event might partially have resulted from the direct aftereffects of previous drug injections (cf., Katz, 1979; Goldberg et al., 1981). Cocaine (e.g., Gonzalez and Goldberg, 1977; Spealman, Goldberg, Kelleher, Goldberg and Charlton, 1977) and nicotine (e.g., Spealman et al., 1981) have both been shown to increase rates of responding early in the interval under fixed-interval schedules of either food presentation or termination of a stimulus associated with electric shock. It is important within this context, however, to note that omitting presentations of brief drug-paired stimuli decreased rates of responding early in the overall interval even under the second-order schedules of cocaine injection. This finding may have implications for programs designed to modify human drug-taking behavior, since presenting drug-paired stimuli not only increased rates of responding maintained by drug injection, but produced these increases at the time drug injection was least imminent.

When stimuli paired with either cocaine or morphine injections were introduced early in the experimental histories of rhesus monkeys, they had profound effects on behavior. Although rates of responding controlled by the drug injections were low, and patterns of responding were erratic, introducing drug-paired stimuli rapidly engendered high rates of responding and a temporal patterning of responses characteristic of the fixed-ratio schedules under which they were produced. Thus, even

before behavior maintained by drug injection had stabilized, stimuli associated with the injections could markedly enhance responding in a manner typifying the process of reinforcement.

Presenting previously drug-paired stimuli during periods of saline substitution had different effects depending on the conditions under which they were presented. When the stimuli were presented throughout the period of saline substitution, response rates declined rapidly and component fixed-ratio patterns of responding were disrupted. Markedly different effects were obtained, however, if responding was first allowed to decline during a period of saline substitution in which the stimuli were not presented. Subsequent reintroduction of stimulus presentations temporarily restored rates and patterns of responding to those maintained when drugs had been injected. Thus, previously drug-paired stimuli can retain their response-maintaining characteristics for a long period of time when they are not repeatedly presented during extinction. Processes similar to those described here with laboratory animals could play a significant role in human relapse to drug self-administration after prolonged periods of abstinence (Wikler, 1965, 1971; Goldberg, 1970).

Direct analogies between the control of human behavior and any given set of laboratory procedures are, of course, tenuous at best. Sufficient amounts of experimental data simply have not been collected, especially on human behavior. Nevertheless, second-order schedules of drug injection appear to resemble in many respects the conditions under which human behavior outside the laboratory is maintained by drug self-administration. Drug injections are not continuously available but are administered intermittently only after progression through a number of sequential stimulus changes and component behavior patterns. The orderly patterns of responding by laboratory animals under second-order schedules of drug injection also compare favorably in terms of their persistence and complexity to those seen in humans. These complex patterns of drug self-administration behavior are extremely sensitive to manipulations of environmental variables and this is another promising field for future research. As yet there seems to be literally no limit to the amount of behavior that can be maintained by drug injections using second-order scheduling contingencies.

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# The Place of Adjunctive Behavior in Drug Abuse Research

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To call a stream of behavior "excessive" is to vilify it. Most excessive behavior is conceived of as bad, although some is seen as exceptional, or even the output of genius. A central question revolves around the sources of unusual amounts of behavior, whether we consider that behavior good, bad, or indifferent. The study of this question can elucidate the genesis of particular excessive behavior that we find obnoxious.

Behavior is labeled and censured as excessive because society finds its personal, medical, or social consequences repugnant. Again, this excessiveness is not a quality of the behavior itself, but of the social sanctions applied. Therefore, perhaps, we should study all manner of behavioral excesses and how they come about, not just those which society has decided are outside its bounds of acceptable behavior. We propose, then, to seek the general sources producing behavioral exaggeration, not just those regarded as pathological.

Both society and its clinical services consider excessive behavior to be invasive or intrusive if it interferes with alternative, adaptive behavior which could and should be occurring in the situation. Much of the current concern with illicit drug seeking and drug taking revolves around this issue. Other excessive behavior is considered undesirable because it produces negative consequences: overeating, cigarette smoking, and child or spouse abuse, for example.

There are several theoretical notions about how excessive behavior is generated. One is that there is an intrinsic defect in some persons. This could be a "bad seed," bad genes, or just a weak will.

Another view is that a person who is basically all right may be the subject of some sort of demonic possession--if not by a literal demon, perhaps a demon-like process, such as exposure to a highly seductive drug. Weakness in the face of overwhelmingly enticing goods or services is not condoned, but some sympathy is felt for those temporarily fallen from grace, since some stimuli have a reputation for being all but irresistible.

A third way in which behavioral excess is believed to be generated is by irritative disinhibition. Some dark and atavistic side of human nature can be released by indulging in dangerous chemical substances. Such agents can weaken the "will" or the "cortical inhibitions," allowing dangerous impulses behavioral egress. These three notions are not mutually exclusive, and it is not unusual to find all of them entwined in accounts of putative mechanisms underlying the control of behavior by drugs having abuse liability.

All of these conceptions are genie-in-the-bottle theories. Something inside the person, when it gets out, is behaviorally intrusive. Environmental conditions, by this view, can trigger or precipitate behavioral excesses, but they are not really determiners of behavior. The important determinants of excessive behavior are seen as structural defects which are innate or are formed by early physical or psychic trauma. There is a kind of internal class struggle: the good, inhibitory responses hold the bad, impulsive responses in check. This point of view has led to a set of beliefs about what will happen when people are given easy access to potent reinforcers such as drugs. Loss of control will occur because these agents both activate the primitive reaction patterns and disrupt our defenses. Some drugs are purported to be like push-pull amplifiers: they pull you because they are euphorics, and they push you because they either release aggression or produce a zombie-like state of carelessness about personal or social consequences. From this perspective, the only way to keep potent reinforcers from producing behavioral excesses, then, is to keep people from getting their hands on them.

In contradistinction to this view, there is an increasing recognition of the socioeconomic determinants of antisocial behavioral excesses. Environmental determinants are now used explicitly to maintain desirable behavior and to attenuate unwanted behavior. Since reinforcing and punishing events have been to some extent used successfully to control behavioral excesses, the assumption has been that perhaps similiar events have contingently engendered the excesses in the first place. While this may be the case, clear proof is lacking. Excessive behavior, by such a view, would be maintained because it is followed by reinforcing consequences.

While it cannot be denied that such a mechanism may be an important underlying factor sustaining substance abuse, it is becoming evident that we also have a different model of excessive and persistent behavior, one which appears counteradaptive in that it is not under the control of obvious contingencies of reinforcement. The phenomenon is called schedule-induced or adjunctive behavior.

## SCHEDULE-INDUCED BEHAVIORS

A number of years ago, I found that a rather ordinary experimental arrangement produced a curious and dramatic result (Falk 1961). When a normal rat was placed into a chamber for about 3 hours each day and required to lever-press to earn most of its food ration, it did so, but it also concomitantly drank inordinate amounts

of water. Enough food was permitted each day to maintain the body weight at about 80 percent of the normal adult free-feeding weight. The rat was free to move about the chamber and press the lever at any time, but a press paid off with a 45 mg food pellet only intermittently, on the average of once per minute. This "variable-interval 1-minute" schedule of reinforcement (Ferster and Skinner 1957) produces a moderate, but persistent, rate of pressing. Among the marks of excessive behavior are that it appears to be counteradaptive and that it tends to be chronic, or at least to reappear frequently. Large and useless amounts of water are drunk by animals as an adjunct to the schedule of reinforcement described above as well as many other schedules (Falk 1969). In the initial experiments with the variable-interval schedule, rats pressed at a moderate rate until a pellet was delivered and then a burst of drinking ensued, followed by a return to pressing. Animals drank after eating almost every food pellet. Drinking in connection with eating is not unusual, but the amount of water ingested over a 3-hour session was most unusual: Animals drank close to one-half of their body weights!

In this initial study, 14 rats were exposed to this schedule. Within a week or two the pressing and drinking pattern had stabilized, with a mean session water intake of 92.5 ml. This was about ten times the average intake of the control animals, rats reduced to 80 percent of their normal, free-feeding weights, but given their food pellets all at once; these drank an average of only 9.5 ml in 3.5 hours. It should be noted that in none of these experiments were the animals ever deprived of water. When they were not in the experimental chambers for their 3-hour session each day, they were housed in individual home cages with free access to water. Extensive study of the conditions that produce session overdrinking revealed no traditional physiological or behavioral considerations which could account for the induction of this persistent overdrinking, or polydipsia, which lasts month after month, as long as the distributed-feeding condition remains in effect.

Unlike drinking produced by the depletion of body water, or by eating highly salted food, this polydipsia is not mitigated by intubating water into the stomach before a session (Falk 1969). Furthermore, the overdrinking does not depend on the intermittent eating of a dry food pellet; it can be produced by a variable-interval schedule of liquid food portions (Falk 1967). Instead of listing classic physiological and behavioral variables which do not account for this schedule-induced polydipsia (for review see Falk 1969, 1971), let us characterize the crucial factors which produce the phenomenon. The experimental arrangement described really contains only two constraints which are not present in the living conditions of most other normal, laboratory-dwelling animals: a limited food ration and a limitation on the rate at which this ration can be eaten. While the reduced food ration in itself does not produce overdrinking, somehow the confluence of the two restraints does.

A powerful behavioral phenomenon, such as schedule-induced polydipsia, is unlikely to be the only excessive behavior generated by such ubiquitous schedule conditions as intermittently delivered food. Indeed, quite similar food intermittency conditions yield schedule-induced aggression or attack. For example, a pigeon earning small portions of food intermittently in an experimental chamber which also contains a semi-restrained second pigeon shows a pattern of directed attack against this pigeon shortly after the delivery of each portion of food (Azrin et al. 1966). As in the case of schedule-induced polydipsia, the attack level is quite excessive as measured against nonintermittent food conditions (either no food available or the ration given as a single large portion). This aggressive behavior can take many forms. For example, squirrel monkeys will repeatedly bite a rubber hose after the intermittent delivery of each small food portion (Hutchinson et al. 1968).

These behavioral excesses are not simply reflexive responses evoked by the periodic delivery of a bit of food. If the water or the restrained pigeon is not freely available in the situation, the animals will work repeatedly to attain access to them (Cherek et al. 1973, Falk 1966). The behavioral excesses, then, reveal the animals' considerable motivation to engage in them, since they will work hard to attain these opportunities.

How widespread are the behavioral excesses produced? Hyperactivity in animals (Levitsky and Collier 1968) and humans (Fallon et al. 1979), consumption of nonfood materials (pica) (Villarreal 1967), escape responses (Azrin 1961), and of particular interest in the present context, the intake of various drugs (Gilbert 1978), have all been investigated. Thus far, we have only mentioned the production of these phenomena in the rat, pigeon, and squirrel monkey. Other studies have revealed them in the mouse, rhesus monkey, gerbil, chimpanzee, and in humans as well (Falk, in press).

Are these behavioral excesses produced only by food deprivation and schedules of food delivery? While most of the experimental work has been done using food schedules, the generation of schedule-induced adjunctive behavioral excesses is not limited to this condition. Schedule-induced activity in rats has been produced by intermittent access to water; conversely, overdrinking has been produced by scheduling running-wheel access. In humans, hyperactivity, polydipsia, and smoking have been induced by the scheduled presentation of monetary rewards, the playing of games, or by problem-solving (Clarke et al. 1977, Fallon et al. 1979, Muller et al. 1979, Wallace et al. 1975, Wallace and Singer 1976). Thus, there is a considerable degree of generality both in the kinds of commodities or behavior sequences whose intermittency generates adjunctive behavior and in the variety of the resulting adjunctive, excessive activities. The scheduling of commodities and activities important to the individual, then, proves to be a major multiplier or exaggerator of ancillary, unexpected behavioral outputs.

## IMPLICATIONS FOR SUBSTANCE ABUSE

It is of critical interest, for our present purposes, to establish whether this excessive behavior bears a homologous relation to those excesses in humans classed as substance abuse. If such a homology is to be considered plausible, at least three points need to be established. First, there must be evidence that adjunctive behavioral excesses do occur in humans under appropriate schedule-induction conditions. This has been confirmed. Second, the schedule-induction conditions should be rather nonspecific in terms of the particular commodity which is being made available on an intermittent basis. That is, it should be sufficient that the commodity or activity be of importance to the individual in a motivational sense. Again, available evidence confirms the generality of this relation: several kinds of scheduled events have been demonstrated to induce various sorts of excessive behavior in humans. Third, schedule induction should be able to institute and maintain drug abuse in animals under conditions that otherwise would not lead to excessive drug taking. Unless such a relation holds true for animals, the human homology would be a difficult argument to sustain. Once again, several drug classes are chronically accepted at excessive levels under appropriate schedule-induction conditions. These include overdrinking of barbiturates, narcotic analgesics, amphetamines, chlordiazepoxide, and ethanol (Gilbert 1978).

Schedule induction can change a weak, oral reinforcing agent into a very powerful one. For example, ethanol was drunk excessively by a group of rats exposed continuously to an intermittent feeding schedule (Falk et al. 1972). On this schedule, a food pellet was delivered to a rat every 2 minutes for a 1-hour feeding period. Feeding periods were each spearated by 3 hours, making six 1-hour feeding periods for each 24-hour cycle. Five percent ethanol was the fluid available for 3 months. The mean alcohol intake for eight animals was 13.1 grams per kilo per day. The blood ethanol level of these animals remained above 100 mg/dl for the major part of the 24-hour cycle, and often lay between 150 and 300 mg/dl. The ethanol solution was preferred to water and some other solutions, and the chronically excessive intake resulted in severe physical dependence on ethanol. Comparable animals maintained under similar nutritional conditions, but not fed on an intermittent schedule, did not drink as much alcohol as the scheduled animals nor did they show evidence of physical dependence (Falk and Samson 1975). A number of studies in animals, using food pellet schedules, have demonstrated schedule-induced excessive intravenous drug self-administration with heroin, methadone, cannabis, and nicotine (Oei et al. 1980, Smith and Lang 1980, Takahashi and Singer 1980).

Many drugs are reinforcers to both animals and humans (Johanson 1978), but under most circumstances, particularly when taken orally, they function as weak reinforcing agents. Some schedules can exaggerate the reinforcing properties of agents, thereby increasing their oral or intravenous self-administration. Both nature and society often provide us with an uneven flow of the commodities

important to survival or the maintenance of an accustomed style of life. Environmental situations, then, in many ways constitute a set of complex, intermittent schedules.

The particular adjunctive behavior that might be induced by such natural schedules would depend upon the available behavior alternatives. Adjunctive behavior is to some extent a function of the opportunities present in the environment. In animals, the presence of a fluid to drink permits excessive drinking. Hyperactivity often occurs if a running wheel is made available in conjunction with an inducing schedule. In humans, the alternative opportunities provided by the environment are probably critical in determining what behavioral excesses occur, be they drug taking, violence, exercise, or creative endeavors.

Clearly, however, even with creative or productive alternatives to drug taking available, there is no assurance that an individual will take advantage of them. Past history and training are critical in enabling a person to utilize a potential opportunity. It is probable that those persons lacking complex behavioral repertoires will turn more readily to easily consumed adjuncts, such as drug taking. Society must take care to provide alternative behavioral repertoires which enable us to make creative and productive choices. If commodity access is limited, as it often is, in such a way that adjunctive behavior occurs persistently, then it is desirable that this excessive behavior be productive, or at the very least, benign.

The induction of excessive, adjunctive behavior by rather simple schedule conditions demonstrates how commodity constraint in one realm can result in excessive behavior in a seemingly unrelated domain. It should be emphasized that these are all normal behavioral processes demonstrable in normal, unselected experimental subjects. Bizarre or extreme manipulations were not imposed. The commerce with life's commodities which is arranged in most of the research described is similiar to that probably encountered by most subjects attempting to exploit an ecological niche in competition with other species and their own neighbors or in just working for a living. From normal sources extreme results can flow. Rather bland environmental conditions of intermittence can produce persistent and problematic excesses, including drug abuse.

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# Discussion

## Complex Schedules and Maintenance of Drug Dependence

James E. Barrett, Ph.D.

Behavioral pharmacology now has available a number of extremely powerful techniques which can illuminate and intensify characteristic aspects of drug seeking and other habitual behaviors. It is often the case that certain problems remain intractable until the development of appropriate procedures renders them subject to experimental assault. Significant advances frequently stem from the widespread application of findings that are fundamentally important (Morse 1975). Clearly, the studies described in this session by Goldberg and Falk represent two major instances where the relatively recent application of technical procedures has permitted the experimental establishment and direct analysis of the persistent, excessive behavior typical of substance abuse. These areas are now ripe for fertile, productive analyses and justify further the relevance of studies with laboratory animals to problems of human drug dependence (Griffiths et al. 1980; Schuster 1975).

These developments are interesting in several other respects. The substantial levels of orderly and well-maintained behavior described in the presentations of Falk and Goldberg arose from two rather different procedures. Falk focused on behaviors that have no specifically arranged consequences (schedule-induced behavior), whereas Goldberg emphasized behaviors remotely maintained by an ultimate consequent event (schedule-controlled behavior). The fact that these different procedures can generate such tremendous amounts of behavior is noteworthy. Whether or not the behaviors occurring under schedule-controlled and schedule-induced conditions are similar in other respects is another area of interest in behavioral pharmacology. Falk (1964) asked several years ago whether the effects of various drugs on schedule-induced behavior are similar to those found with schedule-controlled behavior. A related question is whether drug effects differ depending on whether drinking is induced by schedule variables or by fluid deprivation. It has been shown recently that doses of chlordiazepoxide that increased drinking produced by deprivation decreased drinking induced by an intermittent schedule of reinforcement (Sanger and Corfield-Sumner 1979). Other questions likely to attract increasing attention in the future will center on commonalities among schedule-induced behaviors. What other types of schedule-induced behaviors show the same characteristics as schedule-induced drinking? Are there general induction techniques? Are different schedule-induced behaviors affected similarly by drugs? The answer to these questions awaits further research. However, it is clearly feasible to use pharmacological means to dissect these possible different behaviors.

A particular advantage of the use of second-order schedules described by Goldberg is that behavior is maintained over extended periods by environmental stimuli remotely paired with drug administration. This feature illustrates the importance of environmental stimuli in supporting and sustaining persistent drug-seeking behavior. In addition, techniques where drug injections occur only infrequently minimize the direct effects of the drug and permit the maintenance of performances by drugs from diverse pharmacological classes (Kelleher 1975).

In addition to offering up procedures which permit the resolution of several interesting problems, behaviors maintained under or engendered by these techniques appear to have a great deal of durability, intensity, and persistence. Indeed, the consequences ultimately maintaining or the factors responsible for engendering these behaviors can often seem so remote or insignificant that the behavior itself assumes the quality of having its own volition and appears to be self-sustaining. We might even be inclined to invent or attribute certain pathological or aberrant qualities to behaviors of this type; they appear compulsive, compelling, addictive, and in Falk's words, "counteradaptive." Yet, if we look at the factors responsible for the genesis and maintenance of these behaviors, they reside clearly in the current environment and in the organism's past history.

This emphasis on the significance of environmental variables in drug abuse is not meant to negate or deny the importance of pharmacological variables. An appropriate balance between dynamic forces must always be struck. There are several instances where drugs have remarkably uniform effects over a wide range of conditions (Balster, this volume; Griffiths et al., this volume). This orderliness allows for the screening of new drugs against known standards and permits the prediction of potential abuse liability, analgesia, and other relevant clinical phenomena. However, we have also seen several instances where drugs and other events seem quite malleable (Barrett, this volume; Young et al., this volume). The statement that events are reinforcers under one condition but not others is contradictory only on a superficial level. It does not imply that screening techniques are invalid or that instances where drugs have multiple effects reveal disturbing inconsistencies. Such results highlight the importance of other variables which are nonpharmacological in nature, but nevertheless of obvious import in determining the specific effects a drug will have on behavior. The analysis of variables, both pharmacological and behavioral, that enter into the production of these different effects promises to yield important information for understanding the behavioral pharmacology of human drug dependence.

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# Discussion

## Complex Schedules and Maintenance of Drug Dependence

Nancy K. Mello, Ph.D.

The past decade has been punctuated by drug "epidemics" that often assume crisis proportions. Oscillating waves of congressional rhetoric and public fervor preceded Nixon's "war on drug abuse." Each subsequent furor launched a variety of Federal initiatives targeted to combat the abuse of marijuana, PCP, alcohol, etc. The quasi-random aperiodicity of these intense spotlights on a particular type of drug abuse tends to obscure the fact that drug abuse is a continuing and perennial problem. Even enlightened Federal recognition of the recurrent nature of drug abuse and its complexity (Strategy Council 1973) has not been translated into enduring, rational policies. Also unfortunate is the apparently pervasive illusion that a brief targeted initiative can somehow "solve the problem." Consequently, even the most modest progress on any front may be followed by an abrupt shift of attention (and resources) to another, suddenly visible, problem area.

Yet the most cursory examination of recent history reveals that many contemporary drugs of abuse (e.g., alcohol, morphine, and cannabis) have been used and abused in this country for over 200 years. Opium, alcohol, and cannabis have been available throughout the world for centuries. The fermentation of alcohol allegedly occurred during the Paleozoic era, and the biblical depiction of Noah's drunkenness is a familiar allegory. Opium was readily available in America until about 1909, when emerging prejudice against Chinese and black minorities became associated with fears of opium addiction and eventually led to anti-narcotic legislation in The Harrison Act of 1914 (Musto 1973). Some more recent entries into the illicit and abused drug circle are PCP (Petersen and Stillman 1978), khat (Halbach 1980), and coca paste smoking (Van Dyke and Byck 1981). Tomorrow's new drug problems are as yet unknown, but unquestionably there will be some.

Given the enduring nature of drug abuse in its myriad forms, it is important to develop better and more stable strategies to try to understand and eventually to modify excessive drug use patterns. A consistent and predictable Federal commitment to research on the problems of drug abuse may be more crucial than the types of

research strategies employed. It is the thesis of this essay that a fragmented, intermittent, crisis-oriented approach to drug abuse is an untenable schedule which disrupts and retards research, encourages divisive short-term (often short-sighted) policies, and ultimately contributes more to the maintenance than to the deterrence of drug abuse. Why? Because the externally imposed schedule of research funding is one critical determinant of the type, quality, and innovativeness of research programs and the ultimate scientific product.

There has been relatively little formal attention to the logistics of research grant acquisition as a controlling schedule which affects both the quality and frequency of occurrence of the research end product. However, consider that 2 years of grant support allows the investigator 1 year to work before he/she must reapply for continuation of funds. The 1-year contract is another compelling case in point, which would seem to insure the routine application of today's procedures to yesterday's questions. It may be that short-term, 2- and 3-year funding patterns are potentially counter-productive, since these time constraints facilitate unambiguous and perhaps unimaginative projects and do not encourage development of exploratory programs. Moreover, short-term funding schedules promote a variety of excessive adjunctive behaviors of which continual grant application preparation and the generation of unimaginative reports of safe studies are but two conspicuous symptoms. In the language of behavioral science, a relatively short inter-grant reinforcement interval may generate adjunctive research behaviors which could be eliminated with longer inter-reinforcement intervals, just as schedule-induced polydipsia, the prototypical adjunctive behavior (Falk 1971), tends to decrease in frequency as inter-reinforcement intervals lengthen.[1]

Research scientists justifiably complain that by the time the staff has been hired and apparatus set up to conduct a series of new studies, actual experimental time is limited to a few months before it is necessary to reapply for funds to continue. Prudence dictates that the recipient of a 2-year grant award, funded on December 1st, should submit an application for continued support by February 1st of the following year. Since many institutions have obligatory internal reviews prior to submission of an application to the funding agency, the actual deadline could be as much as 2 months earlier. Any unforeseen event, e.g., delivery delays, subject drop-outs, animal sickness, system down-time, cannot be easily accommodated on this production-line type of schedule. The now familiar (facetious?) lament about trying to fit in some research between grant application preparations approaches the status of a cliche! Despite grumbling to colleagues, academic scientists seldom

1. "The reinforcement intermittence and thwarting conditions which yield adjunctive and displacement behaviors increase the organism's probability of responding in strength to other possibilities in the environmental context by increasing the gain on operant units receiving relatively low, but appreciable facilitation from current environmental stimuli." (Falk 1971, pp. 586-587)

militantly challenge the schedules that control their research behavior. An ambivalent modesty about one's own research and its importance, often qualified to the point of self-depreciation, is a frequent accompaniment of scientific honesty and antithetical to the "hard sell." Whatever the determinants of nonmilitancy in scientists, the problem discussed here is one of the consequences. There are serious questions as to whether or not the prevalent short-term support schedule is most conducive to creativity and productivity.

An alternative model of research support is provided by the intramural laboratories of the National Institutes of Health and of the Alcohol, Drug Abuse, and Mental Health Administration. Assured of stable salary and basic laboratory support, the Federal scientist has more opportunity to begin research programs which involve long-term objectives and to engage in exploratory and developmental projects. Although periodic internal and external reviews determine the budget for the next fiscal period, most Federal scientists are not recurrently faced with the prospect of cataclysmic cessation of funding and unemployment for a trained research staff. The outstanding research record of the National Institutes of Health (NIH 1975) indicates that biennial anxiety infusions are not a necessary prerequisite to research productivity. Perhaps an effort to develop similar long-term support patterns for the extramural scientists would further enhance the overall quality of science in every area. Since "good" science in all of its guises is a common goal for the supporters and supported alike, some extended dialogue between all concerned about the optimal strategies for extramural research support might be a valuable next step beyond sharing our data and ideas as we have in this conference.

We are only beginning to appreciate the complexities involved in the analysis of drugs as reinforcers. The research presented in this volume illustrates the importance of this question. The demonstration that second-order schedules which require extended sequences of behavior leading to drug injection can effectively control operant responding in primate models has profound implications for the clinical situation. The analogy between a monkey responding for over an hour for a single drug injection and an opiate addict procuring negotiable resources, then contacting the supplier for a single "fix," is quite compelling. Use of this available primate model should lead to considerable progress in clarifying this type of symbolic control of behavior. Moreover, research over the past few years has clearly indicated that the reinforcing properties of drugs are not solely a function of the inherent pharmacological properties of the drug. Drugs with many diverse behavioral and physiological actions are abused. Poly-drug abusers may use drugs with antithetical actions (e.g., stimulants and depressants) simultaneously or in rapid succession. Such considerations have led me to postulate elsewhere that perhaps a critical aspect of drug reinforcement is subjective state change and the direction of that change in state, up or down, may be less important than change itself (Mello 1978).

A conceptual framework and technology exist to address these issues effectively. The groundwork has been laid for a comparative analysis of drugs of abuse which may prove more productive than the tradition of studying each drug in isolation. It is my contention that a comparative approach will yield a behavioral analysis of similarities and differences in the ways in which drugs control behavior (Mello 1980). These variables are amenable to systematic study. As we begin to learn some basic principles which transcend the unique pharmacology of particular drugs, we will be better prepared to deal effectively with the drug abuse problems of tomorrow. A better understanding of the way in which drug use behavior is maintained may ultimately lead to improved treatment, prevention, and amelioration of the adverse medical, social, and economic consequences of drug abuse.

The most dedicated commitment to these goals cannot insure realization of that promise. This requires stable support for research which is dissociated from the unpredictable peaks of emotional public response to each "new" drug menace and the effects of that outcry on Congress. Without stable support to study the perennial problem of drug abuse, research in this area becomes an adjunct to the thrice yearly struggle for grant support. Only the obvious and safe research will be done. Insofar as the schedules of reinforcement control a variety of behaviors including research behavior, it is not unreasonable to argue that under a predictable schedule with extended funding periods, innovation and creativity will be encouraged and the great promise that behavioral pharmacology holds for understanding drug abuse may be fulfilled.

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