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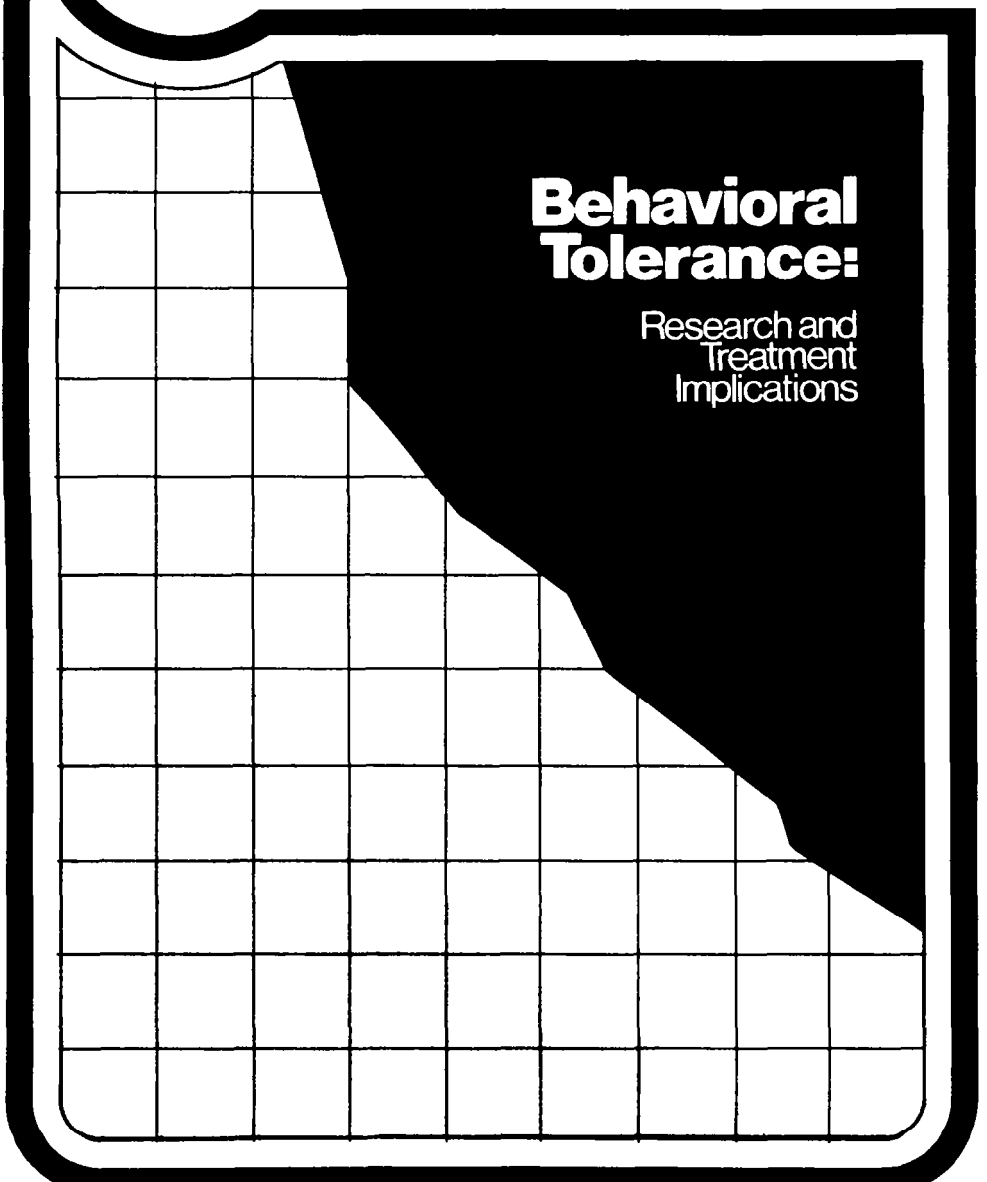

Behavioral Tolerance:

Research and Treatment Implications

US DEPARTMENT OF HEALTH EDUCATION AND WELFARE • Public Health Service • Alcohol Drug Abuse and Mental Health Administration

Behavioral Tolerance: Research and Treatment Implications

Editor:

Norman A. Krasnegor, Ph.D.

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Parklawn Building, 5600 Fishers Lane, Rockville, Maryland 20857

Behavioral Tolerance: Research and Treatment Implications

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Foreword

Tolerance to the effects of abused substances has long been implicated as a causal factor in addiction. Such tolerance is not based entirely on pharmacologic processes; recently the role played by nonpharmacologic factors has become an area of increasing research interest and potential clinical importance. An understanding of the mechanisms of tolerance is a key element in our eventually understanding the larger question of human dependence upon such substances, and ultimately will be useful for developing improved strategies for prevention and treatment.

Aspects of tolerance are being investigated across a broad range of drugs, in humans as well as a variety of animal species. At present, no agreement exists on the mechanisms underlying behavioral tolerance, but as data continue to be added to the base of empirical knowledge, a theoretical synthesis may be approached.

The technical review at which the papers in this monograph were presented was held at the National Institute on Drug Abuse on June 23-24, 1977. At that meeting, past and present research findings on behavioral tolerance in substance abuse were presented; theoretical and experimental approaches to investigation in this field were compared and contrasted; an attempt was made to develop a working definition of behavioral tolerance as it applies to substance abuse; and possible new initiatives for investigating the concept within clinical research and experimental treatment research settings were discussed,

The central purpose of this monograph is to share what was communicated at the technical review, so as to stimulate further interest among the scientific and medical communities in the part played by nonpharmacologic factors in drug tolerance and dependencies, and thus to further the accumulation of new knowledge.

William Pollin, M.D.
Director
Division of Research
National Institute on Drug Abuse

Technical Review Participants

Jack D. Blaine, M.D.
Research Psychiatrist
Clinical-Behavioral Branch
Division of Research, NIDA
5600 Fishers Lane
Rockville, Maryland 20857

Howard D. Cappell, Ph.D.
Head, Psychology
Addiction Research Foundation
33 Russell Street
Toronto, Ontario, Canada M5S2Sl

Stuart M. Deikel, M.A.
Department of Psychology
McGill Universitv
Montreal, Quebec; Canada H3C3Gl
representing
Brooks Carder, Ph.D.
Scientist
Synanon Research Institute
P.O. Box 786
Marshall, California 94940

Peter B. Dews, M.D., Ph.D.
Head, Laboratory of Psychobiology
Department of Psychiatry
Harvard Medical School
25 Shattuck Street
Boston, Massachusetts 02115

John L. Falk, Ph.D.
Professor of Psychology
Rutgers University
Busch Campus
New Brunswick, New Jersey 08903

Douglas P. Ferraro, Ph.D.
Professor of Psychology
University of New Mexico
Albuquerque, New Mexico 87131

Reese T. Jones, M.D.
Associate Professor in Residence
Department of Psychiatry
University of California
401 Parmassus Avenue
San Francisco, California 94143

Eugene Le Blanc, Ph.D.
Director, Strategic Planning
and Research Branch
Addiction Research Foundation
15 Overlea Boulevard
Toronto, Ontario, Canada M4A1A9

Charles P. O'Brien, M.D., Ph.D.
Director, Drug Dependence Treatment and Research Center
c/o Veterans Admin. Hospital
University and Woodland Avenues
Philadelphia, Pennsylvania 19104

Constantine X. Poulos. Ph.D.
Scientist, Clinical Psychology
Addiction Research Foundation
Toronto, Ontario, Canada M5S2Sl

Pierre F. Renault, M.D.
Chief, Clinical-Behavioral Branch
Division of Research, NIDA
5600 Fishers Lane
Rockville, Maryland 20857

Charles R. Schuster, Ph.D.
Professor of Psychiatry
University of Chicago
950 East 59th Street
Chicago, Illinois 60637

Shepard Siegel, Ph.D.
Professor of Psychology
McMaster University
Hamilton, Ontario, Canada L8S4Kl

James H. Woods, Ph.D.
Associate Professor of Pharmacology
University of Michigan
Ann Arbor, Michigan 48104

Technical Review Moderator
Norman A. Krasnegor. Ph.D.
Deputy Chief, Cl&&al-Behavioral Branch
Division of Research, NIDA
5600 Fishers Lane
Rockville, Maryland 20857

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Introduction

Norman A. Krasnegor, Ph.D.

Tolerance to a substance can be demonstrated by the observation that repeated administrations of a fixed dose lead to a diminution of effect. Alternatively, one can demonstrate tolerance by showing that a substance's original effect, diminished in magnitude after sequential exposures to a fixed dose, can be reinstated by an increase in that dose. An understanding of how tolerance influences the dependence processes associated with chronic habitual drug and alcohol use is essential for those who work in the field of substance abuse research because of its reported necessary role in the maintenance of drug addiction and alcoholism. According to this view, drug and alcohol addicts become physically dependent, in part, because the initial effects of a substance diminish with repeated use. In order to attain the original effect that a substance produces in a user, therefore, larger or more frequent doses are consumed. The problem is further compounded for addicts because the diminished response to a fixed dose of an abused substance may lead to the onset of withdrawal symptoms. Thus, the development of tolerance to a substance can contribute to the dependence process by escalating the need for more of that substance to attain a desired effect or to postpone or eliminate abstinence symptoms.

Pharmacologists generally divide the study of tolerance into two broad categories: dispositional and functional. The former subsumes all studies on a substance's effect when changes occur which limit the amount of a substance that bathes its target cells. Such investigations encompass research on altered absorption, distribution, inactivation and/or excretion of a substance from the body. Also included under this rubric is the study of physiological tolerance, i.e., investigations of the altered responsivity of the target cells themselves.

Studies of functional tolerance include all other investigations of tolerance, which are excluded from the dispositional category because the results obtained are not readily understood within the framework of extant pharmacological and/or physiological theories. Behavioral tolerance is an example par excellence of functional tolerance. Study of this phenomenon is important

because it represents a significant conceptual advance. The experimental evidence available shows conclusively that nonpharmacological factors can play a significant role in the development of tolerance. The evidence presented in this monograph demonstrates the relevance of behavioral and environmental variables for this area of research. Even more important, the studies described in this monograph stress the necessity to take the experimental history and the organism's interaction with its environment into account when designing research protocols on tolerance.

Behavioral tolerance can be understood in three ways: empirically, descriptively, and theoretically (Ferraro, this volume). As an empirical term, it is defined relative to the procedures necessary and sufficient to observe it. As a descriptive term, it is defined relative to the aggregate of individual empirical relationships which together constitute the basis for making generalizations and predictions concerning it. As a theoretical term, it is defined relative to underlying mechanisms of action which serve to provide a meta- level explanation for the observed empirical relationships. Behavioral tolerance is used in each of the three ways in this monograph. In this respect, it accurately reflects the state-of-the-art of such research.

At present, there is no acceptable empirical definition for the concept of behavioral tolerance. The consensus of those present at the meeting which led to the publication of this monograph was that the necessary and sufficient conditions and procedures operationally to demonstrate behavioral tolerance are not known. There is an emerging descriptive definition of the concept based upon the continuing empirical work being generated; there is no clear consensus, however, as to whether behavioral tolerance represents the development of tolerance to the behavioral effects of a substance or the effects of behavior on the development of tolerance to the substance's effects. Further research may help to clarify this issue.

There are several theoretical definitions of behavioral tolerance. The elegant experiments of Siegel implicate the role of classical conditioning processes. Carder discusses the possible importance of stress in the development of tolerance. Others, such as Ferraro and Woolverton and Schuster implicate operant principles in the development of tolerance. While there is by no means a consensus, it is apparent that those who have identified learning theory as a mechanism, including Siegel and O'Brien, will actively pursue this line of inquiry. (All of these investigators, this volume.)

It is unclear at present whether research in behavioral tolerance is orthogonal to other types of research paradigms designed to study tolerance in general. Suffice it to say that as the empirical data accumulate, all those who study tolerance will have to integrate such information into their approaches and experimental designs. Future research designed to elucidate the concept of behavioral tolerance could productively focus upon the environment in which the substance abuse occurs. Thus, studies should be

undertaken which investigate the abuser in the social setting and physical surroundings where the habit was acquired and maintained. In addition, the emerging field of human behavioral pharmacology of substance abuse can serve as a framework within which the relationship of self-administration of substance(s) to the development of tolerance can be investigated. Of particular interest would be studies undertaken to determine: why tolerance to a substance develops in some individuals but not others; the relationship of tolerance to the dependence process; and tolerance to the reinforcing effects of substances. Data collected in the human behavioral pharmacology laboratory could serve as a guide for designing studies of substance abuse in the natural environment. For example, the underlying relevant physiological parameters which define the subjective phenomenon of "craving" could then be related to relevant stimuli which occur in the natural environment and help clinicians to treat more effectively those who are dependent.

The possibilities for future research in the field of behavioral tolerance are rich and varied. If what already has been accomplished is an accurate prologue to what will come, we can look forward to much new knowledge which will contribute significantly to our understanding of the dependence processes associated with substance abuse. I am pleased that the National Institute on Drug Abuse has helped contribute to the emergence of this new and exciting field of inquiry and am hopeful that the work presented in this monograph will help to stimulate new and productive research.

I. CONCEPTUALIZATION

Theoretical Basis of Behavioral Tolerance: Implications of the Phenomenon for Problems of Drug Abuse

Charles R. Schuster, Ph.D.

Most studies in the area of behavioral pharmacology involve the determination of the effects of a number of different doses of a drug on a particular behavior. For accuracy in the determination of a drug's potency, such dose-response studies are designed to minimize the interaction of previous drug experience with the effects of each subsequent dose. These studies are essential to determine the profile of behavioral actions of different classes of pharmacologic agents. There are a number of reasons, however, for studying the behavioral actions of drugs given repeatedly under conditions where prior dose experience is likely to modify its subsequent actions. The most compelling reason for conducting such studies is that this is the usual manner in which drugs are taken both for therapeutic reasons and when they are abused.

The most common change produced by prior experience with a drug is a decrease in responsiveness to its effects. When an organism becomes less sensitive to the actions of a drug by virtue of past experience with the drug, we refer to this change as acquired tolerance. If acquired tolerance to one drug confers tolerance to a second drug, we refer to this phenomenon as cross-tolerance.

Investigations of the conditions leading to the development of drug tolerance as well as the mechanisms underlying this change in sensitivity are important areas of investigation for several reasons. Tolerance development complicates the use of a drug in therapeutic conditions demanding its repeated administration. Further, studies of drug tolerance are extremely important in the area of drug abuse, since this phenomenon may be responsible for many of the problems associated with the repeated administration of a drug. The seemingly unending increase in the amount of opiate drugs used by addicts is but one obvious example of the relevance of the study of tolerance to the problems of drug abuse. Of fundamental importance is determining the interrelationship between tolerance development and the development of dependence upon a drug. This interrelationship will be discussed in a later section of this paper.

On the basis of different experimental strategies, pharmacologists have operationally defined tolerance in several ways. Tolerance may be defined as a diminished effect with successive administration of

the same dose of a drug. Tolerance may be further characterized by experiments demonstrating that it is necessary to increase the dose of a drug in order to produce the intensity and/or duration of action originally observed. The most precise manner for defining and quantifying tolerance is to determine dose-response relationships both before and after repeated exposure to a drug. In such experiments a parallel shift in the dose-response curve to the right is an indication that tolerance has developed. In addition, measuring the degree of shift may provide an estimation of the degree of tolerance developed. (There are, however, same reservations regarding the precision of such estimates in whole organism research which will be discussed in a later section.)

Although tolerance is the most common change seen with repeated administration of a drug, in some instances the reverse occurs. Such increased responsiveness to a drug following its repeated administration is termed sensitization. Such sensitization has been reported, for example, for certain of the actions of cocaine (Downs and Eddy 1932; Post 1977; Stripling and Ellinwood 1977; Tatum and Seevers 1929). Although this paper will confine itself to studies of behavioral tolerance, it should be pointed out that identical research strategies are used to study sensitization to a drug.

Subsequent to the establishment of the fact that tolerance does develop to a particular drug, a second stage of research involves the investigation of the mechanisms underlying this change in sensitivity. Many drugs have been investigated in this manner and certain general classes of mechanisms producing tolerance have been established. Tolerance develops to any drug which can induce the synthesis of enzymes responsible for its degradation. Certain barbiturates, for example, are known to increase the concentration of liver microsomal enzymes responsible for their degradation. Thus, when barbiturates are taken repeatedly, we would expect a more rapid elimination of the drug from the body, with a consequent decrease in the intensity and/or duration of the actions of the drug. When amphetamines are administered repeatedly, food intake may be suppressed. Such altered food ingestion causes a change in the pH of the urine, with a consequent effect upon reabsorption of the drug in the kidney. In this case, the drug's disposition is being affected indirectly by a change produced in the organism's eating behavior. When the decreased sensitivity to a drug is explicable on the basis of its altered absorption, distribution, inactivation and/or excretion from the body, we refer to this change as dispositional tolerance. This mechanism, however, cannot account for the tolerance to drugs observed when drug concentrations are equal at the target organs of tolerant and non-tolerant organisms. Under these circumstances, the term functional tolerance is used to suggest some adaptation of the organism to the drug-induced physiologic perturbation. Thus, the term "functional" is used in instances where tolerance cannot be explained on the basis of the drug's altered disposition.

The term "tolerance" is used in relation to a variety of effects. For example in the pharmacologic literature we may read that "cardiovascular tolerance" develops to a drug. Such a term is used purely descriptively to imply that: 1) the drug had some cardiovascular effect, and

2) this effect diminished with repeated administration of the drug. It is in this descriptive sense that I intend to use the term "behavioral tolerance." As this term is being used in this paper it has no mechanistic implications but rather simply means that a drug has some behavioral action which diminishes with its repeated administration. This change in sensitivity to the behavioral actions of a drug may be because of its altered disposition or any functional mechanism.

An excellent review by Kalant et al. (1971) has covered the variables affecting the development of dispositional tolerance to different classes of drugs. In the present chapter, I will concentrate on functional tolerance to behaviorally active drugs, since it is in this area that environmental variables may have influence. Before considering these environmental variables affecting functional behavioral tolerance, we will consider: 1) the strategies for studying behavioral tolerance; 2) strategies for discriminating between functional and dispositional tolerance, and 3) pertinent pharmacologic variables affecting functional tolerance to the behavioral actions of drugs.

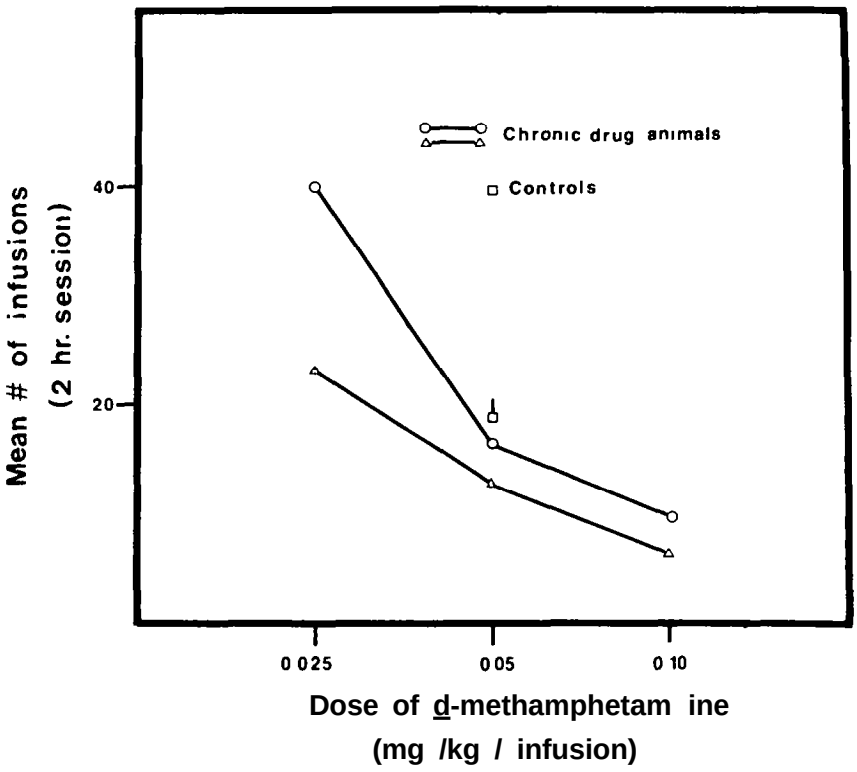
I. STRATEGIES FOR STUDYING BEHAVIORAL TOLERANCE

Potentially any behavior which is affected by a drug could be used in studies of tolerance development. For investigations of the rate and extent of tolerance development, however, the behavior must be quantifiable. Further, there are advantages to using within-subject everimental designs for investigating the effects o repeated administration of a drug. With such designs it is essential that the behavior be stable *over* long periods of time approximating the duration of the repeated drug regimen. The methods of operant conditioning have been shown to generate behavioral baselines which are ideal for the study of both the acute and chronic effects of drugs (Seiden and Dykstra 1977; Thompson and Schuster 1968). These methods emphasize the maintenance of behavior over periods of days, weeks, and months. Further, a wide range of behaviors can be brought under experimental control and precisely measured using these procedures. These attributes make this methodology extremely valuable for the study of drug tolerance. A study from my own laboratory illustrates how such procedures may be used (Fischman and Schuster 1974). In this study, effects of chronic intravenous administration of d-methamphetamine were determined in rhesus monkeys trained to lever press on a Fixed-Ratio 10 schedule of food reinforcement for two hours each day. These animals received an intravenous infusion of drug every three hours beginning at a dose of .0625 mg/kg/infusion. After tolerance developed to the behavioral suppressant effects of the drug, the dose was systematically increased over a six to ten month period to dosage levels as high as 6.5 mg/kg/ . . . It should be obvious that in order to interpret the effects of drugs given repeatedly over an eight to ten month period we must have a procedure which would have generated a stable behavioral baseline if drug had not been given. The methods of operant conditioning are particularly well suited for this purpose, since they have been shown to produce behavioral baselines which remain stable over years (Ferster and Skinner 1957).

In most studies of the effects of repeated administration of a drug on operant behavior, the animals are brought under the discriminative control of lights or tones, and performance is maintained by food or water presentation or the cessation of an aversive stimulus. It is possible, however, to use drugs as discriminative or reinforcing stimuli (Schuster and Balster 1977; Schuster and Johanson 1974; Schuster and Thompson 1969). These studies have obvious implications for the problem of drug abuse. It is of great importance to investigate the development of tolerance to these stimulus functions of drugs. Unfortunately, relatively little systematic work has been done in this area. Recent evidence (Shannon and Holtzman 1976) suggests that tolerance does develop to the discriminative stimulus effects of morphine. However, no systematic studies of tolerance development to the reinforcing actions of morphine have been carried out. Balster and Schuster (1973) presented data showing that there was little change in the reinforcing actions of cocaine over a period of several months. If tolerance developed to the reinforcing actions of the drug, the number of injections taken daily would be expected to increase, and this was not found to be the case. On the other hand, tolerance to the reinforcing actions of cocaine was suggested by the fact that one of the animals in this experiment had a longer past history of self-administering cocaine, and this animal showed a much higher level of intake than the other animals in the study. Clearly, more systematic work must be done to determine whether tolerance develops to the reinforcing actions of cocaine. Such work is now in progress in my laboratory and the data strongly suggests that tolerance to the reinforcing actions of cocaine does not develop.

Observations from my own laboratory also indicate that tolerance does not develop to the reinforcing actions of d-methamphetamine (Fischman and Schuster 1973). This study used two rhesus monkeys previously treated with gradually increasing doses of d-methamphetamine administered intravenously every 3 hours for a period of eight months. During and after the chronic d-methamphetamine regimen it was established that these animals were tolerant to the disruptive effects of the drug on DRL performance maintained by food (Fischman and Schuster 1977). Subsequently, we determined the rate of lever pressing for intravenous infusions of d-methamphetamine delivered under an FR-10 schedule during a Z-hour daily experimental session. Animals were tested with three doses of d-methamphetamine (0.025, 0 .05 and 0.1 mg/kg/infusion) . Figure 1 shows the mean number of drug infusions delivered at each dose of d-methamphetamine. As has previously been shown (Bolster and Schuster 1973), there is an inverse relationship between dose and the number of infusions earned. For comparison purposes the mean number of infusions earned by a group of 5 monkeys never exposed to the chronic drug regimen is also shown in Figure 1 for the dose of 0.05 mg/kg. As can be seen there is no difference in the amount of d-methamphetamine self-administered by the two groups of animals. clearly these observations need confirmation in a more systematic manner. Nonetheless, they strongly suggest that exposure to very high doses of d-methamphetamine does not alter the animal's subsequent responsiveness to the reinforcing actions of the drug. It is important to note that these same animals

FIGURE 1



were tolerant to the disruptive effects of d-methamphetamine on their food-maintained DRL performance. The important point in the present context is that through the use of operant conditioning procedures, tolerance to the discriminative and reinforcing effects of drugs can be studied. More research in this area is needed and should be a high priority item because of its implications for the problems of drug abuse.

To summarize, it is the position of this paper that the methods of schedule-controlled operant conditioning are uniquely suited for the study of the changes in responsiveness to the repeated administration of drugs.

II. METHODS FOR DISCRIMINATING BETWEEN DISPOSITIONAL AND FUNCTIONAL TOLERANCE

Following the observation that tolerance develops to the behavioral actions of a drug, it is important to determine whether this change in responsiveness is due to changes in the disposition of the drug or to functional adaptations to the drug. Ideally, to make this dis-

crimination we would determine whether the concentrations of the drug are the same in the brains of tolerant and nontolerant animals. If the concentrations of the drug are the same in the brains of tolerant and nontolerant animals, we infer that the lowered sensitivity to the drug must be due to some functional change in the organism. If there is a lower drug concentration in the brains of tolerant animals, this suggests that at least in part, the decreased drug responsiveness is caused by dispositional changes. To rule out the involvement of functional changes as well requires giving tolerant animals an increased amount of the drug sufficient to equalize brain concentrations. Only if both groups are then equally responsive may we conclude that the tolerance is completely attributable to dispositional factors.

These ideal strategies, however, are rarely obtainable in practice. With many drugs we are not certain whether metabolites may be pharmacologically active. If they are, then their concentration in the brain as well as the parent compound must be assayed. There is also a question of whether whole brain levels of these substances are the appropriate level of analysis or whether regional distribution of the drug and its metabolites should be measured. In any case, these "ideal" procedures are beyond the capability of most laboratories studying behavioral tolerance. Fortunately there is an alternative strategy which can be utilized to determine whether tolerance to a drug is functional or dispositional. This strategy is based upon the fact that changes in a drug's disposition in the body should result in comparable changes in responsiveness to all of the behavioral actions of a drug. Conversely, it is unlikely that functional tolerance would develop at the same rate or to the same extent to all of a drug's behavioral actions. Thus, if one can demonstrate differential tolerance development to the various behavioral effects of a drug, this strongly suggests that the mechanism is functional. A particularly powerful strategy for showing differential tolerance development is the use of a multiple schedule of reinforcement. This strategy is illustrated in a study by Schuster et al. (1966).

In this study rats were trained to lever press on a multiple fixed-interval (FI)-DRL schedule of reinforcement. When these animals were given repeated administration of d-amphetamine, tolerance developed to the rate-increasing effects in the DRL component but not in the FI component. Clearly, changes in the disposition of d-amphetamine cannot account for the selective tolerance development to the actions of the drug in only one component of the multiple schedule.

This strategy for determining whether behavioral tolerance is functional or dispositional does depend upon the selection of the right behavioral measures. In instances where functional tolerance develops to all the behavioral measures taken, it is impossible to differentiate between functional and dispositional tolerance. This outcome appears unlikely, however, if a broad sample of behavior is obtained.

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III. PHARMACOLOGIC VARIABLES AFFECTING TOLERANCE TO THE BEHAVIORAL ACTIONS OF DRUGS

A. Dosage Regimens

As mentioned in the introduction there are a variety of experimental strategies for demonstrating tolerance development to a drug. In most behavioral experiments investigating the effects of repeated administration of a drug, only one dose of the drug is used. If the effects of this dose diminish with repeated administration, we conclude that tolerance has developed to the drug. In most instances this approach is adequate for this conclusion. It is conceivable, however, that changes in response to the repeated administration of the drug might result from its accumulation rather than tolerance. It is impossible to determine this unless full dose-response relationships are known. For example, an early study of dl-amphetamine tolerance used rats trained on a DRL 17.5 sec. schedule of reinforcement (Schuster and Zimmerman 1961). The acute effect of dl-amphctamine was to increase the animal's response rate. With daily administration of dl-amphetamine, response rates showed progressively smaller increments. This was interpreted as demonstrating tolerance development to the actions of dl-amphetamine on the animal's DRL performance . An alternative explanation of this decrease could be that with repeated daily administration the dl-amphetamine accumulated; therefore, functionally the daily dose was increasing. Since the actions of dl-amphetamine on DRL are biphasic (low doses increase rate and high doses decrease rate), the decreased responding observed could simply represent the effects of a gradually increasing daily dosage level.

One simple manipulation to rule out this alternative interpretation is to determine whether the original effect of the drug can be obtained in tolerant animals by increasing the drug dose administered. This manipulation is a truncated version of the ideal strategy which involves determining a full dose-response curve before, during, and after the chronic drug regimen. Whenever possible this strategy should be utilized. There are, however, some limitations to the use of this ideal strategy in attempting to quantify the degree of tolerance development. These limitations are based upon the fact that when we obtain a dose-response relationship using a behavioral measure, it is highly unlikely that we are dealing with a single effect which varies only quantitatively. This is particularly true when dealing with drug effects which cause a decrease in the rate of an operant response, since many unrelated factors may produce this common outcome. It is argued that a parallel shift in the dose-response curve indicates that we are dealing with the same drug effect. This presumes, however, that the variability in the dose-response relationships is small enough meaningfully to discriminate differences in slopes of the dose-response curves. Unfortunately, behavioral measures often show large variations in response to drugs, thus limiting the usefulness of looking for parallel shifts in dose-response relationships. Clearly this indicates that for quantitative work we must make every effort to improve our behavioral control procedures. It seems quite plausible to speculate that the mechanisms responsible for disruption

of operant performances will vary as a function of the dose of a drug. For example, a low dose of amphetamine might disrupt a food-reinforced lever pressing operant simply because of drug-induced interoceptive changes which function as novel stimuli. As dose is increased the drug may disrupt the ongoing operant by virtue of its interaction with the food deprivation state of the organism. At still higher doses, the drug may elicit stereotypical behaviors, which are greater in strength and incompatible with the operant response. Tolerance may develop to any or all of these actions of the drug. Clearly, the development of tolerance to the novel stimulus effects of the drug could cause a shift in the dose-response curve to the right. However, it is questionable whether in the redetermination we are estimating the degree of tolerance to the novel stimulus effects of the drug or obtaining an unchanged dose response curve for an effect with a higher threshold. This strongly suggests that to investigate fully the development of tolerance to a drug, several dosage levels should be used as the dose given repeatedly.

B. The Selection of Dose for the Chronic Drug Regimen

In the previous section, I have suggested that more than one dose should be studied when investigating whether and to what extent tolerance develops to the behavioral actions of a drug. With drugs which induce enzymes responsible for their degradation, maximal tolerance develops to doses producing maximum enzyme levels. Therefore, studies of this type of tolerance may use relatively high doses of the drug. With functional tolerance, however, the selection of doses is more complicated. If the functional tolerance represents some form of homeostatic adaptation, this adaptation may only be possible across a limited dose range. For behavioral studies, doses somewhere between the ED-25 and ED-75 determined when the drug is given acutely are most appropriate for repeated administration. Higher doses may be tested, but only after tolerance develops to lower doses. If the dose selected for repeated administration causes a complete suppression of the behavior being studied, this may prevent or at least delay the development of compensatory mechanisms which result in tolerante. This is particularly true if the compensatory mechanisms are behavioral in nature and require reinforcement for their strengthening and maintenance. More will be said about this in a later section.

C. Frequency of Drug Administration

Recent work in my laboratory has suggested that more than one type of tolerance can develop to the behavioral actions of the same drug when given with different frequencies. Amphetamines given once daily immediately prior to a session in which rats or monkeys perform on a DRL schedule of reinforcement show the development of tolerance to the drug (Campbell and Seiden 1973; Schuster et al. 1966; Schuster and Zimmerman 1961). Such tolerance development has been shown to be critically dependent upon whether the drug is given before the session or after the session (Campbell and Seiden 1973). When the drug is given chronically after the session, no tolerance develops to its behavioral actions.

This suggests that there is an interaction between the drug and the performance contingencies. On the other hand, we have recently found a marked degree of tolerance to the behavioral actions of d-methamphetamine in rhesus monkeys who did not perform in their behavioral task during the repeated drug regimen. In this case, the repeated drug regimen consisted of twice daily intramuscular injections of d-methamphetamine in gradually escalating dosages from 0.5-16 mg/kg/injection. Following this regimen, the animals showed a 2-4 fold decrease in sensitivity to the disruptive actions of the drug. Neurochemical analysis of the brains of similarly treated monkeys have shown an irreversible depletion in brain monoamines (Seiden et al. 1976). Since the actions of amphetamines in the brain are mediated through monoamines, it seems entirely probable that the tolerance observed in these animals is attributable to the decreased availability of monoamines. Such depletions of monoamines are not seen when low doses of the drug are given to animals daily and hence this cannot be the explanation for tolerance developed when injections are given only once daily. Thus, the mechanism responsible for behavioral tolerance may critically depend on the frequency of administration of the drug during the chronic regimen.

Clearly, systematic investigations of drug tolerance should include the investigation of various doses given at various frequencies. Only in this manner is it possible to define the various conditions under which tolerance may develop. Although such research projects are ambitious, there is no way of shortcutting the task.

IV. ENVIRONMENTAL VARIABLES AFFECTING TOLERANCE DEVELOPMENT TO THE BEHAVIORAL EFFECTS OF DRUGS

In the past few years, studies have begun to appear in the pharmacologic literature demonstrating that environmental variables are of considerable importance in the development of functional tolerance to behaviorally active drugs. In this section I would like to review some of my own work which has convinced me of the central importance of the reinforcement contingencies as a variable affecting behavioral tolerance to a drug. In 1961, I co-authored a paper with Dr. Joseph Zimmerman on the effects of repeated administration of dl-amphetamine to rats trained to lever press on a DRL 17.5 second schedule of milk reinforcement. In this study we observed that the initial effects of. dl-amphetamine were to increase the animals' lever press rate and, as a &sequence, decrease the number of reinforcements received. With repeated administration, however, the animals showed a gradual decline in response rate, a shift in the Inter Response Time (IRT) distribution toward control patterns, and an increase in the number of reinforcements received. Since the effect of the drug declined with repeated administration, we concluded that partial tolerance had developed. In a second study we repeated the original experiment with the addition of obtaining a measure of the animals' general activity every other day. Thus animals were tested on alternate days in the activity apparatus and the operant chamber under the DRl schedule of milk reinforcement. The initial effects of dl-amphetamine were to increase general activity and increase 1ever responding in the DRL sessions. With daily administration of the drug we again observed a gradual shift in the animals' DRL performance towards that observed

under nondrug conditions. In contrast, drug-induced general activity increments were sustained throughout the course of the chronic drug regimen. This development of selective tolerance to one of the behavioral actions of dl-amphetamine and not to another strongly suggested to us that this tolerance was functional and not dispositional. Further, we speculated that the decline in reinforcement frequency in the DRL sessions might have contributed to the development of functional tolerance to the drug. Since there were no reinforcement contingencies associated with the general activity session, the drug-induced behavioral change did not "cost" the animal anything and therefore no tolerance developed.

A later experiment (Schuster et al. 1966) was designed specifically to investigate the role of reinforcement contingencies in the develoopent of functional tolerance to the amphetamines. In this study three rats were trained to lever press on a multiple DRL 30 sec-FI 30 sec schedule of food reinforcement. Following training and the determination of a dose-response curve for single administrations of d-amphetamine, the animals were given 1.0 mg/kg of d-amphetamine daily for 30 consecutive days. Initially for all three-animals d-amphetamine produced a decrement in reinforcement frequency in the DRL component of the multiple schedule. With repeated administration of the drug, however, rate increases and/or temporal patterning of lever pressing gradually returned toward control values with a consequent increase in reinforcement frequency. For two of these animals d-amphetamine caused a rate increase in the FI component but no change in reinforcement frequency. These increased rates in the FI component were maintained over the entire 30 days of the chronic drug regimen. In the third animal, d-amphetamine initially produced a rate decrease and a fall in frequency of reinforcement in the FI component. With repeated administration of the drug, rate and reinforcement frequency returned to control values. These data strongly suggest that tolerance to changes in response rate developed only when these changes produced a decrease in reinforcement frequency. The tolerance developed whether the drug induced increases in responding (DRL) or decreases (FI) provided that the rate change decreased the frequency of reinforcement. In a second experiment in this series rats were trained to lever press in order to avoid an electric shock delivered every 30 seconds. Four of the animals trained under these contingencies continued to receive a number of electric shocks in each daily session. When given 1.0 mg/kg of d-amphetamine for 35 consecutive days their lever press response rate remained consistently elevated. That is, tolerance did not develop to the rate increasing effects of d-amphetamine. It is to be noted that because of the increased response rate the number of shocks received was markedly reduced during the chronic drug regimen.

The data from all of these experiments prompted us to put forth a formal hypothesis stating that: "Behavioral tolerance will develop in those aspects of the organism'sbehavioral repertoire where the action of the drug is such that it disrupts the organisms behavior in meeting the environmental requirement for reinforcements. Conversely, where the actions of the drug enhance, or do not affect, the organism's behavior in meeting reinforcement requirements, we do not expect the development of behavioral tolerance." It was not our intention to

put forth this reinforcement-loss hypothesis as an alternative to other physiological theories of drug tolerance. Rather, we intended to stress that the interaction of the contingencies of reinforcement with the drug-induced behavioral change is an extremely important variable affecting the development of functional tolerance to a drug.

It is beyond the scope of this paper to review those studies which have derived data which support or refute our hypothesis. I am certain it will get a few bruises in the other papers presented in this monograph. It seems clear to me that any such simple hypothesis regarding the interaction of drug effects with contingencies of reinforcement would need great elaboration in order to take into consideration all of the other pharmacologic and environmental variables affecting functional tolerance. To do this at the present time, however, would be largely speculative, since relatively few systematic studies of behavioral tolerance have been done. We need more data before we can further refine our hypothesis. I am in hopes that this symposium may suggest those variables which should be systematically studied in relationship to the reinforcement-loss hypothesis.

V. IMPLICATIONS OF BEHAVIORAL TOLERANCE FOR PROBLEMS OF DRUG ABUSE

We have all been asked by the sponsors of this monograph to speculate about the implications of behavioral tolerance for the problems of drug abuse. Before beginning such speculation, I would like to state that in my opinion we need more systematic experimentation before we can begin properly to appreciate the interrelations between tolerance and the abuse of a drug. Clearly, tolerance develops to most, if not all, drugs commonly abused in our society. An understanding of the pharmacology of these drugs, including the mechanisms underlying the development of tolerance to their behavioral actions, is essential if we are to make any real progress in comprehending the problems of drug abuse.

Now let me indulge in some speculations regarding the importance of studies of behavioral tolerance to the problems of drug abuse.

As stated previously, the chronic administration of a drug for nontherapeutic reasons is complicated by the development of tolerance. The seemingly inexorable escalation of daily dosage which characterizes the abuse of most drugs clearly involves one of the consequences of the development of tolerance. It is not at all clear, however, when such dosage escalation is due to the development of tolerance to the reinforcing effects of a drug or to some other effects which may have initially limited the intake of the drug. For example, when rhesus monkeys are allowed unlimited access to intravenous morphine delivered on an FR-1 schedule of reinforcement they show a gradual increase in responding for the first 40-50 days (Deneau et al. 1969). Thereafter, the number of injections received daily remains stable. It is tempting to attribute the original increase in drug intake to the development of tolerance to the reinforcing effects of the drug. Equally possible, however, is that originally the animals' intake was suppressed by the direct effects of morphine on lever-pressing behavior. As the animals become tolerant to the response-suppressing effects of the drug, the number of injections could increase. Clearly,

this matter needs additional research to clarify the relative importance of these two alternative explanations. This points to a general need for research to clarify under what pharmacologic and environmental conditions tolerance develops to the reinforcing effects of drugs. It seems obvious that if conditions could be arranged so that drug dosage was not continually escalated, many of the social and medical problems associated with drug abuse could be avoided. Stated another way, by studying the variables that give rise to the dosage escalation characterizing drug abuse, it may be possible to develop procedures for aiding drug users to maintain their drug use at lower levels. Such a therapeutic goal is perhaps admissible at this time since it is obvious that the goal of total drug abstinence is probably not obtainable for the vast majority of drug abusers.

I have stated elsewhere that I believe that drug abuse involves not only the self-administration of a drug, but also the demonstration that such drug taking has deleterious consequences (Schuster and Johanson 1974). This means that drugs must be evaluated not only for their reinforcing effects but for their physiological and behavioral toxicity as well. It is clear that tolerance does develop to many of the toxic effects of abused drugs. For example, what might be a behaviorally incapacitating dose of marihuana to the nontolerant individual might actually enhance certain performances of the highly tolerant individual. One must be very careful therefore in defining the drug history of experimental subjects when assessing a drug's possible toxicity. Further, this complicates legal and social policies regarding acceptable levels of drug use. Ultimately it would seem appropriate to base legal decisions as to acceptable levels of drug use on the basis of functional tests rather than on arbitrary blood levels.

A final issue concerns the relationship of tolerance to drug dependence . The WHO (WHO Tech. Report 1964) has stated that drug dependence includes three distinct components: tolerance, physical dependence, and compulsive abuse (psychic craving). Different classes of abused drugs show these three components in differing proportions. Opiates, for example, produce all three components whereas with drugs such as the psychomotor stimulants, the physical dependence component is minimal if not completely absent. It is unclear whether there are common mechanisms underlying both tolerance and physical dependence. On the other hand, it is clear that both tolerance and physical dependence can be separated from a drug's ability to generate compulsive abuse.

Thus, tolerance may occur with all drugs of abuse, but not all drugs producing tolerance are subject to abuse. Clearly, more research is needed to determine the importance of tolerance in the development of drug dependence and the consequent abuse of drugs. I believe we have only begun to do the systematic work necessary to define the pharmacologic, organismic, and environmental variables which affect the development of functional tolerance to the behavioral actions of drugs. As the papers presented in this monograph emphasize, studies of the repeated administration of drugs must take into consideration the complex interaction between drug-induced behavioral change and the consequences of such behavioral change in the organism's adaptation to his environment. I believe that behavioral pharmacologists have a

great deal to contribute to the understanding of the mechanisms underlying functional tolerance to behaviorally active drugs. Ultimately, such understanding is essential for the evolvement of rational preventive and therapeutic approaches to the problems of drug abuse.

REFERENCES

Balster, R.L.,and Schuster, C.R. Fixed-.internal schedule of cocaine reinforcement: Effect of dose and infusion duration. J. Exp. Anal. Behav. 20:119-129. 1973.

Campbell, J.C., and Selden, L.S. Performance influence on the development of tolerance to amphetamine. Pharmac. Biochem. Behav. 1:703-708. 1973.

Deneau, G., Yanagita, T., and Seevers, M.H. Self-administration of psychoactive substances by the monkey. Psychopharmacologia 16:30-38. 1969.

Downs, A.W.,and Eddy, N.B. The effect of repeated doses of cocaine on the rat. J. Pharmac. a Therap. 46:199-200. 1932.

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

Fischman, M.W.,and Schuster, C.R. Unpublished observation, 1973.

Fischan, M.W., and Schuster, C.R. Tolerance development to chronic methamphetamine intoxication in the rhesus monkey. Pharmac. Biochem. Behav. 2:503-508. 1974.

Fischman, M.W., and Schuster, C.R. The effects of long term methamphetamine administration in the rhesus monkey. J. Pharmac. Exp. Therap. (in press). 1977.

Kalant, H., LeBlanc, A.E:,and Gibbins, R.J. Tolerance to, and dependence on, some non-opiate psychotropic drugs. Pharmac. Rev. 23: 135-191. 1971.

Post, R.M. Progressive changes in behavior and seizures following pit cocaine administration: Relationship to kindling and psychosis. : Ellinwood, E.H.,and Kilbey, M.M., eds. Cocaine and Other Stimulants. Advances in Behavioral Biology, vol. 21. New York Plenum Press, 1977. pp.353-372.

Schuster, C.R., and Zimmerman, J. Timing behavior during prolonged treatment with dl-amphetamine. J. Exp. Anal. Behav. 4:327-330. 1961.

Schuster, C.R., Dockens, W.S., and Woods, J.H. Behavioral variables affecting the development of amphetamine tolerance. Psychopharmacoloeia 9:170-182. 1966.

Schuster, C.R., and Thompson, T. Self-administration of and behavioral dependence on drugs. Ann. Rev. Pharm. 9:483-510. 1969.

Schuster, C.R.. and Johanson. C.E. The use of animal models for the study of-drug abuse. In: Poplan, R.E., Schmidt, Wolfgang, and Smart, R. G., eds. Research Advances in Alcohol and Drug Problems, vol. 1. New York: John Wiley Sons, 1974. pp. 1-31.

Schuster, C.R., and Balster, R.L. The discriminative stimulus properties of drugs. In: Thompson, T., and Dews, P.B., eds. Advances in Behavioral Pharmacology. New York: Academic Press, 1977. pp. 85-138.

Seiden, L.S., Fischman, M.W., and Schuster, C.R. Changes in brain catecholamines induced by long-term methamphetamine administration in rhesus monkeys. Drug and Alcohol Dependence 1:215-219. 1976.

Seiden, L.S.,and Dykstra, L.A. Psychopharmacology: A Biochemical and Behavioral Approach. New York: Van Nostrand Reinhold Co., 1977.

Shannon, H.E., and Holtzman, S.G. Evaluation of the discriminative effects of morphine in the rat. J. Pharmacol. Exp. Therap. 198:54-65. 1976.

Stripling, J.S., and Ellinwood, E.H. Sensitization to cocaine following chronic administration in the rat. In: Ellinwood, E.H.., and Kilbey, M.M., eds. Cocaine and Other Stimulants. Advances in Behavioral Biology, vol 21. New York: Plenum Press, 1977. pp. 327-351.

Tatum, A.L ., and Seevers, M.H. Experimental cocaine addiction. J. Pharmac. Exp. Therap. 36:401-410. 1929.

Thompson, T.I., and Schuster, C.R. Behavioral Pharmacology. Englewood Cliffs, New Jersey: Prentice-Hall Inc., 1968.

WHO scientific group report. Evaluation of dependence producing drugs. WHO Tech. Rep. Ser. 287, Geneva. 1964.

AUTHOR

Charles R. Schuster, Ph.D., Professor of Psychiatry, University of Chicago, Chicago, Illinois 60637

I. CONCEPTUALIZATION

Behavioral Tolerance

P. B. Dews, M.D., Ph.D.

Many different mechanisms for the development of tolerance to drugs have been demonstrated, yet for some well-established examples of tolerance, no mechanism has been shown. No doubt, additional mechanisms remain to be discovered. It is, therefore, impossible to infer by exclusion a mechanism in any particular example of tolerance. We are here to discuss a particular mechanism of tolerance: behavioral tolerance. Behavioral tolerance must be identified by positive criteria, not by exclusion. Further, as the various mechanisms of development of tolerance are not usually exclusive, we must expect that more than one mechanism will be involved in the development of tolerance to a drug, even in a single individual at a particular time. A mechanism that has been shown to operate may make only a trivial contribution to the total tolerance in a particular instance. It is, therefore, necessary to measure the contribution of a particular mechanism; for, if the quantitative contribution is not assessed, the major contributors to tolerance may be overlooked. Behavioral tolerance has been discussed only in recent years and relatively few workers have studied it quantitatively. It is the purpose of this essay to contribute to the search for criteria for behavioral tolerance that can be applied in the laboratory and clinic and that lead to quantitative assessments. The presentation will be largely theoretical and forward looking, and will rely heavily on analogies. Quantitative criteria will be sought that will be hard to achieve, and, indeed, comparable precision rarely has been achieved in physiological and biochemical studies. That most physiological and biochemical studies on tolerance do not fulfill precise quantitative criteria is no reason why studies on behavioral tolerance should not seek to do better. The establishment of strict criteria may be useful in suggesting the area of doubt remaining to be resolved in a particular line of investigation; for example, the strict criteria articulated by Paton (1958) for identification of neurohumora1 transmitters may have helped to reduce premature claims for transmitter roles for substances found in the CNS.

Tolerance has been defined as a reduction in the intensity of the effect of a dose of a drug, or the requirement of a larger dose for the original intensity, when the drug has been previously present in a subject. It is preferable, however, to define tolerance as a shift to the right of the dose-effect curve of a drug following appropriate exposure to the drug. This definition emphasizes the importance of exploring dose-effect relations and leads naturally to measurement of the degree of tolerance as the shift in the curve. Pharmacologists have long realized that it is more useful to measure changes in dose-effect curve and not just changes in effect. The shift-to-the-right definition of tolerance also leads to analogies to drug antagonisms that may be useful heuristically. Tolerance is antagonism to the effects of a drug as a result of exposure to the drug itself or to a relative, in which case the effect is called cross-tolerance. Tolerance may be considered as reflexive (in the sense of a reflexive verb) self-antagonism.

We are led to ask whether there are varieties of tolerance corresponding to the varieties of antagonisms. Is there surmountable tolerance in which the full range of effects of the drug can still be achieved, but at consistently higher doses? Tolerance to many of the effects of morphine appears to be of this type. Is there unsurmountable tolerance, in which the full effect of the drug in the nontolerant subject can no longer be achieved at any dose, no matter how large? Tolerance to indirect effects of drugs, the drug liberating pharmacologically active substances from pre-existing body stores, must become unsurmountable if the stores can be depleted. Is there irreversible tolerance in which the effects of a drug in a subject are permanently changed? The tolerance to some behavioral effects of drugs may be of this type: in initial exposures the effects of the drug are enhanced by novelty that is permanently lost in the drug-experienced subject (Dews 1962, p. 438). Negative tolerance clearly occurs in the form of sensitization to the effects of a drug by prior exposure, corresponding to potentiation in the realm of antagonism.

DEFINITIONS

Tolerance may be defined as the reduction in the effect of a constraint on a biological system as a result of exposure to the constraint. Tolerance develops to a variety of physical circumstances such as heat, cold, and delivery of electric shocks. Tolerance develops to exercise and the effects of many brain lesions. Tolerance is a very common biological phenomenon. The changed effect of a drug is called pharmacological tolerance. Three types of pharmacological tolerance can be recognized by the processes they involve: dispositional, physiological, and behavioral. Dispositional tolerance is conceptually the easiest to understand: as a result of exposure to a drug, the physicochemical processes handling the drug in the body are so modified that reduced concentrations of the drug reach the receptive cells, whose modification produces the pharmacological effects of the drug.

The most familiar mechanism of dispositional tolerance is increased rate of metabolism of the drug following repeated administration, as by the induction of higher activity of metabolizing enzymes, typically in cells other than those responsible for the pharmacological effects of the drug. It follows that tolerance to all the effects of the drug will occur, evidenced by a reduction in effect corresponding to a movement left along the dose-effect curve by an amount determined by the reduction in concentration of the drug. Because of the differing slopes and positions of dose-effect curves for different effects of even the same drug, the proportional reduction in the various effects of the drug will not generally be the same even with pure dispositional tolerance. Dispositional tolerance rarely produces a more than 2- or 3-fold decrease in sensitivity, i.e., an 0.5 log unit shift of the dose-effect curve to the right.

Physiological tolerance is a change in the receptive cells, or in cells functionally related to them, such that the effects of a dose of the drug are reduced, even though the receptive cells are subjected to the same concentration of the drug. The changes must be in the specific cells related to the pharmacological effects of the drug. Physiological tolerance may lead to a shift in the dose-effect by one log (10) unit or more to the right. Rarely is much more known about the mechanism.

Behavioral tolerance to a drug is a change in the effect of the drug due to alteration of environmental constraints. In common parlance, subjects learn to cope with the effects of the drug, but "learn" is an undesirable word as it seems to point to a specific process, a gratuitous and meaningless extension.

The distinction between the three types of tolerance is based on the kind of mechanism involved, but the type of tolerance may be recognized without knowing the specific mechanism. Dispositional tolerance may be diagnosed by knowledge of drug levels, without any information on how the levels came to be changed in the tolerant subject. Physiological tolerance may be identified by the reduced responsiveness of isolated tissue from a tolerant subject, also without any information on how the cells have changed their susceptibility. Recognition of type is generally much easier than elucidating mechanism and is usually a prerequisite for the latter.

As with all relatively simple definitions, our definitions of types of pharmacological tolerance should not be considered exhaustive. New types may well be discovered. Indeed, it is easy to think of possible mechanisms of tolerance that would not fit easily into any of the three types. Suppose the reduction in the peripheral blood flow caused by a vasoconstrictor is progressively attenuated because the heart, unaffected directly by the drug, hypertrophies and generates higher arterial pressures. Such a mechanism of tolerance is hardly covered by the definitions. Conversely, the definitions cover some trivial cases of "tolerance." Schuster points out that for a drug with an inverted U-shaped dose-effect curve, in the absence of any change in sensitivity, cumulation can move the effect to the

upper descending limb of the dose-effect curve, simulating tolerance. Rather than elaborating the definitions in a futile attempt to make them perfectly apposite to preconceptions, let us stay with brief, simple definitions and add the limiting and aberrant cases as codicils. Such a course is surely better heuristically than defining behavioral tolerance as tolerance to the behavioral effects of a drug, which merely specifies the obvious dependent variable and provokes no further thought or experiment.

BEHAVIORAL TOLERANCE

Behavioral tolerance, then, is tolerance due to behavioral mechanisms. Generally, behavioral tolerance is thought of only when the behavioral effects of a drug change, but behavioral tolerance may develop to nonbehavioral effects of a drug. For example, a pigeon may continue to work under FR 50 following a dose of pentobarbital that puts a nonworking pigeon to sleep and abolishes its righting reflexes. Behavioral tolerance to the nonbehavioral effects of pentobarbital in producing sleep and abolishing righting reflexes may be developed, therefore, by bringing a subject under the control of a behavioral schedule. (If it be objected that sleep and righting reflexes may be classified as behavior, we may predict confidently that the cardiovascular and respiratory effects of pentobarbital under the above circumstances will be greatly influenced by the behavioral tolerance.) Most of the tolerance to physiological and biochemical effects by behavioral mechanisms is probably indirect, however, as in the example. Obviously, tolerance to the behavioral effects of a drug may be dispositional and physiological as well as behavioral. The different types are not exclusive and usually all occur simultaneously, so it is important to measure the contributions. The rest of the discussion will be devoted to behavioral tolerance to behavioral effects of drugs.

Study of tolerance necessitates repeated measurements on the same subject . If the behavior measured is of a kind that changes with repeated measurements even in the absence of a drug, the assessment of the development of tolerance to the effect of a drug would be so hampered as to be usually unfeasible. In practice, we must seek behavioral activities that are quantitatively repeatable many times, whenever consistent conditions are reimposed. The behavioral activities in relation to their environmental controls during sessions must be in a steady state that persists predictably through successive experimental sessions. For example, subjects under many schedules of reinforcement emit similar patterns of responding and numbers of responses in similar sessions repeated over long periods of time; rhesus monkeys under mult FR FI yielded similar patterns and rates over hundreds of sessions over a period of years (Dews 1977)) and there are many other examples in the literature. Also, the effects of doses of most drugs, judiciously spaced to avoid tolerance, on schedule-controlled responding are qualitatively and quantitatively similar on repeated administration. Unless it has been shown that

under some circumstances the effects of a dose of a drug are replicable in a subject, it is difficult to see how tolerance can be identified and distinguished from metastability of the behavior itself, leading to irreversible change following a single exposure to a variety of more or less nonspecific influences.

Repeatable patterns of behavior and repeatable effects of drugs on the patterns indicate that the drug effect is a modulation of the governing relations between schedule and consequent pattern of responding. With doses of drug insufficient to abolish behavior, the patterns of responding continue to have a recognizable relation to the controlling schedule; for example, under a variety of drugs, clear differences in responding under FR and under FI of a multiple schedule persist, though both patterns may be drastically changed from control patterns. It is as though the schedule continued to exert functional control under the drug, but that the drug had, in effect, changed the parameter values of the functional relationship. When the drug disappears, the parameters return to their prevailing values. The development of behavioral tolerance would be a lessening in the change of parameter with repeated doses of the drug.

One of the difficulties in studying tolerance to a drug is that, as indicated before, the several types are usually operating simultaneously and jointly in the development of tolerance: mechanisms of physiological, dispositional, and behavioral types, and often more than one mechanism within each type. It may be useful in identifying specifically behavioral mechanisms in behavioral tolerance to examine behavioral tolerance to agencies other than drugs. Consider a subject responding consistently in repeated sessions under a particular schedule. If an additional salient, but irrelevant, stimulus is added, the patterns of responding can be modified, as with a drug. Repeated sessions with the new stimulus will lead to a progressive return to the patterns of responding occurring before the introduction of that stimulus. The progressive reduction in the effect of the stimulus may be considered as behavioral tolerance to the stimulus. The progressive reestablishment of original patterns of responding in discrimination-reversal situations, for example, when stimuli of a multiple schedule are interchanged, is behavioral tolerance, although, of course, it has not been discussed in these terms. The advantage of studying such situations to illuminate some of the features of behavioral tolerance to drugs is that the direct effects of the stimuli do not change with the development of tolerance. If we use visual stimuli, the effects of the stimuli on the retina and the resultant discharges in the optic nerves do not change as a stimulus comes to control, e.g., FR rather than FI patterns of behavior. The same is true with auditory stimuli. The evidence for the preceding statements is that with the exception of a few very special circumstances such as visual deprivation in early life, neurophysiologists obtain consistent discharge patterns from eye and ear to specific stimuli from subject to subject without regard to the behavioral history of the subject. Behavioral tolerance to a stimulus can be studied with assurance that the direct impact of the stimulus is

constant. The situation is therefore clearer than for study of behavioral tolerance to a drug, where the development of behavioral tolerance is accompanied by the development of dispositional and physiological tolerances.

Accepting that the behavioral mechanisms involved in behavioral tolerance to a stimulus are the same as those involved in behavioral tolerance to a drug, study of tolerance to a stimulus can provide valuable quantitative information on the rate of development of behavioral tolerance. If the effects of a drug can be even very roughly mimicked by manipulation of salient stimuli, then the amount and rate of development of behavioral tolerance to the stimulus can be used as an estimate of the contribution of behavioral tolerance to the development of tolerance to the drug. There are three possibilities. First, the develoment of tolerance to the drug may be greater than the development of behavioral tolerance to the stimulus. We would conclude that there was a significant contribution from other mechanisms of tolerance developing along with the behavioral tolerance, the extent of the last being estimated from the development of behavioral tolerance to the stimulus. Second, the development of tolerance to the drug may be the same as the development of behavioral tolerance to the stimulus. We would conclude that the develolpment of tolerance to the drug was primarily due to behavioral mechanisms. Third, the development of tolerance to the drug may be less than the developent of behavioral tolerance to the stimulus . We would conclude that some aspects of the effects of the drug were impairing the development of behavioral tolerance more than dispositional and physiological mechanisms were enhancing tolerance. For example, a drug interfering with motor coordination as well as schedule-controlled responding may show little development of behavioral tolerance, because the drug impairs motor execution of the performance and so prevents the normalizing effect of the schedule on the patterns of responding.

As is usual in pharmacology, indeed, in biology, the arguments of the previous paragraph are by no means definitive and conclusive. For example, impairment of the development of behavioral tolerance to some effects of a drug by other effects of the drug may occur even when the development of tolerance to the drug exceeds behavioral tolerance, so that the contribution of dispositional and physiological mechanisms would be underestimated. Such refinements of estimates, however, must surely await until an initial attack has measured the contributions of the various mechanisms to a first order of approximation.

Let us consider another scheme for the measurement of behavioral tolerance to drugs. It is characteristic of schedule-controlled patterns of responding, at steady-state, that the control does not diminish appreciably with the mere passage of time out of the situation. A subject showing stable patterns of responding under, say, mult FR FI may be left without exposure to the schedule for days,

weeks, or even months, and then when re-exposed will give, from the first, patterns of responding indistinguishable from those before the recess. A subject with stable patterns under mult FR FI may be subjected to sessions only once per week or once per two weeks and will continue to respond during the sessions as it does when sessions are daily, or, as is most common, on five days per week. It is possible to have a subject work in daily sessions on an entirely different schedule and still not interfere with responding in interpolated sessions under mult FR FI, provided, of course, that care is taken not to confound stimuli. The property of durability is not peculiar to mult FR FI; it is seen with most schedules that have been studied; mult FR FI is chosen as an example because it is one of the most widely studied schedules in behavioral pharmacology. In the development of dispositional and physiological tolerance, however, the frequency of exhibition of the drug is a crucial variable; it is generally supposed that the more frequent the administration, the greater and faster the development of tolerance. Indeed, the optimum procedure for dispositional and physiological tolerance may be to keep the subject continuously under the influence of the drug, the target cells continuously bathed. If a subject undergoes a daily session of schedule-controlled responding, and if repeated aclministrations of a dose of a drug at one-or two-week intervals yield consistent effects, it is reasonable to assume that the development of dispositional and physiological tolerance is minimal at that frequency of administration. The subject could then be exposed to the schedule only once per week, or once per two weeks, but always under the influence of the drug, the drug not being given otherwise. If tolerance to the effects of the drug develops under this regimen, a clear case would exist for identifying all of the tolerance as behavioral. Interesting variants of the scheme are apparent.

Since the beginning of behavioral pharmacology, there have been two general experimental designs. Some workers have exposed subjects to daily sessions, giving drugs on some days and leaving other days as control days. Other workers have exposed subjects to double sessions daily, the first session being always a control session and the second session being sometimes preceded by administration of a drug. In light of experience, it is unlikely that either design has a decisive general advantage over the other, and they are used interchangeably. With respect to study of tolerance, the difference in the design may make an important difference. Take a drug with a moderate duration of action, say 1/2 time of about 4 hours? to whose behavioral effects tolerance develops when the drug is given daily before a session. If the double session design is used, the control session will start about 20 hours after the previous day's administration of the drug, so that only about 6% of the drug will remain, and performance in the control session would presumably be normal. Sessions under the drug would alternate with normal sessions. Under the single session design, all responding would take place under the influence of the drug. The development of behavioral tolerance would be expected to be more pronounced under the latter regimen. Further, when administration of the drug is discontinued, performance in the first session without drugs would be expected to be abnormal

under the single session design, where all of the previous several sessions had been performed under drug; under the double session regimen, however, there is no reason to expect disturbance even in the first postdrug session, since normal sessions have continued to occur. The general approach offers the advantage that the contribution of behavioral mechanisms to tolerance is assessed during continuing sessions rather than only during occasional probes or once in the course of the experiment. As before, responding in the first session after drug cessation should be abnormal under the single session design, even if enough time is allowed to permit complete dissipation of the physiological and biochemical aftermath of repeated drug administrations.

SUMMARY

Behavioral tolerance is defined as tolerance due to behavioral mechanisms. The study of behavioral tolerance to behavioral effects of drugs requires, in the present state of knowledge, objective and quantitative means of recording behavior. Behavioral activities that do not lend themselves to such recording should probably be left aside in the study of tolerance until the more general quantitative features of tolerance have been measured in quantifiable systems. The behavior selected should occur reproducibly in many successive daily sessions. Many varieties of schedule-controlled patterns of responding fulfill the preceding criteria! and it is likely that study of schedule-controlled responding will play a central role in elucidation of behavioral tolerance in the foreseeable future. Drug and behavior should also be chosen that yield reproducible effects of the drug when dosing is suitably spaced.

In a suitable system, the contribution of behavioral tolerance to a drug tolerance may be estimated by:

1. measuring behavioral tolerance to changes in the environment that grossly mimic the effect of the drug,
2. measuring tolerance development under conditions that permit behavioral tolerance, but minimize other forms of tolerance.

These two criteria are insufficient. Our confidence in our estimate of a contribution of behavioral tolerance depends on the number of independent ways in which the estimate can be made and the closeness in agreement of values arrived at in the different ways. Additional criteria are needed. Understanding of behavioral tolerance may come slowly, but interesting quantitative behavioral pharmacology will be accumulating along the way.

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REFERENCES

Dews, P. B. Psychopharmacology. In: Bachrack, A. J., ed. *Experimental Foundations of Clinical Psychology.* New York: Basic Books, 1962. pp. 423-441.

Dews, P. B. Studies on responding under fixed-interval schedules of reinforcement: The scalloped pattern of the cumulative record. *Journal of Experiental Analysis of Behavior, 1977,* in press.

Paton, W. D. M. Central and synaptic transmission in the nervous system (pharmacological aspects). *Annual Review of Physiology,* 21:431-470, 1958.

AUTHOR

P. B. Dews, M.D., Ph.D., Laboratory of Psychobiology, Harvard Medical School, Boston, Massachusetts 02115

A Pavlovian Conditioning Analysis of Morphine Tolerance[1]

Shepard Siegel, Ph.D.

INTRODUCTION

Many of the effects of a variety of drugs, including morphine, decrease in magnitude over the course of successive administrations, the phenomenon being termed tolerance. Most theories of tolerance stress the physiological consequences of repeated pharmacological stimulation. There is considerable evidence, however, that the display of tolerance is highly dependent upon the organisms' experience with the drug administration environment as well as the drug. The role of such environmental signals of the drug in the development of tolerance has been emphasized in an account of morphine tolerance which stresses Pavlovian conditioning principles (Siegel 1975b; 1976, 1977b). This paper describes this conditioning theory of tolerance and summarizes data which support the theory.

DRUG ADMINISTRATION PAVLOVIAN CONDITIONING, AND DRUG TOLERANCE

A prototypical learning design is that developed by Pavlov (1927) who, in fact, suggested that the usual drug administration procedure was operationally similar to his conditioning situation (Pavlov 1927). The basic conditioning preparation used by Pavlov involves the use of TV cues. The first of these, the "conditional stimulus" is said to be "neutral"; it elicits little relevant activity prior to its pairing with the second stimulus, the unconditional stimulus. As the name implies, the unconditional stimulus is selected because it elicits relevant activities from the outset--unconditionally--prior to any pairings. In Pavlov's well-known conditioning work, the conditional Stimulus was some conveniently manipulated exteroceptive stimulus (bell, light, etc.), and the unconditional stimulus was either food or orally injected dilute acid, both of which elicited a conveniently monitored salivary response. In the case of drug administration, the conditional stimili. are those procedures, cues, or rituals reliably predicting the systemic stimulation induced by the drug, with the actual central effects of the drug constituting the uoconditional stimulus. The development of the association between these stimuli may be revealed if the subject, following a history of administration of the drug, is presented with the usual drug administration procedure

not followed by the usual pharmacological. consequences--rather, for such a conditional response test session, a placebo is administered.

The Compensatory Pharmacological Conditional Response

Following Pavlov's demonstration that responses to drugs can be conditioned, there has been a considerable amount of research concerning such pharmacological learning (see review by Siegel, 1977a). Although many forms of conditional drug responses can be conceptualized, and have been reported, an especially common type of pharmacological conditional response is opposite in direction to many of the effects of the pharmacological unconditional stimilus. Table 1 (next page) summarizes a number of investigations which have reported such conditional responses opposite to the unconditional effects of the drug.

The Compensatory Pharmcological ConditionalResponse and Drug Tolerance

As suggested by Bykov (1959), conditional drug responses' evidenced in anticipation of the actual pharmacological assault should be expected to interact with the drug-induced unconditional response. and thus pharmacological learning may be evidenced by the modulation of the unconditional effects of the drug as it is repeatedly presented in the context of the same situational cues. Since the drug conditional response is often opposite in direction to the drug unconditional. response, the effect of the drug would be expected to became reduced by this compensatory conditional response evidenced in anticipation of the drug's central effects. Because the association between the drug administration procedure and the systemic effects of the drug is strengthened by repeated pairings, the drug's effect would be expected to become increasingly cancelled as the drug-compensatory conditional response grows stronger. Such a decreased effect of a drug, as a function of successive experiences with the drug, defines tolerance.

The Morphine Compensatory Conditional Response and Morphine Tolerance

Of special relevance to the conditioning analysis of morphine tolerance are several. demonstrations that the conditional response following training with morphine consists of a variety of morphine-compensatory responses. As indicated in Table 1, animals with a history of morphine administration (with its analgesic, hyperthemic, and bradycardic effects), when administered a placebo, display hyperalgesia (Siegel 1975b), hypothermia (Siegel, submitted), and tachyardia (Rush, Pearson, & Lang 1970). Since organisms evidence such responses opposite to those induced by morphine confronted with the usual predrug cues, but without actual administration of the drug, it would be expected that when morphine is presented in conjunction with the usual predrug cues, these compensatory conditional responses would attenuate the unconditional responses, thereby decreasing the observed response to the drug over the can-se of successive administrations.

COMPARISON OF THE CONDITIONING THEORY WITH OTHER INTERPRETATIONS OF TOLERANCE

The conditioning interpretation of tolerance may be contrasted with formulations of the phenomenon which do not acknowledge a role for

TABLE 1

COMPENSATORY CONDITIONAL PHARMACOLOGICAL RESPONSES

Unconditional Stimulus	Unconditional Response	Conditional Response	Reference[a]
epinephrine	tachycardia	bradycardia	(1)
epinephrine	gastric secretion	gastric secretion	(2)
epinephrine	hyperglycemia	hypoglycemia	(3)
glucose	hypoglycemia	hyperglycmia	(4)
insulin	hypoglycemia	hyperglycemia	(5)
nicotine	hypoglycemia	hyperglycemia	(6)
atropine	antisialosis	hypersalivation	(7)
chlorpromazine	activity	activity	(8)
amphetamine	02 consumption	O_2 consumption	(9)
dinitrophenol	to consumption, hyperthemia	O_2 consumption hypothermia	(10)
histamine	hypothermia	hyperthermia	(11)
methyl dopa	↓ blood pressure	blood pressure	(12)
lithium chloride	↓ drinking	drinking	(l3)
nalorphine	tachycardia	bradycardia	(14)
morphine	bradycardia	tachycardia	(15)
morphine	hyperthermia	hypothermia	(16)
morphine	analgesia	hyperalgesia	(17)

a (1) Russek & Pina (1962); Subkov & Zilov (1937). (2) Guha, et al. (1974). (3) Russek & Pina (1962). (4) Mityushov (1954); Deutsch (1974); LeMagnen (1975). (5) Siegel (1972a, 1975a). (6) Lundberg & Thyselius-Lundberg (1931). (7) Korol, et al. (1966); Lang, et al. (1966, 1969); Mulinos & Lieb (1929); Wikler (1948). (8) Pihl & Altman (1971). (9) Obal (1966). (10) Obal (1966). (11) Obal, et al. (1965). (12) korol & McLaughlin (1976). (13) Domjan & Gillan (in press). (14) Goldberg & Schuster (1967, 1970). (15) Rush, et al. (1970). (16) Siegel (submitted). (17) Siegel (197%).

associative processes. These alternative theories usually postulate physiological changes, induced by early drug administrations, which functionally reduce the effects of later drug administrations. Such systemic alterations may involve opiate receptors in the brain (e.g., Collier 1965; Snyder & Matthysse 1975), or peripheral changes which hinder the drug from gaining access to central receptors (e.g., Cochin 1971; Mule & Woods 1969). These physiological theories have been extensively reviewed elsewhere (see Hug 1972, Kuschinsky 1977, Takemori 1975).

Some nonassociative interpretations of tolerance! like the conditioning theory, stress the role of homeostatic counter adjustments to the pharmacological stimulation: As the drug is repeatedly administered, these "autonomic hyperreactions" (Himmelsbach 1943) or "opponent processes" (Solomon & Corbit 1974) elicited by the drug become stronger as they are repeatedly exercised, acting increasingly to attenuate the effects of the drug (for a review of many such theories, see Collier 1972). These counteradjustment models, like those models which more particularly specify the nature of the systemic drug-induced alterations, do not incorporate a learning process in the acquisition of tolerance.

In summary, all these traditional interpretations of tolerance are nonassociative. That is, they assert that tolerance results simply from repeated pharmacological stimulation, and specify no role for drug-associated environmental stimuli in the display of tolerance. In contrast, the conditioning interpretation of tolerance indicates that the development of tolerance depends on repeated pairings of environmental cues signalling the drug with the systemic effect of the drug, and ɒot merely the frequency of pharmacological stimulation

A Note on Associative vs. Nonassociative Theories of Tolerance

For purposes of exposition, a conditioning theory of tolerance is distinguished from the more traditional, nonassociative theories. In fact, both associative mechanisms and systemic processes unrelated to associative mechanisms are undoubtedly involved in tolerance. Clearly, processes unrelated to learning are relevant to interpreting tolerance observed when the drug is not repeatedly presented (e.g., pellet implantation studies, Way, Loh, & Shen 1969), or when tolerance is observed in the offspring of rats prenatally treated with opiates (O'Callaghan & Holtzman 1976, 1977), or when tolerance is observed in isolated tissue (e.g., Paton 1957; Takemori 1962). However, it is equally as clear that many tolerance phenomena appear inexplicable without incorporating a learning mechanism in interpretations of tolerance and that until recently the contribution of learning to tolerance has been largely ignored by investigators in the area. The research reported in this paper was designed to clarify the role of conditioning in tolerance, but not to suggest that pharmacological phenomena can best be understood merely with an appreciation of Pavlovian principles.

EVIDENCE FOR THE CONDITIONING THEORY OF TOLERANCE

We have completed a substantial amount of research which provides evidence that association between the drug administration ritual and the systemic effects of the drug plays an important role in the

acquisition of tolerance. The complete reports of most of these experiments have been published, and only the major findings will be briefly summarized here.

General Methods

Certain procedures were common to all the experiments summarized in this section. The subjects were experimentally naive, male, albino rats. All injections were made subcutaneously in the dorsal surface of the neck. The drug dose was 5mg/kg (of a 5 mg/ml solution) of morphine sulfate. All placebo injections consisted of an equivalent volume of physiological saline (i.e., 1 ml/kg).

In some investigations, the analgesic effect of the drug was assessed with the hot plate technique (Fennessy & Lee 1975) which involves the determination of the rat's latency to lick a paw following placement on a warm (54.2" C) surface (with analgesic responses indicated by relatively long paw-lick latencies). In other investigations, analgesia level was assessed with a cammercially available version of the Ramdall-Selitto paw-pressure analgesiometer (Randall & Selitto 1957). To use the analgesiometer, the rat is positioned so that it is free to withdraw its paw from a source of gradually and constantly increasing pressure, with the amount of pressure applied before the paw-withdrawal response occurs providing a measure of pain sensitivity (with analgesic responses indicated by relatively high paw-withdrawal thresholds).

The dose of morphine used in these experiments elevates, body temperature in the rat, the magnitude of this hyperthermic response successively decreasing with successive drug administrations (Gunme 1960, Hermann 1942; Winter 6 Flataker 1953). In same experiments, the role of conditioning in such pyretic tolerance was investigated. 21 these studies, colonic temperature was assessed with an electronic thermometer 30 sec after the probe was inserted 4 cm into the rat's rectum.

In these experiments, unless otherwise indicated, the usual drug administration procedure involved transporting the rat, in its home cage, from the colony room to a different room which, in different experiments, contained either the hot plate, analgesiometer, or temperature assessment apparatus. A constant background of white noise was maintained in this room. The rat was injected in this distinctive environment, and, in sane experiments, the drug's effect was determined on a single occasion, usually one-half hr after the injection. In other experiments, the time course of the drug's effect was determined by sequential assesments on many occasions after administration. The interval between injections differed in different experiments, but was never less than 24 hr.

The Situation Specificity of Tolerance

Although there are many nonassociative interpretations of tolerance, they are all similar in stipulating that tolerance results from systemic changes induced by repeated pharmacological stimulation *However,* there are many demonstrations that tolerance does not result simply from the organism suffering repeated pharmacological stimulation. It does result from repeated administration of the drug in the context of

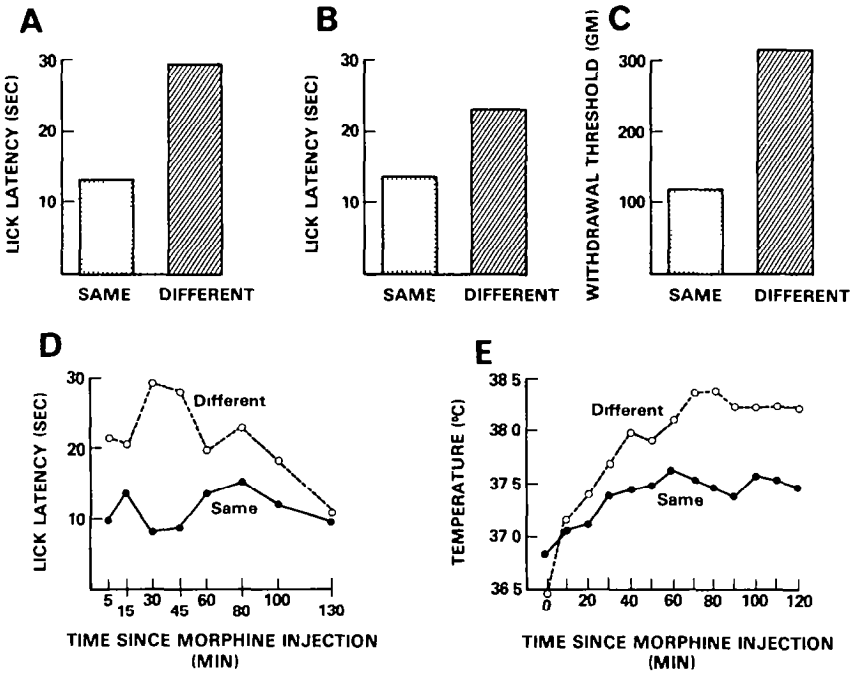
environmental. cues which reliably signal the impending chemical stimulation. A remarkable series of experiments by Mitchell and his colleagues have demonstrated that rats (Adams, Yeh, Woods, & Mitchell 1969, Ferguson, Adams, &Mitchell 1969, Gebhart &Mitchell 1971, 1972; Gebhart, Sherman, & Mitchell 1971, 1972, Kayan, Ferguson, & Mitchell 1973; Kayan &Mitchell 1969, 1972; Kayan, Woods, &Mitchell 1969, 1971) and humans (Ferguson &Mitchell 1969) respond in the expected tolerant manner to the analgesic effect of the last of a series of morphine injections only if this final injection is presented in the same environment as the prior injections in the series. These findings, although not readily interpretable by theories of tolerance which do not acknowledge a role for drug-associated environmental cues in the acquisition of tolerance, are expected on the basis of the conditioning theory of tolerance. According to this conditioning theory, cues that reliably predict the systemic effect of the drug should be crucial to the development of tolerance because they enable the subject to make timely compensatory responses in anticipation of the central responses elicited by the drug.

We have completed a number of studies (Siegel 197fb, 1976, submitted, in preparation) which confirm and extend these previous reports indicating that the display of morphine tolerance is greater in the environment in which the drug has been previously administered than in an alternative environment. The details of the designs of these investigations from our laboratory differ somewhat from experiment to experiment, but they all incorporated two groups, both of which received morphine a sufficient number of times for tolerance to develop, with the effect of the drug being assessed following the Last administration. For one group, this final administration and evaluation of the drug's effect took place in the same environment as that in which the previous injections occurred. For the second group, this tolerance test took place in a different environment than that in which the previous injections occurred. The results of a number of such experiments are summarized in Figure (next page). These experiments have consistently demonstrated that animals tested following drug administration in the same environment in which they had previously experienced the drug respond less (i.e., are more tolerant) than animals tested following drug administration in a different environment from that which they had an opportunity to associate with the drug. The difference between these two conditions, labeled SAME and DIFFERENT in Figure 1, were, in each experiment, statistically significant.[2]

Figure IA indicates the results of one of these experiments (Siegel 1975b, Experiment IA) in which independent groups of rats were tested for the analgesic properties of morphine either in the same environment in which they had previously received the drug, or in a different environment. Rats in the group labeled SAME were injected with morphine on four occasions in the distinctive room, with hot-plate responsivity determined for the first time 30 min following the fourth administration of the drug. The latency to respond to the heat stimulation in this group, which was tested for the effects of the fourth drug administration in the context of the same environmental cues as those present at the time of the three prior administrations, was contrasted with that displayed by rats in the group labeled DIFFERENT, which received the three pretest drug administrations in a different environment, the colony room. As can be seen in Figure lA, Group SAME was more sensitive

FIGURE 1

Summary of results of experiments demonstrating that rats display greates morphine tolerance to the final injection of a series if this final injection is administered in the same environment as the prior injections (SAME) than if the final injection is administered in a different environment (DIFFERENT). Figure IA illustrates hot-plate response latencies reported by Siegel (1975b, Experiment IA), with groups designated SAME and DIFFERENT corresponding to Groups M-CP and M-CAGE, respectively, in the original experiment. Figure IB illustrates hot-plate response latencies reported by Siegel (1976), with groups designated SAME and DIFFERENT corresponding to groups trained with a nonfunctional hot plate and nonfunctional paw-pressure analgesiometer, respectively. Figure 1C illustrates analgesiometer paw-withdrawal thresholds reported by Siegel (1976), with groups designated SAME and DIFFERENT corresponding to groups trained with a nonfunctional analgesiomter and nonfunctional hot plate, respectively. Figure ID illustrates hot-plate response latency time-effect curves, constructed with independent groups at each temporal interval (Siegel, in preparation), Figure 1E illustrates thermal modifications reported by Siegel (submitted), with groups designated SAME and DIFFERENT corresponding to Groups Mor-ROOM/Sal-CAGE and Mar-CAGE/Sal-EWM, respectively, in the original experiment.



to the heat stimulation (i.e., more tolerant to the analgesic effect of the drug) than Group DIFFERENT.

Figure 1B displays the results of another experiment (Siegel, 1976) which similarly demonstrated that, following eight morphine injections, rats responded on the hot plate following a subsequent injection of the drug more rapidly if this test injection was administered in the same environment as the previous injections, rather than in a different environment.

Figure 1C presents the results obtained from additional groups included in Siegel's (1976) study, for which pain sensitivity was assessed with the paw pressure analgesiometer. Once again, rats with a similar history of morphine stimulation do not respond in a similar manner to the final test injection Group SAME subjects were more sensitive to the pressure stimulation (i.e., n-ore tolerant) than Group DIFFERENT subjects.

In a further experiment, the time course of the analgesic response to morphine was assessed (Siegel, in preparation). Independent groups of rats (6 rats per group) were tested on the hot plate at various intervals of time following their sixth morphine injection. That is, time-effect curves were constructed using independent groups at each assessment interval (rather than testing each subject repeatedly). The results are displayed in Figure lD. As may be seen in Figure ID, rats displayed much more tolerance to the analgesic effect of morphine the sixth time it was administered if such administration occurred in the same environment as that in which they were injected on the five prior occasions than if this sixth injectionoccurred in a different environment.

The results of the expertits summarized in Figures IA-D demonstrated that environmental cues are crucial for the display of tolerance to the analgesic effect of morphine. This pain-sensitivity measure of opiate action (althogh the most common in investigations of tolerance) uses an indirect behavioral criterion of pharmacological activity, and it has been suggested that it may be an uncertain manifestation of the drug's effect (Goldstein, Arnow, & Kalman, 1974). Thus, an additional experiment was conducted to determine if environmental cues are also important in the display of hyperthermic tolerance (Siegel, submitted, Experiment IA), The design of this experiment was somewhat different from that of the analgesia experiments. During the pretest phase of the experiment, tolerance was induced in two groups of rats by injecting them with morphine on 10 occasions, one injection every On those alternate days when morphine was not administered, both groups of rats were injected with physiological saline. Morphine and physiological saline were systematically administered in either of two different environments, with the two groups differing only with respect to the environmental cues associated with each injected substance. One group received its morphine injections in the distinctive room and its saline injections in the colony room. The second group received its morphine injections in the colony room and its saline injections in the distinctive roan For both groups, following each injection in the distinctive room, the rat remained in this room for two hr, with colonic temperature assessed immediately after the injection and thereafter at 10-min intervals. Following this tolerance development phase of the experiment, rats in both groups were

administered morphine in the distinctive roan, followed by colonic temperature assessment. It should be emphasized that prior to this final session, both groups had equalexposuretothetestenvironment and temperature assessment procedure For one group, however, this final test session consisted of the usual pre-morphine environmental cues signalling the usual pharmacological consequences (Group SAME). In contrast, for the second group, morphine was administered in the context of cues which, in the past, signalled physiological saline rather than the opiate (Group DIFFERENT). The time course of the mean temperature alteration following this final injection in the distinctive room for each group is shown in Figure I.E. As is obvious in Figure IE, the pyretic effect of the drug was much more pronounced in Group DIFFERENT than in Group SAME. In fact, Group DIFFERENT showed no evidence of pyretic tolerance, the hyperthermic response following this eleventh injection of morphine for Group DIFFERENT did not differ significantly from that which would be expected the first time rats receive the drug.

In all the experiments summarized in this section, prior to the final tolerance test session, both Groups SAME and DIFFERENT suffered the same morphine-induced systemic effects, equally as often, and at the same intervals. The rats in these groups should have been subject to the same metabolic, cellular, or immunifacient modifications that, according to the various nonassociative theories, mediate tolerance. Thus, it would be expected, according to any of these traditional theories of tolerance, that the two groups should not differ in the acquisition of tolerance. In every experiment, it was found that the group which received the drug in a distinctly different environment for the pre-test sessions evidenced little if any indication of tolerance on the test session, suggesting that reliable environmental signals of the drug are important in the development of tolerance. These results are expected on the basis of the conditioning analysis of tolerance, but not of the alternative formulations.

Extinction of Morphine Tolerance

A unique prediction of the conditioning account of morphine tolerance is that tolerance should be subject to the decremental effects of extinction. That is, if morphine tolerance occurs because environmental cues signalling the central effect of the drug elicit a compensatory conditional response, acting to cancel the effect of the opiate, presenting the administration cues without the drug to the tolerant organisn should extinguish these learned responses, and thus cause some recovery of the response to morphine. In other words, according to the conditioning theory of tolerance, repeated placebo sessions should be an effective procedure for attenuating established tolerance.

The results of a number of experiments have, in fact, demonstrated that morphine tolerance is subject to extinction (Siegel 1975b, Experiment 3; Siegel 1977b-, Experiments 1 and 2, Siegel, submitted, Experiment 2). Although there were numerous procedural differences between the experiments, all incorporated two groups, both of which initially received a series of daily morphine injections sufficient to induce tolerance. This constituted the tolerance acquisition phase of each experiment. Some days later, subjects received at least one further injection of morphine. This final experience with the drug constituted the tolerance test phase of each experiment. The two groups differed

only with respect to their treatment during the interval between the tolerance acquisition phase and the tolerance test phase. One group received daily placebo sessions, i.e., they were treated in the same manner as on morphine sessions, except the substance injected was physiological saline rather than the opiate (hereinafter referred to as Group EXT, i.e., extinction). The response of Group EXT to the drug during the tolerance test indicated the effects of repeated presentations of the morphine administration procedure, in the absence of the drug, on tolerance acquired during the tolerance acquisition phase Rats in the second group were simply left undisturbed in their home cages during the period between tolerance acquisition and tolerance testing (hereinafter referred to as Group REST). The response of subjects in Group RED to the drug during the tolerance test provided a measure of any alteration in tolerance attributable simply to the interval that intervened between the tolerance acquisition phase and the tolerance test phase.

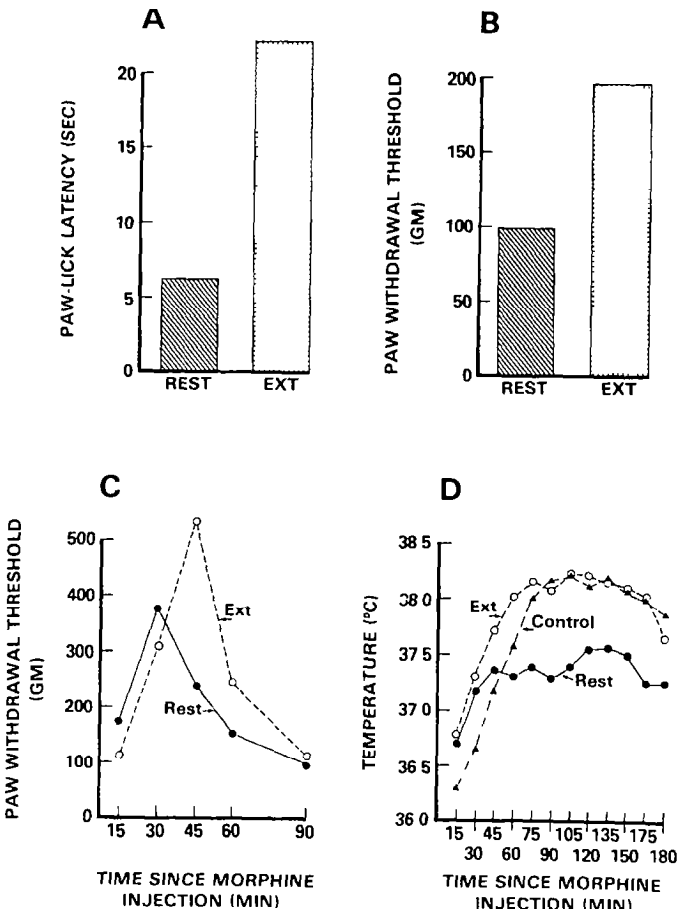
According to the conditioning interpretation of tolerance, presenting drug-associated environmental conditional stimuli without the drug is an extinctionprocedure, and thus the group receiving such treatment subsequent to tolerance acquisition (Group EXT) would be expected to display less tolerance on the tolerance test than would the group with no such extinction experience (Group REST). Results of four experiments demonstrating that such extinction does, in fact, occur, are summarized in Figure 2 (next page). In all experiments, it was found that extinction attenuated tolerance established during the tolerance acquisition phase of the experiment.

Figure 2A illustrates results reported by Siegel (1975b, Experiment 3). In this experiment, rats in Groups REST and EXT were each initially given three, daily, morphine-hot plate analgesia assessment sessions in the distinctive room, which was sufficient for a substantial amount of tolerance to the analgesic effect of the drug to develop (there being no difference between the two groups in the acquisition of analgesic tolerance). Group EXT rats were then given nine daily placebo sessions, and Group REST rats Were left undisturbed for nine days. On the tolerance test session, which occurred on the day after the ninth placebo session (Group EXT) or the ninth rest day (Group REST), all subjects me again injected with morphine. As is obvious in Figure 2A, on this test session, morphine had a me pronounced analgesic effect in Group ExT than in Group REST. (The difference between Groups EXT and REST was statistically significant in this and other experiments summarized in Figure 2.)

Prior to the morphine test session, both groups suffered the systemic effects of morphine equally as often, at the same intervals, and with the same analgesic effect. According to the nonassociative interpretations of tolerance, both groups should display equal tolerance when again injected with the drug on the test session. However presenting the morphine administration ritual unacconpanied by the central effects of the opiate to Group EXT, tolerance subsequently observed in this group was substantially attenuated Such attenuation of tolerance was not due simply the nine-day delay between the end of tolerance acquisition and the tolerance test, since this delay did not affect the tolerance of Group REST (in agreement with other reports that morphine analgesic tolerance dissipates little simply with the

FIGURE 2

Summary of results of experiments demonstrating that morphine tolerance can be extinguished. In each experiment, all subjects were first made tolerant to morphine, and then given a series of either placebo sessions (EXT) or a rest interval (REST) prior to a morphine tolerance test session, with only the results obtained on this tolerance test session illustrated for each experiment. Figure 2A illustrates hot-plate response latencies reported by Siegel (1975b, Experiment 3). Figures 2B and 2C illustrate analgesiometer paw-withdrawal thresholds reported by Siegel (1977b, Experiments 1 and 2, respectively) . Figure 2D illustrates thermal modifications reported by Siegel (submitted, Experiment '2).



passage of time [e.g., Cochin & Kornetsky 1964, Kayan & Mitchell 19721).

Inasmch as no nonassociative interpretation of tolerance would predict that tolerance should be subject to extinction, it was thought desirable to assess the reliability of this confirmation of a unique prediction of the conditioning theory of tolerance with a different analgesia assesment situation. The design of this subsequent experiment (Siege1 1977b, Experiment 1) was similar to that of the earlier hot-plate experiment by Siegel (1975b, Experiment 3), with the following exceptions: Analgesia level was assessed with the paw-pressure analgesiomter; the tolerance acquisition phase of the experiment consisted of six sessions; and subjects received either 12 placebo sessions (Group EXT) or a 12-day rest interval (Group REST) between tolerance acquisition and tolerance testing. The results obtained on the tolerance test session are shown in Figure 2B. It required significantly more pressure to elicit a paw-Withdrawal response in Group EXT rats than in Group REST rats. Once again, Group EXT responded to morphine with a higher level of analgesia (i.e., more tolerance) than Group REST, despite the fact that the two groups did not differ in any manner with respect to their experience with the opiate prior to the test session.

The results of the two experiments described above indicated that presentations of the morphine administration procedure to morphine tolerant rats deleteriously affected the display of tolerance. In both experiments, an attempt was made to make the placebo-initiated extinction sessions as similar as possible to the drug administration sessions, including the application of nociceptive stimulation. Thus, only the group subjected to extinction (Group EXT) had any experience in making the analgesia-indicant response--either paw licking (Figure 2A) or paw withdrawal (Figure 2B)--whilenot drugged. A further experiment was conducted (Siegel, 1977b, Experiment 2) to determine whether extinction is an effective procedure for attenuating established tolerance even if subjects do not practice the analgesia-indicant response during the extinction sessions. In addition, this experiment differed from the previous tolerance-extinction experiments in two other major respects: (a) the time course of the opiate-induced analgesia was assessed (in the previous experiments, the analgesic effect of each administration was assessed on only a single occasion, .5 hr after injection), and (b) the effect of extinction on single dose tolerance was evaluated (previous work has demonstrated that only a single experience with morphine is sufficient to subsequently reduce the analgesic effect of a second administration [Ferguson, et al. 1969; Kornetsky & Bain 19681). During the tolerance acquisition phase of this further extinction experiment, subjects in Groups EXT and REST were injected with morphine on only a single occasion, and evidenced similar analgesic tin-e-effect curves. Group REST subjects were then left undisturbed for four days, while Group EXT subjects received four daily placebo sessions, but without analgesia assessment. On these placebo sessions, Group EXT rats were positioned in the analgesiometer after each of the post-injection assessment intervals, but the apparatus was nonfunctional and no pressure was applied to the paw. Five days following their tolerance acquisition injection of morphine, all subjects received their tolerance test session. Thus, prior to this second morphine session, both groups had but a single experience with opiate stimulation and analgesia assessment.

The time course of the analgesic effect of the drug on the tolerance test session for both groups is shown in Figure 2C. Examination of the time-effect curves reveals that Croup EXT was less sensitive to the pressure stimulation than Group REST, and evidenced peak responsivity to the drug closer to the tin-e of administration than Croup REST--both indicative of less analgesic tolerance (see Siegel, 1977b, Experiment 2). *The results* of this experiment, in *agreement* with the previously described experiments, demonstrated that morphine tolerance is subject to extinction, supporting the conditioning analysis of tolerance. Additionally, the results of this experiment indicated that such extinction of morphine tolerance can be observed after only a single administration of the drug, and is not attributable to any additional practice that extinguished subjects have in responding to the aversive stimulation used to evaluate the effect of the drug.

The results of experiments summarized in Figures 2A-C demonstrated that tolerance to the analgesic effect of morphine can be extinguished. A final experiment in this series was designed to determine whether tolerance to the py-retic effect of morphine similarly could be extinguished (Siegel, submitted, Experiment 2). During the tolerance acquisition phase of this experiment, subjects in Groups REST and EXT were each administered morphine for 12 daily sessions, with the colonic temperature of each subject being determined at 15-min intervals following each injection. Both groups evidenced a similar course of tolerance acquisition. Croup EXT subjects then received 12 daily placebo sessions (which were conducted in the same manner as morphine sessions, except that the substance injected was physiological saline) As WAS the case in the previously described experiments, Group REST was left undisturbed during this period. Finally, all rats received a tolerance test session, which was initiated with an injection of morphine.

To evaluate the extent to which extinction can attenuate tolerance, the design of this hyperthermic tolerance experiment included a group which received morphine for the first time during tolerance testing (Group CONTROL).[3] To the extent that extinction is an effective procedure for attenuating established pyretic tolerance, Croup EXT should, on the tolerance test, evidence a drug-induced hyperthermia resembling that seen in Group CONTROL. The thermic effects of the drug on the tolerance test session, for each group, are shown in Figure 2D. By comparing Croups REST and EXT, it is clear that extinction decreased hyperthermic tolerance. Indeed, the hyperthermic tolerance of Croup EXT was so reduced that the pyretic effect of morphine was similar to that obtained in Group CONTROL, which received the drug for the very first time during the tolerance test. Thus, in this experiment, extinction not only was an effective procedure for attenuating tolerance--in fact, the procedure eliminated tolerance.

It would appear to be well-established that tolerance can be extinguished. Indeed, under sane circumstances, repeated presentations of the drug administration environment in the absence of the drug to the tolerant subject can completely abolish tolerance. Evidence for the extinction of tolerance is robust, having been demonstrated in four experiments encompassing a range of procedural differences and parametric manipulations. These findings that tolerance is subject to extinction (like the previously presented findings on the situation-specificity of tolerance) appear inexplicable by traditional interpretations of

tolerance which stress only the effects of repeated pharmacological stimulation, and ignore the importance of cues present at the time of such stimulation. However, the finding that tolerance can be extinguished is readily interpretable by the conditioning model of tolerance.

Partial Reinforcement of Morphine Tolerance

Results discussed previously demonstrated that extinction, a procedure which decrementally affects established conditional responses, similarly affects established analgesic and pyretic tolerance, thus supporting the conditioning analysis of tolerance. If tolerance is a manifestation of a conditioning process, it would be further expected that manipulations of the putative conditional stimulus (i.e., environmental. cues present at the time of drug administration) known to be effective in retarding acquisition of conditional responses would similarly retard the acquisition of morphine tolerance. One such procedure that is effective in retarding conditional response acquisition is partial reinforcement. if the unconditional stimulus is paired with the conditional stimulus on less than 100% of the trials, conditional response acquisition is generally poor, relative to a situation in which every conditional stimulus is paired with the unconditional stimulus (see Beecroft 1966). Although most studies of partial reinforcement effects in classical conditioning have compared 100% to 50% reinforcement schedules, there is evidence that acquisition rate declines as the percentage of reinforced conditional stimuli decreases, even when the number of reinforced trials is equated in the various reinforcement schedule conditions (i.e., both partially and continuously reinforced groups receive the same number of paired presentations of conditional and unconditional stimuli, with the partially reinforced group receiving additional conditional stimlus-alone trials interspersed between these paired trials).

The implication of the partial reinforcement literature for the conditioning theory of tolerance is clear: A group in which only a portion of the presentations of the drug administration cues are actually followed by morphine (i.e., a partial reinforcement group) should be slower to acquire tolerance than a group which never has exposure to environmental cues signalling the drug without actually receiving the drug (i.e., a continuous reinforcement group), even when the two groups are equated with respect to all pharmacological parameters.

We have completed experiments concerned with the effects of partial reinforcement on both analgesic (Siegel 1977b_, Experiment 4) and pyretic (Siegel, submitted, Experiment 3) tolerance In both experiments, rats were administered morphine a sufficient number of times for tolerance to be evidenced, with the interval between morphine sessions irregularly varied between two and five days. In each experiment, one group was continuously reinforced (Group CRF). For Group CRF all presentations of the drug administration procedure were accompanied by the drug, subjects in this group simply being left undisturbed in their home cages on the days between morphine sessions. A second group in each experiment was partially reinforced (Group PRF). For Group PRF, only a portion (25%) of the presentations of the drug administration procedures were accompanied by the drug. Subjects in this group received the drug on the same days as subjects in Group CRY, but on each of the days between drug sessions they received placebo sessions (that

is, they were treated in the same manner as on morphine sessions, except the substance injected was physiological saline rather than the opiate). Thus, in each experiment, rats in Group CRF and PRF received the same dose of the drug, equally as often, and at the same intervals. The two groups differed only with respect to the reliability of environmental cues as signals for the drug. Group CRF subjects always experienced these cues in conjunction with the drug, and never without the drug. In contrast, Group PRF subjects had extensive experience with these cues, without the drug, between drug sessions.

The results of the two partial reinforcement experiments are summarized in Figure 3 (next page). Figure 3A displays the mean response latency on the hot plate, 30 min following each morphine injection, for both goups in the analgesic tolerance experiment (Siegel, 1977b_, Experiment . As indicated in Figure 3A, both groups displayed analgesic tolerance, that is, decreasing response latency to the thermal stimulation as a function of repeated morphine sessions. However, as may be seen in Figure 3A, tolerance was acquired more rapidly by subjects in Group CKF than by subjects in Group PRF. This difference, which is statistically significant (mixed design analysis of variance, p's <.0l), demonstrates that partial reinforcement retards the development of morphine analgesic tolerance, much as it has been demonstrated to retard learning in more traditional conditioning preparations.

The deleterious effect of partial reinforcement on tolerance was also demonstrated in the investigation of pyretic tolerance (Siegel, submitted, Experiment 3). The results obtained in that experiment are summarized in Figure 3B, which displays the mean colonic temperature two hr following each morphine injection for groups which either did or did not have placebo sessions interspersed between these morphine sessions (Groups PRF and CRF, respectively).[4] Again, both groups evidenced tolerance to the hyperthermic effects of morphine, but this tolerance developed significantly more rapidly in Group CRF than in Group PRF.

It should be emphasized that in both partial reinforcement experiments, Groups CRF and PRF do not differ with respect to pharmacological history, yet they do differ in speed of tolerance acquisition. These experiments clearly demonstrate that the development of tolerance can be affected simply by manipulation of the reliability of environmental cues as signals for morphine. The findings, although not explicable by any interpretation of tolerance which ignores these cues, are to be expected on the basis of the conditioning model of tolerance.

Latent Inhibition of Morphine Tolerance

The results of the experiments described in the previous section indicated that one procedure that is effective in retarding the acquisition of conditional responses, partial reinforcement, is also effective in retarding the development of morphine tolerance, thus supporting the conditioning analysis of tolerance. Another procedure which is known to have a deleterious effect on conditional response formation is preconditioning exposure to the conditional stimulus. It has been reported that in many conditioning preparations, with both human and a variety of infrahuman subjects, presentations of the conditional stimulus prior to the start of acquisition serve to decrease the

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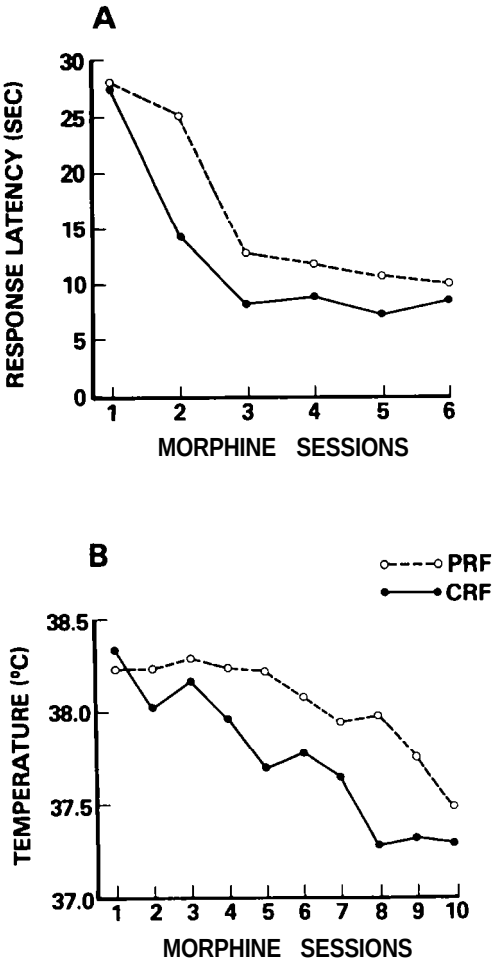
FIGURE 3

Summary of results of experiments demonstrating that the acquisition of morphine tolerance is retarded in a group in which only 25% of the presentations of the drug administration procedure are accompanied by morphine (PRF), compared to a group in which all presentations of the drug administration procedure are accompanied by morphine (CRF). Figure 3A illustrates hot-plate response latencies reported by Siegel (1977b, Experiment 4). Figure 3B illustrates therma1 effects reported by Siege1 (submitted, Experiment 3).



effectiveness of that stimulus when it is subsequently paired with an unconditional stimulus during conditioning. The deleterious effect of conditional stimulus preexposure has been termed "latent inhibition" (Lubow & Moore 1959). Although there is some controversy concerning the mechanism of latent inhibition (see reviews by Lubow, 1973, Siegel 1972b), the theoretical interpretation of the phenomenon is irrelevant for its exploitation as a technique to assess the conditioning theory of morphine tolerance. According to this theory, inasmch as tolerance results from an association between the predrug environmental conditional. stimulus and the pharmacological unconditional stimulus, the course of tolerance acquisition should be affected by the relative novelty of environmental cues present at the time of drug administration. Thus, on the basis of the conditioning theory of tolerance, animals with extensive experience with the administration procedure prior to its actual pairing with morphine should be relatively retarded in the acquisition of tolerance, compared with animals with mininmal prior experience with these environmental cues, despite the fact that both groups suffer the systemic effects of the same dose of the opiate, given the same number of times, at the same intervals.

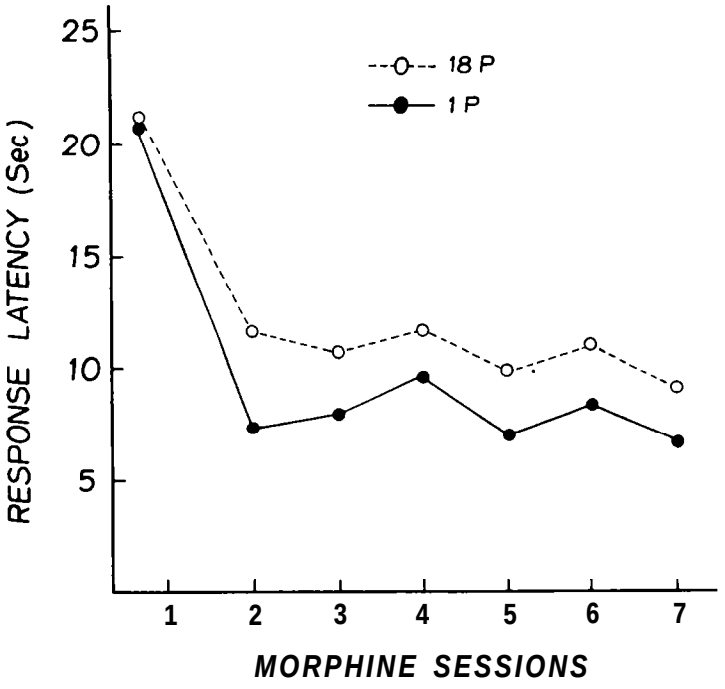
We have reported the results of an experiment designed to assess whether the latent inhibition procedure does, in fact, retard the acquisition of analgesic tolerance (Siegel 1977b, Experiment 3). In this experiment, one group of rats was extensively preexposed to the drug administration cues, in the absence of the drug, before these cues were actually followed by morphine. Rats in this group (Group 18P) received 18 daily placebo sessions prior to seven daily morphine sessions. Rats in a second group received only a single preexposure to the administration procedure prior to this procedure actually signalling the drug (Group 1P). Rats in Group 1P received a placebo session the day before the start of the seven daily morphine sessions.

The mean response latencies of Groups 18P and IP on the hot plate following each morphine injectionare shown in Figure 4 (next page). As can be seen in Figure 4, both groups evidenced similar, highresponse latencies following the first morphine administration, which is a manifestation of the initial analgesic effect of the drug. Response latencies of both groups rapidly decreased on subsequent drug sessions (i.e., analgesic tolerance developed), but this decrease was significantly more rapid [$F(1,20)=6.25, p=.02$] for Group IP than for Group 18P.

On the basis of any of the systemic, nonassociative theories of tolerance, it would be expected that Groups IP and l8P should become equally tolerant to the analgesic effect of morphine. The two groups displayed equivalent levels of analgesia the first time they received the drug, and both groups had equivalent experience with the systemic effects of the drug. However, contrary to this expectation of nonassociative interpretations of tolerance, tolerance was more marked in Group 1P than in Group 18P. This finding that predrug experience with the administration procedure retards the acquisition of tolerance (i.e., that tolerance is subject to latent inhibition) supports yet another unique prediction of the conditioning model of tolerance, and is not explicable by alternative theories of tolerance which do not enphasize the role of drug-associated environmental cues in the development of tolerance.

FIGURE 4

Mean response latency on the hot plate following each of seven morphine injections for groups receiving either 18 preexposures (18p) or 1 preexposure (1P) to the drug administration procedure prior to morphine administration (from Siegel 1977b, Experiment 3).



LEARNING AND TOLERANCE : RESEARCH FROM OTHER LABORATORIES

The results of a number of experiments conducted in my laboratory have been summarized, all supporting the Pavlovian conditioning analysis of morphine tolerance. These investigations have all demonstrated that tolerance (at least in part) is a manifestation of an association between the drug administration ritual and the systemic effects of the drug. Drug preparatory conditional responses, evidenced in anticipation of the actual pharmacological assault, attenuate the pharmcological insult. It should be noted that other investigators, while not committing themselves to a specific associative model of tolerance, have also presented evidence implicating learning or memory processes in the development of morphine tolerance.

Retention of Tolerance

Evidence suggesting that associative processes may be involved in tolerance is provided by experiments indicating that tolerance dissipates little with the passage of time (see Cochin & Kornetsky 1964; Kayan &Mitchell 1972). Indeed, it has been reported that four opiate addicts display profound tolerance to the analgesic effect of morphine as long as eight years after their last experience with the drug (Andrews 1943). Gochin (1970) has suggested that such persistence of tolerance in the absence of any experience with the opiate is not interpretable by many systemic theories of tolerance. However, this great retention of tolerance would be expected on the basis of a learning analysis of tolerance, since learned responses are highly resistant to decrement merely as a result of the passage of time (see Kimble 1961, p. 281). Indeed, Cochin (1972) suggested that since tolerance occurs with very long intervals between drug administrations, "a reaction analogous to memory" (p. 265) may be important in the phenomenon.

Metabolic Intervention and Tolerance

There is evidence that a variety of suppressors of protein synthesis, such as puromycin and cycloheximide, retard the acquisition of certain learned responses (see review by Nakajima, 1976). These drugs also retard the development of morphine tolerance (see review by Ginsburg & cox, 1972). Cohen, Keats, Krivoy, and Ungar (1965) suggested that there may be a parallel between learning and tolerance since metabolic inhibitors have similar effects on both processes.

It has been reported that the ability of metabolic inhibitors to retard learning is antagonized by the pituitary peptide, desglycinamide^{9}-lysine vasopressin (e.g., Lande, Flexner, & Flexner 1972). Furthermore, this vasopressin facilitates sane types of learning (e.g., lande, Witter, & DeWied 1971). Recently, Krivoy, Zimmerman, and Lande (1974) demonstrated that desglycinamide^{9}-1ysine vasopressin facilitated the acquisition of morphine analgesic tolerance, again demonstrating a similarity in the effect of metabolic agents on learning and tolerance.

Consolidation and Tolerance

Learning can be retarded by a variety of cerebrally insulting events presented shortly after the learning experience, such as electrocnvul-

sive shock (ECS) or electrical stimulation of certain brain regions, such as the frontal cortex (see Jarvik 1970; McGaugh & Herz 1972). Recently reported results from two laboratories, obtained in experiments specifically designed to examine the analogy between tolerance and learning, both indicate that ECS retards the development of tolerance to the analgesic effect of morphine (Stolerman, Bunker, Johnson Jarvik, Krivoy, Zimmermann 1976; Kesner, Priano, & Dewitt 1976).[5] Similarly, Kesner, et al. (1976) further demonstrated that stimulation of the frontal cortex following each morphine administration disrupts the acquisition of tolerance, and they concluded:

> .the data from both the ES and discrete brain stimulation experiments provide additional support for a possible parallel between conventional learning and tolerance to drugs (Kesner, et al. 1976, p. 1081).

In summary, investigations from a number of laboratories have demonstrated that the acquisition of tolerance shares many similarities with more conventional learning preparations: Both tolerance and learning are retained over long periods of time, and both are similarly disrupted by ECS, frontal cortical stimulation, and metabolic inhibitors (and both are facilitated by antagonists of metabolic inhibitors). These findings generally support the view that learning plays a role in tolerance and are fully consistent with the conditioning theory of tolerance.

SUMMARY

It has been demonstrated that many conditional responses to a variety of drugs are opposite in direction to the unconditional effects of the drug, and the conditioning analysis of morphine tolerance emphasizes the fact that subjects with a history of morphine administration display morphine-campensatory conditional responses when confronted with the usual administration procedure but without the drug. Thus, when the drug is presented in the context of the usual administration cues, these conditional morphine-compensatory responses would be expected to attenuate the drug-induced unconditional responses, thereby decreasing the observed response to the drug. Research has been summarized which supports this compensatory conditioning model of tolerance by demonstrating that the display of tolerance is specific to the environment in which the drug has been previously administered. Further evidence supporting this theory of tolerance has been provided by studies establishing that extinction, partial reinforcement, and latent inhibition--non-pharmacological manipulations known to be effective in generally affecting the display of conditional responses--similarly affect the display of morphine tolerance. Additional research has suggested many parallels between learning and morphine tolerance. Both processes exhibit great retention, both are disrupted by electroconvulsive shock and frontal cortical stimulation, both are retarded by inhibitors of protein synthesis, and both are facilitated by antagonists of these metabolic inhibitors.

FOOTNOTES

[1]This paper was prepared for a National Institute on Drug Abuse Symposiun on Behavioral Tolerance, June 23-24, 1977. Research by the author smmarized in this paper was supported by NIDA Grant DA-01200.

[2]In addition to groups labeled SAME and DIFFERENT in Figure 1, each of the summarized experiments included additional treatment conditions which, for simplicity, are omitted from the figure. The two groups that are displayed for each of the analgesia experiments (Figures IA-ID) were similarly treated in that, in each case, no subject had any practice in performing the analgesia-indicant response until the final assessment of the drug's effect. The design of the hyperthermic tolerance experiment (Figure lE) was somewhat different, and is described in the text.

[3]The data labeled CONTROL in Figure 2D represent the man of readings for two groups, both of which received morphine for the first time during the tolerance test, and both of which responded to the drug similarly. One of these groups received the same schedule of pretest injections as Group BEST, and the other group received the same schedule of pretest injections as Group EXT; but, in each case, all pretest injections consisted of physiological saline.

[4]In the hyperthermic tolerance experiment, the time course of the temperature alteration on all sessions was determined. For simplicity, Figure 3B displays the temperature measured 120 min following each of the 10 morphine injections. The more complete time-effect data may be found in the original report of the experiment (Siegel, submitted).

[5]It should be noted that the authors of one experiment suggested that their results indicated that post-administration ECS did not affect the development of analgesic tolerance (Ferguson, Adams, & Mitchell 1969). However, examination of their tolerance acquisition data indicates that they, too, obtained an ECS-induced tolerance retardation effect, but the statistical significance of the trend cannot be evaluated from the data presented in the published paper.

REFERENCES

Adams, W.H., Yeh, S.Y., Woods, L.A., & Mitchell, C.L. Drug-test interaction as a factor in the development of tolerance to the analgesic effect of morphine. J. Pharmacol. Exp. Ther., 168:257, 1969.

Andrews, H.L. The effect of opiates on the pain threshold in post-addicts. J. Clin. Invest., 22:511-516, 1943.

Beecroft, R.S. Classical Conditioning Goleta, California: Psychonomic Press, 1966. pp. 126-129.

Bykov, K.M. The Cerebral Cortex and the Internal Organs. Moscow: Foreign Languages Publishing House, 1959. pp. 82-83.

Cochin, J. Possible mechanisms in development of tolerance. Fed. Proc. 29:19-27, 1970.

Cochin, J. Role of possible immune mechanisms in the development of tolerance. In: Clouet, D.H., ed. Narcotic Drugs: Biochemical Pharmacology. New York: Plenum Press, 1971.

Cochin, J. Some aspects of tolerance to the narcotic analgesics. In: Singh, J.M., Miller, L., & Lal, H., eds. Drug Addiction l. Experimental Pharmacology. New York: Futura Press, 1972.

Cochin, J., & Kometsky, C. Development and loss of tolerance to morphine in the rat after single and multiple injections. J. Pharmacol. Exp. Ther. 145:1-10, 1964.

Cohen, M., Keats, A.S., Krivoy, W., & Unger, G. Effect of actinomycin D on morphine tolerance. Proc. Sot. Exp. Biol. Med., 119:381-384, 1965.

Collier, H.O.J. A general theory of the genesis of drug dependence by induction of receptors. Nature (London), 205:181-182, 1965.

Collier, H.O.J. The experimental analysis of drug dependence. Endeavor (Engl. Ed.), 31:123-129, 1972.

Deutsch, R. Conditioned hypoglycemia: A mechanism for saccharin-induced sensitivity to insulin in the rat. J. Comp. Physiol. Psychol., 86:350-358, 1974.

Domjan, M., & Gillan, D.J. Increased drinking associated with the expectancy of lithium malaise. J. Exp. Psychol. : Anim. Behav. Processes, in press.

Fennessy, M.R., & Lee, J.R. The assessment of and the problems involved in the experimental evaluation of narcotic analgesics. In: Ehrenpreis. S., & Neidle, A., eds. Methods in Narcotics Research. New York: Marcel Dekker, 1975.

Ferguson, R.K., Adams, W.J., & Mitchell, C.L. Studies of tolerance development to morphine analgesia in rats tested on the hot plate. Eur. J. Pharmacol., 8:83-92, 1969.

Ferguson, R.K., & Mitchell, C.L. Pain as a factor in the development of tolerance to morphine analgesia in man. Clin. Pharmacol. Ther., 10:372-382, 1969.

Gebhart, G.F., & Mitchell, C.L. Further studies on the development of tolerance to the analgesic effect of morphine: The role played by the cylinder in the hot plate testing procedure. Arch. Int. Pharmacodyn. Ther. , 191:96-103, 1971.

Gebhart, G.F., & Mitchell, C.L. The relative contributions of the testing cylinder and the heated plate in the hot plate procedure to the development of tolerance to morphine in rats. Eur. J. Pharmacol., 18:56-62, 1972.

Gebhart, G.F., Sherman, A.D., & Mitchell, C.L. The influence of learning on morphine analgesia and tolerance development in rats tested on the hot plate. Psychopharmacologia (Berlin), 22:295-304, 1971.

Gebhart, G.F., Sherman, A.D., 4 Mitchell, C.L. The influence of stress on tolerance development to morphine in rats tested on the hot plate. Arch. Int. Pharmacodyn. Ther., 197:328-337, 1972.

Ginsburg, M., & Cox, B.M. Proteins and nucleic acids. In: Mule, S.J., & Brill, H., eds. Chemical and Biological Aspects of Drug Dependence. Cleveland: CRC Press, 1972.

Goldberg, S.R., & Schuster, C.R. Conditioned suppression by a stimulus associated with nalorphine in morphine-dependent monkeys. J. Exp. Anal. Behav., 10:235-242, 1967.

Goldberg, S.R., & Schuster, C.R. Conditioned nalorphine-induced abstinence changes: Persistence in post morphine-dependent monkeys. J. Exp. Anal. Behav., 14:33-46, 1970.

Goldstein, A., Arnow, L., & Kalman, S.M. Principle of Drug Action: The Basis of Pharmacology (2nd ed.). New York: Wiley, 1974, chpt.9.

Guha, D., Dutta, S.N., & Pradhan, S.N. Conditioning of gastric secretion by epinephrine in rats. Proc. Sot. Exp. Biol. Med., 147: 817-819, 1974.

Gunne, L. M. The temperature response in rats during acute and chronic morphine administration: A study of morphine tolerance. Arch. Int. Pharmacodyn. E., 129:416-428, 1960.

Hermann, J.B. The pyretic action on rats of small doses of morphine. J. Phannacol. Exp. Ther., 76:309-315, 1942.

Himmelsbach, C.K. IV. With reference to physical dependence. Fed. proC., 2:201-203, 1943.

Hug, C.C. Characteristics and theories related to acute and chronic tolerance development. In: Mulé, S. J., & Brill, H. , eds. Chemical and Biological Aspects of Drug Dependence.

Jarvik, M.E. The role of consolidation in memory. In: Byrne, W.L., ed. Molecular Approaches to Learning and Memory. New York: Academic Press, 1970.

Kayan, S., Ferguson, K.K., & Mitchell, C.L. An investigation of the pharmacologic and behavioral tolerance to morphine III rats. J. Pharmacol. Exp. Ther., 185:300-306, 1973.

Kayan, S., & Mitchell, C.L. Further studies on the development of tolerance to the analgesic effect of morphine. Arch. Int. Pharmacodyn. Ther., 182:287-294, 1969.

Kayan, S., & Mitchell, C.L. Studies on tolerance development to morphine: Effect of the dose-interval on the development of single dose tolerance. Arch. Int. Pharmacodyn. Ther., 199:407-414, 1972.

Kayan, S., Woods, L.A., & Mitchell, C.L. Experience as a factor in the development of tolerance to the analgesic effect of morphine. Eur. J. Pharmacol., 6:333-339, 1969.

Kayan, S., Woods, L .A., &, Mitchell, C .L. Morphine-induced hyperalgesia in rats tested on the hot plate. J. Pharmacol. Exp. Ther., 177: 509-513, 1971.

Kesner, R.P., Priano, D.J., & Dewitt, J.R. Time-dependent disruption of morphine tolerance by electroconvulsive shock and frontal cortical stimulation. Science (Wash., D.C.), 194:1079-1081, 1976.

Kimble, G. Hilgard and Marquis' Conditioning and Learning. New York: Appleton-Century-Crofts, 1961. p. 281.

Kometsky, C., & Rain, G. Morphine: Single-dose tolerance. Science, 162:1011-1012, 1968.

Korol, B., & McLaughlin, L.J. A homeostatic adaptive response to alpha-methyl-dopa in conscious dogs. Pavlovian J. Biol. Sci., 11: 67-75, 1976.

Korol, B., Sletten, I.W., & Brown, M.L. Conditioned physiological adaptation to anticholinerglc drugs. Am. J. Physiol., 211:911-914, 1966.

Krivoy, W.A., Zimmermann, E., & Lande, S. Facilitation of development of resistance to morphine analgesia by desglycinamide^{9}-lysine vasopressin. Proc. Natl. Acad. Sci. U.S.A., 71:1852-1856, 1974.

Kuschinsky, K. Opiate dependence. Prog. Pharmacol. , 1 :Whole No. 2, 1977.

Lande, S. Flexner , J.B., & Flexner, L.B. Effect of corticotropin tinamide^{9}-lysine vasopressin on suppression of memory by puromycin . Proc. Natl. Acad. Sci. U.S.A., 69:558-560, 1972.

Lande, S., Witter , A. , & DeWied, D. Pituitary peptides, an octapeptide that stimulates conditioned avoidance acquisition in hypophysectomized rats. J. Biol. Chem., 246:2058-2062, 1971.

Lang, W.J., Brown, M.L., Gershon, S., & Korol, B. Classical and physiologic adaptive conditioned responses to anticholinergic drugs in conscious dogs. Int. J. Neurophannacol., 5:311-315, 1966.

Lang, W.J., Bush, M.L., & Pearson, L. Pharmacological investigation of the mechanism of conditional salivation in dogs induced by atropine and morphine. Eur. J. Pharmacol., 5:191-195, 1969.

LeMagnen, J. Olfactory-endocrine interaction and regulatory behaviours . In: Denton, D.A., & Coghlan, J.P., eds. Olfaction and Taste V. New York: Academic Press, 1975.

Lubow, R.E. Latent inhibition. Psychol. Bull., 79:398-407, 1973.

Lubow, R.E., & Moore, A.U. Latent inhibition: The effect of nonreinforced pre-exposure to the conditional stimulus. J. comp. Physiol. Psychol., 52:415-419, 1959.

Lundberg, E., & Thyselius-Lundberg, S. Beitrag zur kenntnis des innersekretorischen gleichgewichtsmechanismus: Die einwirkung des tabakrauchens auf den blutzucker. Acta Med. Scand., Supplement 38, 1931.

McGaugh, J.L., & Hertz, M.J. Memory Consolidation. San Francisco: Albion, 1972.

Mityushov, M.I. Uslovnorleflektor-nay a inkretsiya insulina. (The conditional reflex incretion of insulin.) Zh. Vyssh. Nervn. Deyat., 4:206-212, 1954. (Read in translation.)

Mule', S.J., 6 Woods, L .A. Distribution of N-$C1^4$-methyl labeled morphine. I. In central nervous system of nontolerant and tolerant dogs. J. Pharmacol. Exp. Ther., 168:251-257, 1969.

Mulinos, M.G., & Lieb, C.C. Pharmacology of learning. Am. J. Physiol., 90:456-457, 1929. (Abstract)

Nakajima, S. Cycloheximide: Mechanisms of its amnesic effect. Curr. Dev. Psychopharmacol., 3:26-53, 1976.

Obal, F. The fundamentals of the central nervous control of vegetative homeostasis. Acta Physiol. Acad. Sci. Hung., 30:15-29, 1966.

Obal, F., Vicsay, M., & Madarasz, I. Role of a central nervous mechanism in the acquired tolerance to the temperature decreasing effect of histamine. Acta Physiol. Acad. Sci. Hung., 28:65-76, 1965.

O'Callaghan, J.P., & Holtzman, S.G. Prenatal administration of morphine to the rat: Tolerance to the analgesic effect of morphine in the offspring. J. Pharmacol. Exp. Ther., 197:533-544, 1976.

O'Callaghan, J.P., & Holtzman, S.G. Prenatal administration of levorphanol or dextrorphan to the rat: Analgesic effect of morphine in the offspring. J. Pharmacol. Exp. Ther., 200:255-262, 1977.

Paton, W.D.M. The action of morphine and related substances on contraction and on acetylcholine output of coaxially stimulated guinea-pig ileum. Brit. J. Pharmacol. Chemother., 11:119-127, 1957.

Pavlov, I .P. Conditioned Reflexes. London: Oxford University Press, 1927, pp. 35 ff.

Pihl, R.O., & Altman, J. An experimental analysis of the placebo effect. J. Clin. Pharmacol., 11:91-95, 1971.

Randall, L.O., & Selitto, J. A method for measurement of analgesic activity on inflamed tissue. Arch. Int. Pharmacodyn. Ther. , 61: 409-419, 1957.

Rush, M.L., Pearson, L., & Lang, W.J. Conditional autonomic responses induced in dogs by atropine and morphine. Eur. J. Pharmacol., 11:22-28, 1970.

Russek, M., & Pina, S. Conditioning of adrenalin anorexia. Nature (London), 193:1296-1297, 1962.

Siegel, S. Conditioning of insulin-induced glycemia. J. Comp. Physiol. Psychol . , 78:233-241, 19722.

Siegel, S. Latent inhibition and eyelid conditioning. In: Black, A.H. & Prokasy, W.F., eds. Classical Conditioning II New York: Appleton-Century-Crofts, 1972b.

Siegel, S. Conditioning insulin effects. J. Camp. Physiol. Psychol. , 89:189-199, 1975a.

Siegel, S. Evidence from rats that morphine tolerance is a learned response. J. Comp. Physiol. Psychol., 89:498-506, 1975b.

Siegel, S. Morphine analgesic tolerance: Its situation specificity supports a Pavlovian conditioning model. Science (Wash., D.C.), 193:323-325, 1976.

Siegel, S. Learning and psychopharmacology. In: Jarvik, M.E., ed. Psychopharmacology in the Practice of Medicine. New York: Appleton-Century-Crofts, 1977a.

Siegel, S. Morphine tolerance acquisition as an associative process. J. B. Psychol.: Anim. Behav. Processes, 3:1-13, 1977b.

Siegel, S. The role of learning in the development of tolerance to the hyperthennic effect of morphine, submitted for publication.

Siegel, S. A conditioning model of the situation-specificity of morphine analgesic tolerance, in preparation.

Snyder, S.H., & Matthysse, S. Opiate Receptor Mechanisms. Cambridge, Massachusetts : MIT Press, 1975.

Solomon, R.L., & Corbit, J.D. An opponent-process theory of motivation. Psychol. Rev., 81:119-145, 1974.

Stolerman, I. P. , Bunker, P. , Johnson, C.A., Jarvik, M.E. , Krivoy, W., & Zimmermann, E. Attenuation of morphine tolerance development by electroconvulsive shock in mice. Neuropharmacol., 15:309-313, 1976.

Subkov, A.A., & Zilov, G.N. The role of conditioned reflex adaptation in the origin of hyperergic reactions. Bull. Biol. Med. Exp., 4:294-296, 1937.

Takemori, A.E. Studies on cellular adaptation to morphine and its reversal by nalorphine in cerebral cortical slices of rats. J. Pharmacol. Exp. Ther., 135:89-93, 1962.

Takemori! A.E. Neurochemical bases for narcotic tolerance and dependence . Biochem. Pharmacol., 24:2121-2126, 1975.

Way, E.L., Loh, H.H., & Shen, F. Simultaneous quantitative assessment of morphine tolerance and physical dependence. J. Pharmacol. Exp. Ther. , 67:1-8, 1969.

Wikler, A. Recent progress in research on the neurophysiologic basis of morphine addiction. Am. J. Psychiat., 105:329-338, 1948.

Winter, C., & Flataker, L. The relation between skin temperature and the effect of morphine upon the response to thermal stimuli in the albino rat and dog. J. Pharmacol. Exp. Ther., 109:183-188, 1953.

AUTHOR

Shepard Siegel, Ph.D., Professor of Psychology, McMaster University Hamilton, Ontario, Canada L8S4Kl

II. NARCOTICS

Narcotic Tolerance and Operant Behavior

James H. Woods, Ph.D., and John Carney, Ph.D.

This paper describes the production and measurement of narcotic tolerance as It is reflected in operant behavior. The long-term goals of the project are to describe the variables that control the development and extent of narcotic tolerance; to describe how narcotic tolerance affects different types of operant behavior and vice versa; and, further, to document the types of narcotic tolerance that may exist, as defined by different inducing agents. Additionally, we are interested In particular behavioral consequences of tolerance development, e.g., changes in rate and pattern of narcotic-reinforced responding. Although It is commonly assumed that changes in narcotic self-injection reflect increased tolerance development, to our knowledge no direct evidence bearing on this issue has been offered.

We have devoted most of our attention toward simple characterization of narcotic tolerance. Nevortheless, we have been influenced by evidence that suggests that tolerance to narcotic-induced behavioral changes may be of both a metabolic and nonmetabolic nature (e.g., Goldstein et al. 1973). Moreover, we share the suppositions proposed by a number of participants that dose-effect expressions of tolerance are good measurement tools, and that operant behavior is a good starting point for the analysis of behavioral tolerance. Because of the variety of behavioral circumstances under which we make observations of narcotic tolerance, operant behavior is the only cohesive descriptive system available to us. We will draw particular attention to aspects of our findings on narcotic tolerance where it appears to reflect behavioral mechanisms above and beyond the types of narcotic tolerance noted above.

Narcotics affect a variety of operant behaviors, including behaviors not closely related to painful events (e.g., Dews 1973). Dose-effect relations and relative potency measures of agonists and narcotic antagonism may be obtained with operant behavior in a variety of species (e.g., McMillan 1973), suggesting the suitability of measuring tolerance using this endpoint. There is the suggestion that examples of narcotic tolerance observed

may be characterized as a shift to the right in dose-effect curve of the narcotic (McMillan and Morse 1967). In the following experiments, the generality and degree of narcotic tolerance were assessed in a variety of ways.

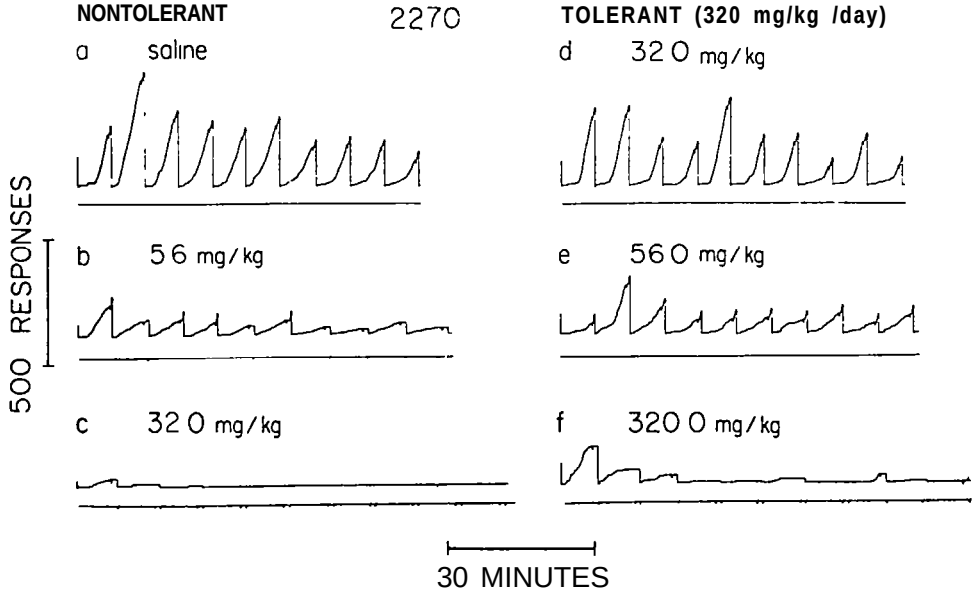
NARCOTIC TOLERANCE AND FOOD-REINFORCED PERFORMANCE

Pigeons

In an experiment with pigeons in which key-peck responses were maintained by occasional food presentations, we gave weekly administrations of morphine to obtain dose-effect relations that would serve as a referent for subsequent tolerance development. Individual cumulative records of performance are shown in Figure 1 for one of the birds from the experiment. Each bird's key peck performance was maintained by 4 sec periods of food access following the first response after five minutes (fixed interval 5 [FI 5]) in the presence of a red key light, or following 30 responses (fixed ratio 30 [FR 30]) in the presence of a blue key light. These schedule conditions alternated following either reinforcement, after 1 min periods of nonresponding under FR 30, or 1 min periods of nonresponding after 5 minutes had elapsed in the FI. Responding was maintained at a lower rate in the FI, and responding gradually increased in rate during the interval (Figure la). Following food delivery, fixed-ratio responding ocurred at a rapid rate until food was delivered again. Morphine at 5.6 mg/kg reduced responding in both components of the schedule (Figure lb) and almost completely eliminated the behavior at 32 mg/kg (Figure lc) . We then delivered the drug daily in gradually increasing doses over the course of six months. At this point, occasional substitutions of larger and smaller doses of morphine were administered; the effects of 32.0, 56.0, and 320 mg/kg are shown in the d-f segments of Figure 1. Clearly, there is loss of sensitivity to morphine in this individual case that suggests a lo-fold change. There do not appear to be other qualitative changes in performance that accompany tolerance development.

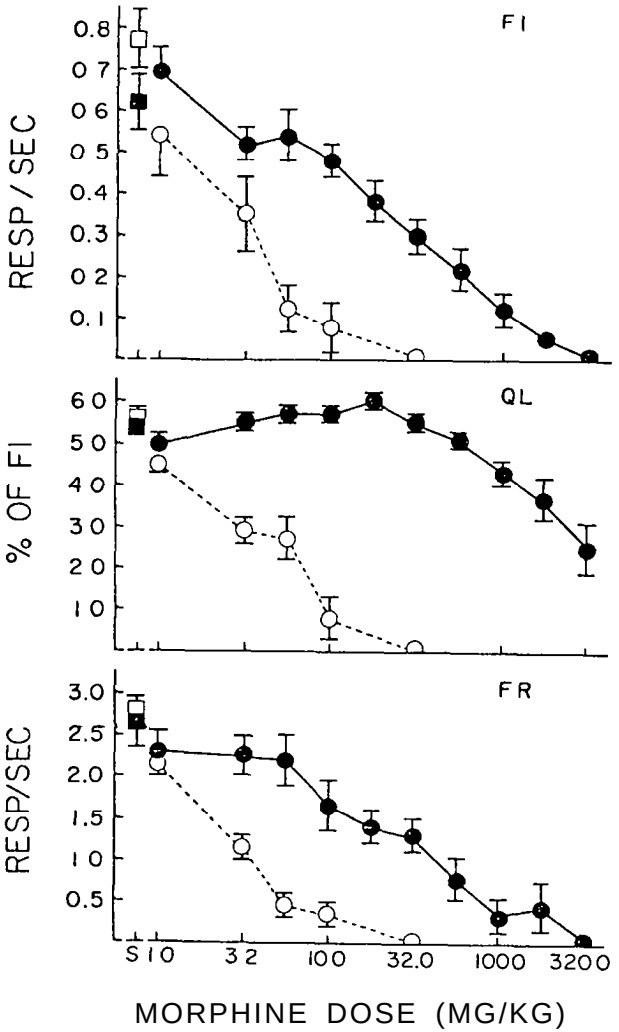
The grouped performances following maintenance for over 50 days at 32.0 mg/kg/day showed an approximately 6- to 10-fold shift to the right of dose-effect curves on response rates for morphine in FI and FR components (Figure 2). Before chronic morphine, a 3.2 mg/kg dose decreased response rates to approximately 45% of control; after daily maintenance at 32.0 mg/kg/day, however, doses of 17.8 and 32.1) mg/kg were required to produce about the same decrease in response rates. Similarly, before daily morphine maintenance, a 32.0 mg/kg dose almost completely suppressed responding. After daily maintenance at 32.0 mg/kg/day, however, a test dose of 320 mg/kg was required to cause about the same degree of response suppression.

FIGURE 1



Cumulative records of a pigeon's performance on a multiple fixed-interval 5 min, fixed-ratio 30 schedule of food presentation. Individual responses step the recorder pen up; diagonal deflections indicate food delivery. The fixed-interval and fixed-ratio components alternate and the recorder pen resets automatically after the completion of the fixed-ratio component . Records a, b, and c are examples of the effects of the pretreatments of saline or morphine in the doses shown when the morphine was delivered at weekly intervals. Records d, e, and f are from a later stage of the experiment in which 32 mg/kg morphine was delivered daily prior to the session and still larger doses were given as probes. This bird developed slightly more tolerance than is presented in subsequent grouped data (from Carney et al. 1977; in press).

FIGURE 2



Effects of morphine test doses and saline (S) on FI and FR response rates and FT quarter-life before chronic morphine (open symbols) and after daily maintenance at 32.0 mg/kg/day (closed symbols). Control values were calculated from 5 non-injection sessions before morphine testing. Each point represents the mean (f S.E.) of nine observations in the nontolerant conditions and 18 observations in the tolerant condition. Morphine and saline were administered intramuscularly immediately before the session (from Carney et al. 1977).

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In both nontolerant and tolerant pigeons, morphine test doses caused dose-related decreases in FI quarter-life. However, in contrast to FI and FR response rates, the dose-effect curve for FI quarter-life was shifted to the right by about 30-fold after daily administration of 32 mg/kg for 50 days. Decreases in FI quarter-life usually represented a tendency for responding to become relatively evenly distributed within FI components, even/ though the actual number of responses emitted may have been reduced substantially.

Thus, the amount of tolerance that develops to the rate-decreasing effects of morphine is substantial and is even greater for the measure of temporal pattern of responding in the interval. This differential tolerance suggests a behavioral mechanism, and it would be interesting to examine temporal patterns of responding on other multiple schedules involving temporal variables in order to generalize this result.

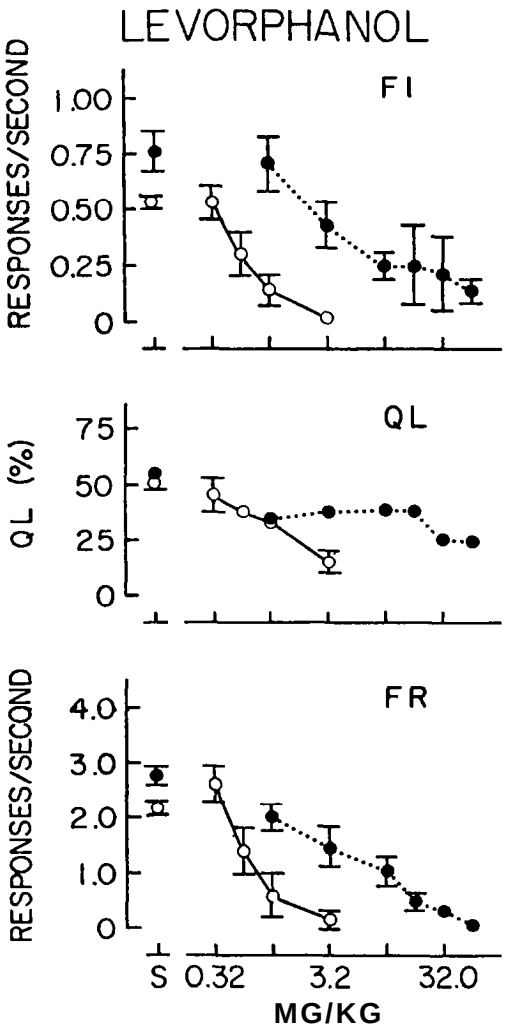
We then examined, in these tolerant birds, the sensitivity to narcotics in which stereoisomers are available. With the morphinans, levorphanol and dextrorphan, only the levorotatory form has a full range of narcotic activity, while dextrorphan lacks many of the actions of narcotics and is thought not to bind to narcotic receptors (e.g., Goldstein et al. 1971). Levorphanol (Figure 3) and dextrorphan (Figure 4) reduce food-maintained key-pecking, with levorphanol being more potent in the case of nontolerant birds. Chronic morphine administration conferred a marked loss of sensitivity to levorphanol but considerably less, if any, tolerance to dextrorphan. Thus, stereospecific tolerance may be conferred by morphine even in situations in which the nonnarcotic has a comparable behavioral activity.

Rhesus Monkeys

We have carried out similar experiments with rhesus monkeys in behavioral situations in which FR 30 responding was maintained by the delivery of 300-mg banana-flavored food pellets. The same paradigm of tolerance assessment was used in that dose-effect relations were obtained before and during chronic administration of morphine. Cross tolerance was assessed by examining changes in sensitivity to levomethorphan and dextromethorphan. Figure 5 shows the extent of tolerance observed under conditions in which 3.2 mg/kg morphine was administered at 8-hour intervals. There was a large shift to the right in the morphine and levomethorphan dose-rate functions without any change in dextromethorphan's effects on FR responding.

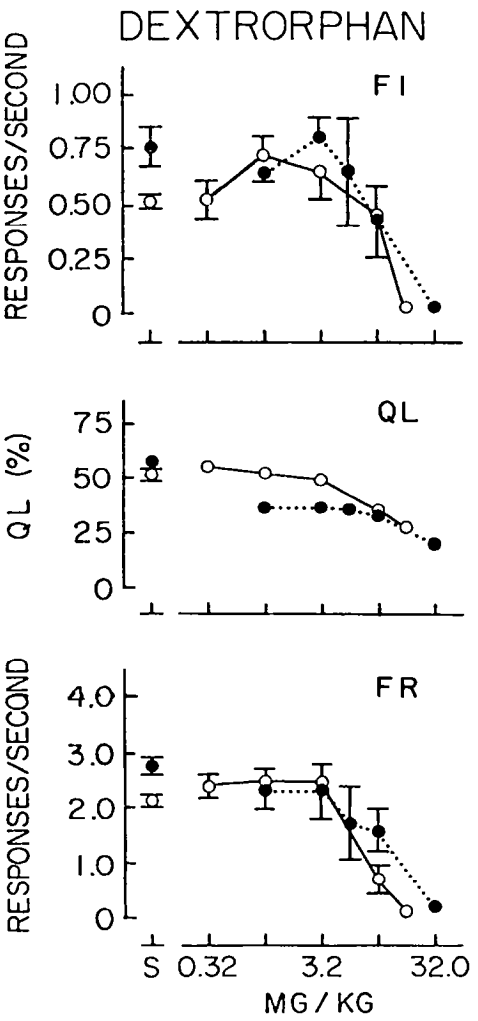
Operant behavior has served us well in describing changes in sensitivity to narcotics and assessing the pharmacological specificity of this effect. A variety of drugs may affect food-reinforced operant behavior, and this fact was taken advantage of in these situations to obtain comparable effects of the stereoisomers. Another important advantage of operant behavior during chronic drug administration is that of being able

FIGURE 3



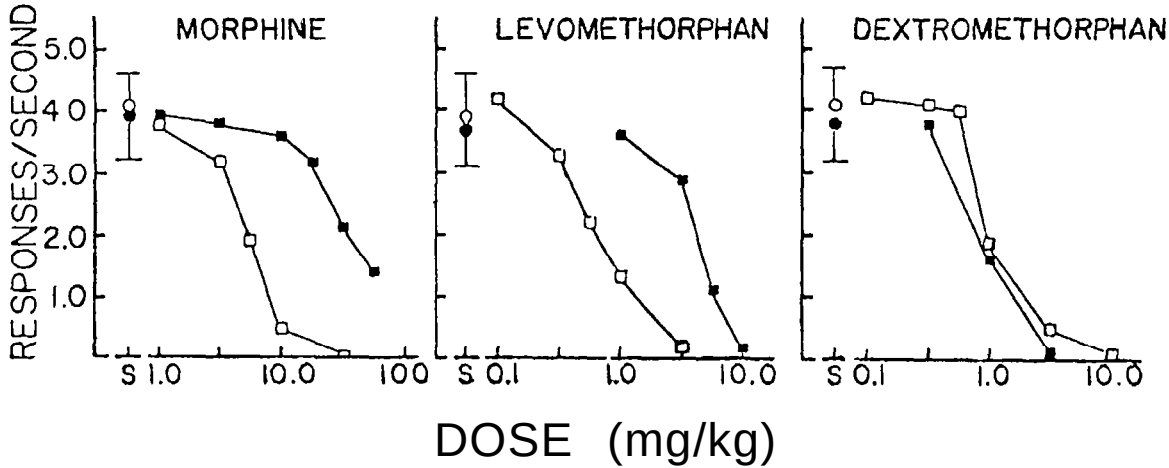
The effects of Ievorphanol on rates of FI responding, quarter-life values and rates of FR responding in nontolerant (open symbols) and morphine tolerant (closed symbols) pigeons. Each point represents the mean (* S.E.)of at least five observations at each dose (from Carney et al. 1977).

FIGURE 4



The effects of dextrorphan on rates of FI responding, quarter-life values and rates of FR responding In nontolerant (open circles) and morphine tolerant (closed circles) pigeons. Each point represents the mean (± S.E.) of at least 5 observations of each dose (from Carney et al. 1977).

FIGURE 5



Effects of morphine, levomethorphan and dextromethorphan on fixed-ratio food-reinforced responding in rhesus monkeys before (open symbols) and during (closed symbols) the chronic administration of 3.2 mg/kg morphine every 8 hours. Each data point represents 3-12 observations. Brackets indicate 1 standard error (from Carney and Woods 1977).

to assess control performance in the absence of drug. In our case, at some times absence of drug yielded behavior that did not differ in rate in any important way from predrug rates. Thus, rates of responding in the presence and absence of tolerance can be comparable, and dose-effect relations may be expressed as shifts from a common starting point.

The extent of narcotic tolerance in the monkey and pigeon was roughly comparable in that there was a 6- to lo-fold increase in the dose-effect relations. These experiments thus provided a good test of the empirical significance of the definition of tolerance in the two species.

NARCOTIC DEPRIVATION: PIGEON AND RHESUS MONKEY

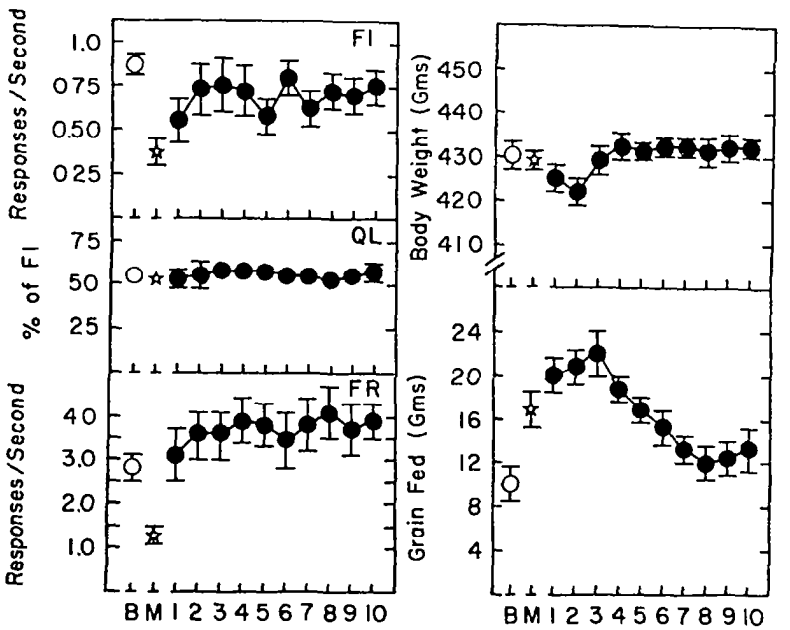
One way of examining other consequences of tolerance development is to deprive the organism of the narcotic. When the pigeons were deprived of morphine, they had been maintained on morphine for about 18 weeks. Saline was substituted for the morphine for ten days. During this time, there was a transient fall in body weight; maximum weight loss occurred 2 days after the last morphine InJection (Figure 6). Thus weight loss required an Increase in daily postsession feeding in an attempt to maintain the 80% deprivation weights. Body weight and amount of grain fed returned to nontolerant control values by the end of the ten-day withdrawal period. Rates of food-reinforced responding generally increased over the ten-day period. After ten days, fixed-interval response rates returned to slightly less than the nontolerant control level. Fixed-ratio response rates not only returned to the nontolerant control level, but increased to 153% of control rate by the end of 10 days.

Thus, morphine deprivation in the pigeon did not result in changes in schedule-controlled responding consistent with the expression of an abstinence syndrome. Similar lack of response disruption by withdrawal in narcotic-tolerant pigeons was reported by Heifetz and McMillan (1971) following 26 days of 5.6 mg/kg/day of methadone or morphine. Morphine deprivation produced a transient weight loss which is consistent with other species and has been taken as an abstinence sign.

The rhesus monkey does not withstand morphine deprivation as readily. If the monkey is deprived of two of the three daily 3.2 mg/kg injections of morphine, the food-reinforced performances are completely suppressed and may be reinstated with a morphine injection Carney and Woods 1977).

These findings taken together with the tolerance definition (a shift in dose-effect relationship) suggest that factors other than a simple equivalent shift of a dose-effect relation are necessary to predict correlates of tolerance development. Any number of factors need to be tracked down in order to supplement the definition in an appropriate way.

FIGURE 6



Effects of morphine deprivation on FI and FR response rates and FI quarter-life (left) and on body weight and amount of grain fed to maintain 80% food-deprivation weights (right). Data for the nontolerant (B) and morphine tolerant (M: 3210 mg/kg/day) conditions are provided for comparison. Prior to morphine deprivation, birds were maintained at 32.0 mg/kg/day. Each point represents the mean (±1 S.E.) of nine observations (from Carney et al. 1977).

TYPES OF NARCOTIC TOLERANCE

Martin and his colleagues (1976) have postulated multiple types of narcotic receptors on the basis of the effects of particular prototype agents that, while antagonized by naloxone, have marked differences in their effects upon various behavioral measures in the chronic spinal dog. Mark Llewellyn, at the University of Michigan, has explored the possibility of developing tolerance to ketocyclazocine in the rhesus monkey. Both morphine and ketocyclazocinc reduce multiple FI 5 FR 30 schedule performances maintained by food presentations. Chronic administration of morphine and ketocyclazocine produced comparable 3-fold shifts to the right in their dose-effect relations. When tested for cross tolerance, however, there was no decrease in sensitivity to morphine of monkeys receiving ketocyclazocine and vice versa. If any change occurred, a slight supersensitivity developed to ketocyclazocine in the monkeys receiving chronic morphine. In this experiment, when we have produced comparable degrees of tolerance to both morphine and ketocyclazocine, drug deprivation leads to marked disruption of food-reinforced responding in the case of morphine, but not with ketocyclazocine.

These data lend support via species and behavioral generality to Martin's conjectures concerning a different type of receptor for compounds of the ketocyclazocine type. They also suggest that cross tolerance tests with narcotics and operant behavior may be an important investigational tool for distinguishing different types of narcotics.

NARCOTIC TOLERANCE AND NARCOTIC-REINFORCED RESPONDING

We have recently adapted the behavioral situations described above to encompass narcotic-reinforced responding (Carney 1976). The situation is a multiple FR 30 schedule of food and codeine delivery. Before the monkey is given access to intravenous codeine for self-injection, a set of dose-effect curves is obtained with FR responding maintained by food presentation. Subsequently, codeine self-injection is added under different cue-light conditions but under the same FR schedule. Drug-reinforced responding is continued for over a month until stable, and then dose-effect relations are obtained again. Decreased drug sensitivity on food-reinforced responding with narcotics would indicate tolerance development; however, we have been able to maintain codeine-reinforced responding at high rates for over a month without obtaining a shift in sensitivity upon food-reinforced responding. Thus, it is possible to sustain narcotic-reinforced responding without inducing significant tolerance development. If the dose of codeine is increased markedly, we can induce tolerance. Under these conditions of tolerance induction, we have not found a

corresponding change in pattern of codeine-reinforced responding. We are confident of the dissociation of tolerance and sustained rates and patterns of narcotic-reinforced responding. We have no direct evidence that tolerance influences narcotic drug self-Injection

SUMMARY

Narcotic tolerance was measured as a shift to the right in dose-effect relations on operant behavior following repeated administration of drug. Tolerance has been observed with operant responding in both pigeons and rhesus monkeys. The amount of tolerance observed with food-reinforced responding is related both to the amount of morphine administered and to the nature of the drug-induced change In operant responding. Pharmacological specificity of the narcotic tolerance has been confirmed by equivalent loss of sensitivity to other narcotics without concomitant changes in sensitivity to nonnarcotic stereoisomers. Tolerant birds do not show disturbed operant behavior when narcotic administration is terminated abruptly.

Tolerance has been induced by narcotic self-injection and Its effects measured on rates and patterns of food- and narcotic-reinforced responding. Tolerance does not necessarily confer changes in narcotic-reinforced responding. Moreover, narcotic-reinforced responding may be initiated and maintained for periods of over one month without conferring tolerance.

REFERENCES

Carney, J .M. Selective modulation of codeine-reinforced responding in rhesus monkeys. Unpublished Ph.D. dissertation, Department of Pharmacology, University of Michigan, 1976.

Carney, J .M. and Woods, J.H. Changes in sensitivity to the behavioral effects of narcotic agonists and antagonlsts in morphine -dependent rhesus monkeys . Submitted to J- Pharmacol. Exp. Therap., 1977.

Carney, J.M., Downs, D.A., and Woods, J.H. Tolerance to effects of morphine on schedule-controlled behavior in pigeons. Submitted to J- Phamracol. Exp. Therap., 1977.

Dews, P. What is analgesia? In: Braude, M. et al., eds. Narcotic Antagonists. Adv. Biochem. Psychopharm., vol. 8. New York: Raven Press, 1973. pp. 235-243.

Downs, D.A., Carney, J.M. and Woods, J.H. Cross tolerance to behavioral effects of narcotics in pigeons. Submitted to J. Pharmacol. Exp. Therap., 1977.

Goldstein, A., Judson, B.A. and Sheehan, P. Cellular and metabolic tolerance to an opioid narcotic. Brit. J. Pharmacol., 47:138-140, 1973.

Goldstein, A., Lowney, L.I., and Pal, B.K. Stereospecific and nonspecific interactions of the morphine congener levorphanol in subcellular fractions of mouse brain. Proc. Nat. Acad. Sci 68:1742-1747, 1971.

Heifetz, S.A. and McMillan, D.E. Development of behavioral tolerance to morphine and methadone using the schedule-controlled behavior of the pigeon. Psychopharmacologia, 19:40-52, 1971.

Martin, W.R., Eades, C.G., Thompson, J.A., Huppler, R.E., and Gilbert, P.E. The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. J- Pharmacol. Exp Therap., 197:517-532, 1976.

McMillan, D.E. Effects of narcotics and narcotic antagonists on operant behavior. In: Braude, M. et al., eds. Narcotic Antagonists. Adv. Biochem. Psychopharm vol 8. New: Raven Press, 1973. pp. 345-360

McMillan, D.E. and Morse, W.H. Some effects of morphine and morphine antagonists on schedule-controlled behavior. J. Pharmacol. Exp. Therap., 157:175-184, 1967.

AUTHORS

James H. Woods, Ph.D., Department of Pharmacology, University of Michigan Medical School, Ann Arbor, Michigan 48109

John Carney, Ph.D., Department of Pharmacology, University of Oklahoma Medical School, Oklahoma City, Oklahoma 73190

II. NARCOTICS

Conditioning Effects of Narcotics in Humans

Charles P. O'Brien, M.D., Ph.D., Thomas Testa, Ph.D., Joseph Ternes, Ph.D., and Robert Greenstein, M.D.

Observations from classical conditioning studies in human narcotic addicts suggest ways in which behavioral tolerance may be involved in human addiction. Narcotic addicts experience sequential drug-related states usually called "highs" drawal, craving) , . Such changes are identifiable by self-reports and by measurable physiological changes. These states are obviously influenced by pharmacological factors (dose, time since last dose, route of administration, etc.), but there is also increasing evidence that they are influenced by learning factors. When environmental stimuli are consistently paired with drug-related states, the stimuli alone may acquire the ability to produce these states or to modify them. The subject's adaptational responses to these states may also be learned. Modification of drug-related states by learning is, of course, related to the phenomenon of tolerance.

CONDITIONED WITHDRAWAL

We have been studying behavioral and autonomic changes in drug-related states and the effects of learning on these changes. The first state we examined experimentally was that of withdrawal. Animal studies [Goldberg 1970) and clinical evidence (Wikler 1973a) indicated that withdrawal can be conditioned. We obtained systematic self-report data from the clinic (O'Brien 197%) and then produced withdrawal as a conditioned response in the laboratory (O'Brien et al. 1975a; O'Brien et al. 1977). SubJects were volunteers, maintained on a steady dose of methadone. Use of confoundine drugs was excluded by daily urine tests. The unconditioned response (UR) was naloxone-precipitated withdrawal. This consisted of brief, dose-related behavioral, subjective, and autonomic signs of narcotic abstinence. It was paired with a complex conditioning stimulus (tone/odor CS) . After 7-10 conditioning trials, a conditioned response (CR) was evident which generalized to the test room and frequently had its onset before the discrete CS. The CR was similar to the UR and in the same direction. The withdrawal consisted

of subjective components (craving, nausea, cramps), behavioral components (yawning, blinking, restlessness, touching of eyes, rubbing of abdomen) , and autonomic components (decreased skin temperature, tearing of the eyes, increased heart rate and respiration, changes in skin resistance and electrogastrogram). Thus a state similar to drug withdrawal was produced by a CS in human subjects under laboratory-controlled conditions.

Concerning conditioning in the natural environment, there is anecdotal evidence that addicts may begin yawning and tearing while discussing drugs during group therapy. We have also reported withdrawal behavior in addicts shown video tapes of drug-administration rituals (O'Brien et al. 1974). Teasdale reported changes in mood scales when addicts were exposed to drug-related slides (Teasdale 1973). The most consistent physiological evidence that we have found to date for a naturally conditioned withdrawal response is a study in which the "cook up" ritual serves as a CS (O'Brien et al. 1977b). Drug-free (detoxified) addicts who perform this ritual develop withdrawal responses (pupillary dilatation, decreased skin temperature) prior to receiving any drug. The CS seems to be a complex of the sight of a bag of heroin, the odor of the "cooker ," and the anticipation of a self-injection. Nonaddicts exposed to the same stimuli showed a novelty response which did not persist the way the addict response did. Thus we have evidence that in some circumstances the withdrawal or drug-negative state can occur as a conditioned phenomenon.

CONDITIONED AGONIST EFFECTS

We have also examined the drug-positive state in detoxified human addicts. When the subject is permitted to go through pre-injection rituals in the laboratory and then inject a narcotic, a sequence of subjective, behavioral, and autonomic changes occurs. bring the pre-injection phase, withdrawal or drug-negative responses usually occur. During the post-injection phase, the withdrawal responses are reversed, and the drug-positive responses occur. The subject reports relief of craving and withdrawal and the presence of pleasant or euphoric feelings. Autonomic responses include pupillary constriction, increased skin temperature, and slowing of respirations and gut contractions. Of course, the intensity and duration of the drug-positive effects depend on the dose and previous drug experience of the subject. We have also found that intensity and duration are influenced by pre-injection rituals and expectation of the subject.

The subjective effects of a narcotic are most influenced by these nonpharmacological factors, but in some subjects even the autonomic changes respond to expectation. A test dose of narcotic tends to produce greater drug-positive effects when self-injected along with rituals than when given over the same time interval through an intravenous infusion with no drug expectation signals to the subject. The conditioning of drug-positive responses is further exemplified by the effects of placebo injections. if a detoxified addict is

permitted to self-inject with rituals either narcotic (4 mg hydromorphone) or saline under double-blind conditions, the saline injection will be followed by a small drug-positive effect. This will extinguish in most subjects after one *or* two trials, especially if the subject has the opportunity to compare the effects of saline and narcotic (cognitive influence).

Addicts who are placed on a narcotic antagonist (cyclazocine or naltrexone) and then allowed to self-inject show an interesting series of responses. Most of those receiving saline extinguish drug-positive responses (high) within 1-3 trials and then show only drug-negative responses (withdrawal) after subsequent injections. Those who self-inject a narcotic show drug-positive responses for a greater number of trials, in spite of the antagonist, but in most cases extinction is complete within 8-10 trials. (There were some notable exceptions, with a few subjects showing euphoric responses for 20-25 trials even with saline injections. It is not clear whether this relates to prior conditioning history or individual variation.) After extinction of drug-positive responses, only drug-negative (withdrawal) responses remain, and these may be persistent and intense. The drug-positive responses probably persist longer when narcotic is injected in the presence of antagonist than when saline is injected, because some of the pharmacological effects of the narcotic are not completely blocked. The cyclazocine or naltrexone acts as a competitive antagonist of narcotic effects, but some narcotic enteroceptive cues apparently still occur. This explanation is supported by the fact that drug-positive effects persist longer when patients self-inject a narcotic while receiving cyclazocine than while receiving naltrexone. Naltrexone, since it has few side effects, can be used in a higher dose and thus can provide an agonist/antagonist ratio more favorable to the antagonist.

Our work with humans, therefore, suggests that both drug-positive and drug-negative effects can be learned. We have interpreted these findings within the framework of Solomon's opponent-process theory (Solomon and Corbit 1974). The findings are also compatible with Wikler's description of conditioned counteradaptive effects (Wikler 1973b) and Siegel's discussion of tolerance as a conditioned phenomenon (Siegel 1975). While Wikler and Siegel deal mainly with conditioning which reduces drug effects (drug-negative phenomena), we also have evidence of conditioned drug-positive effects. The opponent process framework provides a convenient means of describing the interaction between conditioned drug-positive and conditioned drug-negative effects. Briefly stated, it is postulated that a consistent set of rituals reliably signals the appearance of opiates in the body. The adaptive responses provoked by the impact of the drug on homeostatic mechanisms act to oppose the drug effects. These drug-negative responses, after repeated pairings with the antecedent rituals, can be elicited by the rituals alone. This learning of drug-negative responses is facilitated by the fact that the addict frequently is already in a pharmacological state of withdrawal as a result of metabolism of the previous dose by the time he performs the rituals. Thus there are two pathways for the reinforcement of drug-negative responses.

The learned drug-positive effects tend to be briefer and less reliable than drug-negative effects and more easily extinguished. These can be manifested in self-reports of "high" or euphoria and in such autonomic changes as pupillary constriction, decrease in respiratory rate, or increase in skin temperature. These learned responses are similar to what has been called the placebo effect and the "needle freak" phenomenon. Their onset follows self-injection, and they tend to augment rather than reduce the effects of the drug. These effects appear to be more influenced by expectation or cognitive factors than are conditioned drug-negative effects. This may help to explain why addicts continue to report pleasure from street "heroin" which contains minimal, if any, narcotic (O'Brien 1975b).

Our work with conditioned drug states in humans, though still preliminary, suggests that learning does play a role. It is too soon to state how important that role may be or whether the findings will have a direct application to the clinical management of drug dependent people.

REFERENCES

Goldberg, S.R. Relapse to opioid dependence: The role of conditioning . *Adv. Ment. Sci.,* 2:170-197, 1970.

O'Brien, C.P., Chaddock, B., Woody, G., and Greenstein, R. Systematic extinction of narcotic drug use using narcotic antagonists. Proceedings of the NAS/NRC Committee on Problems of Drug Dependence, Washington, D. C. : National Academy of Sciences, 1974. pp. 216-222.

O'Brien, C.P., O'Brien, T.J., Mintz, J., and Brady, J.P. Conditioning of narcotic abstinence symptoms in human subjects. Drug *and Alcohol* Dependence, 1:115-123, 1975a.

O'Brien, C.P. Experimental analysis of conditioning factors in human narcotic addiction. *Pharmacological Reviews,* 27:533-543, 1975b.

O'Brien, C.P., Testa, T., O'Brien, T.J., Brady, J.P., and Wells, B. Conditioned narcotic withdrawal in humans. Science, 195:1000-1002, 1977a.

O'Brien, C.P., Temes, J., Testa, T., and Greenstein, R. Naturally conditioned narcotic withdrawal responses. (Manuscript in preparation) , *1977b.*

Siegel, S. Evidence from rats that morphine tolerance is a learned response. *Journal of Comparative and Physiological Psychology,* 89:498-506, 1975.

Solomon, R.L., and Corbit, J.D. An opponent-process theory of motivation: Temporal dynamics of affect. Psychological *Review,* 81:119-146, 1974.

Teasdale, J. Conditioned abstinence in narcotic addicts. *Int. J. Addict.,* 8:273-292, 1973.

Wikler, A. Dynamics of drug dependence, implication of a conditioning theory for research and treatment. *Arch. Gen. Psychiatry,* 28: 611-616, 1973a.

Wikler, A. Conditioning of successive adaptive responses to the initial effects of drugs. *Conditional Reflex,* 8:193-210, 1973b.

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AUTHORS

Charles P. O'Brien, M.D., Ph.D.
Thomas Testa, Ph.D.
Joseph Temes, Ph.D.
Robert Greenstein, M.D.
Department of Psychiatry, University of Pennsylvania and
Philadelphia Veterans Hospital, Philadelphia, Pennsylvania 19104

III. ETHANOL

Tolerance as a Behavioral Phenomenon: Evidence from Two Experimental Paradigms

A. E. Le Blanc, Ph.D., C. X. Poulos, Ph.D., and H. D. Cappell, Ph.D.

INTRODUCTION

The purpose of this conference is to define and assess the importance of the phenomenon that has come to be known as "behavioral tolerance." Our contribution to this task will be based on two lines of research that have been continuing in the laboratories of the Addiction Research Foundation over the course of many years. During the development of this research, it has become evident to us, as to others, that no comprehensive account of tolerance can ignore behavioral concepts. This is so whether the object of study is drug-induced motor impairment or aversive conditioning by psychoactive drugs.

What Are the Descriptive Requirements of Tolerance?

Before an alteration in drug response can be characterized as tolerance, two requirements must be met:

(a) A drug effect will diminish in magnitude with repeated exposure to a fixed dose.
(b) A drug effect diminished in magnitude by repeated exposure to a fixed dose can be reinstated by an increase in dose.

These requirements imply nothing in particular about mechanisms of tolerance. They merely establish criteria to be applied in order to characterize a reduction in a drug effect as tolerance. It is often the case that investigators invoke the concept of tolerance even when only the first of the above requirements has been met. Usually, this is not a problem because enough is known about the pharmacology of drugs of interest that other characterizations of reduced response can be eliminated. However, reduction of response may be a reflection of tachyphylaxis resulting from depletion of a response mechanism, rather than genuine adaptation (cf. Kalant et al. 1971a). Where tachyphylaxis is involved, the second requirement for the existence of tolerance could not be met.

In the ideal case the production of tolerance should result in a parallel shift in the dose-response curve for the effect under investigation (Kalant et al. 1971a). This would be indicative of a shift in threshold of the dose required to produce the effect. It is not often the case that this ideal is achieved in actual research. In any event, this criterion is only applicable in the relatively simple case of linearity of dose-response function. A parallel shift of a nonmonotonic relationship may be more difficult to demonstrate. The notion of parallel shift is important for reasons of interpretation, since the nature of the alteration of the dose-response curve may be an important clue as to the mechanism of adaptation involved (Kalant et al. 1971a).

Behavioral Tolerance versus Other Kinds: A Preliminary View

The ideation and experimentation that led to the formulating of the concept of behavioral tolerance developed in part as a reaction to more physiologically or pharmacologically based conceptions. (Although "metabolic" tolerance is included as a physiological notion, we are not concerned with it here, especially since it seems not to be important in the studies we are discussing. Our meaning of physiological tolerance refers to changes in sensitivity of receptors at which a drug is presumed to act centrally.) This distinction has been considered in detail by a research group (Kalant et aL 1971a) with no inflexible allegiance to either conception. "Physiological" tolerance was defined as "a compensatory or homeostatic change in the neurons affected by the drug, which renders them less sensitive to it." The implication of such a definition is that tolerance is a necessary consequence of continued contact between a drug and the receptors upon which it acts, unmodulated by conditions other than pharmacological ones such as dose and duration of exposure. What is obviously wrong with such a conception is that it fails to account for numerous examples of adaptation to a drug that are modulated by nonpharmacological variables; perhaps more importantly, it fails to account for the comparative absence of adaptation in instances in which the pharmacological exposure per se was not adequate to evoke an adaptive response (e.g., Carlton & Wolgin 1971; Schuster et al. 1966). The final conclusion of Kalant's review was that there is in fact no qualitative difference between "physiological" and "learned" (the word used in the review) or 'behavioral" (the word adopted for this conference) tolerance. Rather, Kalant et al.argued, behavioral variables contribute to the rate of development of tolerance by modulating the rate of a physiological process common to all manifestations of tolerance. To quote:

> .... it appears that the "learned tolerance" is essentially the same as "physiological tolerance' except that it is acquired somewhat more rapidly. (p.158)

This was not meant to trivialize behavioral factors in tolerance, but only to emphasize the hypothesis that, fundamentally, some common mechanism is at work in various manifestations of the adaptation to the behavioral disruptions produced by drugs. As an

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expression of this conclusion Kalant et al.coined the phrase "behaviorally augmented tolerance" in order to emphasize a fundamental similarity rather than a fundamental difference in varieties of tolerance. It may well be the case that a distinction between behavioral and physiological tolerance is unnecessary in considering an ultimate mechanism of tolerance. Yet it seems also to be the case that any such mechanism is not fully engaged merely by the presence of a drug at a receptor site, independently of other events. The purpose of this paper is to ruminate about what some of these "other events" might be, and to arrive at a conception of tolerance that does no violence to pharmacology, psychology, or fact.

EVIDENCE FROM STUDIES OF MOTOR IMPAIRMENT OF RELATIONSHIPS BETWEEN TOLERANCE AND OTHER FORMS OF ADAPTATION

A reliable consequence of the administration of alcohol and other CNS depressants is motor Impairment. Such impairment can be effectively quantified in rats by means of a test requiring an animal to walk a moving treadmill (Gibbins et al. 1968). Alcohol and barbiturates impair the ability to perform this response, and the method is highly sensitive to small variations in dose. In this test, tolerance is evident as reduced impairment of performance as a result of chronic exposure to a drug. Much of the work reported in this section employed the treadmill test, although occasionally other behavioral tests of impairment have been used. To anticipate somewhat, the thrust of this section is an attempt to draw parallels between tolerance and other forms of adaptation, such as learning. Interestingly, another participant in this conference (Siegel 1975) has viewed the existence of such parallels as an alternative to a purely physiological conception of tolerance to the analgesic effect of morphine. The search for alternatives should not be seen as a dismissal of the relevance of physiology and pharmacology; rather it represents the addition of a novel dimension that is clearly needed to account for certain features of tolerance. We will describe the findings with a minimum of detail since most are available in the published literature and have been reviewed elsewhere recently (Le Blanc &, Cappell 1977).

Cortical Ablations and Tolerance

One strategy for demonstrating a parallel between tolerance and general adaptive processes is to compare the impact of an experimental manipulation designed to interfere with them. The parallels here come from work on ablations of the frontal cortex. An intact frontal cortex appears to be essential in several species for the acquisition of behavior requiring a delay of response or a sensory discrimination in order to receive reward (cf. Grossman 1967). Thus, frontal cortical ablations may interfere with learning. Moreover, lesions of the frontal cortex have been shown to impair the physiological adaptation to thermally elicited tachycardia that is evident in normal animals (Glaser 1966). If tolerance has something in common with these other adaptive phenomena, It should

be possible to interfere with its acquisition by means of comparable ablations. Le Blanc et a1.(1976) tested this hypothesis using alcohol. Using the treadmill test, rats were first made tolerant to the motor impairment produced by alcohol. The animals were allowed to recover from tolerance for a month before being assigned to groups selected for bilateral frontal polar lesions, sham operations, or no operation. Following recovery from surgery, the reacquisition of tolerance was studied under conditions identical to those of initial acquisition. Although all groups were shown to be capable of acquiring tolerance before surgery, only the controls did afterward; the lesioned animals displayed virtually no reacquisition of tolerance. A smaller pilot study yielded similar results with lesions to the occipital cortex.

These results in themselves offer only modest support for our basic thesis. However, they do indicate that alcohol tolerance shares a property in common with complex learning and a physiological adaptation. Moreover, research on amphetamine (Glick 1973) suggests that the involvement of the frontal cortex in tolerance development is not peculiar either to alcohol or to motor impairment.

Protein Synthesis and Tolerance

The evidence on the effects of frontal cortical ablations provided some support for a commonality of process in tolerance development and the acquisition of new responses. To the extent that protein synthesis is involved in learning, another opportunity for pursuing the analogy presents itself. Evidence of a role for protein synthesis in learning is provided in a study by Segal et a1.(1971), who showed that cycloheximide, an inhibitor of central protein synthesis, interfered with the retention of discrimination learning in mice. The effect of cycloheximide on alcohol tolerance was pursued by Le Blanc et a1.(1976) using a design and procedures very similar to those adopted in the ablation study; the major difference was that the effects on reacquisition of tolerance of treatment . with cycloheximide were at issue. During exposure to the initial tolerance-inducing regime, cycloheximide treatment was combined with alcohol in the critical experimental group. On tests of the reacquisition of tolerance to the impairing effects of ethanol the performance of controls improved over time by more than 50%, whereas rats treated with cycloheximide acquired virtually no tolerance whatsoever. Hence, the evidence for our general hypothesis increases, although it is conceded that this experiment does not rule out mechanisms of interference with tolerance acquisition not involving the inhibition of central protein synthesis (e.g., subclinical convulsions) . The effect of cycloheximide on tolerance is not unique to alcohol, since cycloheximide has been found to inhibit the development of tolerance to the analgesic property of morphine in mice (Loh et al. 1969).

Manipulation of Serotonin

A third source of evidence for the tolerance/adaptation parallel derives from recent data on the role of serotonin in the development of tolerance to ethanol. That depletion of serotonin retards habituation to non-drug stimuli has been amply demonstrated in studies of acoustic startle responding (Carlton & Advokat 1973; Connor et al. 1970; Swonger et al. 1970). In all of these studies, serotonin level was manipulated by prior treatment with p-chlorophenylalanine (PCPA), an established depletor of serotonin in the CM. The drug studies (Frankel et al. 1975) employed the moving-belt test to measure tolerance. Both alcohol and pentobarbital were investigated, but since the results were quite similar, only the ethanol work will be presented in any detail.
The essential strategy of the study was to expose animals depleted of serotonin to a schedule of alcohol administration that would be expected to promote tolerance to the impairing effects of a test dose. Treatment with pCPA was given daily for 10 days before chronic exposure to alcohol, and continued for 25 further days during which experimental animals were also exposed daily to large doses of alcohol by gavage. Tests of impairment on the treadmill apparatus were interspersed at intervals during the chronic regime of treatment. Control animals exposed to ethanol but not pCPA clearly developed tolerance to the test dose; rats exposed to pCPA also displayed some tolerance, but the rate of acquisition was significantly impaired, and the level did not approach that of controls during the course of the experiment. Much the same assertion can be made where pentobarbital was concerned.

As with the other data presented in support of our general hypothesis, these findings are by no means free of alternative interpretation. Yet they do seem to enhance the credibility of the hypothesis by providing supporting data from another general domain of investigation. Moreover, there is evidence that comparable manipulations retard the development of tolerance to morphine as well way et al. 1968; Shen et al. 1970).

Topographical Similarity between Tolerance and Learning

A fourth source of parallels between tolerance and adaptation derives from a topographical similarity in one aspect of tolerance and learning. One property of learning that is demonstrable by appealing to both personal experience and the scientific literature (Kimble 1961) is that responses are reacquired after a period of disuse with much greater facility than they are initially mastered. A similar process can be demonstrated in studies of adaptations of a more fundamental physiological nature; for example, physiological adaptation to thermal stimuli proceeds more rapidly to the extent that an organism has a history of adaptation to those stimuli (Glaser 1966). The parallel was illustrated in a study by Kalant et al. (1971b), in which repeated cycles of acquisition of tolerance to alcohol were studied using the treadmill test.

Bats were exposed to as many as 4 cycles of aquisition, with 17-day drug-free intervals between cycles to permit recovery to baseline levels of impairment. The basic finding was that the same Level of tolerance was achieved during each cycle, but that this level was attained in fewer and fewer trials over successive cycles of acquisition. Whereas 13 to 16 days of chronic exposure were required for maximal tolerance to be attained during an initial cycle, maximal tolerance was evident with 4 days of treatment during a fourth cycle.

Effects of Behavioral Manipulations on Tolerance

Although they do not, strictly speaking, provide an example of a parallel between tolerance and learning, studies in which the acquisition of tolerance has been manipulated by behavioral interventions are quite pertinent to our approach. Some studies have explicitly attempted to provide an empirical distinction between 'behavioral" and "physiological" tolerance. Physiological tolerance implies a change in the sensitivity of the neurons directly affected by a drug, and should be a consequence of mere exposure; this is to be distinguished from the functional adaptation (i.e., adaptation to some ultimate behavioral effect of a drug) implied by behavioral tolerance. Experiments that provided evidence of this distinction where amphetamine is concerned have been reported by Carlton and Wolgin (1971) and Schuster et al. (1966). Briefly, these studies showed that tolerance to effects of amphetamine developed to the extent that adaptation was of some "benefit" to the drugged animal; given equivalent pharmacological exposure, tolerance was not observed when there was no "benefit" to be gained thereby. Our discussion focuses on a related phenomenon involving alcohol.

In the study that inspired our own research, Chen (1968) compared groups of rats that first received injections of alcohol either before or after performance was tested on a maze task in which approach behavior was maintained by food reward. On the critical test, all rats received their injection before testing. The finding from this test was that tolerance was evident in the group that had consistently received alcohol before the test, but not in the group that was given alcohol prior to the test for the first time. This outcome seems to indicate clearly that mere exposure to alcohol was not in itself sufficient to provoke tolerance. Chen concluded that this was evidence of a qualitative distinction between physiological and behavioral tolerance. However, Le Blanc et al. (1973) argued that Chen's manipulation may simply have affected the *rate* of tolerance development, and that his results may have depended on the limited number of exposures to alcohol (4 in all} that he employed. Clearly, one would draw different conclusions about the existence of a fundamental difference between behavioral and physiological tolerance if the rate and not the asymptote of a process were the major difference. Le Blanc et al. (1973) tested their hypothesis using a design similar to Chen's, but one which incorporated many more exposures to alcohol prior to the critical test of tolerance . Consistent with the hypothesis, tolerance was acquired more

rapidly if alcohol treatment consistently preceded the behavioral test, but the same final level of tolerance was achieved if during acquisition a sufficient number of exposures to the same dose was given following the behavioral measurement. Le Blanc et al. (1973) concluded from these data that one need not entertain the possibility of a separate cellular mechanism for behavioral and physiological tolerance if behavioral manipulations primarily affect only the rate of tolerance development. For this reason, they proposed the phrase "behaviorally augmented tolerance" to describe the interaction between behavioral demand and the rate of tolerance development, while rejecting the suggestion of fundamentally different mechanisms. Other studies involving opiates (Kayan et al. 1969)) barbiturates (Waslstrom 1968)) and chlorpromazine (Irwin 1963) are consistent with this hypothesis.

In an important extension of this work, it has been found that behaviorally augmented tolerance is not task-specific (Le Blanc et al. 1975). First it was shown that behavioral augmentation of tolerance could be demonstrated on the treadmill test; although this result was not novel, it extends the generality of the phenomenon. More importantly, it was found that the behavioral augmentation of tolerance was transferred to a maze task on which performance was shown to be entirely independent of treadmill performance (i.e., there was no transfer of training in no-drug control conditions). This outcome is of particular Importance because it demonstrates that behaviorally augmented tolerance results in more than an enhancement of learned compensation for the impairment produced in a specific behavioral test. Rather, it appears that behavioral augmentation facilitates\ the development of a fundamental adaptation at neuronal level that is generalizable to an entirely novel behavioral circumstance. Moreover, it is worth noting that behavioral augmentation of physical dependence was also shown in this work.

In summary, it appears that it may not be necessary to think of behavioral and physiological tolerance as independent phenomena that challenge the possibility of a single neural mechanism of tolerance , This resolution ispossible to the extent that we entertain a unitary mechanistic theory of adaptation that allows for the influence of behavioral manipulations on the *rate* of adaptation. The fact that behavioral manipulations do have a clear influence on the rate of adaptation seems to strengthen rather than weaken a unitary theory, although it does require some revision of any thought that mere exposure of the CNS to the drug is the only adaptive stimulus of importance in tolerance development.

SUMMARY

Although our case rests to a large extent on analogy, it is difficult to avoid being impressed by the convergence of all of the foregoing data. It may be possible to dispute the persuasiveness of any or even all of the experimental illustrations taken individually, but the mass of evidence taken together is remarkably consistent with our basic supposition that tolerance and adaptation are quite similar

processes. The parallels hold across a diversity of experimental manipulations and they are not peculiar to any single pharmacological agent. Yet admittedly the argument is still speculative and must remain so until there is some better understanding of the unitary neural mechanism of adaptation that we have suggested.

With our basic thesis established, we can now turn to an area of research that has proceeded somewhat independently from that already described. On the face of it, it would have been difficult to see that these lines of research would ever converge, but they have.

EVIDENCE FROM STUDIES OF GUSTATORY AVOIDANCE CONDITIONING

Our first encounters with gustatory avoidance conditioning some years ago were characterized by a combination of intrigue and puzzlement. Using doses that were known to be positively reinforceing to rats, we were able to condition avoidance behavior with amphetamine (e.g., Cappell & Le Blanc 1973). When the response of drinking saccharin was paired with doses of amphetamine that were not obviously toxic, a phenomenon that looked much like punishment occurred. At first, this behavioral model was intriguing, in large part because it generated an outcome that was nonobvious and apparently paradoxical. Of the possible research avenues to follow, we opted to consider conditioned gustatory avoidance as a model of control of behavior by a pharmacological stimulus, just as intravenous self-administration is. The study of tolerance to the effects that exert such control is obviously important, but intravenous self-administration methods had not been ideally suited for the purpose. For one thing, it is quite difficult to use the intravenous model to generate baselines of drug-maintained behavior that obviate the development of tolerance prior to the acquisition of a stable baseline. Another problem, although not an insuperable one, is that the presentation of the reinforcer might affect the behavior on which it is contingent in such a way as to obscure the measurement of tolerance. Although it has problems of its own, the gustatory conditioning method averts these two.

Since much of this work is already published and the earlier work is reviewed elsewhere (Cappell & Le Blanc 1975a; in press) we will deal briefly with the history and later concentrate more fully on our newer findings. Our first effort in this area (Le Blanc & Cappell 1974) began with an essentially traditional (i.e., "physiological") conception of tolerance. Animals were chronically exposed to regimes of treatment with high and low doses of morphine or amphetamine. Next, their acquisition of avoidance of saccharin conditioned by these drugs was studied. Attenuation of the acquisition of avoidance in this procedure could reflect tolerance to the drug effects that are responsible for avoidance. Pretreatment with amphetamine at both a high (20 mg/kg) and low dose (4 mg/kg) greatly attenuated the degree of gustatory avoidance that could be subsequently conditioned with a dose of 1 mg/kg. These results were corroborated in an analogous experiment with morphine. Although there were several alternative explanations for the results, the best one seemed to be that the pretreatment regimes had produced

tolerance to the effects of the drugs that were responsible for avoidance conditioning (whatever these effects might be).

The next logical series of experiments was also dictated by a traditional contention of tolerance. It was here that the trouble with such a notion first began to emerge. The reasoning (Cappell et al. 1975) was that if pretreatments were effective because they produced pharmacological tolerance, pretreatment with a drug from one pharmacological class should not affect gustatory conditioning by a drug from another class. This prediction was found to be generally true: pretreatments by morphine, amphetamine, or chlordiazepoxide were effective in attenuating conditioned avoidance by themselves, but not by each other. The one strange exception to this was that amphetamine did attenuate conditioning by morphine, although the reverse was not true. We could find only scant evidence to account for this on pharmacological grounds, but the flaw in the tolerance hypothesis still seemed to be outweighed by its merits. Recently, similar anomalies have been reported by other laboratories (Braveman 1975; Vogel & Nathan 1976).

Other experiments were designed specifically to further the interpretation of these pretreatment effects as evidence of tolerance to the unconditioned effects of the drugs. Two parametric studies (Cappell & Le Blanc 1975b) showed that the rate of acquisition and loss of the effectiveness of amphetamine pretreatment corresponded to what might be expected if pharmacological tolerance was at work (Kalant et al. 19719). The effectiveness of pretreatment increased linearly with the number of pretreatments and was lost in linear relationship to the duration of withdrawal following a fixed duration of pretreatment. We also found that the persistence of the effect of pretreatment with morphine outlasted that of amphetamine (Cappell & Le Blanc 1977). This result seemed very persuasive in view of the evidence, admittedly meagre and controversial, that tolerance to morphine is uniquely persistent (Cochin & Kometsky 1964).

In the same paper, however(Cappel1 & Le Blanc 1977), another finding not entirely consistent with a purely physiological conception of tolerance emerged. We compared the effectiveness of 1.5 “massed” and “spaced” pretreatments with morphine and amphetamine in attenuating the acquisition of aversive conditioning by themselves. As far as possible, comparability across the two drugs was attempted by selecting approximately equipotent doses of the two drugs during pretreatment (morphine, 40 mg/kg; amphetamine, 4 mg&kg) and conditioning (morphine, 10 mg/kg; amphetamine, 1 mg/kg). Despite the fact that animals in the “spaced” conditions were injected at intervals of 120 hr compared to 24 hr for the “massed” conditions, the two schedules of pretreatment were highly and equally effective regardless of the drug used. Why is this inconsistent with a purely pharmacological construction of tolerance? According to some empirical evidence and a mathematical model of the kinetics of tolerance acquisition developed in our laboratories (Kalant et al. 197la; Le Blanc & Cappell 1975), a drug treatment schedule should be more effective in producing tolerance to the extent that the adaptive

response to the pharmacological stimulus can accumulate with minimal opportunity for dissipation over time. From this postulate we predicted the greater effectiveness of the massed schedule - incorrectly.

Our prediction was based upon the assumption that there is a decay of the tolerance produced by a single injection of a drug to the point that injections spaced at 120 hr will not provoke much cumulation of tolerance. The loss of the adaptation was assumed to represent a recovery to normalcy, in this case to nontolerant status, in the prolonged absence of a continued pharmacological stimulus to adapt. If this model is not applicable, what kind of interpretation could predict such "savings" of the effectiveness of drug administrations spaced at wide intervals? One possibility that we had considered and rejected earlier (Le Blanc & Cappell 1974) and that has been specifically proposed by Braveman (1975) to account for pretreatment effects is the operation of an associative process. Although Braveman did propose two versions of the operation of an associative mechanism, he was necessarily speculative about how they might work. However, even in the absence of a specific proposal of how such a mechanism might work, in principle it would seem less vulnerable to decay with the mere passage of time than a physiological one such as we had been entertaining. The reason for this is that an active intervention rather than the mere passage of time seems to be required to offset the effectiveness of an associative mechanism,

Further exploration of an associative basis for these pretreatment effects involved an excursion into some principles of conditioning theory. Specifically, pretreatment phenomena were analysed in the context of Rescorla and Wagner's (1972) associative-blocking model of conditioning. First, the operations involved in our typical experimental paradigm were subjected to scrutiny as a conditioning *procedure per se*. Consider first the operations involved in a pretreatment procedure. The animal is repeatedly exposed to a relatively consistent set of cues (i.e., the cues of handling and injection) followed reliably by the pharmacological effects of the administered drug. Formally, this can be considered as the repeated Pavlovian pairing of a CS and a KS. During gustatory conditioning, the animal is exposed to an intended CS (the flavor of saccharin) followed in 5 minutes by handling, injection, and pharmacological effects. That is, during conditioning there is an attempt to establish a new associative link between a flavor (CS2) and a pharmacological effect, although such a link between the cues of handling and injection (CS_1) has already been established. According to an associative-blocking analysis, the prior association of CS_1 and the UCS should 'block" an association between CS_2 and the same UCS because CS_1 has in effect preempted the associabllty of the UCS to other CSs. In an empirical test of this analysis, we specifically attempted to neutralize the association between handling and injection cues and a drug effect by an explicit nonreinforcement procedure, and thus to "unblock" the association between flavor and drug effect. In the interest of brevity, only the results of one experiment that supported this analysis will be presented, although

it should be added that we have successfully replicated and extended the results recently.

On the basis of our analysis, it is evident that the cues requiring neutralization are those that most reliably and immediately precede the drug effect; thus an effective procedure must neutralize the associative value of handling and injection cues. An obvious way to do this is by nonreinforcement- that is, by presenting these cues not followed by a drug effect. In our first experiment designed to test this conceptualization, we examined the effect of a nonreinforcement procedure on the effectiveness of pretreatment by amphetamine (7.5 mg/kg for 12 days). The nonreinforcement procedure simply consisted of administering injections of saline 4 times per day for 4 days prior to the beginning of conditioning trials and on the 2 days intervening between each conditioning trial. The conditioning dose was 1.0 mg/kg of amphetamine. The nonreinforcement procedure had the predicted effect. In the group exposed to the procedure, the usual effect of pretreatment was completely reversed.

This finding can be approached in at least two ways. First, an unelaborated interpretation based on the concept of associative blocking and its reversal suffices on its own. In such an approach, tolerance need not be mentioned, and the information value of the nonreinforcement procedure can be emphasized. Thus it may be that the application of the nonreinforcement procedure tells the rat that the important association in gustatory conditioning is between the flavor and the drug effect, rather than between the handling and injection procedure and the drug effect. Consequently, it learns to avoid the flavor. However, one cannot help but be impressed by the comparability of our nonreinforcement procedure to the associative manipulations that Siegel (reported elsewhere in this monograph) has applied to interfere with analgesic tolerance to morphine. Both involve nonreinforced presentations of a CS intended to interfere with a drug effect that is also associated with the same CS at another point in an experimental procedure. But Siegel (1975) has suggested, and provided direct evidence for, a particular mechanism that mediates the effectiveness of his associative manipulations. Specifically, he has argued that his associative procedures bring under stimulus control the occurrence of a conditioned compensatory response to morphine without which analgesic tolerance will not occur. Could something similar apply to our own procedures?

In theory, it is possible to specify how such a mechanism might work. During pretreatment, a compensatory response might be conditioned to the cues of drug administration by the repeated pairing of these cues with the systemic effects of amphetamine. If this conditioning were allowed to remain intact, these cues would elicit a compensatory response when an injection of amphetamine was paired with the flavor of saccharin during gustatory conditioning. This compensatory response would summate with the actual drug effect and diminish its magnitude. All of this should lead to attenuation

of flavor avoidance, which is of course the result of pretreatment. However, if the drug administration procedure were specifically nonreinforced we would expect a reduction in its ability to evoke the compensatory response. There would be no subtraction from the actual drug effect when it occurred during gustatory conditioning, and avoidance of the flavor should be relatively strong. Of course, this was the effect of our nonreinforcement procedure.

All of this is very plausible in theory. But we cannot avoid the question of whether there is any empirical basis for these arguments. Unfortunately, we can only be highly speculative on this point, but we can specify some of the requirements that any hypothesis of compensatory response activity would need to meet to be applicable to our situation. The most obvious is that it would have to apply in the case of amphetamine, at least to account for our data. We know of no evidence to suggest that the conditioned form of the response to amphetamine administration includes a component that is compensatory. A second requirement is that this hypothetical compensatory response would need to be engaged by a variety of unconditioned stimuli in addition to amphetamine. The reason for this is that pretreatment effects have been obtained even when pharmacologically dissimilar agents have been used during pretreatment and conditioning. As we mentioned earlier (Cappell et al. 1973)) pretreatment with amphetamine attenuated conditioned aversion by morphine; in an extreme case of dissimilarity of unconditioned stimuli, Braveman (1975) found that pretreatment with a number of different pharmacological agents attenuated the gustatory avoidance that could be conditioned by rotation on a turntable. If associatively mediated compensatory conditioning is involved in these examples of "tolerance," clearly the mechanism must be general rather than UCS-specific. We can identify procedural operations of conditioning common to the administration of drugs and rotation that can account in associative terms for successful pretreatment effects using such discrepant manipulations, but specification of a compensatory mechanism remains quite another matter. Where morphine analgesia is concerned, a behavioral compensation is a relatively simple matter to suggest (i.e., analgesia-hyperalgesia) and measure.

One suggestion of a physiological response mechanism that might-be common to the wide variety of manipulations used in studies of pretreatment was made recently by Riley et a1.(1976). They reasoned that the rat's response to the various pharmacological and other manipulations used in gustatory conditioning procedures may be commonly mediated at the level of the hypothalamo-pituitary adrenal axis. In support of this hypothesis they cited a large body of evidence to show that ACTH may be involved in gustatory avoidance conditioning by a variety of agents. Moreover, they cited some evidence purporting to show tolerance in the ACTH response to some drugs. Obviously, a compensatory theory would require that responses compensatory to the effects of ACTH occur and are conditionable for this mechanism to be involved in the mediation of the associative effects that we have found.

Clearly there is no unequivocal evidential basis for making a commitment to ACTH, or for that matter, any particular physiological mechanism, as the final common path underlying pretreatment effects that operate within and between drug classes. We mention this mechanism only because it has been specifically proposed, and because there is at least some evidence in its favor. One might just as easily focus on a neuro-transmitter mechanism, since as we saw earlier, tolerance can be affected by the manipulation of transmitters. The mere suggestion of such a mechanism may, however, bring us full circle to the idea we raised earlier, namely that we can profitably think of tolerance as a special case of adaptation. Physiological mechanisms are certainly important considerations here. What a behavioral perspective has to offer is the idea that the rate and perhaps even the occurrence of such processes is subject to modification by environmental manipulations, including Pavlovian conditioning.

The definitional problems created by the use of the word "tolerance" emerge clearly where the study of tolerance in the context of gus tatory conditioning is concerned. At one level, the reduction in effectiveness of conditioning by pretreatment seems to have all the earmarks of tolerance; there certainly appears to be some form of adaptation involved, and, in fact, habituation has been offered as an alternative to tolerance in accounting for pretreatment effects (Vogel 6 Nathan 1976). Yet there are obvious anomalies. What is intriguing about this is that the puzzling outcomes are anomalous mainly in the context of a strictly pharmacological conception of tolerance. It seems that we are faced with two choices: we can say that it must not be tolerance that we are studying, or we can change our conception of tolerance. It is tempting to prefer the latter choice.

CONCLUSIONS AND IMPLICATIONS

In addition to its obvious forensic relevance (e.g., in relationship to traffic safety), the study of drug tolerance is of special practical importance to the extent that it can help to provide an account of drug consumption. There is ample evidence that increases in alcohol consumption in populations (Schmidt & Popham 1975) are associated with increases in adverse consequences to health. Unfortunately, we cannot yet estimate the precise contribution of tolerance per se to drug consumption. We know much more about tolerance as a *consequence* of drug consumption than we do about its contribution to etiology. Therefore, whatever importance we assign to the contribution of behavioral variables to tolerance cannot be divorced from the importance we assign to tolerance no matter what our theoretical bias is. Whether we study motor impairment, operant behavior, analgesia, or taste aversion, one crucial assumption is that knowledge of adaptation to these *consequences* of drugs provides a basis for making inferences about drug-taking behavior itself.

The case is clear that behavioral factors do contribute substantially to the adaptive response to drugs. The rate of tolerance can be

augmented by behavioral manipulations. Moreover, there are circumstances under which tolerance appears to be substantially controlled by associative conditioning mechanisms. Still, the question of whether such manipulations ultimately have consequences for drug consumption remains one for speculation. As important as it is for us to continue to develop an understanding of the modulation of tolerance to drug effects by behavioral factors, it seems necessary to develop a firmer basis for relating this information to the phenomenon of drug-taking. Our research on gustatory aversion represents an attempt to move in this direction by studying adaptation to the ability of drugs to control behavior. Obviously, this model also requires a considerable inferential leap in order to draw conclusions about drug-taking. Research relating tolerance more directly to drug-taking behavior must, therefore, be considered as a high priority.

Another issue that bears consideration is the relationship of tolerance to physical dependence or withdrawal. Physical dependence is of concern because it can represent a health problem in itself, and also because it may play a role in the maintenance of drug-taking (i.e., by self-medication of withdrawal effects). Earlier we noted that a behavioral manipulation that augmented tolerance had the effect of augmenting physical dependence as well. Thus it seems likely that any increase in our understanding of the behavioral and other factors that affect tolerance may have implications for an understanding of physical dependence. One of the more interesting developments in this area is the evidence that Pavlovian conditioning mechanisms are involved in the adaptive response to drugs. It is tempting to relate the concept of conditioned compensatory response not only to tolerance but to physical dependence as well. Such conditioning has clear implications for relapse to drug use (c.f., Wikler 1973). Conditioning may underly the "savings" observed in repeated cycles of tolerance acquisition (Kalant et al ,1971b), and it may also provide a mechanism whereby the potential for the elicitation of withdrawal is preserved long after apparent recovery has taken place. This suggests that "normalization" of the tolerant-dependent organism may require a process of active behavioral intervention beyond abstinence per se. Further research on the phenomenon in animals should be addressed to its generality, since our knowledge is largely confined to a single drug (morphine), a single response criterion (analgesia), and relatively low doses. Our work with conditioned gustatory avoidance by amphetamine may be a step toward generality, but its relevance is not yet established.

To summarize, there is no question that there is a loss in sensitivity to many of the effects of drugs with repeated exposure. Equally beyond question is that this adaptive process can be manipulated behaviorally. However, the *relative* importance of behavioral and pharmacological or physiological variables in the acquisition of tolerance is not established. Certainly there is no empirical justification for entirely discarding one type of account in favor of the other. And finally, whatever view of tolerance we choose to emphasize, it must always be kept in mind that its etiological significance for drug consumption is still based largely on indirect infe-

rence from effects of drugs (e.g., motor impairment) whose predictive relationship to drug consumption is still presumptive.

REFERENCE

Braveman, N.S. Formation of taste-aversions in rats following prior exposure to sickness. Learn. Mot. ,6:512-534. 1975.

Cappell, H., & Le Blanc, A.E. Punishment of saccharin drinking by amphetamine in rats and its reversal by chlordiazepoxide. J. Comp. Physiol. Psychol.,85:97-104, 1973.

Cappell, H., & Le Blanc, A.E. Conditioned aversion by psychoactive drugs: Does it have significance for an understanding of drug dependence? Add. Behav 1:55-64, 1975s.

Cappell, H., & Le Blanc, A.E. Conditioned aversion by amphetamine : Rates of acquisition and loss of the effects of prior exposure. Psychopharmacologia (Berl.) ,43:157-162, 1975b.

Cappell, H. , & Le Blanc, A.E. Parametric investigations of the effects of prior exposure to amphetamine and morphine on conditioned gustatory aversion. Psychopharmacology, 51:265-271, 1977.

Cappell, H. , & Le Blanc, A.E. Gustatory avoidance conditioning by drugs of abuse: Relationships to general issues in research on drug dependence. In: Milgram, N.W., Krames , L., & Alloway, T.M., eds. Food Aversion Learning. New York: Plenum Press, in press.

Cappell, H., Le Blanc, A.E., & Herling, S. Modification of the punishing effects of psychoactive drugs in rats by previous drug experience. & Camp. Physiol. Psychol.,89:347-356, 1975.

Carlton, P.L., & Advokat, C. Attenuated habituation due to parachlorophenylalanine. Pharmacol. Biochem. Behav.,l:657-663, 1973.

Carlton, P.L., & Wolgin, D.L. Contingent tolerance to the anorexigenic effects of amphetamine. Physiol. Behav.,7:221-223, 1971.

Chen, C. S. A study of the alcohol - tolerance effect and an introduction of a new behavioural technique. Psychopharmacologia (Berl.), 12:433-440, 1968.

Cochin, J., & Kornetsky, C. Development and loss of tolerance to morphine in the rat after single and multiple injections. J. Pharmacol. Exp. Ther.,145:1-10, 1964.

Connor, R.L., Stolk, J.M., Barchas, J.D., & Levine, S. Parachlorophenylalanine and habituation to repetitive auditory startle stimuli In rats. Physiol. Behav. ,5:1215-1219, 1970.

Frankel, D., Khanna, J.M., Le Blanc, A.E., & Kalant, H. Effect of p-chlorophenylalanine on the acquisition of tolerance to ethanol and pentobarbital. Psychopharmacologia (Ber1.),44:247-252, 1975.

Gibbins, R.J., Kalant, H., & Le Blanc, A.E. A technique for accurate measurement of small degrees of alcohol intoxication in small animals. J. Pharmacol. Exp. Ther.,159:236-242, 1968.

Glaser, E.M. The Physiological Basis of Habituation. London: Oxford University Press, 1966.

Glick, S.D. Impaired tolerance to the effects of oral amphetamine intake in rats with frontal cortical ablations. Psychopharmacologia (Ber1.),28:363-371, 1973.

Grossman, S.P. A Textbook of Physiological Psychology. New York: Wiley, 1967.

Irwin, S. Influence of external factors and arousal mechanisms on the rate of tolerance development. Arch. Int. Pharmacodyn.,l42: 152-162, 1963.

Kalant, H., Le Blanc, A.E., & Gibbins, R.J. Tolerance to, and dependence on, some non-opiate psychotropic drugs. Pharmacol. Rev., 23:135-191, 1971a.

Kalant, H., Le Blanc, A.E., & Gibbins, R.J. Pharmacological and behavioral variables in the development of alcohol tolerance. Committee on Problems of Drug Dependence. Nat. Acad. Sci., 2:1283-1296, 1971b.

Kayan, S., Ferguson, R.K., & Mitchell, C.L. An investigation of pharmacologic and behavioral tolerance to morphine in rats. J. Pharmacol. Exp. Ther., 185:300-306, 1973.

KaYan, S., Woods, L.A., & Mitchell, C.L. Experience as a factor in the development of tolerance to the analgesic effect of morphine. Europ. J. Pharmacol., 6:333-339, 1969.

Kimble, G.A. Hilgard and Marquis' Conditioning and Learning (2nd Edition). New York: Appleton-Century-Crofts, 1961.

Le Blanc, A.E., & Cappell, H. Attenuation of punishing effects of morphine and amphetamine by chronic prior treatment. J. Comp. Physiol. Psychol. ,87:691-698, 1974.

Le Blanc, A.E., & Cappell, H. Historical antecedents as determinants of tolerance to and dependence upon psvchoactive drugs. In: Cappell, H., & Le Blanc, A.E:, eds. Biological and Behavioural Approaches to Drug Dependence. Toronto Addiction Research Foundation, 1975. pp. 43-51.

Le Blanc, A.E., & Cappell, H. Tolerance as adaptation: Interactions with behavior and parallels to other adaptive processes. In: Blum, K., ed. Alcohol and Opiates: Neurochemical and Behavioral Mechanisms. New York: Academic Press, 1977. pp. 65-77.

Le Blanc, A.E., Kalant, H., & Gibbins, R.J. Behavioral augmentation of tolerance to ethanol in the rat. Psychopharmacologia (Berl.), 30:117-122. 1973.

Le Blanc, A.E., Gibbins, R.J., & Kalant, H. Generalization of behaviorally augmented tolerance to ethanol, and its relation to physical dependence. Psychopharmacologia (Berl.),44:241-246, 1975.

Le Blanc, A.E., Matsunaga, M. & Kalant, H. Effects of frontal polar cortical ablation and cyclohexunide on ethanol tolerance in rats. Pharmacol. Biocham. Behav. ,4:175-179, 1976.

Loh, H.H., Shen, F. -H. , & Way, E.L. Inhibition of morphine tolerance and physical dependence development and brain serotonin synthesis by cycloheximide. Biochem. Pharmacol., 18:2711-2721, 1969.

Rescorla, R.G., & Wagner, A.R. A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. In: Black, A., & Prokasy, W.F., eds. Classical Conditioning II. New York: Appleton-Century-Crofts, 1972.

Riley, A.L., Jacobs, W.J., & LoLordo, V. Drug exposure and the acquisition and retention of a conditioned taste aversion. J. Comp. Physiol. Psychol., 90:799-807, 1976.

Schmidt, W., & Popham, R.E. Heavy alcohol consumption and physical health problems: A review of the epidemiological evidence. Drug Alc. Dep. ,1:27-50, 1975/76.

Schuster, C.R., Dockens, W.S., E Woods, J.H. Behavioral variables affecting the development of amphetamine tolerance. Psychopharmacologia, 9:170-182, 1966.

Segal, D.S., Squire, L.R., & Barondes, S.H. Cycloheximide: Its effects on activity are dissociable from its effects on memory. Science, 172:82-84, 1971.

Shen, F.H., Loh, H., & Way, E.L. Brain serotonin turnover in morphine tolerant-dependent mice. J. Pharmacol. Exp. Ther., 175:427-434, 1970.

Siegel, S. Evidence from rats that morphine tolerance is a learned response. J. Camp. Physiol. Psychol., 89:498-506, 1975.

Siegel, S. Pavlovian conditioning as a mechanism of tolerance. This monograph.

Swonger , A. K. Chambers, W.F., & Rech, R.H. The effects of alterations in brain 5HT on habituation of the cortical evoked response and the startle response in rats. Pharmacologist, 12:207, 1970.

Vogel, J.R. , & Nathan, B.A. Reduction of learned taste aversion by pre-exposure to drugs. Psychopharmacology, 49:167-172, 1976.

Wahlstrom, G. Differences in tolerance to hexobarbital (enhexymalum NFN) after barbital (diemalum NTN) pretreatment during activity or rest. Acta Pharmacol. (Kbh), 26:92-104, 1968.

Way, E.L., Loh, H.H., & Shen, F.H. Morphine tolerance, physical dependence and synthesis of brain S-hydroxytryptarmine. Science, 162:1290-1292, 1968.

Wikler, A. Dynamics of drug dependence: Implications of a conditioning theory for research and treatment. Arch. Gen. Psychiat., 28:611-616, 1973.

AUTHORS

A. E. Le Blanc, Ph.D., C. X. Poulos, Ph.D., and H. D. Cappell, Ph.D. Addiction Research Foundation, Toronto, Ontario, Canada MSS2Sl

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IV. MARIHUANA

Environmental Influences on Marihuana Tolerance

Brooks Carder, Ph.D.

INTRODUCTION

The concept of behavioral tolerance appears to have evolved from the observation that tolerance to a drug can develop to certain behavioral effects of a drug but not to others. Thus Thompson and Schuster (1968) reported that when rats showed tolerance to the effects of amphetamine on responding to one schedule of reinforcement, they did not show tolerance on a second schedule. They called this phenomenon "behavioral tolerance," because the tolerance appeared to be altered by stimulus, response, and reinforcement conditions.

Along this line, we have shown that tolerance to marihuana develops more rapidly when drug administration is followed by behavioral testing than when it is not (Carder and Olson 1973). This is another example of behavioral tolerance in the sense that we will use the term in this paper. "Behavioral tolerance" applies to those phenomena in which tolerance development is influenced by environmental variables .

It is important to make some qualifications at this point. Previous workers have used such terms as "learned tolerance," "behaviorally augmented tolerance," or "psychological tolerance." These terms frequently lead to assumptions that: 1) Learning is involved in the development of this tolerance; 2) Behavioral tolerance is fundamentally different from "physiological tolerance"; 3) Behavioral tolerance involves an adjustment of behavioral control mechanisms rather than of the biochemical systems which are responsible for the action and metabolism of the drug. This paper is directed at a critical examination of these assumptions. It will examine the phenomenon of behavioral tolerance to marihuana and its principal active constituent 1-A^9-tetrahydrocannabinol (THC). It will describe reasons which lead us to question the role of learning in behavioral tolerance and to question whether behavioral tolerance is fundamentally different from other forms of tolerance. Finally, it will discuss some of the implications of this work for the study of marihuana in humans.

THEORIES OF BEHAVIORAL TOLERANCE

The Instrumental Response Model

In spite of the fact that we will ultimately question this view, we will start where this line of research began, with the hypothesis that instrumental learning plays a role in the development of behavioral tolerance. In one of the early demonstrations of tolerance to THC, McMillan, et al. (1970) first trained pigeons to peck a key for grain on a multiple reinforcement schedule and then gave them daily increasing intramuscular doses of WC. The first application of a dose of 1.8 mg THC/kg impaired performance, but by day 25 a dose of 36 mg/kg left performance unaltered. In this case, the adjustment was ultimately a behavioral one, an increase in responding under the drug. One potential mechanism for behavioral adjustments is, of course, learning. In fact this study could provide an excellent paradigm for tolerance due to learning. Tolerance, or the increase in responding under the influence of the drug, would be reinforced by the increase in frequency of food rewards which accompany the increase in responding.

While we do not wish to engage in an extended discussion of the definition of learning, it is essential to differentiate conditioning from other types of behavioral adjustment. Conditioning requires reinforcement. There are two types of conditioning: instrumental and Pavlovian. In the case of instrumental (operant) conditioning, an organism's response is followed by an event (reinforcer) which increases the future probability of occurrence of that response. Reinforcers are usually events such as the presentation of food to a hungry organism or the termination of painful electric shock. In the case of Pavlovian conditioning, a neutral stimulus (conditional stimulus or CS) is paired with a stimulus which naturally elicits a response (unconditioned stimulus or US). After one or more pairings, the CS elicits a response (conditioned response or CR) which it previously did not. The class of US's and the class of instrumental reinforcers overlap considerably.

In 1972, Olson and I (Carder and Olson 1973) decided to investigate the role of learning in the development of behavioral tolerance to marihuana. Rats were first trained to lever press for positive reinforcers. One study employed food and the second, water. In each study, one group was treated with marihuana extract before each daily training session. The second group was treated marihuana extract, in the same dosage, after each training session. Initially, when the drug was given before session, responding decreased. When the drug-before group demonstrated tolerance to this disruption of responding, the drug-after group was tested for tolerance by giving them the drug before a test session. In both studies the drug-after group showed little or no tolerance. The drug interfered with responding as much as it did in the drug-before group on the first day. Thus the development of tolerance was facilitated when the subjects had the opportunity to respond for reinforcers during the period of drug action as the drug-before group did and the drug-after group did not.

There are a number of other studies which have confirmed the role of practice and/or reinforcement in the development of behavioral tolerance to marihuana and THC. For example, Grilly et al. (1973) described the development of tolerance in chimpanzees on a delayed, matching-to-sample task. Tolerance development was interval specific. That is, tolerance which developed at one delay interval did not transfer when the interval was increased. Grilly et al. proposed that the tolerance involved the learning of compensatory responses which were specific to each particular set of test conditions. This response was reinforced by increases in food which resulted from improved performance under the drug.

Manning (1974) reported the development of tolerance to the effect of MC on free-operant avoidance in rats. He noted that tolerance developed only in those subjects for which the drug-induced depression of responding led to an increase in shock frequency. Of course only these subjects would receive reinforcement (in the form of a decrease in shock frequency) for the development of tolerance.

More recently, Manning (1976) administered THC to rats for 12 days, each time followed by a return to the home cage. When these rats were tested under the drug on a Differential Reinforcement of Low Rate (DRL) schedule, they demonstrated no tolerance. When they were then tested daily under the influence of THC, they developed tolerance at the same rate as rats that had never been exposed to the drug. This study provides strong confirmation for the finding of Carder and Olson (1973) that practice under the drug facilitates the development of tolerance to THC.

In all of these studies, tolerance development may be interpreted as having had an instrumental value for the subject. In the Carder and Olson (1973), Grilly et al. (1973) and Manning (1976) studies, subjects obtained more food reinforcers as they developed tolerance. In Manning's (1974) study of free-operant avoidance, tolerance development was reinforced by a decrease in shock frequency. Thus it is possible to view these demonstrations of behavioral tolerance as instances in which tolerance developed as a learned instrumental response.

It should be noted that there are numerous reports that demonstrate development of tolerance to THC in situations in which no apparent reinforcement was involved. For example, Ten Ham (1977) reported that rats given THC developed tolerance to the effect of the drug on shuttle avoidance and body temperature whether the drug was given before or after testing. The point remains, however, that in many cases, environmental conditions during the period of drug action do exert powerful effects on tolerance development.

The Pavlovian Model

Most investigators seem to have favored an instrumental response model for behavioral tolerance to THC. However, there are at least two other models which can account for most, or perhaps all, of the data which demonstrate behavioral tolerance. The second model we would like to discuss is a Pavlovian model.

Siegel (1975) working with morphine, seems to have been the first to develop a Pavlovian model of learned tolerance, although his work derives from earlier work by Adams et al. (1969), Gebhart and Mitchell (1972), and others. Siegel argued that the administration of morphine produces an unconditioned response, and that over the course of several drug administrations a conditioned response of tolerance develops to the conditioned stimuli associated with intoxication (Particularly the test chamber). According to this hypothesis, instrumental reinforcement is incidental to tolerance development. What is important is that during the period of tolerance development the unconditioned response (UR) which follows drug administration must be paired with the CS of the test chamber. In the test, the CS of the test chamber elicits the conditioned response of tolerance. Siegel showed that rats which received morphine in the home cage failed to demonstrate tolerance to the drug in a hot-plate analgesia test, presumably because the UR produced by the drug was never paired with the CS of the test chamber. Subjects that received daily doses of the drug, followed by exposure to the hot plate, did develop tolerance, whether the plate was hot or cold. Apparently, instrumental reinforcement was not involved, since it is difficult to see how Siegel's subjects could have been instrumentally reinforced for developing tolerance.

Siegel's hypothesis could lead to some very interesting predictions. We know for example that Pavlovian CR's can be brought under discriminative stimulus control. Thus a dog that is reliably fed following a tone (CS+), but not following a light (CS-), will develop a conditioned salivary response to the tone and will not respond to the light. To bring tolerance under stimulus control, rats could be dosed with morphine and then placed in a black chamber (CS+). Placebo injections could be followed by placement in a white chamber (CS-). The CR of tolerance should appear when subjects are tested in the black box, but not in the white. Gebhart and Mitchell (1972) have, in fact, done something like this. They developed tolerance in the hot plate environment and then demonstrated that removing various components of the apparatus, thereby changing the CS, attenuated the tolerance.

The Stress or Arousal Model

Our third hypothesis, which no one seems to have considered yet, is the notion that stress, or arousal, plays a role in tolerance development. When a subject is dosed with a drug and then placed in an experimental test environment, it is presented with the opportunity to associate a CS with the US of the drug and in some cases with the opportunity to obtain instrumental reinforcement for tolerance development. It is also placed in a situation which produces relatively more arousal than does the home cage. Perhaps it is this increase in stress or arousal during the period of intoxication, and not the opportunity to obtain instrumental reinforcement or the exposure to potential Pavlovian conditioning situations, which facilitates the development of tolerance.

EXPERIMENTS

This third hypothesis gives rise to an easily testable prediction. Subjects given a drug and then placed in an arousal-producing situation, even without opportunities for instrumental reinforcement, should develop tolerance to the drug and demonstrate it in a test situation which is quite dissimilar to the situation in which tolerance was developed.

Some pilot studies in our laboratory have addressed this question. In the fundamental experiments, 6 groups of 4 rats were treated as follows: Group THC-cage was treated with 5 daily, intraperitoneal doses of THC an rep aced in the home cage. Group saline-cage was treated with 5 daily doses of saline and also replaced in the home cage. Groups THC-box and saline-box were given the same drug treatment as the first "cage" groups, but 30 minutes following drug administration each rat was placed for 20 minutes in a small experimental chamber. Groups THC-shock and saline-shock also received the same drug treatments and exposure to the experimental chamber, but painful electric shocks were presented during the exposure to the chamber.

On the day following the final day of pretreatment, each rat was dosed with 5 mg THC/kg and tested for swimming escape. The rat was placed in the center of a circular tub of water about 90 an in diameter with a small platform at one edge. The rat could escape by swimming to the platform and mounting it. Rats that did not mount the platform within 60 seconds were removed and given a score of 60. Rats that were unable to swim and sank were immediately removed and given a score of 60. There was one test trial with no pretraining.

The results of the test are presented in Table 1. An analysis of variance revealed a significant effect of pretreatment with THC compared to saline ($F=6.19$, $df=1/18$, $p<.02$) and a significant effect of the pretreatment environment (home cage, box, shock) ($F=7.13$, $df=2/18$, $p<.01$). There was not a significant interaction ($F=0.84$). Thus, either the application of THC, the application of stress in the form of handling, exposure to a novel environment, or electric shock is sufficient to decrease the sensitivity of rats to THC in the swimming escape task.

TABLE 1. Mean escape time as a function of pretreatment.

drug-pretreatment	stress pretreatment: home cage	box	shock
saline	50.0	30.5	16.8
THC	29.8	12.8	13.0

The combination of THC and exposure to either the box or to the box with shock seemed to produce maximal tolerance. Rats tested under

saline in the swimming escape task escaped in a mean of 13 seconds. In rats pretreated with saline, exposure to shock seemed to produce more tolerance than exposure to the box without shock, although this was not statistically reliable ($t=1.25$, $df=6$, $p<.26$).

It should be noted that the stress pretreatment does not produce the appearance of increased tolerance merely by increasing the strength of the escape response. Rats pretreated with saline and 5 daily shock sessions, then tested under placebo, escaped in a mean of 21.25 seconds, indicating that, if anything, shock pretreatment impairs swimming escape.

These data provide strong support for the hypothesis that behavioral tolerance in this situation is not a learned instrumental response, since there was no opportunity for the subjects to be reinforced for tolerance development. Nor does Pavlovian conditioning seem to be involved, since the tolerance was developed in one environment and demonstrated in another. Rather, this appears to be an example of the effect of stress on rats' sensitivity to THC. The presence of stress during the period of intoxication accelerates the development of tolerance to THC.

Perhaps the most interesting aspect of our findings is the fact that stress alone reduced rats' sensitivity to THC in a subsequent test. Pats in the saline-shock group, exposed to the experimental chamber and shocked for 5 daily sessions, escaped faster under THC than did the saline-cage group ($t=3.37$, $df=6$, $p<.02$). We have termed this phenomenon, in which exposure to environmental situations without the application of drugs reduces sensitivity to a drug in a subsequent test, "behaviorally induced tolerance."

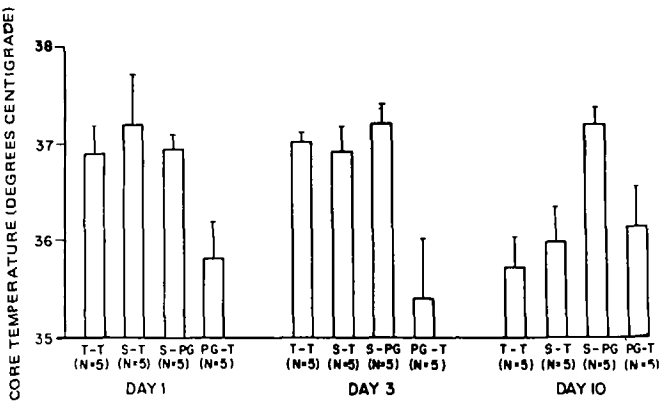
We have followed up this initial finding of behaviorally induced tolerance with several studies designed to explore the dimensions of the phenomenon. The following study demonstrates two very important characteristics of the phenomenon: 1) It has a duration of effect of at least several days, and 2) it extends to physiological as well as behavioral measures of the THC effect.

The temporal characteristics of tolerance to cannabis following chronic administration have been widely detailed. While tolerance reversal has not been consistently noted (Davis et al., 1972), Silva and Carlini (1968) as well as Webster et al. (1973) observed that tolerance to chronic administration of THC was virtually absent 8-11 days after cessation of treatment. In the study below we compared the duration of shock-induced tolerance with the duration of tolerance produced by repeated THC administration. In this experiment, tolerance was assessed by monitoring the hypothermic effect of THC rather than swimming escape.

Sixty rats were randomly assigned to groups I, II, or III for tolerance testing at different intervals following tolerance development. Each group was then subdivided as follows: THC-MC (T-T); shock-THC (S-T); shock-propylene glycol (S-P-G.) ; and propylene glycol-THC (P.G. -T) .

Subjects in the T-T condition were given 7 daily intraperitoneal injections of 5 mg THC/kg and replaced in the home cage. Subjects in S-T and S-P.G. were given 7 daily injections of propylene glycol followed by 20-minute exposures to shock in the experimental chamber, as in the previous study. Subjects in the P.G.-T group were given 7 daily injections of propylene glycol followed by placement in the home cage. Following pretreatment, all subjects were tested for the hypothermic effect of THC. Colonic temperature was measured by a telethermometer via a rectal probe. Pats in group I were tested on the first day following pretreatment? while rats in groups II and III were tested at 3 and 10 days respectively. Rats in groups T-T, S-T, and P.G.-T were given 5 mg THC/kg before the measurement of body temperature, while the rats in group S-P.G. were given propylene glycol before the measurement of body temperature.

FIGURE 1



Mean core temperature as a function of pretreatment and test condition at three intervals following pretreatment.

Figure 1 presents the mean core temperature for all groups and conditions throughout the experiment. Neither the S-T, T-T, nor S.P.G. subjects exhibited noticeable hypothermia on the first day following cessation of pretreatment. In contrast, subjects in P.G.-T demonstrated significant reductions in temperature following THC administration (pc.05). S-T subjects tested 1 or 3 days following cessation of pretreatment exhibited no hypothermia. By day 10, however, all Pretreatment groups had lost their tolerance and showed a hypothermic reaction to THC.

Thus, several brief periods of electric shock can induce a tolerance to the hypothermic effect of THC that persists for at least 3 days. It is important to note that while our previous demonstration of behaviorally induced tolerance employed a behavioral measure of tolerance, this study demonstrates that past environmental conditions can alter a physiological effect of THC.

DISCUSSION

There have been previous studies that show that past experience can alter the effect of a drug. The studies that we are aware of, however, including two from our laboratory (Carder and Olson 1972; Olson and Carder 1974) and the work of File (1973) involve experience with the situation in which the effects of the drug are ultimately tested. This experience would be expected to alter the subject's reaction to the test situation and, therefore, it is not at all surprising that this could alter the effect of a drug in the test situation. The studies described above demonstrate that experiences which involve neither the drug nor the test situation can alter the effect of THC. It is very difficult to explain these findings on the basis of transfer of training.

A possible explanation for the influence of stress on THC tolerance is that the biochemical changes induced by stress and by THC have certain common elements and that it is these common elements that are responsible for the transfer, just as tolerance will transfer between two drugs that have biochemical actions in common. There is considerable evidence, for example, that stress increases catecholamine turnover (Stolk and Barchas 1973). Several biochemical studies (Johnson et al. 1976; Howes and Osgood 1974; Ho et al. 1972; Ho and Johnson 1976; Maitre et al. 1970; Maitre et al. 1973; Poddar and Gosh 1976; Schildkraut and Efron 1971; Singh and Das 1976) indicate that THC increases catecholamine turnover. Recently, behavioral studies (Carder and Delkel 1976; Singh and Das 1976) have indicated that the alteration of catecholamine turnover may underlie some of the behavioral effects of THC. Moreover, the studies provide evidence for cross tolerance between THC and reserpine and tetrabenazine compounds known to increase catecholamine turnover. Thus lt is possible that increased catecholamine turnover may provide the common element between stress and THC that is responsible for behaviorally induced tolerance to THC.

Along this line, Seiden et al. (1975) have proposed that catecholamine alterations underlie the observed rate-dependent effect of amphetamine. A dose which can increase low rates of operant responding will decrease high rates (Dews 1958). Seiden's notion, like the one presented above, is that amphetamine produces different effects on different baseline rates of responding because both the drug and the behavior influence catecholamine metabolism. Therefore the net effect of the drug must depend both on the biochemical effect of the drug and the biochemical effect of the behavior.

It is important to describe how the stress hypothesis can account for tolerance which has been ascribed to Pavlovian or instrumental learning. For example, Siegel (1975) found that the application of morphine, followed by exposure to the test chamber, led to the development of tolerance to morphine. According to Siegel, this was because the CS of the test chamber was paired with the UR produced by the drug, leading to the development of the CR of tolerance. An alternative explanation is that the *test* chamber is a more stressful environment than is the home cage, and that placement in the chamber during intoxication would accelerate tolerance development. A simple test would involve the placement of subjects in a novel environment other than the test chamber during the period of tolerance development. If the

Pavlovian hypothesis is correct, this should not accelerate tolerance development. If the stress hypothesis is correct, this should indeed facilitate tolerance development. In our studies described above, tolerance developed in an operant test chamber was transferred to a swimming escape test, a very different situation. This finding is quite inconsistent with a Pavlovian interpretation.

Those studies such as the Carder and Olson (1973) study, in which tolerance is developed in an instrumental training situation, are also subject to explanation by the stress hypothesis. According to the instrumental learning hypothesis, tolerance develops as a result of the increased reinforcement which accrues to improved performance under the drug. According to the stress hypothesis it is the decrease in reinforcement frequency which accelerates tolerance development. A test which could discriminate between the two explanations is again quite simple. Rats would be trained to press a lever to obtain food. Following THC administration and the consequent reduction in the rate of responding and reinforcement, the rate of reinforcement could be kept low no matter what happened to the response rate. This would prevent the reinforcement of tolerance development and if the instrumental learning hypothesis is correct, tolerance development should be retarded. If the stress hypothesis is correct, the stress created by the continued decrease in the frequency of reinforcement should accelerate the development of tolerance.

CONCLUSIONS

The preceding analysis of environmental influences on marihuana tolerance has implications for both theory and research. We have attempted to expand the concept of behavioral tolerance. Our data indicate that in some cases behavioral tolerance is not a simple learned adjustment which results in a decreased response to a drug. In studying the interaction between environmental factors and tolerance development, we have found that shocking a rat or exposing it to a novel environment, with or without THC, can decrease the rat's response to the drug. While it is possible that some type of learned adjustment may be involved, it is very difficult to see how there could be a transfer of training from inescapable shock to swimming escape. The data indicate that, if anything, the transfer of training is negative.

Another argument against the notion that behavioral tolerance always involves a learned adjustment is our finding of behaviorally induced tolerance to the hypothermic effect of THC. It is difficult to see how learning could lead to an adjustment of mechanisms which control this hypothermic reaction.

In addition, the duration of effect of behaviorally induced tolerance seems to approximate the duration of tolerance to THC produced by repeated THC application: 8-12 days. Learned responses typically persist much longer than this.

I would suggest the view that in their effects in the central nervous system there is no essential difference between pharmacologic and environmental events. The function of the CNS can be altered, either temporarily or permanently, by either. Of course, tolerance to both modes of alteration of CNS function has been described. When a rat

is placed in a chamber and presented with a particular auditory stimulus, it will react in a number of ways, both physiologically and behaviorally. Repeated presentations of the stimulus will lead to an attenuation of this reaction. We call this tolerance which develops to environmental stimulation 'habituation." The attenuation of behavioral and physiological reactions to a drug on repeated application is called "tolerance." There is no a priori reason to expect that the mechanisms of habituation and tolerance should be different. Moreover, the finding that repeated application of shock leads to tolerance to THC suggests some overlap between the mechanisms.

If this is the case, it would appear that it is impossible to study tolerance independently of environmental circumstances. Factors such as handling, adaptation to the apparatus, housing conditions of the subjects , deprivation schedules , and a host of other experimental procedures could play a powerful role in tolerance development. It is essential to begin to assess the contribution of these factors in order to gain an understanding of tolerance to any drug. Behavioral tolerance is not a special case. The term simply refers to the contribution of environmental variables. These appear to be no more or less important than other variables such as route of administration of the drug, frequency of administration, dosage, etc.

The phenomenon of behaviorally induced tolerance is particularly exciting because it may provide us with a model with which to conduct extensive studies of how an organism's past history can alter its reactions to an initial application of a drug. One of the fundamental questions in the field of drug addiction is why some individuals use drugs and become addicted while others use the same drugs but do not develop an addictive pattern. It would be attractive to trace the differing responses to differences in the histories of the individuals. The existence of animal models could help us to define the important variables for such work.

An example of how the animal model might be generalized to research with humans can be developed with the so-called "panic reaction" to marihuana. This reaction is usually seen in naive users, persons who have had no opportunity to develop tolerance through repeated use of the drug. However, the reaction does not occur in all such persons. It also appears that the use of the drug under stressful circumstances IS more likely to lead to a panic reaction, although there is no statistical data on this. Our pilot studies suggest a third variable that may be important: tolerance to stress. A person who had had a great deal of stressful experience and had developed a tolerance to this should be much more resistant *to* developing a panic reaction than a person without this tolerance. This hypothesis could be examined experimentally or evaluated on the basis of existing clinical data.

Of course, marihuana addiction--if such a phenomenon exists--does not appear to present a significant social problem in this country. Thus the most important function of our work may be to provide a model for the study of other drugs. The study of environmental influences on tolerance to narcotics, alcohol, barbiturates, minor tranquilizers, and amphetamines is of the greatest potential interest. Such studies may be fundamental to the development of a scientific understanding of the etiology of drug addiction.

REFERENCES

Adams, W. J., Yeh, S. Y., Woods, L. A., and Mitchell, C. L. Drug-test interaction as a factor in the development of tolerance to the analgesic effect of morphine. *Journal of Pharmacology and Experimental Therapeutics,* 168:251-257, 1969.

Carder, B . , and Olson, J. Marihuana and shock induced aggression in rats. *Physiology and Behavior,* 8:599-602, 1972.

Carder, B . , and Olson, J. Learned behavioral tolerance to marihuana in rats. *Pharmacology, Biochemistry and Behavior,* 1:73-76, 1973.

Carder? B., and Deikel, S. M. Similarities between Δ^{9}-tetrahydrocannablnol (Δ^{9}-THC) and reserpine-like drugs. *Behavioral Biology,* 17:313-332, 1976.

Dews, P. B. Stimulant action of methamphetamine. *Journal of Pharmacology and Experimental Therapeutics,* 122:137-147, 1958.

File, S. E. Interaction between prior experience and the effects of chlorpromazine on exploration in the rat. *Psychopharmacologia,* 32:193-200, 1973.

Gebhart, G. F., and Mitchell, C. L. The relative contribution of the testing cylinder and the heated plate in the hot plate procedure to the development of tolerance to morphine in rats. *European Journal of Pharmacology* , 18:56-62, 1972.

Grilly, D. M., Ferraro, D. P., and Marrott, R. G. Long term interactions of marihuana and behavior in chimpanzees. Nature, 242: 119-120, 1973.

Ham, M. ten. Tolerance to the effects of A^{9}-THC on shuttle-box performance and body temperature in rats. *Pharmacology, Biochemistry and Behavior,* 6:183-186, 1977.

Ho, B. T., and Johnson, K. M. Sites of neurochemical action of A^{9}-tetrahydrocannabiol: Interaction with reserpine. In Nahas, *G. G.,* ed. *Marihuana: Chemistry, Biochemistry and Cellular Effects.* New York: Springer Verlag, 1976.

Ho, B. T., Taylor, D., Fritchie, G. E., Englert, L. F., and McIsaac, W. M. Neurophanacologic study of A^{9}- and A^{8}-tetrahydrocannabinol in monkeys and mice. *Brain Research,* 38:163, 1972.

Howes, J., and Osgood, P. The effect of Δ^{9}-tetrahydrocannabinol on the uptake and release of ^{14}C-dopamine from crude striatal synaptosomal preparations. *Neurophannacology,* 13:1109-1114, 1974.

Johnson, K. M., Dewey, W. L., and Ho, B. T. In vivo alteration of the subcellular distribution of ^{3}H-reserpine in the rat fore-

brain by Δ^9-tetrahydrocannabinol. *Research Communications in Chemical Pathology and Pharmacology,* 15:655-671, 1976.

Maitre, L., Staehlin, M., and Bain, H. J. Effects of an extract of cannabis and some cannabinoids on catecholamine metabolism in rat brain and heart. Agents and Actions, 1:136-143, 1970.

Maitre, L., Waldemier, D. G., and Bauman, P. A. Effects of some tetrahydrocannabinols on the biosynthesis and utilization of catecholamines in the rat brain. In Usdm, E. and Snyder, S., eds. *Frontiers in Catecholamine Research.* London: Pergamon, 1973.

Manning, F. J. Tolerance to the effects of Δ^9-tetrahydrocannabinol on free operant shock avoidance. *Federation Proceedings,* 33:481, 1974.

Manning, F. J. Role of experience in acquisition and loss of tolerance to the effect of Δ^9-THC on spaced responding. *Pharmacology, Biochemistry and Behavior, 5:269-274,* 1976.

McMillan, D. E., Harris, L. S., Frankenhein, J. M., and Kennedy, J. S. 1-Δ^9-trans-tetrahydrocannabinol in pigeons: Tolerance to the behavioral effects. Science, 169:501-503, 1970.

Olson, J., and Carder, B. Behavioral tolerance to marihuana as a function of amount of prior training. *Pharmacology, Biochemistry and Behavior,* 2:243-247, 1974.

Poddar, M. K., and Gosh, J. J. Effect of cannabis extract and delta-9-tetrahydrocannabinol on rat brain catecholamines. *Indian Journal of Biochemistry and Biophysics,* 13:273-277, 1976.

Schildkraut, J. T., and Efron, D. H. The effects of A-tetrahydrocannabinol on the metabolism of norepinephrine in rat brain. *Psychopharmacologia,* 20:191-196, 1971.

Seiden, L. S., MacPhail, R. C., and Oglesby, W. M. Catecholammes and drug-behavior interactions. *Federation Proceedings,* 34:1823-1831, 1975.

Siegel, S. Evidence from rats that morphine tolerance is a learned response. *Journal of Comparative and Physiological Psychology,* 89:498-506, 1975.

Silva, M. T. A., and Carlini, E. A. Lack of cross-tolerance in rats among (-)-Δ^9-trans-tetrahydrocannabinol (Δ^9THC), cannabis extract, mescaline and lysergic acid diethylamide (L.S.D.-25). *Psychopharmacologia,* 13:332-340, 1968.

Singh, P. P., and Das, P. K. Role of catecholamines in the hypothermic activity of cannabis in albino rats. *Psychopharmacology,* 50:199-204, 1976.

Stolk, J. M., and Barchas, J. D. Brain stem norepinephrine:

Behavioral and biochemical differentiation of responses to foot shock in rats. In: Usdin, E. , and Snyder, S. , *eds. Frontiers in Catecholamine Research*. London: Pergamon, 1973. pp. 719-722.

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

Webster, C.D., LeBlanc, A.E., Marshman, J. A., and Beaton, J. M. Acquisition and loss of tolerance to 1-Δ^9-trans-tetrahydrocannabinol in rats on an avoidance schedule. *Psychopharmacologia*, 30:217-226, 1973.

AUTHOR

Brooks Carder, Ph.D., Synanon Research Institute, P.O. Box 786, Marshall, California 94940

IV. MARIHUANA

Behavioral Tolerance to Marihuana

Douglas P. Ferraro, Ph.D.

In the lexicon of behavioral pharmacology, the term *behavioral tolerance* is used in an unfortunately wide variety of ways. In some instances the term is used to refer to a specific empirical event which is observed to occur only in a limited context. In other instances the term is used to refer to a general theoretical mechanism which is assumed to account for a myriad of drug-induced phenomena. Given these extremes of usage, it is little wonder that confusion arises and controversy surrounds the concept of behavioral tolerance.

It should be noted at the outset that either an empirical or a theoretical use of the term behavioral tolerance is acceptable in its own right; neither usage is necessarily more correct or appropriate than the other. But it is necessary that a distinction be drawn between the two and that in any particular instance the intended meaning of behavioral tolerance is made certain. Otherwise, it is difficult to appreciate the arguments of those who embrace and those who eschew the concept of behavioral tolerance.

It is my intention to draw the distinction between empirical and theoretical behavioral tolerance, and to do so with specific reference to the preclinical behavioral pharmacology literature on marihuana effects in animals. The choice of drug is no more than a convenient one; the distinction between empirical and theoretical behavioral tolerance is as readily elaborated and illustrated with many other pharmacological compounds. Indeed, the distinction is a conceptual one which emerges regardless of pharmacological class or behavioral task.

EMPIRICAL BEHAVIORAL TOLERANCE

Empirical Definition of Behavioral Tolerance

A well-framed empirical definition of the concept of behavioral tolerance has the characteristics of being both operational and functional. It is operational in that it states the procedures and

conditions which are necessary to observe the concept. It is functional in that it states what sorts of observable behavioral changes constitute the concept. Take as one instance the following empirical definition of behavioral tolerance to marihuana: Following prior exposure to a fixed dose of marihuana (operational), a specified behavioral effect of marihuana diminishes (functional). A second acceptable example of an empirical definition of behavioral tolerance to marihuana is: Following repeated administrations of marihuana (operational), the dose-effect relationship on some specified behavior shifts to the right (functional).

By way of summary, what it is that makes both of these definitions acceptable, and what would make still others so, is that they specify what is necessary in order to observe behavioral tolerance to marihuana (operationally, to administer marihuana repeatedly), and what observed behavioral change constitutes behavioral tolerance (functionally, a diminution in the behavioral effect induced by marihuana) . Conversely, the empirical definitions imply what behavioral tolerance is not. For example, repeated administrations of marihuana do not constitute behavioral tolerance if they occasion an *increase* in the drug's effect on behavior. Likewise, a diminution of the behavioral effect does not constitute behavioral tolerance if it is produced by some nonpharmacological factor. This is not to deny the possibility of the latter two empirical outcomes. Indeed, they may well be considered as positive instances of some other empirically defined concepts (say, perhaps, reverse tolerance and environmental tolerance). But they are not instances of behavioral tolerance as defined empirically.

Of course, empirically defining behavioral tolerance to marihuana does not assure that instances of the concept actually exist. As it turns out, however, behavioral tolerance to marihuana is readily identified for several unlearned and learned behaviors in a range of animal species and under a variety of marihuana conditions. Indeed, in many instances behavioral tolerance to marihuana is characterized by its rapid development and large magnitude. Among these instances, recently reported, are : spontaneous activity in mice (Anderson et al. 1975) ; dominance status in monkeys (Sassenrath and Chapman 1975); conditioned avoidance learning in rats (Waser et al, 1976); analgesia in dogs (Kaymakcalan et al. 1974) ; and reinforcement schedule performance in pigeons (Bruce and Ferraro 1975).

Empirically defining behavioral tolerance to marihuana also does not serve to explain the concept. Empirical definitions in no way presume or imply anything about the mechanism(s) which underlie the concept defined. That is, the answer to the question of "why does behavioral tolerance to marihuana occur?" is in no way even minimally broached by the empirical definition. This is as it should be, since the specification of underlying explanatory mechanisms is a theoretical matter, not an empirical one. Explanation, in the sense of answering the question Why?", is a reductive process. Identification and description, in the sense of answering the questions "When, where, and under what conditions?", are inductive processes. The inductive-reductive distinction will be discussed further. are might anticipate, however, that empirical and theoretical approaches to the concept of behavioral tolerance differ radically.

Empirical definitions of behavioral tolerance to marihuana are lacking in still another regard. They do not include any specifics about the parameters of the operations that enter into defining the concept. This creates some difficulty for those who are inclined to describe behavioral tolerance empirically. For example, consider the operation of repeatedly administering marihuana. It is not clear from the empirical definition what parameters of this operation are pertinent to describing behavioral tolerance. Several degrees of freedom are available: drug dose and route of administration (Abel et al. 1974; Fried 1976); number of drug administrations and time interval separating successive drug administrations (e.g., Davis and Borgen 1975); drug vehicle and form of the drug (Kosersky et al. 1974); and so on. Further, one may wonder how many times marihuana must be administered before invoking the concept of behavioral tolerance to marihuana is justified. If a completely diminished drug effect on behavior is observed following one marihuana administration (Domino 1971; McMillan et al. 1971)) should this observation qualify operationally as an instance of behavioral tolerance to marihuana?

The lack of parameter specificity inherent in empirical definitions of behavioral tolerance is not peculiar to the operational aspects of the concept. It applies as well to the functional behavioral aspects of the concept. For example, it is not clearly specified by the empirical definition whether the observed diminution in a marihuana-induced behavioral effect should be gradual or abrupt, immediate or delayed, partial or complete. There are two points to be made in this context. The first is the obvious one that it is not always easy to identify an instance of behavioral tolerance to marihuana, even when it is empirically defined because of a lack of parameter specificity inherent in the generic concept. The second point is that empirical definition, while necessary, is not sufficient to provide an empirical description of behavioral tolerance to marihuana.

Empirical Description of Behavioral Tolerance

The empirical description of behavioral tolerance to marihuana is a cumulative affair. It is only through repeated observations that the parameter values of the operations and conditions of behavioral tolerance are progressively elucidated. For example, we now know that behavioral tolerance to the depressant effects of marihuana on reinforcement schedule performance is directly related to the number of marihuana administrations and indirectly related to the treatment interval (Davis and Borgen 1975). With respect to conditions, we now have empirical knowledge that the age of the subject at the time of first exposure to marihuana interacts with later behavioral tolerance development (Parnes and Fried 1974) and that stress may augment behavioral tolerance development (Deikel and Carder 1976). Furthermore, there now exists an extensive listing of those behavioral effects which do and those which do not diminish with repeated administrations of marihuana. To the abbreviated list of confirmed instances of behavioral tolerance to marihuana given above, we may add other instances where a lack of behavioral tolerance development to marihuana has been observed. Briefly, a lack of behavioral tolerance has been found for rodents and monkeys in a wide variety of situations such as: open field behavior (Sjoden

et al. 1973); isolation-induced aggression (Dubinsky et al. 1973); food and water consumption (Gluck and Ferraro 1974); conditioned shock avoidance (Manning 1976); discrimination learning (Adams and Barratt 1976); and performance under a schedule of reinforcement (Snyder et al. 1975).

However, the endpoint of an empirical description of behavioral tolerance to marihuana is not the simple collation of a vast array of specific empirical relationships. Instead, the ultimate goal in this context is the creation of an empirical descriptive system. Such a descriptive system constitutes interrelated sets of empirical relationships which, collectively, generate more implications than each in isolation. Whereas simple empirical description answers the immediate questions of when, where, and under what conditions behavioral tolerance to marihuana occurs, an empirical descriptive system goes beyond the level of present observation to generalize extant empirical relationships and to predict unique relationships regarding behavioral tolerance to marihuana.

An empirical descriptive system is arrived at by a process of induction from the existing data base. Since there are no formal rules for induction (going from the specific to the general) not all behavioral pharmacologists arrive at the same generalizations, even though they are all eventually tied to the same empirical observations. One potential difference among the generalizations is the level of abstractness at which the descriptive system is cast. Nevertheless, the overall objectives remain to generalize from known empirical relationships and to predict unique ones.

For example, one may observe that, "The greater the decrement in performance initially produced by marihuana, the greater the behavioral tolerance." Taken alone this statement implies only that a correlation exists between some measure of performance decrement and some measure of behavioral tolerance. Add to it, however, the statement, "Reinforcement frequency is a direct function of performance level," and it is possible to predict generally that behavioral tolerance will occur *only* when marihuana acts initially to reduce reinforcement frequency. Indeed, just such an induction was arrived at by Schuster, Dockens, and Woods (1966) in their study of the determinants of behavioral tolerance to amphetamine.

One does not always have to be as bold as Schuster et al. (1966) in making predictions from empirical generalizations. Given the present marihuana example, it is acceptable to make the more cautious prediction that behavioral tolerance to marihuana is more likely to occur (or will occur more quickly) when marihuana acts initially to reduce reinforcement frequency. At the least, the latter prediction is more certain to achieve empirical verification than is one couched in absolute terms. Any specific prediction arrived at inductively may be incorrect. However, the empirical generalizations from which the prediction is derived serve abstractly to summarize a number of concrete empirical relationships and to direct further experimentation.

The one task which descriptive systems do not accomplish is that of providing explanations in the earlier-described sense of specifying

the mechanisms underlying behavioral tolerance; they simply do not account for why behavioral tolerance occurs as it does, This may be exemplified by quoting the specific empirical generalization regarding behavioral tolerance to amphetamine which was referred to above:

> Behavior tolerance will develop in those aspects of the organism's behavioral repertoire where the action of the drug is such that it disrupts the organism's behavior in meeting the environmental requirements for reinforcement. (Schuster et al. 1966, p. 181).

No explanatory mechanism is implied here. We are left to ask the question, "Why should behavioral tolerance develop in such a fashion?" But if behavioral tolerance does develop in this way, it may not be necessary to answer the question of why it does so. That is, if we can specify lawful empirical generalizations for the development of behavioral tolerance, we may be better advised to proceed to deal with the implications of these generalizations than to attempt to produce a theoretical explanation for them. After all, explaining the generalizations in no way changes the existence of the generalizations. And once generalizations have been verified empirically, there are no remaining grounds for confusion or controversy about them.

Empirical Generalizations About Behavioral Tolerance

As developed in the preceding section? empirical generalizations regarding behavioral tolerance to marihuana are abstract statements arrived at inductively from specific empirical relationships. As such, empirical generalizations have predictive power but no explanatory power.

In the present section of this chapter, ten empirical generalizations about behavioral tolerance to marihuana will be offered in which the referent behavior change involves an operant/instrumental response. Many of these generalizations have been previously described elsewhere (Ferraro 1976), Consequently, the generalizations will be presented succinctly, and only one of two representative references will be cited for the specific empirical relationships from which each generalization was induced. It will be obvious that several of the empirical generalizations are interrelated and interdependent. This can be simply explained by the fact that all of the generalizations are ultimately tied directly back to a common set of observations.

> Generalization 1. Behavioral tolerance to marihuana is more likely to develop (or will be quicker to develop) if the drug initially produces adverse effects on behavior-environment relationships, such as reductions in reinforcing stimuli or increases in aversive stimuli (Domino 1971; McMillan et al. 1970).
>
> Generalization 2. Behavioral tolerance to marihuana is more likely to continue to develop if drug-induced adverse effects on behavior-environment relationships are maintained (Ferraro 1972).

Generalization 3. Behavioral tolerance to marihuana is less likely to develop (or will be slower to develop) if the drug produces behavioral changes which are not accompanied by adverse effects on behavior-environment relationships (Barry and Kubena 1971; Ferraro 1972).

Generalization 4. Behavioral tolerance to marihuana is less likely to develop if the development of tolerance itself produces adverse effects on behavior-environment relationships (Adams and Barratt 1976; Hirschhom and Rosencrans 1974).

Generalization 5. Behavioral tolerance to marihuana is more likely to develop for some operant/instrumental responses than for others, or for some dependent measures of responses than for others, within the same organism. (Ferraro and Grisham 1972; Harris et al. 1972).

Generalization 6. Behavioral tolerance to marihuana is more likely to develop for simple than for complex operant/instrumental responses (Ferraro and Grilly 1973; Snyder et al. 1975).

Generalization 7. Behavioral tolerance to marihuana is more likely to develop the better the referent operant/instrumental responses are learned (Ferraro and Grilly 1974; Olson and Carder 1974).

Generalization 8. Behavioral tolerance to marihuana is more likely to develop the greater the opportunity to perform the referent operant/instrumental responses under exposure to marihuana (Bruce and Ferraro 1975; Carder and Olson 1973).

Generalization 9. Behavioral tolerance to marihuana which develops under one set of environmental conditions will not transfer completely to another set of environmental conditions; the degree of transfer will be directly related to the similarity of the conditions (Ferraro et al. 1974; Grilly et al. 1973).

Generalization 10. Behavioral tolerance to marihuana which develops under one set of environmental conditions will be relatively permanent under those conditions, even if an extended period of nonexposure to marihuana intervenes (Ferraro et al. 1974).

Of the ten empirical generalizations presented above, the first four pertain specifically to the environmental consequences of behavior, the next four pertain to characteristics of the referent responses, and the last two pertain to environmental antecedents of behavior. In other words, in the instance of behavioral tolerance to marihuana, a dynamic interaction apparently exists

between behavior and the environment. Still other empirical generalizations could be presented which pertain specifically to characteristics of the marihuana treatment (e.g., dose, route of administration, etc.). Thus, behavioral tolerance to marihuana may be reasonably well conceptualized as involving drug-behavior-environment interactions.

Any abstract generalization may be confirmed or discredited empirically. In this regard, it is important that the empirical test of a generalization be carried out within the boundary conditions of the generalization, and that conclusions regarding the suitability of the empirical generalization be correctly formed. For example, a simple demonstration that behavioral tolerance develops to marihuana-induced disruptions in avoidance behavior is not as supportive of Generalization 1 as is an experiment which shows that when marihuana produces an increase in shocks under an avoidance schedule behavioral tolerance occurs, but that when a decrease in shocks is produced no behavioral tolerance occurs (e.g., Manning 1976). Similarly, evidence that behavioral tolerance to marihuana occurs in the absence of adverse behavior-environment relationships, or that behavioral tolerance fails to occur in their presence, does not definitively discredit Generalizations 1-4. All of the generalizations presented above are relative statements about the likelihood and extent of tolerance development to marihuana, and none of them determines the possibility of behavioral tolerance to marihuana in an absolute sense.

This is an important point which can bear elaboration. Take Generalization 8 as a further example. This generalization states that behavioral tolerance to marihuana is more likely to occur the greater the opportunity to respond under the influence of marihuana. This again is a relative generalization. It does not imply that behavioral tolerance cannot occur when marihuana is administered outside of the behavioral situation (Black et al. 1970) or that behavioral tolerance requires repeated exposures to marihuana (McMillan, et al. 1971). Rather, the generalization predicts that behavioral tolerance will develop less quickly if marihuana is administered infrequently and outside of the behavioral situation.

Finally, where a generalization is shown to be inadequate by an empirical test of the predictions made from it, the generalization can be readily dropped and replaced by a new generalization induced from the now enlarged pool of empirical information. However, nothing about this latter process provides an explanation of the generalization.

THEORETICAL BEHAVIORAL TOLERANCE

Theoretical Explanation of Behavioral Tolerance

Providing an explanation of behavioral tolerance to marihuana in terms of the mechanisms which underlie it invades the domain of theory. Theoretical approaches to behavioral tolerance are reductive. That is, explaining empirical relationships regarding behavioral tolerance is done by making reference to a different level of discourse than that at which the empirical relationships exist. This altered level of discourse is reductive in the sense that explanations

are made in terms of molecular processes which occur somewhere inside the organism. These processes may be hypothetical or they may be empirically based, but they are always reductive; they represent the processes that underlie the empirical generalizations which are to be explained.

In the instance of behavioral tolerance to marihuana, one theoretical (reductive) approach is to explain the observed empirical phenomena in terms of pharmacodynamic mechanisms (e.g., McMillan et al. 1971; McMillan and Dewey 1972). In this context any presumed cellular, metabolic, or drug distributional mechanism is worthy of consideration (Davis and Borgen 1975; Dewey et al. 1973; McMillan et al. 1973; Martin et al. 1976).

A second theoretical approach is to account for the empirical generalizations about behavioral tolerance to marihuana in terms of hypothetical or inferred learning processes (Elsmore, 1972; Ferraro and Grisham, 1972; Harris et al., 1972). This latter approach is reductive in that explanatory power is invested in hypothetical learning mechanisms which are presumably located within the organism, but which are not observable.

Both pharmacological and learning theories of behavioral tolerance reside at a distinctly different level of discourse from empirical generalizations of behavioral tolerance. The latter abstractly summarize observed empirical relationships, while the former reductively attempt to explain the latter. Accordingly, the touchstone of a theory of behavioral tolerance is how well it accounts for the relevant empirical generalizations. Actually, there is no more appropriate way to judge the relevance, goodness, truth, or righteousness of a theory of behavioral tolerance than to ascertain how effectively and efficiently it explains the referent empirical phenomena.

It is important here to recognize that no one type of theoretical account is more basic or fundamental than any other. For example, pharmacological theories are not necessarily to be preferred over learning theories because by some metric they may be asserted to be more molecular. Likewise, it is not useful to pursue the truth of one theoretical approach vis-a-vis another. To be sure, if one theory is unable correctly to explain an empirical generalization, then that theory is wrong. But this does not mean that the theory cannot be suitably revised or that an alternative theory must be preferred.

When controversy arises over whether behavioral tolerance to marihuana is learned or pharmacological, the controversy is not an empirical one, nor actually, can it be resolved empirically. The controversy is about what type of theoretical mechanism can best be offered to account for some existing empirical phenomenon. Such controversy is silly, perhaps even nugatory. Either a pharmacological or a learning theory can equally well serve the functions of explaining lawful empirical relationships and of generating future research, and neither type can ever be proved to be true. The behavioral pharmacologist must choose between these approaches or some combination of these approaches (e.g., Kalant et al. 1971; McMillan 1976), actually on the basis of personal preference.

Behavioral tolerance is empirical: whether its basis is learned or pharmacological remains a theoretical issue.

Learning Theory of Behavioral Tolerance

Having drawn a distinction between empirical and theoretical behavioral tolerance, and between learned and pharmacological theories of behavioral tolerance, I should like now to present one version of a learning theory of behavioral tolerance to marihuana. This theory, which was first presented in 1972 (Ferraro 1972) and which has been since elaborated (Ferraro, et al. 1974; Ferraro 1976), is indebted conceptually to Dews (1962) and Schuster (Schuster and Zimmerman 1961; Schuster et al. 1966) for their recognition that learning may explain behavioral tolerance to psychotropic drugs, and to Loewe for his early observation (1944) that behavioral tolerance to marihuana is related to the development of compensatory responses.

The present learning theory is intended specifically to explain the sorts of empirical generalizations presented in a previous section of this chapter and, in fact, it has rather narrow boundary conditions. Specifically, the theory is restricted to operant/instrumental behavior which is maintained by positive or negative reinforcement conditions.

The following summary account of the theory very closely follows that recently presented elsewhere (Ferraro 1976).

It is first assumed that an operant/instrumental response is under the control of antecedent discriminative stimuli, which set the occasion for the response, and of consequent reinforcing stimuli, which determine the probability of response occurrence. A second assumption is that the administration of a behaviorally-effective dose of marihuana can alter responding so as to produce an adverse change in the relationship between responses and discriminative and reinforcing stimuli.

Adverse changes in the behavior-environment relationship produced by marihuana activate compensatory responses to the extent that they are available in the situation. Compensatory responses have the status of a hypothetical construct; they are presumed to exist within the organism but they are not necessarily observable (they are reductive) . Once activated by marihuana-produced adverse changes in the environment, these hypothetical compensatory responses counteract or offset the adverse changes; that is, they function to reestablish the original, more favorable, behavior-environment relationships.

As compensatory responses are repeatedly activated under marihuana, they are gradually learned or associated to the existing stimulus situation. Thus, under repeated administrations of marihuana there is a progressive increase in the strength of learned compensatory responses and a consequent progressive diminution in the drug-induced behavioral alterations. Compensatory responses are learned because they are reinforced by the reductions in the adverse environmental consequences which the compensatory responses themselves produce. By way of overview, the rate and extent of behavioral tolerance to marihuana is hypothesized to be a direct function of the rate and extent to which compensatory responses are activated and learned in

the situation.

Status of The Learning Theory

As with any other theory of behavioral tolerance to marihuana, the usefulness of the present theory is gauged by its ability to explain the empirical generalizations relevant to it. Clearly, the truthfulness of the theory cannot be determined empirically since the central reductive construct of the theory, the compensatory response, is asserted to be hypothetical. There is no problem here. The focus of the behavioral pharmacologist's research attention is more appropriately directed to engendering empirical relationships than to certifying hypothetical theoretical constructs. Where empirical phenomena arise that are not readily explained by the theory, the theory is revised accordingly, if possible. If this is not possible, then the usefulness of the theory is compromised to that extent.

As may already have been anticipated, the present learning theory of behavioral tolerance to marihuana can explain each of the ten empirical generalizations presented earlier. After all, the theory was largely created with these generalizations in mind. Nevertheless, it might be instructive about the theory to discuss briefly how the theory accounts for a few of these generalizations.

The first four empirical generalizations, which in one way or another relate behavioral tolerance to adverse behavior-environment relationships produced by marihuana, follow directly from the theoretical assumption that marihuana-induced adverse environmental consequences activate compensatory responses so that compensatory responses are less likely to occur (but still may) in the absence of drug-produced adversity.

The empirical generalization (Generalization 6) that behavioral tolerance to marihuana is more likely to develop for simple than for complex responses is explained theoretically in terms of the relative availability or effectiveness of compensatory responses. It is assumed within the theory that compensatory responses are less available and/or less effective the more complex the referent response which is affected by marihuana.

Similarly, according to the theory, the opportunity to respond under the influence of marihuana enhances the development of behavioral tolerance (Generalization 8) since the opportunity to learn compensatory responses is greater when the drug is administered inside as opposed to outside of the situation.

Finally, the last two empirical generalizations, which relate behavioral tolerance to antecedent environmental conditions, follow naturally enough from the theoretical supposition that compensatory responses are learned to the environmental stimuli present in the situation. That is, the occurrence of learned compensatory responses will exhibit specificity to the stimulus situation in which they are acquired, although some stimulus generalization could certainly be anticipated (Generalization 9). Furthermore, considered as learned behavior, compensatory responses will be relatively permanently associated to the stimulus situation in which they are initially acquired, unless, of course, explicit procedures are executed to

counteract the learned associations (Generalization 10).

SUMMARY AND CONCLUSIONS

Confusion and controversy sometimes arise regarding the concept of behavioral tolerance. This occurs, in part, because a distinction is not always adequately made between empirical and theoretical behavioral tolerance. Empirical definitions of behavioral tolerance are both operational and functional. As such, empirical definitions permit instances of behavioral tolerance to be identified within limits. However, they do not provide for the description of parmetric relationships regarding behavioral tolerance nor do they explain behavioral tolerance. These latter two functions are accomplished, respectively, by descriptive systems and theoretical systems of behavioral tolerance.

A descriptive system of behavioral tolerance collates individual empirical relationships regarding the parameters of behavioral tolerance and from them inductively arrives at an abstract empirical generalization which generates more implications than each relationship in isolation. In this abstract form, empirical generalizations represent a first-order basis for making predictions regarding the extent and rate of occurence of behavioral tolerance.

Most empirical generalizations regarding behavioral tolerance relate in some manner to antecedent stimuli, response conditions, and consequent stimuli. The implication here is that behavioral tolerance is empirically constituted of various drug-environment-behavior interactions. But since empirical generalizations are arrived at inductively, there is no assurance regarding their correctness. Empirical confirmation of the predictions made from empirical generalizations of behavioral tolerance must be sought within the boundary conditions which apply to the generalizations.

Theories of behavioral tolerance go beyond empirical descriptive systems of behavioral tolerance in attempting to explain the concept in terms of the mechanisms which underlie it. Accordingly, theories of behavioral tolerance are reductive; they resort to presumed processes within the organism to explain observed empirical phenomena. Typically, these are processes described either in terms of pharmacological or learning constructs. Neither type of theory of behavioral tolerance is more fundamental, relevant, appropriate, or correct than the other. Either is acceptable to the extent that the reductive mechanisms it proposes are Capable of explaining the existing empirical generalizations regarding behavioral tolerance. Behavioral tolerance is empirical. Thus. it is inappropriate to debate whether behavioral tolerance is ultimately a learned or a pharmacological process; this remains a theoretical question.

Theories of behavioral tolerance are not necessary. They do, however, represent an efficient, second-order basis for making predictions regarding behavioral tolerance. Accordingly, theories of behavioral tolerance can be quite useful (even if not always correct). In this regard, it is possible to account for several empirical generalizations regarding behavioral tolerance to marihuana with a learning theory which asserts that behavioral tolerance is directly related

to the extent to which compensatory responses are activated and learned under the drug. The important aspect of this learning theory is not its correctness or incorrectness (it is most likely incorrect) but its probability of generating future research and of providing direction regarding the application of behavioral tolerance phenomena to clinical and therapeutic situations. These latter probabilities remain to be determined.

REFERENCES

Abel, E. L., McMillan, D. E., and Harris, L. S. Delta-9-tetrahydrocannabinol: Effects of route of administration on onset and duration of activity and tolerance development. *Psychopharmacologia,* 35:29-38, 1974.

Adams, P. M., and Barratt, E. S. The effects of a marijuana extract on two-choice discrimination learning in the squirrel monkey. *Physiological Psychology,* 4:155-158, 1976.

Anderson, P. F., Jackson, D. M., Chesher, G. B., and Malor, R. Tolerance to the effects of delta-9-tetrahydrocannabinol in mice on intestinal motility, temperature, and locomotor activity. *Psychopharmacologia,* 43:31-36, 1975.

Barnes, C., and Fried, P. A. Tolerance to delta-9-THC in adult rats with differential delta-9-THC exposure when immature or during early adulthood. *Psychopharmacologia,* 34:181-190, 1974.

Barry, H., III, and Kubena, R. K. Repeated high doses of delta-l-tetrahydrocannabinol enhance acquisition of shock avoidance by rats. *Proceedings of the American Psychological Association,* 6:747-748, 1971.

Black, M. B., Woods, J. H., and Domino, E. F. Some effects of (-)-delta-9-trans-tetrahydrocannabinol and cannabis derivatives on schedule-controlled behavior. *Phrmacologist,* 12:258, 1970.

Bruce, P. D., and Ferraro, D. P. Learned tolerance to delta-9-tetrahydrocannabinol in pigeons. Paper presented to Rocky Mountain Psychological Association, Salt Lake, 1975.

Carder, B., and Olson, J. Learned behavioral tolerance to marihuana in rats. *Pharmacology, Biochemistry and Behavior,* 1:73-76, 1973.

Davis, W. M., and Borgen, L. A. Tolerance development to the effect of delta-9-tetrahydrocannabinol on conditioned behavior: Role of treatment interval and influence of microsomal metabolism. *Archives Internationales de Pharmacodynamie et de Therapie,* 213: 97-112, 1975.

Deikel, S. M., and Carder, B. Shock-induced antagonism of delta-9-THC effects in rats. Paper presented to Psychonomic Society, St. Louis, 1976.

Dewey, W. L., McMillan, D. E., Harris, L. S., and Turk, R. F. Distribution of radioactivity in brain of tolerant and nontolerant pigeons treated with 3H-delta-9-tetrahydrocannabinol. *Biochemical Pharmacology,* 22:399-405, 1973.

Dews, P. B. Psychopharmacology. In: Bachrach, A. J., ed. *Experimental Foundations of Clinical Psychology. New* York: Basic Books, 1962.

Domino, E. F. Neuropsychopharmacologic studies of marihuana: Some synthetic and natural THC derivatives in animals and man. *Annals of the New York Academy of Sciences,* 191:166-191, 1971.

Dubinsky, B., Robichaud, R. C., and Goldberg! M. E. Effects of (-)-delta-9-trans-tetrahydrocannabinol and its selectivity in several models of aggressive behavior. Phamnacology, 9:204-216, 1973.

Elsnore, T. F. Effects of delta-9-tetrahydrocannabinol on temporal and auditory discrimination performance of monkeys. *Psychopharmacologia,* 26:62-72, 1972.

Ferraro, D. P. Effects of delta-9-tetrahydrocannabinol on simple and complex learned behavior in animals. In : Lewis, M. F., ed. *Current Research in Marijuana.* New York: Academic Press, 1972.

Ferraro, D. P. A behavioral model of marihuana tolerance. In:Braude, M. C. and Szara, S., eds. *Pharmacology of Marihuana.* New York: Raven Press, 1976.

Ferraro, D. P., and Grilly, D. M. Lack of tolerance to delta-g-tetrahydrocannabinol in chimpanzees. *Science,* 179:490-492, 1973.

Ferraro, D. P ., and Grilly, D. M. Effects of chronic exposure to delta-9-tetrahydrocannabinol on delayed matching-to-sample in chimpanzees. *Psychopharmacologia,* 37:127-138, 1974.

Ferrxo, D. P., Grilly, D. M., and Grisham, M. G. Delta-g-tetrahydrocannabinol and delayed matching-to-sample in chimpanzees. In: Singh, J. M. and Lal, H., eds. *Drug Addiction: Vol. III.* New York: Symposia Specialists, 1974.

Ferraro, D. P., and Grisham, M. G. Tolerance to the behavioral effects of marihuana in chimpanzees. *Physiology and Behavior,* 9:49-54, 1972.

Fried, P. A. Cross-tolerance between inhaled cannabis and intraperitoneal injections of delta-9-THC. *Pharmacology, Biochemistry and Behavior,* 4:635-638, 1976.

Gluck, J. P., and Ferraro, D. P. Effects of delta-9-THC on food and water intake of deprivation experienced rats. *Behavioral Biology,* 11:395-401, 1974.

Grilly, D. M., Ferraro, D. P., and Marriott, R. G. Long-term interactions of marijuana and behavior in chimpanzees. *Nature,* 242:119-120, 1973.

Harris, R. T., Waters, W.,and McLendon, D. Behavioral effects in rhesus monkeys of repeated intravenous doses of delta-9-tetrahydrocannabinol. *Psychopharmacologia,* 26:297-306, 1972.

Hirschhom, I. E., and Rosencrans, J. A. Morphine and delta-g-tetrahydrocannabinol: Tolerance to the stimulus effects. *Psychopharmacologia,* 36:243-253, 1974.

Kalant, A., LeBlanc, A. E., and Gibbons, R. J. Tolerance to, and dependence on, some non-opiate psychotropic drugs. *Pharmacological Reviews,* 23:135-191, 1971.

Kaymakcalan, S., Turker, R. K.,and Turker, M. N. Analgesic effect of delta-9-tetrahydrocannabinol in the dog. *Psychopharmacologia,* 35:123-128, 1974.

Kosersky, D. S., McMillan, D. E.,and Harris, L. S. Delta-g-tetrahydmcannabinol and 11-hydroxy-delta-9-tetrahydrocannabinol: Behavioral effects and tolerance development. *Journal of Pharmacology and Experimental Therapeutics,* 189:61-65, 1974.

Loewe, S. Pharmacological study. In:The *Marihuana Problem in the City of New York.* Lancaster: Jacques Cattell Press, 1944.

Manning, F. J. Chronic delta-9-tetrahydrocannabinol. Transient and lasting effects on avoidance behavior. *Pharmacology, Biochemistry and Behavior,* 4:17-21, 1976.

Martin, B. R., Dewey, W. L., Harris, L. S., and Beckner, J. S. H^3-delta-9-tetrahydrocannabinol tissue and subcellular distribution in the central nervous system and tissue distribution in peripheral organs of tolerant and nontolerant dogs. *The Journal of Pharmacology and Experimental Therapeutics,* 196:128-144, 1976.

McMillan, D. E. Behavioral pharmacology of the tetrahydrocannabinols. In: Dews, P. B., ed. *Recent Advances in Psychopharmacology.* St. Louis: C. V. Mosby, 1976.

McMillan, D. E., and Dewey, W. L. On the mechanisms of tolerance to delta-g-THC. In: Lewis, M. F.. ed. *Current Research in Marijuana,* New York: Academic Press, 1972.

McMillan, D. E., Dewey, W. L., and Harris, L. S. Characteristics of tetrahydrocannabinol tolerance. *Annals of the New York Academy of Sciences,* 191:83-99, 1971.

McMillan, D. E., Dewey, W. L., Turk, R. F., Harris? L. S.,and McNeil, J. H. Blood levels of 3H-delta-9-tetrahydrocannablnol and its metabolites in tolerant and nontolerant pigeons. *Biochemical Pharmacology,* 22:383-397, 1973.

McMillan, D. E., Harris, L. S., Frankenheim, J. M.,and Kennedy, J. S. &-delta-9-trans-tetrahydrocannabinol in pigeons: Tolerance to the behavioral effects. *Science,* 169:501-503, 1970.

Olson, J., and Carder, B. Behavioral tolerance to marihuana as a function of amount of prior training. *Pharmacology, Biochemistry and Behavior,* 2:243-247, 1974.

Sassenrath, E. N., and Chapman, L. F. Tetrahydrocannabinol-induced manifestations of the "marihuana syndrome" in group-living macaques. *Federation Proceedings,* 34:1666-1670, 1975.

Schuster, C. R., Dockens, W. S., and Woods, J. H. Behavioral variables affecting the development of amphetamine tolerance. *Psychopharmacologia,* 9:170-182, 1966.

Schuster, C. R., and Zimmerman, J. Timing behavior during prolonged treatment with d-amphetamine. *Journal of the Experimental Analysis of Behavior,* 4:327-330, 1961.

Sjoden, P. O., Jarbe, T. U. C., and Henriksson, B. G. Effects of long term administration and withdrawal of tetrahydrocannabinols (delta-8-THC and delta-9-THC) on open field behavior in rats. *Pharmacology, Biochemistry and Behavior,* 1:243-249, 1973.

Snyder, E. W., Lewis, E. G., Dustman, R. E.: and Beck, E. C. Sustained ingestion of delta-9-tetrahydrocannabinol and the operant behavior of stump-tailed macaques. *Pharmacology Biochemistry and Behavior,* 3:1129-1132, 1975.

Waser, P. G., Martin, A., and Heer-Corcano, L. The effect of delta-g-tetrahydrocannabinol and LSD on the acquisition of an active avoidance response in the rat. *Psychopharmacologia,* 46:249-254, 1976.

AUTHOR

Douglas P. Ferraro, Ph.D., Professor of Psychology, University of New Mexico, Albuquerque, New Mexico 87131

IV. MARIHUANA

Behavioral Tolerance: Lessons Learned from Cannabis Research

Reese T. Jones, M.D.

INTRODUCTION

From the beginning of our cannabis research we were impressed that so-called nonpharmacologic factors were very important in determining many of the drug's effects. I suppose, right from the start, we were studying the phenomenon this conference is about. However, "behavioral tolerance" and "learned tolerance" are terms I have never felt a great need to use. I'm not sure why. Perhaps it is due to fuzzy thinking, but I would rather think it is due to a belief that the mechanisms of behavioral, learned, physiologic, and other kinds of tolerance are more similar than different. The definition of tolerance:

(a) Diminished effect with repeated exposure to a given dose and

(b) Return of original effect or an increased effect following an increased dose,

assumes nothing about mechanisms. To adopt a terminology like "behavioral" or "learned" tolerance that assumes mechanisms and that may mislead the nonspecialist doesn't seem to be progress to me.

At one point I kept a list of various terms used to describe (and by some to explain) different types of tolerance. These include behavioral, psychological, learned, behaviorally augmented, biochemical, metabolic, cellular, tissue, organic, dispositional, pharmacological, physiologic, central, peripheral, functional, central nervous system, cross, acquired, innate, reverse, negative, and real. Except for the relatively rare instances of "metabolic" tolerance, most of these terms may well be referring to similar processes and common mechanisms. The evidence for this was covered in a review some years ago (Kalant, LeBlanc, and Gibbons 1971) and by other reports in this monograph (LeBlanc, Poulos, and Gappell 1977; Carder 1977).

In my own research strategy I have avoided trying to make clean distinctions between behavioral, physiologic, and mental phenomena. This

is mostly due to a faith that all mental and psychological and behavioral events do, at some level, have physiologic, neurochemical, neuropharmacologic mechanisms in common.

The psychopharmacology of cannabis is such that the behavioral history of the person using the drug and things like set and setting are perhaps more important than with many other CNS-active drugs. Cannabis is a drug that tends to be consumed at fairly low doses by most people, leading to a low level of intoxication. The material available to most users tends to be of low potency or often of hardly any potency at all. The smoked route of administration commonly employed allows easy titration of dose and level of intoxication. Tremendous "adver - tising'" and social and cultural forces tend to shape experienced effects, or at least influence the effects reported by users. It is difficult to think of a drug about whose effects more mythology, fact, and fantasy have been spread. Cannabis' pharmacology, particularly its spectrum of effects, allowing a relatively clear consciousness during intoxication (relative to autonomic and other physiologic effects), perhaps makes psychological factors more important than is the case with CNS depressants like alcohol and barbiturates. The drug's relatively short duration of action and relatively infrequent use (in our culture) tend to make psychological factors more important and such pharmacologic factors as the "bathing of the neuronal pool" less important. All this comes together so as to make expectation, setting, past psychoactive drug experience, personality, associates, time of day, etc., more important determinants of ultimate drug effects than if, for example, we were considering the effects of 150 mg percent blood levels of alcohol or 1 gram doses of LSD (Jones 1971).

That regular smokers of cannabis become more intoxicated when smoking in a group, or more intoxicated when they can smell and taste the smoke, or be more subject to feelings of intoxication after smoking placebos might strike some as having only tangential relevance to behavioral tolerance. So I will describe some data from recent experiments that may have more direct relevance to our topic. The first experiment concerns the effects of practice on marihuana-induced changes in reaction time. The second has to do with behavioral tolerance evident in subjects chronically treated with oral doses of tetrahydrocannabinol ('MC) in a situation where behavior, behavioral tolerance, cardiovascular physiology, cardiovascular tolerance, and other things get conceptually muddled in my mind.

EFFECTS OF PRACTICE AND LEARNING ON MARIHUANA EFFECTS

The reaction time study grew out of a problem that arose when we began studies of 'IX effects over a 4-to 6-week period in hospitalized volunteers who were tested repeatedly (Jones, Benowitz, and Bachman 1976).

In our earlier outpatient studies, largely involving single or a few doses of THC or cannabis given to subjects who visited the lab on only a few occasions, we found what many investigators have--decrements in reaction time and impaired performance on a variety of perceptual, motor, cognitive, and other tasks. Dose-related, to be sure, but fairly predictable.

In contrast, the hospitalized volunteers were tested repeatedly on a daily schedule or even with multiple tests during the day, and most of their waking hours were spent in the lab. The paradigm used with the hospitalized volunteers involved a week or so of practice on a task before administration of the THC or cannabis. Thus, they were well adapted to a test situation, well trained in laboratory rituals, and, specifically, well practiced on the task before being drugged. With such a test schedule we found that the previously reliable drug treatment effects disappeared. Doses of THC that reliably slowed reaction time or impaired performance on a memory task in the out-patients had no effect in the hospitalized subjects. It looked like acquired tolerance developing before any drug was given to them.

We decided to see if this unexpected resistance to drug-induced alterations in behavior was evident in well-practiced outpatient volunteers. It was. Since a full description of this study has been published, I'll only cover a few points here (Peeke, Jones, and Stone 1976). A group of outpatient volunteers practiced on a complex visual reaction time task on four successive test days before receiving marihuana, in order to see whether practice alone in a nondrugged state would alter the response to cannabis. The 34 volunteers all used marihuana two to three times a week during the few months prior to the experiment. They were divided into three experimental groups. Group M-P smoked marihuana (cigarette containing 20 mg WC) during successive daily test sessions 1 through 4 and then smoked a placebo cigarette on session 5. Group P-M smoked placebo cigarettes on sessions 1 through 4 and a marihuana cigarette on session 5. The third group performed the tasks on five daily test sessions, not smoking cigarettes on any. All testing was at the time of peak effects.

A number of tasks were used, but I'll just describe the results on the most difficult one--a categorization task where the subject had to make a judgment as to whether a two-attribute stimulus, varying as to both form and color, matched a preceding two-attribute stimulus. It was a fairly difficult task where four judgments were possible: that is, the Judgment could be (1) same color, same form; (2) same color, different form; (3) different color, same form; and (4) different color, different form. If a correct response was made, the stimulus disappeared to be replaced 368 msec later by the next stimulus requiring another Judgment. The test stimulus about which the judgment was made became the "preceding" stimulus for the next trial and thus had to be retained in memory after the response. Thus the memory trace for a stimulus served in different capacities on two successive trials. During an experimental session the task was run for five blocks, each containing 40 trials. In the data in figure 1 tire mean reaction time for each block of trials was computed, yielding five data points per session for each Judgment.

As judged by the mean reaction times, the task was a fairly difficult one. Initial reaction times of over one second were common. The group M-P, who had received no practice before performing the task under marihuana, showed considerable impairment during the first test session. The short duration of the impairment was surprising. The M-P group showed considerable improvement during session 1 (that is,

FIGURE 1

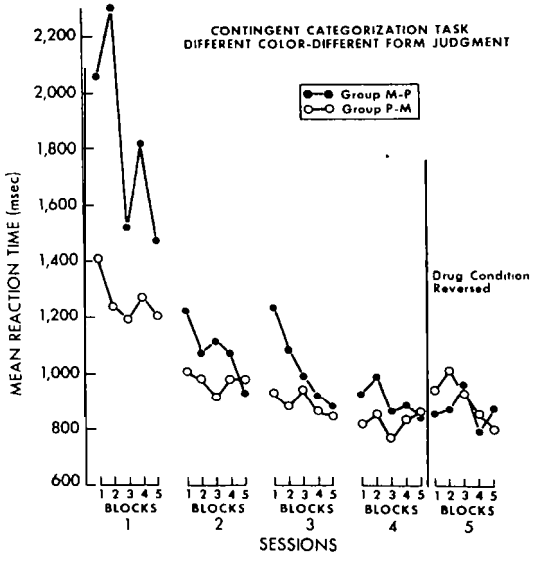


Fig 1 Mean reaction time for drug treatment groups for each block of trials within each session for the Different Color- Different Form Judgment of the Contingent Categorization task

during their first exposure to marihuana in the laboratory) and by the end of session 2 (that is, their second laboratory day smoking marihuana) , their performance was indistinguishable from the performance of the group that had been smoking placebo only. Remember that each data point in the figure represents 40 trials on the task for each subject, so that by block three, when the greatest performance gain is seen, the subjects had already received considerable practice on the task. Despite the disappearance of marihuana effects on performance, the physiological and subjective responses to the marihuana diminished only slightly over the four daily sessions. These included salivary flow, pulse rate, and self reports of intoxication levels. Practice while intoxicated improved performance. The rate of improvement differed for the M-P and the P-M groups; however, the final level of performance was comparable for both groups.

The performance of the group who smoked nothing was not different from the P-M group on the first four sessions nor different from M-P on the fifth session. Thus, the well-practiced outpatients resembled our well-practicedinpatients in terms of diminished magnitude of drug effects. Our hunch is that with practice, particularly on a complex perceptual task, such things as the importance of attention are

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gradually reduced and behavior becomes far more automatic. Thus, the demands of the task may well change and resulting drug effects diminish. The alternate explanation--a fundamental adaptation at the neuronal level with practice and consequent drug effect differences--is also plausible and intriguing.

BEHAVIORAL TOLERANCE : IN THE HEART OR IN THE HEAD?

The utility of considering both behavioral and physiologic data when trying to understand what might seem to be behavioral tolerance I hope is illustrated in the next example. The data is from our tolerance studies with hospitalized volunteers (Jones, Benowitz, and Bachman 1976). The dose of tetrahydrocannabinol was 20 mg given orally every three hours. Our goal in this study was to produce tolerance as rapidly as possible so as to study drug interactions in the tolerant and nontolerant state. Hence, the dosage schedule was selected so that we could maintain a fairly constant tissue level of cannabinoids, or "continually bathe the neuronal pool," as Seevers and Deneau (1963) said a bit more poetically some years ago when discussing optimal conditions for the appearance of tolerance and dependence to opiates. It would be handy if we could implant a pellet of THC or use some similar strategy. This, of course, is difficult to do in human studies, so the every-three-hour dosage schedule used in our current studies is a compromise.

The behavioral tolerance that I'll discuss has to do with behavior that I'll term "falling down." Many of our experimental subjects frequently become dizzy and some fall down early during the period of the THC administration. Even though the MC is continued, the falling down behavior rapidly decreases and disappears, fulfilling part of the definition of tolerance. It returns if the THC dose is rapidly increased. The change in behavior is most dramatic. In most subjects the falling tends to disappear completely within 24 to 48 hours after the THC is begun, indicating rapid development of tolerance. One might assume that such behavioral tolerance to falling down is indicative of some sort of so-called "functional" or "CNS" or other nonmetabolic mechanisms. Although we are looking hard, we as yet find no evidence for metabolic tolerance sufficient to account for the phenomenon. However, by following some fairly simple cardiovascular changes, we can partially account for the behavioral tolerance and, I hope, to a small extent illustrate the utility of not distinguishing too sharply between physiological and behavioral tolerance.

The falling down behavior tends to occur after a subject has just stood up following a period of being supine or sitting. Of course, whenever a person stands up from a prone or supine position, drugged or not, there is a transitory drop in blood pressure. Tetrahydrocannabinol and many other drugs produce fairly dramatic drops in blood pressure when measured right after standing. When symptoms appear we call this orthostatic hypotension. These changes are described in a recent report from our laboratory (Benowitz and Jones 1975).

The pattern of blood pressure change in a typical subject is shown in figure 2. The change in systolic blood pressure from supine to quiet standing for one minute is plotted over the one-month course of the study. me pressures were all measured at 7 a.m. when the subject first got out of bed. The drops in BP can be dramatic- -for example, on day 11. The 20 mg doses of oral THC had been begun at 8 p.m. on day lo, so the subject had a total of four 20 mg doses prior to the BP recording. The BP drops diminished over the next four days. on day 17 the THC was stopped at 11 p.m., so that the BP recorded at 7 a.m. on day 18 was 8 hours after the last dose of THC . Note the increase in BP on day 18. The drug was restarted at bedtime on day 18 (11 p.m.). Note the apparent decrease in degree of tolerance at the 7 a.m. recording on day 19.

Some might view the blood pressure changes as being more evidence of physiologic tolerance than of behavioral tolerance. An orthostatic BP drop is not ordinarily viewed as behavior even though one must engage in behavior to evoke it, i.e., stand up. At least standing BP requires more behavior on the part of the subject than does supine BP.

The subject in figure 2 showed fairly typical changes in body weight during the experiment. During the first 5 days on THC he gained 12 pounds. Although one might consider this to be due to the 'munchies" or other THC-induced changes in appetite and diet, our data indicates it is largely, if not entirely, due to an increase in body water, mainly increased plasma volume (Benowitz and Jones 1975). When a person experiences episodes of orthostatic hypotension, various mechanisms are often triggered so as to increase plasma volume (Weil and Chidsey 1968). In a sense the organism "learns" and adapts to the BP drops. During THC administration, tolerances does not develop or develops slowly to the weight gain or increase in plasma volume. Thus, the behavioral impairment produced by MC (falling down) disappears after a complicated set of homeostatic cardiovascular changes. The performance of certain behaviors (for example, getting up and walking around) is probably of great importance in determining whether the homeostatic cardiovascular changes take place.

We have not yet done the crucial experiment, but I'm fairly certain how it would come out, so I will speculate a bit. Suppose the behavior I'm interested in (falling down) did not occur during the period of THC administration. Would the weight gain and tolerance to the postural BP drops still develop? What if the person never had occasion to stand up while drugged and thus never became dizzy, faint, and weak, never experienced precipitous BP drops, and subsequently fell down? Under such conditions I think the tolerance to the hypetension would develop much more slowly, if at all. The rapid tolerance to the orthostatic hypotension (and to falling) in our test situation I think is a good example of behaviorally augmented tolerance.

Others have speculated that: "Stimulus to the development of tolerante.. .would not be the presence of the drug itself, but the degree of impairment of required neuronal functions which the drug produces (Frankel et al. 1975)." Those investigators were talking about CNS neuronal functions, but cardiovascular system measures make the same

FIGURE 2

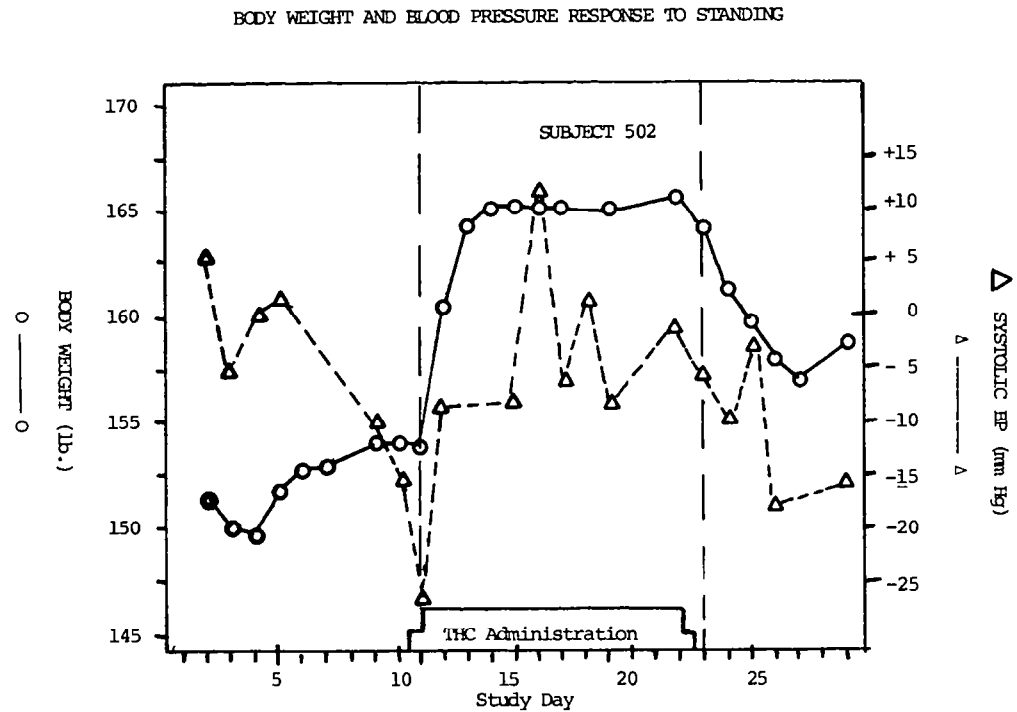


Figure 2. Body weight and change in systolic blood pressure from supine to standing for one minute. Measures all taken at 7 A.M. Maximum THC dose was 20 mg every 3 hours. THC began at 8 P.M. on Day 10 and stopped 8 P.M. on Day 22.

point. If our hospitalized patients were kept in bed in a supine position for the first few weeks of THC administration, I'm reasonably sure there would be marked hypotension when they then first stood up, i.e., there would not be the rapid tolerance shown by the patient in figure 2. In fact, just lying prone for a week without any THC administration would, of course, be associated with a certain degree of "acquired" hypotension upon standing. This maybe reflects the loss of some other sort of "tolerance" (nondrug-related) to postural BP changes. If the subject was never exposed to an episode of hypotension, the necessary stimulus for the increase in plasma volume would not occur and the large gain in body weight would not follow. Tolerance in our test situation clearly has instrumental value for the subject but, if no BP drop occurs, such homeostatic changes would have no instrumental value.

We have not yet done such an experiment, but have observed that subjects who stay in bed when the THC is begun have less weight gain and more problems with persistent hypotension. Subjects who are successfully encouraged to get up slowly and keep moving despite the hypotension and other symptoms develop tolerance very rapidly (as in the case of the subject in figure 2).

I have an impression that our subjects tend to demonstrate more rapid and profound tolerance to many cannabis effects than is the case in other chronic administration experiments. It may well be that our particular dose schedule, i.e., around-the-clock administration, in a sense forces the subjects into an optimal behaviorally augmented tolerance paradigm. That is, our subjects can't smoke a number of marihuana cigarettes and then go to bed, as happens in other studies. Even though intoxicated, subjects in our experiment are required frequently to perform and behave. These subjects very rapidly develop tolerance.

Does all this mean that BP and plasma volume changes are to be considered part of behavioral tolerance? Or are they examples of physiologic tolerance? I'm inclined to agree with those (Kalant, LeBlanc, and Gibbons 1971) who emphasize the similarities rather than differences in varieties of tolerance.

REFERENCES

Benowitz, N. L.,and Jones, R. T. Cardiovascular effects of prolonged delta-9-tetrahydrocannabinol ingestion. Clin. *Pharmacol. Ther.* , 18:287-297, 1975.

Carder, B. Environmental influences on marihuana tolerance. This monograph.

Frankel, D., Khanna, J., LeBlanc, A., and Kalant, H. Effect of p-chlorophenylalanine on the acquisition of tolerance to ethanol and pentobarbital. *Psychopharmacologia,* 44:247-252, 1975.

Jones, R. T. Marihuana- induced "high": Influence of expectation, setting, and previous drug experience. *Pharmacol. Rev.,* 23:359-369, 1971.

Jones, R. T. , Benowitz, N. L.,and Bachman, J. Clinical studies of cannabis tolerance and dependence. *Ann. New York Acad. of sci.,* 282:221-239, 1976.

Kalant, H., LeBlanc, A. E., and Gibbons, R. J. Tolerance and dependence on some non-opiate psychotropic drugs. *Pharmacol. Rev. ,* 23:135-191, 1971.

LeBlanc, A. E., Poulos, C. X., and Cappell, H. D. Tolerance as a behavioral phencomenon: Evidence from two experimental paradigms. This conference.

Peeke, S. C., Jones, R. T., and Stone, G. C. Effects of practice on marihuana induced changes in reaction time. *Psychopharmacology,* 48: 159-163, 1976.

Seevers, M. H.,and Deneau, G. A. Physiological aspects of tolerance and physical dependence. Review in: Root, W. S., and Hofmann, F. G., eds. *Pharmacology : A Comprehensive Treatise.* New York: Academic Press, 1963. pp. 565-640.

Weil, J. V., and Chidsey, C. A. Plasma volume expansion resulting from interference with adrenergic function in normal man. *Circulation,* 37:54-61, 1968.

AUTHOR

Reese T. Jones, M.D., Department of Psychiatry, University of California, San Francisco, California 94143

V. STIMULANTS

Behavioral Tolerance to Cocaine

William L. Woolverton, Ph.D., and
Charles R. Schuster, Ph.D.

Conflicting reports regarding the development of tolerance to the effects of cocaine have appeared in the literature. It has been reported (Jaffe 1975; Kosman and Unna 1969) that human cocaine addicts can tolerate doses as high as 10 grams per day. However, whether this tolerance is acquired or simply the result of normal variability in initial tolerance in the population is unclear. In the animal laboratory, the consensus is one of increased sensitivity (reverse tolerance) to many of the behavioral effects of cocaine. As early as 1924, Lewin stated that

> as opposed to morphine, animals cannot become accustomed to cocaine; they even exhibit an increasing sensibility to the drug (Byck 1974, p. 245).

Indeed, numerous reports of increased sensitivity to the central stimulant effects of cocaine in rats (Downs and Eddy 1932; Post 1977; Stripling and Ellinwood 1977),. dogs (Tatum and Seevers 1929) and rhesus monkeys (Tatum and Seevers 1929; Post 1976) have appeared in the literature. Doses of cocaine which initially produced a mild stimulation induced convulsions and often death during repeated administration. However, changes in sensitivity to the effects of cocaine on conditioned behaviors in laboratory animals have not been studied.

With these considerations in mind, we have been studying the effects of repeated administrations of cocaine in rats in several behavioral situations. Both tolerance and increased sensitivity to cocaine have been observed, depending upon the relationship of time of injection to the experimental session. Further, cross tolerance between cocaine and d-amphetamine, as well as increased sensitivity to d-amphetamine, has also been observed. The findings support the hypothesis of Schuster et al. (1966) that behavioral tolerance develops to the effects of a drug that interfere with the ability of the organism to meet the contingencies of reinforcement.

GENERAL PROCEDURE

Two basic experimental procedures were used to test the effects of single and repeated administrations of cocaine in rats.

Milk Drinking Procedure. Daily experimental sessions consisted of 15 minutes access to 50 ml of a sweetened condensed milk solution. At the end of this period, the quantity of milk remaining was measured to determine milk intake.

Operant Procedure. Rats were trained in a standard operant chamber to press a lever for food delivery on a schedule of reinforcement that required that responses be spaced by at least 20 seconds (differential reinforcement of low rates 20 seconds: DRL 20"). The effects of cocaine on lever pressing frequency were measured.

All animals in both procedures experienced 1) initial dose-effect determinations of cocaine or d-amphetamine, 2) a period of repeated administration of cocaine or d-amphetamine, 3) dose-effect redetenminations of cocaine or d-amphetamine. These procedures were carried out in the following manner:

1) Initial Dose-Effect Determinations. Initially all animals were injected (i.p.) 15 minutes before the session with 1 ml/kg 0.9% saline. When behavior had stabilized (less than 10% variation in mean intake or number of food pellets delivered for at least 3 consecutive days) a dose of drug was substituted for the injection of saline before the session. Doses of cocaine (4.0, 8.0, 16 and 32 mg/kg) or d-amphetamine (0.5, 1.0, 2.0, and 4.0 mg/kg) were administered once each in an ascending order in the milk drinking procedure. Doses of cocaine (4.0, 8.0, 16, and 32 mg/kg) were administered once in an ascending and once in a descending order to rats responding in the operant procedure. d-Amphetamine was not tested in the operant procedure.

2) Repeated Administration. A dose of cocaine or d-amphetamine that reduced milk intake to at least 50% of levels observed following saline injections was chosen for daily administration to rats in the milk drinking procedure. Similarly, a dose of cocaine that decreased number of reinforcements to less than 50% of that observed following saline injections was chosen for daily administration to the rats trained in the operant procedure. Daily drug administration continued for between 75-110 days. When milk intake reached a new stable level, dose-effect redeterminations were begun in the milk intake procedure. In the operant procedure, dose-effect redeterminations were begun on day 61 of repeated administration.

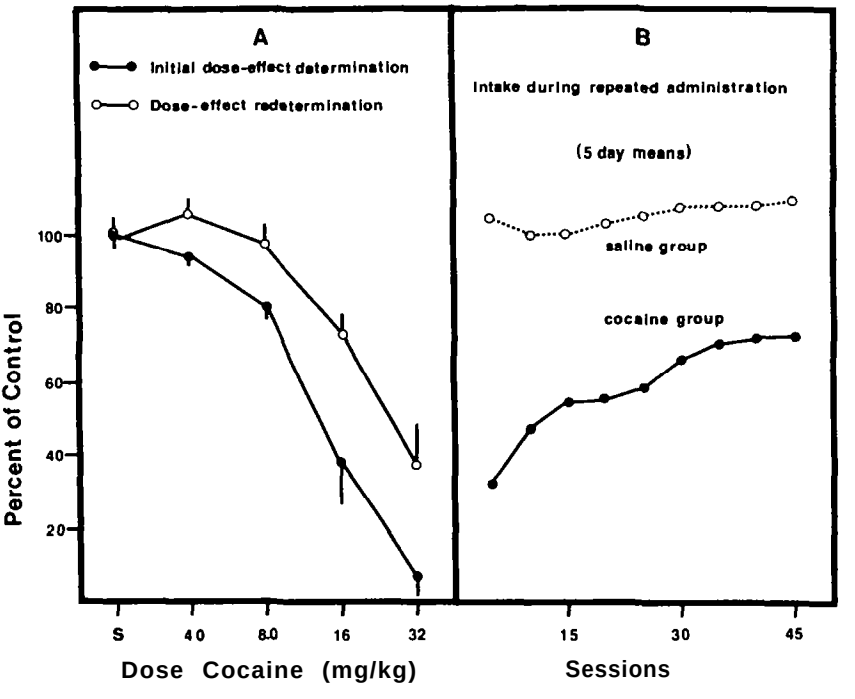
3) Dose-Effect Redeterminations. Dose-effect redeterminations were conducted in the following manner. On selected days, test doses of saline, cocaine, or d-amphetamine were substituted for the usual drug or saline injection. Test doses were given in an ascending order in the milk drinking procedure and in an ascending and descending order in the operant procedure. There were at

least 3 sessions between test doses of drug in which the animal was injected with the usual daily injection. Thus, it Was possible to measure the effect of each dose of both drugs during the period of repeated administration of either drug.

RESULTS

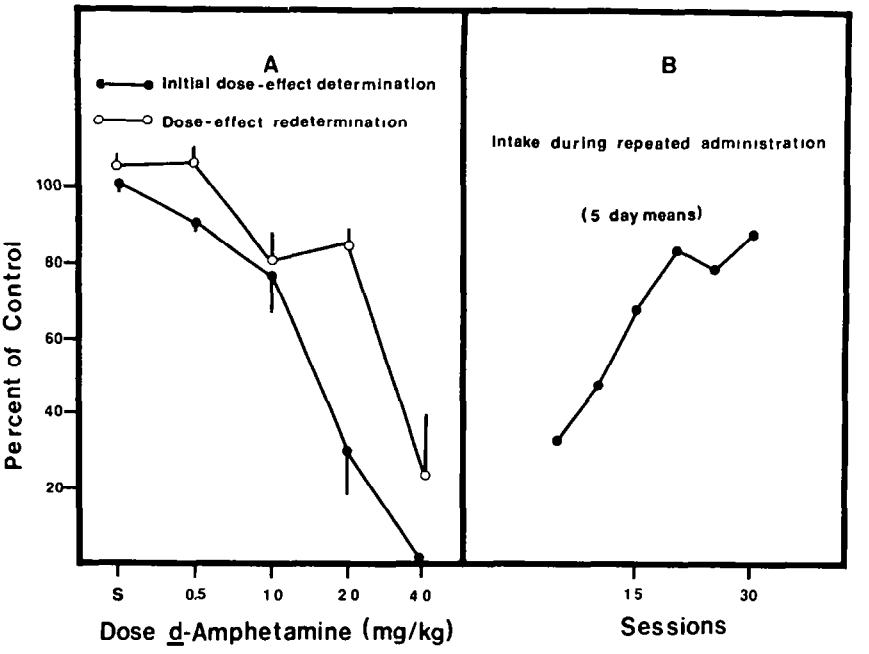
Milk Drinking Procedure. In the initial dose-effect determinations, cocaine and d-amphetamine produced dose-related decreases In milk intake [Figs, IA, 2A, 3A, & 5). When the two highest doses of cocaine (16 and 32 mg/kg) or d-amphetamine (2.0 and 4.0 mg/kg) were given, stereotyped behaviors including sniffing and head bobbing were observed.

FIGURE 1



Left Panel (A). Effects of injections of cocaine on mean milk intake of rate in Part 1, before (0-r) and during (0-0) a period of repeated daily injections of cocaine (16 mg/kg). Drug effects are expressed as percent of non-drug control levels. Vertical lines represent the standard error of the mean. The points above S represent the effects of saline injection on intake. Right Panel (B). Effects of repeated administration of cocaine (16 mg/kg) or saline on mean milk intake. Drug effects on milk intake are *expressed* as *percent of non-drug control Levels. Each data point is the mean of* 5 consecutive sessions.

FIGURE 2

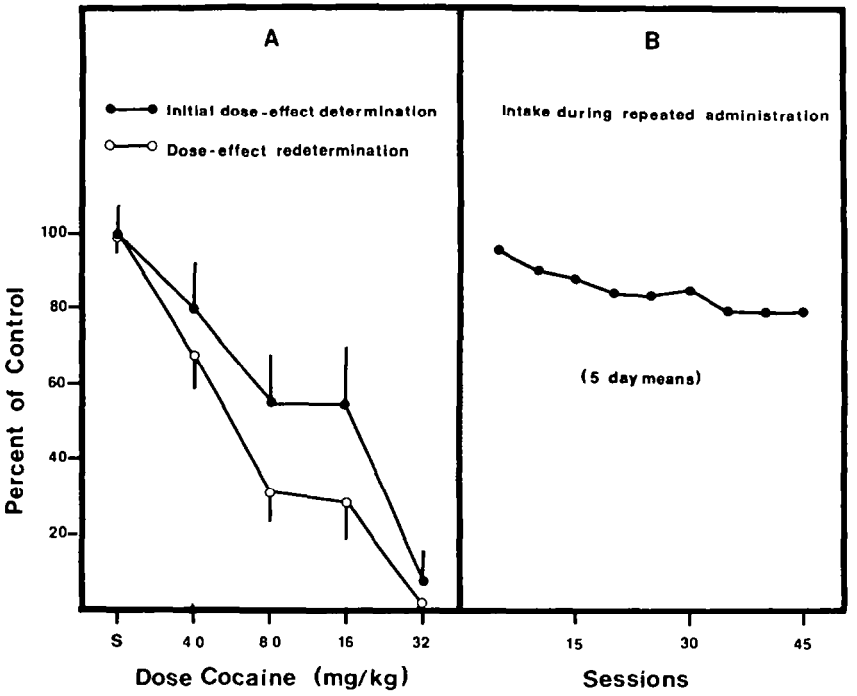


Left Panel (A). The effects of d-amphetamine on the mean milk intake of the rate in Group B of Experiment II before (0-O) and during (O-O) a period of repeated administration of d-amphetamine (2.0) mg/kg) . Drug effects are expressed as percent of non-drug control levels. The points above S represent the effects of saline injections on intake. vertical lines represent the standard error of the mean.
Right Panel (B). Effects of repeated administration of d-amphetamine (2.0 mg/kg) on the mean milk intake of the rats in Group B from day 1 to day 30. Each point is the mean of 5 consecutive seesions.

The dose of 16 mg/kg cocaine initially reduced milk intake to about 30% of control levels and was chosen for daily administration. During the first 45 days of repeated cocaine administration milk intake increased from 30% of control levels to about 70% of control levels. Milk intake of rats receiving saline daily remained at about 100% of control levels throughout this period (Fig. 1B). In a group of animals receiving cocaine after the session during this period, milk intake decreased to about 80% of original control levels (Fig. 3B).

The dose of 2.0 mg/kg d-amphetamine reduced intake initially to about 30% of control levels. Intake increased during the first 30 days of repeated administration to about 85% of original control levels (Fig. 2B).

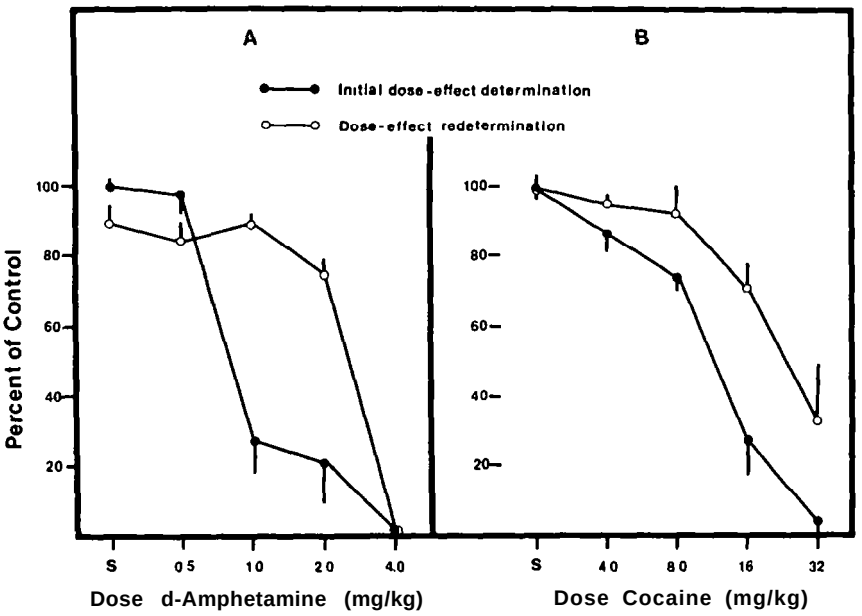
FIGURE 3



Left Panel (A) ; Effects of cocaine on mean milk intake before (0-0) and during (0-0) a period of daily injections of cocaine (16 mg/kg) given after the session. Milk intake is expressed as percent of control levels. The points above S represent the effects of saline injections on intake. Vertical lines represent the standard error of the mean.
Right Panel (B). The effects of repeated administration of cocaine (16 mg/kg) on milk intake of the rats in Part 2. Injections of cocaine were given immediately after the 15 minute access period. Intake is expressed as percent of control levels.

After tolerance had developed to the disruptive effects of 16 mg/kg cocaine, the dose-effect function of cocaine was shifted to the right in animals receiving cocaine daily before the session (Fig. l.A) (F=16.6, d.f. 3,48, p<.00l) . Furthermore, when the dose-effect function of cocaine on milk intake was redetermined in rats receiving d-amphetamine before the session, it was similarly shifted to the right (Fig. 4B) (F=13.2, d.f.=1, 40, p<.00l). In contrast, when cocaine dose-effect function was redetermined in rats receiving cocaine daily after the session, a shift to the left in the function was observed (Fig. 3A) (F=4,97, d.f.=1,40 P<.05).

FIGURE 4



Left Panel (A). Effects of d-amphetamine (0.5 - 4.0 mg/kg) on milk intake in Group-A before (0-0) and during (0-O) a period of daily injections of cocaine (16 mg/kg). Drug effects on intake are expressed as percent of non-Drug control levels. The points above S represent the effects of saline injections on intake. Vertical lines represent the standard error of the mean. Right Panel (B). Effects of cocaine on milk intake of the rate in Group B before (0-0) and during (0--0) a period of daily injections of d-amphetamine (2.0 mg/kg). Drug effects are expressed as in the left panel (above).

Following the redetermination of the cocaine dose-effect function in animals receiving pre-session cocaine, all injections were stopped. On selected days (4 and 10) after termination of injections, the effect of 16 mg/kg on intake was again determined. On day 4, the animals were still tolerant to the effects of this dose on intake. However, on day 10 the effect of 16 mg/kg on intake was the same as that observed in the initial dose-effect function, indicating that the animals were no longer tolerant (Table 1).

TABLE 1

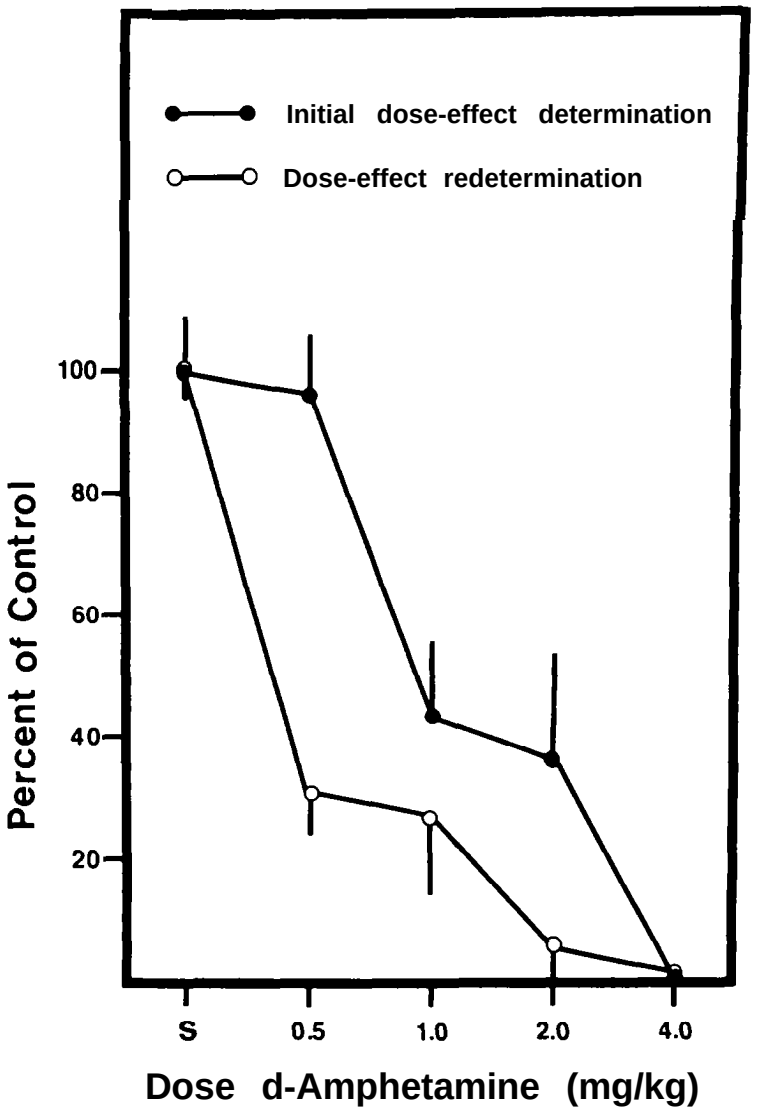
THE EFFECTS OF 16 MG/KG COCAINE ON MILK INTAKE BEFORE, DURING, AND AFTER THE DAILY COCAINE REGIMEN

Condition	Intake (ml)
Initial dose-effect determination	13.6 ± 4.61 (S.E.M.)
Dose-effect redetermination	25.6 ± 1.96 (S.E.M.)
4 days after daily cocaine administration	27.3 ± 3.13 (S.E.M.)
10 days after daily cocaine	14.3 ± 5.4 (S.E.M.)

After tolerance had developed to the effects of 2.0 mg/kg d-amphetamine on milk intake, the dose-effect function of d-amphetamine was shifted to the right in animals receiving daily d-amphetamine before the session (Fig. 2A) ($F=18.7$, d.f.=1, 40, $p<00l$). When the dose-effect function of d-amphetamine on intake was redetermined in animals receiving cocaine daily before the session, a similar shift in the d-amphetamine dose-effect function was observed (Fig. 4A) ($F=35$,-d.f.=3,48, $p<.001$). On the other hand, when the d-amphetamine dose-effect function was redetermined in animals receiving cocaine after their daily session, a shift to the left in the function was observed (Fig. 5) ($F=30.9$, d.f.=1,40, $p<.00l$). Thus, whether tolerance or supersensitivity developed to the effects of cocaine on milk drinking was dependent on the relationship of the drug administration to the period of access to milk.

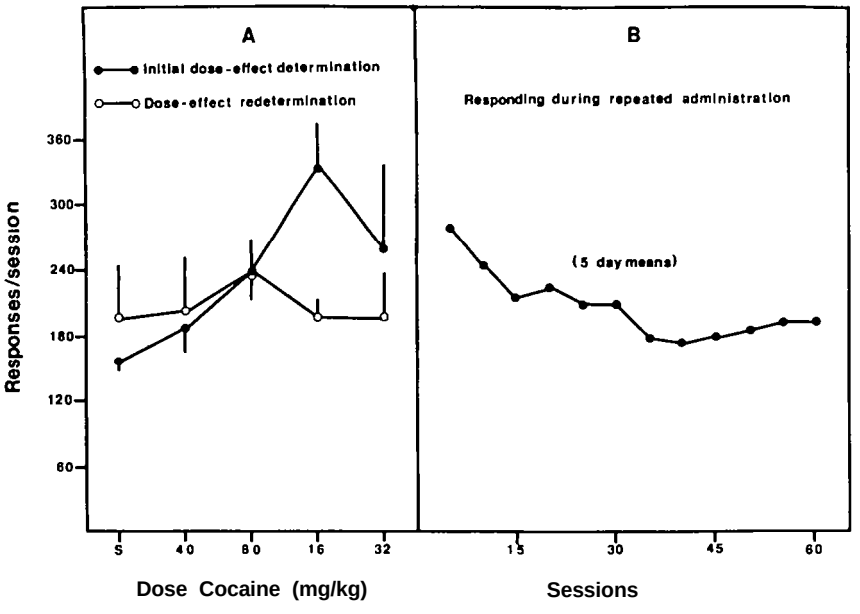
Operant Procedure. In the initial dose-effect determinations single injections of cocaine resulted in a dose-related increase in responses per session (Fig. 6A) and a decrease in the number of reinforcements received (Fig. 7A). The IRT distribution (Fig. 8A) was shifted to the left with increasing dose of cocaine. A dose of 16 mg/kg was chosen for repeated administration since it decreased reinforcements by at least 50% in all cases.

FIGURE 5



Effects of d-amphetamine on mean milk intake before (0-0) and during (0-O) the period of repeated daily injection of cocaine (16 mg/kg). Injections of cocaine were given immediately after the session. Milk intake is expressed as percent of control levels of intake.

FIGURE 6

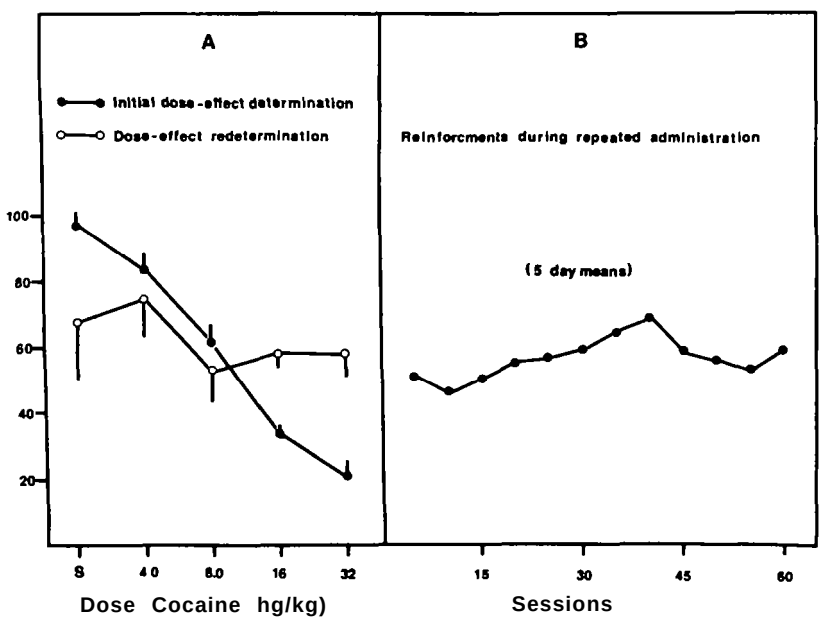


Left Panel (A). Effects of single injections of cocaine on the mean numver of responses/session for the rats (N=4) responding on a DRL 20" schedule for food before (0-O) and during (0-O) a period of daily injection of cocaine (16 mg/kg). The points above S represent the effects of saline injection on responding. Vertical lines represent the standard error of the mean. Right Panel (B). Effects of repeated administration of cocaine (16 mg/kg) on responses/session for the rats (N==4) responding on a DRL 20" schedule for food during the period of repeated administration. Each point is the mean of 5 consecutive sessions.

During the first 60 days of repeated administration, responses per session decreased from 278.1 (+ 25.2 s.e.m.) for days l-5 to 195 (+ 12.6 s.e.m.) for days 55-60-(Fig. 6B). Furthermore, in the initial dose-effect determinations, responses per session following 16 mg/kg averaged 336 (+ 34 s.e.m.) while an average of 195 (+ 18.9 s.e.m.) responses per session was observed following this dose on days 59 and 60. The decrease in responding was maximal at about day 40 and relatively stable thereafter. The change in mean number of reinforcements per session over the first 60 days

of daily cocaine injections is shown in Fig. 8B. During this period, reinforcements per session increased from 51.1 (+ 6.0 s.e.m.) for days 1-5 to 59 (+ 5.4 s.e.m.) for days 55-60. Reinforcements per session for days l-5 is high since this point is an average. Most importantly, in the initial dose-effect determinations, reinforcements per session averaged 32.5 (+ 2.5 s.e.m.) while an average of 57 (+ 9.4 s.e.m.) food pellets was delivered for sessions 59 and-60. The increase in number of reinforcements per session was maximal at about day 40 and relatively stable thereafter,

FIGURE 7



Left Panel (A). Effects of single injections of cocaine on the mean number of reinforcements per session for the rats (N=4) responding on a DRL 20" schedule for food before (0-0) and during (0-O) a period of daily injection of cocaine (16 mg/kg). The points above S represent the effects of saline injection on number of reinforcements. Vertical tines represent the standard error of the mean.

Right Panel (B). Effects of repeated administration of cocaine (16 mg/kg) on number of reinforcements per session for rats (N-4) responding on a DRL 20" schedule for food during the period of repeated administration. Each point in the mean of 5 coneecutive sessions.

FIGURE 8

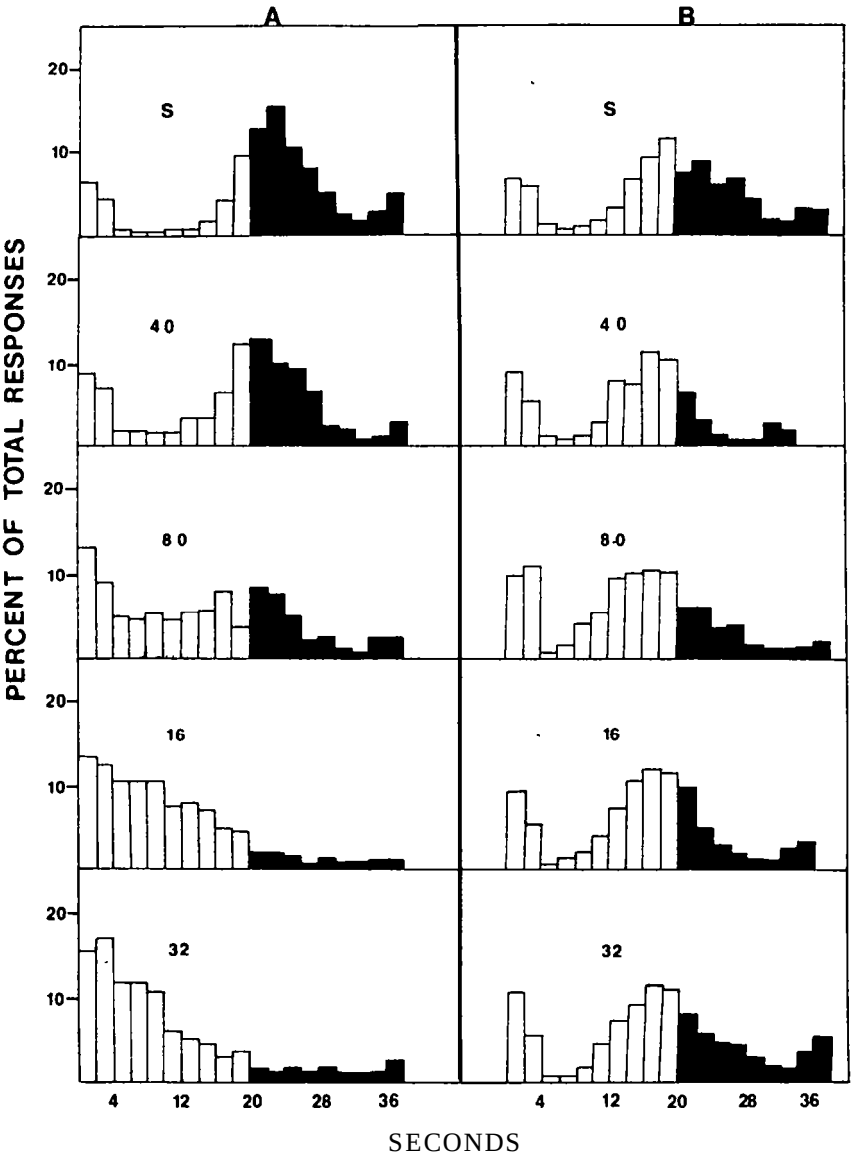


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Figure 8

Left Panel (A). Effects of single injections of cocaine on the IRT distributions of the rata responding on a DRL 20" schedule for food before the repeated administration of cocaine (16 mg/kg). Each IRT histogram is divided into 2 second bins and contains the percent of the total responses per session that occurred in that bin. Each histogram is the mean of two determinations of the effects of each drug dose in all 4 rats. The IRT distribution following saline injection (S) is the mean of 10 control sessions. Doses of cocaine (mg/kg) are indicated on the left side of each bin. Solid bins are 20" and represent reinforced IRT's.
Right Panel (B). Effects of single injections of cocaine on the IRT distributions of the rats responding on a DRL 20" schedule for food during the period of repeated administration of cocaine (26 mg/kg). Histograms are as described above. Each is the mean of two redeterminations of the effects of each dose in all 4 rats.

Figure 6A shows the effects of single injections of cocaine (4.0 - 32 mg/kg) on number of responses per session during the redetermination of the dose-effect function. There was no effect of dose of cocaine on number of responses per session in the redetermination. Relative to the initial dose-effect function, a two-way analysis of variance revealed a significant interaction between dose and daily treatment indicating non-parallel dose-effect curves before and during daily administration. The decrease in responses per session was significant ($p<.0l$) at the 16 mg/kg dose. Changes observed at 4.0, 8.0, and 32 mg/kg were not significant due to high variability in the effects of these doses in different rats during the redetermination.

A one-way analysis of variance revealed no effect of dose of cocaine on the number of reinforcements per session in the redetermination (Fig. 7A). Relative to the initial dose-effect function, a two-way analysis of variance revealed a significant effect of daily treatment and a significant interaction between daily treatment and dose of cocaine ($F=4.44$, d.f.=1,56, p (.05; $F=4.87$, d.f.= 3,56, $p<.01$ respectively) indicating non-parallel shifts in the dose-effect function during the period of repeated administration. Further analysis revealed no change in the number of reinforcements per session following injections of saline, 4.0 and 8.0 mg/kg. `However, a significantly greater number of reinforcements was delivered at 16 and 32 mg/kg during the dose-effect redeterminations, ($p<.01$ in both cases).

The average IRT distributions for the group during the redetermination of the dose-effect function are shown in Fig. 8. Consistent with the response and reinforcement data presented above, there is little noticeable effect of dose of cocaine on the IRT distribution during the redetermination. Relative to the initial dose-effect data, the IRT's following saline injection were shifted slightly to the left as were IRT's following 4.0 mg/kg. Following 8.0 mg/kg, there is some shift in the IRT's toward the 20-22 second bin, but the percent of IRT's that were reinforced remained the same as was observed initially. Following 16 and 32 mg/kg,

there was a distinct shift in the IBT distribution to the right relative to those observed initially, indicating a decrease in response bursting and a higher percentage of reinforced IRT's.

SUMMARY

The experiments reported here demonstrated that single injections of cocaine caused a dose-related disruption of both milk intake and scheduled controlled behavior of rats. Cocaine increased the low response rates of animals responding on a DRL 20" schedule. In this regard, cocaine is similar to all other psychomotor stimulant drugs (Sanger and Blackman 1976). Furthermore, high doses of the drug (16 - 32 mg/kg) produced stereotyped behaviors that were similar to those reported for other psychomotor stimulant drugs (Ellinwood and Balster 1974; Randrup and Munkvad 1970).

Attenuation of the effects of a single dose of a drug and a shift to the right in the dose-effect function during repeated administration are evidence for tolerance to a drug. Pre-session administration of an intermediate dose of cocaine on a daily basis to animals allowed to drink milk resulted in the development of tolerance to the disruptive effects of cocaine on milk intake. This tolerance was lost, however, by the tenth day following the cessation of daily administration of cocaine. In contrast, when the same dose of cocaine was administered post-session to animals allowed to drink milk, increased sensitivity to the disruptive effects of cocaine was subsequently observed. This increased sensitivity was shown as well to d-amphetamine. In addition, cross-tolerance was clearly observed between cocaine and d-amphetamine, suggesting a common mechanism of tolerance to both drugs. The repeated administration of cocaine to animals trained to lever press on schedules of reinforcement generating low response rates resulted in tolerance to the behavioral effects of cocaine that result in a decreased rate of reinforcement.

Thus, tolerance develops to the effects of cocaine that disrupt milk intake and DRL 20" performance. These data are consistent with the hypothesis of Schuster et al. (1966) which states that behavioral tolerance will develop to the effects of a drug that interfere with the ability of the organism to meet the contingencies of reinforcement. In this respect, cocaine is similar to many other drugs for which behavioral tolerance has been demonstrated. In view of the numerous reports of increased sensitivity to the behavioral effects of cocaine (Downs and Eddy 1932; Stripling and Ellinwood 1977; Tatum and Seevers 1929) it is significant that this effect was only observed when cocaine administration did not decrease reinforcement density. It is possible that increased sensitivity to cocaine is the major pharmacological effect of repeated administration but that environmental influences (e.g., reinforcement loss) are capable of activating compensatory mechanisms resulting in the development of tolerance.

ACKNOWLEDGMENT

This research was supported in part by grants from the National Institute on Drug Abuse DA-00250-06, DA-00085-06 and DA-00024-07, Charles R. Schuster, Principal Investigator, and from the National Institute on Mental Health PHS l-T32, MH-14274.

REFERENCES

Byck, R. The Cocaine Papers (by Sigmund Freud). New York Stonehill Publishing Co., 1974.

Downs, A.W., and Eddy, N.B. The effect of repeated doses of cocaine in the rat. J. Pharma. Exp. Ther ., 46:199-200, 1932.

Ellinwood, E.H., and Balster, R.A. Rating the behavioral effects of amphetamine. Eur. J. Pharm., 28:35-41, 1974.

Jaffe, J. Drug addiction and drug abuse. In: Goodman, L.S.,a.nd Gilman, A., eds. The Pharmacological Basis of Therapeutics. New York: McMillan Co., 1975.

Kosman, M.E., and Unna, K.R. Effects of chronic administration of amphetamine and other stimulants on behavior. Clin. Pharma. Ther., 9:240-254, 1968.

Post, R., Kopanda, R.T., and Black, K.E. Progressive effects of cocaine on behavior and central amine metabolism in rhesus monkeys: Relationship to kindling and psychosis. Biol. Psychiat., 11:403-417, 1976.

Post, R.M. Progressive changes in behavior and seizures following chronic cocaine administration: Relationship to kindling and psychosis. In: Ellinwood, E.H. and Kilbey, M.M., eds. Cocaine and Other Stimulants. New York: Plenum Press, 1977. pp. 353-372.

Randrup, A., and Munkvad, I. Biochemical, anatomical and psychological investigations of stereotyped behavior induced by amphetamines. In: Costa, E. and Garatini, S., eds. Amphetamines and Related Compounds. New York: Raven Press, 1970. pp. 695-714

Sanger, D.J., and Blackman, D.E. Rate dependent effects of drugs: A review of the literature. Pharmacol. Biochem. Behav., 4:73-83, 1976.

Schuster, C.R., Dockens, W.S., and Woods, J.H. Behavioral variables affecting the development of amphetamine tolerance. Psychopharmacologia, 9:170-182, 1966.

Stripling, J.S.. and Ellinwood, E.H. Sensitization to cocaine following chronic administration in the rat. In: Ellinwood, E.H. and Kilbey, M.M., eds. Cocaine and Other Stimulants. New York: Plenum Press, 1977. pp. 327-352.

Tatum, A.L., and Seevers, M.H. Experimental cocaine addiction. J. Pharma. Exp. Ther., 36:401-410, 1929.

AUTHORS

William L. Woolverton, Ph.D., Department of Pharmacological and Physiological Sciences, University of Chicago, and
Charles R. Schuster, Ph.D., Professor of Psychiatry, University of Chicago, Chicago, Illinois 60637

Behavioral and Pharmacological Components of Phenobarbital Tolerance

Maisy Tang, Ph.D., and John L. Falk, Ph.D.

While the degree of tolerance development to barbiturates is not as great as to opioids, it is well documented (Kalant et al. 1971) and its physiological basis is a combination of both drug metabolic and central nervous changes (Goldstein, Aronow, and Kalman 1974). Tolerance can develop to the behavioral effects of a drug: as well as to its physiological effects. The development of behavioral tolerance to repeated drug administration could be due to progressive, general, physiological consequences of the drug regimen, or to a more specific development of behavioral changes that allow the organism to accommodate to the drugged condition. One method for distinguishing these possibilities is to compare the development of tolerance to repeated daily drug doses when they are given prior to sampling behavior versus after such sampling (Campbell and Seiden 1973; Carlton and Wolgin 1971; Chen 1968; LeBlanc et al. 1973, 1976). The present experiment used this method to evaluate the behavioral tolerance which develops to the repeated administration of phenobarbital. Both schedule-dependent and schedule-induced behaviors were examined to determine If these behaviors would be differentially sensitive either to the degree of behavioral tolerance developed, or to the dosing regimen in relation to the tolerance developed.

METHOD

Animals. Eight male, albino, Holtzman rats with an initial mean body weight of 369 g (range: 350-389 g) were used. Except during the dally 3-hr experimental session, all animals were housed individually in standard Acme stainless steel cages in a temperature-controlled room with a 12-hr light-dark illumination cycle (lights on 7 AM-7 PM). Water was continuously available in the home cage from calibrated Richter-type drinking tubes.

Experimental chamber. Individual chambers consisted of Plexiglas boxes (25.5 x 25.5 x 30.3 cm) with stainless steel rod floors. An

operant lever and a food-pellet magazine were mounted on one side of each box. On an adjacent side, a metal drinking spout attached to a calibrated water reservoir was available. Licks on the drinking spout were recorded with a drinkometer.

Drugs. Sodium phenobarbital was dissolved in isotonic saline (0.9% Naci). The vehicle solution was made from isotonic saline solution titrated with 0.1 N sodium hydroxide to match the pH of the sodium phenobarbital solution (pH 10.0). All doses were given subcutaneously into the loose sldn on the back.

Procedure. Animals were reduced to 80% of their free-feeding body weights and held at that level for the duration of the experiment by limiting food rations. They were trained to lever press on a fixed-ratio 1 schedule (FR 1) which delivered 45-mg Noyes food pellets and were then shifted to a fixed-interval one min (FI 1 min) schedule. A lever press delivered a pellet only after at least one min had elapsed since the last pellet delivery. All other lever presses were ineffective but were recorded. No programmed stimulus informed the animal when such one-min periods had elapsed. Animals were given 3-hr FT 1 min sessions every day and then returned to their cages and allowed a food ration supplement (Purina Laboratory chow, pelleted) sufficient to maintain them at 80% of their initial free-feeding weights. Number of lever presses, licks on the water spout, and pellets obtained were recorded both on counters and with cumulative recorders (Ralph Gerbrands Co.). The volume of water consumed during each session also was measured. When the values of the above measures became stable from session to session for individual animals, the effects of phenobarbital doses (20, 40 and 80 mg/kg, specified as the salt) given 15 min presession were studied. Each dose was given to each animal twice, first in an ascending and then in a descending order. At least 5 noninjection sessions separated drug-injection days. Two vehicle injections were given, one at the beginning and one at the end of the drug series. Seven days after the second vehicle injection, the animals were divided into two equal groups (N = 4). One group received daily phenobarbital injections of 80 mg/kg 15 min presession (Before Group), while the other group received the same dose 15 min postsession (After Group). These daily dosing regimens remained in effect for the duration of the experiment except on dose-effect redetermination days when animals from both groups received their particular dose 15 min presession. The dose-effect relation redetermination began on the fourteenth day of the chronic dosing regimen and subsequent doses in the redetermination series were at least 8 days apart. On inter-days, the group dosing regimens continued as previously described. The Before Group was given dose-effect relation redetermination doses in the order: 120, 160, 100 and 120 mg/kg; the order for the After Group was 120, 80, 100 and 120 mg/kg. A vehicle injection was administered to After Group animals 6 days after the last dose-effect determination dose. No corresponding vehicle injection was given to the Before Group as this would have constituted a withdrawal condition.

RESULTS

The initial dose-effect relations and their redeterminations are shown for both the Before and After Groups in Figure 1.

FIGURE 1

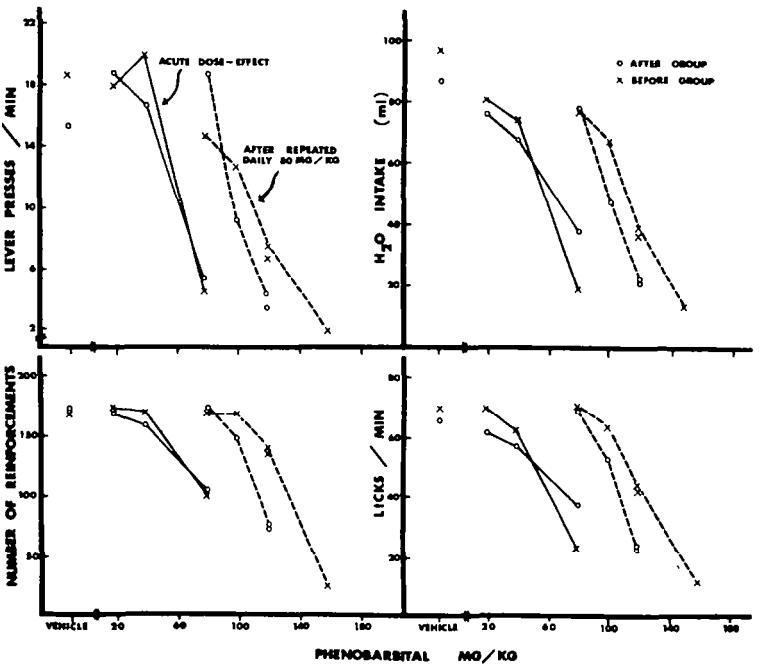

Fig. 1. Initial dose-effect relations for 2 groups (N = 4 each) for phenobarbital. (mean of an ascending and a descending dose order for all animals) shown as solid line functions, and mean dose-effect relation redeterminations following 13 days of daily 80 mg/kg doses given either presession (Before Group) or post-session (After Group).

The solid-line functions on the left side of each quadrant reveal that prior to exposure to the different repeated-dose regimens both groups responded in a similar fashion to phenobarbital doses on all measures. Relative to the mean vehicle-injection levels, phenobarbital doses had either no effect or a suppressive one on all measures in the initial dose-effect determination, except for lever-pressing rate which showed an enhanced rate at 20 mg/kg for one group and at 40 mg/kg for the other. In contrast to the other measures, water intake was decreased by the 20 mg/kg dose. Water

intake levels for both groups under day-to-day and vehicle-injection conditions were at polydipsic levels characteristic of schedules such as FI 1 min (Falk 1966; 1971).

Both groups developed tolerance to the 80 mg/kg repeated dose regimen, but the tolerance was not complete. Fig. 2 shows that only "number of reinforcements" (pellets earned) attained its previous level for both groups.

FIGURE 2

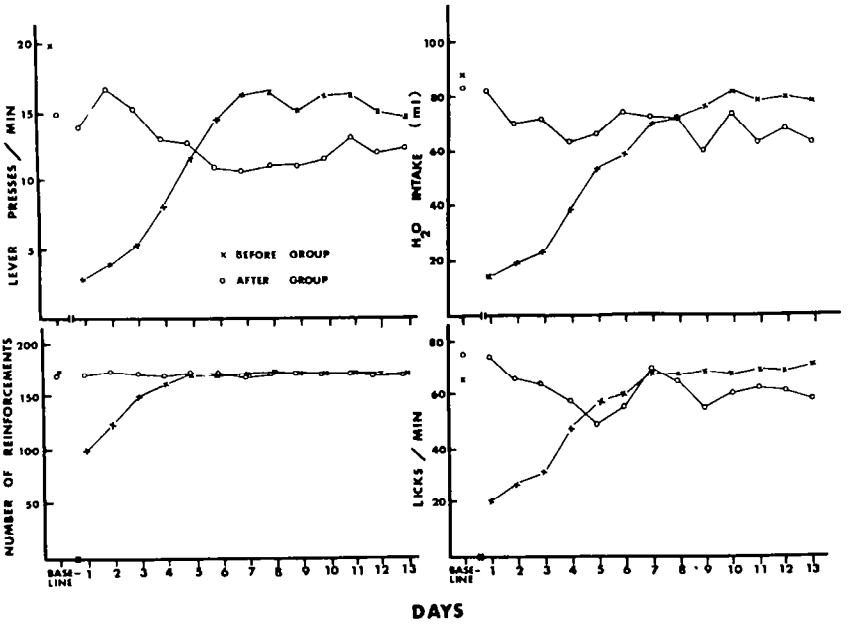

Fig. 2. Mean dally session measures for 2 groups (N = 4 each) given 80 mg/kg phenobarbital dally-injections either presession (Before Group) or postsession (After Group). Baseline = mean of 6 sessions preceding start of dally phenobarbital Injections.

The other measures remained below the former baseline level for both groups, except the "licks/min" measure for the Before Group. (Mean baseline values shown In Fig. 2 are the means of values for the sessions preceding the beginning of the repeated-dose regimen). The functions to the right in each quadrant of Fig. 1 (dashed lines) reveal that the Before Group had developed greater tolerance to phenobarbital than the After Group, as shown by the greater shift to the right of the Before Group's dose-effect relation re-

determination. Tolerance to repeated 80 mg/kg doses, while not complete for either group (Fig. 2), was equivalent for the two groups when the presession effect of this 80 mg/kg dose was compared (Fig. 1). However, when larger doses were explored, the greater tolerance of the Before Group, relative to the After Group, became evident as a greater shift to the right in the dose-effect relations. The reliability and lack of any serial-order effect in the redetermination relations is indicated by the replicability of the 120 mg/kg points, as this dose was the first and the last dose given in the series.

DISCUSSION

Both the Before and After repeated-dose regimens produced marked tolerance to phenobarbital. However, tolerance was incomplete, as indicated by the incomplete return 'co previous baseline levels of most of the behavioral indices (cf. Fig. 2). Suppressive effects of phenobarbital on running in rats revealed a similar failure to develop complete tolerance under repeated dosing (Schmidt

Both schedule-dependent (lever pressing) and schedule-induced (polydipsia) behaviors developed tolerance to repeated phenobarbital dosing (cf. Fig. 1). Moreover, both kinds of behavior were affected in a similar way by the differential effect of the two dose regimens. The enhanced FI lever-pressing rate produced by low doses of phenobarbital agrees with similar findings in the pigeon given low doses of barbiturates under FI schedules (Dews 1955, 1964; Rutledge and Kelleher 1965). Low to intermediate doses of barbiturates increase water intake in the rat (Jones 1943; O'Kelly and Weiss 1955; Schmidt 1958), but decrease it under schedule-induction conditions (Falk 1964). The present study confirms this latter result.

LeBlanc and his associates (LeBlanc et al. 1973, 1976) studied the acquisition of tolerance to ethanol using a Before and an After Group design as well. They concluded that both groups developed the same level of tolerance and only differed as to the rate at which the tolerance developed. In their experimental designs, the repeated-maintenance and testing doses were at the same level. We too would have come to the same conclusion if our testing (redetermination) doses had been limited to the maintenance dose (80 mg/kg). In Fig. 1 it is evident that the groups did not differ at 80 mg/kg in the redetermination phase; both showed a similar tolerance. But the larger doses revealed the different tolerance levels of the groups. Other investigators have used the Before versus After Group design to explore tolerance to d-amphetamine (Campbell and Seiden 1973; Carlton and Wolgin 1971). It was concluded that the After Groups showed little evidence of tolerance development. But again a single level of the test dose was administered rather than a determination and redetermination of dose-effect relations. Such a procedure might have unmasked some level of pharmacological tolerance development in the After Groups.

In conclusion, while the major portion of tolerance development to phenobarbital in this study was explicable in terms of pharmacological exposure to the drug, nevertheless the greater shift to the right of the Before Group's dose-effect redetermination functions revealed an additional behavioral tolerance component.

ACKNOWLEDGMENT

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REFERENCES

Campbell, J.C. and Selden, L.S. Performance influence on the development of tolerance to amphetamine. Pharmac. Biochem. Behav., 1.: 703-708, 1973.

Carlton, P.L. and Wolgin, D.L. Contingent tolerance to the anorexigenic effects of amphetamine. Physiol. Behav., 7:221-223, 1971.

Chen, C. S. A study of the alcohol-tolerance effect and an lntroduction of a new behavioural technique. *Psychopharmcologia,* 12: 433-440, 1968.

Dews, P.B. Studies on behavior. I. Differential sensitivity to pentobarbital of pecking performance In pigeons depending on the schedule of reward. *J. Pharmacol. Exp. Ther.,* 113:393-401, 1955.

Dews, P.B. A behavioral effect of amobarbital. *Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol.,* 248:296-307, 1964.

Falk, J.L. Studies on schedule-induced polydipsia. In; Wayner, M.J. ed. *Thirst: Proceedings of the First International Symposium on Thirst in the Regulation of Body Water.* 'New York: Pergamon Press, 1964. pp. 95-116.

Falk, J.L. Schedule-induced polydipsla as a function of fixed interval length. *J. exp. Analysis Behav.,* 9:37-39, 1966.

Falk, J.L. The nature and determinants of adjunctive behavior. *Physiol. Behav.,* 6:577-588, 1971.

Goldstein, A., Aronow, L. and Kalman, S.M. Principles of Drug *Action: The Basis of Pharmacology.* 2nd ed. New York: John Wiley & sons, 1974. pp. 569ff.

Jones, M.R. The effect of phenobarbital on food and water intake, activity level and weight gain in the white rat. *J. Comp. Psychol.,* 35:1-10, 1943.

Kalant, H., LeBlanc, A.E. and Gibbins, R.J. Tolerance to, and dependence on, some non-opiate psychotropic drugs. *Pharmacol. Rev.,* 23:135-191, 1971.

LeBlanc, A.E., Gibbins, R.J. and Kalant, H. Behavioral augmentation of tolerance to ethanol *In* the rat. *Psychopharmacologia,* 30: 117-122, 1973,

LeBlanc, A.E., Kalant, H. end Gibbins, R.J. Acquisition and loss of behaviorally augmented tolerance to ethanol in the rat. Psychopharmacology,48: 153-158, 1976.

O'Kelly, L.I. and Weiss, H.H. The effects of ether and a barbiturate on water regulation in the rat. *J. Comp. Physiol. Psychol.,* 48:123-125, 1955.

Rutledge, C.O. and Kelleher, R.T. Interactions between the effects of methsaphetamine and pentobarbital on operant behavior in the pigeon. *Psychopharmacologia,* 7:400-408, 1965.

Schmidt, Jr., H. Pentobarbital facilitation of water ingestion in the albino rat. *J. Comp. Physiol. Psychol.,* 51:26-28, 1958.

Schmidt, Jr., H., Summe, J.P., and Coby, W.F. Phenobarbital withdrawal end behavioral disruption in the rat. *Physiol. Behav.,* 5: 1473-1479, 1970.

AUTHORS

Maisy Tang, Ph.D., and John L. Falk, Ph.D., Department of Psychology, Rutgers University, New Brunswick, New Jersey 08903

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