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## Fixed-Ratio Size as a Determinant of the Development of Tolerance to Morphine

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**FIXED-RATIO SIZE AS A DETERMINANT OF THE DEVELOPMENT  
OF TOLERANCE TO MORPHINE**

by

**Mark J. Nickel**

A Thesis  
Submitted to the  
Faculty of The Graduate College  
in partial fulfillment of the  
requirements for the  
Degree of Master of Arts  
Department of Psychology

**Western Michigan University  
Kalamazoo, Michigan  
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# **FIXED-RATIO SIZE AS A DETERMINANT OF THE DEVELOPMENT OF TOLERANCE TO MORPHINE**

**Mark J. Nickel, M.A.**

**Western Michigan University, 1992**

The acute and chronic effects of morphine were examined in pigeons exposed to a multiple schedule with fixed ratio 5, 25, and 125 components. Acute exposure to morphine (0.56-10.0 mg/kg) resulted in rate reductions under each component when the dose was 1 mg/kg or higher. With chronic exposure to 5.6 mg/kg, tolerance to the rate-reducing effects of morphine was evident under each fixed ratio component. The development of tolerance was determined to some extent by fixed-ratio size, a result similar to earlier findings with cocaine.

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## INTRODUCTION

The effects of drugs on behavior are of great interest to humans. For many years, the medical model has provided the focus and orientation for pharmacological research. In medical pharmacology, mechanisms of drug action are identified via direct examination of *biochemical* processes such as absorption, distribution, biotransformation, and excretion (Poling, 1986). The type and concentration of drug administered constitutes the independent variable. The dependent variable is expressed in biochemical measures such as blood-drug concentration levels and drug metabolites.

More recently, however, pharmacology researchers have recognized that psychological variables influence dramatically the effect of drugs on behavior. With the introduction of operant conditioning techniques, which emphasize the environmental determinants of behavior (Skinner, 1953), psychology researchers began to play a more prominent role in experimental pharmacology. Behavioral pharmacology, an integration between operant psychology and medical pharmacology, examines how *behavioral* mechanisms of drug actions modulate behavior (Thompson & Boren, 1977). In other words, behavioral pharmacologists evaluate the extent to which *environmental* variables alter the behavioral effects produced by psychoactive agents.

Using the experimental methods of operant conditioning, behavioral pharmacologists investigate how behavioral factors such as stimulus variables, consequence variables, motivational variables, reinforcement schedule considerations, and sensation and perception processes alter drug actions during the acquisition and maintenance of a response (Thompson & Boren, 1977). Similar to traditional medical pharmacology, the drug type and concentration constitute the independent variable.

Unlike medical pharmacology, environmental conditions which generate behavior also function as independent variables. Observed changes in the response patterns, response rates or response accuracy represent the primary dependent variables. However, just as in medical pharmacology, it has become increasingly common to report behavioral measures as well as biochemical correlates.

The experiment depicted below provides an example of how the scope of pharmacological research has expanded since the inception of behavioral pharmacology. The study emphasizes how environmental variables modulate the behavioral effects produced by a stimulant, d-amphetamine.

Urbain, Poling, Millam, and Thompson (1978) demonstrated clearly that behavioral factors in the absence of drug administration can influence the behavioral change produced by a drug. The experimenters hypothesized that response rates in the absence of d-amphetamine administration would alter the behavioral effect produced by the d-amphetamine. Two groups of rats were trained to lever press for food reinforcement. Each group was exposed to a different schedule of food reinforcement. Group one was trained under a fixed-ratio (FR) schedule of food reinforcement. Group two was trained under an inter-response-time greater than  $t$  seconds ( $IRT > t$ ) schedule of food reinforcement. By arranging two different schedules of reinforcement, the experimenters generated high rates of responding for group one (FR) and low rates of responding for group two ( $IRT > t$ ).

During the drug evaluation stage of the experiment, both groups were placed on a common fixed-interval (FI) schedule of food reinforcement. Under a FI schedule, a response is reinforced only after a fixed amount of time has elapsed. The fixed-interval schedule of food reinforcement typically produces low rates of responding immediately after reinforcement delivery and moderate rates of responding before reinforcement delivery (Ferster & Skinner, 1957). Urbain et al. (1978) selected the fixed-interval

schedule because the FI schedule would not markedly influence the emergence of different response rates and response patterns than those patterns established during the training period.

Urbain et al. (1978) found that d-amphetamine administration produced different effects depending on the environmental conditions under which the groups were trained. d-Amphetamine administration *reduced* response rates in the subjects trained under the FR schedule but *increased* response rates of subjects trained under the IRT > t schedule. The experimenters concluded that the rate of behavior in the absence of d-amphetamine administration influenced the behavioral effects produced by the drug.

As the Urbain et al. (1978) study shows, environmental variables can influence the effects that drugs have on behavior. Pharmacology researchers, as a whole, needed to consider more carefully psychological and environmental influences of behavior rather than focus solely on biochemical assays. The introduction of behavioral pharmacology expanded the focus and orientation of pharmacology research to include areas such as reinforcement controlled behavior and the effects of drugs, punishment controlled behavior and the effects of drugs, avoidance controlled behavior and the effects of drugs, drug-induced stimulus control, drug self-administration, drug tolerance, and even behavioral toxicology (see Blackman & Sanger (1978) for a more comprehensive review). Stated more simply, the behavioral pharmacologist arranges variations of reinforcement, punishment, and avoidance schedules and determines the extent to which acute and chronic drug administration changes the acquisition (i.e., learning), maintenance, and/or extinction processes of the response in question.

The preponderance of behavioral pharmacology research comprises the analysis of acute drug effects on a particular behavior or response pattern (Schuster & Johanson, 1981). By arranging a particular set of reinforcement (or punishment)

contingencies, a baseline pattern of responding is generated against which acute drug administration can be introduced. Acute drug administration refers to a drug regimen wherein test doses are widely spaced (Poling, 1986). Acute drug administration procedures minimize the influence of prior drug experience while allowing the investigator to complete procedural replications on the same subject. One subject can be exposed to a range of drug dose levels.

Drugs often produce different effects at different dose levels. A fundamental principle in pharmacology states that the magnitude of the drug effect is related in an orderly way to the quantity of the drug administered (Poling, 1986). Generally, a low dose produces a small effect and a high dose produces a large effect. A dose-response curve can be generated by plotting the dependent variable (usually a response measure per unit time) on the ordinate and the drug dose levels (usually expressed in log units) on the abscissa (Hamilton & Timmons, 1990). Given the number and parameters of environmental variables to investigate, it is not surprising that behavioral pharmacologists have concerned themselves mainly with the analysis of acute drug effects.

More recently, however, behavioral pharmacologists have broadened their research scope to include the analysis of chronic drug effects. A chronic drug regimen refers to repeated administration of a particular drug dose (Poling, 1986). The most common effect produced by repeated administration of a drug is *tolerance*.

Tolerance refers to an organism's decreased sensitivity to the actions of a drug due to the organism's experience with the drug (Corfield-Sumner & Stolerman, 1978). Tolerance is evident when (a) the subject is exposed repeatedly to the same drug dose and the drug produces less behavioral impairment upon each exposure to the drug or (b) when a subject is exposed repeatedly to the same drug dose and a higher dose is necessary to produce the same level of behavioral impairment. Tolerance, formally

depicted in a figure, can be viewed as a right-ward shift in the chronic dose-response curve as compared to the acute dose-response curve (Thompson & Boren, 1977).

After demonstrating the development of tolerance to a psychoactive agent, the mechanisms responsible for the organism's decreased sensitivity to drug actions should be examined. Here again, one can draw a distinction between the approach used by medical pharmacologists and the approach used by behavioral pharmacologists.

Medical pharmacologists typically examine the mechanisms of drug tolerance as they relate to dispositional factors. Alterations in the organism's absorption, distribution, biotransformation, and excretion processes are referred to as *dispositional* tolerance. For example, repeated administration of amphetamine produces suppression of food intake. The absence of food results in an increase of urinary pH. The more alkaline urinary pH decreases the efficacy of the drug reabsorption process in the kidney (Kuhn & Schanberg, 1978). Given a less efficient absorption process, a higher drug concentration is required to produce the same biological effects.

Biochemical explanations of tolerance provided by the medical pharmacologist are necessarily reductionistic and should not maintain an existence independent of the actual behavior generated. Behavioral pharmacologists emphasize how environmental determinants influence the development of tolerance. In fact, behavioral pharmacologists stress the development of *functional or behavioral* tolerance to a drug. Schuster and Johanson (1981) refer to the term functional tolerance as follows:

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 the instances where tolerance cannot be explained on the basis of the drug's altered disposition. (p. 64)

According to Poling (1986), behavioral tolerance refers to an organism's decreased responsiveness to drug effects due to the organism emitting the response in question during the drug state. Drug exposure is a necessary but not sufficient

condition for the development of behavioral tolerance.

Conceptually, dispositional mechanisms of drug tolerance do not explain adequately the behavioral differences observed in non-tolerant and tolerant subjects when equivalent drug concentrations are present within the respective target organs of both non-tolerant and tolerant subjects. Clearly, Schuster and Johanson (1981), as well as Poling (1986), espoused that environmental variables can modulate the development of drug tolerance. The remainder of the introduction addresses more specifically the experimental literature related to behavioral mechanisms of drug tolerance.

The evaluation of chronic effects of drugs is important for many reasons: (a) drug dependence and drug abuse often are associated with repeated drug administration (Wikler, 1973); (b) drug therapy routinely involves chronic administration of a psychoactive agent; (c) chronic drug therapy may produce undesirable secondary effects such as the induction of certain forms of paranoid schizophrenia (Kokkinidis & Anisman, 1981); and (d) drug tolerance can be conceptualized as an adaptive process and as such, "learning" within the organism's can be investigated at the level of biological systems (Le Blanc & Cappell, 1977).

The literature on behavioral tolerance to psychoactive agents in nonhumans is appreciable (see reviews by Kalant, LeBlanc, & Gibbins, 1971; Corfield-Sumner & Stoleran, 1978; Krasnegor, 1978; Goudie & Demellweek; 1986; Wolgin, 1989). Many environmental variables influence the development of tolerance to drugs (e.g., Corfield-Sumner & Stoleran, 1978; Siegel, 1978). When the response in question is an operant, the reinforcement contingencies under which behavior is maintained may be one such class of variables (Corfield-Sumner & Stoleran, 1978). The next section describes how behavioral pharmacologists identified and demonstrated behavioral tolerance by manipulating reinforcement contingencies.



In 1961, Schuster and Zimmerman proposed that environmental variables can influence the development of behavioral tolerance to psychoactive drugs. Schuster and Zimmerman (1961) examined reinforcement contingencies as a variable that influenced the development of drug tolerance. Their initial investigation contained two experiments.

In experiment one, rats were trained to lever press under a differential reinforcement of low rate of responding schedule of milk reinforcement (DRL 17.5-s). A DRL schedule engenders low rates of responding due to reinforcement being arranged only after a specified amount of time has passed between successive responses (Ferster & Skinner, 1957). In this experiment, a response was not followed by milk delivery unless the response was preceded by 17.5-s of not responding. After obtaining low, stable response rates, d-amphetamine was administered *chronically*.

Predictably, d-amphetamine, a stimulant, produced an increase in response rates. The increase in response rates resulted in a decrease in reinforcers earned under the DRL schedule of milk reinforcement. After repeated exposure to the drug, however, Schuster and Zimmerman observed a decrease in response rates and a concomitant increase in reinforcers earned. Repeated exposure to the same dose of d-amphetamine produced a diminution of effect. Tolerance to the behavioral effects of d-amphetamine had been demonstrated.

Experiment two constituted a systematic replication of experiment one with one exception: the experimenters, in addition to measuring response rates during the experimental session, measured general activity level of each rat outside of the experimental session. On alternate days, rats were placed either (a) in the experimental chamber and exposed to the DRL 17.5-s schedule of milk reinforcement or (b) in an activity apparatus. Baseline performance was recorded after which a chronic d-amphetamine regimen was initiated.

As in experiment one, under the DRL schedule of reinforcement, d-amphetamine produced an initial increase in response rates followed by a gradual return to baseline levels. The findings in general activity, however, did not reflect the pattern of responding under the DRL schedule. Similar to the response rates under the DRL, d-amphetamine produced initial increases in general activity level. However, general activity level remained high throughout the chronic drug regimen. Repeated exposure to d-amphetamine did not result in an attenuation of the behavioral effects produced by the drug. The same subject, under the same drug regimen, exhibited tolerance in the experimental session but not the activity session.

Although no biochemical data was collected, Schuster and Zimmerman (1961) suggested that dispositional mechanisms of drug tolerance did not explain adequately the behavioral differences observed in the experimental session and the activity session. Their logic was straight forward. The same dose of d-amphetamine was administered each day. Presumably equivalent drug concentrations were present within the blood plasma and respective target organs of the subjects during experimental and activity sessions. Schuster and Zimmerman speculated that the selective tolerance was somehow influenced by environmental factors.

Schuster and Zimmerman (1961) identified one critical difference between the experimental session and the activity session. In the experimental session, milk reinforcers were specifically arranged under a DRL schedule. In the activity session, however, no explicit reinforcement contingencies were programmed. Schuster and Zimmerman (1961) concluded that the initial loss of reinforcers under the DRL schedule of milk reinforcement modulated the development of tolerance to d-amphetamine. Tolerance developed to the rate increasing effects of d-amphetamine because the drug interfered with the organism's ability to meet the contingencies of reinforcement. Tolerance did not develop to the rate increasing effects of d-

amphetamine during the activity session because the drug-induced behavioral change did not interfere with the organism's ability to meet the contingencies of reinforcement: no explicit contingencies of reinforcement had been arranged.

Following Schuster's lead, behavioral pharmacologist attempted to more clearly rule out dispositional mechanisms of drug tolerance by demonstrating that behavioral variables affected the development of drug tolerance during the *same* session within the same subject. Multiple schedules of reinforcement (and punishment) became the tools by which researchers manipulated environmental conditions within the same experimental session.

A multiple schedule consists of two or more alternating, independent schedules or conditions of reinforcement, each of which is correlated with a particular stimulus condition. Each schedule and its associated stimulus defines a component of the multiple schedule (Ferster & Skinner, 1957). One could conceptualize loosely the Schuster and Zimmerman (1961) experiment as a multiple schedule in which twenty four hours separated the schedule components of DRL and activity sessions. A much more powerful demonstration of behavioral tolerance could be arranged by programming two distinct schedules of reinforcement within the same experimental session. Schuster, Dockens, and Woods (1966) used this logic and arranged a 2-ply multiple schedule of food reinforcement in experiment one of their study.

The multiple schedule comprised a fixed-interval 30 second (FI 30-s) and a differential reinforcement of low rate of behavior 30 second (DRL 30-s) schedule of reinforcement. Subjects were exposed to alternating 10 minute components of DRL and FI schedule components. After performance stabilized across both schedule components, an acute d-amphetamine dose-response curve was obtained. A chronic d-amphetamine regimen was then initiated. Similar to previous findings (Schuster & Zimmerman, 1961), chronic d-amphetamine administration produced increased

responding under both DRL and FI components. Responding under the DRL schedule gradually declined over the course of the chronic regimen. Tolerance developed to the rate increasing effects of d-amphetamine under the DRL component. d-Amphetamine also produced response increases in the FI component. However, the increased responding sustained throughout the chronic drug administration and tolerance did not develop under the FI component.

The increase in response rates resulted in reinforcement loss under the DRL schedule whereas increases in response rate under the FI schedule did not result in reinforcement loss. Tolerance developed under the DRL schedule but not under the FI schedule. Consistent with the earlier findings, reinforcement loss appeared to be affecting the development of tolerance. Schuster, Dockens, and Woods (1966) extended their investigation to determine the extent to which behavioral tolerance would develop when the effect produced by the drug enhanced the subject's ability to meet avoidance contingencies.

Chronic d-amphetamine administration produced uniform rate increases in subject's responding to avoid electrical shock. The rate increase produced a concomitant decrease in the number of shocks received. Tolerance, however, did not develop to d-amphetamine. Schuster, Dockens, and Woods (1966) concluded that tolerance did not develop under the shock avoidance contingencies because the d-amphetamine did not interfere with the subject's ability to meet the escape contingencies.

Schuster, Dockens, and Woods (1966) formally introduced what is referred to today as the *reinforcement loss hypothesis* :

Behavioral tolerance will develop in those aspect 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 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. (p. 181)

This is not to say that the reinforcement loss hypothesis constituted an adequate or complete explanation of the mechanisms responsible for the development of tolerance. Schuster et al. (1966) cautioned researchers that the purpose of their hypothesis was not to replace the traditional medical pharmacology treatment of drug tolerance. Rather, the reinforcement loss hypothesis was "put forth as an additional variable which may be operative in those behavioral situations where tolerance develops in a manner not predictable from the classical conceptions" (p. 181). In fact, recent research on the behavioral determinants of drug tolerance has called into question the adequacy of the reinforcement loss hypothesis. (See Corfield-Sumner & Stoleran (1978) for a more complete discussion.)

The research conducted by Schuster and associates provided the impetus for behavioral pharmacologists to study the extent to which behavioral factors influenced the development of drug tolerance. Research on environmental determinants of tolerance became increasingly important as drug use and abuse proliferated within society. Rather than investigate behavioral tolerance in its own right, researchers began to structure their investigations around highly abused drugs such as alcohol, cocaine and opioids. The initial step in such research programs is demonstrating the existence of tolerance under different environmental conditions.

Many environmental variables influence the development of tolerance to opioids and other drugs (e.g., Corfield-Sumner & Stoleran, 1978; Siegel, 1978). When the response in question is an operant, the schedule of reinforcement under which the behavior is maintained is one such class of variables (Corfield-Sumner & Stoleran, 1978). Numerous studies have demonstrated the development of tolerance to drugs under two-component multiple schedules of reinforcement (e.g., Thompson,

Trombley, Luke, & Lott, 1970; Heifetz & McMillan, 1971; Gilbert, 1974; Smith, 1979; and Woods & Carney, 1979). Of the aforementioned studies, only one evaluated the extent to which a three-component multiple schedule of reinforcement influenced the development of tolerance.

Hoffman, Branch, and Sizemore (1987) examined the effects of cocaine under a multiple schedule of food reinforcement with three fixed-ratio (FR) components. One fixed-ratio component was "small" (FR 5), one "medium" (FR 25), and one "large" (FR 50 or FR 125). With chronic exposure to 5.6 mg/kg cocaine, tolerance developed under the two smaller fixed-ratio components, but no tolerance or less tolerance occurred under the largest fixed-ratio component. These findings suggest that the amount of responding required for reinforcement may affect the development of tolerance to cocaine.

Whether fixed-ratio size affects the development of tolerance to other drugs is not known. To begin to address this question, the present experiment replicated methodologically and procedurally the research of Hoffman, Branch, and Sizemore (1987). A multiple schedule of food reinforcement with fixed-ratio 5, 25, and 125 components was used to examine the extent to which fixed-ratio size influenced the development of tolerance to morphine. In view of previous findings with cocaine and that the development of tolerance is a characteristic feature of all opioid drugs (Jaffee & Martin, 1985), it was hypothesized that tolerance to morphine would develop less readily under a fixed-ratio 125 schedule of food reinforcement than under either a fixed-ratio 5 or fixed-ratio 25 schedule of food reinforcement.

## METHODS

### Subjects

Four adult female White Carneau pigeons (numbered 2895, 775, 6048, and 6211) were maintained at 80% of their free-feeding weights. Except during experimental sessions, subjects were housed individually in a climate controlled colony with a 18:6 hr light/dark cycle. Subjects were given unlimited access to grit and water. Supplemental feeding of mixed grain occurred as necessary after daily sessions.

All subjects had various experimental histories including drug exposure. Each pigeon had served in a prior experiment that investigated the effects of mephentyoin on schedule-controlled responding in the pigeon (Pelletiere, Delaney, Schlinger, & Poling, 1988). All pigeons were drug free for at least six months prior to the start of the experiment proper. Approval was obtained from the Western Michigan University Institutional Animal Care and Use Committee prior to the start of the experiment.

### Apparatus

Three translucent plastic response keys and a rectangular food aperture were located on the front wall of four Lehigh Valley Electronics (BRS/LVE) operant conditioning chambers with internal dimensions of 32 by 35 by 35 cm. In each chamber, three response keys were mounted in a horizontal row 23 cm above the floor. The center response key was located 17.5 cm from the outer edge of the front wall. The side response keys were juxtaposed 5.5 cm to the left and to the right of the center response key. Only the right key was operative during experimental sessions. The response key could be transilluminated by either white, red or blue-green stimulus

lights. A minimum static force of 0.2 N was required for a microswitch to detect a key-peck response.

A food hopper, located behind an aperture 15.5 cm below the center key, provided access to mixed grain. Ambient chamber illumination was provided by a 7-W white bulb, centrally mounted 2 cm below the ceiling. White noise and a continuously operating ventilation fan masked extraneous noise. In an adjacent room, a Digital Equipment Corporation PDP-8/A ® minicomputer scheduled experimental events and collected data. The PDP-8/A ® minicomputer was programmed with SUPERSKED® software (Snapper & Inglis, 1978).

### Behavioral Procedure

Due to prior experimental experience with fixed-ratio (FR) schedules of food reinforcement, subjects required no hopper or key-peck training. Subjects were systematically exposed to progressive fixed-ratio values ranging from FR 10 to FR 125 on randomly selected white, red and blue-green stimulus lights. After each subject could reliably complete 45 trials of FR 125, the final schedule arrangement was initiated. Key colors were counterbalanced and assigned across the respective multiple fixed-ratio schedule of food reinforcement for each subject.

The terminal schedule consisted of a three-block, three-component multiple schedule of fixed-ratio food delivery with component schedules of FR 5, 25, and 125. Each component schedule was correlated with a particular color of key illumination. The session began with the illumination of a ceiling light and one of the three randomly selected stimulus lights transilluminating the response key. The selected fixed-ratio schedule was in effect until the programmed ratio was completed 5 times. After the delivery of the fifth reinforcer of a component, a 60 second blackout ensued. During the blackout period, all lights in the operant chamber were darkened and key pecking



produced no programmed consequences. After the blackout period elapsed, the computer randomly selected the next fixed-ratio component from the two remaining components. After completion of the five ratios in the second component, the chamber lights were again darkened for 60 seconds, after which the third component ratio was in effect until the programmed ratio was completed five times. At that time, the chamber lights were darkened for 60 seconds and the schedule arranged initially was repeated. This process continued until each component schedule was arranged on three occasions. The experimental session ended after the delivery of 45 3-second mixed grain food reinforcers or a maximum of 107 minutes.

Time requirements were also superimposed on each fixed-ratio component. Subjects were allotted 2-min, 6-min, and 25-min to complete the FR 5, FR 25, and FR 125 components respectively. Failure to complete a component within the allotted time resulted in termination of the component and initiation of the 60-s blackout. The blackout was followed by the routine presentation of the next component. These time requirements are identical to those employed in the procedure after which this study is fashioned (Hoffman, Branch, & Sizemore, 1987). The time-based completion requirements affords the experimenter the opportunity to assess any differences in drug effects across the three fixed-ratio schedules of food reinforcement.

Experimental sessions occurred at approximately the same time each day. During the determination of acute drug effects, sessions were conducted once, daily, 6 or 7 days a week. Sessions were conducted once, daily, seven days a week during chronic drug exposure.

### Pharmacological Procedure

After the overall response rate of each subject under all three components of the multiple schedule was stable (i.e., 10 consecutive sessions with no visible trends), an

injection regimen was initiated. Commercially prepared morphine sulfate (Sigma Chemical Company, St. Louis, MO) was diluted with a 0.9% sodium chloride (saline) solution. Injection volume was 1 ml/kg and subjects received exposure to 5 dose levels of morphine (0.56 mg/kg, 1.0 mg/kg, 3.16 mg/kg, 5.56 mg/kg, and 10.0 mg/kg). With the exception of 10.0 mg/kg, all doses were administered twice during the acute phase. 10.0 mg/kg was administered as the final dose of the second series because 5.56 mg/kg did not markedly suppress the overall response rate of one subject (P 6048) in the FR 5 of the first component. Injections were made into the pectoral muscle 30-min prior to selected sessions.

Drug injections were given according to a BBBBCD design where B represents baseline sessions (no injection), C vehicle control sessions (saline injection) and D drug sessions. To limit the development of acute tolerance, the acute drug injections were separated by a minimum of five days. This time period allowed the morphine and any metabolites to be deactivated, removed from the blood plasma, and excreted from the body of the pigeon before a subsequent test probe was given. Ascending series were employed throughout the study to facilitate the detection of systematic changes in the dose-response curve over successive drug assessments.

Ten consecutive non-injection (i.e., baseline) sessions interposed acute and chronic phases of the experiment. The chronic drug regimen consisted of daily administration of 5.6 mg/kg of morphine 30-min prior to each session. This dose was selected because acute administration of 5.6 mg/kg was the lowest dose that markedly suppressed (i.e., greater than 50 percent) response rates across all three fixed-ratio sizes. Daily alternation of injection site, from left to right pectoral muscle, minimized muscle bruising. Although behavior began to recover within a few sessions after the start of chronic drug administration, responding was judged to be stable (i.e., 10 consecutive sessions with no visible trend) after 56, 15, 16, and 20 injections for

pigeons 2895, 775, 6048, and 6211 respectively. Substitution doses other than 5.6 mg/kg of morphine were then evaluated.

With the exception of saline probes, the pattern of dose substitution resembled that of the acute drug administrations. Saline test probes were introduced as the first injection of each ascending series (saline, 0.56, 1.0, 3.16, 5.56, and 10 mg/kg). To maintain the general drug evaluation pattern (BBBBCD) used during the acute phase, test doses were separated by at least 5 days. Supplemental morphine injections occurred immediately after each test session to preserve the integrity of the 5.6 mg/kg chronic administration.

## RESULTS

To evaluate the acquisition of tolerance within an experimental session, overall response rates were collected separately for each FR component. During drug and control sessions, data were similar across the three exposures to each component schedule; therefore, only aggregate overall response rates for the FR 5, FR 25, and FR 125 are reported. Results of the study are summarized in Figure 1.

In the absence of drug, the highest response rates occurred under the FR 25 component and the lowest response rates occurred under the FR 125 component. When administered acutely, morphine at 0.56 mg/kg had no systematic effect. Higher doses generally reduced response rates relative to vehicle control levels under all fixed-ratio components. The relative and absolute magnitude of rate reductions were not obviously related to FR size, but were generally related directly to dose. Throughout the study, differences in the sensitivity to morphine under different fixed-ratio schedules did not appear to correlate with differences in the time spent in the initial schedule.

With daily exposure to 5.6 mg/kg, tolerance developed to the rate-reducing effects of morphine. In general, acute and chronic dose-response curves were less clearly separated under the FR 125 component than under the FR 5 or FR 25 components, which suggests that ratio size affected the development of tolerance. However, two of the four subjects (P 2895 and P 6211) demonstrated substantial tolerance under the FR 125 component. The degree of observed tolerance, however, should not be considered a simple inverse function of ratio size. For three of the four subjects, response rates to the 10 mg/kg test probes during chronic administration,

response rates were higher under the FR 125 component than under the FR 25 component for three of the four subjects.

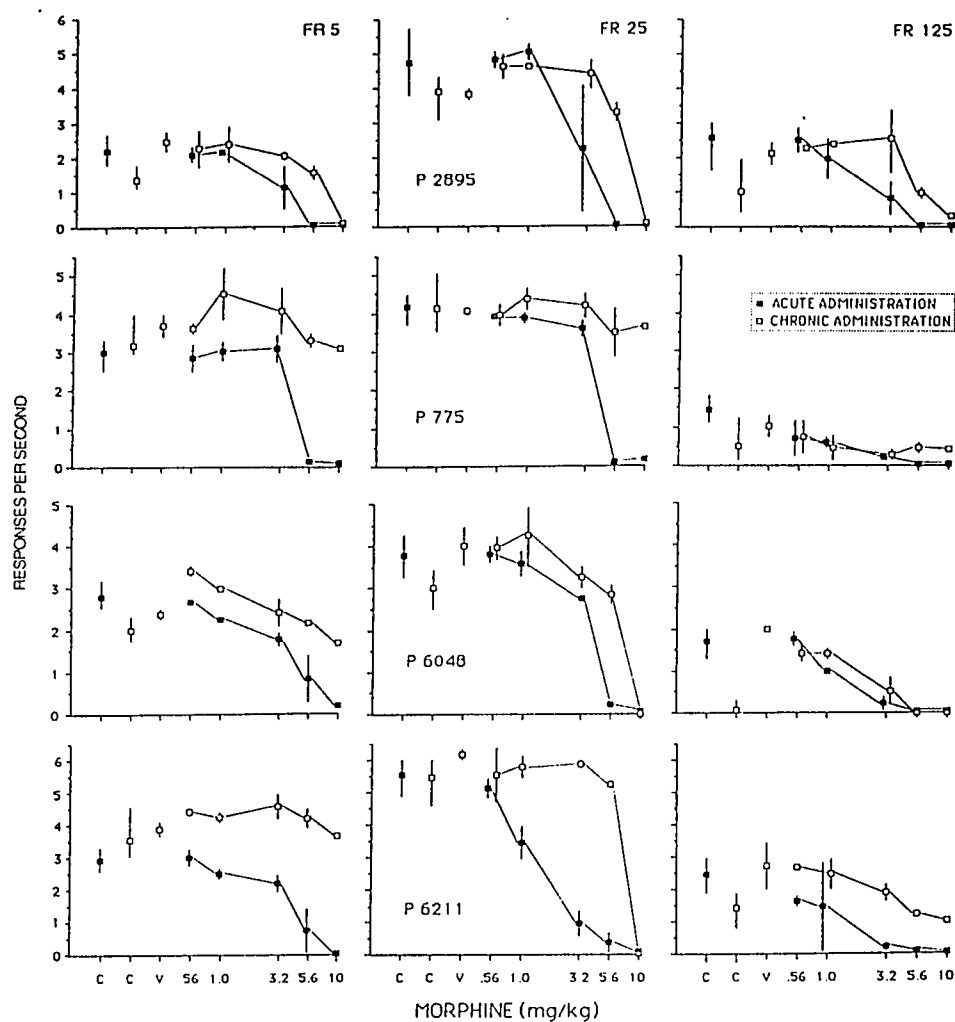


Figure 1. Mean Overall Response Rates as a Function of Morphine Dose.

Closed squares are data from acute administrations. Open squares are data from substitution probes tested during daily chronic administration of 5.6 mg/kg morphine. Vertical lines represent ranges. Closed squares above C show means from all vehicle sessions immediately preceding acute morphine administration. Open squares above C represent the 5.6 mg/kg administration prior to substitution probes during chronic morphine administration. V refers to the vehicle probes administered during the chronic regimen. Each row depicts data for one pigeon and each column, from left to right, shows data from the FR 5, 25, and 125 components respectively.

## DISCUSSION

Under nondrug conditions, the relationship between overall response rates and fixed-ratio values reported herein is consistent with previous findings. Boren (1961) arranged small fixed-ratio values ( $<FR\ 30$ ) and demonstrated that increases in ratio size produced increases in overall response rates. While investigating post-reinforcement pause, Felton and Lyon (1966) and Powell (1968) examined much larger fixed-ratio values and reported that higher fixed-ratio values ( $FR\ 150$ ) produce marked decreases in overall response rates. Integrating the three aforementioned studies, a general relationship between fixed-ratio size and overall response rates can be described as follows: increases in fixed-ratio values produce higher overall response rates up to a point after which additional increases in fixed-ratio values result in lower overall response rates. The present data portray this very pattern.

The overall response rate under the  $FR\ 25$  was higher than the overall response rate under the  $FR\ 5$ . The overall response rates under the  $FR\ 125$  were lower than those observed under either the  $FR\ 5$  or  $FR\ 25$ . These overall response rates serve two functions. First, they corroborate with previous experimental findings. Second, these findings suggest that subjects employed in the current experiment were typical to subjects used in prior non-drug experiments. Before discussing the acute and chronic drug effects, one characteristic of the non-drug data should be addressed.

Greater baseline stability enhances the detection and evaluation of drug effects (Thompson & Boren, 1977). Larger fixed-ratio schedules of reinforcement engender lower overall response rates. Moreover, less stability is associated with performances on larger fixed-ratio values. Low response rates and increased variability in performance are conditions less than optimal to examine drug effects. Suffice it to say,

especially conservative statements are rendered during this discussion of the FR 125 data. With this cautionary note, the discussion below focuses on the acute and chronic drug effects produced by morphine.

Recall a basic tenet of behavioral pharmacology that states the qualitative and quantitative behavioral effects produced by the drug are related directly to the amount of the drug administered (Poling, 1986). In the present study, acute administration of morphine produced dose-related decreases in overall response rate across all three fixed-ratio values. This finding is consistent with the results of other studies that examined the effects of morphine on responding maintained by fixed-ratio schedules of food reinforcement.

Prior studies have revealed that morphine characteristically reduces response rates under fixed-ratio schedules of food delivery and that some tolerance develops to its rate-decreasing effects (e.g., Thompson, Trombley, Luke, & Lott, 1970; Heifetz & McMillan, 1971; Gilbert, 1974; Smith, 1979; Woods & Carney, 1978; Craft, Picker, & Dykstra, 1989; Negus, Picker, & Dykstra, 1989). The role of fixed-ratio size as a determinant of tolerance was not examined directly in those studies, which characteristically employed relatively low fixed-ratio values ( $< \text{FR } 50$ ) and higher chronic morphine doses than those used in the present study. Due to these and other procedural differences (e.g., subject species) between prior studies and the present investigation, it is difficult to determine whether the degree of tolerance evident in the present study is comparable to that observed in other investigations using smaller fixed-ratios.

In an earlier investigation, similar in procedure to the present study, fixed-ratio size clearly and strongly modulated the development of tolerance to cocaine (Hoffman, Brand, & Sizemore, 1987). For example, in two pigeons exposed to FR 5, 25, and 125 components, tolerance failed to develop under the FR 125, but was evident under



the other components. In the present study, fixed-ratio size appeared to modulate the development of tolerance in a similar fashion.

The extent to which tolerance developed to morphine appeared to depend on the fixed-ratio value. Under the FR 5 schedule, tolerance developed for all three subjects. Similarly, all subjects demonstrated tolerance under the FR 25 schedule. However, less separation in the acute and chronic dose-response curves occurred under the FR 125 schedule. This consistent pattern across all subjects suggests that tolerance may, in general, be less likely to occur under relatively long fixed-ratio schedules than under relatively short fixed-ratio schedules.

The results reported herein are consistent with previous studies that report the development of tolerance to one schedule component of a multiple schedule of reinforcement but not another (e.g., Schuster, Dockens, & Wood, 1966; Sizemore, Branch & Hoffman, 1987). Demonstrating behavioral tolerance, however, is much different than identifying the mechanism underlying behavioral tolerance. The behavioral mechanism through which fixed-ratio size modulates the development of tolerance remains unclear. The following sections discuss the present results within the conceptual framework of four theories related to the extent to which behavioral factors influence the development of drug tolerance: the reinforcement loss hypothesis, effort or behavioral cost, response strength, and rate-dependency.

The reinforcement loss hypothesis constitutes the most acknowledged theory concerning behavioral tolerance. The reinforcement loss hypothesis states that the development of tolerance to a drug effect is more likely when the drug interferes with the subject's ability to meet the reinforcement contingencies (Corfield-Sumner & Stolerman, 1966; Schuster, Dockens, & Woods, 1966). The present study was not designed to explicitly test the reinforcement loss hypothesis. However, the data are at least partially reconcilable with the reinforcement loss hypothesis.

Decreases in overall response rate under fixed ratio schedules of food reinforcement produce decreases in reinforcement frequency. Morphine, administered acutely, produced decreases in overall response rate under the FR 5, FR 25 and FR 125 schedules. Tolerance was clearly evident in four subjects under the FR 5 and FR 25, and to a lesser extent under the FR 125 (P 2895 and P 6211). Consistent with the reinforcement loss hypothesis, tolerance developed under the schedules in which acute drug administration produced decreases in reinforcement frequency. A closer inspection of the FR 125 schedule suggests, however, that the reinforcement loss hypothesis does not adequately address all aspects of the data.

Morphine administration produced a more marked decreases in reinforcement frequency under the FR 125 schedule than under either the FR 5 or FR 25 schedules. The reinforcement loss hypothesis predicts that tolerance would develop more readily under the FR 125 schedule. In the present study, however, acute and chronic dose-response curves were less clearly separated under the FR 125 component than under the FR 5 or FR 25 component. As Hoffman, Branch, and Sizemore (1987) suggest, the fixed-ratio size may present "boundary conditions beyond which reinforcement loss contributes less to the development of tolerance" (p. 373).

Failure to demonstrate tolerance consistently under the FR 125 schedule may be due to the multiple schedule context in which the FR 125 is embedded. Due to the use of time limits in each component, subjects may have stopped responding in a particular component and proceeded to obtain reinforcers in subsequent component. It is unclear the extent to which tolerance would be observed under an FR 125 schedule that was studied either in isolation or within a multiple schedule context wherein the FR 125 constituted the smallest fixed-ratio value. Future investigations should examine the context in which the FR occurs as well as the extent to which the generative power of the schedules in question allow response patterns to vary within a particular trial.

Given that the reinforcement loss hypothesis did not explain adequately all aspects of the data, the data was reconceptualized in terms of response effort as a factor that could modulate the development of tolerance.

In the present experiment, effort can be operationally defined as the number of responses required to produce food delivery. The more robust demonstration of tolerance under the FR 5 and FR 25 schedules than under the FR 125 schedule may have been related to the effort or behavioral cost associated with each component. This conceptualization of the data is consistent with previous findings that suggest cocaine tolerance may be related to the amount of behavior necessary to produce reinforcement (Branch & Dearing, 1982).

Suppose that drug administration produced comparable rate reductions under all three schedules. In terms of access lost to food per unit time relative to baseline performance, the effect would be more costly under the FR 5 and FR 25 than under the FR 125. Reinforcement frequency, rather than effort, may have influenced the development of tolerance. The FR 125 yielded far less access to food per unit time than the FR 5 or FR 25. A conclusive statement about the present results as they relate to response effort cannot be made because effort was confounded with reinforcement loss. The reinforcement loss hypothesis in this form does not account for the differential development of tolerance under the three schedule components.

In addition to differing in access to reinforcement per unit time, fixed-ratio schedules of dissimilar lengths vary with respect to inter-reinforcement time and access to reinforcement required for each response. In the present study, each response under the FR 5 resulted in 0.6-s access to food. Each response under the FR 25 resulted in 0.12-s access and each response under the FR 125 resulted in 0.024-s access to food. When conceptualized in this way, the difference in the relative payoff of the three schedules is even greater than when they are compared in terms of total access to

reinforcement per unit time. It is possible that the relatively low payoff of the FR 125 schedule compared to the FR 5 and FR 25 schedule, rather than the variables previously discussed, retarded the development of tolerance.

Until studies are conducted that separate the effects of effort per se from those of other reinforcement variables such as inter-reinforcement interval, relative response payoff, and relative reinforcement loss, any conclusions concerning effort as a determinant of tolerance are premature.

Somewhat related to response effort is the notion of response strength as a determinant to the development of tolerance. Nevin (1974, 1979) indexed response strength by evaluating performances maintained under multiple schedules of reinforcement. Each schedule component was exposed uniformly to a rate decreasing factor. According to Nevin (1974), "the component performance that undergoes the smaller reduction, relative to its stabilized baseline, may be identified as the stronger of the two performances" (p. 390).

Using Nevin's logic, acute morphine administration serves as the rate decreasing factor applied uniformly across all three fixed-ratio components. Acute drug effects can then be used to index response strength. At a given dose, the greater the reduction in overall response rates, the lower the response strength.

Response strength appears to predict tolerance in the Hoffman, Branch, and Sizemore (1987) study and in the present experiment. In both studies, acute drug administration tended to produce greater behavioral disruption under the FR 125 than under the FR 5 or FR 25. Tolerance was quite evident under the FR 5 and FR 25 schedules and less apparent under the FR 125 schedule. It follows that tolerance would develop more readily to behavior more resistant to change.

Magnitude of acute drug effects, however, does not appear to be a good general predictor of the development of tolerance. For example, pigeons responding under a

delayed-matching-to-sample procedure, acute administrations of methsuximide and mephentyoin produced greater disruptions when the delay was six seconds than when it was shorter, yet comparable tolerance developed across all delays (Schlinger & Poling, 1988). Also, in pigeons responding under a multiple fixed ratio 50, fixed-interval (FI) 90-second schedule of food reinforcement, acute administration of mephentyoin at 240 mg/kg produced greater rate reduction under the FR component, but with chronic exposure comparable tolerance developed under the fixed-ratio and fixed-interval schedule of food reinforcement (Pellettieri, Delaney, Schlinger, & Poling, 1988). Thus it appears that the development of tolerance to drugs does not relate in any simple fashion to response strength as indicated by resistance to change.

To complete the analysis, the data was aligned according to a more traditional, behavioral pharmacological theory of rate-dependency. The following paragraphs address the rate-dependency analysis.

The response rate in the absence of drug is often related in an orderly fashion to behavioral disruption produced by the drug (see Dew & Wenger, 1977 for a review). In the present experiment, overall response rates under the FR 25 were higher than response rates on either the FR 5 or FR 125 schedules. Response rates under the FR 125 schedule component were lower than those produced by the FR 5 schedule. The rate-dependency description predicts that the degree of suppression produced by acute administrations of morphine should be directly related to baseline responding. More behavioral suppression should occur under schedules which engender higher the rate of responding than a schedule that engenders a lower rate of responding. This rate dependency analysis, however, does not hold true for the present data. For a given dose level of morphine, more response suppression was evident under the FR 125 schedule than under the FR 5 or FR 25 schedule. Clearly, a simple relationship between degree of response suppression and baseline responding did not exist.

The present findings and the results of prior studies appear to show that the amount of responding required for reinforcement may affect the development of tolerance to psychoactive agents. However, these demonstrations of behavioral tolerance do not identify explicitly the mechanisms underlying the development of drug tolerance. The behavioral mechanism through which fixed-ratio size modulates the development of drug tolerance remains unclear. Additional research is necessary to separate the effects of effort per se from those of other reinforcement variables such as inter-reinforcement interval, relative response payoff, and relative reinforcement loss. Moreover, the identification of behavioral mechanisms does not rule out a biochemical basis for tolerance (e.g., changes in receptor sensitivity). Behavioral pharmacologists should use wisely their opportunities to collect biochemical data and integrate the behavioral and biochemical data. Researcher should heed the warning of Schuster, Dockens, and Woods (1966):

This hypothesis is not intended as a replacement for the classical physiological theories of drug tolerance....Rather this hypothesis is put forth as an additional variable which may be operative in those behavioral situations where tolerance develops in a manner not predictable from the classical conceptions. (p. 181)

**Appendix A**  
**Institutional Animal Care and Use Committee Approval Form**

## INVESTIGATOR CERTIFICATION

Title of Project LSD\* tolerance: Acute versus chronic effects as dependent  
upon fixed-ratio size.

If any of the above procedures are changed, I will submit a new protocol. \*Note, Morphine and Cocaine will also be used if supplied.

I understand that any failure to comply with the *Animal Welfare Act*, the provisions of the *DPHS Guide for the Care and Use of Laboratory Animals* and requirements set down by the IACUC may result in the suspension of my animal studies.

Mark Nickel (Mark Nickel for Al Poling) Psychology 2/20/89  
 Signature: Principal Investigator Department Date

## REVIEW BY THE INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE

Disapproved

X Approved

Approved with the provisions listed below

Provisions:

or

Explanation

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Donald Seuring  
 IACUC Chairperson

2-24-89  
 Date

Researcher's Acceptance of Provisions:

Mark Nickel  
 Signature: Principal Investigator

20 February 1989  
 Date

IACUC Chairperson Final Approval

Date

Approved IACUC Number 0030

Revised June, 1988



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