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Schedule-induced Polydipsia and Oral Intake of Drugs*

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In 1971, Falk (3) defined adjunctive behaviors as those which are maintained at a high probability by stimuli whose reinforcing properties are primarily derived from schedule parameters which govern the availability of another class of reinforcers. According to this definition, schedule-induced polydipsia is a form of adjunctive behavior, which apparently is not maintained by direct or by adventitious reinforcement. In the 15 years since schedule-induced polydipsia was first reported by Falk (2), this phenomenon has been found to have wide generality. Excessive fluid intake in nonfluid deprived animals, as a function of schedule control has been shown in a number of species. Other schedule generated behaviors such as air-licking, pica, aggression, and escape have been included with polydipsia in the general descriptive category of adjunctive behaviors (*cf.* Falk (3) for review).

Lester (15) was the first to show that schedule-induced polydipsia was an effective procedure for inducing alcohol intoxication in rats. Lester did not report evidence of physiological dependence with this procedure. A number of other investigators have also reported high levels of alcohol intake induced in rodents by variations on a schedule-induced polydipsia technique, but none has reported production of physiological dependence (9, 10, 17, 18, 29).

The first successful application of the polydipsia paradigm for inducing physiological dependence upon alcohol in the rat was reported by Falk *et al.* (4). This model met the several criteria of alcohol dependence (21, 34) insofar as the polydipsic animals ingested more alcohol through time, showed evidence of intoxication, and signs of physiological dependence upon alcohol withdrawal. Moreover, signs of physiological dependence clearly reflected the removal of alcohol rather than intercurrent illness or nutritional deficiency. A critical advantage of the polydipsia procedure is its capacity to maintain high levels of alcohol ingestion in the presence of adequate food intake. Schedule-induced polydipsia can occur when animals are maintained between 80 and 85% of ad lib weight. This avoids the potentially confounding effects of severe weight reduction in several other models of alcohol dependence (*cf.* 21, 29 for discussion).

The papers in this volume by Falk and Samson (5), Meisch (16), and Leander and McMillan (14) unquestionably demonstrate the efficacy of schedule-induced polydipsia in inducing oral intake of noxious tasting opiate and ethanol solutions in the rat. In most instances, a polydipsia procedure is superior to a situation in which the drug solution is provided as the only fluid in the home cage, in terms of the quantity of drug solution consumed by the animal. Falk and Samson (5) have been able to maintain intake of 5% ethanol solutions (v/v) in daily doses up to 13 g/kg with associated blood alcohol levels which

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usually ranged between 150 to 300 mg/100 ml. Leander and McMillan (14) report polydipsia-induced ingestion of morphine and methadone solutions (1 mg/ml) up to 37.5 mg/kg per hr as compared with doses ranging between 60 and 100 mg/kg per 24 hr in home cage, forced-choice situations (1, 14).

In addition to ensuring a high volume of fluid intake, schedule-induced polydipsia permits the investigator to control both the periodicity and the duration of fluid ingestion. This degree of temporal control is essential insofar as sustained high blood levels of addicting drugs appear to be the critical factor in inducing physiological dependence. Falk and Samson (5) have re-emphasized the importance of programming polydipsia sessions so that frequent high doses of drug solutions are consumed, if the goal is to produce a physiologically dependent animal. These data confirm and extend the observation that 3 hr access to intravenous self-administration of ethanol is not sufficient to produce physiological dependence (34). This important general pharmacological principle has been carefully demonstrated by Yanagita and Takahashi (36) in their comprehensive study of the optimal regimens for the induction of barbiturate dependence. All investigators who have reported successful techniques for inducing alcohol dependence have developed procedures which produce sustained high blood alcohol levels or frequent high alcohol peaks (*cf.* 21 for review).

The extent to which physiological dependence and/or sustained exposure to a noxious drug solution will effect subsequent *preference* for that drug solution has been examined in different ways by each of the investigators in this Section. Preference can be evaluated in some form of free or forced choice paradigm, or in an operant reinforcement paradigm. In an elegant dissection of ethanol *vs.* dextrose or saccarine preference curves, Falk and Samson (5) have shown that an animal physiologically dependent upon alcohol, requires a "sweeter" solution to change preference from alcohol to the sweet solution than does the nondependent animal. The qualification of relative preference as a function of the concentration of a competing solution (*e.g.*, dextrose) may offer a more precise and powerful assessment technique than the usual approach which compares water with various concentrations of drug solutions.

A second approach to examining the extent to which prolonged exposure to a drug solution may effect subsequent preference, is to determine if an animal will work to produce the drug solution in an operant paradigm. Leander and McMillan (14) report that rats will "follow" a source of etonitazene after 15 days exposure to that drug even when water was also available. Moreover, rats exposed to etonitazene will subsequently respond under a fixed interval schedule of presentation of the etonitazene-quinine solution in a dipper feeder. Responding of control rats was not maintained by the quinine solution (14).

Comparable data have also been reported for alcohol selection after a period of alcohol exposure. In 1964, Mello and Mendelson (23) reported that after a period of 75 days free choice exposure to ethanol in a home-cage situation, rats trained to lever press for a milk reinforcer on a multiple 25-response fixed-ratio, 5-min fixed-interval schedule, sustained responding for a 5% ethanol solution (v/v) for 20 to 40 hourly sessions, albeit at a progressively lower rate. Subsequently, it was found that rats trained to drink a 10% (v/v) solution of ethanol from a drinkometer on a rate-contingent ratio schedule of 64 (with a licking rate requirement of 36 responses per min) for a milk reinforcer, continued to drink 10% ethanol from the drinkometer to obtain a 10% ethanol reinforcer over a period of 10 days (24). These early observations have been confirmed and extended by Meisch (16) and by Meisch and Thompson (18). Meisch (16) reports that after a single 6-hr exposure to an 8% ethanol solution,

rats will lever-press to produce more ethanol presentations than water presentations from a dipper feeder. Meisch (16) emphasizes the fact that comparable data can be obtained after a variety of alcohol acquisition histories.

It is clear that exposure to a noxious drug solution may be associated with subsequent shifts in "preference" for that solution. However, induced "preference" may be transitory or extremely variable. In the case of alcohol, removal of factors such as noxious stimuli used to accelerate preference, is usually accompanied by a marked decrease in alcohol intake. Moreover, preference may be totally unrelated to the production of physiological dependence upon the drug solution. A dissociation of alcohol "preference" from physiological dependence is important insofar as the primary impetus for developing self-administration techniques has been to produce a physically dependent animal. In the past, many investigators have failed to distinguish between a transitory "preference" for alcohol and physical dependence upon alcohol, leaving a legacy of enduring confusion in this literature (*cf.* 19, 21, 27 for review).

Oral Intake of Drugs: Some methodological Issues

Polydipsia can be a powerful tool for inducing comsumption of doses of opiates and alcohol sufficient to produce physiological dependence in experimental animals. However, there are several methodological problems which are inherent in any oral self-administration procedure, as contrasted to an intravenous self-administration procedure. These methodological problems include: 1) ensuring ingestion of the fluid; 2) monitoring drug blood levels; 3) controlling variables which effect delay of absorption. Specification of criteria used to assess physical dependence is, of course, important in any type of drug self-administration procedure. A brief discussion of each of these issues follows.

1. Control of fluid intake. In any oral self-administration procedure which involves a nonpreferred or noxious tasting liquid, there is always a question as to whether the animal does, in fact, consume the fluid. Since reinforcement is usually lick-contingent rather than ingestion-contingent, there is no assurance that fluid consumption accompanies licking behavior. Alternatively, the fluid tube could leak, the animals could jiggle the fluid tube or splash liquid from a reservoir, or even spit out the fluid. In the course of our own efforts to induce rhesus monkeys to drink large volumes of alcohol solution with a polydipsia procedure (25) or an electric shock-avoidance procedure (26), we became particularly sensitized to the problem of ensuring that the animal in fact consumed the drug solution. A brief review of these data will illustrate these problems.

Four rhesus monkeys were trained to drink an alcohol solution from a drinkometer in order to avoid a noxious electric shock, in a paradigm in which licking the drinkometer tube was the operant response. Both bourbon and ethanol solutions were presented in concentrations ranging from 5 to 25% (v/v). A 6-hr period on a shock postponement schedule (32) was alternated with a 6-hr rest period during which no shocks occurred. Experiments were run 24 hr a day 7 days a week. Each monkey learned to drink (lick) at a rate sufficient to avoid virtually all possible shocks. However, the amount of fluid consumed varied across the ethanol and bourbon concentrations. Although the rate of lick responses remained the same, fluid consumption decreased linearly as a function of increasing alcohol concentrations. Consequently, it appeared that the monkey had learned a dual avoidance response in which it was possible to postpone the occurrence of a noxious shock by making a lick response, and also to avoid consuming an aversive fluid by modulating the duration of the lick response. Measurement of lick response durations revealed that as the

ethanol concentration was increased, the mode of the lick duration distributions was shifted towards shorter durations (fig. 1). Shorter lick-durations presumably resulted in smaller amounts of fluid dispensed per lick (26).

The apparatus was then modified so that only discrete licks of a specified duration were effective in postponing shock. Monkeys were studied for 60 days with a 10% alcohol solution (v/v) and lick duration requirements were increased in 50 msec increments. Each monkey's lick response duration increased in accordance with the programmed lick duration requirements (fig. 2). Despite the increase in lick duration, the volume of alcohol consumed did not increase. Monkeys drank about 2.5 g/kg per day and blood alcohol levels ranged between 30 and 70 mg/100 ml (26).

Since the required lick duration was controlled by the operant program, these data suggest that the monkey learned to control the amount of fluid dispensed by manipulating the displacement of the ball valve in the drinking tube. In a subsequent series of studies, this variable was also placed under experimental control. The monkey's task was 3-fold: to lick, to lick for a specified duration of time, *and* to displace the ball in the fluid tube enough to break a photocell. This combination of requirements was designed to ensure that the monkey did in fact consume fluid in the course of emitting the required avoidance response. Given our long history of difficulty with this procedure, we also arranged for a leakage collection device so that any fluids which did not go into the monkey would go into a tube and a calibrated bottle located outside the experimental chamber (22a).

As before, all monkeys were able to successfully avoid all noxious shocks. The contingencies for lick duration and fluid tube ball displacement were consistently met. However, it appeared that the monkeys had now learned a quadruple avoid-

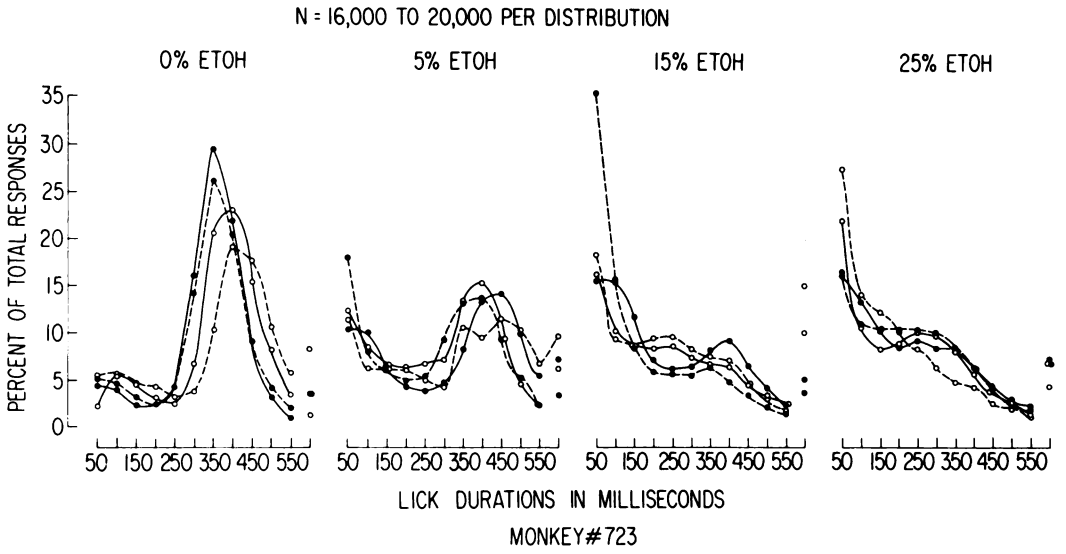

FIG. 1. Distribution of lick response durations as a function of the concentration of the ethanol (w/v) in the avoidance-contingent bottle for an individual monkey. Each distribution at each concentration reflects the total number of lick avoidance responses on a single day. These data were recorded with an automatic distribution counter. The first and last data bin contain all responses of equal and shorter, and of equal and longer, duration than the number indicated on the abcissa. The number of actual responses falling in each duration interval is expressed here as a percentage of the total responses across all duration intervals. [Reprinted from N. K. Mello and J. H. Mendelson, The Effects of Drinking to Avoid Shock on Alcohol Intake in Primates. *In* Biological Aspects of Alcohol, ed. by M. K. Roach, W. M. McIsaac, and P. J. Creaven, pp. 313-332. University of Texas Press, Austin, 1971, by permission of the publisher (26).]

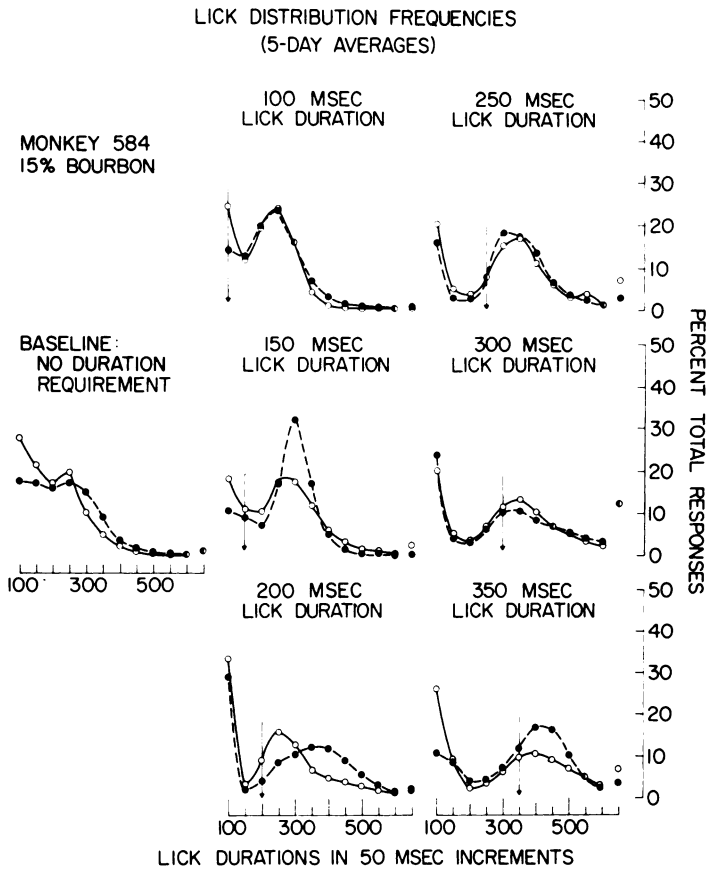

FIG. 2. Lick distributions for an individual monkey maintained on a 15% bourbon solution (w/v) are shown as a function of the duration required for successful avoidance of shock. The actual number of responses in each duration interval is expressed as a percentage of the total number of responses that occurred. The spontaneous baseline lick duration frequencies on water (open circles) and on 15% bourbon (closed circles) are shown at the left of the figure. Lick duration distributions as a function of increasing duration requirements are shown in columns two and three, reading from top to bottom. The downward arrow in each distribution indicates the minimum duration necessary to avoid shock successfully. Each distribution pair represents two consecutive 5-day averages in which the open circle distribution occurred first. The lick duration requirements for monkey 584 were increased gradually from 100 to 350 msec in 50 msec increments. [Reprinted from N. K. Mello and J. H. Mendelson, The Effects of Drinking to Avoid Shock on Alcohol Intake in Primates. *In* Biological Aspects of Alcohol, ed. by M. K. Roach, W. M. McIsaac, and P. J. Creaven, pp. 313-332, University of Texas Press, Austin, 1971, by permission of the publisher (26).]

ance response insofar as they still failed to consume significant amounts of alcohol. Blood alcohol levels were in the range previously observed, 30 to 70 mg/100 ml. No monkey showed evidence of intoxication or of physiological dependence upon removal of alcohol. Direct observation of the animals during an avoidance period suggested that animals were letting the alcohol solution run off their chins and drip into the collection cup. In any event, there was a highly orderly relationship between the amount of alcohol removed from the fluid reservoir and the amount of fluid which appeared in the leakage collection bottle (22a). These data testify to the monkey's aversion to alcohol and ingenuity in evading our efforts to force them to ingest a 10% alcohol solution.

The use of food as a reinforcer for drinking was even less effective in inducing high levels of alcohol consumption in rhesus monkeys. Monkeys were required to make a consummatory (lick) response from a

"contingent" fluid bottle to earn banana pellets on an intermittent schedule of reinforcement in a daily three hour session (25). Monkeys had free access to a 43% bourbon solution during the remaining 21 hr of each day. During the *water* baseline period, it was found that the amount of fluid consumed from a second (noncontingent) water bottle was far greater than the water consumed from the response "contingent" bottle and it appeared that the animals were engaging in adjunctive drinking. Subsequently, alcohol concentrations in the response contingent bottle were gradually increased from 5 to 15% in 5% steps and alcohol concentrations in the noncontingent bottle were increased at a slower rate in an effort to manipulate alcohol intake through concentration comparisons. Although monkeys ingested volumes of 5% ethanol from the "contingent" bottle equal to or exceeding baseline water consumption (200 ml within 3 hr) a sustained intake of higher concentrations of alcohol was not observed. This consumption level yielded an alcohol dose which averaged about 3 g/kg with blood alcohol levels which averaged about 50 mg/100 ml. No monkeys showed signs of gross intoxication or signs of physiological dependence despite approximately 10 months exposure to these procedures. During this period, there was no progressive increase in alcohol intake in the polydipsia situation and no increase in preference for 43% bourbon (25).

Polydipsic drinking has been shown in monkey when nonaversive fluids, *e.g.*, water is provided (30). The use of relatively low alcohol concentrations (2.5% w/v) has been more effective in producing severe intoxication in monkeys in a polydipsia paradigm (34). Total volumes of alcohol consumption which exceeded 1000 ml in a 24-hr period were sometimes observed in monkeys with a previous history of intravenous alcohol administration. Oral alcohol doses as high as 7.1 g/kg were consumed. Monkeys with a history of intravenous self-administration of alcohol did drink more alcohol in a 2.5- to 4-hr polydipsia paradigm than naive controls, during the first 3 to 4 weeks of exposure to this schedule. Subsequently naive controls reached a level of intake comparable to that of the alcohol experienced animals. Five of six animals showed signs of intoxication and blood alcohol levels which ranged between 150 and 200 mg/100 ml (34a). However, signs of physiological dependence were not observed in these monkeys under these conditions.

2. *Assessment of drug blood levels.* It is obvious from the foregoing that without determination of blood levels of an orally administered drug, there is no way to ensure that the number of milliliters gone from a fluid reservoir or the number of reinforcements (*e.g.*, dipper presentations of a noxious drug solution) does in fact bear any relationship to the actual ingestion behavior of the animal. Although techniques for assessing intoxication and tolerance are available [*cf.* Kalant *et al.* (12) for review], most investigators tend to rely upon a visual assessment of the animals with the attendant problems inherent in any nonsystematic observation. The correlation between blood alcohol levels and behavioral indices of intoxication is often poor in human alcohol addicts because of the development of behavioral tolerance. However, in the absence of sensitive behavioral procedures to assess intoxication in animals, blood drug levels are the only way to monitor the efficacy of any oral self-administration procedure.

There are a number of techniques available for determination of blood alcohol levels. Since alcohol is distributed equally throughout the body fluids, there is a good reason to believe that blood alcohol levels may have a fixed relationship to brain alcohol levels. Techniques are available to determine blood alcohol levels on the basis of as little as 0.2 ml of plasma. Determination of blood morphine and blood methadone levels are more difficult, but can be

accomplished with radioimmunoassay techniques. The relation of peripheral opiate levels to central nervous system levels may be somewhat less certain than the relation of peripheral to central alcohol levels. However, on a qualitative basis it should be possible to establish that blood morphine levels are higher on occasions when an animal presumably ingested 150 mg/kg than when it ingested only 50 mg/kg. Without blood-drug level data, the utility of oral ingestion procedures is greatly limited.

3. Control of variables affecting absorption. Intravenous drug self-administration procedures have the particular advantage that each drug infusion is rapidly distributed throughout the circulatory system and presumably the conditions for "immediate reinforcement" are in effect. In contrast, oral self-administration of drug solutions is less likely to produce "immediate reinforcement" because of the delay in rate of absorption of the drug solution from the gut. Delay of absorption of an alcohol solution is influenced by the number of hours of fasting, the amount of food in the stomach, and the concentration of the alcohol solution. Comparable factors also influence the delay in absorption of opiate solutions. Given that drug solutions are absorbed after the passage of some period of time and high blood drug levels are achieved only after absorption, a drug-related change in state may occur 2 to 3 hr later. The extent to which animals are capable of learning to associate the initial noxious taste of the drug solution with the delayed effect is unknown. Garcia and co-workers have shown that conditioned taste aversion can be learned in a single trial even though the consequence (vomiting) may be delayed by several hours [*cf.* Garcia and Koelling (7) for review].

In a single session paradigm of oral self-administration of alcohol or opiate solutions, it is important that the investigator specify and control the factors known to influence absorption delay. Hours of fasting before initiation of the session should be specified. Moreover, it is possible to do a series of time-related dose response curves to estimate the time course of drug absorption and consequent maximal blood drug levels. This can be done easily by administering a known dose of the drug solution through nasogastric intubation to a fasted animal and taking periodic blood drug levels. In rhesus monkey, fasted for 22 hr, the peak blood level is reached only after 1 or 2 hr, as is illustrated in figure 3 (20).

4. Assessment of physical dependence. Although the importance of maintaining careful measures of body weight and standardized measures of physical dependence upon the particular drugs studied is not unique to oral drug self-administration procedures, it is necessary to emphasize that the absence of such data makes the interpretation of other behavioral data at best ambiguous. It is essential to specify the criteria used to conclude that physiological dependence has been established and to determine the reliability and validity of these criteria. The assessment of physiological dependence through withdrawal signs is based primarily upon visual observation. The difficulties and ambiguities involved in the examination of withdrawal signs in animals and in human addicts are similar. However, accurate assessment of the relative severity of withdrawal signs is a prerequisite to meaningful comparisons between laboratories. It is unfortunate that the development of appropriate technological devices *or* application of existing physiological monitoring techniques to standardize assessment of withdrawal signs has not commanded much interest in the field [*cf.* Mello (21) for discussion]. However, determination of the presence or absence of specific withdrawal signs can be done with a reasonable degree of confidence when frequent periodic observations are made. Seevers and Deneau (31) have provided comprehensive behavioral rating scales for assessment of opiate dependence. A rating scale based on the

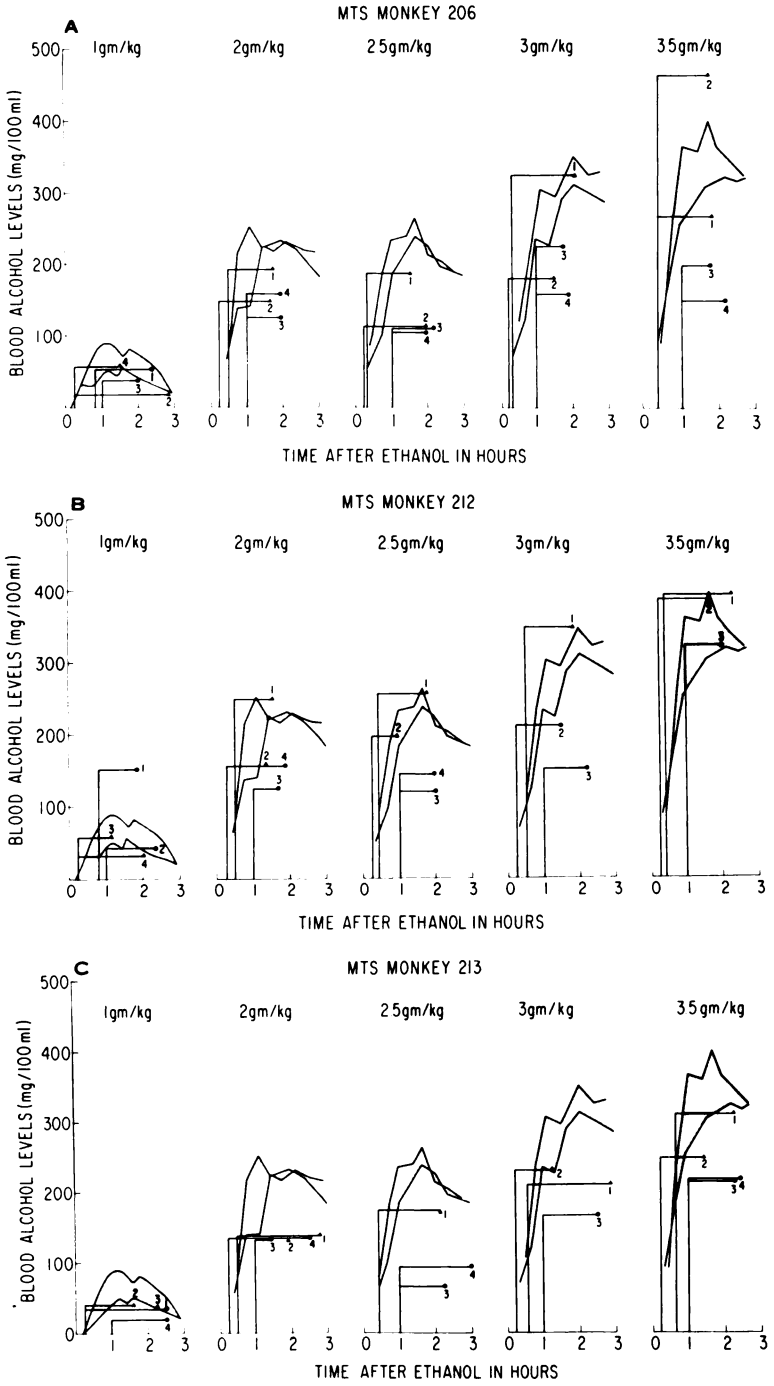

FIG. 3. Standard blood alcohol curves, displayed as shaded gray envelopes, are based on the average of two determinations (in duplicate) on samples from three naive rhesus monkeys (*Macaca mulata*). Monkeys were fasted for 22 hr before administration of 1.0, 2.0, 2.5, 3.0, 3.5, and 4.0 g of ethanol per kg. Each acute dose trial was separated by at least 48 hr. Blood samples were taken every 20 min for 3 hr after administration of 25% alcohol (w/v) *via* nasogastric intubation. The vertical lines superimposed on the blood alcohol curve indicate when each experimental session began after intubation. The superimposed horizontal lines indicate the terminal blood alcohol levels after each training session at each ethanol dosage. [Reprinted from N. K. Mello: Alcohol effects on delayed matching-to-sample performance by rhesus monkey. Physiol. Behav. **7**:77-101, 1971, by permission of the publisher (20).]

Seevers-Deneau data has been suggested by Mello (21). Comprehensive behavioral rating scales for signs of physiological dependence in mouse have also been developed by Freund (6), Goldstein (8), and Irwin (11).

Experimental Questions: The Need for More Explicit Definition

The foregoing comments have been concerned with some specific methodological issues. A more general problem, not specific to oral drug self-administration procedures or even to the discipline of behavioral pharmacology, involves the all too frequent absence of any clearly defined experimental question. It often seems as if a legitimate concern with methodological problems and techniques becomes a preoccupation which takes precedence over the original issues the techniques were developed to address. The need for careful parametric studies cannot be denied. However, the number of possible combinations of drug concentrations and feasible behavioral paradigms renders our discipline vulnerable to the generation of pseudoparametric studies which are in fact "questionless" experiments.

It is essential to distinguish between a clearly defined experimental question and a "relevant" question. Since "relevance" is often a capricious and transitory value judgment, this discussion only argues for the urgent need for explicit questions. Usually if questions are clearly defined, they are not formulated without attention to their broader implications and significance.

Comparable sentiments have been expressed more eloquently by many scientists commenting on numerous areas of research. In warning of the possible dangers inherent in research on psychophysics, S. S. Stevens states,

> "The trouble with the narrow conception of psychophysics is that it mistakes procedures for problems and precision for goals." (33, p. 31).

This volume is a testimony to the many recent conceptual and methodological achievements in behavioral pharmacology. However, it is obvious that continued advances in behavioral pharmacology will be contingent, in part, upon an increased effort by all investigators to make more explicit the hypotheses which are to be tested and the questions which are to be asked. Moreover, the significance of these questions for clarifying the effects of drugs on behavior, in the broadest sense, should be fully discussed. There are so many fascinating unresolved issues which invite the attention of behavioral pharmacologists (*cf.* 22, 28 for discussion) that any trend towards mistaking procedures for problems is perhaps best dismissed as a problem in individual focus. Indeed the frenetic acquisition of data *in vacuo* may resemble the adjunctive behaviors discussed earlier.

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