*ORAL DRUG SELF-ADMINISTRATION IN RHESUS MONKEYS:
INTERACTIONS BETWEEN DRUG AMOUNT AND
FIXED-RATIO SIZE*

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During daily 3-hr sessions, 5 rhesus monkeys drank drug solutions and water that were concurrently available. The drug solutions were: 1 milligram per milliliter (mg/mL) pentobarbital (2 monkeys), 1 mg/mL pentobarbital plus 0.5% ethanol (1 monkey), 1 mg/mL pentobarbital plus 1% ethanol (1 monkey), and 8% ethanol (1 monkey). The drug solution and water were available under identical two-component tandem fixed-ratio continuous-reinforcement *N* schedules. Two variables were manipulated: the size of the fixed-ratio component and the number of liquid deliveries (*N*) in the second component. Deliveries of the drug solution maintained higher rates of responding than did deliveries of the drug vehicle, water. The number of drug deliveries per session increased with increases in the number of deliveries per fixed ratio and decreased with increases in fixed-ratio size. Analysis of the results in terms of the proportion of deliveries to responses showed that the number of drug deliveries per session was directly related to the size of this quotient. Finally, when fixed-ratio size was repeatedly doubled, the following orderly relationship emerged: The greater the number of available drug deliveries per fixed ratio, the less was the percent decrease in the number of fixed ratios completed per session. It was concluded that increases in the number of liquid deliveries per fixed ratio resulted in increases in reinforcing efficacy.

Key words: drug self-administration, oral route, pentobarbital, ethanol, relative reinforcing efficacy, tandem schedule, fixed-ratio size, reinforcer magnitude, rhesus monkeys

Response rate has not been a reliable index of reinforcing efficacy (e.g., see Neuringer, 1967; Nevin, 1974). Response rates in some studies have varied directly with reinforcer magnitude (e.g., Bradshaw, Szabadi, & Bevan, 1978; Shettleworth & Nevin, 1965), but in other studies they have not (e.g., Catania, 1963; Morse, 1966; Neuringer, 1967). Response rates in drug self-administration studies are especially likely to be ambiguous indicators of reinforcing efficacy. Generalized effects following drug intake can disrupt responding (Spealman & Goldberg, 1978); these effects tend to increase with increasing intake (Young, Woods, Herling, & Hein, 1983); and, finally, high enough doses of any drug will eliminate responding (Kelleher & Morse,

1968). Depending on the schedule values and the drug doses or concentrations employed, the relationship between response rate and dose or concentration of a self-administered drug has been variously found to be an inverse one (e.g., with intravenous self-administration of cocaine under fixed-interval (FI) schedules by rats [Dougherty & Pickens, 1973] and by monkeys [Pickens & Thompson, 1972]), an inverted U-shaped one (e.g., with monkeys intravenously self-administering cocaine [Kelleher & Goldberg, 1977] or one of several narcotics [Young, Swain, & Woods, 1981]), or a direct one (e.g., with intravenous delivery of cocaine reinforcing monkeys' responding under a relatively lengthy FI schedule [Balster & Schuster, 1973]).

Because of problems with response rate as a measure of reinforcing efficacy, several strategies have been developed as alternatives to rate measures. Studies of drug-reinforced behavior that have focused on this problem can be categorized as choice experiments or as scaling experiments.

Choice experiments necessarily involve concurrent schedules (for a review, see de Villiers, 1977). Concurrent-scheduling studies directly gauge the relative ability of different reinforcers to maintain behavior, and such studies have been successfully conducted with

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drug reinforcers (e.g., with monkeys intravenously self-administering cocaine [Iglauer & Woods, 1974] and cocaine or methylphenidate [Johanson & Schuster, 1975]). It has typically been found that the distribution of responding between schedules favors the schedule under which the higher drug dose is available.

Several experimental designs have been used to scale different reinforcer magnitudes according to relative efficacy. The shared aim of these experiments was to quantify the amount of operant behavior that can be maintained by different reinforcer magnitudes (see discussions in Valenstein, 1964; Verhave, 1963). In scaling studies, different reinforcer magnitudes are presented sequentially for blocks of sessions. To date, progressive-ratio paradigms have mainly been used. For example, monkeys' responding that was reinforced by intravenous injections of cocaine or one of three amphetamine derivatives (Griffiths, Brady, & Snell, 1978) or one of several opiates (Hoffmeister, 1979) has been examined, as has responding of humans reinforced by oral delivery of a pentobarbital solution (McLeod & Griffiths, 1983). Findings of these studies generally parallel those of choice experiments: Within effective dose ranges, higher drug doses are more efficacious than low doses in maintaining behavior leading to their delivery.

In the present study, reinforcer magnitude was controlled by varying the amount of drug solution delivered. This was done by changing the number of consecutive liquid deliveries available on a continuous reinforcement (CRF) schedule at the end of each fixed-ratio (FR) sequence. Different numbers of CRF deliveries were presented during successive blocks of sessions. Each drug amount was studied at several FR values. The purpose of the experiment was to systematically replicate an earlier study in which reinforcer magnitude was altered by using different drug concentrations (Lemaire & Meisch, 1984).

In the earlier study, reinforcing efficacy increased with increases in pentobarbital concentration (Lemaire & Meisch, 1984). The increased reinforcing efficacy was inferred from the greater ability of higher drug concentrations to maintain behavior, relative to baseline levels, when FR size was increased. The present study sought to determine whether the previous finding of a direct relationship

between reinforcing efficacy and quantity of drug delivered could be replicated when drug quantity was varied by changing the amount of a drug solution delivered, instead of its concentration.

METHOD

Subjects

Five male rhesus monkeys (M-LA, M-CR, M-D, M-C, and M-S2), 3 of which had histories of oral drug self-administration, served as subjects. The mean weights of the monkeys during the experiment were 9.9, 9.5, 9.3, 8.2, and 7.6 kg, respectively, which were 64, 71, 70, 72, and 82% of their unlimited free-feeding (24-hr-a-day access to unlimited amounts of food) weights. The monkey that weighed the most was reduced the greatest amount, and the monkey that weighed the least was reduced the least amount. These percentages are potentially misleading because under free-feeding conditions most of the singly housed monkeys became moderately obese. Thus, experimental weights expressed as percentages of free-feeding weights may appear low. Each animal's appearance was consistently healthy and vigorous during the experiment. The monkeys were food deprived because a previous study demonstrated that much higher levels of pentobarbital-reinforced responding occurred under food-deprivation conditions (Kliner & Meisch, 1982). Monkeys M-S2 and M-LA had each participated in a previous study with pentobarbital (DeNoble, Svikis, & Meisch, 1982, and Lemaire & Meisch, 1984, respectively). Monkey M-C had been in a prior ethanol self-administration experiment (Henningfield & Meisch, 1979). Monkeys M-CR and M-D were experimentally naive.

For the 3 monkeys not having a self-administration history with the drug solution used in the current study (M-C, M-D, and M-CR), these drugs were established as reinforcers for the animals according to the following procedures. A 1 mg/mL pentobarbital solution was established as a reinforcer for M-C by first adding pentobarbital in a small amount (0.0078 mg/mL) to a 4% ethanol solution that was serving as a reinforcer for the monkey. The amount of pentobarbital in the solution was gradually increased across sessions, while the ethanol concentration was gradually de-

creased. Finally, ethanol was eliminated from the solution altogether. An 8% ethanol solution was established as a reinforcer for M-D by first substituting a 0.5% solution for the water that had previously been available under a CRF schedule during sessions. The monkey readily drank this solution, and the ethanol concentration was increased across sessions to 8%. The fixed-ratio requirement was then increased from one to eight responses over a number of sessions. Finally, water was reintroduced under a concurrently operating FR 8 schedule. Monkey M-CR was initially given his daily food allotment 1 hr into each day's session, during which water was available on a CRF schedule. Next, a 0.0078 mg/mL pentobarbital solution was made available during sessions instead of water. The concentration of the drug solution present during sessions was slowly increased. The quantity of food given during sessions was gradually decreased, and finally food was eliminated from the sessions. As a final measure, a low concentration of ethanol (1%) was added to the pentobarbital solution, for more stable behavior was obtained with the ethanol-pentobarbital combination. Ethanol is known to enhance absorption of barbiturates (Sharpless, 1970), and to exacerbate the CNS-depressant (Harvey, 1980) and ataxic (Ritchie, 1980) effects of the barbiturates. Monkey M-S2 also received a pentobarbital solution containing a low concentration (0.5%) of ethanol.

Apparatus

Monkeys were individually housed in primate cages (Hoeltge, No. HB-108) both during and between experimental sessions. The cages measured 77 by 76 by 100 cm. The fronts of these cages were barred. One of the side walls was modified to accept a work panel, which attached to the outside of the wall. Two brass spouts and stimulus lights were attached to the work panel, entering the cage through holes cut in the wall. Stimulus lights (2.8 W) covered with jewel lenses were located 15.5 cm either side of the work panel midline, 64 cm above the cage floor. Twelve cm directly below each of these lights a brass spout (1.2 cm outside diameter, 0.2 cm inside diameter) extended 2 cm into the cage. Four 1.1-W lights, two covered with white and two with green translucent lenses, were located behind

a recessed Plexiglas disk that surrounded each spout. These lights were each 3 cm from the spout. The white-lensed lights were on either side of the spout, 180° apart; the green-lensed lights were similarly situated, but shifted 90° from the white lights. Details of the work panel have been described elsewhere (Henningfield & Meisch, 1976; Meisch, Henningfield, & Thompson, 1975). The cages were in a room maintained at 27 °C. Constant masking white noise and a 12-hr light/dark cycle were present.

Liquids were contained in covered stainless-steel reservoirs mounted on a T-shaped bar attached to the back of the work panel, outside the cage. Polyethylene tubing conducted the liquids from the reservoirs to solenoid-operated valves attached at the rear of each spout. All liquids consumed by the monkeys, both during and between sessions, were delivered via this apparatus.

When water was available at a spout (both during and between experimental sessions), the jeweled light above the spout was constantly illuminated, and each mouth contact with the spout (the reinforced operant response) illuminated the pair of white translucent-lensed lights for the duration of the response. During sessions, when drug solution was available at a spout, the jeweled light above that spout flickered at a rate of 10 Hz and the green-lensed lights were illuminated for the duration of each response.

Completion of the response requirements of the reinforcement schedule in effect at a spout resulted in operation of the solenoid for a maximum of 150 ms, allowing approximately 0.64 mL of liquid through the spout. To prevent liquid spillage, solenoid operation terminated if a monkey withdrew from contact with the spout before completion of the normal, 150-ms delivery. Solid-state programming and recording equipment were located in an adjacent room.

Drugs

Concentrations of ethanol are expressed in weight/volume percentages. Ninety-five percent ethanol was added to tap water in appropriate amounts. Stock solutions of sodium pentobarbital (6.25 mg/mL) were prepared with tap water at 7- to 10-day intervals and stored at 3 °C. Daily solutions were mixed by adding tap water to appropriate amounts of

stock solution approximately 2 hr prior to sessions.

The constituents and concentrations of the drug solution available to each monkey during sessions remained constant throughout the experiment. Monkeys M-C and M-LA received a 1 mg/mL pentobarbital solution; M-S2 and M-CR's drug solutions contained, in addition to 1 mg/mL pentobarbital, 0.5 and 1% ethanol, respectively; M-D received an 8% ethanol solution.

Procedure

The operant response was a mouth contact (usually a lip contact) with a brass drinking spout. The response topography varied from one in which the mouth completely surrounded the spout, to a pattern in which the head moved up and down, with the lower and upper lips alternately contacting the spout. Some licking of the spout was also observed. The purpose of reinforcing a class of mouth-spout-contact responses was to allow immediate delivery of the liquid reinforcer and to prevent spillage.

Experimental sessions were 3 hr in length and were conducted daily, 7 days per week. A 1-hr timeout (TO), during which stimulus lights were off and responding had no programmed consequences, was in effect just prior to each session. During this time the monkeys' water consumption values for the intersession period were recorded and solutions for the session were placed in each monkey's reservoirs. Following sessions there was a second 1-hr TO, during which data from the session were recorded and water was placed in one of each monkey's reservoirs, where it was available on a CRF schedule between sessions. One hour of access to water followed the postsession TO; this was succeeded by the third 1-hr TO of the day, at which time the animals received their daily allotment of Purina Monkey Chow. During the remaining 17 hr of the day, water was again available under a CRF schedule.

The monkeys were tested with drug solution and water available concurrently under identical tandem FR- X CRF- N schedules, with side positions of the liquids reversed daily. Each condition was tested with a subject until 10 sessions of stable behavior were obtained. Stability was defined as the absence of an observable increasing or decreasing trend

in the number of liquid deliveries over the 10-day period. The number of sessions required to reach stability across values of the tandem schedule ranged from 10 to 26; the majority of conditions required fewer than 15 sessions, and the modal number of sessions at a particular condition was 10.

Under the tandem FR- X CRF- N schedule, the FR size (X) and number (N) of consecutive CRF liquid deliveries following FR completions were systematically varied. The quantity of drug solution available following completion of each fixed ratio was manipulated by varying the number (N) of liquid deliveries programmed to occur under the CRF schedule. The value of N was varied across blocks of sessions at each FR size that was tested.

At each FR size an initial CRF- N value was tested, followed by testing at progressively lower values of N . The value of N was decreased by half after each block of 10 sessions of stable responding. The progressive decreases in the value of N continued until either (1) the mean number of drug deliveries obtained at a particular value of N fell below 25% of the mean number obtained when that N was first used (as an initial CRF- N value of an earlier FR series), or (2) the CRF-1 condition was reached. After testing at the lowest value of CRF- N in an FR series, monkeys were retested at the CRF- N value used at the beginning of the series.

After the retest condition of each FR series, both the FR size and the value of CRF- N were doubled, and testing proceeded through a new series of CRF- N halvings at the higher FR size. The experiment terminated when one of two criteria was met: Either a monkey completed, on the average, only one fixed ratio per session at the initial CRF- N condition of a new FR series, or a monkey's responding declined to low levels within a series and responding under the retest condition was markedly lower than under the initial test condition.

Four of the monkeys began the experiment at schedule values of FR 8 CRF-2: After 8 responses were emitted, each of the next 2 responses produced a liquid delivery. Monkey M-LA began at FR 16 CRF-4, for under these conditions he showed greater separation between the numbers of drug and water deliveries. Table 1 lists the order in which values

Table 1
Sequence of tandem reinforcement schedule values tested with Monkey M-S2.

Fixed-ratio size	Number of available second-component liquid deliveries (CRF-N)							
	128	64	32	16	8	4	2	1
8							1, 3 ^a	2
16						4, 7	5	6
32					8, 12	9	10	11
64				13, 18	14	15	16	17
128			19, 23	20	21	22		
256		24, 28	25	26	27			
512	29, 33 ^c	30	31	32 ^b				

^a The second number appearing at initial schedule values of each FR delivery-manipulation series indicates a retest condition.

^b Monkey M-S2 was mistakenly tested at one extra CRF-N value in his FR-512 series, after having met the criterion for shifting to the retest condition (see text). This was the only exception to the criteria set for terminating a CRF-N-halving series that occurred for any of the monkeys.

^c A second retest condition for this subject, obtained following exposure to a reacquisition procedure instituted subsequent to low levels of responding during the original retest.

of the tandem FR-X CRF-N schedule were tested for one representative monkey, M-S2.

The first of the two criteria mentioned above for halting a CRF-N series can be illustrated by a specific example. When Monkey M-S2 was tested at FR 32, the CRF value of 8 was introduced for the first time (Table 1). Under these conditions the monkey obtained a mean of 462 drug deliveries. At the CRF-8 condition at FRs of 64 and 128, this monkey obtained a mean of 368 and 224 drug deliveries, respectively; because both of these numbers are greater than 25% of 462, the value of *N* continued to be halved to values lower than 8 in each of these series (see Table 1 for the sequence of test conditions). However, at FR 256, M-S2 obtained a mean of 41 drug deliveries at FR 256 CRF-8; because this is less than 25% of 462, the retest condition immediately followed the test at FR 256 CRF-8 (Table 1).

The overall proportion of deliveries to responses at each condition can be calculated by dividing the number of deliveries per FR by the size of the FR. Larger values of this proportion indicate greater amounts of available drug per FR response. The doubling of both the FR size and the number of deliveries available per FR for the beginning of each new series permitted the proportion of liquid deliveries to FR responses to remain constant (1:4) across the initial schedule condition of each FR series. This proportion was also constant across the second condition of each series (1:8), the third condition (1:16), and so on.

Limiting the maximum value of CRF-N at low FR values, and doubling it with each doubling of FR size, also prevented drug overdosing.

RESULTS

Figure 1 shows that rates of responding maintained by drug deliveries generally exceeded rates maintained by water deliveries. As FR size increased, maximum rates occurred at progressively larger numbers of deliveries per ratio. For both drug- and water-maintained responding, rates tended to decline as FR size increased. At FR values of 8, 16, and (for 3 monkeys) 32, response rates increased as the number of deliveries per ratio was halved (Figure 1). However, these increases were not great enough to maintain a constant number of deliveries per session within these FR series (Figure 2). At higher FR values, rates declined when the fewest deliveries per FR were available.

Figure 2 illustrates that the number of drug deliveries per session increased with increases in the number of drug deliveries per FR. For 3 monkeys, water deliveries showed a pattern similar to that for drug deliveries. However, with 2 monkeys, the number of water deliveries remained uniformly low. At each FR value, as the number of liquid deliveries per ratio decreased, water deliveries declined more rapidly than did drug deliveries. Maximum pentobarbital intakes for Monkeys M-LA, M-C, M-S2, and M-CR were 31, 43, 45, and 35

Fig. 1. Mean response rates maintained by deliveries of drug solution or water, as a function of number of deliveries per FR. Circles connected by solid lines represent mean response rates ($n = 10$) maintained by drug deliveries. Triangles connected by broken lines represent mean response rates ($n = 10$) maintained by water deliveries. Disconnected points within each FR series represent retest values. Brackets denote SE_M ; absence of brackets at a point indicates that the SE_M fell within the area occupied by the point. At each FR size, CRF- N values are listed in order of ascending value, which is the reverse of the order in which they were tested. Asterisks indicate a second retest condition, obtained after a reacquisition procedure that followed the retest condition of the final series. This second retest was conducted as the final experimental condition with the 3 monkeys whose responding during the original retest did not recover to levels comparable to those of the series' initial test condition.

Mean liquid deliveries per 3-hr session

Fixed-Ratio size

Fig. 2. Mean numbers of liquid deliveries per session as a function of number of deliveries per FR. Circles connected by solid lines represent mean numbers of drug deliveries ($n = 10$). Triangles connected by broken lines represent mean numbers of water deliveries ($n = 10$). Brackets denote SE_M ; absence of brackets at a point indicates that the SE_M fell within the area occupied by the point. At each FR size, CRF-N values are listed in order of ascending value, which is the reverse of the order in which they were tested. Asterisks are as in Figure 1.

Fig. 3. Representative cumulative records of Monkey M-S2's performance at each CRF-*N* condition at FR 64. Records are from sessions in which the total number of drug deliveries was closest to the monkey's overall mean for that condition. At each condition, upward steps of the upper pen recorded mouth-contact responses on the drug spout. Downward deflections of this pen marked drug deliveries. Deflections of the pen on the horizontal line below the record of drug-reinforced responding marked water deliveries.

mg/kg/3-hr session, occurring at the 1:4 delivery-to-response proportion at FRs 32, 64, 8, and 32, respectively. Monkey M-D's greatest ethanol intake, 1,550 mg/kg/3-hr session, occurred at the 1:4 delivery-to-response proportion during his FR 16 series.

Figure 3 presents representative cumulative records for Monkey M-S2 from sessions at each CRF-*N* condition at FR 64. Responding was characteristic of behavior maintained under FR schedules. Many drug deliveries were obtained during an initial bout of drinking at the beginning of each session, followed by pauses that were interrupted by later, shorter periods of drug responding.

Figure 4 depicts the total numbers of drug deliveries obtained per session at the different delivery-to-response proportions tested. These are the same drug delivery values seen in Fig-

ure 2, but plotted differently. Total deliveries are plotted as a function of FR size for proportions of 1 delivery per 4, 8, 16, 32, and 64 responses. In general, the maximum number of drug deliveries was obtained at the highest delivery-to-response proportion, 1:4. For all subjects but M-LA, an approximately constant number of drug deliveries was obtained across FR sizes at this most favorable proportion. However, for some of the monkeys the number of drug deliveries began to decline at this proportion at the higher FR values. Although not shown in Figure 4, all monkeys that underwent a retest condition during their final, highest FR series showed a substantial diminution in drug deliveries at the 1:4 proportion under these retest conditions. With each decrease in the proportion of deliveries to responses, the number of drug deliveries per session declined at each FR size, and there was a more rapid decline to low levels in the number of drug deliveries across doublings of FR size. Finally, Figure 4 reveals that there was a minimum proportion between deliveries and responses (1:32 or 1:64, across monkeys) below which behavior was not maintained within any FR series.

Monkey M-S2 at times showed behavioral signs of severe intoxication (gross ataxia and anesthesia) during sessions at delivery-to-response proportions of 1:4; behavioral signs of moderate intoxication (moderate ataxia and incoordination, inability to move without losing balance) were evident during sessions when the proportion was 1:8; signs of mild intoxication (slowness of responsiveness and movement, mild drowsiness) were observed at proportions of 1:16; and very mild signs of intoxication, or none at all, were observed at lower proportions. The pattern revealed by behavioral observation was similar for Monkeys M-CR and M-LA, except that signs of mild intoxication persisted under some schedule combinations where the delivery-to-response proportion was 1:32. Monkey M-C's motor behavior was severely affected at proportions of 1:4 and 1:8, moderately affected at proportions of 1:16, and not visibly affected at lower proportions. No behavioral signs of intoxication were observed with Monkey M-D, who received 8% ethanol.

Figure 5 shows the effects of doubling FR size on the relative number of fixed ratios completed per session. For each case in which

Fig. 4. Mean numbers of drug deliveries per session ($n = 10$) as a function of FR size, plotted according to the overall proportion of deliveries to responses. This proportion was calculated for each condition by dividing the number of CRF deliveries per FR by the size of the FR. The larger the value of this proportion, the greater the amount of available drug per FR response, overall. Brackets are as in earlier figures. Retest conditions are not shown.

a particular number of deliveries per FR was tested at two consecutive FR values, the number of fixed ratios completed at the higher FR is expressed as a percentage of the number of ratios completed at the lower FR value. Doubling FR size always resulted in a decrease in the number of fixed ratios completed, regardless of the number of CRF deliveries avail-

able. What is of particular interest is that doubling FR size had the greatest relative effect at low amounts of drug per FR, and progressively less effect as drug amount increased. In other words, when FR size was doubled, the percent change in behavior varied inversely with the magnitude of the reinforcer: The larger the magnitude, the less the

Mean fixed ratios completed at the higher FR, as a percentage of fixed ratios completed at the preceding FR

Fig. 5. Mean numbers of fixed ratios completed per session ($n = 10$), as percentages of the mean numbers of fixed ratios completed at identical CRF-N values during the immediately preceding FR series. These percentages were calculated for each case in which a particular number of deliveries per FR was tested at two consecutive FR values. Along the abscissa, current-FR-series values are listed as numerators and preceding-FR-series values are listed as denominators. Within each bar, numerators and denominators indicate, respectively, the mean numbers of fixed ratios completed during the current series and during the previous series at the listed CRF-N value, rounded to the nearest whole integer. The height of the bars indicates actual percentages; the mean numbers of fixed ratios completed are included at each bar as an indication of absolute values, although the values are inexact due to the rounding procedure. As an illustration: When one drug delivery was available per FR, Monkey M-LA completed 186 and 401 fixed ratios at FRs 32 and 16, respectively (numerator and denominator in the far-left bar in M-LA's graph). Dividing 186 by 401, then multiplying by 100, yields 46%. Thus, at FR 32 and one delivery, the monkey completed 46% of the mean number of fixed ratios that were completed at FR 16 and one delivery. Note that retest conditions do not appear.

percent change. This relationship is illustrated in Figure 5: Across rows of bars comparing consecutive FR values, the height of the percentage bars generally increases as the amount of drug per FR increases.

DISCUSSION

Reinforcer magnitude can be manipulated in two ways when an orally delivered solution is used as a reinforcer—by varying the concentration of the reinforcing substance or by varying the amount of solution that is delivered while maintaining its concentration at a constant value. In the present study the amount (mg) of drug per FR was manipulated by varying the number of drug deliveries per FR. In an earlier study the amount of drug per FR was manipulated by varying drug concentration (Lemaire & Meisch, 1984). Many of the findings of the present experiment parallel those of the earlier study. The drug solutions served as reinforcers, as demonstrated by the higher rates of behavior maintained by their delivery than by delivery of the vehicle, water. As FR size was increased in both studies, the amount of drug that maintained maximum response rates shifted to higher values. In both studies, drug intake (mg of drug per kg of body weight per 3-hr session) increased with amount of drug per FR. Finally, in both studies, the larger the amount of drug delivered per FR, the less was the relative decrease in number of FRs completed when FR size was increased. In the present study, the functional relationships between independent and dependent variables held regardless of whether pentobarbital, ethanol, or a combination of the two drugs served as the reinforcer.

Nevin (1974) defined the strength of an operant as the relative resistance of its response rate to change when contingencies are altered. Analogously, Lemaire and Meisch (1984) discussed the relative reinforcing efficacy of a reinforcer in terms of its ability to maintain behavior, relative to baseline levels, when schedule requirements are increased. The findings of the present study suggest that larger drug amounts had greater relative reinforcing efficacy, in that the larger the amount of drug per FR, the less was the relative decrease in the number of ratios completed when FR size was doubled.

One unusual feature of the present study

deserves comment. In this experiment the same class of responses occurred in both the FR and the CRF liquid-delivery components of the tandem schedule. In contrast, other studies typically have involved different responses—one to meet reinforcement contingencies (e.g., a rat's lever press), and another to consume the reinforcer (e.g., the rat's eating a food pellet). In spite of this unusual feature, the findings of the present study were consistent with previous studies, in that FR response patterning was similar to the pattern of responding seen under FR schedules in other studies, and there was a decrease in the number of fixed ratios completed with increases in FR size.

Several difficulties are encountered when the quantity of orally delivered drug is manipulated by changing the concentration of a drug solution. Factors such as drug solubility and palatability impose a ceiling on the concentrations that can be tested. Also, with each change in concentration both taste and rate of absorption are altered. In contrast, such conditions were held constant in the present study, in which monkeys were progressively permitted to take more deliveries of a readily self-administered drug solution at the end of each ratio. Delivery of large amounts of drug upon completion of schedule requirements in the current study made possible the maintenance of behavior at larger FR values than in previous studies (e.g., Carroll, Stotz, Kliner, & Meisch, 1984; Lemaire & Meisch, 1984), and with most subjects a wider range of reinforcer magnitudes was tested than in the earlier study (Lemaire & Meisch, 1984).

In the present study of interactions between FR size and reinforcer magnitude, performance varied as a function of the quotient of reinforcer size and FR size (Figure 4). An earlier study (Schwartz, 1969) demonstrated similar results but employed pigeons as subjects, food as the reinforcer, and concurrent chained schedules. In Schwartz's study, two FI 90-s schedules were in effect on separate side-keys, as the initial links of concurrently operating chained schedules. With a probability of .5, completion of the response requirement of either FI schedule resulted in entrance into a second component, consisting of an FR requirement followed by presentation of grain. Both the size of the FR and the duration of grain access were varied systematically. Particular combinations of FR size

and feeder-access duration were presented concurrently for blocks of sessions. Response rates in the FR components were relatively invariant across the range of feeder-access durations. Also, response rates in the two FI schedules, relative to each other, were not discernibly related to the two independent variables—relative reinforcement time following completion of the FRs of the two schedules and the reciprocals of the two FR values—when either of these two variables was considered alone. However, relative FI response rates were directly related to the interaction of the two variables—relative feeder-access time per ratio response. That is, response rates in the initial FI links, relative to each other, were proportional to the relative reinforcer durations per FR response in the second links of the concurrent chained schedules. Thus, data from Schwartz's study and from ours indicate the importance for behavior of the proportion, reinforcer size divided by FR size.

Schwartz (1969) also noted that an increase in feeder-access time systematically compensated for the effects on FI response rate of an increase in FR requirement. He suggested that one could make up for a doubling in FR size by doubling the magnitude of the reinforcer. Over the range of values he studied, FR 5 to FR 75, doubling the feeder-access time did compensate for the effects of a doubling in FR value. The findings of the present study were partially consistent with those of Schwartz. In Figure 4, perfect compensatory relationships between doublings of FR and CRF-*N* values would have been indicated by horizontal, parallel lines at different delivery-to-response proportions. Across low and moderate FR sizes, fairly stable performances were maintained by most subjects at high delivery-to-response proportions (1:4 and 1:8) when both FR size and drug amount were proportionately increased. However, as FR size was further increased, performance was not maintained, despite continued proportionate increases in available drug amount per FR. Thus, compensation did not hold indefinitely as reinforcer size and response requirement were repeatedly increased. At lower proportions of deliveries to responses, the compensating effects of a simultaneous doubling in reinforcer size with doubling of FR size were weaker, as the negatively sloped lines of Figure 4 indicate.

There is a convergence of evidence demonstrating that reinforcers of larger magnitude are, in general, more efficacious in maintaining behavior (e.g., Nevin, 1974; Shettleworth & Nevin, 1965), and, specifically, that within reinforcing dose ranges the same is true of larger drug quantities. The several experimental designs employed in studies of drug-reinforcer efficacy yield results that are in good agreement (Griffiths, Brady, & Bradford, 1979). Results of the present experimental procedure are consistent with this body of data and lead us to stress again (see Lemaire & Meisch, 1984) the desirability, in investigations of comparative reinforcing efficacy, of examining behavior maintained by reinforcer magnitudes spanning an appreciable range, across several schedule values. Relationships between behavior and reinforcer magnitude can then be observed at several schedule values, and relative changes in behavior can be compared across shifts in behavioral requirements. Pooling information from analyses of both absolute and relative aspects of reinforced behavior will provide a fuller account of the relation of behavior to reinforcer magnitude.

REFERENCES

- Balster, R. L., & Schuster, C. R. (1973). Fixed-interval schedule of cocaine reinforcement: Effect of dose and infusion duration. *Journal of the Experimental Analysis of Behavior*, **20**, 119-129.
- Bradshaw, C. M., Szabadi, E., & Bevan, P. (1978). Relationship between response rate and reinforcement frequency in variable-interval schedules: The effect of the concentration of sucrose reinforcement. *Journal of the Experimental Analysis of Behavior*, **29**, 447-452.
- Carroll, M. E., Stotz, D. C., Kliner, D. J., & Meisch, R. A. (1984). Self-administration of orally-delivered methohexital in rhesus monkeys with phencyclidine or pentobarbital histories: Effects of food deprivation and satiation. *Pharmacology Biochemistry and Behavior*, **20**, 145-151.
- Catania, A. C. (1963.) Concurrent performances: A baseline for the study of reinforcement magnitude. *Journal of the Experimental Analysis of Behavior*, **6**, 299-300.
- DeNoble, V. J., Svikis, D. S., & Meisch, R. A. (1982). Orally delivered pentobarbital as a reinforcer for rhesus monkeys with concurrent access to water: Effects of concentration, fixed-ratio size, and liquid positions. *Pharmacology Biochemistry and Behavior*, **16**, 113-117.
- de Villiers, P. (1977). Choice in concurrent schedules and a quantitative formulation of the law of effect. In W. K. Honig & J. E. R. Staddon (Eds.), *Handbook of operant behavior* (pp. 233-287). Englewood Cliffs, NJ: Prentice-Hall.

- Dougherty, J., & Pickens, R. (1973). Fixed-interval schedules of intravenous cocaine presentation in rats. *Journal of the Experimental Analysis of Behavior*, **20**, 111-118.
- Griffiths, R. R., Brady, J. V., & Bradford, L. D. (1979). Predicting the abuse liability of drugs with animal drug self-administration procedures: Psychomotor stimulants and hallucinogens. In T. Thompson & P. B. Dews (Eds.), *Advances in behavioral pharmacology* (Vol. 2, pp. 163-208). New York: Academic Press.
- Griffiths, R. R., Brady, J. V., & Snell, J. D. (1978). Progressive-ratio performance maintained by drug infusions: Comparison of cocaine, diethylpropion, chlorphentermine, and fenfluramine. *Psychopharmacology*, **56**, 5-13.
- Harvey, S. C. (1980). Hypnotics and sedatives. In A. G. Gilman, L. S. Goodman, & A. Gilman (Eds.), *Goodman and Gilman's The pharmacological basis of therapeutics* (6th ed., pp. 339-375). New York: Macmillan.
- Henningfield, J. E., & Meisch, R. A. (1976). Drinking device for rhesus monkeys. *Pharmacology Biochemistry and Behavior*, **4**, 609-610.
- Henningfield, J. E., & Meisch, R. A. (1979). Ethanol drinking by rhesus monkeys with concurrent access to water. *Pharmacology Biochemistry and Behavior*, **10**, 777-782.
- Hoffmeister, F. (1979). Progressive-ratio performance in the rhesus monkey maintained by opiate infusions. *Psychopharmacology*, **62**, 181-186.
- Iglauer, C., & Woods, J. H. (1974). Concurrent performances: Reinforcement by different doses of intravenous cocaine in rhesus monkeys. *Journal of the Experimental Analysis of Behavior*, **22**, 179-196.
- Johanson, C. E., & Schuster, C. R. (1975). A choice procedure for drug reinforcers: Cocaine and methylphenidate in the rhesus monkey. *Journal of Pharmacology and Experimental Therapeutics*, **193**, 676-688.
- Kelleher, R. T., & Goldberg, S. R. (1977). Fixed-interval responding under second-order schedules of food presentation or cocaine injection. *Journal of the Experimental Analysis of Behavior*, **28**, 221-231.
- Kelleher, R. T., & Morse, W. H. (1968). Determinants of the specificity of behavioral effects of drugs. *Ergebnisse der Physiologie Biologischen Chemie und Experimentellen Pharmacologie*, **60**, 1-56.
- Kliner, D. J., & Meisch, R. A. (1982). The effects of food deprivation and satiation on oral pentobarbital self-administration in rhesus monkeys. *Pharmacology Biochemistry and Behavior*, **16**, 579-584.
- Lemaire, G. A., & Meisch, R. A. (1984). Pentobarbital self-administration in rhesus monkeys: Drug concentration and fixed-ratio size interactions. *Journal of the Experimental Analysis of Behavior*, **42**, 37-49.
- McLeod, D. R., & Griffiths, R. R. (1983). Human progressive-ratio performance: Maintenance by pentobarbital. *Psychopharmacology*, **79**, 4-9.
- Meisch, R. A., Henningfield, J. E., & Thompson, T. (1975). Establishment of ethanol as a reinforcer for rhesus monkeys via the oral route: Initial results. In M. M. Gross (Ed.), *Advances in experimental medicine and biology: Vol. 59. Alcohol intoxication and withdrawal: Experimental studies II* (pp. 323-342). New York: Plenum Press.
- Morse, W. H. (1966). Intermittent reinforcement. In W. K. Honig (Ed.), *Operant behavior: Areas of research and application* (pp. 52-108). New York: Appleton-Century-Crofts.
- Neuringer, A. J. (1967). Effects of reinforcement magnitude on choice and rate of responding. *Journal of the Experimental Analysis of Behavior*, **10**, 417-424.
- Nevin, J. A. (1974). Response strength in multiple schedules. *Journal of the Experimental Analysis of Behavior*, **21**, 389-408.
- Pickens, R., & Thompson, T. (1972). Simple schedules of drug self-administration in animals. In J. M. Singh, L. H. Miller, & H. Lal (Eds.), *Drug addiction: Vol. 1. Experimental pharmacology* (pp. 107-120). Mount Kisco, NY: Futura.
- Ritchie, J. M. (1980). The aliphatic alcohols. In A. G. Gilman, L. S. Goodman, & A. Gilman (Eds.), *Goodman and Gilman's The pharmacological basis of therapeutics* (6th ed., pp. 376-390). New York: Macmillan.
- Schwartz, B. (1969). Effects of reinforcement magnitude on pigeons' preference for different fixed-ratio schedules of reinforcement. *Journal of the Experimental Analysis of Behavior*, **12**, 253-259.
- Sharpless, S. K. (1970). Hypnotics and sedatives. I. The barbiturates. In L. S. Goodman & A. Gilman (Eds.), *The pharmacological basis of therapeutics* (4th ed., pp. 98-120). New York: Macmillan.
- Shettleworth, S., & Nevin, J. A. (1965). Relative rate of response and relative magnitude of reinforcement in multiple schedules. *Journal of the Experimental Analysis of Behavior*, **8**, 199-202.
- Spealman, R. D., & Goldberg, S. R. (1978). Drug self-administration by laboratory animals: Control by schedules of reinforcement. *Annual Review of Pharmacology and Toxicology*, **18**, 313-339.
- Valenstein, E. S. (1964). Problems of measurement and interpretation with reinforcing brain stimulation. *Psychological Review*, **71**, 415-437.
- Verhave, T. (1963). Towards an empirical calculus of reinforcement value. *Journal of the Experimental Analysis of Behavior*, **6**, 525-536.
- Young, A. M., Swain, H. H., & Woods, J. H. (1981). Comparison of opioid agonists in maintaining responding and in suppressing morphine withdrawal in rhesus monkeys. *Psychopharmacology*, **74**, 329-335.
- Young, A. M., Woods, J. H., Herling, S., & Hein, D. W. (1983). Comparison of the reinforcing and discriminative stimulus properties of opioids and opioid peptides. In J. E. Smith & J. D. Lane (Eds.), *The neurobiology of opiate reward processes* (pp. 147-174). Amsterdam: Elsevier/North Holland Biomedical Press.

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