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# Drug Effects on an Effortful Operant: Pentobarbital and Amphetamine

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NEWLAND, M. C. AND B. WEISS. *Drug effects on an effortful operant: Pentobarbital and amphetamine.* PHARMACOL BIOCHEM BEHAV **36**(2) 381–387, 1990.—The behavioral effects of amphetamine and pentobarbital depend upon the conditions maintaining behavior. For example, amphetamine usually decreases the rate of operant behavior maintained by fixed ratio schedules while pentobarbital either increases it or leaves it unaffected. However, when considerable exertion is required, as in situations that require endurance, amphetamine tends to enhance performance while barbiturates degrade it. These differences complicate predictions of the effects of these two drugs on effortful operants. The present experiment was designed to characterize effortful responding behaviorally and pharmacologically. Cebus monkeys were trained to operate a lever by flexing their arms and extending their legs; this response exerted a force approximating their body weight. This operant was maintained by a multiple fixed ratio fixed interval (Mult FR FI) schedule. The two schedules maintained dramatically different response patterns. The FR schedule maintained vigorous, high rate responding characterized by a narrow IRT distribution centered at 0.5 sec. The FI schedule maintained very low overall rates of responding characterized by a variable IRT distribution with a median of 1.5 to 2 sec. Despite very low rates of responding during the FI component, no consistent rate increases appeared after amphetamine, and 0.3 mg/kg eliminated responding altogether. Pentobarbital increased overall rate but also shifted the interresponse time (IRT) distribution toward longer IRTs. The increase in overall rate arose from an earlier onset of responding during the FI component and occurred simultaneously with response slowing. The present studies do not support suggestions of a generalized enhancement of effortful performance by amphetamine or a generalized degradation by pentobarbital.

Effort Operant Fixed ratio Fixed interval Schedule-controlled behavior Primate Cebus monkey Drugs Amphetamine Pentobarbital Behavior

ALMOST all of the data describing the modification of schedule-controlled performance by drugs derive from studies of operants, such as key pecks and lever presses, that require minimal effort. Little is known about drug effects on operants that require substantial physical effort and the effects of amphetamine and pentobarbital illustrate the ambiguous predictions that might be made on the basis of the available literature.

Amphetamine is generally held to enhance athletic performance (23). Enhancing effects of amphetamine have been observed in highly motivated subjects, such as competitive swimmers (16, 22, 25), but amphetamines also enhance the swimming and treadmill endurance of rats (2, 12, 13, 22). Amphetamine's enhancing effects are clearest in performance impaired by sleep deprivation or with tasks that are tedious and repetitious (30,33). It also has been reported to enhance wakefulness and vigilance in human volunteers (25, 30, 33).

Amphetamines and barbiturates differ in their effects on performance degraded by fatigue. In situations where amphetamine enhances wakefulness, pentobarbital produces sleepiness (30), and where amphetamine enhances athletic performance, secobarbital degrades it (25,26). Such effects have also been reported in animal studies; pentobarbital disrupts swimming endurance in rats, an effect directly opposite to that of amphetamine (2,18).

Amphetamine's and pentobarbital's reputed effects on performance are based upon studies of fatigue and wakefulness, but these studies offer little guidance on how these drugs might affect effortful, schedule-controlled behavior. Of the large number of reinforcement schedules that have been studied, fixed-ratio (FR) schedules might seem the best suited to the study of response effort because they impose a direct and manipulable cost on behavior: the number of responses required for each reinforcer. However, the effects of both pentobarbital and d-amphetamine on conventional fixed-ratio performance differ from what might be predicted from their effects on endurance. As in the endurance studies, amphetamine and pentobarbital have contrasting effects on FR performance, but the direction of change is different. Moderate doses of d-amphetamine usually decrease the rate of FR responding (7,24) by introducing long pauses in otherwise high-rate responding (19,32). Moderate doses of pentobarbital, however, frequently increase the overall rate of FR responding (5, 25, 31). These rate increases result from pentobarbital's tendency to reduce or eliminate very long pauses, such as those following reinforcement or which appear early in the ratio (32).

Fixed-interval (FI) schedules provide a useful contrast to FR schedules when examining drug effects. Under FI schedules, the reinforcement rate is less directly tied to the rate of responding and the typical response pattern and topography selected by the

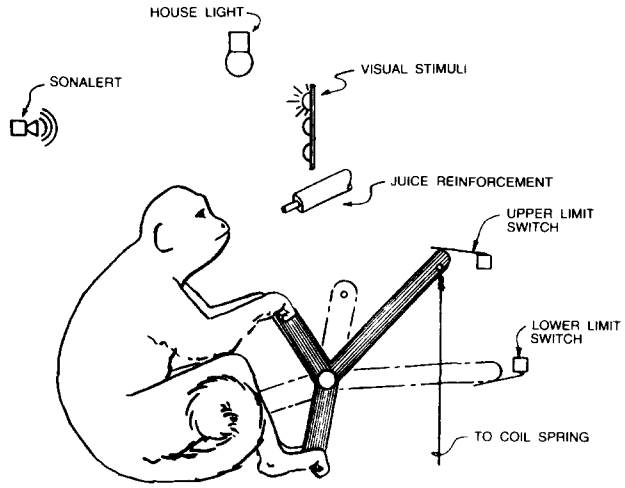


FIG. 1. Schematic showing the operation of the response manipulandum. The monkey pulled the lever with its arms while simultaneously pushing with its legs. A response was defined in three steps: 1) closing the lower limit switch, 2) opening the upper limit switch, and 3) opening the lower limit switch. To accomplish this the manipulandum had to be moved through an arc length of 10 cm against a 40 N (4 kg) spring. A brief Sonalert pulse followed each successful response. The visual stimuli indicated which schedule component was in effect.

schedule differ markedly from those seen under FR schedules. Small doses of amphetamine tend to increase the rate of responding maintained by FI schedules and larger doses tend to decrease it. Both increases and decreases in overall response rate have been reported after pentobarbital (5, 15, 24).

The present study was designed to characterize effortful operants. The literature provides no firm basis on which to predict schedule or drug effects. FI and FR schedules of reinforcement were selected for study both becuase performance under these schedules have been examined under a variety of conditions and because these two schedules engender different patterns of responding. Pentobarbital and amphetamine were selected for the study because of the extensive literature and their contrasting behavioral effects.

## METHOD

### *Subjects*

Two wild-caught, male adult Cebus monkeys *(C. apella)*, CM842 and CM904, weighing 3.2 kg and 3.9 kg, respectively, served in the experiments. The monkeys were housed in individual cages in an AAALAC-approved facility and had free access to Purina Monkey Chow. They were water deprived at about 1600 hours and tested in the morning the following day. The monkeys had not participated in prior experiments and had received no prior drugs.

### *Apparatus*

Monkeys perched in a Plexiglas primate chair that was open at the front and provided only neck restraint. The chair was placed in front of a response device as illustrated in Fig. 1. The monkey pulled on the top bar with its arm while simultaneously pushing the lower bar with its legs, executing a motion resembling that requried by a rowing machine. The manipulandum was attached to a constant force, spring-driven reel (Neg'ator™), and moved through an angle of about 45 degrees and an arc length of 10 cm. This permitted nearly full extension of the arms at the beginning of the response and substantial extension of the legs at the peak of the response. The spring resisted movement in one direction with a force of 39 to 41 Newtons (corresponding to a 4.0 to 4.2 kg mass), and returned the lever to resting position when the animal released the bars.

Monkeys were tested in a sound-deadened chamber, 171 by 56 by 86 cm ($H \times W \times D$, inside dimensions). Air was circulated by connecting a floor vent spanning the back of the chamber to a circulating exhaust system. This pulled fresh air through a 7 cm shaft situated at the top of the chamber. A fluorescent house light and white noise remained on throughout the sessions. All events were controlled and monitored with 0.01 sec resolution by a PDP-8 computer operating under the Supersked™ system (28).

### *Procedure*

The operant consisted of moving the lever through an arc length of 10 cm and allowing it to return to the home position. Limit switches detected the extremes of movement and a 0.1-sec tone burst from a Sonalert sounded after each complete response. The reinforcement cycle consisted of a 1.5-sec train of Sonalert bursts (0.25 sec on, 0.25 sec off) followed by 1 ml of fruit juice delivered in 0.1 sec through a spout located in front of the monkey's mouth.

After the animal learned to drink from the spout, he was trained to grip the bar and, in a series of steps, to move it until the extreme limit switch was activated. The operant was acquired after about two hours of shaping. Both monkeys were initially trained under a fixed ratio 1 (FR 1) schedule, in which each complete response produced the reinforcement cycle. As the FR parameter was increased gradually to 20 (20 responses required for each reinforcer), a fixed interval 5-sec (FI 5 sec) schedule was introduced. During the FI 5-sec schedule, the reinforcement cycle followed the first response to occur after 5 sec elapsed. Both the FR and FI parameters were changed as behavior permitted. Final performance was maintained by a Multiple FR 20 FI 90-sec (Mult FR 20 FI 90) schedule. Three white lights situated in front of the animal were lit when the FI schedule was in effect and were dark when the FR schedule was in effect. A fluorescent houselight was on during the entire session. The schedule changed after each reinforcer delivery. Sessions lasted until 50 reinforcers were delivered or two hours had elapsed.

### *Drugs and Dosing*

Drugs were administered after behavior had stabilized on the multiple schedule. Stability criteria included the lack of systematic changes in postreinforcement pausing in both schedule components, number of responses per FI, and the time to complete the FR schedule.

d-Amphetamine sulfate and sodium pentobarbital were dissolved in sterile physiological saline in a concentration such that 0.1 ml/kg solution was injected. The sequence of doses was irregular. The drugs were injected in the thigh muscle 10 minutes before the session began. Vehicle sessions were interspersed among the drug sessions. Experimental sessions conducted on the day before a drug or vehicle session provided noninjected control data. Drug injections were administered no more than twice weekly and were separated by at least 48 hours.

The effects of 0.01, 0.03, 0.1, and 0.3 mg/kg of d-amphetamine sulfate and of 1, 3, 6.5 and 10 mg/kg of sodium pentobarbital (all calculated as the salt) are reported. After a complete series of d-amphetamine sessions, the multiple schedule was

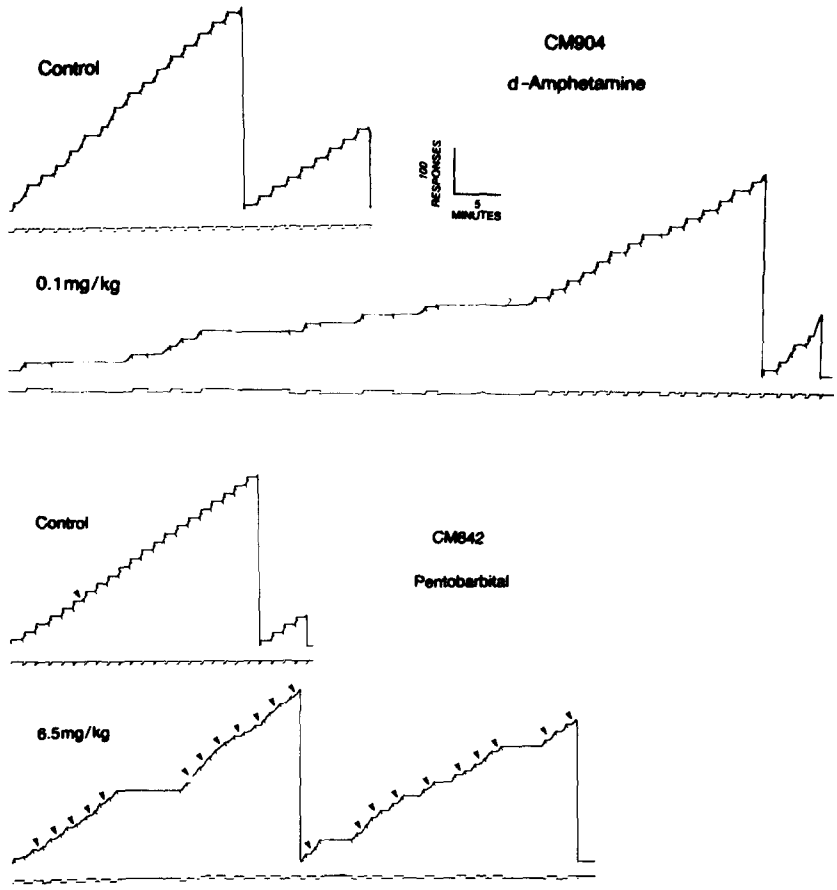


FIG. 2. Cumulative records showing typical control performance and the effects of amphetamine for CM904 (top two records) and control performance and the effects of pentobarbital for CM842 (bottom two records). The response pen advanced for each successful response, deflected for each reinforcer, and reset after 500 responses. The event pen was down for the fixed ratio component and up for the fixed interval component. Following 0.1 mg/kg of d-amphetamine, responding was interrupted by long pauses during the first half of the session but control-like performance was restored after about an hour. To highlight the major effect of pentobarbital, arrows show FI components during which more than five responses occurred. An increase in response output during the FI component is indicated by an increase in the number of intervals containing more than five responses and by the elevated location of the response pen at the end of the pentobarbital session.

rearranged so that the session began with the FI component and some doses of d-amphetamine were readministered.

*Statistical Analyses*

A one-way analysis of variance was performed on each dose-effect relationship described in the Results section. The significance of an overall effect was determined by nonparametric randomization procedures described by (8). Briefly, this involves randomly redistributing the data among treatment groups iteratively, computing the F ratio for each permutation, and tabulating the number of F ratios with a more extreme F ratio than the one obtained from the experimental data. Randomization procedures make no assumptions about the underlying probability distribution, and groups with unequal numbers of data points can be accommodated. Because the number of permutations of each data set was large, a random sample of 10000 permutations of the data for each dose-effect relationship was analyzed.

If a dose-effect relationship was significant, then each dose was compared with the data from control sessions by *t*-test. The *p*-value was determined by randomization tests.

## RESULTS

*Control Sessions*

Appropriate schedule control appeared under noninjection control conditions, although the FI component was marked by an unusually low number of responses per interval. Responding was stable in all indices of performance throughout the series of amphetamine and pentobarbital injections. Typical patterns of responding are displayed by the cumulative records taken from noninjected control sessions and shown in Fig. 2.

Responding during the FR component was characterized by a postreinforcement pause of 5 to 15 seconds followed by an unbroken burst of responding that persisted until reinforcement.

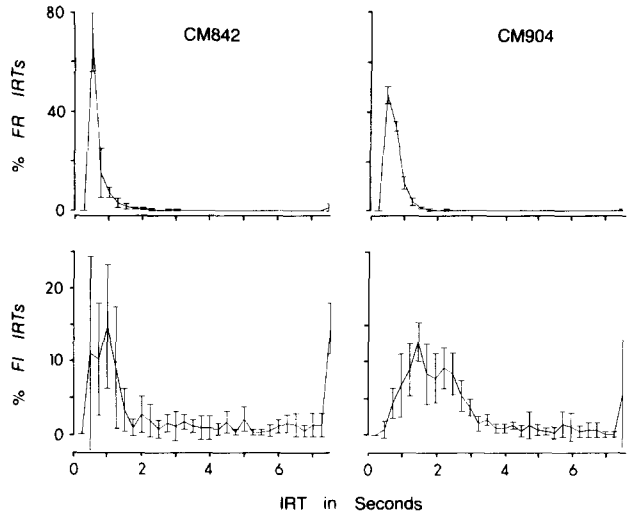


FIG. 3. Interresponse time distributions in 0.25-sec intervals from 5 sequential, drug-free sessions for each animal from the fixed-ratio and fixed-interval components. Error bars show ±two standard errors. All IRTs longer than 7 seconds are summed in the rightmost point.

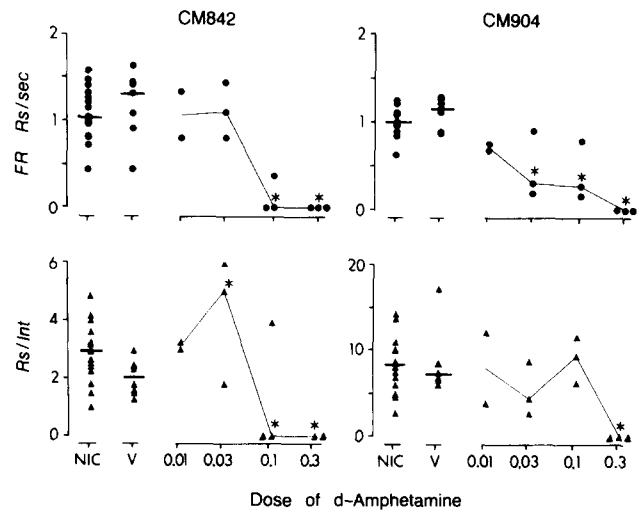


FIG. 4. Overall response rates during the fixed-ratio component (top) and total responses/fixed interval (bottom) for CM842 (left) and CM904 (right) during noninjected control (NIC), vehicle (V), and d-amphetamine sessions. Each point represents a single session and lines connect the medians. The points at 0.3 mg/kg represent 3 sessions during which no responding occurred. The asterisks represent points that are significantly different from control. Note the different scales on the ordinates.

The monkeys were observed perching on the hand and foot bars and operated the manipulandum rapidly without interruption during this component.

Responding during the FI component appeared as a series of slow, separate responses rather than as the coherent burst observed during the FR component. During control sessions, CM842 consistently emitted 1 to 5 responses/interval and CM904 emitted between 2 and 15 responses/interval. Observations revealed a more relaxed topography than that seen during the FR component. The bar was pulled slowly, responses did not occur in bursts, and the animal was not observed perching on the bars while responding.

The distribution of interresponse times (IRTs) reflected the different response topographies found in the FR and FI components (Fig. 3). The IRT was the time between the onset of a response and the onset of the next response. More than 95% of the IRTs during the ratio component fell between 0.5 and 1.25 seconds, with a pronounced break at 0.5 seconds and almost no IRTs longer than 2 seconds.

The IRT distribution taken from the FI component offered a sharp contrast with FR distribution, both in the number of IRTs and in the pattern of the distribution. The FI distributions were multimodal for both animals. The highest peak (ignoring the overflow bin at >7.5 sec) lay at 1 second for CM842 and 1.5 seconds for CM904; the distributions were much broader than those representing the FR component. The area between 0.5 and 1.75 seconds of CM842's distribution included only 54% of the total IRTs. The upper 95% bounds were >7.5 seconds and 5 seconds for CM842 and CM904, respectively.

*d-Amphetamine*

The cumulative records in Fig. 2 illustrate the major effects of d-amphetamine. During the beginning of the session selected to exemplify the effect of 0.1 mg/kg, long pauses separated periods of responding, but the coherent bursts of responding that typify FR performance remained intact. After about one hour, control-like performance returned. Neither monkey responded following 0.3 mg/kg of d-amphetamine, although both monkeys appeared alert. This was true regardless of whether the FI or the FR component began the session.

Doses of 0.1 to 0.3 mg/kg of d-amphetamine lowered FR rates or eliminated responding for both animals (Fig. 4). The number of responses/interval, an indication of FI responding, did not increase for CM904, but CM842 showed a slight increase at 0.03 mg/kg from a median of 3 responses/interval to a median of about 5 responses/interval. Examination of IRT distributions revealed no consistent effects of d-amphetamine on either component (data not shown). The rate decreases observed in the FR component correspond with the long periods of pausing seen in the cumulative records.

*Pentobarbital*

Pentobarbital increased overall FI responding at moderate doses and decreased it at the highest dose studied (Fig. 5). A cumulative record from a typical pentobarbital session is shown in Fig. 2. During the control session only 1 FI contained more than five responses but following 6.5 mg/kg, 22 did. The slope of the cumulative records during the FR component was shallower following pentobarbital indicating that, although the cohesion of responding during the FR component remained intact, the rate decreased appreciably. Higher doses of pentobarbital were sufficiently incapacitating that the animals could not sit upright in the chair without support.

Pentobarbital produced a dose-related decrease in FR response rate at 6.5 mg/kg for both monkeys (Fig. 5); at 10 mg/kg responding was eliminated altogether. Overall FI responding, as indicated by the number of responses per interval, displayed nearly a three-fold increase at 6.5 mg/kg for both monkeys at the same time FR responding suffered a reduction in rate.

The top panels of Fig. 6 present cumulative IRT distributions taken from sessions following 6.5 mg/kg of pentobarbital. The IRTs were calculated as described above and the cumulative distributions from the FR and FI components were summarized

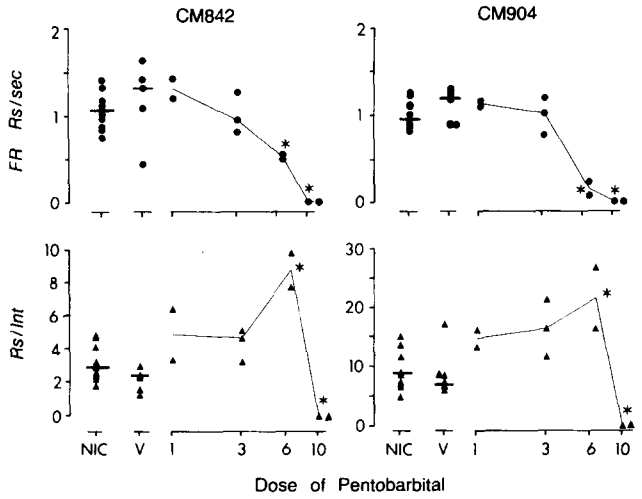


FIG. 5. Overall response rates during the fixed-ratio component (top) and total responses/fixed interval (bottom) for CM842 (left) and CM904 (right) during noninjected control (NIC), vehicle (V), and pentobarbital sessions. Each point represents a single session and lines connect the medians.

using 20 and 10 centiles, respectively. The greater number of responses during the FR component enabled finer resolution in the description of the distribution. The distributions from the two sessions following 6.5 mg/kg were combined and the control distributions in Fig. 6 were taken from sessions preceding the 6.5 mg/kg sessions.

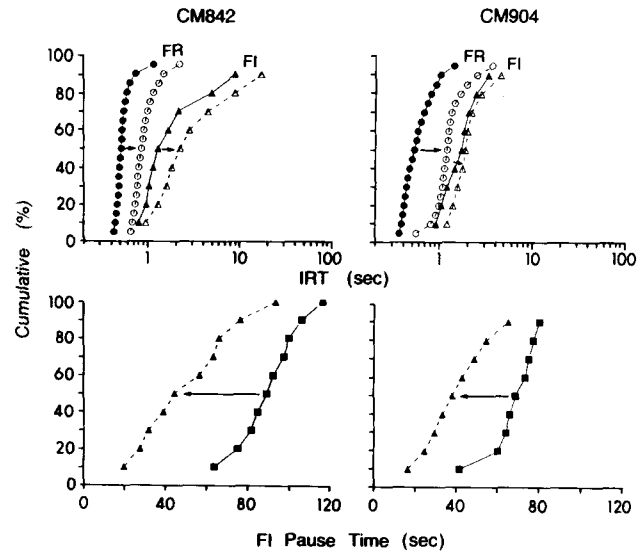


FIG. 6. Cumulative IRT distributions (top) and FI pause time distributions (bottom) for CM842 (left) and CM904 (right) showing the effects of 6.5 mg/kg of pentobarbital (dashed lines, open symbols) compared with control sessions from the previous day (solid lines). The distributions for the FR component (dashed lines) contain 20 points representing the 5th, 10th, . . . 95th centiles of the distribution.The distribution of FI IRTs and FI pause times component contain 10 points representing the 10th, 20th, . . . 90th centiles of the distributions. An arrow connects the median of a control distribution with that of the distribution taken from a drug session on the following day.

Distributions from the control sessions reflected the characteristics of the IRT distributions presented in Fig. 2. The medians were about 0.5 sec and the distribution was very narrow: 95% of the IRTs were less than 1.25 sec. The control FI distribution was shifted toward longer IRTs and was broader (the slope is shallower) than that taken from the FR component.

Pentobarbital shifted both the FR and FI distributions toward longer IRTs in both monkeys, although the shift seen in CM904's FI responding was small. The shift was slightly more pronounced at longer IRTs (toward the top of the curves), especially for CM842. However, the FR IRT distribution remained narrow after pentobarbital and the FI distributions remained broad; the distinction in the two schedules' behavioral effects remained intact at this dose.

The source of increased FI responding is revealed in the bottom panels of Fig. 6, which plot cumulative distributions of FI pause times. The pause time was the time from the onset of the FI component to the first completed response. Median pause times during control sessions for CM842 and CM904 were about 90 and 70 seconds, respectively. During the control sessions, half of the FI pauses for CM842 were longer than the FI parameter of 90 sec so these intervals contained only one response. Only about 10% of the FI pauses for CM904 were longer than the FI parameter. Following 6.5 mg/kg of pentobarbital, FI pause time decreased by 50%; the medians for CM842 and CM904 fell to about 45 and 35 sec, respectively.

## DISCUSSION

### *Behavioral Patterns*

The FR and FI components maintained dramatically different response topographies in the present experiment. Under the FR component, responding occurred in a tight burst until the schedule requirement was fulfilled. The coherence of this burst is best seen in the narrowness of the IRT distribution, which reflected a response topography of perching on the bottom bars and responding at an exceedingly high rate until reinforcement delivery. The observation that the FR component consists of an unbroken stream of responses corresponds with other reports that the FR pattern appears as a single response unit (20, 32, 34).

FI schedules of reinforcement usually maintain a distinctive pattern of responding and a substantial, if highly variable, number of responses in each interval (9, 11, 34). However, in the present experiment, an unusually small number of responses appeared during the FI component. Although this may reflect species differences or any of the other details in which experiments differ, the great species generality observed in FI patterns suggests that these details are less important than the reinforcement contingency itself (21).

The effort and extended displacement required to execute the operant seem the most cogent explanation for the low response rate. This suggestion is consistent with reports that increasing effort lowers rate (4) and enhances the sensitivity of response rate to reinforcement contingencies (19). Indeed, McDowell and Wood (19) showed that force does more than merely reduce overall rate of responding. In humans, increased response force amplified the influence of reinforcement magnitude on response rate,; at high forces (25–146 Newtons) response rate was sensitive to reinforcer magnitude while at lower forces (1–11 Newtons) no relationship emerged.

In the present experiment, the IRTs during the FI component were much longer and more variable than those observed during the FR component and responding appeared more relaxed. The animals were observed sitting in the chair pulling intermittently on

the bar rather than perching on the bar and responding at a high rate.

In most respects, the IRT distributions from the FI component resembled those seen when pigeons peck a key under minimal force requirements (11). In the present study and in Gentry *et al.*, the median IRT was moderate in length, the distribution was bimodal or multimodal, and one mode appeared in an overflow bin collecting long IRTs, or pauses. The IRT distributions from the FI component in the present experiment differ from those presented by Gentry *et al.* (11) in the lack of a mode representing very short IRTs. The absence of very short IRTs is consistent with observations that these IRTs reflect the selection of nibbling or other response topographies that permit certain response devices to oscillate rapidly about the criterion response (32). Such a topography is impossible in the present experiment since the response entailed moving a force of about 40 Newtons through 10 cm.

### *d-Amphetamine*

Amphetamine's effects on FI performance in the present experiment differed from its reported effects on FI performance when more conventional operants are used. Amphetamine usually engenders more uniform responding through the interval than seen under nondrug conditions, an effect that results in higher overall rates (3). This summary of amphetamine's effects suggests that in the present experiment rate increases should have occurred. However, only a slight, and inconsistent, rate increase appeared in one monkey at one dose during the FI component.

Amphetamine's rate-decreasing effects in the present experiment resemble its effects on behavior under FR schedules (1, 7, 17, 24). Such decreases arise from the interpolation of long pauses into otherwise cohesive, vigorous performance (10,32). The rate decreases observed in FR performance may reflect concomitant increases in other, less effortful, behavior. Bacotti (1) demonstrated amphetamine-induced rate decreases on FR schedules simultaneous with rate increases on concurrently available FI or variable interval schedules. There were no programmed consequences for concurrent activities in the present experiment, but informal observations of the monkeys suggested that the rate decreases seen after amphetamine coincided with an increase in facultative behavior, as described by Staddon (29), such as grooming, stroking support bars on the chair, and looking about the chamber.

The present results do not support hypotheses based upon a generalized enhancement of effortful performance by amphetamine. The low response rates during the FI component provided ample opportunity for such enhancement to occur, but it did not appear reliably. However, it should be noted that the present experiments do not address directly the question of amphetamine's effects on endurance. To do so it would be necessary to continue the sessions until the animals showed evidence of impaired physical capacity. In addition, endurance studies often include an aversive consequence, such as falling into water or onto an electrified grid, if the animal fails to respond.

### *Pentobarbital*

Pentobarbital increased overall responding during the FI component. This increase was not due to a shortening of IRTs but, rather, to an earlier onset of responding in the interval. Indeed, increases in responding occurred in spite of *lengthening* of IRTs during both the FI and FR components. Although 6.5 mg/kg of pentobarbital substantially slowed responding, it did not destroy the coherence of the FR burst by introducing long pauses such as those that occurred after amphetamine. Nor did pentobarbital eliminate differential control over responding maintained by the stimuli associated with the two schedule components; the IRT distributions from the FR and FI components remained distinct. Weiss and Gott (32) also reported that pentobarbital, rather than disrupting FR responding, actually enhances its coherence by shortening long IRTs found early in the FR and leaving the short ones in the rest of the ratio sequence unaffected.

### *Summary and Conclusions*

The response patterns maintained by the FR and FI schedules of reinforcement when responding required considerable effort resembled in many ways the patterns maintained by these schedules when the operant is less physically demanding. But distinct differences lay in the low number of responses and absence of very short IRTs during the FI component. The imposition of marked physical effort may have amplified the different response topographies seen under FR and FI schedules. The present results extend to effortful operants the observations of others that, under certain conditions, pentobarbital increases, and amphetamine decreases, response rates. IRT analyses showed that the rate increases observed following pentobarbital occurred simultaneously with increases in the time between response initiations.

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