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DRUGS AND PUNISHED RESPONDING I: RATE-DEPENDENT EFFECTS UNDER MULTIPLE SCHEDULES[1]

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The effects of drugs were studied in pigeons whose responses were punished with electric shock during one component of a multiple fixed-interval 5-min fixed-interval 5-min schedule of food presentation. Most of the drugs analyzed for rate-dependent effects increased low rates of both punished and unpunished responding, while increasing higher rates less, or decreasing them; however, low rates of punished responding sometimes were increased more by pentobarbital, diazepam, and chlordiazepoxide than were matched rates of unpunished responding. In contrast, *d*-amphetamine and chlorpromazine usually increased low rates of unpunished responding more than matched rates of punished responding. These two drugs also decreased high rates of unpunished responding less than they decreased high rates of punished responding. Thus, the effects of drugs on punished responding depend on the control rate of punished responding; however, the rate-dependent effects of drugs on punished responding are not always the same as they are for unpunished responding.

When responding maintained with food as a reinforcer is punished with electric shock, the response-produced shock subsequently suppresses the responses that produced it. Pentobarbital, amobarbital, phenobarbital, meprobamate, hedonal, emylcamate, and urethane have been shown to decrease the suppression of behavior produced by response-produced electric shock in rats or monkeys (Geller and Seifter, 1960, 1962; Geller, Kulak, and Seifter, 1962, 1963; Morse, 1964; Kelleher and Morse, 1964, 1968; Wuttke and Kelleher, 1970). In contrast, amphetamines, morphine, chlorpromazine, promazine, and trifluoperazine usually do not attenuate the suppression of behavior by response-produced electric shock (Geller *et al.*, 1962; Geller and Seifter, 1960; Kelleher and Morse, 1964), although under some conditions morphine (Leaf and Muller, 1965) and chlorpromazine (Dinsmoor and Lyon, 1961) may increase punished responding.

There have been a number of attempts to determine the mechanism by which some drugs attenuate the suppression of responding produced by punishment. For example, Kelleher and Morse (1968) suggested that drugs that attenuate suppression produced by punishment do not act by producing analgesia, since morphine does not increase the rate of punished responding (Geller *et al.*, 1963; Kelleher and Morse, 1964).

Kelleher and Morse (1968) also have argued that increases in the rate of punished responding do not represent a nonspecific enhancement of responding by drugs that are particularly effective in increasing low rates of responding (Dews, 1958; Smith, 1964; Clark and Steele, 1966; McMillan, 1969), since the amphetamines do not increase low rates of responding when the low rates have resulted from the suppressive effect of punishment (Geller and Seifter, 1960; Hanson, Witoslaw-

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ski, and Campbell, 1967). Nevertheless, many drugs that attenuate the suppressive effect of punishment have been shown to increase low rates of responding in a number of situations (Kelleher, Fry, Deegan, and Cook, 1961; Cook and Kelleher, 1961; Herrnstein and Morse, 1957; Dews, 1964), so it is possible that drugs that increase the rate of punished responding do so primarily because punished responding occurs at a low rate.

In an attempt to separate the specific effects of drugs on the mechanisms controlling punished behavior from their tendency to increase low rates of responding, Cook and Catania (1964) equated rates of punished and unpunished responding by punishing responses intermittently with electric shock and reinforcing them with food during a punishment component, while reinforcing unpunished responses with food less often during a nonpunishment component. They found that both meprobamate and chlordiazepoxide increased the rate of punished responding more than they increased matched rates of unpunished responding. Although Cook and Catania's data might in part reflect interactions between the drug effects and the frequency of food presentation, their data strongly suggest that the ability of minor tranquilizers to increase punished responding does not depend entirely on their tendency to increase low rates of responding.

Recently, Wuttke and Kelleher (1970) used fixed-interval schedules to generate a wide range of rates of both punished and unpunished responding. For one group of pigeons, every thirtieth response was punished with electric shock while fixed-interval responses were not punished for a second group. There was a considerable overlap among local rates of punished and unpunished responding during different segments of the fixed-interval for the two groups of birds; however, drugs that increased low rates of punished responding increased low rates of unpunished responding to the same degree. Thus, Wuttke and Kelleher (1970), in contrast to Cook and Catania (1964), concluded that chlordiazepoxide (as well as two other benzodiazepines) has a general tendency to increase low rates of responding, rather than a specific effect on responding suppressed by punishment.

The present experiments used multiple fixed-interval schedules of food presentation, where responses were punished under one component but not under the other component, to match rates of punished and unpunished responding and to study the rate-dependent effects of drugs on punished and unpunished responding.

METHOD

Subjects

Four male White Carneaux pigeons with no previous training, weighing between 540 and 600 g under a regimen of free food and water were reduced to 80% of their free-feeding weights. They were maintained at these weights throughout the experiments. During the course of the experiments, one of the birds died and was replaced by another bird whose 80% of free-feeding weight was within the range of the 80% weights of the other birds.

Apparatus

Pigeons were implanted with electrodes around the pubis bone according to the method of Azrin (1959). Electric current (110 V ac, 60 Hz) was delivered through an adjustable resistor to a fixed resistance of about 11,000 ohms. The range of shock intensity was varied between 2.5 and 5.2 mA through the adjustable resistor and the intensity of shock that would give a moderate suppression of responding was determined empirically for each bird. For most experiments, the shock duration was 50 msec, but during the experiments with meprobamate and oxazepam, shock duration was increased to 100 msec and shock intensity was 2.5 to 3.4 mA.

The experimental chamber, a modification of that of Ferster and Skinner (1957), was sound attenuating. A translucent plastic response key, 0.75 in. (2 cm) in diameter, was mounted in the center of a wall inside the chamber about 8 in. (19 cm) above the chamber floor. A feedback relay behind the wall operated whenever 15 g (0.14 N) of force was applied to the key. Directly below the response key at a point 1.75 in. (4 cm) above the floor of the chamber was a rectangular opening through which the pigeon could be given 4-sec access to grain. The chamber was illuminated by a 25-W bulb and white noise was present in the chamber at all times. Conventional relay, scheduling and recording apparatus were housed in a different room from the one containing the test chambers.

Procedure

The birds were trained to key peck to obtain food and then were placed under a multiple fixed-interval 5-min fixed-interval 5-min schedule of food presentation (*mult* FI 5-min FI 5-min). Under this schedule, in the presence of a red keylight the first peck after 5 min resulted in 4-sec access to grain, and in the presence of a green keylight, the first key peck after 5 min also resulted in 4-sec access to grain. The two schedule components alternated. If no response occurred within 1 min after 5 min in the presence of either key color, the schedules alternated without food delivery. Two birds always started a session with a green keylight and the other two with a red keylight. The session terminated after nine presentations of each schedule component (approximately 90 min).

After behavior had stabilized under *mult* FI 5-min FI 5-min all responses during one of the two FI components produced electric shock (punishment component). Two birds were shocked only for pecks on the green key and two birds were shocked only for pecks on the red key. Two birds always began the session with the punishment component (one bird with a red keylight and one bird with a green keylight) and two birds always began the session without shock (one bird with a red keylight and one bird with a green keylight). Shock levels were adjusted over a period of about a month in an attempt to produce rates of responding during the punishment component that were less than half the rates during the unpunished component. This was done so that the rate of punished responding was free to vary in either direction when drugs were given, and so that there would be a high enough rate of punished responding late in the punishment component to permit the matching of the rate of punished responding with approximately equal rates of unpunished responding earlier in the unpunished component.

Drugs were used in the following forms: chlordiazepoxide and diazepam as the commercial preparations (Librium® and Valium®); oxazepam and meprobamate as the powders; pentobarbital as the sodium salt; tetrabenazine as the methanesulfonate; morphine and *d*-amphetamine as the sulfates; imipramine, mescaline, and chlorpromazine as the hydrochlorides; *l*-Δ^9- and *l*-Δ^8-*trans*-tetrahydrocannabinol (Δ^9-THC and Δ^8-THC) as the synthetic preparations available from the NIMH. Doses were given as the above forms. Distilled water was used as the injection vehicle for chlorpromazine, morphine, *d*-amphetamine, tetrabenazine, imipramine, mescaline, and pentobarbital; dimethylsulfoxide for meprobamate; 1% Tween 80 for oxazepam, the commercial solvents for chlordiazepoxide and diazepam (Tween 80, benzyl alcohol, maleic acid, propylene glycol, sodium hydroxide to adjust pH to 3.0 and water for chlordiazepoxide; benzyl alcohol, ethyl alcohol, propylene glycol, sodium benzoate, benzoic acid to adjust pH to 6.55 and water for diazepam) and 5% Triton X-100 (by volume) for Δ^9-THC and Δ^8-THC.

Control injections of the above solvents were given into the breast muscle 10 min before the start of a session, or 2 hr before the start of a session for Triton X-100. Injection volumes were on the basis of 1 cc/kg. All drugs except meprobamate and oxazepam were studied in four birds. Due to the death of one bird after a concentrated solution of Tween 80, only three birds were studied for meprobamate and oxazepam. A fourth bird was added after these two drugs were studied.

Two birds received the drugs in an ascending dose series beginning with a control injection and two birds received the drugs in a descending dose series terminating with a control injection. Injections were not given more often than twice weekly. The drugs were studied in the order listed in Table 1. Drug injections were intramuscular, 10 min before a session, except that Δ^8-THC and Δ^9-THC were given 2 hr before a session. Usually, single observations were made in each bird at each dose level, but occasionally duplicate or triplicate observations were made in each bird. When more than one observation was made in each bird, the number of observations is shown beside the point it represents (Figure 1).

Measurement of Drug Effects

Average rates of responding during the entire session were computed in responses per second from elapsed time meters and counters for both components. Days immediately before injection days were used as control days to determine a control mean, a control range, and a standard error. Since these experiments were conducted over a period of many months,

Table 1

Control means in responses per second with three standard errors above and below the control mean as %. At least one of the observations contributing to the control mean is a vehicle-injection control. Data show the drift in rates from October 1968 to September 1970, as well as the short-term variability.

	PUNISHED RESPONDING		*UNPUNISHED RESPONDING*	
DRUG	*Pre-Drug Control Mean as Responses/ Seconds*	*±3 Standard Errors Around the Pre-Drug Mean as %*	*Pre-Drug Control Mean as Responses/ Seconds*	*±3 Standard Errors Around the Pre-Drug Mean as %*
Before shock	0.67	—	0.66	—
Chlordiazepoxide	0.36	86-114	0.81	91-109
d-amphetamine	0.29	83-117	0.82	89-111
Tetrabenazine	0.34	88-112	0.92	89-111
Diazepam	0.25	69-131	0.92	88-112
Morphine	0.25	68-132	0.92	96-104
Chlorpromazine I	0.21	71-129	0.92	89-111
Pentobarbital I	0.20	65-135	0.76	83-117
Meprobamate	0.21	85-115	0.76	86-114
Oxazepam	0.11	82-118	0.97	94-106
Δ^9-THC	0.15	91-109	1.07	91-109
Imipramine	0.19	84-116	1.16	86-114
Chlorpromazine II	0.21	81-119	1.15	91-109
Pentobarbital II	0.21	94-106	1.25	90-110
Δ^8-THC	0.19	58-142	1.33	76-124
Mescaline	0.21	90-110	1.21	97-103

there was some drift in the control means and ranges; therefore, the group curves (Figure 1) have been plotted as a percentage of the control mean to facilitate comparison between drugs when the control means differed. Actual control values in responses per second are shown for each drug in Table 1.

For the analysis of rate-dependent drug effects, responses were cumulated during each tenth (30 sec) of the FI component for both schedule components during each session, so that average rates of punished and unpunished responding during 10 different segments of each FI component could be determined for pre-injection-control sessions and for injection sessions. The logs of the 10 control rates were averaged for pre-injection sessions and plotted on the abscissa, and the logs of the post-injection rates as percentages of the average pre-injection rate were plotted on the ordinate. Points were not plotted if the control rates were less than 0.001 responses per second, or if the injection decreased the post-injection rate to less than 1% of the control rate. Lines were fitted to the points by the method of least squares.

To summarize the rate-dependent effects of the drugs across doses and subjects (Tables 2 to 4) the slopes of the regression lines were converted to degrees and averaged across birds for each dose. The value on the Y axis (rate of responding after drug as a percentage of the control rate) when the value on the X axis (the mean control rate) equalled 1.0 responses per second, was also averaged across birds. These data permit the drawing of mean regression lines.

RESULTS

Effects of the Punishing Stimulus on Responding Under Multiple FI FI

The mean rate of responding (averaged for the entire FI component for the four birds) under the FI component to be punished was 0.67 responses per second during the final session before shock was introduced, while the mean rate during the other FI component was 0.66 responses per second.

Table 1 shows the effects of punishing responses during one of the FI components. The rate of responding during the punishment component decreased to levels that usually were less than half the rates before punishment was introduced. However, as the rate decreased during the punishment component, there was

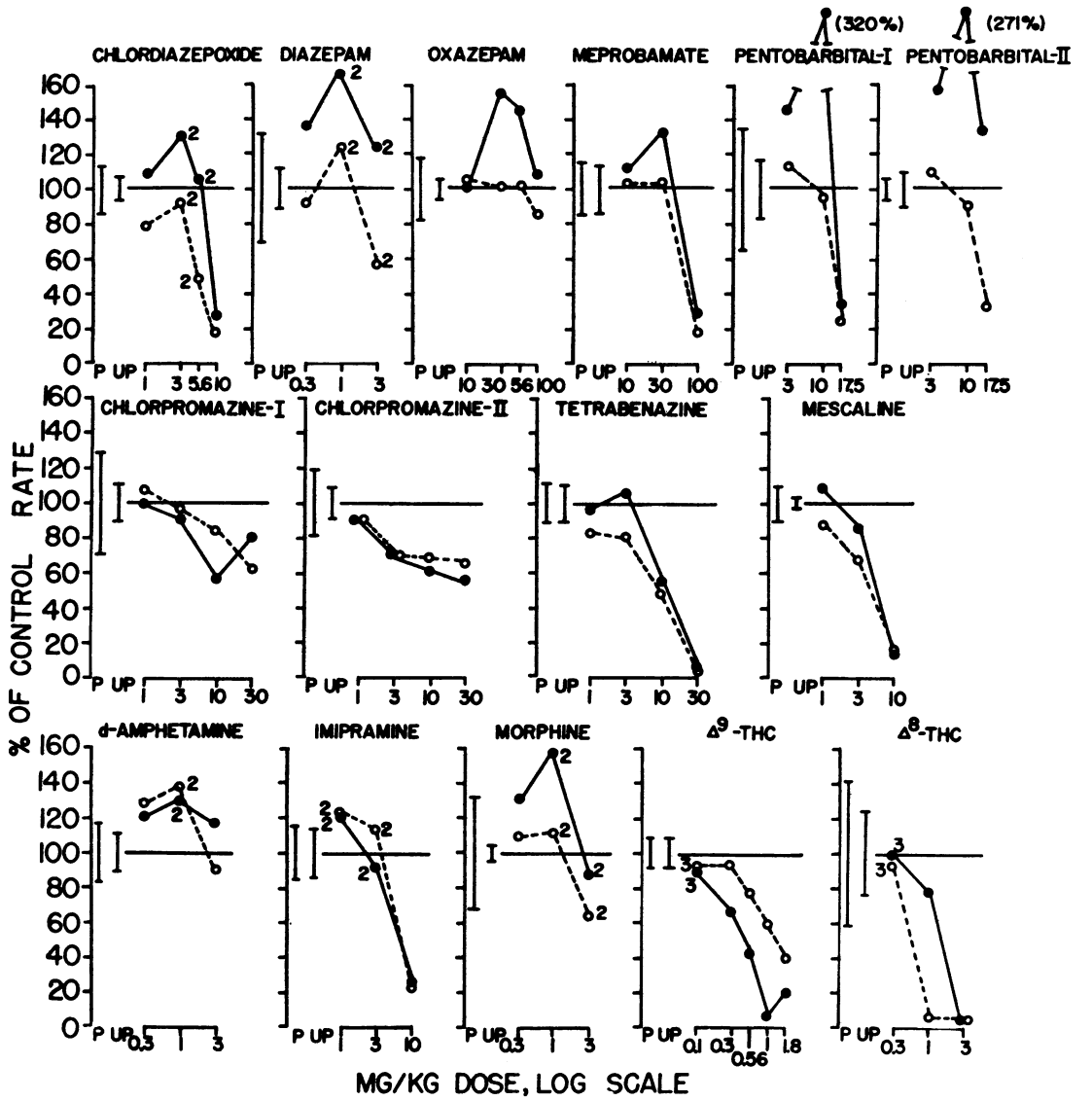

Fig. 1. Effects of drugs on punished and unpunished responding. Abscissa: mg/kg dose, log scale. Ordinate: rate of responding as a percentage of the mean rate of responding on non-injection control days (see Table 1 for these mean rates) during an entire session for each component. The brackets represent the range of unpunished (at UP) and punished (at P) rates of responding on the days immediately preceding injections. Each range is based on at least five observations, one of which was an injection vehicle control session. The filled circles and solid lines are for punished responding and the open circles and broken lines are for unpunished responding. Each point is the mean of a single injection in each of four birds (three birds for oxazepam and meprobamate), except where numbers beside the points represent more than one observation in each bird.

an increase (contrast effect; Reynolds, 1961) in rate during the unpunished component of the multiple FI FI.

Drug Effects On Overall Rates of Responding

The effects of all 13 drugs on mean rates of responding during punished and unpunished components of the *mult* FI 5-min FI 5-min schedule are shown in Figure 1. Three benzodiazepines (chlordiazepoxide, diazepam, and oxazepam) increased the rate of responding during the punishment component by about 50% at doses that had little effect on the rate of responding during the nonpunishment component. At higher doses, the rate of re-

Table 2

Average slope of the regression line and average rate after injection as % control, when the control rate is one response per second for punished and unpunished responding after chlordiazepoxide, diazepam, and pentobarbital. Data are means from four birds.

DRUG AND MG/KG DOSE		PUNISHED RESPONDING		UNPUNISHED RESPONDING	
		Slope	Y as % X, when X = 1/sec	Slope	Y as % X, when X = 1/sec
Chlordi-	0	− 9°	112	1°	98
azepoxide	1	−20°	79	7°	81
	3	−13°	117	12°	91
	5.6	−15°	91	8°	45
	10	−18°	15	−25°	18
Diazepam	0	− 8°	91	− 4°	91
	0.3	−15°	87	− 7°	87
	1	−15°	110	−12°	96
	3	−38°	20	−13°	26
Pento-	0	−13°	63	4°	93
barbital	3	−23°	81	−17°	129
	10	−37°	113	−25°	107
	17.5	−38°	37	−34°	37

sponding during the punishment component returned to control levels, while the rates of responding during the nonpunishment component were decreased (chlordiazepoxide and diazepam), or unaffected (oxazepam). The potency order for increasing the rate of punished responding was: diazepam > chlordiazepoxide > oxazepam.

Figure 1 also shows a dose-response curve for the effect of meprobamate on rates of responding under the multiple schedule, and two determinations of a pentobarbital dose-response curve. Both of these drugs increased the rate of responding under the punishment component at doses that did not affect the rate of responding under the nonpunishment component; however, pentobarbital caused much larger increases in the rate of responding under the punishment component than did meprobamate or any of the benzodiazepines.

In the second row of Figure 1, two dose-response curves for the effects of chlorpromazine and a dose-response curve for the effect of tetrabenazine are shown. Both chlorpromazine and tetrabenazine decreased the rates of both punished and unpunished responding. The second row of Figure 1 also shows the dose-response curve for the effects of mescaline. Like chlorpromazine and tetrabenazine, mescaline decreased the overall rates of responding

Table 3

Average slope of the regression line and average rate after injection as % control, when the control rate is 1/sec for punished and unpunished responding after *d*-amphetamine and chlorpromazine. Data are means from four birds.

DRUG AND MG/KG DOSE		PUNISHED RESPONDING		UNPUNISHED RESPONDING	
		Slope	Y as % X, when X = 1/sec	Slope	Y as % X, when X = 1/sec
d-amphet-	0	− 9°	138	−14°	110
amine	0.3	− 8°	91	−20°	118
	1	−15°	85	−26°	151
	3	−29°	13	−12°	48
Chlorprom-	0	− 1°	91	− 1°	112
azine	1	−14°	93	−16°	115
	3	−26°	32	−15°	83
	10	−38°	16	−26°	51
	30	−36°	11	−14°	49

Table 4

Average slope of the regression line and average rate after injection as % control, when the control rate is one response per second for punished and unpunished responding after imipramine and morphine. Data are means from four birds.

DRUG AND MG/KG DOSE		PUNISHED RESPONDING		UNPUNISHED RESPONDING	
		Slope	Y as % X, when X = 1/sec	Slope	Y as % X, when X = 1/sec
Imipramine	0	1°	132	15°	87
	1	− 2°	129	−14°	126
	3	−11°	39	3°	107
	10	−43°	34	−25°	53
Morphine	0	10°	115	17°	96
	0.3	−12°	107	10°	107
	1	−21°	110	− 5°	105
	3	− 1°	43	−23°	53

under both schedule components. Both Δ^9-THC and Δ^8-THC (3rd row) also only decreased overall rates of both punished and unpunished responding. Δ^9-THC was slightly more potent than Δ^8-THC. The rate-decreasing effects of Δ^9-THC and Δ^8-THC were still apparent 24 hr after the highest dose levels (not shown).

Figure 1 (3rd row) also shows dose-response curves for the effects of morphine, *d*-amphetamine, and imipramine on the rates of punished and unpunished responding. Morphine increased the overall rates of punished responding to about the same extent as the benzodiazepines. *d*-Amphetamine may have produced very small increases in punished responding, but these effects are marginal. However, *d*-amphetamine clearly increased the overall rate of unpunished responding. Imipramine had little effect, except for the higher doses, which suppressed responding during both schedule components.

Another effect observed was an increase in the rate of punished responding after some of the injection vehicles were administered. In the 15 dose-response curves of Figure 1, in seven instances the rate of punished responding after the control injection was higher than the rate during any non-injection control session. Since the mean control rate for each drug was based on at least five observations, there would be only one chance in five (or three in 15) of the injection vehicle observation being the highest observation, yet this occurred seven times in 15 observations, suggesting a "placebo effect" for punished responding. However, the increases in punished responding after vehicle control injections were not nearly as large as those produced by morphine or by the drugs in the top row of Figure 1.

Analysis of Rate-Dependent Effects

Figure 2 shows the rate-dependent effects of three different drugs at selected dose levels for three different birds (6535, 5470, and 3575). The injection vehicles produced slight rate-dependent effects for punished responding; however, these effects were quite variable and there was no consistent relationship between punished and unpunished responding. Chlordiazepoxide, diazepam, and pentobarbital all produced marked rate-dependent effects on both punished and unpunished responding at the doses shown in Figure 2. In general, low rates of responding tended to be increased by these drugs while higher rates were increased less or decreased in these individual birds.

Figure 2 also suggests that the rate-dependent effects of these drugs are not the same for punished and unpunished responding at all dosages. For all three drugs, there is a tendency for the punishment regression lines to be steeper than the nonpunishment regression lines. One effect of the steeper punishment regression lines is to make it appear that low rates of punished responding are increased more than matched rates of unpunished responding. At higher control rates of responding, the drugs seem less able to affect punished and unpunished responding differentially.

Table 2 shows the mean slope (in degrees) of the regression lines for all four birds after all doses of chlordiazepoxide, diazepam and

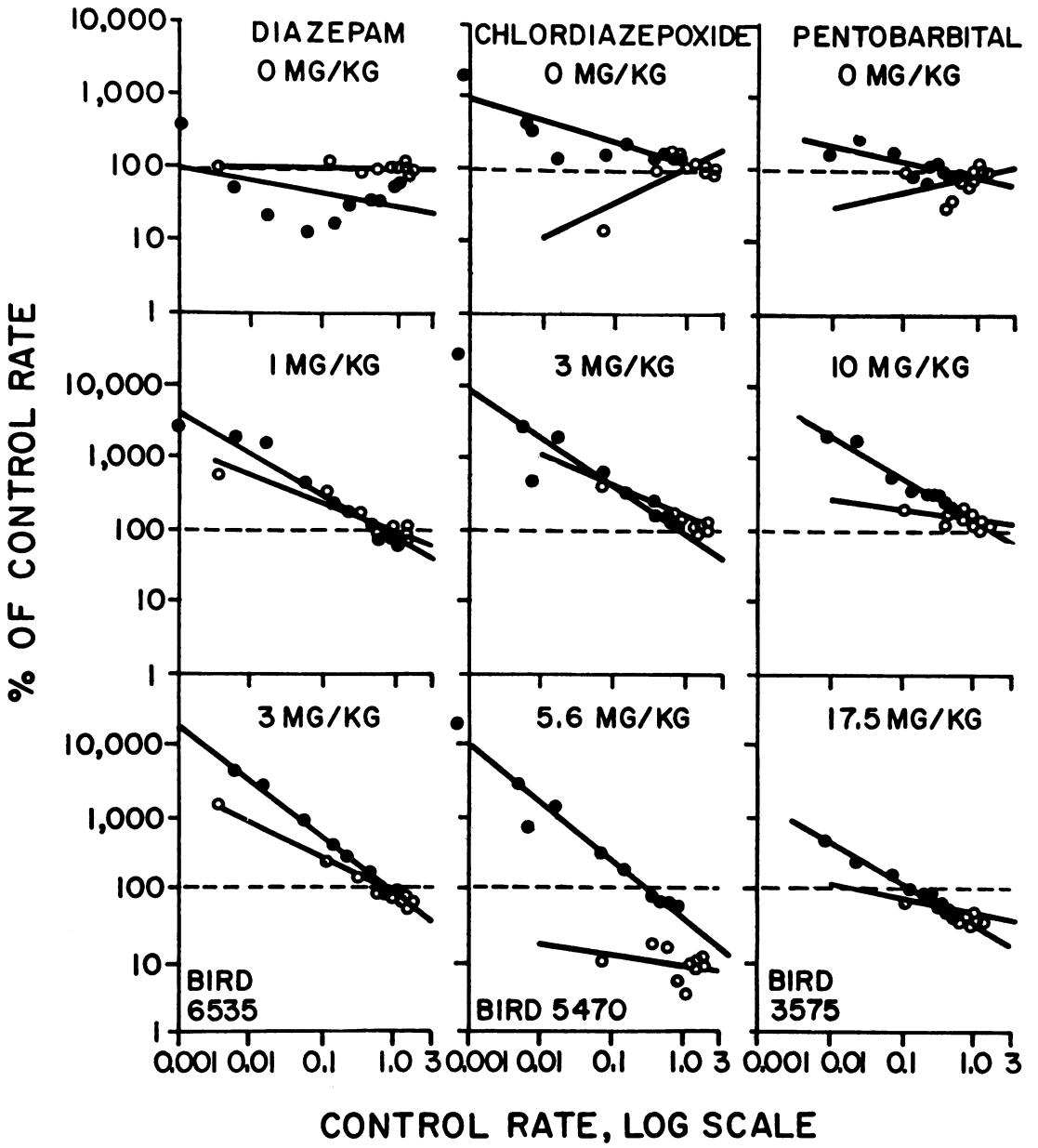

Fig. 2. Log-log plots for the effects of diazepam, chlordiazepoxide, and pentobarbital on punished and unpunished responding. Abscissa: control rate of responding averaged over at least four non-injection sessions, log scale. Ordinate: rate after drug as a percentage of the control rate, log scale. Open circles are for unpunished responding and filled circles are for punished responding. Each point is the mean rate of responding during one of the 10 successive 30-sec segments of the fixed interval, averaged over the session for a single bird.

pentobarbital (first determination of the pentobarbital dose-response curve). With the exception of the lower doses of chlordiazepoxide all the mean regression lines after drug appear to have a greater negative slope than that after the control injection. Aside from the slight degree of positive slope for unpunished responding after low doses of chlordiazepoxide, the negatively sloped regression lines show that low rates of both punished and unpunished responding are increased, while higher rates are increased less, or decreased.

Table 2 also shows that there is a tendency for the negative slope of the mean regression

lines to increase as the dose of diazepam, or pentobarbital increases. Thus, the rate-dependent effects of the drugs become more pronounced at the higher dose levels.

Figure 3 shows the rate-dependent effects of *d*-amphetamine and chlorpromazine in individual birds (6535 and 5470) at selected doses. There is little tendency for rate-dependent effects to occur after vehicle injections; however, after both *d*-amphetamine and chlorpromazine low rates of both punished and unpunished responding are increased while higher rates are increased less or decreased. In contrast to the effects seen after pentobarbital and the benzodiazepines, Figure 3 shows clearly that *d*-amphetamine and chlorpromazine increase low rates of unpunished responding more (or decrease higher rates of unpunished responding less) than matched rates of punished responding.

Table 3 shows the mean slope of the regression lines for all four birds after all doses of *d*-amphetamine and chlorpromazine.

The rate-dependent effects of imipramine and morphine were also determined. The mean slopes from all four birds are shown for these drugs in Table 4. Again rate-dependent effects appear to occur for both punished and unpunished responding, as evidenced by the negative slopes of the mean regression lines after drug. Unfortunately, there are reversals in the dose-effect relationships for both these drugs.

DISCUSSION

When the rate-dependent effects of some of the drugs studied in these experiments were analyzed, all the drugs increased low rates of responding, and increased higher rates of responding less, or decreased them. This quantitative relationship between the control rate of responding held for both punished and unpunished responding; however, *d*-amphetamine and chlorpromazine increased unpunished responding more than matched rates of punished responding, while diazepam, chlordiazepoxide, and pentobarbital tended to increase very low rates of punished responding more than matched rates of unpunished responding.

There is much evidence that the benzodiazepines increase low rates of responding in a variety of behavioral situations (Kelleher and Morse, 1968); however, only two previous experiments have compared the rate-dependent effects of benzodiazepines on punished and unpunished responding. In the earliest of these experiments, Cook and Catania (1964), studied the effects of chlordiazepoxide in squirrel monkeys. They used a multiple variable-interval 2-min (punishment component) variable-interval 6-min (nonpunishment component) schedule of food presentation to match control rates of punished and unpunished responding. Chlordiazepoxide increased control rates of punished responding more than matched rates of unpunished responding, which suggests that chlordiazepoxide has effects on punished behavior that cannot be explained simply in terms of rate dependence.

More recently, Wuttke and Kelleher (1970) studied the effects of three different benzodiazepines on responding maintained by fixed-interval schedules of food presentation. Some of these birds worked under a simple FI 5-min schedule (followed by a 1-min timeout) while every thirtieth response of other birds under the same schedule was punished with electric shock. They found that diazepam, chlordiazepoxide, and nitrazepam all increased the low rates of both punished and unpunished responding at the beginning of the fixed-interval schedule, a finding that agrees with the present findings. However, Wuttke and Kelleher (1970) did not find any indication that very low rates of punished responding were increased more than matched rates of unpunished responding.

Wuttke and Kelleher's failure to find differential effects of benzodiazepines on matched rates of punished and unpunished responding is in contrast to the findings of Cook and Catania (1964), as well as to those of the present study. The procedures used in these experiments differed in several ways. Wuttke and Kelleher used different birds to study punished and unpunished responding, while multiple schedules were used to study punished and unpunished responding in the same birds in the present studies. Wuttke and Kelleher punished responding intermittently, while each response was punished during the punishment component in the present study. Despite these differences, it is clear from both studies that the rate-dependent effects of the benzodiazepines hold for both punished and unpunished responding, and that these rate-dependent effects go a long way toward de-

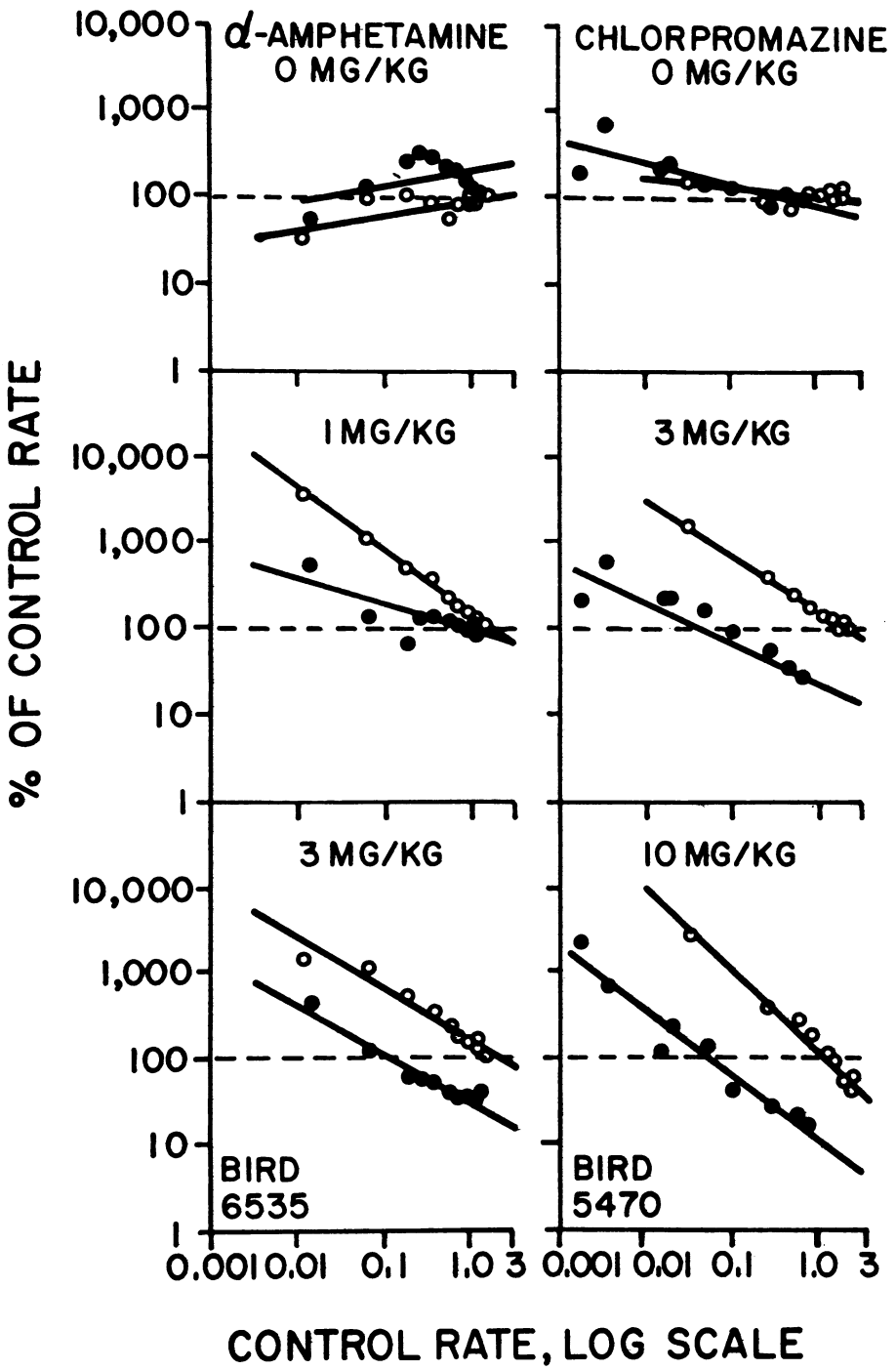

Fig. 3. Log-log plots for the effects of *d*-amphetamine and chlorpromazine on punished and unpunished responding. Abscissa: control rate of responding averaged over at least four non-injection sessions, log scale. Ordinate: rate after drug as a percentage of the control rate, log scale. Open circles are for unpunished responding and filled circles are for punished responding. Each point is the mean rate of responding during one of the 10 successive 30-sec segments of the fixed interval, averaged over the session for a single bird.

scribing the drug effect. However, the present experiments, as well as those of Cook and Catania (1964), suggest that under some conditions other variables can modify the rate-dependent effects of the benzodiazepines, and perhaps these "other variables" relate specifically to drug interactions with punished behavior.

Both the ability of the barbiturates to increase responding suppressed by punishment (Geller and Seifter, 1960; Morse, 1964) and the rate-dependent effects of the barbiturates are well known (Dews, 1964; Kelleher and Morse, 1968). However, previous experiments with barbiturates have not compared rate-dependent effects on unpunished responding with rate-dependent effects on punished responding. In the present experiments, the rate-dependent effects of the barbiturates were similar to the rate-dependent effects of the benzodiazepines; that is, pentobarbital increased low rates of both punished and unpunished responding, while higher rates were increased less, or decreased. As with the benzodiazepines, pentobarbital tended to increase very low rates of punished responding more than matched rates of unpunished responding.

The rate-dependent effects of the amphetamines have been studied more widely than the rate-dependent effects of any other drugs. The notion that amphetamines increase low rates of responding and decrease high rates was suggested by Dews (1958). Since that time, a host of investigators have demonstrated the wide applicability of this statement (Smith, 1964; Clark and Steele, 1966; McMillan, 1969). Among the few exceptions to amphetamine's tendency to increase low rates of responding, is punished behavior (Geller and Seifter, 1960; Hanson *et al.*, 1967; Kelleher and Morse, 1968). In the present experiments, *d*-amphetamine increased low rates of both punished and unpunished responding, while increasing higher rates less, or decreasing them. However, in a contrast to the effects of pentobarbital and the benzodiazepines, *d*-amphetamine increased rates of unpunished responding more than matched rates of punished responding. Although the effects of *d*-amphetamine are clearly rate-dependent for both punished and unpunished responding, it is clear that some other factor modifies the usual rate-dependent effects of *d*-amphetamine when responses are punished.

Chlorpromazine produced rate-dependent effects resembling those of *d*-amphetamine. Although chlorpromazine increased low rates of both punished and unpunished responding and increased higher rates less or decreased them, there was a clear tendency for low rates of unpunished responding to be increased more after chlorpromazine than were matched rates of punished responding.

These experiments offer evidence for the wide generality of the rate-dependency phenomenon. Drugs of diverse pharmacological classification produced rate-dependent effects on both punished and unpunished responding. All of these drugs increased low rates of both punished and unpunished responding more than higher rates, which often were decreased. However, the drug effect on matched rates of punished and unpunished responding were different for different drugs. Although the rate-dependency phenomenon accounts in large part for the increases in punished responding observed with the benzodiazepines and pentobarbital, as yet undetermined factors may elevate very low rates of punished responding more than matched rates of unpunished responding, while with *d*-amphetamine and chlorpromazine, other undetermined factors seem to prevent rates of punished responding from increasing to the same extent as matched rates of unpunished responding.

All of the drugs studied that might be classified as minor tranquilizers or sedative-hypnotics, increased the overall mean rate of responding during the punishment component, while chlorpromazine and tetrabenazine, which are classified as major tranquilizers, did not increase the rate of responding during the punishment component. These findings are in agreement with those of previous investigators (Geller and Seifter, 1960, 1962; Geller *et al.*, 1962, 1963; Morse, 1964; Kelleher and Morse, 1964, 1968; Wuttke and Kelleher, 1970). However, the increases in the overall rate of punished responding observed after morphine have not been reported by other investigators (Geller *et al.*, 1963; Kelleher and Morse, 1964), although at least one other laboratory (Leaf and Muller, 1965) has reported that morphine will increase the number of shock-punished licking responses on a drinkometer. The procedural differences in these experiments include: the species, the schedule of food presentation, the schedule of presentation of the

punishing stimulus, the shock intensity and duration, and the complexity of the schedule. Which if any of these variables are important cannot be determined without extensive parametric studies of the interaction of drugs with punished behavior.

Of possible relevance in explaining some of these drug effects might be the influence of contrast effects on baseline rates of responding. Before responses were punished, rates during both components of the multiple FI FI were nearly equal (0.66 to 0.67 responses per second). When responses were punished during one FI component, response rates during this component decreased to about 0.2 responses per second; however, response rates increased to about 1.0 responses per second during the unpunished component. To what extent the drug effects on punished responding may have been influenced by these contrast effects will require comparisons between multiple and simple schedules.

Because so many factors may influence the effects of drugs on punished behavior, any simple description of the effects of a drug on punished behavior is probably an oversimplification. It may be as inappropriate to make the generalization that a drug increases the rate of punished responding, as it has already been shown to be inappropriate to make the generalization that a drug increases the rate of food-reinforced responding. In both cases, a host of schedule parameters may interact to produce the drug effect.

The only group of drugs in these experiments that has not been studied previously in punishment experiments is the tetrahydrocannabinols. Both Δ^8- and Δ^9-THC only decreased the rates of responding under both punishment and nonpunishment components. Kubena and Barry (1970) suggested that Δ^9-THC may have tranquilizer activity. Since Δ^8- and Δ^9-THC do not appear to increase the overall rates of responding during the punishment component, these tetrahydrocannabinols do not seem to act in a manner similar to the minor tranquilizers or sedative hypnotics.

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