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NEGATIVE REINFORCING PROPERTIES OF SOME PSYCHOTROPIC DRUGS IN DRUG-NAIVE RHESUS MONKEYS[1,2]

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ABSTRACT

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Rhesus monkeys, previously trained to avoid electric shock, pressed a lever to extinguish a light associated with an intravenous drug infusion scheduled to occur 30 seconds after the onset of the light. Each response when the light was on terminated the light for a 1-minute time-out period (avoidance); a response during the infusion terminated the infusion (escape). Under these conditions the monkeys tolerated a high number of saline infusions. Saline was replaced by different doses of chlorpromazine, lysergic acid diethylamide (LSD) and pentobarbital each for six successive daily 2-hour sessions. Infusions of chlorpromazine (5.0–20 μg/kg/infusion) or LSD (1.0–2.5 μg/kg/infusion) generated and maintained avoidance/escape behavior, whereas most of the infusions of pentobarbital (10–100 μg/kg/infusion) were tolerated. In rhesus monkeys with no previous drug experience, chlorpromazine and LSD, but not pentobarbital, have negative reinforcing properties.

A previous paper (Hoffmeister and Wuttke, 1973) reported that drug-naive rhesus monkeys avoid injections of nalorphine and cyclazocine but not naloxone if they are performing under a schedule which allows them to avoid or escape injections of these drugs. From these experiments, it was concluded that nalorphine and cyclazocine have negative reinforcing (*i.e.*, aversive) properties.

The aim of the present study was to establish whether such negative reinforcing effects can also be demonstrated with psychotropic drugs such as chlorpromazine and LSD which are known not to be self-administered, when studied with conventional self-administration techniques (Schuster and Thompson, 1969; Seevers, 1973; Hoffmeister and Goldberg, 1973). The effects of these drugs were compared with those of pentobarbital which is self-administered by naive and drug-experienced rhesus monkeys (Schuster and Thompson, 1969; Schlichting *et al.*, 1970).

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Methods

Animals. Eight rhesus monkeys (male and female *Macaca mulatta*) weighing between 2.5 and 5 kg were used. Under sodium pentobarbital anesthesia (30 mg/kg i.v.), monkeys were surgically prepared with chronic silicone rubber (Vivosil) catheters (outside diameter 2.2 mm, inside diameter 1.0 mm) which were passed through the internal jugular vein to the level of the right atrium.

Gold plate electrodes were placed subcutaneously under the skin of the head below the major occipital nerve.

Apparatus. The monkeys were fitted with metal harnesses for restraint. Each monkey was housed in an individual cubicle (76 cm wide, 91 cm high, 66 cm deep) fitted with a jointed metal restraining arm which was attached to the harness and allowed the animal almost complete freedom in the cubicle. The front of the cubicle was open for observation and maintenance of the monkey. The surgically implanted catheter and the leads connecting to the electrodes passed subcutaneously to the back of the monkey where they were brought out through the skin and then passed through the restraining arm to an infusion pump (Cole Palmer Masterflex) mounted behind the cubicle or to an electric stimulating device. A key (lever: Lehigh Valley Electronics, model 1380) and a white stimulus light (2.4 w) were mounted on the back wall of the cubicle. The device for delivering electric shock and the infusion pump were activated by automatic programming equipment. Each activation of the infusion pump delivered 0.2 ml/kg of solution. Infusion time (approximately 10 seconds) was regulated according to the weight of the animals. One saline infusion was delivered automatically every 4 hours except during experimental sessions to prevent blood from clotting in the catheter. Details of the catheterization procedure and of the apparatus have been reported by Yanagita *et al.* (1965) and Deneau *et al.* (1969).

Procedure. After the monkeys had been catheterized and implanted with electrodes, they were placed in individual cubicles where they lived for the duration of the experiment. Food and water were freely available. To prevent tuberculosis, monkeys received 10 mg/kg of isoniazid in sweets daily.

After the subjects had recovered from surgery (2 weeks), they were trained to press a lever to turn off a white light which was associated with electric shock of 10 seconds duration (American Electronics Laboratory stimulator 104; 50 cycles; impulse duration, 1 msec; voltage, 7 V) scheduled to occur every 30 seconds after the onset of the light. Each response, when the light was on, turned it off for a 60-second time-out period and prevented the shock (avoidance). A response during the 10-second electric shock terminated the shock (escape) and also terminated the light for a time-out period during which responses had no scheduled consequences.

After the subjects responded to avoid, or at least to escape, most of the electric stimuli during two to four daily 2-hour sessions, electric shocks were no longer delivered. Avoidance/escape behavior extinguished within 2 weeks. After this 2-week extinction period, 10-second infusions of saline solution were introduced instead of the 10-second electric shocks. During this period, the subjects became accustomed to the noise of the infusion pumps. When the monkeys tolerated most of the saline infusions, that is, when they did not press the lever to avoid or escape them, saline infusions were replaced by different doses of the drugs to be studied. Each unit dose was offered over a period of 6 (chlorpromazine up to 12) days during successive daily 2-hour sessions. Avoidance and escape from the infusions was recorded.

The following data were recorded.

1. Mean number of avoidance/escape responses per 2-hour session was calculated for the first and the second 3 days, respectively, of the 6-day replacement period.

2. The number of infusions tolerated. In order to account for the volume of solution administered by responses which terminated infusions (escape), the number of infusions was calculated as follows: the total intake in milliliters per session was divided by 0.8 (the volume of one total infusion). By this procedure, apparent differences between the number of responses and drug intake, owing to different types of behavior, are eliminated; for example, if a subject when presented with a given dose of a drug emits escape responses in the 9th second of the ongoing 10-second infusion only, it will receive much higher doses of the drug as compared to an animal emitting the same number of responses as avoidance responses.

3. The total intake of the drugs per session. The 6-day drug period was always followed by a saline extinction period which continued until the subjects again tolerated the saline infusion (6–14 days). The number of saline infusions tolerated by each monkey during the last 6 days of each extinction period served as control. The mean numbers of saline infusions tolerated during control periods for individual monkeys are summarized in table 1. Then saline was again replaced by the next dose of the drug to be studied. Each dose of the drugs was tested in three to six different monkeys; the different doses were offered in decreasing sequence always starting with the highest. For assignment of drugs and doses to monkeys, no strict rule was observed.

Drugs. Chlorpromazine, pentobarbital and lysergic acid diethylamide (LSD) were used. All drugs studied were dissolved in saline solution. Doses refer to the base of the drugs.

TABLE 1

Number of avoidance/escape responses and the number of tolerated infusions of individual monkeys during the first and the second 3-day component of the extinction (saline) periods

No. of Monkey	1–3 Days[a]		4–6 Days	
	No. of responses	No. of infusions	No. of responses	No. of infusions
M 2.9	33.0	117.3	43.0	102.0
	36.3	112.3	42.7	102.7
	35.7	115.3	39.0	109.7
	25.0	132.7	16.7	147.3
	40.0	103.0	40.3	103.3
	58.0	71.0	33.7	114.7
	21.0	138.0	37.3	109.3
	43.3	99.7	47.0	96.0
	24.0	133.7	52.7	86.0
	27.0	127.3	42.3	100.7
$\bar{X}$	34.5	115.0	39.5	107.2
M 5.9	17.3	144.7	14.7	150.0
	43.0	101.0	8.3	167.3
	44.7	97.0	32.0	121.3
	33.3	115.7	42.7	102.0
	24.3	136.7	30.0	121.3
	3.7	171.0	9.7	161.0
	4.0	170.7	9.3	161.3
	23.7	135.7	37.3	111.0
	13.3	152.0	28.0	122.7
$\bar{X}$	23.2	136.1	23.6	135.3
M 7.6	9.0	161.0	16.0	147.3
	38.4	113.3	5.3	168.7
	17.4	149.7	0.7	176.3
	41.3	106.7	22.7	138.0
	37.0	112.7	14.3	152.3
	33.3	119.0	9.3	160.0
	15.7	151.7	5.0	168.5
$\bar{X}$	27.5	130.6	10.5	158.7
M 8.10	38.0	108.7	36.0	111.0
	52.7	77.7	14.7	150.3
	37.7	109.3	29.0	121.3
$\bar{X}$	42.8	98.6	26.6	127.5
M 6.6	48.0	90.3	13.0	150.7
	38.0	108.3	31.0	119.7
$\bar{X}$	43.0	99.3	22.0	135.2
M 8.11	1.6	175.0	0.3	177.3
	4.7	169.3	1.3	174.3
$\bar{X}$	3.2	172.2	0.8	175.8
M 6.7	34.3	116.7	23.3	138.0
	9.3	159.0	5.7	167.3
	1.0	175.3	1.0	175.0
$\bar{X}$	14.9	150.3	10.0	160.1
M 11.11	19.3	144.7	15.3	150.0
	30.3	123.7	0.0	177.3
	13.7	153.7	6.6	166.0
$\bar{X}$	21.1	140.7	7.3	164.4
$\bar{X}$[b]	27.6	128.2	22.0	137.9

[a] Days of replacement.
[b] n = 39 extinction periods.

Results

Figure 1 shows representative cumulative records of one monkey (subject 8.11) performing under the above described experimental conditions. As indicated by record A, the subject avoided most of the electric stimuli.

On the 3rd day of the extinction period, during which electrical shocks were replaced by saline infusions avoidance/escape behavior was extinguished (fig. 1B). When the animal was given LSD (2.5 μg/kg/infusion) for the first time, it tolerated 22 successive infusions before avoidance/escape behavior was initiated (fig. 1C). Record 1D shows the behavior on the 4th day of presentation of LSD. On this day, the animal did not tolerate complete infusions. Ten infusions were terminated by escape responding. Record E demonstrates performance on the 3rd day of the extinction period during which LSD was again replaced by saline infusions. Avoidance/escape behavior was almost completely extinguished.

Figure 2 summarizes the results obtained with all doses of LSD. Figure 2A indicates the mean percentage of LSD infusions tolerated by

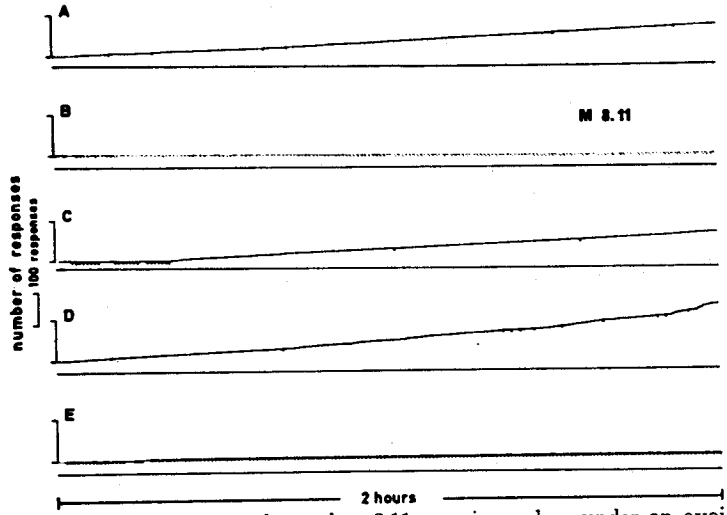

FIG. 1. Representative performance of monkey 8.11 pressing a key under an avoidance/escape procedure with either electric stimuli (A) or infusions of saline or LSD. Ten-second infusions of saline solution (B and E) or 10-second infusions of 2.5 μg/kg of LSD (C and D) were scheduled to occur every 30 seconds in presence of a white light. Each response during the 30-second light period terminated the light period (avoidance); each response during the 10-second infusion period terminated the infusion and the light period (escape); light periods were followed by 60-second time-out periods during which key pressing had no scheduled consequences. Ordinate: cumulative number of responses, short diagonal strokes indicate delivery of electric stimuli (A) or infusion (B–E). Abscissa: time (2-hour session). A. Performance with presentation of electric stimuli. B. Third day of extinction period during which electric stimuli (record A) were replaced by saline infusions. Record C. First day of LSD presentation (2.5 μg/kg/infusion). Record D. Fourth day of LSD presentation (2.5 μg/kg/ infusion). Record E. Third day of extinction period during which LSD infusions were replaced by saline infusions.

the monkeys, plotted as means of the values of the first and the second 3 days of the 6-day replacement period. The individual data are represented as percent of saline infusions tolerated by the same subjects during both components of the extinction (saline) periods. As indicated by figure 2A, infusions of 0.5 μg/kg of LSD are tolerated to almost the same extent as saline infusions during all 6 days of the replacement period. Infusions of 1 μg/kg/infusion initiate and maintain avoidance/escape behavior during the 4th to the 6th day, but not during the first 3 days of the replacement period. As compared to saline only, 10 to 20% of infusions of 2.5 μg/kg of LSD are tolerated during both of the two 3-day components of the replacement period.

Figure 2B shows the effects of LSD infusions on avoidance/escape behavior. Number of responses increases with increasing doses (fig. 2B). LSD intake is highest with infusions of 1 μg/kg of LSD, probably due to the delayed onset of avoidance behavior with presentation of this dose (fig. 2C).

Chlorpromazine (1–20 μg/kg/infusion), during the first 3 days of the replacement period, abolished avoidance/escape behavior completely and increased the percentage of tolerated infusions above saline level (fig. 3A). During the second 3-day component of the replacement period, infusions of 5 to 20 μg/kg initiated avoidance/escape behavior resulting in a decrease of the percentage of tolerated infusions of the saline value to 50 to 60% at infusion doses of 10 μg/kg (fig. 3A). Infusions of 50 and 1 μg/kg chlorpromazine were tolerated almost like saline infusions.

Number of responses is lower than saline values with replacement of 1 mμ/kg/infusions of chlorpromazine during all 6 days of replacement. With higher doses, the number of responses increased, depending on dose, up to the saline level during the first 3 days of the replacement period. There was a marked increase in responding during the second 3 days of replacement with infusions of 5 to 50 μg/kg. The highest number of responses occurred with infusions of 10 μg/kg (fig. 3B).

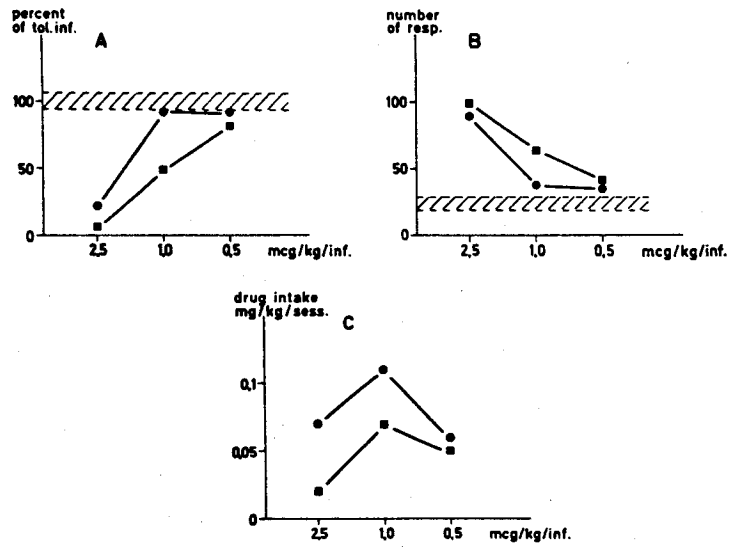

FIG. 2. Effects of varying LSD infusion doses on the number of infusions tolerated, number of avoidance and escape responses and drug intake during the first and the second 3-day component of the 6-day replacement period. ●——●, means of the 1st to the 3rd day of replacement; ■——■, 4th to the 6th day of replacement; [[, confidence limits of saline infusions tolerated. A. Effects of infusion dose (abscissa) on the number of infusions tolerated per 2-hour session plotted as percentage of saline infusions tolerated by the same subjects during extinction periods. Individual symbols represent means of all monkeys involved in the replacement experiments with different infusion doses. B. Effects of infusion dose (abscissa) on mean number of responses per 2-hour session of all monkeys involved in the replacement experiments with different infusion doses. C. Effect of infusion dose (abscissa) on mean drug intake per 2-hour session of all monkeys involved in the replacement experiments with different infusion doses.

These experiments demonstrate that the onset of avoidance/escape behavior is delayed when animals are presented with chlorpromazine; the percentage of infusions avoided never exceeded 50%. In order to establish whether avoidance/escape behavior would increase after prolonged exposure to chlorpromazine, replacement of 10 μg/kg of chlorpromazine was extended to 12 days. Figure 4 shows the time course of this experiment. The number of tolerated infusions decreased from the 9th to the 12th day of replacement to less than 10% of the saline level. The number of responses increased correspondingly (fig. 4B). When saline replaced chlorpromazine, extinction of avoidance behavior took up to 24 days, indicating long-lasting negative reinforcing properties of chlorpromazine after prolonged exposure to infusions of 10 μg/kg.

Infusions of pentobarbital (10 and 100 μg/kg/infusion) were tolerated better than saline infusions (fig. 5A). There was no significant increase in avoidance/escape behavior (fig. 5, B–D). Monkeys were heavily sedated during and after pentobarbital infusions. The same applied to the chlorpromazine experiment except when the subjects avoided the infusions. LSD infusions (when not avoided) caused pronounced excitation together with apparent hallucinatory behavior.

The data of all monkeys involved in the study are represented in detail in tables 1 and 2.

Discussion

The experiments described above show that infusions of chlorpromazine or LSD restore avoidance and escape behavior which had been extinguished in drug-naive rhesus monekys. These findings complement results of earlier investigators (Schuster and Thompson, 1969; Hoffmeister and Goldberg, 1973; Seevers, 1973) who found that chlorpromazine caused a sudden suppression of responding in monkeys pressing a key for infusions of codeine or cocaine. These effects of chorpromazine are comparable to those of other events that punish behavior (Holz and Azrin, 1963).

In contrast to chlorpromazine and LSD, pen-

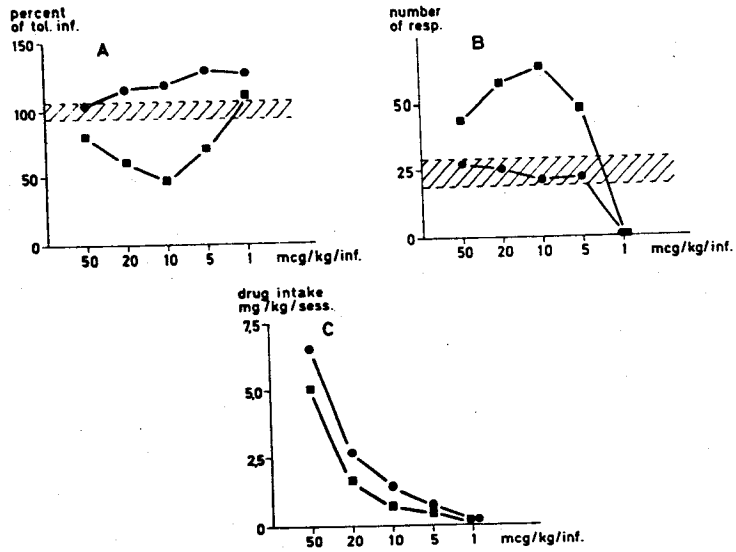

FIG. 3. Effects of varying chlorpromazine infusion doses on the number of infusions tolerated, number of avoidance and escape responses and drug intake during the first and the second 3-day component of the 6-day replacement period. ●——●, means of the 1st to the 3rd day of replacement; ■——■, means of the 4th to the 6th day of replacement;]], confidence limits of saline infusions tolerated. A. Effects of infusion dose (abscissa) on number of infusions tolerated per 2-hour session plotted as a percentage of saline infusions tolerated by the same subjects during extinction periods. Individual symbols represent means of all monkeys involved in the replacement experiments with different infusion doses. B. Effects of infusion dose (abscissa) on mean number of responses per 2-hour session of all monkeys involved in the replacement experiments with different infusion doses. C. Effect of infusion dose (abscissa) on mean drug intake per 2-hour session of all monkeys involved in the replacement experiments with different infusion doses.

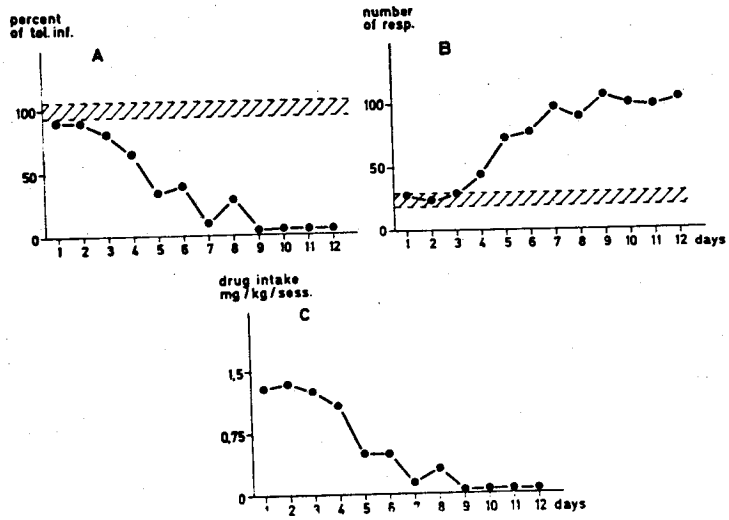

FIG. 4. Effect of 10 μg/kg/infusion of chlorpromazine on the number of infusions tolerated, number of avoidance and escape responses and drug intake at the individual days of a 12-day replacement period.]], confidence limits of saline replacement. A. Effect on mean number of infusions tolerated per 2-hour session plotted as a percentage of the saline infusions tolerated per 2-hour session (ordinate) by the same subjects during the extinction periods. Symbols represent means of all monkeys involved in the replacement experiment. B. Effect on mean number of responses per 2-hour session of all monkeys involved in the replacement experiment. C. Effect on mean drug intake per 2-hour session of all monkeys involved in the replacement experiment.

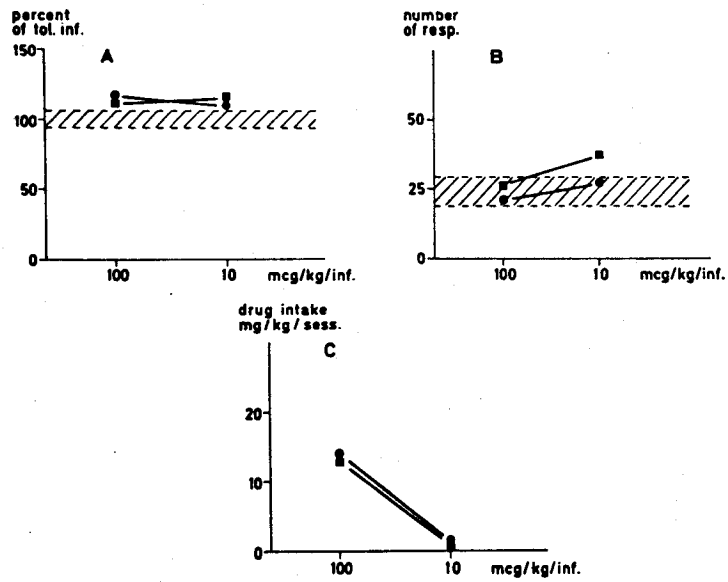

FIG. 5. Effects of varying pentobarbital infusion doses on the number of infusions tolerated, number of avoidance and escape responses and drug intake during the first and the second 3-day component of the 6-day replacement period. ●——●, means of the 1st to the 3rd day of replacement; ■——■, means of the 4th to the 6th day of replacement; [[, confidence limits of saline infusions tolerated. A. Effects of infusion dose (abscissa) on the number of infusions tolerated per 2-hour session plotted as a percentage of infusions tolerated by the same subjects during extinction periods. Individual symbols represent means of all monkeys involved in the replacement experiments with different infusion doses. B. Effects on infusion dose (abscissa) on mean number of responses per 2-hour session of all monkeys involved in the replacement experiments with different infusion doses. C. Effect of infusion dose (abscissa) on mean drug intake per 2-hour session of all monkeys involved in the replacement experiments with different infusion doses.

tobarbital in the dose range investigated does not induce avoidance/escape behavior. The failure of pentobarbital to initiate avoidance behavior cannot be attributed to the sedative action of the compound since rhesus monkeys press a lever in order to self-administer the drug in doses comparable to those injected in this study (Hoffmeister, 1974).

The negative reinforcing effects of chlorpromazine occur after a latent period of 3 (2–4) days. During the first 3 days of the 6-day replacement period, the animals tolerated all studied doses of chlorpromazine either to the same or to a greater extent than saline. During the second 3 days, avoidance behavior was initiated leading to a dose-dependent decrease of tolerated infusions. The maximum effect was seen with infusions of 10 μg/kg. Extending the replacement period from 6 to 12 days caused a further decrease of the number of tolerated infusions during the second 6 days of the replacement period.

The pattern of avoidance/escape behavior generated by LSD is different from that induced by chlorpromazine. LSD (0.5 μg/kg/infusion) does not initiate avoidance behavior during both components of the 6-day replacement period. LSD (1 μg/kg/infusion) generated avoidance/escape behavior during the second 3 days of the replacement period, and LSD (2.5 μg/kg/infusion) initiated avoidance/escape behavior beginning with the first day of the replacement period. Thus the behavioral effects of LSD (at least with the 2.5 μg/kg/infusion dose) are similar to those of nalorphine (Hoffmeister and Wuttke, 1973).

That high doses (50 μg/kg/infusion; 5–7 mg/kg/session) of chlorpromazine are less effective in generation of avoidance behavior than lower doses might be explained by the long-lasting rate depressing and sedative effects of the drug. Possibly these effects last longer than 24 hours and are thus still effective at the onset of the next drug exposure. Since the action of LSD is of much shorter duration, rate depressing or behavioral disruptive effects

TABLE 2

Number of avoidance/escape responses and percentage of tolerated infusions of individual monkeys during the first and the second 3-day component of the replacement periods

Substance	Dose	No. of Monkey	1–3 Days			4–6 Days		
			No. of responses	% of tol. saline infusions	Intake	No. of responses	% of tol. saline infusions	Intake
	μg/kg/ infusion				*mg/kg*			*mg/kg*
Chlorpromazine	50	2.9	68.0	55.5	2.99	31.7	111.3	6.10
		5.9	5.7	123.7	8.39	19.4	105.5	7.15
		7.6	6.7	133.9	8.27	81.0	24.0	1.92
		$\overline{X}$	26.8	104.4	6.55	44.0	80.3	5.06
	20	5.9	7.0	121.3	3.30	37.7	82.2	2.26
		7.6	37.7	92.3	2.29	85.4	26.8	0.79
		8.10	30.7	127.3	2.43	48.7	70.5	0.77
		$\overline{X}$	25.1	113.6	2.67	57.3	59.8	1.61
	10	2.9	58.7	66.6	0.75	87.6	25.0	0.28
		6.6	12.7	154.3	1.52	56.7	54.2	0.76
		7.6	13.7	126.3	1.57	60.6	46.3	0.73
		8.10	15.0	146.3	1.44	65.3	47.7	0.57
		8.11	7.7	94.3	1.62	71.0	34.6	0.60
		11.11	15.0	114.4	1.52	35.0	71.8	1.17
		$\overline{X}$	20.5	117.1	1.40	62.7	46.6	0.69
	5	6.6	21.3	142.2	0.69	48.7	71.2	0.47
		7.6	9.3	127.8	0.80	67.6	40.8	0.31
		8.10	35.0	115.0	0.56	27.3	99.9	0.62
		$\overline{X}$	21.9	128.3	0.68	47.9	70.6	0.47
	1	6.7	0.3	117.9	0.18	0.0	110.8	0.18
		11.11	0.3	134.1	0.18	0.3	108.4	0.18
		$\overline{X}$	0.3	126.0	0.18	0.2	109.6	0.18
LSD	2.5	2.9	84.3	27.9	0.08	99.0	9.5	0.03
		5.9	82.0	30.7	0.10	101.0	6.8	0.02
		8.11	100.7	4.7	0.02	97.3	1.5	0.01
		$\overline{X}$	89.0	21.1	0.07	99.1	5.9	0.02
	1	2.9	47.0	85.0	0.10	81.3	29.2	0.03
		5.9	36.0	81.1	0.11	38.3	78.8	0.11
		7.6	31.0	109.6	0.13	71.7	38.9	0.06
		$\overline{X}$	38.0	91.9	0.11	63.8	49.0	0.07
	0.5	2.9	56.0	71.8	0.04	55.0	72.6	0.04
		5.9	13.3	111.2	0.08	28.0	91.1	0.06

TABLE 2—*Continued*

Substance	Dose	No. of Monkey	1–3 Days			4–6 Days		
			No. of responses	% of tol. saline infusions	Intake	No. of responses	% of tol. saline infusions	Intake
	μg/kg/ infusion				*mg/kg*			*mg/kg*
		$\overline{X}$	34.7	91.5	0.06	41.6	81.9	0.05
Pentobarbital	100	2.9	12.3	115.6	15.50	11.3	182.9	15.70
		7.6	8.0	108.8	16.50	5.7	99.1	16.70
		5.9	43.7	126.4	9.90	62.0	54.1	6.50
		$\overline{X}$	21.4	106.9	14.00	26.3	112.0	13.00
	10	2.9	42.3	81.7	1.04	46.4	95.6	0.96
		5.9	19.0	154.3	1.42	11.0	149.9	1.56
		11.11	21.0	92.8	1.43	53.7	100.0	0.79
		$\overline{X}$	27.4	109.6	1.30	37.0	115.2	1.10

might not interfere with avoidance behavior 24 hours after the presentation of LSD.

The results achieved with chlorpromazine and LSD are surprising since these drugs suppress signalled avoidance responding in the monkey (Cook and Catania, 1964; Brown and Bass, 1967; Clark and Samuel, 1969) as well as other species (Kelleher and Morse, 1968; Wray, 1972). Obviously, these direct behavioral effects do not affect responding when the consequences of such responding are avoidance or escape from infusions of the drug.

It is interesting that monkeys previously presented with higher doses of chlorpromazine and LSD tolerated lower doses of the compounds for two to four successive daily sessions before avoidance/escape behavior was induced. Possibly higher doses of these compounds exert behavioral effects qualitatively different from those of lower doses. This might explain the delayed onset of responding since subjects with presentation of each dose of a compound would be confronted with a pharmacological action hitherto unknown to them. Induction of responding would then be the consequence of a "learning process," requiring two to four exposures to the particular dose of a drug. Apart from these speculations, the experiments reported here indicate that it is possible to analyze further the reinforcing effects of drugs which are not self-administered in cross-self-administration techniques.

That chlorpromazine has strong negative reinforcing effects in the rhesus monkey corresponds with the general experience with major tranquilizers in man. On the other hand, hallucinogenic drugs seem to be aversive in rhesus monkeys independent of their euphorigenic (LSD) or dysphoric (nalorphine, Hoffmeister and Wuttke, 1973) properties in man.

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References

BROWN, H. AND BASS, W. C.: Effect of drugs on visually controlled avoidance behavior in rhesus monkeys: A psychophysical analysis. Psychopharmacologia **11**: 143–153, 1967.

CLARK, R. AND SAMUEL, G. K.: Drug effects on a discrete conditioned avoidance response in dogs, rhesus monkeys and rats. Psychopharmacologia **14**: 106–114, 1969.

COOK, L. AND CATANIA, A. C.: Effects of drugs on avoidance and escape behavior. Fed. Proc. **23**: 818–835, 1964.

DENEAU, G. A., YANAGITA, T. AND SEEVERS, M. H.: Self-administration of psychoactive substances by the monkey: A measure of psychological dependence. Psychopharmacologia **16**: 30–48, 1969.

HOFFMEISTER, F.: Positive and negative reinforcing properties of psychotropic drugs in rhesus monkeys. Neuro-Psycho-Pharmacology **133**: 36, 1974.

HOFFMEISTER, F. AND GOLDBERG, S. R.: A comparison of chlorpromazine, imipramine, morphine and *d*-amphetamine self-administration in cocaine-dependent rhesus monkeys. J. Pharmacol. Exp. Ther. **187**: 8–14, 1973.

HOFFMEISTER, F. AND WUTTKE, W.: Negative reinforcing properties of morphine-antagonists in naive rhesus monkeys. Psychopharmacologia **33**: 247–258, 1973.

HOLZ, W. C. AND AZRIN, N. H.: A comparison of several procedures for eliminating behavior. J. Exp. Anal. Behav. **6**: 99–106, 1963.

KELLEHER, R. T. AND MORSE, W. H.: Determinations of the specificity of behavioral effects of drugs. Ergeb. Physiol. **60**: 1–56, 1968.

SCHLICHTING, U. U., GOLDBERG, S. R., WUTTKE, W. AND HOFFMEISTER, F.: D-Amphetamine self-administration by rhesus monkeys with different self-administration histories. *In* Proceedings of the 12th Meeting of the European Society for the Study of Drug Toxicity, Uppsala. Excerpta Med. Int. Congr. Ser. **220**: 62–69, 1970.

SCHUSTER, C. R. AND THOMPSON, T.: Self-administration of and behavioral dependence on drugs. Annu. Rev. Pharmacol. **9**: 483–502, 1969.

SEEVERS, M. H.: Discussion remark. *In* Psychic Dependence, Definition, Assessment in Animals and Man, Theoretical and Clinical Implications, ed. by L. Goldberg, and F. Hoffmeister, p. 87, Springer-Verlag New York, 1973.

WRAY, S. R.: A correlative evaluation of cyclazocine, LSD and naloxone on continuous discriminated avoidance in rats. Psychopharmacologia **26**: 29–43, 1972.

YANAGITA, T., DENEAU, G. A. AND SEEVERS, M. H.: Evaluation of pharmacologic agents in the monkey by long-term intravenous self- or programmed administration. Excerpta Med. Int. Congr. Ser. **87**: 453–457, 1965.