INFLUENCE OF HALOPERIDOL (R 1625) AND OF HALOPERIDIDE (R 3201) ON AVOIDANCE AND ESCAPE BEHAVIOUR OF TRAINED DOGS IN A "JUMPING BOX"

BY CARLOS J. E. NIEMEGEERS AND PAUL A. J. JANSSEN

From the Research Laboratorium Dr. C. Janssen, Beerse, Belgium

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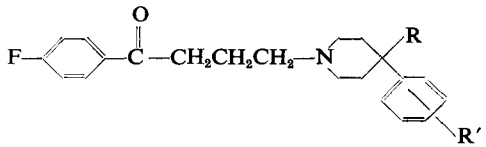
The experimental details of a technique for establishing conditioned responses on the basis of escape and avoidance behaviour of dogs in an electrically charged "jumping box" are described. The method is similar to the well-known Warner technique for rats. The influence of two new neuroleptic agents, haloperidol (R 1625) and haloperidide (R 3201), on the behaviour of trained dogs is reported. One and five hours after injection the effects of both compounds are qualitatively and quantitatively indistinguishable. Haloperidol has a longer duration of action. These results are of particular interest in view of the fact that haloperidide is about ten times more active than haloperidol as an antagonist of apomorphine-induced emesis in dogs.

THE literature contains many descriptions of techniques for establishing conditioned responses on the basis of an escape response of the animal as a whole from an electrically charged grill. The first apparatus of this sort—referred to as a "jumping box" in this paper—was described for rats in 1932 by Warner [1,2]. It consists of a box with two compartments separated by a partition. The floor of each compartment is a grill which can be charged electrically. The rat can escape the aversive stimulus (shock) by making the only appropriate "escape response", that is to jump into the other compartment. The rat can also avoid the aversive stimulus by making a conditioned "avoidance response" when presented with a warning signal, for example the sound of a buzzer or bell, a short time before presentation of the shock. Many modifications of this "jumping box" technique are described for rats[1–13].

The purpose of this paper is to describe the experimental details of a "jumping box" technique for dogs which we have tried to standardise. To illustrate the technique, the effects of two drugs on the behaviour of trained dogs will be described. Both compounds are neuroleptics of the butyrophenone-series and were originally synthesised in this laboratory.



Haloperidol (R 1625): R = OH; R′ = *p*-Cl

Haloperidide (R 3201): R = CON⟨ ⟩ ; R′ = *m*-Cl

Pharmacological and clinical properties of haloperidol have been described by many authors[14–55]. The pharmacology of haloperidide will be described in detail in subsequent papers from this laboratory. One point of particular interest in connection with this study is the extremely high activity of haloperidol and of haloperidide as antagonists of apomorphine-induced emesis in dogs. One to eight hours after subcutaneous injection we find haloperidide (ED50 = 0·0025 mg./kg. s.c.) about 10 times more active than haloperidol (ED50 = 0·025 mg./kg. s.c.) in this test[35,37,47].

METHOD

Subjects. Eight adult male mongrel dogs of unknown age were the subjects. They had initial weights in kg. (dog 1: 12·5; 2: 13·2; 3: 10·8; 4: 8·5; 5: 10·9; 6: 8·2; 7: 9·7; 8: 11·2).

Administration of the drugs. Aqueous solutions of haloperidol and of haloperidide were prepared for subcutaneous injection of 0·5 ml./kg. weight. Each dog received at random, using an 8 × 8 latin square design, all eight of the following doses at weekly intervals:

haloperidol (R 1625):	0·005 mg./kg.	$= x_1$
	0·02 mg./kg.	$= x_2$
	0·08 mg./kg.	$= x_3$
	0·31 mg./kg.	$= x_4$
haloperidide (R 3201):	0·005 mg./kg.	$= y_1$
	0·02 mg./kg.	$= y_2$
	0·08 mg./kg.	$= y_3$
	0·31 mg./kg.	$= y_4$

Apparatus (jumping box). The cage, Figure 1, consists of a steel frame, 2 m. long, 1 m. wide and 1 m. high, made of L-shaped steel. The bottom is made of $\frac{3}{4}$ in. thick wood. The top is covered with 2 cm. square galvanised wire gauze, the walls are made of $\frac{1}{8}$ in. thick asbestos cement

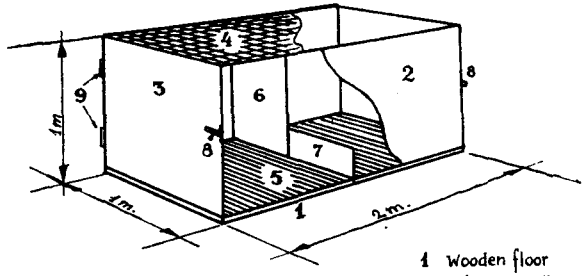


FIG. 1.

sheets. Both ends of the cage can be opened and are used as doors. They are covered with asbestos cement and provided with hinges and bolts. The floor consists of a grate made of 8 mm. iron bars, electrically isolated in two groups dividing the cage in two compartments (A and B), alternatively being connected to the shock source.

In the middle of the cage, separating the two compartments a perspex wall of 50 cm. wide and $\frac{5}{8}$ in. thick, bars half of the transit from one compartment into the other. The free half shows a smaller wall or hurdle of about 20 cm. high of the same material, which the animal must jump over to reach the other compartment.

By means of a variac (1 k. VA.) a voltage of $\pm$30–50 V., a.c. at 50 c.p.s. is given to the floor grid of one compartment. This voltage may be

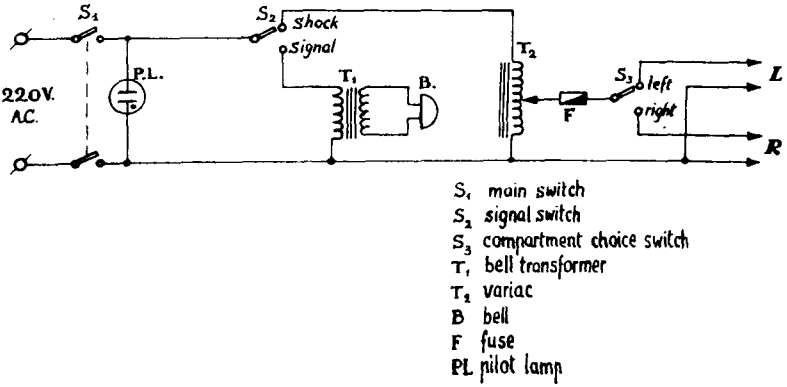


FIG. 2.

switched off by the two-way signal switch to connect the signal bell (5 V., with step-down transformer). During the signal period a second two-way switch makes it possible to electrify the second compartment. By switching back the signal switch to shock-position, the shock-voltage will be connected to the first compartment (Fig. 2).

Description of one cycle. Avoidance conditioning in dogs was progressively achieved by subjecting the animals twice a day, except Saturday and Sunday, at 5-hour intervals to a series of 10 cycles of conditions. Each cycle, Figure 3, has a duration of 1 minute (T_3) and consists of periods T_1 (1 to 15 seconds) and T_2 (59 to 45 seconds).

The dog is placed on the unelectrified grid floor of compartment A of the box.

(*a*) Warning stimulus: a bell (S_1) is rung for a maximum of 15 seconds (T_1) or until the animal jumps from compartment A into B. If jumping occurs during the 15 second period (T_1) it stops the bell and is defined as an "avoidance response" (R_1). During the T_1 period both compartments of the box are current-free.

(*b*) Aversive stimulus: if the animal does not leave its compartment during the signal period S_1, a continuous electric shock (S_2) is delivered during a period T_2 with a maximal duration of 45 seconds. The T_2 period can be terminated by an "escape response".

(*c*) "Silence stimulus" (S_3), that is, absence of S_1 or S_2. A new response occuring during the same cycle under S_3 is stimulated by shock, necessitating another escape response, and defined as a "paradoxal response" (R_3). R_3 may obviously occur after R_2 during the same cycle.

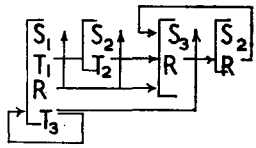
A series of 10 cycles of 10 minutes' total duration is defined as a session.

Training period. During the training period the eight dogs were subjected daily to a morning and afternoon session, with 5 hours in between, except on Saturdays and Sundays. Except for the first day of the training period, the observer did not actively interfere with the behaviour of the dogs. Training was continued until 20 out of 20 avoidance responses (R_1) were observed on a given day. Such an animal was considered to be "adequately" trained.

Design of the experiment. The eight "adequately" trained dogs were subjected to two daily sessions 5 days a week for 8 weeks.

	Sessions		Hours before (−) or after (+) injection	
	a.m.	p.m.	a.m.	p.m.
Monday	−4	−3	−48	−43
Tuesday	−2	−1	−24	−19
Wednesday	1	2	+1	+5
Thursday	3	4	+25	+30
Friday	5	6	+49	+54

On Wednesday morning each animal was given a subcutaneous dose of haloperidol (x_1 to x_4) or of haloperidide (y_1 to y_4) as described above. At the end of the 8 weeks each dog had received all doses of both compounds in a random order.



S_1 = warning stimulus (bell).
T_1 = duration of S_1 (1 to 15 seconds).
S_2 = aversive stimulus (shocks).
T_2 = duration of S_2 (1 to 45 seconds).
S_3 = "silence" stimulus with a duration of 0 to 59 seconds.
T_3 = 60 seconds, i.e., the period with which these conditions recycle.
R = "response", i.e., jumping from one compartment to the other.
R_1 = R occurring under S_1 (avoidance response).
R_2 = R occurring under S_2 (escape response).
R_3 = R occurring under S_3 (paradoxal response).

FIG. 3. Symbolisation of one cycle (ref. 56).

RESULTS AND DISCUSSION

1. *Training Period*

The relevant data concerning the behaviour of the eight dogs during the training period are summarised in Tables I, II and III.

All dogs were trained for 8 or more days. A minimum of 5 and a maximum of 11 days was required for adequate training.

Table I shows the significance of the criteria $\overline{T}_1$, $\overline{T}_2$, fR_2 and fR_3 to decrease as a function of time. $\overline{T}_1$ reaches a lower limit of roughly 3 seconds after about 2 weeks of training, whereas $\overline{T}_2$, fR_2 and fR_3 approaches zero.

It is obviously easier for a dog to learn how to avoid aversive stimulation in situation S_1 (bell) than in situation S_3 (silence). Escape or avoidance responses were observed in all trials throughout the training period.

TABLE I

TRAINING PERIOD (8 DAYS): DAILY VALUES FOR THE 8 DOGS (20 CYCLES PER DAY)

d	$\overline{T}_1$*	$\overline{T}_2$	fR_2	fR_3†	fR
1	8·6	1·5	5·8	4·0	160
2	6·5	0·41	3·1	5·8	160
3	5·8	0·44	2·4	3·9	160
4	5·2	0·15	1·1	4·0	160
5	4·6	0·06	0·38	0·88	160
6	4·3	0·09	0·50	1·4	160
7	3·8	0·02	0·25	0·63	160
8	3·4	0·07	0·25	0·63	160

* $\overline{T}_1$: mean duration of T_1 per cycle (max. 15 seconds).
$\overline{T}_2$: mean duration of T_2 per cycle (max. 45 seconds).
fR_2: mean frequency of R_2 per 20 cycles (max. 20).
fR_3: mean frequency of R_3 per 20 cycles (max. 20).

† Frequency computed on the basis of a simple alternative criterion: response or no response in a given cycle. It should be noted, however, that several responses R_3 per cycle were sometimes observed.

Table II summarises relevant data on the individual characteristics of the behaviour of each dog during the 8 days.

On the basis of these data the following alternative criteria are proposed for the purpose of classifying the eight dogs in four categories A, B, C and D:

(1) "slow dog": $\overline{T}_1 > 5$ seconds.

(2) "quick dog": $\overline{T}_1 < 5$ seconds.

(3) $fR_3/fR_2 < 1$.

(4) $fR_3/fR_2 > 1$.

Hence

		fR_3/fR_2	
		<1	>1
$\overline{T}_1$	slow	Dog 7 (A)	Dogs 1, 2, 3, (B)
	quick	Dog 5 (C)	Dogs 4, 6, 8, (D)

For the six dogs of categories B and D we found a highly significant positive correlation between $\overline{T}_1$ and $\overline{T}_2$ ($\overline{T}_2$ = 0·19, 0·19 and 0·45 for category B and T_2 = 0·01, 0·06 and 0·06 for category D). Dogs No. 5 and 7, however, making relatively less paradoxal responses (R_3), are characterised by high values of $\overline{T}_2$ (0·81 and 0·82).

Table III shows that there is no striking correlation between the frequency of R_2 and of the *n*th cycle, the probability of occurrence varying from 6 to 17/128 per cycle. Paradoxal responses, however, occur most frequently ($P < 0{\cdot}05$) during the first cycles of a given session. No significant correlation was found between body weight and any of these training period data.

Pre-injection period. Throughout the eight experimental weeks all eight dogs were subjected to two daily sessions of 10 cycles each on both

TABLE II

TRAINING PERIOD (8 DAYS): MEAN VALUES FOR EACH DOG (160 CYCLES PER DOG)

	Dog No.							
	1	2	3	4	5	6	7	8
$\overline{T}_1$*	6·5	6·2	5·7	4·1	4·5	3·4	7·4	3·9
	(2)	(3)	(4)	(6)	(5)	(8)	(1)	(7)
$\overline{T}_2$	0·45	0·19	0·19	0·01	0·81	0·06	0·82	0·06
	(3)	(4½)	(4½)	(8)	(2)	(6½)	(1)	(6½)
fR_2	17	19	14	2	11	7	34	6
	(3)	(2)	(4)	(8)	(5)	(6)	(1)	(7)
fR_3	35	32	26	16	8	17	14	23
	(1)	(2)	(3)	(6)	(8)	(5)	(7)	(4)
$fR_2 + fR_3$ ..	52	51	40	18	19	24	48	29
	(1)	(2)	(4)	(8)	(7)	(6)	(3)	(5)
fR_3/fR_2	2·1	1·7	1·9	8·0	0·73	2·4	0·41	3·83
	(4)	(6)	(5)	(1)	(7)	(3)	(8)	(2)

* $\overline{T}_1$: mean duration of T_1 per cycle (max. 15 seconds).
$\overline{T}_2$: mean duration of T_2 per cycle (max. 45 seconds).
fR_2: total frequency of R_2 (max. 160).
fR_3: total frequency of R_3 (max. 160).

TABLE III

TRAINING PERIOD (8 DAYS) TOTAL FREQUENCY OF R_2 (fR_2) AND OF R_3 (fR_3) FOR THE 8 DOGS (MAXIMUM FREQUENCY: 8 DOGS × 8 DAYS × 2 SESSIONS = 128)

			Ranking of	
*n**	fR_2	fR_3	fR_2	fR_3
1	7	26	9	1
2	12	23	5	2
3	17 } 57	21 } 109	1	3
4	13	20	3½	4
5	8	19	8	5
6	6	14	10	8
7	13	12	3½	9
8	14 } 53	16 } 62	2	6
9	9	15	7	7
10	11	5	6	10
	110/1280	171/1280		

* n = the n th cycle of a session.

pre-injection days, i.e., on Monday and on Tuesday. Only two "errors" (of type R_3) occurred in these 2,560 (8 dogs × 8 weeks × 2 days × 20 cycles) cycles, showing that all subjects were "adequately" trained.

Table IV summarises the most important data pertaining to the behaviour of the dogs during the pre-injection period. Obviously $\overline{T}_1$ is not correlated with a particular week, showing the absence of significant after-effects of previous doses. Neither are the $\overline{T}_1$-values correlated with the sessions, the reaction time remaining about the same throughout.

There are no significant differences between morning and afternoon experiments as far as $\bar{T}_1$ is concerned.

Surprisingly, we found no correlation of the average reaction time per dog for the training period and for the pre-injection days as shown by the following rankings of $\bar{T}_1$:

Dog	Training period	Pre-injection days
1	6·5 (2)	1·9 (6)
2	6·2 (3)	3·6 (3)
3	5·7 (4)	1·8 (7)
4	4·1 (6)	4·1 (1)
5	4·5 (5)	3·7 (2)
6	3·4 (8)	1·6 (8)
7	7·4 (1)	3·2 (4)
8	3·9 (7)	3·0 (5)

The effects of haloperidol and of haloperidide. All eight dogs were treated at random and at weekly intervals with eight different doses, as described. The effects of each dose were measured at six time intervals

TABLE IV

PRE-INJECTION DAYS

Week	$\bar{T}_1$	Dog	$\bar{T}_1$	Cycle	$\bar{T}_1$ a.m.	$\bar{T}_1$ p.m.
1	2·7	1	1·9 (6)	1	2·8	2·8
2	3·1	2	3·6 (3)	2	3·3	3·1
3	2·7	3	1·8 (7)	3	3·2	3·3
4	2·9	4	4·1 (1)	4	3·2	3·4
5	2·8	5	3·7 (2)	5	3·3	3·4
6	3·1	6	1·6 (8)	6	3·3	3·4
7	3·0	7	3·2 (4)	7	3·3	3·3
8	2·9	8	3·0 (5)	8	3·1	3·3
average	2·9	average	2·9	9	3·3	3·2
				10	3·2	3·1
				average	2·9	2·9

after injection. A total of 1920 post-injection cycles (8 dogs × 4 doses × 6 sessions × 10 cycles) are therefore available for each drug. The frequency of the various types of responses was computed as follows:

	fR	fR_1	fR_2	fR_3	Maximum
Haloperidol ..	1726	1557	69	14	1920
Haloperidide ..	1786	1719	67	9	1920
Total	3512	3276	136	23	3840

The animals failed to respond 194 times after haloperidol and 134 times after haloperidide. Avoidance responses were observed more frequently after haloperidide ($fR_1 = 1719$) than after haloperidol (1557). The frequency of escape responses (fR_2) and paradoxal responses (fR_3) after haloperidol was also slightly greater. On the basis of these figures, haloperidol seems to be somewhat more active than haloperidide.

This difference in activity, however, is mainly due to the longer duration of action of haloperidol (Table V). One and 5 hours after injection both substances are about equi-active. The second day, however, haloperidol

is still strikingly active and haloperidide much less so. The two lower dose levels of both compounds (0·005 and 0·02 mg./kg.) have no influence on escape behaviour. They do produce, however, a slight but significant

TABLE V

EFFECTS OF HALOPERIDOL AND OF HALOPERIDIDE AT VARIOUS INTERVALS AFTER INJECTION (SEC.)

	Dose*	1st day		2nd day		3rd day		Maximum
		a.m.	p.m.	a.m.	p.m.	a.m.	p.m.	
$\bar{T}_1$	x_1	3·2	3·4	3·0	2·8	3·0	2·9	15
	x_2	3·7	3·3	3·2	3·2	3·2	2·9	15
	x_3	11·6	12·0	3·1	3·6	2·3	3·2	15
	x_4	13·1	14·4	8·8	10·3	4·4	4·3	15
	Σx	8·1		4·8		3·4		15
	y_1	3·4	3·7	2·7	2·7	2·6	2·5	15
	y_2	3·6	4·7	3·5	3·2	3·1	2·8	15
	y_3	9·4	13·2	3·4	3·2	3·1	2·9	15
	y_4	12·5	14·1	5·6	4·4	3·6	3·4	15
	Σy	8·1		3·6		3·0		15
$\bar{T}_2$	x_1	—	—	—	—	—	—	45
	x_2	0·04	—	—	—	—	—	45
	x_3	17·2	15·6	—	—	—	—	45
	x_4	27·9	32·1	10·3	11·8	—	—	45
	Σx	11·6		2·8		0		45
	y_1	—	0·16	—	—	—	—	45
	y_2	—	0·14	—	—	—	—	45
	y_3	12·0	16·4	—	—	—	—	45
	y_4	25·3	27·8	—	—	—	—	45
	Σy	10·2		0		0		45
fR	x_1	80	80	80	80	80	80	80
	x_2	80	80	80	80	80	80	80
	x_3	50	52	80	80	80	80	80
	x_4	33	29	62	60	80	80	80
	Σx	484		602		640		640
	y_1	80	80	80	80	80	80	80
	y_2	80	80	80	80	80	80	80
	y_3	60	53	80	80	80	80	80
	y_4	38	35	80	80	80	80	80
	Σy	506		604		640		640
fR_1	Σx	432		485		640		640
	Σy	439		640		640		640
fR_2	x_1	—	—	—	—	—	—	80
	x_2	1	—	—	—	—	—	80
	x_3	13	12	—	—	—	—	80
	x_4	10	16	4	13	—	—	80
	Σx	52		17		0		640
	y_1	—	1	—	—	—	—	80
	y_2	—	3	—	—	—	—	80
	y_3	11	20	—	—	—	—	80
	y_4	11	21	—	—	—	—	80
	Σy	67		0		0		640
fR_3	x_1	—	—	—	—	—	—	80
	x_2	3	1	2	—	—	—	80
	x_3	—	3	3	1	—	—	80
	x_4	—	—	1	—	—	—	80
	Σx	7		7		0		640
	y_1	—	2	—	—	—	—	80
	y_2	—	1	—	1	—	—	80
	y_3	—	2	2	—	—	—	80
	x_4	—	—	—	1	—	—	80
	Σy	5		4		0		640

* See text for details.

increase of the reaction time of the avoidance response as well as a few paradoxal responses. After injection of 0·08 mg./kg. of both drugs these same effects were much more pronounced and significant inhibition of escape behaviour was observed with both drugs up to 5 hours after dosage.

The highest dose (0·31 mg./kg.) produced essentially similar effects. The duration of action of this dose is clearly more prolonged. The frequency of the paradoxal responses (fR_3), however, was significantly lower (Table V). As shown in Table VI we find considerable variation among dogs during the post-injection period. On the basis of different individual total frequencies of avoidance (fR_2) and escape-loss (480-fR) the eight dogs may be classified in four categories (A to D).

	fR_2	480-fR	Dogs
A	normal	high	No. 7
B	normal	normal	No. 2, 5, 6, 8
C	normal	low	No. 1, 3
D	high	low	No. 4

There is no significant relation between the behaviour of the animals during the training period and their sensitivity to haloperidol and haloperidide. We found furthermore no correlation between the frequency

TABLE VI

INDIVIDUAL FREQUENCIES OF THE VARIOUS TYPES OF RESPONSE (R, R_1, R_2 AND R_3) AFTER INJECTION (COMBINED DATA PER DOG FOR ALL EIGHT DOSES AND ALL SIX SESSIONS AFTER INJECTION)

Dog No.	fR	fR_1	fR_2	fR_3
1	463 (7)	459 (7)	4 (8)	3 (4)
2	438 (5)	421 (6)	17 (4)	2 (5½)
3	479 (8)	466 (8)	13 (5)	1 (7)
4	457 (6)	411 (3½)	46 (1)	2 (5½)
5	428 (3)	409 (2)	19 (2)	6 (1)
6	429 (4)	411 (3½)	18 (3)	0 (8)
7	389 (1)	381 (1)	8 (7)	4 (3)
8	424 (2)	412 (5)	12 (6)	5 (2)
Max.*	480	480	480	480
Total	3507	3370	137	23

* 1 dog × 8 doses × 6 sessions × 10 cycles = 480.

of paradoxal responses (fR_3) observed during the training- and the post-injection periods (Tables II and VI) or between the individual sensitivity of the animals to the drugs and their average reaction times (T_1) during the pre-injection days (Table IV).

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