The Neuroleptics. Mod. Probl. Pharmacopsychiat., Vol. 5, pp. 85–108
ed. by D.P. Bobon, P.A.J. Janssen and Jean Bobon, Liège
(Karger, Basel/München/Paris/New York 1970)

Chapter 5
Animal Behavior

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Behavior may be defined, for our present purposes, as the observable activity of an animal with mainly intact control of the motor system initiated by its higher integrated centers. Thus, coma cannot be regarded as a behavior, nor can paralysis caused by neuromuscular block. Convulsions, *e.g.* after strychine or picrotoxin, must also be excluded. It may be disputed whether catalepsy caused by neuroleptics or stereotypy caused by amphetamine may be called behavior, although many do.

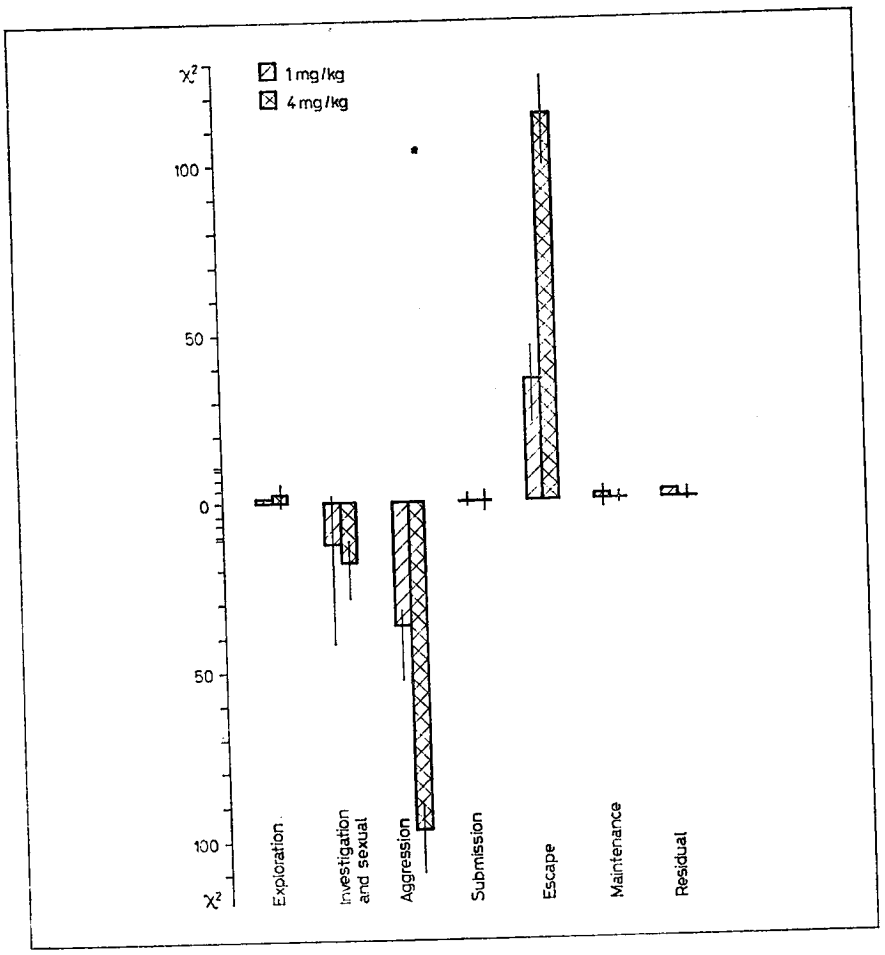
A host of experiments on the influence of drugs on behavior have been done, and obviously it was impossible for our group to cover all aspects. Many important problems such as taming, imprinting and orientation reflexes, had to remain undiscussed. And, with one exception, the very important point of species and strain differences was also left out.

The discussion was mainly focussed on the factors able to elicit a well defined behavior, and the influence of drugs on this behavior. Among the many techniques which have been used in this type of study, the program had chosen only a few which were thoroughly discussed.

The *ethological approach* to the behavior problem consists of giving the animals as much scope as possible. That is, they are placed in a situation in which they will show behavior of several kinds, so that one kind of behavior can act as a control for other, non-specific effects. Here the behavior of two male rats placed together was reported. Their behavior was found to be composed of a relatively few identifiable units, such as rising on the hind legs and grooming. These units are easy to recognize and are recorded on tape during the experiment. Some drugs have a typical in-

1 Conclusions of Round Table no. 5 at the 'Semaine Interdisciplinaire des Neuroleptiques' (Liège, May 11–16, 1969). Leader: M. Richelle; main discussant: E. Jacobsen.

fluence [SILVERMAN, 1965]. Chlorpromazine, for example, reduces the overall activity, especially the faster moving elements. It reduces aggression and increases escape behavior and submission. Chlorpromazine can also increase avoidance in response to an ambivalent stimulus, as is shown in some conflict experiments (see p. 96). Other activities such as eating, grooming, etc. are not really affected by chlorpromazine [SILVERMAN, 1966a] (fig. 1). Drugs different from the neuroleptics have different effects. Thus, small doses of barbiturates increase aggressive behavior [SILVERMAN, 1966b] (fig. 2). Amphetamine increases apparent exploration and, like chlorpromazine, increases avoidance, and it reduces eating, grooming, etc.



[SILVERMAN, 1966a]. A still different effect is seen after administration of nicotine [SILVERMAN, in prep.] (fig. 3).

The most commonly used – and most discussed – technique is the observation of a single defined response selected by the experimenter. It is often a response that would occur only rarely if not specifically conditioned in the experimental situation. Such techniques are used mainly with the conditioned reactions and the conflict situations. The conditioning technique may be the *classical Pavlovian*. The animals are trained to react on a certain signal associated with a positive or negative unconditioned stimulus [RAY, 1963]. In the *operant conditioning* the situation itself is acting as the conditioned signal. The technique has been varied in many ingenious ways but is basically the same. The animals have learned to do some task, such as manipulating levers or pressing buttons, in order to obtain a reward which may be food, drink, or stimulation of sites in the brain from which pleasant feelings are generated. The animals may have been conditioned to avoid a punishment such as an electric shock or stimulation of sites in the brain from which unpleasant feelings are triggered. The speed with which the task is done, such as the frequency of lever pressing, is recorded and reflects the effect of the drug given.

At the beginning, the discussion was concentrated on the type and intensity of the reactions. Simple reactions, such as lever pressing, seem to be virtually identical in all examined animals, including man. Humans were placed in the same situation as were the experimental animals. Without any oral or written instruction they had to find out by themselves that by pressing a lever they obtained a reward or avoided an electric shock. The development of the reactions and their pattern closely resembled that of animals

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Fig. 1. Effect of chlorpromazine on the social behavior of laboratory rats (A.P.S.)[2]

Male rats were isolated 7 days, then introduced into the home cage of a 'partner' and observed for 10 min. Experimental and control rats met the same partners in a counterbalanced order. The figure shows the difference from saline controls of 6 rats injected with chlorpromazine 1 mg/kg i.p. and of 6 given 4 mg/kg, immediately before introduction.

Rectangles represent the χ^2 value of the difference between experimentals and controls for each category of behavior. The lines give an estimate of the variability of the elements included in that category [SILVERMAN, 1965].

Chlorpromazine reduced behavior involving approach to the other rat (Investigation and sexual, aggression) but unlike benactyzine, for example [SILVERMAN, 1966a], also increased escape away from the partner. It is to be noted that exploration of the physical environment, the most frequent of all these categories, and behavior directed to the self (maintenance, *i.e.* eating, grooming etc.) is not affected in this situation.

2 Initials of group member presenting the material.

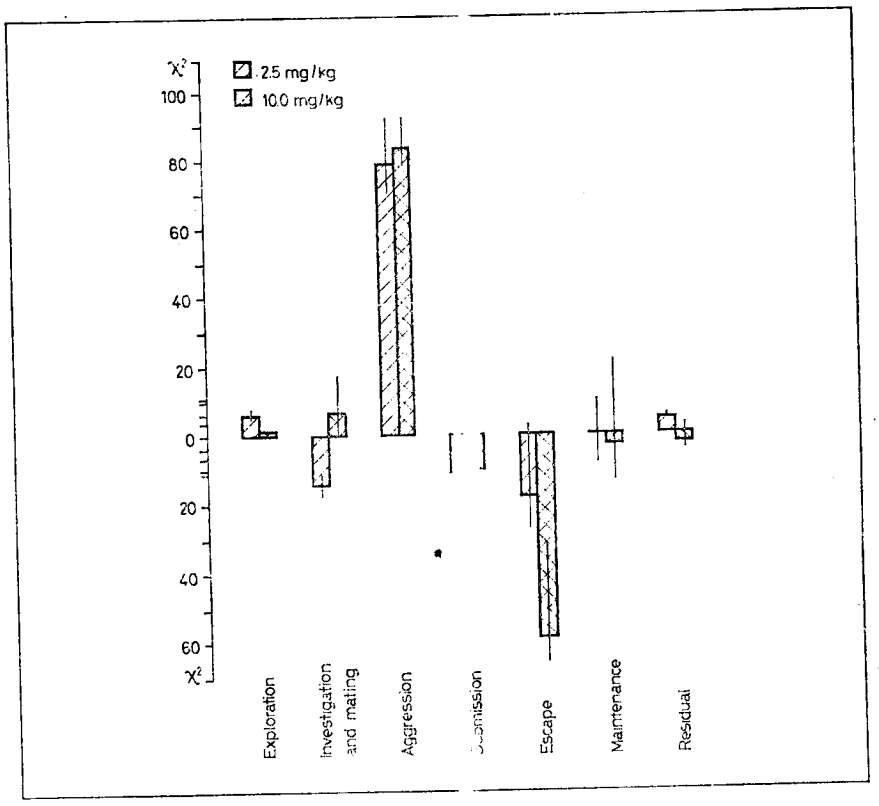

Fig. 2. Effect of small doses of amobarbital sodium on the social behavior of rats (A.P.S.)

Method as described for figure 1. Barbiturates at the given doses have opposite effects to chlorpromazine, *i.e.* aggression is increased, submission and escape are reduced. The two latter forms of behavior might be equivalents to behavior that, in man, is associated with anxiety.

and the influence of drugs was the same as that observed in the animals [Cook].

It was once more stated that the neuroleptics inhibit most conditioned responses, whether positively or negatively reinforced, and whether classical or operant [Cook and Catania]. Earlier experiments, which indicated that the more fixed a conditioned response is, the less it is inhibited by neuroleptics, were not stressed when presented to the Round Table. Lack of knowledge of this fact is possibly the cause of much disagreement about the effects of neuroleptics.

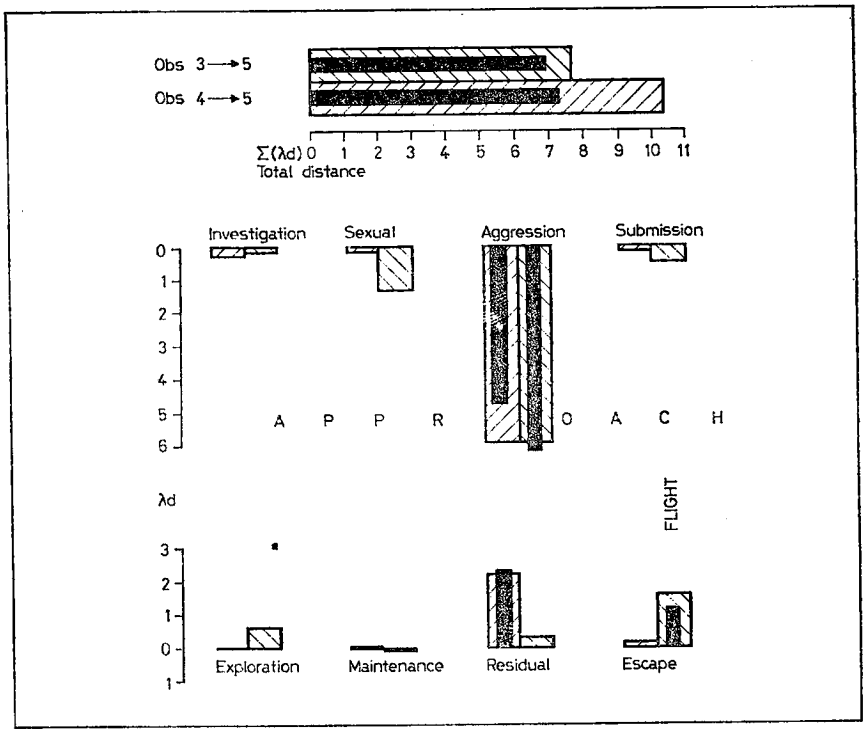

Fig. 3. Effect of nicotine on the social behavior of rats (A.P.S.)

The change in behavior between experimental and control condition is observed. The dose given was 25 μg/kg s.c., about equivalent to that inhaled by a man smoking a cigarette.

Male rats were housed in pairs, separated daily for 6 h, and observed weekly for 6 min on return. After 2 baseline observations, the 3rd immediately followed the injection of nicotine to 16 of the rats and saline to the other 16; the 4th followed the last of 4 daily injections to the same rats. Finally, a 'crossover' observation followed the injection of nicotine to the former controls, saline to rats formerly receiving nicotine.

The figure illustrates the effect of nicotine within the groups of rats, *i.e.* it compares the change in behavior of experimentals and controls from observations 3 and 4 respectively to observation 5. The former group received nicotine in observation 3 and 4, the latter in observation 5.

The effect is measured by discriminant analysis. The 'total distance' measures the difference in the pattern of behavior. Hatched bars represent the distance as first computed, in both cases significant at $p < 0.001$. Solid bars represent a recalculation after variables not contributing significantly to the total distance have been rejected. The solid bars are, therefore, of great interest in analyzing the contribution of each category of behavior to the overall difference in pattern – they show that the major significant effect of nicotine in this situation was to reduce aggression. [From SILVERMAN, in prep.]

If the fixation of the response is expressed by the probability that it will occur, further analysis could be conveniently carried out, if a commonly used formula from general psychology was adapted and expressed in the following way:

$$P = \left\{ H \times D \times K \times I \times T \times \ldots\ldots\ldots\ldots \times \frac{1}{C} \times \ldots\ldots \right\} +$$

where P stands for the probability that the response will occur, H is the habit, *i.e.* the length of the training, D the drive, K the quality of the unconditioned stimulus, I its intensity, T the actual *tonus* of the central nervous system. P increases with all these factors. C is the complexity of the conditioned reaction, which decreases P.

The specific influence of neuroleptics on the habit (H), was found to be small, and only dependent on its influence on P. The influence of C was probably increased by the drugs, but this point was not especially discussed.

As could be expected, the intensity of the conditioned stimulus was shown to have a crucial influence [RAY, 1964a, b, 1965]. Within certain limits, P increases with increasing intensity (I), and consequently, the more difficult it is to establish the conditioned reaction on a given unconditioned stimulus, the smaller are the doses of neuroleptics necessary to suppress it. Some examples were demonstrated. It was possible to condition animals by means of intravenous injections of adrenaline or acetylcholine as a conditioned stimulus. The endoceptive conditioning with adrenaline required much more trials than, for example, an exteroceptive conditioning with a tone. The conditioned response elicited by adrenaline was very easily inhibited by neuroleptics in doses which had little influence on the conditioned response elicited by a tone. Peripheral effects such as increase in blood pressure and changes of heart rate following the adrenaline injection were the same as in the controls not given neuroleptics [COOK and CATANIA].

The influence of drugs on the drive (D) and the quality of the unconditioned stimulus were submitted to an extensive analysis. In earlier literature the question was much discussed as to whether the influence of neuroleptics on conditioned responses depends on the type of unconditioned stimulus. In particular, it had been shown that a reaction reinforced by punishment is more sensitive to neuroleptics than is one reinforced by reward [*e.g.* RAY, 1963]. However, this seems to be a question of intensity rather than quality, and more recent experiments presented to us showed clearly that if the intensity of the reinforcement was balanced, no differ-

ence was seen between neuroleptic effects on punishment-reinforced reactions and on reward-reinforced reactions. It was apparent that the same pattern of reaction was seen independently of the type of reinforcement [RAY and BIVENS]. As other experiments with different techniques have indicated the same trend [COOK and CATANIA], it may now be accepted as a fact that the effects of neuroleptics in principle are absolutely independent of the type of reinforcement, although in practice there may be a partial and quantitative dependence.

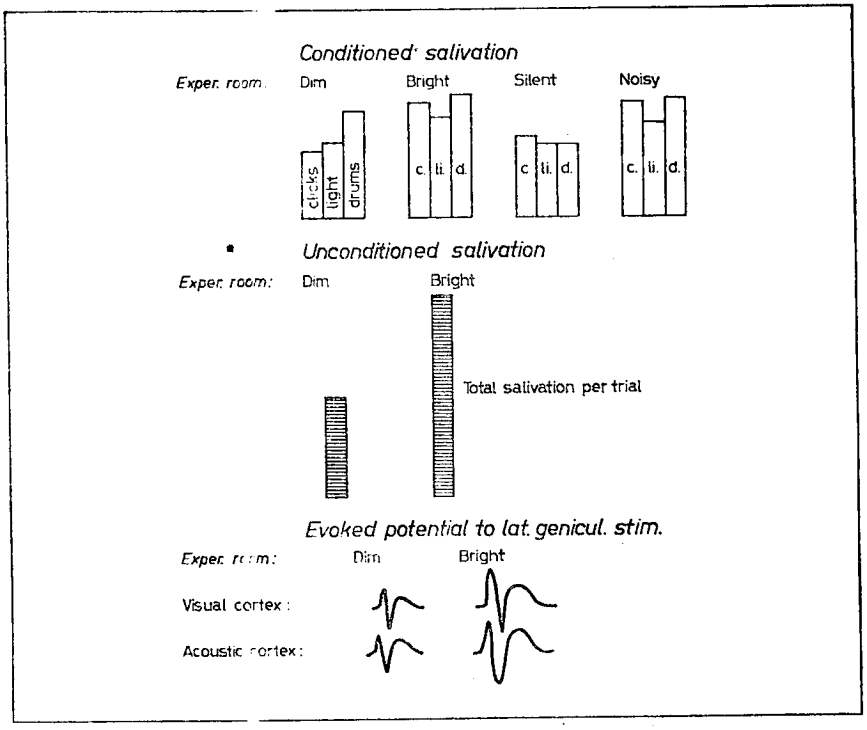

Fig. 4. The interrelations between unspecific stimuli on the amount of conditioned and unconditioned salivation and on the amplitude of cortical evoked potentials (C.G.)
The unspecific stimuli were the general illumination of the experimental room or the level of noise. Top tracing from KUPALOV [1948], dogs. Middle tracing from KOSTENETZKAYA [1965], dogs. Lower tracing from CHANG [1952], cats.

The general tonus of the central nervous system (T) seems to play a major role in the effect of the neuroleptics. The tonus may depend on various intrinsic factors, but it also depends on the input of sensory stimuli in general, so that a series of non-specific stimuli, given together with the

specific conditioned stimuli, seem to faci ate the conditioned response, provided that they are not disturbingly in nse. Such stimuli are illumination, slight noise, etc.

A closely analogous phenomenon c n also be shown electrophysiologically. For example, the electric respon e from the visual and auditory cortex upon the electrical stimulation of th lateral geniculate body is more intense if the experimental animals are plac d in light instead of in darkness.

Various intrinsic factors may also influence the state of the tonus (and different neural mechanisms are poss ly involved) responsible for the general state of alertness, or for selective a ention, or both (fig. 4).

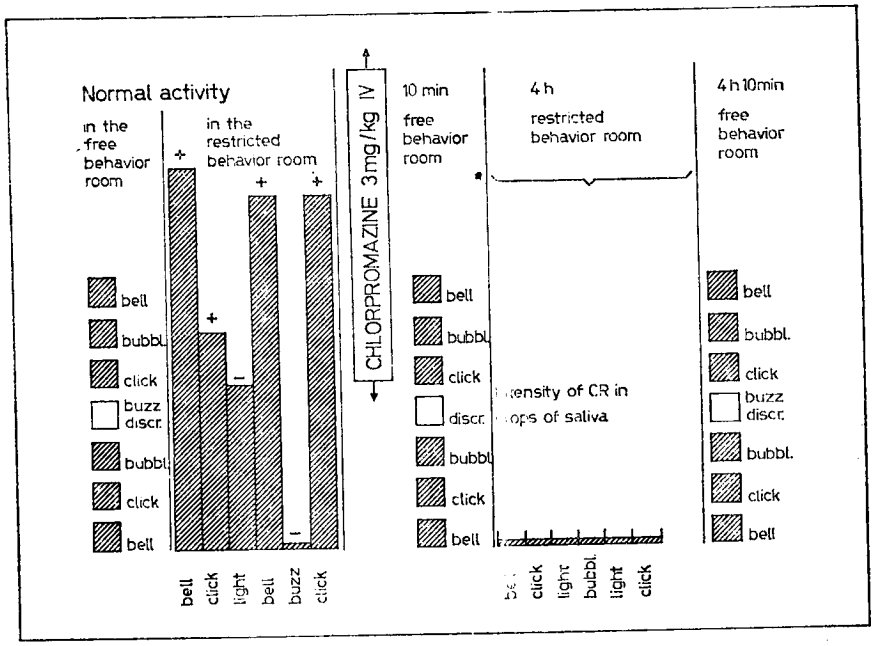

Fig. 5. Dependence of the chlorpromazine effect on the experimental conditions (dog *Dingo*) (C.G.)

Left (normal activity): a) In the free behavior room: darkened squares mean normal response to positive conditioned stimuli; white square means normal response to negative (discriminatory) conditioned stimuli. b) In the restricted behavior room: each column represents the amount of saliva to the conditioned stimuli; note that no secretion is obtained at buzzer (discrimination); the signs + or – represent the presence or absence of a conditioned motor reaction which usually accompanies the salivary response.

Right (after chlorpromazine): a normal conditioned reflex activity is maintained in the free behavior room while all conditioned reflexes are suppressed in the restricted behavior room.

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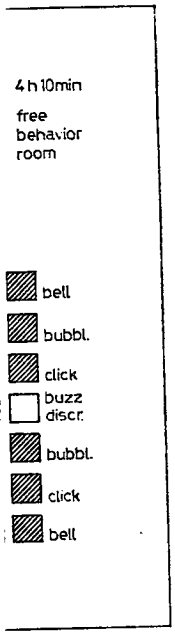

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The influenc ɔf the cerebral tonus on the neuroleptic effect was clearly demonstrated ɔ the group. The response to chlorpromazine differs with the situation ir which the conditioned experiments are done. Dogs were conditioned wit the classical technique in two different situations and their reaction to chl promazine tested. If the dogs were tested in a sound-proof compartment, estricted by a harness, chlorpromazine inhibited the conditioned reflexes nade the animals drowsy and even cataleptic, but if the same dogs were ested unrestricted in a room not soundproofed, the same dose of chlorpı mazine was practically without effect. This difference was seen in several t ɔes of experiments and was evidenced even if the animal was observed fo its behavior in front of the free-behavior room or in front of the restricte -behavior room, without actually entering the room. It was proposed tha the physiological mechanism of the last-mentioned phenomenon is a 'sh tened' type of conditioned reflex to the experimental milieu, a possible c dico-reticular conditioned reflex by which a conditioned enhancement f central tonus is able to counteract significantly the effect of chlorpromaz ne [GIURGEA] (figs. 5 and 6).

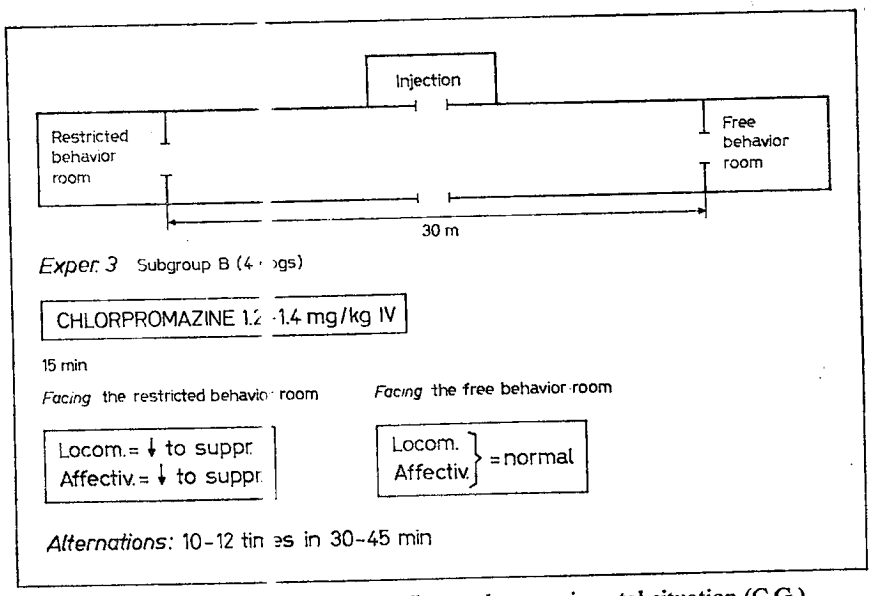

Fig. 6. The 'shortened' conditioned reflex to the experimental situation (C.G.)
When the anim l is placed in front of the free behavior room his motor activity and affectivity a e normal while when he is placed in front of the restricted behavior room a maxim l effect of chlorpromazine is seen. Ten to twelve times during 30–45 min these cha ges in motor behavior were observed when placing the dog alternatively in front of ne or the other experimental room.

The question was discussed as to whether chlorpromazine directly influenced the cerebral tonus elicited by he unspecific stimuli in the free room, or the conditioning was less fixed a the diminished cerebral tonus in spite of the fact that the animals were con litioned to stereotypy. The question is still open and requires more experi ients to be solved.

Although most of the experiments presented were done with chlorpromazine as a representative of the grou of neuroleptic drugs, some were also done with other neuroleptics. In a se ies of phenothiazine-type neuroleptics tested, a fair to good correlation b tween the doses effective in rats on the conditioned avoidance responses nd the clinically effective doses was found [COOK and CATANIA; RAY and BIVENS]. However, some species differences were shown; and for instance a better correlation was found in experiments with squirrel monkeys than i experiments with rats (table I).

Table I. Effect of chlorpromazine and thioridaz ne on two types of conditioned avoidance (L.C.)

	Discrete avoidance			Sidman avoidance
	Conditioned pole-climb response ED_{50} mg/kg, p.o.			Conditioned lever-press response MED mg/kg, p.o.
	Rat	Squir	l monkey	Squirrel monkey
Chlorpromazine	11	5.2		1.3
Thioridazine	600	4.2		1.2
	126			

The conditioned pole-climb avoidance behavior procedure in squirrel monkeys was carried out similarly to the method des ribed by COOK and WEIDLEY [1957]. The values of ED_{50} for thioridazine in rats re present the results of two different studies. Sidman avoidance behavior is a continuc is avoidance schedule with response-shock and shock-shock values of 30 sec. The re ults indicate that the poor effects of thioridazine on conditioned discrete avoidance in rats are likely due to species differences, and not to differences in the response of the two test methods.

Only quantitative differences were found for the neuroleptics, perhaps with a single exception, which will be mentioned later.

The effects of other drugs in comparison with the neuroleptics were also discussed. As a general rule it could be stated that the conditioned reactions were enhanced by drugs of the amphetamine type, which is consistent with the general antagonism found between the amphetamines and

the neuroleptics. Tranquilizers such as meprobamate and chlordiazepoxide were without any effect on conditioned reactions[3].

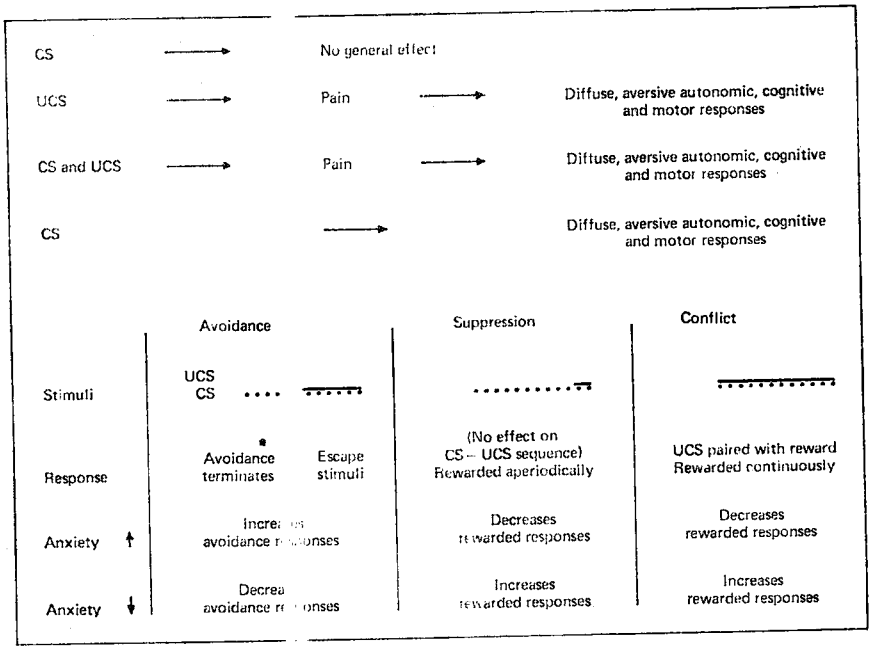

Fig. 7. The development and monitoring of three types of experimental 'anxiety' (O.S.R.)

The upper part is a summary of the classical conditioning. The animals are exposed to a conditioned stimulus (CS) (light, tone, etc.) which in itself does not have any effect on behavior. If they are exposed to an unconditioned stimulus (UCS) (electric shock, etc.) they respond characteristically. If the CS are combined with the UCS, the response to the CS will be the same as the response to the UCS.

If the animals are conditioned to respond to the CS by a certain action – *e.g.* pressing a lever which will terminate the stimulus and in this way avoid the shock *(conditioned avoidance behavior)* – an increase in 'anxiety' increases avoidance responses and shortens the response latency, while a decrease in 'anxiety' has the opposite effect. In the *conditioned suppression* a neutral stimulus is terminated with an unavoidable shock. Animals trained to work – e.g. pressing a lever – to obtain a reward of food or water with aperiodical intervals, will decrease work in case of increased anxiety, and increase it in case of decreased anxiety. In the *approach–avoidance conflict* each positive reinforcement – such as pressing a lever for a reward – is paired with a negative stimulus – such as an electric shock. An increased anxiety causes a decrease of the responses while a decreased anxiety causes an increase of the responses.

3 The 1967 W.H.O. classification of psychotropic drugs sealed the fate of the expression *major* and *minor* tranquilizers.

Much discussion was devoted to he effect of drugs on *conflict situations*. Several techniques have been eveloped to study the conflict situations, generally with rats as experime al subjects, but also with many other species. Figure 7 gives a summary the methods used to provoke *anxiety* in rats. In some experiments, the a mal has to overcome a noxious impulse, for example an electric shock, in rder to get the reward, either in connection with the reward itself [NAESS a l RASMUSSEN; COOK and CATANIA], *e.g.* when it attempts to eat or drink or as it approaches to reward. *e.g.* when it has to pass electrified grids [G LER and SEIFTER; RAY, 1964a], or the *telescope alley* [MILLER and BARRY] The intensity of the shock can be varied, and the willingness of the animals to overcome the negative reinforcement is generally taken as a measure of the intensity of the induced conflict.

A much used principle is the *conditioned emotional response* (CER) or *conditional suppression*. Animals trained to press a lever for food are exposed at intervals to a sound ending with an electric shock [BRADY; RAY, 1964a, 1965].

In all types of experimental techniques the animals generally stop the lever pressing, or at least decrease the rate substantially. The decrease of lever pressing is taken as a measure of the influence of the aversive stimulus, and a re-establishment towards a normal rate of lever pressing as a measure of a positive effect of a given drug. Here, repeated administration of reserpine seems to have an effect, but meprobamate and chlorpromazine failed to show any effect in this special experimental technique [RAY, 1964a] (table II).

Table II. Drug effects on experimental anxiety behavior (O.S.R.)

Compounds	Avoidance	Experimental procedure	
		Suppression	Conflict
Chlorpromazine	Decreases avoidance responses	No effect	No effect
Reserpine	Decreases avoidance responses	Increases approach responses during shock-paired stimulus	No effect
Meprobamate	Decreases avoidance responses	No effect	Increases shock-paired approach responses

The conflict situation may be pressed so high that a so-called *experimental neurosis* is developed. Animals are trained to release a food pellet into a box. When well conditioned, the animals are at intervals given a frightening air blow from the box instead of a food pellet. A conflict is thus established between the attraction to the box and the fear of it, and consequently a characteristic syndrome is developed. After some days there appears a delay in the performance combined with displacement activities. Autonomic signs with diarrhea, retching or vomiting may also develop. The syndrome may persist between the experiments and may last for days or weeks [MASSERMAN and YUM; JACOBSEN and SKAARUP].

Regardless of the way in which the conflict situation has been developed, all tranquilizers have an effect on the experimental neurosis syndrome. For example, after meprobamate, animals will work in spite of the noxious stimulus [RAY, 1963, 1964b], and if displacement activities have developed they will be abolished (fig. 8).

On the other hand, no effect has been demonstrated with the neuroleptics, partly because they suppress conditioned reactions, which, up to now, are a prerequisite for provoking the animal experimental neurosis. Under special experimental conditions some effect of neuroleptics can be observed. If the rat made two separate responses on two separate levers, one for milk reward and one for shock avoidance, chlorpromazine selectively reduced lever pressing for food reward. If, however, a single conditioned stimulus signals a possible combination of reward and punishment, the lever pressing was suppressed by chlorpromazine. An exception, perhaps of importance, was shown with low doses of trifluoperazine which seems to act like the tranquilizers [DAVIDSON and COOK], but high doses showed the same suppression as the other neuroleptics (fig. 9). Reserpine given in repeated doses also showed some effect [RAY, 1964a].

The effect of amphetamine is also nil, or it produces further suppression of the response by its effect in increasing avoidance behavior. The effect of some types of drugs on experimental anxiety behavior is shown in table II.

The physiological and biochemical background of drug effects on the behavior is very important. Generally, all drugs with a behavioral effect seem to have an *influence on the EEG,* although some exceptions may be found. Especially remarkable are the anticholinergic drugs, such as atropine and benactyzine. In most animals these drugs elicit a synchronization of the EEG in spite of the fact that the animals do not appear drowsy or go to sleep, as should be expected from the EEG pattern. Psilocybine or mes-

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Increases shock-paired approach responses

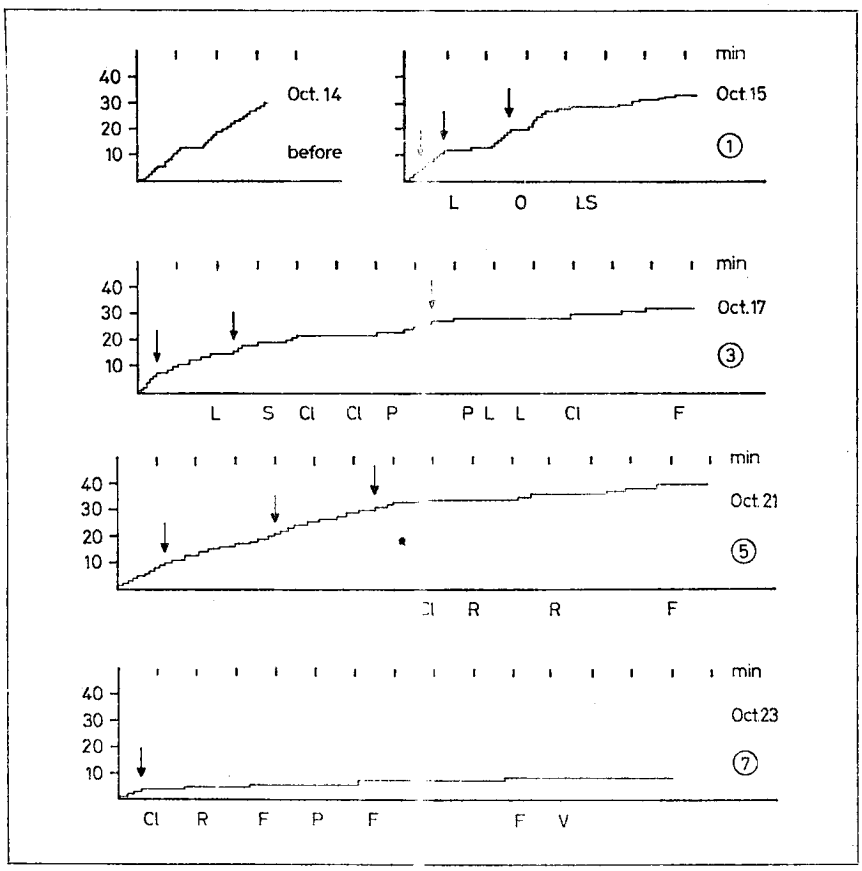

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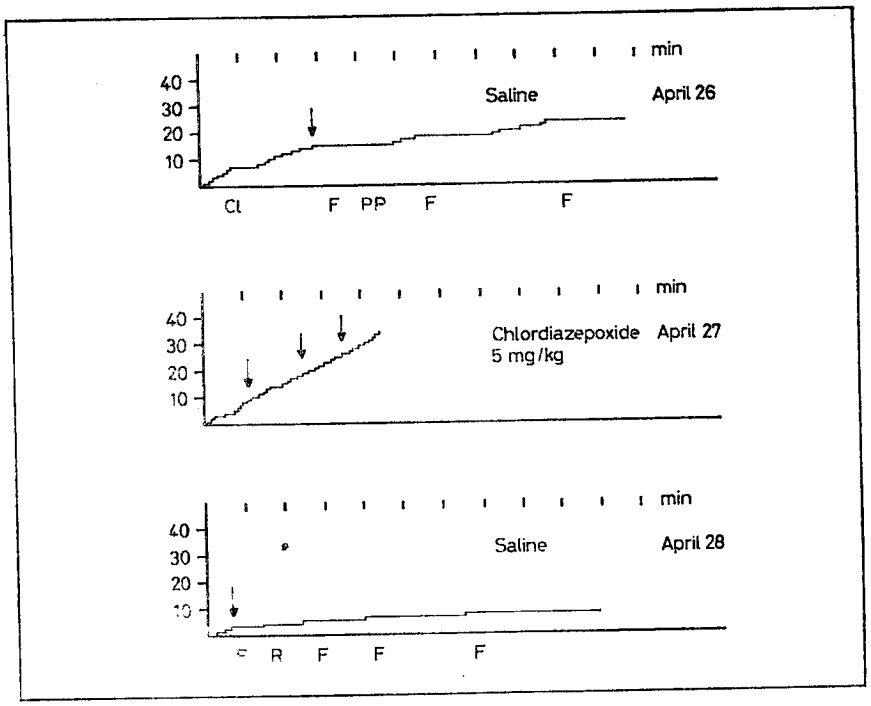
Fig. 8 a–c. Development of experimental conflict neurosis in cats and the influence of psychotropic drugs thereon (E.J.)

The experimental cage is about 1.00×0.60×0.50 m. In one wall is a lever which will release a food pellet into the feeding box with a hinged lid, placed at the opposite wall. The feeding box is further furnished with a narrow tube through which an air blow accompanied by a loud hiss, imitating the warning signal of cats, can be given.

Cats are trained to press the lever, open the box, eat the food pellet and repeat the procedure *ad libitum*, which they do about 30–40 times even if they are not starved. One feeding cycle takes from 2 to 5 sec, varying from individual to individual. The conflict neurosis is established by giving the cats an air blow from the box about every tenth feeding cycle. At first, the air blow has little effect, but during 5–8 daily repetitions the conflict syndrome develops, consisting of delay in the feeding cycle, breakdown of the conditioned pattern and the appearance of displacement activities. a) Development of the experimental conflict neurosis. Abscissa: time. Ordinate: number of feeding cycles completed. Arrow: air blow. Only every second experiment is given. Displacement activities: L = licking; S = scratching; Cl = sharpening claws;



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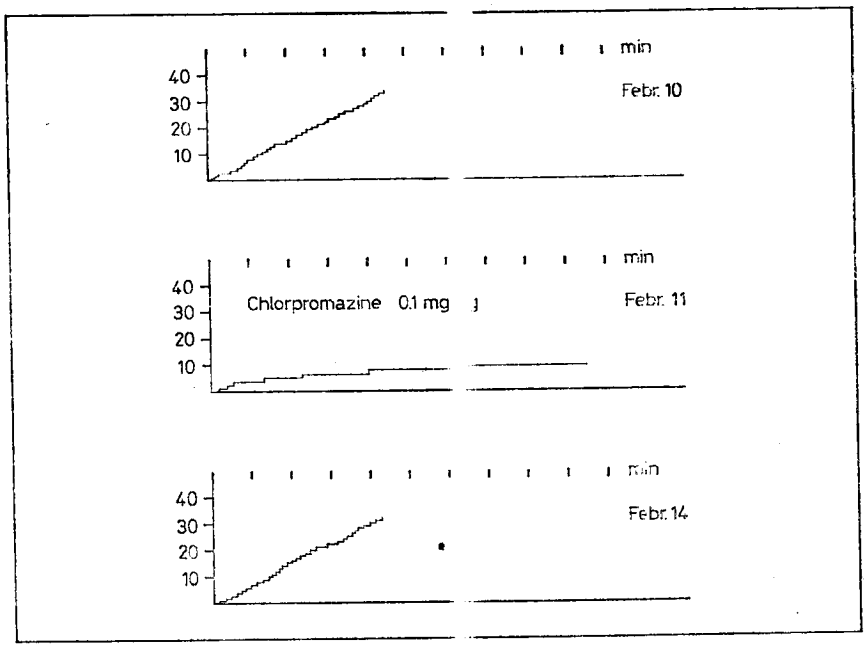
caline show a similar pattern; they induce an EEG pattern of drowsiness in spite of increased somatic activity (fig. 10). The discrepancy between lack of EEG arousal and somatic arousal has generally been regarded as an unspecific and characteristic effect of the anticholinergics. It was, nevertheless, demonstrated that cats conditioned to press a button under the influence of the centrally-acting anticholinergic drug, Ditran®, were unable to work unless they showed and EEG arousal (fig. 11). A failing desynchronization was always followed by a failing reaction. On the other hand, the animals were apparently awake [ROUGEUL *et al.*, 1965, 1966].

R = rolling on the floor; F = lying down on the floor; V = vomiting; P = pressing lever without opening box; O = opening box without pressing lever. b) Effect of 5.0 mg/kg chlordiazepoxide. c) Inhibitory effect of chlorpromazine s.c. 0.1 mg/kg on the operant behavior of not *neurotic* cats. Doses between 0.05 and 2 mg/kg had no effect on the *neurotic* behavior except a further delay of the feeding cycles. No difference in the effect of chlorpromazine, haloperidol and chlorprothixene in varied doses was observed.



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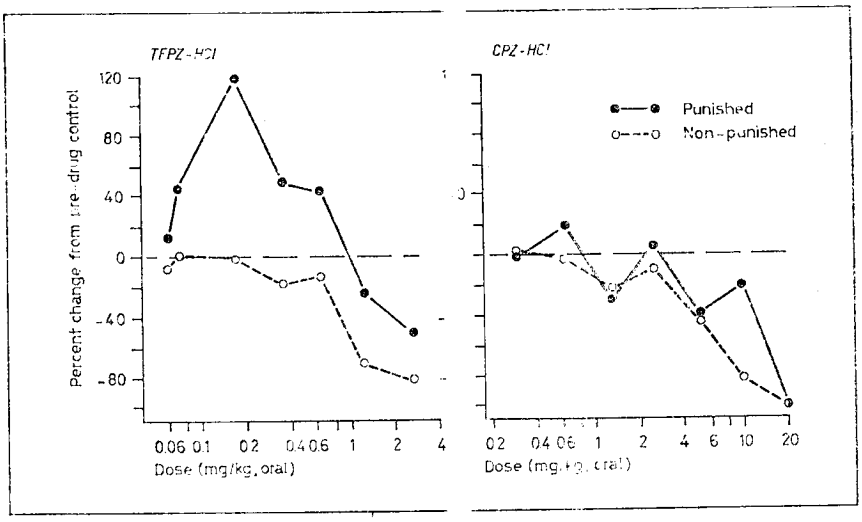
An arousal is provoked both by centrally-acting cholinomimetics and by centrally-acting adrenomimetics but neuroleptics act fundamentally differently against the arousal effect of the two types of drugs. Cholinomimetics in low doses activate EEG pattern without changing behavior,



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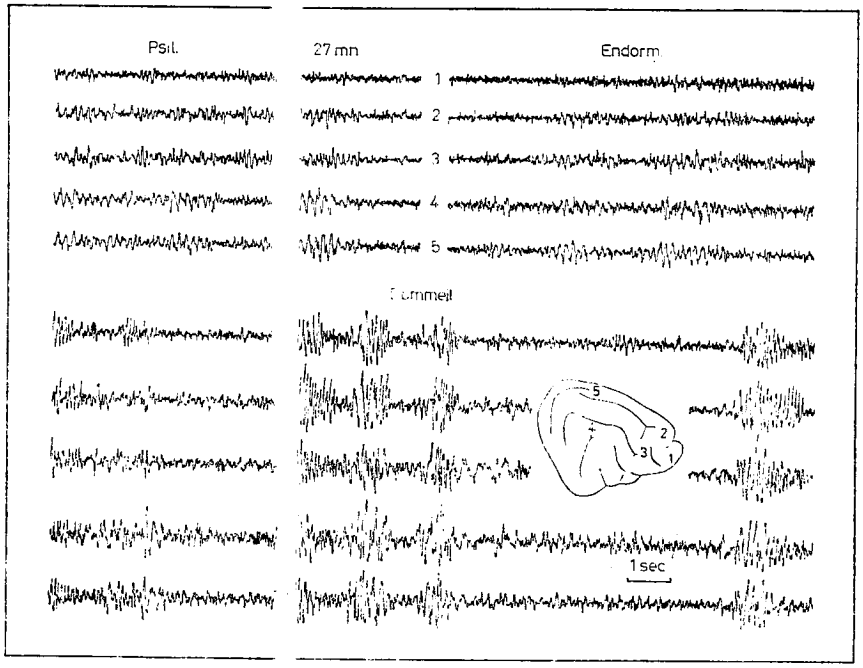

Fig. 10. Comparison of el trocortical activities during awake states under psilocybine, during natural drowsi s and 'slow' sleep (P.B.)

Note the similarity etween the normal drowsy state (endorm.) and the effect of 0.5 mg/kg psilocybine. I he first case the animal is immobile, in the second he is very active and alert. The rowsiness-like' pattern induced by psilocybine may last for two hours, whereas tl normal drowsy state is only transitory, lasting a few minutes.

Fig. 9. Effects of trifluop razine (TFPZ) and chlorpromazine (CPZ) on rat conflict–punishment behavior (L.C.)

The procedure is a ultiple VI (food only) – FR 10 (food + shock) schedule. Periods of punishment (2 n n each) alternate with periods of non-punishment (5 min each). The figure illustrate he effects of drug treatment on each of these two types of behavioral responses, as percentage change from non-drug control baselines. Increase of punished behavi represents increased rate of punishment–suppressed responding, *i.e.*, attenuation he suppressant effects of punishment.

but adrenomimetics activate both the EEG and the behavioral pattern. All tested neuroleptics, such as chlorpromazine, reserpine and haloperidol, diminish or completely block both the EEG and the behavioral activation after amphetamine or apomorphine [Vorontsova and Dyntarova] (fig. 12).

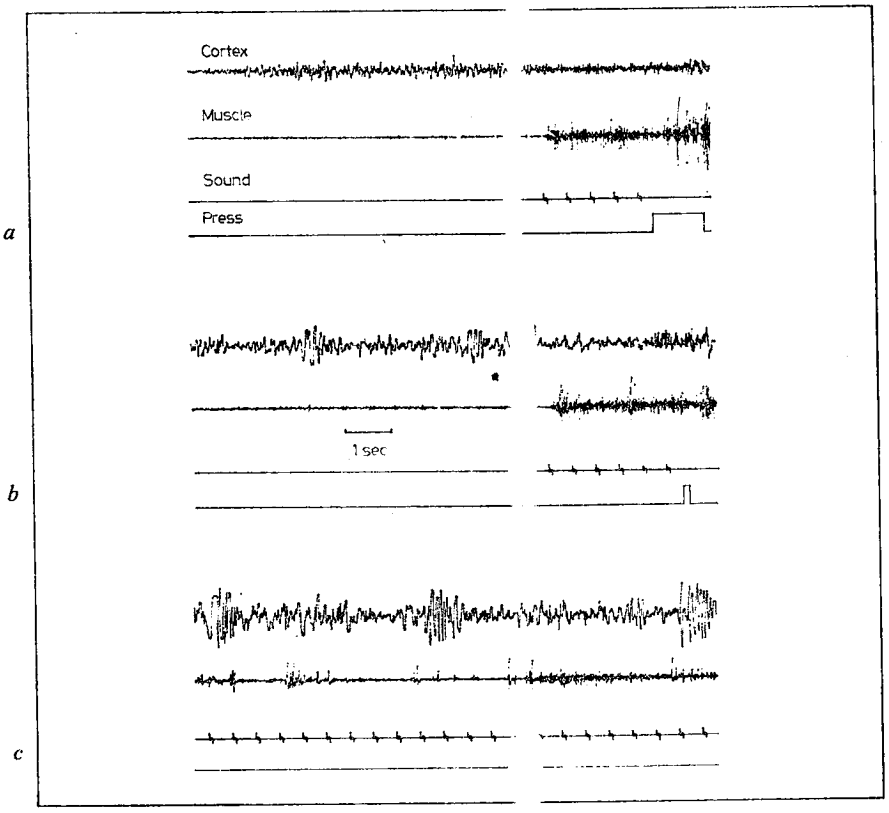

Fig. 11. Relationship between electrocortical activity and behavior in cat under Ditran® (P.B.)

The animal is trained to press a bar (press) to receive food at a given signal (clics at 2/sec, marked 'sound' on 3rd channel). Movements of the anterior paw are indicated by activity in clavotrapezius muscle (channel 2). Electrocortical activity is recorded from right sensorimotor cortex with bipolar electrodes (channel 1). a) Control trial before drug injection. Note electrocortical activation at start of movement. b) 18 min after injection of 1 mg/kg of Ditran®. Cortical spindles have appeared, but the animal is still able to perform the learned task, performance being again accompanied by electrocortical arousal. c) 23 min later, the animal is very active (see E.M.G.), but does no more press the bar, despite long repetition of conditional signals. Electrocortical spindles develop throughout the whole sequence of desoriented activity. [From Rougeul *et al.*, 1965]

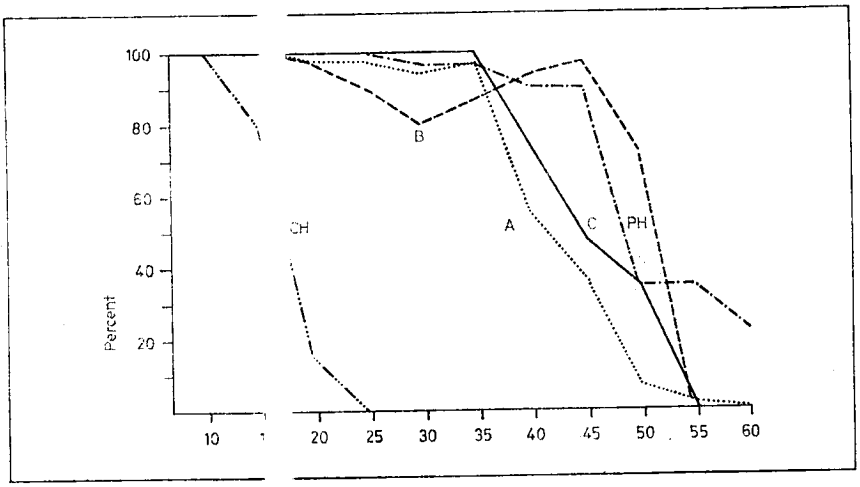

Fig. 12. Effect of chlorpr azine, benactyzine, phenobarbital or amitriptyline on the EEG desynchronization ev ed by apomorphine (Z.V.)

The experiments re done in rats with chronic implanted electrodes in the cortical and hippocampal as of the brain. All drugs were injected i.p., apomorphine 10 min before the other gs tested or saline solution. On the ordinate: desynchronization expressed in per tage; on the abscissa: time in minutes after the administration of tested drugs. C es represent the results of 10 adult male rats, tested five times in one-week interval

Only chlorproma ine significantly shortened the EEG desynchronization evoked by apomorphine.

C = saline sol (0 ml/100 g i.p.), PH = phenobarbital (20 mg/kg), B = benactyzine (0.2 mg/kg), CH chlorpromazine (5 mg/kg), A = amitriptyline (5 mg/kg).

The EEG activation pr luced by cholinomimetics, such as physostigmine, is not changed in inte ity and may even be prolonged by pretreatment with the neuroleptics te ed. The behavioral excitation after higher doses of cholinergics is also uni luenced. The same negative effect of neuroleptics was also seen on the E G activation and behavioral excitation caused by nicotine and arecoline /OTAVA, 1967a] (fig. 13). From these experiments it may be concluded th the activation caused by cholinergic- and adrenergic-acting drugs have a ifferent localization or a different mode of action, or both [VOTAVA, 1967].

The presence o wo different special systems in the central nervous system, important not ly for the types of behavior discussed but also for

the action of drugs, was clearly demonstra l: the *medial forebrain bundle,* from which the reward reaction in genera d, and the *periventricular system,* from which the punishment reaction s generated [STEIN, 1969a, b] (fig. 14). From the former system, stimula on of implanted electrodes will release a self-stimulation, and it is doubtfu if any substantial self-stimulation can be released from electrodes place outside the bundle.

A stimulation of the medial forebr in bundle has almost the same effect on behavior as have small doses of mphetamine, and chlorpromazine specifically inhibits the effect of both. That its function is closely connected with adrenergic neurons appears fr m the facts that the presence of noradrenaline is demonstrated histochem cally, that noradrenaline is released from this site during local stimula on [STEIN and WISE], and that central administration of noradrenaline cilitates brain self-stimulation [WISE and STEIN]. It is to be supposed tha this place is the site of action of chlorpromazine, at least for the effect on c nditioned reactions.

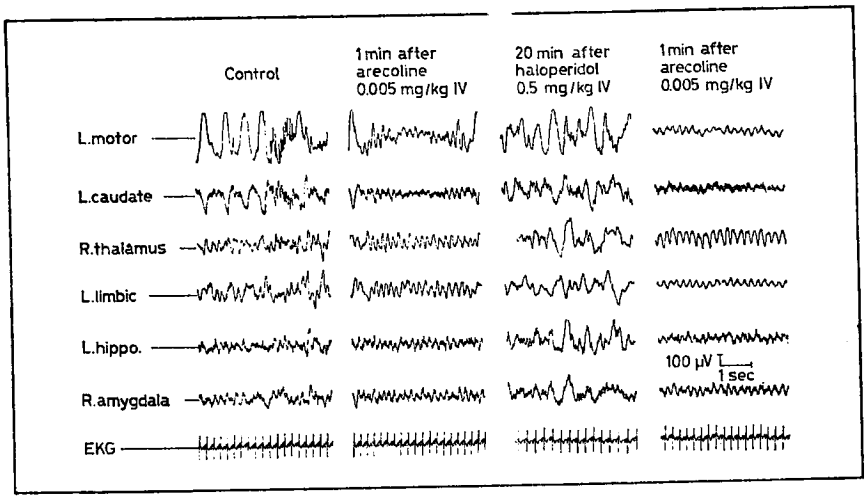

Fig. 13. Effect of haloperidol on the EEG desynchronization evoked by arecoline in rabbits (Z.V.)

From left to right: localization of electrodes and EKG recording, control EEG recording (saline injection), desynchronization evoked by arecoline injection (0.005 mg/kg). EEG resting pattern 20 min after the injection of haloperidol (0.5 mg/kg). Arecoline injected one minute later in the same dose as previous, caused the same EEG desynchronization, indicating that there was no central anticholinergic effect of haloperidol. The same was found using nicotin (0.02 mg/kg i.v.) or physostigmine (0.05 mg/kg i.v.) as desynchronizing drugs.

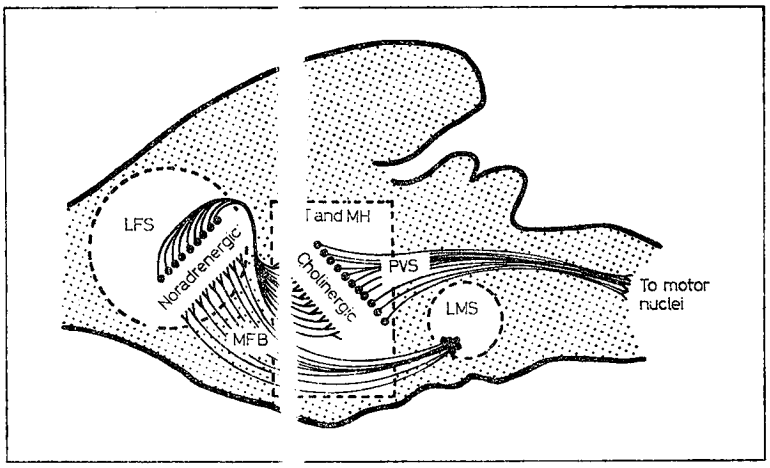

Fig. 14. Diagram representi · hypothetical relationships between reward and punishment mechanisms (L.S.)

A rewarding stimulus releases behavior from periventricular system (PVS) suppression by the followi sequence of events: 1. activation of medial forebrain bundle (MFB) by stimuli eviously associated with reward (or the avoidance of punishment) causes release the inhibitory transmitter, noradrenaline, into amygdala and other forebrain suppre r areas (LFS). 2. Inhibitory action of noradrenaline suppresses activity of the LFS hus reducing its cholinergically mediated excitation of medial thalamus and hypot lamus (MT & MH). 3. Decreased cholinergic transmission at synapses in MT & H lessens the activity in the PVS, thereby reducing its inhibitory influence on mot nuclei of the brain stem.

The periventricu ar system seems mainly to be cholinergic [MARGULES and STEIN] and s ms to play a role in the extinction of the conditioned reactions. This stem is influenced not only by anticholinergic drugs but is also specific ly inhibited by all tranquilizers.

During the discu ion it was possible to reach a common idea about the effects on the condit ned reactions of some groups of drugs, especially the neuroleptics, the am netamines (here including apomorphine) and the tranquilizers (meprobam te, diazepam, chlordiazepoxide). It appears as if all the data presented c ld be explained from a common concept of the drug action.

Behavioral man stations developed and maintained by outer influences are inhibited b the neuroleptics. These outer influences may be the influence of the su oundings, of another animal, of a conditioned signal, or of a reward c punishment presented in the operational condition, the type of motivat n being unimportant.

In most cases the amphetamines pl ; apomorphine – *i.e.* the central catecholamine releasers – enhance these r ctions. The amphetamines and the neuroleptics are mutually antagonisti On the other hand, the tran-quilizers have an inhibitory effect on all f ors which, for some reason or other, suppress the behavior which ought) be developed or retained by outer influences. It is thus easy to distingu between a neuroleptic, a tran-quilizer and a drug belonging to the amph mine group.

But by means of behavioral studie lone, it has not yet – with the exception mentioned – been possible to (tinguish between the different types of neuroleptic drugs. First of all, be use there are too many gaps in our data; the effects of the butyrophenone have only rarely been included in the series presented to the group. Howe r there are other reasons, espe-cially the complexity of the effect. The do effect curve generally does not follow what is expected and required by e pharmacologists. Low doses may have an effect which will completely abolished if the dose is raised, because it is masked by new inhibitory e cts, and the ratio between en-hancing and inhibitory effects may vary fr 1 drug to drug.

The theoretical background of dr influence on behavior is little known, but it seems nevertheless possible suggest tentatively some rea-sonable explanation, not only about the s of action of the neuroleptics but also about their mode of action on the ellular basis. However, the data available are still too meagre to allow a de nite conclusion.

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