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BEHAVIOURAL EFFECTS OF A LONG-TERM TREATMENT WITH MEPROBAMATE IN CATS*

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Summary—The action of meprobamate on conditioned behaviour was studied with cats. The subjects were trained to press a lever for food in a Skinner-box on a fixed-interval schedule of reinforcement. They develop a typical pattern of behaviour, characterized by a spontaneous temporal discrimination. Meprobamate increases the rate of responding and disrupts the temporal discrimination. These effects are similar to those obtained with chlordiazepoxide.

Both effects are reduced and disappear with prolonged treatment (150 mg meprobamate daily). The tolerance extends to the general motor symptoms observed at the beginning of the treatment. When chlordiazepoxide is again administered after tolerance to meprobamate has developed, its effects on conditioned behaviour are still observed, though those on general motor behaviour are not (partial cross-tolerance).

Animals treated with high doses show withdrawal reaction when the drug is no longer administered.

INTRODUCTION

THE PROBLEM of the development of tolerance is crucial in the assessment of psychotropic drugs, both from the clinical and the public health points of view. Surprisingly little attention has been given to it by experimenters. Especially in the field of behavioural research with animals, where chronic treatment is not barred by moral or technical restricting factors, most studies are limited to exploring the effect of a few doses, administered once or twice. Little is known about the effects of repeated administration for a long period of time, even for classical compounds of current use in clinical practice.

The aim of the present study was to analyse some behavioural consequences of long-term treatment with meprobamate in cats. The drug was found to induce modifications of spontaneous and conditioned behaviour which were reduced with repeated administration. As the modifications of behaviour observed under meprobamate were similar to those induced by chlordiazepoxide, tests for generalization of tolerance, or *cross-tolerance*, were made. Finally, some aspects of the habit-forming properties of meprobamate were investigated.

Meprobamate (MPB) is known as a myorelaxant (BERGER, 1954, 1955; HENDLEY *et al.*, 1954), and anti-convulsive drug (HENDLEY *et al.*, 1956). Its tranquillizing properties recognized by clinicians have been related, more or less appropriately, to various behavioural effects studied in animals: reduction of spontaneous motor activity (SCHALLEK

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et al., 1956; KINNARD and CARR, 1957; LA BARRE and DESMAREZ, 1960); reduction of irritability induced by septal lesions (TEDESCHI *et al.*, 1959); reduction of "isolation induced aggression" in mice (COOK and WEIDLEY, 1960). However, high ataxic doses are necessary to modify the aggressive behaviour of rats toward mice (KARLI, 1960).

Chlordiazepoxide (CDZ), also used as a tranquilizer with human patients, has an action in many respects similar to that of MPB: it is myorelaxant and anticonvulsive (FROMMEL *et al.*, 1960; RANDELL *et al.*, 1960); it reduces various kinds of aggressive behaviour and the spontaneous motor activity (HEISE and BOFF, 1961; RANDELL *et al.*, 1960; and WEIDLEY, 1960; KARLI, 1960; SCHALLEK and NAUTA, 1960).

METHODS

Apparatus

The experimental cage was a classical Skinner-box designed for cats. It was equipped with a response-lever and an electromagnetic tap controlling the flow of the milk used as reinforcer. The experiment was automatically programmed by means of relays and timers located outside the experimental room. Results were automatically recorded on a cumulative pen recorder and a series of digital counters.

Subjects

Four cats were used as subjects: two males numbered 6 and 9, and two females numbered 4 and 8. The weights of the animals, at the beginning of the experiment were 2·6; 3; 2·5 and 3·2 kg for cats 4, 6, 8 and 9 respectively. They lived in large individual home-cages in the animal room. None of these animals was experimentally naïve: they had been experimental subjects for 1–3 years, undergoing a number of pharmacological tests (mainly with methylphenidate and CDZ) in operant conditioning situations. They were already used to the particular schedule of reinforcement used in this experiment.

Cat 8 was submitted only to the last part of the experiment concerned with the habit-forming properties of MPB; the reasons for this will appear clearly in the next section. Cat 4 died before the last phase of the experiment. Complete results were available for cats 6 and 9.

Schedule of reinforcement

The particular contingencies relating the response to its consequence, the reinforcement, in an operant conditioning situation, may be varied in a number of fashions. The procedure used in this experiment is known as *fixed-interval schedule of reinforcement* or FI (FERSTER and SKINNER, 1957). A reinforcement is delivered following a response only after a given delay (2 min in this experiment) has elapsed since the last reinforcement. Responses emitted in the interval have no consequences.

Administration of the drug

MPB was administered *per os*, mixed with a small amount of a commercially supplied food for cats. It was given to the animals 30 min before the experimental session. Because of the bitter taste of the drug cats probably would not accept high doses. When doses greater than 150 mg were given, the excess was injected i.p.

CDZ was absorbed *per os* mixed with the same kind of food, at all doses used, 30 min before the session.

Mephenesin was injected 10 min before the session.

Experimental program

The experiment continued for six months, from 16 September 1962 to 20 March 1963. Experimental sessions lasted 1 hr and took place approximately at the same time in the afternoon. As was said, the subjects had been trained in the FI schedule in previous experiments and were only *retrained* during fifteen daily experimental sessions until a stable base line was recovered.

The pharmacological tests starting thereafter are divided into three experimental phases, according to the following calendar:

Experimental phase	Date	Doses administered	Experimental sessions	Subjects
Exploration of the effect of various doses of MPB	17·10–9·11	50 mg MPB 100 mg MPB 150 mg MPB 100 mg CDZ	5/week	4, 6, 9
Long-term treatment with MPB	13·11–21·12	150 mg daily	daily	
	interruption	—	—	(4 died)
	21·12–15·1			
	16·1–2·3	150 mg MPB daily	5/week	6, 9
	3·3	100 mg CDZ		6, 9
Withdrawal Reactions	6·3 7·3 8·3	200 mg MPB	daily	6, 8, 9
	9·3	250 mg MPB test for withdrawal reaction I		6, 8, 9
	10·3 11·3	200 mg MPB		6, 8, 9
	12·3	test for withdrawal reaction II		6, 8, 9

Evaluation of the drug action

The action of the drugs is evaluated in two ways: by analyzing the automatic records of experimental data and by systematic observation of various typical motor reactions.

(a) *Experimental data.* The automatic pen recorder draws a cumulative curve showing the rate and the general pattern of responding. Reinforcements and timing cycles of the FI program are recorded on the same graph.

A set of eight digital counters provides for a precise quantification of the frequency of responses emitted in the successive parts of the 2 min interval. The interval is divided into eight 15-sec periods. To each of these periods corresponds one counter. By means of a stepper, a given response is recorded by the counter corresponding to the 15 sec period during which it is emitted. Using the total number recorded by each counter at the end of an experimental session, we can build a frequency distribution reflecting the temporal discrimination developed by the subject.

(b) *Systematic observation.* Since the drugs used are myorelaxant, and are known to have disturbing effects on motor coordination, it was interesting to test a few classical reflexes.

Cats 6 and 9 used to run by themselves from their home-cages to the experimental cage. This implied running 35 m, climbing sixteen steps up to the second floor and jumping 1 m into the experimental cage. Both motor coordination and space orientation are required to perform this simple habit. The effects of the drugs were carefully noted.

Finally, other aspects of spontaneous behaviour were observed, e.g. general motor activity in home cage, simple emotional reactions to caretakers and experimenters, food acceptance, toilet behaviour and the like.

RESULTS

I. Action of MPB on the behaviour controlled by FI schedule of reinforcement

The FI schedule generates a typical pattern of behaviour, illustrated by cumulative curve A, Fig. 1. Long pauses followed each reinforcement, indicating a fairly accurate

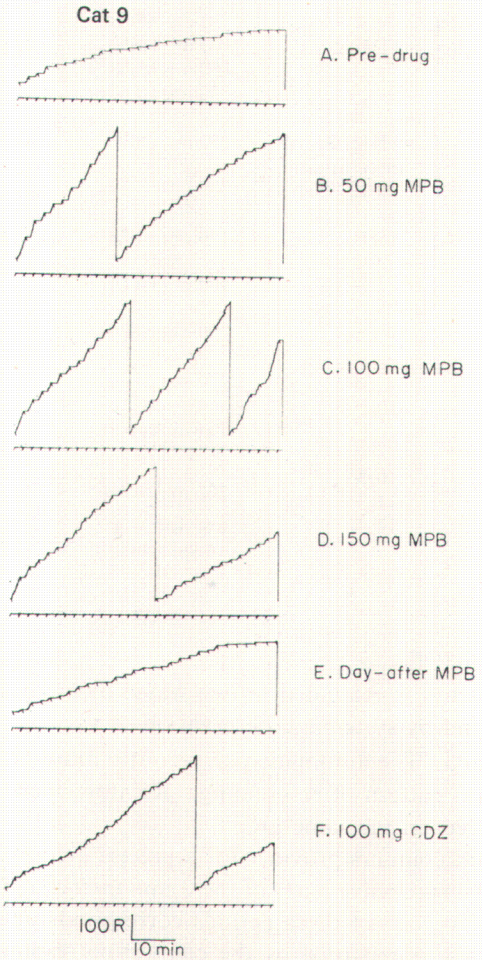

FIG. 1. Cumulative curves from Cat 9 on the fixed-interval schedule of reinforcement, under normal conditions and with various doses of meprobamate and chlordiazepoxide. Responses are cumulated on the ordinate as the paper unrolls from left to right. The pen resets automatically to its origin on the ordinate after 500 responses. Oblique pips on the cumulative curves indicate the reinforcement. The pen tracing the horizontal line at the lower part of each graph is kept in the down position when the 2 min interval is over and comes up again as soon as the reinforced response is emitted.

time discrimination; the subject resumed response toward the end of the 2 min interval, and the rate is accelerated until the reinforcement is obtained. It should be remembered that the temporal discrimination is not the condition for reinforcement; it is a kind of economic, spontaneous adjustment to the particular contingencies arranged in the environment.

Meprobamate increased the number of responses and disrupted the temporal discrimination. The number of responses emitted during the 1 hr session under normal conditions and under the various doses of MPB, for each animal, are given in Table 1. The values for normal conditions are averaged from the last ten sessions of the stabilization phase. Other values are raw numbers from individual sessions.

TABLE 1. NUMBER OF RESPONSES PER SESSION UNDER NORMAL CONDITIONS (PRE-DRUG), UNDER VARIOUS DOSES OF MPB. PRE-DRUG VALUES ARE AVERAGED FROM THE LAST TEN SESSIONS BEFORE PHARMACOLOGICAL TESTS

	Cat 4	Cat 6	Cat 9
Pre-drug	228	232	267
50 mg MPB	693	228	972
80 mg MPB	850	319	1353
100 mg MPB	1183	740	1343
150 mg MPB	1307	567	749
Day-after MPB	515	207	283
100 mg CDZ	774	887	665
Day-after CDZ	364	737	655

The increase of conditioned activity was observed in all three animals, with individual differences in degree and in critical doses. In Cat 4, the number of responses was multiplied by three with the dose of 50 mg and reached its maximum with 150 mg, being multiplied by 5·7. In Cat 9, a similar effect was observed with 50 mg, but a peak is reached at 80 mg when the number of responses is multiplied by 5. The behaviour of Cat 6 is altered slightly with 80 mg (1·3 times the normal level) and reached its maximum with 150 mg (3·1 times the normal level). The cumulative curves B, C and D, Fig. 1, show the modification of behaviour under drug action in Cat 9.

The distribution of responses during the successive 15 sec periods of the 2 min interval provides a good way to appraise the disruption of timing behaviour. The numbers recorded by the eight digital counters at the end of the experimental session were reduced to percentages of the total number of responses emitted during the session. The obtained values are represented in the form of histograms in Fig. 2. *Pre-drug* histograms are based on results averaged from ten sessions. *Drug* histograms are for individual sessions. Each block correspond to one of the eight 15 sec periods dividing the interval. The higher the block, at the right end of the histogram, the better the temporal discrimination. It can be

seen that the timing behaviour, remarkably developed in the pre-drug performance, is impaired in all the subjects, though not to the same degree in each of them. Cat 6, again, seems relatively more stable.

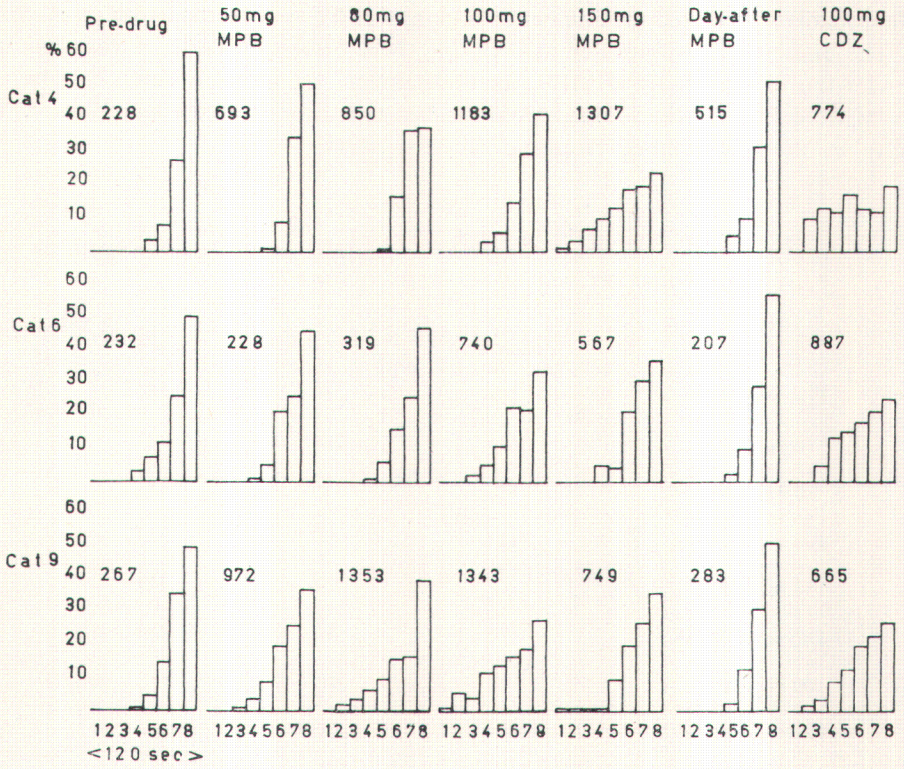

FIG. 2. Distributions of percentages of responses emitted during the eight successive 15-sec periods composing the 2-min interval, for each individual subject, under normal (pre-drug) conditions and with various doses of meprobamate and chlordiazepoxide. The higher the proportion of responses in the last period (at the right end of the histogram), the better the temporal discrimination. Figures above histograms indicate the number of reponses emitted in the 1-hr session.

The behaviour returns close to its normal level, both from the point of view of activity and of temporal discrimination, on the day following the last test with MPB. Results are given for comparison in Table 1 and in Fig. 1 (Curve E) and Fig. 2 (Day-after MPB).

The action of MPB on muscle tonicity can be observed with 80 mg and higher doses, i.e. with 150 mg most of the reflexes investigated were clearly altered. Motor coordination was seriously impaired. The subjects were staggering. Cats 6 and 9 were unable to climb upstairs as they usually do. The ataxic behaviour was still more pronounced in Cat 4. General motor activity in home cages was reduced, though the animals still reacted adequately to usual stimulations in their environment (presence of caretakers or experimenters, food, etc.). None of the effects described was observed on the day following the administration of MPB; experimental data and systematic observations are parallel.

Chlordiazepoxide (100 mg) induces a motor syndrome in most respects similar to that provoked by MPB: muscle hypotony, incoordination, ataxia. However, in contrast with MPB, CDZ makes the animals hyperactive and agitated in their home-cages in the presence of humans. The effects of CDZ on general motor behaviour persists on the day following administration of the drug, as do the effects on conditioned behaviour.

II. *Action of prolonged treatment with MPB*

It will be remembered that there were two periods of prolonged treatment with a daily dose of 150 mg, providing experimental results for a first series of forty sessions and for a second series of twenty sessions, separated from the first by a 25–day interval. Data are complete for Cats 6 and 9, incomplete for Cat 4 which died during the interval.

Results were treated for six successive groups of ten sessions. For each of these six groups, we computed the mean number of responses per session and the percentages of responses emitted in each part of the 2-min delay. The evolution of behaviour throughout the treatment will appear by comparing the results from one group of sessions to the next one, using the pre-drug values as reference base-line.

TABLE 2. EVOLUTION IN RATE OF RESPONSES DURING THE PROLONGED TREATMENT WITH MPB. MEAN NUMBERS OF RESPONSES PER SESSION COMBINED FOR SIX SUCCESSIVE GROUPS OF TEN SESSIONS.

	Cat 4	Cat 6	Cat 9
Pre-drug	228	232	267
Treatment sessions: 1–10	704	817	1079
11–20	579	320	541
21–30	600	336	137
31–40	400	358	219
41–50	—	168	162
51–60	—	239	127

Table 2 gives the mean numbers of responses per session in the six successive phases of the treatment. The activity comes back progressively to the pre-drug level. The initial effect of the drug on temporal discrimination also disappears, as evidenced by the distribution shown in Fig. 3. It should be noted that behaviour does not simply return to its pre-drug characters. In some respects, the final performance is different from the initial level; in Cat 9, for example, the number of responses dropped down to about one half of the pre-drug level, and the temporal discrimination was improved, with more than 60 per cent responses emitted during the last 15 sec of the interval, as opposed to 50 per cent in the pre-drug sessions.

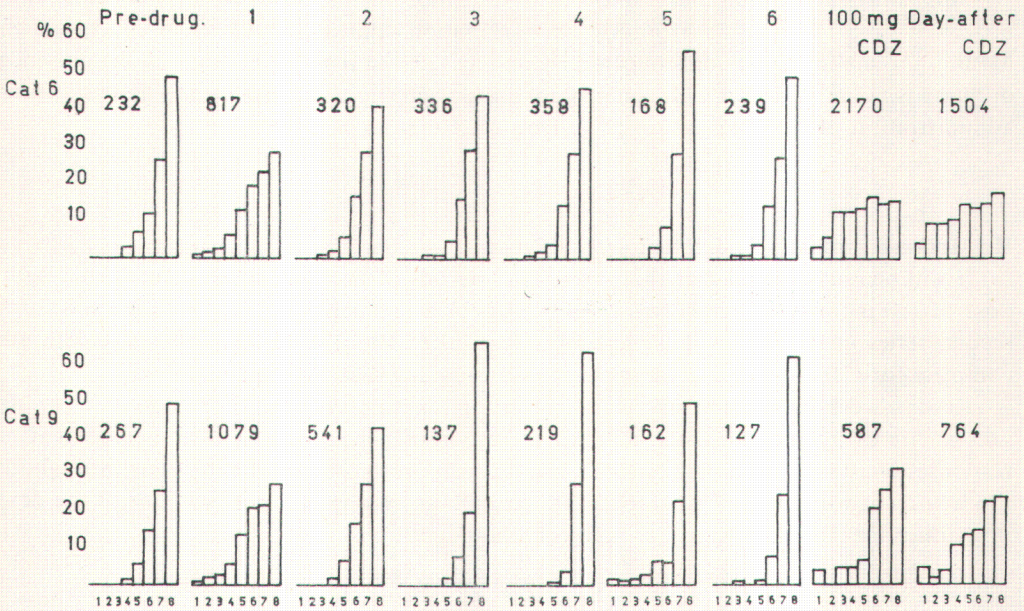

FIG. 3. Evolution of temporal discrimination through prolonged treatment with meprobamate, for Cats 6 and 9. See Fig. 2 for key to reading. Pre-drug histograms and histograms numbered 1–6 (prolonged treatment with MPB) are based on averaged results from groups of ten experimental sessions. Histograms for tests with chlordiazepoxide are drawn from individual sessions.

The tolerance is clearly observed in general motor behaviour; all signs of motor impairment described above disappear more or less rapidly. Cat 6 seemed to recover normal muscle tonicity on the fifth day, while Cat 4 required about 20 days.

The tolerance developed by repeated administration of the drug persists after the 25-day interruption. None of the initial effects is observed when the treatment is reinstated.

Chlordiazepoxide (100 mg) was again administered to Cats 6 and 9 on the day following the last administration of MPB in prolonged treatment. The effects on motor coordination and muscle tonicity observed, under the same dose, in the first part of the experiment, *were not observed* here; both subjects presented normal reflexes and were able to run their way up from their home-cage to the experimental cage. In contrast with this reduction of effect on general motor ability, CDZ did deteriorate operant behaviour as it did before the MPB treatment, increasing the rate of responses and disrupting the temporal discrimination. Both aspects of its action were even much more pronounced in Cat 6, which emitted more than 2000 responses. The modifications of conditioned behaviour persisted on the day following administration of the drug. Signs of ataxia could be observed again when 200 mg were administered.

III. *Withdrawal reactions after high doses of MPB*

It was seen in parts I and II of the experiment that no particular observable reaction followed when MPB was not administered. The effects of MPB were shown not to last

beyond the day of administration, and nothing was observed that could be called a *withdrawal reaction*. The absence of withdrawal reaction might be related to the dosage used. A test was made, on Cats 6, 9 and 8, to check a possible withdrawal reaction following administration of higher doses. Doses as high as 200 mg (Cats 6 and 9) and 250 mg (Cat 8) were given during three days.

These doses altered, but did not suppress, operant behaviour. Twenty-four hr after the last administration, the subjects were put into the experimental cage without previous administration of the drug. Operant behaviour was completely suppressed. General behaviour was also dramatically modified; the animals were hyperactive, agitated, irritable, they ran away from the experimenter, showed unusual fear reactions; diarrhoea, tachycardia and vomiting were observed.

Each animal was then injected with 200 mg mephenesin and returned to the experimental cage 10 min later. Cats 6 and 9 did not emit any response. Cat 8 emitted a few randomly, now and then. They kept lying down quietly in the cage. Mephenesin, at this dose, did not reduce motor coordination in these animals pretreated with MPB.

Each subject received then 200 mg MPB, and was put in the experimental cage for the third time in the same day, 30 min later. All the symptoms observed in general behaviour disappeared. The conditioned activity was reinstated, though the performance was irregular.

During the next 2 days, the subjects received a daily dose of 200 mg MPB. Twenty-four hr after the last dose, the withdrawal syndrome was observed again in general behaviour and operant behaviour as well. A test with mephenesin, again, gave negative results. CDZ (200 mg), administered on the same day, appeared to have a positive effect; the animals responded in the Skinner-box; the agitation was reduced. This effect persisted for three days. Then, abnormal symptoms reappeared and became more and more serious; vomiting, refusing food, fear reactions, sialorrhea, loss of toilet behaviour, loss of weight. After five days, an attempt was made to cancel out these symptoms by giving a small dose of MPB (80 mg), repeated twice at 3 days interval. The cats ate, gained weight and came back to normal behaviour.

DISCUSSION

Meprobamate, considered as a tranquilizer, has a paradoxical effect on the kind of behaviour studied in this experiment. It increases the conditioned activity and alters the quality of the adjustment to the environment previously developed by the organism. This action of MPB has been described for rats and monkeys, in FI schedule and in DRL schedule (Differential Reinforcement of Low rates)—both schedules involving a temporal regulation of behaviour—(KELLEHER *et al.*, 1961; BOREN, 1961; COOK and KELLEHER, 1962).

Our results also confirm previous studies on chlordiazepoxide. The action of the latter is similar in FI and DRL schedules of MPB. This was shown in cats, rats and monkeys (COOK and KELLEHER, 1961; RICHELLE, 1962; RICHELLE *et al.*, 1962; RICHELLE and DJAHANGUIRI, 1963).

The effects of MPB, at doses which do not produce withdrawal reactions, are no longer observed on the day after administration. In contrast, the effects of CDZ are long-lasting: in our experiment, we observed them for 3–5 days after the administration of the drug. Similar observations were made on cats (RICHELLE, 1962) and on monkeys (COOK and KELLEHER, 1962).

Several hypotheses have been proposed to explain the persistence of drug action beyond the day on which it is administered. The persistance is so long in some cases that it seems hard to explain by some particularly slow rate of metabolization. Behavioural hypotheses suggest that initial behaviour deteriorated by the drug is to be reacquired (RICHELLE, 1962) or that the drug induces compensatory mechanisms which do not disappear as soon as the physiological effect of the drug is over. The latter hypothesis is advocated by DEWS in the following terms: "New patterns of behavior acquired under the influence of a drug as would be expected, frequently persist after the drug has been eliminated, just as a tossed mariner may stagger a while after he reaches terra firma. This is undoubtedly the main source of 'day after' effects produced by drugs that are known in the body in significant concentrations for only a few hours" (DEWS, 1962).

However sensible such a hypothesis might sound at the theoretical level, it leaves unexplained the fact that one drug, CDZ, has long lasting effects, while another, MPB, has not, though both compounds induce comparable modifications in general and conditioned behaviour. Why should "new patterns of behaviour", similar in both cases as far as the way to assess them was accurate, be more persistent in one case than in the other? If the modified behaviour observed under the influence of the drug is to be considered as a newly acquired behaviour, it should be expected to be more persistent when it has been given the opportunity to develop throughout a series of sessions than when one single experimental session with drug took place. What we observe with MPB and CDZ goes exactly in the opposite direction; the test for "day-after" persistance was done after four sessions with MPB, after one session with CDZ. It is worth remembering, also, that rats did not show any "day-after" effects to CDZ (RICHELLE *et al.*, 1962; RICHELLE and DJAHANGUIRI, 1963).

The concept of tolerance refers to a reduction of the effects of a drug after it is administered repeatedly. Tolerance is rarely general, homogenous: some effects are attenuated and eventually disappear, though others are maintained, or become even more pronounced. Tolerance to MPB has been described by experimenters (TADDEI and PANNI, 1959; OXBURY, 1961; PHILIPS *et al.*, 1962; MOHR and MEAD, 1958; SHAGASS *et al.*, 1959).

Our data shows, unequivocally, the development of a tolerance to MPB in the three subjects under experiment. The initial action of a drug disappears progressively, in general motor ability and in two measures of operant behaviour (rate of responding and temporal discrimination).

The behavioural description does not, so far, explain the mechanism of tolerance. Part, if not the whole of it, is to be explained at the metabolic level. When MPB is repeatedly injected, the rate of metabolization of the compound is accelerated by induction of microsomal liver enzymes activity (EMERSON *et al.*, 1960; KATO *et al.*, 1961, 1962). This, however, as KATO himself points out, does not account for several aspects of the phenomenon of tolerance, especially as the process goes on long after the first few days of prolonged treatment. Other mechanisms are likely to be at work, such as changes in the sensibility of the central nervous system, or as far as behavioural aspects of tolerance are concerned, the development of corrective patterns of behaviour (DEWS, 1962). In the latter hypothesis, behavioural interaction between the organism and its environment would be essential for tolerance to show up; the repetition of the drug administration alone would be sufficient in the first case. We lack, at the present time, experimental

evidence to support either interpretation, or to delineate the respective part of each in specific contexts.

Cross-tolerance introduces new complications in the general problem of tolerance. A cross-tolerance between MPB and CDZ was observed in general motor activity, but was not observed in the experimentally controlled behaviour. This dissociation can only be explained hypothetically. It might be related to a difference in degree of automaticity between the two categories of behaviour; corrective behaviour could be developed more easily and more rapidly for more automatized activities. It might be related to partial differences in the sites of action of the two drugs: their effects on general motor behaviour might be mediated through a common site, while their effects on operant behaviour would depend on different sites. This would suppose that similar behavioural changes are to be traced to different causes—a perfectly admissible possibility.

Withdrawal reactions are shown to follow the administration of high doses of MPB. It should be emphasized that prolonged treatment is not necessary to obtain the withdrawal syndrome; one of the animals (Cat 8) was not submitted to the prolonged treatment. The dosage appears to be more critical than the length of the treatment. Withdrawal reactions to MPB have been described by experimenters, working on mice and dogs (SWINYARD *et al.*, 1957; ESSIG and AINSLIC, 1957) and by clinicians (KLEK *et al.*, 1957; HOLLISTER and GLAZENER, 1960; JUDAK *et al.*, 1961). High doses were used in all studies (up to 5·8 g day in psychiatric patients). Mephenesin, a myorelaxant substance, also derived from propanediol, does not cancel out the withdrawal reaction. Mephenesin is known to act mainly at the level of medullar associative neurons, but lacks the central action of MPB. CDZ, on the other hand, is, at least to some extent, an effective substitute for MPB.

Résumé—L'action du méprobamate est étudiée sur le comportement conditionné du chat. Dans une cage Skinner, les animaux sont entraînés à presser sur une pédale pour obtenir de la nourriture, suivant un programme de renforcement à intervalle fixe. Ils développent spontanément un type de comportement caractérisé par de la discrimination temporelle. Le méprobamate détermine une augmentation du nombre de réponses et une détérioration de la discrimination temporelle. Ces effets sont similaires à ceux engendrés par le chlordiazepoxide.

Par traitement prolongé (150 mg *pro die*), ces deux types d'effets sont réduits ou disparaissent. La tolérance concerne également le syndrome moteur général observé au début du traitement.

Le chlordiazepoxide, administré à nouveau après développement de la tolérance au méprobamate, induit encore les mêmes effets sur le comportement conditionné mais plus sur la motricité générale (tolérance croisée partielle).

Avec des doses élevées, le syndrome de sevrage apparaît lors de l'interruption de l'administration.

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