

A NOTE ON BEHAVIORAL TOLERANCE TO  
MEPROBAMATE<sup>1</sup>

MARC RICHELLE

UNIVERSITY OF LIÈGE, BELGIUM

Behavioral tolerance to meprobamate was demonstrated in a cat, on an FI schedule, without behavior taking place during the chronic treatment. Behavioral factors, such as the development of corrective patterns of behavior, do not explain behavioral tolerance in this case.

The role of behavior as an independent variable accounting for the effects of psychotropic drugs has been repeatedly demonstrated by psychopharmacological research. It has been suggested that tolerance to the behavioral effects of a drug can take place through the development of corrective patterns of behavior (Dews, 1962). Tolerance of this kind to a given drug should develop only in those cases where the behavior used as a criterion actually takes place during the chronic treatment. Otherwise, the development of corrective behavior would seem inconceivable.

Behavioral tolerance to meprobamate in cats was demonstrated by Xhenseval and Richelle (in press), using an FI schedule of reinforcement with a pharmacological treatment extending over several months. Behavioral effects of 150 mg (absolute dose)—*i.e.*, increased total output and disruption of temporal discrimination—subsided within two or three weeks.

Is it necessary, for this effect to show, to run the animals in the experimental cage during the treatment? If the answer is yes, the results will support Dews' behavioral hypothesis. If it is no, the behavioral tolerance to meprobamate cannot be explained as the development of corrective behavior with prolonged experience of working under the drug.

## METHOD

Three cats with a 2-yr history of FI 2 min were used. They developed a very stable

behavior, showing a fairly constant rate of responding even on the first experimental session after a four to six week vacation period. This stability made them especially appropriate for the purpose, *i.e.*, to treat them daily for three weeks with meprobamate, testing them twice in the experimental cage, for the initial effect on the first day and for eventual tolerance on the last day. To match the experimental conditions used by Xhenseval and Richelle, the drug was administered *per os*, mixed with a small amount of raw meat or fish. After the first administration, two cats obstinately refused the compound, presumably because of its taste, and the experiment was limited to the third animal. The results for this *S* are so clearcut that they leave little doubt as to the solution of the problem.

The cat (#10, female, 2.250 kg) was run in a home-made Skinner-box. Pressing a telegraph key was the response. Two ml of milk were delivered as reinforcement on an FI 2-min schedule. The experimental cage was isolated in a sound-proof compartment. Responses and reinforcements were recorded on a Gerbrands cumulative recorder. A set of eight digital counters yielded the distribution of responses in the 2-min interval, subdivided into eight, 15-sec periods. This provides for a quantitative analysis of the temporal pattern of responding. Experimental sessions lasted 1 hr.

After a number of sessions without drug, where the baseline behavior was confirmed, a dose of 200 mg of meprobamate was administered 45 min before the session. The same dose was given daily during the following 15 days, but no experimental session took place until the 16th day of the treatment. On the 16th day, the cat was run in the experimental

<sup>1</sup>Reprints may be obtained from the author, Laboratoire de Psychologie Institut de Thérapeutique Expérimentale, Université de Liège, 32 Boulevard de la Constitution, Liège, Belgium.

cage under the same conditions as used on the first day of treatment. An amount of milk equal to the amount usually obtained as reinforcement was given in the home-cage throughout the treatment.

## RESULTS

Results are summarized in Fig. 1 and 2, showing the cumulative curves and the distribution of responses in the interval. Curve A

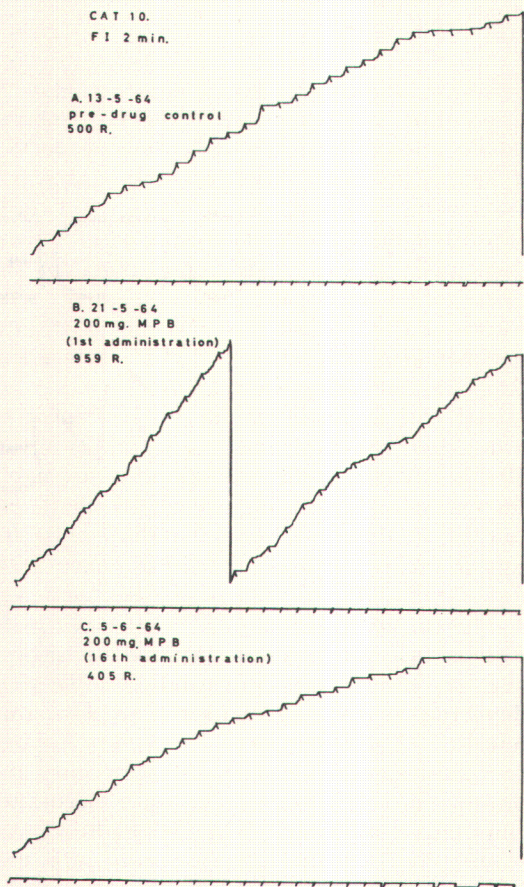


Fig. 1. Cumulative curves showing tolerance to meprobamate without conditioned behavior taking place during treatment. The pen tracing the cumulative curves returns to point zero on the ordinate after 500 responses. Oblique pips on the cumulative curve indicate the reinforcements. The fixed pen tracing the line at the bottom of each graph is deflected when the 2-min delay is over, and remains in that position until the reinforced response is emitted. Each graph is from a 1-hr session.

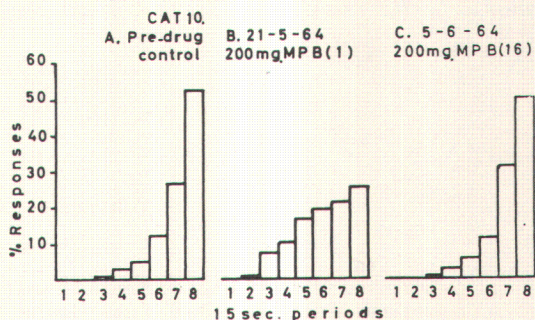


Fig. 2. Distribution of responses in the 2-min interval. The eight successive periods of 15 sec are numbered 1 to 8.

of Fig. 1 is a pre-drug sample. Histogram A (Fig. 2) is based on averaged results from the last 10 pre-drug sessions.

Curve B shows the effects of this first administration of meprobamate: the total output is drastically increased and the regular FI pattern is disrupted. This latter effect is best illustrated by comparing histogram B to histogram A in Fig. 2. The proportion of responses emitted during the last 15-sec period drops from 50 to 25%.

Curve C and histogram 6 are from the last day of the treatment: the animal resumed immediately its normal pattern of behavior and its temporal discrimination is at its best.

## CONCLUSIONS

The tolerance seen in these experiments does not seem to be the result of a behavioral adaptation. This does not mean, of course, that such an explanation might not be correct for other drugs, other types of behavior, or other species. However, the hypothesis that behavioral tolerance is but one aspect of general pharmacological tolerance should, as a rule, be considered first.

## REFERENCES

- Dews, P. B. Psychopharmacology, in A. J. Bachrach, Ed., *Experimental foundations of clinical psychology*, New York, Basic Books, 1962.
- Xhenseval, B. and Richelle, M. Behavioral effects of a long-term treatment with meprobamate in cats, *Int. J. Neuropharmacology*, (in press).

Received July 16, 1964