1968), and in mice retested without drugs one week later (Bradley *et al.*, 1968).

Although the dose-dependence of these effects has not yet been explored in great detail, it was clear from the present experiments that the amount of activity on the second trial was reduced by a constant proportion regardless of the actual doses administered at trial 1. Such a re-emergence of the dose-response curves on the second trial could not have been predicted from the results of previous experiments.

These findings suggest that dose-related behaviour patterns can be elicited long after the original administration of drugs; this may be relevant to clinical practice.

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## Disappearance in rats with septal lesions of the stimulatory effect of hyoscine on exploratory behaviour

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Electrocoagulative lesions were stereotactically placed in the septal region of male Wistar rats weighing 80–100 g, according to the coordinates of the rat atlas of Konig & Klippel (1963). Three days later the rats were rated for aggressiveness and hypermotility using the scale and procedure described by King (1958). Only those animals which showed a score close to the maximum were used.

Exploratory behaviour was investigated in a symmetrical Y shaped runway (Marriot & Spencer, 1965) counting the number of complete entries into the arms of the runway. Unoperated rats were used as controls. Neither operated nor unoperated rats had any previous experience of the experimental apparatus.

All the drugs were injected subcutaneously 30 min before testing. At the end of the experiments the operated rats were killed and the extent of the lesion was checked by histological examination.

The results are listed in Table 1. They show a marked difference between the effects of hyoscine on the exploratory behaviour of controls and that of septal rats. Hyoscine increases such behaviour in unoperated rats and decreases it in the septal rats. Amphetamine stimulates exploratory activity in both groups of animals.

TABLE 1. *Effects of drugs on the exploratory behaviour of septal rats placed in a Y-box*

| Drug | Dose mg/kg s.c. | Mean entries in the arms ± S.E. Controls | Septal rats |
|---|---|---|---|
| Saline | — | 3·06±0·44 (16) | 5·12±0·75 (8)‡ |
| Hyoscine | 0·5 | 8·31±1·25 (16)* | 1·9±0·73 (8)†§ |
| Amphetamine | 5·0 | 10·56±1·89 (16)* | 15·0±4·18 (8)† |

Number of rats in brackets.
* Different from saline with $P=0{\cdot}01$. † Different from saline with $P=0{\cdot}01$.
‡ Different from controls with $P=0{\cdot}02$. § Different from controls with $P=0{\cdot}01$.

These results support the view that the septum plays a role in the central cholinergic pathways as also suggested by the work of Lewis, Shute & Silver (1967) and of Szerb (1967).

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## The brain acetylcholine system in barbitone-dependent and withdrawn rats

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Hypotheses to explain development of physical dependence and central nervous tolerance suggest that the mechanisms involved represent a compensatory reaction to the altered pattern of nervous activity produced by the drug in question. One type of theory supposes that the synthesis, release and/or destruction of transmitter(s) is affected, while a second type supposes that neuronal sensitivity to normal amounts of transmitter is altered (Collier, 1965, 1968). Although many workers have studied the effect of chronic morphine administration and withdrawal on brain neurochemical systems, few have studied drug dependence of the barbiturate type.

Female Wistar rats were made dependent on barbiturate by the administration of up to 400 mg/kg per day of barbitone sodium in the drinking water for 4 weeks. Withdrawal was effected by replacing barbitone solution with drinking water.

Chronic barbitone administration and withdrawal did not produce any change in the following, all determinations being made on the brains removed from control, barbitone-dependent and 48 h withdrawn animals: (1) acetylcholine content, cholinesterase and choline acetyltransferase activity of frozen brain removed from animals killed by total submersion in liquid air; (2) the ability of cerebral slices to synthesize acetylcholine; (3) the ratio of "free" to "bound" acetylcholine extracted from freshly excised brain.