test, and at 0·03–0·12 mg/kg in the electroshock test. Eserine was active only in the phenylbenzoquinone test, at 0·03–0·06 mg/kg, being ineffective in the electroshock test at 0·3 mg/kg. Both agents were antagonized by atropine sulphate, 0·5 mg/kg, in both tests. As with morphine and nalorphine, eserine (0·03 mg/kg) potentiated oxotremorine in the phenylbenzoquinone test, but at 0·1 mg/kg antagonized it in the electroshock test.

By the use of crossed agonist and antagonist experiments we investigated the possibility that these two classes of agents were producing their anti-nociception by an action on the same system. The following results were obtained. Eserine (0·045 mg/kg) potentiated both morphine and nalorphine in both tests; morphine and nalorphine were not antagonized by atropine sulphate (0·5 mg/kg) in either test; neither oxotremorine nor eserine were affected by naloxone (2·5 mg/kg).

From these results it appears probable that there are at least two separate, centrally-sited, systems which can be involved in anti-nociception.

REFERENCES

BURN, J. H., FINNEY, D. J. & GOODWIN, L. G. (1950). *Biological Standardisation.* Oxford Univ. Press.

HENDERSHOT, L. C. & FORSAITH, J. (1959). Antagonism of the frequency of phenylquinone-induced writhing in the mouse by weak analgesics and non-analgesics. *J. Pharmac. exp. Ther.*, **125**, 237–240.

LESLIE, G. B. (1969). The effect of anti-parkinsonian drugs on oxotremorine-induced analgesia in mice. *J. Pharm. Pharmac.*, **21**, 248–250.

PARKES, M. W. & PICKENS, J. T. (1965). Conditions influencing the inhibition, by analgesic drugs. of the response to intraperitoneal injections of phenylbenzoquinone in mice. *Br. J. Pharmac. Chemother.*, **25**, 81–87.

## A quantitative method for the assessment of physical dependence on narcotic analgesics in mice

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In the past most quantitative assessments of the physical dependence properties of narcotic analgesic drugs were made in humans, monkeys and, more recently, in rats. It was generally agreed that mice were unsuitable for this type of study because their responses were too variable to permit objective measurement.

Following chronic treatment with morphine three times daily for one week, mice, when injected with nalorphine, exhibited signs of withdrawal which were characterized by persistent jumping. Other signs of withdrawal such as diarrhoea, micturition and piloerection were also present.

This characteristic jumping was also seen when chronic morphine administration was discontinued. Under these conditions the response was rather more variable and less intense than that elicited by nalorphine. This reduced intensity of withdrawal is consistent with the findings of numerous workers in other species.

The purpose of the investigation was to determine whether the number of jumps elicited by nalorphine in groups of mice could be used as a method of measuring the intensity of the withdrawal syndrome. The relationship between the number of jumps occurring in a given time and the dose of drug, the interval between injections and the dose increment was studied using morphine, methadone and pethidine.

It was possible to obtain a significant number of jumps after only six injections when morphine was administered three times daily in increasing doses. The number of jumps was a monotonic increasing function of both the number of injections and the total dose injected. When the same amount of morphine was given at each injection no such consistent relationship was found.

The behaviour of mice treated with methadone and pethidine was slightly different. It appeared necessary to inject pethidine more often (every three hours) to demonstrate physical dependence. Methadone, however, could be injected less frequently than morphine and still produce a significant number of jumps. This is consistent with what is found in man (Isbell & White, 1953). Way, Loh & Shen (1969) have published a quantal method for assessing precipitated abstinence in mice. In our method the response is graded and more detailed information about the abstinence syndrome can be obtained using fewer mice.

In conclusion it is suggested that the number of jumps elicited by an antagonist in chronically narcotized mice can be used as a quantitative measure of the withdrawal syndrome.

REFERENCES

ISBELL, H. & WHITE, W. M. (1953). Clinical characteristics of addiction. *Am. J. Med.*, **14**, 558–565.
WAY, E. L., LOH, H. H. & SHEN, F.-H. (1969). Simultaneous quantitative assessment of morphine tolerance and physical dependence. *J. Pharmac.*, **167**, 1–8.

**Behavioural effects of a " smoking dose " of nicotine in rats**

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Armitage, Hall & Morrison (1968) showed that nicotine can cause EEG activation and behavioural arousal, in terms of operant responding for water, with variations depending on the individual rat, the dose (in the range 50–400 $\mu$g/kg) and on the rate of injection. They estimated that a rat given 15–30 $\mu$g/kg intravenously receives a dose of nicotine equivalent to that inhaled by a man smoking a cigarette.

In the present experiments, the social behaviour of rats of two laboratory strains was observed, following the subcutaneous injection of nicotine base (25 $\mu$g/kg in 1 ml./kg of dilute saline). Paired male rats were separated daily and observed for 6 min after reintroduction. Acts and postures described by Grant & Mackintosh (1963) were recorded, and interpreted statistically by discriminant analysis.

There was a barely significant difference between the randomly selected experimental and control animals in the baseline observations. However, the difference was much greater after the administration of nicotine, and was greater still after the last of four daily injections intended to control for habituation. In a crossover test, where rats formerly given nicotine were injected with saline, and vice versa, the difference between the groups fell to insignificance. There seem to be individual differences between rats to which the effects of nicotine are additive. The latter were therefore shown more clearly by considering rats as their own controls.