biton sodium (35–45 mg/kg) anaesthesia, as described by FELDBERG and SHERWOOD[5]. Penicillin was administered postoperatively and a 3–5-day interval elapsed before the first experiment. All solutions were injected slowly under aseptic conditions in volumes of 0.2 ml and washed in with 0.1 ml of 0.9% NaCl. The cats were observed continously for 2–6 h and intermittently for 24 to 48 h. The drugs used were nicotine hydrogen tartrate and tetraethylammonium chloride.

The most striking effect of nicotine after its intraventricular injection in doses from 1.0 to 4.0 mg was a condition of catalepsy. The signs of catatonia appeared within 10 min and persisted for about 40 min. When fully developed the cat could be placed in nearly erect position with forepaws over the rung of an inverted stool. The cat remained in this position for about 15 sec. Thereafter the cat slowly climbed down. Moreover, when the cat was induced to walk, it ceased moving after a few steps and stood motionless for a few minutes. Finally, it lay down on its belly. During this time the eyes were half open and the cat showed little interest in its surroundings with no signs of affection. When the stage of catalepsy wore off, no spontaneous movements were observed and the cat would sit usually under a bench motionless for hours if undisturbed. The sedation and stupor lasted up to 12 h. It is interesting to note that in some experiments catalepsy developed after convulsions.

Intraventricular administration of tetraethylammonium in dose of 2 mg potentiated the signs of catalepsy. When the intraventricular injection of tetraethylammonium was preceded by an intraventricular administration of nicotine, the cat could be placed in nearly erect position with its forepaws over the rung of an inverted stool for about 90 min.

Apart from the signs of catalepsy an intraventricular administration of nicotine in doses from 1.0 to 4.0 mg produced mydriasis, salivation, piloerection, vomiting, ataxia, tremor, respiratory embarassements, rigidity, convulsions and sometimes akathisia. Control injections of 0.4 ml of 0.9% saline caused no visible changes.

The present experiments show that nicotine produced catalepsy in conscious cats when injected into the cerebral ventricles. Intraventricular application of bulbocapnine[6], anticholinesterase[7], morphine[8] and prostaglandin[9] in unanaesthetized cats and rabbits also produced catalepsy. Furthermore, experimental syndrome of catatonia can be obtained by placing electrolytic lesions in the upper brain stem[10]. The lesions of the border between upper tegmentum and the posterior hypothalamus are known to produce catatonic syndrome[11]. These regions might be reached by intraventricular injection of nicotine from the third ventricle. Nicotine in high doses is known to interrupt nervous pathways by producing a block of synaptic transmission in autonomic ganglia or in neuromuscular junction. By analogy, it can be supposed that nicotine in high doses injected intraventricularly produced a kind of pharmacological lesion paralyzing nerve cells and interrupting probably some specific pathways, causing catalepsy.

Résumé. La nicotine, aux doses de 1.0 à 4.0 mg, injectée par voie intraventriculaire à des chats non-anesthésiés, provoque la catalepsie, la sédation et la stupeur. Les signes de catalepsie apparaissent d'ordinaire 10 min après l'injection et disparaissent au bout de 40 min. L'application intraventriculaire de tétra-éthyl-ammonium potentialise les symptômes de catalepsie dûs à la nicotine.

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Development of Behavioural Tolerance to Nicotine in the Rat[1]

Although chronic self-administration of nicotine (as a constituent of tobacco) is widespread, most studies of the behavioural effects of this drug on experimental animals have been concerned with the consequences of acute administration. Vertical rearing activity in rats has been shown to be susceptible to the acute effects of nicotine in a number of studies[2–5]. This component of the general activity of the rat is also useful in the assessment of the effects of repeated administration of drugs since it is known to stabilize when animals are repeatedly exposed to the same test situation[6], thereby providing a constant baseline against which drug effects can be assessed.

Repeated administration of a drug often results in a diminished effect due to the development of tolerance[7]. It has also been found[8,9], that when drugs are given repeatedly before animals are exposed to a behavioural test, drug withdrawal can have behavioural consequences even though physiological dependence may not be apparent.

There is evidence that drug effects on behaviour may be greater when the drugs are administered before exposure to completely novel, as against familiar, situations[10–12]. This effect could be confused with the development of tolerance in experiments in which drug administration is repeatedly followed by exposure to some test situation. In order to minimise this possibility the present study was so designed that animals had already received several exposures to the experimental situation before drug administration was commenced.

Materials and method. 16 Roman control (RCA) strain rats, aged 180 days, were used in the study. All the rats were males.

The apparatus used to measure rearing activity consisted of a transparent acrylic plastic tube 63 cm high with an internal diameter of 23 cm. A stainless steel band, 1.3 cm wide, attached to the outer circumference of the tube 25 cm from the base, functioned as the probe of a proximity meter (capacitance transducer). Vertical movement of the rat resulted in a capacitance change proportional to the distance between the animal's head and the probe. This capacitance change caused the proximity meter to produce a varying voltage output which was then recorded as an analogue print-out curve on a moving-pen recorder.

A rear was defined as a pen deflection of at least 1 cm from the baseline on the analogue curve (corresponding to a 1-volt variation in proximity meter output). Rearing frequency was assessed as the total number of rears in a 10-min test period.

Each rat was given a total of 6 daily 10-min exposures to the rearing apparatus, after which the rearing behaviour was judged to be sufficiently stable for drug administration to begin. On the 7th day of testing the rats were divided into experimental and control groups each containing 8 animals. Experimental animals were given 0.5 mg/kg of nicotine hydrogen tartrate dissolved in physiological saline: controls received saline only. All injections were made s.c. in the dorsal flank 20 min before testing. The sequence of drug injection followed by exposure to the test situation was repeated for 10 consecutive days. On the 11th day the drug and control conditions were reversed: those animals which had been given nicotine now received saline before testing (to investigate any possible withdrawal effects), whilst the group previously given saline was transferred to nicotine administration (to assess the possible effects of a larger number of drug-free exposures to the test situation on initial drug response).

Results. An analysis of variance was carried out on the data from the first 9 days of the experiment. The days factor was reduced to 3 levels by combining the data from consecutive 3-day periods (Table I). There was a significant drug × days interaction ($P < 0.001$). While nicotine initially reduced rearing frequency, the effect diminished with repeated administration, until after 9 days there was no difference between experimental and control groups: in fact, the difference between the groups was significant only on days 1 to 3 ($P < 0.01$). Analysis of the data from the final day (day 11) of the experiment, when drug and saline treatments were reversed, was carried out by comparing them with the scores of the previous day (day 10). The data are summarized in Table II. Rearing frequency in the group which had previously received chronic nicotine administration was significantly increased when saline was substituted ($P < 0.01$). There was a slight reduction in rearing frequency in the animals transferred to nicotine following chronic saline treatment, but this was not statistically significant.

Discussion. The present findings accord with those of MORRISON and LEE[5] who have reported a depressant effect of acutely administered nicotine on rearing activity in rats. Nicotine has, however, been found to enhance rearing in some strains of rats[2–4], a contrary finding which may be partly accounted for by strain differences since there is evidence that this is an important determinant of reactivity to nicotine[4,5]. Recovery from the depressant effects of nicotine on discrimination performance in rats has been reported[13] to follow repeated administration of the drug. No attenuation of the stimulant activity of nicotine on motor activity was found, however, even after several months of daily injections[14]. It is difficult to make comparisons between these earlier results and the findings of the present experiment because of considerable differences between the experimental procedures employed.

It is not clear from the present results whether or not the observed attenuation of nicotine effects with repeated administration was due to tolerance development or to some other factor, such as an interaction between the drug effect and length of exposure to the test situation, but the fact that the chronic saline group (which received an extended pre-nicotine exposure to the test situation) was little affected by the drug lends tentative support to the latter view.

Nicotine withdrawal produced a rebound effect in a direction opposite to the original drug action. Although rather similar effects have been reported for other drugs in different test situations[8,9], little is known about the mechanisms involved in this phenomenon. One possibility is that animals can counteract drug effects by making behavioural adjustments, drug withdrawal then leading to a behavioural over-reaction.

Résumé. On a donné de la nicotine à des rats une fois par jour, pendant 10 jours. L'activité des animaux a d'abord diminué, mais après quelques administrations de la drogue, on constata une accoutumance à ces effets. L'administration terminée, l'activité a augmenté.

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Table I. Change in rearing frequency of rats given nicotine or saline over a 9-day period

Treatment	Days 1–3	Days 4–6	Days 7–9
Nicotine	20.5[a]	26.3	32.1
Saline	31.8	31.0	29.9

Values are given as the total number of rears in 10 min averaged over successive blocks of 3 days. The days × drug interaction was significant beyond the $P < 0.001$ level. [a] Significant against saline control beyond the $P < 0.01$ level.

Table II. Change in rearing frequency between days 10 and 11 as a result of interchanging saline and nicotine treatments

Days 1–9	Day 10		Day 11	
Treatment	Treatment	Rearing frequency	Treatment	Rearing frequency
Nicotine	Nicotine	28.6[a]	Saline	37.4[a]
Saline	Saline	27.6	Nicotine	24.2

Values are given as the total number of rears in 10 min. [a] Difference between day 10 and day 11 scores significant beyond the $P < 0.01$ level.

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