number of ejaculations. The order of testing the drugged or abstinent dependent rats was counterbalanced.

Dependent, drugged rats, which were more active, made more contacts with the females but these were brief and the rats responded to the females inappropriately. There were no attempts at mounting or any other sexual interactions. However, in acute abstinence these same rats appeared to respond normally to the females and were now indistinguishable from controls (see Table 1).

After two weeks of abstinence, the post-addicts and the controls showed no differences (Test III) but when both groups were tested after an injection of morphine (30 mg/kg), the controls were sedated and their sexual behaviour was virtually suppressed. The post-addicts showed significantly less attenuation of the number and duration of contacts which indicates that there was still some tolerance to morphine 16 days after withdrawal.

The effects of morphine on eating and drinking (Kumar *et al.* 1977) and on the sexual activity of dependent rats follow different courses over time; sexual behaviour is disrupted while the rats are drugged and seems to be unaffected during acute abstinence.

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Effect in the rat of chronic morphine treatment on the behavioural response to apomorphine

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A growing body of biochemical (Kuschinsky & Hornykiewicz, 1974) evidence suggests that morphine interacts with dopamine (DA) containing neurones. Behavioural evidence for such an interaction is contradictory (Kuschinsky, 1975; Smee & Overstreet, 1976). In the present experiments the effect of chronic morphine treatment on the behavioural response to the DA agonist, apomorphine, was investigated in normal rats and in rats with bilateral lesions to the caudate DA terminals. Apomorphine in low doses induces a marked stimulation of locomotor activity in the rat.

In Experiment 1, 6 rats and their controls received escalating i.p. injections of morphine sulphate (20–40 mg/kg) for 5 days. One and five days after the last dose of morphine, the response to 0.1 mg/kg apomorphine (s.c.) was measured. Morphine injections were then reinstated twice per day in dosages up to 120 mg/kg. The response to apomorphine was again tested 1, 5 and 16 days after the last morphine injection. Motor activity was measured for 1 h after apomorphine with photocell recording methods and stereotypy was rated every 10 min with a non-linear scale which classifies motor behaviour into one of 6 characteristic topographies (Creese & Iversen, 1975). In experiment 2, essentially the same procedures were followed but in this case the effect of morphine pretreatment was studied in rats with bilateral 6-OHDA (8 μg in 2 μl each side) lesions to the caudate nucleus and their appropriate controls. At the completion of this experiment the levels of caudate DA were measured with a radio-enzymatic assay (Cuello, Hiley & Iversen, 1973).

In Experiment 1, after the second morphine treatment regime, significantly higher locomotor activity was recorded 10 and 20 min after apomorphine in the morphine treated group compared to the saline controls (24 h post morphine injection, 10′ $P<0.013$, 20′ $P<0.047$; 5 days post morphine injection, 10′ $P<0.008$, 20′ $P<0.004$). In Experiment 2, after chronic morphine treatment, the caudate lesioned animals showed a different apomorphine response from that observed in saline treated caudate lesioned animals. In the latter animals intense confined stereotypy was seen after apomorphine whereas in the morphine treated animals apomorphine stereotypy was severely disrupted by long bursts of locomotor activity.

It has been established that the mesolimbic DA system mediates locomotor responses to DA agonists (Kelly, Seviour & Iversen, 1975) and thus it is suggested that morphine interacts principally with non-striatal DA substrates to modify the apomorphine response. This is supported by the observation that locomotor activity predominates in morphine treated caudate lesioned animals, where the enhanced responsiveness of the post-synaptic striatal receptors normally results in persistent stereotyped responding to low doses of apomorphine (Kelly *et al.*, 1975).

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A study of the potentiation of morphine antinociception by hydroxyzine in the rat

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Hydroxyzine, a minor tranquillizer with antiemetic, antihistaminic and antispasmodic actions, has been shown in man to possess analgesic properties and to potentiate morphine (Beaver & Feise, 1976) and meperidine analgesia without altering its pharmacokinetic and metabolism (Stambaugh & Weiner, 1976). However these findings were not confirmed by Kantor & Steinberg (1976). In this study we investigated the antinociceptive properties of hydroxyzine chloride.

Antinociception was evaluated by the method of Paalzow & Paalzow (1973). The tail of adult male rats was stimulated for 1 s using square waves at a frequency of 125 pulse/s, pulse width 1.6 ms, through thin needles inserted subcutaneously. In each animal the thresholds for motor response (tail withdrawal and hind quarter movement), for vocalization response and for vocalization after-discharge were determined before and 30 min after drug administration. According to Hoffmeister & Kronenberg (1966) the motor response is of spinal origin, the vocalization response involves the medulla, the vocalization after-discharge the thalamus, hypothalamus and rhinencephalon and represents the affective component of pain.

Hydroxyzine (12.5 mg/kg i.p.) exerted no antinociception; however at a dose of 25 mg/kg it reduced slightly the motor response and at 50 mg/kg exerted a weak antinociceptive action as shown in Table 1. Morphine sulphate (2.5 mg/kg s.c.) exerted a well detectable antinociceptive effect. Hydroxyzine potentiated the effect of morphine on the motor response and on the vocalization after-discharge. A small effect on the vocalization response occurred with 25 mg/kg. Hydroxyzine seems therefore to affect mostly the spinal and emotional components in the pain reaction. A comparison between hydroxyzine and other minor tranquillizers is in progress.

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Table 1 Effect of morphine, hydroxyzine and their combination on nociceptive reaction in the rat

			% increase of threshold (mean ± s.e. mean)		
Drugs	*Dose (mg/kg)*	*Route*	*Motor response*	*Vocalization*	*Vocalization after-discharge*
Hydroxyzine	25	i.p.	18.5 ± 0.9^{+}	1.6 ± 0.03	11.1 ± 0.6
Hydroxyzine	50	i.p.	45.4 ± 2.7^{++}	21.3 ± 1.7	24.2 ± 1.4^{+}
Morphine	2.5	s.c.	29.3 ± 1.3^{++}	75.6 ± 4.8^{++}	84.7 ± 6.2^{++}
Morphine	5	s.c.	32.7 ± 2.8^{+}	88.9 ± 15.2^{++}	143.1 ± 29.4^{++}
Hydroxyzine + Morphine	12.5 2.5	i.p. s.c.	*38.8 ± 0.5^{++}*	72.9 ± 7.0^{++}	*151.7 ± 28.3^{++}*
Hydroxyzine + Morphine	25 2.5	i.p. s.c.	*36.2 ± 1.1^{++}*	*110.6 ± 4.8^{++}*	*280.1 ± 32.7*

Groups of 5 rats
Differences from thresholds before treatment: P values $^{+}<0.05$ $^{++}<0.01$
The italicized figures are significantly different when compared with morphine 2.5 mg/kg with $P < 0.01$.