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Disturbed patterns of behaviour in morphine tolerant and abstinent rats

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Summary

1. Eating, drinking and spontaneous motor activity were studied in rats receiving large daily doses of morphine. These forms of behaviour were largely suppressed when the rats were made abstinent and were restored when morphine was given again.

2. Compensation for depressions of behaviour during abstinence did not seem sufficient to account for all the stimulant effects of morphine in tolerant rats. Morphine also had slight stimulant actions in non-tolerant rats.

3. In tolerant rats, the repeated pairing of the effects of morphine with the re-emergence of behaviour such as eating and drinking may intensify the rewarding value of the drug.

Introduction

Theories of physical dependence on opiates have sometimes been concerned with the more rapid development of tolerance to the 'depressant', than to the 'stimulant' effects of morphine (Tatum, Seevers & Collins, 1929; Seevers & Deneau, 1963). Dependence may be associated with long-lasting changes in the excitability of the central nervous system or in levels of presumed neurotransmitter substances (Jaffe, 1970). However, relationships between changes in the nervous system and overt behaviour are sometimes difficult to establish, partly because the terms 'stimulation' and 'depression' have been rather loosely applied to such diverse effects as increased motor activity, convulsions and emesis on the one hand, and to sedation, analgesia and respiratory depression on the other.

Martin, Wikler, Eades & Pescor (1963) used rating scales to obtain a compound measure of 'activity' in tolerant rats, and reported increased activity scores after injections of morphine; the rats also 'consumed food and water voraciously, if allowed'. Abstinence from morphine in rats has been characterized by reduced motor activity, losses in weight, increased aggressiveness and other changes (Kaymakcalan & Woods, 1956; Weeks, 1962; Martin *et al.*, 1963; Thor & Teel, 1968; Stolerman & Kumar, 1970). The first experiment described here was a comparative study of the time course of eating, drinking and spontaneous motor activity in morphine tolerant rats, both when drugged and when abstinent. We also tested the possibility, suggested by experiments on sleeping and drinking (Wikler, Martin, Pescor & Eades, 1963; Khazan, Weeks & Schroeder, 1967), that prolonged treatment with morphine might disrupt the normal diurnal rhythms of behaviour. The second experiment was a more detailed analysis of the restoration

of behaviour after giving morphine to abstinent rats and finally, in experiment 3, we tested some effects of a range of doses of morphine in non-tolerant rats.

Methods

Animals

The animals were male hooded rats aged 80–100 days at the start of experiments 1 and 3 and 130–160 days in experiment 2. They had been housed twelve per cage since weaning. The ambient temperature was $22 \pm 1°$ C and a regular (non-reversed) light/dark cycle was imposed throughout by electric lighting. The lights were on between 9 a.m. and 5.30 p.m. and during the experiments the rats were housed in single cages in a sound-insulated room.

Food and water intake

The amounts of food and water consumed were determined by weighing the food containers (open cups) and the water bottles before and after each test period. The amounts of food spilt were also measured and appropriate allowances determined by preliminary experiments were made for leakage, whenever water bottles were inserted into the animals' cages.

Spontaneous activity

Four photocell activity cages were fitted with food containers and water bottles. Each cage had dimensions of $27 \times 27 \times 27$ cm and was crossed at a height of 4 cm by two beams of infrared light at right angles to each other. Interruptions of the beams of light were recorded on counters. Uses and limitations of this apparatus have been discussed in detail elsewhere (Krsiak, Steinberg & Stolerman, 1970).

Delay before eating in a new environment

A cage $36 \times 26 \times 20$ cm, made of wire mesh, was fitted with a food container and illuminated by a 60 watt bulb placed 60 cm above it. The rats were put in the cage individually and the experimenter recorded the delays before eating began. Powdered diet was used and the criterion for eating was 10 s of continuous chewing (Bolles, 1965). Each rat was tested once only, so that the cage served as a new environment. All tests stopped after 15 min, even if no eating had occurred.

Drugs

Morphine hydrochloride was dissolved in pyrogen-free water and was injected intraperitoneally throughout. Isotonic saline was used as the control solution.

Experiment 1

Eighteen rats were divided into two groups ($n=9$ each) by a random method and were housed singly throughout the experiment. Group 1 (tolerant rats) received injections of morphine twice a day for 6 days ; the initial dose was 15 mg/kg per injection, and this was increased to 30 mg/kg and 60 mg/kg on the third and fifth days, respectively. From the seventh day onwards, the total daily dose of 120 mg/kg was given in a single injection at 10 a.m. ; the rats were weighed both then and at

5 p.m. This regime continued when the rats were moved to the activity cages on the fourteenth day. Group 2 (non-tolerant controls) was treated in a similar way throughout, but received saline injections whenever group 1 was given morphine.

Preliminary experiments showed that the diurnal patterns of activity in the photocell cages stabilized after about 2 days (Stolerman, 1969). From 10.15 a.m. on the sixteenth day, the numbers of photocell counts were printed automatically every hour for 24 h and the food and water intakes were measured after 4 and 24 hours. Hourly measurements of food and water intake were not made because of their possible influence on activity. Owing to apparatus failures, activity scores were obtained for only seven of the nine rats.

On the seventeenth day, the drug treatments were reversed: group 1 was given saline instead of morphine, group 2 was given morphine, 20 mg/kg ; the large dose (120 mg/kg) previously given to group 1 would probably have killed the non-tolerant rats in group 2.

Experiment 2

Tolerance to morphine was induced in nine rats by injecting them with increasing doses of morphine as in experiment 1. Seven rats received the same number of saline injections. The tolerant rats were then maintained on a single daily dose of morphine (120 mg/kg at 10 a.m.) for about 2 weeks, while the controls continued to receive saline. Seven days were then allowed for adaptation to the powdered food, which was substituted for the usual pellet diet. On the eighth day, the amounts of food and water consumed were measured at hourly intervals for 6 h, beginning at 10 a.m. and also after 24 hours. On the ninth day, saline was substituted for the morphine usually given to the tolerant group, and the measurements of food and water intake were repeated.

The injections of morphine were then resumed for 7 days before the last stage of the experiment, which consisted of measuring the delays before the rats began eating when they were placed in a new environment. This test was used as an additional measure of hunger ; the greater the amount of previous food deprivation, the shorter is the delay (Chance & Mead, 1955 ; Bolles, 1965). The tolerant rats were tested in this way 1 h after their usual daily injection of morphine (120 mg/kg) ; the only time they were deprived of food was the hour between the injection and the test. In order to provide a basis for comparison, the controls were tested in a similar manner, but after being deprived of food for 48 hours.

Experiment 3

For one week before testing, rats which had never had morphine before were housed singly and given powdered food instead of the usual pellets. On the eighth day they were all deprived of food for 24 h and were then allocated to five treatment groups by a random method (saline or morphine 2·5, 5·0, 10·0 or 20·0 mg/kg, $n=8$ each). One hour after injection, the delay before eating in a new environment was measured for each rat. Following this the rats were returned to their home cages and the intakes of food and water were measured after 2, 4 and 24 hours.

Analysis of results

The significance of differences between groups was examined by the Mann-Whitney test, or by the Wilcoxon test when rats served as their own controls (Siegel,

1956). Non-parametric trend tests were also used (Jonckheere, 1954); in many cases the scores were not normally distributed, mainly because appreciable numbers of rats did not eat or drink at all in some conditions. For example, in the tests of delays before eating in a novel environment, a high proportion of rats receiving the largest dose of morphine did not eat and were therefore assigned delay scores of 15 minutes.

Results

Experiment 1

The non-tolerant control rats consumed food and water slowly during the 4 h after the daily injections of saline at 10 a.m., but more quickly during the remainder of the 24 h test (Fig. 1). As one would expect, they gained weight overnight and lost it during the day; on average, the weights at 10 a.m. were 3–6 g higher than at 5 p.m. The motor activity of the control rats was also greater at night. These daily patterns are consistent with previous findings; that is in rats maintained under similar conditions, eating, drinking and motor activity occur mainly at night (Cofer & Appley, 1964). Figure 1 also shows that morphine changed these daily patterns. During the 4 h following the regular daily injections of the drug, the tolerant rats consumed about 3 times as much food and water as did the controls ($P<0{\cdot}01$ for food intake, $P<0{\cdot}05$ for water intake). However, 5–24 h after the injection, the situation was reversed; the controls ate and drank more than the tolerant rats ($P<0{\cdot}01$ for both food and water intake). The findings with body weights were consistent; the tolerant rats gained an average of 6·5 g during the day and lost weight at night. The total amounts of food and water consumed every day were greater for control than for tolerant rats (Table 1).

Motor activity also strikingly increased after the daily injection of morphine (Fig. 1). The differences between the tolerant and control groups were very large for the first 4 h after injection ($P<0{\cdot}001$), and were still apparent 4–8 h after injec-

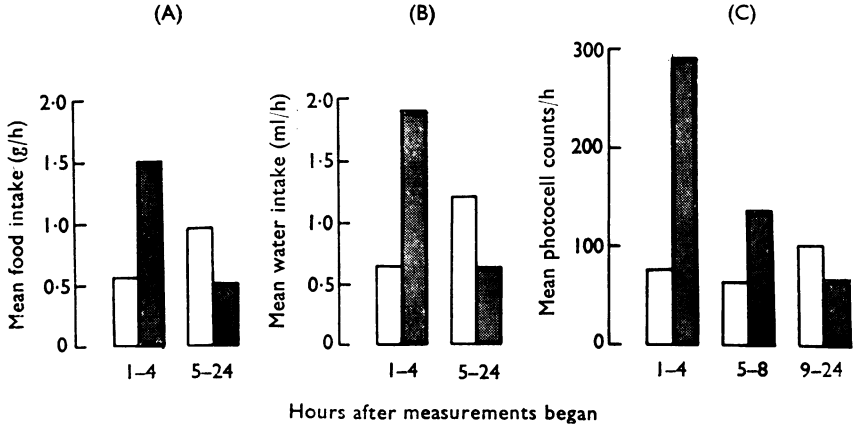

FIG. 1. Changed diurnal patterns of three forms of behaviour in rats tolerant to morphine. In controls ($n=9$), the amounts of eating, drinking and spontaneous motor activity (photocell counts) were low between 10 a.m. and 2 p.m., but increased subsequently. This pattern was reversed in tolerant rats ($n=9$, except for activity, where $n=7$), so that relatively large proportions of the daily totals of these forms of behaviour occurred after the morphine was given at 10 a.m., 30 min before measurements began. (A), Eating; (B), drinking; (C), activity. (Shaded columns), tolerant (morphine i.p.); (open columns), controls (saline i.p.).

tion ($P<0.05$). A more detailed analysis of the daily pattern of activity in Fig. 2 shows that activity of the tolerant rats then fell below that of the controls ($P<0.05$ for each of the periods 13–16, 17–20 and 21–24 h after the injection). The time of the change from high to low activity conforms with previous reports of the onset of abstinence (Martin *et al.*, 1963). Effectively therefore, the usual daily pattern of motor activity in the tolerant rats was reversed, as compared with that in the controls. The total amount of activity during the 24 h was greater (Table 1) but this was not significant.

Substituting saline for the usual daily dose of morphine approximately halved the amounts of food and water consumed during the following 24 h (Table 1) and the weights of the rats fell by a further 19·5 g. Motor activity was markedly reduced and no hyperactivity 'conditioned' to the injection procedure could be seen. During the night, activity was lower than in controls but not below the level in the night following one of the usual injections of morphine at 10 a.m. (Fig. 2). These

TABLE 1. *Total amounts of eating, drinking and spontaneous activity (photocell counts) during* 24 *h after injections of morphine or saline at* 10 *a.m.*

Group	Treatment	Food intake	Water intake	Activity
Control	Saline	20·2g	27·4 ml	2161
	Morphine (20 mg/kg)	16·2g†	25·1 ml*	2420
Tolerant	Saline	9·3g‡	9·9 ml‡	1608
	Morphine (120 mg/kg)	16·2g‡	19·9 ml‡	2770

The tolerant group had been maintained on morphine (120 mg/kg) for 7 days before testing, following a regime of increasing doses, but the controls received only a single dose of morphine (20 mg/kg). Significant differences from controls (saline): * $P<0.05$; † $P<0.01$; ‡ $P<0.001$.

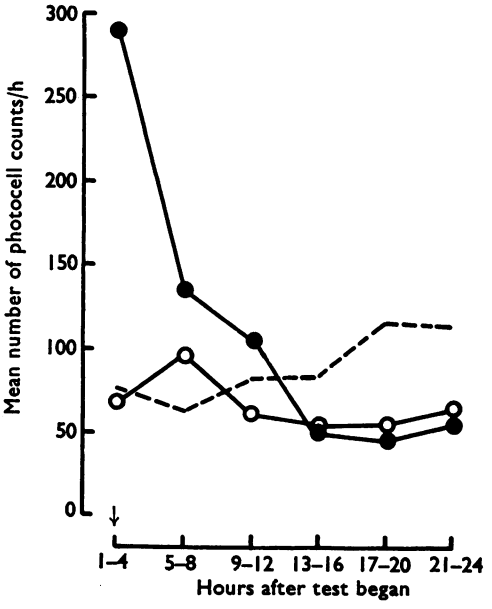

FIG. 2. Changed diurnal patterns of spontaneous motor activity (photocell counts) in rats tolerant to and abstinent from morphine. For at least 8 h after a large dose of morphine, the tolerant rats were more active than the controls. This situation was reversed 13–24 h after the injection when the rats were effectively abstinent. Hyperactivity was not apparent when saline was substituted for the regular daily dose of morphine. (●——●), Tolerant, tested after morphine (120 mg/kg i.p. at 10 a.m.) ($n=7$). (○——○), Tolerant but saline substituted for morphine ($n=7$). (– – –), Controls (saline) ($n=9$). ↓ Injections (10 a.m.).

results suggested that the changed diurnal rhythms were directly controlled by the repeatedly imposed cycles of morphine treatment and abstinence. The drug did not seem to have brought about persistent changes by affecting ' biological clocks '.

The single dose of morphine (20 mg/kg) administered to the control group slightly reduced the total intake of food (Table 1), but the drug seemed to have a complex, biphasic time course of action (Stolerman, 1970). The food intake was higher than that after saline during the first 4 h (3·8 g as compared with 2·2 g, $P<0·05$), but a subsequent drop in eating more than compensated for the initial rise. Stimulant effects for 4 h after the injection were also obtained with water intake and spontaneous activity ($P<0·05$), but no clear depressant actions were apparent subsequently with these measures.

Experiment 2

The results for food and water intake were consistent with those of experiment 1: the tolerant rats ate and drank more than the non-tolerant controls during 6 h after injection, but less during the night, when the controls consumed most of their daily food and water (Fig. 3).

The time course of these stimulant effects is shown in more detail in Fig. 4, together with results for spontaneous activity taken from experiment 1. Control rats consumed very small amounts of food or water for 6 h following the usual daily saline injections, and also showed little spontaneous activity. For the first hour after injections of morphine, the tolerant rats consumed no more food than the controls (Fig. 4A) but clear increases were apparent during the second and third hours ($P<0·05$ and $P<0·001$ respectively). Subsequently there were no significant differences.

Figure 4B shows that the results for water intake were similar, but that the increased drinking began about 1 h later than the eating; the differences from controls were significant during the third, fourth and fifth hours after injection

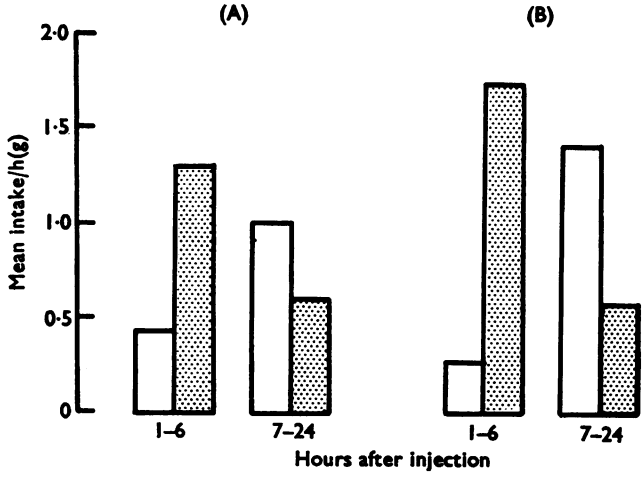

FIG. 3. Changed diurnal patterns of eating and drinking in rats tolerant to morphine. The reversal of the normal cycles confirms the results shown in Fig. 1. (A), Food intake; (B) water intake. (Shaded columns), tolerant (morphine (120 mg/kg) at 10 a.m. daily), $n=9$; (open columns), controls (saline daily), $n=7$.

($P<0{\cdot}01$ in all cases). The total amounts of food and water consumed in the 6 h after injection of morphine were measured again later in the experiment without disturbing the rats at hourly intervals, and similar results were obtained. Close correlations between food and water consumption have been reported previously in rats (Lepkovsky, Lyman, Fleming, Nagumo & Dimick, 1957; Cizek & Nocenti, 1965). Spontaneous activity, which was measured in different groups of rats (experiment 1), also showed a clearly defined time course after morphine (Fig. 4C), and was higher than that of controls during the second, third and fourth hours ($P<0{\cdot}01$ in all cases). For all three measures, the maximum stimulation occurred at about the same time, that is, 2–3 h after injection.

Following the substitution of saline for the morphine usually given at 10 a.m., the amounts of eating, drinking and activity did not increase, that is, there did not appear to be any effects 'conditioned' to the injection procedure.

Control rats, which had been deprived of food for 48 h, began eating in the new environment after a mean delay of 312 seconds. The tolerant rats, tested 1 h after the daily injection of morphine, started to eat after a mean delay of only 186 s, which was significantly shorter ($P<0{\cdot}05$). Although these rats had had free access to food until they were injected, they now appeared to be more hungry than the controls. Tatum *et al.* (1929) found that following injections of morphine, tolerant cats developed a 'voracious appetite' and an 'unusual desire to play in water'. A contributing factor may be that morphine reduced the inhibitory effects of novelty on eating.

Additional observations were made on the tolerant rats in their home cages after they had been injected with morphine. During the first hour they tended to remain immobile and showed a form of muscular stiffness, previously described as 'lead-pipe rigidity' (Janssen, 1964). However, when prodded they were able to walk and run very quickly, although with a 'curious gliding motion' (Joel & Ettinger, 1926). About 2–3 h after receiving the morphine, they began eating and drinking, but at

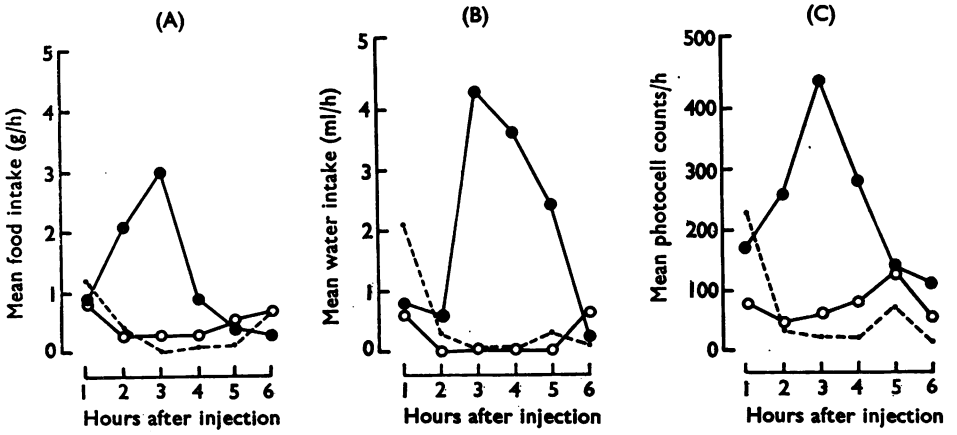

FIG. 4. Time courses of the increased eating, drinking and motor activity (photocell counts) in tolerant rats after injections of morphine (120 mg/kg i.p.). Very similar effects can be seen with all three forms of behaviour. Substituting saline for the morphine did not bring about 'conditioned' increases in these forms of behaviour. (A), Eating; (B), drinking; (C), activity. (●——●), Tolerant, tested after morphine given at 10 a.m. (○——○), Tolerant, saline substituted for morphine at 10 a.m. (– – –), Controls (saline).

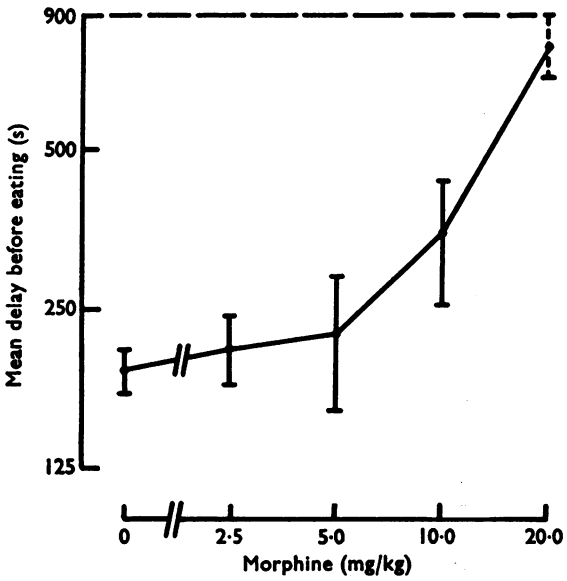

FIG. 5. Increased delays before non-tolerant rats injected with morphine begin to eat in a new environment. All injections were intraperitoneal 1 h before testing ($n=8$ at each dose). The vertical bars show one standard error on each side of the mean.

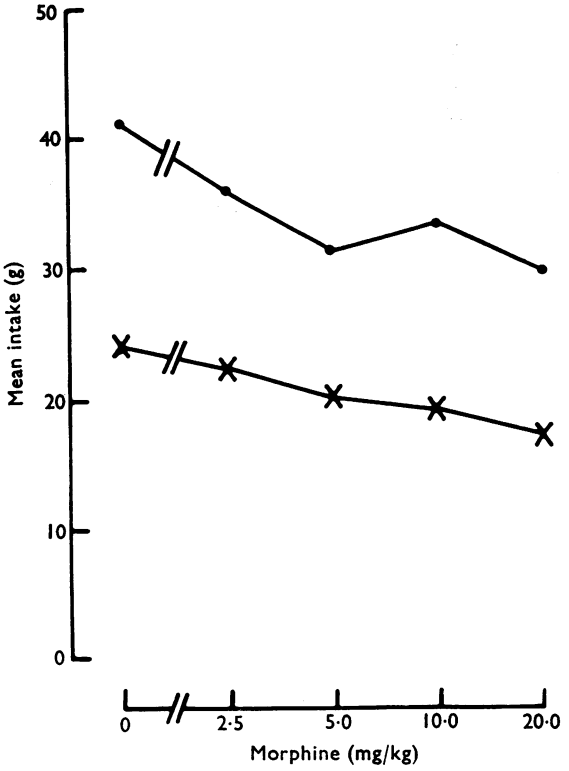

FIG. 6. Reduced eating and drinking during a 24 h test beginning 1 h after non-tolerant rats were injected with morphine intraperitoneally ($n=8$ at each dose). None of the doses used had detectable stimulant effects, which is consistent with the measurements of delays before eating in a new environment. (•——•), Water ; (×——×), food.

times were seen just holding pellets of food in their mouths without chewing. They also seemed to be hyperexcitable and ravenously hungry ; they continued eating or drinking while being handled, and grabbed any food pellets which came within their reach. This seemed a most striking phenomenon.

Experiment 3

Experiment 3 was a study of the effects of morphine on appetite in non-tolerant control rats, and was a test for any possible direct stimulant effects of the drug. Figure 5 shows that the larger the dose of morphine, the longer the delay before the rats began to eat in the new environment ($P<0{\cdot}01$). None of the doses used shortened the delay and the largest dose (20 mg/kg) largely inhibited spontaneous motor activity ; seven of the eight rats receiving that dose failed to eat before the arbitrary 'cut-off' after 15 min, and all very clearly showed the characteristic muscular rigidity produced by morphine in rats. It may be noted that the saline control rats started to eat sooner than those in the previous experiment ; this may be because the rats in experiment 2 were older (Bolles, 1965) and had been repeatedly handled and injected with saline. Figure 6 shows that morphine also reduced eating and drinking during the following 24 h ($P<0{\cdot}001$ and $P<0{\cdot}05$, for food and water intake respectively). There were no stimulant effects during any of the component intervals. These findings may be contrasted with those of experiment 1, where a dose of 20 mg/kg seemed to have transient stimulant actions in undeprived rats. Withholding food for 24 h before the tests in experiment 3 may have masked such effects.

Discussion

The regime of large doses of morphine given at 10 a.m. each day disturbed, and to some extent even reversed, the characteristic diurnal patterns of the rats' behaviour. Shortly after being injected with morphine they began to eat, drink and be active, and this lasted for 6–8 hours. In the periods of abstinence before the daily injections, these forms of behaviour were reduced, which supports earlier observations (Martin *et al.*, 1963 ; Wikler *et al.*, 1963). The results are also consistent with findings on altered patterns of sleep and wakefulness in rats (Khazan *et al.*, 1967), but do not support the view (Seevers & Deneau, 1968) that withdrawal of morphine results in the 'unmasking' of some longer lasting stimulant effects, at least in the cases of eating, drinking or motor activity. It might be possible to obtain different results by using other doses, antagonists or longer periods of abstinence (Martin *et al.*, 1963 ; Weeks & Collins, 1968).

The reduced eating and drinking during the nightly phase of withdrawal can be regarded as major factors contributing to the losses in weight recorded here and previously (Martin *et al.*, 1963 ; Akera & Brody, 1968 ; Neal, 1968 ; Stolerman & Kumar, 1970). Increases in urination and defaecation also occurred. It is not clear whether the tolerant rats ate and drank more after the morphine injections merely to compensate for the diminished overnight food and water intake, or whether the drug also had some direct stimulant effects. Other experiments in which a second dose of morphine was given 6 h after the first, failed to demonstrate unequivocal stimulant effects (unpublished observations). However, experiment 2 showed that tolerant rats receiving a dose of morphine can be hungrier than controls deprived of all food for 48 h ; mere recovery from approximately 17 h of morphine abstinence

does not seem sufficient to account for this. It also seems unlikely that the increased activity found in experiment 1 occurred simply in compensation for the low overnight levels, but in part this might reflect movements related to eating and drinking. It has also been reported that repeated doses of morphine can produce 'stereotyped' or repetitive behaviour (Joel & Ettinger, 1926; Fog, 1970), and the photocells might have picked this up (Krsiak *et al.*, 1970).

A related question concerns the nature of the stimulant effects of morphine in non-tolerant rats. For example, in experiment 1 we found transient increases in eating, drinking and motor activity after 20 mg/kg, but we were unable to replicate these in experiment 3. Earlier workers have also reported stimulation several hours after similar doses of morphine (Joel & Ettinger, 1926; Sloan, Brooks, Eisenman & Martin, 1962) and more recently, very small doses (1–2 mg/kg) have been shown to stimulate some forms of motor activity (Fog, 1970; Katz & Steinberg, 1970) and learned behaviour rewarded with food (Thompson, Trombley, Luke & Lott, 1970). In non-tolerant animals of other species, it is well known that opioids can act as stimulants; for example, by inducing 'running fits' in mice (Sharkawi & Goldstein, 1969). However, in tolerant rats the almost simultaneous stimulation of eating, drinking and motor activity is very striking, and analogous results have been reported with learned behaviour in monkeys and cats (Thompson & Schuster, 1964; Djahanguiri, Richelle & Fontaine, 1966). These observations are difficult to reconcile with the view that morphine depresses all biological needs and drives (Wikler, 1953; Jaffe, 1970 p. 278). It seems that the repeated association of morphine with the restoration of normal behaviour may intensify the value of the drug as a reward.

An analogy can be drawn between the properties of morphine in tolerant subjects and the effects of electrical stimulation of some 'reward' areas of the brain (Collier, 1969); it has recently been shown that morphine given systemically results in 'seizure' activity in the hypothalamus of rats and monkeys (Eidelberg, personal communication). Both morphine and hypothalamic stimulation can increase eating and drinking and both may serve as powerful rewards for maintaining learned behaviour (Weeks, 1962; Deneau, Yanagita & Seevers, 1969; Nichols, 1968; Hoebel, 1969; Mogenson, 1969; Stolerman & Kumar, 1970). However, there may be differences in the patterns of responding for these two sorts of reward and there seem to be factors which limit the intake of morphine. Nevertheless, these results are consistent with the possibility that morphine might affect hypothalamic 'reward' mechanisms and that these may be involved in the development of dependence.

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