

ENVIRONMENT IS NOT THE MOST IMPORTANT
VARIABLE IN DETERMINING ORAL MORPHINE
CONSUMPTION IN WISTAR RATS¹

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Summary.—The role of differential housing on sucrose-morphine consumption in outbred Wistar rats was investigated in two studies. The results of earlier research, indicating rats housed in a quasinatural colony drank significantly less sucrose-morphine than rats isolated in standard laboratory cages, could not be replicated, as the consumption of sucrose-morphine by the isolated animals in the present two studies was reduced. It is possible that during a colony conversion the supplier inadvertently introduced strain differences making the present rats more resistant to xenobiotic consumption. Discussion documents the role of genetics in morphine consumption.

It has been repeatedly demonstrated that rats rapidly learn to self-administer opiates orally in large quantities, often in preference to water when given a choice (Bardo & Gunion, 1982; Khavari, Peters, Baity, & Wilson, 1975; Khavari & Risner, 1972; Risner & Khavari, 1973; Wikler, Martin, Pescor, & Eades, 1963; Wikler & Pescor, 1967; Wikler, Pescor, Miller, & Norrell, 1971). These findings are often taken to suggest that mammals in general have a natural affinity for opiates (Goldstein, 1972, 1976). However, one feature the above studies have in common is that the animals used were all housed singly in standard laboratory cages during their exposure to the opiates. Lore and Flannelly (1977) indicated that rats have highly complex social interactions, are curious, wide ranging, and well adapted to group living. These social attributes are therefore greatly curtailed in an isolated existence, and, contrary to Goldstein's (1972, 1976) hypothesis about natural affinity, it is very possible that this social deprivation may account for the amount of opiate consumption in isolated animals.

A series of studies by Alexander and coworkers (Alexander, Beyerstein, Hadaway, & Coombs, 1981; Alexander, Coombs, & Hadaway, 1978; Hadaway, Alexander, Coombs, & Beyerstein, 1979), using outbred rats purchased from Charles River Canada, Inc., found that rats housed singly at the time of intake testing drank significantly more morphine solution than did animals housed in a quasinatural colony. This phenomenon was found in animals that had been pretreated with unsweetened morphine (Alexander, *et al.*, 1978) and in naive rats that were exposed to progressively more palat-

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able sucrose-morphine solutions (Alexander, *et al.*, 1981; Hadaway, *et al.*, 1979). These three studies therefore suggest that the consumption of opiates by animals in conditions of self-administration may be strongly facilitated by the typical isolated housing conditions present during intake testing.

A problem with the studies on the effects of housing was the unreliability of the apparatus used to measure individual drinking in rat colonies (Coombs, Alexander, Davis, Hadaway, & Tressel, 1980). During the Alexander, *et al.* (1981) study a persistent electronic malfunction caused the loss of eight days of data. Hence, only three-quarters of the potential data could be analyzed. In the present experiments, therefore, a computer-controlled system was used to collect data on the drinking of individual animals in the colony (Petrie, Gabert, Toms, Tressel, Alexander, & Beyerstein, 1985).

The first study reported here was designed to examine the computerized system's capability for data collection by comparing morphine consumption of rats in the colony versus that of isolated animals. These rats had no prior exposure to morphine, and all the animals were given the choice between water and progressively more palatable sucrose-morphine solutions.

EXPERIMENT 1

Method

Subjects.—There were 10 male and 10 female Wistar rats of Charles River Canada, Inc. origin, in both the isolated and colony groups. The animals were raised from weaning (21 days of age) in their respective environments, and were 113 days of age when the experiment started.

Apparatus.—Isolated rats were housed from weaning in standard rat cages (18 × 25 × 18 cm) with sheet metal walls that prevented visual contact with adjacent animals. To collect wastes, paper was placed on trays under the cages. These rats received fluids through stainless steel drinking tubes from plastic bottles (Girton, Millville, PA) fastened on the outside of each cage. Purina rat chow was provided *ad libitum* by means of inside feeders (11 × 13 × 5.5 cm). Bottles attached to two empty control cages allowed for the calculation of spillage and evaporation that might occur in a 24-hr. period.

Colony rats lived together from weaning in an open-topped wooden box with a floor area of 8.8 m². The box contained a layer of kiln-dried cedar shavings (Hyon Bedding) and two large open-topped metal cages (40 × 25 × 18 cm) from which two feeders (24 × 12.5 × 5 cm) containing Purina rat chow were hung. The animals had continuous access to a common drinking source. To drink, each animal climbed a pole (41 cm long; 4 cm circumference) triggering a videotaped recording of that rat's identifying hair dye mark (L'Oreal Excellence—Napoli Black, Cosmair Canada, Inc.) and drank from one of two nipples (Edstrom Industries, Inc. A115 Adjustable Flow

Valve No. 10443). The computer-controlled system noted the weight of each of two fluids consumed (resolution of 0.1 gram) for each visit to the site by a rat. The time and duration of the visit were also recorded. Rats learned to operate the system within three days of its introduction to the colony. This drinking system is described fully elsewhere (Petrie, *et al.*, 1985).

The white fluorescent lighting in both environments was on a 12-hr. light-dark cycle controlled by a single timer (Tork Time Switch Model 7102). Red lights (Sylvania 25- and 60-watt bulbs) were on in both environments at all times.

Procedure.—The animals were placed in individual cages or the colony at 21 days of age. At 86 days of age the colony rats were dye-marked for identification and at 99 days of age the control animals had a second bottle of fluid attached to their cages. Intake testing began at 113 days of age, and all rats were weighed at 114 days of age. Intake testing concluded when the animals were 142 days of age and all rats were weighed again and killed at 143 days of age.

During intake testing all animals were given 24-hour access to tapwater and the alternative experimental fluid. The seven phases of testing were each four days in length, and unlike experiments with the older apparatus, no data were lost due to malfunctioning equipment.

In the first and seventh phases, access to tapwater and to a 10% sucrose solution was provided to assess whether housing conditions had any effect on consumption of sucrose.

The second phase compared the intake of tapwater to that of a solution of 10% sucrose with 0.05 mg/ml quinine sulfate, to check for the effects of housing on preference for bitter-sweet solutions. To the human palate, this sucrose-quinine solution tasted the same as the sucrose-morphine solution used in the 0.25 morphine hydrochloride phase.

Phases 3 through 6 entailed continuous access to water and to progressively decreasing concentrations of morphine hydrochloride (MHCl) in 10% sucrose. Phase 3 included 1.0 mg MHCl/ml 10% sucrose. Phase 4 consisted of 0.5 mg MHCl/ml 10% sucrose. Phase 5 involved 0.25 mg MHCl/ml 10% sucrose. Phase 6 comprised 0.125 mg MHCl/ml 10% sucrose (see Table 1).

Left-right positions of water and the experimental fluid were reversed every two days in both environments.

Results

Two-way repeated-measures analyses of variance corrected for multiple comparisons were carried out separately for each phase on the proportion of experimental fluid to total fluid consumed; on milligrams of experimental substance ingested per kilogram of body weight; on grams of experimental fluid consumed; and on total fluid consumption (grams). Significant interac-

TABLE 1
ORDER OF EXPERIMENTAL PHASES: IN EACH PHASE THE RATS OF BOTH GROUPS
HAD A CHOICE BETWEEN TAP WATER AND THE SOLUTION DESCRIBED

Phase	Experimental Fluid	Days
1. Pretest	Water + 10% sucrose	4
2. QSO ₄	0.05 mg QSO ₄ /ml water + 10% sucrose	4
3. 1.0 mg MHCl	1.00 mg MHCl/ml water + 10% sucrose	4
4. 0.5 mg MHCl	0.50 mg MHCl/ml water + 10% sucrose	4
5. 0.25 mg MHCl	0.25 mg MHCl/ml water + 10% sucrose	4
6. 0.125 mg MHCl	0.125 mg MHCl/ml water + 10% sucrose	4
7. Posttest	Water + 10% sucrose	4

tions were analyzed using a Newman-Keuls *a posteriori* comparison (Ferguson, 1971).

The colony animals consumed significantly more experimental fluid in proportion to water drunk than did the isolated animals in Phases 2 ($F_{1,34} = 32.6$, $p < .05$), 3 ($F_{1,34} = 55.2$, $p < .05$), and 7 ($F_{1,33} = 11.7$, $p < .05$). In Phase 4 female rats consumed significantly more experimental fluid in proportion to water drunk than did the males ($F_{1,33} = 4.5$, $p < .05$).

Female rats consumed significantly more mg/kg of experimental fluid than did the male rats in Phases 1 ($F_{1,34} = 15.8$, $p < .05$), 3 ($F_{1,34} = 6.1$, $p < .05$), 4 ($F_{1,33} = 12.1$, $p < .05$), 5 ($F_{1,33} = 4.7$, $p < .05$), 6 ($F_{1,33} = 5.7$, $p < .05$), and 7 ($F_{1,33} = 14.5$, $p < .05$). Colony animals drank significantly more mg/kg of experimental fluid than did the isolated animals in Phase 3. Also in Phase 3, females in the colony drank significantly more mg/kg of experimental fluid than isolated males ($df = 34$, $p < .05$), isolated females ($df = 34$, $p < .05$), and colony males ($df = 34$, $p < .05$). Colony males drank significantly more mg/kg of the experimental fluid than did isolated males ($df = 34$, $p < .05$) and isolated females ($df = 34$, $p < .05$).

Animals in the colony consumed significantly more of the experimental fluid in Phase 2 ($F_{1,34} = 18.8$, $p < .05$) and 3 ($F_{1,34} = 80.98$, $p < .05$), while females consumed significantly more of the experimental fluid than did males in Phase 4 ($F_{1,33} = 8.4$, $p < .05$). An interaction of housing \times gender showed colony females drinking significantly more of the experimental fluid than colony males in Phases 1 ($df = 34$, $p < .05$) and 7 ($df = 33$, $p < .05$). During Phase 7 the isolated males drank significantly more of the experimental solution than did the colony males ($df = 33$, $p < .05$).

Colony-housed animals drank significantly more total fluid than did the isolated animals in Phases 2 ($F_{1,34} = 6.3$, $p < .05$), 3 ($F_{1,34} = 11.4$, $p < .05$), and 4 ($F_{1,33} = 17.5$, $p < .05$). Interactions of housing \times gender showed that colony females drank significantly more total fluid than colony males ($df = 34$, $p < .05$) in Phase 1, while in Phase 3 colony females drank significantly more total fluid than did isolated females ($df = 34$, $p < .05$) and isolated males ($df = 34$,

$p < .05$). Colony males in Phase 3 drank significantly more total fluid than did isolated females ($df=34$, $p < .05$). In Phase 4, colony females consumed significantly more total fluid than did isolated females ($df=33$, $p < .05$), isolated males ($df=33$, $p < .05$), and colony males ($df=33$, $p < .05$). Colony males in Phase 4 consumed significantly more total fluid than did isolated females ($df=33$, $p < .05$). In Phase 7, isolated males drank significantly more total fluid than did colony males ($df=33$, $p < .05$). Colony females drank significantly more total fluid than did colony males ($df=33$, $p < .05$); see Table 2.

TABLE 2
AVERAGE NUMBER OF GRAMS OF FLUID CONSUMED DAILY: FIRST SUCROSE-MORPHINE STUDY

Phase	Isolated Animal Summary		Colony Animal Summary	
	Water	Experimental Fluid	Water	Experimental Fluid
1. Pretest	2.5	103.2	1.3	108.3
2. QS0 ₄	26.3	33.4	5.5	75.0
3. 1.0 mg MHCl	39.5	0.0	58.8	3.6
4. 0.5 mg MHCl	44.5	0.5	74.6	1.3
5. 0.25 mg MHCl	33.9	15.7	49.5	18.3
6. 0.125 mg MHCl	23.2	30.2	19.6	42.8
7. Posttest	8.8	81.4	0.7	79.6

Note.—Pre- and posttest experimental fluids were 10% sucrose. All other experimental fluids were quinine sulfate or morphine hydrochloride in 10% sucrose solution.

Discussion

The results of this study do not replicate some of the earlier research on housing and morphine consumption. Females drank significantly more of the experimental fluids (mg/kg) in all of the four sucrose-morphine phases. This is consistent with Hadaway, *et al.*'s (1979) observation that females generally drank more morphine solution than did males.

The major finding of the earlier research on housing that rats housed in the colony at the time of testing drank significantly less morphine than did the isolated rats was not confirmed. In fact, during the 1.0-mg MHCl/ml 10%-sucrose phase, the colony rats in the present study drank significantly more than did the isolated animals on all four measures, although the magnitude of the differences was small. There were no significant differences in morphine consumption between the colony and caged animals in either the 0.5-mg, 0.25-mg, or 0.125-mg MHCl/ml 10%-sucrose phases.

The possibility exists that either the results of this study or the three studies conducted with the older technology could be artifacts of the measurement procedure. Therefore, the second study reported was designed without any kind of automated equipment to measure the fluid intake of the

colony animals. Although this way of measuring fluid intake precluded the gathering of any individual fluid-consumption patterns in the colony rats, the amount of fluid taken from colony reservoirs could be weighed and compared to the amount of fluid being removed from the control cages during the same time interval.

EXPERIMENT 2

Method

Subjects.—There were 10 male and 10 female Wistar rats of Charles River Canada, Inc. origin, in both the isolated and colony groups. The animals were raised from weaning (21 days of age) in their respective environments and were 113 days of age when the experiment started.

Apparatus.—Except for the automated drinking system, the apparatus used in both the isolated and colony conditions was identical to that used in the previous study. In the colony condition the animals had continuous access to a common drinking source. The 41-cm pole present in the first study was removed and the automated drinking system disabled. At the base of the wall on which the drinking system was hung, two holes were drilled and two nipples (Edstrom Industries, Inc. AL 113 Adjustable Flow Valve-No. 10441) were positioned in these holes. From each nipple ran a one metre length of plastic tubing (Tygon R-3603) into a one-gallon plastic reservoir situated on a 60-cm high stool. Each reservoir was filled with the assigned fluid and weighed daily. Beside each reservoir there was another identical container filled with the same fluid, with an identical length of hosing leading down to a similar nipple at the end. The nipple for this container was placed against the outside wall of the open-topped wooden box and was not touched by the rats. These containers served as control reservoirs and allowed for the calculation of any evaporation that might occur in a 24-hr. period.

Procedure.—Except for the automated drinking system, the experimental protocol followed was identical to the procedure in the previous study.

Results

Although there could be no inferential analysis of the colony group's data since there was no way of identifying individual animals' fluid consumption, the averages obtained indicate that the colony animals outdrank the isolated animals during the 1.0-mg sucrose-morphine phase ($M=4.3$ gm., $M=0.3$ gm. per day); whereas the isolated animals outdrank the colony animals during the 0.5-mg sucrose-morphine phase ($M=9.4$ gm., $M=3.0$ gm. per day); the 0.25-mg sucrose-morphine phase ($M=17.4$ gm., $M=10.9$ gm. per day), and the 0.125-mg sucrose-morphine phase ($M=44.4$ gm., $M=33.1$ gm. per day); see Table 3.

The differences between the two groups in this study were never as

TABLE 3
AVERAGE NUMBER OF GRAMS OF FLUID CONSUMED DAILY: SECOND SUCROSE-MORPHINE STUDY

Phase	Isolated Animal Summary		Colony Animal Summary	
	Water	Experimental Fluid	Water	Experimental Fluid
1. Pretest	0.9	116.2	4.2	104.5
2. QSO ₄	25.9	26.3	56.3	10.4
3. 1.0 mg MHCl	33.9	0.3	54.5	4.3
4. 0.5 mg MHCl	30.9	9.4	60.8	3.0
5. 0.25 mg MHCl	23.7	17.4	66.6	10.9
6. 0.125 mg MHCl	11.9	44.4	41.1	33.1
7. Posttest	5.2	104.2	4.3	94.9

Note.—Pre- and posttest experimental fluids were 10% sucrose. All other experimental fluids were quinine sulfate or morphine hydrochloride in 10% sucrose solution.

large as the differences observed in the eight male and eight female rats that were maintained in their original environments in the Alexander, *et al.* (1981) study. The continuously isolated animals in that study drank up to seven times as much sucrose-morphine as the rats that lived in the colony from weaning to the end of the study.

Discussion

The results of this study are consistent with those obtained in the first study using the automated system to monitor colony drinking. Therefore, the results of the two studies reported indicate that the results of the earlier housing research were not replicated.

GENERAL DISCUSSION

Alexander, *et al.* (1981) found that rats allowed to pursue a quasynatural existence consume much less morphine than do isolated animals, even if that morphine is contained in a 10%-sucrose vehicle, a solution that rats drink in large quantities when it is free of morphine regardless of their housing condition. Both experiments reported here did not replicate the results of Alexander, *et al.* (1981). The second study indicated that the cause of the nonreplication in the first study could not be ascribed to automated equipment.

It is apparent that the difference between the two experiments reported here and the Alexander, *et al.* (1981) study is in the response of the isolated animals. The isolated animals in the two present experiments drank much less sucrose-morphine solution than did the isolated rats in the Alexander, *et al.* (1981) study, whereas there was no appreciable difference in the sucrose-morphine consumption of the colony Wistar rats in all three studies.

These differences in sucrose-morphine consumption are all the more striking when it is realized that the Wistar rats used in the Alexander, *et al.*

(1981) study drank *less* sucrose, as measured in Phases 1 and 7, than did the Wistars used in the two present studies. Clearly the isolated animals in the two studies reported here were avoiding the consumption of morphine.

This finding leads to the issue of differences between rat strains in psychopharmacological research. The possibility exists that the Wistar rats used in the two studies reported here differed from the Wistar rats used in the Alexander, *et al.* (1981) study. The Alexander, *et al.* study that the research reported here was designed to replicate was published in 1981. However, the research for that publication was done from April to July in 1979. In November 1979, the animal supplier changed outbred Wistar rat colonies. Therefore the Wistars used in the Alexander, *et al.* (1981) study were Old Colony Wistars, while the rats used in the present research were New Colony Wistars.

The reasons for the changing of the colonies included health, housing, and breeding. A number of viruses that compromised long-term studies were eradicated; the quality of the animal housing was improved while breeding ratio and productivity were increased (J. Goyer, Managing Director, Charles River Canada, Inc., St. Constant, Ont., personal communication, May, 1985).

It is well known that there are strain differences in responsivity to drugs in both mice and rats (Bardo & Gunion, 1982; Collins & Whitney, 1978; Horowitz, Whitney, Smith, & Stephan, 1977; Oliverio, Castellano, Racagni, Spano, Trabucchi, & Cattabeni, 1978; Shearer, Creel, & Wilson, 1973). It is quite possible that, if a genetic alteration were inadvertently introduced when the animal supplier changed from Old Colony to New Colony animals, this genetic shift could be manifest in New Colony animals that responded differently to psychoactive substances than did Old Colony animals.

Experimental evidence suggests that the Old and New Colony Wistars respond differently to equivalent levels of psychoactive substances. Ton, Blair, Holmes, and Amit (1983) compared the effects of chronic naltrexone injection on amphetamine locomotor activity on individually housed Old and New Colony male rats. Rats were tested for locomotor activity in the open field with or without white noise. During the testing period the New Colony animals showed a significant attenuation in amphetamine locomotor activity in the absence of noise only. In contrast, chronic naltrexone significantly decreased amphetamine activity in Old Colony animals only under noise conditions. Ton, *et al.* (1983) thought that the differential effects may reflect predispositional differences across animal populations in the modulation of dopamine function by opioid peptides via opiate receptors.

Another difference between Old and New Colony Wistars includes levels of voluntary alcohol ingestion, with consumption by New Colony Wistars being greatly attenuated when compared to intake of Old Colony rats (F. J.

Boland, Queen's University, Kingston, Ont.; C. Pang, Department of Pharmacology, University of British Columbia, Vancouver, BC; personal communications, May, 1985). Nichols and Hsiao (1967) indicated that preference for oral morphine and alcohol intake has a genetic basis.

Therefore, the fact that Ton, *et al.* (1983) found differences in response to equivalent levels of psychoactive substances between the two colonies and that Boland and Pang (personal communications) indicated differences in voluntary drug consumption between Old and New Colony Wistars, suggest the possibility that the New Colony rats are genetically different from the Old Colony animals.

Even considering the limitations of the Alexander, *et al.* (1981) study and the nonreplication of those results by the two present studies, the data in all three studies are a strong disconfirmation of Goldstein's "natural affinity" hypothesis (1972, 1976). When given the opportunity for unlimited ingestion of an opioid made palatable by the addition of sucrose, rats did not consume more morphine as the study progressed, as Goldstein's hypothesis would suggest. Rather, these animals continued to consume approximately the same amount of absolute morphine and only increased their consumption of the sucrose-morphine solution when the morphine content decreased, suggesting that they were consuming the solution not because of its morphine content, but for its sucrose content. Indeed, it is more likely that the animals had an affinity for sucrose rather than morphine!

In conclusion, the results of earlier studies (Alexander, *et al.*, 1981; Alexander, *et al.*, 1978; Carroll & Meisch, 1979; Hadaway, *et al.*, 1979; Khavari, *et al.*, 1975; Khavari & Risner, 1972; Risner & Khavari, 1973; Wikler, *et al.*, 1963; Wikler & Pescor, 1967; Wikler, *et al.*, 1971) which, taken together, suggest that in the appropriate housing conditions, rats will self-administer opiates in large quantities, appear now to be confounded by a factor or factors that must be more fully explored. These factors are most likely genetic in nature and are most probably the reason for the variation in the results obtained in the oral sucrose-morphine consumption of the Old and New Colony Wistars.

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