

**BLOCKADE OF ORAL MORPHINE CONSUMPTION
IN THE MALE ALBINO RAT BY HYPOPHYSECTOMY**

David Ziskind

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David Ziskind

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ALBINO RAT BY HYPOPHYSECTOMY

ABSTRACT

Because previous studies had shown that lesions of the lateral hypothalamus inhibit the oral intake of a morphine solution and because the hypothalamic areas are intimately related anatomically and functionally to pituitary function, it seemed reasonable to expect to find evidence of pituitary involvement in the control of oral morphine intake. Hypophysectomized animals refused a morphine solution in a forced-choice situation. An isoaversive quinine solution was ingested, indicating that taste factors alone did not control the behavior. Barbiturate consumption was unaffected, while the results with alcohol were intermediate between the effects on morphine and barbiturate consumption. Animals which were tested three months after hypophysectomy showed some recovery of morphine drinking. Evidence is presented that the morphine dosage delivered in this study is pharmacologically effective and that the blockade of intake may be mediated by central effects of the morphine. Possible physiological modes of control of morphine intake behavior are discussed.

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INTRODUCTION

Previous studies have implicated specific central nervous system structures as being involved in appetitive (Anand and Brobeck, 1951; Devor, Wise, Milgram, and Hoebel, 1970) and drug directed behaviors (Stern and Amit, 1972). These are discussed in relation to the experimental design of using an oral intake route of drug self-administration and in terms of a possible theoretical framework which may account for the observed blockade of morphine consumption.

Different methods of drug self-administration in small animals have been developed. Goldstein and Judson (1971) have housed mice in sealed containers to which a controlled atmosphere containing ethanol vapor was introduced. While this technique is not strictly a voluntary intake paradigm, more volitional techniques are available.

The presentation of drug solutions in drinking tubes has been used with rats to deliver ethanol (e.g. Amit and Stern, 1971; Masserman and Yum, 1946; Richter, 1940; Wayner, Greenberg, Tartaglione, Nolley, Fraley and Cott, 1972), morphine (Risner and Khavari, 1973; Stolerman and Kumar, 1972; Trafton and Kahn, 1974; Wikler and Masserman, 1943), hashish resin (Corcoran and Amit, 1974), diazepam (Amit and Cohen, 1974), and other unrelated drugs.

Beach (1957) manually injected rats with morphine upon entrance to the proper arm of a Y-maze.

An intra-gastric fistula designed to deliver a solution directly to the stomach and activated by a bar press, was used

by Amit and Stern (1969) and by Epstein and Teitelbaum (1962) to deliver ethanol and even varying food concentrations to the albino rat.

Weeks (1962), Wilson and Schuster (1973), Yokel and Wise (1975), and others have employed an intravenous catheter attached to a bar-press actuated pump for the delivery of amphetamine, morphine, cocaine and other drugs.

Khavari and Risner (1973) have added morphine to the food presented to their rats in order to produce intake of the drug.

There are also a number of techniques available for initiating and maintaining drug intake behavior. The technique of presenting the animal with a "forced choice" of not drinking at all or of drinking a drug solution in tap water (Kamano and Arp, 1964) or in a solution made more palatable by the addition of sucrose (Wikler and Pescor, 1967) saccharin (Risner and Khavari, 1973) or milk (Masserman and Yum, 1946) has been widely used.

To facilitate drinking Veale and Myers (1969) and Amit, Stern, and Wise (1970) have used gradually increasing concentrations of drug solutions to "acclimate" the animals. A schedule of alternate day presentation of ethanol was found to increase intake by Amit, Stern, and Wise (1970), Wise (1973), and by Wayner and Fraley (1972).

In 1970, Amit reported that electrical stimulation of the lateral hypothalamus increased ethanol ingestion in male albino rats. Amit subsequently reported that the technique

of stimulating the lateral hypothalamus daily (for 30 days) and presenting a free-choice between water and ethanol on alternate days, resulted in animals which developed a permanent preference for ethanol over water at a concentration above that which they had previously rejected.

Masserman and Yum (1946) reported the temporary induction of drinking of ethanol in a milk solution by cats placed in a conflict situation. A bar-press effected delivery of a choice between milk or a milk-ethanol solution plus an aversive air blast. This technique yielded ethanol intake during the period in which the air blast contingency was in effect, which shifted back to a preference for the pure milk when the air blast was discontinued.

In 1961, Falk reported the phenomenon of "schedule induced polydipsia." Rats placed on a schedule of intermittent food reinforcement and provided with water ad libitum in the experimental chamber were found to consume very large quantities of water. If a drug solution is substituted for water in this procedure, enhanced drug intake may be obtained, but the results have been reported to be temporary (Lester, 1961; Senter and Sinclair, 1967).

An oral, "forced-choice" mode of drug self-administration was employed in this study. There are several disadvantages to this technique, both procedural and theoretical. Most drugs investigated are aversive in taste beyond all but the lowest concentrations. Thus, a basis must be established for deciding that the pharmacological effect of the drug,

and not its taste, is the relevant variable controlling intake. It is possible to employ very dilute drug solutions in testing, but the problem then arises that the animal must ingest very large quantities of liquid in order to obtain a "pharmacologically active" dose of the drug. In addition to drug concentration, it is also necessary to consider the time course of drinking in order to evaluate the quantity of drug present in the system at any time. It is important to note in this respect that George and Way (1959) have reported behavioral effects with intra-peritoneal (i.p.) doses of morphine in normal rats as low as 0.1 mg/kg, of body weight. While the rate of absorption and speed of onset of drug effect varies with oral, intra-peritoneal, intravenous or subcutaneous routes of administration, it may be reasonably postulated that a .02% morphine solution (0.2 mg/ml or 2.0 mg/10 ml) may produce a pharmacological, rather than merely a taste or gustatory, effect. March and Elliott (1954) report that the elimination of morphine from the rat after injection requires up to 48 hours to be complete.

The rate of absorption of a drug via the oral route is also an important factor in terms of the delay of reinforcement resulting from drug ingestion. It thus becomes difficult to account for an animal's ingestion behavior or lack of this behavior in operant terms if a requirement of close temporal contiguity is demanded. It has been shown, however, that very long delays between CS and UCS may still result in learning in rats when the alimentary system is

involved (cf. Garcia and Koelling, 1966; Kalat and Rozin, 1970; Rozin and Kalat, 1971; Seligman, 1970).

A number of studies have indicated that selective destruction of the lateral hypothalamus will produce aphagia and adipsia, to varying degrees (e.g. Montemurro and Stevenson, 1957; Teitelbaum and Epstein, 1962). Destruction of the ventromedial hypothalamus, while producing hyperphagia, has also been reported (Corbit, 1965; Schachter, 1971) to produce an increased sensitivity to normally only mildly aversive adulterants in food. Investigations involving oral drug intake in combination with CNS manipulation or even peripheral manipulation may therefore suffer from contamination by spurious taste or motivational factors.

There are also a number of serious disadvantages involved in the use of the other available techniques of evaluating drug self-administration behavior in animals. Masserman and Jacques (1948) trained cats to respond to electric shocks and air blasts as feeding signals and to "self-administer" these stimuli in order to receive food. After the food reward was discontinued, however, the cats continued to administer the air blast to themselves and two cats continued to administer the electric shock. Since responding or the absence of responding for drug presentation is the indicator of its reward value in techniques which rely on instrumental conditioning, it is important to be able to state that the animal does in fact respond for reward, not punishment. In addition to the lack of clarity in

inferring reward from the observation of reinforcement, it has also been shown that the interacting effect of a drug in combination with a particular schedule of reinforcement will differentially affect responding. MacPhail (1971) has shown that amphetamine injections will increase the rate of responding during intervals when responding is normally low, while decreasing the rate of responding during periods when responding is normally high. In addition to the effect of the amphetamine, the particular value of fixed interval schedule which was employed exerted control over the rates of response.

One method of obtaining a direct measure of responding for a drug would entail the use of a continuous reinforcement (CRF) schedule of drug presentation. However, this procedure is rarely used with the intravenous catheter technique because of the effects of the drug itself on responding. Weeks and Collins (1968), for instance, presented 10 mg/kg of morphine intravenously after every 10 responses to animals which had already been subjected to extensive passive experience with morphine in order to develop tolerance. The presentation of a large amount of morphine after every response in a naive animal would soon have produced ataxia.

Various schedules of intermittent reinforcement produce characteristic temporal patterns of responding (Ferster and Skinner, 1957) and various drugs produce characteristic disruptions to these patterns of responding

(Schuster and Thompson, 1969). Thus the use of differing schedules of drug presentation may produce differing "schedule artifacts."

Another possible "artifact" arises from the demonstration that rats "titrate" their intake of morphine (Collins and Weeks, 1965; Weeks, 1962). As the dosage per administration is increased, responding per unit of time decreases. Pickens and Thompson (cited in Thompson and Schuster, 1969) have reported that responding for cocaine exhibits a pattern of equal inter-self-administration intervals. MacPhail (1971) has shown that responding on different schedules of reinforcement is differentially affected by various drugs. There is thus the possibility that interpretation of responding for a particular drug may be obscured by factors such as drug dosage and concentration, density of reinforcement, or schedule of reinforcement.

An issue of special importance with regard to studies involving the effects of organismic manipulation on subsequent affective response to drug injections is still unresolved. An increase in responding could indicate that each individual reinforcement is of smaller reward magnitude and that the animal is thus responding more in order to receive an increased reward. Alternatively, the same observation of an increase in responding for a drug could indicate that each reinforcing event is of greater reward magnitude and therefore more powerful in maintaining or increasing the behavior which preceded it. Various drugs

could act differentially in this respect. The issue of the effect of reward magnitude on responding is also important because of the possibility of a changing drug tolerance affecting reward magnitude and subsequent responding.

Thus, there are valid objections to the rigid interpretation of drug intake patterns evinced by all of the methods discussed. However, of the techniques available, the use of an oral mode of drug presentation suffers least in clarity of interpretation and freedom from artifact. The oral presentation technique does not involve any post-operative discomfort and does not raise the issue of possible analgesic effects of some drugs. The technique is fast and easy to use, and particularly appropriate in testing an experimental manipulation which seeks to block intake behavior. In a forced-choice design, the animal must drink the solution in question or not drink at all. Thus, the strength of the statement that a "blockade of intake" has been achieved is increased when this blockade of intake cannot be overcome by extreme dehydration. In a forced-choice, oral intake testing procedure such as the one used in the present study, increased "finickyness" can be tested for by offering the animals a quinine solution and by offering a variety of pharmacologically active ingredients. Total blockade of all intake, of course, indicates that the drug in question may not be the sufficient stimulus to suppress intake. Selective blockade of intake of certain drugs, however, is an indication that the experimental manipulation has affected

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a system which in some way functions to avoid further contact with the drug stimulus. The earlier cited work of Garcia and Koelling, and Rozin and Kalat has demonstrated that gustatory cues can associate to organismic states over periods of very long delay, adding further credence to the assumption that, even though slow-acting via the oral route, the ingestion of drug solution, if aversive, will result in a decrease in the intake behavior.

Humans normally self-administer morphine and its derivative, heroin, by the i.v. rather than oral route. However, it should be pointed out that this research is not directed toward control of drug use or toward the development of a rat analogue of human drug use. Since morphine produces reproducible and pronounced behavioral effects and is easily administered, it is a useful tool in investigating CNS changes as correlated with changes in behavior.

To borrow one illustration from the human research literature: Himmelsbach (1943) reported that regular heroin users will voluntarily undergo withdrawal in order to lower their tolerance to the drug and thereby lower their daily dosage to an affordable level. This report, besides being at odds with the prevailing conception of "drug addicts", also points to the significance of the positive reinforcing effects of the drug on the organism, as opposed to the organism's avoidance of aversive effects, as controlling drug intake behavior. Thus, the approach in this study has been to use morphine and CNS manipulations as a tool in

asking questions of the form, "What CNS structures or systems interact with a drug stimulus in such a way as to lead to the development of an acquired motivation? What is the site or physiological representation of this acquired motivation?"

The present study stems from the finding by Amit and Corcoran (1972) that lesions of the LH block oral morphine consumption and the later finding (by Amit, Corcoran, Amir, and Urca, 1973) that lesions of the ventral portion of the LH is sufficient for oral morphine intake blockade. Both Pozuelo and Kerr (1972) and Amit and Stern (1971) have suggested that drug self-administration is a consummatory and regulatory behavior, and therefore it is likely to be controlled to some degree by the hypothalamus. In addition, a large body of evidence indicates that the lateral hypothalamus is intimately involved in regulation of and interaction with the pituitary. As Turner and Bagnara (1971, p. 51) put it, "It is apparent that the whole pituitary gland is predominantly subservient to and has partially evolved from the hypothalamic portion of the brain".

It has been established that the hypothalamus and pituitary are interrelated by direct neuronal connection, neuronal chemical transport and storage, and hormonal communication by the hypophyseal portal system and through the general circulation both directly and via secondary hormonal effects from glands affected by the pituitary (cf. Briggs and

Munson, 1955; Everett, 1964; Kaplanski and Smelik, 1973; Meites, 1970; O'Conner, 1947; Raisman, 1970; Roth, Glick, Yalow, and Berson, 1963; and Zolovick and Labhsetwar, 1973).

The hypothalamus has been implicated in the mediation of both short and long term motivational effects (cf. Levison and Flynn, 1965; Schacter, 1971) and has been shown to be intimately related to pituitary function. Since manipulation of the hypothalamus has led to the observation of a circumscribed blockade of oral drug intake (Amit et al., 1973), it seemed both reasonable and worthwhile to investigate the effects of manipulations "downstream" (Green and Harris, 1947; Popa and Fielding, 1930; Wislocki and King, 1936) from the hypothalamus on oral drug intake behavior.

This study was designed to investigate the effect of pituitary ablation on oral morphine intake and to obtain a preliminary indication of the effect of this manipulation on the intake of other drug solutions.

METHOD

Subjects

The subjects were male Wistar rats obtained from Canadian Breeding Farms and Laboratories. At the beginning of the study they weighed from 175 to 225 grams. The animals were housed in stainless steel cages with standard lab chow and a 5% (w/v) solution of sucrose in tap water available ad libitum unless otherwise stated.

Hypophysectomy was performed by the breeder by the method for transauricular hypophysectomy described by Falconi and Rossi (1964), at a weight of 200-225 grams. The animals were delivered one day after hypophysectomy and allowed a week to recover from the acute effects of the procedure before further manipulation.

Solutions and Injections

All drinking solutions were mixed with tap water. Concentrations are expressed as percent by weight of solute in volume of solvent. One kilogram per liter = 100% w/v.

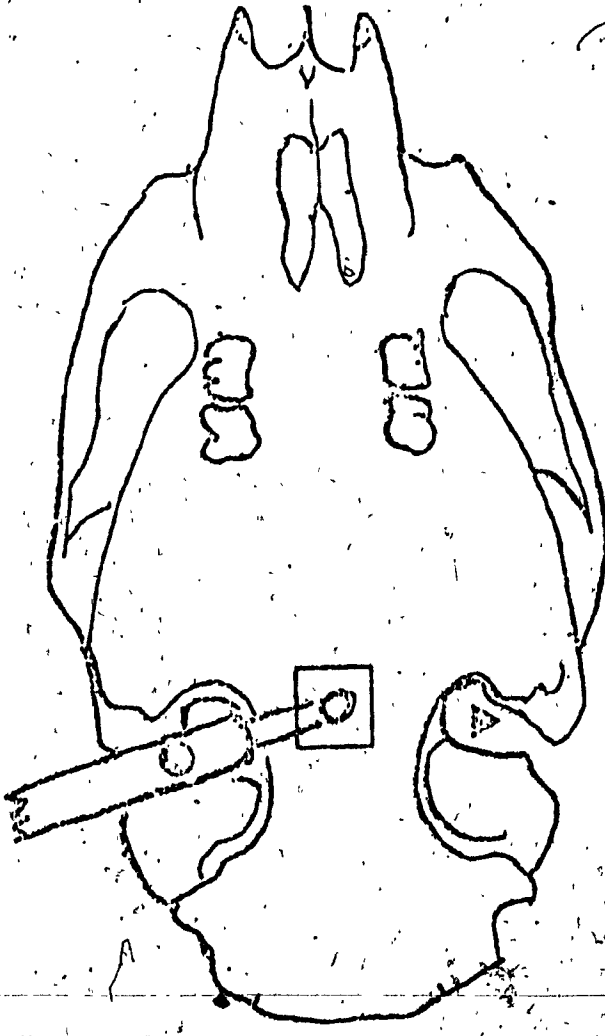
Ethanol solutions are expressed as volume of ethanol per volume of tap water percent.

Injection solutions of morphine hydrochloride were prepared with Ringer's solution.

Verification of Surgical Procedure

Those rats which were successfully hypophysectomized showed very retarded growth and an absence of the coarse, yellowish hair of a mature Wistar rat. Three groups of hypophysectomized animals (n=18) were killed. The adrenals

Figure 1. Schematic position of the pituitary in the rat. Note relationship to interaural line and external meatus. (Redrawn from de Groot, 1959, and from Falconi and Rossi, 1964).



were removed, dissected free of fat, and placed in physiological saline. They were then weighed within one hour of removal (Brain and Nowell, 1969).

A group of normal animals (n=4) which were received on the same date and were of the same age as the hypophysectomized animals was subjected to the same procedure and adrenal weights were compared.

Procedure

Before testing the effects of hypophysectomy on drinking of the various solutions, it was desirable to establish a morphine concentration that would not only be ingested in reasonable quantity by normal animals, but would also be "equiaversive" to a solution of quinine which would be ingested by normal animals. A pilot study indicated that a solution of .0125% quinine sulphate (w/v) and 5% sucrose (w/v) in tap water would be equally preferred to a solution of .02% morphine hydrochloride (w/v) and 5% sucrose in tap water. The sucrose was added to make both solutions more acceptable to the animals.

Twelve naive animals were presented with a free-choice between the above morphine and quinine solutions in standard type glass graduated Richter tubes for 14 consecutive days. Drinking tube positions were alternated daily to eliminate the effects of position preference.

Although the mean daily intake of the morphine-sucrose solution was 16.6 ml and the mean daily intake of the quinine-sucrose solution was only 6.3 ml, a t-test for

related samples indicated that there was no significant difference in preference for the solutions ($t=2.10$, $p .05$, two-tailed test).

All other determinations of fluid ingestion and acceptability were determined using a one-tube, forced-choice procedure in which the animal could drink the test solution or not drink at all. Each test group consisted of naive animals.

In all cases, the expression "mean daily intake" denotes the following procedure: The mean daily consumption of the fluid in question was determined for each animal by averaging its intake over the days of the drinking test. The "mean daily intake" of a group is the average of the mean daily intake of each animal. Thus, a rat drinking two, four, six and eight millilitus, respectively, over four days, would be described as having drunk a mean daily intake of five millilitus of test solution.

To begin a preliminary consideration of the specificity of the effect of hypophysectomy on the oral intake of various pharmacologically active agents, the acceptability of .05% (w/v) sodium pentobarbital in 5% sucrose was compared for normal (Group PBN, $n=6$) and hypophysectomized (Group PBH, $n=6$) rats. A similar test was employed using 6% ethanol in tap water and using 20% ethanol and 5% sucrose in tap water. The two ethanol solutions were offered to both normal and hypophysectomized animals.

The following morphine intake tests were conducted:

Group HM (n=6) was hypophysectomized and tested for morphine intake by the procedure described. Group NM (n=5) consisted of normal animals which were tested for morphine drinking.

Four animals (Group HQ) were hypophysectomized and tested for quinine solution intake.

In order to get an indication of the time course of the blockade of morphine intake effect, eight animals (Group HRM) were hypophysectomized, provided with 5% sucrose solution for two weeks, housed in standard stainless steel cages and provided with Purina Rat Chow and water ad libitum for three months, and then tested for their intake of the morphine test solution.

The groups and treatments are summarized in Table I.

TABLE 1

Summary of Groups and Treatments

Group	n	Procedure
Morphine Intake		
NM	5	Normal, test morphine drinking
HM	6	Hypophysectomy, test morphine drinking
HQ	4	Hypophysectomy, test quinine drinking
HRM	8	Hypophysectomy, three months recovery, test morphine drinking

Specificity of effect - other pharmacologically active
preparations

PBH	6	Hypophysectomy, test sodium pentobarbital drinking
PBN	6	Normal, test sodium pentobarbital drinking
AlcN6	6	Normal, test drinking of 6% ethanol (without sucrose)
AlcH6	6	Hypophysectomy, test drinking of 6% ethanol (without sucrose)
AlcN20	6	Normal, test drinking of 20% ethanol
AlcH20	6	Hypophysectomy, test drinking of 20% ethanol

RESULTS

Verification of Surgery

Two "hypophysectomized" animals which had shown obvious coarse hair development also exhibited adrenals of normal weight, otherwise the groups did not overlap. A two-tailed t-test for independent samples indicated that the groups differed significantly ($t=5.78$, $p < .001$). The mean adrenal weight (per pair of adrenals) of the normal animals was 33.97 gm., while the mean adrenal weight of the hypophysectomized animals was 13.87 gm.

Experimental Results

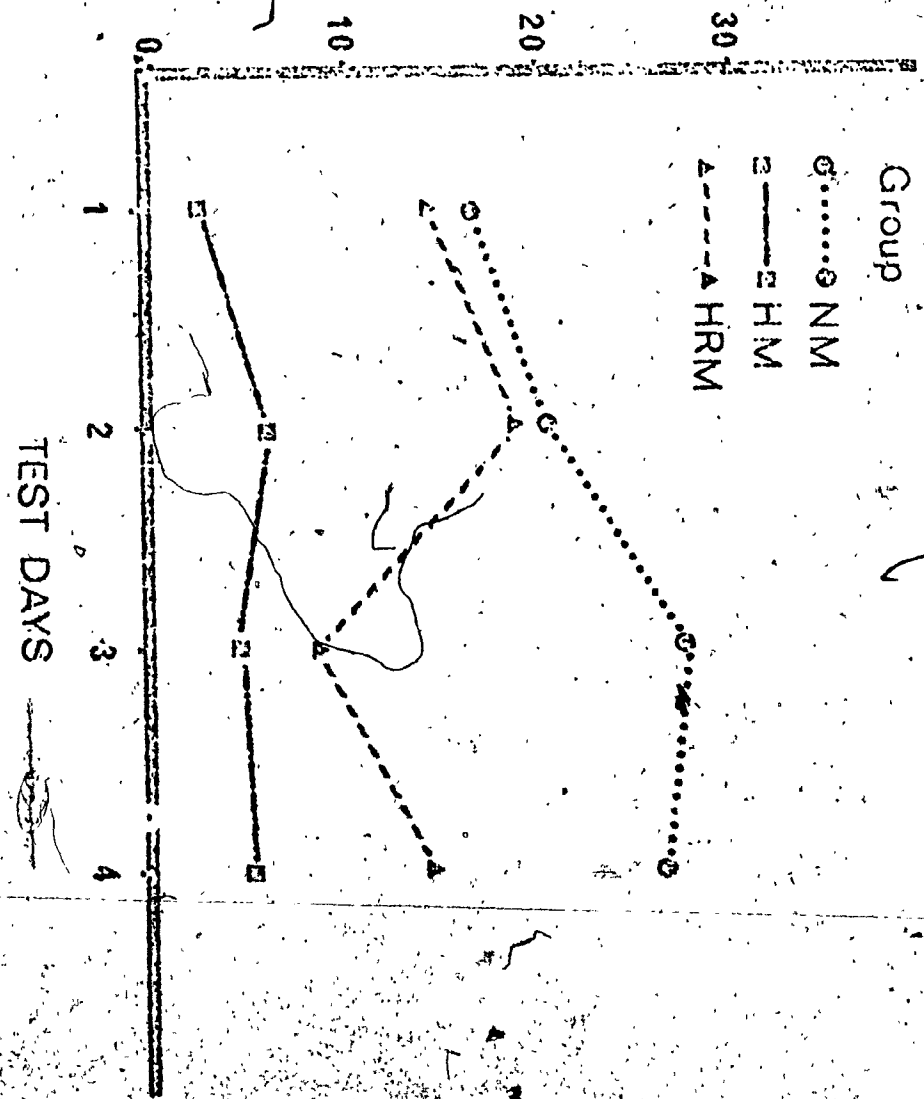
Hypophysectomy resulted in animals which almost totally rejected the morphine in sucrose solution. The mean daily intake of fluid of the operated animals (Group HM, $n=6$) was 4.2 ml while the mean daily morphine solution intake of the normal control animals (Group NM, $n=5$) was 22.8 ml. A two-tailed t-test for independent measures indicated that the difference in intake was significant ($t=6.22$, $p < .001$). A two-tailed t-test for related measures also indicated that the difference from baseline sucrose solution consumption to morphine-in-sucrose solution consumption of the operated animals (Group HM) was also significant ($t=6.84$, $p < .01$). These animals dropped from a mean daily intake of 23.8 ml of sucrose to a mean daily intake of 4.2 ml of morphine solution.

These results are summarized in a portion of Figure 2.

The observed blockade of morphine intake does not seem to be based on a reaction to taste, as indicated by a comparison of quinine solution to morphine solution drinking.

Figure 2. Mean daily intake of a solution of .02% morphine hydrochloride (w/v) and 5% sucrose (w/v) in tap water by animals subjected to hypophysectomy (Group HM), by normal animals (Group NM) and by "recovered" hypophysectomized animals (Group HRM).

MEAN DAILY MORPHINE SOLUTION INTAKE (ML)



Four animals (Group HQ) were hypophysectomized, and tested for their intake of a .0125% quinine HCl in 5% sucrose solution. Mean daily intake was 16.8 ml. The difference in intake between the two groups of hypophysectomized animals receiving either morphine or quinine was significant ($t=2.65$, $p < .05$, two-tailed t-test for independent measures).

These results are summarized in Figure 3.

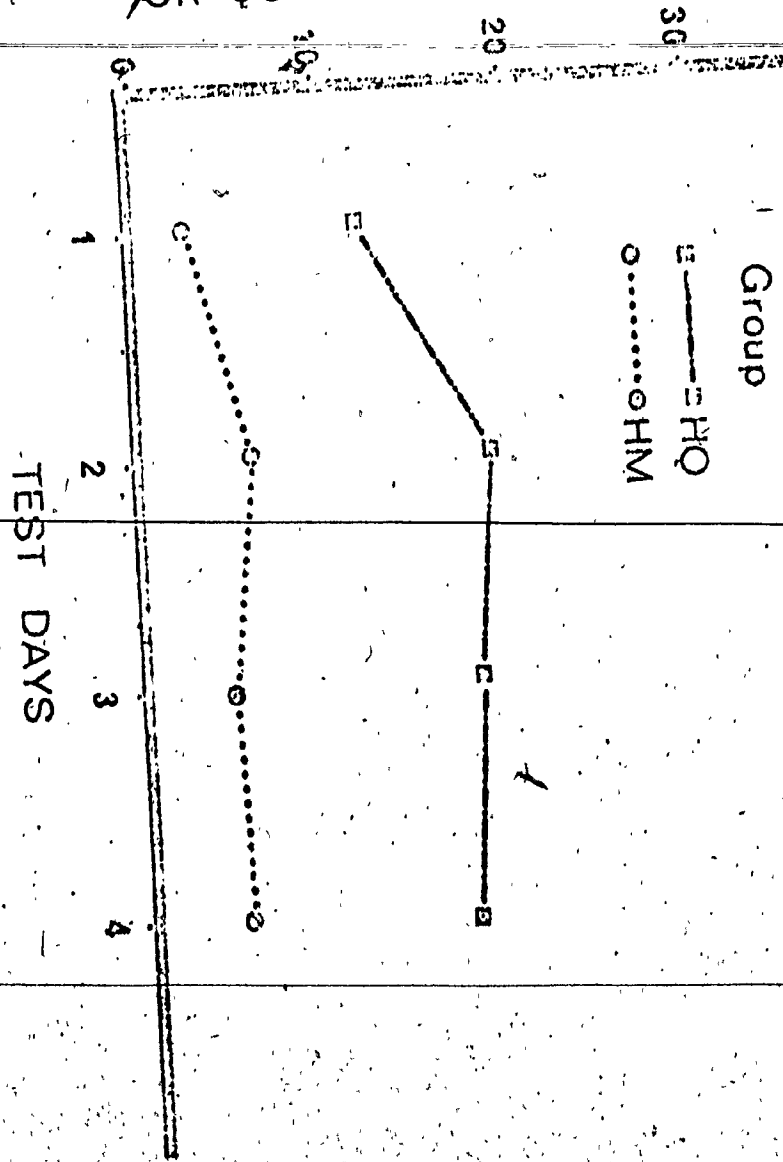
Although hypophysectomy exerted its most pronounced blocking effect on morphine drinking, ethanol consumption was also reduced. There was a significant effect on intake levels, but not as total as the effect on morphine intake. The post-hypophysectomy baseline water drinking of Group AlCH6 (n=6) was compared to its intake of a 6% ethanol solution. The animals of this group, subjected to an alcohol concentration which is normally acceptable to rats, dropped from a mean daily intake of 25.4 ml of water to a mean daily intake of 20.0 ml of 6% ethanol. This difference was significant ($t=5.71$, $p < .01$, two-tailed t-test for related measures).

A comparison of the intake levels of 6% ethanol by normal animals (Group AlCN6) versus hypophysectomized animals (Group AlCH6) also revealed a significant difference in intake (two-tailed t-test for independent samples, $t=5.26$, $p < .001$). The mean daily intake of 6% ethanol by the normal animals was 32.2 ml while the mean daily intake of the hypophysectomized animals was 20.2 ml.

A similar comparison of post-hypophysectomy sucrose solution baseline intake versus drinking of a solution of

Figure 3. Mean daily intake of a solution of .0125% quinine sulphate (w/v) and 5% sucrose (w/v) in tap water by hypophysectomized animals (Group HQ) compared to the morphine solution intake of hypophysectomized animals (Group HM).

MEAN DAILY MORPHINE
OR QUININE INTAKE (ML)



a significant drop in intake from a mean of 42.8 ml of sucrose solution daily to a mean of 15.2 ml daily of 20% ethanol in sucrose. This test was performed to observe the effects of hypophysectomy on the intake of an alcohol solution which is normally not preferred by rats in a free-choice situation. (See Figure 4).

Comparison of intake of this concentration of ethanol by normal and hypophysectomized animals (Group AlcN20 vs AlCH20) indicated significantly differing intake levels ($t=3.60$, $p < .01$, two-tailed t -test for independent measures). The mean daily 20% ethanol solution intakes were 24.1 ml for Group AlcN20 and 15.2 ml for Group AlCH20.

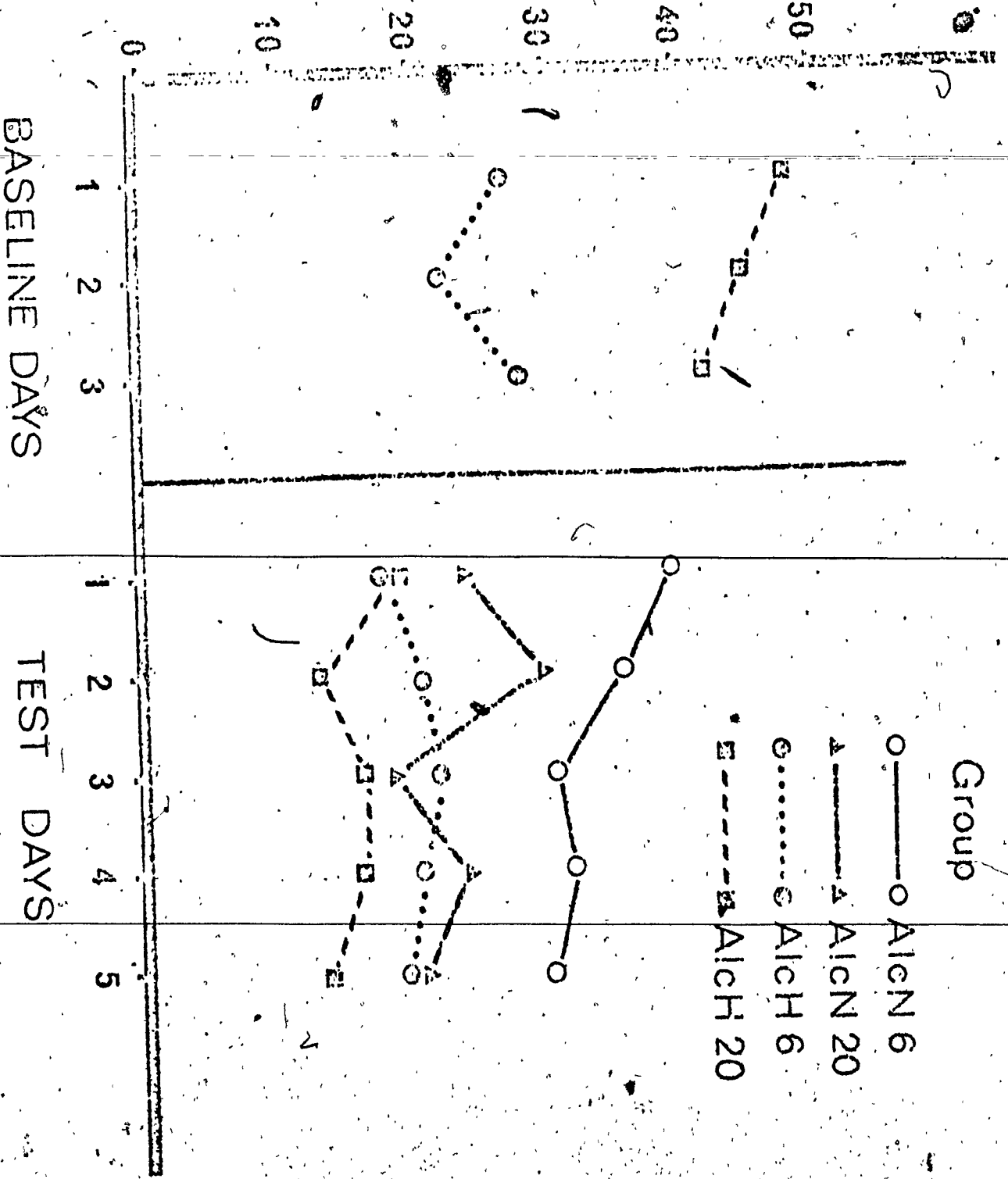
The acceptability of a solution of .05% sodium pentobarbital in 5% sucrose relative to the acceptability of a 5% sucrose solution did not seem to be affected by hypophysectomy (two-tailed t -test). Baseline drinking of sucrose was a mean of 32.7 ml daily (Group PBH, $n=6$), while the mean sodium pentobarbital solution intake was 32.3 ml daily.

In addition, a comparison of sodium pentobarbital intake of hypophysectomized animals (Group PBH) and a group of normal animals (Group PBN) revealed no significant difference in drug solution drinking (two-tailed t -test). The mean daily intake of the normal animals was 49.5 ml and the mean intake of the hypophysectomized animals was 32.3 ml. (See Figure 5).

Eight animals (Group HRM) were hypophysectomized, allowed to recover for three months, and tested for their willingness

Figure 4. Baseline water intake of hypophysectomized animals compared to their intake of 6% ethanol in tap water (Group AlCH6) and compared to the intake of 6% ethanol by normal animals (Group AlcN6). Similar comparison is made for normal (AlcN20) and hypophysectomized animals (AlCH20) receiving 20% ethanol in a 5% sucrose solution.

MEAN DAILY FLUID INTAKE (ML)



Group

○—○ AICN 6

▲—▲ AICH 20

●—● AICH 6

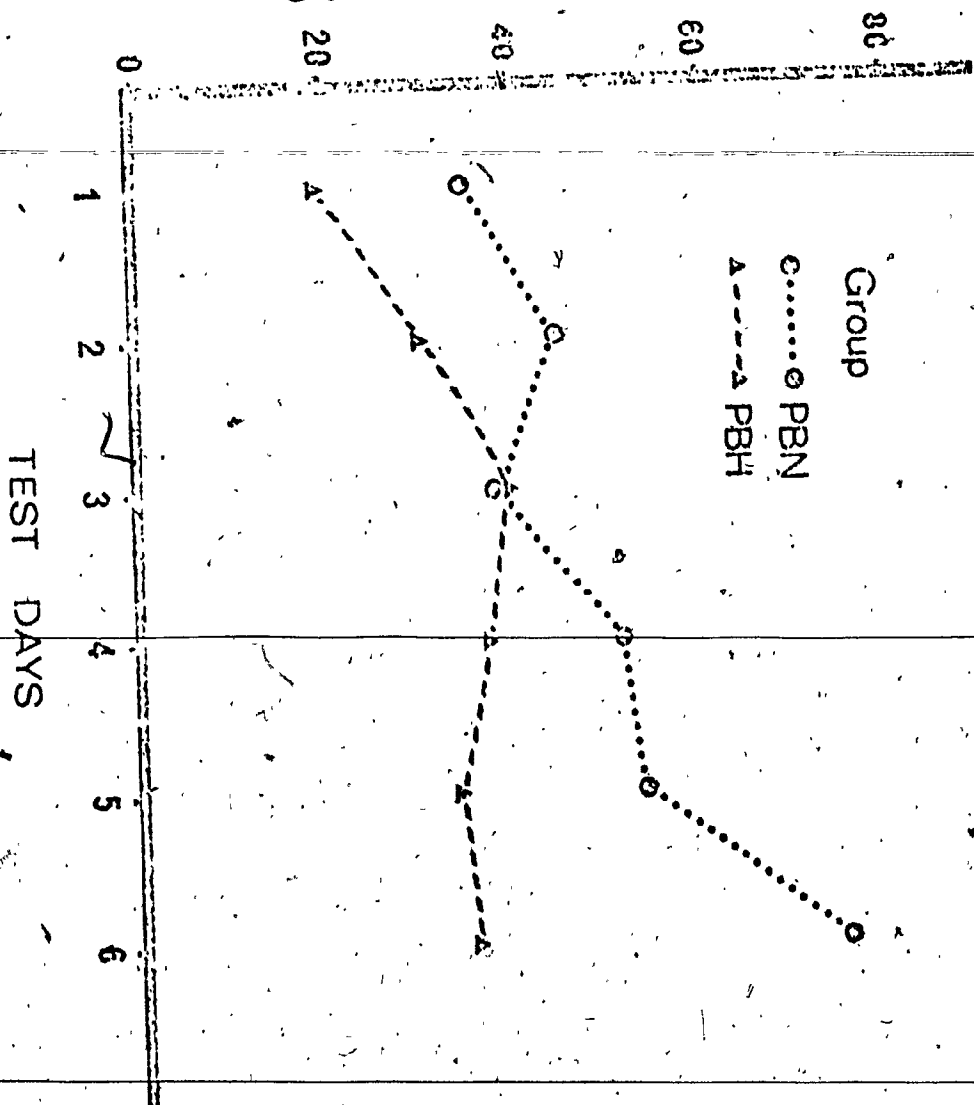
■—■ AICH 20

BASILINE DAYS

TEST DAYS

Figure 5. Mean daily intake of .05% sodium pentobarbital (w/v) and 5% sucrose (w/v) in tap water, of hypophysectomized (PBH) and normal (PBN) animals.

MEAN DAILY BARBITURATE
SOLUTION INTAKE (ML)



to drink the morphine test solution. Two two-tailed t-tests for independent samples indicated that this group's mean daily intake of 14.0 ml of morphine solution was significantly different from the intake of either the normal or hypophysectomized animals ($t=4.76$ and 3.61 , respectively, $p < .01$). There is thus some indication that recovery occurs from the effects of hypophysectomy on morphine intake. (See Figure 2). Unfortunately, the adrenal weights of this group are not available.

DISCUSSION

The use of morphine and other drugs to affect the CNS, in combination with ablation of selected structures, is appealing because of the strong possibility of obtaining a robust phenomenon which may justify a statement of cause and effect. When dealing with the hypothalamo-pituitary axis, however, there is always a strong possibility of an overwhelming effect of influencing a behavioral measure by a manipulation too general to lead to inferences of meaningful relationships. In this respect it is worthwhile to note that while the relatively discrete manipulation of a vagotomy raised the lateral hypothalamic self-stimulation threshold by over 100 percent in rats (Ball, 1974), lateral hypothalamic self-stimulation was unaffected by hypophysectomy (Phillips and Shapiro, 1973).

As demonstrated by this study, hypophysectomized rats will drink a solution of quinine which in normal animals is equiaversive with a morphine test solution which is rejected by hypophysectomized animals.

Because of considerations of initial acceptability to the normal animal, it is our opinion that the finding of an intermediate acceptability (between that of morphine and barbiturate) of ethanol after hypophysectomy is equivocal. Further research will indicate whether this is a fruitful line of enquiry. However, the results with barbiturate are extremely interesting: Intake levels after hypophysectomy remained high. A number of workers have reported the

hyperdipsic effects of barbiturates (cf. Schmidt, 1965). Whatever the mechanisms of action of the barbiturate induced hyperdipsia, it is still functional in the hypophysectomized rat.

Pickford (1969, p. 59) refers to an increased sensitivity to taste and smell with hypoadrenalism. Again, the finding of the experimental animals' willingness to drink quinine, barbiturate or alcohol, argues against this explanation of the observed "finickyness" toward morphine.

In an attempt to narrow the possible factors involved in the blockade of morphine consumption, Gelfand, Amit, and Ziskind (Note 1) have instituted a replacement therapy of ACTH to hypophysectomized rats and found that this treatment abolishes the observed blockade of oral morphine intake.

That this ACTH reversal of blockade is not mediated through an adrenal effect is suggested by the finding by Hébert, Amit, and Ziskind (Note 2) that adrenalectomy does not affect morphine solution drinking. There is thus an indication that ACTH affects a central structure which does not receive ACTH in a hypophysectomized animal and which must receive ACTH in order to "allow" morphine drinking.

Scapagnini and Preziosi (1973) suggest that central noradrenergic neurons are responsible for a tonic ACTH secretion inhibition in the rat. They administered alpha-methyl-para-tyrosine (AMPT, a drug which inhibits catecholamine synthesis by inhibition of tyrosine hydroxylase activity) systemically and determined hypothalamic catecholamine

level and plasma corticosterone level. The AMPT caused an increase in adrenocortical activity, indicative of a release of ACTH. Intraventricular administration of a systemically ineffective dose of AMPT also increased the plasma corticosterone concentration. Selective depletion of NE by bis 4-methyl-1-homopiperazinylthiocarbonyl - disulfide (FLA-63), an inhibitor of dopamine-beta-hydroxylase, resulted in a clear-cut adrenocortical activation. Selective depletion of dopamine failed to result in this adrenocortical activation.

The preceding is intended to present an argument for the notion that a NE system could inhibit ACTH release. ACTH release (and its subsequent action at an unidentified CNS site) is necessary in order to observe oral morphine intake, and so any manipulation which lowers the NE content of the ACTH inhibiting system will result in enhanced morphine intake while a manipulation (such as hypophysectomy) which lowers ACTH content will inhibit morphine intake. Again, since the study by Hébert et al. showed that adrenalectomy has no effect on morphine drinking, this ACTH effect should be a direct one on a CNS structure, and not mediated through an adrenocorticoid inducing effect and the subsequent action of one or more induced hormones on a central site. Further evidence for this line of reasoning is presented by Fuxe, Hokfelt, Jonsson, and Lidbrink (1973), who point out that adrenocortical hormones decrease NE turnover and that ACTH induces both an increase in NE

turnover and an increase in adrenocortical activity. Therefore, the ACTH induced NE turnover must be mediated extra-adrenally.

Returning to the design of the present study, a major consideration is the fact that the dosage of morphine delivered via the drinking solution was only 2 mg/10 ml. It should be restated, then, that George and Way (1959) found that a dose of morphine as small as .1 mg/kg was effective in producing an antidiuretic effect in normal rats.

Morphine has been shown to have a dual action on the CNS. The low dose effect is one of stimulation, while at high doses depression occurs (George, 1973). Lorens and Mitchell (1973) have demonstrated the development of tolerance to the depressant effect of morphine with a concurrent lack of tolerance to the stimulant effect of the drug, as measured by patterns of lateral hypothalamic self-stimulation after drug administration. They found that an injection of 5, 10 or 20 mg/kg of morphine sulphate subcutaneously, resulted in an initial drop in responding for rewarding brain stimulation (ESB), followed approximately five hours after injection by an increase above baseline responding for ESB. With repeated daily injections, the depression in responding for ESB returned to baseline levels, while the later increase in responding was not attenuated. Lotti, Lomax, and George (1965) have also recorded the dual depressant and stimulant effects of morphine, as indicated by the direct action of morphine on the thermoregulatory

areas of the hypothalamus. They reported hyperthermia and excitation upon micro-infusion of morphine directly to the caudal hypothalamus and respiratory depression and hypothermia resulting in the rostral hypothalamus. These findings fit with the finding by Lomax, Kokka, and George (1970) of the development of tolerance to the effects of morphine infusion to the rostral hypothalamus and the lack of tolerance with infusions to the caudal hypothalamus. The measure used was inhibition of radioactive iodine release by the thyroid as a result of thyroid stimulating hormone (TSH) release in response to TSH releasing hormone (TRF) by the hypothalamus.

Sherman and Mitchell (1972) have demonstrated a differential effect of morphine on whole brain metabolism in chicks depending upon the presence or absence of a concurrent stress (heat) stimulus. They found evidence of decreased whole brain metabolism in the presence of stress or morphine injection alone. Brain metabolism returned to normal levels if the stress was applied to a morphinized preparation. Sherman and Mitchell (1972) therefore suggested that the behavioral state of the organism should be considered when investigating the effects of morphine, since this factor may change the metabolic state on which the drug acts. It is interesting to note in this context that George and Way (1959) found that anterior median eminence lesions abolished the adrenocortical response to morphine.

At the time of this writing the original finding of a

blockade of oral morphine intake by hypophysectomy has been replicated in the same laboratory, the reinstatement of morphine drinking after hypophysectomy by ACTH injections has been demonstrated, and the absence of a straightforward adrenocortical involvement in the phenomenon has been demonstrated with adrenalectomized animals. The possibility still exists that a reinstatement of morphine drinking after hypophysectomy may be accomplished by means other than the replacement of ACTH to the system and the possibility also exists that ACTH exerts its effect on morphine drinking indirectly, perhaps via the induction of a CNS hormone or perhaps even by the induction of some peripheral effect. An elimination of alternate possible modes of action to account for the phenomenon cannot be accomplished by the demonstration of lack of effect of a particular manipulation. Even the positive demonstration of the effects of ACTH in reinstating morphine drinking does not preclude the possibility that ACTH is interacting with some other hormone in order to exert its effect. An obvious first step in elucidating the mode of interaction of ACTH and morphine will be the infusion of small quantities of morphine directly into hypothalamic areas which may react to the infusion by releasing corticotrophin releasing factor.

If this site can be established, then it may be reasonable to expect to isolate an area (by selective lesioning) which may "allow" morphine drinking when affected by ACTH. Since the amount of drug which is effective in

blocking intake is very small, it is reasonable to search for an effect in an area of the hypothalamus which has been shown to be stimulated by morphine and which does not demonstrate tolerance.

The observed willingness of hypophysectomized rats to drink a barbiturate solution provides the possibility of identifying a site which must remain functional in order for barbiturate drinking to continue. Preliminary studies (in progress) have shown that the LD_{50} for both morphine and barbiturate are significantly lowered after hypophysectomy, but not after adrenalectomy. This may provide an excellent opportunity to develop an understanding of very specific brain-drug interactions and the nature of the observed lethal effect.

A phenomenon of considerable significance has been the observation that many self-administration phenomena are drastically altered by the factor of experience with a drug prior to a manipulation which in naive animals blocks subsequent voluntary intake (Amir, Note 3). The technique of micro-infusion to specific areas may serve to identify the areas which are affected by initial drug exposure and the nature of the changes occurring with drug experience.

At this point, it seems that continued research into the factors and structures controlling oral morphine intake may prove useful in elucidating the interactions involved in the acquisition of new approach - avoidance tendencies and may contribute to an understanding of the long delays

in reinforcement which have been demonstrated to be effective with gustatory cues. In terms of the question of drug approach motivated behavior, it will be very interesting to investigate the differential effects of certain CNS manipulations such as hypophysectomy on subsequent drug approach behavior which does not consist of an oral intake mode of self-administration. It may well be that the particular sequence of behaviors involved in obtaining (or approaching) a drug will be the major factor influencing its motivational effects.

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APPENDIX

Raw data for the groups described in the text.

Values expressed are in milliliters.

Group NM

(Normal, tested for morphine drinking)

<u>Animal</u>	<u>Day</u>			
	1	2	3	4
1	27	35	30	35
2	13	20	25	22
3	19	22	25	25
4	4	5	34	30
5	21	22	21	21

Group HM

(Hypophysectomized; tested for morphine
drinking)

<u>Animal</u>	<u>Day</u>			
	1	2	3	4
1	1	1	-	-
2	2	1	5	6
3	1	0	0	1
4	8	8	5	12
5	0	0	0	-
6	5	26	12	1

Group HQ

(Hypophysectomized, tested for quinine drinking)

<u>Animal</u>	<u>Day</u>			
	1	2	3	4
1	22	22	24	19
2	1	2	0	0
3	1	26	28	29
4	25	26	20	21

Group HRM

(Hypophysectomized, allowed to recover,
tested for morphine drinking)

<u>Animal</u>	<u>Day</u>			
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>
1	19	23	10	15
2	18	22	14	18
3	13	17	12	11
4	4	19	2	15
5	11	10	3	12
6	16	24	8	12
7	14	16	8	17
8	19	21	11	16

Group PBN

(Normal, tested for sodium pentobarbital
drinking)

<u>Animal</u>	<u>Day</u>					
	1	2	3	4	5	6
1	53	50	36	43	50	84
2	37	38	75	78	82	115
3	39	48	41	64	60	97
4	20	32	21	28	35	31
5	21	51	35	57	58	90
6	35	49	24	37	33	33

Group PBN

(Hypophysectomized, tested for sodium
pentobarbital drinking)

<u>Animal</u>	<u>Day</u>					
	1	2	3	4	5	6
1	15	17	24	23	35	36
2	23	55	91	94	80	40
3	19	32	33	26	28	28
4	14	21	26	19	28	17
5	27	29	40	29	36	35
6	16	27	21	28	22	24

Group AlcN6

(Normal, tested for drinking of 6% ethanol in water)

<u>Animal</u>	<u>Day</u>				
	1	2	3	4	5
1	28	27	28	29	28
2	32	35	30	36	33
3	34	31	28	32	33
4	33	33	26	28	26
5	41	50	34	35	35
6	39	37	28	29	30

Group Alch6

(Hypophysectomized, tested for drinking
of 6% ethanol in water)

<u>Animal</u>	<u>Day</u>				
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>
1	21	24	24	24	24
2	10	15	16	17	12
3	22	24	24	24	22
4	17	17	16	15	17
5	17	24	23	22	16
6	18	24	28	23	26

Group AlcN20

(Normal, tested for drinking of 20%
ethanol in sucrose solution)

<u>Animal</u>	<u>Day</u>				
	1	2	3	4	5
1	27	33	15	22	27
2	32	44	21	25	21
3	25	27	20	22	3
4	19	27	20	30	21
5	23	27	21	27	24
6	16	20	12	18	17

Group AlCH20

<u>Animal</u>	<u>Day</u>				
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>
1	17	17	20	17	13
2	17	10	13	16	12
3	22	14	14	11	10
4	14	18	19	18	12
5	18	14	14	11	15
6	21	16	17	23	17