

AVERSIVENESS OF ORALLY ADMINISTERED

MORPHINE IN RATS

by

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Abstract

Recent animal research in opioid addiction has led some authors to suggest that morphine is positively reinforcing, and if it were freely available, any mammal would become addicted. Such variables as route of ingestion, environment, personality, and social factors are considered largely irrelevant. We believe that this conclusion is an over-generalization of the animal studies, in which subjects housed in small individual cages self-inject morphine as their sole source of stimulation. The reinforcing properties of morphine may obtain only with these experimental methods. Evidence from our laboratory shows that rats housed in a large colony cage consume substantially less morphine than individually caged rats. Also, findings from our laboratory and elsewhere suggest that morphine is aversive when it is administered orally.

The present experiment is a further investigation of the aversion to orally administered morphine. Typically, rats reject the drug in oral form, but this has been attributed to its bitter taste. In this experiment, two methodologies were combined (represented as two phases), to overcome the taste problem. In the first phase, the only liquids available to the rats were morphine solution and a much more bitter quinine solution. Ten out of 18 animals

persisted in avoiding the morphine and selected quinine. In the second phase, a morphine antagonist was added to both solutions to neutralize the effects of morphine. Seventeen animals then consumed 90% morphine, indicating that the morphine aversion in the first phase was due to the pharmacological effect of morphine, not the taste. Furthermore, there are several pieces of evidence that the 8 animals which selected mostly morphine in the first phase also found the drug aversive. First, they avoided the morphine solution in the first few days of drinking. Second, they drank only enough morphine to meet minimum fluid requirements, unlike the relatively large amounts of an equally bitter quinine solution consumed in a comparison experiment.

A third and final phase of the experiment was a demonstration that no radical taste interactions had occurred between morphine and the antagonist, and that the antagonist did not cause changes in bitterness aversion.

This experiment provides strong evidence that morphine is sometimes aversive to rats, and disputes the notion that free availability of the drug in any form is sufficient to lead to addiction.

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Introduction

Historical Overview

Man has self-administered psychoactive substances since before written history (Lewin, 1931/1964). Of all these substances, opium has been one of the most pervasively used. Mesopotamia is believed to have been the original home of the opium poppy (Papaver somniferum). The Sumerians, who settled there in 5000 or 6000 B.C., refer to opium on tablature dating from about 2000 B.C. This anonymous writing speaks of the efficacy of the plant in relieving pain and inducing sleep (Emboden, 1972). The Sumerian ideogram used for opium means "joy", or "rejoicing" (Terry and Pellens, 1928/1970).

Opium was also often cited in the literature of ancient Greece. Homer frequently mentions nepenthe, a drink made from opium poppies. In the Odyssey (ca. ninth century B.C.), Helen of Troy offers a filter of nepenthe to Telemachus that will "lull pain and bring forgetfulness of sorrow." Hippocrates (466-377 B.C.) advocated poppy wine as a medicine. In some connection, the poppy is mentioned by almost every major writer of Greek and Roman antiquity, including Aristotle, Virgil, and Pliny The Elder. This is perhaps not surprising, since the curative properties of

sleep were highly esteemed in Greece, and opium was seen as an herbal vehicle to that state. Called the "potent destroyer of grief", opium poppies appeared on coins, vessels, jewelry, utensils, and figurines. Its use was associated with Nyx, goddess of night; Thanatos, god of death; Hypnos, god of sleep; and Morpheus, god of dreams. Images of these deities are frequently represented in association with opium flowers and capsules (Emboden, 1972, p.23).

From Grecian times to the present, opioids have continued to be of interest to the Western World. They have been used as a remedy for a wide variety of human ills, and they constituted the main therapeutic agent for medical men for over two thousand years (Terry and Pellens, 1928/1970). In nineteenth century America, physicians often referred to morphine as "G.O.M." -- "God's Own Medicine." In Dr. H. H. Kane's textbook, The Hypodermic Injection of Morphia, Its History, Advantages and Dangers, the author lists 54 diseases which were relieved by morphine. Of course few if any of these diseases were in fact cured by morphine, nor were essential symptoms eliminated; only the pain, discomfort, and worry associated with illness were alleviated. Nevertheless, opioids were palliatives of enormous clinical value (Brecher, 1972, p.8).

It may be argued that it is precisely this overreliance

on opioids which placed them in jeopardy of eventual prohibition. Szasz (1974) suggests that there is a strong tendency in human society to consider particular drugs to be either panaceas, or panapathogens (i.e. completely harmful). He points out that the status of many drugs has undergone reversals of public opinion, in a way that never befits the actual pharmacology of the drug (because each has beneficial and deleterious side effects). This leads to its improper use -- either unnecessary prohibition, or indiscriminate overuse.

In spite of the fact that these drugs were so widely used, for so many reasons and for so long, there is no evidence that they ever succeeded in addicting entire populations. In fact, in view of the current popular conception of the powerfully addictive properties of opioids, their addicting efficacy seems to have been surprisingly weak (Terry and Pellens, 1928/1970).

Through the course of history, the motivations for opioid use have varied considerably. In earliest times, opium was used as a tranquilizer, pain reliever, and sedative. Since that time they have been used by wounded soldiers to alleviate pain, by Chinese laborers to tolerate aversive working conditions, and by housewives for menstrual cramps and menopause. Infants were frequently given the drug as a teething, or choleric remedy. Currently, opioids

are used as analgesics, antitussives, and antidiarrheals. Also, of course, they have often been used for the euphoria they produce in certain individuals.

There has also been considerable variation in the socio-cultural groups using these drugs. In the nineteenth century, most narcotics users were women, outnumbering men by two to one (Lindesmith, 1968, p.210) or three to one (Brecher, 1972, p.17). They were typically middle or upper class, and between twenty-five and fifty-five years old, averaging about 40 years of age for both females and males (Brecher, 1972, p.18). Some apparently became habitual users by medical prescription, or by self-medication with patent medicines such as Laudanum.

In contrast, the current population of North American "street addicts" are approximately eighty percent male (Brecher, 1972, p.17). They obtain their heroin on the black market, and are predominantly of the lower class. In the United States, the majority are under thirty-five (Brecher, 1972, p.18).

There are at least three important factors which have contributed to these changes in opioid use. First, the isolation of morphine from opium in 1803 by Serturmer permitted individuals to easily ingest large purified quantities of opioids (Brecher, 1972, p.46).

Second, the invention of the hypodermic syringe

permitted an individual to inject potent amounts of morphine in a manner which produced immediate effects.

Third, opioids were prohibited in North America and elsewhere. This inhibited casual use, but it consolidated the remaining opioid consumers into a clique of outlaws, who tended to support each others' behavior. Furthermore, the increased prices resulting from black market trading strongly encouraged users to resort to intravenous injections in order to receive maximum and most rapid benefits from the least amount of the drug (Brecher, 1972, p.46).

It should also be noted that opioids seem to have a more pleasurable effect when a person is undergoing stress of some sort (Sandoz, 1922; Jaffe and Martin, 1975), and may have "no pleasurable effect at all on a prosaic and stolid person with no sense of strain or conflict" (Lindesmith, 1968, p.27). Hence, the act of criminalizing opioid possession has the effect of reducing casual use, but it may worsen the quality of addiction for persistent users by increasing the strain they experience. The poverty, malnutrition, poor housing, distrust, conflict with thieving friends, the sense of life-failure, and the constant need to avoid the police all may contribute to a highly stressful lifestyle.

Contemporary Patterns of Opioid Use

The most obvious characteristic of the contemporary "street addict's" behavior is an intense craving and striving for heroin. This desire is not casual or vague, but is a powerful conscious motive driving him or her to seek gratification in the face of unbelievable sacrifices and almost insuperable obstacles. All treatment methods which attempt to detoxify this type of addict and return him or her to the home environment are almost completely unsuccessful, with usually more than ninety-two percent of treated individuals relapsing within five years (Dansauer and Rieth, 1931; O'Donnell, 1965; Lindesmith, 1968, p.53).

For other groups, however, the prognosis for addiction treatment is much better. Physicians, for instance, have a problem with opioid addiction -- about one percent are morphine addicts (Nichols, 1965). However, when they are threatened with the certainty of losing their licences to practice medicine if they remain addicted, most are able to stop using the drug. In at least one follow-up study, ninety-two percent were able to stop using opioids for a period of five years (O'Donnell, 1965).

Patients receiving morphine as part of medical treatment also have an extremely low addiction rate (Jaffe, 1975; Zinberg, 1974). Dansauer and Rieth (1931) reported on

a large number of patients who were given oral and parenteral opioids for long periods (in some instances for more than ten years) without inducing subsequent drug-seeking behavior. These individuals usually suffer withdrawal if the drug is stopped abruptly. However, drug craving is not expressed verbally, and they only rarely seek out morphine from illicit sources. Often the patient states that he or she has no desire for the drug, or that the effects are aversive.

The addiction careers of U.S. soldiers returning from Vietnam also differ from "street addicts". In 1971, about 42% of U.S. enlisted men in Vietnam used opioids at least once, and approximately half of these reported that at some time during their year there they were physically dependent (Robins, 1974). However, very large numbers of users were able to successfully give up heroin after returning to civilian life (Bourne, 1974).

Social and Personality Theories of Addiction

These highly varied addiction careers have been variously interpreted. A large number of investigators have theorized that there is an "addiction prone personality" (Yorke, 1970; Braucht et al., 1973). Khantzian et al. (1974) proposed that addicts have resorted to heroin in

order to help them deal with uncontrollable anger, fear, and other problems of stress. Based on the M.M.P.I., Gilbert and Lombardi (1967) concluded that the addict is characteristically depressed, inadequate, irresponsible, impatient, lacking persistence, and egocentric. Clinical studies have shown that addicts tend to be psychoneurotic (Rosenberg, 1968; Felix, 1944), and to have a low tolerance for frustration (Bender, 1963; Zimmering et al., 1952).

However, these findings cannot be taken as unchallengeable, since they suffer from basic flaws (Jamison, 1972). First, addicts are seldom compared to matched control groups. In a careful Canadian study, Gendreau and Gendreau (1970) compared addicts to controls matched for intelligence, socio-economic status, criminal experience, age, and opportunity for drug use. They found no significant differences in psychiatric dimensions. Stevenson et al. (1956) found similar results in a study of prisoners in British Columbia. The personality characteristics of the drug-using group were very similar to those of the non-drug-using group. The second flaw is that clinical assessments of addicts are based on an ex post facto analysis: it is virtually impossible to distinguish those personality characteristics which caused addiction from those which are the result of addiction. A third problem is that most addict samples are derived from those

heroin users who come to the attention of the authorities; these may not represent the true addict population.

Sociological and situational factors also apparently play a part in the addiction process. Encouragement and peer pressure may induce individuals to begin experimentation with opioids (Chein and Rosenfeld, 1957; Hughes and Crawford, 1972; Stevenson et al., 1956).

The addict's family environment also appears to be important. A very high proportion of young addicts come from single-parent homes (Vaillant, 1966; Willis, 1969; Chein et al., 1964), lacking cohesiveness, and characterized by open hostility between family members (Chein et al., 1964). In two parent families where the addict lives at home, the parents are extremely overindulgent toward the addict, and both addict and parents view the addict as overly passive and dependent (Alexander and Dibb, 1975; 1977) ..

Physiological Theories of Addiction

The increasing frustration with the ineffectiveness of addiction psychotherapy and social adjustment programs has led some researchers to conclude that the principal cause of addiction is biochemical. There is a growing body of evidence to support this view (Dole, 1972).

A number of researchers have shown that morphine produces measurable and enduring physiological changes in mammals. Signs of abstinence seem to continue in a mild way for long periods of time, often as long as craving endures. Himmelsbach (1942) studied addict patients at the United States Public Health Hospital who had remained abstinent for months, and found persistent signs of withdrawal, such as hyperthermia, mydriasis, increased blood pressure, and increased respiratory rate. Martin and Jasinski (1969) confirmed these findings, and showed that these signs persisted, and later reversed themselves (changing to hypothermia, miosis, decreased blood pressure and decreased sensitivity of the respiratory center to carbon dioxide). Congruent with this is the finding that rats also show protracted metabolic abnormalities in similar phases.

Tolerance also persists for long periods in rats, and demonstrable differences in response to morphine between opioid treated rats and controls have been shown to occur for as long as a year after termination of morphine (Cochin and Kornetsky, 1964). Even a single injection of morphine produces persistent tolerance (Dole, 1972). Way et al. (1969) have argued that tolerance is an alternate expression for physical dependence. If this is so, the persistence of tolerance suggests that physical dependence and craving are also enduringly present.

Certainly signs of physical dependence seem to persist. Khazan and Colasanti (1971) have treated post-addict rats with opioid antagonists as long as six months after exposure to morphine, and produced E.E.G. and behavioural responses similar to withdrawal symptoms.

The conviction that addiction is physiologically based has been further reinforced by the findings of Nichols (1967), who was able to selectively breed rats to increase their susceptibility to morphine addiction, and the findings of Snyder (1977), Hughes (1976), and others, who have discovered endogenous opioid-like substances (enkephalin and Beta-lipotropin), and have made progress in pinpointing morphine and enkephalin binding sites.

One theory (under dispute) which arises from this work is that morphine and heroin act by binding to, and overloading the enkephalin receptors. One consequence might be negative feedback to reduce the production of enkephalin. This progressive reduction potentially explains the phenomenon of tolerance, since the addition of morphine would only briefly increase the total opioid supply (morphine plus enkephalin) in the body. It could also explain physical dependence, since if the morphine were suddenly withheld, the reduced enkephalin production would temporarily be unable to supply sufficient opioid for normal physiological functioning. If this were in fact true, and

related to physical dependence as it is now defined, it is possible that chronic opioid use permanently disrupts and reduces enkaphalin production, leaving the addict in a mild and enduring state of withdrawal which opioids could alleviate. This might be synonymous with opioid craving.

However, attractive as it may be, the theory that addiction is purely physiologically based has several problems. First, these findings fail to conclusively prove that the continuation of morphine's physiological effects or withdrawal symptoms are in any way related to the continuation of psychological craving.

Second, it should be pointed out that the physiological changes accompanying opioid exposure do not seem to become more marked as addiction increases. Wei et al. (1973) performed an experiment in which two groups of rats were made physically dependent on morphine and then withdrawn from the drug. One group experienced this cycle repeatedly, the other only once. After a final morphine free period, rats were injected with an opioid antagonist to measure enduring withdrawal symptoms. No difference was found between the groups.

Third, there is good evidence to dispute the theory that exposure to morphine, by itself, results in addiction. As mentioned previously, many individuals, such as morphine using doctors, hospital patients, and veterans of the

Vietnam war have demonstrated that it is possible to give up heroin or morphine completely, and to experience virtually no sensations of psychological craving. In fact, only "street addicts" typically show patterns of compulsive drug use and continual relapse.

Fourth, there are reasons to doubt the capacity of opioids to cause enduring addiction in even "street addicts". Many spontaneously give up opioids. Winick (1962) carried out a cross sectional study of the records of arrest for U.S. narcotics users. In these records, addicts are listed as 'inactive' when a period of five years has elapsed since the last police contact for drug related crime. Approximately 80% of the subject sample became inactive by the time they were age 38.

In a longitudinal study, Robins and Murphy (1967) reviewed the drug use careers of a random sample of normal St. Louis negro men, and found that about 7% both reported being addicts, and had an official record of selling, use, or possession of narcotics during adolescence and early adulthood. Of these, at the time of the study, when the subject population ranged between the ages of 30 and 35, at least three quarters had ceased to be addicts, using the combined criteria of personal statement, and a period of five years since last drug arrest.

Viewed in the light of these findings, it would seem

unlikely that the mere exposure to opioids, even on a repeated basis, is sufficient to cause certain and irrevocable craving and addiction. But the notion that opioids induce enduring physiologically based craving is an important one and it warrants careful consideration. It is quite conceivable that slight physiologically based craving does in fact persist for long periods of time. Only further research in this area can tell.

Conditioning Theories of Addiction

Few researchers maintain that drug biochemistry is the only ingredient to the addiction process -- most believe that conditioning also plays an important role (e.g., Dole, 1972; Wikler, 1971). Nichols et al. (1956) were the first to show that conditioning procedures can induce morphine addiction in rats. Their technique was to inject animals with morphine daily for one month, and then commence avoidance conditioning. The rats underwent withdrawal distress for two days and on the third day they were permitted to drink only morphine solution. By this means, rats learned that morphine has a powerful ability to alleviate withdrawal symptoms. After several such learning trials, the animals came to consume substantial amounts of morphine. Nichols proposed a drive reduction theory of

addiction, which states that morphine is reinforcing because it reduces a wide variety of important drives, such as hunger, sex and anxiety. (However, this latter theory of addiction has been questioned by the subsequent work of Woods and Schuster (1968) which indicates that monkeys will self inject morphine and initiate lever pressing for self injected doses of 10 mcg/kg, which did not interfere with other normal activities such as eating or drinking).

Stimulus control is another conditioning factor which can affect opioid consumption. Thompson and Ostlund (1965) have found that rats which have been made physically dependent on morphine, then withdrawn, and re-exposed to morphine in a new environment, are more susceptible to readdiction than are rats which have been re-exposed to morphine in the original environment. Conversely, re-exposing a rat to morphine in the same environment where withdrawal took place reduced readdiction susceptibility. Similarly, in human research, Vaillant (1966) found in a 12-year follow-up study that addicts who successfully remained abstinent tended to have undergone withdrawal in their home environment, and many abstainers had moved to different environments from those in which the original drug dependence had developed. * *the key has to be maintained yourself*

Secondary reinforcement was a variable in work by Stolerman and Kumar (1970), in which rats were first made

physically dependent on orally administered morphine, then withdrawn, and finally, given access to quinine water (as an equally bitter substitute to the morphine). The animals drank substantial amounts of quinine solution, indicating that they had come to associate bitterness with the effects of morphine.

Perhaps the most powerful contribution to the conditioning theory view of addiction originates with the demonstration by Weeks (1964) that self injections of morphine can be reinforcing. In his research, rats were fitted with indwelling jugular vein catheters, which were connected to an injection pump. This apparatus permitted the animal to be relatively unrestrained, and able to self-inject morphine by means of a lever press. In his initial work (1962), he premedicated rats with morphine prior to exposure to the self-injection apparatus. Since then, however, other workers (Deneau et al., 1965, Woods and Schuster, 1968) have shown that no pretreatment is necessary. Some mammals will initiate lever-pressing for an intravenous injection of morphine, even in such comparatively low doses as 10 mcg/kg.

Based on these data (particularly the self-injection research), a number of theorists (e.g., Goldstein, 1972; 1976; Schuster and Thompson, 1969; Dole, 1972) have concluded that morphine possesses intrinsic positive

reinforcing properties which of themselves can induce rats, monkeys and humans to self administer the drug. Of this issue, Goldstein (1976) says:

If heroin were universally available and there were no constraints on its use, it is probable that heroin addiction would be much more prevalent than it is now. Other primates, when given the opportunity in the laboratory, self administer opiates to the exclusion of normal activities. This is not the anomalous behaviour of a few, but the predictable behaviour of all. Thus, on fundamental biological grounds, we may infer that were it not for countervailing influences on human society, narcotic addiction might well be the norm rather than an aberration. (p.353)

The Reinforcing Properties of Opioids

These ideas are vital to an understanding of opioid addiction and mark the central topic of this thesis. It is the belief of this author that the widely accepted conclusions reached by Goldstein are predicated on extreme

overgeneralizations of the evidence. It cannot be denied that there are certain circumstances in which mammals find morphine reinforcing. The aforementioned research on self-injection clearly demonstrates that in some circumstances, rats and monkeys will self-administer morphine. What is at issue, however, is the proposition that opioids are universally positively reinforcing.

Opioids are not always positively reinforcing for humans. ^{"please define"} Normal human subjects who have not been previously exposed to morphine do not generally respond positively to the drug. Lasagna et al. (1955) extensively studied the effects of morphine (8mg and 15mg S.C.) and heroin (2mg and 4mg S.C.) on opioid naive subjects. Of those who received the high morphine dose (N = 11) 6 considered it highly unpleasant, and 5 considered the experience as a whole to be dysphoric. At the lower dose of morphine (N = 9) 3 felt that the drug was pleasurable, 2 considered it neutral, and 4 thought it unpleasant.

For the higher dose of heroin (N = 11), 2 found the drug pleasurable, 2 found it neutral, and 7 considered it unpleasant. For the lower dose (N = 9), 3 felt that the drug was pleasurable, 2 neutral, and 3 unpleasant. From this work, it is evident that neither heroin nor morphine are usually reinforcing on initial exposure to humans.

*bad
conclusion
what human
all human?*

With respect to the self-administration research on animals, it could be argued that many of these results are based on negative reinforcement, in which opioids are used by rats for attenuating the impact of aversive experiences, such as unnatural laboratory conditions, handling, and restraint. Morphine and many of its congeners have powerful anxiety reducing effects which must be taken into account (The word "tranquilize" was coined in connection with opium by Thomas De Quincey in his book Confessions of an English Opium Eater, 1821/1930).

An extensive literature search by this author found that every experiment which has purported to show that mammals find opioids positively reinforcing was characterized by restraint or laboratory conditions very unlike their environment of evolutionary adaptiveness, such as frequent handling by humans, confinement of social animals to individual cages, installation of catheters, restraint by self-injection apparatus, and/or the use of restraining chairs. With regard to this issue, Khantzian (1974) concurs:

I believe that it is unwarranted to conclude that laboratory animals addict themselves because of the euphorogenic actions of opioids. It is just as reasonable to infer that the animal prefers opioids

because of its ability to relieve stress induced by laboratory conditions and handling, situations for which the animal is ill equipped instinctively. (p.64)

*a common
deliberate
with a purpose*

The need for caution is exemplified by work in spontaneous addiction carried out by Woods and Schuster (1968). In this study, rhesus monkeys were placed in restraining chairs for long periods each day and were fitted with indwelling jugular catheters. Humans fitted with venous catheters often report that these devices are uncomfortable, and sometimes painful. Placing a monkey in a restraining chair appears to be distressing for the monkey (B.K. Alexander, Personal Communication, 1977). Hence, in these conditions, it is possible that for these animals, negative reinforcement played a role in sustaining morphine self-administration.

The role of handling conditions and housing circumstances is very important. Alexander et al. (1978) and Hadaway et al. (in press) hypothesized that small individual cages may be aversive to rats, and that such housing may render them prone to addiction. They found that rats raised in a large colony cage are much more resistive to addiction than individually caged animals. This was the case for addiction-producing methodologies used by both

Nichols et al. (1956) and Khavari and Risner (1973). Hadaway et al. concluded, "It seems clear that the reinforcement properties of opiates, like those of other reinforcers, are highly situation dependent". *but it should be a cause*

In a number of other studies, *and others?* it would appear that when aversive contingencies are lessened, the certainty of inducing addiction in animals is also reduced. This was the case, for example, in the research performed by Claghorn et al. (1965). In their experiment, 4 rhesus monkeys were given ad libitum access to morphine sulfate (1%) solution or tap water. They were apparently kept in small individual cages, but not subjected to other conditions of stress. One monkey drank morphine solution for one week, then stopped voluntarily. A second monkey commenced drinking, but began reducing its consumption and deteriorated physically, so was dropped from the experiment. A third monkey increased its consumption to reach substantial amounts of morphine on the 80th day, but reduced its intake to baseline by the end of the experiment. The fourth animal progressively increased its morphine intake over the course of the experiment, reaching a maximum of 520 mg/morphine/day. Hence, only one monkey progressively increased its morphine consumption in a pattern which would suggest that morphine is positively reinforcing (Thor, 1972). It would appear that for these subjects, the reinforcing value of morphine varies across

animals, and, within each animal, over time.

Similar conclusions arise from work by Deneau et al. (1965). In this experiment, rhesus monkeys were individually housed, and although not placed in restraining chairs, were subjected to catheterization and fitted with a harness of stainless steel tubing which connected to a restraining arm. Thus, the monkey was permitted some activity, but was definitely not permitted free movement. One might expect that under these conditions, monkeys would self-inject opioids somewhat less readily than in restraining chairs. This was indeed the case, and not all animals self-injected opioids in the experiment. Deneau stated in a later article (1968): "The monkey shows a similar range of susceptibility to drug abuse as does man, in that some animals are highly susceptible, some are only moderately so, some are indifferent, and some are completely resistant" (p.205). *Can we compare animals to man - does man respond automatically to stress?*

This statement, when compared to Goldstein's, suggests that the conclusions reached by the researchers themselves are much more cautious than conclusions reached by some of those who assess the work.

It should be noted here that this review discusses both oral and parenteral self-administration studies, because both routes of administration are relevant to human and rat addiction. Morphine is readily absorbed from the

gastrointestinal tract, the nasal mucosa, the lung, and from subcutaneous, intravenous, and intramuscular sites of injection (Jaffe and Martin, 1975, p255). Although these routes differ regarding speed of onset, route of absorption, and the intensity of effects produced by a given dose, once absorbed, most of the pharmacodynamics are the same. In general the differences between parenteral and oral routes are that oral doses are about 1/6 to 1/15 as effective as parenteral administration (Jaffe and Martin, 1975, p258), and the duration of action is somewhat longer with the oral route (Jaffe and Martin, 1975, p255). All routes produce analgesia, drowsiness, changes in mood, mental clouding, respiratory depression, nausea, decreased colonic propulsive contractions, and increased biliary tract pressure.

Furthermore, morphine is addicting in either oral or parenteral forms. A survey of heroin users in New York city suggests that a sizable proportion, possibly a majority, prefer illegal, non-injectable methadone to illegal injectable heroin (Agar and Stephens, 1975). During the U.S. military presence in Vietnam, when heroin was abused extensively by servicemen, a substantial proportion of users took the drug orally (Brecher, 1972, p191).

Addiction to orally administered opiates was also common in the United States prior to their legal prohibition (Brecher, 1972, p3-6). Opiates were freely sold for oral use

by physicians, pharmacies, grocery stores, general stores, and by mail order. Opium was sold in penny sticks and pills, as well as such forms as Mrs. Winslow's Soothing Syrup, Darby's Carminative, Godfrey's Cordial, McMumm's Elixer of Opium, Dover's Powder, Ayers Cherry Pectoral, and Laudanum. Some of these substances may have been consumed for their alcohol content, but much of the opiates sold did not contain alcohol.

Much of the research which demonstrates that mammals will self-administer morphine is based on a type of negative reinforcement, paradigm, which is interpreted as showing that the animal acquires a preference for morphine by learning that it alleviates withdrawal symptoms.

This was most dramatically demonstrated by Nichols et al. (1956), who, as described above, forced rats to drink morphine solutions while they underwent withdrawal. This induced a drug preference which endured even when a tap water alternative was made available.

Withdrawal aversion may also explain experimental results obtained at the University of London (Kumar et al., 1968; Stolerman and Kumar, 1970; Kumar, 1972; Kumar and Stolerman, 1973). These researchers' typical procedure was to limit rats' access to fluid to a period between 10.00h and 17.00h each day. For two days, only morphine was available (forced trials), and on the third day, morphine

solution and tap water (choice trials). Withdrawal symptoms almost certainly developed in the 17 hours of fluid deprivation. Morphine consumption on choice trials increased substantially over baseline. In general, the experimental design resembles that of Nichols et al. (1956), and it is conceivable that the increased morphine selection is attributable to the same cause: learned avoidance of withdrawal symptoms.

It should also be emphasized that there is a substantial body of research which supports the conception that opioids are clearly aversive for rats and monkeys.

Some of the earliest work on morphine reinforcement was carried out by Spragg (1940). He demonstrated that chimpanzees would choose morphine if they were undergoing withdrawal, but not after the withdrawal symptoms had worn off. In his experiments, the animals were injected by the investigator in a special room. Chimpanzees undergoing withdrawal would clamour to be taken to the room, and on one occasion, a chimpanzee went to a cupboard to obtain a hypodermic syringe and handed it to the investigator and waited. These animals would also choose the syringe over a banana or orange when food deprived but undergoing withdrawal. However, these preferences disappeared after the effects of withdrawal had subsided.

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Using an entirely different paradigm, Beach (1957) found that physically dependent rats which had learned to associate one arm of a Y maze with an injection of morphine to alleviate withdrawal symptoms would prefer that arm after they had been withdrawn from the drug for three weeks. In an attempt to distinguish between the change-in-state effects of the drug immediately after injection, and the more enduring euphoric effects of the drug, Beach injected some animals 20 minutes prior to maze running. These animals did not come to prefer the morphine-associated arm, and Beach concluded that "euphoric effects of morphine do not constitute a reinforcement which makes for a durable habit".

Opioid-naive rats do not spontaneously drink significant amounts of morphine solution when they have a tap water alternative (Stolerman and Kumar, 1970). This has frequently been interpreted as reflecting the bitter taste of morphine rather than drug avoidance (Kumar et al., 1968). However, there is accumulating evidence that the pharmacological effects are also aversive.

One of the most convincing demonstrations of this was carried out by Chipkin and Rosecrans (1978). They employed methadone, which is qualitatively identical to morphine pharmacologically, except that it is more effective when given orally, and has a more extended duration of action in

suppressing withdrawal symptoms in physically dependent individuals (Jaffe and Martin, 1975). Chipkin and Rosecrans' technique was to present rats with a choice of drinking quinine or methadone solutions, both in varying concentrations. Experimental animals received daily injections of naltrexone, a potent, long acting, and nearly pure opioid antagonist (Blumberg and Dayton, 1974).

Control animals did not receive naltrexone injections. When the quinine concentration was low enough, all animals preferred quinine solution, and when the quinine concentration was high, the rats selected methadone. However, when the two fluids were taste balanced, the rats treated with naltrexone drank equal amounts of each fluid, while saline treated rats avoided the methadone. The aversion appeared to become more pronounced over the course of the 20 day experiment. Chipkin and Rosecrans concluded that methadone is aversive for rats, that taste factors alone cannot explain these observations, and that the aversion is caused by the narcotic effect of methadone, since naltrexone blocked it.

Opioid aversion was also observed by Wikler and Pescor (1970). They gave rats access to etonitazene (which is tasteless in the concentrations they used; Goldstein, 1976), either (group one) after a four month dependence inducing regimen or, (group two) after no previous opioid exposure.

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group one
group two

In the following 336 days, rats were given 8 'relapse tests', which were two bottle choice tests using tap water and etonitazene solution (5 mcg/ml). Group one consistently consumed more than group two, but reduced their etonitazene solution intake from approximately 40 ml to approximately 10 mls per day. Group two consumed about 10ml the first day, but subsequently reduced their intake to virtually zero. The downward trends of these data seem incompatible with the idea that opioid exposure by itself produces craving of sufficient intensity to support continued self-administration. This especially applies to group two, which seemed to avoid etonitazene after a few exposures.

Huidobro (1964) used different methods, but arrived at similar results. Although he failed to submit his data to rigorous statistical analyses, he found that:

(1) rats avoid morphine if given a choice between it and tap water.

(2) they also avoid morphine solutions if the major gustatory nerves (lingual and glossopharyngeal) are sectioned.

(3) when given a choice, rats will choose water over morphine solution even with gustatory denervation and when undergoing withdrawal distress.

Using another method, similar results were obtained by Coombs (1977). His experiment was to derive by taste

testing the solutions, equally bitter concentrations of Quinine Sulfate (.1mg/ml) and Morphine Hydrochloride (.5mg/ml). Both were in 5% sucrose solution, and the morphine solution contained a weak concentration of 'Tang' artificial orange juice which would permit the rat to distinguish the fluids. Rats were presented with both fluids for 21 days. In the first few hours of the experiment, equal amounts of each fluid were consumed. Within a few days, however, morphine consumption dropped to nearly nil. The authors proposed that this was due to the aversive qualities of morphine.

Very strong evidence for the negative aspects of morphine arises from work with conditioned taste aversions (CTA). The essence of this technique (first reported by Garcia et al., 1955) involves permitting an animal to consume a novel food or liquid, and then inducing illness in the animal in a variety of ways. The animal then typically avoids the novel stimulus, even if the experience of illness did not occur until several hours after consumption. Garcia et al. (1974) and others have hypothesized that in rats and primates, any substance which is perceived to cause

Recent research has used a variety of drugs in this paradigm to induce taste aversion. Some workers (Jacquet, 1973; Cappell et al., 1973; Le Blanc and Cappell, 1974; Farber et al., 1976) have used morphine. All of these investigators have demonstrated that after several pairings of morphine injections with the presentation of a novel fluid, the animals subsequently avoid that fluid. The narcotic properties of morphine appears to be the specific cause of the CTA, because Le Blanc and Cappell (1975) have demonstrated that the formation of tolerance, which reduces the morphine effects, also reduces the strength of the aversion. Furthermore, narcotic antagonists can prevent the aversion from occurring. This seems to represent clear evidence that in this paradigm, morphine has aversive properties.

The Present Experiment

In summarizing this body of research, the question of whether morphine is reinforcing or punishing remains unanswered because of conflicting evidence. The answer is difficult to obtain, because self-injection paradigms contain an ineradicable stress component, and in oral paradigms, any rejection of morphine may be attributed to the drug's bitterness. The present experiment's purpose is

to present morphine to rats in such a way that bitterness does not influence the pattern of self-administration, and stress is minimized. For this purpose, the oral route of ingestion was selected.

The present experiment made use of the two bottle choice test technique, with a very bitter quinine alternative. This was to ensure that any morphine aversion could not be attributed to taste, and to impel each animal to sample the drug. Relative bitterness was determined by taste testing -- there is excellent evidence that rats have similar bitter taste thresholds to humans (see Discussion). Sugar was added to both fluids to increase palatability, and to reduce mortality from dehydration, which was observed in earlier research (Alexander et al., 1978). The presence of sugar in both alternatives ensured that the nutritive value would not affect preferences.

In the event that some of the animals rejected the morphine and drank quinine, it was decided to implement a subsequent phase of the experiment, in which an opioid antagonist would be introduced. By cancelling the narcotic effect of the morphine, the antagonist would make it possible to compare fluid preferences with and without the narcotic effect. For this purpose, naltrexone was selected. Naltrexone (N-cyclopropylmorphine) is a potent, nearly pure morphine antagonist of high oral efficacy and

long duration of action which completely blocks the pharmacological effects of morphine (Blumberg and Dayton, 1974). In order to avoid the stress of injections, and to ensure that the antagonist was administered contiguously to the morphine dosage, it was decided to administer it orally, by adding it to the existing fluids.

Finally, a third phase was thought necessary, in which the quinine was removed in order to determine if radical taste interactions occur between naltrexone and morphine, and if naltrexone caused changes in bitterness aversion.

Method

Subjects

The subjects were 9 male and 9 female rats of Wistar origin purchased from the University of British Columbia colony, 45-55 days old at the beginning of the experiment. The animals had lived in individual cages since weaning, 20 days before the experiment began. None of these rats had been previously exposed to opioid drugs. Food was available ad libitum throughout the experiment, and tap water was present until the first day.

Apparatus

The rats were housed in standard 18 cm by 15 cm by 18 cm wire bottomed laboratory cages. Liquid was dispensed from standard laboratory water bottles, with rubber stoppers and stainless steel nipples. Fluid consumption was measured by daily weighing of the water bottles on each cage. A correction factor for spillage, leakage and evaporation was generated by the use of four control bottles attached to empty cages. The daily values of the correction factor varied between .5 and 2.5 g. Bottle position was reversed on days 5, 12, 19, and 26 of the experiment to guard against position preference.

Procedure

Prior to the beginning of the experiment, the rats were given a choice of tap water and 8% sucrose solution for three days. This was to reduce the novelty of sucrose solutions. The subsequent 31 days were divided into three experimental phases, distinguished by the choice of fluids offered the animals (see Table I). Throughout the experiment, the rats had a choice of two fluids, both of which consisted of tap water plus 8% sucrose, plus some concentration of morphine hydrochloride, quinine sulfate, and/or naltrexone hydrochloride.

Phase One: Days 1-14

The rats were offered a free choice between .5 mg/ml morphine hydrochloride in the sucrose vehicle and .2 mg/ml quinine sulfate in the sucrose vehicle. In previous research, (Coombs, 1977), it was found that for rats and humans, .5 mg/ml morphine was about equally palatable to .1 mg/ml quinine. In this experiment, the quinine concentration was doubled to ensure that it was more bitter than the morphine. Thus, on the grounds of palatability, rats would be impelled to drink the morphine. To the human palate, the morphine tasted sweet and slightly bitter --

much like tonic water -- while the quinine solution was sweet, but very much more bitter.

Phase Two: Days 15-21

In this phase, .1 mg/ml naltrexone hydrochloride was added to both fluids used in Phase One. At this concentration naltrexone did not appreciably change the taste of either fluid, but it cancelled the psychoactive effects of the morphine (Blumberg and Dayton, 1974), so that fluid preferences were determined only by taste.

Phase Three: Days 22-31

In the third phase, quinine was removed from the second fluid. Thus, the rats had a choice between .5 mg/ml morphine plus .1 mg/ml naltrexone, in the sucrose vehicle, and .1 mg/ml naltrexone in the sucrose vehicle.

TABLE I. Fluid choices in the three experimental phases.

	PHASE		
	1	2	3
CHOICE 1	.5 mg/ml morphine hydrochloride	.5 mg/ml morphine hydrochloride and .1 mg/ml naltrexone hydrochloride	.5 mg/ml morphine hydrochloride and .1 mg/ml naltrexone hydrochloride
CHOICE 2	.2 mg/ml quinine sulfate	.2 mg/ml quinine sulfate and .1 mg/ml naltrexone hydrochloride	.1 mg/ml naltrexone hydrochloride

Results

Phases One and Two

During the first two days of the experiment, total fluid consumption by all animals was substantially below normal. Several animals drank almost nothing. Within five days, most animals had resumed drinking normal quantities (see Figure 1). Several showed evidence of dehydration, and one (number 8) showed such critical signs that it was necessary on day 12 of the experiment to inject 7 ml of physiological saline intraperitoneally in order to maintain body fluid levels. The animal subsequently recovered.

Because very little fluid was consumed during the first two days, the validity of proportion calculations for these days is suspect, since they are based on very small quantities. For example, an animal which consumed .1 g quinine and no morphine technically preferred 100% quinine, even though .1 g amounts to a few drops of fluid, and the average daily spillage was approximately 1.5 g. For these reasons, all data analyses using proportions omit the first two days of consumption.

In Phase One, the total fluid consumption of the rats was approximately one half morphine and one half quinine solution. In Phase Two, the rats consumed almost 90%

naltrexone-morphine solution. Morphine consumption as proportion of total fluid intake was compared in the two phases by means of the Wilcoxon matched pairs signed ranks test (Siegel, 1956). The change in fluid preference was significant ($N= 18$, $T= 11$, $P<.01$, two tailed). This pattern was present in both males and females (see Figure 2) ..

However, the distribution of fluid preferences in Phase One was strongly bimodal, and this trend became more pronounced over the course of this phase, until each animal came to prefer one or the other fluid almost exclusively (see Figure 21). Because of the bimodality, no animals were accurately represented by any measure of central tendency. These features of the data made parametric statistics, with their assumption of an underlying normal distribution, inappropriate. Furthermore, it was clear that two separate populations had emerged in Phase One: animals which consumed mostly quinine, and animals which consumed mostly morphine.

The predominant change between Phases One and Two was that the quinine consuming rats shifted to the naltrexone-morphine, while the morphine consuming rats did not shift, selecting naltrexone-morphine in Phase Two. Most rats entered into these categories unambiguously, as is evident from visual inspection of their preference records

(Figures 3-20). In order to verify this, non-parametric statistical analyses were undertaken. The proportion of morphine solution to total fluid intake of each animal was treated as a separate collection of observations for Phases One and Two, which were then compared by the Mann-Whitney U test (Siegel, 1956). Based on the results of these tests, it was possible to classify each rat according to the presence or absence of a significant ($\alpha = p < .05$, two tailed) change in fluid preference between Phases One and Two (see Table II). Rats were classified as:

QM Subjects (N=10; 6 females, 4 males). Those which consumed mostly quinine solution in Phase One, and consumed mostly naltrexone-morphine in Phase Two. These rats all showed a significant increase in morphine preference between Phase One and Phase Two.

MM Subjects (N=7; 2 females, 5 males). Those which consumed mostly morphine solution in Phase One, and mostly naltrexone-morphine in Phase Two. These rats did not show a significant change in morphine preference between Phase One and Phase Two.

MQ Subjects (N=1; female). Those which consumed mostly morphine in Phase One, and mostly naltrexone-quinine in Phase Two. This rat showed a significant decrease in morphine preference between Phase One and Phase Two.

QQ Subjects (N=0). Those which consumed mostly quinine in Phase One and mostly naltrexone-quinine in Phase Two. Although no animals were present in this category, they would have been expected to show no significant change in quinine preference between Phase One and Phase Two.

In Phase Three, the fluid consumption shifted again, so that most rats strongly preferred the naltrexone solution over the naltrexone-morphine. The Wilcoxon matched pairs signed ranks test (Siegel, 1956) was used to compare Phase Two and Phase Three. The decrease in naltrexone-morphine consumption was significant ($N= 18, T= 0, p<.01$, two tailed). The variance was relatively large, but the distribution of preferences was not bimodal (see Figure 21). Although all animals preferred naltrexone solution for the first two days of Phase Three, as it progressed, there was a general upward trend in naltrexone-morphine consumption. The Wilcoxon matched pairs signed ranks test was used to compare the first three days of Phase Three with the last three days. This revealed a statistically significant increase ($N= 18, T= 18, p<.01$, two tailed).

TABLE II. Assignment of rats to categories according to results of Mann-Whitney U tests.

RAT	GENDER	U	N_1	N_2	P	CATEGORY ASSIGNMENT
1	F	31.5	7	10	N.S.	MM
2	F	7	7	10	<.02	QM
3	F	9	7	10	<.02	QM
4	F	2	7	8	<.002	QM
5	F	13	7	10	<.05	QM
6	F	0	7	10	<.002	QM
7	F	4	7	9	<.02	MQ
8	F	21	7	9	N.S.	MM
9	F	7	7	10	<.02	QM
10	M	0	7	10	<.002	QM
11	M	34	7	10	N.S.	MM
12	M	24	7	10	N.S.	MM
13	M	21	7	7	N.S.	MM
14	M	22	7	8	N.S.	MM
15	M	2	7	9	<.002	QM
16	M	0	5	9	<.002	QM
17	M	29	7	9	N.S.	MM
18	M	0	5	10	<.002	QM

Figure 1. All subjects -- Total fluid consumption (M+Q) in Phase One.

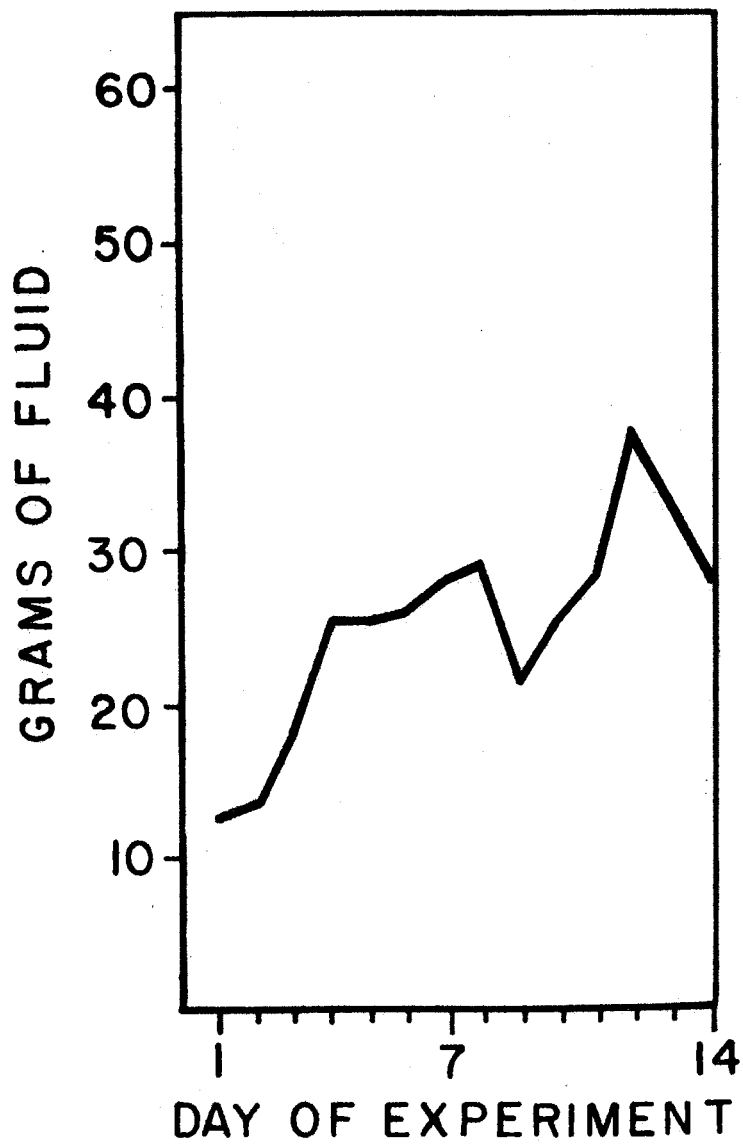


Figure 2. Female, Male subjects -- Morphine consumption as proportion of total fluid intake.

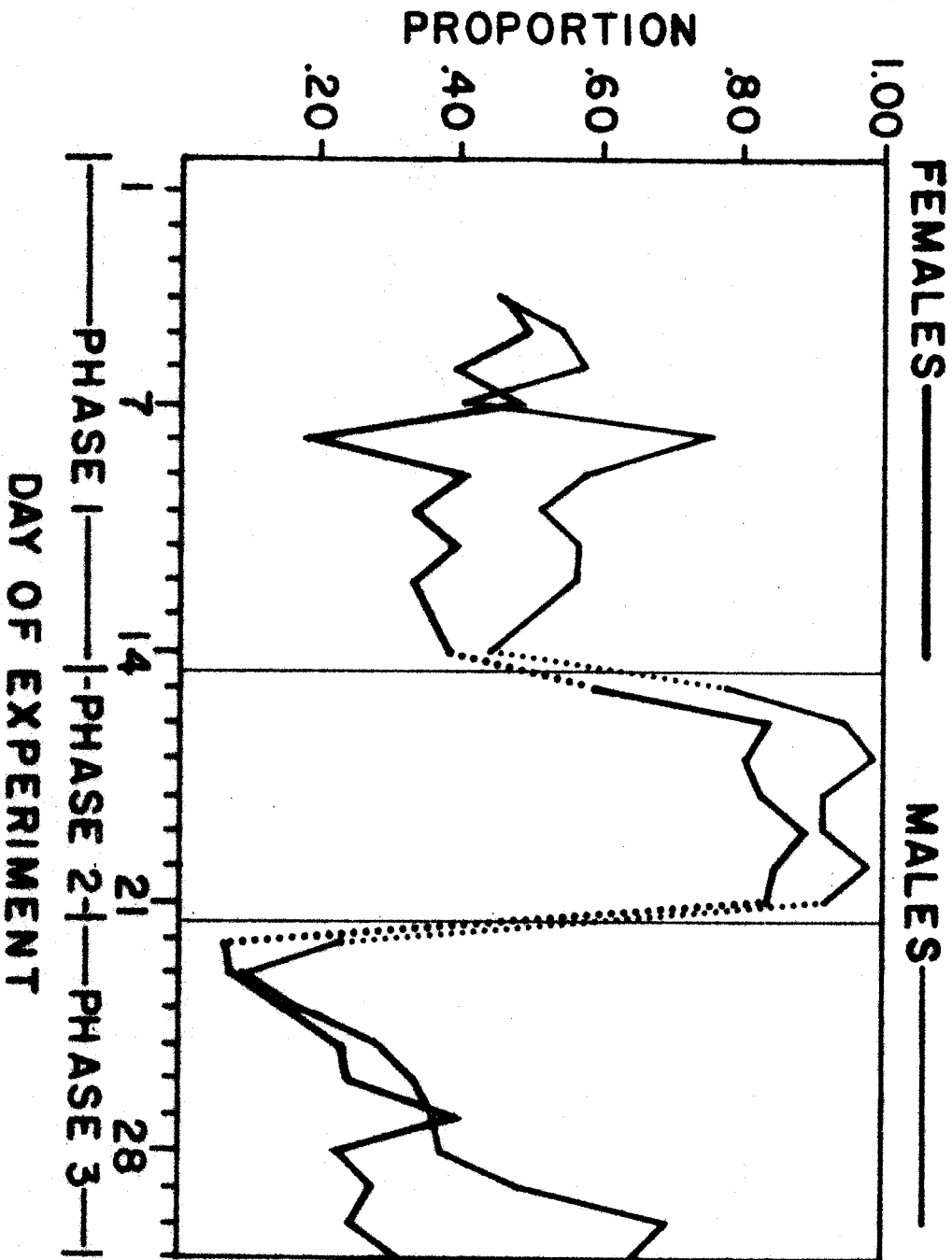
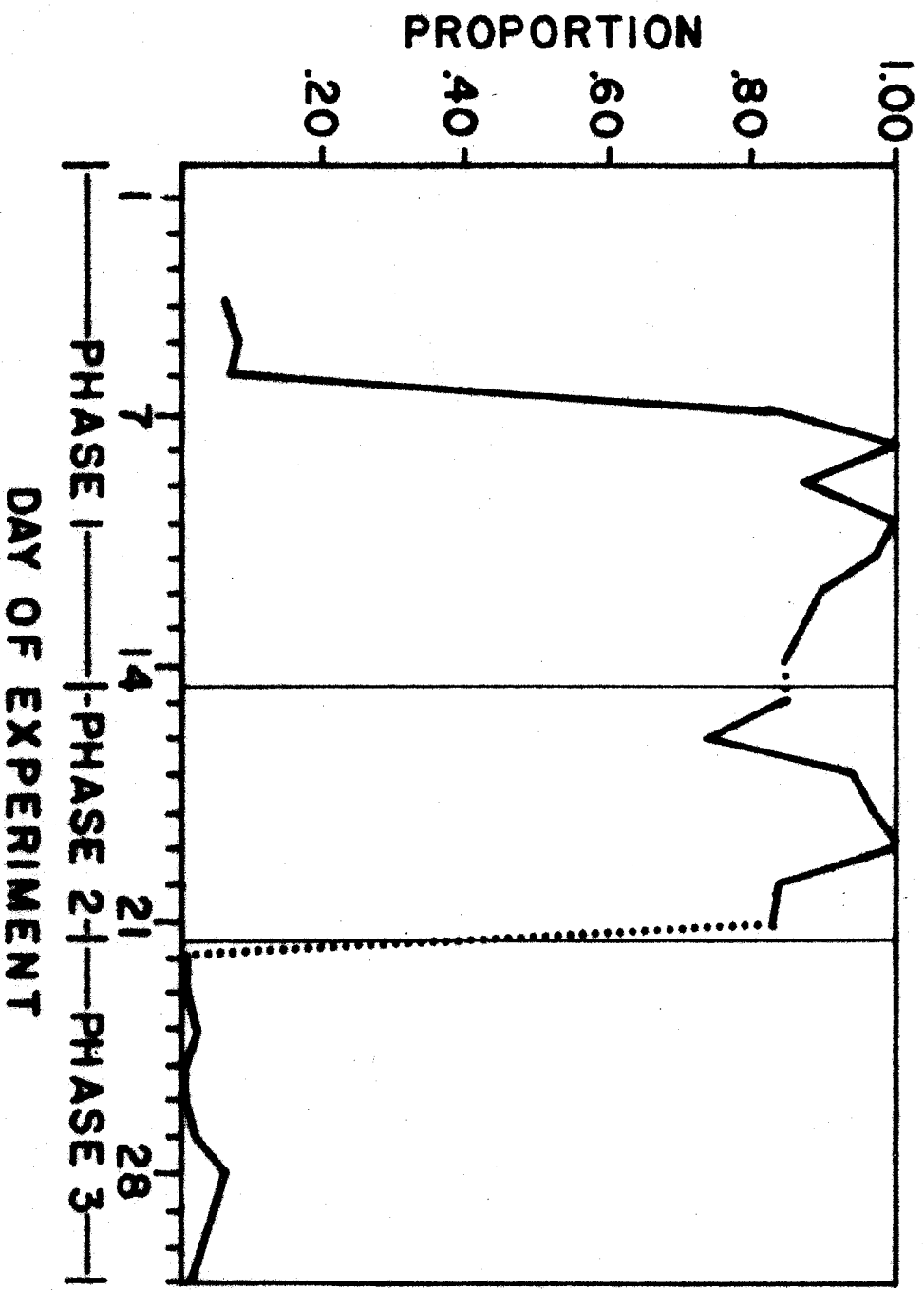


Figure 3. Rat 1 (female; category MM) Morphine consumption as proportion of total fluid intake.



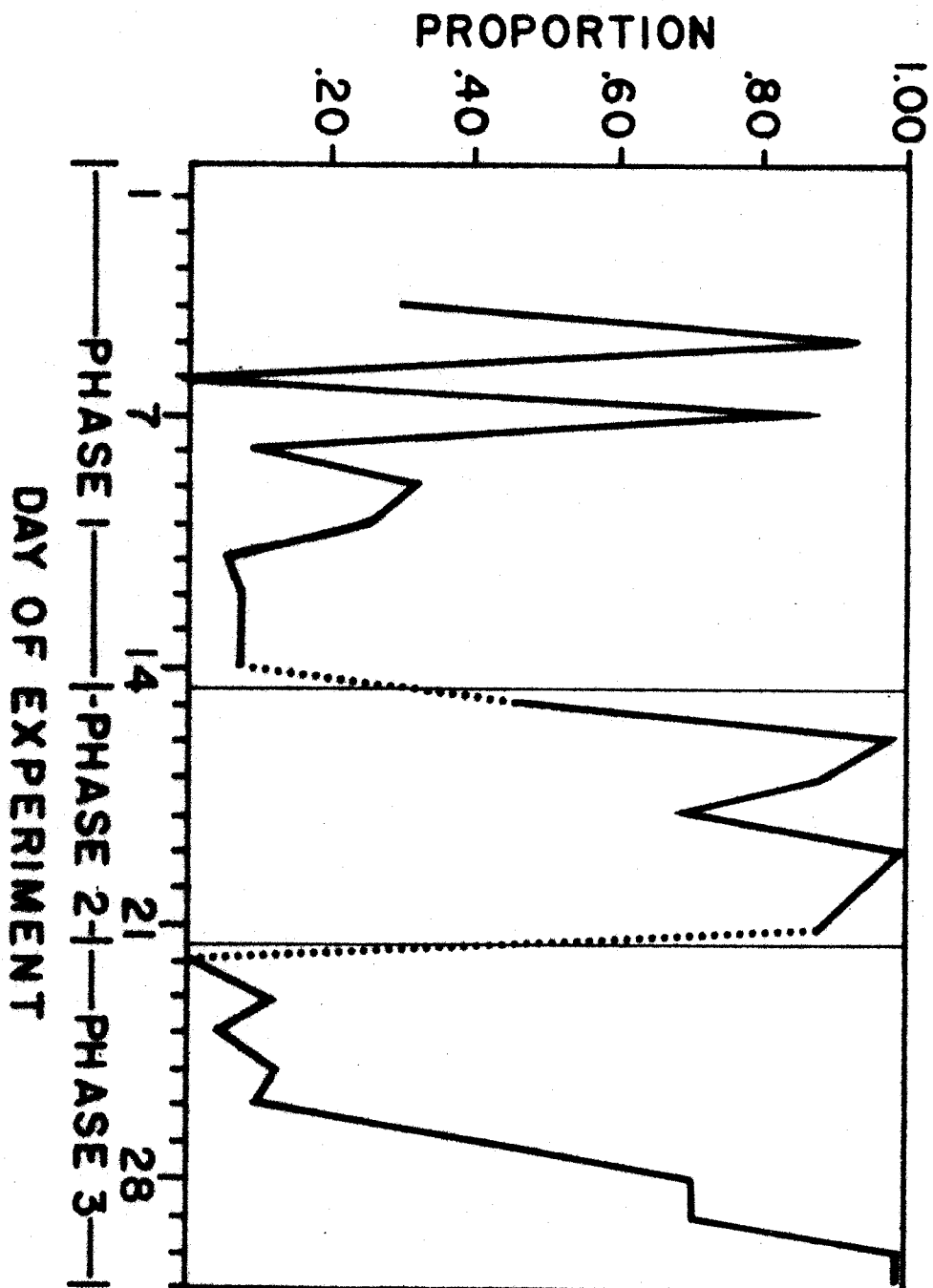


Figure 4. Rat 2 (female, category QM) Morphine consumption as proportion of total fluid intake.

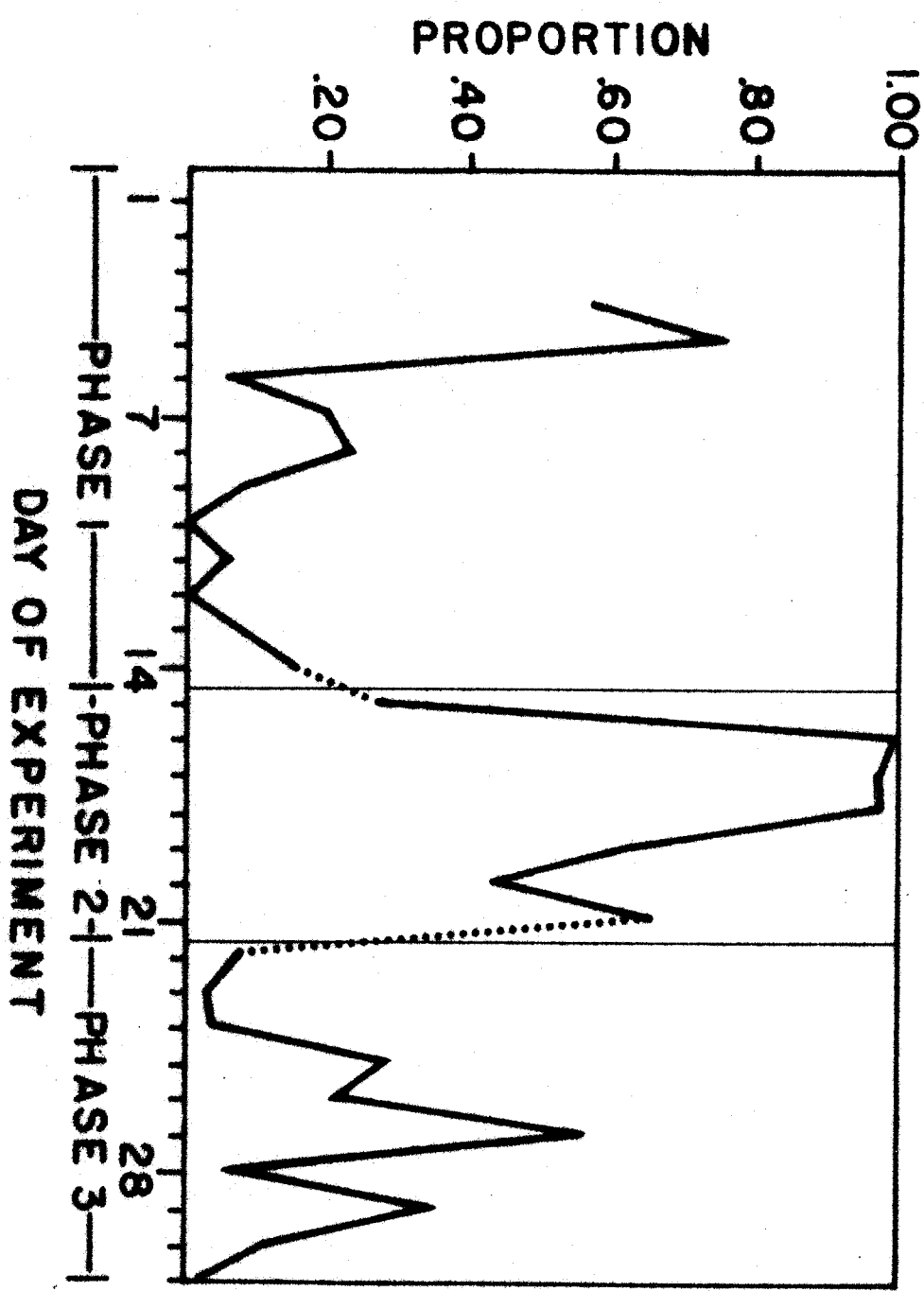


Figure 5. Rat 3 (female, category OM) Morphine consumption as proportion of total fluid intake.

Figure 6. Rat 4 (female, category Q4) Morphine consumption as proportion of total fluid intake.

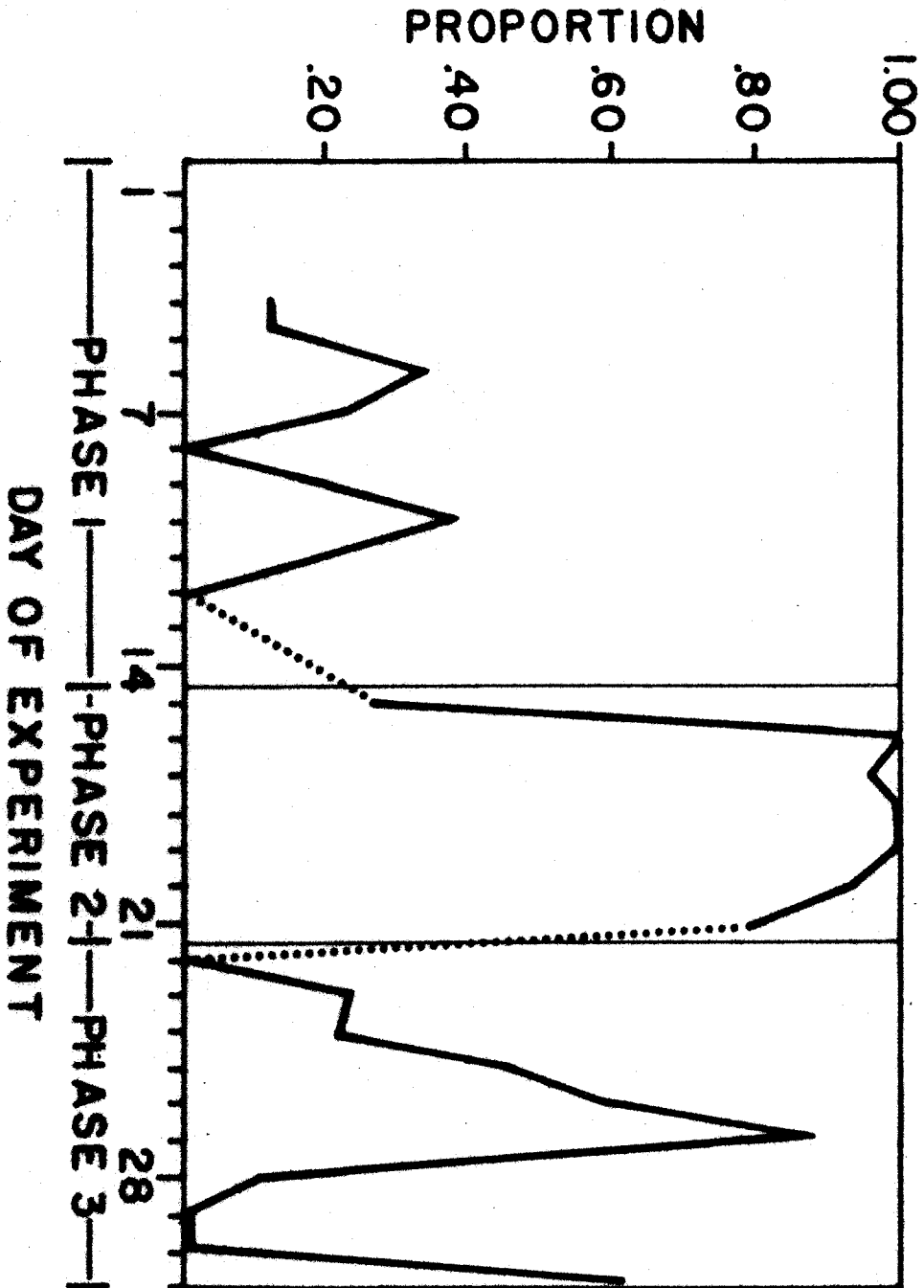


Figure 7. Rat 5 (female, category Q4) Morphine consumption as proportion of total fluid intake.

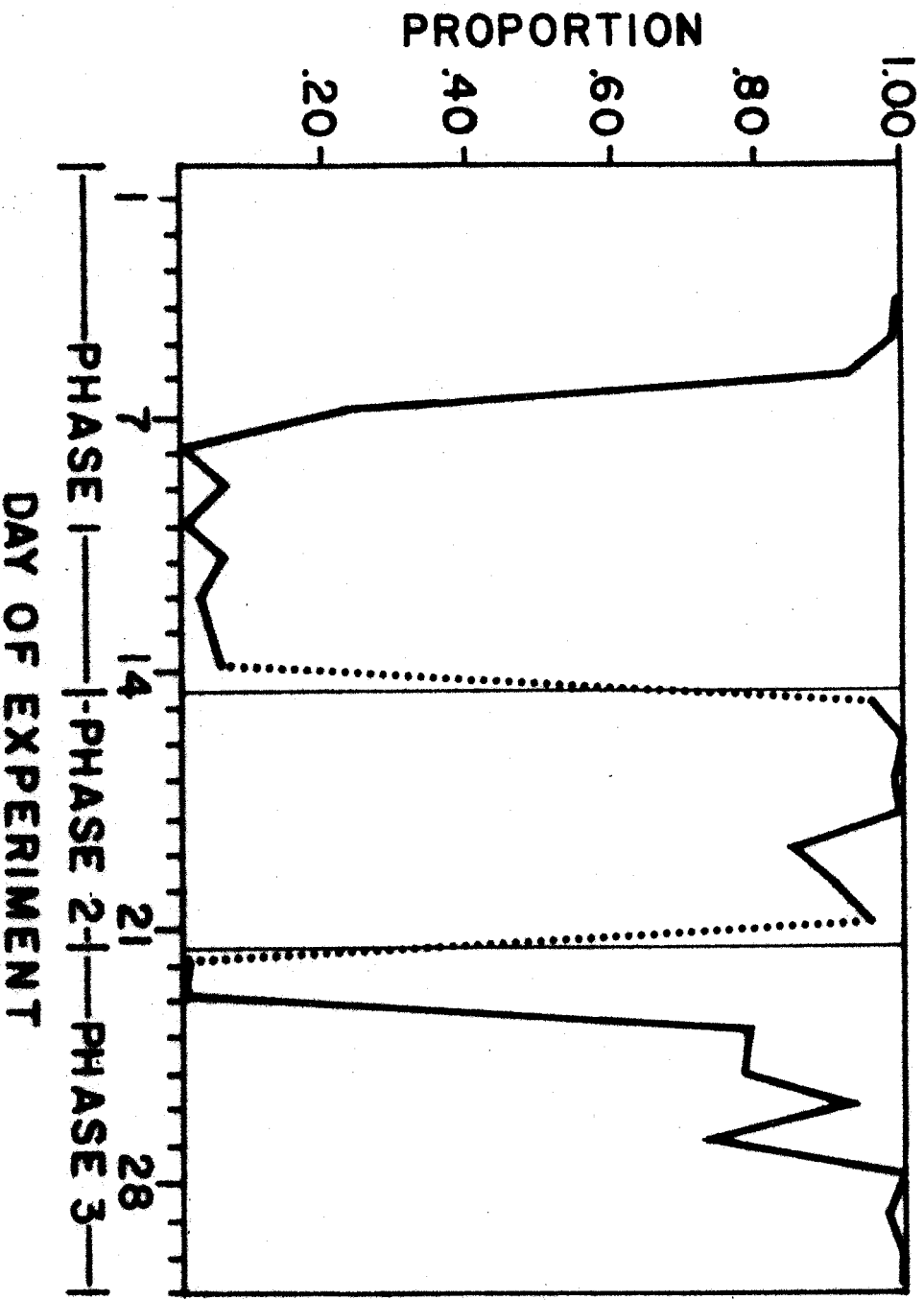


Figure 8. Rat 6 (female, category OM) Morphine consumption as proportion of total fluid intake.

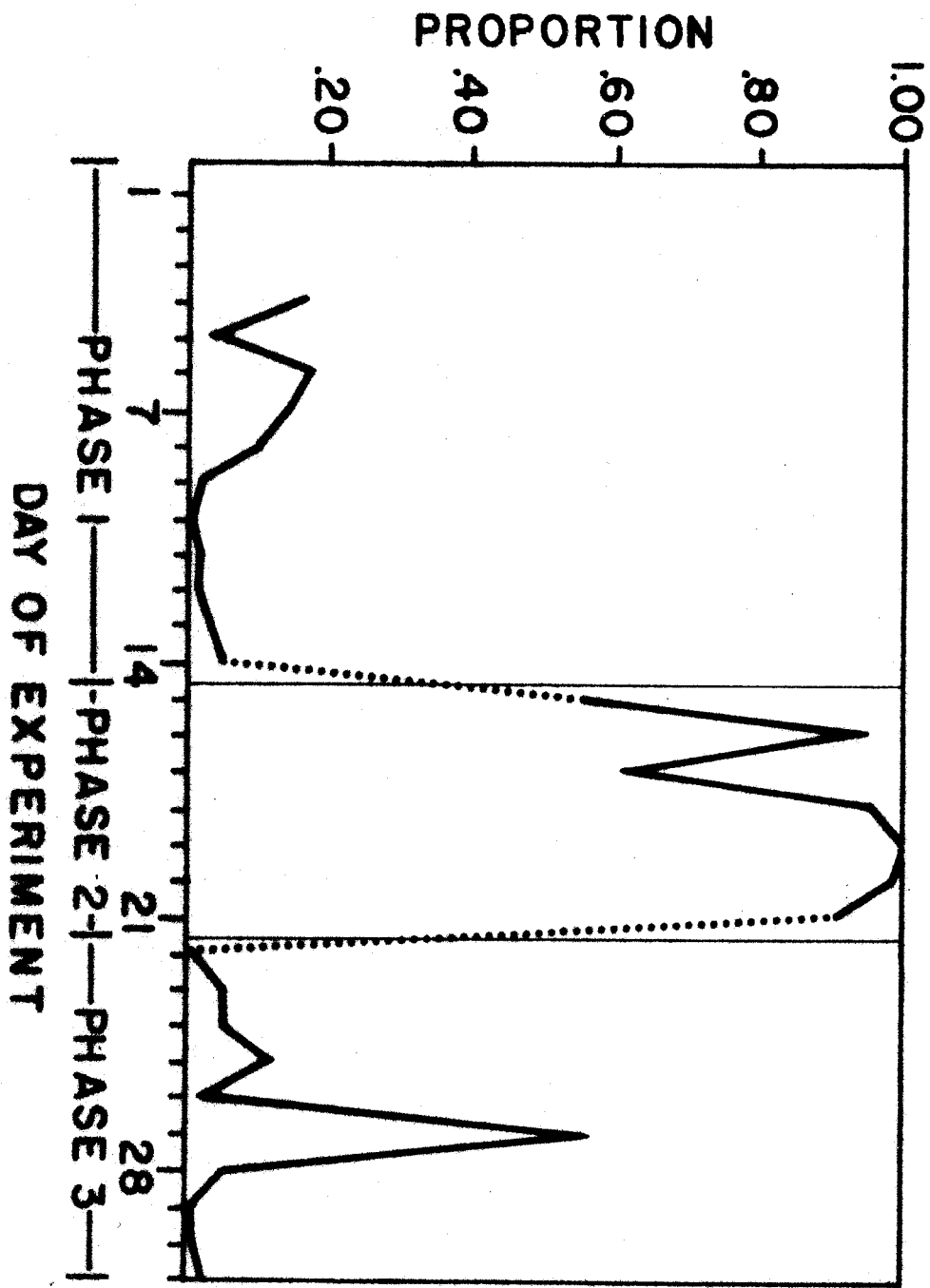


Figure 9. Rat 7 (female, category MQ) Morphine consumption as proportion of total fluid intake.

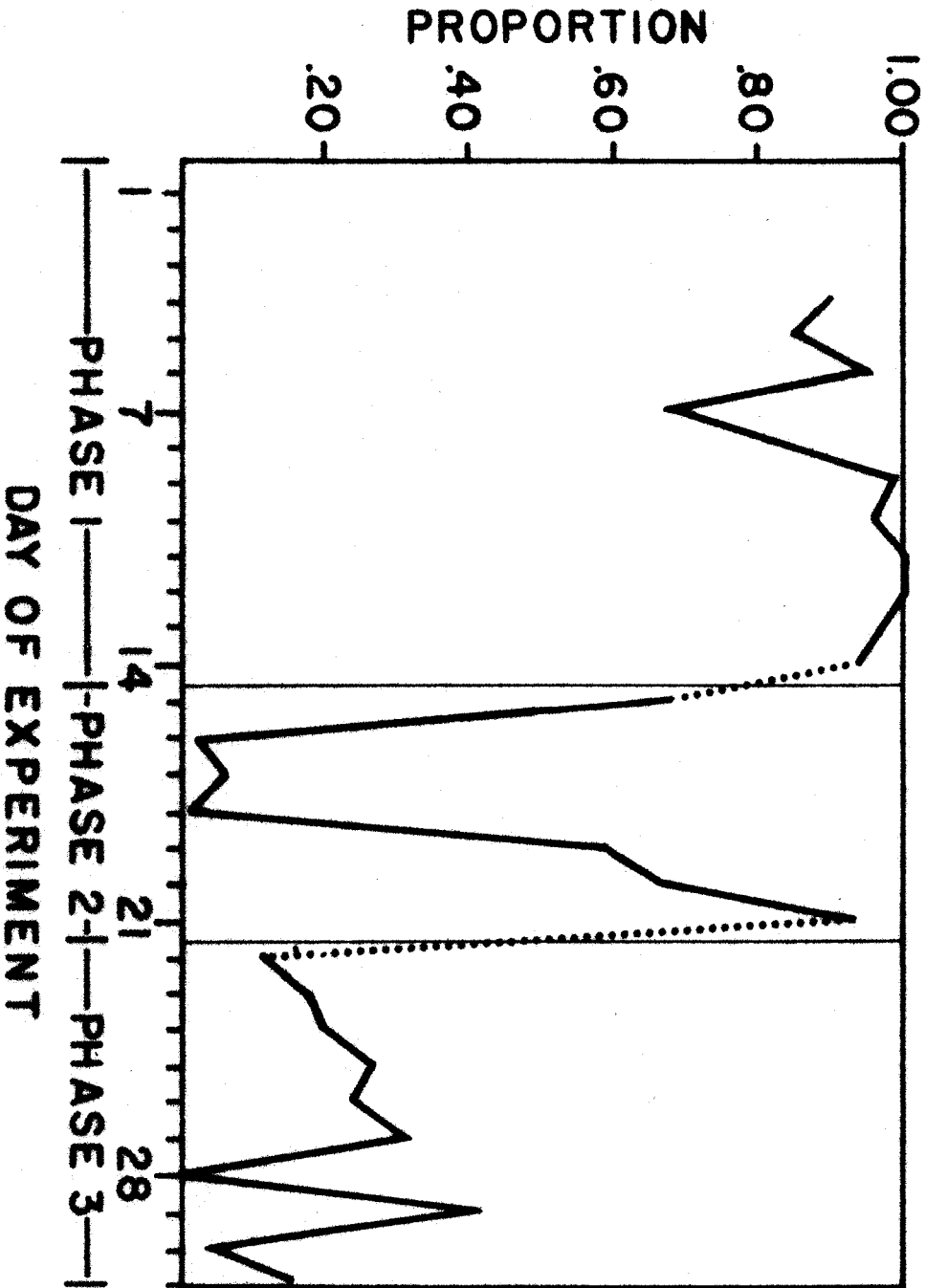


Figure 10. Rat 8 (female, category MM) Morphine consumption as proportion of total fluid intake.

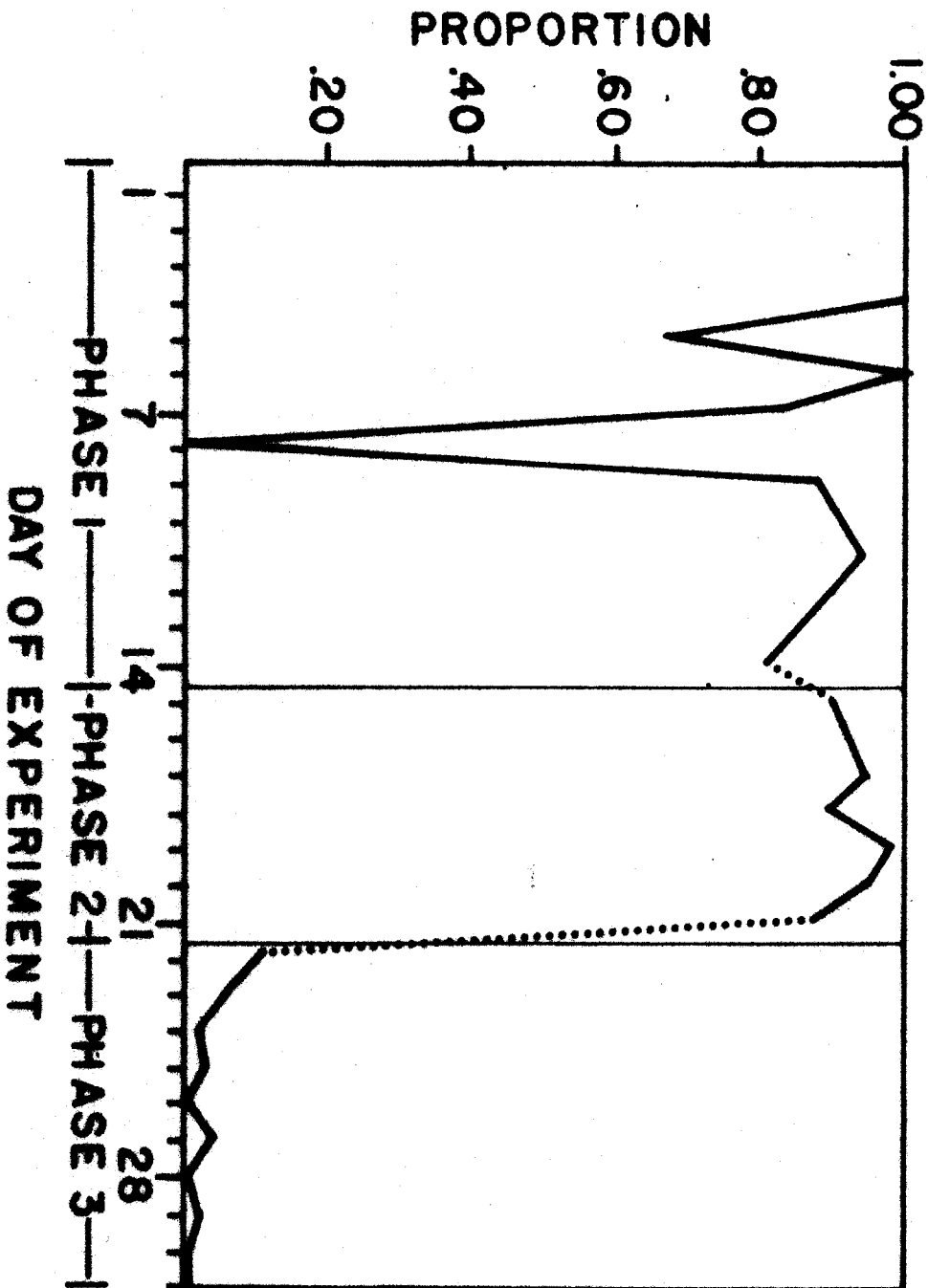


Figure 11. Rat 9 (female, category QM) Morphine consumption as proportion of total fluid intake.

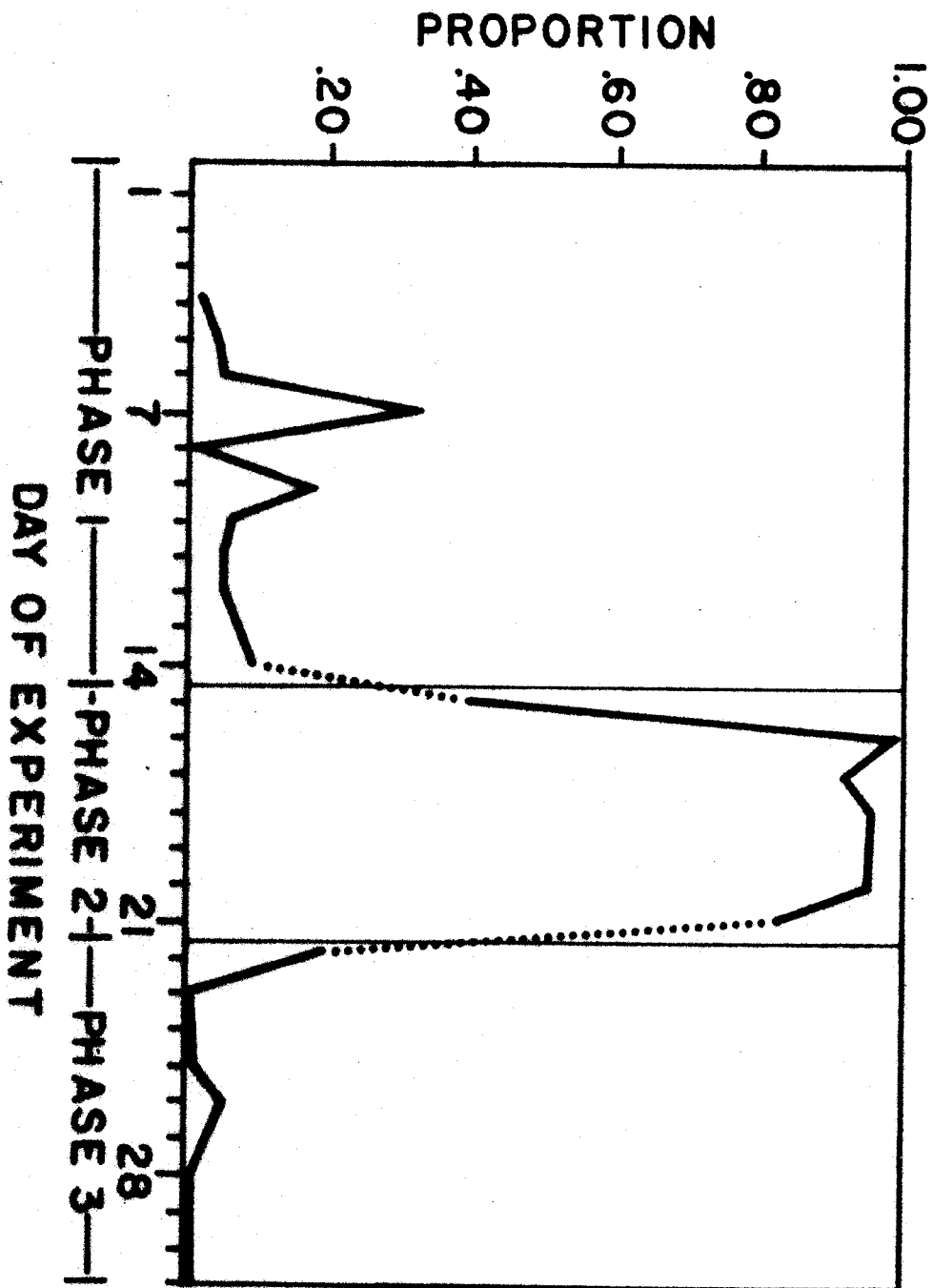


Figure 12. Rat 10 (male, category QM) Morphine consumption as proportion of total fluid intake.

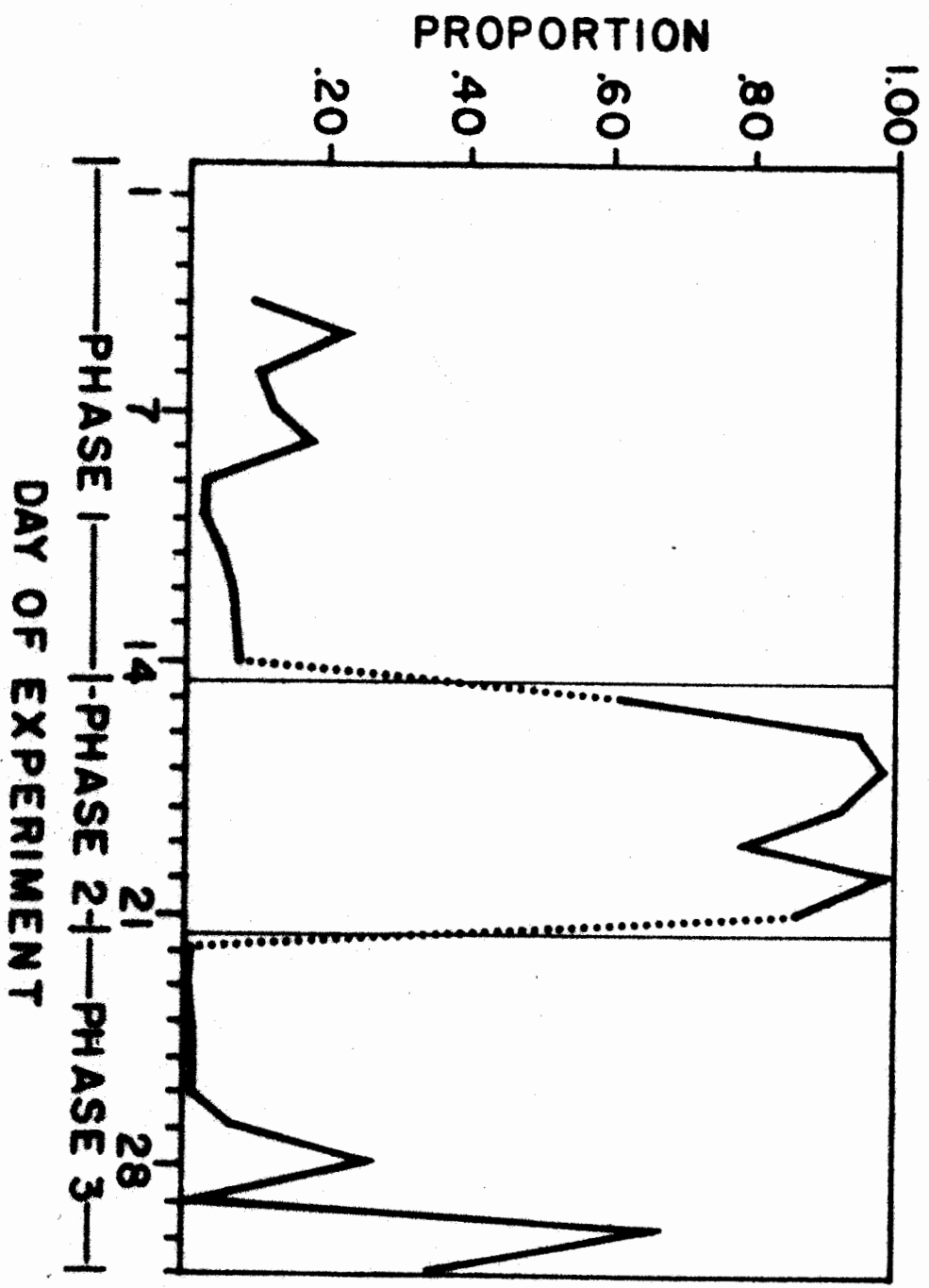


Figure 13. Rat 11 (male, category MM) Morphine consumption as proportion of total fluid intake.

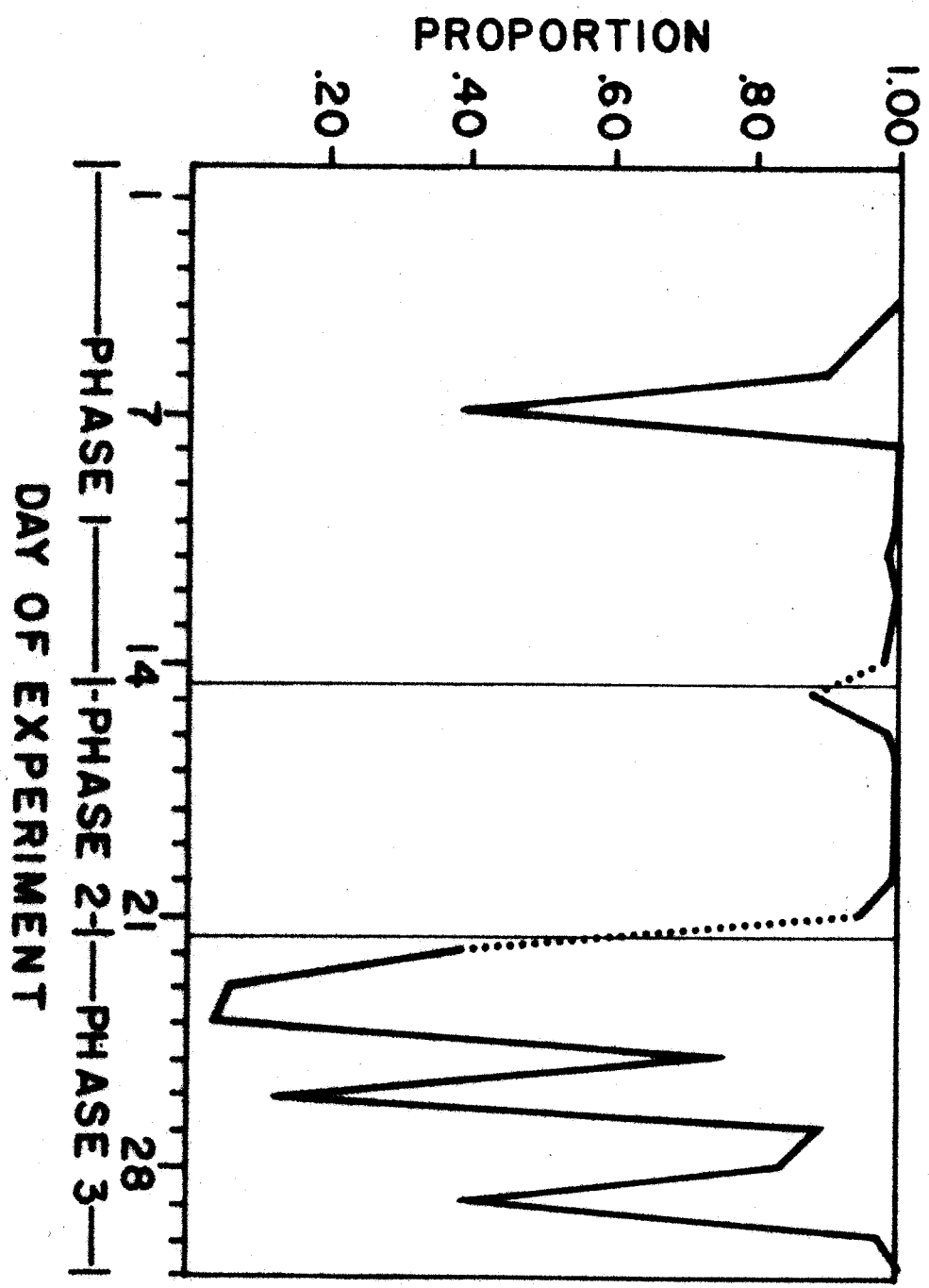


Figure 14. Rat 12 (male, category M1) Morphine consumption as proportion of total fluid intake.

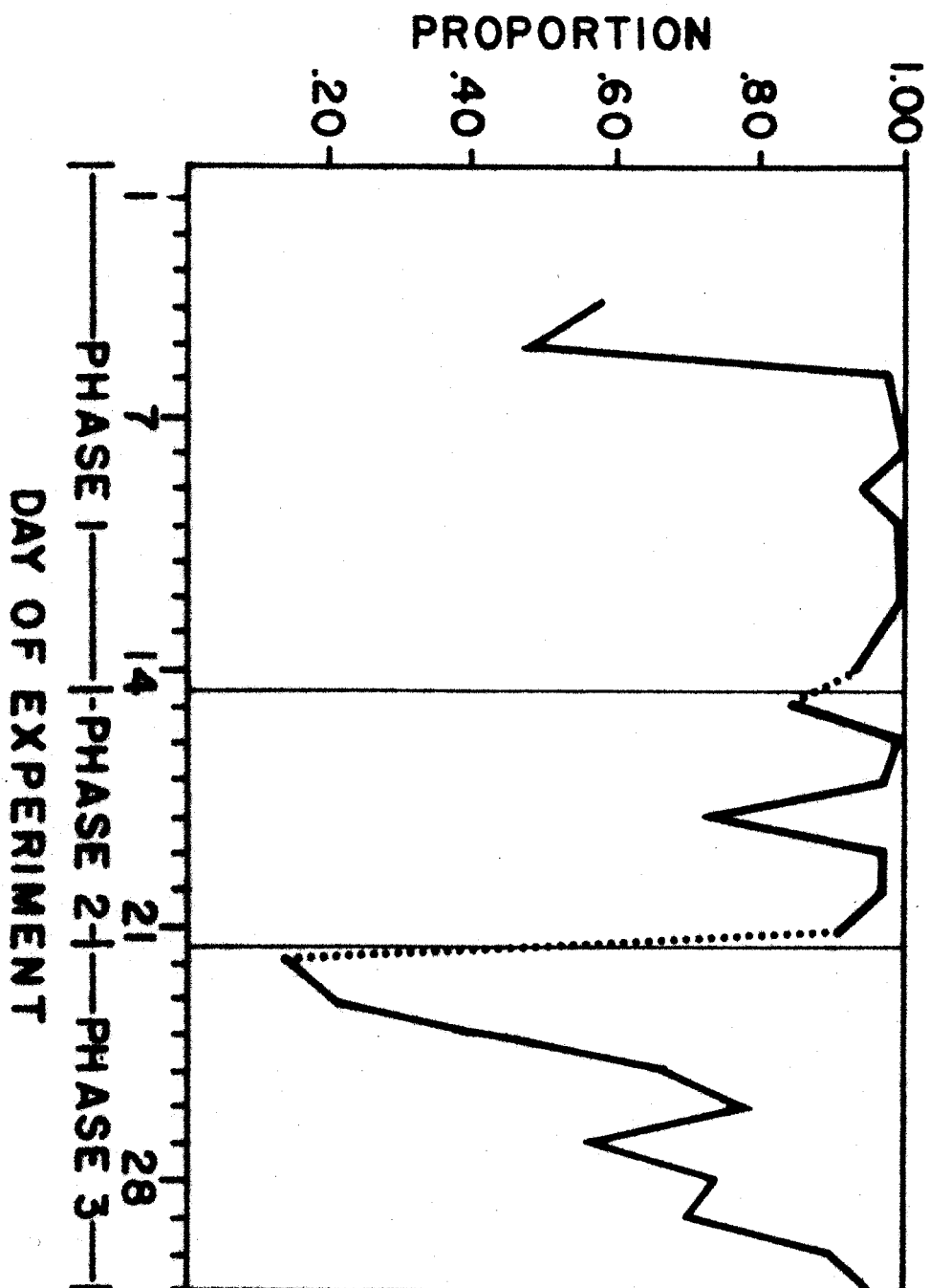


Figure 15. Rat 13 (male, category MM) Morphine consumption as proportion of total fluid intake.

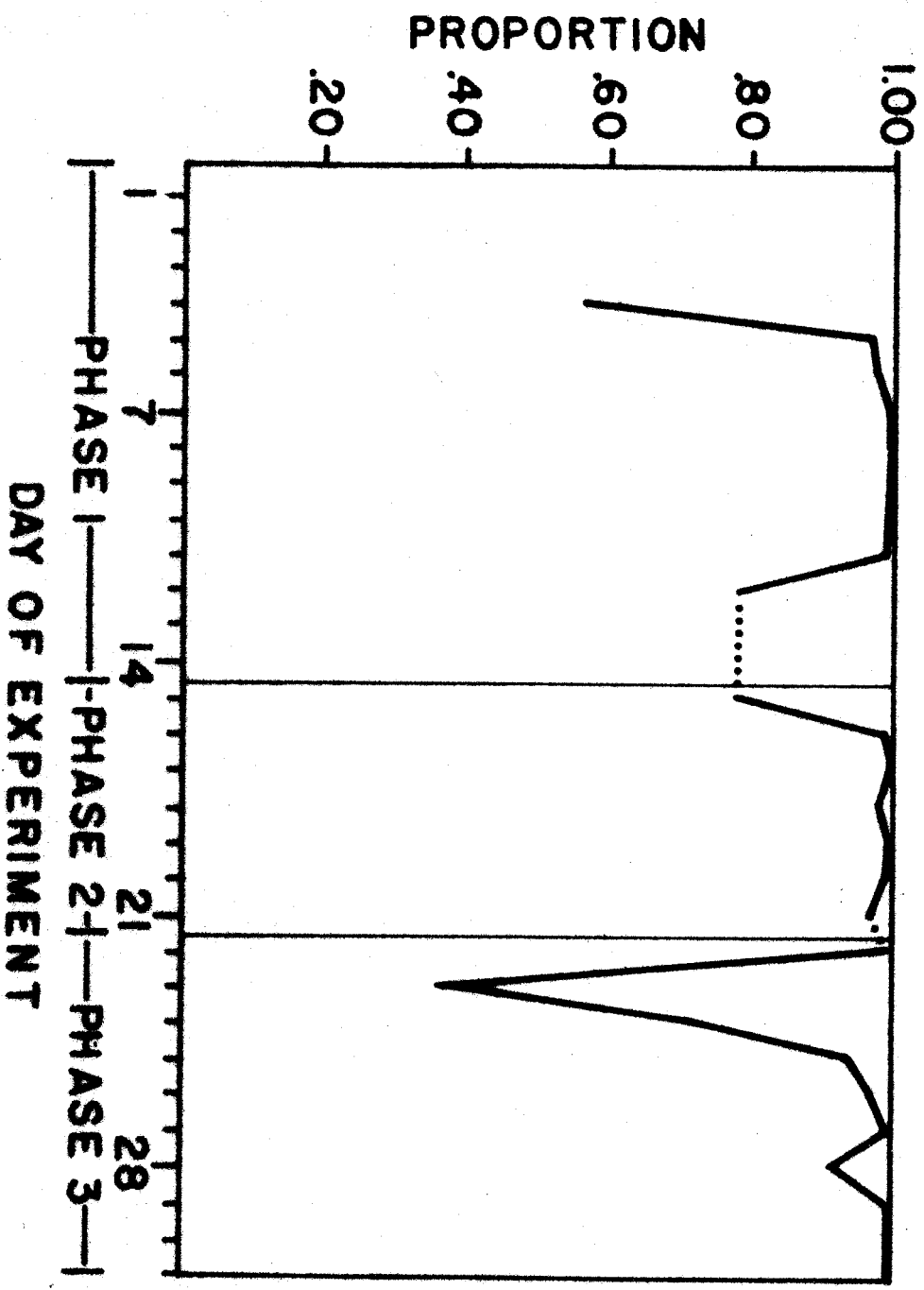


Figure 16. Rat 14 (male, category MM) Morphine consumption as proportion of total fluid intake.

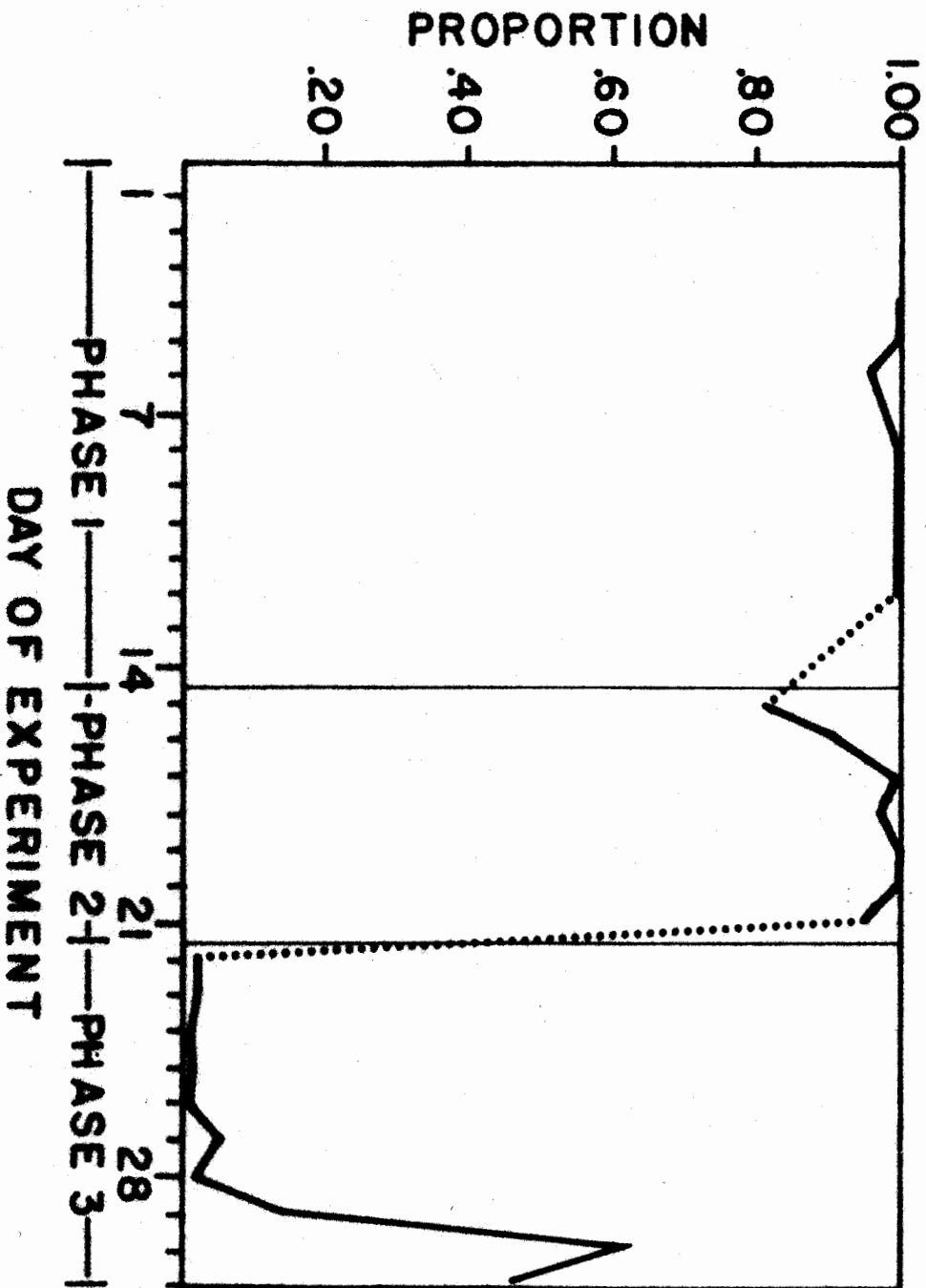


Figure 17. Rat 15 (male, category QM) Morphine consumption as proportion of total fluid intake.

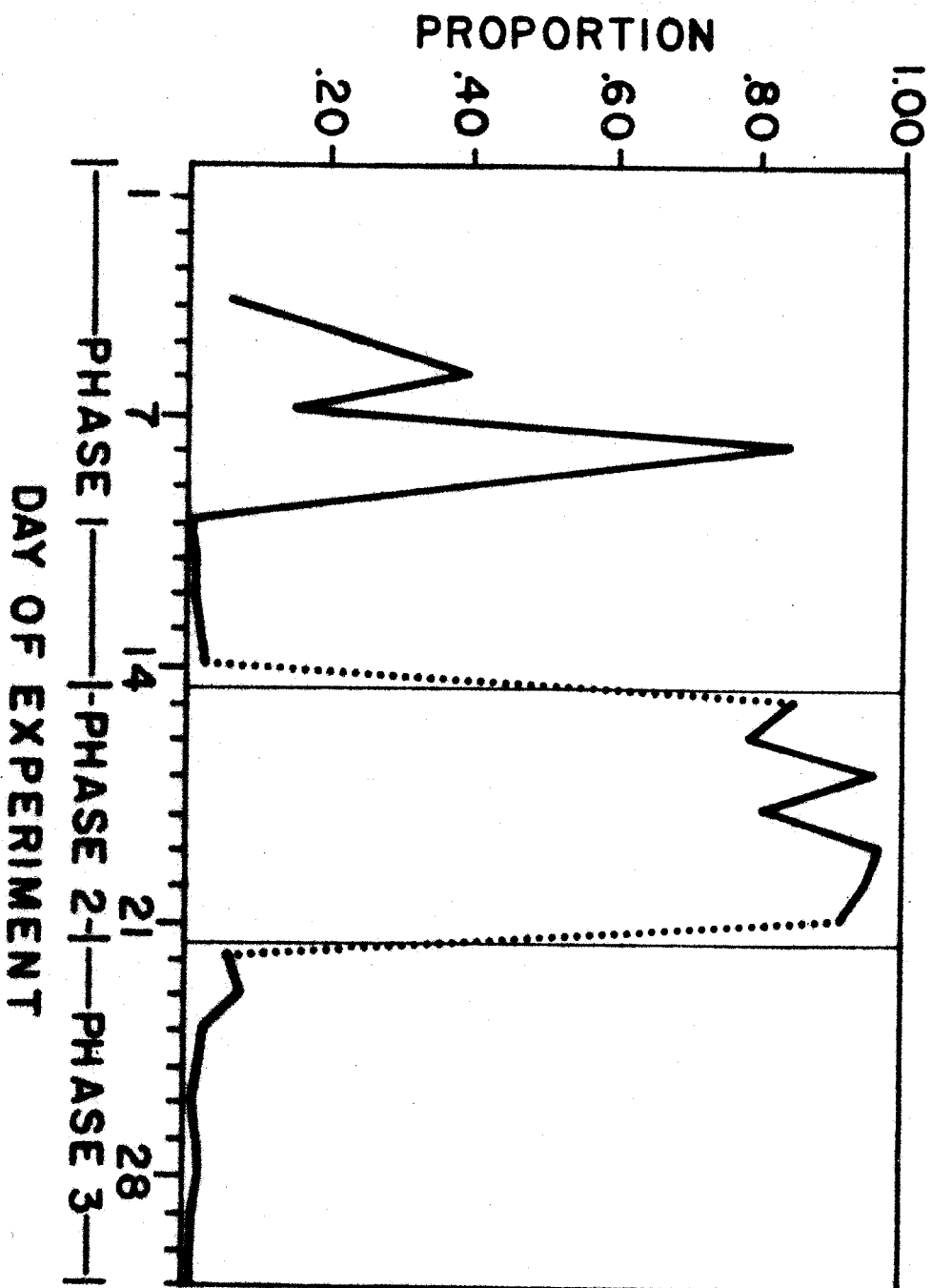


Figure 18. Rat 16 (male, category Q1) Morphine consumption as proportion of total fluid intake.

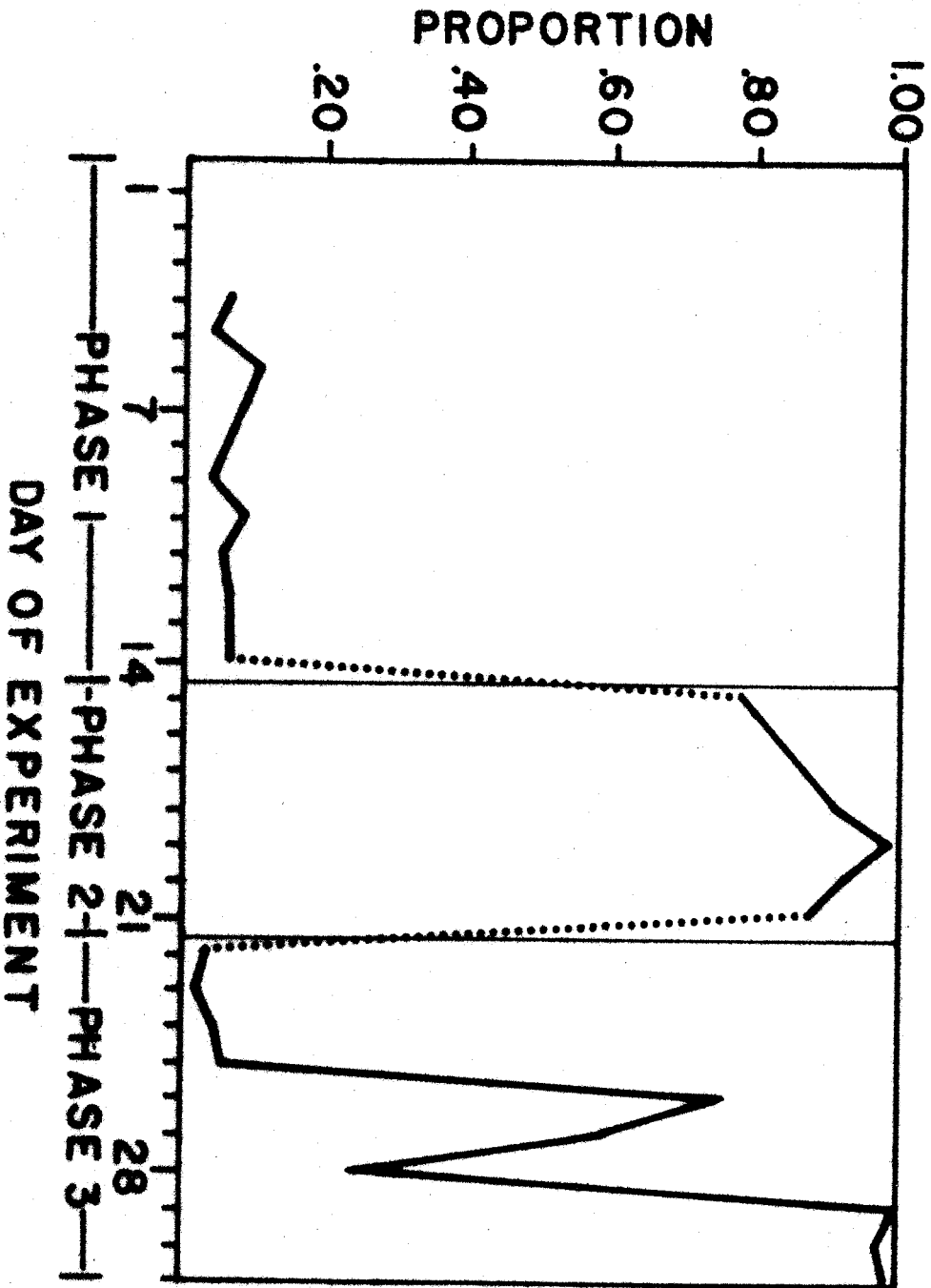


Figure 19. Rat 17 (male, category M) Morphine consumption as proportion of total fluid intake.

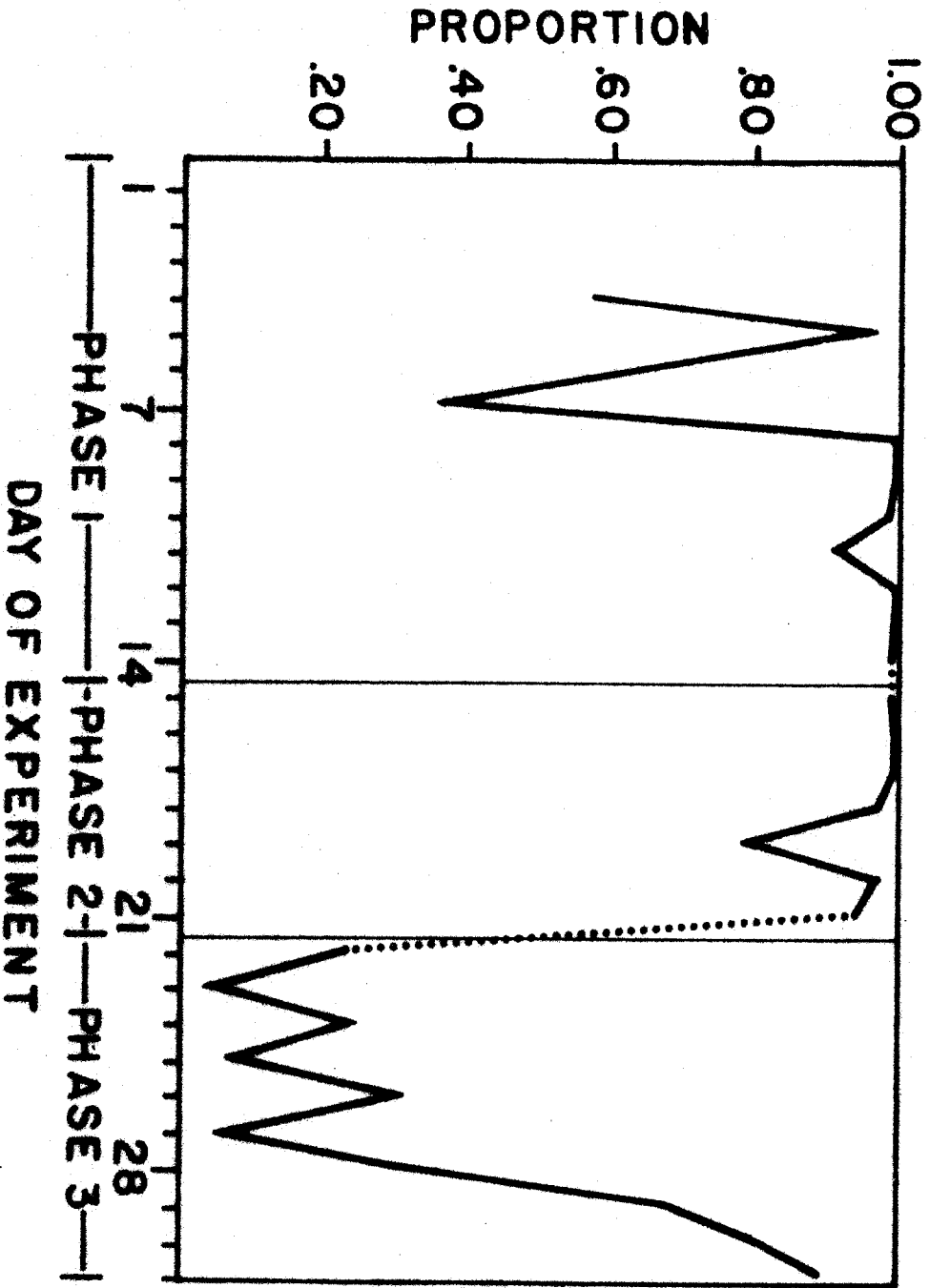
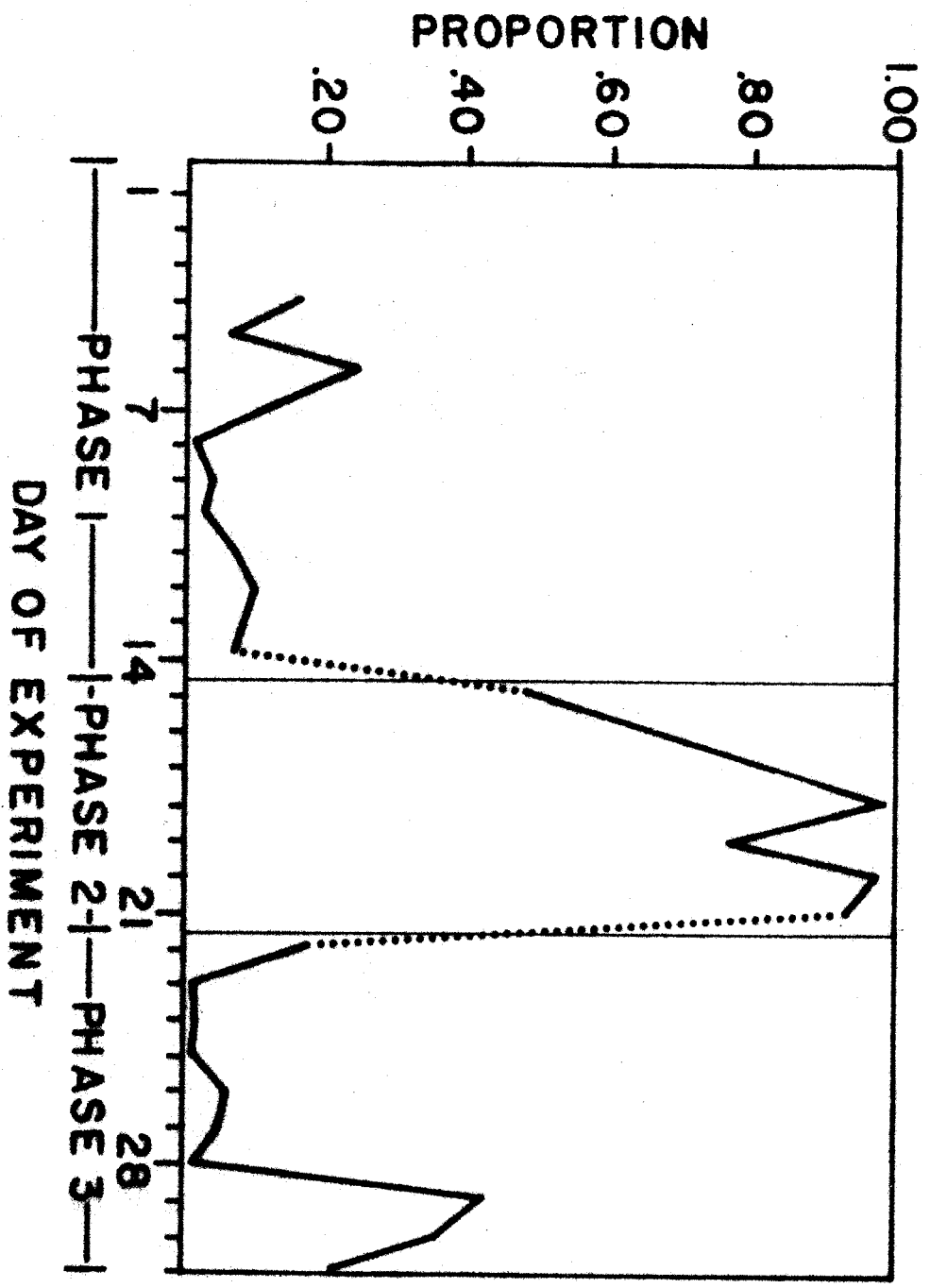


Figure 20. Rat 18 (male, category QM) Morphine consumption as proportion of total fluid intake.



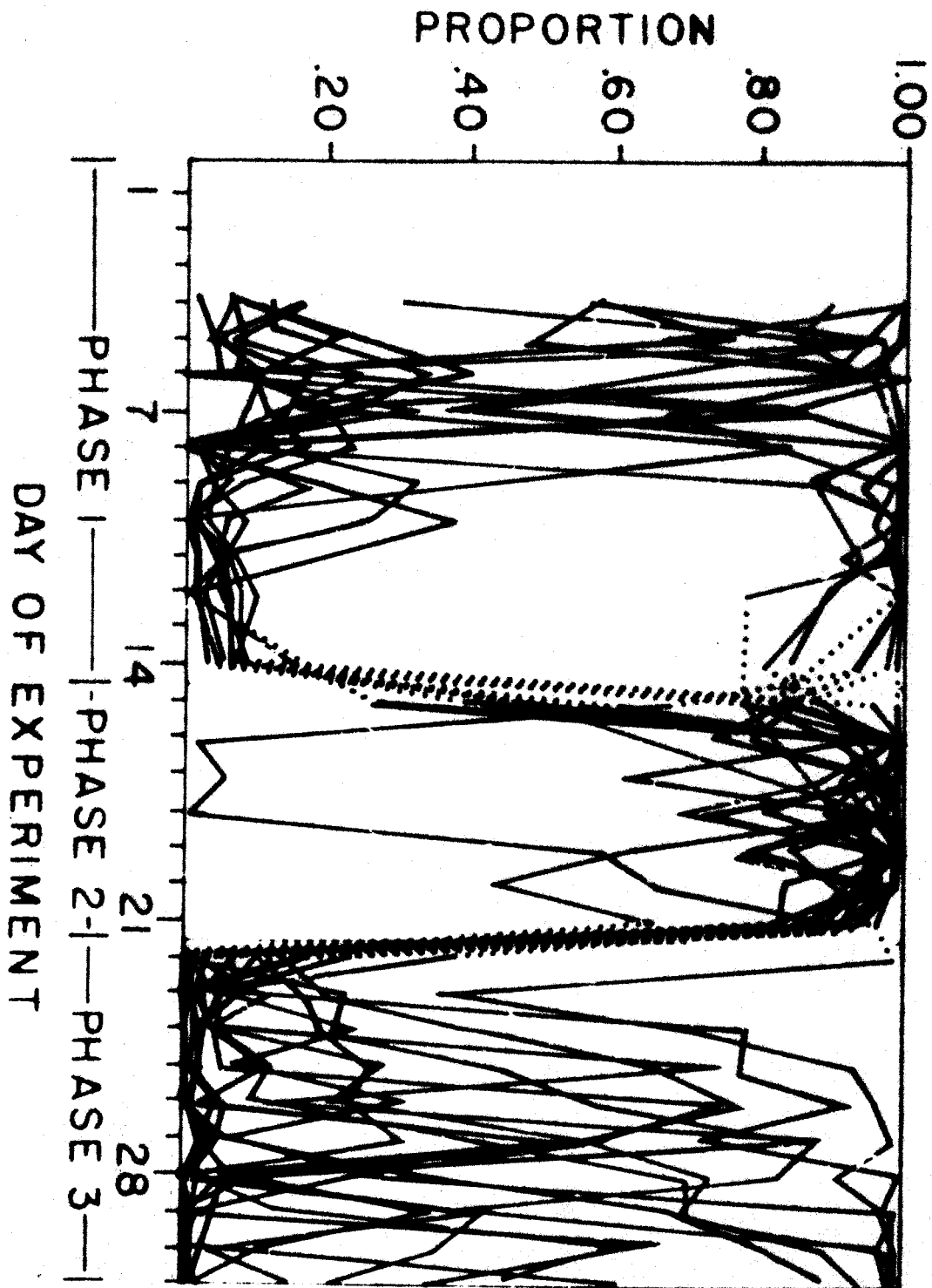


Figure 21 - All subjects, each represented separately. Morphine consumption as proportion of total fluid intake.

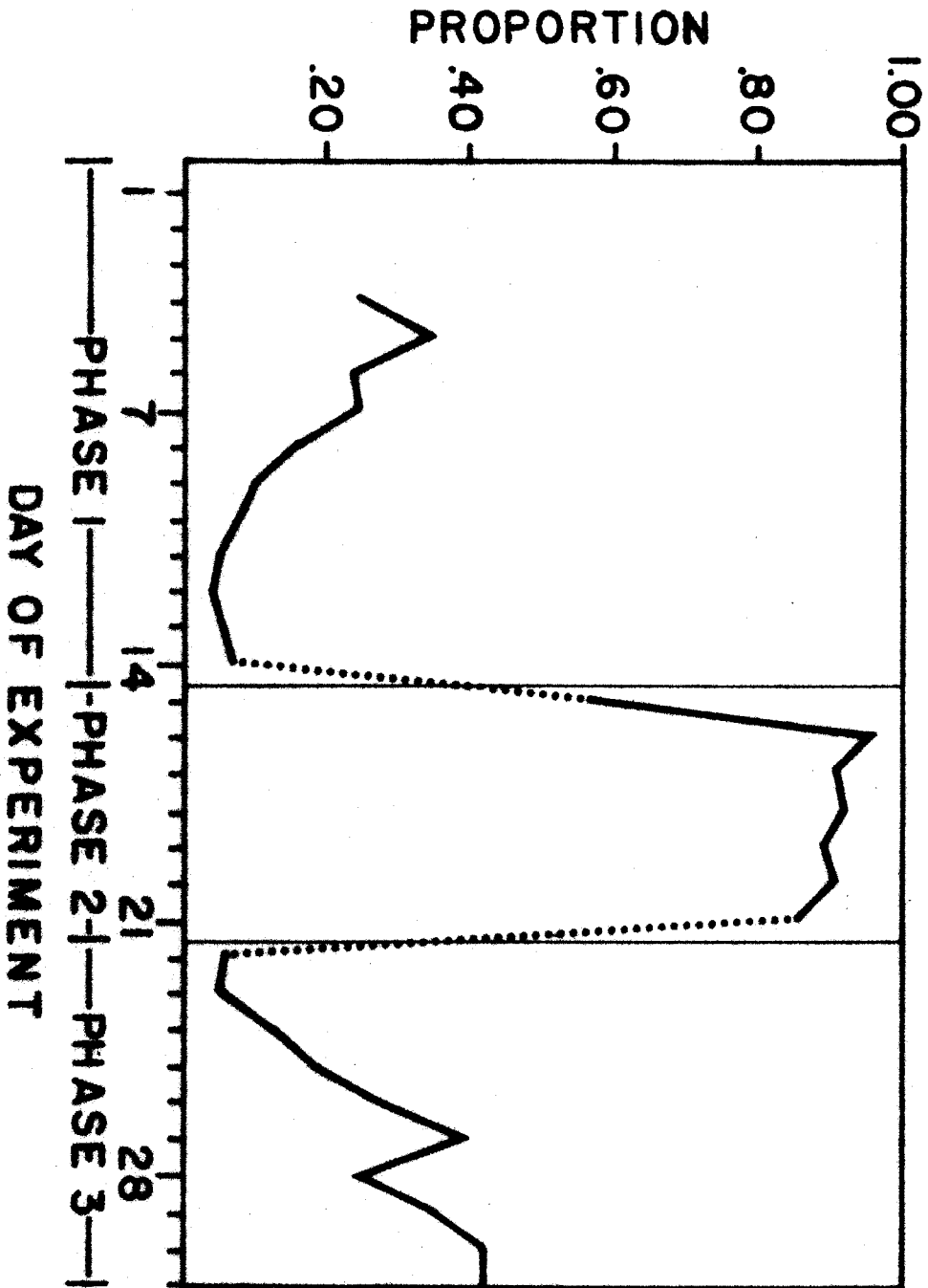


Figure 22. QM Subjects -- Morphine consumption as proportion of total fluid intake.

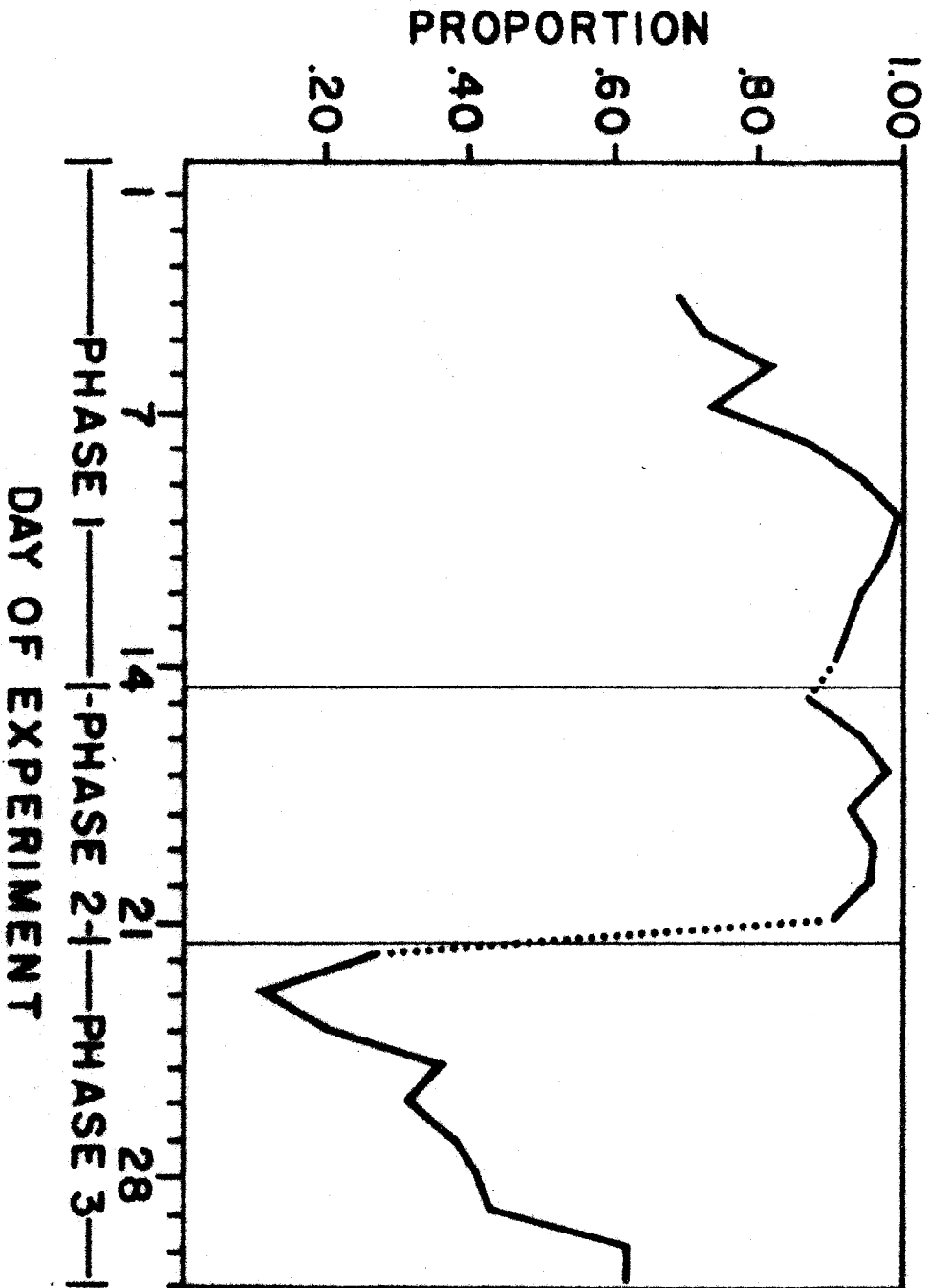
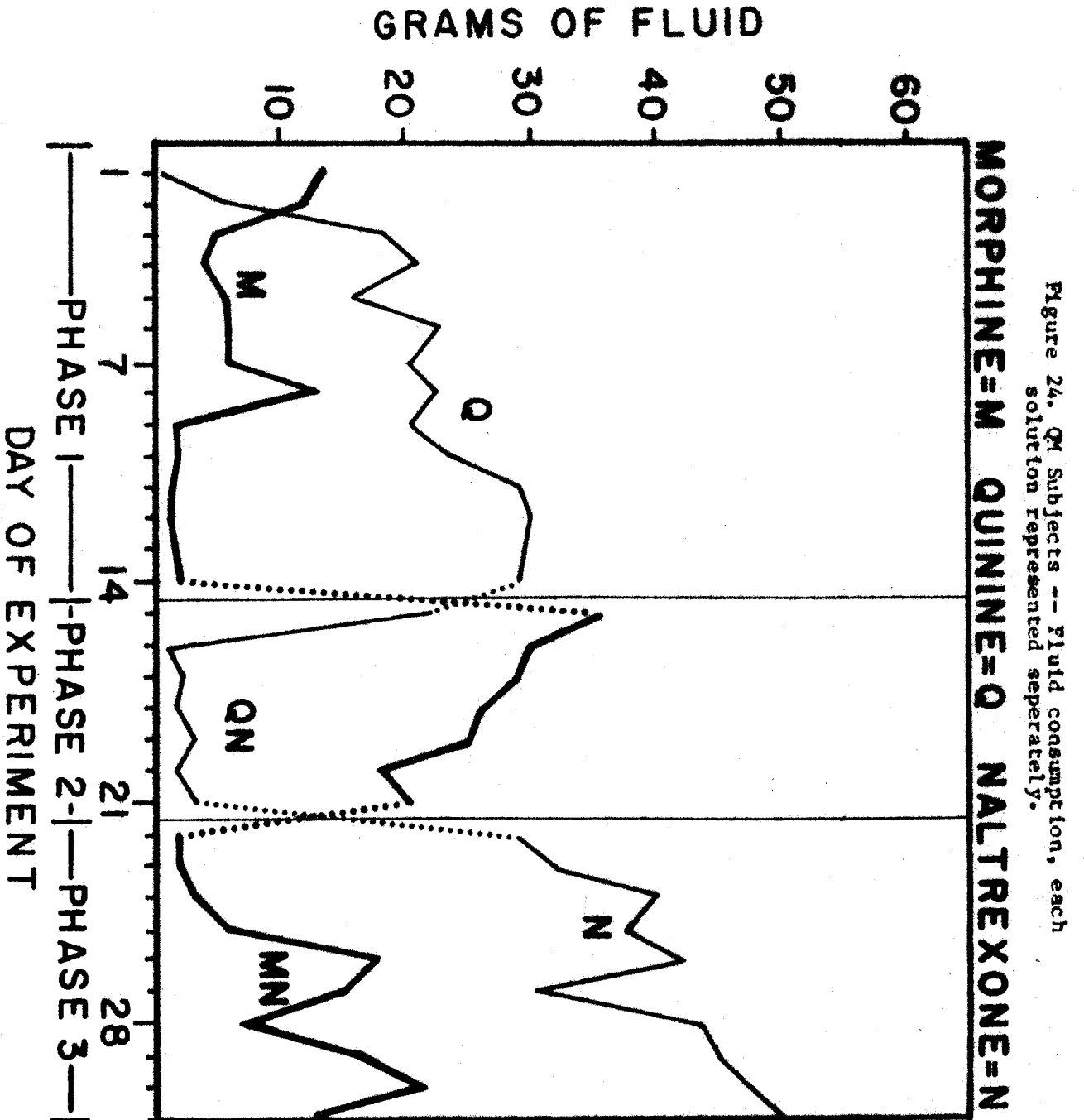


Figure 23. MM Subjects --- Morphine consumption as proportion of total fluid intake.



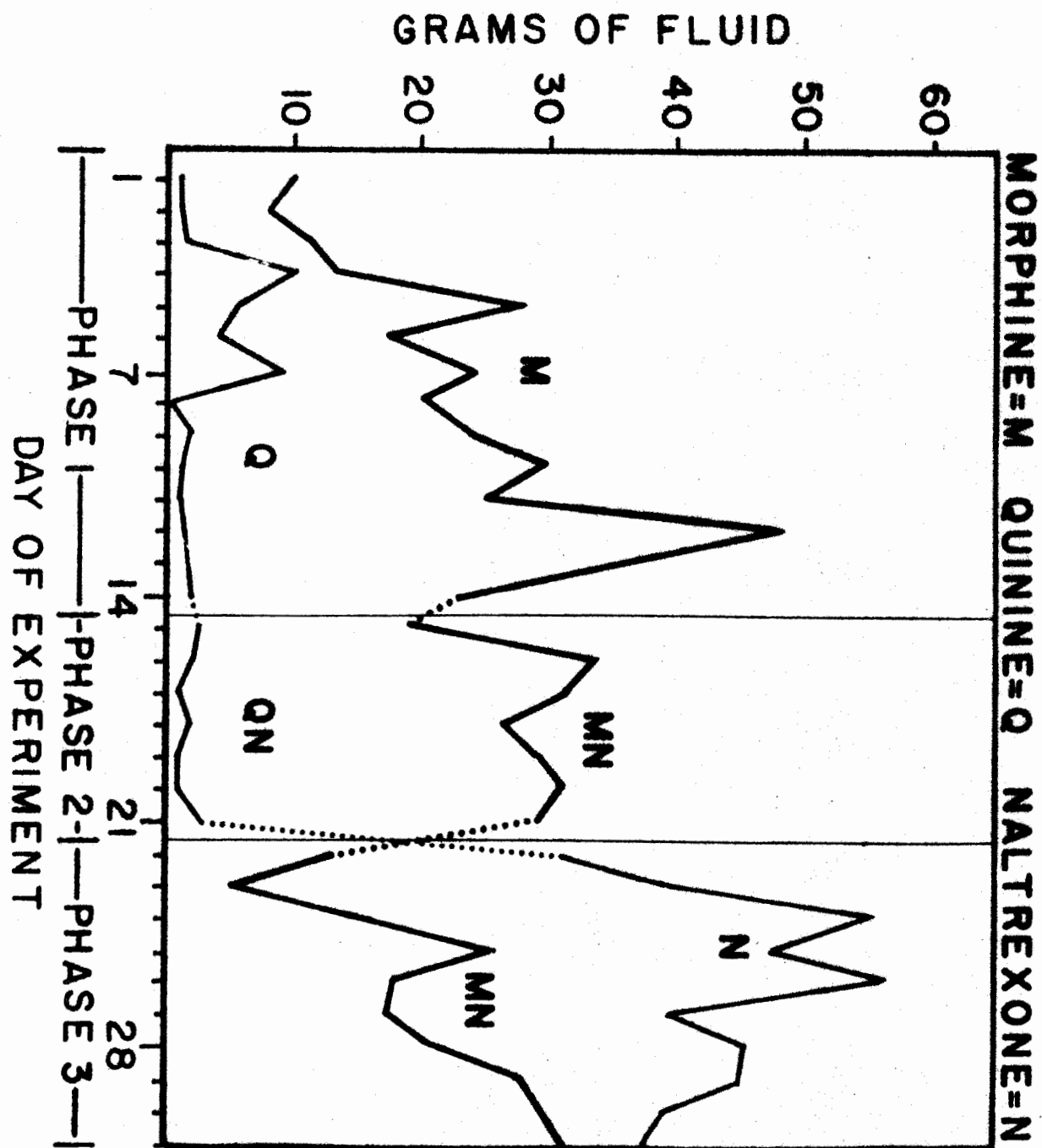


Figure 25. MM Subjects -- Fluid consumption, each solution represented separately.

Discussion

The results of this experiment are complex, but they demonstrate that the psychoactive effect of morphine was aversive to these rats. QM and MM subjects will be discussed seperately.

QM Subjects

The 10 QM subjects afford clear evidence of an aversion to morphine's psychoactive effects (see Figure 2). In Phase One, they selected quinine even though it was much more bitter than the morphine, and without exception, all preferred the pharmacologically neutral naltrexone-morphine in Phase Two. Thus, the aversion to morphine in Phase One was attributable to the psychoactive effect, rather than the taste.

Rat Taste Responses

The role of rat taste responses is an important issue in the interpretation of this experiment, and it merits detailed consideration. This is because it may be argued by some that it is impossible to know what a rat's taste experiences are, and therefore it is impossible to draw firm

conclusions from this experiment. It might be hypothesized that taste could interfere with the interpretation in two ways. The first is the possibility that rats' perceptions of the bitterness of the morphine and quinine are actually the opposite of man, and the QM rats preferred quinine in Phase One simply because it was the least bitter solution to them. Second, perhaps complex taste interactions occurred between the morphine, quinine, and the 8% sucrose vehicle, so that the most strongly bitter quinine in some way acquired the most preferable taste.

However, these arguments are extremely unlikely because of a large body of findings on the physiology and psychophysics of taste responses (e.g. Denton and Coghlan, 1975; Beidler, 1971). Taste research has been very productive, because taste is, apparently, simpler than other sense modalities (for example, vision and audition), and because it is relatively similar across mammalian species. The great bulk of taste research concentrates on humans and the laboratory rat. Extensive studies have been conducted on such topics as taste psychophysics, tongue anatomy and histology, neural response patterns to taste stimuli, central projections of the gustatory system, taste stimuli chemistry, the role of postingestional effects on taste responses, and comparative studies of gustation.

These and other results of comparative studies on taste have led many workers to conclude that the gustatory responses of rats and humans closely resemble one another. For example: "Laboratory rat...responses to many taste stimuli are similar to those of men." (Kare, 1971) or, "Man and rat...are remarkably similar in their thresholds and preferences to gustatory stimuli. The behavioral similarities are based on the animal's having similar gustatory systems, similar convergence on gustatory and internal afferents to the nucleus solarius, and similar regulatory mechanisms." (Garcia et al., 1974). These similarities are most likely due to the fact that, "The sense of taste, in contrast with vision and hearing, appears to have undergone relatively little evolutionary development in morphology of the receptor and central neural connections." (Pfaffmann, 1975).

Several methods now exist for measuring taste preferences in rats, such as: two bottle choice tests (e.g. Young, 1957); comparison of bar press rates to obtain one of two positively reinforcing substances (e.g. Guttman, 1954); or measurement of bar pressing to stop a mouth fistula infusion of an unpalatable solution (Kissileff, 1975).

Gustatory sensation can now be studied by direct recording of taste receptor impulses, which are principally carried by the chorda tympani and glossopharyngeal nerves.

It is possible to derive meaningful results from this method because of the good agreement in both rats and humans between the perception of taste and the firing patterns of gustatory neurons. The work on humans has been carried out in the laboratory of Y. Zotterman (Diamant and Zotterman, 1959; Borg et al., 1967; Zotterman, 1971) on subjects undergoing otological operations, in whom the chorda tympani had been severed. Impulses which originated in the taste receptors were recorded at the severed end. Peak amplitudes of the summated neuronal responses represented the strength of the taste response. Prior to the operation, the patient's perception of taste was measured by Steven's (1957) method of magnitude estimation (subjects were well trained in this technique). The agreement between the psychophysical and physiological responses were generally of a very high order (see Figures 26, 27).

This type of agreement is also present in rats. There is generally good rank order correlation between the amplitudes of rat chorda tympani impulses for a particular taste, and a rat's behaviorally demonstrated strength of preference for that taste. Also, Sato (1971) has conducted extensive studies of the magnitudes of neural responses in the rat chorda tympani, and concluded that they are approximately the same as humans.

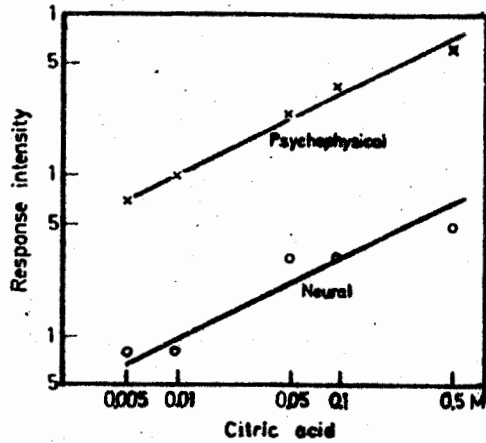


Figure 26 - Graphs from one patient, showing subjective intensity and neural response plotted against molarity of citric acid in a log-log scale (after Zotterman, 1971).

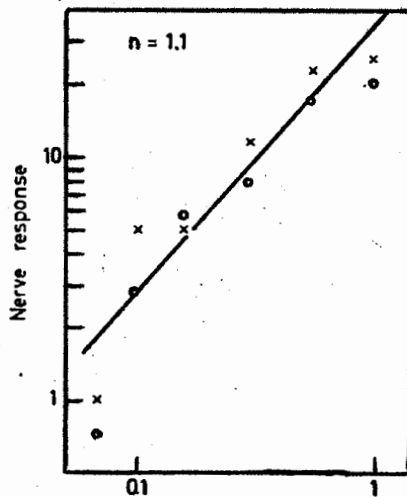


Figure 27 - Responses (open circles) and subjective estimation plotted against molarity of sucrose solution (after Zotterman, 1971).

Thus, although it is not possible to know directly what a rat subjectively experiences when tasting any substance, there are strong similarities in the underlying taste physiology in man and rat, and, in both species, the strength of responses emitted by the physiological structures are closely associated with demonstrated taste preferences.

One of the most important subjects to this discussion is taste chemistry. Generally, chemicals which taste the same tend to share distinctive properties. For example, nearly all sour tastes are caused by acids (Pfaffmann et al., 1971). The stimulatory strength of an acid depends upon the hydrogen ion and its degree of dissociation in solution. Salt taste is caused by sodium chloride, and many other salts. Sweet taste is predominantly induced by low molecular weight monosaccharides and oligosaccharides (Shallenberger and Acree, 1971). Most bitter chemicals are alkaloids or glycosides; both substances are found naturally occurring in plants. The glycosides are acetal derivatives of the cyclic forms of the sugars pyranose and furanose. Some of these substances taste sweet as well as bitter. The common cause of bitterness amongst glycosides is not well understood (Shellenberger and Acree, 1971). Much more is known about the commonalities of structure which occur in the bitter alkaloids. Generally, they contain a

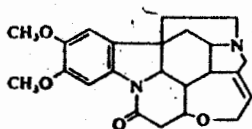
heterocyclic nitrogen ring such as is found in purine, pyridine, pyrrole, quinoline, and isoquinoline. They are usually levorotatory, and of high molecular weight. The sensation produced by alkaloids is usually a purely bitter taste. Some important alkaloids which are bitter to man include morphine, quinine, cocaine, strychnine, brucine, caffeine, nicotine, solanine, and codeine (see Table III).

Morphine is an alkaloid, containing a heterocyclic nitrogen ring, and it is an isoquinoline derivative (Leavitt, 1974, p.388). It is of high molecular weight, and the pharmacologically active stereoisomer is the levorotatory form (Snyder, 1977). Like many bitter alkaloids, it is psychoactive, and toxic in high doses.

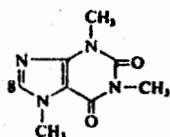
Based on what is known about taste chemistry, it is very likely that morphine is also bitter to rats. This is mainly because, of the alkaloids of this same class which have been tested on rats, all are avoided. Although it is not possible to directly test rats' taste preferences for all alkaloids (because many are toxic, or psychoactive, and therefore may be avoided for these reasons rather than bitterness alone), some can be measured directly, by such means as the two bottle choice test. The most frequently tested of these is quinine (both hydrochloride and sulfate forms). It is avoided by all rats and monkeys (*Macaca mulatta*) tested (Patton and Ruch, 1944). This aversion

TABLE III. Molecular structures of some important bitter alkaloids, and quinoline, isoquinoline.

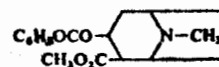
Brucine



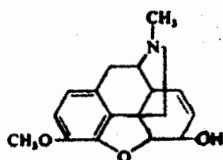
Caffeine



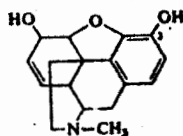
Cocaine



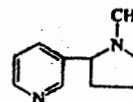
Codeine



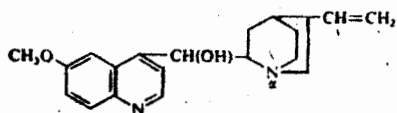
Morphine



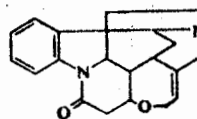
Nicotine



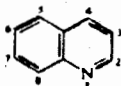
Quinine



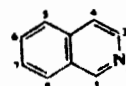
Strychnine



Quinoline



Isoquinoline



response is so reliable that it is used as a determinant of taste thresholds; i.e. it is assumed that when an animal can taste quinine solutions, it will avoid them. Quinine also fits very well into the class of bitter alkaloids, and closely resembles morphine in bitterness criteria; it contains heterocyclic nitrogen rings, it is derived from quinoline (which closely resembles the morphine parent, isoquinoline), it is of high molecular weight, and it is levorotatory. However, in the dosages used in this experiment, it is neither psychoactive or toxic.

Interesting evidence concerning bitterness perception in rats arises from experiments by Frank (1975) and Pfaffmann et al., (1967). Until their work, most neurophysiological investigations of taste were carried out on the chorda tympani, because this nerve predominantly transmits the most interesting and thoroughly studied sensations of sweet, salty, and sour (bitter substances elicit only very sparse chorda tympani responses). These researchers, however, studied the glossopharyngeal nerve, which innervates the back of the tongue for both man and rat, and responds most vigorously to bitter substances (Pfaffmann et al., 1967).

Their technique was to free the glossopharyngeal from other tissue, cut it centrally, and split it into fine strands from which differentially amplified signals from single fibers could be recorded. Stimulation of the

circumvallate papillae taste receptors at the back of the tongue was performed via an inserted pipette. Fibers were classified according to which of the four basic stimuli (sucrose, NaCl, HCl, quinine HCl) they responded best. It was then possible to obtain response profiles of these fibers, and to compare the profiles of responding to different stimuli of the same class.

Two findings from this work are relevant to this discussion. First, a type of fibre exists which responds distinctively and quite specifically to quinine stimulation (see Figure 28). It is the most common and most 'highly tuned' of rat glossopharyngeal circumvallate fibers, in the sense that it responds quite exclusively to bitter stimuli. The second best response of these neurons was to hydrochloric acid, which was less than 20% of the quinine response. This presents strong evidence that rats have quinine receptors.

Second, the pattern of responses to chemicals which are also bitter to man are generally in agreement with the patterns elicited by quinine (see Table IV). Note that caffeine, which is a heterocyclic nitrogenous alkaloid, correlates best with quinine stimulation.

The pattern of taste responding in the chorda tympani is also very similar in rats and non-human primates. Approximately the same proportions of chorda fibres respond

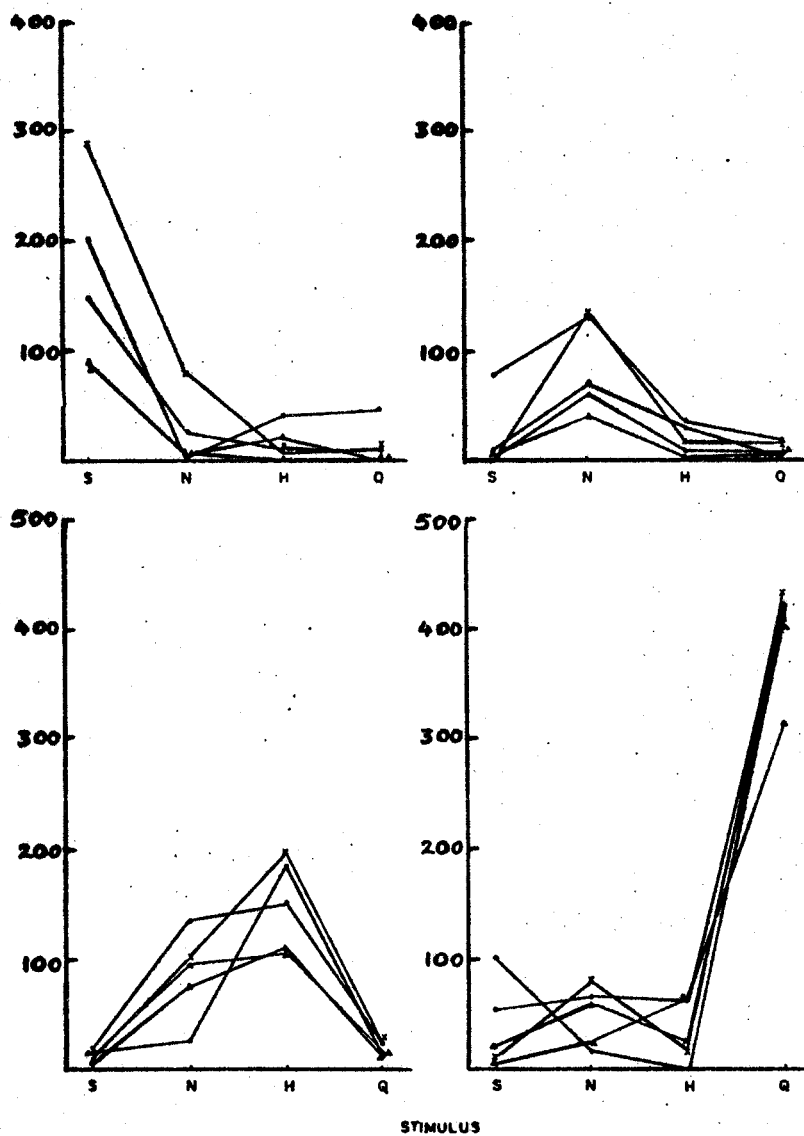


Figure 28 - Twenty rat glossopharyngeal-circumvallate nerve fiber response profiles to 4 tastes: for 5 fibers which respond best (largest number of spikes in 5 s) to .3 M sucrose (S), .3 M NaCl (N), .003 M HCl (H), and .001 M quinine HCl (Q) (after Frank, 1975).

TABLE IV. Rank order correlation coefficients between responses of rat glossopharyngeal nerve fibers to 4 common tastes and 4 bitter tastes with circumvallate stimulation (after Frank, 1975).

	SUCROSE	NaCl	HCl	QUININE	N+
MgSO ₄	+0.27	+0.14	-0.13	+0.22	15
Urea	-0.26	-0.24	+0.49	+0.59	15
S.O.A.	-0.14	+0.22	+0.45	+0.52	23
Caffeine	-0.24	+0.16	+0.40	+0.60*	22

* $p < .01$, t test.

The molarities for the common tastes are: .3 sucrose, .3 NaCl, .003 HCl, and .001 quinine hydrochloride. For the other tastes they are: .3 MgSO₄, 1.0 Urea, .0003 sucrose octa-acetate (S.O.A.), and .03 caffeine. N is the number of fibers whose responses were used in each correlation.

to salt, sugar, acid, and quinine in both the macaque monkey and the rat (Sato, 1975).

In addition to the rat, a large number of other animal forms reject stimuli which humans perceive as bitter. Garcia and Hankins (1975) outline the evidence supporting this conclusion:

Morgan's scientific canon against anthropomorphism limits our generalizations concerning inferences of bitter sensations in organisms other than humans old enough to verbally report the quality of the test substance. However, it is difficult to resist the anthropomorphic temptation when one observes the characteristic grimace displayed by neonate humans and nonhuman primates induced by quinine solutions, or for that matter, the characteristic grooming observed in rats when they encounter bitter food. In fact, species from virtually every phylum reject solutions which are also rejected by man who describes them as bitter.

For example, Schaeffer (1910) reports that Stentor caeruleus, a protozoan, will not feed on materials which have been soaked in quinine and then rinsed. When the stream of quinine food reaches the oral disc, the stentors contract, or bend away; Parker (1910) has found that both the ostia and ocula of sponges Stylotella heliophila close when small amounts (.0002M) of strychnine, a bitter compound, contracts them. Quinine in .0003M solution inhibits the feeding of wireworms Agriotes Spp. and .003M quinine reduces biting by 75% (Crombie and Darrah, 1947). Earthworms Lumbricus terrestris are apparently much more sensitive, withdrawing immediately from .00001M quinine hydrochloride applied to the prostomium (Laverack, 1960).

Another fascinating example is the ancient arthropod Limulus, or the horseshoe crab which is equipped with chemical sensors

on its mandible and on its legs. The leg receptors are extremely sensitive (Patten 1894, Barber 1956). Arthropods provide many other examples. Both adult and larval insects are sensitive to bitter substances. For example, von Frisch (1934) reported that some bees would reject .0008M quinine in 1 M sucrose solution, and Dethier (1937) found that lepidopterous larvae Porthotera dispar "spit out" bitter substances.

The molluscs and echinoderms appear to be extremely sensitive to bitter materials. Measuring the oral tentacular retraction of oysters Ostrea virginica, Hopkins (1935) found clear retraction responses to .000046M quinine sulfate, and Wells (1963) using a behavioral task found that octopi Octopus vulgaris could discriminate .0000015M quinine sulfate in sea water.

Olmsted (1917) found that sea cucumbers Synaptula hydriformis withdrew from .0001M quinine. Sessile tunicates Ascidia atra retract their siphon to .00005M quinine sulfate (Hecht 1918).

Aversive reactions to bitter substances have been reported for all classes of chordates. Quinine stimulation of oral receptors in fish produce avoidance reactions (Sheldon, 1909; Herrick, 1902; Bardach and Case, 1965; Bardach and Atema, 1971). Little work has been done with the sensitivity of amphibia, but some salamanders Triturus do respond to bitter taste qualities (Bardach, 1967). Feral pigeons, Columba livia, (Duncan, 1960) and rats Rattus norvegicus (Cicala and McMichael, 1964) reject quinine hydrochloride in all detectable concentrations. (p. 40)

This behavior can be expected to be deeply rooted in the physiological makeup of such wide ranging, curious, and omniverous animals as rats and humans, because there is a substantial adaptive advantage to the avoidance of bitter tastes. More than ten percent of plant species contain bitter and toxic alkaloids and/or glycosides (Kingsbury,

1964). Hence animals (especially wide-ranging omnivores) which have mechanisms to reject bitter substances, have a good chance to avoid fatal poisoning. Not surprisingly, rats' responses to either toxic or intensely bitter food is very similar. They dig it out of the food dish, then groom themselves vigorously and rub their muzzles on the floor (Garcia and Hankins, 1975).

Many bitter substances are naturally occurring chemicals which have no apparent purpose in the plant's metabolism. Some are quite complex, and require a considerable expenditure of energy to produce. Brower (1969) suggests that some of these may be synthesized specifically for their toxic properties. In addition, he presents a typical example of a bitter toxin, the digitalis-like cardiac glycosides produced by the Milkweed, Asclepiaga curassavica. These substances are powerful emetics to mammals, and as a result, cattle and other herbivores learn to avoid this plant. The larvae of the Monarch butterfly Danaus plexippus, however, feeds on the milkweed, assimilating and storing the poison -- apparently without toxic effect. But when birds feed on the butterfly, they become ill and subsequently avoid it.

The opium poppy Papaver somniferum might well synthesize opiates for the same reason: to generate toxicosis. Opiates are produced by the seed pod immediately

prior to the ripening and dispersal of the seeds. This is a crucial part of the plant's life cycle, and it would make adaptive sense to defend the large, conspicuous, juice laden seed pod from herbivores. Morphine, in addition to being bitter to man, often produces nausea, vomiting, and dysphoria when first administered (Jaffe and Martin, 1975).

From this evidence, it is reasonable to conclude that rats respond to nitrogenous alkaloids in the same way as humans, and that they therefore could be expected to reject both morphine and quinine because of taste.

Let us now turn to the central question regarding taste: whether the rats found the morphine less bitter than the quinine in the present experiment. There is good evidence that rats rank taste intensities as humans do, and this also appears to be the case with the three other taste modalities.

Unfortunately, not enough research on the ranking of taste intensities has been carried out for bitterness. "Bitterness scores", or finely discriminated stimulus ratings for closely related compounds are not available. At best, bitter tastes have been ranked as "slightly bitter", "bitter", or "extremely bitter" (Shallenberger and Acree, 1971). Also, when measuring neural responses, there is a tendency to choose the chorda tympani in preference to the glossopharyngeal, since the former best represents three

taste modalities, the latter only one. This leaves the bitter taste response much less frequently investigated.

Nevertheless, some work has been done in this area. Coombs et al., (1977) found that, to the experimenter's palates, 0.1 mg/ml quinine sulfate in 5% sucrose solution, and 0.5 mg/ml morphine hydrochloride in 5% sucrose solution, were about equally bitter. In the first few hours of free-choice exposure, rats consumed about equal amounts of these same concentrations (Coombs, 1977). We concluded that these solutions are about equally preferable, prior to the onset of pharmacological effects.

Stolerman and Kumar (1970) used two groups of rats to arrive at a similar conclusion. Group 1 was given a choice between quinine hydrochloride solution (.25mg/ml) or tap water. Group 2 was given a choice between morphine hydrochloride solution (.5mg/ml), or tap water. Both groups had access to these fluids for a seven hour period. The mean amount of morphine or quinine solution consumption expressed as proportion of total liquid intake were .15, and .18 for groups 1 and 2 respectively. Since these did not differ significantly, the authors conclude: "It therefore appears that the quinine (hydrochloride) solution of .25mg/ml was about as aversive as the morphine (hydrochloride) solution of .5mg/ml." These two findings are comparable, with the exception that Coombs et al. used

.1mg/ml quinine sulfate, whereas Stolerman and Kumar used .25mg/ml quinine hydrochloride. However, for humans, quinine sulfate is about twice as bitter as quinine hydrochloride (the taste thresholds are .1mg/ml and .2mg/ml, respectively; Pfaffmann et al., 1971).

Doubling the quinine sulfate concentration to .2mg/ml in the present experiment made it much more bitter than .5mg/ml morphine for humans, and it would be expected to do the same for rats, in view of research on the psychophysical scaling of taste. The relationship between sensation and intensity is most closely described by Stevens' Power Function (1960):

$$R = KS^n$$

Where R = response as measured by unit of sensation
 K = proportionate constant
 S = stimulus intensity
 n = an exponent characteristic of the different sense modalities

For taste, the exponent is generally around 1 (Pfaffmann, 1971). Sato (1971) reports that this exponent is approximately valid for both psychophysical and neural responses in humans, and is also valid for neural responses in the rat. Therefore, it is reasonable to conclude that for rats, the morphine solution used in the present experiment was much more palatable than the quinine solution.

A second important question regarding rat taste responses is whether complex taste interactions occurred between the morphine, quinine, and the 8% sucrose vehicle, so that the most strongly bitter quinine in some way acquired the most preferable taste. For example, although, .5mg/ml morphine hydrochloride solution by itself is more palatable than .2mg/ml quinine sulfate, could it be that rats find 8% sucrose excessively sweet, and therefore prefer the addition of a strongly bitter taste to counteract it?

There is substantial evidence that such complex taste interactions do not occur in either rats or humans. The most relevant research on human taste interaction was carried out by Kamen et al., (1961). Their findings are based on careful psychophysical testing of 80 subjects using caffeine and sucrose solutions as stimuli. They show that increasing the caffeine concentration of a sucrose-caffeine solution does not alter the subjective intensity of the sweet taste (see Figure 29). This is true for all concentrations used. The effect of sucrose on bitter taste is somewhat more complex. It would appear that increasing the sugar concentration in a caffeine-sucrose solution reduces the subjective intensity of the bitter taste. This occurs in a curvilinear way, with bitterness attenuated to an increasing extent as sucrose concentration increases. However, this effect is fairly constant for all levels of

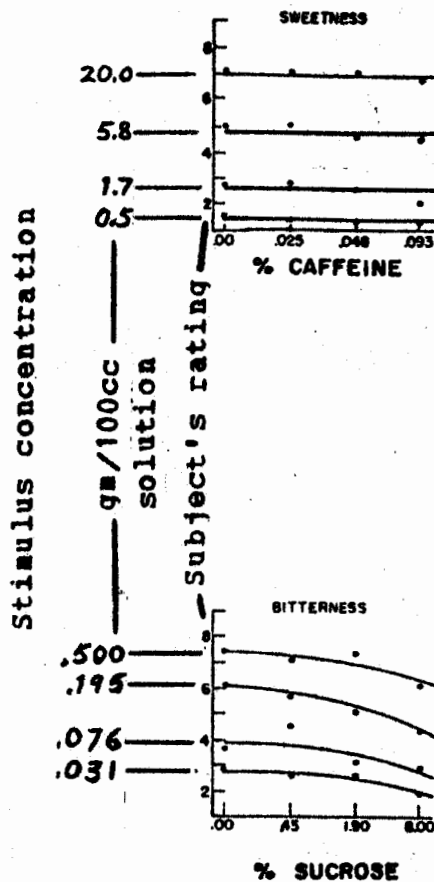


Figure 29 - Summary of taste interactions (after Kamen et al., 1961).

The abscissa represents increasing concentrations of the secondary stimulus. The four curves on each graph are for the four levels of the primary stimulus whose taste quality is shown on the inner scale of the ordinate. Primary stimulus concentrations are on the outer scale. Curve fitting was guided by the significance of the sources of variation in the analyses of variance, rather than by least squares methods.

bitterness; and complexities such as cross-overs do not occur. In summary, in humans, bitter tastes do not have the effect of counteracting sweet tastes, but the 8% sucrose solution should have had a reducing effect on bitterness. However, this would affect both solutions equally: the morphine should still be more palatable than the quinine.

Phase One Morphine Aversion Responses

There is another issue to be considered regarding the drinking patterns of the QM rats -- they continued to sporadically drink very small amounts of morphine in Phase One (see Figure 24). It might be argued that these rats in fact find morphine rewarding, but in low doses. However, there are four reasons why this interpretation is unlikely to be correct.

First, the morphine consumption in the group of rats which drank mostly quinine was very sporadic; some days none was consumed. These preferences do not appear to be related to the days on which bottle position was shifted (Figure 24). Regular consumption did not occur in any of these rats.

Second, if morphine were reinforcing to this group of rats, one would expect stable consumption, or a gradual increase, in order to overcome the effect of progressive tolerance. Instead, morphine consumption decreased slightly

over the course of Phase One. Morphine preference in QM rats, expressed as proportion of total fluid intake, measuring mean preferences in two independent blocks of measures (days 3-6 vs. 11-14) decreased significantly (Wilcoxon Matched Pairs Signed Ranks test, Siegel, 1956, $N=10$, $T=0$, $P<.01$, two tailed). Total morphine consumption measured as mg morphine/day also declined. The mean morphine consumption for this group of rats in the last 4 days of Phase One was .8mg.

Third, the morphine solution was substantially more palatable than the quinine solution. Therefore, all animals would have been motivated to consume morphine, and some sampling is not surprising.

Fourth, it should be pointed out that in previous work with this strain of rat, it has become clear that they are extremely resistant to the effects of morphine -- it is very unlikely that these small amounts are a pharmacologically effective dose for them.

Possible Aversive Properties of Naltrexone

There is another alternative explanation of the behavior of the QM Subjects, which rests on two postulates. The first concerns naltrexone's biochemical activity. The most widely accepted theory of action of morphine

antagonists is that they compete with morphine for stereospecific opioid receptor sites, and thereby prevent morphine from having any effect (Jaffe and Martin, 1975). The first postulate asserts that the corollary is also true; that by competing with naltrexone at the binding site, morphine is a "naltrexone antagonist", capable of blocking any pharmacological effects of the naltrexone.

The second postulate then focuses on the pharmacological effect of naltrexone, and suggests (without proof) that naltrexone is aversive to rats.

If both postulates are true, then the addition of naltrexone in Phase Two would have affected the morphine and quinine solutions differently. The naltrexone would have increased the aversiveness of the quinine, but would not have added to the aversiveness of the morphine, because the morphine would have "antagonized" (i.e. neutralized) naltrexone's aversiveness.

This means that when the quinine preferring rats of Phase One shifted preference to naltrexone-morphine in Phase Two, they did so because the quinine had become more aversive. This disputes the explanation that the quinine preferring rats switched to naltrexone-morphine because naltrexone had neutralized morphine's aversive pharmacological properties.

Some support for the two postulates may subsist in the results of Phase Three, where 3, or possibly 4 of the 10 QM Subjects eventually came to consume more naltrexone-morphine mixture than the naltrexone-only solution (see Figures 4, 6, 7, 12, & 18). Their preference for naltrexone-morphine may be evidence that naltrexone's hypothesized aversiveness is attenuated when it is combined with morphine.

However, there is good evidence that these arguments are false. A key question is whether naltrexone by itself is aversive. In humans, there is little or no subjective effect of naltrexone, and naltrexone-morphine mixtures are, if anything, slightly aversive. Martin et al., (1973) extensively studied the psychopharmacological effects of naltrexone on humans. They concluded that, "it is virtually devoid of agonistic activity, including the ability to induce nalorphine-like dysphoric effects." Of eleven prisoner postaddict subjects who received naltrexone subcutaneously, most identified it as a "blank", and reported that it produced either no subjective changes, or relaxation, which is also a common response to a placebo. Most of those who received the drug orally also reported no effect, although two subjects became sleepy and identified naltrexone as a barbiturate. Table V summarizes the results of an experiment to compare oral naltrexone (30mg/70kg) to the cherry syrup vehicle. Measures of sensation, mentation,

TABLE V. Effects of naltrexone (30 mg orally) on physiologic changes and subjective state * (after Martin et al. 1973).

	VEHICLE	NALTREXONE	DIFFERENCE
Systolic blood pressure	23.4	51.1	27.7
Diastolic blood pressure	1.6	31.6	30.0**
Pupillary diameter	2.6	1.0	-1.6
Temperature	2.1	1.0	-1.1**
Pulse rate	9.6	12.4	2.8
Respiratory rate	6.2	1.0	-5.2
Opiate signs	4.6	3.2	-1.4
Opiate symptoms	0.2	2.0	1.8
Liking -- observers	1.2	1.2	0
Liking -- patients	0	0	0
L.S.D. ***	26.4	27.3	0.9
M.B.G. ***	0	1.2	1.2
P.C.A.G. ***	25.6	23.2	2.4

* Each value is the mean, for five subjects, of the sum of the differences between the mean control value and the treatment values or the sum of observations for the first 5 hours after drug administration.

** This symbol indicates those differences that were statistically significant at the .05 level (t-test).

*** L.S.D. is the L.S.D. scale; M.B.G. is the morphine-benzadrine group scale which measures feelings of euphoria and well being; and P.C.A.G. is the pentobarbital-chlorpromazine-alcohol group scale which measures feelings of apathetic sedation.

and affect for subjects, and their behavior and symptoms as monitored by observers, were derived from a subjective effect questionnaire (Jasinsky et al., 1968). It would appear from these data that naltrexone may produce measurable changes in diastolic blood pressure and body temperature, but no apparent subjective effects in humans.

The neutrality of naltrexone-only solutions is supported by the drinking patterns in Phase Three. Rats require approximately 25-35 ml of water per day to meet fluid requirements. In the present experiment, total fluid consumption rose from a mean of approximately 30 ml to a mean of approximately 50 ml in Phase Three. This shift is mainly attributable to the consumption of naltrexone-only solution, of which most animals consumed substantially more than was required to meet their fluid needs (see Figures 24 & 25). Therefore, the second postulate of the argument is untenable, since naltrexone did not appear to be aversive to these rats.

Moderate doses of naltrexone and morphine mixtures also appear to have only mild consequences. Table VI summarizes the results of an experiment by Martin et al. (1973) to measure the effects of chronically administered oral naltrexone on subcutaneously administered morphine. The control group received 15 or 30 mg of morphine, while the experimental group received 50 or 100 mg of morphine plus 15

TABLE VI. Effects of chronically administered naltrexone (15 mg twice a day orally) on subcutaneously administered morphine * (after Martin et al., 1973).

DOSE OF MORPHINE (mg)	CONTROL		NALTREXONE	
	15	30	50	100
Feel effect -- patients	2.4	4.9	0.4	0.7
Feel effect -- observers	5.9	5.7	5.3	3.3
Identification -- patients	1.3	3.5	0	0
Identification -- observers	5.6	5.7	5.1	3.3
Symptoms	2.6	19.6	0.3	0.7
Signs	12.7	20.4	15.7	11.4
Liking -- patients	2.5	9.7	0	0.7
Liking -- observers	6.6	11.6	7.3	4.9
M.B.G. scale	4.3	14.0	2.9	2.6
Pupils	8.6	9.8	1.9	4.2

* Each value represents the mean, for six subjects, of the sum of responses for the first five hours after the administration of morphine for subjective responses. For pupils the mean is for the sum of the differences between the mean control value and the observations for the five hour period following the administration of morphine.

mg of naltrexone twice daily. Note that the subjects were unable to identify the drug, and showed no apparent like or dislike of the effects.

Martin et al., (1973) also report on a 9 subject experiment using naltrexone-morphine combinations (morphine, 240 mg/day; naltrexone, 30 or 50 mg/day) for 14 days followed by abrupt termination of the morphine. Subjects were unable to identify the drug state in either condition. They reported a mild aversion to the combination of the two drugs, and generally felt somewhat worse for about one week after the termination of the morphine. Approximately half identified this as a withdrawal experience. The authors suggest two possible reasons for the mild dislike of the naltrexone-morphine combination: "(1) When subjects were stabilized on morphine, the ingestion of naltrexone would precipitate mild signs and symptoms of abstinence which would become manifest within 15 to 30 minutes and would subside over the following hour. (2) The fact that the patients did not experience euphoria with the administration of morphine was a disappointment to them." In summary, it would appear that in moderate doses, neither naltrexone nor naltrexone-morphine combinations are aversive to humans. In very high doses of the agonist-antagonist combination, however, some mildly disagreeable sensations may emerge.

One must use extreme caution in generalizing these results to rats, but they suggest that in Phase Two of the present experiment, if anything, the naltrexone-morphine may have become slightly aversive. However, this possible slight aversion could not have influenced the results, since 17 of 18 rats strongly preferred the naltrexone-morphine solution.

It should also be pointed out that the hypothesized aversiveness of naltrexone, and the antagonism by morphine of this aversiveness, is an explanation only for events in Phases Two and Three. It does not account for the central finding of this experiment, which is that the QM rats rejected morphine in Phase One even though it had the most preferable taste. Therefore, to challenge the validity of the conclusions of this experiment with such an hypothesis requires the use of another explanation for the observed drinking in Phase One. This author would argue that such a combination of explanations violates the Law of Parsimony, since it is not the simplest way to explain the data. It requires that two independent and unlikely explanations be invoked to account for Phases One and Two. In contradistinction, the morphine aversion hypothesis is unitary, simple, and likely.

MM Subjects

There are several possible explanations for the drinking patterns of those seven rats which consumed mostly morphine in Phase One. One is that the narcotic effect of the morphine was aversive, but the rats selected it because the taste of the quinine alternative was even more repellant. Another explanation is that the morphine was positively reinforcing, and the rats chose it both because of its preferable taste, and because of its psychoactive effects. A third is that morphine's psychoactive effects were completely neutral to these animals, and they selected morphine simply because of its preferable taste.

There is some evidence in support of the first explanation. In the first 3 days of Phase One, the mean total fluid consumption is much less than the normal daily tap water intake of 25-35g. Day 1 was 12.4g, Day 2 was 13.6g, and Day 3 was 18.1g, indicating that both fluids were initially aversive (see Figure 1). This obtained equally for MM and QM subjects. However, morphine combined with naltrexone is not aversive. As depicted in Figure 25, rats consumed substantial amounts of naltrexone-morphine solution in Phase Three. They did this under no compulsion, since the naltrexone solution, which was the alternative, was very sweet. The positively reinforcing character of this

alternative is evident in that substantial quantities of it were consumed. Therefore, the naltrexone-morphine solution cannot be aversive, since the rats consumed substantial quantities of it when there was no compulsion to do so.

There is additional evidence of this aversiveness on days 4 to 14 in Figure 25. On these days, the mean daily morphine consumption of the MM rats was 25.2g. This is sufficient to sustain life, but is much less than what one would expect if the psychoactive effect were rewarding or even neutral. In a previous experiment (Coombs 1977) rats of the same age, strain, sex, and housing condition were given access to .1 mg/ml quinine sulfate in a 5% sucrose solution. For human judges this was about equally palatable to the .5 mg/ml morphine hydrochloride in 5% sucrose which was the rats' alternative. Thus, the quinine solution in this previous experiment could be expected to be less palatable than the morphine in this experiment, but in fact the rats consumed substantially more of it -- a mean of 58.9g for days 4 - 13. The difference is attributable to the aversiveness of the psychoactive effects of morphine.

However, in spite of these arguments, it is nevertheless true that the MM rats did consume mostly morphine in Phase One of the present experiment, and one cannot say with certainty whether the morphine was or was not reinforcing to them.

Some Unexpected Results

One unexpected outcome of this experiment was that no sex differences in morphine consumption were observed. In earlier experiments (Alexander et al., 1978; Hadaway et al., in press; Hill, 1978), strong sex differences had been observed, with the females consuming substantially more morphine than the males.

Another puzzling observation was the behavior of rat number seven (Figure 9). This animal preferred morphine in Phase One, but rejected naltrexone-morphine in Phase Two, which suggests that she was consuming morphine in Phase One because it was reinforcing.

Summary

The results of the present experiment contradict the commonly held view that opioids are addictive because they produce intensely pleasurable effects. To this author, the notion that opioids are always powerfully pleasurable is a misconception which constitutes a central misunderstanding of the causes of addiction. As shown in the introduction, many eminent researchers also seem to be subject to this misconception, although to them, the word 'pleasure' is

usually translated into the term 'positive reinforcement'.

But morphine and heroin are not pleasurable to all humans (Lasagna et al., 1955). Similarly, as demonstrated by the present experiment, morphine is not positively reinforcing for other mammals.

It would appear desirable for future research to attend more carefully to the situational factors of opioid effects. For example, ex-addicts given morphine in anxiety provoking situations exhibit a much more intense narcotic effect than otherwise (Jaffe and Martin, 1975). Similar effects have been demonstrated in rats (Hill et al., 1954). Other environmental variables also affect morphine responses (Katz and Steinberg, 1970; Defeudis et al., 1976; Sklar and Amit, 1977; Alexander et al., 1978). This type of research may provide important information regarding the causes of addiction.

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