NARCOTIC AND NARCOTIC ANTAGONIST ANALGESICS[1]

By H. F. Fraser
Lilly Research Laboratories, Indianapolis, Indiana

AND

L. S. Harris
Department of Pharmacology, University of North Carolina, Chapel Hill, North Carolina

Introduction

The last decade has witnessed a ferment in the field of analgesics. Compounds have been discovered which have a potency nearly 10,000 times that of morphine (1). On the other hand, drugs have been developed which quite effectively relieve severe pain in man yet, in major part, fail to show antinociceptive properties in the usual animal test procedures (2, 3). Additionally, a real separation has been achieved between strong analgesics and addiction liability (4, 5). Because of this development and many careful structure-activity studies, our ideas concerning a specific site for morphine-like action and the nature of the site have been seriously questioned (6, 7).

Many physiological findings have paralleled these pharmacological advances. The concept of pain as a specialized sensory system with a distinct central activation has been challenged (8–10). Despite earlier reports to the contrary in anesthetized animals (11), Casey (12), in a careful microelectrode study of the thalamic area of unanesthetized awake monkeys, could find no units which responded exclusively to noxious stimuli. These findings and others such as those of Beecher (13) concerning the psychological variables associated with the perception of pain have led to a reconsideration of the concepts of pain and of its evaluation (14, 15).

The present review is concerned with recent pharmacological developments in the field of analgesics of the narcotic and narcotic-antagonist type. The viewpoint is a specialized and critical one. No attempt has been made to be comprehensive.

Analgesia and Abuse Liability of Narcotic-like Drugs

Laboratory evaluation of analgesics.—This subject has recently been reviewed by Winter (16), who indicated that one of the most important facets of any method is its predictive value in man. In the last few years, the classical tests for strong analgesics have been found to be faulty. Methods such as the mouse hot-plate and rat tail-flick tests, although highly predictive of clin-

[1] The survey of the literature pertaining to this review was concluded in June 1966.

ical analgesic activity, failed to select the narcotic antagonists which are capable of relieving severe pain in man. Indeed, these tests appeared to be as good indicants of addiction liability as they are of clinical analgesia and thus have tended to hinder the search for nonaddicting strong analgesics (2). Recently, new tests have been devised and older tests have been modified with the hope that these shortcomings will be overcome.

A number of types and modifications of operant conditioning have been employed. Weiss & Laties reported a shock titration procedure in rats (17) and monkeys (18). The animals were trained to press a lever to step-down a constantly and regularly increasing shock intensity, which they would then maintain at a relatively constant level. This level could be raised by morphine and other agents (18, 19). In the monkey, the potent narcotic-antagonist analgesic cyclazocine was active, and its potency relative to morphine paralleled that seen in man (18). On the other hand, nalorphine, the classical narcotic-antagonist analgesic, was devoid of activity. Weitzman & Ross (20) and Vernier et al. (21) used a similar technique in which the shocks were applied to selected portions of the brain. Again, morphine and related drugs produced dose-related increases in the threshold. Other agents, such as pentobarbital, chlorpromazine, methamphetamine, and procaine, altered performance but appeared to be qualitatively different. The narcotic antagonists alone have apparently not been assessed in this procedure.

Evans (22, 23) reported a flinch-jump test whereby rats were submitted to varying intensities of shock and were observed to exhibit either a "flinch" or a "jump" response. Changes in the threshold for these responses in the presence of drug were then recorded. The narcotic antagonists nalorphine and pentazocine were, like morphine, active analgesics in this test. In addition, their relative potencies paralleled their clinical activity as analgesics. Evans also found activity for amphetamine and observed the recognized ability of this drug to potentiate the activity of morphine and the antagonists. Pearl et al. (24) used a similar technique, with vocalizing and jumping as the end points. Unknown drugs were compared with a group of narcotic antagonists having known clinical activity. They found that the effects on vocalizing correlated better with analgesia in man than those of jumping. However, they concluded that the test had too many shortcomings to be a useful laboratory procedure for the evaluation of narcotic antagonists with analgesic properties.

Recently, McMillan & Morse (25) have been studying the effects of morphine and various morphine antagonists on schedule-controlled behavior in the pigeon. They used a multiple fixed-ratio, fixed-interval schedule of food presentation. Both morphine and the antagonists increased the response rate under the fixed-interval schedule at appropriate doses. The rate of response under both schedules was decreased by higher doses. The potencies observed for both effects roughly followed those seen in man for pain relief.

Ward, Foxwell & Funderburk (26), using a modification of the Randall-

Selitto test, reported the easy detection of analgesic effects by the morphine antagonists. Winter & Flataker (27), using a variety of narcotic antagonists in a more complete study, found little relationship between the clinical efficacy of these compounds and the dose necessary to raise the threshold to pressure on the inflamed paw.

The effects of various analgesics on the mouse phenylquinone writhing test have recently been re-examined. Taber, Greenhouse & Irwin (28) and Blumberg, Wolf & Dayton (29) compared morphine and various antagonists for their ability to block writhing. There appears to be some correlation between activity in this test and clinical effectiveness. Pearl & Harris (30), however, have examined a large series of antagonists in this test procedure and found certain inconsistencies. These were confirmed by Archer & Pierson (31), who found a correlation between the central muscle-relaxant properties of the compounds tested and their antiwrithing ability. Lim and his colleagues (32) have refined his technique of using bradykinin-induced visceral pain in dogs to distinguish classes of analgesics. The narcotic-antagonist analgesic pentazocine has been shown to be a centrally acting agent in this procedure (33). Interestingly, both morphine and nalorphine, although active in the mouse writhing test, are not additive. The two narcotic analgesics morphine and methadone are additive; the two antagonist-analgesics nalorphine and pentazocine are also additive (34). Because of these data, some investigators have suggested that these two classes of drugs are exerting their analgesic activity by different mechanisms.

An interesting modification of the tail-flick reflex, using ultrasound as the noxious stimulus, has been reported (35). Further work will be necessary to ascertain the applicability of this method. Potentials evoked in various portions of the brain by stimulation of the tooth pulp have been used in an attempt to provide a more specific analgesic evaluation (36). A variety of agents were employed, but the observed effects could not be related to the analgesic properties of the drugs. Morphine and meperidine have been shown to depress post-tetanic potentiation in the spinal cord (37).

An interesting *in vitro* method for detecting possible analgesics has been described by Jaques (38). This test is based on the ability of the compound to block the stimulation of the guinea pig ileum by arachidonic acid. Nalorphine is inactive in this test procedure, although the anticholinergic agents are quite active.

The effect of various stress situations on the action of morphine has been investigated by Frommel (39). He reports that severe muscular and sensorial stress leads to an increased sensitivity to the analgesic activity of morphine. It would be of interest to ascertain whether the narcotic-antagonist analgesics would show activity under these conditions. We can conclude that, despite the progress being made, there is as yet no ideal single laboratory test procedure for the evaluation of strong analgesics.

Laboratory methods for evaluating the abuse liability of narcotic analgesics.— In 1964, the World Health Organization (WHO) Expert Committee of Addic-

tion-Producing Drugs (40) recommended substitution of the term "drug dependence" for the terms "drug addiction" and "drug habituation." The WHO Scientific Group (41) endorsed this recommendation. Drug dependence is defined as a state arising from the repeated administration of a drug on a periodic or continuous basis. It includes the attributes "physical" or "psychic" dependence or both. Its characteristics vary with the agent involved, but it is a general term selected for its applicability to all types of drug abuse and carries no connotation in regard to degree of risk to the public or need for a particular type of control.

In order to take cognizance not only of the concept "drug dependence" but also of "degree of risk to the public," in this review abuse is defined as follows: "Abuse of a drug exists if its use so harmfully affects the individual, society, or both as to require its control" (42).

It would be advisable to have screen tests in animals and man not only to predict "drug dependence" but also to predict, if possible, the degree to which drugs might be abused by society. This review will indicate that, in the case of narcotic drugs and narcotic antagonists, considerable competence has been attained in developing a multiplicity of tests in animals and man that are reasonably predictive of abuse liability by man.

This subject has recently been reviewed by Halbach & Eddy (43), the WHO Scientific Group (41), and Fraser (42), so only limited aspects will be discussed.

An acute test for tolerance and physical dependence in the dog has been described (44). Morphine sulfate was infused slowly over an eight-hour interval. Physical dependence was unmasked by nalorphine. The syndrome produced by this procedure was distinct and reproducible and consisted of restlessness, apprehension, violent tremor, lacrimation, salivation, rhinorrhea, urination, defecation, vomiting, mydriasis, and tachycardia. Tolerance is readily recognizable during the course of the infusion and can be demonstrated the following day by use of the standard test dose of morphine. This test should be a satisfactory preliminary screen for physical-dependence-inducing agents because of its brevity and reproducibility. However, insofar as predictability for abuse in man is concerned, this test has been extended to only a limited number of morphine-like drugs.

Martin et al. (45) have addicted male rats to progressively larger doses of morphine sulfate by starting with 5 mg/kg administered twice daily and increasing to a total daily dosage of 320 mg/kg by the 35th day. In this study, they made observations during preaddiction and addiction and even continued them up to six months after abrupt withdrawal of morphine. The abstinence syndrome was divided into two phases: (*a*) The early phase, classified as "primary abstinence," consisted of weight loss, an increased number of "shakes," increased activity, and a fall in body temperature and metabolic rate. The primary abstinence syndrome became definite within 8 to 16 hours following the last dose of morphine and persisted for approxi-

mately 72 hours. (*b*) The secondary abstinence syndrome that developed thereafter consisted of a rapid gain in body weight, elevated body temperature and metabolic rate, and an increase in water consumption. This syndrome was protracted, and differences between addicted and control animals persisted for as long as four to six months after withdrawal of morphine.

Buckett (46) has developed a test for dependence in rats. Two injections of morphine hydrochloride were given intraperitoneally each day, and the dose was increased from 20 mg/kg on the first day to a total of 420 mg/kg on the 11th day. The rats were then maintained on 400 mg/kg daily. Symptoms of abstinence (writhing, squealing, diarrhea, teeth chatter, ptosis, and "wet dog") were given "weighted" point scores, and dependence on unknown drug was tested by the ability of the unknown to decrease the abstinence score. This test is analogous to that which Seevers & Deneau (47) employed in monkeys and is comparable to the substitution tests originated by Himmelsbach (48) in man.

During both chronic intoxication and withdrawal, morphine-like drugs induce a pattern of effect different in the rat from that observed in man. Nevertheless, the rat should be a very satisfactory species for evaluating physical dependence on unknown morphine-like agents. Furthermore, it is advantageous to have both parameters evaluated in the same species, and analgesic potency is readily measured in the rat.

In mice, the abstinence syndrome which follows abrupt withdrawal of morphine is erratic. Huidobro et al. (49) were able to develop a consistent abstinence syndrome in mice by implanting pellets of morphine and then precipitating abstinence with nalorphine or levallorphan. They found that morphine and nalorphine influenced the intensity of the abstinence syndrome and that low intensity was observed when both these drugs were employed in small quantities. The most intense abstinence syndrome was obtained with high doses of morphine and nalorphine. An abstinence syndrome of moderate intensity was consistently observed with nalorphine and morphine in doses that were not extreme. The doses of nalorphine used were 1, 1.75, 2.50, 5.0, 10.0, 50.0, and 100 mg/kg. The average daily absorption of morphine from the pellets was 100, 200, 300, and 400 mg/kg. In these mice, the concurrent chronic administration of morphine and nalorphine reduced the intensity of the morphine abstinence syndrome, an observation which had previously been reported in man by Isbell & Fraser and cited by Fraser (50). Although the method of Huidobro and his collaborators, using pelletized morphine implantation to develop physical dependence in mice, has not been exploited as a mechanism for detecting physical dependence of unknown drugs, there is no logical reason why it could not be utilized for this purpose.

Rats have been used for the self-differential selection of various narcotic analgesics when the drugs were given orally (51–54). An ingenious technique developed by Weeks (55) permitted the rat to self-inject drugs directly into the right side of the heart via catheter. This technique has been extended to

monkeys by Yanagita et al. (56). Of the drugs evaluated so far in monkeys, the following results have been obtained with respect to spontaneous development of self-administration (psychic dependence):

Cocaine:	In 5 of 5 monkeys
Amphetamine:	In 5 of 5 monkeys
Morphine:	In 8 of 11 monkeys; in the other 3, during the first week of programmed injections
Morphine and cocaine: (simultaneously available)	In 4 of 4 monkeys
Codeine:	In 4 of 5 monkeys; in the other, during the first week of programmed injections
Alcohol:	In 4 of 5 monkeys. The 5th animal began self-administration during the first week of programmed injections but later discontinued spontaneously.
Pentobarbital:	In 5 of 5 monkeys.

On the other hand, monkeys have not developed self-administration patterns with nalorphine (4 animals), mixtures of morphine and nalorphine (4 animals), mescaline (7 animals), and chlorpromazine (8 animals). The significance of these experiments is tremendous, since the major types of drugs abused by man (cocaine, amphetamines, morphine, morphine with cocaine, codeine, alcohol, and pentobarbital) were all abused by the monkey. Furthermore, these experiments illustrate that the monkey is selective in the drugs that he elects not to self-inject (nalorphine, mixtures of morphine and nalorphine, mescaline, and chlorpromazine). This group of drugs has not been abused by man. The investigators realize that these methods as now carried out are not quantitative. Nevertheless, the experiments indicate that it may be possible to quantitate psychic dependence in animals.

Methods for evaluating analgesics in man, using experimental pain as a model.—Beecher (13) has long contended that clinical pain is a pathological condition and differs from experimental pain. Consideration of the matter confirms Beecher's concept, since there are many apparent differences. For example, the degree of anxiety associated with clinical pain is undoubtedly greater than that which accompanies most tests which make use of experimental pain. Clinical pain has a much more chronic course than that observed with the usual methods for provoking experimental pain. In addition, the intensity of experimental pain, because of the methods employed (heat to the forehead, electric shock to the teeth, pinpricks of the skin), is usually less severe than that which may be experienced in the case of clinical pain.

It should be realized, however, that clinical pain is not constant, even in the same individual, and may be influenced by environmental situations. For example, in the study of men in battle, Beecher (57) found a very low incidence of pain that was severe enough to require a narcotic. These severely wounded soldiers were clear mentally, were not hypotensive nor in shock, had received no morphine in many cases and if morphine had been adminis-

tered, it was given at least four hours before questioning them about their pain. In a study of 225 such soldiers, only 25 per cent, when directly questioned shortly after entry to the field hospital, said that their pain was severe enough for them to want pain-relief therapy. On the other hand, Beecher (58) observed in civilians undergoing pain postoperatively that 80 per cent of such patients had enough pain to want something done about it.

To date, there has been only limited progress in the use of experimental pain for evaluating analgesics. Some of the reasons why difficulties are experienced in this area are illustrated in the classical studies of Hill and his collaborators (59). They studied, in former narcotic addicts, the effects of 15 mg of morphine sulfate and a placebo under two situations: (*a*) an anxiety-generating situation and (*b*) an anxiety-allaying situation. In the anxiety-generating environment, tests were conducted in a darkened room surrounded by complex electronic equipment. From the time the subject was called to the testing room until he was dismissed, the relations between the experimenter and the subject were strictly impersonal but not unfriendly. In this group, electric shocks were administered by the experimenter after a warning light was flashed. On the other hand, with the anxiety-allaying group, the experimenter adopted a very casual manner. He conversed with the subject in the waiting room, described the experiment as much as feasible without divulging its purpose, explained the operation of the apparatus, had a light in the testing room during the explanation, demonstrated the method of shocking (he applied the electrodes and shocked himself), offered the subject cigarettes, and generally attempted to create an atmosphere of congeniality. In this group, electric shocks were self-administered by the subject after a warning light was flashed. Both groups received six consecutive series of nine stimuli in each experiment, and the subjects were required to state whether each stimulus was "stronger" or "weaker" than a standard stimulus.

The results of this study were as follows. The anxiety-generating group interpreted a significantly greater number of test stimuli as being "stronger" than the standard stimulus. These errors were significantly reduced by the administration of morphine but were not altered by placebos. On the other hand, in the case of the anxiety-allaying group, verbally reported judgments of test stimuli were extremely accurate and were practically identical with those of the standards. Neither morphine nor placebos had any significant effect on the estimation of the intensities of painful stimuli in this group.

These experiments by Hill et al. point out two important features of experimental pain: (*a*) The threshold for pain may be altered by the extent to which anxiety is a factor in the situation. (*b*) When anxiety is a significant component of the situation, morphine changes the interpretation of stimulus intensity. It is, however, ineffective in a nonanxiety environment.

A corollary of these observations might well be that drugs capable of inducing euphoria—such as morphine and codeine—could be calibrated in an experimental pain situation if anxiety is deliberately included in the experimental test procedure. On the other hand, one would not expect drugs with minimal euphoric properties—for example, aspirin—to be satisfactorily

assayed in an experimental pain situation; this is supported by the studies of Wolff et al. (60) and other investigators.

Methods for evaluating analgesics in man, using clinical pain as a model.—Houde, Wallenstein & Beaver (61) have reviewed this subject very comprehensively. Only a limited number of the facets they discuss will be touched on in this review. As in experimental pain, there are many factors in evaluating clinical pain which influence the choice of yardsticks which would be most practical and meaningful. Some investigators prefer quantal measures—for example, "at least 50 per cent relief of pain" (62, 63), "complete relief of pain" (64), "presence or absence of comfort" (2), or "better," "no change," or "worse" days (65). Other investigators have either used scales which measure "pain intensity" (66–68) and "pain relief" (68, 69) or have used a combination of "change in pain intensity" and "pain relief" (70) scales. Still others use "therapeutic indices," which, according to Houde et al. (61) confound analgesia with side effects.

Although measurements of pain using "experimental pain" as a model have met with difficulties, there are reasons for success with clinical measurement of analgesia. These are:

(*a*) Recognition that pain is a subjective sensation. Therefore, the bias of the patient and of the observer must be avoided or distributed evenly insofar as feasible by carrying out studies in a double-blind manner. The observer must avoid emotional involvement with the outcome of the test or with the disease of the patient. To attain this goal, it is necessary to have full-time observers who are interested in their work but make their observations with the same emotional detachment as that with which they would brush their teeth or eat lunch. Such standards cannot be achieved by nurses who make the observations as a sideline in connection with other duties or by observers who are assigned on a temporary basis.

(*b*) Recognition that the determination of the relative potency of analgesics is a complex task and may require a negative control, as well as at least two dose levels of an appropriate standard such as morphine, codeine, or aspirin, and two or more dose levels of the unknown (61). Also, investigators are alert to the undesirability of stating the analgesic potency in absolute terms. Such absolute estimates may vary considerably even when the same method is used within the same institution, but at different times. For example, Denton & Beecher (62) stated that the AD_{90} of morphine was 7–9 mg per 150 lb body weight. Subsequently, Keats et al. (63), at the same institution, stated that the mean percentage of patients reporting relief from a dose of 10 mg per 150 lb body weight was 75.5, with a high and low range of 94 and 55 per cent among subgroups. The use of internal standards permits relative potency estimates of the unknown as compared with the standard and considerably neutralizes variations caused by different patient population groups. [As pointed out by Houde et al. (61), this feature of the experimental design is not as widely appreciated as it should be.]

Potency evaluation is also complicated by the fact that different drugs—

or even the same drug administered by different routes—develop their effects at different rates and may well have differences in duration of action. Consequently, both peak effects and total effects must be taken into consideration.

(*c*) Recognition by investigators that the crossover design has limitations insofar as analgesic assays are concerned, especially in postoperative and postpartum situations in which the intensity of pain is rapidly subsiding. This applies especially to postpartum pain which usually requires abandonment of the crossover design and the evaluation of a single dose of only one drug in each subject. In postoperative pain, the reduction in intensity is not as rapid and may be handled by randomization of treatment, but even in this case, there is a limit to the number of drugs which may be evaluated in each patient. On the other hand, the pain of cancer has less fluctuation and is preferable for crossover evaluations (61).

(*d*) Recognition by investigators of the significance of the placebo reaction and that the response which follows a placebo is affected to a considerable extent by the potency of the medication given immediately preceding the placebo [Kantor et al. (71)].

A survey of the methods used in the clinical evaluation of analgesics discloses a primary weakness in this field of research. There is a paucity of investigators who have evaluated the effects of repeated doses of analgesics. Few carefully controlled studies are reported in which the unknown drug is given for several days and the effects compared, as is done when single doses are used, with appropriate negative and positive controls. As a matter of fact, in only a limited number of studies are even two successive doses of the unknown compared with two successive doses of a standard drug. Since analgesics are usually given in repeated doses, erroneous impressions may be gained from evaluation of single doses. For example, although single doses of methotrimeprazine do not induce a significant degree of sedation (72), multiple doses provoke pronounced sedative effects (73, 74) and limit its analgesic usefulness.

Experimental methods for evaluating the abuse liability of narcotic analgesics, using former narcotic addicts as subjects.—The methods referred to below for evaluating abuse liability of drugs in man are those employed at the Addiction Research Center in Lexington, Kentucky. The subjects used are male prisoner volunteers in good physical condition with a long history of asocial behavior, including abuse of opiate-like drugs, and with a poor prognosis for recovery. Except for certain refinements, the methods are based on the classic studies of Kolb & Himmelsbach (75) and Himmelsbach (48) and include the following procedures: (*a*) administration of single doses for detection of morphine-like subjective (euphorigenic) effects, morphine-like induced behavior, or both; (*b*) substitution of the test drug for morphine in human subjects addicted to morphine in order to ascertain its effectiveness in preventing symptoms of abstinence; (*c*) direct addiction by chronic drug administration in increasing doses as tolerated for 7, 18, and 60 or more days, followed by abrupt withdrawal to ascertain the presence and degree of

physical dependence (in addition, nalorphine may be administered subcutaneously after various intervals of chronic drug administration in an attempt to precipitate abstinence phenomena); (*d*) a short-term intravenous preference test in which addicts are given sample doses of drugs on a double-blind basis so that they may select the drugs which they wish to take in subsequent seven-day intoxication tests. Insofar as the studies at Lexington are concerned, the effects of single doses, of substitution tests of Himmelsbach, and of direct addiction procedures have been adequately covered by previous reviews (42, 43).

The only significant recent development is the short-term intravenous preference test (76). In this technique, each of six to eight subjects is given intravenously, in random order, a sample dose of each of a series of drugs, including a standard such as 30 mg of morphine sulfate, codeine, or *d*-propoxyphene.

The observer is aware of the characteristics of all drugs, but the subject is not. The subjects are then asked to rate the drugs in the order of their "liking" for them and subsequently they may elect to take none of them, one or more, or all of them intravenously on an increasing dosage schedule for seven days. Subjects may discontinue a drug at any time during the chronic phase. In each instance, stopping of the medication is followed by a withdrawal period of three days, and then another drug of the patient's selection is given in randomized order in a similar manner. At the conclusion of the chronic test, each subject is again asked to rate the drugs in order of preference. Nalorphine or placebo is given intravenously on a randomized double-blind basis three hours after the last dose of experimental drug on the sixth or seventh day of the experiment. This short-term intravenous procedure has several advantages: (*a*) it is less rigid than the customary direct addiction procedure; (*b*) it allows subjects an opportunity to choose from a number of drugs and to decide how long they wish to take any agent before trying another; and (*c*) it rapidly brings out differences among drugs regarding the quality of the subjective effects, since all drugs are given by the intravenous route, the route of preference of North American addicts. One of the major deficiencies of this method is that the test period is of insufficient duration to evaluate adequately the relative degree of physical dependence induced by the various drugs.

Another area in which advances have been made is the evaluation of psychic dependence in post addicts (77). A high correlation was observed between the ability of post addicts with wide drug experience to identify new drugs as narcotics [morphine or heroin-like "dope"] and the capacity of the same drugs to induce physical dependence. Furthermore, it has been possible on a double-blind basis to obtain dose response and relative potency assays of morphine-like subjective effects and to compare them with certain physiological measurements concurrently performed, such as pupillary diameter (77).

However, these investigators pointed out the need for caution in inter-

preting the significance of psychic effects of narcotic drugs and the fact that single-dose tests are inadequate unless the drug has a very morphine-like pattern. For example, some of the drugs tested at Lexington provoked side effects such as nausea, vomiting, nervousness, and insomnia, which the subject did not like because he was accustomed to the balance of sedation and stimulation obtained from heroin or morphine. In addition, even though addicts might have been satisfied with the effects of single doses, their voluntary discontinuance of a drug while participating in a chronic schedule was considered valid evidence that they would not abuse that drug. Furthermore, certain drugs may irritate the tissue and progressively occlude veins so that an addict is incapable of chronically abusing such drugs by this route. Another important factor in psychic abuse is that the addict prefers to have subjective effects develop in maximal intensity immediately.

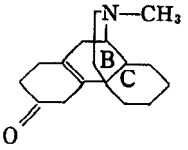
A good example of a drug which does not exhibit these qualities is 1-(3-cyano-3,3-phenylpropyl)-4-phenyl-4-piperidine carboxylate hydrochloride (R-1132, diphenoxylate) (78). When diphenoxylate was injected intravenously into nontolerant morphine addicts, the onset of effects was very gradual and no definite identification of opium-like effects was made until 10 to 20 minutes after injection; however, after 30 minutes the effects were pronounced. The most probable reason for this delay was that the drug is extremely insoluble in water and must be dissolved in pure propylene glycol. If even one drop of water was present in the syringe, diphenoxylate precipitated out *in toto*. When injected into the vein, diphenoxylate evidently precipitated promptly and was available for its pharmacological action very slowly. It is obvious that the potential abuser of diphenoxylate would need to carry a solvent like propylene glycol; this would also significantly interfere with his abuse of the drug.

Tests for tolerance and physical dependence under clinical conditions.—Such a procedure can be carried out when there is a sufficiently large group of patients with persistence of severe pain—for example, inoperative malignancies. Here also attempts to compare the unknown drug with a standard such as morphine for degree of tolerance and especially for evidence of physical dependence are made by utilizing the nalorphine abstinence precipitation test (79). This technique, however, as pointed out by the WHO Scientific Group (41), is time consuming and requires close supervision by an interested clinical investigator. Difficulties have been encountered in evaluating drugs administered orally or drugs with a weak potency, since such agents usually do not produce a sufficient degree of dependence in therapeutic doses to demonstrate differential degrees of tolerance and physical dependence.

Newer Agents of the Narcotic Type

Morphinans.—There has been little activity in this area in the last few years. Pirkle & Gates (80) have prepared the hydro-aromatic analogues

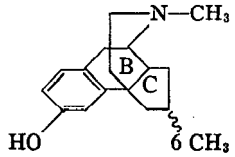
(I and II) of the potent analgesic 1-3-hydroxy-N-methylmorphinan. The *cis*-fused compound (1) was inactive while the *trans*-fused compound was active only at near toxic doses. Reduction of the aromatic ring markedly reduced analgesic activity and thus points to the importance of the planar ring.



I B/C *cis*

II B/C *trans*

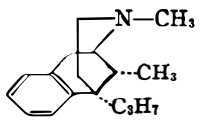
Sawa and his colleagues (81, 82) reported the synthesis of some C-nor-morphinan derivatives characterized by a 5-membered C-ring (III and IV). These compounds were respectively 19 and 12 times more active than morphine.



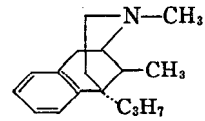
III B/C *cis*

IV B/C *trans*-6-oxo

Benzomorphans.—May and his colleagues (83-86) have continued their elegant work in this area. They have prepared a number of *cis*- and *trans*-pairs such as V and VI. The *trans*-compounds tend to be considerably more potent than the *cis*-compounds. The *cis*-compounds still behave anomalously in that they have little or no ability to substitute for morphine in the addicted monkey. It has been reported (85) that the analgesic (hot plate) ED_{50} values



V

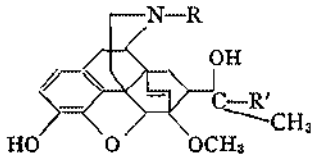


VI

obtained in a new type of Caesarean-derived general-purpose mice were approximately half those previously obtained at the same institution. These healthier, faster-growing mice would appear to be more susceptible to analgesics.

An interesting modification of the benzomorphan nucleus has been reported by Kametani and his colleagues (87, 88). They prepared 1,2,3,4-tetrahydro-6H-1,5-(e)(1,4)diazocine and 1,2,3,4,5,6-hexahydro-2,6-methano-benzo-(e)(1,4)diazocine, two azabenzomorphans. It will be interesting to ascertain whether these aza-derivatives retain the analgesic properties of the parent ring system.

Oripavine derivatives.—One of the most interesting disclosures in recent years concerns the finding by Bentley and his colleagues that ring expansion of morphine to the six-ring 6,14-endoethenotetrahydrothebaine or oripavine structure (VII) leads to analgesics of surpassing potency (1, 89, 90).



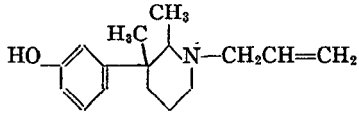
VIIa: R=CH_3, R'=$(CH_3)_2CHCH_2CH_2$

VIIb: R=△-CH_2, R'=CH_3

VIIc: R=△-CH_2, R'=$(CH_3)_2CHCH_2CH_2$

The compound VIIa was found to be nearly 8000 times more potent than morphine (89). This high potency has led to the widespread use of these agents to immobilize wild animals. These compounds can be readily utilized in "darting," and their safety ratio in four-legged animals is high. Narcotic antagonists have also been prepared in this series. However, their behavior is not typical. Thus, the N-cyclopropylmethyl derivative (VIIb) is a potent antagonist (35X nalorphine), while the analogous compound with a longer C-side-chain (VIIc) behaves more like a strong analgesic. Some qualitative differences between this compound and morphine do exist (90, 91). Keats (92) has attempted to evaluate VIIb in man as an analgesic but found a high incidence of nalorphine-like side effects.

Piperidinoids.—Despite the fact that over 4000 meperidines have been prepared, work in this area continues unabated. Hardy, Lister & Sterm (93) described several homologous series of normeperidines which were assayed for analgesic activity. Peak activity occurred consistently when the nitrogen side-chain skeleton had an overall length of 7–9 Å. Within different series of compounds, increasing the length of the N-side-chain produced relatively the same changes in analgesic potency. Their investigations point out that this may be caused by equivalent effects on rates of transport to the active site or by similar changes in affinity for that site. Kugita and his colleagues (94), continuing their earlier work with 3-alkyl-3-phenylpiperidines, prepared a series of 3-alkyl-2-methyl-3-arylpiperidines, some of which were as potent as morphine. Of particular interest was the N-allyl derivative VIII. This

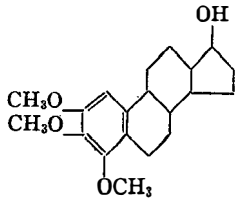


VIII

compound was devoid of analgesic activity and proved to be an antagonist. This differs markedly from the meperidine series in which the N-allyl derivative is a straightforward analgesic. Archer & Harris (6) postulated that antagonistic activity may be related to a phenethylamine fragment of

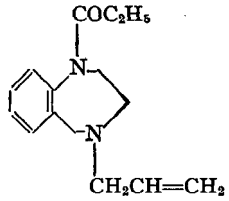
the molecules. This structural feature, shared by VIII and other narcotic antagonists, is lacking in N-allyl-normeperidine.

Miscellaneous.—A non-nitrogenous steroid (IX) has been reported to have strong analgesic properties in laboratory animals and man (95, 96).



IX

Of additional interest is the report by Carabateas & Harris (97) of a series of analgesic antagonists in the benzodiazepine series of the type X. These compounds proved to be relatively specific, albeit weak (1/100 nalorphine) antagonists.



X

It is noteworthy that members of this series having nitrogen substituents which are usually associated with strong analgesic properties (i.e., methyl and phenethyl) were inactive in this regard. Indeed, some were quite active antagonists.

Narcotic Antagonists as Analgesics

Introduction.—One of the most fascinating areas of analgesic research concerns a group of compounds known as narcotic antagonists. These drugs have the remarkable property of specifically reversing the major pharmacodynamic actions of the narcotics (6, 50, 98, 99); the more potent ones are capable of inducing an immediate and intense withdrawal syndrome when administered to narcotic addicts (5, 100). Perhaps the most interesting and provocative fact about the narcotic antagonists is that many of them are capable of relieving severe pain in man (3, 101–104). The first discovery of the analgesic properties of nalorphine, the classical antagonist, was born from the hopes of Eddy (105) that a mixture of morphine and nalorphine could be found which would reduce the respiratory-depressant and other side effects of morphine without interfering with the analgesic effects. It was in the careful study (101) designed to put this hypothesis to the test that the analgesic action of nalorphine itself was uncovered. This was very surprising since, by and large, the narcotic antagonists are relatively inactive as

antinociceptive agents in laboratory animals. Although of great theoretical importance, these findings also have an equally great practical implication since some of the narcotic-antagonist analgesics are free from morphine-like addiction potential. They do not support morphine addiction, addicts do not like their effects, and, after prolonged administration, abrupt withdrawal leads to relatively mild and atypical withdrawal symptoms (4, 5, 106–108). Indeed, one of these compounds, cyclazocine, appears to have some utility in the treatment of narcotic addicts (109–111). There is reason to hope that, through these compounds, some progress has been made toward finding a clinically acceptable, nonaddicting strong analgesic.

Laboratory evaluation.—A number of tests have been devised to assess the ability of narcotic antagonists to prevent or reverse the analgesic action of morphine and other narcotic analgesics (6). The method of Green, Ruffell & Walton (112) measures the dose of antagonist required to reduce by 50 per cent the morphine-induced doubling of the pain threshold to pressure and heat. The methods of Winter, Orahovats & Lehman (113) and Harris & Pierson (114, 115) involve the ability of the antagonist to prevent the delay in response time induced by morphine or meperidine on the rat tail-flick response. These tests are in relatively good agreement (6) and have been the most extensively used in the evaluation of new compounds. Antagonists evaluated by these methods now exist in the oripavine (90), morphine (6, 98–100), oxymorphone (116), morphinan (117), benzomorphan (2), and a piperidine series of analgesics (94). These antagonists vary in potencies from weak (approximately 1/100 nalorphine) to potent (30 times nalorphine.) In general, the stronger the parent analgesic, the more potent the antagonists (6). This concept breaks down in the meperidine series, where the N-allyl compound is not an antagonist, but this may be because of structural features, since another series of piperidine analgesics does yield antagonists (94). Again, in the oripavine series there is evidence of discrepancy. The N-cyclopropylmethyl derivative of the most potent analgesic of this group is not an antagonist (90). It behaves more like a strong analgesic with some marked qualitative differences from morphine (118). N-cyclopropylmethyl derivatives of weaker analgesics in this series have, however, afforded very potent antagonists (90).

The ability of the narcotic antagonists to reverse the respiratory and cardiovascular depression produced by a variety of narcotic analgesics has also been utilized for evaluation (6, 98–100, 118). There is some reason to believe that nalorphine and other antagonists are more effective in reversing the respiratory than the cardiovascular depression. Some of the newer antagonists are less effective than nalorphine, and this is probably a result of their inherent depressant properties. Indeed, despite the clinical reports of respiratory depression produced by nalorphine, there is little to support this from studies in laboratory animals (98). On the contrary, large doses of nalorphine stimulate respiration (98, 119), a fact which might account for earlier reports on the usefulness of this agent in the treatment of barbiturate-

induced respiratory depression (98). Recently, Keats & Telford (120) have noted that the respiratory-depressant effects of certain antagonists in man level off. Small doses produce about the same depression as does morphine, but larger doses give no further increment of depression. Similar behavior with other antagonists is seen in laboratory animals. Thus, even very large doses of the benzomorphan antagonists only rarely produced apnea (118).

Another method of ascertaining the antagonistic properties of these agents makes use of their ability to reverse the somatic and behavioral effects of morphine or meperidine in the unanesthetized dog (118, 121). Dogs are medicated with large doses of narcotic, and the behavioral and somatic changes are noted and scored. The antagonists are then given intravenously and the degree of reversal assessed. When the effects of the antagonists alone were studied in the unanesthetized dog, analgesia was occasionally noted. This occurred, however, only at high doses and may be related to the general central depression seen (118).

Evaluation of the analgesic properties of these agents was discussed in an earlier section. A good laboratory procedure for predicting the analgesic effectiveness of the narcotic antagonists in man is not available. This holds true also for our ability to predict the potential of these compounds to cause psychic disturbances. It has been reported (115, 121) that certain of the N-cycloalkyl antagonists have potent and selective polysynaptic blocking properties. It was also noted that small doses produced an enhancement of both the polysynaptic and monosynaptic reflexes. With one of the compounds, cyclorphan, the enhancement was much greater in the spinal animal (121). Wikler & Carter (122) had noted earlier that large doses of nalorphine in the chronic spinal dog produced an excitant effect on the ipsilateral flexor and crossed extensor reflexes. How this relates to the bizarre psychic effects produced by these drugs in man remains to be seen.

Initially, investigators postulated that the narcotics and the narcotic antagonists competed for a common receptor site in the central nervous system (98, 115). Archer & Harris (6) tested twenty diverse antagonists for their ability to reverse nearly equianalgesic doses of phenazocine, morphine, and meperidine. The potencies of the antagonists varied over a one-thousand-fold range, while the potencies of the analgesics varied over a one-hundred-fold range. Spearman rank-order correlations for antagonistic potency versus that of the three analgesics used were very high (>0.95). This would tend to support the hypothesis of a common mechanism of action. More convincing are the results of a carefully controlled study by Grumbach & Chernov (123). They carried out Gaddum drug-ratio studies in rats with nalorphine and levallorphan and a variety of analgesics. The ratios for four pairs of drugs were constant over a wide dose range which indicated that the antagonism is a "surmountable" one and that the drugs are competing for a common receptor site. Cox & Weinstock (124), reporting on the ability of nalorphine to reverse the lenticular opacities produced by a number of narcotic analgesics, presented similar evidence.

Clinical evaluation and uses of narcotic antagonists.—The clinical methods for evaluating narcotic antagonists as analgesics are similar to those employed for assessing narcotic analgesics. There are two important differences which are related to the pharmacology of the antagonists: first, the clinician must be alert for psychotomimetic effects and, second, if the antagonist is potent in counteracting the effects of morphine, the antagonist should not be given to patients dependent on or chronically receiving opiate-like drugs because a severe abstinence syndrome may be precipitated (50).

Certain of the antagonists have important uses in medicine, for example (*a*) as analgesics (125, 127), particularly pentazocine; (*b*) to counteract overdoses of various morphine-like drugs (125–128); and (*c*) to test for physical dependence on narcotic drugs which may either be experimental (1, 100, 129) or used as a diagnostic tool to determine whether a narcotic addict has relapsed in a setting designed to prevent abuse of narcotic-like drugs (130–132).

Tests in man for evaluating the abuse liability of narcotic antagonists and their pharmacological pattern.—Essentially, these tests are the ones enumerated for narcotic analgesics. In addition, a very important factor is the potency of these antagonists to counteract the effects of morphine. A potent morphine antagonist such as nalorphine is shunned by narcotic addicts because, if they are dependent on opiates, 5 to 10 mg of nalorphine will precipitate a very severe abstinence syndrome (100, 129, 133).

The three narcotic antagonists that have been studied most extensively in respect to their abuse potential are nalorphine, pentazocine, and cyclazocine (42).

Schrappe (134) reported that a mild but typical morphine-like abstinence syndrome developed after abrupt withdrawal of nalorphine in two psychotic patients. Isbell (106), on the other hand, observed no significant signs of abstinence in chronic administration tests with nalorphine. Martin & Gorodetzky (107) conducted a direct addiction test with nalorphine in which the dosage was gradually raised to 240 mg per 70 kg and, after 72 days, the drug was abruptly withdrawn. A moderate abstinence syndrome, with many of the characteristics of morphine, promptly developed. However, the complete pattern was qualitatively different and, except for its speed of onset, was more similar to the abstinence of cyclazocine. There was no drug-seeking behavior during withdrawal of nalorphine. In a patient chronically intoxicated on cyclazocine (12.3 mg daily), nalorphine was substituted for an interval of 14 days (108), and an abstinence syndrome similar to that described by Martin & Gorodetzky (107) developed when the substituted nalorphine was withdrawn abruptly.

Pentazocine is a weak narcotic antagonist which, in single doses, showed significantly less morphine-like effects than intravenous morphine and *d*-propoxyphene. When pentazocine, in the maximum tolerated and accepted dosage, was substituted for morphine in morphine-dependent subjects, addicts did not like the effects induced and there was no significant suppres-

sion of abstinence symptoms. Furthermore, when pentazocine was chronically administered, it was disliked by opiate addicts. Seven of eight subjects elected to stop taking it, whereas none discontinued morphine in parallel experiments. The eighth subject (who continued on pentazocine for 25 days despite a severe inflammatory reaction at the injection sites) showed a mild but definite abstinence syndrome when the drug was discontinued, but no physical dependence was demonstrated by the nalorphine tests. It was concluded from these studies that pentazocine has minimal, if any, abuse liability.

Cyclazocine is a potent narcotic antagonist which was evaluated in a manner similar to that used for pentazocine (5). In single-dose tests, cyclazocine was qualitatively different from morphine and its effects more closely resembled those of barbiturates when doses of 1 and 2 mg per 70 kg were employed. Cyclazocine does not suppress abstinence in subjects physically dependent on morphine; on the contrary, it precipitates abstinence in a manner similar to that of nalorphine. Subjects who were chronically intoxicated with cyclazocine followed a dosage schedule which was gradually increased to an average maximum of 13.2 mg per 70 kg; they showed definite tolerance to cyclazocine and cross-tolerance to nalorphine, and exhibited a definite abstinence syndrome when cyclazocine was withdrawn. The predominant signs of abstinence from cyclazocine were an increase in body temperature, miosis, loss of appetite, decrease in body weight, and tachycardia. This abstinence syndrome was slow to develop; it first became apparent on the third or fourth day following withdrawal and reached a maximum on the seventh day. Minimal signs of abstinence were seen as long as six weeks after withdrawal. Even though abstinence signs were present, addicts showed no evidence of drug-seeking behavior. Because cyclazocine is effective orally and has a relatively long length of action, as mentioned above, Martin et al. (109) have advocated the use of its antagonistic properties to prevent the development of physical dependence and to counteract the euphoria induced by narcotic analgesics.

The antagonists may well lead us, as investigators, to change our attitude with respect to requirements for abuse—namely, although physical dependence (development of an abstinence syndrome) is highly presumptive evidence that a drug will be abused, it is not conclusive evidence unless the agent in question develops subjective effects which result in drug-seeking behavior.

Biochemical Considerations

Distribution and fate.—The distribution and metabolism of morphine and its surrogates have recently been exhaustively reviewed by Way & Adler (135). Little that is new has been added concerning the addicting narcotics. Chernov & Woods (136) compared the distribution and metabolism of morphine in the cat with those found in the dog. This study revealed little difference between the species despite the marked disparity in behavioral response. Way, continuing his work on the metabolism of heroin, presented

convincing evidence that the pharmacologic effects are dependent on the formation of monoacetylmorphine (137). Heroin is de-esterified to monoacetylmorphine, which then acts as a carrier to facilitate the access of morphine to receptor sites in the central nervous system.

Tritium-labeled dihydromorphine (DHM-H^3) was studied by Hug & Mellett (138, 139). Minimal qualitative differences in the pattern of excretion and metabolism were found between DHM-H^3 and morphine. Qualitatively, the biological fates of the two compounds were nearly identical (139). It was also reported that DHM-H^3 was actively secreted by the renal tubules of dogs and monkeys (139). Highly tolerant monkeys did not differ from nontolerant animals in this regard.

McMahon, Culp & Marshall (140) reported that, among the simpler synthetic molecules, the major metabolic pathway for *α-dl*-acetylmethadol is by enzymatic N-demethylation to the analgesically active *α-dl*-noracetylmethadol. The nor-compound is, in turn, N-demethylated but at a much slower rate, which tends to permit accumulation of the secondary amine in the body. Ester hydrolysis does occur but to a lesser extent. N-dealkylation was also shown to be an important biotransformation pathway for anileridine (141). In this case, normeperidine and *p*-aminophenylacetic acid were isolated and identified from the urine of rats receiving anileridine.

In the area of narcotic antagonists, Mulé (142) reported a statistically significant lowering of the levels of morphine in the central nervous system of dogs after the administration of nalorphine. This change was even more apparent in other tissues. Plasma levels of free morphine were lower in the nalorphine-treated animals than in the controls. This discrepancy between displacement from tissue sites and lowered plasma levels may be accounted for by higher plasma levels of morphine glucuronide in the antagonized animals.

Ferrari (143) studied the distribution of pentazocine in the cat. Tissue distribution and rate of uptake by the brain closely resembled those reported for nalorphine. A later study (144) reported a comparison with morphine in the subcellular distribution in the brain. Differences were noted in the degree of binding. Mulé & Gorodetzky (145) studied the physiological disposition of cyclazocine in nontolerant, tolerant, and abstinent dogs. Little difference in the recovery pattern and plasma levels was seen in the various animals studied. The central nervous system levels were relatively high in the first hour and then rapidly fell off. The highest levels of free and conjugated cyclazocine were found in bile.

Postulated molecular mechanisms.—On the basis of several studies in which steric factors were related to biological activity, Portoghese (7) has postulated different modes of analgesic-receptor interactions depending on the type or series of agent. He conceived of the receptor as having a charged anionic site as a common pivot point around which the analgesic may be bound more or less tightly depending on its structural and conformational characteristics.

Ungar and his colleagues (146, 147) have continued to explore the earlier work of Kornetsky & Cochin (148) which related tolerance development to protein or peptide formation in the central nervous system. Thus, extracts of brains from morphine-tolerant rats and dogs imparted tolerance to the analgesic effects of morphine in mice (146). Again, development of tolerance to morphine could be delayed by pretreating animals with actinomycin D. In this regard, the work of Clouet and her associates is relevant (149, 150). They have found both *in vitro* and *in vivo* that morphine decreased the ability of rat-brain ribosomes to incorporate C^{14}-leucine into protein.

Of great interest is the recent work of Kakunaga, Keneto & Hano (151), who found that Ca^{++} strongly antagonized the analgesic action of morphine and other opiates. Conversely, intercisternally administered decalcifying agents such as EDTA enhanced the analgesic activity of the opiates. The calcium complexes of these chelating agents were without effect, as were a number of other cations. These findings strongly suggest that calcium in the central nervous system plays an important role in the opiate-produced analgesic process, and further work along these lines would appear to be promising.

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