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OPIOID ANTAGONISTS

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I. INTRODUCTION

The history of the development of antagonists of morphine is well known and their basic and clinical pharmacology has been the subject of several reviews (6, 7, 64, 65, 81, 86a, 91, 136, 212, 323, 352, 365). In 1915, proceeding on the premise that the allyl compounds stimulated respiratory processes, Pohl (277) studied the effects of N-allylnorcodeine, synthesized by Von Braun (337). In addition to describing the ability of N-allylnorcodeine to antagonize respiratory depression produced by morphine and heroin, he recognized that it accelerated respiratory rate in its own right and that it was more effective in antagonizing respiratory depression produced by morphine than by ether, chloroform or chloral hydrate. He postulated that both morphine and N-allylnorcodeine were taken up by the same haptophore and suggested that they produced opposite effects. Although Pohl's work was confirmed in 1923 by Meissner (252), its significance was not fully recognized. The development of N-allylnormorphine (nalorphine, Nalline) and the chemical problems concerning its synthesis have been reviewed (6, 65, 212). After its synthesis was reported (247, 344), its morphine antagonistic properties were described by Hart (139), who also confirmed Pohl's work (138), Unna (331) and Hart and McCawley (138, 140). This property was not exploited clinically until 1951 when Eckenhoff *et al.* (58) demonstrated that nalorphine was an antidote for morphine poisoning in man. In quick succession followed the observation of Wikler *et al.* (356) that nalorphine could precipitate the abstinence syndrome in morphine-dependent subjects and that of Lasagna and Beecher (214) that nalorphine was a potent analgesic. Each of these fundamental observations has opened fertile areas for research.

A large number of agents that antagonize the effects of morphine, with diverse chemical structures, have been synthesized and subjected to extensive pharmacological study. The therapeutic and diagnostic use of this group of agents has been greatly extended. Further, they have provided powerful tools for studying the mode and site of action of morphine, for assisting in the understanding of the fundamental processes involved in tolerance and physical dependence to narcotic analgesics, and for delineating their own modes of action. It is the purpose of this review not only to critically summarize the large body of work that has been done with the narcotic antagonists, but to explore the theoretical implications of these findings, particularly with regard to their modes of action and the nature of tolerance to and physical dependence on morphine and certain antagonists of morphine. In preparing this manuscript, some references dealing with the narcotic antagonists have been intentionally omitted because they had little relevance to the main thesis. There are undoubtedly other omissions that are oversights, for which the author apologizes.

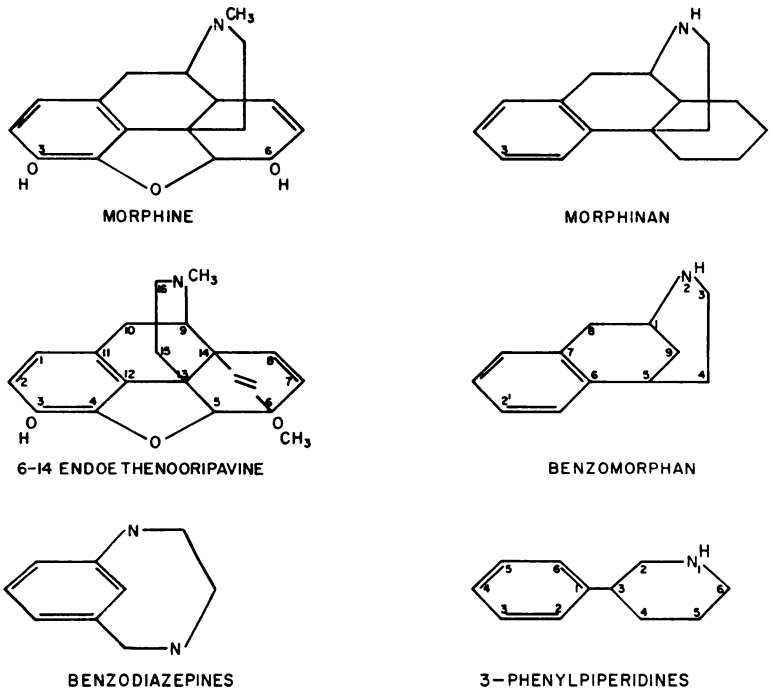
The terminology of both morphine-like agents and nalorphine-like antagonists has become unsatisfactory for designating and classifying many of the newer related drugs for several reasons. (a) Narcotic antagonists have both agonistic and antagonistic effects. Further, the agonistic effects of certain narcotic antagonists are qualitatively different from those produced by morphine. We have adopted the term *opioid*, which was proposed by Professor George H. Acheson,

to designate those analgesics whose pattern of pharmacological and agonistic effects is similar to that of morphine, and have called this pattern of effects the *opioid syndrome*. This term has the same general connotation as the terms *strong*, *potent* and *narcotic analgesics*, except that it carries no implications about either potency or activity (see below). The pattern of agonistic effects produced by nalorphine and nalorphine-like drugs will be called the *nalorphine syndrome*, and agents that produce this type of syndrome will be called *opioid antagonists*, *narcotic antagonists*, or *antagonists of the nalorphine type*. Within this framework, applying the term antagonist to agents that are also agonists is misleading; however, under appropriate circumstances a partial agonist (see below) may antagonize the effects of a more active agonist. For historical reasons, it seems worthwhile to retain the term antagonist but to broaden its meaning to include partial agonists, which produce either the *opioid* or *nalorphine* syndrome, and antagonists (agonists with no activity). It is important that the possibility be recognized that even in cases where agonists such as nalorphine and morphine produce similar effects (*e.g.*, analgesia) these effects may be a consequence of the drug's interaction with different receptor populations. (b) One of the major points of this review is that agents that occupy receptors that are responsible for causing agonistic effects of both the opioid and the nalorphine-like antagonist type differ in their ability to initiate these changes. *Activity* will be used in this review in a manner closely related to the concept of *intrinsic activity* (8), to indicate the maximal effect of the agonist. The terms *agonist with low activity* and *partial agonist* are synonymous.

The terms *opioid* and *opioid antagonist*, which designate pharmacological syndromes, also have implications concerning modes of action of these agents. An attempt will be made to reconcile a number of observations by using the concepts of *competitive antagonism*, *competitive dualism* (8), and *receptor dualism*. *Competitive antagonism* will designate the interactions between an agonist and an agent that can occupy the agonist receptor but that does not have agonistic activity in its own right. *Competitive dualism* designates the interaction of two agonists that produce their effects by occupying the same receptor but that differ from each other in their levels of activity. *Receptor dualism* designates the resulting interactions of agonists that produce the same effect by occupying different receptor populations.

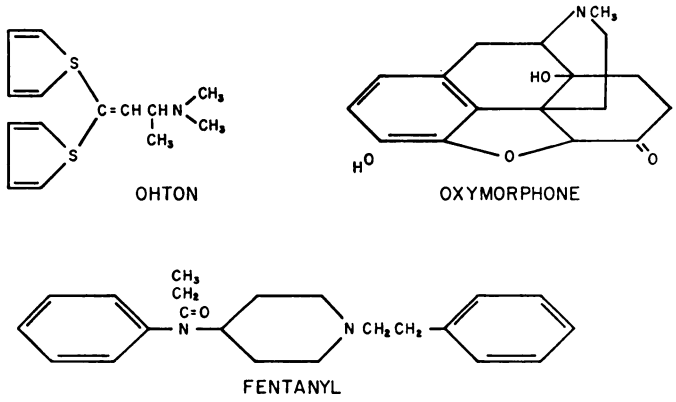
II. CHEMICAL STRUCTURE OF NARCOTIC ANTAGONISTS

Figure 1 shows the basic structure of the rings which, when appropriately substituted, have yielded narcotic antagonists and includes the morphine (331), morphinan (102), 6,14-endoethenooripavine (19), benzomorphan (137), the benzodiazepine (36) and the 3-phenyl piperidine (208, 209) ring structures. A variety of substitutions can be made on the nitrogen of these ring structures to yield antagonists, including ethyl, propyl, allyl, dimethylallyl, propargyl, butyl, isobutyl, crotyl, 2-ketopropyl, methylcyclopropyl, methylcyclobutyl and chlorallyl (114, 137, 363). Optical isomerism of these compounds also determines their activity as both analgesics and antagonists. The *l*-isomers of the morphine,



BASIC RING STRUCTURES OF NARCOTIC ANTAGONISTS

FIG. 1a. Basic ring structures of narcotic antagonists



STRUCTURES OF SELECTED OPIOIDS

FIG. 1b. Structure of some of the less well known opioids referred to in the text

morphinan, and benzomorphan series are more potent than the *d*-isomers, both for agonistic and antagonistic actions of these drugs. Further, the cis-trans isomerism involving the 5,9 position of the benzomorphan nucleus affects both antagonistic and agonistic activity of this series; for some analogs the cis is more

potent than the trans, while for others the trans is more potent than the cis (7, 244, 273). Although the N-methyl derivatives are for the most part devoid of antagonistic actions, recent findings suggest that even certain of them may be antagonists. Although N-allylnormeperidine does not antagonize the analgesic actions of a variety of opioid analgesics, in very large doses it antagonizes the respiratory depressant effects of these agents. Recently, the N-allyl derivatives of 3-phenyl- and 3-methyl-3-phenylpiperidines were found to antagonize the analgesic activity of morphine in the mouse (208, 209). It is of interest that substitution of a methyl group in the 3 position markedly reduces analgesic potency. As Harris (136) has pointed out, this finding strengthens the proposal of Archer and Harris (6) that the phenethylamine moiety is associated with antagonism.

The following agents will play a major role in the following discussion: Nalorphine (N-allylnormorphine, Nalline), naloxone (N-allyl-noroxymorphone), levallorphan (*l*-3-hydroxy-N-allylmorphinan, Lorfan), cyclorphan (3-hydroxy-N-cyclopropylmethylmorphinan), cyclazocine (2-cyclopropylmethyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan), and pentazocine [2-(3,3-dimethylallyl)-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan, Talwin].

III. BIOCHEMICAL CONSIDERATIONS

A. Metabolism

Seibert and Huggins (297) first studied the conjugation of nalorphine *in vitro* in dog liver slices and found that it was conjugated at about the same rate as morphine, but *in vivo* in the dog Woods and Muehlenbeck (367) found that nalorphine was conjugated more rapidly and more completely than morphine. Concentrations of both conjugated and free nalorphine in tissues other than brain were lower than those of morphine after comparable doses of morphine had been administered. It has been presumed that nalorphine is conjugated at the phenolic hydroxyl group as a glucuronide.

Although much less is known about the metabolism of levallorphan than nalorphine, its metabolism is certainly more complex (339, 340). Only a small portion of doses of levallorphan administered to dogs (33) and rats (225) has been recovered and identified. In rats, levallorphan as well as its metabolites could be conjugated; levallorphan was dealkylated to 3-hydroxymorphinan; and a third metabolite was identified but not characterized chemically (225). From 60 to 80% of administered cyclazocine is excreted in the free or conjugated form; the remainder is unaccounted for (261).

Both nalorphine and levallorphan have been shown to be N-dealkylated, both *in vivo* and *in vitro* (10, 90, 225, 340). Nalorphine inhibits the N-demethylation of morphine probably in a noncompetitive manner (10). It is of interest that maximal inhibition of demethylation of morphine by nalorphine is about 75% and is obtained with a concentration of 4×10^{-4} M nalorphine. Chronic administration of morphine, nalorphine, or normorphine depresses the enzymatic demethylation of morphine. Chronic administration of morphine produces a modest suppression of enzymatic deallylation of nalorphine; but chronic administration of nalorphine

or normorphine does not (43). When nalorphine (43) or levallorphan (226) is chronically administered in combination with morphine, the suppression of N-demethylation of morphine is unaffected. These data will be considered again in the section on the site of action of opioids and opioid antagonists (III C).

B. Distribution

Nalorphine is rapidly taken up by the blood and plasma when administered subcutaneously, reaching a peak concentration as the free drug within 30 minutes (157, 366). Maximal concentrations in the gray areas of the brain are also reached in about 30 minutes. Decay is rapid, only trace amounts being present after 4 hours (157). The decay of nalorphine levels in brain is much more rapid than that of morphine and is more rapid than the decrement in the agonistic effects of nalorphine (249). The brain concentrates nalorphine to a much greater extent than it does morphine (255, 336). The concentration in the brain is even greater in the hepatectomized rat and is probably lessened in the intact rat because of rapid conjugation (336). Morphine was concentrated to a greater extent than nalorphine *in vitro* by slices of guinea pig cerebral cortex (260). The change in concentration of nalorphine in the white matter lags somewhat behind that in the gray matter.

In the dog the uptake of subcutaneously administered cyclazocine and its appearance in the brain are quite rapid. Although the decay in brain levels of cyclazocine is not as precipitous as the decay of nalorphine, it is considerably faster than that of morphine (261) and than that of its own agonistic effects (249).

Information about the effects of opioid analgesic antagonists on the distribution of opioid analgesics is limited, and the facts that are known are not easily reconciled one with the other. In the nontolerant dog, nalorphine increases the levels of morphine in both gray and white matter of the brain regardless of whether the nalorphine is given before, at the same time as, or after morphine (263). Nalorphine does not produce consistent changes in the gray:white concentration ratio of morphine. In the tolerant dog, nalorphine consistently decreases the levels of morphine both in gray and white matter without increasing the plasma levels of morphine (259). In the rat, the administration of morphine with nalorphine results in higher brain concentrations of nalorphine than when nalorphine is administered alone, but the concentration of morphine in the brain is unaffected by nalorphine (182, 184).

Nalorphine is concentrated by dog renal cortical slices and by rabbit choroid plexus to about the same extent as morphine and dihydromorphine. Further, nalorphine competitively inhibits the incorporation of dihydromorphine into both tissues (156). It is of interest that hexamethonium also competitively inhibits the uptake of dihydromorphine (156). Nalorphine increases the rate of excretion of morphine by the kidney and decreases the proportion conjugated (1, 2).

Chronic administration of morphine does not affect the intracellular distribution of morphine in the brain or liver of guinea pigs, nor does nalorphine, in either the nontolerant or morphine tolerant guinea pig (262).

Certain of these observations can be explained; others cannot. The fact that both nalorphine and cyclazocine are rapidly absorbed and quickly gain entry into the brain is due, at least in part, to the fact that the allyl-substituted nitrogen of the opioids is less well ionized, and hence more lipid soluble, than the methyl-substituted nitrogen (366). The fact that brain levels of both nalorphine and cyclazocine decay more rapidly than their agonistic actions can be explained by assuming they are bound to active receptors more tightly than to inactive receptors. The fact that nalorphine, while antagonizing the effects of morphine on the brain, does not alter in a consistent way the brain concentration or intracellular distribution of morphine does not seem consistent with the hypothesis that nalorphine competitively displaces morphine from active receptors, but it may be that the number of active and critical receptors in both the tolerant and nontolerant animal is small compared to the number of inactive receptors and that the antagonists have a selective affinity for active receptors. On the other hand, the observation that both nalorphine and cyclazocine seem to enter and leave the brain more rapidly than morphine is not easily reconciled with the idea that they are bound more tightly to the active receptors than agonists.

C. Site of action

The effects of opioid antagonists on enzyme systems concerned with the metabolism of neurohumors are discussed in section V D 3. The determination of the site of action of opioids and opioid antagonists at an enzymatic or receptor level has proved to be a difficult problem.

Nalorphine inhibits DPN-cytochrome-*c* reductase activity and is a more potent inhibitor than morphine or other narcotic analgesics that also inhibit this enzyme (338). Morphine increases glucose 6-phosphate dehydrogenase activity of the brain. Nalorphine also does so to a small degree and does not antagonize this effect of morphine (321).

Axelrod and Cochin (10, 43) have pointed out the similarities between the morphine receptor responsible for analgesic activity and the enzyme that N-demethylates morphine, namely, (a) that nalorphine and other narcotic antagonists antagonize the analgesic effects of morphine and inhibit N-demethylation of morphine as well as other narcotic analgesics (298), and (b) that as tolerance develops to the analgesic effects of morphine, the activity of the N-demethylating enzyme decreases (9, 43). They have suggested that the N-demethylase enzyme may serve as a model for the morphine receptor (9, 43). Yet although both *d*- and *l*-3-hydroxy-N-allylmorphinan inhibit the demethylation of levorphanol (322), only the *l*-isomer is an antagonist. 3-Hydroxy-N-3′-hydroxypropylmorphinan antagonizes morphine analgesia in the rat but does not affect N-demethylation (283). Further, chronically administered levallorphan, nalorphine, and cyclazocine inhibit the development of dependence on morphine (174, 239, 296). Because of the close association between tolerance and dependence, the fact that neither nalorphine (43) nor levallorphan (226) inhibits the suppression of N-demethylation activity induced by chronically administered morphine does not support this hypothesis.

Mulé (260) found that morphine stimulates the incorporation of phosphate into a number of phospholipids and inhibits its incorporation into phosphatidyl choline. Both the inhibitory and stimulatory effects of morphine decrease as the concentration of morphine decreases. Nalorphine, like morphine, in high concentrations stimulates the incorporation of phosphate into certain phospholipids while inhibiting their incorporation into others. It is of interest that at lower concentrations the inhibition of phosphate incorporation into phosphatidyl choline seen with high concentrations is converted into stimulation. At very high concentrations, nalorphine (10^{-2} M) antagonizes some of the effects of morphine but not others. In lower concentrations (10^{-6} M), it enhances some of the effects of morphine.

Morphine as well as other narcotic analgesics inhibits the growth of *Escherichia coli*. It is of interest that levallorphan is a more potent inhibitor of growth than levorphan and nalorphine is more potent than morphine (301).

IV. AGONISTIC ACTIONS

It is important in understanding the interactions between opioids and opioid antagonists to recognize that drugs classed as narcotic antagonists may be at the same time agonists. To facilitate discussion and to concisely summarize the work done in describing the agonistic and antagonistic actions of a wide variety of narcotic antagonists on certain functions, the reader is referred to table 1. In developing a theoretical framework for interpreting interactions between narcotic antagonists and narcotic analgesics, the agonistic actions of the narcotic antagonists will be discussed first, and then their antagonistic actions.

In many respects the agonistic actions of the narcotic antagonists are similar to those of morphine and related narcotic analgesics. Thus, these two classes of agents produce analgesia (IV A), respiratory depression (IV B), miosis (IV G) and depression of certain reflexes (IV D). With regard to certain other effects, they are quite different. Thus, the subjective effects produced by the agonistic narcotic antagonists are quite different from those produced by narcotic analgesics (IV C).

A. Analgesia

Hart and McCawley (140) first reported that nalorphine produced analgesia in the rat using the procedure of D'Amour and Smith (52), but Unna (331) could detect no analgesia in mice using electrical stimulation applied to the abdominal skin with nalorphine in dose levels of 10 mg/kg and only slight analgesia with 100 mg/kg. Smith *et al.* (305) found that nalorphine had a weak analgesic action in rats but none in dogs. In rats anesthetized with barbital, Tullar (330) found that nalorphine produced analgesia, using a radiant heat method. Isbell (unpublished observation, *cf.* 175) found that nalorphine elevated pain threshold in human subjects tested with the Wolff-Hardy technique. Lasagna and Beecher (214) observed that nalorphine in dose levels of 10 and 15 mg/kg produced relief of postoperative pain comparable to that produced by 10 mg of morphine. Keats and Telford (192) confirmed these findings.

TABLE 1

Antagonistic and agonistic actions of narcotic antagonist congeners

Narcotic Antagonist Congeners	Analgesia				Respiratory Depression				Subjective effects
	Antagonist		Agonist		Antagonist		Agonist		Agonist
	Animals	Man	Animals	Man	Animals	Man	Animals	Man	
I. *Morphine congeners*									
A. Normorphine									
N-ethyl	(363)								
N-propyl	(114, 363)			(325)		(325)		(325)	(325)
N-isopropyl	(363)								
N-allyl (nalorphine)	(108, 114, 218, 267, 268, 291, 331, 363)		(24, 249, 273, 291, 315, 360)	(152, 192, 214)	(47, 140, 159, 283, 331)	(3, 25, 27, 39, 56, 58, 60, 62, 98, 210, 241, 309, 356)		(59, 83, 97, 161, 214, 286, 326)	(130, 160, 174, 192, 193, 214, 237, 275, 356)
N-propargyl	(114, 363)								
N-2-ketopropyl	(363)								
N-butyl	(114)								
N-amyl	(363)		(363)						
N-crotyl	(114, 363)								
N-methylcyclopropyl			(360)						
N-methallyl				(325)		(325)			
N-2-bromallyl	(363)								
B. Norcodeine									
N-propyl	(114, 363)								
N-allyl	(114, 363)				(138, 252, 277)				
C. Normonoacetylmorphine									
N-allyl	(363)								
D. Nordiacetylmorphine									
N-propyl	(363)								
N-allyl	(114, 363)		(114)						
E. Dihydronormorphine									
N-propyl	(363)								
N-allyl	(363)								
N-methylallyl	(363)								
N-isobutyl	(363)								
F. Nordiacetyldihydromorphine									
N-propyl	(363)								
N-allyl	(363)								
G. Nordiproprionylmorphine									
N-allyl	(114)		(114)						
H. Nordesoxymorphine									
N-propyl	(363)								
N-allyl	(363)								
I. Nordesoxydihydromorphine									
N-propyl	(363)								
N-allyl	(363)								
J. Nordesoxycodeine									
N-allyl	(363)								

TABLE 1—*Continued*

Narcotic Antagonist Congeners	Analgesia				Respiratory Depression				Subjective effects
	Antagonist		Agonist		Antagonist		Agonist		Agonist
	Animals	Man	Animals	Man	Animals	Man	Animals	Man	
I. *Morphine congeners—Continued*									
K. Nordihydrodesoxycodeine									
N-propyl	(363)								
N-allyl	(363)								
L. Nordihydrohydroxymorphinone									
N-allyl (naloxone)	(24, 248, 273)	(285)		(213)	(21)	(55, 82, 85–87)			
M. Nordihydrocodeinone									
N-propyl	(363)								
N-allyl			(363)	(325)		(325)		(325)	(325)
II. *Levorphan congeners*									
A. Morphinan									
N-propyl				(325)	(283)	(325)		(325)	(325)
N-allyl (levallorphan)	(47, 48, 102, 242, 334, 363, 370)	(117, 251)	(24, 370)		(18, 47, 102, 253, 334, 370)	(4, 60, 86, 88, 117, 131, 311)	(253, 370)	(211, 312, 329)	(181, 312)
N-propargyl				(325)	(41, 283, 350)	(251, 325)		(325)	(325)
N-methylcyclopropyl (cyclorphan)	(273)		(273)	(213)					
III. *Benzomorphan congeners*									
A. 2′-Hydroxy-5,9-dimethyl-6,7-benzomorphan									(194)
2-allyl (SKF-10047)	(5, 273)			(194)					
2-dimethylallyl (pentazocine)	(137, 273)		(24, 273, 315, 360)	(13, 37, 89, 195, 284, 307)				(89, 195)	
2-methylcyclopropyl (cyclazocine)	(137, 273)		(24, 137, 249, 315, 360)	(215)				(215)	(130, 215, 236)
2-chlorallyl	(137, 273)			(194)					(194)
2-methylcyclobutyl	(273)		(273)						
B. 2′-Hydroxy-5-ethyl-9-methyl 6,7-benzomorphan									
2-allyl				(194)		(194)			
2-dimethylallyl	(273)		(273)	(194)		(194)			(194)
IV. *Meperidine congeners*									
A. 1-Allyl-4-phenyl-4-carbethoxypiperidine	(363)		(*cf.* 47)		(47)				
B. 1-Allyl-2-methyl-3-methyl-3-(3-hydroxyphenyl) piperidine	(209)								
C. 1-Allyl-3-methyl-3-(3-hydroxyphenyl) piperidine	(208)		(208)						

Animal testing procedures such as the tail flick (114, 137, 363), hot plate [Eddy (unpublished observation, see 214), 137], tail pressure (114) and the monkey aversive threshold technique (349) can usually demonstrate little or no analgesic activity for nalorphine. Nalorphine, pentazocine, and cyclazocine do depress the tail flick response in the mouse pretreated with liminally analgesic doses of physostigmine (136a). Nalorphine does not block vocalization evoked in the dog by bradykinin (127). It is of interest that although both Weiss (348) and Hill *et al.* (145) have shown that nalorphine can suppress the bar pressing rate for food, Hill could not find that nalorphine significantly reduced the conditioned suppression of bar pressing. Conditioned suppression has been shown to be reduced by analgesics such as morphine (146–148). Yim *et al.* (370) found that levallorphan and levorphan would partially suppress chewing movements evoked by tooth stimulation in the rabbit.

There are, however, several procedures in which nalorphine produces measurable analgesia. Nalorphine and cyclazocine (249), like morphine (354, 355) and other opioid analgesics (234), depress spinal cord reflexes of the chronic spinal dog. Nalorphine produces only partial depression of the flexor reflex which is near maximal at a dose level of 1 mg/kg. The degree of depression is inversely related to the strength of stimulus employed, and over a dose range up to its ceiling effect, nalorphine and morphine are equipotent.

The "flinch jump" procedure described by Evans (76) has also been used for the study of analgesic activity of narcotic antagonists (77, 78). With this technique, nalorphine produces a maximum elevation of the current threshold necessary to elicit the jump response at doses of 1.0 to 1.5 mg/kg, and up to these dose levels seems to be as effective as morphine; but higher doses do not further elevate the threshold, whereas higher doses of morphine do. Pearl *et al.* (274) were unable to show an analgesic effect with nalorphine with a method similar to Evans', involving different procedures for presenting and analyzing the data.

Taber *et al.* (315), Blumberg *et al.* (24), and Pearl and Harris (273) have studied a variety of narcotic antagonists including nalorphine with the phenylquinone writhing test (300) and have found nalorphine to be approximately equipotent to morphine. Winter and Flataker (360) have found that nalorphine, pentazocine, cyclazocine, cyclorphan, and N-cyclopropylmethyl-normorphine produce a significant degree of analgesia using the pressure method on the "yeast edematous paw" described by Randall and Selitto (281).

The analgesic activity of a variety of narcotic antagonists has been studied clinically. Telford *et al.* (325) have compared several levorphan derivatives with morphine. *l*-3-Hydroxy-N-propargyl morphinan, like nalorphine, is both an effective antagonist and analgesic; however, it shares with nalorphine a variety of side effects including the production of dysphoric subjective effects. It is of interest that 5 mg/70 kg produced maximal analgesia, *i.e.*, the same as that of 10 and 15 mg/70 kg. The analgesic activity of levallorphan has only recently been studied (197), and it has been found that 8 mg/70 kg is nearly as active as 10 mg/70 kg of morphine. Cyclorphan, synthesized by Gates and Montzka (109), is both an analgesic (213) and opioid antagonist (273).

There has been great interest in the narcotic antagonists of the benzomorphan series. The major groups of congeners synthesized in this series are the N-substituted 2′-hydroxy-5,9-dimethyl and the 2′-hydroxy-5-ethyl-9-methyl derivatives. 2-Allyl-2′-hydroxy-5,9-dimethyl benzomorphan, a potent antagonist, is a relatively weak analgesic but produces marked psychotomimetic changes (5). The dimethylallyl congener (pentazocine) is a weak antagonist (137), devoid of analgesic activity by the tail flick method, a weak analgesic on the hot plate test (137), and about one-half to one-sixth as potent as nalorphine and morphine as judged by the phenylquinone writhing test (24, 273, 315). The racemic mixture has been estimated to be from one-sixth as potent to equipotent to morphine in man (13, 37, 89, 195, 284, 307). Most of the analgesic activity resides in the *l*-isomer (89, 273).

Cyclazocine (2-cyclopropylmethyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan), like pentazocine, is only weakly active as an analgesic according to the tail flick and hot plate methods (137); but, it has at least four to five times the potency of nalorphine and morphine when assessed by the phenylquinone writhing test and depression of the flexor reflex of the chronic spinal dog (24, 249, 273, 315). In man, it is probably about 40 times more potent than morphine as an analgesic (215).

A most interesting antagonist whose actions have contributed greatly to theoretical concepts concerning narcotic antagonists is N-allylnoroxymorphone (naloxone). Naloxone has no analgesic activity when tested by the hot plate and phenylquinone writhing tests (22). Small doses do not affect the magnitude of the flexor reflex of the chronic spinal dog; whereas larger doses (20 mg/kg) enhance this reflex (249). Finally, in pathological pain 2 mg produces a mild degree of analgesia, whereas 8 mg/kg produces less analgesic effect than would have been produced by a placebo (213).

In interpreting the studies on the analgesic effects of narcotic antagonists, it is necessary to attend to the issue of the sensitivity of the analgesic testing methods (357). Table 2 summarizes some data dealing with the sensitivity of methods commonly employed in the study of analgesic activity of both narcotic analgesics and narcotic antagonists. As can be seen, the tail flick, radiant heat, hot plate and tail pressure methods are all relatively insensitive methods requiring several milligrams or more of morphine per kilogram to attain an analgesic threshold. On the other hand, the phenylquinone writhing test, depression of the flexor reflex of the chronic spinal dog and pathological pain are much more sensitive and can detect the analgesic activity of a fraction of a milligram of morphine per kilogram.

McClane and Martin (249) have suggested that sensitivity of the analgesic testing procedure may be an important factor in detecting and measuring the analgesic activity of the narcotic antagonists. Several lines of evidence indicate that the intensity of stimulation affects the sensitivity of the method. Woolfe and MacDonald (368) investigated the effects of temperature in assessing analgesics, with the hot plate technique. Their data clearly indicate that sensitivity decreases as temperature is increased. With the hot plate temperature at 55°C,

TABLE 2

Analgesic thresholds and analgesic dose 50's for morphine as obtained using a variety of techniques

Technique	Analgesia Threshold	AD50
Tail flick	>6 mg/kg (52)	*ca.* 8 mg/kg (52) 3.2 mg/kg (115)
Radiant heat	*ca.* 4 mg/kg (73)	6 mg/kg (73)
Hot plate	*ca.* 5 mg/kg (368) *ca.* 2 mg/kg (67)	5.5 mg/kg (137)
Tail pressure	2 mg/kg (115)	3.2 mg/kg (115)
Aversive threshold in monkey	*ca.* 1 mg/kg (349)	
Phenylquinone writhing		0.45 mg/kg (mouse) (315) 0.59 mg/kg (mouse) (24) 0.20 mg/kg (rat) (24)
Flexor reflex in spinal dog	<0.25 mg/kg (234)	
Pathological pain in man	<0.1 mg/kg	

the threshold analgesic dose of morphine was about 5 mg/kg. When the temperature was increased to 70°C, over 25 mg/kg of morphine were required to produce an equivalent degree of analgesia. Similarly, when clamps of different strength are used to evoke the flexor reflex of the chronic spinal dog, the more intense the stimulation, the less effective were morphine, cyclazocine, and nalorphine (249).

Further, narcotic antagonists differ in their analgesic activity. McClane and Martin (249) found that, in contrast to morphine and cyclazocine, naloxone did not depress the flexor reflex of the chronic spinal dog at all and that nalorphine produced partial depression. Although the degree of depression produced by nalorphine was inversely proportional to stimulus strength, the maximal depressant dose was 1 mg/kg. A similar effect for nalorphine has been reported by Evans, using the flinch jump procedure (77). It was concluded, on the basis of these experiments, that the analgesia of the narcotic antagonist type with low activity probably could be detected only with sensitive methods (249). Thus, methods whose sensitivity can measure the analgesic effect of morphine in doses less than 1 mg/kg can detect the activity of nalorphine, whereas those whose sensitivity is less than 1 mg/kg of morphine by and large failed to detect its analgesic action.

B. Respiratory effects

Eckenhoff *et al.* (59) first recognized respiratory depressant effects of nalorphine in man. Nalorphine in doses of 5 and 10 mg, although having no consistent effect on respiratory rate, decreased minute volume about 35%. These results have been confirmed by a number of investigators (83, 97, 161, 214, 286, 326). Nalorphine produces little respiratory depression in the newborn (63). In addition, a number of other narcotic antagonists induce respiratory depression in adult man: levallorphan (211, 312, 329), N-allylnordihydrocodeinone (325), 1,3-

hydroxy-N-propargylmorphinan (325), N-N-propylnormorphine (325), pentazocine (195), and cyclazocine (215). Wendel and Lambertsen (349a) compared the effects of 10 mg/70 kg of morphine and nalorphine on respiratory sensitivity to CO_2 and concluded that nalorphine was half as potent as morphine on a molar basis in depressing sensitivity. The respiratory depressant effects of nalorphine have been studied over a range of doses (0.25 to 1.0 mg/70 kg) in normal subjects by Keats and Telford (196), using displacement of the respiratory stimulus response curve. Nalorphine shifts the CO_2 minute volume curve to the right, and maximal respiratory depression occurs at low doses, probably around 10 mg. Morphine on the other hand, while producing a comparable degree of respiratory depression to nalorphine at the 10 mg dose level, produces further progressive respiratory depression up to 0.50 mg/kg (*ca.* 36 to 70 mg total dose). It is of interest that although nalorphine, like morphine, shifts the respiratory stimulus-response curve to the right, it increases its slope, whereas morphine decreases the slope.

Cyclazocine in doses ranging from 0.25 and 1.0 mg produces the same degree of respiratory depression, which is less than that produced by 10 mg of morphine. Lasagna *et al.* (215) concluded that respiratory depression is maximal at 0.25 mg. Naloxone is devoid of respiratory depressant actions (83, 197, 240).

Although a number of nalorphine-like antagonists depress respiration in man, this action is not so generally seen in other species. Transient stimulation of respiration by nalorphine has been seen in rabbits anesthetized with urethane (331) and dogs anesthetized with barbital (158, 159), but in the rat anesthetized with urethane, levallorphan depresses both respiration and blood pressure (30). Further, in lethal and convulsant doses, nalorphine produces respiratory stimulation in the monkey (171). In the rabbit, nalorphine antagonizes the respiratory depression induced by ethanol (103). Related are the findings that in the guinea pig nalorphine has been found to antagonize sleep induced by phenobarbital, meprobamate, or chlordiazepoxide; but it does not antagonize hexabarbital sleep in the mouse or thiopental sleep in the rabbit (104). Further, it does not antagonize the toxicity of secobarbital in the mouse and increases the secobarbital sleeping time (119). In man, nalorphine has been reported to stimulate respiration in patients heavily sedated with thiopental or thiamylal (57). In the dog anesthetized with pentobarbital or chloralose plus urethane, the respiratory stimulation by nalorphine was not a consequence of its hypotensive effect, nor was it affected by denervation of either the carotid body or the carotid sinus or by vagotomy (16, 335, 336). Nalorphine stimulates respiration in the unanesthetized decerebrate dog (336), but does not increase the sensitivity of the respiratory center to CO_2 (187). Nalorphine also increases respiratory rate and minute volume in the decerebrate cat (235).

C. Subjective effects

The subjective effects of narcotic antagonists have been characterized clinically by a number of investigators (130, 160, 174, 192, 193, 213, 214, 236, 237, 275, 336, 352a) and can be classified into several distinct groups (236). (1) At

low dose levels (*e.g.*, 5 to 10 mg of nalorphine), these agents can produce feelings that are likened to euphoria, "high", exhilaration, relaxation and sensations like those induced by morphine. (2) Some symptoms that occur are likened by post-addicts to those produced by sedatives, hypnotics, and tranquilizers and consist of feelings of sleepiness, tiredness, grogginess and drunkenness. (3) The third group of symptoms has been characterized as dysphoric effects and consists, in their mild form, of uncontrolled racing thoughts, inability to concentrate and feelings of irritability. When these are severe, the subjects may experience either pleasant or unpleasant delusions and hallucinations. Subjective effects produced by graded doses of the narcotic antagonists nalorphine and cyclazocine have been objectively and systematically studied by Haertzen (130) with the Addiction Research Center Inventory, a 550-item questionnaire containing a large number of questions which test for a variety of subjective effects produced by drugs. It was found in this study that both nalorphine and cyclazocine produce similar spectra of subjective effects and that valid and reliable dose response relationships and potency estimates were obtained on four scales: (1) The lysergic acid diethylamide scale (LS) which contains items which measure psychotic states; (2) the pentobarbital-chlorpromazine-alcohol group scale (PCAG) which consists of items responsive to the three aforementioned drugs and measures sensations of fatigue and lethargy; (3) the efficiency scale (Ef) which measures subjective, social, and cognitive efficiency; and (4) a general drug effect scale (GDE), which consists of a number of items that are responsive to a large number of drug conditions representing nonspecific and general effects of drugs.

With items from the LS and PCAG scales that were most responsive to nalorphine and cyclazocine, as well as items from the morphine-benzedrine scale, which measures euphoria, a short questionnaire has been developed for studying other narcotic antagonists. On the basis of responses to these questionnaires, levallorphan produces subjective effects similar to those of nalorphine and cyclazocine, whereas naloxone produces no subjective changes (181). This latter finding clearly indicates that the antagonistic action of the narcotic antagonists is independent of their capacity to produce subjective changes (181). Jacob and his collaborators (176, 177) have pointed out that in the rabbit nalorphine differs from a variety of other psychotomimetics in that it does not produce an elevation in body temperature. As previously mentioned (IV A), 2-allyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan (SKF 10047) seems to exhibit some selectivity in producing dysphoria and psychotomimetic changes (194, 273).

Nalorphine not uncommonly produces feelings of drunkenness, yet even persons receiving large doses do not exhibit gross ataxia or dysarthria. Unsteadiness and some incoordination can often be seen after nalorphine when subjects attempt heel-to-toe walking. Cyclazocine in doses of 1.0 mg or larger produces gross ataxia and drunkenness.

D. Neurophysiological effects

The narcotic antagonists have certain properties in common with both barbiturates and interneuron depressants, as well as narcotic analgesics. Wikler and

Carter (354) found that nalorphine produces a slight depression of the flexor and crossed extensor reflexes of the chronic spinal dog, but they found no predictable dose-response relationship. The effects on the extensor thrust and patellar reflexes were "small and variable." Subsequent studies (232) indicated that nalorphine does depress the ipsilateral extensor thrust reflex but not the patellar reflex. In the cat a dose of 20 mg of nalorphine per kg depressed spinal cord potentials evoked by stimulating the splanchnic nerve, whereas doses of 10 mg/kg or less were inactive (266). Cyclazocine depressed the linguo-mandibular reflex but not the patellar reflex of the cat anesthetized with chloralose, whereas neither nalorphine nor pentazocine, nor two other substituted benzomorphan antagonists, has these effects (137). With an inclined screen test for assessing motor incoordination, nalorphine was inactive, whereas a series of substituted benzomorphan derivatives were active, with cyclazocine being the most potent (137). A systematic investigation of the dose-response relationship for the depressant effects of the narcotic antagonists on the flexor reflex (249) revealed that cyclazocine almost completely suppressed this reflex, nalorphine depression had a ceiling effect dependent on the stimulus strength, while naloxone had no depressant action. Naloxone actually enhanced the flexor reflex at subconvulsant dose levels (20 mg/kg). Cyclazocine, like nalorphine, depresses the ipsilateral extensor thrust reflex in the chronic spinal dog (236).

Two generalizations can be made about the effects of narcotic antagonists on motor coordination and somatomotor reflexes: (1) Compounds of this group differ with regard to their maximal activity or ceiling; and (2) they possess certain neurophysiological and clinical actions that are similar to those produced by barbiturates, interneuron depressants and morphine. The antagonists depress the ipsilateral extensor thrust reflex, like barbiturates and interneuron depressants; whereas, morphine enhances this reflex (155, 236). On the other hand, the narcotic antagonists share with morphine the ability to suppress a variety of nociceptive and polysynaptic reflexes.

Wikler (351) found that nalorphine produced a sleep pattern in the dog EEG like that produced by morphine but not associated with behavioral depression, as morphine's effect is. Gangloff and Monnier (107), in an extensive electrophysiological comparison between morphine and levorphan on the one hand and levallorphan on the other, found their activities quite different in the unanesthetized rabbit. Levallorphan, after a transient period of high-voltage, slow-wave activity in the EEG produced a low-voltage, high-frequency "arousal" pattern. It also enhanced the "attention" and "activation" reflexes evoked by stimulation of the midbrain reticular formation and depressed the recruitment response; and it depressed the cortical and subcortical responses to rhinencephalic stimulation. In all instances, these changes were opposite in direction to those produced by morphine and levorphan. On the other hand, Goldstein and Aldunate (112) found that nalorphine, like morphine, increased electrogenesis (electrically integrated EEG output) and EEG spindling in the rabbit. Both agents produced sedation, and in this regard, nalorphine was approximately ten times more potent than morphine. On stimulation of the tooth pulp in the cat, Straw and Mitchell

(308) found that both morphine and nalorphine enhanced potentials evoked in the nucleus ventralis posterolateralis and depressed potentials in the periaqueductal gray and the mesencephalic tegmentum, whereas pentazocine and pentobarbital depressed all of these evoked potentials. Neither morphine nor nalorphine produced changes in the electroencephalogram.

E. Guinea pig ileum

Morphine depresses the peristaltic reflex as well as the twitch response of the guinea pig ileum evoked by electrical stimulation (203, 270, 288, 289). Morphine does so by preventing the release of acetylcholine from cholinergic neurons (49, 270, 290). There is a very good correlation between the ability of the opioid analgesics to suppress the peristaltic reflex and twitch response of the guinea pig ileum and their analgesic activity (129, 270). Several narcotic antagonists [nalorphine (270), N-methylallylnormorphine, levallorphan, cyclazocine, pentazocine and 2-allyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan (SKF-10047)] also depress these reflexes (128). The antagonists, however, differ from the narcotic analgesics in several respects: (1) tachyphylaxis of the depressant actions develops more rapidly than with morphine (128, 270); (2) small doses of the antagonists produce more profound tachyphylaxis for subsequent doses of morphine than does morphine (128); and (3) the tachyphylaxis (antagonism) recovers more rapidly after the narcotic analgesics (agonists) than after the antagonists. In studying the dose relationship for depression of the twitch, a clear-cut ceiling effect was seen only for the antagonist levallorphan; however, recent unpublished studies by Kosterlitz clearly indicate that the narcotic antagonist naloxone does not depress the twitch response in its own right and competitively antagonizes the depression produced by morphine.

Further, Cox and Weinstock (49) have shown that although nalorphine is very nearly as potent as morphine in depressing the twitch response, very small nondepressant doses of nalorphine antagonize the depressant effects of morphine.

F. Tolerance and dependence

Isbell (174) first studied the addiction liability of nalorphine and reported that although partial tolerance to the dysphoric subjective effects of nalorphine developed, it was not sufficient to permit elevation of the dose to above 100 to 130 mg/day. Abrupt withdrawal of this dose was not followed by overt signs of abstinence. Schrappe (292) reported a morphine-like abstinence syndrome in one patient who had been given nalorphine chronically in a dose of 130 mg daily. Seevers and Deneau (296) found and reported to the Committee on Drug Addiction and Narcotics that monkeys chronically intoxicated with nalorphine or levallorphan did not develop physical dependence; yet the monkeys exhibited scratching following abrupt withdrawal of the agent. Cochin and Axelrod (43) found that rats receiving nalorphine chronically were cross tolerant to the analgesic effects of morphine. Contreras *et al.* (46) attempted to determine if chronic administration of nalorphine or levallorphan to mice caused the development of tolerance to their convulsant actions as well as to restlessness, exophthalmos,

and the Straub phenomenon. They concluded that tolerance did not develop to these effects, but it is difficult to reconcile this conclusion with their data concerning the convulsant effect of nalorphine. Martin *et al.* (236) reported the development of a high level of tolerance to the subjective effects of cyclazocine in subjects chronically intoxicated with this agent on a slowly increasing dose schedule. Subjects tolerant to cyclazocine were cross tolerant to nalorphine. When cyclazocine was abruptly withdrawn, a definite abstinence syndrome emerged, which was qualitatively different from the morphine abstinence syndrome. Further experiments (237) revealed development of a high level of tolerance to the subjective effects of nalorphine in subjects chronically treated with this agent, as well as cross tolerance to cyclazocine. An atypical abstinence syndrome emerged upon abrupt withdrawal of nalorphine.

Although the abstinence syndromes of cyclazocine and nalorphine are not identical, they are strikingly similar. Subjects dependent on nalorphine have sensations of itching and scratch when they become abstinent. It will be recalled that Seevers and Deneau (296) also reported scratching during withdrawal in monkeys that had been chronically intoxicated with nalorphine and levallorphan. This sign and symptom of abstinence has not been seen in subjects dependent on cyclazocine. With this single exception, the abstinence syndromes of cyclazocine and nalorphine are nearly identical. They share the following characteristic: one of the early signs of abstinence is an ill-defined sensation that has been likened by some subjects to electric shocks to the head and described by others as lightheadedness. This sensation can be precipitated by drinking hot or cold fluids and may be especially prevalent when the abstinent subject is dropping off to sleep. The sensation does not appear to be a convulsive phenomenon, but this possibility has not been completely excluded. As the abstinence syndrome develops, signs and symptoms such as lacrimation, rhinorrhea, yawning, chills and diarrhea become manifest although their frequency of appearance is less and their intensity is much milder than during morphine abstinence.

Fever and loss of body weight and appetite, are also prominent signs of the abstinence syndrome. In contrast to the morphine abstinence syndrome, increased blood pressure and respiratory rate play only a minor role. Of greater interest is the fact that the narcotic antagonist abstinence syndrome is not associated with either an apparent drug need or drug-seeking behavior.

The question should be raised as to why the phenomena of tolerance and dependence should be considered agonistic actions. The following will argue that both tolerance and physical dependence are consequences of the agonistic and not the antagonistic actions of the narcotic antagonists. The first observation supporting this hypothesis is that although subjects who receive nalorphine and cyclazocine chronically become highly tolerant to their ability to produce subjective changes, as well as sedation and incoordination (236, 237), tolerance does not develop to their antagonistic effects (239). Thus, subjects receiving 4 mg of cyclazocine a day chronically had only minimal subjective effects (238) but were protected against the respiratory depressant, euphoric, miotic and physical dependence-producing properties of morphine and heroin (239). Further, at-

tempts have been made to make subjects dependent on the narcotic antagonist naloxone which has at best only liminal agonistic properties (181). Naloxone is seven times more potent than nalorphine in precipitating abstinence. In subjects chronically intoxicated with 90 mg daily (15 mg every 4 hour), equivalent to 630 mg daily of nalorphine, naloxone did not produce any subjective or objective changes nor did signs of abstinence develop when it was withdrawn. Nalorphine in a dose of 240 mg/day produces definite dependence (237). Further, naloxone continued to antagonize the miotic and euphoric effects of morphine throughout the period of chronic intoxication. These findings clearly indicate that the agonistic, not the antagonistic, properties of the narcotic antagonists are responsible for both tolerance and physical dependence.

G. Pupillary changes

The pupillary constricting effects of nalorphine in man were first described by Wikler *et al.* (356) and have been confirmed by others (97, 160). Levallorphan (71), pentazocine (96), and cyclazocine (236) also constrict the pupil in man. Since naloxone is devoid of miotic activity in man (181), it is clear that the miotic effects of the narcotic antagonists can be completely dissociated from their antagonistic properties.

In animals, the effects of narcotic antagonists on pupils are more complex. Nalorphine dilates pupils in the cat (331) and constricts them in the dog (231, 232). Its effects in the rabbit (176) are variable, with miosis being the more frequent change. Cyclazocine in large doses dilates the pupils in the dog (249).

Only partial tolerance develops to the miotic effects of nalorphine (237) and cyclazocine (236). Nalorphine antagonizes the miotic effects of narcotics in man (97) and in the dog (232). In both acutely and chronically dependent man (356) and dogs (231, 232), nalorphine causes pupillary dilation. Naloxone (181) also antagonizes the miotic effects of morphine and cyclazocine in man. Naloxone (181), levallorphan (181), and cyclazocine (236) cause pupillary dilation in dependent subjects. The diagnostic use of the pupillary responses in man are discussed in section VI C.

H. Endocrine effects

Nalorphine in doses of 40 and 80 mg has been reported to release ACTH in the pentobarbital anesthetized rat (34), but other studies have reported no release (110, 332). In man, reports are also conflicting. Fraser *et al.* (92) reported that nalorphine caused no significant changes in urinary excretion of 17-hydroxycorticoids in postaddicts; whereas, McDonald *et al.* (250) observed a decrease in excretion after 10 mg of nalorphine and a larger decrease after morphine. Both nalorphine and morphine decrease binding of iodine by the thyroid gland (80).

I. Summary

Opioid antagonists such as nalorphine and cyclazocine have many agonistic effects and properties such as analgesia, respiratory depression, depression of nociceptive reflexes, prevention of release of acetylcholine by the gut, pupillary

constriction, and suppression of ACTH secretion, which are also produced by morphine. In producing some of the effects, the opioid antagonists clearly are acting as partial agonists, and at least one potent antagonist, naloxone, has verv little, if any, agonistic activity.

Some of the agonistic actions of opioid antagonists such as the subjective effects and certain neurophysiological changes are different from those produced by morphine. Even when the effects of nalorphine and morphine are superficially similar (*e.g.*, analgesia), they may be produced by interactions with different receptor populations (see section V A). The agonistic effects of the antagonists induce tolerance and physical dependence; but the abstinence syndrome is qualitatively different from the morphine abstinence syndrome.

V. ANTAGONISTIC ACTIONS

A. ANALGESIA

Unna (331) first showed that nalorphine could either prevent or antagonize the analgesic action of morphine in the mouse. Studies of the interaction between the analgesic activity of nalorphine and morphine have been of interest from two points of view: (1) It was hoped that by mixing nalorphine with other narcotic analgesics it would be possible to selectively antagonize the respiratory depressant effect of the narcotic without attenuation of the analgesic activity; and (2) it was further hoped that the abuse potentiality of the mixtures would be significantly less than the narcotic alone. The ability of nalorphine and other narcotic antagonists to antagonize the analgesic effect of morphine (see table 1) and other narcotic analgesics has been confirmed repeatedly (47, 48, 102, 121, 218, 242, 267, 268, 285, 334, 362, 369, 370). It is generally assumed that there is no specificity of the antagonist against the analgesic action of various narcotic analgesics, but Costa and Bonnycastle (47) found that levallorphan antagonizes the analgesic effects of morphine, *l*-methadone, alphaprodine, and meperidine, but not that of levorphan. Nalorphine was an effective antagonist of all of the above-mentioned analgesics except morphine.

In man the interactions between narcotic antagonists and narcotic analgesics are much more complicated. In the first report showing nalorphine to be an analgesic, Lasagna and Beecher (214) found that the analgesic effect of a mixture of 10 mg of morphine and 2 mg of nalorphine was not significantly different from that of 10 mg of morphine alone. Further, nalorphine failed to antagonize the analgesic effect of 10 mg of levorphan when a dose ratio of 1:10 was used (61), as well as 50 and 100 mg of meperidine in a dose ratio of 1:80 (151). Cappe and Pallin (35) found that mixtures of nalorphine and morphine produced sleep and analgesia. Houde *et al.* (152, 153) investigated the ability of graded doses of nalorphine to antagonize the analgesic activity of 5 and 10 mg doses of morphine and found that partial antagonism was seen in a ratio of 1:8 (nalorphine to morphine). In a ratio of 1:4 complete antagonism was attained, but in a ratio of 1:2 partial antagonism again resulted. When the ratio was 1:1, analgesia was further increased, but the emergence of undesirable subjective effects precluded

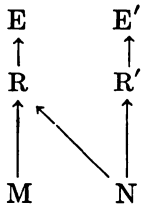
completion of the study. The significance of the biphasic dose-response curve that these investigators obtained will be discussed (this section).

Studies of the nature of the analgesic and antagonistic effects of morphine antagonists must be classified on the basis of the analgesia testing procedure.

1. *Studies with procedures in which the antagonist is not analgesic.* Cox and Weinstock (48) studied the interaction of nalorphine with methadone, morphine and 3-0-acetyl-6,14-*endo*-etheno-5,7,8,8-tetrahydro-7α-(2-hydroxypent-2-yl)oripavine (M-183), using the hot plate test, and have shown that the "pA_2" value for nalorphine in antagonizing these analgesics was about 4.0 and concluded that the three analgesics occupied the same receptor and that nalorphine competed with them for the receptor. Grumbach and Chernov (121), in an extensive study of the interactions of nalorphine and levallorphan with morphine, methadone, ketobemidone, phenazocine, meperidine and a series of meperidine congeners, concluded that both nalorphine and levallorphan were competitive antagonists for the following reasons: (a) The antagonistic dose-50 against an analgesic dose-80 of several classes of analgesics for both nalorphine and levallorphan fell within a narrow range; (b) when the degree of antagonism of analgesia was plotted against dose of nalorphine or levallorphan, the response lines were linear and parallel; (c) the Gaddum dose ratios (ratio of dose of agonist to antagonist to produce a fixed response) for both nalorphine and levallorphan were constant for two analgesic meperidine congeners. It is important to emphasize that in both of these studies the degree of antagonism increased as the dose of the antagonist increased. Zetler *et al.* (373) studied the interactions between nalorphine, levallorphan, mephenesin or reserpine and morphine, levorphan, methadone, or mephenesin in the mouse. In this species nalorphine seemed to be a competitive antagonist against methadone and meperidine, but not against morphine and levorphan. In contrast, levallorphan seemed to antagonize competitively the analgesic actions of morphine and methadone, but not levorphan and meperidine. Of interest was the finding that reserpine also shifted the morphine and methadone dose-response curves to the right but did not alter their slopes. Blane *et al.* (19a) studied the antagonistic effects of nalorphine and M285 [N-cyclopropylmethyl-7α-(1-hydroxy-1-methylethyl)-6,14-endoethenotetrahydronororipavine] on the analgesic actions of etorphine [M99, 7α-(1-hydroxy-1-methylbutyl)-6,14-*endo*etheno-oripavine] and morphine in the rat and concluded that both antagonists acted competitively against both agonists. Thus, in preparations in which the opioid antagonists are devoid of analgesic activity, with some exceptions, they seem to act competitively.

2. *Studies with procedures in which the antagonists have analgesic effects.* As previously mentioned, interaction studies between nalorphine and morphine on analgesia in man indicate that the dose-response curve is biphasic, with increasing antagonism as the dose of antagonist is increased to a certain level and then reemergence of analgesia as the dose is further increased (152, 153). Houde *et al.* (153) have interpreted these findings to indicate that "at the lower ratios nalorphine interferes with the morphine effect, while in the higher ratio exerts its own analgesic action." Similarly, Yim *et al.* (370) found that maximal antagonism of

the analgesic effects of levorphan by levallorphan was attained when the ratio was 10:1. As the ratio was increased to 5:1, 2.5:1 and 1:1, analgesia increased (although the increase was not statistically significant for any of the ratios). It is of interest that the degree of analgesia was greater for all of these ratios than for the 10:1 ratio and that the degree of analgesia with the 1:1 mixture was identical to that seen with levallorphan alone. Combinations of nalorphine, levallorphan, or 3-hydroxy-N-3′-hydroxypropylmorphinan with morphine in different ratios produced a biphasic analgesic effect in the rat, using a radiant heat method. Maximum antagonism was observed with a molar ratio of about one (283). These observations are of great importance. They cannot be explained by assuming that the agonist and antagonist produce their agonistic actions by occupying the same receptor and differ from each other only in intrinsic activity and affinity. The theoretical formulation of competitive dualism (8) would predict that as the concentration of the antagonist is increased for any fixed dose of agonist, the level of effect should approach that that would be produced by the antagonist alone. The biphasic dose-response curve can be explained by assuming that the analgesic effect of the antagonist is produced by occupying another receptor that is stereochemically similar to the narcotic analgesic receptor but different. Such a circumstance would be characterized as having both receptor and competitive dualism. Proceeding on this assumption, the following theoretical model of receptor dualisms seems plausible:



M (morphine-like agent) interacts with receptor R to form a drug receptor complex MR and to produce effect E (*e.g.*, analgesia).

(1) $M + R \rightleftarrows MR$

(2) $\frac{[M][R]}{MR} = K_A,$

where K_A is the dissociation constant.

(3) $E = \alpha\, MR$ where α is the intrinsic activity of M in producing E.

N (nalorphine-like agent) also interacts with receptor R to form a drug receptor complex NR.

(4) $N + R \rightleftarrows NR$

(5) $\frac{[N][R]}{NR} = K_B$

where K_B is the dissociation constant.

N, however, has no intrinsic activity ($\beta = 0$) and produces no effect (analgesia) when interacting with this receptor. Therefore:

$$(6)\ E = \frac{\alpha r}{\frac{NK_A}{MK_B} + \frac{K_A}{M} + 1}$$

where r is the total number of R receptors. N also reacts with R′.

$$(7)\quad N + R' \rightleftarrows NR'$$

$$(8)\ \frac{[N][R']}{NR'} = K'_B$$

where K'_B is the dissociation constant.

The effect E′ (analgesia) is:

$$(9)\ E' = \gamma NR' = \frac{\gamma r'}{\frac{K_B}{N} + 1}$$

where r′ is the total number of R′ receptors and γ is the intrinsic activity of N in producing E′.

It is assumed that the effect when mixtures of M and N are administered will be:

$$(10)\quad E_T = E + E'$$

or

$$(11)\ E_T = \frac{\alpha r}{\frac{NK_A}{MK_B} + \frac{K_A}{M} + 1} + \frac{\gamma r'}{\frac{K_B}{N} + 1}$$

Figure 2 illustrates the types of dose response relationships that can be obtained for this type of interaction. The curves in graph A were taken from an experiment conducted in the chronic spinal dog (249). Hypothetical dose-response curves for mixtures of morphine with fixed doses of nalorphine are also given. Two circumstances are illustrated. The solid lines for which the nalorphine doses are designated by "N" illustrate the condition in which nalorphine has a greater affinity for R than morphine and are based on data obtained by Grumbach and Chernov (121) in the rat. The light dotted lines for which the nalorphine doses are designated by "n" illustrate the condition in which nalorphine has a lesser affinity for R than morphine. On the basis of these curves, the effect of morphine in the presence of graded doses of nalorphine acting as a competitive inhibitor without intrinsic activity on receptor R was added to the effects of nalorphine resulting from its interaction with R′. In graph B, the results of the interaction when nalorphine has a greater affinity for R than M are presented. As can be seen, the resulting curves are biphasic and concave downward and are similar in configuration to curves obtained by Houde and Wallenstein (152), Rubin *et al.* (283) and Yim *et al.* (370). The circumstance in which nalorphine

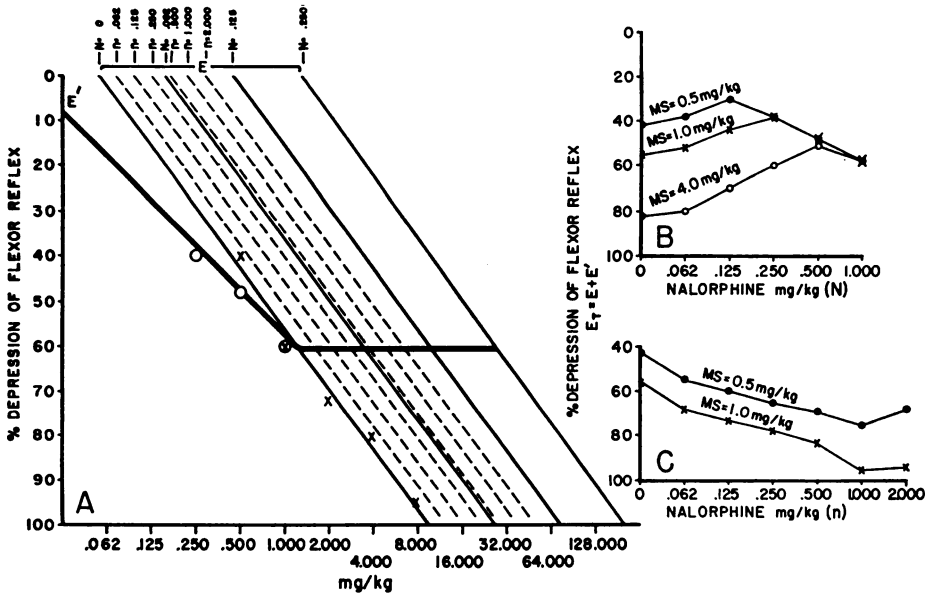


Fig. 2. Hypothetical dose-response relationship for nalorphine and morphine, and their interactions in depressing the flexor reflex of the chronic spinal dog.

A. Open circles (O) and heavy line indicate the effect of nalorphine. The crosses (X) indicate the effect of morphine. The line parallel to the morphine dose-response curve represents its displacement by various doses of nalorphine. The solid lines illustrate the circumstance where nalorphine has a greater affinity for the morphine receptor than morphine (N); the dashed line, where nalorphine has a lesser affinity than morphine (n).

B. The interaction of nalorphine and morphine where nalorphine has the greater affinity. The effects of various doses of morphine (0.5, 1.0 and 4.0 mg/kg) in the presence of various doses of nalorphine (0, 0.62, 0.125, 0.250, 0.500 and 1.000 mg/kg) were added to the effects of these doses of nalorphine.

C. The interaction of nalorphine and morphine where nalorphine has the lesser affinity.

has a lower affinity for R than morphine is presented in graph C. Here, where the increment due to nalorphine's agonistic activity is greater than the decrement due to its antagonistic activity for smaller ratios, the curve is also biphasic but the concavity is upward. This type of interaction has been seen in the spinal dog (233a).

Veatch *et al.* (334), in studying the analgesic activity of the optical isomers of α-acetylmethadol, methadone and levorphan administered intraventricularly, found that the analgesia produced by the more active isomer was readily antagonized by nalorphine while the analgesia produced by the less active isomer was not; this suggested that narcotics could produce analgesia through several modes of action. Further, Kong (201) found that bilateral injection of nalorphine into the lateral periventricular gray of the third ventricle antagonized the analgesic effects of morphine. Microinjection of nalorphine into midbrain reticular formation, lateral thalamus and septum did not antagonize the analgesic activity of morphine. Kong used radiant heat to the hindleg as a nocicep-

tive stimulus and a large dose of morphine (8 mg/kg). Veatch *et al.* (334) have postulated that the site of action of narcotic analgesics at which nalorphine is an antagonist is supraspinal inhibitory centers that are stimulated by the analgesic; whereas the site at which nalorphine is not an antagonist is in the spinal cord. This hypothesis is based on the observations (154, 169, 316, 358) that morphine is more potent in abolishing the skin twitch and polysynaptic reflexes in the intact rat, dog and cat than in spinal preparations; however, there is a body of information based on studies of the hindlimb withdrawal reflex and flexor reflex of the intact and chronic spinal dog that would indicate that the important variable is the reflex, not the region of the brain. The flexor reflex of the chronic spinal dog is much more sensitive to depressant effects of morphine than both withdrawal and skin twitch reflexes in the intact dog (231, 232, 234). Further, the narcotic antagonists nalorphine and naloxone are quite effective in antagonizing the depressant effects of morphine on the flexor reflex of the chronic spinal dog (232, 248). Nalorphine may have a lower affinity for morphine receptors in the spinal cord than in the brain stem (see above).

Naloxone, in addition to antagonizing the effects of narcotic analgesics, has been shown to antagonize the analgesic effects, in the phenylquinone writhing test, of the agonistic narcotic antagonists pentazocine, nalorphine, cyclazocine, cyclorphan, and levallorphan (23). In nonstimulatory doses, naloxone also antagonizes the depressant effect of cyclazocine on the flexor reflex (248), as well as the respiratory depressant and psychotomimetic effects of cyclazocine in man (240). These data clearly indicate that the receptors responsible for the analgesic, respiratory depressant and psychotomimetic effects must be stereochemically quite similar and in some instances identical to the morphine receptor.

B. Respiratory depression

The observations that N-allylnorcodeine (138, 252, 277) and nalorphine (140, 331) antagonize the respiratory depressant effects of morphine have been extended to show that nalorphine also prevented or antagonized respiratory depression produced by morphine, dihydromorphinone, codeine and methadone, but not meperidine, in the dog anesthetized with barbital (159). In 1951and 1952, Eckenhoff *et al.* (58) reported that nalorphine was effective in combatting respiratory and circulatory depression induced by morphine and meperidine in man. Further clinical studies demonstrated or confirmed that nalorphine antagonized the respiratory depressant effect of morphine (3, 210, 241, 272), methadone (98, 356), dihydromorphinone (39, 62), levorphan or racemorphan (27, 39, 56), heroin (309, 356), metopon (methyldihydromorphinone) (60), alphaprodine (60), meperidine (39, 58), pantopon (25) and propoxyphene (310).

Other morphine surrogates that are antagonists of the respiratory depressant effects of narcotic analgesics in man and in animals are presented in table 1. Of these, two in addition to nalorphine have undergone extensive clinical trial: levallorphan and naloxone. Levallorphan was first shown to antagonize respiratory depression of levorphan (18, 102) in rabbits. In the rat, it antagonizes the

respiratory depressant effects of codeine, ethylmorphine and normethadone, but not that of dextromethorphan (4). Clinical studies have demonstrated that levallorphan antagonizes the effects of morphine (60, 86, 131, 211), levorphan (60, 86, 117, 131, 329), meperidine (131, 311, 312), alphaprodine (314), oxymorphone (86) and fentanyl [N-(1-phenethyl-4-piperidinyl)propioanilide] (86). Levallorphan is five to eight times more potent than nalorphine as an antagonist of narcotic-induced respiratory depression (83, 85, 88). This potency estimate is based on comparisons with single doses of both antagonists and agonists.

Naloxone antagonizes the respiratory depressent effect of oxymorphone in the rabbit (21). Clinical studies have shown that it antagonizes and prevents respiratory depression produced by morphine (54, 86), oxymorphone (54, 55, 82, 87, 285), meperidine (54, 82, 86, 87) and fentanyl (86, 87). Naloxone is thought to be about 30 times more potent than nalorphine in antagonizing narcotic-induced respiratory depression (88). In this regard, it should be recalled that naloxone appears to be devoid of agonistic activity as a respiratory depressant.

The interaction between narcotics and narcotic antagonists on respiratory function is quite complex. A number of reports clearly indicate that nalorphine may not only fail to antagonize the respiratory depressant effect of small doses of morphine (60, 97, 190, 191, 272), but actually cause an enhancement (214); however, the antagonistic effects of narcotic antagonists on respiration become manifest if respiration is markedly depressed or if subjects have received several doses of a narcotic analgesic (191, 214). These observations have suggested two hypotheses concerning the nature of nalorphine's antagonistic action: (1) Landmesser *et al.* (210), recognizing that nalorphine itself is a respiratory depressant, proposed that high levels of carbon dioxide that had accumulated as a consequence of the depression of the respiratory center by morphine were the respiratory stimulus and suggested that nalorphine acted by displacing morphine and partially resensitizing the respiratory center to CO_2; (2) independently, Lasagna (212) and Wikler [cited by Lasagna (212)] proposed that the antagonistic effect of nalorphine became manifest when subjects became acutely (or chronically) dependent on morphine and that the stimulatory effects were signs of abstinence. There are really several issues involved in these hypotheses which force one to examine the concepts of "stimulation" and "dependence" carefully. After the administration of nalorphine to persons whose respiration has been severely depressed by a narcotic analgesic, there is an initial marked phasic increase in respiration which subsides as a tonic equilibrium condition is established. The phasic response usually far exceeds pre-existing control values. The tonic equilibrium state following the phasic response may exceed control values in certain instances and not in others, but it is greater than the level in morphine-depressed subjects. Evidence has been presented which complements that of Landmesser *et al.* (210) that the initial phasic stimulation is due to excessive concentrations of CO_2 driving the respiratory center resensitized by the narcotic antagonist (230, 235). The resensitization has only to be partial for this force to become manifest. Since nalorphine is probably a respiratory depressant whose intrinsic activity is less than that of morphine, even though on

a mg/kg basis it is probably nearly as potent as morphine over a limited range of doses, it would tend to move the level of sensitivity of the respiratory center toward that produced by a maximally depressant dose of nalorphine [probably that produced by 10 mg in man (196)]. This concept is not entirely inconsistent with the concept advanced by Lasagna and Wikler (212) if a broad definition of dependence is used. A sign of precipitated abstinence has been defined as one "which cannot be attributed to a combination of the independent actions of nalorphine (*antagonist*) and morphine (*agonist*)" (231). The concept of Landmesser *et al.* (210) has been extended into a general homeostatic theory of acute tolerance and physical dependence (230), which postulates that when a narcotic antagonist rapidly resensitizes a homeostat that has been altered by a narcotic, a large error force is established which acts as a strong drive to compensatory mechanisms. When the error force is reduced, the level of function of the physiologic compensatory systems diminishes. In addition to this process, narcotics can induce a state of hyperexcitability in a number of functional systems not concerned with homeostasis. This type of physical dependence can also develop at a very rapid rate and will be discussed below (see section V D).

Wendel and Lambertsen (349a) have proposed that, when nalorphine and morphine are administered in a ratio of 0.56 or less, antagonism is seen and, when used in a ratio of 0.88 or more, synergism is seen. Lambertsen (209a) has estimated "that nalorphine has approximately twice the affinity of morphine for the respiratory mechanism responding to CO_2 but only about ½ its potency as a respiratory depressant."

Miller *et al.* (253) have summarized some additional complexities in interpreting interaction studies between narcotics and narcotic antagonists on respiration. These authors pointed out that morphine and the narcotic antagonists have both respiratory stimulant and respiratory depressant effects. Thus, the maximum respiratory depressant effect of morphine occurs at a dose level around 16 mg/kg in the rabbit, and further increases in dose cause stimulation. In their study, levallorphan also produced both respiratory depression, which was modest compared to that produced by morphine, and at higher dose levels (10 mg/kg) transient respiratory stimulation. These authors found that as the dose of the antagonist was increased, the degree of antagonism also increased. Of particular interest is the observation that the larger doses of the antagonists (5 and 10 mg/kg of levallorphan) transiently increases respiratory minute volume in the morphine-depressed animal beyond control values. This stimulation could not be accounted for in its entirety by either the stimulant action of the antagonist alone or by the resensitization of the respiratory center to carbon dioxide. Yim *et al.* (369) studied the effects of different mixtures of levallorphan and levorphan on minute volume. Maximum antagonism was observed at a ratio of 10:1 (0.2 pg of levallorphan per kg to 2 pg of levorphan per kg). Increasing the proportion of levallorphan did not change the degree of antagonism. It is of interest that the respiratory depression seen with ratios of 10:1, 5:1, 2.5:1 and 1:1 was not greatly different from that seen with levallorphan alone (2 pg/kg). In contradistinction to the analgesic studies by these same authors,

as the proportion of the antagonists was increased, the degree of antagonism of respiratory depression increased to a maximum and then remained at that level. For this reason, there seems to be no need at the present time to postulate receptor dualism for the effects of the antagonists on respiration, and one can assume that the antagonists produce respiratory depression by occupying the same receptor that is occupied by morphine. On the other hand these data do not preclude the possibility of receptor dualism, for if the antagonistic effect increases at the same rate as the agonistic effect, a flat dose-response curve can be obtained over a range of doses. The fact that naloxone antagonizes the respiratory depressant effects of both morphine and cyclazocine is consistent with this observation (240). In this regard, Telford and Keats (324) have shown that methylphenidate antagonizes the respiratory depressant effects of pentazocine. Gruber (118) found, in studying the effects of nalorphine on morphine toxicity in the mouse, that when nalorphine was given in quantities in excess of those that produced optimum protection, toxicity of nalorphine and morphine was additive.

To suggest that all of the antagonistic effects of the narcotic antagonists on respiratory depression are the consequence of competitive dualism would be unrealistic. The following hypotheses, which are not necessarily mutually exclusive, must still be considered as possible important forces: (1) The antagonists have a direct respiratory stimulant action, the nature of which is unknown; (2) the narcotic analgesics have both respiratory stimulant and respiratory depressant actions, and the narcotic antagonists selectively antagonize the respiratory depressant effects (295); (3) large doses of narcotic analgesics induce acute physical dependence both by shifting the level of sensitivity of the homeostat and by altering its normal level of function. Antagonists not only rapidly resensitize the homeostat but further reveal its increased level of sensitivity (230).

Neurophysiological studies have shown that levallorphan antagonizes the depressant action of morphine on respiratory acceleration produced by electrical stimulation of the pneumotaxic center and the vagus nerve. Further, apneustic breathing seen in rostral pontine preparations is antagonized by morphine and is restored in morphine-treated preparations by levallorphan. Only the elevation of inspiratory threshold produced by morphine is not antagonized by levallorphan (265).

C. Convulsions

From a theoretical point of view, the effect of opiod antagonists on the convulsive effects of opioids is of great importance. Although the mechanism whereby narcotic analgesics produce convulsions is not known, there is general agreement that the convulsion is an invariant prototype of the excitant actions of these agents. Narcotic antagonists themselves may produce convulsions (171, 182, 216, 249). Both morphine (50 mg/kg s.c.) and nalorphine (20 mg/kg s.c.) prolong the tonic and clonic phases of electroconvulsions in the guinea pig (104). The evidence about antagonism of the convulsant effects of opiods by narcotic antagonists is conflicting. Thus, Koppanyi and Karczmar (202) could not antag-

onize the convulsant actions of morphine with nalorphine in the mouse and rat. Further, nalorphine is less effective in preventing death caused by convulsions than by respiratory depression produced by opioids (359). On the other hand, nalorphine lowers the incidence, shortens the duration and/or increases the latency of convulsions produced by meperidine (280) and *d*-propoxyphene (38, 134, 224, 282, 310).

D. Tolerance and physical dependence

1. Antagonism of tolerance and dependence. Chronic administration of mixtures of nalorphine and morphine (1:32 and 1:64) prevents the development of tolerance to the analgesic effect of morphine as assessed using the tail flick procedure in the rat (267). Similarly, the administration of a mixture of levallorphan and levorphan (1:5) delays the onset of tolerance to the analgesic action of levorphan (369). Narcotic antagonists also inhibit the development of physical dependence. Isbell (173) studied the effects of chronic administration of mixtures of nalorphine and morphine and reported:

"Three patients have been experimentally addicted to the one to ten mixture of Nalline and morphine, three to the one to five mixture and two to the one to three mixture. With these experiments 'addicting' dosage schedules were used, the total amount of drug given being pushed upward as rapidly as seemed safe. Mixtures were administered every three to four hours, day and night. Experiments were continued for 28 to 30 days, and the total dosages reached were 360 mgm. of morphine with 36 mgm of Nalline in the case of the one to ten mixture, 210 mgm. of morphine plus 42 mgm. of Nalline in the case of the one to five mixture and 180 mgm. of morphine combined with 60 mgm. of Nalline in the case of the one to three mixture. One other patient was started on the one to three mixture but withdrew after several days addiction. The results with the mixtures were similar. The patients disliked the mixtures intensely from the very beginning of the experiment and complained that the drug had 'no drive', that it did not 'pick them up.' At times, they insisted they were being given water. Despite these complaints, their pupils were tightly constricted, respiratory rate was depressed, all were severely constipated and all showed alternate somnolence and wakefulness. All patients complained of bad dreams and involuntary twitching and jerking of the arms and legs. After a few days all patients began to perspire profusely after each dose and complained of alternating hot and cold sensations, a sense of constriction in the chest and severe headaches. The symptoms would appear in a few minutes after the injection of a dose of the mixture and subsided in about 20 min, only to reappear after the next dose. Symptoms were strongly suggestive of the precipitation of mild abstinence with each dose of the mixture. Following abrupt withdrawal of the mixtures, all eight patients showed definite but mild symptoms which resembled abstinence from morphine. Two of the patients who received the one to five mixture and both those who received the one to three mixture appeared to be semi-stuporous and confused during the first day of abstinence. All three patients who received the one to ten mixture, two of the patients who received the one to five mixture, and both

those who took the one to three mixture have now been put through a cycle of addiction to morphine, using morphine in the same amounts and with the same schedule as was administered in the mixture. Following withdrawal of morphine, abstinence was far more intense in every patient than was the case after withdrawal of mixtures. Attempts have now been made to addict six of the patients to Nalline, following the same dosage schedules that were used with the mixtures. There has been no clear-cut evidence of morphine-like abstinence following withdrawal of Nalline in any of these patients."

Wikler (352b) found that adminstering a mixture of nalorphine (1.25 mg/kg) and morphine (3.75 mg/kg) every 6 hours retarded the development of tolerance to the depressant effects of morphine on the flexor reflex of the chronic spinal dog. In other experiments in which he administered 5 mg of nalorphine/kg every 3 hours and 2.5 mg of morphine/kg every 6 hours to chronic spinal dogs for 28 days, nalorphine failed to evoke signs of abstinence and only modest hyperreflexia was seen when the drugs were withdrawn.

Seevers and Deneau (295) also found that by giving mixtures of morphine and levallorphan chronically to the monkey, dependence on morphine could be attenuated or completely antagonized. Martin et al. (239) demonstrated that chronic adminstration of cyclazocine could prevent the development of physical dependence to morphine. Of especial interest in this regard is a series of experiments that have been conducted by Huidobro and collaborators. These authors found that if repeated doses of nalorphine were administered to mice made tolerant to and dependent on morphine by implanting compressed pellets of the free base of morphine, the precipitated abstinence syndrome decreased in intensity. If the injections of nalorphine were frequent enough, signs of morphine intoxication (seen after first implanting the pellet) again became apparent (163, 168). These results, which will be discussed in greater detail below (Section V D 2c) can be interpreted as indicating that nalorphine, as well as a variety of other narcotic antagonists (166), can in the presence of morphine reduce the level of both tolerance and dependence.

Tolerance to morphine confers cross tolerance to the lethal effect of nalorphine in the rat (182).

2. Precipitation of abstinence; definitions and theories. The observation of Wikler *et al.* (356) that nalorphine could precipitate abstinence in morphine dependent man has been of both practical and theoretical importance. Subsequent studies have shown that narcotic antagonists of the nalorphine type can precipitate abstinence in the narcotic dependent mouse (168), rat (51, 132, 150, 189), guinea pig (50, 51), dog (231, 354), and monkey (170).

The nature of precipitated and withdrawal abstinence in the rat deserves special comment. Kaymakcalan and Woods (189), Hosoya *et al.* (150) and Maynert and Klingman (245) found that nalorphine produces sedation in the dependent rat, while Hanna (132) and Gunne (124) have observed hyperirritability. Before discussing the theoretical importance of these observations, it may facilitate the reading of the subsequent discussion to present definitions of terms that will be used (232).

"*Precipitated* or *acute* abstinence refers to an abstinence syndrome produced by a morphine antagonist such as nalorphine in either acutely or chronically physically dependent animals. Further, the *precipitated abstinence syndrome* refers to any group of signs 'which cannot be attributed to a combination of the independent actions of the narcotic and the narcotic antagonist.' *Withdrawal* or *chronic* abstinence refers to an abstinence syndrome that becomes manifest when morphine-like agents are withdrawn from physically dependent animals. *Chronic abstinence* has also been used to describe the protracted signs of abstinence that persist long after the initial and violent signs have subsided. To differentiate the early and late signs of abstinence the terms 'primary' and 'secondary' have also been employed.

"By *acute physical dependence* is meant a state in which abstinence can be demonstrated or precipitated following either a single dose or a short-term infusion of morphine. In contradistinction, *chronic physical dependence* designates a state in which an abstince syndrome can be precipitated or becomes manifest when the drug is withdrawn following a prolonged course of administration of morphine or similar agents."

Several theories have been offered to explain the ability of nalorphine to precipitate physical dependence. Some of these theories are based on the hypothesis that the narcotic antagonists are competitive antagonists of the actions of morphine and other narcotic analgesics.

a. Seevers and Deneau (295) suggested that the narcotic antagonists selectively antagonize the depressant effects of morphine, thus leaving the excitatory actions unopposed. In a reevaluation and critique of the dual-action hypothesis of tolerance and physical dependence, Seevers and Deneau (294) advanced strong and convincing arguments that in chronically dependent subjects signs of withdrawal abstinence cannot be explained by the persistence of the excitatory effects of the dependence-producing narcotic analgesics; in the acutely dependent animal, however, they felt that signs of precipitated abstinence could be explained by this hypothesis. In support of the latter position is the fact that monkeys pretreated with either nalorphine or levallorphan showed "piloerection, motor restlessness, muscular rigidity, tremors, salivation and occasional vomiting" shortly after being given morphine. Because these signs emerge quickly after the injection of morphine and because the effects of morphine that are associated with tolerance and dependence are blocked, it is unlikely that they have the same cause as signs of withdrawal abstinence. Some of these same phenomena occur in the chronic spinal dog pretreated with nalorphine when given morphine; they include lacrimation, rhinorrhea, salivation, emesis, restlessness, tachycardia, and increased respiratory rate (230). Even these signs, which can be seen during precipitated or withdrawal abstinence, cannot be clearly interpreted, for morphine by itself causes emesis, lacrimation, rhinorrhea, salivation and panting in the dog. On the other hand, in the nalorphine-pretreated animal morphine does not cause mydriasis, increased body temperature, or enhancement of the flexor and crossed extensor reflexes, which are signs of precipitated abstinence in both the acutely and the chronically dependent dog.

It has been concluded, therefore, that the dual-action theory may account for some, but not all, signs of precipitated abstinence in the acutely and chronically dependent animal (230).

b. Martin (230) has proposed a homeostatic theory of both acute and chronic physical dependence. This theory suggests that in acute dependence morphine alters the level of function of homeostats and the accompanying equilibrium state, and that nalorphine rapidly restores the level of function of the homeostats. At the time of restoration, a difference (error force) between the existing morphine-altered equilibrium state and the resensitized homeostat provides a strong drive for restorative physiological functions. The alteration in function of the restoring physiological functions is a sign of precipitated abstinence. Evidence has been obtained indicating that the precipitated abstinence sign of trembling in the dog may be a heat generating mechanism (232), responding when the thermoregulatory homeostat in the morphine depressed animal is resensitized by nalorphine. Similarly, in the morphine-treated decerebrate cat, hyperpnea is initiated by the hypercapnia when the respiratory center is resensitized by nalorphine in the morphine-depressed preparation. In chronically physically dependent and tolerant people, it appears that the homeostat adapts to the effects of morphine by becoming hypersensitive (235) and that this effect becomes unmasked during abstinence, and is probably unmasked by the administration of a narcotic antagonist. It is important to recognize that the homeostatic theory of dependence and precipitated abstinence only partially explains signs of abstinence, for abstinence signs can be precipitated in the spinal cord of the chronic spinal dog, a neuronal substrate that as far as is known is not concerned with homeostasis.

c. By an argument of exclusion, it has been postulated that in both acute (235) and chronic (294) physical dependence occupation of sites by morphine with the concomitant initiation of a pharmacological effect (181, 230) gives rise to contra-adaptive changes. The nature of these changes is unknown, but several hypotheses have been offered, including supersensitivity by denervation (179, 298, 299), functional hypertrophy of redundant pathways (230), and induction of enzymes and receptors (44).

As previously mentioned, Huidobro and collaborators have made the interesting observation that when repeated doses of nalorphine are administered to mice chronically tolerant to and dependent on morphine not only does the intensity of precipitated abstinence decrease, but also signs of morphine intoxication to which the animal had become tolerant reappear. These investigators have presented evidence that has been interpreted as indicating that tolerance does not develop to nalorphine (46, 167). As has been previously discussed (Section IV F), studies in man have clearly shown that tolerance does develop to the agonistic actions of nalorphine (237) and other antagonists (236), but not to their antagonistic actions (181, 229, 239). Further, these investigators have obtained no evidence that nalorphine markedly affects the metabolism of morphine (167). By an argument of exclusion, and because intraventricularly administered nalorphine does not precipitate abstinence, Huidobro and collab-

orators have proposed that possibly the abstinence syndrome induces some biological variable (167) ("although this variable is not explicitly identified, it could be considered a type of accommodation"), and more recently, that nalorphine must be converted into an "active substance" (223) to exert its antagonistic effect. The experiments of Lotti *et al.* (219) and Kong (201) (see section V H) clearly indicate that nalorphine can act as an antagonist when injected directly into the brain substance. A simpler interpretation of the results of Huidobro is that chronic injection of nalorphine reduces the degree of tolerance and physical dependence (See section V D 1).

3. Neurohumors and dependence. Attempts have been made to modify the nalorphine precipitated abstinence syndrome, as well as withdrawal abstinence, with agents that affect neurohumoral transmission. Reserpine (221), as well as deserpidine, rescinamine, tetrabenazine or bretylium, but not 10-methoxy deserpine, syrosingopine or guanethidine (222), enhances precipitated abstinence. LSD, methysergide (1-methyl-D-lysergic acid butanolamide) and dopa also enhance the precipitated abstinence syndrome (164). Several compounds have been found that reduce the precipitated abstinence syndrome in the mouse: DL-tryptophan, tyrosine, phenylalanine, serotonin (after pretreatment with iproniazid) and L-5-hydroxytroptophan (164); iproniazid, β-phenylisopropyl hydrazine, phenelzine, nialamide, but not marplan (221); and alanine, serine, nicotinamide, desoxypyridoxine, and KCN (165). Curiously, DL-tryptophan, in addition to diminishing precipitated abstinence reduces morphine analgesia (162). Compounds that do not modify the precipitated abstinence syndrome *in toto* include serotonin (164), pentobarbital, phenobarbital, diphenylhydantoin, trimethadione, scopolamine, chlorpromazine, meprobamate, and diphenhydramine (221).

The relationship between morphine dependence and the metabolism of catecholamines, serotonin, γ-hydroxybutyric acid and acetylcholine has been the subject of a large number of studies. The effects of single doses or chronic administration of morphine on catecholamine metabolism are quite complex and depend on the doses of morphine employed as well as the species and tissues. In general, brain catecholamine levels increase when marked behavioral depression is produced and decrease when excitation or convulsions are induced (123, 125, 245, 302). Injection of morphine into the lateral ventricles of the cat causes a fall in hypothalamic norepinephrine (257). Chronic administration of morphine may cause no changes in brain catecholamine levels if no excitatory changes are manifest during the stabilization period (125, 245) as is seen in the dog, or may increase if the effect is stimulatory, as it is in the rat (101, 126, 303). Both Maynert and Klingman (245) and Gunne (125) observed that nalorphine, which itself has no marked effect on brain catecholamine levels, markedly decreases brain norepinephrine in the morphine dependent dog and rabbit. In contrast, nalorphine did not cause a significant change (126, 149, 245) or caused a decrease (149) in brain norepinephrine levels in the morphine dependent rat. By way of comparison, the effects of withdrawal abstinence on brain catecholamine levels in the rat are conflicting. Gunne (126) reported no change, whereas Sloan *et al.*

(303) found that they returned to control levels at 24 and 48 hours after withdrawal of morphine. These findings have suggested that the stimulatory action of morphine causes an initial depletion of catecholamines (126, 245, 302) and a later acceleration of their synthesis (126, 245). Further, the excitatory signs of abstinence are associated with a depletion and possibly an increased utilization of depots of norepinephrine in the brain and the periphery.

In an attempt to assess the role of increased liberation of catecholamines in the genesis of withdrawal abstinence in the chronic spinal dog, it was found that either amphetamine or methoxamine produced spinal reflex changes that were qualitatively similar to those seen in precipitated and withdrawal abstinences. These changes could be completely antagonized by phenoxybenzamine but in the abstinent morphine dependent preparation, phenoxybenzamine did not suppress spinal cord signs of abstinence. These results suggest that although increased liberation of norepinephrine in the central nervous system may either be responsible for or associated with certain signs of abstinence, it is not a necessary condition for signs of abstinence to become manifest (233).

Takagi and Nakama (317) found that morphine also decreases brain levels of dopamine in the mouse. Nalorphine does not decrease brain levels of dopamine and antagonizes this action of morphine.

Brain concentrations of serotonin are not altered by single doses or chronic administration of morphine (126, 246, 303), by nalorphine (126, 246) or by abrupt withdrawal of morphine (126, 303) in the morphine dependent rat or dog. Neither are brain concentrations of γ-aminobutyric acid changed by single doses or chronic treatment with morphine or by nalorphine in the morphine dependent rat (246).

Although small and analgesic doses of morphine do not alter brain levels of acetylcholine in the rat (144, 183), large doses increase the levels in both the rat and the mouse (133, 144). Large doses, however, fail to alter brain levels of acetylcholine in the tolerant mouse. Hayashi (142) found that morphine increased the bound and total acetylcholine content of mouse brain but decreased free acetylcholine. In contrast, meperidine, ohton (dimethylthiambutene) and 2-(N-2-methylphenethylaminoethyl-proprionamido) thiophene decreased all fractions of brain acetylcholine. None of these changes was antagonized by nalorphine. The brain levels of acetylcholine in both the morphine dependent and the abstinent mouse are not different from those of control animals. In this regard, it is of interest that atropine partially suppresses spinal cord signs of morphine abstinence in the chronic spinal dog (233).

Like a number of opioids, both nalorphine and levallorphan are inhibitors of true cholinesterase from a variety of sources including brain (20, 84, 144, 371), as well as of serum cholinesterase (20, 74, 84, 184). The significance and importance of cholinesterase-inhibiting properties of narcotic analgesics and narcotic antagonists is not clear. As previously mentioned, levallorphan does not alter brain acetylcholine (144), although it is a potent inhibitor of acetylcholinesterase *in vitro* (144, 371). Johannesson and Milthers (184) have postulated a relationship between inhibition of brain cholinesterase and the lethal effects of morphine and nalorphine.

Cholinesterase enzymes, however, have served as narcotic receptor models for studying the nature of the receptors and their kinetics. Ettinger and Gero (74, 75) have strong evidence, using cholinesterase from human serum, that there are two narcotic receptor sites, one the hydrolytic site, and another which is responsible for the acceleration of hydrolysis. Nalorphine is a competitive inhibitor at the hydrolytic site. Further, methadone seemingly has a preferential inhibitory action on the hydrolytic enzyme which is competitively inhibited by nalorphine. At the stimulatory site nalorphine and methadone act as noncompetitive inhibitors. Levallorphan, like morphine, acts as both a competitive inhibitor at the hydrolytic site and an agonist at the stimulatory site.

Levallorphan (10^{-3} M), as well as levorphan and dextrophan(*d*-3-hydroxy-N-methyl-morphinan), stimulates the activity of choline acetylase; whereas, levallorphan (10^{-5} M) and morphine inhibit its activity. Nalorphine is inactive (258).

E. Cardiovascular effects

The effects of the narcotic antagonists on the cardiovascular system vary from one individual to another and between conditions and species. Nalorphine produces only small changes in normal people. Eckenhoff *et al.* (59) found that nalorphine either had no effect on blood pressure or produced a fall. Wikler *et al.* (356) noted a modest slowing of heart rate and an increase in blood pressure in postaddicts. These same findings were obtained by Huggins *et al.* (161) but Huggins and Moyer (160) found no consistent change in blood pressure or pulse rate in another study. Cyclazocine in analgesic doses does not affect blood pressure in man (364).

In anesthetized animals, narcotic antagonists have more marked effects. Nalorphine may cause a moderate to severe hypotension (331). Levallorphan (30) and the benzomorphan derivatives cyclazocine and pentazocine (135) can also depress blood pressure. In the anesthetized dog, cyclazocine depresses pulse rate (135), while in the unanesthetized dog it accelerates it (249). Nalorphine does not affect pulse rate in the unanesthetized dog (231). In the decerebrate cat, nalorphine does not affect pulse rate and produces only a modest and transient fall in blood pressure (235).

Morphine and other opioids depress blood pressure. Several mechanisms have been proposed: a direct effect on vascular smooth muscle, release of histamine, depression of central vasomotor centers, and the diminution of psychic factors that may elevate blood pressure. In patients and animals, nalorphine antagonizes the vasodepressor and cardiac-slowing effects of a variety of opioids [morphine (3, 59, 62), meperidine (3, 59, 62), pantopon (62), methadone (62), dihydromorphinone (62), levorphan (86, 87), oxymorphone (86, 87) and fentanyl (86, 87, 108)]. Naloxone and levallorphan can also antagonize and prevent the circulatory changes produced by narcotics (82, 86, 87).

In patients dependent on morphine, nalorphine and other narcotic antagonists produce a marked elevation in blood pressure (356). In the acutely or chronically dependent dog, nalorphine antagonizes morphine-induced bradycardia and con-

verts it into a tachycardia (231, 232). In the decerebrate cat that has received a large dose of morphine, nalorphine not only antagonizes both the cardiac-slowing and the vasodepression, but also causes tachycardia (235).

F. Gastrointestinal effects

Hart and McCawley (140) first found that the spasmogenic effect of morphine on the intestine could be antagonized by nalorphine. Subsequent investigators confirmed this observation and extended it to other narcotic analgesics (12, 113, 120). In one patient, after the intravenous injection of nalorphine, there was an initial increase in contractility and tonus in the jejunum which was followed by depressed motility (12). Nalorphine antagonizes and prevents increased pressure in the common bile duct induced by morphine (287). Levallorphan also antagonizes the contraction produced by morphine or meperidine on the gall bladder (29). The effects of nalorphine and morphine on the gut vary greatly from one experimental setting to another. In the jejunum of the isolated rabbit or puppy, opioids cause spasm; whereas, nalorphine and levallorphan produce relaxation. In these preparations, the narcotic antagonists do not markedly affect the spasmogenic actions of barium, histamine, methacholine or serotonin (113). In other preparations, morphine is an antagonist of the constricting effects of serotonin (106, 203), nicotine (106, 203, 243) and barium (203); and nalorphine and levallorphan (203, 243) also antagonize the actions of serotonin (203, 243, 318) and nicotine (243). In high concentrations, both nalorphine and morphine cause contraction in the isolated rat intestine (188). In the rat, morphine suppresses gastric secretory activity in dose levels of 1 to 16 mg/kg and produces fever (section V H 5). Nalorphine antagonizes both the inhibition of gastric secretions and the fever (32).

Margolin (227) found that microgram quantities of morphine, methadone, or codeine injected intracranially in the mouse inhibit gastrointestinal propulsive activity. Nalorphine, like meperidine, was less potent. This action of morphine is not antagonized by cord section, adrenalectomy, atropine, papaverine, dibenamine, or physostigmine. Margolin concluded that the inhibitory effect of morphine on gastrointestinal activity may be due to the release of an unidentified substance from the brain into the blood.

There are conflicting reports of the effects of nalorphine on the small intestine of the tolerant and dependent rat. Mattila (243) reported an enhancement of the relaxing effects of large doses of nalorphine; whereas, Kaymakcalan and Temelli (188) found that small doses increased contractions. Both morphine and levallorphan antagonized the contracting effect of serotonin in the morphine dependent guinea pig (318). The intestine of the morphine tolerant guinea pig is less responsive to the blocking of nicotine and serotonin effects by morphine than the intestine of the nontolerant guinea pig.

Unna (331) demonstrated that nalorphine antagonized the emetic action of morphine in the dog. In man, a wide range of doses of morphine (15 to 130 mg) and heroin (10 to 100 mg), which normally produce nausea and vomiting, has been administered to patients who are receiving cyclazocine chronically without producing nausea or emesis (230a).

Pentazocine delays gastric emptying time and causes a modest inhibition of small intestine propulsive activity in the rat (53) and duodenal tone in the dog (52a). It decreases the propagation of bioelectric slow wave in the pyloric antrum but does not affect pyloric sphincter tone in the dog (52a). Chronic administration of cyclazocine causes constipation in man (239).

Opioid antagonists have both agonistic and antagonistic effects on the gastrointestinal tract.

G. Lenticular changes

Weinstock and collaborators (345, 347) have shown that a number of analgesics cause lenticular opacities and that there is a good correlation between the analgesic activity of these agents and their activity in producing lenticular opacities. Nalorphine antagonizes and prevents both the analgesia and the opacities produced by a variety of narcotic analgesics (345) and causes opacities to disappear more rapidly (346). Smith *et al.* (304) have shown that levallorphan inhibits the uptake of levorphanol-H^3 by the lens.

H. Neurophysiological changes

1. Peripheral nerve. Krivoy (205) found that several narcotic analgesics, including morphine, augment the positive afterpotential in peripheral nerve and that this augmentation is antagonized by levallorphan. The effects of narcotics and narcotic antagonists on potassium conductance have not been studied, but Grundy (122) found that morphine, meperidine and nalorphine decrease the short circuit current across the skin of the *Rana temporaria* and this decrement is not seen after ouabain. These authors suggested that these agents may decrease sodium conductance.

Kosterlitz and Wallis (204) found that morphine suppressed transmission in the superior cervical ganglion which had been partially blocked with hexamethonium and that nalorphine antagonized this effect. Nalorphine in very high concentrations (254 μM) suppressed preganglionic axonal conduction in this preparation.

2. Spinal cord. Wikler and Carter (353, 354) first showed that nalorphine can antagonize the depressant effect of morphine on the flexor and crossed extensor reflexes in the spinal dog. After either a single dose or an infusion of morphine, nalorphine in a dose that would depress the flexor reflex not only antagonizes the depressant effect of morphine but may enhance the reflex above the control level and produce fragmentary and protracted running movements (232, 354). Nalorphine, like morphine, depresses the dorsal root V (DRV) potential in the cat, but also antagonizes the depressant effect of morphine on this potential. DRV is thought to arise, at least in part, as a consequence of interneuron activity. Nalorphine also antagonizes the depressant effects of morphine and ohton on spinal cord and cortical potentials evoked by stimulation of the splanchnic nerve in the cat (266) and the depressant effect of morphine on potentials evoked in the nucleus of the spinal tract of the trigeminal nerve in the dog (256).

Nalorphine enhances the flexor and crossed extensor reflexes in the spinal cat, and it antagonizes and prevents the depressant effect of morphine (353). Whereas nalorphine depresses the flexor reflex in the chronic spinal dog, naloxone enhances

this reflex in subconvulsant doses (248, 249). Like nalorphine, it antagonizes the depressant action of morphine in doses too low to enhance the reflex (248). Naloxone also antagonizes the depressant effect of the narcotic antagonist cyclazocine (248) on this reflex.

3. Endocrine changes. A. ANTIDIURETIC HORMONE. The effects of narcotic analgesics on the release of antidiuretic hormone are quite complex. The antidiuretic actions of morphine and levorphan and the accompanying increase in liberation of the antidiuretic hormone are antagonized by nalorphine (111, 291, 361) and levallorphan (116). Nalorphine has no antidiuretic action in its own right (111, 361) and does not antagonize the antidiuretic action of vasopressin in the rat (361), but in man Becker and Moeller (14) found that levallorphan partially antagonizes the effect of "hypophysin" on glomerular filtration and reabsorption. Further, they indicated that the antidiuretic effect of morphine results from a direct action on the kidney as well as release of antidiuretic hormone. The fact that the antagonism of morphine antidiuresis by levallorphan is complete implies that the sites of its antagonistic action are both central and renal. In addition to the direct antidiuretic effect, morphine and meperidine antagonize the antidiuretic response evoked by stimulation of the ulnar nerve or certain brain stem areas, but not that evoked by stimulating the vagus nerve (254). Nalorphine also blocks this antagonistic effect of meperidine. The antidiuretic effect of morphine in the rat is due in part to inhibition of absorption of water from the gastrointestinal tract and in part due to a decreased rate of urine formation. Nalorphine and levallorphan antagonize both effects (105, 291).

B. ACTH. The effects of morphine on the hormones of the adrenal cortex are dependent on the preparation studied. In the unanesthetized rat, morphine decreases the ascorbic acid levels in the adrenals and increases the release of ACTH (31, 264). Depletion of adrenal ascorbic acid produced by morphine or *l*-methadone is antagonized by nalorphine (110, 332), whereas, the depleting effects of *d*-methadone and aspirin are not (110, 332), and that of histamine is slightly antagonized. It is of interest that reserpine and chlorpromazine, but not phenoxybenzamine, also antagonize the depleting effect of morphine (209). In the rat anesthetized with pentobarbital, morphine depresses the release of ACTH evoked by stress, and this effect is also antagonized by nalorphine (34, 72). In this phenomenon, nalorphine appears to be a competitive inhibitor of morphine and has a dose ratio of approximately five (34).

C. MORPHINE-INDUCED HYPERGLYCEMIA. Nalorphine (199, 372), levallorphan (276) and cyclazocine (249) do not change blood sugar levels in the dog; however, the antagonist 3-hydroxy-N-propargyl-morphinan causes hyperglycemia (28). Nalorphine, levallorphan, and 3-hydroxy-N-propargyl-morphinan antagonize the hyperglycemic effect of morphine and those of a variety of other narcotic analgesics (28, 198, 199, 276, 372). Borison *et al.* (26) have shown that the injection of minute quantities of morphine into the lateral ventricle of the cat causes hyperglycemia; they propose that there are chemoreceptors for morphine "at or near the cerebral ventricular surface" that are responsible for the depletion of hypothalamic norepinephrine, indirect stimulation of the adrenal medulla, release

of epinephrine, and hyperglycemia (257). Intraventricularly administered nalorphine (2 mg) also causes a transient hyperglycemia, but it antagonizes the hyperglycemic effect of intravenously administered morphine for over 24 hours (26).

4. EEG and evoked potentials. Morphine depresses the augmenting and recruitment responses in the cat, and these effects are antagonized by nalorphine (266). Chin and Domino (42) have conducted a detailed study of the effects of morphine and its interaction with nalorphine on potentials evoked by electrical stimulation of the tooth pulp and sciatic nerve and recorded from brain stem and cortical sites of the dog. Neither morphine alone nor morphine followed by nalorphine had any significant effect on evoked primary cortical potentials. The effects of either morphine or nalorphine on potentials evoked by tooth pulp stimulation in the diffusely projecting and association nuclei of the thalamus were variable; depending upon the site, both the amplitude and the latency were increased, decreased or unaffected. Potentials evoked in the midbrain and medulla were enhanced by morphine, and this enhancement was antagonized by nalorphine. In contrast, Mizoguchi (256) found that morphine depressed the augmenting, recruitment, and EEG activating responses in the dog, and these changes were antagonized by levallorphan. Morphine and levallorphan also enhanced cortical potentials in the dog evoked by sensory and transcallosal stimulation; however, levallorphan antagonized the enhancement of transcortical potentials produced by morphine (256).

Nalorphine antagonized the EEG slowing and suppression of local cortical potentials produced by an analgesic of the aminothiophene series in the rabbit (143). Gangloff and Monnier (107) found in the rabbit that levallorphan antagonizes the EEG changes, the depression of attention, and the enhancement of the recruitment response produced by large doses of morphine (40 mg/kg). It was less effective in antagonizing the depression of the activating reponse produced by morphine. Goldstein and Aldunate (112) found that nalorphine (3.2 μmoles/kg) antagonized the increase in electrogenesis (measured by integrating the EEG) by morphine (2.5 μmoles/kg); however, in contrast to the studies of Gangloff and Monnier, these authors found that both morphine and nalorphine independently produced an increase in electrogenesis.

5. Temperature regulation. Nalorphine antagonizes the hyperthermic response of morphine in 10-day-old mice (11), the cat, and the rat (32). Nalorphine and morphine in doses that, when given separately, do not affect body temperature produce hyperthermia in the guinea pig when given together (104). Both morphine and nalorphine antagonize the hyperthermic response produced by Pyrexal (lipopolysaccharide of *Salmonella equi*) (104). In the dog (231), systemically administered nalorphine does not affect body temperature, but in man a modest decrease in temperature has been observed (97, 356). Chronically administered cyclazocine decreases body temperature, and tolerance to this effect develops (236). Nalorphine antagonizes the hypothermic response of morphine in the dog (232).

Lotti *et al.* (219) found that nalorphine injected either intravenously or into the

anterior hypothalamus could antagonize the hypothermic effect of morphine administered either intravenously or by microinjection into the anterior hypothalamus and converted it into a hyperthermic response. Further, they found that nalorphine injected into the anterior hypothalamus produced hyperthermia after a long latency.

6. Miscellaneous. Takemori (319) found that the increased oxygen consumption of rat cerebral cortical slices induced by KCl is depressed by nalorphine in concentrations of 10^{-3} M, but not in lower concentrations. The lower concentrations antagonize the depressant action of morphine on oxygen consumption in this preparation. More striking was the demonstration that nalorphine could antagonize the tolerance developed to morphine-induced respiratory depression in the chronically morphinized rat (319), as well as cross tolerance to meperidine and methadone (320).

Krivoy *et al.* (207) have observed that morphine reduces the amplitude variation of the electric discharge of the knife fish and that nalorphine antagonizes this effect.

Cook and Catania (45) have shown that morphine and other narcotic analgesics suppress the conditioned avoidance response in the rat. Nalorphine when administered with morphine reduces the suppression of conditioned avoidance.

Weeks and Collins (343) have demonstrated that an infusion of nalorphine will increase the voluntary intake of morphine in morphine dependent rats, presumably in response to precipitated abstinence.

7. Conclusions. Studies of the opioid antagonists clearly show that they have both agonistic and antagonistic actions in many parts of the nervous system (*e.g.*, peripheral nervous system, spinal cord, medulla, mesencephalon, hypothalamus, thalamus, and cerebral cortex). The ubiquitous distribution of the sites of actions of opioids and opioid antagonists in the central nervous system indicates that these agents affect a fundamental function of nervous tissue and that this function is mediated or modulated by a relatively specific drug receptor interaction. Although many of the neurophysiological studies are apparently conflicting, some can be reconciled by recognizing the fact that antagonists may act as partial agonists. As more selective antagonists and agonists become available, many of these apparent conflicts may be resolved. Further, by recognizing the consequences of competitive dualism (8), a theoretical basis for selecting doses and dose ratios of the agonists and the antagonists can be established that would facilitate the designing of more definitive experiments. The technique of locally instilling antagonists in circumscribed areas of the brain of animals treated either locally or systemically with agonists is a powerful tool for sharply localizing the site of actions of opioids and could be profitably extended.

VI. CLINICAL APPLICATIONS AND OTHER USES

The narcotic antagonists have had four basic clinical uses: (1) Antidotes for severe narcotic analgesic intoxication (see V B); (2) production of analgesia (see IV A); (3) diagnosis of narcotic dependence; and (4) treatment of narcotic addiction.

A. Respiratory depression

The use of the narcotic antagonists as antidotes for severe intoxication by narcotic analgesics has been previously discussed (sections V B and V D 2). They antagonize the respiratory depression, coma and convulsions produced by a wide variety of narcotics. As previously mentioned, they appear to be most effective when patients are severely depressed and perhaps have developed a degree of acute or chronic tolerance. One of the potential hazards of using the narcotic antagonists nalorphine and levallorphan is that they have respiratory depressant activities in their own right which may summate with existing respiratory depression. One of the newer antagonists, naloxone, has no discernible respiratory depressant action in its own right in man and may prove particularly useful in combatting respiratory depression that is presumed to be due to narcotic analgesics.

B. Analgesia

Among the narcotic antagonists there are a number of analgesics, but their psychotomimetic effects have limited or precluded their use for this purpose. Pentazocine, which is a weak antagonist, has proved to be an effective and clinically useful analgesic (13, 37, 79, 186, 195, 269, 284, 307). It has been estimated to be one-half (196) to one-sixth (13) as potent as morphine. It has a shorter duration of action than morphine (13, 79, 195) and a 40 mg dose is as effective as 60 mg of codeine orally (186). It produces respiratory depression (17, 195), as great as or greater than that of morphine with equianalgesic doses. Respiratory depression produced by pentazocine is not markedly antagonized by nalorphine or levallorphan (195). On the other hand, pentazocine partially antagonizes the respiratory depression produced by morphine (195). Intravenous doses may cause hypertension and tachycardia (195). The untoward subjective effects of pentazocine are similar to those produced by morphine, but dizziness and lightheadedness may be somewhat more common, and hallucinations have been reported in an occasional patient (13). Side effects after oral pentazocine seem to be more common in women than in men (186). Pentazocine has a low potentiality for abuse. It does not suppress abstinence and, when given in maximally tolerated doses, produces only a mild dependence, which is atypical in that nalorphine does not precipitate abstinence (96). In substitution studies using morphine dependent subjects, pentazocine neither prevented nor precipitated abstinence when abstinence was measured from the 14th to 24th hour of substitution (96). Pentazocine (80 mg) will precipitate abstinence in morphine-dependent subjects when administered several hours after their last stabilization dose (181a). In patients suffering from chronic pain who have received narcotics chronically, pentazocine has precipitated a mild abstinence syndrome (13). For this reason, Beaver *et al.* (13) recommended that the dose of pentazocine be increased cautiously in patients who have been receiving narcotics chronically. The same authors found that cross tolerance to pentazocine in patients receiving opiates was low.

C. Diagnosis of dependence of the morphine type

Isbell first recognized the value of the narcotic antagonists as agents for the diagnosis of narcotic addiction and first proposed and used nalorphine for this purpose (68, 172). The procedure used by Isbell has been described by Fraser (91). Narcotic antagonist when administered to subjects with even a very low level of physical dependence on narcotic analgesics precipitates signs of abstinence. Terry and Braumoeller (327) first used nalorphine as a diagnostic procedure for medico-legal purposes in subjects suspected of narcotic abuse. Whereas Isbell (172) stresses the importance of the entire abstinence syndrome, Terry and Braumoeller emphasize the pupillary response as "an accurate, efficient and sensitive index" of narcotic addiction. Their criteria were that 3 mg of nalorphine in the non-user produced pupillary constriction of 0.5 to 2.0 mm; in the occasional user of narcotic analgesics, nalorphine produced no change; and in the dependent subject, an increase of 0.5 to 2 mm could be obtained. Not only is the nalorphine test being used for the diagnosis of narcotic use and dependence but as a deterrent to narcotic use (279, 328). A positive test has been defined as one in which 3 mg of nalorphine produces an increase in pupillary diameter of 0.25 mm or more (306).

Although the primary purpose of this section is to discuss the validity and reliability of the nalorphine test for opioid dependence, because of the close relationship between opioid dependence and crime, a physician should be aware of the possible legal implications of administering this test and his responsibilities. The state of being dependent on an opioid is not in itself necessarily a crime, although criminal acts are frequently committed in obtaining opioids to induce and maintain dependence. Courts in the United States may regard evidence obtained using a diagnostic test or a drug without the patient's consent as inadmissible. Poze (279) has also pointed out that since nalorphine may precipitate an intense and potentially dangerous abstinence syndrome, the physician who administers nalorphine without the patient's consent may be "subject to both civil suit and professional censure."

Because of the importance of pupillography in this testing procedure, a great deal of attention has been given to various techniques for measuring pupillary diameter and to their precision and reproducibility. Four procedures have been employed: Card pupillography using either (1) graded sized filled circles or (2) holes; (3) the slit lamp; and (4) photography of pupils. The pupil matching procedure usually has a precision of no more than 0.5 mm and a reproducibility between observers of no more than 0.25 mm (71). The precision and reproducibility between observers of the photographic method is 0.1 mm; but it has a significant variability between replications, which may exceed 1.0 mm as often as 1 in 10 replications in both dependent (180) and nondependent persons (71, 185).

Elliott *et al.* (70) found that a reliable positive nalorphine test could be obtained 2 to 4 hours after a single 15-mg dose of morphine, 2 hours after a 150-mg dose of meperidine, for more than 6 hours after 15 mg of methadone, for at least 2 hours after 5 mg of heroin and for 2 hours after 10 mg of oxycodone. Nalorphine does not produce mydriasis after single systemic or oral doses of codeine, but

does if codeine is administered chronically in increasing doses or is infused for 8 hours (69, 70). These results also suggest that the development of acute tolerance and dependence may contribute to the antagonistic properties of nalorphine. The concordance between the nalorphine test and chemical tests made on the urine is quite good (70, 341). A positive nalorphine test is obtained in approximately 60% of subjects who have received a single 15-mg dose of morphine if the test is performed within 4 hours of receiving the narcotic (70). In patients using relatively large doses of narcotics chronically, the test is positive over 80% of the time if it is administered within 4 hours of the last dose of narcotic (342).

It is possible that other drugs can modify the nalorphine test. In experiments conducted in rabbits, it has been found that homatropine and physostigmine abolish the response to nalorphine and that chlorpromazine and amphetamine convert a positive response into a negative one (40). Although the nalorphine test does not appear to be as sensitive as chemical methods as a diagnostic procedure for drug use, it is still a useful procedure for the diagnosis of dependence on narcotic analgesics. It also is a convenient and economical procedure for screening purposes.

D. Treatment of abstinent narcotic abusers

As previously mentioned, during chronic administration of narcotic antagonists, tolerance develops to their agonistic effects but not to their antagonistic activities. This has provided a basis for the ambulatory treatment of abstinent addicts. Cyclazocine, a potent, long acting (12 to 24 hours), orally effective narcotic antagonist, when administered in doses of 2 mg twice daily orally, will markedly antagonize the euphoria-producing properties of morphine and heroin, as well as the development of physical dependence (239). In order to obtain this dose level, cyclazocine must be administered initially in small doses and the doses then slowly increased as tolerance develops to the psychotomimetic and sedative actions of this agent. It has been suggested that this type of treatment might provide several benefits to the abstinent addict (229, 238): (1) it would minimize the continuation of drug use due to physical dependence that developed during spree use; (2) it could facilitate the extinction of conditioned abstinence and conditioned drug-seeking behavior; and (3) it would provide an optimal circumstance in which protracted abstinence could diminish by preventing the reestablishment of dependence.

Jaffe and Brill (178) have reported on 11 abstinent addicts who were accepted for cyclazocine treatment. At the time their paper was published, nine of the patients had been stabilized on cyclazocine and were by and large making satisfactory social adjustments. Freedman (100) has also stabilized 15 patients on cyclazocine. One of the interesting effects of cyclazocine observed by this investigator was an increase in sexual drive. Both Freedman and Jaffe have confirmed the observation that cyclazocine antagonizes the euphoric effects of heroin. Further, this technique seems to have potential value in the management of abstinent narcotic addicts.

E. Determination of the abuse potential of analgesic drugs

In patients who had received morphine, methadone, or heroin, Wikler *et al.* (356) were able to precipitate signs of abstinence with nalorphine and concluded that it unmasked physical dependence. Subsequent studies have shown that nalorphine can precipitate abstinence in subjects who have received normorphine (99), oxymorphone (66), anileridine (66), *d*-propoxyphene (93), codeine (95), norcodeine (95), or diphenoxylate (94) chronically. This observation has served as one criterion for assessing dependence of the morphine type.

F. Immobilization of game

One of the more interesting uses of etorphine [M99, 7-(1-hydroxy-1-methylbutyl)-6,14-endoetheno-oripavine], an opioid that is more than a thousand times more potent than morphine (19, 217), is for the tranquilization and immobilization of wild hoofed animals, such as the rhinoceros, elephant, giraffe and zebra (141, 200). Nalorphine, as well as M285 [N-cyclopropylmethyl-7-(1-hydroxy-1-methylethyl)-6,14-endoethenotetrahydronororipavine] a potent opioid antagonist, has been used to reduce or terminate the narcotic effect abruptly when the need for it no longer exists (141, 200).

VII. SUMMARY AND CONCLUSIONS

Several investigators have postulated that nalorphine acts competitively in antagonizing the effects of opioids (293), but the corollary of this hypothesis that opioids are agonists was first explicitly stated by Van Rossum (333). In arguing the point whether morphine was the agonist or antagonist and nalorphine the antagonist or agonist, Van Rossum felt that morphine was more likely the agonist and nalorphine the antagonist because nalorphine had a larger group substituted on the nitrogen. Archer and Harris (6) buttressed this argument by summarizing studies in which narcotic antagonists appeared to act competitively against narcotic analgesics. The argument is further strengthened by the finding that naloxone acts as an antagonist in dose levels that are devoid of agonistic or contrastimulatory effects.

The nature of the agonistic action of morphine in the central nervous system has not been demonstrated. There is no question that its action on the intestine in inhibiting acetylcholine release is a competitively antagonizable agonistic effect, but acetylcholine antagonists and anticholinesterases do not respectively mimic or antagonize the central actions of morphine. Although these facts do not conclusively reject inhibition of acetylcholine release as a mechanism of morphine's central action, they do not support this hypothesis, even though morphine prevents the release of acetylcholine in the brain (15). Either directly or indirectly, morphine causes changes in the release of norepinephrine, epinephrine, dopamine, histamine, and serotonin. With such broad actions on neurohumors, the possibility that it alters the release of yet other unidentified neurohumors cannot be excluded.

Whatever the mode of action of opioids, clearly agents that occupy the receptor sites of the opioids differ in their ability to induce pharmacological ac-

tions. Near the two extremes of activity are morphine, representative of an active agonist, and naloxone, representative of an agonist with no activity and a competitive antagonist. Differences in degrees of activity among opioid antagonists have been seen in a number of functional systems, including those responsible for analgesia, respiratory depression, miosis, and inhibition of the release of acetylcholine. The possibility that opioids could have different levels of intrinsic activity has been proposed (228). Obviously, the basis for differences in activity between the agents that seem to occupy the opioid receptor cannot even be rigorously studied until the modes of action of the opioids have been elucidated, and possibly the basic mechanisms governing the release of neurohumors and the excitability of neurons discovered; however, for heuristic reasons it may be worthwhile enumerating some of the possible mechanisms that have been proposed for other agonists and systems.

Ariëns *et al.* (8) have suggested that the magnitude of intrinsic activity is associated with effectiveness of the drug-receptor interaction, *i.e.*, with the intimacy of binding at all necessary sites. Alternatively, they have suggested that the agonist could serve as a cofactor, some agonists being effective cofactors (*e.g.*, furnishing hydrogen ions), while others would be less effective. The effectiveness would be independent of the tightness of the union of the cofactor with the enzyme. The known facts about opioid analgesics and antagonists do not really allow critical testing of these hypotheses.

Paton (271) has proposed that the rate of occupation of receptors by the agonist may determine the magnitude of effect. This theory predicts that activity is directly related to the dissociation constant at an equilibrium state and that agents that are more tightly bound would be weaker agonists, and conversely, more effective antagonists. This hypothesis cannot be rejected for the narcotic analgesics, but the following observations argue against it: (1) The duration of action of antagonists and partial agonists as antagonist would be expected to be longer than their actions as agonists and longer than the actions of pure agonists. Naloxone, an antagonist which is nearly devoid of agonistic activity, has a shorter duration of action than cyclazocine, an active agonist and antagonist. An even more critical piece of evidence is that both the agonistic and antagonistic effects of the narcotic antagonist cyclazocine persist for many hours. (2) Nalorphine egresses from the brain more rapidly than morphine. This observation is not critical, because, as has been pointed out, the agonistic actions of nalorphine persist longer than its presence in the brain. This suggests that chemical determinations are not primarily measuring drug bound to active receptors.

Mackay (220) has suggested that the agonistic actions of drugs may be related to the density of their influx through the effector membrane. This hypothesis does not fit with the observation that pharmacological actions, as well as brain levels of both opioid and opioid antagonists, continue at high levels at times when the plasma concentrations have decreased to negligible levels.

At the present time, the most attractive drug-receptor hypothesis is that opioids' action is a consequence of two factors: the proportion of the receptors occupied by the analgesic, and the intrinsic activity of the analgesic. Testing of

this hypothesis in a number of functional systems is complicated by the fact that they are concerned with homeostatic regulation and that acute tolerance and dependence develop in them. Antagonists need only partially antagonize the effects of the opioid on a homeostatic mechanism to create an error force that will drive compensatory mechanisms above their control level of function. A similar situation may exist for systems that are either acutely or chronically dependent.

Among the observations that argue against accepting the concept that opioid antagonists are competitive antagonists are the facts that: (1) Under some circumstances, the actions of nalorphine add to those of morphine, while under other circumstances they antagonize the actions of morphine; and (2) nalorphine exhibits contrastimulatory actions in its own right. With regard to the former observation, when the properties of partial agonists (agents with moderate or low intrinsic activity) are recognized, as well as the importance of homeostasis and dependence in the response to them, many of the paradoxical observations can be adequately explained.

In attempting to explain the contrastimulatory properties of the opioid antagonists, one is forced to reconsider the nature of the agonistic actions of the narcotic analgesics. One can assume, for argument sake, that opioids mimic a naturally ongoing process. If this hypothesis is true, then it would not be unreasonable to assume that those antagonists with low intrinsic activity would antagonize not only morphine-induced activity, but the naturally ongoing activity that is similar in nature to the effects of morphine with the result that an antimorphine effect would become manifest. The effects of the opioid antagonists on several functional systems, such as EEG changes in the rabbit, respiratory changes in certain anesthetized preparations and the extensor thrust reflex in the spinal dog, seem consistent with this formulation, but the preponderance of observations indicates that for most systems either the opioid antagonists have no action or their actions resemble those of morphine. It can be assumed that for some sites affected by opioids there is no natural morphine mimetic ongoing process, whereas there are naturally ongoing morphine mimetic processes at other sites.

A more serious problem bearing on the issue of competitive inhibition is the biphasic dose response curves obtained by Houde and Wallenstein (152), Rubin *et al.* (283) and Yim *et al.* (370) for the analgesic activity of mixtures of opioids and opioid antagonists. This type of dose response relationship cannot be obtained by assuming there is one analgesic receptor and that competitive antagonism or competitive dualism obtains. It can be explained by assuming that there are two analgesic receptors, one where morphine acts as an agonist and nalorphine as a competitive antagonist, and the other where morphine is inactive and nalorphine is an agonist. The fact that nalorphine and morphine produce different types of subjective effects is also consistent with the idea that they may act at different sites. This is buttressed by the observation that subjects tolerant to subjective effects of morphine are not cross tolerant to the psychotomimetic effects of cyclazocine. The fact that subjects dependent on the narcotic antagonists nalorphine and cyclazocine exhibit an abstinence syndrome that is qualita-

tively different from the morphine abstinence syndrome also supports this hypothesis. The fact that naloxone can antagonize the agonistic actions of both the narcotic antagonists and the narcotic analgesics would indicate that although these receptors are distinguishable they must have very similar stereochemical configurations. In this regard, Portoghese (278), on the basis of structural considerations, has also suggested that there may be several species of analgesic receptors. Taber *et al.* (315) have also suggested that the narcotic antagonists may have a different site of action from that of the opioids in producing analgesia, and base their argument on the difference in slopes of the dose response curves of opioid and analgesic opioid antagonists.

The observation that the agonistic antagonists nalorphine and cyclazocine can induce tolerance to their agonistic effects, but not to their antagonistic effects and physical dependence, whereas the antagonist naloxone does not induce either tolerance or dependence, strongly suggests that both tolerance and dependence are induced by the agonistic effect, not by receptor occupation. When naloxone is administered chronically, its blocking action persists, indicating receptor occupation; however, neither tolerance nor dependence is induced.

Studies with opioid antagonists clearly indicate that morphine and other narcotic analgesics act at all levels of the central nervous system and in the peripheral nervous system, and that whatever their mode of action, it is on a very fundamental, basic, and widespread neuronal process.

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