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Pharmacology of Opioids*

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* This article is the fourth of a series of reviews on various aspects of opioid pharmacology arranged with the help of Hans W. Kosterlitz, Aberdeen, and Eric J. Simon, New York, as Consulting Editors. The Editor and Associate Editors are grateful for their assistance. The first two articles of this series, "Animal Models for Dependence" by W. L. Woolverton and C. R. Schuster and "Opioid Receptors: Autoradiography" by J. K. Wansley, appeared in the first issue of this volume. The third article in the series, "Electrophysiology of Opioids" by A. W. Duggan and R. A. North, precedes this one in this issue. Other topics will follow.

I. Introduction

THE PHARMACOLOGY of opioid-like drugs has been the subject of numerous monographs, reviews, texts, and symposia (27, 40, 153, 154, 203, 226, 237, 124). It is not the purpose of this article to authoritatively review the pharmacology of the opioids, which would be an enormous undertaking for the citations bearing on this subject must now number in the tens of thousands. Rather, the purpose of this article will be to view the action of opioids in terms of receptor pharmacology. It has become increasingly apparent that opioid analgesics are agonists that interact with a variety of receptors. The approach to the identification of receptors has involved two processes: 1) The characterization of unique pharmacological profiles or syndromes with opioid agonists and antagonists of varying degrees of selectivity; and 2) the study of kinetics of saturable and stereospecific binding of opioid agonists and antagonists to various tissue fractions. The characterization of the receptor binding site and the coupling mechanisms that are responsible for the initiation of pharmacological actions, as well as the interaction between these components of the receptor, remains a fundamental and unsolved problem in pharmacology. It is evident that these two types of methodologies have limitations and that in the end the two methodologies yield complementary data that must be reconciled by unifying concepts. The study of opioid analgesics has provided a unique opportunity for formulating theories about subtypes of opioid receptors. Thousands of opioid analgesics of diverse structures have been synthesized and investigated to varying degrees for their analgesic, antidiarrheal, antitussive, and dependence-producing properties. As a consequence, several analgesics have been identified that have been classified as either opiates or morphine-like drugs, or as opioid analgesics which generally differ from morphine in their pharmacology.

There are two general ways in which non-opiate opioids differ from opiates: a) They may exhibit antagonistic activity to opiates and in this regard may be either competitive antagonists of the opiate type or partial agonists of the opiate type. b) They may exert pharmacological effects that are different and distinguishable from those of opiate analgesics. There is reason to believe that some opioid analgesics are at the same time competitive antagonists, partial agonist, and strong agonist, exhibiting each of these pharmacological properties at different opioid receptors.

Both pharmacological and binding studies have provided evidence of multiple opioid receptors. With regard to brain function, the presence of multiple receptors has implications far broader than is present in peripheral tissues. This is because a) the various opioid receptors appear to be present on different and distinguishable types of neurones involved in the same and diverse physiological and pharmacological functioning; b) the diverse neurones and their associated pathways both converge and diverge and are thus involved in both similar and different physiological and pharmacological effects.

A. Pharmacological Dualism

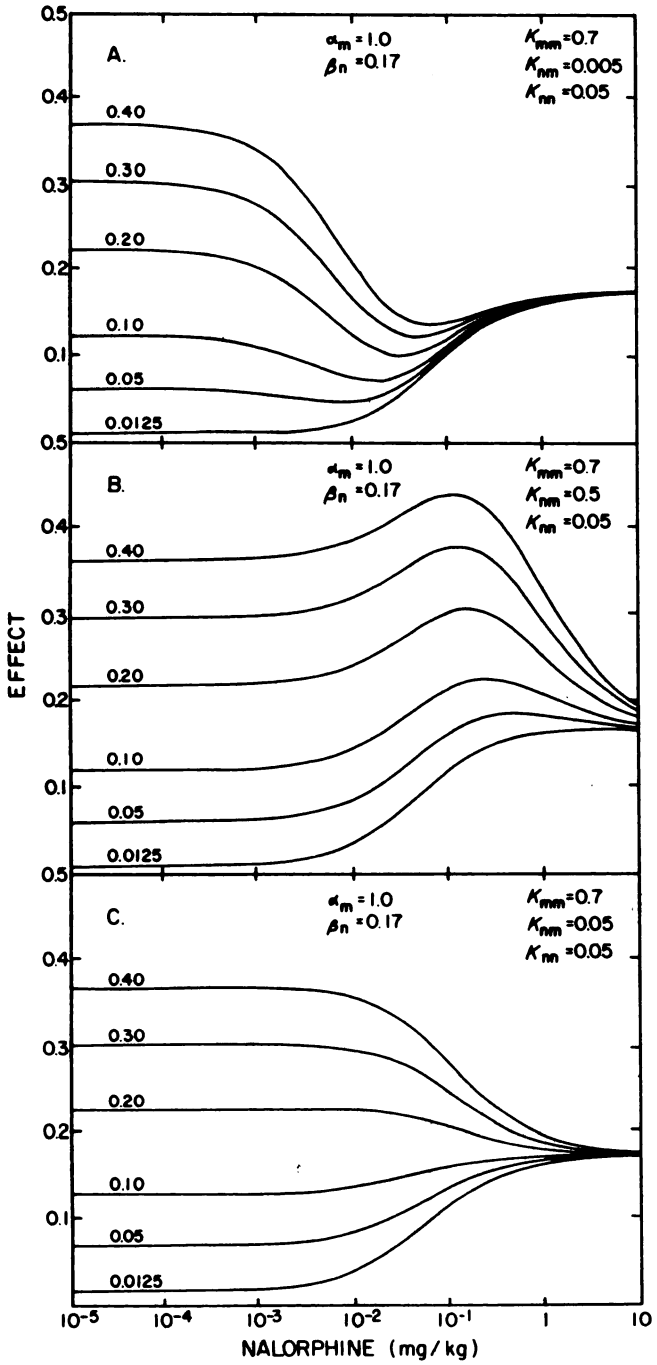
The term "pharmacological dualism" indicates that the activation of several neuronal pathways through different and distinguishable receptor mechanisms results in the same pharmacological action (173). Figure 1 illustrates pharmacological redundancy for the situation in which two pathways with two different receptor mechanisms produce a pharmacological effect and an equation that defines dose response relationships for this particular circumstance. Several types of dose response relationships can result from these complex interactions when graded doses of mixed agonists-antagonists (nalorphine) are administered in the presence of a strong agonist (morphine) (188).

Three families of dose response lines are presented in figure 1 for the situation in which one drug (M) is a strong agonist at one receptor (m) and the other drug (N) is a competitive antagonist at one (m) receptor and a partial agonist at another receptor (n). If N has a higher or a lower affinity for m than does M, a biphasic dose response curve results. Whether the curve is concave upward or downward depends on the relative affinity of N for m as compared to its affinity for n. If N's affinity for m is greater than for n the curve will be concave upward because the antagonism of the effects of M will occur at lower doses than the manifestation of N's agonistic actions at receptor n (fig. 1A). On the other hand if N has a higher affinity for n than m the curve will be concave downward (fig. 1B). If the affinity of N for m is the same as n, the partial agonistic action of N on n will be seen (fig. 1C). Empiric data has been developed that shows these characteristics (see section II A 1 and 2).

The type of dose response relationships that are obtained for central nervous system functions are more complicated than those based on peripheral tissues because of multiple receptors and pharmacological dualism.

B. Drug Syndromes

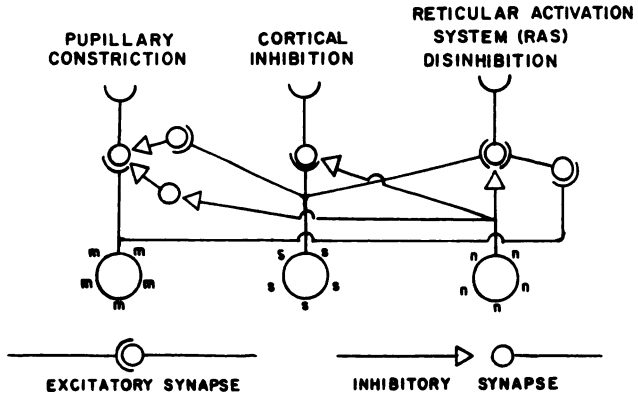
Pharmacological dualism is a phenomenon related to the convergence of pathways with different receptor mechanisms on a common pathway. *Drug syndromes* are related phenomena tht are concerned with divergence of pathways containing the same or different receptors. The mapping of brain receptors, with their pathways and related functions, is an emerging area of pharmacology. A hypothetical example of neuronal pathways involved in producing a syndrome is presented in figure 2 in which three neuronal pools with three different receptor populations project to the Edinger-Westphal nucleus, the cerebral cortex, and the reticular activating system over



$$\frac{E_{nm}}{E_{max}} = \frac{\alpha_m M K_{nm}}{M K_{mm} + M K_{nm} + K_{mm} K_{nn}} + \frac{\beta_n N}{N + K_{nn}}$$

FIG. 1. Theoretical dose effect curves for an interaction between a drug M (morphine) which is a strong agonist at receptor *m* and drug N (nalorphine) which is a competitive antagonist at receptor *m* and a partial agonist at receptor *n*. The intrinsic activity of M and N are designated by α and β and dissociation constants by K (from Martin et al. (188)).

both inhibitory or facilitative pathways. In this simplified scheme three distinct syndromes result for the prototypic agonists, M, K, and S. We can speculate as to yet other hypothetical syndromes that could result if a mixed agonist or a mixed agonist-antagonist was given.



AGONIST	EFFECT: PUPILS	EFFECT: CORTICAL CONTROL	EFFECT: RAS
M	MIOSIS	NO CHANGE	AROUSAL
S	MYDRIASIS	UNCONTROLLED THOUGHTS	AROUSAL
N	MIOSIS	DECREASED ABILITY TO MAKE ASSOCIATIONS	SLEEP

FIG. 2. Neuronal nets and drug syndromes. Three neurones with three different opioid receptors (*m*, *s*, *n*) which project to and modulate three different effector systems are illustrated. The three different syndromes which result from the activation of the three prototypic neurones (or neuronal pools) by selective agonists are presented in the bottom box.

There is ample evidence from a variety of types of experiments, including iontophoretic and microinjection studies of agonists into the brain as well as histochemical and pharmacological studies, that different CNS neurones differ in their complement of receptor subtypes. It is thus evident that agonists with different specificities may produce different pharmacological syndromes. Thus the demonstration of different pharmacological syndromes is a necessary piece of evidence in the identification and delineation of multiple central nervous system receptors.

C. Receptor Agonist and Antagonist Nomenclature

The nomenclature for designating types of analgesics and related drugs and receptors is evolving and at this time definitions at best should be considered ad hoc. The terms agonist, competitive antagonist, irreversible (nonequilibrium) antagonist, and partial agonist have well established definitions and are used in discussing opioid drugs in their conventional sense.

The term "opioid" is one whose definition has changed with time. Acheson (see 173) first coined and used the term to designate drugs whose actions resembled morphine but whose chemical structure could be quite different from opiate analgesics. The definition of the term was broadened to include both agonist and antagonists whose spectrum of activity and specificity include related drugs of diverse chemical classes some members of which exhibit a opiate spectrum activity.

The terms "agonist-antagonist" or "mixed agonist-

antagonist" have been used to designate two distinct types of pharmacological activity: a) Some agonists-antagonists are partial agonists (e.g. propiram, profadol, buprenorphine, and nalbuphine) which exhibit an agonist effect when administered alone or in the presence of small quantities of a strong agonist but which diminish or antagonize the effect of a large dose of a strong agonist and precipitate abstinence in opioid dependent animals. b) Other agonists-antagonists are competitive antagonists at one opioid receptor and agonists at other related receptors (receptor dualism).

A "mixed agonist" is a drug that acts as an agonist on several receptor types. Similarly a drug that is a competitive antagonist at several receptors is a "mixed antagonist."

II. Pharmacology of Opioids

A. Analgesia

1. General Issues. Studies of the analgesic actions of opioid analgesics in man have failed to distinguish among several agents that diminish the response to different types of nociceptive stimuli to different degrees and in different ways in animals. Valid potency estimates of analgesic potency have been obtained by comparing such diverse agents as morphine, heroin, pentazocine, nalorphine, and buprenorphine on several types of pathological pain in man (121a). The criteria of a valid bioassay were met in these studies indicating that the slopes of the dose response lines of these various agonists were parallel. Thus the relief of pathological pain alone does not distinguish between analgesics with different modes of action. As will be discussed later, interaction studies between drugs with different modes of action, although used infrequently, have generated provocative data which indicates that there is opioid receptor heterogeneity in man. It may be worthwhile to speculate about why studies of the analgesic actions of drugs in man with pathological pain have not distinguished among analgesics with apparently different modes of action in relieving experimental pain. 1) It is possible that they do not have different modes of action in man; however, the fact that they produce different subjective (section II B 1), cardiovascular (section II C), and respiratory (section II B) effects argues against this possibility. 2) The doses of agonists and agonist-antagonists used in clinical studies are from the low end of the dose response line. Thus the doses used in studies of the analgesic actions of morphine in man fall within the range of 0.1 to 0.5 mg/kg. A rough approximation of the dissociation constant (K_d) of morphine in man is 1.0 mg/kg (188). Thus the effects produced by commonly used clinical doses of morphine predicted by this assumption would be 0.1 to 0.3 of its maximal effect. Data from this part of a dose response line is not the best for estimating its slope. 3) There may be fundamental differences between pathological pain in man and nociceptive responses and reflexes in animals used to study analgesics.

2. Suppression of Nociceptive Responses and Reflexes in Animals by Opioid Agonists and Antagonists. The use of animals for studying analgesia and estimating the effectiveness and potency as analgesics has been reviewed by Winter (288) and Taber (258). Table 1 summarizes the relative potencies of a variety of prototypic agonist and agonist-antagonists on several types of responses to nociceptive stimuli in the mouse, rat, dog, and monkey. Morphine is used as a standard for these comparisons and is assigned the relative potency of 1. The estimates of the AD50 (or its approximation) of morphine are presented in parenthesis.

There are several generalizations concerning table 1 that are worthy of mention.

A. SENSITIVITY. As can be seen there are differences in the sensitivities of different analgesic tests as indicated by their AD50. Thus the writhing tests in the mouse (AD50 = 0.2–0.8 mg/kg) and rat (AD50= ca 0.2 mg/kg) can detect analgesic doses of morphine of the order of magnitude 0.1 mg/kg. This method is 5 to 10 times more sensitive than the hotplate test with mice and the tail flick test with rats. The flexor and skin twitch reflexes of the chronic spinal dog may approach the writhing tests in sensitivity in detecting analgesic activity. The tail squeeze, flinch jump, intracarotid bradykinin, and monkey stimulus titration tests may be intermediate in sensitivity to the mouse and rat writhing tests on the one hand and the mouse hotplate and rat tail flick tests on the other.

B. STIMULUS STRENGTH. Many agonists-antagonists are either ineffective or have a low order of potency in suppressing the rat tail flick reflex and several hypothesis have been advanced to explain this lack of efficacy. One possibility is that the intensity of the stimulus is great in this assay (see 173) and that partial agonists are incapable of producing a sufficient degree of analgesia to yield a valid assay. Several investigators have addressed this issue. Gray et al. (92) studied the analgesic activity of several agonists and agonist-antagonists on the rat tail flick evoked by four strengths of radiant heat that yielded mean reaction times of 12, 8, 4.8, and 3.6 seconds, respectively. There was little difference between morphine dose response lines for the four strengths of stimuli although morphine had greater potency when assayed with the lowest heat intensity. Similarly the meperidine dose response lines for the three lowest strengths of stimuli had similar slopes. The dose response line for the highest strength of stimulation had a lesser slope or a ceiling. The slopes of the pentazocine dose response lines showed a progressive decrement in slope with increasing strengths of stimulation. Nalorphine exhibited liminal analgesic activity only when the lowest strength of stimulation was used. Tyers (269) used two temperatures of water (50°C and 55°C) to evoke a tail flick in rats. Neither nalorphine, pentazocine, nor ketacyclazocine exhibited analgesic activity at either temperature whereas ethylketazocine exhibited analgesic activity at both tem-

TABLE 1

*Relative potency of opioid analgesics and agonist-antagonist in producing analgesia with several nociceptive reflexes in the mouse, rat, dog, and monkey**

	Mouse			Rat			Dog			Monkey
	Hot plate	Writhing	Tail flick	Tail squeeze	Writhing	Flinch jump	Bradykinin	Flexor	Skin twitch	Stimulus titration
Morphine	1 (1.2[18], 2.7[7], 3.1[19], 5.5[6], 1.7[31])	1 (0.26[19], 0.28[20], 0.6[1,2], 0.8[4])	1 (1.2[20], 2.5[11,19])	1 (0.5[20], 0.65[24], 2.5[20], 3.0[12])	1 (0.16[19], 0.26[4])	1 (ca 2[8,9])	1 (1.1[1], 2.3[28])	1 (0.1–0.5 [10,15,16])	1 (0.5–1.0[10,15,16])	1 (0.25–1.0[22,23,26])
Codeine	0.16[18], 0.11[31]	1.1[8]	0.1[5], 0.4[6]	0.14[24]		0.05[8]	0.03[11]	0.05[14]	0.1[16]	
Meperidine	0.25[18], 0.22[31]		0.05[5], 0.1–0.2[11]	0.25[24]		0.01[8]		–†	0.26[16]	
Methadone	2.0[7]		1.1[5]	2.3[12]		0.5[8]				
Propiram	0.13[30]	0.05[20]		0.04[20]				0.14–0.17[10]	–	
Profadol	0.37[30]		sl‡[21]	1.0[25]						
Buprenorphine	32.5[30], 1.1[31]	14[20]	sl[21]	61[20]			575[29]	118–160[15]	69[15]	
Ketocyclazocine	3.1[30], sl[31]	5.6[11]	1.9[27], 2.4[20]	0.6[20]			3.4[28], 22[27]	2.1[15]	–	
Nalbuphine	sl[3]	2.0[3]	sl[21]		4.3[3]		6.8[21]			
Butorphanol	0.5[19]	5.1[7], 6.7[11]	0.1[19]	1.2[20]	4.0[19]				>0.2[19]	
Pentazocine	0.04[13], 0.09[18] 0.27[19], 0.06[31]	0.07[19], 0.14[17] 0.16[4], 0.2[1,21], 0.3[3], 0.35[20]	0§[13,19] 0.04–0.06[11]		0.17[19], 0.2[4]	0.2[9]	0.6[1]	0.27–0.33[10]	ca 0.4[10]*	–
Cyclazocine	0.05[18], 0.36[13] 1.2[19]	2.8[20], 5.6[19] 4.5[17,21], 21[1]	0[13,19]		5.5[19], 17[4]		12[28]	4.3–4.8[10]	0[10]	ca 1[22], 2[26]
Nalorphine	0.03[12], 0.08[19] inactive[31]	0.3[1,19], 0.5[21] 0.8[17], 1.7[4], 2.1[20]	0[13]	<0.05[20]	0.3[19], 1[4]	1[8]	0.2[1]	0.53–0.58[10] 0	<0.2[19], 0[10] 0	0[22]
Naloxone	0[18], <0.01[19], 0[22]	<0.008[4,17,20] *, >0.01[19]	*, 0[19,20]	0[20]	0[4], <0.01[19]					
Naltrexone	0[18], 0[22]	0[4]			1.9[4]					

* All potency values are expressed as the number of milligrams of morphine equivalent to 1 mg of the drug. Values in parentheses are the analgesic dose 50 (AD50) of morphine in mg/kg. Superior figures are reference numbers.

† –, Not a valid assay.

‡ sl, slight analgesia.

§ 0, No analgesia.

[1] Blane (15).
[2] Blumberg et al. (20)
[3] Blumberg et al. (19)
[4] Blumberg and Dayton (17)
[5] Bonnycastle and Leonard (23)
[6] D'Amour and Smith (48)
[7] Eddy et al. (57)
[8] Evans (61)
[9] Evans and Bergner (62)
[10] Gilbert and Martin (86)
[11] Gray et al. (92)
[12] Green and Young (93)
[13] Harris and Pierson (108)
[14] Martin et al. (182)
[15] Martin et al. (184)
[16] Martin et al. (186)
[17] Pearl and Harris. (212)
[18] Perrine et al. (214)
[19] Pircio et al. (217)
[20] Rance (223)
[21] Taber et al. (258)
[22] Weiss and Laties (282)
[23] Weitzman and Ross (283)
[24] Winder et al. (286)
[25] Winder et al. (287)
[26] Yaksh and Rudy (292)
[27] Michne et al. (199)
[28] Pierson and Rosenberg. (personal communication)
[29] Pierson, Sterling Research Institute (personal communication)
[30] May (personal communication)
[31] Tyers (269)

peratures. Different temperatures have been used for testing analgesics by the hotplate technique. Although it is difficult to detect (obtain a valid bioassay of) the analgesic effect of many agonists-antagonists by the conventional hotplate technique (54.5°C), O'Callaghan and Holtzman (208) found that by reducing the temperature of the hotplate to 49.5°C, an analgesic action of pentazocine, nalorphine, cyclazocine, and levallorphan could be detected in the rat and that the analgesia was antagonized by naloxone. Although the strength of stimulus may be of some importance in detecting the analgesic effects of opioid agonist-antagonist and partial agonists, it does not appear to be either a significant influence in or the only explanation for the lack of effectiveness of opioid agonist-antagonist in depressing the rat tail flick reflex.

C. SPINAL CORD REFLEXES. McClane and Martin (196) used three strengths of stimuli with manual toe squeezers to evoke the flexor reflex of the chronic spinal dog. There was little difference in the potency of morphine or cyclazocine for the three strengths of stimuli. Nalorphine, which exhibited a ceiling effect, produced a greater depression of the flexor reflex when the weakest stimulus was used. In a subsequent experiment (86) in which three strengths of stimuli were used with a programmed pneumatic toe squeezer, nalorphine's ability to suppress the flexor reflex was the same for the three strengths of stimulation. Although narcotic analgesics such as fentanyl, morphine, meperidine, and methadone depressed the rat tail flick response when administered into the subarachnoid space of the lumbosacral region of the spinal cord, the agonists-antagonists cyclazocine, pentazocine, and nalorphine were inactive (292). Codeine and ethylmorphine were also inactive. The spinal cord effects of agonist-antagonist in the rat appear to be quite different than they are on spinal cord flexor reflex of the chronic spinal dog in which cyclazocine and pentazocine depress the flexor reflex in a dose-related manner (86). Existing data suggests that the rat spinal cord is devoid of κ receptors in contrast to the spinal cord of the chronic dog which is rich in them.

D. MEPERIDINE AND PENTAZOCINE: THE RAT TAIL SQUEEZE AND TAIL FLICK TEST. Although most investigators have reported valid assays when comparing meperidine and morphine with the rat tail flick procedure, Davies et al. (50) and Green and Young (93) found that the meperidine dose response lines had a lesser slope than morphine's when their analgesic activity was assessed in the rat by using the tail flick and tail squeeze techniques. Hoffman and Difazio (117) found that morphine and meperidine reduced the concentration of cyclopropane necessary to suppress the response to tail pinch in the rat in a dose responsive way and that meperidine was 0.14 times as potent as morphine. Pentazocine produced a similar effect except that the dose response curve plateaued at 20 mg/kg, a dose that was equivalent to about 2 mg/kg of morphine.

E. MOUSE AND RAT WRITHING TESTS. Although the writhing test has yielded valid potency estimates in comparisons of agonists-antagonists and morphine, the slope of the agonists-antagonists dose response lines are less steep than morphine's (259).

F. RAT FLINCH JUMP TEST. Evans (61) and Evans and Bergner (62) studied the effects of morphine, codeine, meperidine, methadone, nalorphine, and pentazocine on the jump response to electrical stimulation in Long-Evans hooded rats. A ceiling effect for raising the jump threshold currently was seen with nalorphine, meperidine, and pentazocine (table 1).

G. BRADYKININ TEST. Guzman et al. (100) studied the autonomic and affective changes produced by intra-arterial injection of KCl, acetylcholine, histamine, serotonin, and bradykinin in the dog. Morphine, 1 mg/kg, was effective in preventing vocalization produced by these substances (101). This technique has subsequently been adapted to the rat in which bradykinin is administered in the carotid artery and causes turning of the head (51). Although the sensitivity of this technique appears to be about the same as the tail flick, the bradykinin response is depressed by agonist-antagonists.

H. SPINAL DOG SKIN TWITCH REFLEX. The dose response line for μ partial agonists such as propiram and buprenorphine in suppressing the skin twitch reflex have shallower slopes than strong μ agonists such as morphine, codeine, and *d*-propoxyphine. These partial agonists give valid assays in depressing the flexor reflex. The agonist-antagonists nalorphine, diprenorphine, and oxilorphan, which are probably partial agonists of the κ type, do not significantly alter the skin twitch reflex of the chronic spinal dog. Pentazocine, ketazocine, and ethylketazocine increased the latency of the skin twitch reflex in a dose-related manner but the slope of their dose response lines are significantly less steep than those of strong narcotic analgesics.

I. MONKEY STIMULUS TITRATION TECHNIQUE. Several stimulus titration techniques have been developed for measuring the analgesic actions of drugs in the monkey. Weiss and Laties (282) used electrical stimulation of the feet, Boren and Malis (24) brain-stem stimulation, and Weitzman and Ross (283) stimulation of the Gausserian ganglia as nociceptive stimuli. These methods have sensitivity and can detect levels of morphine of the order of magnitude of 0.1 mg/kg (283). The foot stimulation seems to have a lesser sensitivity in detecting analgesic activity than stimulation of the Gausserian ganglia. Weiss and Laties (282) and Yaksh and Rudy (292) were able to obtain a dose-related elevation of shock threshold with morphine and cyclazocine. Nalorphine was inactive (282). Yaksh and Rudy (292) compared the ability of naloxone to antagonize the analgesic effect of morphine and cyclazocine. They found that naloxone was more effective in shifting the morphine dose response line to the right than in shifting the cyclazocine dose response lines. Their calculation pA_2 for morphine was 7.16 and 6.13 for cyclazocine.

3. Narcotic Antagonists. A. ANALGESIC ACTIVITY. Nal-

oxone and naltrexone are largely devoid of analgesic activity with conventional analgesic tests (see table 1) except for the following observations. Blumberg and Dayton (17) found that naltrexone had analgesic activity in the rat but not in the mouse by using the writhing test. Naloxone prolongs the latency of the tail flick response in mice pretreated with physostigmine (107). Recently Kamerling et al. (144) found that naltrexone depresses the skin twitch reflex of the intact dog. Naloxone administered intrathecally in rats increased the threshold of vocalization in a dose of 15 μg and decreased it in a dose of 60 μg (56a).

B. ANTIANALGESIC ACTIVITY. Jacob et al. (126) found that naloxone produced a dose-related decrease in the latency of the jumping response in the hot plate test in mice and rats but it did not alter the latency of the licking response except in one experiment with mice when the temperature of the hot plate was 50°C. The results were confirmed by Grevert and Goldstein (95), who, by using the hot plate technique, found that 10 mg of naloxone shortened the latency to jumping but not to foot-licking in mice. Pinsky et al. (216) found that naloxone increased rearing and leaping but diminished forepaw licking in rats on a hot plate. Similar results were obtained by Frederickson et al (76) who also found that the latency of the jump response showed diurnal variation being longest during the night. Naloxones hyperalgesic effect was also greatest at night. Bonnet et al. (22) found that both naloxone and naltrexone decreased foot shock threshold. Naloxone failed to alter foot shock escape latency (2 mg/kg) in Fischer strain rats (91) or the response to formalin (10 mg/kg) in Sprague-Dawley rats (206). Carmody et al. (32) found that naloxone (0.05 and 0.1 mg/kg) shortened the latency of a foot flick response to a hot plate in mice and rats. The 0.05-mg/kg dose of naloxone markedly reduced the analgesic effect of morphine. King et al. (151) found that naloxone shortened the latency of the rat tail flick response. Kokka and Fairhurst (152) and Ramabadran and Jacob (222) have shown that naloxone increased acetic acid writhing in rats and mice. This activity resided in the *l*-isomer. Naltrexone and dextrallorphan did not alter writhing and levallorphan and diprenorphine suppressed it in mice (222). Naloxone also antagonizes the prolongation of the latency of jumping of mice on a hot plate induced by haloperidol, pimozide, benperidol, as well as by arecoline and eserine (221). Naloxone did not produce hyperalgesia in mice pretreated with buprenorphine (127). Naloxone antagonizes analgesia evoked by brain-stem stimulation (2) and peripheral stimulation (30, 218). Naloxone, naltrexone, and nalorphine enhance the amplitude of the C-fiber reflex evoked by both electrical and heat stimulation (8). Harris et al. (107) observed that physostigmine pretreatment revealed the ability of nalorphine, pentazocine, cyclazocine, and cyclorphan but not naloxone to prolong the latency of the mouse tail flick. Further naloxone antagonized oxotremorine-induced analgesia. Pedigo et al. (213) found that naltrexone, naloxone, cyclazocine, nalorphine, and pentazocine antagonized the analgesic effect of intra-ventricularly administered acetylcholine (ACh) as assessed by the phenylquinone writhing test. Although these agents were less potent in antagonizing ACh than morphine analgesia, their relative potencies were about the same.

The issue of whether narcotic antagonists affect the perception of pathological or experimental pain in man cannot be answered with certainty. Lasagna (156) reported that naloxone in a dose of 2 mg produced a modest degree of analgesia while 8 mg produced a slight degree of hyperalgesia in pathological pain. El-Sobky et al. (58) were unable to detect any effect of naloxone (0.4 to 0.8 mg) on experimental pain evoked by increasing electrical stimulation. Neither the threshold current for the sensation of pain or the current required to produce severe or maximally tolerated pain were changed by naloxone.

In a series of studies in man, naloxone failed to alter hypnosis-induced analgesia or enhance pain produced by either an ischemic technique or by cold (89, 94, 96). Buchsbaum et al. (29), with an experimental protocol similar to that used by El-Sobky et al. (58), divided the patient population into pain insensitive and sensitive subjects. They also recorded electroencephalographic (EEG) potentials from the somatosensory cortex. They found that naloxone (2 mg) both enhanced and decreased pain perception in the insensitive group (enhanced perception appeared to be somewhat greater) and tended to decrease pain perception in the sensitive subjects. Naloxone also enhanced the cortical-evoked potential in the insensitive but not the sensitive group. Levine et al. (165) studied the effect of naloxone on the level of pain in patients who had undergone a tooth extraction. It had no effect in patients who were not placebo responders. In placebo responders 0.4 and 2 mg produced analgesia and 7.5 and 10 mg hyperalgesia. Houde and Wallenstein (122) found that low doses of nalorphine antagonized the analgesic effect of morphine while higher doses produced a lesser degree of antagonism.

C. ANTAGONISTIC ACTIVITY AGAINST NARCOTIC ANALGESICS AND AGONIST-ANTAGONISTS. The ability of narcotic antagonists to antagonize the analgesic activity of morphine-like drugs has been well documented [see Martin (173) for older citations]. Cox and Weinstock (47) and Grumbach and Chernov (98) were the first to clearly show that nalorphine and levallorphan would shift the dose response of narcotic analgesics to the right suggesting that morphine was an agonist and nalorphine was a competitive antagonist. Cox and Weinstock (47) calculated the pA_2 of nalorphine for several analgesics. Blumberg et al. (18) with the mouse writhing test and McClane and Martin (196) with the flexor reflex of the chronic spinal dog showed that naloxone could also antagonize the analgesic action of agonist-antagonists; however, larger quantities were required than needed to antagonize morphine-like agents. Table 2 compares the work of several investigators who studied the interactions between antagonists and agonist-antagonists. As

TABLE 2

ED50 of naloxone in antagonizing the analgesic action of narcotic analgesics and agonist-antagonists using the mouse and rat writhing tests

	Mouse	Rat
Morphine	0.11[2]	
Oxymorphone		0.045[1]
Butorphanol	0.61[2]	
Cyclazocine	0.76[2], 0.20[1]	0.11[1]
Pentazocine	0.78[2], 0.20[1]	0.09[1]
Nalorphine	0.80[2], 0.21[1]	0.24[1]
Levallorphan	1.7[1]	0.55[1]

[1] Blumberg et al. (18).
[2] Pircio et al. (217).

TABLE 3

pA_2 of naloxone in antagonizing the analgesic action of narcotic analgesic and agonist-antagonists by using the mouse writhing test

	pA_2 (95% Confidence Limits)	Slope (S.E.)
Narcotic analgesic		
Morphine[1,2]	7.08 (6.86–7.29)	−0.83 (0.03)
	7.07 (6.96–7.16)	−0.83 (0.06)
Levorphanol[1]	6.87 (6.65–6.77)	−0.97 (0.04)
Etorphine[2]	6.58 (6.39–6.77)	−1.24 (0.06)
Methadone[1]	6.98 (6.71–7.24)	−0.79 (0.09)
Agonist-Antagonists		
Nalorphine[1]	6.21 (5.99–6.42)	−1.46 (0.10)
Pentazocine[1,2]	6.20 (6.01–6.40)	−1.74 (0.05)
	6.45 (6.19–6.71)	−1.39 (0.11)
Cyclazocine[1]	6.50 (6.39–6.60)	−1.53 (0.12)

[1] Smits and Takemori (252).
[2] Takemori et al. (261).

can be seen the ratio of the amounts of naloxone required to antagonize agonist-antagonists nalorphine, cyclazocine, and levallorphan to the amount required to antagonize morphine and oxymorphine varies from 2 to 8. Blane and Dugdall (16) found that naloxone and M5050 also antagonized the analgesic actions of nalorphine, pentazocine, and levallorphan, as well as several oripavine agonist-antagonists, with the bradykinin test. Blane and Dugdall (16) found that naloxone and diprenorphine were more potent in antagonizing some agonist-antagonists than others. Taber et al. (259) found that naloxone was almost equieffective in antagonizing the analgesic actions of morphine and nalorphine.

The ability of naloxone to antagonize agonist-antagonists were pursued in a systematic way by Takemori and his associates by using Schild plots to analyze data obtained by the mouse writhing test. Some of their data is summarized in table 3 (252, 261). Hayaski and Takemori (109) found that naloxone had about the same pA_2 and its Schild plots had about the same slope (mean = 1.10) in antagonizing morphine analgesic activity in the mouse when using the hot plate, tail flick, or writhing test. As can be seen the pA_2 for opiate analgesics tends to be higher than for the agonist-antagonists. The mean difference between the pA_2s of opiate analgesics and agonist-antagonists is 0.56 suggesting naloxone is 3 to 4 times more potent in antagonizing narcotic analgesics than agonist-antagonists. The difference in pA_2 of the narcotic analgesic etorphine is not significantly different from the pA_2 of pentazocine or cyclazocine. It also should be noted that the slope of the Schild plots are steeper for the agonist-antagonists than for the narcotic analgesics. This issue has been discussed by Tallarida et al. (262) who have pointed out that constraining the slope of the Schild plot to 1 may decrease some differences between pA_2s. It should also be noted in table 3 that the narcotic analgesic may have Schild plots with slopes both significantly greater than and less than 1. Whether the affinity of the antagonists or agonists for the receptor changes as the receptors become increasingly occupied by the antagonist cannot be answered.

Relationship between agonist and agonist-antagonist may be more complicated in animals. Yim et al. (293) found that small doses of levallorphan produced a dose-related decrease in levorphanol analgesia while large doses produced a lesser degree of antagonism. In contrast to these studies, Taber et al. (260) did not see antagonism of morphine analgesia with low doses of nalorphine, but did see an additive effect with large doses of nalorphine.

4. Conclusions. It is clear that opioid analgesics must have several modes of action in obtunding pain and nociceptive reflexes. 1) Agonist-antagonists produce a dose-related analgesia in some tests (e.g. mouse and writhing or stretching) but not in others (e.g. rat tail flick). 2) Naloxone is more potent in antagonizing narcotic analgesics than agonist-antagonists. Although this issue is not completely settled, the preponderance of evidence supports this conclusion. 3) When graded doses of nalorphine are given in the presence of an effective dose of a narcotic analgesic, a biphasic dose response results.

The issue of identifying competitive antagonist is difficult and categorical classifications cannot be made at this time. When Jasinski et al. (134) first proposed that naloxone was a pure antagonist, it was already recognized that it had action not readily explained by its opioid antagonistic activity. Four considerations confound their classification: 1) The existence of weak agonistic properties which can be identified in some functional systems but not others; 2) the presence or absence of spontaneous and endogenous opioid peptide tone; 3) the antagonist may be a competitive antagonist at one opioid receptor but a partial agonist at another; 4) there may be subtle but significant differences between receptors of different strains or species (177–179, 190). Since then, more experimental evidence indicates that classifying of antagonists may be dependent on the experimental situation, the phenomenon, and the species. Blane and Dugdall (16) were unable to identify any activity of buprenorphine in the mouse, yet Gilbert and Martin (86) found it to be a partial agonist in the chronic spinal dog. Naloxone has been reported to produce analgesia, hyperalgesia, and to have no effect on pain.

"Pure" antagonists such as naloxone and naltrexone produce both hyperalgesia and analgesia under certain experimental conditions. Their hyperalgesic effect is

most commonly ascribed to their antagonizing existing tone of endogenous opioid peptides whose activity has been increased by such influences as sensory stimulation, cholinergic tone, and decreased dopominergic tone. The explanation for their analgesic effects are not readily explained. The possibility that endorphinergic processes are also involved in facilitating as well as inhibiting nociceptive processes cannot be excluded. Wu et al. (289a) have observed that ethylketazocine produces a naloxone antagonizable hyperalgesia in the acutely decerebrated dog and Kamerling et al. (144a) have shown that ethylketazocine produced hyperalgesia when administered in the fourth ventricle of the intact dog. These observations suggest that there is a medullary κ hyperalgesic center.

B. Respiration

1. Narcotic Analgesics. The older literature on the effects of opioid agonists and agonist-antagonists on respiration has been extensively reviewed (25, 173, 226). In brief, narcotic analgesics interact with respiratory modulator processes principally by decreasing the responsivity of the respiratory center to CO_2 and may have some selectivity in depressing neuronal modulation of the respiratory center (82, 83). Narcotic analgesics also exert a stimulatory effect on respiration in some species, probably by effecting hypothalamic thermoregulatory mechanisms (70). Denavit-Saubie et al. (52) applied morphine, levorphanol, and methionine-enkephalin iontophoretically on respiratory neurones in the nucleus ambiguus, tractus solitarious, and nucleus parabrachialis medialis of the cat. Spontaneous unit activity associated with phrenic nerve activity as well as activity evoked by the iontophoretic application of glutamate was depressed in two thirds, excited in about one eighth, and not affected in one fourth of the units. Neither dextrophanol nor naloxone influenced unit activity. The depressant effects of morphine, levorphanol, and methionine enkephalin were antagonized by naloxone.

Narcotic analgesics alter respiratory rate, rhythmicity and pattern (28), and minute volume and responsivity to CO_2. Each of these changes has been used to investigate the effects of opioids on respiration. In addition blood pH and CO_2 concentration are useful measures that are used for assessing the respiratory depressant effects of opioids. In man, morphine shifts the CO_2 stimulus-respiratory response curve to the right in a dose-related manner and produces a modest depression of its slope (193, 244). Several agonists-antagonists differ in certain respects from narcotic analgesics in their affect on respiration. In the intact and chronic spinal dog, morphine increases respiratory rate by inducing panting which is associated with the lowering of body temperature (180, 181). The partial opioid agonists, propiram and butorphanol, do not change respiratory rate in the chronic spinal dog (86).

Morphine increases pulmonary resistance and decreases pulmonary compliance, probably as a consequence of its histamine-releasing property.

2. Nalorphine and Cyclazocine. Telford et al. (267) found that 10 mg/70 kg of morphine and nalorphine were about equieffective in producing respiratory depression. In a subsequent and more extensive study of the respiratory actions of morphine and nalorphine, Keats and Telford (150) found that graded doses of nalorphine (0.25 to 1.0 mg/kg) administered intravenously produced only a modest shift of the respiratory CO_2 stimulus response curve to the right (less than would have been predicted for 2 mg/70 kg of morphine) and increased its slope. Further, all doses produced approximately the same shift to the right, indicating a ceiling effect.

Both nalorphine and cyclazocine stimulate respiratory rate in the chronic spinal dog (86, 87) although very large doses of nalorphine are required to produce this effect. In the pentothal-barbital-anesthetized dog, cyclazocine markedly depressed respiratory minute volume, pentazocine produced a lesser depression, and nalorphine little effect if any (106).

3. Pentazocine. Interpretation of data on the effects of pentazocine on respiration in man is difficult primarily because of differences in techniques used and in the way data was analyzed. Bellville and Green (10) compared morphine (5 and 10 mg) with pentazocine (10, 20, and 40 mg) and found that the dose response lines of morphine and pentazocine for shifting the CO_2 stimulus respiratory response curve to the right had similar slopes and differed only in that morphine was twice as potent. The respiratory depressant effect of pentazocine resides mostly in the *l*-isomer. The *d*-isomer produced only slight respiratory depression in doses of 30 and 60 mg (9).

Keats and Telford (148) found that the dose response line of pentazocine was somewhat less steep than morphine's. Engineer and Jennett (59) found that the slope of the CO_2 stimulus respiratory response line was less depressed by pentazocine than by meperidine and that the depression was the same for 22.5- and 45-mg dose levels of pentazocine whereas a dose response relationship was obtained with meperidine. Tammisto and Mattila (263) found that the slope of the dose response line for elevating alveolar CO_2 concentrations was less steep for pentazocine than for morphine, meperidine, fentanyl, or dextromoramide. Successive doses of pentazocine (3 mg/kg; total dose) given at 15-min intervals increased minute volume in conscious volunteers (5) while meperidine (5 mg/kg) and fentanyl (0.005 mg/kg) decreased it (264). Repeated doses of meperidine administered to women prior to delivery produce greater respiratory depression than repeated doses of equianalgesic dose of pentazocine in newborns (224). Repeated doses of morphine also produce a greater degree of respiratory depression than repeated doses of pentazocine (59). Keats and Telford (148) were unable to antagonize respiratory

depression produced by pentazocine or levallorphan with nalorphine. Naloxone will antagonize pentazocine-induced respiratory depression.

Pentazocine does not alter respiratory rate in the chronic spinal dog. McGilliard et al. (197, 198) found that the pA_2 of naloxone for antagonizing pentazocine-induced respiratory depression in mice was not different from its pA_2 in antagonizing morphine.

4. Nalbuphine. Nalbuphine (10 to 40 mg) shifts the CO_2 stimulus respiratory response curve to the right and decreases its slope (228). The slope of the nalbuphine dose response line (10, 20, 30, and 40 mg) was less steep than morphine's. Indeed there was no statistically significant difference between doses. There was more cumulation of effect when nalbuphine was administered chronically than with chronic morphine administration. Naloxone, nalorphine, and levallorphan will antagonize the respiratory depressant effects of nalbuphine but they are less effective than they are in antagonizing an equally effective respiratory depressant dose of morphine.

5. Butorphanol. Butorphanol produces respiratory depression in man by increasing blood CO_2 concentrations and decreasing pH (219) but has little respiratory depressant effect in the dog or rat (217). Butorphanol depresses the slope and shifts the CO_2 stimulus respiratory response line to the right in a manner similar to morphine; however, the slope of the dose response for the shift of the CO_2 stimulus respiratory response line is less steep for butorphanol than for morphine (204). This suggests that butorphanol may be a partial agonist (see section II D 2). Butorphanol does not increase pulmonary resistance or release histamine (242).

6. Naloxone and Naltrexone. Neither naloxone (68, 72, 134, 234) nor naltrexone (97, 192) alter respiratory rate or tidal volume (285) in adults or infants. The effects of naloxone and naltrexone on respiratory rate in the dog are controversial. Jacob and Michaud (125) observed tachypnea in the intact dog with doses from 0.01 to 3 mg/kg; however, these changes were not statistically significant. Martin et al. (184) conducted two studies of the effects of naltrexone (0.5, 2.0, and 8.0 mg/kg) on respiratory rate in the chronic spinal dog ($n = 6$ in both experiments). In both experiments the rate was slowed. In one experiment the changes were statistically significant, in the other they were not. Lawson et al. (160) found that naloxone (0.4 mg/kg) increased phrenic nerve activity, respiratory frequency, and peak phrenic nerve activity in the chloralose-urethane-anesthetized cat. Similar results were obtained in the decerebrate cat except the effect of naloxone on peak phrenic nerve activity was more erratic. These observations seem in keeping with those of Florez and Mediavilla (71) who found that methionine-enkephalin applied to the brain stem of the pentobarbital-urethane-anesthetized cat produced a naloxone antagonizable depression of respiration. Naloxone enhances the respiratory stimulant action of CO_2 in the anesthetized rat (256) and rabbit (14). Naloxone increases respiratory minute volume and frequency in the acutely decerebrated unanesthetized dog (289). Holaday and Faden (119) observed an increase in respiratory rate in acute spinal anesthetized rats after administration of *l*-naloxone but not after *d*-naloxone. Naloxone initiates respiration of apneic fetal sheep in utero and enhances the respiratory stimulant action of CO_2 (202). Farber and Maltby (67) found that naloxone enhanced respiration in the young opossum. Since it was associated with increased somatic muscle activity they concluded the respiratory stimulation was part of a general arousal.

The effects of naloxone on respiratory function in patients with chronic obstructive pulmonary disease has been studied with conflicting results. Santiago (236) found that naloxone stimulated respiration while Butland (31) found no effect. Naloxone did not alter respiratory function in healthy males (69).

7. N-Allylnormetazocine (SKF 10047). N-Allylnormetazocine produced a dose-related increase in respiratory rate in the chronic spinal dog (184).

8. Ketazocine, Ethylketazocine (Win 35, 197-2), Oxalorphan, and Diprenorphine. Neither ketazocine, ethylketazocine, oxalorphan, or diprenorphine over a wide range of doses significantly altered respiratory rate in the chronic spinal dog (86, 184).

9. Conclusion. Opioid analgesics and agonist-antagonists have diverse effects on respiration in man. Morphine and nalorphine clearly alter the slope of CO_2 stimulus respiratory response curve; the former depressing and the latter increasing its slope. Pentazocine probably occupies an intermediate position. It is possible that the psychotomimetic effects of certain agonist-antagonists may be related to increasing the slope of the CO_2 stimulus respiratory response line and may be related to the respiratory rate stimulant action of N-allylnormetazocine (184; Wu and Martin, in preparation). The dose response lines for depressing respiration of a variety of agonist-antagonists including pentazocine, butorphanol, and nalorphine have slopes significantly less than those of narcotic analgesics such as morphine. Whether respiratory depression dose response lines with lower slopes is characteristic of κ agonists cannot be critically evaluated at this time. Partial agonist and κ agonist do not appear to alter respiratory rate in the unanesthetized dog. The observations reported by McGilliard et al. (198) on the antagonistic actions of naloxone on pentazocine and morphine-induced respiratory depression indicate that pentazocine and morphine may interact with the same receptor in producing respiratory depression in the mouse.

C. Cardiovascular Effects

The effects of morphine-like drugs on the cardiovascular system are extremely complex varying from species

to species, the type of preparation (e.g. anesthetized or not; intact central nervous system or not), the dose, the drug, and whether the subject is tolerant or not. Despite studies of the actions of opioids on the cardiovascular system which now extend over a century, many of their effects are not clearly understood. This discussion will focus on several issues: 1) a brief review of the sites of actions of morphine cardiovascular effects; 2) interactions between opioids and anesthetics; and 3) the role of opioids and opioid antagonists in the physiology and pathophysiology of cardiovascular regulation.

1. Sites of Action of Morphine. In man, morphine in most circumstances has only a modest depressant effect on blood pressure and heart rate but decreases systemic and pulmonary resistance (41, 295). The decrease in vascular resistance is antagonized by naloxone (42). In the dog and the cat large doses of morphine administered intravenously cause a fall in blood pressure to which tolerance develops rapidly. This effect of morphine is probably due to the dilation of blood vessels and is most easily demonstrated in anesthetized animals. Histamine release may account for some but not all of this action and a central component probably plays a role (60, 240). The morphine-induced depressor response is also seen in the acute decerebrate and spinal cat. Evans et al. (60) found that pyrilamine antagonized morphine's depressor response in the spinal cat. Morphine also produces a vasopressor response in the unanesthetized cat that is diminished by anesthetics and prevented by spinal cord transection and by ganglionic and α-adrenergic blocking drugs (147). In the pentobarbital-anesthetized dog fentanyl or dextromoramide administered intravenously, by the vertebral artery or intracisternally, decreased blood pressure, sympathetic outflow, and pulse rate in a dose-related manner [see Laubie et al. (157)]. These investigators found that oxotremorine and physostigmine administered intracisternally or into the cerebral artery antagonized the bradycardia and hypotension produced by dextromoramide. In the pentobarbital-anesthetized cat morphine produces a pressor effect followed by a depressor effect (279). The pressor effect is diminished by adrenalectomy. Fentanyl enhances the baroreceptor reflex and decreases blood pressure and pulse rate in the pentobarbital-anesthetized dog whose nucleus tractus solitarious was lesioned bilaterally. It had a similar effect in the baroreceptor deafferented dog (158). Fentanyl perfused through the fourth ventricle of the unanesthetized dog slowed the heart rate and reduced blood pressure; however, the baroreceptor vasopressor response was not altered but evoked tachycardia was diminished (81). The effects of fentanyl on blood pressure and heart rate were antagonized by naltrexone. Intrathecally administered morphine produces both a pressor and depressor response associated with bradycardia in the chloralose-anesthetized rat (21). Laubie et al. (159) injected morphine into the nucleus ambiguus of chloralose-anesthetized dogs and observed hypotension and bradycardia. Similar observations have been made by Wu and Martin (unpublished observations) when fentanyl is administered into the nucleus ambiguus of the unanesthetized acutely decerebrated dog. This effect is antagonized by naloxone.

2. Agonist-Antagonists. A. PENTAZOCINE, CYCLAZOCINE, AND NALORPHINE. The cardiovascular effects of the agonist-antagonist pentazocine have been most extensively studied in man. Five successive doses of pentazocine administered at 15-min intervals to a total dose of 3 mg/kg increased blood pressure and pulse rate in unanesthetized subjects. Meperidine (5 mg/kg) and fentanyl (0.005 mg/kg) produced a lesser increase in blood pressure. Meperidine increased pulse rate while fentanyl decreased it (264). Lee et al. (162) found that pentazocine (60 mg) increased systemic and pulmonary pressure and resistance in patients who had an acute myocardial infarction. Morphine (15 mg) and meperidine (100 mg) did not produce a significant increase in systematic pressure and resistance nor a lesser increase in pulmonary pressure than did pentazocine. In the thiopental-barbital-anesthetized dog pentazocine and, to a lesser degree, nalorphine decreased blood pressure. Cyclazocine produced a greater fall in blood pressure (106) and a dose-related decrease in heart rate. Pentazocine also decreased heart rate while nalorphine had little effect.

B. KETAZOCINE AND ETHYLKETAZOCINE. Ketazocine depressed diastolic blood pressure and slowed heart rate in the pentobarbital-anesthetized dog (43). Martin et al. (184) and Gilbert and Martin (86) found no significant changes in heart rate in the chronic spinal dog after graded doses of ketazocine or ethylketazocine. Ethylketazocine slows heart rate and decreases blood pressure in the acutely decerebrated unanesthetized dog, effects which are naloxone antagonizable (289a).

C. N-ALLYLNORMETAZOCINE. N-allylnormetazocine administered intravenously in the acutely decerebrate dog produced a transient fall in blood pressure and an increased pulse rate.

D. BUTORPHANOL. Butorphanol produces little effect on or a slight fall in blood pressure in the pentobarbital-anesthetized dog (217, 242). In man, it does not appear to decrease blood pressure, heart rate, or systemic resistance but does increase pulmonary resistance (219).

E. NALBUPHINE. Romagnoli and Keats (227) studied nalbuphine in patients with coronary artery disease who underwent cardiac catheterization. Neither nalbuphine (10 mg) nor morphine (10 mg) produced a significant alteration on any parameter. Lee and Mason (162a) on the other hand found that nalbuphine slowed heart rate and produced a transient increase in pulmonary resistance.

3. Antagonists. Narcotic antagonists have been reported to increase, decrease, and produce no effect on blood pressure and pulse rate; however, they clearly

antagonize the vasodepressor and the cardiac slowing effect of opiate-type analgesics [cf, Martin (173)]. Naloxone under usual circumstances has little effect on blood pressure or pulse rate in man (73, 243, 285). Under certain conditions narcotic antagonists do affect blood-pressure. Naloxone decreases the fall in blood pressure associated with sleep in man (232) and the increase in blood pressure associated with skin stimulation in the halothane-anesthetized dog (161). Conscious rats made hypotensive by bleeding (63), and *Escherichia coli* endotoxin (64, 118) as well as pentobarbital- and halothane-anesthetized rats made hypotensive by spinal cord transection (C-7) showed a significant increase in blood pressure after the administration of naloxone. The *l*-isomer of naloxone produced this effect while the *d*-isomer was inactive in rats treated with endotoxin (65). Naloxone also increases blood pressure in pentobarbital-anesthetized dogs made hypotensive by bleeding and endotoxin (120). Dashwood and Feldberg (49) found that naloxone increased blood pressure in cats that had undergone extensive surgical procedures; this effect was abolished by a renalectomy and a partial sympathectomy.

Naloxone increases blood pressure and pulse rate in the acutely decerebrated dog (289). Both Martin et al. (192) and Gritz et al. (97) found that naltrexone increased diastolic blood pressure in man. Jacob and Michaud (125) and Martin et al (184) found that naloxone and naltrexone produce an erratic increase in pulse rate in the intact and chronic spinal dog.

4. Conclusions. Morphine appears to have two effects on vasomotor systems of the central nervous system—a stimulatory effect that may be a consequence of activation of a chemoreceptor in the subfornical area (26), with a consequent increase in sympathetic tone; and a depressant effect in which neurones in the brain stem are depressed, decreasing sympathetic tone and increasing vagal tone. These actions are antagonized by naloxone and other narcotic antagonists. The vasodepressor effect seems to predominate in anesthetized animals. It also stimulates some brain-stem neurones; however, this effect is not antagonized by naloxone. The overall effect of narcotic analgesics in man is to produce a modest decrease in peripheral resistance and heart rate. Agonist-antagonists seem to produce a modest increase in vasomotor tone. This may be a consequence of their antagonizing an endogenous ligand or a consequence of another type of agonistic activity. κ-Agonists, which appear to have only modest effects on cardiovascular function in the intact dog, have a marked depressant effect in the acutely decerebrated dog. The σ-agonist N-allylnormetazocine appears to activate some brain-stem vasomotor processes. Under certain pathological processes, endogenous opioid processes are recruited, which have a pernicious depressant action on cardiovascular function probably at a medullary level. These actions can be antagonized by narcotic antagonists. It would seem on the basis of existing data that endogenous opioid peptides have little effect on blood pressure regulation under normal circumstances in man.

D. Pupils

1. Narcotic Analgesics. The predominant effects of narcotic analgesics on pupillary diameter vary from species to species. Constriction predominates in dog, rabbit, and man whereas dilation predominates in the cat and monkey. Although the miotic effect of narcotic analgesics has been generally assumed to be due to its actions on the oculomotor nucleus, direct evidence for this has been obtained only in the dog. Lee and Wang (163) found that intraventricularly administered morphine caused pupillary constriction. Even large doses of morphine did not cause miosis after destruction of the oculomotor nerve. Intraocular morphine did not cause miosis. Pupillary constrictor neurones of the oculomotor nucleus exhibited an increase in firing rate when morphine was administered intravenously. In the cat, the mydriatic effect of morphine is not only abolished by adrenalectomy, adrenalectomy reveals a miotic effect (280). The mydriatic action of morphine in the cat may be related to its hyperglycemic effect (see section II C). Fanciullacci et al. (66) have shown that naloxone applied topically to one eye of a morphine-dependent subject causes mydriasis in that eye (anisocoria). This finding suggests that there may be opioid receptors in the eye.

2. Effects in Man. A. NARCOTIC ANALGESICS. Fraser et al. (75) emphasized the value of measuring pupillary diameter in studying the time action course and relative potency of narcotic analgesics. Subsequently the ability of several drugs to constrict pupils in man have been compared by using morphine as a reference drug. Table 4 shows the relative potency of several prototypic agonists and agonist-antagonists in constricting pupils with their ability to produce analgesia. A more extensive analysis of data that was acquired at the Addiction Research Center on the effects of analgesics on pupillary diameter can be found in the definitive review of Jasinski (128). As can be seen there is excellent agreement between the potencies of narcotic analgesics in producing miosis and analgesia in man. Man is quite sensitive to the miotic actions of morphine with 0.5 mg/kg producing a near maximal degree of miosis. Chronic administration of morphine and methadone produce a tonic constriction of pupils which does not change even though patients may be chronically intoxicated with these drugs for months (189, 191).

The morphine-like partial agonist propiram and profadol produce maximal miosis and the dose response lines have slopes similar to morphine's (134).

B. AGONIST-ANTAGONISTS. The miotic effect of nalorphine was first described by Wikler et al. (284). Levallorphan and pentazocine also constrict pupils [see Mar-

TABLE 4

Relative potency of narcotic analgesics, partial agonists, and agonist-antagonist in producing miosis and analgesia in man and dogs. Relative potencies are expressed as milligrams of morphine equivalent to 1 mg of the drug

	Pupils		Analgesia		
	Man	Dog	Man	Dog, flexor reflex	Dog, skin twitch reflex
Analgesics					
Codeine (IM and IV)	0.06–0.07[2]	0.07–0.14[5]	0.05–0.06[2]	0.06[5]	0.1[8]
d-Propoxyphene (IV, 0)	0.06[2]	ca 0.16[7]	0.03[2]	0.12–0.19[7]	0.12[7]
Meperidine (SC)	0.07[2]	Dilates[8]	0.09[2]	DRNP*,[8]	0.26[8]
Partial agonists					
Propiram (IV, SC)	0.12[2]	0.11[4]	0.10[2]	0.14–0.17[4]	DRNP[4]
Buprenorphine	25–50[2]	95[7]	30–40[2]	118–160[7]	69[7]
Agonist-antagonists					
Pentazocine	0.17 (DRNP)[2]	0.24[4]	0.16[1]	0.3	0.25[3], DRNP[4]
Nalorphine	1	0.24[4]	0.7[6]	0.55[4]	DRNP[4]

* DRNP, dose response lines not parallel.
[1] Beaver et al. (6).
[2] See Jasinski (128) for primary references.
[3] Jasinski et al. (135)
[4] Gilbert and Martin (86).
[5] Martin et al. (182).
[6] Martin et al. (185).
[7] Martin et al. (184).
[8] Martin et al. (186).

tin (173) for citations]. In man, both cyclazocine and nalorphine produce a dose-related decrease in pupillary diameter and the slopes of the dose response lines are similar to morphine's (185). In one study the cyclazocine dose response curve plateaued at a dose level of 2 mg/70 kg and may have become biphasic (185). The slope of the pentazocine dose response line for producing pupillary constriction was less steep than morphine's and 40 mg/70 kg of pentazocine was judged to produce the same degree of miosis as 10 mg/70 kg of morphine (135). Nalbuphine in doses of 8, 24, and 72 mg/70 kg produced miosis equivalent to 10 mg/70kg of morphine. A clear-cut ceiling effect was observed (133). Butorphanol (2, 4, and 8 mg) produced a biphasic effect on pupillary diameter. A dose-related miosis was observed with the 2 and 4 mg with butorphanol being 3 to 4 times more potent than morphine. The 8-mg dose of butorphanol produced a lesser degree of miosis than the 4-mg dose.

C. NALOXONE AND NALTREXONE. Neither naloxone nor naltrexone administered in single doses produced any significant effect on pupillary diameter (134, 192). Very large doses of naloxone administered chronically did not alter pupillary diameter.

3. Effects in Dogs. Narcotic analgesics and opioid agonist-antagonist produce miosis in the dog. The dog is less sensitive to the miotic actions of morphine than is man. Whereas 0.5 mg/kg of morphine produces maximal miosis in man, over 2 mg/kg are necessary to produce maximal miosis in the dog. Further there are indications of spurious reactions to some presumed opioid analgesics (see table 5). Thus meperidine does not produce miosis in the dog and large doses (4 mg/kg) produce mydriasis. However, the strong agonists propoxyphine as well as partial agonists of the morphine type such as propiram and buprenorphine (184) produce a dose-related miosis. There was no difference in the degree of miosis produced by 0.016 and 0.064 mg/kg of buprenorphine. Nalorphine, pentazocine, and butorphanol produce a modest degree of miosis equivalent to about 0.4 mg/kg of morphine (86, 217); and larger doses did not produce more miosis. Very large doses of nalorphine (64 mg/kg) produced mydriasis (87). A small dose of cyclazocine (0.016 mg) produced a modest degree of miosis while larger doses produced mydriasis (86, 196). A biphasic pupillary diameter dose response curve in which low doses produced miosis and larger doses produced mydriasis was more obvious for diprenorphine. Both ketocyclazocine and ethylketocyclazocine produced a dose-related miosis. The slope of ethylketocyclazocine dose response curve was steeper than morphine's while ketocyclazocine was less steep. N-allylnormetazocine produced a dose-related mydriasis. Naltrexone did not alter pupillary diameter in the dog.

4. Conclusions. Table 5 summarizes the slopes and configurations of dose response relationship for the effect of opioid agonists, agonists-antagonists and antagonists on pupillary diameter in comparison to morphine in the dog. All agents constrict pupils except naltrexone and meperidine. The fact that naltrexone does not dilate pupils would argue for two propositions: 1) There are no natural opioid agonists modulating pupillary diameter under the conditions of the experiments conducted in the chronic spinal dog; and 2) it is unlikely that the mydriatic action of agonist-antagonists and N-allylnormetazocine are a consequence of the antagonistic action. The nature of meperidine's mydriatic action is not known but could be a consequence of its cholinolytic activity.

The agonist-antagonists cyclazocine, nalorphine, and butorphanol as well as N-allylnormetazocine produce

TABLE 5

Effects of narcotic analgesics (agonists and partial agonists), κ agonist, agonist-antagonists, σ agonist and antagonists on pupil diameter, slopes of dose response lines and subjective effects in comparison to morphine

	Miosis	Same or Greater Slope	Lesser Slope	Plateau	Biphasic	Mydriasis	Psychotomimetic in Man
Narcotic analgesics							
Propoxyphene	+*	+	0†	0	0	0	0
Propiram	+	+	0	0	0	0	0
Buprenorphine	+	+	0	0	0	0	0
Meperidine	+	0	0	0	0	+	0
			0				
κ Agonists							
Ethylketocyclazocine	+	+	0	0	0	0	−‡
Ketocyclazocine	+	0	+	0	0	0	−
Agonist-Antagonists							
Cyclazocine	+	−	−	−	+	+	+
Nalorphine	+	+	0	+	+	+	+
Pentazocine	+	+	0	+	−	−	+
Butorphanol	+	+	0	+	−	−	+
Diprenorphine	+	+	0	0	+	+	−
σ Agonists							
N-allylnormetazocine	0	0	0	0	0	+	+
Antagonists							
Naltrexone	0	0	0	0	0	0	0
Naloxone	0	0	0	0	0	0	0

* +, Produces effect.
† 0, Does not produce effect.
‡ −, Effect not known.

mydriasis in the dog and are psychotogens in man. It is not known whether diprenorphine is a psychotogen in man. These agents as well as ethylketocyclazocine and ketocyclazocine also produce miosis. The configuration of their miotic dose response lines are different. Thus ethylketocyclazocine has a steeper dose response than morphine's and ketocyclazocine has a less steep slope. Further the slope of the linear portion of nalorphine's and butorphanol's dose response lines are the same as morphine's yet they exhibit a plateau indicating that these drugs are partial agonists. These observations are perplexing for the slope of the dose response line of a partial agonist should be less steep than that of a strong agonist. The plateau of the nalorphine is broad extending over a 20-fold range of doses while the diprenorphine dose response curve has a V-shaped configuration. This can be explained by assuming that nalorphine is a partial agonist at the κ receptor and agonist at the σ receptor whose affinity for the κ receptor is 10 or 20 times greater than its affinity for the σ receptor. In contrast diprenorphine affinity for the κ receptor may only be 2 or 3 times its affinity for the σ receptor. The difference between cyclazocines affinity for the κ and σ receptor may be even less than diprenorphine's which would be consonant with clinical observations. In man hallucinations induced by agonist-antagonists are associated with miosis and are produced by small doses only several times necessary to produce analgesia. In the dog over 10 times the analgesic dose of cyclazocine and nalorphine are required to produce mydriasis and canine delirium (86, 87). This suggests that the dysphoric and hallucinatory effects of these drugs may not be associated with their mydriatic action.

E. Electroencephalogram (EEG) Changes, Convulsions, and Levels of Consciousness

1. EEG Changes. The older literature concerning the effects of opioid analgesics and antagonists on the EEG have been reviewed by Martin and Kay (194) and the primary reference for the following generalizations can be found in this publication. In man several narcotic analgesics including morphine, meperidine, methadone, ketobemidone, and heroin slow α activity and increase δ activity. Fentanyl also decreases awareness and produces a slow wave EEG. These effects are antagonized by naloxone (155). Volavka (277, 278) found that both naloxone and naltrexone produced a slight slowing of α rhythms in man. In animals including cats, dogs, monkeys, rats, and rabbits several opiates of diverse chemical structures (morphine, meperidine, dextromoramide) increased δ activity and on some occasions increased spindle activity. Opiate analgesics have generally been reported to decrease activation of the EEG produced by nociceptive stimuli as well as other sensory modalities. Not all studies have supported this conclusion, however (201, 220).

After either intravenously or intraventricularly administered morphine in the dog or rabbit, a period of EEG desynchronization is frequently seen associated with behavioral activation, increased respiratory rate, and bradycardia (3, 207). This is followed by behavioral sedation and a predominantly synchronized EEG. Albus and Herz (3) administered morphine in the third and fourth ventricles. There was little change in the EEG or the threshold for EEG activation produced by electrical stimulation of the paw when morphine was administered

into the third ventricle; however, when morphine was restricted to the fourth ventricle, EEG synchrony as well as an increase in activation threshold was observed. These authors suggest that morphine may be activating a medullary synchronizing center. Fentanyl produced a modest slowing of the frequency of the EEG of the cerveau isole cat while increasing the EEG frequency of the intact cat (77). Freeman and Ingvar (77) suggested that fentanyl had an excitatory action mediated through the reticular formation. Wettstein, Kamerling, and Martin (unpublished observations) have observed that microinjection of fentanyl into the periaqueductal gray (PAG) matter produces a dose-related increase in EEG synchrony. Neither ethylketazocine nor naltrexone had this action. Naltrexone given intravenously and into the fourth ventricle produced EEG slowing and synchronization.

Morphine may increase spindle activity in the medial thalamus of the rat and decreases unit activity and evokes paroxysmal spiking in the hippocampus (166). It did not markedly alter hippocampal unit activity. The effects of morphine, methadone, *l*-α-acetylmethadol (LAAM), norLAAM, and dinorLAAM on the EEG and behavior have been studied in the rat (170). Both methadone and morphine produce alternating episodes of stuporous behavior and arousal for all doses. LAAM, norLAAM, and dinorLAAM also produced alternating episodes of stupor and arousals; however, a greater percentage of time was spent in a state of arousal than stupor.

Pickworth and Sharpe (215) found that ethylketazocine and ketazocine as well as morphine increased δ activity (1 to 3 Hz) in the intact dog. These changes were associated with stupor, immobility, catalepsy, and ataxic walking. The EEG and behavioral effects were antagonized by naloxone; however, it took about 30 times as much naloxone to antagonize ethylketazocine and ketazocine effects as it did to antagonize morphine's effects. Young et al. (294) studied the EEG changes of the prototypic agonists; morphine (μ), ethylketazocine (κ), and N-allylnormetazocine (σ) in the rat. Morphine greatly enhanced slow wave EEG activity below 10 Hz while ethylketazocine increased activity in the 4 to 7 Hz range. N-allylnormetazocine produced an increase in EEG activity at about 7 to 8 Hz. Morphine and ethylketazocine produced behavioral depression and N-allylnormetazocine behavioral arousal.

2. *Opiate-induced Convulsions.* Animals that exhibit high slow waves and repetitive apparent spindles after the administration of narcotic analgesics may abruptly exhibit convulsive activity characterized by high voltage high frequency spikes. Spike and wave configurations may also be seen. The convulsions produced by opiates differ in their overt manifestations. Heroin, propoxyphene, and meperidine produce clonic convulsions in mice and death infrequently ensues. Large doses of naloxone produce tonic-clonic seizures. Death does not commonly result. Noremeperidine and thebaine produce tonic-clonic seizures and death. Naloxone was more effective and potent in antagonizing *d*-propoxyphene and heroin than meperidine-, normeperidine-, or thebaine-induced seizures (85). Naloxone is effective in antagonizing seizures produced by γ-hydroxybutyrate (254). Limbic seizures evoked by the intraventricular administration of β-endorphin in the rat are also prevented by naloxone. Diazepam and phenytoin attenuated but did not abolish β-endorphin-induced seizures while haloperidol, amphetamine, apomorphine, and scopalamine were devoid of antagonistic activity (112). Leucine-enkephalin injected into the lateral ventricle of rats caused cortical seizures which were antagonized by ethosuximide, trimethadione, and sodium valproate but not by clonazepam, phenobarbital, or phenytoin. Diazepam produced some attenuation of seizures (253). Repeated injections of methadone produced EEG spikes in monkeys and naloxone treatment evoked convulsions in these animals (255).

Morphine and methionine-enkephalin and leucine-enkephalin administered intraventricularly evoked cortical seizure activity and increased firing of neurones of the PAG (79, 270). Methionine-enkephalin injected into the dorsal medial nucleus of the thalamus produced seizure activity; methionine-enkephalin injected into the PAG produced analgesia (79). Naloxone antagonizes these seizures (80). When morphine and levorphanol are injected unilaterally into the anterior amygdala, high voltage spikes and slow waves were produced which projected to the contralateral anterior amygdala. Dextrorphanol was devoid of activity (266). Aloisi et al. (4) studied the effect of intraventricularly administered morphine as well as several opioid peptides including leucine and methionine-enkephalin on seizure activity in the rabbit. Morphine produced a brief period of excitation followed by both EEG and motor convulsive activity including grand mal seizures. The opioid peptides produced EEG synchrony and spikes, blockade of the arousal responses and associated stupor, rigidity, and catatonia. In the rat both morphine and the opioid peptides produced EEG and behavioral seizures. Nalorphine antagonized seizure activity in both rats and rabbits.

Cowan et al. (44) have studied the effects of several opioids in altering fluothyl-induced seizure in rats and have identified four classes of drugs: 1) Those that attenuate fluothyl seizures but whose anticonvulsant effect is not antagonized by naloxone (N-allylnormetazocine and cyclazocine); 2) those whose anticonvulsant activity is antagonized by naloxone (morphine, methadone, phenazocine, levorphanol, buprenorphine, and etorphine); 3) those that had little anticonvulsant activity (ketazocine, ethylketazocine, nalorphine, normorphine, and nalbuphine); and 4) those that lowered fluothyl seizure threshold [pentazocine (particularly the +-isomer), meperidine and normeperidine]. The proconvulsant effect of the group 4 opioids was enhanced by a subconvulsant dose of naloxone.

3. *Levels of Consciousness.* Although opiates increase

EEG slow wave activity they also decrease sleep. Kay et al. (145) found that morphine produced a dose-related increase in waking time and light sleep (stages 1 and 2), a decrease in deep sleep (stages 3 and 4), and a decrease in rapid eye movement (REM) sleep in human subjects who had a history of heroin use. Heroin produced similar changes and in this regard was 1.2 to 2.0 times more potent than morphine (146). This potency estimate is similar to its estimated potency in producing analgesia (see section II A), constricting pupils (see section II D), and producing subjective effects (see section III).

4. Conclusions. Perhaps the oldest view of opioid drugs is that they alter consciousness by decreasing sensory input particularly by attenuating transmission of painful impulses, thus increasing the probability of sleep, the production of stupor, and a slow wave EEG. In animals stupor and a slow wave EEG are preceded by a period of arousal and EEG desynchronization. Both are apparently due to a central action of morphine since these changes are seen following both intracerebral and systemic administration.

The significance of the EEG slow wave activity produced by opioids is not known. The work of Young et al. (294) is particularly important in that it indicates that the prototypic μ, κ, and σ agonists produce different EEG slow wave patterns suggesting that opioid-induced changes in EEG rhythms cannot be placed on a sleep-wakefulness continuum. The ability of opiates to produce generalized seizures is well recognized and has been for the most part viewed as an undesirable side effect. It is apparent that opioids exert both their convulsant and anticonvulsant activity through several modes of action and probably through several receptor mechanisms which may well be distinct from better characterized opioid receptors. Further, these receptors and possibly endogenous opioid agonists may have psychopathological implications particularly as they regulate the functioning of the limbic system.

F. Temperature Regulation

The effects of opioid analgesics on body temperature are complex and dependent upon dose, species, presence of tolerance and dependence, ambient temperature and the time after administration. It now appears that there are multiple opioid receptors involved in temperature regulation. Clark (35) has recently reviewed much of the literature from 1970 to the present which bears on the issue of multiple opioid receptors and temperature regulation.

1. Phenomenology of Effects of Opioid Analgesics on Body Temperature. The literature on the effects of opioid analgesics on body temperature in different species is extensive. Only a small portion of it will be cited to illustrate several important principles with regard to the effects of opioid analgesics in several species.

Rosow et al. (229) studied the effects of different doses of a variety of opiates on body temperature of mice treated with several narcotic analgesics and observed at different ambient temperatures (20°, 25°, and 30°C). Morphine produced both hypo- and hyperthermia. The hypothermic response predominated at 20°C and hyperthermia at 30°C. Hydromorphone, levorphanol, oxymorphone, methadone, etonitazene, fentanyl, etorphine, and anileridine generally shared this pattern. Hypothermia was seen at 20°C following administration of meperidine and codeine; however, significant hyperthermia was not seen at 30°C. Cowan and MacFarland (45) found that cyclazocine and morphine lowered body temperature in mice. Very large doses of naloxone and naltrexone decreased body temperature in mice while a dose of naloxone well above that which antagonized both the hypo- and hyperthermic effect of morphine was without effect (230). The hypothermic effect of naloxone and naltrexone was greatest at lower ambient temperatures. Rosow et al (231) also studied a series of agonist-antagonists among which were κ-σ agonists, μ antagonists, and partial agonists. The partial agonists, nalorphine, buprenorphine, and nalbuphine produce modest hyperthermia at ambient temperatures of 20°C and 30°C. Ketazocine, a κ agonist, like morphine produced a dose-related fall in body temperature at 20°C and a modest rise at 30°C. N-allylnormetazocine, a μ antagonist and σ agonist, produced predominantly hyperthermia. Of the other drugs studied, only cyclazocine and pentazocine have been well characterized in the spinal dog and man. These drugs are μ antagonists and κ agonists with differing degrees of σ agonistic activity. Low doses of cyclazocine produced hyperthermia at both 20° and 30°C. The hyperthermic effect of a low dose of pentazocine was smaller. Larger doses of both drugs produce hypothermia at 20° and 30°C. The hypothermia effect seen at 30°C was also produced by levallorphan and butorphanol. There is reasonably good agreement between the relative potency of these opioids in producing hypothermia and analgesia (hotplate technique) in mice; however, the doses required to produce hypothermia were 100 times greater than those required to produce analgesia.

Morphine also produces a biphasic effect on body temperature in the rat (99, 113, 211, 249). Hypothermia preceded hyperthermia and is dose-related. Hyperthermia may be the predominant effect of analgesic dose levels. Lotti et al. (168) produced hypothermia in rats by injecting morphine into the anterior hypothalamus. Morphine injected into the ventromedial hypothalamus produced a dose-related increase in body temperature and an increase in food consumption (268). Rudy and Yaksh (233) found that morphine in doses as low as 2 μg injected subdurally in the lumbar region of the spinal cord of rats produced an increase in rectal temperature. The degree of hyperthermia was independent of the ambient temperature. Naloxone administered intraperitoneally and intrathecally antagonized the hyperthermic effects of morphine injected intrathecally and intraperitoneally, respectively. Methadone and meperidine as well as morphine may produce a modest hypothermia which is enhanced by lowering ambient temperature (209). In rats

pretreated with *p*-chlorophenylalanine, morphine causes a hyperthermia (209, 211). Raphe lesions abolish both the hypo- and hyperthermia actions of morphine (235). Cyclazocine and diprenorphine decreased body temperature in the rat while morphine produced hyperthermia (45). Naloxone (0.5, 3.0, and 10 mg/kg) may produce both a small to moderate decrease (45, 90) and a small increase (46) in the body temperature of the rat. Large doses of naltrexone (80 and 160 mg/kg) produce hypothermia (5). Martin et al. (192) and Gritz et al. (97) observed that naltrexone produced a small but significant decrease in body temperature in man. Hyperthermia produced by a low dose (4 mg/kg) of morphine was not antagonized by naloxone. Hyperthermia in the acutely dependent rat can probably be antagonized by naloxone (46). Adler et al. (1) classified opioid analgesics into four groups on the basis of their effects on rat body temperature: 1) Analgesics that produced a low dose hyperthermia and a high dose hypothermia which were stereo specific and naloxone antagonizable (morphine and levorphanol); 2) opioids that produced only hyperthermia (buprenorphine); 3) hypothermia (ethylketazocine); or 4) little effect (N-allylnormetazocine).

Nalorphine produced a modest hypothermia when injected into the anterior hypothalamus of the rat (169). Pentazocine and buprenorphine produced hyperthermia when administered systemically to rats (1). In contrast, ethylketazocine and normeperidine produced hypothermia while N-allylnormetazocine had little affect on temperature [also see Ward et al. (281)]. Ward et al. (281) found that ketazocine produced hyperthermia in the rat. The effects on temperature produced by buprenorphine and normeperidine were not antagonized by naloxone. Naloxone administered into the ventromedial hypothalamus of the rat did not alter body temperature (268).

Morphine produces hyperthermia in the cat while in the dog it produces a dose-related hypothermia. Other morphine-like drugs such as codeine, *d*-propoxyphene, fentanyl, as well as FK 33-824, depress body temperature in the chronic spinal dog. Nalorphine, pentazocine, cyclazocine, normorphine, propiram, and buprenorphine also produced some depression of body temperature; however, the slope of their dose response lines were less steep than morphine's. Meperidine, oxilorphan, diprenorphine, naltrexone, ketazocine, ethylketazocine, and apomorphine did not alter body temperature at any doses studied (84, 86, 184, 186). N-allylnormetazocine did not significantly alter body temperature in the chronic spinal dog although there was a trend toward hyperthermia. Although morphine depresses the temperature homeostat in the dog, homeostasis is maintained at a lower level utilizing heat conserving, producing, and dissipating mechanism (174). Morphine produced hypothermia in both the low (T-10) and high (C-5 or C-6) spinal dogs indicating that the spinal cord actions of morphine plays little role in this response in the dog (181). Naloxone and naltrexone do not appear to alter body temperature of the chronic spinal dog (184).

Morphine hyperthermia in the cat can be evoked by either parenteral or intracerebrally administered morphine and antagonized by naloxone (34, 45, 78, 200). It is not dependent on the ambient temperature (36). Naloxone and naltrexone do not alter body temperature in the cat (34, 78) and naloxone does not antagonize fever induced by leukocyte pyrogen injected into the third ventricles of cats (37).

Pentazocine produces a biphasic effect on temperature in the cat when injected into the third ventricle. Initially, there is a hypothermia persisting several hours followed by a long-lasting hyperthermia. Neither effect was antagonized by naloxone (34). Ketazocine also produces hyperthermia in the cat and this effect is not antagonized by naloxone (45).

In contrast to morphine, small doses intracerebrally injected, D-Ala^2-methionine-enkephalinamide (D-Ala) causes a naloxone antagonizable hyperthermia in the cat that is dependent upon the ambient temperature. Larger doses of D-Ala produce hypothermia in the cat which is also antagonized naloxone. FK 33-824 (Tyr-*d*-Ala-Gly-MePhe-Met-(0)-ol) is exceptionally effective in producing a temperature dependent, naloxone antagonizable hyperthermia when injected into the third ventricle (39). These observations have led Clark to postulate four opioid receptors [μ (ν_1,) ν_2, ν_3, and ν_4] involved in temperature regulation in the cat (35).

2. Conclusions. It is clear that opioid analgesics alter body temperature by acting at several sites including the spinal cord, medullary raphe system, and the anterior and the ventromedial hypothalamus. The opioid analgesics also exert their effect on temperature regulation through both naloxone antagonizable as well as naloxone resistant mechanisms. Opioid peptides may exert their effects through yet other receptor mechanisms. Clark has postulated that the cat has brain receptors involved in temperature regulation that have not been identified in dog, rat, or mouse. The fact that neither naloxone nor naltrexone markedly alter body temperature suggest that endogenous opioid transmitters probably play a modest role in temperature regulation under normal physiological conditions.

III. Psychological Effects of Opioids

The psychological effects of opioids have been dealt with in depth by Lal (155a). It is the intent of this section to briefly review the subjective effects produced by a variety of opioid analgesics and agonist-antagonists and the results of experiments with these same drugs that have been studied as discriminative stimuli in animals particularly as to their bearing on the concept of multiple opioid receptors.

A. Subjective Effects in Man

1. Nalorphine, Cyclazocine, and Morphine. The early literature on the subjective effects produced by agonists-antagonists in abstinent prisoner narcotic addicts has been reviewed by Martin (173) and Haertzen (103, 104).

In studies of cyclazocine, three distinct types of subjective effects produced by these agonist-antagonists were identified: 1) Feelings of well being; 2) sedation, tiredness, grogginess, drunkenness, and sleepiness; and 3) dysphoria which consisted of a variety of changes including racing thought, irritability, inability to concentrate, and delusion and hallucinations. Feelings of well being produced by narcotic analgesics (185) are difficult to distinguish from those produced by agonist-antagonists; however, this constellation of subjective effects is clearly different from those produced by narcotic analgesics. Haertzen (102), while developing a subjective effect scale for narcotic antagonists by using the Addiction Research Center Inventory (ARCI), compared cyclazocine (0.6 and 1.2 mg/70 kg) and nalorphine (16 and 32 mg/70 kg) with morphine (15 and 30 mg/70 kg) and pentobarbital (125 and 250 mg/70 kg). Both cyclazocine and nalorphine produced a dose-related elevation of the General Drug Effect; Pentobarbital, Chlorpromazine, and Alcohol pattern (PCAG) and the LSD scales and a dose-related decrease of the Morphine Empirical and Efficiency scale scores. Relative potencies obtained with these scales indicated that cyclazocine was from 15 to 26 (mean = 22) times more potent than nalorphine. These potency data, by and large, agreed with observations made with the Addiction Research Center Single Dose Questionnaire in which single doses of both nalorphine and cyclazocine produced a dose responsive increase in feelings of sleepiness, drunkenness, and dysphoria (185, 187). An unexplained discrepancy between reported subjective feelings and behavior was the observation that cyclazocine produced gross ataxia while nalorphine produced only a barely detectable degree of ataxia.

l-Cyclazocine was twice as potent as *d,l*-cyclazocine in precipitating abstinence in morphine-dependent subjects and twice as potent as *d,l*-cyclazocine in elevating scores on the LSD and PCAG scales (140); these effects were observed with small doses of *l*-cyclazocine (0.2, 0.4 and 0.8 mg/kg). *l*-Oxilorphan also produced elevated scores on the LSD and PCAG scales as did large doses of dextromethorphan (139). Naloxone decreased the subjective effects produced by cyclazocine as well as its miotic and respiratory depressant effects (138).

2. *Morphine-like Agonists.* A short item questionnaire was constructed which contained items from ARCI LSD, PCAG, and Amphetamine [also morphine-benzedrine group (MBG)] scales (134). These groups of items were intended to identify the dysphoric (LSD), sedative (PCAG), and euphoric (MBG) subjective effects produced by opioid agonist-antagonists.

Morphine was used as control drug for most studies of the agonist-antagonists. In most studies morphine produced a dose-related increase in the Amphetamine or MBG subscale scores as did the strong opioid agonists heroin, methadone (139), dilaudid (131), meperidine (140), and codeine (129). The effects of morphine on PCAG scale scores have varied from one study to another. In some studies morphine produced a dose-related increase in the PCAG scale scores (134, 135, 141), in other studies no change (136). Jasinski et al. (141) found that the increase in PCAG scores appeared after the elevation of the MBG scale scores and persisted longer. Partial morphine-like agonists such as profadol, propiram, and buprenorphine also produced dose-related increases in both MBG and PCAG scale scores (136, 141).

Smith and Beecher (250) and Smith et al. (251) compared the effects of heroin (4 mg) and morphine (10 mg) on subjective state and mental functioning in young college students. Both drugs produced mental clouding, feelings of dejection, unfriendliness, anxiety, insecurity, and a slowing of performance on a variety of psychological tests. These subjects reported little in the way of feelings of well being and euphoria as has been observed in abstinent narcotic addicts although an improvement of mood was observed in subjects who had received heroin during a free period in which subjects were not involved in test taking. The taking of long and complicated psychological questionnaire may decrease narcotic and opiate-induced feelings of well being and increase feelings of apathetic sedation.

3. *Pentazocine.* Pentazocine produces psychotomimetic and dysphoric effects (6, 105) in a clinical setting. In a systematic assessment of the subjective effects produced by graded doses of pentazocine (10, 20, 40, 60 mg/70 kg), Jasinski et al. (135) found that only the 40 mg/70 kg-dose of pentazocine produced a significant elevation of the MBG scale score which was equivalent to that produced by 10 mg of morphine. Only the 60 mg/70 kg-dose of pentazocine produced a significant elevation of the PCAG and LSD scale scores which were equivalent to that produced by 10 mg/70 kg of nalorphine. Hamilton et al. (105) also observed the emergence of psychotomimetic effects with a 60-mg dose of pentazocine in preoperative female patients.

Jasinski et al. (135) observed severe psychotomimetic effects in patients, who were dependent on 240 mg of morphine a day in addition to signs of abstinence following doses of 120 to 140 mg/70 kg of pentazocine. The psychotomimetic effects persisted longer than signs of precipitated abstinence. These observations indicate that there was no cross tolerance to pentazocines psychotomimetic effects in morphine-tolerant patients. However, patients receiving pentazocine chronically in doses of over 110 mg every 4 hr did not report dysphoric or psychotomimetic effects (135). The dysphoric and psychotomimetic effects of pentazocine can be antagonized by naloxone (W. T. Beaver, personal communication).

4. *Nalbuphine.* The subjective effects of graded doses of nalbuphine (8, 24, and 72 mg/70 kg) have been compared to morphine (10 and 30 mg/70 kg) in imprisoned abstinent narcotic addicts. The 24 and 72 mg/70 kg produced liminal elevations of the MBG and LSD scale scores. The effect of 72 mg on the MBG was similar to that produced by 8 mg of morphine. Nalbuphine produced a dose-related increase of the PCAG scale scores (133).

5. Butorphanol. Two studies were conducted by Jasinski et al. (130) comparing the subjective effects of butorphanol with morphine in one and with morphine, cyclazocine, and pentazocine in the other. Butorphanol (2, 4, and 8 mg) did not produce a significant elevation of the MBG score in either study and resembled cyclazocine and pentazocine in this regard. Like pentazocine and cyclazocine it produced significant and dose-related elevations of the PCAG and LSD scale score whereas morphine did not.

6. Oxilorphan (l BC 2605). Oxilorphan produced a dose-related increase on the PCAG and LSD scale scores (140).

7. Naloxone and Naltrexone. The subjective effects of doses of 6, 12, and 24 mg/70 kg of naloxone were studied in imprisoned abstinent heroin addicts and were not different from those produced by a placebo. Nalorphine (15 and 30 mg/70 kg) and levallorphan (3.6 and 12 mg/70 kg) on the other hand produced significant and dose-related increases of LSD and PCAG scale scores (134). Naloxone in a dose of 1 mg completely antagonized the effects of 25 mg of morphine (192). When naloxone was administered chronically (90 mg every 4 h), observers reported that subjects were intermittently sleepy, tired, and irritable; however, no equivalent observations were made in control subjects so the importance of the observation were not evaluated (134). Although Grevert and Goldstein (94) found that naloxone enhanced feelings of anxiety and tension in patients participating in an experimental pain study, this finding was not confirmed in another study (96).

No consistent subjective effects were produced in imprisoned addicts by naltrexone (0.01 to 80 mg) in dose-ranging studies (192). Further, the subjective effects of a 30-mg dose of naltrexone administered orally were not different from those observed following the administration of the vehicle. Gritz et al. (97) found that naltrexone decreased scores on the MBG scale of the ARCI, a scale which measures feeling of well being.

Patients participating in studies in which they received large doses of naltrexone chronically for the treatment of narcotic addiction have reported feelings of tiredness, sleepiness, sluggishness, irritability, nausea, vomiting, and decreased appetite as well as insomnia [225, 239; also see Julius and Renault (143) and Martin (176) for references]. These are signs and symptoms of abstinence and thus could have been a consequence of precipitated abstinence in patients with a liminal degree of residual opioid physical dependence. The incidence of side effects in a group of narcotic addicts receiving large doses of naltrexone chronically for the experimental treatment of narcotic dependent was not different from a comparable population receiving a placebo [National Research Council Committee's report on Clinical Evaluation of Narcotic Antagonists (205)].

8. N-allylnormetazocine (SKF 10047). N-allylnormetazocine produced hallucination and dysphoria in subjects but little or no analgesia in maximally tolerated doses (149). Similar activity was seen with a close congener (*Win 29M*) in which a Cl was substituted for a H on the terminal carbon of the allyl moiety.

B. Opioids as Discriminative Stimuli in Animals

Attempts to dissect interoceptive cues and centrally mediated changes in feeling states produced by opioid analgesics in animals have used the phenomenon of state dependent learning. Several procedures have been used. A Y maze in which the floor was shock activated except for a safe area at the end of one arm of the maze when the drug was administered and at the end of the other arm when the animal received the vehicle was one of the earliest procedures used. Animals could be trained to discriminate between the two arms of the maze depending on the drug treatment. Experimental drugs were then administered to the trained animals to determine which arm of the maze would be selected. Modifications of this procedure have consisted of an operant situation in which the animal presses a bar to avoid shock or to obtain a reward. The animal is then given the opportunity of pressing two bars. The pressing of one bar will be rewarding in animals that have received a drug, the pressing of the other bar will be rewarding when the animal has received a vehicle or another type of drug. The details of this methodology are reviewed in detail by Lal (155a) as are the use of opioids as discriminative stimuli. These procedures will be discussed here only as they pertain to multiple opioid receptors and relate to the effects of opioid analgesics and agonist-antagonists in man.

When animals are trained by using morphine as a discriminative stimulus, they generalize to most morphine-like analgesics. Shannon and Holtzman (245–247) found that rats trained on 1.75, 3.0, and 5.6 mg/kg of morphine generalized to profadol and pentazocine over a wide range of doses. Rats trained on 1.75 mg/kg generalized to nalbuphine over a wide range of doses but only partially to cyclazocine. When trained on 3.0 and 5.6 mg/kg of morphine they only partially generalized to nalbuphine and not at all to cyclazocine (5.6 mg/kg). Rats trained on 3.0 mg/kg of morphine generalized to butorphanol and naloxone, and only partially to cyclazocine, nalorphine, levallorphan, ketazocine, and not all to oxilorphan, dextrorphanol, ketamine, or mescaline. Rats trained to discriminate cyclazocine (0.3 and 1.0 mg/kg) generalize to ketazocine, N-allylnormetazocine, phencyclidine, and ketamine but not to mescaline (265). Those rats trained on 0.3 mg/kg of cyclazocine generalized to ethylketazocine, pentazocine, and levallorphan and partially to morphine and nalorphine. Those trained on 1.0 mg/kg only partially generalized to pentazocine, and levallorphan and did not generalize to ethylketazocine, morphine, or nalorphine at all. The discriminative properties of morphine (245) and cyclazocine (265) can

be surmountably antagonized by naltrexone; however, the discriminative properties of morphine appear to be antagonized by smaller doses of naltrexone than those of cyclazocines.

Shearman and Herz (248) found that rats trained with ethylketazocine as a discriminative stimulus generalized to cyclazocine and bremazocine but not to N-allylnormetazocine. Partial generalization to fentanyl and morphine was observed. Rats trained with fentanyl as a discriminative stimulus generalized to morphine but not to cyclazocine, N-allylnormetazocine, and bremazocine. Partial generalization to ethylketazocine was seen. When rats were trained with bremazocine as a discriminative stimulus, they generalized to ethylketazocine, cyclazocine, and N-allylnormetazocine but not to morphine and partially to fentanyl. Naloxone, N-allylnormetazocine, and MR2266 [(1-)-2-(3-furyl-methyl)-5,9-diethyl-2-hydroxy-6,7-benzomorphan] surmountably antagonized the discriminative stimulus properties of both fentanyl and ethylketazocine. Naloxone showed the greatest selectivity for fentanyl, while MR2266 showed the greatest selectivity for ethylketazocine.

Both the squirrel and rhesus monkey have been used in discrimination studies of agonist-antagonists. The squirrel monkey trained with morphine generalized to fentanyl, oxymorphone, levorphanol, methadone, and meperidine but not to dextrorphanol. Naloxone surmountably antagonized the discriminative effect of morphine (238). Rhesus monkeys trained with ethylketazocine as a discriminative stimulus (110), generalized to nalorphine, cyclazocine, cyclorphan, N-allynormetazocine, ketazocine, and 2-(2-methyl-3-furyl-methyl)-2-hydroxy-5,9-dimethyl-6,7 benzomorphan methane sulfonate. They did not generalize to morphine, codeine, pentazocine, etorphine, or levorphanol. Some monkeys generalized to phencyclidine, ketamine, dextrorphan, and meperidine but others did not. Hein et al. (111) argue that the discriminative effects of ethylketazocine are central because monkeys generalized to nalorphine but not its quaternary analogue and because naltrexone but not its quaternary derivative surmountably antagonized ethylketazocine's discriminative properties.

C. Conclusions

The effects of several prototypic agonist-antagonists on subjective effects and analgesia are presented in table 6. As can be seen there is complete concordance between their ability to produce dysphoria and their ability to increase scores on the LSD scale. Further there is selectivity among these drugs in altering subjective states. Thus N-allylnormetazocine is effective in producing dysphoria and psychotomimetic effects while nearly devoid of euphoric, sedative, and analgesic activity. Butorphanol, cyclazocine, and nalorphine have sedative, psychotomimetic, and analgesic activity but produce liminal euphoria. Morphine and related drugs produce euphoria in some subjects and sedation in others but no dysphoria. Why morphine is perceived as sedative by some subjects but not others has not been explained. We have identified several hypothesis which may be worth pursuing: 1) As indicated above, the length of the questionnaire and the time required to complete it may interact with the drug in determining subjective effects. Thus when a patient is sedated, and the effort to complete a questionnaire is great, the task may be onerous and the patient may perceive the drug effect as discomforting whereas completing a short questionnaire may not disrupt drug-induced changes in mood. 2) The personality of the drug recipient may also affect the drug response. Thus the euphoric effects of a drug may be more prominent in subjects who have hypophoric feeling states than in individuals who have predominant feelings of well being. These individual differences in predominant mood state and personality could reflect differences in activity of neurotransmitters involved in mood regulation or their associated receptors. 3) Another factor that may determine the effect of a psychoactive drug may be drug history. Thus it may be that the heroin abusers have a greater degree of residual tolerance to the sedative effects of opioids than to their euphoric effects.

TABLE 6

Comparison of the analgesic and subjective effects produced by morphine-like drugs and agonist-antagonists

	Analgesia	MBG*	PCAG	LSD	Dysphoria
Morphine and morphine-like drug	+†	+	0‡ or +	0	0
Naloxone	0	0	0	0	0
Naltrexone	0	0	0	0	0
Pentazocine	+	+	+ (only dose of ≥60 mg)	+ (only dose of ≥60 mg)	+
Nalbuphine	+	+ (liminal)	+ (dose-related)	+ (liminal)	+ (slight)
Butorphanol	+	0	+	+	+
Cyclazocine	+	0	+	+	+
Nalorphine	0	0	+	+	+
N-allylnormetazocine					+

* Abbreviations used are: MBG (Morphine-Benzedrine Group); PCAG (Pentobarbital, Chlorpromazine, and Alcohol Group); LSD (D-lysergic acid).

† +, Indicates the drug produces the effect or elevates scale score.

‡ 0, Indicates the drug does not produce the effect or elevate scale score.

TABLE 7

Degree of generalization to other drugs in rats and monkeys trained to discriminate morphine, fentanyl, ethylketazocine, or cyclazocine

Morphine	Fentanyl	Ethylketazocine	Cyclazocine
Rats			
Generalization			
Profadol	Morphine	Cyclazocine	Ketazocine*
Pentazocine		Bremazocine	Ethylketazocine*
Nalbuphine			Pentazocine*
Butorphanol			N-allylnormetazocine*
Naloxone			Phencyclidine*
Partial generalization			
Cyclazocine	Ethylketazocine	Fentanyl	Morphine*
Nalorphine		Morphine	Nalorphine*
Levallorphan			Pentazocine†
Ketazocine			Levallorphan†
No generalization			
Oxilorphan	Cyclazocine	N-allylnormetazocine	Mescaline
Dextrophan	N-allylnormetazocine		Ethylketazocine†
	Bremazocine		Morphine†
			Nalorphine†
Monkeys			
Generalization			
Fentanyl		Nalorphine	
Oxymorphone		Cyclazocine	
Levorphanol		Cyclorphan	
Methadone		N-allylnormetazocine	
Meperidine			
Partial generalization			
		Phencyclidine	
		Ketamine	
		Dextrorphan	
		Meperidine	
No generalization			
Dextrorphan		Morphine	
		Codeine	
		Pentazocine	
		Etorphine	
		Levorphan	

* Rats trained with 0.3 mg/kg as a discriminative stimulus.

† Rats trained with 1.0 mg/kg as a discriminative stimulus.

The results obtained in the rat and monkey by using discriminative techniques are summarized in table 7. With regard to the use of rats there is reasonable concordance between data using the opioid agonist-antagonists in discrimination experiments and data obtained measuring subjective effects in man. Unfortunately many of the critical and criterion drugs have not been studied in sufficient depth in man. Thus quantitative data on the subjective effects of ethylketazocine, N-allylnormetazocine, and fentanyl in man have not been obtained. It is known that profadol, pentazocine, nalbuphine, butorphanol, nalorphine, and cyclazocine in certain doses and in certain subjects will produce morphine-like subjective effects. Pentazocine, nalorphine, and levallorphan, in appropriate doses, also produce subjective effects that are similar to those of cyclazocine. On the other hand it is known that post-addict subjects can distinguish larger doses of pentazocine and butorphanol from morphine. Data obtained in the monkey with opioid agonists and agonist-antagonists are not sufficient to allow any generalizations.

IV. Physical Dependence

A. Theoretical Considerations

The theoretical basis for using physical dependence and its associated abstinence or withdrawal syndromes for characterizing opioid agonists and identifying selective agonists has recently been reviewed (195). Only opioid agonists (not antagonists) produce dependence, maintain physical dependence, and suppress the abstinence syndrome. Hence dependence on opioid analgesics is a consequence of agonist activity. The degree of physical dependence is dependent on the number of receptors occupied and the intensity of abstinence is a function of the number of receptors that have been vacated by the agonist (Gilbert, Martin, and Jasinski, in preparation). Further agonists that differ in specificity occupy different constellations of receptors which are on different neurones that mediate or modulate the activity of different functional systems. The contra-adaptive mechanism recruited by different types of agonists that act on different

parts of the nervous system are different and are thus responsible for different abstinence signs and syndromes.

B. Direct Addiction Studies in Man

The first systematic studies of the comparative qualitative characteristics of abstinence syndromes of opioid agonists were conducted in man in which morphine, cyclazocine, and nalorphine (185, 187) were studied. In these studies the intensity of various signs of abstinence (1+ signs; 2+ signs, caloric intake, restlessness, emesis, fever, hyperpnea, increase in systolic blood pressure and weight loss) using the Himmelsbach (115) scoring system were estimated and the proportion that each sign score contributed to the total score was calculated.

Comparisons of sign syndromes was made by using either a rank order or, in some studies, a product moment correlation coefficient. With data obtained by E. G. William and H. F. Fraser [see Martin (172)] it was found that the morphine abstinence syndrome over a wide range (40 to 240 mg/day) of stabilization doses given for varying lengths of time (7 to 30 days) did not change its characteristics. The character of the abstinence syndrome does change with level of dependence in the dog and rat [see Martin and Sloan, (195) for primary references]. It was found that the cyclazocine and nalorphine abstinence syndromes were milder than the morphine abstinence syndrome and were qualitatively different from morphine abstinence syndrome. Because the morphine abstinence syndrome did not change with levels of dependence of intensity of abstinence, it was felt that qualitative differences between abstinence syndromes were not a consequence of the level of dependence or the intensity of the abstinence syndrome. The characteristics of the withdrawal abstinence syndrome of several opioid agonists are summarized in table 8. The Spearman rank order correlation coefficients between the morphine and cyclazocines withdrawal abstinence syndromes are presented as well. As can be seen morphine, profadol, propiram, and GPA 1657 produced similar types of dependence. The cyclazocine, nalorphine, pentazocine, and propiram abstinence syndrome were also similar to each other. The nalbuphine abstinence syndrome differed from that of both morphine and cyclazocine.

C. Direct Addiction Studies in Animals

Comparatively little has been done in conducting direct addiction studies and comparing abstinence syndromes in species other than man except in monkeys and to a lesser extent the dog. Studies of the dependence-producing properties of many agonist-antagonists have been conducted in the Rhesus monkey at the University of Michigan. Some of these studies of critical and prototypic drugs will be briefly reviewed.

1. Cyclazocine. Cyclazocine did not suppress but precipitated abstinence in the morphine-dependent monkey. When cyclazocine was administered chronically (8.0 mg/kg) tolerance to cyclazocine depressant actions were seen and when large doses of naloxone were administered a mild precipitated abstinence syndrome was observed which consisted of restlessness, yawning, scratching, and a 0.6°C increase in body temperature (272). The latter sign is not observed in morphine-dependent monkeys who exhibit hypothermia when abstinent (121). These latter observations are in keeping with observations in man (185) where hyperthermia is the predominant sign of the cyclazocine abstinence syndrome. A closely related benzomorphan, pentazocine, did not suppress or precip-

TABLE 8

Relative percentages and the various sources of "Himmelsbach" points which contribute to the abstinence syndrome of human subjects made dependent on prototypic opioid agonists and Spearman correlation coefficients between these percentages for morphine or cyclazocine and the other drugs

	Morphine[4]	Cyclazocine[4]	Nalorphine[5]	Pentazocine[1]	Profadol[2]	Propiram[2]	GPA 1657[2]	Nalbuphine[3]	Butorphanol[6]
+ Signs	4.4	12.8	11.0	9.4	12.6	17.7	12.5	17.3	11.1
++ Signs	9.3	16.7	3.8	29.2	17.4	21.4	18.1	26.2	18.3
Caloric intake	1.9	5.5	6.7	3.2	2.3	2.2	1.9	4.8	13.0
Restlessness	0.8	0	1.1	0	5.2	1.2	5.4	0.8	0.5
Emesis	2.8	0.7	0	4.6	2.6	0	0	0.8	5.4
Fever	12.3	33.9	35.8	15.5	17.5	26.8	15.5	12.9	18.4
Hyperpnea	31.1	11.1	10.8	26.2	13.5	23.6	28.8	20.2	4.6
Increase in systolic blood pressure	25.5	3.1	9.9	3.5	16.4	3.4	14.4	8.8	13.8
Weight loss	11.5	15.8	20.9	8.4	12.5	4.4	3.4	8.2	15.0
Spearman rank order correlation coefficients compared with:									
Morphine	1.00	0.47	0.60	0.60	0.72*	0.70*	0.70*	0.64	0.37
Cyclazocine	0.47	1.00	0.72*	0.78*	0.67	0.85*	0.50	0.60	0.80*

* $P < 0.05$.

[1] Jasinski et al. (135).

[2] Jasinski et al. (137).

[3] Jasinski and Mansky (133).

[4] Martin et al. (185).

[5] Martin and Gorodetzky (187).

[6] Jasinski et al. (142).

itate abstinence in morphine-dependent monkeys in doses up to 30 mg/kg (55). No direct addiction studies of pentazocine were conducted in the monkey.

Morphine and cyclazocine dependence have been compared in the chronic spinal dog by using the naltrexone precipitated and the withdrawal abstinence syndromes (86). The precipitated abstinence syndrome in cyclazocine-dependent dogs was distinguishable from precipitated abstinence syndrome in morphine-dependent dogs in that tachypnea, mydriasis, gnawing, emesis, and salivation were major signs of the precipitated cyclazocine syndrome while hind limb stepping, hyperthermia, tachypnea, tachycardia, and mydriasis were the major signs of precipitated morphine abstinence. Similarly withdrawal abstinence syndromes were different. Tachypnea, mydriasis, gnawing, and panting were the major signs of the withdrawal cyclazocine abstinence syndrome whereas continuous hind limb stepping, hyperthermia, tachycardia, and whining were the most prevalent sign of withdrawal morphine abstinence. The morphine and cyclazocine abstinence syndromes can be distinguished in man, the dog, and the monkey.

2. Profadol. Profadol was a particularly interesting drug since it is an effective analgesic in several species (287) which precipitated but did not suppress abstinence in the monkey (56). When it was administered chronically, a severe abstinence was precipitated by both nalorphine and naloxone; however, only a mild to moderate abstinence syndrome was seen when it was abruptly withdrawn (271, 274). The dependence-producing property resided primarily in the *l*-isomer (275).

3. GPA 1657 (β-[−]-5-phenyl-9-methyl-2′-hydroxy-2-methyl-6,7benzomorphine). GPA 1657 precipitated but did not suppress abstinence in the morphine-dependent monkey. In monkeys who had received GPA 1657 chronically, neither nalorphine nor abrupt withdrawal produced signs of abstinence (273).

4. Nalbuphine. Nalbuphine precipitated, but did not suppress, abstinence in the morphine-dependent monkey. In monkeys who had received nalbuphine chronically, naloxone, but not nalorphine, precipitated abstinence. Abrupt withdrawal of nalbuphine results in a morphine-like abstinence syndrome (276).

D. Suppression and Precipitation Studies

The use of the suppression technique to classify opioid analgesics has been used in both man and dogs. A complete description of the suppression technique as developed by Himmelsbach (114) and a summary of results obtained in man has recently been published (128). This technique was further developed and applied by Dr. Maurice Seever to morphine-dependent monkeys at the Department of Pharmacology of the University of Michigan [see Deneau (53); Martin and Jasinski (190)]. It is unfortunate that a summary of these data from the University of Michigan program has not been published in an archival source; however, they are available in the minutes of the Committee on Problems of Drug Dependence. A similar technique has been developed in both the morphine- and cyclazocine-dependent chronic spinal dog (183, 184, 186, 190). Himmelsbach (114) felt that if a drug could suppress abstinence in morphine-dependent patients and thus substitute for morphine, it had morphine-addicting properties. This line of argument has been extended through the use of receptor theory as being another index of receptor specificity (173). It is important in this regard, to recognize that the entire abstinence syndrome must be examined and compared sign by sign and symptom by symptom. The importance of this type of analysis is illustrated by recent studies with clonidine to treat the morphine and methadone withdrawal syndrome (88). A close analysis of the ability of clonidine, an α_2-catecholaminergic agonist, to suppress signs of abstinence showed that it was more potent in suppressing autonomic signs than it was in relieving the discomfort of abstinence (132). Table 9 summarizes the ability of certain prototypic agonists and antagonists to suppress and precipitate abstinence in morphine- and cyclazocine-dependent subjects (man, monkey, and dog).

E. Suppression Substitution Studies

1. Strong Agonists. Strong opiate analgesics will suppress signs and symptoms of abstinence in a dose-related manner and parallel line bioassays can be obtained [(74; also see Jasinski (128)]. Jasinski (128) has summarized most of the suppression studies in man in which relative potencies were obtained. Opiate analgesics that are effective in producing a dose-dependent suppression of abstinence include morphine, codeine, propoxyphene, phenazocine, codoxime, and diphenoxylate. Of course many other opiate analgesics will suppress the morphine abstinence syndrome and substitute for morphine analgesics. Many hundreds of opiate analgesics have been shown to suppress abstinence in the morphine-dependent monkey by investigators at the University of Michigan program. The results of this program have been published as addenda to the reports of the annual meeting of the Committee on Problems of Drug Dependence (formerly the Committee on Drug Addiction and Narcotics). The only drug among the typical and well studied opiate analgesics in which suppression studies in the monkey over estimated the ability of a drug to suppress abstinence in man was meperidine. Whereas meperidine could completely suppress signs of abstinence in morphine-dependent monkeys (54), it could only partially suppress abstinence in man (116). A much smaller number of opiate analgesics have been studied for their ability to suppress abstinence in the dog. Morphine, oxycodone, dilaudid, etorphine, levorphanol, phenazocine, methadone, propoxyphene, ketobemidone, and fentanyl (186) produced a dose-related suppression of abstinence and the relative potencies agreed very well with potencies obtained in man ($r = 1.0$).

2. Partial Agonists and Agonist-Antagonists. Beginning

TABLE 9

Ability and relative potency of opioid antagonists and agonist-antagonists in suppressing and precipitating abstinence in morphine-dependent monkeys and men and morphine and cyclazocine-dependent dogs

The relative potencies are expressed as the number of milligrams of the experimental drug that will produce the same amount of suppression of the morphine abstinence syndrome as 1 mg of morphine or the number of milligrams of the experimental drug that will precipitate abstinence in the morphine dependent subjects to the same degree as 1 mg of naloxone.

	Monkey		Man		Dog			
					Morphine dependent		Cyclazocine dependent	
	Suppression	Precipitation	Suppression	Precipitation	Suppression	Precipitation	Suppression	Precipitation
Morphine	+*	0†	1.0	0	1.0	0	1[1]	0
Naloxone	0	+	0[4]	1.0[4]	0[8]	1.0[8]	—‡	—
Naltrexone	0	+	0[7]	0.6[7]	0[8]	0.3[8]	—	1[1]
Butorphanol	0	+	sl§,[6]	sl[6]	0[10]	—	—	—
Buprenorphine	0	+	—	—	sl[9]	sl[9]	—	—
Propiram	0	+	10[4]	1920[4]	6.7[1]	1789[1]	—	—
Profadol	0	+	3.2[4]	435[4]	5.0	—	—	—
Pentazocine	0	+	0[3]	512[3]	0[1]	522[1]	5.2[1]	—
Nalbuphine	0	+	—	37[5]	—	—	—	—
Nalorphine	0	+	0[4]	10[4]	0[8]	12.5[8]	42[1],‖	111[1]
Levallorphan	0	+	—	3.7[2]	—	—	—	—
d,l-Cyclazocine	0	+	0	1.2[4]	0[8]	2.1[8]	1.0[1]	—
Diprenorphine	0	+	—	—	—	0.2	—	1.5[1]
N-allylnormetazocine	0	+	—	—	—	7.7	—	—
GPA 1657	0	+	0.7[4]	0[4]	—	—	-	—
Buprenorphine	0	+	—	—	—	0.2[9]	—	—

* +, Effect.
† 0, No effect.
‡ —, Not studied.
§ sl, Slight effect.
‖ Ceiling effect or low slope.
[1] Gilbert and Martin (86).
[2] Jasinski et al. (134).
[3] Jasinski et al. (135).
[4] Jasinski et al. (136).
[5] Jasinski and Mansky (133).
[6] Jasinski et al. (130).
[7] Martin et al. (191).
[8] Martin et al. (183).
[9] Martin et al. (184).
[10] Martin et al. (186).

in 1963, a systematic effort was made to identify partial agonists in man and in the chronic spinal dog. Two tactics were taken to identify partial agonists by using suppression studies. In man, subjects were made dependent on different stabilization doses of morphine. The theories underlying these studies were that in the dependent subject opioid agonists continued to exert their agonistic activities and that the physical dependence and apparent tolerance was a consequence of hypertrophy of parallel adaptive redundant pathways. Further, the degree of adaptation and consequently the intensity of the abstinence syndrome were related to the proportion of receptors occupied by the agonists (174, 175). Thus patients dependent on a low level of an agonist would have only a portion of the receptors occupied and would have recruited only a portion of their adaptive capacity. A partial agonist whose maximal effect was equal to that produced by a small dependence dose of a strong agonist could substitute for the strong agonist and suppress abstinence.

On the other hand, when patients were dependent on large doses of narcotics, they would have most of their opiate receptors occupied and would have near maximally recruited adaptive processes. A partial agonist would reduce agonistic activity and precipitate abstinence. The K_D of morphine in man has been estimated to be about 1 mg/kg (188). Indeed it was found that propiram and profadol suppress abstinence in patients dependent on 60 mg/day and precipitated abstinence in patients dependent on 240 mg/day (136). On the other hand, the agonist-antagonists, pentazocine and nalbuphine, would not suppress abstinence in subjects dependent on daily doses of morphine as low as 30 mg/day (139).

A different approach to identifying partial agonists was used in morphine-dependent dogs (86, 184). In these studies dogs were allowed to become maximally abstinent and observed from the 40th to 43rd hr of abstinence. The rationale for these studies was that when dogs were maximally abstinent most of the opioid receptors were free of their exogenous ligand and that suppression of

abstinence with graded doses of agonists would provide an accurate characterization of the agonist dose response line. In these studies it was found that the partial agonist buprenorphine did suppress abstinence but that the slope of the dose response line was one-third that of morphine. This suggested that the intrinsic activity of buprenorphine was about 0.3. On the other hand, the suppression dose response line of propriam was parallel to that of morphine. Data obtained in man suggested that it, too, is a partial agonist with agonistic activity greater than that of buprenorphine. Pentazocine, ketazocine, and ethylketazocine did not suppress abstinence in morphine-dependent dogs. In cyclazocine-dependent dogs, nalorphine partially suppressed abstinence while pentazocine, cyclazocine, ketazocine, ethylketazocine, and morphine produced parallel and dose-related suppression. These data suggest that nalorphine is a partial agonist at the κ receptor and that pentazocine, cyclazocine, ketazocine, ethylketazocine, and morphine are strong κ agonists.

F. Precipitation Studies

Precipitation studies were first used to measure the relative antagonistic potency of opioid antagonists in human subjects dependent on morphine (134). Subsequently Martin et al. (184) and Gilbert and Martin (86) used similar techniques in morphine- and cyclazocine-dependent dogs. There is excellent agreement between the relative potencies of these antagonists in precipitating abstinence in morphine-dependent man and dogs (correlation coefficient = 1.0). Both in the dog and in man partial agonists are relatively impotent antagonists when compared to competitive antagonists. Further the antagonistic actions of agonist-antagonists are dissociated from their agonistic actions. Thus cyclazocine is nearly as potent an antagonist as naltrexone in dogs and naloxone in man as measured by its ability to precipitate abstinence in morphine-dependent subjects, yet it is a potent agonist and is nearly as effective as ethylketazocine (RP = 4.4) in suppressing abstinence in cyclazocine-dependent dogs.

G. Tolerance and Cross-Tolerance

Although tolerance and cross-tolerance are well recognized as being associated with physical dependence, they have not been extensively used in classifying the agonistic properties of opioid analgesic. However tolerance can be quantified [see Martin and Sloan (195)]. Jasinski and Nutt (140) found that when cyclazocine was administered to morphine-tolerant subjects, the higher doses produced cyclazocine-like dysphoria thereby suggesting that morphine-tolerant subjects were not cross-tolerant to the psychotomimetic effects of cyclazocine. Schulz et al. (241) have studied the effects of several prototypic agonists on guinea pig ilia obtained from animals tolerant to morphine (μ agonist), fentanyl (μ agonist), DADL (D-alanine-1-D-leucine-5-enkephalin) (δ agonist), ethylketazocine (κ agonist), and other agonists. In brief they found ilia from guinea pigs who had been pretreated with morphine, fentanyl, or DADL were tolerant and cross-tolerant to each other but were not cross-tolerant to κ agonists such as ethylketazocine. Ilia from guinea pigs that had been treated with ethylketazocine and other κ agonists were tolerant and cross-tolerant to each other but to a much lesser degree to morphine, fentanyl, and DADL. These data indicate that the phenomena of tolerance and cross-tolerance can be used to classify opioid agonists.

H. Conclusions

The use of physical dependence to identify opioid analgesics with different mechanisms of action has proved to be a powerful technique. The reason for this is that opioid analgesics with different mechanisms of action alter the function of neurones located in different parts of the nervous system which in turn participate in different functional systems. The contra-adaptation that takes place in the central nervous system to the actions of the opioids represents a complementary image of the map of the opioid depressed foci and the signs and symptoms of abstinence are their manifestation when the brain is released from the effect of the opioids.

Precipitation studies have been particularly useful in distinguishing two types of agonist-antagonists, partial agonists, and mixed agonist-antagonists which are agonist at one subspecies of receptors and competitive antagonists at another. The partial agonist will suppress in the maximally abstinent animal and precipitate in the maximally stabilized dependent animal. The slope of the dose response lines will indicate the intrinsic activity of the partial agonist. Mixed agonist-antagonists on the other hand will precipitate but not suppress abstinence in animals dependent on a drug which is an agonist for the receptor subtype for which it is a competitive antagonist. It will substitute for but not precipitate abstinence where it and the drug of dependence are both agonists.

The abstinence syndrome with its diverse signs and symptoms can be quantified. The Himmelsbach scoring system as well as its modifications (183) are comprised of nominal, ordinal, and ratio numbers. Despite the complexity of the abstinence score, both precipitation and suppression scores are linearly related to dose and to signs that can be measured by using a ratio scale (e.g. pupils). These complicated numbers can thus be mapped against ratio numbers (257) and bioassay parametric statistics can be used to characterize dose response curves and calculate relative potencies. The use of the dependent animal has allowed agonists to be studied over a wider range of doses than can be readily studied in the nondependent animal. This characteristic has facilitated the study and identification of partial agonists.

The relative potency values obtained in precipitation and suppression studies in chronic spinal dog agree very well with those obtained in man. Further, the relative potencies obtained in precipitation and suppression stud-

ies in man agree well with potency estimates obtained in non-dependent addicts and in patients who are receiving narcotics for the treatment of pain. These correlations speak to the validity of these methods which have been developed in tolerant and dependent subjects.

V. General Conclusions

A. Multiple Opioid Receptors: A Steric Theory of Opioid Agonists, Competitive Antagonists, Agonist-Antagonists, and Partial Agonists

It is quite clear that the specificity of opioid receptors and their topograpy is determined by species, tissue, and even by the region of tissue (e.g. region of the brain) as judged by agonist specificity, antagonist specificity, and by pharmacological actions. Multiple opioid receptors were the first receptors to be identified and characterized in the brain and the first clues of their existence were provided by selective agonists and by the existence of opioid antagonists [see Martin (173)]. The diverse opioid receptors which have been identified thus far are summarized in table 10. These pharmacological characterizations and putative receptors do not account for all of the effects produced by opioid drugs and other receptors will undoubtedly be postulated. This richness and diversity of opioid receptors needs comment particularly since there seem to be more subtypes of opioid receptors than for other receptors which also exhibit multiplicity of selectivity and specificity.

In order to gain a better insight about the topography of the opioid receptors, three-dimensional models of the opioid receptor were made from modeling clay to conform to an opioid molecule which has all of the moieties that have been shown to influence the activity of opioid agonists, agonist-antagonists, and antagonists (fig. 3B) and which include substitutions at 3, 6, 7, 10, 14, and N positions of the morphine molecule. Opioid molecules were made by using Framework Molecular Models (Prentice-Hall, Inc., Englewood Cliffs, N.J.). A plaster impression of the clay model was constructed. The active sites were color coded to indicate the approximate and relative magnitude of the bond strength between the opioid ligand and the receptor (figs. 3, A and C, and 4). The position of the receptor sites were identified in rectangular coordinates in which the X-Y plane is that of the flat site (A), the X axis is directed from the center of the flat site to the projection of the anionic site (B) on the X-Y plane and the origin (0, 0, 0) is the center of the flat site (fig. 4).

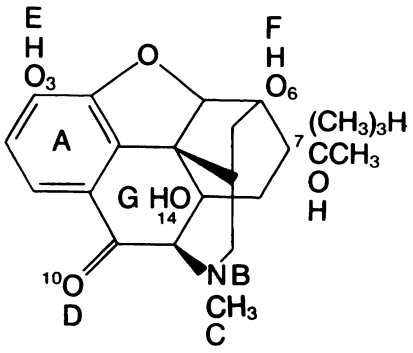
Figure 4 also designates 11 active sites (A, B, B′, C, D, E, F, F′, G, G′, and H). The A site is the flat place of the opioid receptor which interacts with the benzene moiety of the general opioid agonist through van der

TABLE 10
Opioid receptor subtypes

Receptor	Agonist	Antagonist	Species and Tissue	Pharmacological Effect
δ[5]	Leucine-, methionine-enkephalin	Naloxone	Mouse vas deferens	Inhibition of contraction
ϵ[10]	Endorphins	Naloxone	Rat vas deferens	Inhibition of contraction
κ[9]	Ethylketazocine; dynorphin	Naloxone	Rabbit vas deferens	Inhibition of contraction
			Dog CNS	Miosis, hyporeflexia, sedation
$\mu(\nu_1)$[1,6,7]	Fentanyl; morphine	Naloxone	Dog CNS[1]	Miosis, analgesia, bradycardia, hypothermia
			Cat CNS (hypothalamus)	Hyperthermia
ν_2[2]	D-Ala[2] methionine-enkephalin-amide	Naloxone	Cat CNS (hypothalamus)	Hyperthermia
ν_3[2]	D-Ala[2] methionine-enkephalin-amide	Naloxone	Cat CNS (hypothalamus)	Hypothermia
ν_4[3]	FK 33-824	Naloxone	Cat CNS (hypothalamus)	Hyperthermia
σ_1[8]	Cyclazocine	Naloxone	Man CNS	Dysphoria and hallucinations
σ_2[8]	N-allylnormetazocine; phencyclidine	?	Dog CNS	Canine delirium, tachycardia, tachypnea, mydriasis
Type 1[4]	N-allylnormetazocine; cyclazocine	?	Rat	Anticonvulsant
Type 2[4]	Morphine	Naloxone	Rat	Anticonvulsant
Type 3[4]	Ethylketazocine		Rat	No effect on fluothyl seizures
Type 4[4]	Pentazocine	?	Rat	Proconvulsant

[1] Clark and Cumby (36).
[2] Clark and Ponder (38).
[3] Clark et al. (39).
[4] Cowan et al. (44).
[5] Lord et al. (167).
[6] Martin et al. (184).
[7] Martin et al. (186).
[8] Martin [see Chang and Cuatrecasas (33)].
[9] Oka et al. (210).
[10] Wuster et al. (291).

B



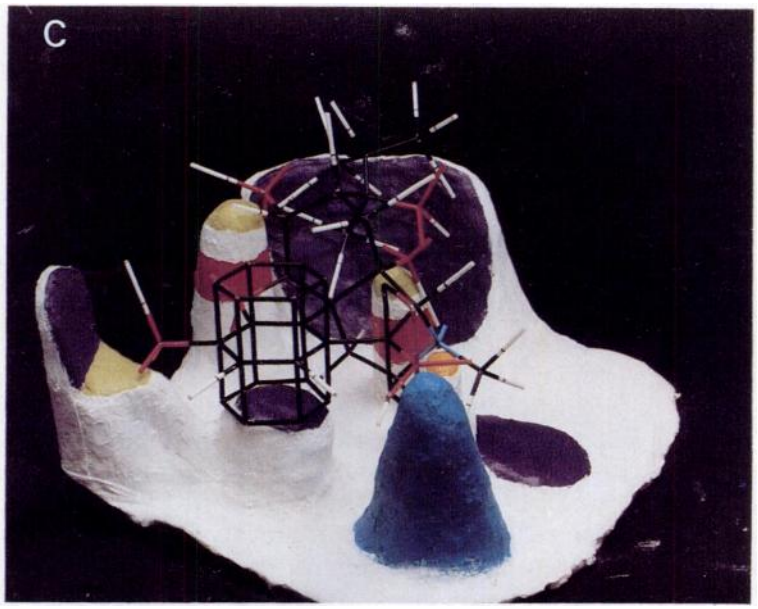


FIG. 3. Topographic model of a hypothetical opioid receptor. A. A top-oblique view of the opioid receptor model. B. The structure of a general opioid ligand that provided the basis for the construction of the model. C. A frontal-oblique view of the opioid receptor model with a framework molecular model of the general opioid ligand in place. See text and figure 4 for description of procedures for constructing the receptor model, the designation of the reactive sites, and the color coding of the receptor model.

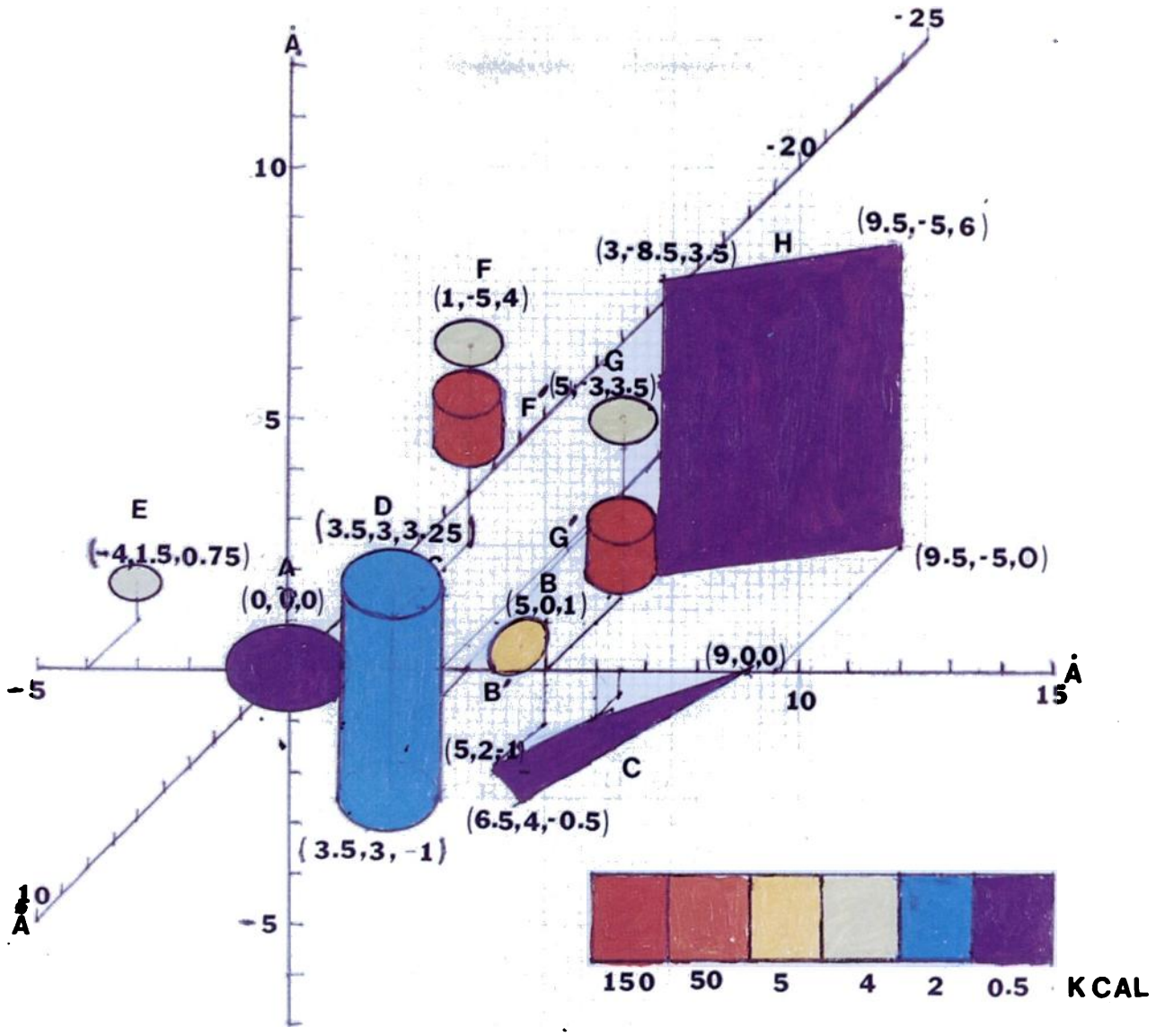


FIG. 4. A schematic oblique view of the hypothetic opioid receptor based on the model presented in figure 3. The reactive sites are designated with alphabetical letters and their X, Y and Z coordinates in Angstroms are in parenthesis. The color coding of presumed bond strength of the reactive sites are indicated. See text for the description of the various sites. The receptor volume is somewhat larger than 15 × 14.5 × 7 Å.

Waal forces. Site B is the anionic site of the μ receptor which interacts with the charged nitrogen of opioid agonist molecules. This site is postulated in the Beckett et al. (7) morphine receptor model. Loh et al (166a) believe that this site is the sulfate moiety of cerebroside sulfate. B′ is the anionic site for the κ opioid receptor and is approximately 1 Å clockwise from the B site. C is the site at which the substitutions on the nitrogen of the μ agonist interact through van der Waal forces.

Site D interacts with the ketonic oxygen in the 8-position of ethylketazocine (10-position of the morphine molecule). It also interacts with the bulky heads of allyl- and cyclopropylmethyl substitutions on N. Methyl and ethyl substitutions on N of the morphine molecule neither have the bulk nor proximity to permit an interaction with site D. This particular site is present in both the μ and the κ receptors but, as will be described subsequently, plays different roles for these two receptors. Site E interacts with the 3-OH. As indicated this interaction may involve hydrogen bonding and/or van der Waal forces. Further steric hinderance may also occur at this site. F is the site with which the 6-hydroxyl group interacts, probably through hydrogen bonding. The F′ is a site at which covalent bonding can occur to yield irreversible antagonists such as chlornaltrexamine (219a). G is the site with which the 14-hydroxyl group of the opioid molecule interacts through hydrogen bonding and G′ is a site where covalent bonding can occur (4a). H is a large

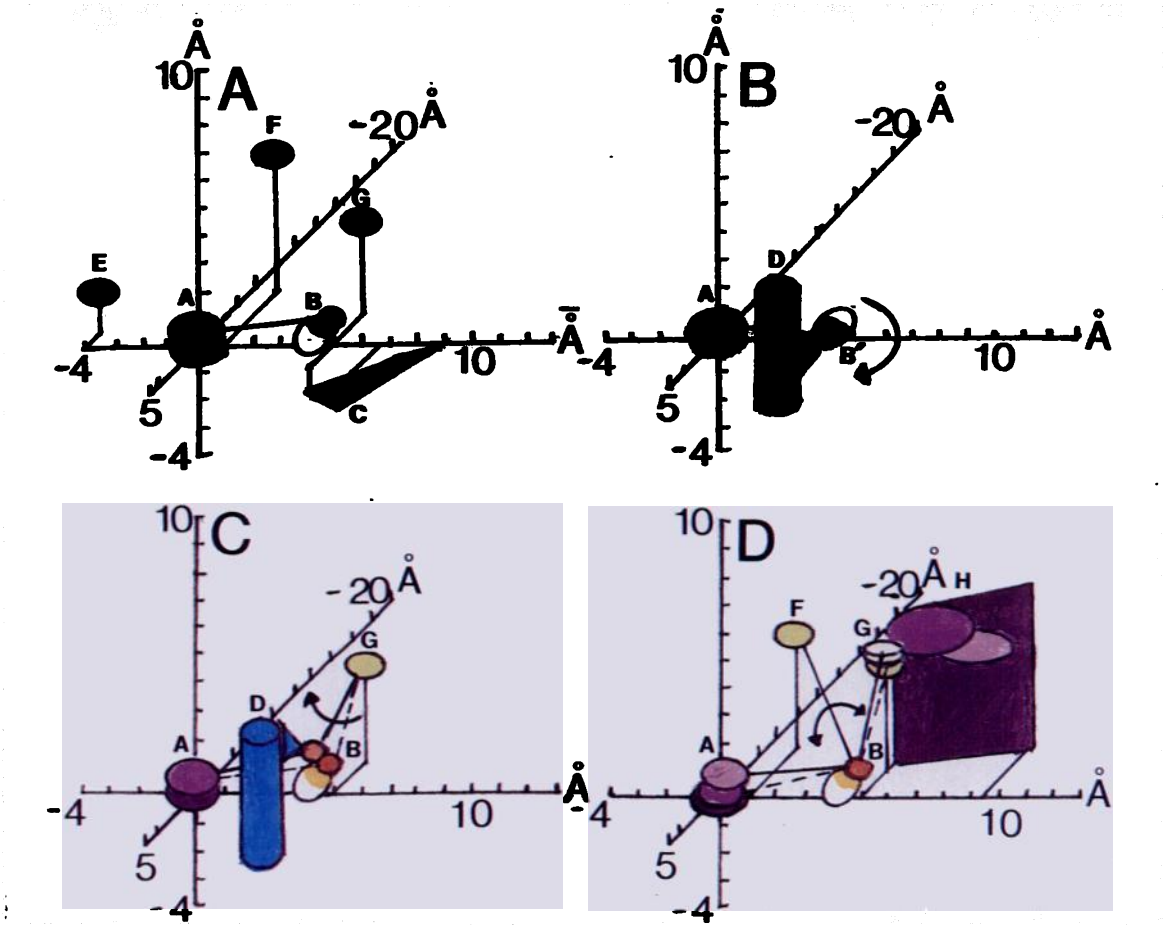


FIG. 5. Schematized oblique drawing of salient and necessary aspects of the opioid receptor in explaining μ and κ agonistic, competitive antagonistic, and partial agonistic activity. Sites are labeled with alphabetical letters as indicated in figure 4. The important features of the reacting drug are also schematically indicated and designated with off colors (e.g. violet, reddish orange, and yellow green. A. The μ receptor with its nuclear (A and B) and satellite sites (C, E, F and G). The violet and reddish figures are a superimposed μ agonist. B. The presumed steric effect of a methyl-cyclopropyl substitution on the N position of the agonist (κ)-antagonists (μ)-ligand on the μ and κ receptors. The arrow indicates how the opioid ligand is rotated by the methyl-cyclopropyl moiety interacting with the D site moving the piperdine nitrogen (orange) of the ligand from the B to the B′ position. C. The presumed steric effect of the 14-OH substitution on a methyl-cyclopropyl substituted antagonist ligand. The arrow indicates that the methyl-cyclopropyl moiety interacting with the D site does not rotate the ligand clockwise in the X, Y plane but because of the constraining influence of the 14-OH–G site interaction lifts the ligand up and off of both the B and B′ sites giving a μ and κ antagonist. D. The presumed steric effect of a large lipophilic substitution on the 7-position of the opioid interacting with the H site of the receptor. The arrow indicates that the ligand can be in one of two positions: the A-B agonist position or its rotation around the BF axis into the BFH position because of the interaction of the 7-position substitution with the H site. This gives rise to a partial agonist. See text for a further description.

area, postulated by Bentley and Lewis (11) to which large moiety substituted on the 7-position can bind through van der Waal forces.

1. *The μ Receptor.* As illustrated in figure 5A the active moieties of the μ receptor which are responsible for the agonistic activity of μ agonists are sites A, B, and possibly C. These are the μ receptor nuclear sites which must be occupied by an agonist for an effect to occur. The μ receptor does not have a B′ site. Sites C, D, E, F, and G play the role of enhancing the binding of μ agonists to this receptor and are called satellite sites. The C site may be necessary for activity in some but not all species and tissues.

2. *μ Antagonists.* The substitution of an allyl or cyclopropylmethyl group on the nitrogen of morphine, levorphanols, and benzomorphans convert these μ agonists to μ competitive antagonists [cf. Martin (173)]. Figure 5B illustrates the effect of adding a cyclopropylmethyl or an allyl group on the nitrogen of a morphine-like molecule which is interacting with a μ receptor. This moiety now interacts with the D site by providing a large area for a van der Waal interaction. This rotates the agonist clockwise around the Z axis as indicated by the arrow pulling the molecule toward the D site and moving the nitrogen away from the B site. The molecule loses its μ agonistic activity; however, because it is still in close proximity to the receptor it inhibits the binding of μ agonist molecules to the receptor.

3. *The κ Receptor.* The nuclear sites of the κ receptor are A, B′, and D. The substitution of allyl and cyclopro-

pylmethyl groups as well as other related groups on the nitrogen not only converted the μ agonist into a μ competitive antagonist, they also frequently endowed these compounds with different types of agonistic activity which is attributed to their interaction with a κ and a σ receptor (184). It was subsequently shown that a substitution on a position equivalent to the 10-position of the morphine molecule (the 8-position of the benzomorphan molecule) conveyed κ agonistic activity to the metazocine molecule (86, 184); however, this substitution did not confer μ antagonistic activity. To explain these observations it is proposed that κ agonistic activity is conferred by the molecule interacting with the opioid receptor at the A, B′, and D sites. The B′ site is located approximately 1 Å clockwise and somewhat higher than the B site. The κ receptor does not have a B site. Figure 5B also illustrates the κ agonist interacting with the κ receptor.

4. The Pure Antagonists, Naloxone and Naltrexone. The addition of a hydroxyl group in the 14-position yields μ congeners (oxymorphone and oxycodone) that appear to have activity and potency similar to their parent compounds (hydromorphone and hydrocodone). However, the 14-OH substitution on the N-allyl or N-cyclopropylmethyl congeners of oxymorphone are competitive antagonists not only of μ agonists but also of κ agonists. It is for this reason that they are referred to as pure antagonists (134). The effects of this substitution alters the effect of the N-allyl and cyclopropylmethyl substitutions on both the μ and κ receptor. The constraining effect of the binding of the 14-OH group at the G site prevents the rotation of the nitrogen moiety to the B′ site of the κ receptor. Rather the attraction of the N-allyl and methylcyclopropyl groups to the D site must occur at higher location on the D locus which lifts the N off of the B and B′ site. To state it differently, since the distance between the N and 14-OH position is fixed and the shortest distance between the G site and the D locus will be in the XY plane going through G, the N-allyl and methylcyclopropyl moieties will cause the N to be rotated clockwise in this plane and in a direction with vectors along both the positive Y and Z axes as illustrated in figure 5C. The fact that the N of the 14-OH antagonists cannot occupy either the B or B′ sites yet covers them, confers both μ and κ competitive antagonistic properties to both naloxone and naltrexone.

5. Partial Agonists. The concept and phenomenology of partial agonists has been difficult to explain mechanistically. Belleau (8a) proposed that agonists could react with receptors to yield active or inactive receptor complexes which have different conformations. Changeux et al. (33a) and Karlin (144b) proposed that there is equilibrium between active and inactive forms of receptors and that partial agonists interact with both forms of the receptor having a slightly greater affinity for the active than the inactive form. Feinberg et al. (67a) have proposed that the opiate receptor can exist in an agonist or an antagonist conformation that are in equilibrium. Kolb (152a) has formulated a one-receptor agonist-antagonist model in which the antagonists (e.g. allyl) and agonists (e.g. methyl) substitutions on the N nitrogen determine the configuration of the piperdine ring (chair or boat form) and the position (direction) of the N-lone pair electron lobe of the unprotonated N. This would allow an interaction of the nitrogen with either an agonist or an antagonist site on the receptor. Archer and Michne (4b) have proposed that an agonist will alter an allosteric site making the allosteric site complementary to and able to react with an antagonist. When the allosteric site interacts with an antagonist it prevents the agonist from inducing an effect. Portoghese and Takemori (personal communication) have proposed that antagonists act at a distinct and separate site which causes an allosteric change in the opiate receptor. They propose that a partial agonist would be active at both the opioid receptor and at the allosteric site.

I have felt that in the opioid tolerant and dependent animal opioids continue to exert their full agonistic activity (see section IV) and that for opioid drugs there is no need to postulate an antagonist, inactive or desensitized form of the opioid-receptor complex. Although it may be subsequently demonstrated that one of these forms of the opioid-receptors may exist, a new steric theory of partial agonist is presented which does not necessitate a separate antagonist receptor conformation, allosteric changes in the receptor, or the receptor existing in an active or inactive form.

The principle is that because of the complexities of the opiate receptor some ligands can bind to it in several ways. To illustrate this principle, buprenorphine, which has many of the properties of a partial μ agonist in the dog (184) will be used. It is proposed that buprenorphine can bind to the μ receptor configuration. It binds at sites A, B, C, E, and F. The N-methylcyclopropyl moiety cannot rotate the molecule to the μ antagonist or κ agonist configuration (fig. 5B and C) because of steric hinderance at the B and F site thus causing buprenorphine to have μ agonistic activity. However, the substitution on the 7-position allows it also to bind to the B, F, and H moieties causing the molecule to rotate about the B-F axis which lifts the benzene ring off of the A site. Thus we have the situation in which the molecule can bind to the A and B sites and exhibits μ agonistic activity or can bind to the B, F, and H sites lifting it off of the A site such that it loses its agonistic activity and becomes a competitive antagonist at the μ site. It is apparent that under both circumstances the drug is bound to the μ receptor. Its agonistic activity or efficacy will depend on the relative affinity of the drug for these two binding configurations. Thus if the drug has a very high affinity for the A, B configuration and a very low affinity for the B, F, and H configuration, the drug would have a high intrinsic activity. On the other hand when the drug is tightly bound to the B, F, and H configuration

and has a low affinity for the A, B configuration, it would have low intrinsic activity. If the affinities for the two sites are approximately equal the drug would have an intrinsic activity of about 0.5. When the drug (D) is bound to the A, B configuration it is designated as [DR]′ and when bound in the BFH configuration as [DR]″. The intrinsic activity (α) of the drug is

$$\alpha = \frac{[DR]'}{[DR]' + [DR]''}. \quad (1)$$

The dissociation constant at the A B site is designated K′ and at the BFH sites K″ as defined by equations (2) and (3).

$$\frac{[D][R]}{[DR]'} = K' \quad (2)$$

$$\frac{[D][R]}{[DR]''} = K'' \quad (3)$$

Then

$$\alpha = \frac{[DR]'}{[DR]' + [DR]''} = \frac{\frac{[D][R]}{K'}}{\frac{[D][R]}{K'} + \frac{[D][R]}{K''}} = \frac{K''}{K' + K''}. \quad (4)$$

Thus the larger K″ is (the lower affinity of D to BFH configuration) the larger will be α.

Propiram and profadol have been shown to be partial agonists of the μ type in man (137). These drugs can hypothetically also occupy the μ receptor in two positions (179a). Nalorphine has been shown to be a partial agonist of the κ type in the chronic spinal dog (see section V D 1). When nalorphine occupies the κ receptor (sites A, B′, and D) the 3- and 6-OH hydroxyl groups are rotated clockwise away from the E and F sites. Nalorphine can also occupy the receptor in a competitive antagonist position (ADEF) which results in a rotation of nalorphine around the AD axis lifting the nitrogen above the B′ site. Another factor that may determine at which positions the drugs can occupy the receptor is the axis of rotation and the lever arms of the interactions. In the situation in which nalorphine can occupy the two positions (AB′D vs ADEF) by teetering around the AD axis the lever arms over which the interaction at the E and F sites occur are longer than the lever arm of the B′ site interaction. Even though the B′ site interaction is stronger than the E and F site interactions, the E and F site interactions may be equally as effective as the B′ site interaction because their forces have a longer lever arm.

The nature of the drug receptor interactions may have many dimensions which include the strength of the interactions, the position and the number of the reactive sites, and the lever arm of the forces and points or axes of rotation. It is important to emphasize that the reactive moieties play at least three classic roles in the drug receptor interaction: 1) The strength of the interaction or affinity; 2) the initiating of a pharmacological effect or efficacy; and 3) a role in orienting the drug on the receptor (good steric fits).

The fact that there are so many reactive moieties whose spatial relationships and chemical nature can be altered by genetic and inductive influences may be the fundamental reason for the many opioid receptor subtypes. It seems reasonable that the number of receptor subtypes that exist is proportional to the number of reactive moieties of the receptor(s) and hence to its complexity. Loh et al. (166a) have identified flat (A) and anionic (B) sites in cerebroside sulfate; however, the other postulate sites are absent. He has also shown that the rat brain opiate binding site is comprised of cerebroside sulfate and a protein component (Loh, personal communication). It is possible that the D, E, F, F′, G, G′, and H sites could reside in the protein part of a lipoprotein receptor.

What determines which receptor subtype predominates or exists? Clues are available which suggest certain influences. Hereditary influences must play an important role. Thus in the vas deferens of the mouse the δ receptor predominates (167), while the ϵ receptor predominates in the rat (164, 291), and the κ receptor in the rabbit (210). Villarreal (272) and Martin and Jasinski (190) have commented on the marked difference between species in their response to opioid agonists of different classes and chemical structure; Martin and Jasinski (190) speculated that this could be due to subtle differences in chemical structures of opioid receptors in different species.

By using the previously described methods for exploring steric receptor relationships, insight into the role of species differences in response to opioids of different structures has been obtained. Thus if the C site (fig. 4) is located 1 Å counterclockwise, the N-methyl group of meperidine will no longer interact with it. The interaction at the C site is important in the dog for normorphine does not have morphine-like activity in this species (184). Thus only a slight rearrangement of the positions of the moieties of the opioid receptor may have profound influences on the specificity and selectivity of agonists. Thus minor changes in the position of the C site of the opioid in the monkey and the dog could account for the fact that meperidine is a typical morphine-like drug in the monkey and devoid of morphine-like activity in the dog.

The differences between the syndromes that opioid analgesics produce is most readily explained by assuming they affect different neurones or parts of neurones (e.g. pre- and postsynaptically) in the same brain in different ways. Why there are subtle differences between neurones from different parts of the brain and between parts of the same neurone must be a subject for speculation at

this time. Among influences that can be considered are: 1) inductive influences of neighboring nerves or tissues, 2) local influences within the cell which may physically strain the membrane in which the receptor is located; 3) alterations in the receptor as it is being transported from its place of synthesis to the membrane; and 4) differences in the composition of the membrane in which the receptor imbeds in different parts of the neurone.

Receptors, characterized pharmacologically, form a fundamental concept in the development of both selective agonists and antagonists as well as mixed agonist-antagonists. If the topography of the receptor and the spatial relationships of its active moieties are determined by a diversity of influences whose nature can only be speculated about at this time, receptor nomenclature may well have to reflect these factors (179). Whether multiple receptors have a unique and invariant number of reactive moieties whose spatial relationships are determined by a variety of influences and forces of varying strengths and stability or have different chemical structures is an unanswered question; however, new drugs of unique selectivity can be developed and identified regardless of the mechanisms which give rise to multiple receptors.

B. The Role of Multiple Opioid Receptors in Function

Do opioid agonists occupy receptors and exert their pharmacological actions by mimicking endogenous opioid peptide neurotransmitters or neurohumors? Three questions must be posed in considering this issue: 1) Whether there are opioid receptors for which there are no physiological endogenous agonists; 2) whether all opioid receptors for which there are endogenous ligands are in or on neurones which are innervated by opioid peptides containing neurones; and 3) whether endogenous ligands are mobilized continuously or only under special conditions. Thus we can divide the action of opioid agonist into pharmacological, physiological, and pathological.

"Pharmacological" actions are of two types: 1) Where the agonists interact with receptors for which there is no endogenous ligand; and 2) where the agonist interacts with a receptor for which an endogenous ligand exists but not in the vicinity of the receptor. Under these "pharmacological" conditions an agonist may produce an effect for which there is no physiological counterpart. If there is no endogenous agonist, a competitive opioid antagonist would not be expected to produce any pharmacological changes. There are at least two pitfalls in this line of argument: 1) The measure or experimental circumstances may be inappropriate; 2) there may be mutually antagonistic endogenous opioid systems. Under such a circumstance the antagonist would diminish the effect of both functions with little or no net change. Indeed such a circumstance may have already been demonstrated. Wu et al. (289a) have suggested a medullary hyperalgesic as well as spinal cord and perhaps supramedullary analgesic κ agonistic processes perhaps mediated by a dynorphinergic mechanism. To date, however, no one has reported that either naloxone or naltrexone alters pupillary diameter in either man or in dogs. Further naloxone in dose levels that would probably antagonize the actions of endogenous μ and κ ligands produce little or no change in subjective state although Gritz et al. (97) found that chronic naltrexone produced a modest decrease in feelings of well being. Naltrexone and naloxone produces a slowing of the EEG (Wettstein, Kamerling, and Martin, in preparation); however, these changes are very similar to those produced by fentanyl and ethylketazocine. It is thus difficult to ascribe a physiological role of endogenous opioids to these functions at present.

Naloxone lowers body temperature in mice and naltrexone in man. Naltrexone does not significantly alter body temperature in the dog. The changes produced by naltrexone are modest. These results suggest that endogenous ligands may play a role in temperature regulation in some species but a lesser role in others. Nevertheless opioid receptors which can alter body temperature appear to be ubiquitously distributed throughout the nervous system and may be used by temperature regulating centers.

Although the effects of opioids in endocrine function have not been discussed in this article, opioid antagonists enhance the release of luteinizing hormone and decrease the release of prolactin and growth hormone indicating that endogenous opioid peptides are involved in the regulation of the release of these hormones. The role of endogenous opioids in regulation of perception of nociceptive stimuli is extremely complicated and no unifying concept has been elucidated. There is increasing evidence that opioid peptides can not only be released by neurones in the central nervous system but by the pituitary and adrenal glands. Thus the body has a variety of mechanisms available for modifying unpleasant stimuli. How these mechanisms are mobilized and the pathophysiological consequences of their mobilization has yet to be clarified. The possibility that endogenous opioid ligands may participate in enhancing perception of nociceptive stimuli emphasizes one of the difficulties in delineating the physiological role of endogenous ligands with antagonists. It also raises an important issue about the evolution of brain hyperalgesic and analgesic systems and whether enhancing or diminishing suffering best serves species. There is also evidence that endogenous opioids may be involved in the negative feedback control of respiration and that they may achieve pathological significance in patients with chronic obstructive pulmonary disease.

Although endogenous opioid processes may play a minor role in the regulation of cardiovascular function under normal circumstances, they may play a major role in certain pathological circumstances such as shock.

For most functional systems of the central nervous system, not all (e.g. cardiovascular) exogenously admin-

istered opioids seem to produce much larger effects than are produced by endogenous ligands as judged by studies with opioid antagonists. This can be tentatively interpreted as indicating that the majority of opioid receptors are not participating in physiological processes although this varies in degree from one functional system to another.

It would also appear that there is functional redundancy for opioid receptors. Thus both μ and κ agonists constrict pupils, produce analgesia, and lower body temperature. Indeed this "receptor dualism" gives rise to complicated interactions between opioid agonists and agonist-antagonists (173).

C. *The Relationship of Opioid Receptors and Binding Sites*

The discovery of opioid binding sites has provided a basis for understanding the mechanism of action of opioid analgesics. Lord et al. (167) were the first to obtain evidence of binding site heterogeneity with brain homogenate binding techniques. More recently Magnan et al. (171) have completed an extensive binding study with guinea pig brain homogenates, a variety of opioid agonists, agonist-antagonists, and antagonists and putative μ (D-Ala^2, MePhe^{4}Gly-ol^5 enkephalin), δ (D-Ala^2, D-Leu^5 enkephalin), and κ (ethylketazocine) radioligands. The results of some of these studies are summarized in table 11. In addition the effects of these same drugs in depressing the flexor reflex of the chronic spinal dog (column VII) and precipitating (column IX), and suppressing abstinence (column VIII) in morphine-dependent chronic spinal dogs are also summarized. The inhibition constants (K_I) at the μ receptor for all drugs are presented in column I. Columns II, III, and IV show the relative potencies of each of the drugs in preventing the binding of the μ, δ, and κ ligands and are expressed as the ratio of κ and δ K_I to their K_I at the μ binding sites. Thus it takes, respectively, 50 and 176 times more morphine to inhibit the binding of the δ and κ ligand as the μ ligand. Column V presents the potency of the drugs relative to morphine in inhibiting μ binding and column VI presents the potency of the mixed agonist-antagonists relative to morphine μ agonistic activity (e.g. M is 0.56 as potent as EKC at the μ binding site and EKC is twice as potent at the κ as the μ binding site).

Column V and IX allow a comparison of a group of drugs that are competitive μ antagonists in the dog and man. There is relatively good agreement between their μ binding potencies in the guinea pig brain and in precipitating abstinence in the morphine-dependent chronic spinal dog for the antagonists as well as for the agonist-antagonist cyclazocine. However, the agreement for the other agonist-antagonist is poor. Thus ethylketazocine has a high affinity for the μ ligand site but does not appear to have either morphine agonistic or antagonistic effects in the morphine-dependent dog. Further NANM, pentazocine, and nalorphine are, respectively, 8, 34, and 12 times less potent in precipitating abstinence as they are in inhibiting the binding of the μ ligand. These differences cannot be explained completely by differences in distribution of the drugs for the ratio of potency for κ agonistic activity of the agonist-antagonists is quite different. Thus pentazocine, cyclazocine, ethylketazocine, and nalorphine are, respectively, 4, 1.2, 3, and 2.6 times more potent as κ agonists in the dog than they are in inhibiting κ ligand binding, findings that are incon-

TABLE 11

Comparison of the relative potency (R.P.) of opioid agonists, agonist-antagonists, and antagonists to inhibit the binding of μ, δ, and κ ligands (columns I–VI) and in suppressing the flexor reflex (VII) and suppressing (VIII) and precipitating (IX) abstinence in the non-dependent and morphine dependent chronic spinal dog (see text for a fuller explanation)

	I μ K_I	II μ R.P.	III δ K_I R.P. δ/μ	IV κ K_I R.P. κ/μ	V μ B.K_I R.P.	VI κ B.K_I R.P.	VII Dog* κ agonist R.P.	VIII Dog† μ agonist R.P.	IX Dog‡ μ antagonist R.P.
Agonists									
Morphine (M)	1.8	1	50	176	1	1	1.0	1	—§
Methadone (Me)	4.2	1	3.6	387	2.3			0.2	—
Fentanyl (F)	7.0	1	21.0	67	3.9			0.014	—
Phenazocine (Ph)	1.5	1	2.3	5.3	0.8	4.3		0.12	—
Normorphine (NM)	4.0	1	77.0	37	2.2			—	—
Agonist-Antagonists									
N-allylnormetazocine (NANM)	2.0	1	4.4	1.6	1.1				7.7
Pentazocine (Pe)	7.0	1	15.0	3.2	3.9	12.4	3.0		522.0
Cyclazocine (Cy)	0.3	1	6.8	1.4	0.17	0.23	0.2		0.5
Ethylketazocine (EKC)	1.0	1	5.5	0.5	0.5	0.3	0.1		—
Nalorphine (NL)	1.8	1	4.1	4.4	1	4.4	1.7		12.5
Antagonists									
Naloxone (Nal)	1.8	1	15.0	9.7	1				1
Naltrexone (Ntx)	1.1	1	6.1	7.9	0.6				0.3
Diprenorphine (Dpr)	0.8	1	1.7	2.7	0.4				0.2

† Suppression of abstinence signs in morphine dependent dogs.
‡ Precipitation of abstinence signs in morphine dependent dogs.
§ —, no activity.

sistent with the idea that the agonist-antagonists do not readily gain access to the μ receptors.

A similar comparison of columns V and VIII show that, whereas there is good agreement between the potency of morphine and phenazocine in inhibiting μ ligand binding and suppressing abstinence in the morphine-dependent dog, methadone and fentanyl are, respectively, 11.5 and 278.5 more potent in suppressing abstinence. Furthermore, normorphine is not a morphine-like drug in the dog.

Although subtypes of opioid binding can be clearly identified in guinea pig brain homogenates, they do not covary with opioid pharmacological effects in the dog. It is important to recall that with regard to these pharmacological variables there is excellent agreement between results obtained in man and the dog. As indicated above it is unlikely that the lack of correlation between results obtained with binding studies and pharmacological effect can be attributed entirely to difference in distribution and must in part be related to other variables, possibly species. As efforts in receptor classification evolve, it is necessary that these types of differences be reconciled.

D. Classification of Opioid Analgesics and Identification of Prototypic Agonists

The identification of multiple opioid receptors was a consequence of clinical studies and efforts to develop a non-toxic, non-addicting analgesic. The great need for safe analgesics and the consequent financial rewards for developing them provided the incentive for synthesizing and investigating the pharmacology of thousands of new chemicals. There have been several ambiguities in how these objectives should be obtained as they relate to economic, legal, and health issues and these ambiguities have confounded scientific issues related to receptor classification. From a health perspective, the major objectives would be analgesia, acceptable subjective effects, the absence of undesirable side effects, and an absence of the ability to induce tolerance and physical dependence which gives rise to drug-seeking behavior unrelated to the treatment of pain. These objectives have been partially obtained. Thus the partial agonist buprenorphine has enough agonistic activity to produce a clinically significant degree of analgesia, is well accepted by patients, but does not produce enough agonistic activity to produce significant dependence or toxicity. The agonist-antagonist pentazocine is an effective and accepted analgesic which has been proven to be particularly safe. Partial agonists and antagonists such as nalbuphine, butorphanol, and cyclazocine probably will share these properties.

1. Partial Agonists. Partial agonists have proved to be relatively easy to classify particularly those with predominantly μ agonistic activity.

A. PROFADOL, PROPIRAM, AND BUPRENORPHINE. These drugs appear to be partial agonists of the morphine type because they have been shown to both precipitate and suppress abstinence in morphine-dependent men or dogs. In man, profadol and propiram have been shown to have these properties, and in the dog, propiram and buprenorphine. In single-dose studies these drugs produce miosis and morphine-like subjective effects in man. They could not be distinguished from morphine on the basis of any of their dose response line slopes. In the dog buprenorphine, but not propiram, gave an indication of a ceiling effect; however, both drugs produced the same constellation of morphine-like signs.

B. NALORPHINE. The dissection of the pharmacological actions of nalorphine along with those of pentazocine and cyclazocine have also been of critical importance in developing ideas of multiple opioid receptors. The most parsimonious interpretation of the modes of action of nalorphine is that it is a competitive antagonist at the μ receptor, a partial agonist at the κ receptor, a σ_1 agonist of intermediate potency, and low affinity agonist at the σ_2 receptor. It will not suppress but precipitate abstinence in the morphine-dependent dog, the monkey, and man. It both precipitated and suppressed abstinence in the cyclazocine-dependent dog. It exhibited a ceiling effect in the dog but not in man.

The constellation of signs seen after administration to non-dependent patients and dogs and after withdrawal in nalorphine-dependent patients were similar to those of cyclazocine and ethylketazocine. Further, the abstinence syndrome observed in patients dependent on nalorphine resembles that of cyclazocine but not of morphine. It would also seem that the analgesic effect of nalorphine (κ) is dissociated from its psychotomimetic effects (σ). Whereas peak analgesia in man is obtained with 10 mg of nalorphine, psychotomimetic changes increase in a dose-related manner at least to 32 mg (102).

C. NALBUPHINE. Nalbuphine has been extensively studied in man and the monkey but not in the chronic spinal dog. It precipitates abstinence in morphine-dependent men and the monkey. It is not known whether it can suppress abstinence or not in man or the dog. The nature of the abstinence syndrome of patients dependent on nalbuphine did not significantly resemble either morphine or cyclazocine abstinence syndrome and was mild in degree. It exhibits a ceiling effect in producing respiratory depression. It elevates the PCAG (apathetic sedation) scale score but produced only liminal changes in LSD scale scores. These data would suggest that nalbuphine is a partial agonist of the κ type. Whether it has agonistic or antagonistic effects on the μ or σ receptors cannot be answered at this time.

2. Agonist-Antagonists. A. CYCLAZOCINE AND PENTAZOCINE. Cyclazocine and pentazocine have been extensively studied in man and the chronic spinal dog and are competitive antagonists at the μ receptor and strong κ and σ_1 agonists. Both cyclazocine and pentazocine precipitate but will not suppress abstinence in the morphine-dependent monkey, man, and the dog. They suppress but do not precipitate abstinence in the cyclazo-

cine-dependent dog. The abstinence syndromes of patients dependent on cyclazocine and pentazocine resemble each other but not that seen in abstinent patients dependent on morphine. The pharmacological syndrome produced by them in non-dependent men and dogs are similar, but different from the morphine syndrome, and differ only in their potency in producing σ effects. In man both pentazocine and cyclazocine produce dysphoric and psychotomimetic effects; however, at equianalgesic or equimiotic doses, patients receiving cyclazocine are more likely to have psychotomimetic effects than patients receiving pentazocine.

B. BUTORPHANOL. Butorphanol produces only a slight suppression and precipitation of abstinence in patients dependent on morphine. It did not suppress abstinence in chronic spinal dog dependent on morphine. When subjects were made dependent on butorphanol and then withdrawn, an abstinence syndrome emerged which resembled the cyclazocine abstinence syndrome. Butorphanol did not produce morphine-like subjective effects but, like cyclazocine, caused apathetic sedation and dysphoria. Butorphanol thus appears to be a strong κ agonist which is neither a μ agonist or antagonist. It also has significant σ agonistic activity.

E. Summary

The concept of multiple opioid receptors reconciles a large body of clinical and pharmacological data. Recent studies have shown that there are also multiple opioid binding sites. It would appear that there is considerable variability between species in both the specificity and selectivity of opioid receptors. This issue has not been explored systematically regarding opioid binding sites. Better characterization of the pharmacological profiles and receptor binding specificity for different species may help resolve some of the apparent disparities. The number of putative receptors now number nearly a dozen. Already subspecies of μ, κ, and σ receptors are being postulated. Both pharmacological and neurochemical methods may reveal even more. Some of the newer κ agonists differ in their pharmacology from the prototypic κ agonist ethylketazocine.

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