REVIEW ARTICLE

NARCOTIC–NARCOTIC ANTAGONIST MIXTURES

JANE TELFORD, M.D., AND ARTHUR S. KEATS, M.D.

THE introduction of nalorphine (N-allylnormorphine) into clinical medicine by Eckenhoff, Elder and King in 1952 [27] occurred at a time when great interest existed among many investigators in identifying an improved potent analgesic of the morphine type. All newly discovered potent analgesics possessed seemingly obligatory side actions of respiratory depression, sedation, nausea, vomiting, constipation and addiction. It was postulated by some investigators that a combination of a narcotic with a narcotic antagonist would fulfill this objective by antagonizing the side actions of narcotics without antagonizing the primary desirable action of analgesia. Stimulated by this novel approach, many reports appeared in the ensuing years both supporting and denying the validity of the postulate. It was the purpose of this review to summarize and critically examine the data pertaining to the pharmacological effects of narcotic-narcotic antagonist mixtures. In the course of achieving this objective, it was found necessary to review in some detail certain aspects of the antagonism of narcotics by narcotic antagonists, to provide a background against which the data on mixtures could be appraised. The primary question addressed was whether or not it was possible to inhibit selectively the side actions of narcotics by a combination of narcotic and antagonist in a specific dose ratio without interfering with analgesia. The side actions whose elimination was considered most desirable were respiratory depression and addiction liability.

The pharmacology of the narcotic antagonists has been reviewed extensively recently with emphasis on aspects other than that undertaken here.[32, 41, 89, 133, 139] These reviews contain a complete bibliography of the early work. Therefore, in this review preference was given to more recent data even though priority for original observation belonged to an earlier investigator.

The authors are in the Division of Anesthesiology, Baylor University College of Medicine, Houston, Texas.

GENERAL CONSIDERATIONS

The narcotic antagonists in a generic sense include nonspecific and specific antagonists. Nonspecific antagonists (or analeptics, such as caffeine and methylphenidate) are drugs which are effective against the central nervous system depression of narcotics, barbiturates and anesthetics. This discussion will be confined to the specific antagonists, or drugs whose antagonism is limited to the narcotics including both the central and peripheral effects of narcotics.

Many narcotic antagonists have been developed in recent years. Both Clarke *et al.*[18] and Green, Ruffel and Walton [52] found morphine antagonists among a series of N-substituted normorphine derivatives which they studied. Winter, Orahovats and Lehman [138] compared the antimorphine potencies of a large series of morphine antagonists chemically related to morphine, morphine derivatives, and the synthetic narcotics. Chernov, Miller and Mannering [17] reported on a series of morphinan derivatives which were morphine antagonists, one of which was subsequently studied in man.[99, 121, 132] However, most pharmacological data have been obtained from studies of nalorphine and levallorphan. Except in the number of milligrams of each drug employed and hence the ratios of narcotic to antagonist, there existed little evidence that there was any large difference in pharmacological effects between the narcotics used, between levallorphan and nalorphine, or between the various combinations used as mixtures. Therefore, morphine and nalorphine were used as prototypes. When evidence existed for a difference between drugs or drug combinations, this was mentioned specificially.

TABLE 1

PHARMACOLOGICAL EFFECTS OF NALORPHINE SIMILAR TO AND DIFFERENT FROM MORPHINE IN MAN

Drug Effect	Reference Numbers
Respiratory depression	43, 70, 91, 112, 120
Analgesia	80, 91
Sedation	16, 69, 81, 91, 106, 112
Dizziness	69, 81, 91
Euphoria and dysphoria	16, 43, 91, 106
Nausea and vomiting	69, 81, 91, 106
Sweating	69, 81
Miosis	43, 69, 106, 112
Decreased rectal temperature	43, 135
Increased cerebrospinal fluid pressure	78
Antidiuresis	115
Antitussive	12
Bradycardia and hypertension	70, 135
Little change in pulse or blood pressure	32, 43, 69
Postural hypotension	27
Decreased gastric emptying	127
Decreased plasma hydrocortisone	97
Different from Morphine	
Visual hallucinations, bizarre day dreams and anxiety	16, 69, 81, 91, 106
Disruption of psychomotor performance	7 (greater than morphine)
No increase in choledochal pressure	113 (three patinets)
Increased oxygen consumption	70 (see text)
Antispasmotic on gastrointestinal tract	8 (one patient)

In the past some confusion has existed in assessing the pharmacological effects of narcotic antagonists because of a failure to appreciate two seemingly obvious facts. (1) Although the effects of nalorphine in man when given alone were strikingly similar to those of an equal milligram dose of morphine, the same relationship was not true in animals. Nalorphine produced relatively little effect when given to animals in sublethal doses. Therefore, the problem of transferring animal observations to man was greater than usual in this area. (2) The effects observed after nalorphine in man were highly dependent on the precise relationship between the administration of the antagonist and the administration of a narcotic. Nalorphine given alone produced morphine-like effects in man. When given before morphine, it blocked morphine actions. When given after a large dose of morphine, it produced antagonism. Unfortunately, the distinction between data obtained from simultaneous administration of narcotic and antagonist and the administration of an antagonist just before or just after a narcotic has often been disregarded. The data reviewed are presented with regard for these distinctions.

EFFECTS OF NARCOTIC ANTAGONISTS ADMINISTERED ALONE

Man. In table 1, we have summarized the major pharmacological effects of nalorphine given to man without previous narcotic. Obviously the reported circulatory effects of nalorphine were not consistent or great. The similarity in the effects of nalorphine and morphine are apparent even though the data in some areas were meager. A total of 4 patients provided all the known information on the gastrointestinal and biliary tract and we have been unable to confirm the isolated observation of increased oxygen consumption after nalorphine.[83] In the few similar studies with levallorphan alone, the only documented pharmacological effect observed was that of respiratory depression.[120, 125] One important difference between nalorphine and morphine not listed in table 1 was the failure to demonstrate either psychic or physical dependence to nalorphine after chronic administration.[72] This has been interpreted to mean that nalorphine was not an addicting drug in man.[80] However, because of the unpleasant psychic effects of nalorphine in this study,[72] dose levels equivalent to those used for experimental morphine addiction could not be achieved. For the same reason tolerance development could not be adequately studied, but Fraser[41] stated that tolerance did develop to the hallucinations of nalorphine in man.

Animals. Most of the narcotic effects listed in table 1 have been reported to occur to some degree after nalorphine in some species of animal (mouse, rat, guinea pig, rabbit, cat, dog, or monkey).[89, 139] In addition, recent studies on the effects of nalorphine and morphine on the bronchial and intestinal smooth muscle of animals indicated that their effects were similar.[50, 51, 101]

There were important differences however. In man nalorphine was approximately as potent as morphine in producing its effects. In animals nalorphine was a much weaker drug when given in sublethal doses. Despite this, the LD_{50} of nalorphine in mice was approxi-

mately the same as for morphine.[54, 57] In animals, nalorphine in doses similar to morphine was a mild sedative, produced little analgesia as measured by the increase in pain threshold, and did little else. In contrast to morphine, it did not produce a typical Straub tail in mice, antidiuresis in the rat,[115, 137] excitement in the cat, nor an increase in blood sugar in the rabbit and dog,[84, 107, 143] all of which were characteristic of narcotics. Similarly, levallorphan did not increase the blood sugar in the dog.[84, 107] The rate of tolerance development to nalorphine was low when compared to that of morphine in the rat.[75] Large intravenous doses of nalorphine produced a transient stimulation of respiration in rabbits and dogs [62, 68] and convulsions preceded death in mice.[62] Levallorphan in low doses depressed respiration in the rabbit; in high doses it produced marked initial stimulation of respiration, then depression.[100] In monkeys, nalorphine produced anxiety, crying, vomiting, hallucinatory behavior and clonic convulsions in large doses.[71] Nalorphine was more disruptive to adaptive or learned behavior in the mouse than was morphine which paralleled the experience in man.[7, 130]

Central Nervous System Stimulation by Nalorphine. Wood [139] concluded that nalorphine was an atypical central nervous system stimulant in man (anxiety and hallucinations). This was supported by observations of stimulation of respiration, convulsions, anxiety, and hallucinatory behavior reported in animals. In addition several investigators showed that the respiratory rate and minute volume of rats and dogs anesthetized with pentobarbital or chloralose-urethane were increased by large doses of nalorphine.[139] In the case of rats, the dose of nalorphine or levallorphan required to reduce pentobarbital induced respiratory depression was twice that of pentobarbital.[20] Kao and Belford [74] found that a large dose of nalorphine (30 mg./kg.) did not alter the respiratory center sensitivity of decerebrate dogs as measured by change in the slope of the $P_{A_{CO_2}}$-VA curve. However, their data also showed a parallel shift of this curve to the left which represented respiratory stimulation, although not necessarily due to increased respiratory center sensitivity.[11] On the other hand, nalorphine was found to increase the sleeping time of secobarbital in mice without altering the LD_{50} of secobarbital.[55] More recently Boyd and Pearl [14] were unable to alter the mortality rate from thioamylal in rabbits and dogs by several dose levels of nalorphine given as an antagonist. In a similar study, Weakley and Bergner [129] found that nalorphine increased the respiratory depression of intravenous secobarbital in both animals and man. Many observers [2, 26, 27, 30, 88, 112] failed to observe any stimulation of respiration by nalorphine or levallorphan given to patients depressed by barbiturates or anesthetics. The only exception to this overwhelming evidence is a single report of two patients whose barbiturate-induced respiratory depression was lessened by nalorphine.[25] From these data any central nervous system stimulation by the antagonists would seem to be similar to that of the non-specific analeptics and to require high doses.

Some recent unpublished data pertain to this problem.[83] Nalorphine in doses of 10 mg./70 kg. depressed the respiration of normal man to approximately the same degree as morphine when measured by shift in $P_{A_{CO_2}}$-VA curves obtained in response to CO_2 inhalations. However, when given in doses of 1 mg./kg. intravenously, the depression of morphine was much greater than that of nalorphine. Measurements after successive small increments of nalorphine indicated that respiratory depression was maximum after 10–20 mg. and subsequent doses did not increase the depression. This was not observed after similar increments of morphine. In addition, no increase in oxygen consumption was observed after either small or large doses of nalorphine in contrast to the increase in oxygen consumption which followed methylphenidate. Obviously nalorphine was not a typical analeptic in these doses in man.

Blocking Action of Narcotic Antagonists

When the antagonist was administered before the narcotic, the narcotic effects which were reported to have been blocked are listed in table 2. In some studies in man designed to elicit blocking effects, the patients studied were premedicated with a narcotic before

TABLE 2

NARCOTIC ACTIONS BLOCKED BY PRIOR ADMINISTRATION OF A NARCOTIC ANTAGONIST IN ANIMALS AND MAN

Drug Effect	Reference Numbers	
	Animals	Man
Death	Rat, rabbit, mouse—57, 136	
Respiratory depression	Rabbit—62, 126	27, 29
Analgesia	Rat—126, 138	
Sedation or hypnosis	Rat—117 Dog—126	
Bradycardia and hypotension		27
Vomiting	Dog—126	
Euphoria		43
Increased intestinal tone	Dog—50	8
Increased choledochal pressure		113

the experiment.[40, 121-123] These data were omitted because it was not clear whether antagonism or a blocking effect was demonstrated, especially since control values were obtained after the narcotic.

It was not always possible to determine from the reports whether the blocking action of a narcotic antagonist was complete or partial. For such effects as death, vomiting, and increased intestinal tone in animals, a complete block was observed. For respiratory depression and analgesia in animals, the degree of block varied with the doses of antagonist and narcotic used. For euphoria and increased choledochal pressure in man, only a partial block occurred.

The only notable failure of a narcotic antagonist to block a narcotic action was reported by Siker *et al.*[116] Pretreatment of patients with 0.02 mg./kg. of levallorphan intravenously only partially prevented the hypotension, tachycardia and postural hypotension which followed 1.5 mg./kg. of meperidine intravenously.

NARCOTICS FOLLOWED BY ANTAGONISTS

Antagonism of Large Doses of Narcotics. The antagonism of the effects of large doses of narcotic by an antagonist has been demonstrated for all narcotic actions listed in table 3. In all instances, antagonism was accomplished by a dose of antagonist smaller than the narcotic dose. In most of the animal studies all degrees of antagonism (partial, complete, more than complete) could be observed, depending on the parameter studied, and the absolute and relative doses of narcotic and antagonist used. However, in many studies in man, it was difficult to estimate the degree of antagonism which had occurred because predrug values were not recorded.

Antagonism of Therapeutic Doses of Narcotics. For the purposes of this discussion therapeutic doses will be considered as 15 mg. of morphine for the 70 kg. man or its equivalent in other narcotics. In every study listed in table 3, with the exception of those concerning vomiting, the intestine and biliary tract of man, a morphine antagonist was administered after one or more doses of narcotic which totaled 30 mg. or more of morphine or its equivalent. In all animal studies the doses of narcotic were far in excess of therapeutic doses in man. The reviewers have been unable to find a single instance of failure of antagonism of narcotic action when large doses of narcotic were followed by an antagonist. Similarly, the reviewers have not found any systematic study in which the administration of an antagonist after a single therapeutic dose of narcotic resulted in more than transient or slight antagonism. These studies are listed in table 4. The only exceptions found to these statements were: (1) The effects of single therapeutic doses of narcotics on the biliary or gastrointestinal tract

TABLE 3

NARCOTIC ACTIONS ANTAGONIZED BY NARCOTIC ANTAGONISTS IN ANIMALS AND MAN

Narcotic Effect	Reference Numbers	
	Animal	Man
Death (overdosage in man)	Rat, mouse—136	Many reports
Respiratory depression	Rabbit—62, 100 Rat—19	87, 102, 123
Analgesia	Rat—19 Mice—126 Dog—63	34, 102
Sedation or hypnosis	Rat—104 Dog—126	60, 87, 88
Miosis	Dog—117	43
Bradycardia	Dog—117	87
Hypotension	Dog—58, 104	27, 36
Vomiting	Dog—126	2
Euphoria		43
Increased cerebrospinal fluid pressure		78, 118
Decreased cerebral O_2 consumption		102
Hypothermia	Dog—117	
Antidiuresis	Rat—137	
Hyperglycemia	Rabbit—84	
Increased intestinal tone	Dog—50	8, 23, 24
Increased choledochal pressure		113

TABLE 4

FAILURES OF ANTAGONISM OF THERAPEUTIC DOSES OF NARCOTICS BY ANTAGONISTS IN MAN

Reference	Narcotic	Time Interval	Antagonist	Parameter Measured	Effect
105	Morphine 15 mg. subcutaneous	30 minutes	Nalorphine 10 mg.	Respiratory minute volume Unpleasant side effects	Stimulation followed by greater depression No antagonism
91	Morphine 15 mg. subcutaneous	2 hours	Nalorphine 5 mg. subcutaneous	Minute volume response to CO_2	Transient stimulation in one of four subjects
79	Morphine 10 mg. intravenous	1 hour	Nalorphine 10 mg. intravenous	Alveolar ventilation Alveolar carbon dioxide tension	No antagonism
69	Morphine 15 mg. or Meperidine 100 mg.	5–15 minutes	Nalorphine 25 mg.	Blood pressure, pulse, respiratory rate Sedation	No consistent change Increased
43	Morphine 30 mg. subcutaneous	105 minutes	Nalorphine 10 mg.	Miosis Euphoria Depressed minute volume Hypothermia	Antagonized Transient antagonism No antagonism No antagonism
96	Premedication narcotic	3–4 hours	Nalorphine	Minute volume response to CO_2	No antagonism (Ether anesthesia used)
120	Morphine 11 mg. subcutaneous	1 hour	Levallorphan 5–10 mg.	Minute volume and respiratory rate	No consistent change

have been antagonized by a single dose of nalorphine.[1, 3, 8, 23, 24, 113] The total experience in these six reports consists of observations on 13 patients. (2) There were case reports of patients who were excessively depressed by a therapeutic dose of narcotic and in whom the hypotension or respiratory depression was antagonized by nalorphine. Bodman [13] reported respiratory stimulation after 1–3 mg. of nalorphine in an unstated percentage of patients depressed by meperidine 50 mg. or pantopon 20 mg. No quantitative data were given. Finestone and Eksterowicz [35] antagonized the respiratory depression of 10 mg. of methadone with 10 mg. of nalorphine in one patient. Adriani and Kerr [2] reported respiratory stimulation by nalorphine in 11 patients presumably depressed by the narcotic given for premedication and a return of blood pressure to normal in 5 patients similarly depressed. They also reported 15 similar patients with respiratory depression and 5 with hypotension in whom nalorphine had no antagonistic effect. There may be other case reports which have not come to our attention and which provide additional exceptions. No comparable studies in animals utilizing doses in this range have been reported.

Degree of Antagonism. The primary determinant of the degree of antagonism seemed to be the dose of narcotic administered. After therapeutic doses of narcotic, little or no antagonism occurred (table 4). With moderate or large doses, partial to complete antagonism occurred (table 3). In the narcotic tolerant animal or the human counterpart, the narcotic addict, more than complete antagonism followed the narcotic antagonist. In the addict, a small dose of antagonist not only abolished morphine effects, but precipitated an acute abstinence syndrome (lacrimation, rhinorrhea, mydriasis, hyperpnea, tachycardia, hypertension, hyperpyrexia, restlessness, diarrhea and muscle twitching). In experimental morphine addiction, 15 mg. of nalorphine after 2–3 days of morphine treatment produced a mild abstinence syndrome. After several weeks of morphine, 1–2 mg. of nalorphine produced a severe abstinence syndrome.[135]

Additional evidence from other sources supported this relationship between narcotic dose and degree of antagonism. (1) In contrast to the experience in table 4, patients in whom accidental narcotic overdosage had occurred [89] or patients who received multiple small doses of narcotics as a supplement to anesthesia obtained dramatic antagonism from a small dose of antagonist.[88, 89] (2) Eckenhoff, Hoffman, and Dripps [30] noted that when nalorphine was given to parturient mothers just prior to delivery good antagonism of neonatal narcosis occurred in infants born of mothers moderately

or deeply depressed by 200 mg. of meperidine, but no measurable antagonism occurred in mothers who received less meperidine. In another extensive study by this group,[31] it was difficult to demonstrate any benefit to the infant from nalorphine given to parturient mothers who had received narcotics before delivery, except in those who were heavily sedated. They reported a similar relationship when levallorphan was used.[28] (3) Keats and Mithoefer [79] showed that 10 mg. of nalorphine did not antagonize the respiratory depression of 10 mg. of morphine given intravenously one hour apart. However, antagonism did occur if a "priming" dose of 15 mg. of morphine were given 5–8 hours before the second dose of morphine. (4) In chronic spinal dogs, antagonism of morphine-depressed spinal reflexes by nalorphine was greater when the reflex depression by morphine was greater. Antagonism could be demonstrated if many small doses or if one large dose of morphine had been administered.[134] (5) When a morphine-nalorphine mixture was given chronically to rats, the analgesic effect of the mixture decreased more rapidly with time than in comparable animals given morphine alone. This was considered to be the result of the proportionately greater antagonistic effect of nalorphine as the total dose of morphine increased.[103]

Differential Antagonism of Narcotic Actions by Antagonists. Studies suggesting that all narcotic actions were not antagonized equally appeared early. In 1952 Fromherz and Pellmont [44] reported that levallorphan was less active than nalorphine in antagonizing analgesia compared to their respective activities in antagonizing respiratory depression. A much later report on several antagonists chemically similar to levallorphan supported the original study.[17] The N-propargyl analog of levallorphan was found to be a potent antagonist of respiratory depression in the rabbit, but not of analgesia in the rat. Conversely the N-propyl derivative was a potent antagonist of analgesia but not of respiratory depression. Gray [50] noted that antagonist doses which reversed intestinal spasm and prevented vomiting did not antagonize narcotic sedation in dogs. The studies of Costa and Bonnycastle [19] suggested that a chemical specificity existed as well as differential antagonism with an optimal dose ratio. Using rabbits, they found that a dose of nalorphine could be found which would antagonize the respiratory depression but not the analgesia of morphine. This was also true of levallorphan against levorphan (current generic name is levorphanol). The converse, however was not true. Both levallorphan against morphine, and nalorphine against levorphan resulted in equal antagonism of analgesia and respiratory depression. Additional support for a drug specificity came from the observation that the respiratory depression of meperidine in the dog was not antagonized by nalorphine [68] and that it was difficult to precipitate an abstinence syndrome with nalorphine in meperidine addicts.[133] In man, Fraser, Van Horn, and Isbell [43] noted antagonism of morphine miosis and euphoria by nalorphine without antagonism of respiratory depression. We have repeatedly observed during studies in man of antagonism of large doses of morphine by nalorphine that even when respiratory depression was dramatically antagonized, subjects remained slightly groggy, or dizzy, or had difficulty concentrating.[83] This was noted by Eckenhoff, Elder and King,[27] as well as in several case reports.

Narcotic-Antagonist Ratios. The ratio of antagonist dose to narcotic dose for production of maximum antagonism seemed to depend primarily on the narcotic action measured and the dose of narcotic used. This latter point was illustrated by Miller, Gilfoil and Shideman [100] who showed in the rabbit that the optimal ratio of levallorphan to morphine for complete antagonism of the respiratory depression of 4 mg./kg. of morphine was 2:4. However, when rabbits were given 32 mg./kg. of morphine this ratio decreased to 5:32. On the other hand, in the antagonism of the electroencephalographic electrogenesis of morphine by nalorphine, an all or none response, either complete or no antagonism, was observed.[47] Complete antagonism occurred with nalorphine-morphine ratios ranging from 1:600 to 1:3. Increasing the nalorphine percentage increased the duration but not the degree of antagonism. Similarly Gray [50] has clearly shown that no critical or constant narcotic-antagonist dose ratio ex-

isted for antagonism of the increased intestinal tone induced by 4 narcotics in the dog. Regardless of the dose of narcotic (which ranged over one hundred fold) or the order of administration, the absolute amount of antagonist necessary to prevent or reverse the narcotic effect remained fairly constant. This last observation may be pertinent to the exceptions noted above in antagonism of the effects of therapeutic doses of narcotics on the intestinal and biliary tract and suggested that the mechanism involved in antagonism of central nervous system actions of morphine may be different from that of smooth muscle actions. In general, the dose of narcotic seemed to be the primary factor in determining whether or not antagonism would occur, the degree of antagonism and the dose of antagonist (ratio) producing maximum antagonism.

Simultaneous Administration of Narcotic and Antagonist

The clinical use of narcotic-antagonist mixtures was based on studies in animals which showed that some actions of narcotics were more readily antagonized than others. This has been amplified to suggest that certain combinations of narcotic and antagonist in an optimal dose ratio elicited this differential effect to its greatest degree and this would also occur when both drugs were administered simultaneously. This has been difficult to document because there have been few well-controlled studies in which more than one parameter of drug action were studied. Unfortunately in many studies [118, 119, 122, 123] the subjects were given morphine or meperidine before study and antagonism in a highly selected situation was actually studied.

The acceptable data in animals and man have been summarized in tables 5 and 6. Only two studies (table 5) in animals were directed to simultaneous mesaurement of more than one parameter of narcotic action and successfully demonstrated a dissociation.[104, 141] A third failed to demonstrate dissociation.[115] The data of Orahovats, Winter, and Lehman [104] clearly showed that a 32:1 ratio of morphine to nalorphine could produce anal-

TABLE 5

Simultaneous Administration of Narcotic and Antagonist in Animals

Drugs	Dose of Narcotic	Narcotic-Antagonist Ratio	Narcotic Action Studied	Results	References
Levorphan-Levallorphan	8 mg./kg.	64:1 32:1	Analgesia Tolerance to analgesia	Incomplete antagonism Inhibited tolerance development	103 Rat
Levorphan-Levallorphan	4–16 mg./kg. 2 mg./kg.	8:1, 16:1 32:1, 64:1 13:1	Analgesia and hypnosis Analgesia, emesis, bradycardia, hypotension	At 32:1 ratio hypnosis antagonized, but not analgesia All except analgesia antagonized	Rat 104 Dog
Morphine-Nalorphine or Levallorphan	Many	Many	Mortality	Decreased mortality rate but not complete protection	Mouse 54 56
Morphine-Nalorphine	10 mg./kg.	1:2.5, 6:1 12:1	Analgesia Antidiuresis Delayed gastric emptying	At all ratios, there was incomplete antagonism of all three actions studied	Rat 115
Levorphan-Levallorphan	0.002–0.008 m.M./kg.	Many 1:1 to 15:1	Analgesia Respiratory depression	At all ratios except 5:1 both actions antagonized equally and incompletely. (See text)	Rabbit 141
Levorphan-Nalorphine	2 mg./kg.	1:1 moles	Hyperglycemia	Transient antagonism	Dog 107
Levorphan-Levallorphan	0.008 m.M./kg.	5:1	Tolerance to analgesic action	Inhibited tolerance development	Rabbit 142
Morphine-Nalorphine	1.6 mg./kg.	8:1, 4:1, 2:1	Learned behavior	Addition of antagonist in any ratio disrupted adaptive behavior	Rat 130
Morphine or Normorphine-Nalorphine	10 mg./kg. (intracisternal)	1:1	Analgesia	Incomplete antagonism	Rat 93
Morphine Nalorphine	10 mg./kg.	10:1, 3:1, 1:1, 1:3	Delayed charcoal meal propulsion in small intestine	Complete antagonism 1:1. Incomplete at other ratios	Rat 51
Meperidine-Levallorphan	8–16 mg./kg.	40:1, 160:1	Analgesia	Decreased analgesia to 50 per cent	Rat 95

TABLE 6

SIMULTANEOUS ADMINISTRATION OF NARCOTIC AND ANTAGONIST IN MAN

Drugs	Dose of Narcotic	Narcotic-Antagonist Ratio	Narcotic Action Studied	Results	Reference
Morphine-Nalorphine	10 mg. or 15 mg. subcutaneous	5:1, 3:1	Analgesia Respiratory depression Subjective effects	No antagonism Increased No antagonism	91
Levorphan-Levallorphan	10 mg. subcutaneous	10:1	Sedation Respiratory depression	Increased "Less." Did not measure	45
Levorphan-Levallorphan	3–5 mg. subcutaneous	10:1, 1:1	Analgesia Respiratory depression	No antagonism No antagonism	29
Levorphan-Levallorphan	0.054 mg./kg. intravenous	5:1	Respiratory depression	Incomplete antagonism	125
Morphine-Nalorphine	20 mg. subcutaneous	1:2.5	Antidiuresis	Slight to no antagonism	115
Morphine-Nalorphine	8 mg. subcutaneous	8:1, 4:1, 2:1	Psychomotor performance	Addition of nalorphine disrupted psychomotor performance. Side actions (sweating, vomiting) greater after mixture	7
Morphine-Nalorphine	30 mg. subcutaneous	10:1, 5:1, 3:1	Miosis Respiratory depression Hypothermia Euphoria	Incomplete antagonism No antagonism No antagonism Antagonized for 2–3 hours then reappeared	43
Heroin-Nalorphine	10 mg. subcutaneous	1:1	Miosis Respiratory depression Hypothermia	Incomplete antagonism Increased No antagonism	
Morphine-Nalorphine	10 mg. subcutaneous	2:1, 1:1, 8:1, 4:1	Respiratory depression Subjective effects Analgesia	No antagonism, increased Increased Antagonizes at high ratios then exerts its own analgesia at low ratios	66
Morphine-Nalorphine	10 mg./70 kg.	1:1	Respiratory depression	No antagonism	131
Meperidine-Levallorphan	22.5 mg. subcutaneous	300:1, 150:1	Pain threshold elevation (heat)	No antagonism. 300:1 ratio better than meperidine alone	64
Levorphan Levallorphan	3 mg. subcutaneous	10:1	Respiratory depression	No antagonism	128
Morphine-Levallorphan Meperidine-Levallorphan	10 mg. subcutaneous 100 mg. subcutaneous	20:1, 5:1 80:1	Increased choledochal pressure	Incomplete antagonism (Statistical significance?)	96
Meperidine-Levallorphan	50–100 mg. intramuscular 1 mg./kg. intravenous	80:1	Analgesia Nausea, vomiting, sweating Respiratory depression	No antagonism No antagonism Incomplete antagonism	65
Levorphan-Levallorphan	3 mg. intramuscular 3 mg. intravenous	10:1	Respiratory depression	Depressed minute volume and respiratory rate	109

gesia without sedation in rats and analgesia without emesis and with less circulatory depression in dogs. Lower ratios antagonized analgesia as well as hypnosis and larger ratios produced no antagonism of either. Respiratory depression was not measured. In fact morphine stimulated the respiration of the dogs (panting). In the other study using rabbits,[141] only by administering high narcotic doses and only at one narcotic-antagonist ratio could a statistically significant decrease in the respiratory depression with maintenance of analgesia be demonstrated. The other studies simply demonstrated some antagonism of a single narcotic action by a mixture.

In man, Fraser, Van Horn and Isbell [43] were able to show antagonism of miosis and euphoria by administration of a combination of morphine and nalorphine to postaddicts, but observed no antagonism of the hypothermia and respiratory depression of morphine. Two sets of investigators [66, 91] using several combinations of morphine and nalorphine found the same or greater respiratory de-

pression following the combination than after morphine alone. One of these groups [66] also reported an antagonism of analgesia and an increase in unpleasant subjective side actions with the combination compared to morphine alone. The other [91] reported no antagonism of analgesia or side actions. Eckenhoff *et al.*[29] corroborated the lack of antagonism of respiratory depression by combinations of racemorphan and levallorphan, as did Wallenstein, Bellville and Houde [128] with mixtures of levorphan and levallorphan. However, two other groups [25, 65] reported partial antagonism of respiratory depression on simultaneous administration of narcotic and antagonist. Hossli and Bergman [65] found no difference in the analgesia of meperidine alone compared to meperidine with levallorphan in a 80:1 ratio in postoperative patients. This same ratio of drugs given intravenously to unpremedicated patients produced significantly less depression of respiratory rate and minute volume than meperidine alone in a second group. This study will be discussed later. The more refined studies of Thomas and Tenney [125] utilizing unpremedicated normal subjects also showed that a combination of levallorphan with levorphan was significantly less depressant to the respiration than levorphan alone. The remainder of the studies demonstrated no antagonism or slight antagonism by a mixture for some single narcotic action only. Additional studies concerning simultaneous administration will be discussed below.

Clinical Studies

Analgesia. One report in this area concerned changes in pain threshold after various combinations of antagonist with narcotic in man.[64] Beecher,[10] has described the limitations of data obtained in this manner especially in terms of applicability to analgesia in man. He also pointed out the controls necessary for an adequate study of analgesia in man such as double blind conditions, coded drugs, randomization of doses, crossover design and use of a standard for comparison.[9] Unfortunately most studies purporting to show that the narcotic-antagonist mixtures maintain analgesia while antagonizing respiratory depression ignored these essential controls.

In the studies reviewed, there were two major difficulties. First, while respiratory depression was quantitated in some way, either by change in respiratory rate, minute volume, or response to CO_2 inhalations (overlooking the failure to measure carbon dioxide tension, a requisite for quantitation of drug effects on respiration,[11, 29]) no attempt was made to measure analgesia with any similar precision. Acceptable techniques to quantitate analgesia in man are complex and tedious.[10, 67, 76, 90] Even with adequate controls, small differences are difficult to distinguish. Studies which showed antagonism of respiratory depression did not demonstrate complete antagonism but rather "less" depression and the differences were not great. To detect an equivalent percentage difference in analgesia, elaborate techniques would have been necessary. It is, therefore, difficult to rely on data of investigators who concluded an absence of antagonism of analgesia by casual observations of pain relief classified as excellent, good, fair and poor. Secondly, some investigators have used subjects who received narcotics in the recent past. Under these circumstances, antagonism of respiratory depression was most likely to occur (see previous section). A narcotic abstinence period of four to six hours was not sufficient, since it has been shown that a single dose of morphine five to eight hours prior to the administration of a second narcotic dose enabled antagonism to occur where it had not previously.[79]

Cullen and Santos [21] and Auerbach and Coakley [4] both showed that a narcotic-antagonist mixture produced less depression of respiratory rate or minute volume than the administration of the narcotic alone. In one study analgesia was graded. In the other, it was simply stated that pain was relieved. Patients in both studies probably had had narcotics four or more hours prior to the administration of the mixture. Shiffrin, Balagot, and Sadove [114] studied 6 patients with chronic pain who had been receiving narcotics. They were able to demonstrate significantly less depression of minute volume 30 minutes after a meperidine-levallorphan mixture than after meperidine alone. Their analgesic and side action data were too few to be meaningful, but they claimed no loss of analgesia. A

larger study by this group using postoperative patients in the recovery room was directed to the same problem.[111] The respiratory depression, analgesia, sedation and other side actions following 25 and 50-mg. doses of meperidine were compared to those of three dose ratios of meperidine-levallorphan containing either 25 or 50 mg. of meperidine. Double blind conditions, placebo control, and coded drugs were used. However, approximately 75 per cent of their subjects received meperidine premedication, and 10 per cent received meperidine as a supplement during the anesthetic. Despite this, all drug combinations except the placebo and the meperidine (25 mg.)-levallorphan (0.25 mg.) mixture produced significant depression of minute volumes compared to predrug controls. The investigators then showed that the average of all the postinjection minute volume values for all narcotic-antagonist mixtures and placebo was significantly less than the postdrug values of meperidine alone. However, the predrug minute volumes for the 25 mg. and 50 mg. meperidine groups were 10–25 per cent lower than predrug minute volumes for the mixture groups, and this difference was not leveled by converting to percentage changes. They found no statistically significant difference in mean analgesia scores between meperidine alone and meperidine-levallorphan mixtures. They were also unable to show any significant difference in the mean analgesia score between 25 mg. and 50 mg. of meperidine. Since their analgesia measuring technique could not detect the effects of a 100 per cent increase in dose, it seemed unlikely that they could have detected the degree of antagonism of analgesia comparable to the antagonism claimed in their respiratory data. As to side action liability, their 50-mg. data actually suggest an increase in sedation and in "other reactions" with all mixtures over meperidine alone. Some of the same criticisms apply to a more recent study by Hossli and Bergmann.[65] They showed that a 80:1 combination of meperidine and levallorphan, when given as 1 mg./kg. of meperidine intravenously, produced significantly less depression of minute volume and respiratory rate in unpremedicated patients than did meperidine alone in a second group of 15 patients. They then compared the analgesic effect and side actions in postoperative patients. They found no difference in analgesia or side actions between the mixture and the narcotic alone. However, their data showed that there was also no difference in the analgesia scores when the dose of meperidine-levallorphan was increased from 50 to 75 and 100 mg., indicating either that their technique was too insensitive or that antagonism of analgesia occurred at the higher doses.

Mergerian, White, and Marcus[99] studied the effects of many ratios of alphaprodine and levallorphan or its N-propargyl derivative on minute volume, respiratory rate, and "responsiveness" in postoperative patients in the recovery room. Although not stated, all patients probably received a narcotic prior to operation. Certain of the ratios studied were considered optimal in that they produced no significant respiratory depression (minute volume) but did produce "diminished responsiveness." An identical study was carried out using meperidine and levallorphan.[88] In both studies, the patients probably did not have pain at the time of study. In no sense can their "diminished responsiveness" be equated with analgesia. Barbiturates, other hypnotics, and promethazine all diminish responsiveness without relieving pain to any great degree.[82] Even morphine can produce sedation and sleep ("diminished responsiveness") without relief of pain.[76]

There were two studies in which all essential controls were observed and concerned analgesia with narcotic-antagonist mixtures. Lasagna and Beecher[91] compared the analgesic effect of 10 mg. of morphine with that of a mixture of 10 mg. of morphine and 2 mg. of nalorphine in postoperative patients. The analgesia following the mixture was less than that of morphine but the difference was not statistically significant. In this study, morphine and the mixture were alternated in the same patients and all patients probably received a preoperative narcotic. Whether the added nalorphine acted as an antagonist or not depended on the order of drug administration in each patient. It was, therefore, difficult to evaluate their data. Houde and Wallenstein[66] found definite antagonism of analgesia when morphine was combined with nalorphine and compared to the effects of morphine alone.

These investigators used patients with chronic pain of cancer in a complete crossover study. Probably these patients had been receiving narcotics prior to this study and could be considered narcotic tolerant to some degree. This may be the reason the antianalgesic activity of nalorphine was so readily demonstrated.

Most of the studies discussed above were limited to the use of a single or at most several doses of a narcotic-antagonist mixture in each patient. There is little information on chronic use of mixtures. However, their utility would seem to be limited, since with successive injections increased morphine physical dependence would develop and the activity of the antagonist would increase with each dose. Cullen and Santos [21] noted in their few patients treated chronically that if the antagonist content of their levorphan-levallorphan mixture was increased, patients complained of nervousness, restlessness and intensification of pain rather than analgesia. All these can be considered signs of morphine antagonism (abstinence syndrome). Fraser [41] reported that after 2 to 3 days of regular administration of morphine-nalorphine mixtures to postaddicts, morphine abstinence signs (sweating and disturbing mental effects) began to appear with each injection and euphoria was no longer present. The chronic use of a 3:1, 10:1, and 15:1 mixture of morphine-nalorphine in their postaddicts did not prevent the appearance of an abstinence syndrome on acute withdrawal, although the syndrome was less intense than the one after morphine alone in these same subjects.

As A Supplement to Anesthesia. The basis for supplementing general anesthesia with narcotic-antagonist mixtures was the same as for its use as an analgesic, namely, to provide analgesia without respiratory depression. Their use during nitrous-oxide thiopental anesthesia was first suggested by Hamilton and Cullen [59] who injected levallorphan during anesthesia and noted that subsequent doses of meperidine, levorphan or morphine produced less respiratory depression than expected. Subsequently the same investigators [60] observed that if levallorphan were given during thiopental-nitrous oxide-meperidine anesthesia, respiration increased and anesthesia "lightened." However subsequent meperidine doses did not depress respiration but did deepen anesthesia. It was assumed that analgesia was maintained but respiratory depression was blocked by levallorphan.

Subsequently Foldes and his group advocated the use of narcotics and antagonists as supplements to thiopental-nitrous oxide anesthesia.[37, 38, 39] Minor variations in techniques have been introduced by others,[85, 94] but the results described in all reports were similar. Patients premedicated with narcotics were given levallorphan (0.02 mg./kg.) intravenously followed by alphaprodine (1 mg./kg.) or meperidine (2 mg./kg.) 3 to 6 minutes later. Nitrous oxide-oxygen (80 per cent) was then administered. If anesthesia was inadequate further increments of the narcotic were given intravenously. Whenever adequate anesthesia could not be maintained by the narcotic alone without depression of the respiratory rate below 12 per minute, a small dose of thiopental was given. If excessive respiratory depression occurred, additional doses of levallorphan were given. The mg./minute requirements for narcotic and thiopental were calculated for these patients and compared to a group similarly treated except that levallorphan was omitted. In all three reports thiopental requirements were decreased to 25–50 per cent of that of the control group while the narcotic dosage was increased 300–500 per cent over the control group. Thus, the administration of the antagonist prior to anesthesia enabled the anesthesiologists to use one-fourth the amount of thiopental (a weak analgesic) and required them to use five times as much meperidine or alphaprodine (potent analgesics) to accomplish the same thing. To the reviewers these data constitute a powerful argument supporting the antagonism of analgesia as well as respiratory depression. It was also clear from these data that depth of anesthesia was not synonymous with analgesia, since depth of anesthesia could be increased equally as well by thiopental as by a narcotic. There is a considerable difference in the analgesic potency of these two classes of compounds.

Use in Obstetrics. The use of nalorphine in obstetrics to prevent or treat neonatal apnea, respiratory depression or narcosis was studied promptly after its introduction into clinical

medicine.[30, 31] It was soon learned that nalorphine given intravenously to mothers ten minutes before delivery reduced the time of onset of breathing in newborns when mothers were moderately or markedly depressed by narcotics. Obviously, nalorphine passed through the placenta readily. In addition, nalorphine injected into the umbilical vein of newborns depressed by narcotics resulted in striking stimulation of respiration.[31] The beneficial results of the latter technique were confirmed in a subsequent study by Prescott [108] who found that newborns given nalorphine were easier to resuscitate. However, just as narcotic antagonists failed, in general, to antagonize therapeutic doses of narcotics, so nalorphine had no beneficial effect in newborns of mothers who were only mildly depressed by narcotics.[30] From these reports, it was also apparent that careful observations of mother and newborn were required to demonstrate any beneficial effects of nalorphine even when large doses of narcotic had been given to the mother.

More recent obstetrical studies on the use of narcotics combined with or followed by antagonists contributed little additional information. In most, no control group of patients (narcotics without antagonist) was available for comparison. When analgesic efficacy was evaluated, none of the requisite controls mentioned above were used. In evaluating neonatal apnea or depression, breathing or crying times, measurements of ventilation, or Apgar ratings were usually not recorded. Such reports accomplish little more than to testify that a certain combination of drugs was not lethal in a specified number of patients.

The merit of various combinations of narcotics and antagonists was the subject of seven reports.[33, 46, 48, 49, 53, 61, 92] In none of these was control observations made and the results could not be evaluated. Baker [6] tried a mixture of meperidine and nalorphine for analgesia in labor. In two groups of patients, each with a simultaneous control group, the analgesia, amnesia, and incidence of fetal depression was approximately the same whether meperidine alone or combined with nalorphine (20:1 and 50:1) was used. In a third group in which meperidine-nalorphine (20:1) was used in a second trial, no control patients were used and the results were far better than in the first trial. The author therefore recommended the 20:1 ratio for improved analgesia and amnesia with a reduction neonatal depression.

Backner, Foldes and Gordon [5] studied an alphaprodine-levallorphan (50:1) mixture in obstetrics. There was no control group for comparison of analgesic effectiveness. A control group was available for one portion of their data, although they give no information about it except that the patients received no levallorphan. They showed that the mean breathing and crying times of infants born of mothers receiving the mixture were significantly less than the means of infants whose mothers received unspecified amounts of narcotics without antagonist provided the mothers also received nitrous oxide-oxygen-ether anesthesia. There was no significant difference between the two groups when regional anesthesia was used. In their alphaprodine-levallorphan group 160 patients received regional anesthesia, and only 40 received general anesthesia. Each was compared to a control group of 100 patients. In the general anesthesia control group there were 3 infants who did not breathe for 15, 17, and 18 minutes. These results were just the reverse of those of Eckenhoff, Hoffman and Funderberg [31] who could demonstrate the effectiveness of nalorphine in infants born of mothers with regional anesthesia but not with general anesthesia.

In a study similar to Baker's,[6] Bullough [15] reported on four groups of obstetrical patients who received either meperidine alone, a 50:1 meperidine-nalorphine mixture, a 20:1 meperidine-nalorphine mixture or a 50:1 meperidine-levallorphan mixture. There were approximately 100 patients in each group. The milligrams of meperidine used per patient and per hour of labor was increased when either antagonist was added to meperidine. Analgesia was estimated by the patient on the day following delivery (retrospective evaluation) and the percentage of "good analgesia" increased when the mixtures were used. Amnesia (according to the midwife's assessment) was also greater after the mixture. (With greater amnesia, what of the validity of greater analgesia based on retrospective information?) The incidence of neonatal asphyxia was less.

Few if any of the differences noted would prove to be statistically significant had they been tested. As the author admitted, the study has other limitations in that the patient groups were not randomly selected and the groups were studied consecutively over a five-year period instead of simultaneously. In this study, as in all the recent ones mentioned above, double blind conditions were not observed.

Finally, Roberts *et al.*[110] measured the mean minute volume of 177 newborns whose mothers received meperidine analgesia for labor and compared this to the mean minute volume of 178 newborns of mothers who had received meperidine-levallorphan (150:1) analgesia. There was no significant difference in minute volumes between the two groups of newborns.

None of these studies could be considered to have demonstrated that the use of mixtures decreased the hazard of neonatal apnea, narcosis or depression while providing equal or better analgesia. Disregarding the failure to measure analgesia in an acceptable way, the investigators have not satisfactorily demonstrated any decrease in the incidence of neonatal asphyxia. Three investigators [6, 15, 48] have been impressed with their ability to use higher and more frequent doses of meperidine for analgesia when it was combined with an antagonist. They did not suggest that perhaps the reason was that analgesia was also antagonized and higher doses were required. The conclusion of Lasagna [89] in 1954 seems equally pertinent today. "These results strongly suggest that there is little reason to assume the arrival of a pharmacological millennium in obstetrics because of the availability of nalorphine."

Comment

It would be appropriate at this point to review the mechanisms postulated to underlie antagonism of narcotics by antagonists. However Wikler has recently reviewed this subject [133] and newer data would not alter his appraisal. Obviously, simple preferential substitution of nalorphine molecules at receptor sites occupied by morphine molecules could account for only a portion of the observations made. The relationship of degree of antagonism to dose of narcotic and the fact that abstinence symptoms (not characteristic of either narcotic or antagonist effects) appeared after an antagonist in narcotic tolerant animals and addicted humans strongly supported a mechanism suggested by both Lasagna [89] and Wikler.[133] They proposed that narcotic antagonists were effective only when narcotic administration had been sufficient to produce physical dependence. Stated differently, narcotic antagonism was the result of the release of whatever cellular alterations constituted physical dependence. Wikler, Fraser, and Isbell [135] have shown that postaddicts readdicted experimentally, developed demonstrable physical dependence after only nine injections of morphine. We have suggested that two morphine injections were sufficient when antagonism of respiratory depression was measured.[77] Woods [139] postulated a modified molecular substitution theory based on the dual action concept of narcotic action. In this theory the narcotic antagonist substituted only at sites responsible for the depressant actions of narcotics but not for the stimulant actions either because of differing receptor affinities or cell membrane characteristics.* Obviously, these theories are not mutually exclusive, nor all-inclusive. For example, a simple molecular substitution theory explains well the observations on antagonism of morphine effects on the gastrointestinal and biliary tract, especially since current evidence indicates that nalorphine actions on smooth muscle are different from morphine in man. On the other hand, the physical dependence mechanism accounts nicely for the antagonism of central nervous system effects, especially the failure of antagonism of therapeutic doses of narcotics. It would also account nicely for the differential antagonism which appeared when large doses of narcotic were antagonized. Tolerance to the euphoric, analgesic, respiratory depressant, miotic, and smooth muscle actions of morphine develop at differing rates in man.[133] The development of tolerance to narcotics is associated with the development of physical dependence, although these two are not necessarily related. However, a differing rate of physical dependence development for several

* This theory has been recently retracted by its major proponent, M. H. Seevers.

narcotic effects could account for differential antagonism when antagonists follow a narcotic.

Regardless of theory, accumulated evidence indicates that narcotic antagonists do not produce antimorphine effects in the absence of previously administered narcotic and are only slightly or not at all effective as an antagonist unless the previously administered narcotic is in excess of therapeutic doses. The effects of simultaneously administered narcotic (in therapeutic dose) and antagonist could, therefore, not be expected to be antagonistic, but rather to be the resultant of the effects of the individual drugs. Since the effects of antagonists given alone are qualitatively similar to those of narcotics (exceptions noted in table 1), the resultant effect should be similar to that of a narcotic. If there are quantitative differences between antagonist and narcotic in potency for specific drug actions, for example, analgesia or respiratory depression, then the degree to which the specific effect would appear after a mixture would depend on the degree to which each drug was effective. Since these drugs compete for receptor sites, additive effects would not be expected. Unfortunately, insufficient data are available on the quantitative effects of antagonists alone to enable predictions of the effects of mixtures. However, since both have the same effect, any difference in degree between the effect of a narcotic compared to a mixture is likely to be small. This has been the general experience of studies in man.

The results of one study only [43] are not in accord with such an explanation. In this, patients received 30 mg. of morphine, a dose in excess of a therapeutic dose, combined with nalorphine, and euphoria and miosis did not appear. In this study, because of the amount of morphine given, antagonism may have occurred. Other studies in man were not considered by the reviewers to have satisfactorily demonstrated differential antagonism of analgesia and respiratory depression on simultaneous administration. A similar explanation could apply equally well to the animal data even though much larger narcotic doses were used and antagonism probably did occur. Since nalorphine is a much less potent drug in animals than in man, a decreased narcotic action on simultaneous administration should be more readily demonstrated either by antagonism or competitive effects. This too has been the general experience. In only one animal study [104] has differential antagonism of morphine effects been impressively demonstrated on simultaneous administration and this did not include respiratory effects. In other studies using simultaneous administration, either all parameters studied were decreased to approximately the same degree or antagonism of only one narcotic action was studied. The critical question of differential antagonism seems to have been avoided in most studies.

In accord with this speculation is the fact that only two well-conducted studies in man demonstrated a lesser respiratory depression by a mixture compared to the narcotic and in these the drugs were given intravenously.[65, 125] The drugs were given subcutaneously or intramuscularly in all studies which failed to show a difference.[29, 43, 66, 91, 128] † Since Woods [140] demonstrated that nalorphine enters the dog brain three to four times more rapidly than morphine, the difference in the route of administration may account for the different results. The higher blood concentration obtained by the intravenous route may have permitted relatively more antagonist than narcotic to enter the brain. If the antagonist (levallorphan) were a less potent respiratory depressant than the narcotic (meperidine or levorphan), then lesser respiratory depression would result from a mixture or an antagonist blocking action would result. In view of this, a more pertinent comparison might be the effect of a mixture compared to the effect of the antagonist content alone. Against this argument is the recent observation [47] that in rabbits the electroencephalographic changes after intravenous nalorphine develop only after a latent period of 15–30 minutes in contrast to the prompt electroencephalographic effects observed after intravenous morphine. Obviously, the relative ease of penetration of the drugs into the brain is an important consideration and there are no such data for man.

The data reviewed here provide no pharmacological basis for the clinical use of narcotic-

† Unpublished data of Lasagna failed to show antagonism of the respiratory depression and other side actions of levorphan by the addition of levallorphan.

narcotic antagonist mixtures. It is yet to be demonstrated satisfactorily that the simultaneous administration of therapeutic doses of narcotic and antagonist to patients who have received no previous narcotic will result in lesser side actions while maintaining analgesia. On the other hand, the administration of such mixtures to patients who have received narcotics in the recent past can be expected in some circumstances to produce lesser effects than if the narcotic alone were administered. However, it is yet to be demonstrated that this antagonism does not apply equally well to analgesia as to respiratory depression. There is no pharmacologic basis at present for the use of narcotic-antagonist mixtures for preanesthetic medication, as a supplement to anesthesia, or in the treatment of postoperative or labor pain. The problems associated with the chronic administration of mixtures, especially the appearance of withdrawal symptoms, have been discussed above. Mixtures have not been found useful either for the treatment of chronic pain nor to prevent tolerance development and addiction in man.

Summary

The pharmacological and clinical data pertaining to the use of mixtures of narcotics and narcotic antagonists administered simultaneously to animals and man have been reviewed. To evaluate these data critically, certain aspects of the pharmacology of the narcotic antagonists, when used alone and in relationship to narcotics, have also been reviewed. Data pertaining to the degree of antagonism of narcotic effects by antagonists and to differential or preferential antagonism of narcotic effects have been emphasized. Clinical studies designed to show that simultaneous administration of antagonist and narcotic provide analgesia equal to that of the narcotic alone with lesser respiratory depression have been reviewed in the greatest detail. From these studies as well as from theoretical considerations, the achievement of this objective by the use of mixtures of antagonist and narcotic does not seem likely with drugs studied to date.

Addendum

Since preparation of this manuscript, several pertinent publications have come to our attention and merit inclusion. L. Grumbach and H. I. Chernov (*Fed. Proc. 20: 165, 1961*) reported an extensive study of the analgesic effectiveness of combinations of narcotics and narcotic antagonists simultaneously administered to the rat. The analgesic effect of ten analgesics given alone and in various combinations with nalorphine and levallorphan were measured. They found that the dose of antagonist required to reduce the analgesia of any narcotic studied by 50 per cent was a constant for each antagonist regardless of the relative potency or chemical nature of the analgesic. These results indicated that the analgesics studied have the same mode of action regardless of chemical nature and that their antagonism by nalorphine and levallorphan is effected by a common mechanism independent of the relative potencies of the analgesic.

A. C. Posner (*Brit. Med. J. 1: 124, 1960*) in a letter to the editor reported the results of a double blind study in which meperidine and meperidine combined with levallorphan (80:1) were used to treat the pain of labor in 1,420 patients. Posner measured the breathing time, crying time, and sustained breathing time of the newborns. The newborns were grouped according to time intervals between administration of the last dose of analgesic and delivery. For some of the time intervals, the breathing time, crying time and sustained breathing time of infants whose mothers received the meperidine-levallorphan mixture were significantly shorter than those of mothers who received meperidine alone. The magnitude of the differences was not reported and no mention was made of the relative analgesic efficacy of the two treatments. Proper evaluation of this report must await publication of the data.

Eddy *et al.* (*Eddy, N. B., Piller, M., Pirk, L. A., Schrappe, O., and Wende, S.: Bull. Narcotic 12: 1, 1960*) studied the effect of the addiction of levallorphan on the rate of tolerance and physical dependence development to morphine in man. Morphine and a morphine-levallorphan mixture (50:1) were administered in a double blind fashion to 19 patients with chronic pain for periods up to 14 weeks. Tolerance development was estimated by rate of increase in dose required for pain relief and physical dependence was estimated by the intensity of withdrawal signs after periodic administration of nalorphine. Their data suggest that the addition of levallorphan decreased the rate of development of tolerance and physical dependence. However, after 4 weeks of treatment with the mixture, tolerance was definitely present in 2 of 9 patients and physical dependence was definitely present in 4 of 8 patients. When compared to the results in patients who received only morphine, the differences were not great and suppression by levallorphan was of short duration. The incidence of side effects decreased from week to week in patients who received morphine. However, in patients who received the mixture, side actions continued to appear throughout the treatment period. The authors postulated that either the addition of levallorphan deferred the develop-

ment of tolerance to the side effects of morphine, or that the persisting side effects were abstinence symptoms precipitated by the levallorphan in the mixture. From the similar experience of others, the latter explanation seems the more likely to the reviewers. In this paper the authors mentioned unpublished observations of Seevers and Deneau on chronic administration of several morphine-levallorphan mixtures to monkeys. They found that the intensity of the abstinence syndrome following mixtures was definitely less than that usually seen after morphine and that a 1:1 morphine-levallorphan mixture completely suppressed physical dependence development in the monkey.

The unpublished investigations referred to in this review were supported by a grant awarded by the Committee on Drug Addiction and Narcotics, National Academy of Sciences–National Research Council, from funds contributed by a group of interested pharmaceutical manufacturers.

REFERENCES

1. Adelman, M. H., and Rosenthal, A. I.: Nalorphine in treatment of morphine induced biliary colic, J. Mount Sinai Hosp., New York **25**: 36, 1958.
2. Adriani, J., and Kerr, M.: Clinical experiences in use of N-allylnormorphine (Nalline) as antagonist to morphine and other narcotics in surgical patients, Surgery **33**: 731, 1953.
3. Alper, M. H., and Vandam, L. D.: Morphine, biliary spasm and nalorphine–case report, ANESTHESIOLOGY **20**: 713, 1959.
4. Auerbach, J., and Coakley, C. S.: Effect of Nisentil (alphaprodine) HCl and Lorfan (levallorphan) tartrate on respiration, Anesth. Analg. **35**: 460, 1956.
5. Backner, D. D., Foldes, F. F., and Gordon, E. H.: Combined use of alphaprodine hydrochloride and levallorphan tartrate for analgesic in obstetrics, Amer. J. Obstet. Gynec. **74**: 271, 1957.
6. Baker, F. J.: Pethidine and nalorphine in labor, Anaesthesia **12**: 282, 1957.
7. Bauer, R. O., and Pearson, R. G.: Effects of morphine-nalorphine mixtures on psychomotor performance, J. Pharmacol. Exp. Ther. **117**: 258, 1956.
8. Beal, J. M., and Schapiro, H.: Effect of N-allyl-normorphine on gastrointestinal motility, Surgery **33**: 65, 1953.
9. Beecher, H. K.: Appraisal of drugs intended to alter subjective responses, symptoms, J. A. M. A. **158**: 399, 1955.
10. Beecher, H. K.: Measurement of pain–prototype for quantitative study of subjective responses, Pharmacol. Rev. **9**: 59, 1957.
11. Bellville, J. W., and Seed, J. C.: Effect of drugs on respiratory response to carbon dioxide, ANESTHESIOLOGY **21**: 727, 1960.
12. Bickerman, H. A., and Barach, A. L.: Experimental production of cough in human subjects induced by citric acid aerosols. Preliminary studies on evaluation of antitussic agents, Amer. J. Med. Sci. **228**: 156, 1954.
13. Bodman, R. I.: Depression of respiration by opiates and its antagonism by nalorphine, Proc. Roy. Soc. Med. **46**: 923, 1953.
14. Boyd, E. M., and Pearl, M.: Can nalorphine hydrochloride prevent respiratory depression and death from overdose of barbiturates? Canad. Med. Ass. J. **73**: 35, 1955.
15. Bullough, J.: Use of premixed pethidine and antagonists in obstetrical analgesic, Brit. Med. J. **2**: 859, 1959.
16. Cahal, D. A.: Some effects of nalorphine on behavior of healthy human volunteer, J. Mental Sci. **103**: 850, 1957.
17. Chernov, H. I., Miller, J. W., and Mannering, G. J.: Possible relationships between antagonism of morphine-induced respiratory depression and analgesia and in vitro demethylation of 3-methoxy-N-methylmorphinan by N-substituted analgesics of 1-3-OH-morphinan, Fed. Proc. **18**: 376, 1959.
18. Clarke, R. L., Pessolano, A. A., Weijlard, J., and Pfister, K., 3rd.: N-substituted epoxymorphinans, J. Amer. Chem. Soc. **75**: 4963, 1953.
19. Costa, P. J., and Bonnycastle, D. D.: Effect of levallorphan tartrate, nalorphine HCl, and WIN 7681 (1-allyl-4-phenol-4-carbethoxypiperidine) on respiratory depression and analgesia induced by some active analgetics, J. Pharmacol. Exp. Ther. **113**: 310, 1955.
20. Costa, P. J., and Bonnycastle, D. D.: Effect of levallorphan and nalorphine upon barbiturate induced respiratory depression in rats, Proc. Soc. Exp. Biol. Med. **90**: 166, 1955.
21. Cullen, S. C., and Santos, C. C.: Analgesia for chronic pain without respiratory depression, A.M.A. Arch. Surg. **69**: 410, 1954.
22. Cullen, S. C., and Santos, C. C.: Analgesia for postoperative pain without respiratory depression, ANESTHESIOLOGY **16**: 674, 1955.
23. Daniel, E. E., and Bogoch, A.: Mechanical and electrical activity of ileal segments isolated for uretero-ileal anastomosis, Canad. Med. Ass. J. **80**: 95, 1959.
24. Daniel, E. E., Sutherland, W. H., and Bogoch, A.: Effects of morphine and other drugs on motility of the terminal ileum, Gastroenterology **36**: 510, 1959.
25. Dulfano, M. J., Mack, F. X., and Segal, M. S.: Treatment of respiratory acidosis with N-allyl-normorphine (Nalline), New Engl. J. Med. **248**: 931, 1953.
26. Eckenhoff, J. E., Elder, J. D., and King, B. D.: Effect of N-allylnormorphine in treatment of opiate overdose, Amer. J. Med. Sci. **222**: 115, 1951.

27. Eckenhoff, J. E., Elder, J. D., and King, B. D.: N-allylnormorphine in treatment of morphine or Demerol narcosis, Amer. J. Med. Sci. **223**: 191, 1952.
28. Eckenhoff, J. E., and Funderburg, L. W.: Observations on use of opiate antagonists nalorphine and levallorphan, Amer. J. Med. Sci. **228**: 546, 1954.
29. Eckenhoff, J. E., Helrich, M., Hede, M. J. D., and Jones, R. E.: Combination of opiate antagonists and opiates for prevention of respiratory depression, J. Pharmacol. Exp. Ther. **113**: 332, 1955.
30. Eckenhoff, J. E., Hoffman, G. L., Jr., and Dripps, R. D.: N-allylnormorphine: an antagonist to opiates, ANESTHESIOLOGY **13**: 242, 1952.
31. Eckenhoff, J. E., Hoffman, G. L., Jr., and Funderberg, L. W.: N-allylnormorphine: antagonist to neonatal narcosis produced by sedation of parturient, Amer. J. Obstet. Gynec. **65**: 1269, 1953.
32. Eckenhoff, J. E., and Oech, S. R.: Effects of narcotics and antagonists upon respiration and circulation in man, Clin. Pharmacol. Ther. 1: 483, 1960.
33. Eckerling, B., Goldian, J. A., and Gans, B.: Combined intravenous use of Pethedine, Phenergan and Lorfan for analgesia in obstetrics, Obstet. Gynec. **14**: 331, 1959.
34. Eddy, N. B., Lee, L. E., Jr., and Harris, C. A.: Rate of development of physical dependence and tolerance to analgesic drugs in patients with chronic pain: comparison of morphine, oxymorphone and anileridine, Bull. Narcotics **11**: 3, 1959.
35. Finestone, A. J., and Eksterowicz, F. C.: Treatment of acute narcotic poisoning with N-allylnormorphine, Amer. Practit. **4**: 640, 1953.
36. Foldes, F. F., Duncalf, D., Robbins, R. S., D'Sousa, P. B., and Conte, A. A.: Production of controllable apnea in anesthesia, combined use of narcotic analgesics and their antagonists, J. A. M. A. **166**: 325, 1958.
37. Foldes, F. F., and Ergin, K. H.: Levallorphan and meperidine in anesthesia, study of effects in supplementation of nitrous oxide-oxygen-thiopental sodium anesthesia, J. A. M. A. **166**: 1453, 1958.
38. Foldes, F. F., Lipschitz, E., Weber, G. M., Swerdlow, M., and Pirk, L. A.: Levallorphan (Lorfan) and alphaprodine (Nisentil) in anesthesia: study of effects in supplementation of nitrous oxide, oxygen-thiopental (Pentothal) sodium anesthesia: J. A. M. A. **160**: 168, 1956.
39. Foldes, F. F., Swerdlow, M., Lipschitz, E., Weber, G., and Pirk, L. A.: Combined use of Nisentil hydrochloride and levallorphan tartrate, for supplementation of nitrous oxide-oxygen anaesthesia, preliminary report, Canad. Anaesth. Soc. J. **2**: 362, 1955.
40. Foldes, F. F., Zeedick, F. J., and Koukal, L. R.: Effects of narcotic analgetics and narcotic antagonists on respiration, Amer. J. Med. Sci. **233**: 153, 1957.
41. Fraser, H. F.: Human pharmacology and clinical uses of nalorphine (N-allylnormorphine), Med. Clin. N. Amer. **41**: 393, 1957.
42. Fraser, H. F., and Isbell, H.: Morphine antagonists, Fed. Proc. **14**: 340, 1955.
43. Fraser, H. F., Van Horn, G. D., and Isbell, H.: Studies on N-allylnormorphine in man: antagonism to morphine sulfate and Heroin and effect of mixtures of N-allylnormorphine and morphine, Amer. J. Med. Sci. **231**: 1, 1956.
44. Fromherz, K., and Pellmont, B.: Morphinantagonisten, Experientia **8**: 394, 1952.
45. Gaard, R. C.: Preoperative use of a combination of Levo-Dromoran tartrate and a new narcotic antagonist, Minn. Med. **38**: 637, 1955.
46. Gabriels, A. G., Jr., and Fitzgerald, W. J.: Morphine and Nalline in obstetric analgesic observations in 150 patients, New York J. Med. **55**: 3113, 1955.
47. Goldstein, L., and Aldunate, J.: Quantitative electroencephalographic studies on effects of morphine and nalorphine on rabbit brain, J. Pharmacol. Exp. Ther. **130**: 204, 1960.
48. Gordon, D. W. S., and Pinker, G. D.: Increased Pethidine dosage in obstetrics associated with the use of nalorphine, J. Obstet. Gynec. Brit. Emp. **65**: 606, 1958.
49. Gottschalk, C., Orkin, L. R., and Rovenstine, E. A.: Nisentil: preliminary screening study of its clinical applicability, New York J. Med. **55**: 90, 1955.
50. Gray, G. W.: Some effects of analgesic and analgesic-antagonist drugs on intestinal motility, J. Pharmacol. Exp. Ther. **124**: 165, 1958.
51. Green, A. F.: Comparative effects of analgesics on pain threshold respiratory frequency and gastrointestinal propulsion, Brit. J. Pharmacol. **14**: 26, 1959.
52. Green, A. F., Ruffel, G. K., and Walton, E.: Morphine derivatives with antianalgesic action, J. Pharm. Pharmacol. **6**: 390, 1954.
53. Griffin, E. L., and Clement, J. E.: Use of promazine and levallorphan to improve obstetrical sedation, South. Med. J. **53**: 655, 1960.
54. Gruber, C. M., Jr.: Effects of N-allylnormorphine upon toxicity of morphine, J. Pharmacol. Exp. Ther. **111**: 404, 1954.
55. Gruber, C. M., Jr.: Effects of N-allylnormorphine in presence of secobarbital, J. Pharmacol. Exp. Ther. **111**: 409, 1954.

56. Gruber, C. M., Jr.: Effect of levallorphan tartrate upon toxicity of morphine, Proc. Soc. Exp. Biol. Med. **88**: 189, 1955.
57. Gruber, C. M., Jr.: Combined toxicity of morphine sulfate, nalorphine hydrochloride and levallorphan tartrate, Arch. Internat. Pharmacodyn. **103**: 489, 1955.
58. Haggart, J., Woods, L. A., and Seevers, M. H.: Studies on antagonism of morphine hypotension in dog, J. Pharmacol. Exp. Ther. **110**: 23, 1954.
59. Hamilton, W. K., and Cullen, S. C.: Effect of levallorphan tartrate upon opiate induced respiratory depression, ANESTHESIOLOGY **14**: 550, 1953.
60. Hamilton, W. K., and Cullen, S. C.: Supplementation of nitrous oxide anesthesia with opiates and new opiate antagonist, ANESTHESIOLOGY **16**: 22, 1955.
61. Harris, H., Tafeen, C. H., Freedman, H. L., and Fogarty, E.: Intravenous use of Demerol, scopolamine and Nalline in labor, Amer. J. Obstet. Gynec. **75**: 39, 1958.
62. Hart, E. R., and McCawley, E. L.: Pharmacology of N-allylnormorphine as compared with morphine, J. Pharmacol. Exp. Ther. **82**: 339, 1944.
63. Heng, J. E., and Domino, E. F.: Effects of morphine and nalorphine upon tooth pulp thresholds of dogs in alert and drowsy state, Psychopharmacologia **1**: 433, 1960.
64. Herxheimer, A., and Sanger, C.: Analgesic action of pethidine-levallorphan mixtures in man, Brit. Med. J. **2**: 802, 1957.
65. Hossli, G., and Bergmann, G.: Combination of analgesic and antagonist in postoperative pain, Brit. J. Anaesth. **32**: 481, 1960.
66. Houde, R. W., and Wallenstein, S. L.: Clinical studies of morphine-nalorphine combinations, Fed. Proc. **15**: 440, 1956.
67. Houde, R. W., Wallenstein, S. L., and Rogers, A.: Clinical pharmacology of analgesics: method of assaying analgesic effect, Clin. Pharmacol. Ther. **1**: 163, 1960.
68. Huggins, R. A., Glass, W. G., and Bryan, A. R.: Protective action of N-allylnormorphine against respiratory depression produced by some compounds related to morphine, Proc. Soc. Exp. Biol. Med. **75**: 540, 1950.
69. Huggins, R. A., and Moyer, J. H.: Some effects of N-allylnormorphine on normal subjects and review of literature, ANESTHESIOLOGY **16**: 82, 1955.
70. Huggins, R. A., Spencer, W. A., Geddes, L. A., Deavers, S., and Moyer, J. H.: Respiratory functions in man following intravenous administration of morphine, N-allylnormorphine, and N-allylnormorphine after morphine, Arch. Internat. Pharmacodyn. **111**: 274, 1957.
71. Irwin, S., and Seevers, M. H.: Acute and antagonistic effects of nalorphine in monkey, Fed. Proc. **13**: 369, 1954.
72. Isbell, H.: Attempted addiction of nalorphine, Fed. Proc. **15**: 442, 1956.
73. Isbell, H., and Fraser, H. F.: Addiction to analgesics and barbiturates, Pharmacol. Rev. **2**: 355, 1950.
74. Kao, F. F., and Belford, J.: Analysis of central respiratory action of nalorphine in decerebrate dogs, Brit. J. Pharmacol. **11**: 15, 1956.
75. Kaymakcalan, S., and Woods, L. A.: Nalorphine induced "abstinence syndrome" in morphine tolerant albino rats, J. Pharmacol. Exp. Ther. **117**: 112, 1956.
76. Keats, A. S.: Postoperative pain: research and treatment, J. Chron. Dis. **4**: 72, 1956.
77. Keats, A. S.: New concepts in action of analgesic drugs, South. Med. J. **49**: 1285, 1956.
78. Keats, A. S., and Mithoefer, J. C.: Mechanism of increased intracranial pressure induced by morphine, New Engl. J. Med. **252**: 1110, 1955.
79. Keats, A. S., and Mithoefer, J. C.: Nature of antagonism of nalorphine to respiratory depression induced by morphine in man, Fed. Proc. **14**: 356, 1955.
80. Keats, A. S., and Telford, J.: Nalorphine, a potent analgesic in man, J. Pharmacol. Exp. Ther. **117**: 190, 1956.
81. Keats, A. S., and Telford, J.: Subjective effects of nalorphine in hospitalized patients, J. Pharmacol. Exp. Ther. **119**: 370, 1957.
82. Keats, A. S., Telford, J., and Kurosu, Y.: "Potentiation" of meperidine by promethazine, ANESTHESIOLOGY **22**: 34, 1961.
83. Keats, A. S., Telford, J., and Papadopoulos, C. N.: Unpublished data.
84. Keith, E. F., Jr., and De Boer, B.: Effect of N-allylnormorphine on narcotic induced hyperglycemia, Arch. Internat. Pharmacodyn. **101**: 481, 1955.
85. Kepes, E. R., and Margolius, B. R.: Effect of Nisentil hydrochloride and Lorfan tartrate on respiration during nitrous oxide oxygen anesthesia, Amer. J. Surg. **91**: 761, 1956.
86. Kjellgren, K.: Influence of morphine and Pethidine in combination with levallorphan on biliary duct pressure after cholecystectomy, Brit. J. Anaesth. **32**: 2, 1960.
87. Landmesser, C. M., Cobb, S., and Converse, J. G.: Effects of N-allylnormorphine upon respiratory depression due to morphine in anesthetized man with studies on respiratory response to carbon dioxide, ANESTHESIOLOGY **14**: 535, 1953.
88. Landmesser, C. M., Formel, P. F., and Converse, J. G.: Comparative effects of new narcotic antagonist (levallorphan tartrate) upon respiratory responses to carbon dioxide during narcotic and barbiturate de-

pression in anesthetized man, ANESTHESIOLOGY 16: 520, 1955.
89. Lasagna, L.: Nalorphine (N-allylnormorphine): practical and theoretical consideration, A.M.A. Arch. Int. Med. 94: 532, 1954.
90. Lasagna, L.: Clinical measurement of pain, Ann. New York Acad. Sci. 86: 28, 1960.
91. Lasagna, L., and Beecher, H. K.: Analgesic effectiveness of nalorphine and nalorphine-morphine combinations in man, J. Pharmacol. Exp. Ther. 112: 356, 1954.
92. Lloyd, T. S., Jr.: Levallorphan in obstetrics, Virginia Med. Monthly 83: 551, 1956.
93. Lockett, M. F., and Davis, M. M.: Analgesic action of normorphine administered intracisternally to mice, J. Pharm. Pharmacol. 10: 80, 1958.
94. Margolius, B. R., and Kepes, E. R.: Meperidine-levallorphan in anesthesia: study of usefulness of such mixtures in supplementation of nitrous oxide-oxygen anesthesia, Amer. J. Surg. 95: 787, 1958.
95. Masson, A. H. B., and Stephenson, R. P.: Antagonism of Pethidine by levallorphan in rats, Anaesthia 14: 345, 1959.
96. May, G., Phillips, M., and Adriani, J.: Effect of N-allylnormorphine and levallorphan on respiration during and after ether anesthesia, ANESTHESIOLOGY 18: 871, 1957.
97. McDonald, R. K., Evans, F. T., Weise, V. K., and Patrick, R. W.: Effect of morphine and nalorphine on plasma hydrocortisone levels in man, J. Pharmacol. Exp. Ther. 125: 241, 1959.
98. Megirian, R., and White, C. W., Jr.: Evaluation of respiratory and sedative effects of meperidine hydrochloride combined with levallorphan tartrate in postoperative patients, New Engl. J. Med. 257: 849, 1957.
99. Megirian, R., White, C. W., Jr., and Marcus, P. S.: Alphaprodine hydrochloride with levallorphan tartrate or RO 1-7780 postoperatively, ANESTHESIOLOGY 18: 610, 1957.
100. Miller, J. W., Gilfoil, T. M., and Shideman, F. E.: Effects of levallorphan tartrate on respiration of rabbits given morphine, J. Pharmacol. Exp. Ther. 115: 350, 1955.
101. Mitchell, H. S., and Cooke, W. R.: Studies on effect of morphine sulfate and related compounds on bronchial muscle, Canad. Med. Ass. J. 73: 45, 1955.
102. Moyer, J. H., Pontius, R., Morris, G., and Hershberger, R.: Effects of morphine and N-allylnormorphine on cerebral hemodynamics and oxygen metabolism, Circulation 15: 379, 1957.
103. Orahovats, P. D., Winter, C. A., and Lehman, E. G.: Effect of N-allylnormorphine upon development of tolerance to morphine in the albino rat, J. Pharmacol. Exp. Ther. 109: 413, 1953.
104. Orahovats, P. D., Winter, C. A., and Lehman, E. G.: Pharmacological studies of mixtures of narcotics and N-allylnormorphine, J. Pharmacol. Exp. Ther. 112: 246, 1954.
105. Payne, J. P.: Effects of N-allylnormorphine on healthy subjects premedicated with morphine, Brit. J. Anaesth. 26: 22, 1954.
106. Pennes, H. H., and Hoch, P. H.: Psychotomimetics, clinical and theoretical consideration: Harmine, WIN-2299, and Nalline, Amer. J. Psychiat. 113: 887, 1957.
107. Pittinger, C. B., Gross, E. G., and Richardson, O. M.: Effect of Nalorphine, levallorphan and analogues of levallorphan upon the hyperglycemic response of dogs to levorphan, J. Pharmacol. Exp. Ther. 114: 439, 1955.
108. Prescott, F.: Nalorphine in prevention of opiate-induced neonatal narcosis, Canad. Anaesth. Soc. J. 3: 39, 1956.
109. Radney, P. A.: Nitrous oxide, oxygen anesthesia supplemented by Levo-Dromoran and Lorfan tartrate, J. Int. Coll. Surg. 26: 155, 1956.
110. Roberts, H., Kane, K. M., Percival, N., Snow, P., and Please, N. W.: Effects of some analgesic drugs used in child birth, Lancet 1: 128, 1957.
111. Sadove, M. D., Schiffrin, M. J., Nickerson, W. R., and Grove, W. J.: Use of meperidine and meperidine-levallorphan mixtures in recovery room, J. A. M. A. 166: 1432, 1958.
112. Salomon, A., Marcus, P. S., Herschfus, J. A., and Segal, M. S.: N-allylnormorphine (Nalline) action on narcotized and non-narcotized subjects, Amer. J. Med. 17: 214, 1954.
113. Schapiro, H., and Beal, J. M.: Effect of N-allylnormorphine on choledochal sphincter action, Surgery 34: 870, 1953.
114. Schiffrin, M. J., Balagot, R. C., and Sadove, M. S.: Some effects of levallorphan on responses to meperidine, Canad. Anaesth. Soc. J. 4: 372, 1957.
115. Schneiden, H., and Blackmore, E. K.: Effects of nalorphine on the antidiuretic actions of morphine in rats and men, Brit. J. Pharmacol. 10: 45, 1955.
116. Siker, E. S., Brunn, H. M., Crawford, J. F., and Foldes, F. F.: Circulatory effects of narcotics and narcotic antagonists in man. ANESTHESIOLOGY 21: 115, 1960.
117. Smith, C. C., Lehman, E. G., and Gilfillan, J. L.: Antagonistic action of N-allyl-normorphine upon the analgetic and toxic effects of morphine methadone derivatives and isonipecaine, Fed. Proc. 10: 335, 1951.
118. Swerdlow, M.: Further CSF pressure studies, Anaesthesia 11: 149, 1956.

119. Swerdlow, M.: Respiratory effects of Pethidine and levallorphan, Anaesthesia **12**: 174, 1957.
120. Swerdlow, M.: Levallorphan, Anaesthesia **13**: 318, 1958.
121. Swerdlow, M.: Duration of action of levallorphan, Anaesthesia **14**: 178, 1959.
122. Swerdlow, M., Foldes, F. F., and Siker, E. S.: Effects of Nisentil hydrochloride and levallorphan tartrate on cerebrospinal fluid pressure, Brit. J. Anaesth. **27**: 244, 1955.
123. Swerdlow, M., Foldes, F. F., and Siker, E. S.: Effects of Nisentil HCl and levallorphan tartrate on respiration, Amer. J. Med. Sci. **230**: 237, 1955.
124. Telford, J., Kurosu, Y., and Keats, A. S.: Studies of narcotic antagonists as analgesics, ANESTHESIOLOGY **21**: 117, 1960.
125. Thomas, D. V., and Tenney, S. M.: Effect of levorphan and levallorphan on respiratory mechanism of normal man, J. Pharmacol. Exper. Ther. **113**: 250, 1955.
126. Unna, K.: Antagonistic effect of N-allylnormorphine upon morphine, J. Pharmacol. Exp. Ther. **79**: 27, 1943.
127. Van Liere, E. J., and Northup, D. W.: Effects of nalorphine on gastric emptying in man, Proc. Soc. Exp. Biol. Med. **91**: 619, 1956.
128. Wallenstein, S. L., Bellville, J. W., and Houde, R. W.: Respiratory effects of levorphan and levallorphan in man, Fed. Proc. **17**: 417, 1958.
129. Weakley, L. D., and Bergner, R. P.: Respiratory effects of N-allylnormorphine in secobarbital sodium narcosis, ANESTHESIOLOGY **18**: 603, 1957.
130. Weiss, B.: Effects of various morphine-N-allyl-normorphine ratios on behavior, Arch. Internat. Pharmacodyn. **105**: 381, 1956.
131. Wendel, H., and Lambetsen, C. J.: Mechanism of action of N-allylnormorphine in morphine induced respiratory depression in man, Fed. Proc. **15**: 497, 1956.
132. White, C. W., Jr., Megirian, R., and Marcus, P. S.: RO 1-7780, potent antagonist of alphaprodine, Proc. Soc. Exp. Biol. Med. **92**: 512, 1956.
133. Wikler, A.: Mechanisms of action of opiate and opiate antagonists, Public Health Monograph 52, U. S. Dept. of Health Education & Welfare. Public Health Service Publication No. 589, U. S. Government Printing Office, Washington, 1958.
134. Wikler, A., and Carter, R. L.: Effects of single doses of N-allylnormorphine on hind limb reflexes of chronic spinal dogs during cycles of morphine addiction, J. Pharmacol. Exp. Ther. **109**: 92, 1953.
135. Wikler, A., Fraser, H. F., and Isbell, H.: N-allylnormorphine: effects of single doses and precipitation of acute "abstinence syndromes" during addiction to morphine, methadone, or Heroin in man (postaddicts), J. Pharmacol. Exp. Ther. **109**: 8, 1953.
136. Winter, C. A., and Flataker, L.: Effect of N-allylnormorphine on massive doses of narcotic drugs, Proc. Soc. Exp. Biol. & Med. **93**: 158, 1956.
137. Winter, C. A., Gaffrey, C. E., and Flataker, L.: Effect of N-allylnormorphine upon the antidiuretic action of morphine sulfate, J. Pharmacol. Exp. Ther. **111**: 360, 1954.
138. Winter, C. A., Orahovats, P. D., and Lehman, E. G.: Analgesic activity and morphine antagonism of compounds related to nalorphine, Arch. Internat. Pharmacodyn. **110**: 186, 1957.
139. Woods, L. A.: Pharmacology of nalorphine (N-allylnormorphine), Pharmacol. Rev. **8**: 175, 1956.
140. Woods, L. A.: Comparative distribution of morphine and nalorphine in dog brain, J. Pharmacol. Exp. Ther. **120**: 58, 1957.
141. Yim, G. K. W., Keasling, H. H., Gross, E. G., and Mitchell, C. W.: Simultaneous respiratory minute volume and tooth pulp threshold changes following levorphan, morphine, and levorphan-levallorphan mixtures in rabbits, J. Pharmacol. Exp. Ther. **115**: 96, 1955.
142. Yim, G. K. W., Keasling, H. H., and Gross, E. G.: Simultaneous respiratory minute volume and tooth pulp threshold changes following chronic administration of levorphan and a levorphan-levallorphan mixture in rabbits, J. Pharmacol. Exp. Ther. **118**: 193, 1956.
143. Zauder, H. L.: Antagonistic effect of N-allyl-normorphine on morphine induced hyperglycemia, Fed. Proc. **11**: 405, 1952.