ANESTHESIOLOGY

The Journal of

THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC.

Volume 14 NOVEMBER, 1953 Number 6

EFFECTS OF N-ALLYLNORMORPHINE UPON THE RESPIRATORY DEPRESSION DUE TO MORPHINE IN ANESTHETIZED MAN WITH STUDIES ON THE RESPIRATORY RESPONSE TO CARBON DIOXIDE *

CHARLES M. LANDMESSER, M.D., SANFORD COBB, M.D., AND J. GERARD CONVERSE, M.D.

Albany, New York

Received for publication February 20, 1953

More than a generation ago, and following experiments of Von Braun (1) and Heimann (2) regarding the molecular structure of morphine, codeine and other related alkaloids and its influence on their pharmacologic activity, Pohl (3) reported that N-allylnorcodeine, although almost inactive when given alone, antagonized the respiratory depression of morphine whether given before or after morphine. Furthermore, he described an experiment in which N-allylnorcodeine temporarily aroused a dog from sleep induced by morphine.

These observations apparently remained unnoticed for a quarter of a century until they were confirmed on rabbits by Hart (4) in 1941. This led McCawley, Hart and Marsh (5) to attempt the synthesis of N-allylnormorphine (NANM), but its first successful synthesis was reported by Weijlard and Erickson (6) in 1942 † (fig. 1).

Hart (7), in 1943, confirmed the preliminary conclusion (5) that N-allylnormorphine has an action similar to that of N-allylnorcodeine in antagonizing the effects of morphine on the respiratory mechanism,

* From the Department of Anesthesiology and the Cardio-pulmonary Function Laboratory of the Albany Medical College of Union University and the Albany Hospital, Albany, New York.
† Weijlard and Erickson (6) reported that their many efforts in the Merck research laboratories to repeat the preparation of N-allylnormorphine as outlined by McCawley, Hart, and Marsh (5) had failed. They described a different product of their own preparation which they proved to have the chemical requirements of N-allylnormorphine. Subsequently, Hart and McCawley (9) reported that re-investigation of their original product led to the conclusion that the original material prepared by them was N-allyl-o-allylnormorphine.

535
and Unna (8) and Hart and McCawley (9) studied \(N\)-allylnormorphine pharmacologically in comparison with morphine in animals. In 1950, Huggins, Glass and Bryan (10) showed that the antagonistic action of \(N\)-allylnormorphine on the respiratory depression produced by morphine in dogs extends to certain morphine derivatives and synthetic substances of related structure. Although they claimed meperidine (demerol\(^\circ\)) to be an exception, further studies in animals (11, 12) showed that \(N\)-allylnormorphine does have a protective action against demerol.

The first report of the effect of \(N\)-allylnormorphine on man was published by Wikler (13) in 1951 when he described the subjective sensations it produced in 12 postaddicts.

The clinical use of \(N\)-allylnormorphine for the treatment of opiate overdose was first reported by Eckenhoff, Elder and King (14) in 1951. They found that, given intravenously, it resulted in a twofold or threefold increase in respiratory rate and a 200 to 300 per cent increase in the respiratory minute volume when respiration was depressed with either morphine or demerol. A slight but not unusual analeptic action was produced by the drug. \(N\)-allylnormorphine had no effect on depression produced by cyclopropane, pentothal\(^\circ\) or ether. Administered intravenously (5 or 10 mg.) to 5 normal male volunteers, the drug

![Chemical structure of \(N\)-allylnormorphine hydrochloride.](image)

did not affect the respiratory rate remarkably, and respiratory minute volume was uniformly diminished. Eckenhoff, Elder, and King (15) later elaborated upon these findings, and presented 2 cases of morphine overdosage demonstrating the therapeutic effectiveness of \(N\)-allylnormorphine. Subsequently, the successful treatment with \(N\)-allylnormorphine of two patients with methadone poisoning (16) and overdosage with dilaudid\(^\circ\), dromoran\(^\circ\) and demerol all in one patient on three different occasions (17) was reported. An additional case report of the successful treatment of combined morphine and demerol overdosage in one patient by the administration of \(N\)-allylnormorphine was included in a recent publication by Eckenhoff, Hoffman and Dripps (18) concerning studies which showed this drug to be an effective antagonist not only to depression produced in surgical patients by morphine, meperidine, pantopon\(^\circ\), dilaudid and methadone, but also to neonatal depression due to analgesic drugs administered to the mother in the final stages of labor.

In a recent editorial (19), in which are briefly reviewed the history of the laboratory and clinical development of \(N\)-allylnormorphine as a narcotic antagonist, it was concluded that although it appears that \(N\)-allylnormorphine may prove a useful addition to the physician’s
Effects of N-allylnormorphine

Armamentarium further studies will be required to delineate its clinical usefulness and toxic potentialities. The opinion has been expressed that the site of action of N-allylnormorphine is probably central (8, 15) and that the suggestion is apparent that the drug acts in a competitive fashion with the opiate for certain receptors (15). Reports that the “abstinence syndrome” can be produced in “addicted” animals (20) and that during active addiction to morphine or methadone in man acute “abstinence syndromes” appear within fifteen minutes after subcutaneous injection of single doses of N-allylnormorphine (21) strongly suggest that this agent may compete with opiates for certain receptors. Actually, however, there is little if any conclusive information yet available regarding the mechanism by which N-allylnormorphine antagonizes the respiratory depression produced by narcotics.

On the basis of the recent reports (14–19) concerning the effectiveness of N-allylnormorphine in combating the respiratory depression accompanying narcotic overdosage, we conducted a clinical trial with N-allylnormorphine in several isolated cases of respiratory depression following nitrous-oxide oxygen anesthesia for various surgical procedures during which relatively large doses of morphine or demerol or both were administered to supplement the anesthesia. The interesting results obtained in these isolated cases stimulated us to undertake the present study in an attempt to gain additional information which might help to explain the mechanism by which N-allylnormorphine antagonizes the respiratory depression produced by morphine and other narcotics.

Method

The subjects selected for this investigation were patients brought to the operating room for thyroidectomy. Pilot experiments were conducted on 24 patients to determine and perfect a suitable standard method of procedure. After this was accomplished, 13 additional patients were studied, with technically successful results in 9. The data included in this report were obtained from these 9 patients (females, 20 to 65 years old) and, compared with the fragmentary data obtained from the omitted cases, are thought to be representative.

All patients were prepared for surgery and anesthesia with morphine and scopolamine given hypodermically one hour before operation after (except in one case) preliminary sedation with morphine given hypodermically two hours before operation. Two patients received a barbiturate by mouth along with the preliminary injection of morphine, but this was intentionally avoided in all other cases in order to eliminate possible respiratory depression from any drug other than morphine.

Upon arrival of the patient at the operating room, an intravenous infusion of 5 per cent glucose in water was started and additional morphine was given intravenously through the infusion tubing immediately before anesthesia was started, or subsequently or both, as was considered necessary for a smooth operative course. The total amount of
<table>
<thead>
<tr>
<th>Experiment</th>
<th>Patient</th>
<th>Age, Years</th>
<th>2 hrs. Preop.</th>
<th>1 hr. Preop.</th>
<th>During Operation, Morphine, Mg.</th>
<th>Total Morphine, Mg.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Morphine Mg.</td>
<td>Other, Mg.</td>
<td>Morphine Mg.</td>
<td>Scopolamine, Mg.</td>
</tr>
<tr>
<td>1</td>
<td>M. S.</td>
<td>44</td>
<td>10.5</td>
<td>Nembutal</td>
<td>10.5</td>
<td>0.64</td>
</tr>
<tr>
<td>2</td>
<td>M. D.</td>
<td>50</td>
<td>16.0</td>
<td></td>
<td>16.0</td>
<td>0.64</td>
</tr>
<tr>
<td>3</td>
<td>M. H.</td>
<td>26</td>
<td>16.0</td>
<td>Secomaline</td>
<td>16.0</td>
<td>0.64</td>
</tr>
<tr>
<td>4</td>
<td>P. P.</td>
<td>65</td>
<td>10.5</td>
<td></td>
<td>10.5</td>
<td>0.64</td>
</tr>
<tr>
<td>5</td>
<td>C. K.</td>
<td>38</td>
<td>16.0</td>
<td></td>
<td>16.0</td>
<td>0.64</td>
</tr>
<tr>
<td>6</td>
<td>M. B.</td>
<td>44</td>
<td>16.0</td>
<td></td>
<td>16.0</td>
<td>0.64</td>
</tr>
<tr>
<td>7</td>
<td>P. M.</td>
<td>39</td>
<td>16.0</td>
<td></td>
<td>16.0</td>
<td>0.64</td>
</tr>
<tr>
<td>8</td>
<td>H. W.</td>
<td>40</td>
<td>16.0</td>
<td></td>
<td>16.0</td>
<td>0.64</td>
</tr>
<tr>
<td>9</td>
<td>R. McD.</td>
<td>36</td>
<td>—</td>
<td></td>
<td>16.0</td>
<td>0.64</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td>43</td>
<td>13.0</td>
<td></td>
<td>14.8</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Morphine given any one patient ranged from 32 to 80 mg. (average, 50.4 mg., table 1).

Before the surgical procedure was started, the pharynx and larynx of each patient were topically anesthetized with pontocaine hydrochloride (1 per cent), and orotracheal intubation was performed with auffed endotracheal tube. General anesthesia was induced and maintained with nitrous-oxide and oxygen (4:1½ liters per minute) administered by a semiclosed circle system incorporating a carbon dioxide absorption canister, and procaine hydrochloride (0.5 per cent) was used for local infiltration by the surgeon. Respirations were assisted or controlled during the operation when indicated for adequate ventilation.

Immediately after the operation, the calibrated bellows breathing bag of an apparatus previously described (22), and suitably modified to function as a simple quantitative spirometer, was substituted for the regular breathing bag of the anesthesia machine without interrupting the nitrous oxide-oxygen anesthesia. Subsequently, the patient was allowed to breathe spontaneously without assistance.

After a Cournand needle was placed in the brachial artery, the anesthesia circle system was closed and anesthesia was continued using 100 per cent oxygen at a flow rate equilibrated with the metabolic requirements of the patient. A continuous kymographic tracing of the patient's respirations was obtained from an ink writer directly connected to the calibrated bellows breathing bag. In routine sequence, and in continuity, a tracing was obtained of each patient's respirations (a) during a control period, (b) during a period of rebreathing carbon dioxide for approximately five minutes while the carbon dioxide absorption canister was by-passed, (c) during a recovery period of approximately five minutes, (d) during the administration of N-allylnormor-
Effects of N-allylnormorphine

Phine † (5 mg. in 1 cc., injected rapidly into and flushed through the intravenous infusion tubing) and the response period of approximately five minutes which followed, and (e) during a second period of rebreathing carbon dioxide while the carbon dioxide canister again was bypassed. From this tracing, respiratory rate and minute volume at the end of each of these five test periods were measured directly, and the average tidal volume for the same time was calculated.

At the end of each of the five test periods, and before the next test period was started, arterial blood specimens were collected in 10 cc. syringes by our modification of the anerobic technic of Scholander (23).§ In certain instances we were unable to collect a full set of blood specimens owing to technical difficulties. Oxygen and carbon dioxide contents were determined on 1 cc. samples of blood in duplicate (with few exceptions) by the method of Van Slyke and Neill (24). Oxygen capacity was determined by the technique of Sendroy (25). Volumes per cent were corrected to standard temperature and pressure values (0° C. and 760 mm. of mercury) and the oxygen figures were corrected for physically dissolved gas as recommended by Comroe (26). All blood specimens were collected and analyzed by one of us (S. C.).

Blood pressure and pulse rate were determined by auscultation and palpation, respectively, at frequent intervals (approximately each minute) during the experiment.

Results

The results of a typical experiment are illustrated in figure 2. Although the absolute values for respiratory rate, tidal volume, minute volume, arterial oxygen content and arterial carbon dioxide content varied from patient to patient, the relative values followed a definitely similar pattern during the course of each of the five test procedures in each of the 9 patients studied (fig. 3).

I. Before Administration of N-allylnormorphine:

(a) Respirations:

Considering that morphine depression of the respiratory system is primarily reflected in the respiratory rate (27), the degree of respiratory depression in the 9 patients studied varied from marked (3 respirations per minute) to slight (17 respirations per minute) during the control period. The respiratory rate in all but one patient was 11 per minute or less, and the average for all 9 patients was less than 9 per minute. Respirations were definitely periodic (Cheyne-Stokes) in 2 patients and tended to be periodic in 4 others. Tidal volume varied

†Nalline, a brand of N-allylnormorphine, was generously provided for this study by Merck & Co.

§ We have modified this technique merely by occluding the hub of the syringe with a round toothpick instead of a mercury filled syringe cap.
Fig. 2. Kymographic record of respirations from Experiment 1, showing respiratory response to rebreathing of carbon dioxide in morphone-depressed patient before administration of N-allylnormorphine (top), respiratory effect of N-allylnormorphine (middle), and respiratory response to rebreathing of carbon dioxide after administration of N-allylnormorphine (bottom). The three tracings are in continuity except that a small section representing a recovery period of three and a half minutes was removed from the end of the top tracing. Values for respiratory activity and corresponding arterial oxygen and carbon dioxide contents are indicated.

among the 9 patients from 323 cc. to 1,081 cc. (average, 523 cc.), and minute volume varied from 2,450 cc. to 6,575 cc. (average, 3,981 cc.). ||

Rebreathing carbon dioxide increased the respiratory rate, tidal volume and minute volume in each of the 9 patients. The average increases were 44.4 per cent, 78.8 per cent and 193.1 per cent, respectively. Rebreathing carbon dioxide also abolished periodic breathing in all patients who exhibited this during the control period.

During the recovery period, the respirations of each of the 9 patients became similar to those observed before the rebreathing of carbon dioxide. The respiratory rate, tidal volume and minute volume returned to values closely approximating those which existed during

|| Discrepancies in the average values for rate, tidal volume and minute volume are due to the fact that slight inaccuracies which could not be avoided in measuring rate and minute volume directly from the kymographic tracings were reflected in calculating tidal volume for each patient and magnified in calculating averages for all patients.
Effects of N-allylnormorphine

Fig. 3. Comparative values for respiratory activity and blood gases as determined in each of 9 patients during (a) first control period before administration of N-allylnormorphine, (b) rebreathing of carbon dioxide before administration of N-allylnormorphine, (c) second control period before administration of N-allylnormorphine, (d) period of stability following administration of N-allylnormorphine and (e) rebreathing of carbon dioxide after administration of N-allylnormorphine. Average values are indicated numerically.

the original control period, and the pattern of respiration characteristic of the original control period returned in each case.

(b) Blood Gases:

During the original control period, the average arterial oxygen content for 8 of the 9 patients studied was 19.7 volumes per cent, and the arterial oxygen saturation of each of these 8 patients was 100 per cent or more. Hypoxia could not be demonstrated in any of these 8 patients in spite of the existing respiratory depression. The average arterial carbon dioxide content for the same 8 patients during this period was 54.3 volumes per cent (49.6 to 59.0 volumes per cent), a significant elevation compared with the "normal" value of 48.3 volumes per cent (28).#

† The blood specimen for the ninth patient taken during the control period was inadvertently spoiled, so that no oxygen or carbon dioxide determinations could be made for this patient's control period.

# We realize that arterial carbon dioxide content values alone are meaningless in so far as acid-base balance studies are concerned but, for the purposes of this investigation, we consider their relative values a significant index of respiratory efficiency.
Rebreathing carbon dioxide had no significant effect upon arterial oxygen content in any of the 9 patients but, as would be expected, it consistently raised the arterial carbon dioxide content (average increase, 4.6 per cent).

At the end of the recovery period, arterial oxygen content remained essentially unchanged (average, 19.3 volumes per cent), and arterial carbon dioxide content returned to values closely approximating those which existed during the original control period. In all but one instance, however, the arterial carbon dioxide content at the end of the recovery period was slightly less than during the original control period (average decrease, 2.9 per cent), possibly due to the effect of hyperpnea during the rebreathing of carbon dioxide upon previously poorly ventilated areas of lung tissue.

II. Effect of N-allylnormorphine:

(a) Respirations:

Rapid intravenous administration of 5 mg. (0.5 cc.), of N-allylnormorphine had a remarkable effect upon the respirations in each of the 9 patients. Within thirty to sixty seconds the respiratory rate suddenly increased from a control rate averaging less than 9 per minute (3.5 to 15 per minute) to a normal rate averaging slightly more than 20 per minute (17 to 26 per minute). This represented an average rate increase of more than 122.2 per cent. This increased rate was well maintained in each of the 9 patients for the remainder of the observation period.

At the time the rate increase first became apparent, the tidal volume increased in varying degrees for a brief period (usually less than one to two minutes) in each of the 9 patients, then gradually decreased to become relatively stable after approximately five minutes. At this point of stabilization the tidal volume was either definitely less than during the control period or not significantly changed (average decrease, 27.4 per cent).

The minute volume, which increased greatly at first when the tidal volume reached its peak during the first moments of increased respiratory rate, subsequently declined along with the tidal volume. Even after stabilization, however, it remained above the control value (average, 82.3 per cent above) in every instance, due to the fact that the increase in rate overbalanced the decrease in tidal volume.

(b) Blood Gases:

The administration of N-allylnormorphine did not significantly alter the arterial oxygen content, as determined from blood samples collected when respirations became stabilized. This would be expected since arterial oxygen saturation already was complete in all patients even before N-allylnormorphine was administered.

One of the most striking features of this investigation, however, was
Effects of *N*-allylnormorphine

the marked decrease in arterial carbon dioxide content which consistently occurred following the administration of *N*-allylnormorphine as determined on blood specimens collected approximately five minutes later when respirations had become stabilized. The arterial carbon dioxide content fell from control levels of 50.1 to 55.8 volumes per cent (average, 52.7 volumes per cent) to new levels of 47.2 to 51.2 volumes per cent (average, 49.3 volumes per cent). This change represented an average decrease of 6.5 per cent.

(c) Circulatory Changes:

During this study, significant changes in blood pressure and pulse rate did not occur regularly following the administration of *N*-allylnormorphine. Definite increase in both blood pressure and pulse rate were observed in 5 of 9 patients, but the magnitude of these increases was in no way alarming. In the others, there was no significant change. No arrhythmias were detected in the pulse during the administration of *N*-allylnormorphine. As was to be expected, slight elevations of blood pressure and pulse rate occurred in some but not all of the patients during the rebreathing of carbon dioxide both before and after the administration of *N*-allylnormorphine.

(d) Anaesthetic Effect:

Six of the 9 patients began to respond (swallowed, coughed or moved) shortly (three to twelve minutes) after the administration of *N*-allylnormorphine. The other 3 patients remained quiet enough to allow the final test procedure (the rebreathing of carbon dioxide) to be completed, and in one of these the arterial carbon dioxide content determinations proved to be grossly out of line and had to be discarded. The 3 patients who remained sufficiently quiet for the completion of their study did so for sixteen, twenty and twenty-one minutes, respectively, after the administration of *N*-allylnormorphine, and subsequently responded promptly when extubated and allowed to breathe room air. Three of the 6 who responded prematurely did so before the rebreathing of carbon dioxide and the other 3 did so during this final test procedure before blood specimens could be collected.

III. After Administration of *N*-allylnormorphine:

(a) Respiration:

When respirations had become stabilized after the administration of *N*-allylnormorphine, an attempt was again made to test the response of each patient to the rebreathing of carbon dioxide. Because of the anaesthetic effects of *N*-allylnormorphine described in the preceding section, this could be satisfactorily accomplished in only 5 of the 9 patients. In each of these, the rebreathing of carbon dioxide was accompanied by a further increase in respiratory rate, tidal volume and
minute volume. The average increases were approximately 40 per cent, 111 per cent and 185 per cent, respectively, changes of a magnitude similar to those produced by the rebreathing of carbon dioxide before the administration of N-allylnormorphine.

(b) Blood Gases:

Although the analeptic effect of N-allylnormorphine made it technically impossible to collect satisfactory arterial blood specimens for gas analyses in all but 3 of the 9 patients during the subsequent rebreathing of carbon dioxide, the results obtained in this limited number of cases were considered significant. Arterial oxygen content again did not significantly change in any of the 3 cases studied (average change was a decrease of only 4.1 per cent). However, as would be expected, the arterial carbon dioxide content rose from 50.4 to 54.0 volumes per cent in one patient and from 49.1 to 52.7 volumes per cent in another patient (average increase, approximately 7 per cent). The value for arterial carbon dioxide content determined from the specimen collected from the third patient was grossly out of line (33.2 volumes per cent) and had to be discarded.

IV. Relationship of Respiratory Activity To Arterial Carbon Dioxide Content Before And After Administration of N-allylnormorphine:

An attempt was made to correlate arterial carbon dioxide content with respiratory rate, tidal volume and minute volume, respectively, both before and after the administration of N-allylnormorphine (fig. 4). The average values for rate, tidal volume and minute volume during the control period, during the rebreathing of carbon dioxide and at the end of the recovery period following the rebreathing of carbon dioxide, both before and after the administration of the drug, were plotted against the corresponding average values for arterial carbon dioxide content. Lines drawn between the points representing the values before administration of N-allylnormorphine had essentially the same slope as lines drawn between the points representing the values after its administration. This was true for each of the three component parts of respiratory activity (rate, tidal volume and minute volume), and suggested that the sensitivity of the respiratory center, as tested by its response to carbon dioxide (29, 30), was essentially the same before as after the administration of N-allylnormorphine in the patients studied. Closer scrutiny made it evident, however, that though the slopes of the lines were essentially similar, those representing the respiratory response to carbon dioxide after administration of N-allylnormorphine were below and to the right of those before its administration. It thus became evident that, although the rebreathing of carbon dioxide elevated the arterial carbon dioxide content and produced corresponding increases in rate, tidal volume and minute volume both before and after the administration of N-allylnormorphine, the
arterial carbon dioxide content was consistently higher for corresponding degrees of respiratory activity before than after its administration. Although the respiratory responses to carbon dioxide before and after administration of N-allylnormorphine were similar, they were at different thresholds.

**Discussion**

The results of this investigation reaffirm the findings of others (14, 15, 18,) that N-allylnormorphine is an effective antagonist toward the respiratory depression produced by morphine in man. In addition, they provide evidence to further elucidate the mechanism of action of N-allylnormorphine. Hart (7), who was one of the first to observe its antagonistic actions against morphine, suggested in his incomplete report on rabbit experiments published ten years ago, that N-allylnormorphine antagonizes the respiratory depressant effect of morphine by increasing the sensitivity of the respiratory center to carbon dioxide. He stated: "When given before morphine, the allyl compound causes no stimulation of respiration and no change in the sensitivity of the respiratory center to carbon dioxide. However, when the allyl derivative is given after morphine the respiration is stimulated beyond the normal level and the respiratory center becomes more sensitive to carbon
dioxide than before morphine. The hyperpnea and hypersensitivity last only a few minutes and the respiration then becomes normal."

From the results of our present investigation, and in the light of the additional information concerning N-allylnormorphine which has accumulated in the literature since Hart's report, we feel obliged to revise Hart's statement regarding the mechanism of its action as follows: "When given before morphine, the allyl compound causes not only no stimulation of respiration but, indeed, a depression (14, 15) which is probably due to a decrease in the sensitivity of the respiratory center to carbon dioxide as is usually effected by morphine derivatives and other respiratory depressants (29, 30). However, when the allyl derivative is given after morphine the respiration is stimulated beyond the normal level, not by the drug itself, but by the excessive concentration of carbon dioxide which has accumulated during the morphine depression and which has a greater stimulating effect upon respiration once the sensitivity of the respiratory center is returned toward normal from its pre-existing state of morphine depression. This return toward normal is effected by N-allylnormorphine, which probably displaces morphine from certain receptors in a competitive fashion (7, 15). Although slightly depressant to the respiratory center itself, it is less depressant than morphine (8). Displacement of morphine from the respiratory center immediately eliminates the characteristic slowing effect of morphine on the rate (27) and increases the sensitivity of the respiratory center to carbon dioxide (29, 30). The resultant increase in respiratory rate, together with the exaggerated tidal volume, promptly effects the reduction of the increased carbon dioxide concentration in the blood toward a more physiologic level. The exaggerated tidal volume lasts only a few minutes, and the respiration then becomes normal since at this time the rate is no longer slowed by morphine nor the tidal volume increased by excessive concentrations of carbon dioxide."

In objection to this proposed explanation of the mechanism by which N-allylnormorphine antagonizes the respiratory depression produced by morphine, it might be argued that the antagonistic action of N-allylnormorphine might just as well be explained by attributing the initial respiratory stimulation following its administration to a direct stimulatory effect of the drug upon the respiratory center, and the associated decrease in carbon dioxide concentration in the blood to the normal train of events which would be expected to accompany the increased respiratory activity. This argument, however, is incompatible with the fact that N-allylnormorphine is not a direct respiratory stimulant: (a) It has no stimulating effect upon respiration when given to unmedicated animals (7, 8) and even has a slightly depressant effect when given to normal volunteers (14, 15), and (b) has no antagonistic effect toward the depression produced in man by cyclopropane, pentothal, ether or seconal® (14, 15, 18).

On the other hand, in support of the proposed explanation, based on
the phenomenon of drug competition, that N-allylnormorphine antagonizes the respiratory depression produced by morphine by displacing morphine from the respiratory center, three categories of facts may be presented. A) Chemical: The close relationship between the chemical structure of N-allylnormorphine and its specificity of action is strongly suggested by the fact that it apparently antagonizes the depression produced only by morphine and other narcotics structurally related to morphine such as codeine (morphine methyl ether), dilaudid® (dihydromorphinone), metocon® (methylidihydmorphinone), methadone® (6-dimethylamino-4, 4-diphenyl-3 heptanone hydrochloride) and its derivatives, demerol® (ethyl 1-methyl 4-phenylpiperidine 4-carboxylate-hydrochloride), dromoran® (3-hydroxy-N-methyl-morphinan hydrobromide), and pantopon (pantopium hydrochloride) (10-12, 14-19).** B) Pharmacologic: Along with its chemical structure, N-allylnormorphine shares with morphine many of its narcotic properties in a milder or slightly varied degree (8, 9, 13, 14, 15, 20), and its cholinesterase inhibiting property in a slightly greater degree (32). C) Physiologic: The ability of N-allylnormorphine to displace morphine from certain receptors in a competitive fashion is strongly suggested by three physiologic phenomena exemplifying this apparent action: (a) When injected in mice after morphine, N-allylnormorphine rapidly abolishes the analgesic effect of morphine and reduces the threshold for pain perception to the level obtained by N-allylnormorphine alone (7). (b) When injected in cats after morphine, N-allylnormorphine abolishes the restlessness, marked irritability, incoordination and extreme mydriasis produced by morphine (8). (c) N-allylnormorphine produces acute "abstinence syndromes" within fifteen minutes when given subcutaneously to morphine addicts (21).††

The theory that N-allylnormorphine displaces morphine at certain receptors in a competitive fashion would explain not only its antagonistic effect toward the respiratory depression produced by morphine, but also toward the circulatory depression produced by morphine (34). This would account for the occasional rises in blood pressure and pulse rate following the administration of N-allylnormorphine in narcotic depression as observed during this investigation and reported by others (11, 15, 18). This theory also would explain the observed and reported (14-18) analeptic action of this drug given in the presence of narcotic depression for, although N-allylnormorphine itself has mild narcotic properties (8, 9, 13, 14, 15, 20), in displacing a drug having stronger narcotic properties it would render the subject more responsive.

** Huggins, Glass and Bryan (10) state: "The structural formula for demerol® and methadone can be written to simulate the morphine structure." Sexton (31) states: "When written on paper, the relationship between these two molecules" (morphine and demerol) "is obscure, but three-dimensional models reveal a close similarity of pattern which can hardly be fortuitous."

†† It is interesting that in an addict receiving enough morphine to keep him in undisturbed addiction balance, an injection of physostigmine, also a powerful inhibitor of cholinesterases, likewise brings about withdrawal symptoms (33).
SUMMARY

The antagonistic effect of N-allylnormorphine toward the respiratory depression produced by morphine in man was quantitatively recorded and studied.

Even in the absence of hypoxia, concentrations of carbon dioxide in the blood during morphine depression were demonstrated which consistently were in excess of those demonstrated after the respiratory depression produced by morphine had been antagonized by the administration of N-allylnormorphine.

Correlations of respiratory activity with arterial carbon dioxide content indicated that, although the respiratory responses to carbon dioxide were similar both during morphine depression and after its antagonism by N-allylnormorphine, the arterial carbon dioxide content was consistently higher for corresponding degrees of respiratory activity before than after the administration of N-allylnormorphine.

Evidence supporting the theory that N-allylnormorphine antagonizes morphine depression by the mechanism of drug competition and the displacement of morphine from certain receptors was discussed, and it was suggested that by such a mechanism N-allylnormorphine restores the respiratory center to a more normal state of sensitivity to carbon dioxide and thus increases respiratory activity when given during morphine narcosis.

Occasional indications of increased vasomotor activity and of analeptic effect following the administration of N-allylnormorphine in the presence of morphine depression also were observed and considered compatible with the suggested mechanism of action of N-allylnormorphine.

ACKNOWLEDGMENT

The authors wish to express their appreciation for his interest and cooperation to John C. McClintock, M.D., upon whose surgical patients these studies were conducted.

REFERENCES