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## Effect of N-Allyl Normorphine on Excretion of C-14-Labeled Morphine in Mice. (20752)

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The use of N-allyl normorphine in the treatment of respiratory depression resulting from overdosage of morphine or one of its synthetic substitutes(1,2) has been indicated by the many favorable responses which have been obtained both experimentally and clinically. The practical application of this antagonism, however, precedes any reasonable explanation of the mechanism involved in the spectacular recoveries reported in the literature. The experiments reported here indicate that N-Allyl normorphine is capable of producing at least two secondary effects in intact, morphinized animals, in addition to central stimulation. These results were obtained in the course of studies on the excretion of C-14-labeled, biosynthesized(3) morphine, utilizing small amounts of the drug; the quantity of alkaloid was not sufficient to cause central depression of remarkable degree.

Morphine has been shown to produce an antidiuretic response in experimental animals (4); the mouse shares this property of the alkaloid. This finding and other data suggested that a partial explanation of N-Allyl normorphine's action might rest in an increased ability to excrete morphine, free or conjugated, by activation of renal or other mechanisms, thereby decreasing the time that the drug could exert its effects.

*Methods.* Eight mice weighing 20 g each were injected intraperitoneally with 0.070 mg of C-14-labeled morphine base, each dose equivalent to 2100 counts (the specific activity of the compound isolated from Papaver somniferum was 30000 counts per mg per minute). Four of the animals were then injected intraperitoneally with 500 $\gamma$ of N-allyl normorphine ("Nalline", Merck). The Straub reaction appeared in each animal approximately 2 minutes after injection of the C-14 morphine.

The urine was collected hourly in glass metabolism cages and suitable aliquots of each sample were plated on copper discs and counted in open window, gas-flow counters; results are expressed as counts recovered per hour. As the most significant findings appeared within 6 hours after injection, only

TABLE I. Excretion of C-14 Morphine, Counts/Hr.

| Hr | I | | II | | III | | IV | |
|---|---|---|---|---|---|---|---|---|
| | Morphine | Morphine and Nalline | Morphine | Morphine and Nalline | Morphine | Morphine and Nalline | Morphine | Morphine and Nalline |
| 1 | 0 | 26 | 19 | 7 | 26 | 9 | 0 | 0 |
| 2 | 47 | 1580 | 11 | 766 | 11 | 1336 | 10 | 1036 |
| 3 | 28 | 0 | 375 | 43 | 13 | 0 | 0 | 28 |
| 4 | 1347 | 0 | 50 | 98 | 6 | 0 | 0 | 656 |
| 5 | 77 | 13 | 41 | 27 | 49 | 0 | 0 | 56 |
| 6 | 134 | 0 | 228 | 14 | 39 | 187 | 1189 | 164 |

TABLE II. Percentage of Dose Excreted.

| Hr | I | | II | | III | | IV | |
|---|---|---|---|---|---|---|---|---|
| | Morphine | Morphine and Nalline | Morphine | Morphine and Nalline | Morphine | Morphine and Nalline | Morphine | Morphine and Nalline |
| 1-2 | .022 | 76.5 | .014 | 36.8 | .017 | 64.0 | .004 | 49.3 |
| 3-4 | 65.5 | 0 | 20.2 | 6.7 | .9 | 0 | 0 | 32.6 |
| 5-6 | 10.0 | .619 | 12.8 | 1.95 | 4.19 | 8.9 | 56.6 | 10.4 |

data obtained during this period will be presented here. The results of Table I and II were obtained in this study.

The data in Table I and II indicate that in each instance in which N-allyl normorphine was administered, a large portion of the injected dose appeared in the urine before the release of morphine by the control animal. These findings suggest that N-allyl normorphine produces in the morphinized animal effects in addition to the central stimulation for which it is well known. Such *secondary* effects could include(1) antagonism of antidiuretic hormone formation by the posterior pituitary or (2) facilitation of excretion by direct effect on the renal threshold. The antagonism by Nalline of morphine antidiuresis has been tested(5) and it has been found that Nalline significantly increases the volume of urine excreted by a group of morphine-treated animals as compared to morphinized controls. Other compounds have been found to antagonize the anti-diuretic action of morphine(5), and the mechanism of action of both these possible *secondary* effects is being studied further.

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## Presence of Elastase in Teleost Islet Tissue.* (20753)

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Balo and Banga(1) recently described an enzyme, elastase, which solubilizes elastic tissue and is exclusively extractable from pancreas. Elastase, which is apparently specific for elastic tissue, acts upon the substrate without the release of peptides or amino acids. It appears to effect a conversion of this insoluble fibrous protein to a soluble globular form. Elastase has been effective in unravelling the chemical morphology of elastic fibers(2). Partially solubilized elastic fibers of horse ligamentum nuchae have been shown to contain fine, longitudinally oriented fibrils bound together by a matrix material of the same or

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