

utilization of thyroid hormone is diminished with age, or whether the slight degree of decline in radioiodine uptake represents some extraneous mechanism which affects the rate of iodine accumulation but which does not influence the overall secretory activity of the gland.

The persistently higher radioiodine uptake by women over men raises the same question of biological versus statistical significance. The higher uptake by women does not correspond with the lower basal metabolic rate found in this sex compared to men of the same age. No ready explanation for the uptake difference is at hand, but the data serve to emphasize that other factors influence basal metabolic rate(10) besides the level of thyroid hormone secretion.

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10. Werner, S. C., Proc. of the First Clinical ACTH Conference. The Blakiston Co., Phila., 1950, p. 120.

*Summary.* 1. The percentage of a tracer dose of radioactive iodine deposited in the thyroid gland at the end of 24 hours was determined by measurement of radio-activity directly over the gland in 1,050 tests in 1952 apparently euthyroid individuals. 2. It is concluded that, within the New York area, there is statistically no effect of season, on the average uptake of radioiodine by the thyroid gland of the euthyroid individual. 3. The 24-hour uptake of radioiodine decreases progressively but slightly with each decade of age. The extent of fall is statistically, but not clinically, significant. 4. Women in all age groups show a slightly higher average uptake than men. The difference is not clinically significant.

Appreciation is expressed to Dr. John Fertig of the School of Public Health, Columbia University for reviewing the statistical material.

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Received May 9, 1950. P.S.E.B.M., 1950, v75.

### Protective Action of N-Allyl-Normorphine Against Respiratory Depression Produced by Some Compounds Related to Morphine.\*† (18257)

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Some of the pharmacological properties of N-allyl-normorphine have previously been investigated by Unna(1) and Hart and McCawley(2). These studies demonstrated that N-allyl-normorphine prevents, or abolishes, certain actions of morphine, *i.e.*, the respiratory depression, the excitatory action in cats, and increased the lethal dose. No in-

formation seems to be available showing whether the protection of the respiratory center afforded by N-allyl-normorphine against morphine extends to other narcotics, therefore, data on this point were collected for the following: codeine (methymorphine), Dilaudid (dihydromorphinone), Demerol (ethyl 1-methyl-4-carboxylate-hydrochloride), Metopon (methyl-dihydromorphine), and Methadon (6-dimethylamino-4, 4-diphenyl-3-heptanone hydrochloride).

*Methods.* The dogs were anesthetized with sodium barbital 250 mg/kg and a sound passed down the left carotid into the aorta for the registration of blood pressure with a Hamilton manometer(3). Respiratory rate was recorded by attaching a chest plethysmograph to a Hamilton manometer. Two pro-

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\* This study was supported in part by a grant from the Eli Lilly and Company.

† We wish to express our appreciation to the following for making certain drugs available: Dr. George A. Emerson, University of Texas Medical Branch, Galveston, Texas, N-allyl-normorphine, Dr. Karl H. Beyer, Sharp & Dohme, Metopon, and Mr. Kenneth M. Smoot, Winthrop-Stearns, Inc., Methadon.

1. Unna, Klaus, *J. Pharm. and Exp. Therap.*, 1943, v79, 27.

2. Hart, E. R. and McCawley, E. I., *J. Pharm. and Exp. Therap.*, 1944, v82, 339.

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3. Hamilton, W. F., Brewer, G. and Brotman, I., *Am. J. Physiol.*, 1934, v107, 427.

TABLE I. Lethal Doses of Various Narcotics in Dogs.

| No. of dogs                | Drug     | Dose, mg/kg | No. dogs dying of respiratory failure | Time until death, min. |
|----------------------------|----------|-------------|---------------------------------------|------------------------|
| Sodium barbital, 250 mg/kg |          |             |                                       |                        |
| 6                          | Demerol  | 10          | 4                                     | 2 to 5                 |
| 3                          | "        | 15          | 3                                     |                        |
| 6                          | Methadon | 2.5         | 4                                     | 1 to 2                 |
| 3                          | "        | 3.0         | 3                                     |                        |
| 3                          | Metopon  | 0.5         | 1                                     | 1 to 2                 |
| 2                          | "        | 1.5         | 2                                     |                        |
| 2                          | "        | 2.5         | 2                                     |                        |
| 4                          | Dilaudid | 2.0         | 4                                     | 1 to 2                 |
| 2                          | Codeine  | 15          | 1                                     | 2 to 5                 |
| 6                          | "        | 20          | 6                                     |                        |
| Chloralose, 120 mg/kg      |          |             |                                       |                        |
| 6                          | Methadon | 2.5         | 6                                     | 30 to 60               |

TABLE II. Effect of N-Allyl-Normorphine on Respiration in Dogs Receiving Lethal Doses of Various Narcotics.

| No. of dogs                                                  | Drug     | Dose | No. dogs dying of respiratory failure |
|--------------------------------------------------------------|----------|------|---------------------------------------|
| N-allyl-normorphine, 20 mg/kg, administered after narcotic.  |          |      |                                       |
| 4                                                            | Demerol  | 10   | 3                                     |
| 2                                                            | "        | 15   | All                                   |
| 2                                                            | "        | 30   | "                                     |
| 3                                                            | Methadon | 2.5  | 0                                     |
| 3                                                            | "        | 5    | 0                                     |
| 3                                                            | Metopon  | 2    | 0                                     |
| 3                                                            | "        | 4    | 0                                     |
| 3                                                            | Dilaudid | 2.5  | 0                                     |
| 3                                                            | "        | 5    | 0*                                    |
| 3                                                            | Codeine  | 20   | 0                                     |
| 3                                                            | "        | 40   | 0                                     |
| N-allyl-normorphine, 20 mg/kg, administered before narcotic. |          |      |                                       |
| 6                                                            | Demerol  | 10   | 5                                     |
| 4                                                            | Methadon | 2.5  | 0                                     |
| 6                                                            | Metopon  | 2    | 0                                     |
| 6                                                            | Dilaudid | 2.5  | 0                                     |
| 6                                                            | Codeine  | 40   | 0                                     |

\* 2 required additional amounts after 30-60 min.

cedures were used in this study. One, the N-allyl-normorphine 20 mg/kg was given i.v. and 20 minutes later the lethal dose of one of the narcotics was given. The other, was to give a lethal dose of a narcotic and after respiration had stopped for approximately 30 seconds to administer the N-allyl-normorphine. In addition to the lethal dose, twice that amount was also tried for each drug.

**Results.** N-allyl-normorphine 20 mg/kg may have a transient effect on respiration and circulation. The respiratory rate either

remains unchanged or there may be an increase for 1 or 2 minutes. There is usually a slight fall in blood pressure but it returns to the control level within 5 to 15 minutes.

It was necessary to determine, at least approximately, the lethal amounts of the various narcotics used under the conditions of these experiments. These data are included in Table I. In 6 dogs in which Methadon was used chloralose was substituted for the sodium barbital to test whether there might be a significant difference in the lethal dose as a result of a different anesthetic. The use of chloralose instead of barbital did not effect the lethal dose but respiratory arrest when chloralose was used did not occur for 30 to 60 minutes after injection. Respiration during the interval after injection until respiratory arrest was in the majority of instances of the Cheyne-Stokes type but in 2 dogs Biot's breathing occurred.

When N-allyl-normorphine, Table II, was injected either before or 30 to 45 seconds after lethal amounts of the other drugs there was no evidence of a significant decrease in either rate or depth of respiration except with Demerol. N-allyl-normorphine did not protect against a lethal dose of Demerol.

**Discussion.** The antagonistic action which N-allyl-normorphine has on the respiratory depression produced by morphine has been shown to extend to certain morphine derivatives and synthetic substances of related structure, with the exception of Demerol. The structural formulae for Demerol and Methadon can be written to simulate the morphine structure but there is some doubt whether this is warranted. However, since N-allyl-normorphine antagonizes the respiratory depression produced by Methadon but not that of Demerol, it tends to support the validity of considering Methadon to be related to morphine in structure.

**Conclusions.** 1. N-allyl-normorphine prevents or antagonizes the respiratory depression produced by codeine, Dilaudid, Metopon and Methadon. 2. It did not provide protection against the respiratory depression caused by Demerol.

Received September 11, 1950. P.S.E.B.M., 1950, v75.