Since the precise nature of the underlying metabolic disturbance of Graves' disease is as yet unknown, the relation between it and our present findings is undetermined. It has been found that hyperthyroid patients require more oxygen to perform a given physical task than normal subjects.[10] These findings as well as our own suggest that in Graves' disease a disproportionate amount of the energy available to the organism is dissipated as heat, and that Graves' disease may not be looked upon merely as a quickening to the same relative extent of all metabolic functions, but represents a different level of dynamic equilibrium, with an excess of certain exothermic catabolic oxidations, or a relative decrease in certain endothermic anabolic changes.

Summary. In 4 cases of Graves' disease with an average basal metabolic rate of +33%, the arterio-venous oxygen difference was found to be decreased by 37%. The average cardiac output was 8.1 liters per minute compared to a normal of 4.2, representing an increase of 93%. The relation of the present findings to those previously reported, to the question of method of cardiac output determination, and to the possible nature of the underlying metabolic disturbance in Graves' disease is briefly discussed.

8711 P

Barbiturate-Coriamyrtin Antagonism.

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At the time when we established the antidotal action of picrotoxin on the barbiturates[1] we indicated our intention of investigating the action of other picrotoxin-like substances. This paper reports the antidotal action of coriamyrtin in rabbits subjected to lethal doses of amytal, pernoston and nembutal.

The same method of procedure was followed in this work as in our early investigations of picrotoxin.[1, 2] The animals were given

[10] Boothby, W. M., and Sandiford, S., *J. Am. Med. Assn.*, 1923, **81**, 795.

[1] Maloney, A. H., Fitch, R. H., and Tatum, A. L., *J. Pharm. and Exp. Therap.*, 1931, **41**, 465.

[2] Maloney, A. H., and Tatum, A. L., *J. Pharm. and Exp. Therap.*, 1932, **44**, 337.

single lethal doses of the barbiturate in increasing increments up to the limit of effective therapeusis and as soon as narcosis occurred coriamyrtin was administered in fractional doses at intervals P.R.N.

The initial dose of coriamyrtin was so graded as to elicit a mild state of reflex stimulation, evidenced by an increased rate of respiration and a manifestation of such gross reflexes as the whisker twitch, winking and (or) nystagmus, jerking movements of the limbs and ears, and coarse body tremors. Great care was taken in the lower barbituratized groups to grade the initial dose of coriamyrtin so as to avoid throwing the animal into violent convulsions. Mild seizures in such cases are inconsequential and pass off within a few minutes. When the respiration rate became slow again and the gross reflexes disappeared, to determine the degree of depression pinching the tip of the tail or ear was done. This served as an index for the quantitative estimation of the succeeding dose of coriamyrtin. Our technique was to try to maintain such a degree of sensitivity as to elicit a reaction of resistance to this mechanical mode of stimulation at all times. This procedure was repeated until the effects of the barbiturate were palpably beginning to wear off, as evidenced by the persistence of the induced hypersensitivity. The barbiturates were administered intraperitoneally as a 5% aqueous solution while the coriamyrtin was injected intravenously as a 0.1% solution.

Preliminary experiments to determine the pharmacodynamic activity of our sample of coriamyrtin showed that the glucoside has a minimal convulsive potency of 0.14 mg./kg., and a minimal lethal potency of 0.40 mg./kg., both intravenously, in the rabbit. In most instances 75% of the normal lethal intravenous dose was adequate to produce initial stimulation in the animals subjected to the lower ranges of the barbiturate dosages. However in the higher levels we have frequently had to give 1.5-2 mg./kg. as a single first dose to initiate the desired stimulatory effects.

With amytal sodium 100% recoveries were obtained up to a little more than 1.5 beyond the M.L.D. (150 mg./kg.). At twice the M.L.D. 33.3% recovered. This dosage bordered on the upper limit of effective therapeusis. The antidotal ratio of coriamyrtin and amytal for the total number that recovered was 1:43.4

Coriamyrtin was 100% effective against 1 and 1.3 times the M.L.D of nembutal. At 1.7 times the M.L.D. its efficiency was 80%. Beyond this level, however, we were unable to save any animal, 3 trials each having been made with doses of 125 mg./kg.

(1.9×M.L.D.), 150 mg./kg. (2.4×M.L.D.), and 200 mg./kg. (3.1×M.L.D.). The antidotal ratio of coriamyrtin and nembutal for the total number of survivals was 1:20.55.

In the pernoston series 70% recovered at a dosage slightly above the M.L.D. (1.2) and 60% recovered at a dosage 2.1 times the M.L.D. This dosage level represented the upper limit of effective therapeusis. The results in this series corroborate our previous observations[3] of the wide range of therapeutability of pernoston as compared with the non-halogenated barbiturates. The antidotal ratio of coriamyrtin and pernoston for the total number of survivals was 1:34.6.

The action of coriamyrtin is as quick as that of picrotoxin but is of much shorter duration. This necessitates constant surveillance of the severely poisoned animal and the prompt administration at rather frequent intervals of small fractional doses of coriamyrtin as soon as indicated. Further detailed studies are in progress on coriamyrtin and tutin.

We wish to express appreciation to the Eli Lilly Research Laboratories for supplying amytal and coriamyrtin, the Abbott Laboratories for nembutal and the Riedel de Haen Company for pernoston used in this study.

8712 P

Poliomyelitis Histology in Rhesus Monkeys: Virus Introduced Via Gastrointestinal Tract.*

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When poliomyelitic virus was injected intracerebrally into *M. rhesus* monkeys no histologic evidence of its presence was observed in sections of tissues from the central nervous system until at least 3 days (usually 4 days) had elapsed following the injection. This corresponded to the time when symptoms of the disease began to appear.[1] When virus was injected directly into the median nerves

[3] Maloney, A. H., *J. Pharm. and Exp. Therap.*, 1933, **49**, 133.

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[1] Fairbrother, R. W., and Hurst, E. W., *J. Path. and Bact.*, 1930, **33**, 17.