

by the appearance, after similar hydrolytic treatment, of ninhydrin-positive impurities in the comparable chromatographic fraction of the control bile or urine. Further purification to facilitate identification of these metabolites is being carried out.

Some of these results were presented before the Pacific Coast Section of the Society for Experimental Biology and Medicine, San Francisco, on February 20, 1957.

While this manuscript was in preparation, Krebs and Brauer<sup>8</sup>, utilizing alumina columns, were also able to isolate unidentified metabolites of sulphobromophthalein from bile.

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### Anti-Thyroid Action of $\beta$ -Aminoethylisothiuronium Dibromide in Rats

DURING the development of a screening test for goitrogenic activity of drugs,  $\beta$ -aminoethylisothiuronium dibromide, a radiation protective agent<sup>1</sup>, was observed to have anti-thyroid activity. In view of possible long-term administration of this substance for prophylactic protection against irradiation, we are reporting our findings.

$\beta$ -Aminoethylisothiuronium dibromide was prepared from ethylene imine and thiourea. 13.5 ml. ethylene imine (Chemirad Corp., Port Washington, New York) was dissolved in 80 ml. ether and the sediment removed. To this solution, chilled in a salt-ice bath, was added slowly a solution of 19.0 gm. thiourea and 57.8 ml. 48 per cent hydrobromic acid (s.g. 1.49) in 80 ml. methanol. After 6 hr., the precipitate of  $\beta$ -aminoethylisothiuronium dibromide which formed was removed and recrystallized three times from 80 per cent ethanol. The final product had a melting point of 194° C., corrected. Infra-red spectra of this material and authentic  $\beta$ -aminoethylisothiuronium dibromide obtained from Dr. D. G. Doherty were identical and a mixture melting point of the two was not depressed.

Female Sprague-Dawley rats weighing about 100 gm. were divided at random into six experimental groups of eight animals each and fed Rockland rat diet (1.20 mgm. iodide/100 gm. diet) *ad libitum*. The animals were given: (1) 400 mgm.  $\beta$ -aminoethylisothiuronium dibromide/kgm. body-wt./day; (2) 50 mgm. 6-propylthiouracil/kgm. body-wt./day; (3) 120 $\gamma$  L-thyroxine/kgm. body-wt./day; (4) 400 mgm.  $\beta$ -aminoethylisothiuronium dibromide + 120 $\gamma$

L-thyroxine/kgm. body-wt./day; and (5) 50 mgm. 6-propylthiouracil + 120 $\gamma$  L-thyroxine/kgm. body-wt./day by gavage daily as a freshly prepared suspension in 10 per cent gum acacia. A control group was given 10 per cent gum acacia alone. Daily weights were obtained. On the last day of drug administration, 0.05  $\mu$ c. iodine-131 in 0.1 - 0.2 ml. solution was injected intraperitoneally. The animals were killed 24 hr. later, and the larynx with the thyroid gland attached was removed and assayed for radioactivity. The thyroid then was dissected carefully from the larynx and weighed.

The results are summarized in Table 1. The administration of  $\beta$ -aminoethylisothiuronium dibromide resulted in less iodine uptake and in some thyroid enlargement ( $P < 0.05$ ). 6-propylthiouracil, which is known to be a powerful goitrogen, produced similar, though greater, changes. The increase in thyroid weight was prevented in both cases by the simultaneous administration of L-thyroxine. Thiourea derivatives are known to block the formation of thyroid hormone<sup>2</sup>. It is not surprising, therefore, that  $\beta$ -aminoethylisothiuronium dibromide, which is related structurally to these compounds, results in depression of iodine uptake and thyroid enlargement. While hypothyroid animals perhaps are somewhat more resistant to irradiation<sup>3</sup>, the radiation protective action of  $\beta$ -aminoethylisothiuronium dibromide is greatest during the half-hour immediately following its administration, and in acute radiation experiments it is not likely that the anti-thyroid action of  $\beta$ -aminoethylisothiuronium dibromide explains any radiation protective action. However, it is of interest that cysteamine, another radiation protective compound, also has anti-thyroid activity<sup>4</sup>.

Table 1. EFFECT OF  $\beta$ -AMINOETHYLISOTHIURONIUM DIBROMIDE (AET) AND PROPYLTHIOURACIL (PTU) ON THE IODINE UPTAKE AND THYROID WEIGHT OF RATS

Drug and dosage (10 days)	Average body-weights		Thyroid weight (mgm./100 gm. body- weight)	24-hr. radiiodine uptake (per cent)
	Initial (gm.)	Final (gm.)		
400 mgm. AET/kgm. daily	140	180	9.56 $\pm$ 1.0	3.64 $\pm$ 0.40
50 mgm. PTU/kgm. daily	160	210	16.0 $\pm$ 0.73	0.68 $\pm$ 0.18
120 $\gamma$ L-thyroxine/ kgm. daily	160	200	6.06 $\pm$ 0.88	1.62 $\pm$ 0.48
400 mgm. AET + 120 $\gamma$ L-thyroxine/ kgm. daily	135	190	7.14 $\pm$ 0.68	0.19 $\pm$ 0.04
50 mgm. PTU + 120 $\gamma$ L-thyroxine/kgm. daily	140	180	8.12 $\pm$ 0.74	0.25 $\pm$ 0.10
Control (10 per cent gum acacia)	140	190	7.82 $\pm$ 0.33	16.0 $\pm$ 1.0

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