

Studies on Histamine Sensitivity and Anaphylactic Response. The Effect of Thyroid Extract.

LAURENCE FARMER AND RENÉE FRIBOURG. (Introduced by
A. Bernhard.)

*From the Allergy Clinic and the Achelis Laboratory, Lenox Hill Hospital, New
York City.*

Administration of large amounts of thyroid extract enhances the anaphylactic response of guinea pigs.¹ It has further been demonstrated in this species that administration of thyroid extract (or of thyroxine) depletes the ascorbic acid² and cholesterol stores³ of the adrenals. Depletion of the ascorbic acid content of the adrenals in guinea pigs in turn leads to depletion of their "cortin" content.⁴

Cortin deficiency, in our opinion, leads to increased histamine sensitivity and thereby to enhanced anaphylactic response. On the basis of these considerations we would expect that administration of thyroid extract leads to increased histamine sensitivity. The following experiments were undertaken to ascertain whether this assumption is correct.

Experimental. Young adult male guinea pigs weighing on an average 350 g were used. They were fed a diet consisting of oats, carrots and greens. As there possibly exists a seasonal variation in the guinea pig's sensitivity to histamine, control experiments and thyroid experiments were done during the same season.

I. Experiments in guinea pigs fed thyroid extract. 1. Control Experiments. Forty-four guinea pigs were used. They were divided into 2 groups consisting of 18 and 26 animals. The first group received 0.3 mg histamine phosphate per kilo of body weight, the second group 0.35 mg histamine phosphate. The histamine injections were given intravenously (jugular vein) 18 to 24 hours after the last feeding. In the first group, 2 animals or 11.1% and in the second group, 9 animals or 34.6% died in shock.

2. Administration of Thyroid Extract. a. In these experiments, 36 guinea pigs, which were divided into 2 groups of 21 and 15 ani-

¹ Képinow, L., *Compt. rend. Soc. de biol.*, 1915, **78**, 198.

² Demole, V., and Ippen, F., *Z. f. physiol. Chem.*, 1935, **235**, 226; Mosonyi, J., *Ibid.*, 1935, **237**, 173; Plaut, F., and Bülow, M., *Klin. Wchnschr.*, 1935, **14**, 1318; Nespor, E., *Compt. rend. Soc. de biol.*, 1936, **122**, 427.

³ Hoen, E., Langefeld, H., and Oehme, C., *Endokrinologie*, 1939, **21**, 305.

⁴ Giroud, A., and Santa, N., *Compt. rend. Soc. de biol.*, 1939, **131**, 1176; Giroud, A., Santa, N., and Martinet, M., *Ibid.*, 1940, **134**, 23; Giroud, A., Santa, N., Martinet, M., and Bellon, M. T., *Ibid.*, 1940, **134**, 100.

mals, received orally 5 doses of 0.02 g thyroid extract U.S.P. per 100 g of body weight by mouth over a period of 5 to 6 days. Eighteen to 24 hours after the last thyroid administration and last feeding the animals received 0.3 and 0.35 mg histamine phosphate per kilo of body weight respectively. In the first group, 18 or 85.7% and in the second group 11 or 73.3% died in shock.

b. To exclude the possibility that the high percentage of deaths observed in the thyroid-fed guinea pigs was due to instability of the autonomous nervous system and not to the injected histamine, another group of 10 animals was given thyroid extract in the above described manner. Eighteen to 24 hours after the last administration of thyroid, each animal received 0.2 cc physiological saline intravenously. No reaction to this injection was observed in any animal. Twenty-five minutes later, each guinea pig received intravenously 0.3 mg histamine phosphate per kilo of body weight. Eight of the guinea pigs died in severe shock.

II. Ascorbic Acid Determinations. Various authors² have shown that administration of thyroid extract leads to depletion of the ascorbic acid stores of the tissues. Assays were done to determine the degree of depletion of ascorbic acid in the adrenals in our experiments. The method used was that of Bessey and King.⁵ The determinations were made in February and March.

The ascorbic acid content of the adrenals of 11 normal guinea pigs ranged from 64 mg % to 132 mg %. The average value was 95 mg %.

Eight guinea pigs were fed 0.02 g thyroid per 100 g of body weight 5 times over a period of 5 to 6 days. The ascorbic acid determinations were done 18 to 24 hours after the last administration of thyroid. The values found ranged from 33 mg % to 57 mg %. The average value was 47 mg %, a marked decrease.

Conclusions. In our experiments, administration of thyroid extract to normal guinea pigs greatly enhanced their sensitivity to histamine shock. We believe that the enhanced sensitivity to histamine which follows administration of thyroid extract explains the enhanced anaphylactic response observed after administration of this hormone.

Administration of thyroid extract to normal guinea pigs led to marked decrease of the ascorbic acid content of the adrenals. Depletion of the ascorbic acid stores of the adrenals of guinea pigs leads to depletion of their cholesterol and cortin contents. We suggest that the enhanced sensitivity to histamine observed in our guinea pigs is due to depletion of the cortin content of their adrenals.

⁵ Bessey, O. A., and King, C. G., *J. Biol. Chem.*, 1933, **103**, 687.