

THYROTROPHIC ACTIVITY AND EXOPHTHALMOS-PRODUCING SUBSTANCE IN HUMAN PLASMA*

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Techniques for the biological assay of thyrotrophin and allied substances were developed and used in the study of endocrine problems.

Thyrotrophin

The assay for thyrotrophin was based on the most specific effect of this substance—the ability to discharge organically bound iodine from the thyroid gland.

Weanling female mice received 8 $\mu\text{c.}$ of I^{131} intraperitoneally, followed by thyroxine subcutaneously and orally to suppress endogenous thyrotrophin secretion. Four days later, mouse whole blood was counted for radioactivity before and 2 hours after the intravenous injection of 3 dose levels of USP thyrotrophin standard, a saline control and the 'unknown' plasma samples. By this means, a standard log-dose response line was constructed for each experiment. The increase in radioactivity following the 'unknown' substances was plotted in relation to the log-dose response line, and translated into an absolute value for thyrotrophin, being finally expressed in milliunits (mu.) per 100 ml. of plasma. A sensitivity of the order of 5-10 mu. per 100 ml. allowed the detection of thyrotrophin in untreated plasma.

Exophthalmos-producing Substance

The exophthalmos-producing substance of the anterior pituitary (EPS) was assayed by a technique involving the induction of measurable degrees of proptosis in goldfish. The intercorneal distance was measured before and 3 hours after the intracoelomic injection of saline, plasma and an anterior pituitary extract rich in EPS. An attempt was made to standardize an otherwise crude procedure and compensate for seasonal and other variations by expressing the increase in intercorneal distance (ICD) invoked by an 'unknown' substance as a percentage of that produced by the fixed dose of standard. Such percentages were graded 0 to ++++ (200%), in which terms EPS activity was ultimately expressed. An adequate dose response trend was established.

Long-acting Thyroid Stimulator

The recent demonstration in the blood of patients with exophthalmos or Graves' disease of a substance with a slow but sustained thyrotrophin-like action has aroused considerable interest. This substance, currently named long-acting thyroid stimulator (LATS), was assayed by the same technique used for the estimation of thyrotrophic activity. However, in addition to the measurement of the discharge of radioactivity 2 hours after the injection of appropriate plasma, a further reading was made at 7 hours to detect 'late' activity.

Results

Using the techniques outlined, assays for the presence of one or more of the 3 substances were performed on approximately 150 aliquots of plasma or tissue homogenate.

A mean of 23 mu. thyrotrophin per 100 ml. of plasma was found in 15 normal volunteers, while EPS was convincingly shown in only 1 of 10 such persons. In hypothyroidism, great extremes of thyrotrophic activity were assayed, varying from 0 to 310 mu. per 100 ml., while the values in hyperthyroidism lay in the normal range. EPS was found more consistently in hyperthyroidism, the level being higher in exophthalmic subjects.

All except 1 of 22 euthyroid persons with goitre had normal plasma thyrotrophic levels. These appeared to bear no relationship to the thyroidal I^{131} uptakes, since both high and low uptake groups had similar activity. The cause of raised I^{131} uptakes in euthyroid goitrous subjects remains obscure, but appears to be independent of raised plasma thyrotrophic activity.

Plasma thyrotrophin was either low or absent in 3 cases of Hashimoto's disease, absent in hypopituitarism, and normal in acromegaly (though LATS was found in 1 case with high thyroidal and RBC I^{131} uptakes).

LATS was assayed in the plasma of euthyroid patients with lid lag and lid retraction, post-thyroidectomy malignant exophthalmos and hyperthyroidism (where the level appeared to be directly related to the degree of exophthalmos), and in enormous amounts in both the plasma and homogenates of pretibial tissue of 3 patients with the pretibial myxoedema syndrome. LATS was either absent or present in minute amounts in homogenates of fat from 2 of the 3 subjects used as controls.

Collaborative assays suggested the separate identities of LATS and EPS.

Serial assays, performed while hyperthyroid or euthyroid patients with exophthalmos received various forms of therapy, suggested that methimazole might cause a transient elevation of LATS activity, and that corticosteroids in high dosage might effectively suppress the elevated LATS values associated with progressive exophthalmos and thus provide a rational basis for such therapy. The results must remain speculative, however, in view of the small number of patients on whose plasma serial estimations have so far been attempted.

Finally, it was shown that the ability of high doses of triiodothyronine to suppress the elevated thyroidal I^{131} uptake in euthyroid subjects with large goitres was dependent on a complete suppression of plasma thyrotrophic activity, while the lack of such effect so characteristic of the hyperthyroid state appeared to be associated with the persistence of high levels of plasma LATS activity.

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