ASSAY OF BLOOD AND URINE FOR THYREOTROPIC HORMONE IN THYROTOXICOSIS AND MYXEDEMA

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ASSAY OF BLOOD AND URINE FOR THYREOTROPIC HORMONE IN THYROTOXICOSIS AND MYXEDEMA[1]

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Rogowitch (1) demonstrated hypertrophy of the anterior pituitary body following thyroidectomy in rabbits and dogs as early as 1889. Niepce (2) in 1851 recorded that both man and animals with large parenchymatous goiters had greatly enlarged pituitaries. Boyce and Beadles (3) in 1892 described enlargement of this gland along with colloid in the anterior lobes of the pituitary in cases of human myxedema. This finding was confirmed in 1917 by Hale White; and Wegelin (4) described similar findings in a case of cachexia thyreo priva. Degener (5), Kojima (6) and Kamo confirmed the findings of Rogowitch in animals.

In 1914 Adler (7) demonstrated that destruction of the pituitary in tadpoles depressed metamorphosis and the development of the thyroid gland. Allen (8) and Smith (9) in 1916 independently studied the same relationship in tadpoles. Gudernatch (10) had described the rôle of the thyroid hormone in metamorphosis in 1912 and it was therefore logically suspected that the inhibition of metamorphosis following pituitarectomy was in some way related to secondary diminution in thyroid function. Allen's work (11) in 1921 indicated that pituitary transplants induced premature metamorphosis following thyroidectomy only if some residual tissue was present. Smith and Smith (12) were able to induce metamorphosis in pituitarectomized tadpoles by the intraperitoneal administration of anterior lobe of sheep. Schwartzbach and Uhlenhuth (14) showed that thyroidectomized salamander larvae could not be made to undergo metamorphosis with large doses of pituitary extracts which were readily effective in the presence of the thyroid.

In extending the above concepts to mammals Smith (15) clearly demonstrated that following pituitarectomy in the rat regression could be prevented or repaired by implantation of anterior lobes of rat pituitaries. Aron (16) demonstrated thyreotropic activity of anterior pituitary extracts in the guinea pig. Later studies by Smith and Siebert (17) indicated that extracts of anterior lobe substance increased the metabolic rate in the presence of the thyroid in the guinea pig.

Schockaert (18) reported the production of a syndrome of exophthalmos, thyroid hyperplasia, decreased thyroid iodine and increased metabolic rate in the duck. He noted the tendency of the hyperplastic thyroid to involute in a few of his animals after prolonged treatment with anterior pituitary material. Schockaert drew the analogy between anterior pituitary induced hyperthyroidism and Graves' disease in the human.

Histologic studies by Hertz and Kranes (20) pointed to an exhaustion of the

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thyroid epithelium after prolonged administration of the thyreotropic factor. The 'natural remission' despite prolonged thyreotropic administration had been noted in the metabolic studies of Friedgood, Loeb and Collip. Friedgood (21) published metabolic data and an account of anterior pituitary-induced exophthalmos and hyperthyroidism in the guinea pig. He also drew attention to the cyclic nature of the thyroid response to stimulation by the thyreotropic factor in a later publication (22).

Attempts to extend the anterior pituitary hypothesis to the pathological mechanism operative in human Graves' disease have been made. Marine (24) in a recent review on thyroid physiology stressed the resemblance between the hyperthyroidism produced in animals by injection with thyreotropic hormone and exophthalmic goiter in man and infers that there is an over-production of thyreotropic principal in Graves' disease. He suggests as an alternative possibility that exophthalmic goiter may occur in man when the capacity to produce an antithyreotropic material is impaired. He also states that a decreased production of thyreotropic hormone is probably the immediate cause of myxedema.

Aron (25) tried to obtain evidence of increased thyreotropic activity of the pituitary in human cases of Graves' disease. He used young guinea pigs as test animals and depended upon minor histologic changes such as vacuolization of the colloid as criteria in reading the test. It was with a similar view that the studies of Krogh and Okkels (26) were made. In their early experiments they attempted to repeat the technique of Aron. They agreed that there was no evidence of increased thyreotropic material in the urine of patients with Graves' disease, but added that the histologic assay method was not reliable. By using metabolic rate determinations in their assay technique these workers could find no further evidence of thyreotropic hormone in the urine of thyrotoxic patients, even after its concentration.

Castillo and Magdalena tried to verify Aron's work and used his method of assay. Their results forced them to the conclusion that guinea pigs were unsuitable for assay of thyreotropic action of sera. They found that of 10 hypophysectomized dogs, 3 had sera which gave a positive reaction by Aron's technique and criteria. Obviously the results of Aron must be regarded in the light of this nonspecificity of his assay method.

We therefore devised our own method of assay for thyreotropic factor using the pituitarectomized rat as test object. In so doing we followed the work of Collip and his co-workers in their attempts to purify thyreotropic hormone from pituitary tissue. This method can be regarded as specific for thyreotropic factor since it depends upon a principle similar to that underlying the substitutional transplant method used by Smith in his original contributions to the thyreotropic field.

METHOD AND RESULTS OF ASSAY

The method of assay which we finally developed and consider suitable for assay of biologic fluids for thyreotropic activity is as follows. White rats of Wistar strain were used throughout our experiments. Males weighing between 150 and 200 grams were selected. They were pituitarectomized by a modified Selye* technique. Five days were allowed postoperatively for recovery. Intramuscular injections of urine or serum were then instituted and carried on

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