THE AETIOLOGY OF THYROTOXICOSIS*

JOHN S. RICHARDSON, *M.V.O.*, M.A., M.D., F.R.C.P.

Physician, St. Thomas's Hospital, and Consulting Physician to the Metropolitan Police, New Scotland Yard, London

Very little of fundamental significance is known about the aetiology of thyrotoxicosis. Heredity may play some part but its importance is in no way clearly defined. The incidence of thyrotoxicosis is world wide, but there is some concentration of toxic goitres in areas where simple goitres are endemic. There is, as far as I know, no satisfactory explanation why it is about 7 times commoner in women than in men, but almost all agree that stress, either physical or mental, tends to precipitate hyperthyroidism, and this is particularly true of emotion. It is natural, therefore, that workers should turn to possible relationships between the thyroid, the central nervous system and the other endocrine glands when considering the aetiology of the thyrotoxic state.

The study of the interdependence of the endocrine glands, one upon another, is not only one of the most complex but also the most fascinating of the problems of internal medicine. The great strides which have been made in this field of research over many years are largely due to the discovery that the pituitary body can be removed from certain experimental animals without damaging the adjacent brain tissue. The early results that followed the working out of this procedure (Smith, 1918 and 1930) showed the importance of the control of the pituitary body over the other endocrine glands, and the discovery in the anterior lobe of a specific thyrotrophic hormone (Loeser, 1931; Anderson and Collip, 1933), and of adrenocorticotrophin (Collip *et al.*, 1933), has linked further the activity of both the thyroid and the adrenal cortex to the hypophysis.

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THYROID-ADRENAL RELATIONSHIP

The first experimental work on a thyroid-adrenal relationship dates from 1897 when Cohen gave dried suprarenal gland to patients with hyperthyroidism and recorded in them a gain of body weight. These results were non-specific as a like gain in weight was found by Oppenheim (1905) and by Hoffe (1918) using desiccated ovarian tissue and corpus luteum.

It will thus be seen that as early as the beginning of this century some workers were not satisfied that the thyroid alone was responsible for the syndrome of thyrotoxicosis.

Marine and Bauman began in 1921 to publish a series of experiments designed to disentangle the problem of the relationship of the thyroid to the adrenal glands, and built up a large body of information which was reviewed by Marine in 1935. Oehme (1936) a year later was able to show that the effect of thyroxine could be counteracted by cortin in guinea pigs, and in 1938 Richardson, also using guinea pigs, found that cortin inhibited the stimulating effect of the thyroid stimulating hormone (T.S.H.) on the thyroid. He showed that the normal increase in body weight in young animals took place, and that the weight and activity of their thyroid glands did not increase, if cortin was given with the T.S.H.

The first series of patients to be treated with adrenal extract was reported by Shapiro (1924), who treated 20 cases

orally with a glyceryl extract of adrenal cortex, and claimed that there was improvement in strength and weight, but found no change in the basal metabolic rate.

By 1930 Marine had treated 50 cases with a similar preparation, with like results, and in addition he found a fall in the basal metabolic rate, but this was delayed until between 2 and 4 months after the onset of treatment, and his findings are thus open to certain objections.

Richardson (1939) obtained a definite but temporary fall in the basal metabolic rate in 6 out of 7 patients treated with Eucortone (cortin) over a 4-day period, but found no clinical improvement and concluded that the adrenal cortical extract of that day had little part to play in the treatment of hyperthyroidism.

Interest in this aspect of the aetiology of thyrotoxicosis has persisted, and has been increased by a recent paper by Harris and Woods (1956). They were initially investigating the relationship between the central nervous system and thyroid activity, and set out to study the effect on thyroid function of prolonged (1-7 days) electrical stimulation of the hypothalamus by remote control. They tested thyroid activity by the ^{131}I output method, and the blood concentration of protein-bound radio-active iodine.

They found thyroid acceleration in only 2 out of 37 experiments and thus felt that some other factor might be inhibiting or masking the effects of an increased secretion of thyrotrophic hormone in their experiments. They thought this might be the result of the increase in secretion of corticotrophin which is known to accompany stimulation of the tuber cinereum (de Groot and Harris, 1950). They then stimulated the hypothalamic region in 14 rabbits on whom bilateral adrenolectomy had been carried out, and found a marked increase in thyroid activity in 20 experiments on 10 of these animals, whereas before adrenalectomy hypothalamic stimulation on the same animals had produced no increase, or even reduction in the thyroid activity. They thus showed that electrical stimulation of the hypothalamus in the region of the tuber cinereum rarely induced an increase in thyroid activity unless it was preceded by adrenalectomy. The possibility of an inhibitory action by the adrenal cortex on the thyroid is also suggested by depression of thyroid uptake of ^{131}I in man and in experimental animals following the administration of corticotrophin or cortisone. Corticotrophin does not produce this effect in patients with Addison's disease, or after adrenalectomy, and cortisone is similarly ineffectual after hypophysectomy. The inhibitory action upon the thyroid is therefore probably mediated through depression of secretion of T.S.H. by the anterior pituitary.

Harris and Woods further pointed out that the frequency of the occurrence of psychological trauma before the development of hyperthyroidism is generally accepted, and it might be expected that a stress reaction, with overactivity of the adrenal cortex, would develop. In fact, however, adrenocortical function is normal or often impaired, and they suggested that there may be either a relative or absolute reduction in adrenocortical function in response to stress in thyrotoxic subjects, with increased thyroid activity, a state of affairs which is the reverse of the normal.

RECENT CLINICAL STUDIES

Hill *et al.* (1950) treated 6 patients suffering from Graves' disease with corticotrophin in doses of 40 to 200 mg. per day for 5 to 23 days. In all these patients there was an initial period of increased thyrotoxicity for 4 to 24 hours following the start of treatment. After the full course of treatment 2 patients showed no significant improvement in any respect; 2 patients showed a moderate decrease in serum protein-bound iodine and in the size of the thyroid gland, and one of these also showed a decrease in the rate of thyroid uptake of radio-iodine. A fifth patient showed a similar decrease in rate of iodine uptake, with a reduction in the size of the gland and a coincident improvement in the clinically mild hyperthyroid state. Cessation of treatment in this patient was followed by a transient exacerbation of the hyperthyroidism and then by remission, which was complete 3 months later. The last patient experienced an almost complete remission, as evidenced by both clinical and laboratory findings, with reduction in the size of the goitre. This patient then had a sub-total thyroidectomy with 14 days of corticotrophin as the only pre-operative preparation.

Thus 4 of the 6 patients showed biochemical improvement, and in 2 of these a clinical remission was reported.

Various other descriptions of the use of cortisone and corticotrophin have been reported, but on the whole the results have been disappointing (Moseley and Merrill, 1950; Szilagyi *et al.*, 1952; and Warner, 1950). There have, however, been occasional cases where success has been claimed. Engel (1950) reported improvement in a patient who had thyrotoxicosis, auricular fibrillation and congestive failure. The basal metabolic rate fell from + 44 % to + 4 % after 10 days of corticotrophin, coincidentally with improvement in the patient's general condition. Three weeks after the cessation of this therapy there was no clinical evidence of hyperthyroidism, the basal metabolic rate was + 15 % and the goitre had practically disappeared. The value of the basal metabolic rate as an estimate of thyroid function in the presence of the cardiac failure is, however, questionable.

In order to demonstrate more clearly the therapeutic value, if any, of corticotrophin in hyperthyroidism, a further clinical investigation has been started in conjunction with my colleague, Dr. H. J. Galbraith. So far 6 patients have completed the course of treatment and assessment.

DESIGN OF INVESTIGATION

Each patient is admitted to hospital and confined to bed. No treatment is given for 10 to 14 days, and during this period the diagnosis is confirmed and the severity of hyperthyroidism established by the collection of clinical data and a series of tests.

The basal metabolic rate is estimated by the Benedict-Roth method on at least 3 separate days towards the end of the period of assessment.

Radio-active iodine studies are bing undertaken by Dr. J. S. Staffurth. These include the estimation of urinary excretion and thyroid uptake, the plasma radio-active iodide, the protein-bound radio-active iodine and also the serum protein-bound iodine by the chemical method.

Adrenocortical function is assessed by the urinary excretion of 17-ketosteroids and 17-ketogenic steroids over at least two 24-hour periods (Prof. F. T. G. Prunty's laboratory) This is proving of some interest as the level of the 24-hour excretion of 17-ketosteroids in all patients before the start of treatment was either pathologically low or in the lower

ranges of normal. The levels of 17-ketogenic steroid excretion were normal. These findings are in accordance with the results obtained by previous workers.

Tests for the presence of complement-fixing and precipitating thyroid auto-antibodies are also being made. This is being done because the recent very interesting work on Hashimoto's disease, in which auto-antibodies have been found, has led to the occasional demonstration of complement-fixing auto-antibodies in thyrotoxicosis. Their significance is far from being understood, but we did not wish to lose an opportunity of seeking them and of attempting to assess whether corticotrophin, with its recognized effect on lymphoid tissue and antibody formation, resulted in any alteration in these tests. So far no antibodies have been detected.

When the tests of thyroid function are completed, corticotrophin gel is given twice daily by injection for a period of 2 to 4 weeks, the duration depending on the patient's response. The initial dosage is 20 units twice daily. Excessive fluid retention is combated by a low-salt diet and twice weekly injections of mersalyl. When, in spite of these measures a weight-gain of about 10 lb. is produced, the dose is reduced to 10 units twice daily. Potassium chloride is given by mouth concurrently with the corticotrophin.

Corticotrophin of the same batch is being used in each case. Its potency has previously been demonstrated in a healthy subject by estimation, after injections from this batch, of an increase in the urinary excretion levels of 17 keto- and 17-ketogenic steroids.

During the last few days of corticotrophin administration and, in some cases, during the course of treatment, the clinical and laboratory measurements are repeated, the injections of mersalyl being stopped while urine collections are being made. Confirmation of the efficiency of the adrenocortical stimulation was obtained by the fluid retention produced in each case and by the increase in the levels of urinary excretion of 17 keto- and 17 ketogenic steroids.

RESULTS

Six patients have so far been treated with corticotrophin. Four had diffuse goitres and 2 nodular goitres. Only one patient showed significant reduction in the degree of hyperthyroidism during treatment. He was a man aged 40 with a diffuse goitre whose symptoms were of only 4 months' duration.

A reduction in the size of the goitre was thought to have occurred in one woman of 45 with a diffuse enlargement during the first fortnight of treatment, but further improvement was not seen although corticotrophin was given for another 2 weeks.

One patient, a woman aged 40 with a nodular goitre, has been treated under similar conditions with Prednisone, 40 mg. daily for 18 days. No significant change in her condition was observed.

Review of the reported cases, including ours, leads one to the provisional conclusion that little clinical benefit will result from treatment of thyrotoxicosis with corticotrophin or cortisone. There is, however, evidence that in a number of patients some of the methods of estimation of thyroid function, notably in the protein-bound iodine, show a tendency to revert nearer to normal, and for this reason it seems worth while to continue our studies.

It has been claimed that corticotrophin has led to an unexpectedly smooth post-operative period when used pre-operatively with Lugol's iodine (Szilagyi *et al.*, 1952). Schlicke and Berhan (1954) used corticotrophin in 7 thyrotoxic patients undergoing sub-total thyroidectomy in whom an unsatisfactory reponse to conventional medical preparation had made possible the occurrence of some acute post-operative complication. Corticotrophin was given on the day of operation and for a few days subsequently to all 7 of them, and in 5 for two or three days before operation. This was in addition to the usual iodine and antithyroid drugs. All the patients were said to have had a notably smooth post-operative course.

Since the report of Hill *et al.* (1950) there have been several descriptions of the use of corticotrophin and adrenocortical steroids in malignant exophthalmos and in thyrotoxic crises. In the former most writers agree that a reduction in oedema occurs without any improvement in proptosis or ophthalmoplegia. In the latter it appears that corticotrophin may play an important part in ensuring or accelerating recovery, although the situation is invariably confused by the administration of other forms of treatment as well.

SUMMARY

1. It would seem from the results of corticotrophin treatment so far reported that a significant clinical improvement in hyperthyroid patients will only be noted occasionally, but some tests for thyroid function notably for protein-bound iodine may revert to normal.

2. The post-operative course following subsequent thyroidectomy may be made smooth by this treatment, but this is difficult to assess objectively without a very large series.

3. One effect of corticotrophin appears to be reduction in the size of the goitre, and this has been observed in about a third of the patients.

4. There is some evidence that corticotrophin plays an important part in the management of thyrotoxic crises, and is of some value in malignant exophthalmos.

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