

"STUDIES ON THE DIAGNOSIS AND MANAGEMENT OF THYROID DISEASE"

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REFERENCES

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3. TOFT, A.D., BARNES, E.W., HUNTER, W.M., SETH, J., IRVINE, W.J. Raised plasma thyroid stimulating hormone levels in thyrotoxic patients treated with iodine-131. *Lancet* ii, 644-645 (1973).
4. TOFT, A.D., SETH, J., HUNTER, W.M., IRVINE, W.J. Plasma thyrotrophin and serum thyroxine in patients becoming hypothyroid in the early months after iodine-131. *Lancet* i, 704-705 (1974).
5. TOFT, A.D., IRVINE, W.J., HUNTER, W.M., SETH, J. Plasma TSH and serum T-4 levels in long-term follow-up of patients treated with ¹³¹I for thyrotoxicosis. *British Medical Journal* 3, 152-153 (1974).
6. TOFT, A.D., IRVINE, W.J., HUNTER, W.M., RATCLIFFE, J.G., SETH, J. Anomalous plasma TSH levels in patients developing hypothyroidism in the early months after ¹³¹I therapy for thyrotoxicosis. *Journal of Clinical Endocrinology and Metabolism* 39, 607-609 (1974).
7. TOFT, A.D., IRVINE, W.J., SETH, J., HUNTER, W.M., CAMERON, E.H.D. Thyroid function in the long-term follow-up of patients treated with iodine-131 for thyrotoxicosis. *Lancet* ii, 576-578 (1975).
8. TOFT, A.D., IRVINE, W.J. Partial failure of anterior pituitary and thyroid presenting as myxoedema. *Acta Endocrinologica* 79, 688-690 (1975).
9. TOFT, A.D., IRVINE, W.J., CAMPBELL, R.W.F. Assessment by continuous cardiac monitoring of minimum duration of preoperative propranolol treatment in thyrotoxic patients. *Clinical Endocrinology* 5, 195-198 (1976).
10. TOFT, A.D., IRVINE, W.J., HUNTER, W.M. A comparison of plasma TSH levels in patients with diffuse and nodular non-toxic goiter. *Journal of Clinical Endocrinology and Metabolism* 42, 973-976 (1976).
11. TOFT, A.D., IRVINE, W.J., McINTOSH, D., MACLEOD, D.A.D., SETH, J., CAMERON, E.H.D., LIDGARD, G.P. Thyrotoxicosis treated by subtotal thyroidectomy under cover of propranolol. *ibid* (1976) (In press).
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SUMMARY

Serum thyrotrophin (TSH) levels have been measured by radioimmunoassay in a large series of new patients referred to the Endocrine Clinic, Royal Infirmary, Edinburgh with suspected thyroid disease. The normal range for the assay has been established at undetectable - 5.7 mU/l. Raised levels of serum TSH have been found in patients with untreated primary hypothyroidism and in patients with impaired reserve of thyroid function, and it has been shown that a single estimation of serum TSH gives similar information about thyroid reserve as the time-consuming TSH stimulation test. It has not been possible, on the basis of a single estimation of serum TSH, to differentiate the euthyroid patient from the hyperthyroid patient. However, a lack of response of the serum TSH level to thyrotrophin-releasing hormone (TRH) intravenously has been shown to be compatible with a diagnosis of thyrotoxicosis. The measurement of serum TSH level before and at twenty minutes after TRH showed good correlation with the results of the triiodothyronine suppression test, and the TRH test should therefore replace the suppression test in the investigation of patients with suspected thyrotoxicosis in whom the results of routine thyroid function tests are equivocal. Serum TSH levels have been found to be significantly lower in patients with simple non-toxic nodular goitre than in euthyroid non-goitrous patients or in patients with simple non-toxic diffuse goitre, and may be a reflection of thyroid autonomy in nodular goitre.

Thyroid function has been assessed in patients treated with iodine-131 for thyrotoxicosis. Due to a suppression of the brain-thyroid axis in patients previously exposed to high circulating levels of thyroid hormones, the total serum thyroxine level was a better index of

impending hypothyroidism than the serum TSH level in the early weeks after radioiodine treatment. Raised levels of serum TSH have been found in over 50% of patients euthyroid six to eighteen years after iodine-131 therapy for thyrotoxicosis. The patients with a raised serum TSH level were shown to be at risk of developing hypothyroidism at a rate of 2-5% per annum over a period of three years of study, whereas no patient with a normal serum TSH level developed hypothyroidism over the same study period. It is suggested that the long-term follow-up policy for the ever-increasing number of patients who have been treated with radioiodine for thyrotoxicosis could be rationalised on the basis of the serum TSH level measured at one year after therapy.

The efficacy of treating patients with thyrotoxicosis by subtotal thyroidectomy under cover of propranolol has also been demonstrated. The time for recovery of the suppressed brain-thyroid axis in such patients has been shown to be between four and eight weeks. The phenomenon of temporary clinical hypothyroidism in the early weeks after subtotal thyroidectomy has been described in terms of total serum triiodothyronine and thyroxine and TSH levels and attention has been drawn to the possibility that the timing of postoperative review may be related in part to the postoperative incidence of hypothyroidism.

CHAPTER 1 Serum TSH levels in thyroid disease

Since the description of a sensitive and specific radioimmunoassay of human serum thyrotrophin (TSH) by Odell et al. (1965) and Utiger (1965) the estimation of circulating TSH in the investigation of patients with thyroid disease has proved a valuable additional test of thyroid function (Hall et al. 1971; Hershman and Pittman, 1971; Mayberry et al., 1971; Patel et al., 1971). The development of a double-antibody radioimmunoassay for serum TSH in Edinburgh has afforded the opportunity of measuring serum TSH levels in a large series of patients referred to a thyroid clinic. The present report is concerned with the definition of a normal range for serum TSH and with the evaluation of serum TSH levels in the diagnosis of patients with suspected thyroid disorders.

PATIENTS AND METHODS

A total of five hundred and eighty-one new patients were studied who had been referred to the Endocrine Clinic, Royal Infirmary, Edinburgh for the investigation of suspected thyroid disease. In each case the thyroid status was determined clinically and on the basis of the following tests of thyroid function: total serum thyroxine (T_4) by competitive protein-binding analysis (Seth, 1973) or radioimmunoassay (Seth et al., 1975), effective thyroxine ratio (ETR) (Thorson et al., 1972; Toft et al., 1973a), circulating thyroid autoantibodies (Doniach and Roitt, 1975) and the 4 hour uptake of iodine-132 by the thyroid gland supplemented when necessary by TSH stimulation or triiodothyronine (T_3) suppression. In addition thyroid biopsy was performed in some of the patients with suspected Hashimoto's thyroiditis.

No evidence of thyroid disease could be found in two hundred and twenty

of the patients (185 females, 35 males) with a mean age of thirty-eight years, of whom twenty-nine patients were taking an oestrogen containing oral contraceptive agent at the time of presentation. Circulating thyroid autoantibodies were present in thirty-five of the patients (16%) in this group.

Three patients, all female, were considered to have exophthalmic Graves' disease, on the basis of unilateral exophthalmos associated with thyroid autoantibodies and an abnormal T_3 suppression test result.

A diagnosis of Hashimoto's thyroiditis was made in sixteen patients (15 female, 1 male) with a mean age of forty-three years. In each case a firm, symmetrical enlargement of the thyroid gland was present and was associated with clinical and biochemical evidence of hypothyroidism in five patients, and in three of these five patients thyroid autoantibodies were present in the serum. The remaining eleven patients with Hashimoto's thyroiditis were euthyroid, although the TSH stimulation test was abnormal in eight: in six of the euthyroid patients, thyroid autoantibodies were either undetectable or present in the serum in weak titre and the diagnosis of Hashimoto's thyroiditis was confirmed by histological examination of the gland; in the other five patients the combination of a firm symmetrical goitre and a tanned red cell haemagglutination titre of 1:2500 or more and/or a complement fixation titre of $\geq 1:32$ was considered adequate for diagnostic purposes.

Thirty-three patients (31 females, 2 males) with a mean age of fifty-three years were found to have primary (non-goitrous)

hypothyroidism. Three of the patients had previously been treated with iodine-131, and two by subtotal thyroidectomy for thyrotoxicosis. In all cases a low total serum T_4 level and a low ETR was associated with a lack of response of the 4 hour iodine-132 uptake by the thyroid gland to exogenous TSH stimulation. Thyroid autoantibodies were present in 75% of the patients.

Secondary hypothyroidism as a result of anterior pituitary or hypothalamic dysfunction was present in ten patients (4 females, 6 males) with a mean age of forty-two years. In each case low circulating levels of thyroid hormone were associated with a normal TSH stimulation test result. In three of the patients the hypothyroidism was associated with idiopathic panhypopituitarism, in two patients it was secondary to a hypothalamic lesion and in four patients it was the result of hypophysectomy for a pituitary adenoma. The remaining patient was considered to have a combination of partial thyroid and partial pituitary failure.

A simple non-toxic goitre was present in one hundred and fifteen patients and was classified as diffuse or nodular on clinical grounds alone in the majority. In fifty-two patients (50 females, 2 males) with a mean age of twenty-nine years the thyroid gland was diffusely enlarged. A nodular goitre was present in sixty-three patients (60 females, 3 males) with a mean age of forty-seven years. A solitary nodule was present in eight of these patients and in six a partial thyroidectomy was carried out and the histology shown to be that of a benign thyroid adenoma. Partial thyroidectomy was also performed in fourteen of the patients with multinodular goitre and in each case the histological appearances confirmed the clinical diagnosis and did

not indicate Hashimoto's thyroiditis. Thyroid autoantibodies were present in five patients with diffuse goitre and in fifteen patients with nodular goitre. The titres in the complement fixation test and in the tanned cell haemagglutination test in no case exceeded 1 in 8 and 1 in 250 respectively which are below the levels suggestive of Hashimoto's thyroiditis and which commonly occur in control populations.

Thyrotoxicosis was diagnosed in one hundred and eighty-four patients (155 females, 29 males) with a mean age of forty-two years, and thyroid autoantibodies were present in the serum of 65% of the patients.

The radioimmunoassay of serum TSH was carried out using a modification of the double antibody method of Odell et al. (1967a). Purified human TSH (Preparation DE-32-3) for iodination was provided by Dr. A. Stockell Hartree, Cambridge University, and the Medical Research Council human TSH standard A was used as a standard. Guinea-pig anti-TSH serum was raised by the MRC Radioimmunoassay Team, Edinburgh, and rabbit antiserum to guinea-pig γ -globulin was used as the precipitating antibody. In ten consecutive assays the mean and range of binding to antibody of the 50 ng/l iodine-125-TSH tracer was 47.3 (41.9-54.5)%, while 25%, 50% and 75% inhibition of this binding was given by 0.55 (0.49-0.60), 1.30 (1.10-1.35) and 3.70 (2.50-3.80) mU/l incubate respectively. Serum was assayed at 1:4 or greater dilution as appropriate. No attempt was made to equalise the serum content of the incubates by incorporating human TSH-free serum in the standards because the small intrusion of non-specific interference as represented by the response of different samples of

non-primate serum was inconstant. Responses which were not greater than 10% binding below the 'O' standard were recorded at less than the appropriate value. The mean value for this threshold was 1.84 (range 1.60-2.12) mU/l serum in the ten assays described above.

RESULTS

The levels of serum TSH recorded in the five hundred and eighty-one patients with suspected thyroid disease are shown in Fig. 1.1 in relation to the final diagnosis.

Normal Range

The normal range for the TSH assay was calculated from the serum TSH levels of the one hundred and ninety-one patients (156 females, 35 males) in whom no evidence of thyroid disease could be found and who were not receiving an oestrogen containing oral contraceptive agent. The results conformed to a log normal distribution and the mean serum TSH level and the 95% tolerance limits calculated on this basis were 2.7 and <1.8-5.7 mU/l respectively. The normal range for serum TSH was therefore considered to be <1.8-5.7 mU/l.

The euthyroid patients represented in Fig. 1.1 include the twenty-nine females taking oestrogen containing oral contraceptives, and the three females with exophthalmic Graves' disease. Forty (18%) of the total two hundred and twenty-three euthyroid patients had a serum TSH level of <1.8 mU/l. It is of interest that thyroid autoantibodies were detected in the serum of three of the four euthyroid patients with the highest serum TSH levels. Serum TSH levels were uninfluenced by age, sex or oestrogens.

Hashimoto's thyroiditis

The serum TSH levels were elevated in all but three of the patients with Hashimoto's thyroiditis. The five patients who were clinically hypothyroid had serum TSH levels ranging from 25.2-93.0 mU/l, and the eight euthyroid patients with raised serum TSH levels had values of 6.2-19.8 mU/l.

Primary hypothyroidism

In all patients with primary hypothyroidism the serum TSH levels were markedly elevated, ranging from 21.2 - 512.0 mU/l. There was no apparent relationship between serum TSH concentration and age, duration of symptoms or titre of thyroid autoantibodies.

Secondary hypothyroidism

In three patients in this category the serum TSH level was undetectable and in four patients lay between 1.8 and 5.7 mU/l. In the two patients with hypothalamic lesions, the serum TSH level was minimally raised at 5.9 and 6.4 mU/l. In the remaining patient in whom a diagnosis of hypothyroidism secondary to a combination of partial thyroid failure and partial pituitary failure was made, the serum TSH level was 30.0 mU/l. In view of the unusual aetiology of hypothyroidism in this latter patient, the case will now be described in more detail: the patient was a 58 year-old female schoolteacher who presented with the features of myxoedema. There was no goitre. The total serum T_4 was <25 nmol/l, serum TSH 30.0 mU/l and antibodies were detected to thyroglobulin in a titre of 1:2500 by the tanned cell haemagglutination method. Antibodies against thyroid cytoplasm were not detected. The 4 hour iodine-132 uptake by the

thyroid gland increased normally from 13-26% in response to exogenous bovine TSH, 10 i.u. intramuscularly daily for three consecutive days, suggesting a diagnosis of secondary hypothyroidism. Tomography of the pituitary fossa was normal and the visual fields were intact. Urinary luteinising hormone (LH) measured by haemagglutination inhibition was low for a post-menopausal female at 23.3 IU/24 hours (normal >36 IU/24 hours). A standard insulin tolerance test was performed, using 0.1 units soluble insulin/Kg - body weight. The plasma glucose fell to <1.0 mmol/l, but the serum growth hormone (GH) level measured by radioimmunoassay (HGH-125 Imusay, Abbott Laboratories) was undetectable throughout the test. The plasma 11-hydroxycorticosteroids (11-OHCS) (Mattingly, 1962) and the plasma prolactin measured by radioimmunoassay (Cole and Boyns, 1973) increased normally from 480 to 1250 nmol/l and from 0.19 to 0.59 U/l respectively. The elevated basal serum TSH level of 30.0 mU/l indicative of primary thyroid failure was unchanged however, at twenty and sixty minutes after the rapid intravenous injection of 200µg thyrotrophin-releasing hormone (TRH), suggesting that the pituitary thyrotrophs were already secreting TSH to their maximum capacity. When the patient had been taking l-thyroxine 0.15 mg daily for five months the brain-thyroid axis was reinvestigated. She was clinically euthyroid, with a total serum T₄ of 100 nmol/l and a serum TSH level of <1.8 mU/l which remained undetectable following 200 µg TRH intravenously. Urinary LH remained low at 26.2 IU/24 hours. Serum GH increased on this occasion to 8.0 mg/l during insulin-induced hypoglycaemia, the plasma glucose falling to <1.0 mmol/l. Plasma 11-OHCS and prolactin levels rose normally during the test. The patient has been followed up for three years and remains well. There is no clinical or radiological evidence of pituitary tumour. The

degree of impaired function of either thyroid or pituitary gland alone would not have caused the clinical presentation, and the only satisfactory explanation of the results of the various investigations is that the myxoedema was a consequence of a combination of partial failure of the thyroid gland and the anterior pituitary gland.

Simple non-toxic goitre

The serum TSH levels in the patients with diffuse enlargement and in the patients with nodular enlargement of the thyroid gland are shown in Fig. 1.2. The serum TSH levels in the one hundred and ninety-one patients with no evidence of thyroid disease are included for comparison. The results conformed to a log normal distribution and the mean levels and the 95% tolerance limits calculated on this basis are shown in Table 1.1. Although the mean serum TSH levels of the two groups of patients with simple non-toxic goitre lay within the normal range, it was apparent that a different distribution of serum TSH levels existed between the patients with nodular goitre and those with diffuse goitre or those euthyroid patients without goitre in that a greater proportion of patients with nodular enlargement of the thyroid gland had undetectable levels of TSH in the serum of <1.8 mU/l (57%) when compared with the patients with diffuse thyroid enlargement (29%) or with those without goitre (18%). Due to the uncertain nature of the distribution of the serum TSH results below 1.8 mU/l the Mann-Whitney U test was employed as a non-parametric test of significance (Siegel, 1956) to determine any difference in serum TSH levels in the three groups of patients. Using this test, the serum TSH levels in the patients with nodular goitre were significantly lower than those recorded in either the patients with

diffuse thyroid enlargement or the non-goitrous euthyroid patients ($P < 0.01$ and $P < 0.0001$), and this difference was maintained when the patients with evidence of circulating thyroid autoantibodies were excluded ($P < 0.0001$ and $P < 0.0001$). The difference between the groups could not be accounted for by age, as there was no apparent relationship between serum TSH levels and age in the control group. There was, however, no statistical difference in serum TSH levels between patients with diffuse goitre and non-goitrous euthyroid patients with or without evidence of circulating thyroid autoantibodies ($P > 0.8$ in each case).

It is of interest that seven of the patients with diffuse thyroid enlargement had raised serum TSH levels which on the one hand may represent the initial stimulus to goitre formation, but on the other hand may be the result of undetected autoimmune thyroiditis or dysshormonogenesis. In three of the five patients with nodular goitre and elevated serum TSH levels, antibodies to thyroid microsomes were detected by immunofluorescence, but the complement fixation titre was less than 1:4 and thyroglobulin antibodies were absent in each case.

Thyrotoxicosis

The serum TSH level was undetectable at < 1.8 mU/l in one hundred and sixty-nine (92%) of the patients with thyrotoxicosis. The remaining fifteen patients with thyrotoxicosis had serum TSH levels of between 1.8 and 5.7 mU/l which is the upper limit of normal established for the euthyroid patients with no evidence of thyroid disease. No patient with thyrotoxicosis had a raised level of serum TSH.

DISCUSSION

All published reports of the radioimmunoassay of TSH have established a normal range from serum TSH levels found in hospital in-patients and healthy volunteers. Such a method is epidemiologically unsatisfactory (Masi, 1965) and there are alternative approaches for the determination of a normal range for serum TSH. One method is to measure circulating TSH levels in a large scale community survey and it is of interest that the upper limit of normal for serum TSH on this basis in the Newcastle-upon-Tyne area is 5.0 mU/l (Evered et al., 1975), which is significantly higher than the upper limit of normal of 2.8 mU/l proposed by Hall et al., (1971) utilising the same radioimmunoassay system, but depending upon a small number of hospital controls. The other approach is to calculate a normal range or more precisely a clinic euthyroid range, from the levels of serum TSH estimated in patients referred to a thyroid clinic with suspected thyroid disease, but who are ultimately found to be clinically and biochemically euthyroid with no evidence, past or present, of thyroid disease. It is felt that such a group of patients is well matched with the patients who are found to have disordered thyroid function, since each group has been selected only on the basis of suspected thyroid disease from the same population and by means of the same hospital referral system. It is of interest that the normal range so established of <1.8-5.7 mU/l has an upper limit of normal close to that reported from the population survey in Newcastle of 5.0 mU/l. The lower limit of sensitivity of the present assay of 1.8 mU/l is higher than that reported in many other assay systems, but can be mainly accounted for by the fact that in the Edinburgh assay binding responses which are less than 10%

below the 'O' standard of the standard curve are recorded as undetectable levels of serum TSH.

The only comprehensive study of serum TSH levels in autoimmune thyroiditis is that of Greenberg et al., (1970) who estimated thyroid function in children with chronic lymphocytic thyroiditis in whom there was histological confirmation of the diagnosis in each case. Raised serum TSH levels were found in nineteen of the thirty-two euthyroid patients. Serum TSH levels showed a good correlation with the degree of follicular epithelial atrophy within the thyroid gland. There is no similarly detailed study available in adult patients with Hashimoto's thyroiditis. Mayberry et al., (1971) reported elevated serum TSH levels in 38% of euthyroid patients with Hashimoto's thyroiditis, but histological confirmation of the diagnosis was available in only half of the patients and no attempt was made to relate serum TSH levels to thyroid histology. Eight of the eleven euthyroid patients with Hashimoto's thyroiditis in the present series had raised serum TSH levels, but the number is too small to permit informed comment. There is no doubt, however, that a raised serum TSH level in a patient with a symmetrical goitre and with circulating thyroid autoantibodies prevents the need for histological confirmation of the diagnosis of autoimmune thyroiditis since serum TSH levels in patients with simple goitre and carcinoma are normal or low. Although patients with congenital dysmorphogenesis may have high levels of serum TSH, antibody titres are rarely significantly increased (Anderson et al., 1959). It remains to be seen whether the natural history of Hashimoto's thyroiditis in a patient with a normal serum TSH level and presumably mild disease will differ from that of the patient with a raised serum TSH level and

more extensive destruction of the thyroid gland.

The serum TSH level exceeded 20.0 mU/l in all the patients with primary hypothyroidism, a total of one hundred and nine patients if the patients described in the TSH stimulation test and TSH 'short-feedback' studies are included. There is therefore a range of TSH in the serum from 5.7-20.0 mU/l which is seen in patients who are euthyroid but have some degree of impairment of thyroid reserve. Prior to the development of overt hypothyroidism a patient must pass through two stages of impaired reserve of thyroid function. In the first stage there is a tendency for thyroid hormone levels to deviate downwards from the optimum level and for pituitary TSH secretion to increase, but while there is adequate thyroid reserve the total serum T₃ and T₄ are returned to normal levels. Such patients, who are asymptomatic, have been classified as having subclinical or preclinical hypothyroidism (Evered and Hall, 1972; Evered et al., 1973a). Some aspects of preclinical hypothyroidism have been described in terms of circulating thyroid autoantibodies (Bastenie et al., 1967a; Bastenie et al., 1967b; Vanhaelst et al., 1967; Bastenie et al., 1971; Gordin et al., 1972; Gordin et al., 1974) or in terms of raised serum cholesterol concentrations (Fowler and Swale, 1967; Fowler et al., 1970). Although some patients with preclinical hypothyroidism will have circulating thyroid autoantibodies and/or a raised serum cholesterol level, neither of these phenomena is specific, and the definition should be retained for asymptomatic patients with a raised serum TSH level and normal levels of circulating thyroid hormones. In the second stage of impaired reserve of thyroid function, despite rising levels of serum TSH, the concentrations of total serum T₃ and T₄ are not maintained

and deviate downwards although still within the normal range. Many of these patients are considered to have mild hypothyroidism on the basis of non-specific symptoms and a subjective response to thyroxine replacement therapy (Evered et al., 1973a). However, the greatest incidence of patients with thyroid hormone levels in the lower part of the normal range and raised serum TSH levels occurs following treatment of thyrotoxicosis with radioiodine or surgery. In several large series (Tunbridge et al., 1974; Evered et al., 1975; Toft et al., 1973c, 1974a, 1975 and Chapter 5) such patients have not been considered to have mild hypothyroidism as they have not received replacement therapy with thyroxine. It is evident that there is no agreement about where the division lies between impaired thyroid reserve and hypothyroidism and in Edinburgh it is felt that the diagnosis of primary hypothyroidism requires a demonstration of a low circulating level of total serum thyroxine which will be invariably associated with serum TSH concentration of >20.0 mU/l. Patients with total serum T_4 levels in the lower range of normal associated with raised serum TSH levels are considered to be euthyroid although it is possible that long-term studies of this group of patients may prove that the withholding of thyroxine replacement therapy is detrimental.

On the basis of the current understanding of the brain-thyroid axis, serum TSH levels should be undetectable in patients with hypothyroidism secondary to pituitary or hypothalamic disease. However, the spectrum of results for serum TSH recorded in patients with secondary hypothyroidism in the present series, from undetectable to slightly raised levels, is an agreement with the reports of other investigators (Patel and Burger, 1973; McLaren et al., 1974). The

finding of detectable levels of serum TSH within the normal range in secondary hypothyroidism may be explained by the lack of sensitivity of the assay. It is more difficult to account for the presence of raised serum TSH levels in such patients unless there is associated primary thyroid failure as suggested in the patient in the present study in whom a serum TSH level of 30 mU/l was detected which did not rise further after TRH, and in whom the TSH stimulation test result was normal and autoantibodies were present in high titre to thyroid tissue. Patel and Burger (1973) reported almost 50% of a series of patients with secondary hypothyroidism to have slightly raised serum TSH levels, although concomitant thyroid failure based on the presence of circulating thyroid autoantibodies and a lack of thyroidal response to exogenous TSH was present only in the minority. However, the recent description of autoantibodies to prolactin secreting cells of the human pituitary in patients with one or more autoimmune endocrine diseases (Bottazzo et al., 1975) gives credence to the possibility that pituitary and thyroid failure may coexist in the same patient. It is also possible that biologically inactive fragments or precursors of TSH which cross-react with the TSH anti-serum are released in some of the patients with secondary hypothyroidism. Whereas the serum TSH level is of value in determining whether a patient has primary or secondary hypothyroidism, it was hoped that the serum TSH response to TRH would demonstrate whether the site of functional impairment was of pituitary or hypothalamic origin. An absent or subnormal serum TSH response to TRH is found in patients with hypopituitarism (Anderson et al., 1971; Haigler et al., 1971; Hall et al., 1972) and a serum TSH response to TRH of normal magnitude but delayed time course occurs in patients with hypothalamic disease (Costom et al., 1971; Hall et al., 1972).

However, since absent, subnormal or delayed responses may occur in patients who are euthyroid or hypothyroid with pituitary or hypothalamic disease (Foley et al., 1972; Patel and Burger, 1973; McLaren et al., 1974; Snyder et al., 1974), and since high basal levels of serum TSH with exaggerated responses to TRH have been reported in patients with pituitary tumours (Faglia et al., 1972; Schalch et al., 1972; McLaren et al., 1974) the significance of the patterns of serum TSH response to TRH is not always clear.

The cause of sporadic non-toxic goitre is not known and from the present study it is evident that a raised serum TSH level is not required for the maintenance of thyroid enlargement, unlike the situation in areas of severe iodine deficiency where serum TSH levels are raised in association with goitre (Buttfield et al., 1966; Pisarev et al., 1970; Wahner et al., 1971; Beckers and Cornette, 1971; Delange et al., 1971; Ogihara et al., 1972; Kochupillai et al., 1973). Although it is possible that the thyroid gland of patients with sporadic goitre is more sensitive to the goitrogenic action of TSH, as is the case in both iodine-deficient rats and man (Bray, 1968; Kajubi, 1975) the initial thyroid hyperplasia may be TSH induced. It is of interest in this respect that Young et al., (1975) found higher circulating TSH levels in patients with idiopathic euthyroid goitre of less than one year's duration than in patients whose goitre had been present for more than one year. They also found serum TSH levels to be higher in the goitrous patients compared with control subjects, unlike the present series, but did not measure thyroid autoantibodies and therefore probably underestimated the incidence of autoimmune thyroiditis. It is noteworthy that the serum TSH level was elevated in seven of the present series of patients with diffuse thyroid enlargement. Two of

these seven patients were available for follow-up after one year and although the serum TSH level fell in one case, it was unchanged in the other, raising the possibility of previously undiagnosed dyshomogenesis or autoimmune thyroiditis. It is considered that in time, the diffuse non-toxic goitre of youth becomes the nodular goitre of middle age and the autoradiographic and histological studies of Taylor (1953; 1956; 1973) have shown that nodular goitre is the end result of recurrent focal hyperplasia and degeneration with the majority of nodules inactive but the functioning nodules behaving autonomously. It would appear from the present study that the transition from diffuse to nodular goitre is associated with a significant reduction in serum TSH levels which may reflect the autonomy of function of nodular goitre. The proportion of patients with detectable serum TSH levels associated with diffuse or nodular goitre approximates to the reported success rate in inducing goitre shrinkage with thyroid hormone therapy (Greer and Astwood, 1953; Astwood et al., 1960; Lamberg et al., 1960; Shimaoka and Sokal, 1974). If the majority of patients with nodular goitre and undetectable serum TSH levels have autonomous thyroid function, shrinkage of the gland by exogenous thyroid hormone would not be expected.

Thyroid autonomy, in terms of lack of suppression of the radio-iodine uptake of the thyroid gland by oral T_3 , has been reported in some 25% of patients with euthyroid multinodular goitre (Werner and Spooner, 1955). Although the patients with multinodular goitre in the present series were clinically euthyroid with normal total serum T_4 levels, a possible explanation of the reduction in serum TSH levels is that a subgroup exists of patients with subclinical thyrotoxicosis, in whom the total serum T_3 levels would be raised and in whom there would be

a lack of response of serum TSH to TRH. Evered et al., (1974) have described raised total serum T_3 levels, associated with absent serum TSH responses to TRH, in euthyroid patients with solitary autonomous thyroid nodules, but similar studies in patients with multinodular goitre do not seem to have been reported.

The majority of patients with thyrotoxicosis in the present series had undetectable levels of TSH in the serum, but 8% had levels which were detectable between 1.8 and 5.7 mU/l. The radioimmunoassay of TSH is therefore not sufficiently sensitive to differentiate the euthyroid patient from the patient with thyrotoxicosis on the basis of a single serum TSH estimation. Although a normal response of serum TSH to TRH excludes a diagnosis of thyrotoxicosis, a lack of response of serum TSH to the releasing hormone, invariably seen in thyrotoxicosis, may also occur in patients with exophthalmic Graves' disease (Lawton et al., 1971; Ormston et al., 1973) and in euthyroid patients with solitary autonomous thyroid nodules (Evered et al., 1974). The total serum T_3 levels in these two groups of euthyroid patients may be at the upper limit of normal or slightly raised and is an indication of the narrow range of total serum T_3 and T_4 concentrations in which the serum TSH response to TRH is normal (Snyder and Utiger, 1972a; 1973). This range will be much narrower for an individual patient than the normal range of thyroid hormone levels for the population. Furthermore, a temporary lack of response of serum TSH to TRH occurs in patients rendered euthyroid either by iodine-131 or subtotal thyroidectomy, as a result of the suppression of the pituitary thyrotrophs previously exposed to high circulating T_3 and T_4 levels when the patient was thyrotoxic (Chapter 6).

In summary by estimating serum TSH by radioimmunoassay in five hundred and eighty-one new patients referred to an Endocrine Clinic it has been possible to:

- i) define a normal range for serum TSH in patients with no evidence of thyroid disease of $<1.8-5.7$ mU/l.
- ii) demonstrate serum TSH levels of >20.0 mU/l in patients with primary hypothyroidism and therefore not only differentiate between primary and secondary hypothyroidism but also exclude a diagnosis of primary hypothyroidism on the basis of a single estimation of serum TSH.
- iii) confirm that serum TSH levels may be normal or raised in patients with Hashimoto's thyroiditis.
- iv) demonstrate that serum TSH levels are significantly lower in patients with simple non-toxic nodular goitre than in euthyroid non-goitrous patients or patients with simple non-toxic diffuse goitre.
- v) confirm that although serum TSH levels are undetectable in the majority of patients with thyrotoxicosis, a single estimation of serum TSH level will not differentiate the euthyroid from the hyperthyroid patient.

Fig. 1.1

Serum TSH (mU/l) levels in 581 new patients referred to the Endocrine Clinic, Royal Infirmary, Edinburgh with suspected thyroid disease. The upper limit of normal for the assay of 5.7 mU/l is indicated by the horizontal continuous line. The numbers (%) in the boxed areas represent the patients in the various diagnostic categories with undetectable levels of TSH in the serum of <1.8 mU/l, in addition to the euthyroid patients with serum TSH levels in the normal range. The solid symbols represent patients in whom circulating thyroid autoantibodies were detected. The patient indicated by the arrow had myxoedema due to a combination of partial failure of the pituitary and the thyroid gland.

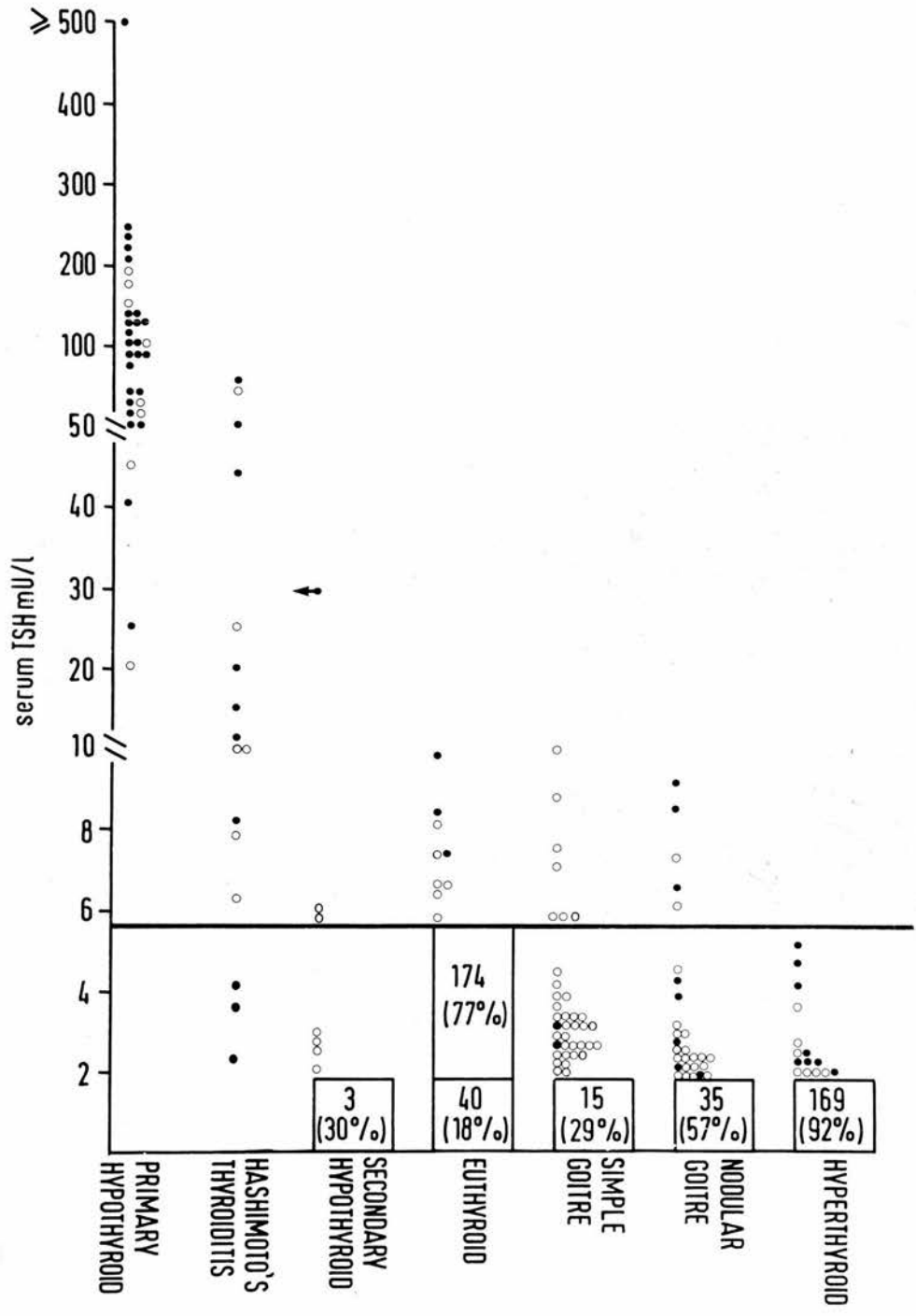
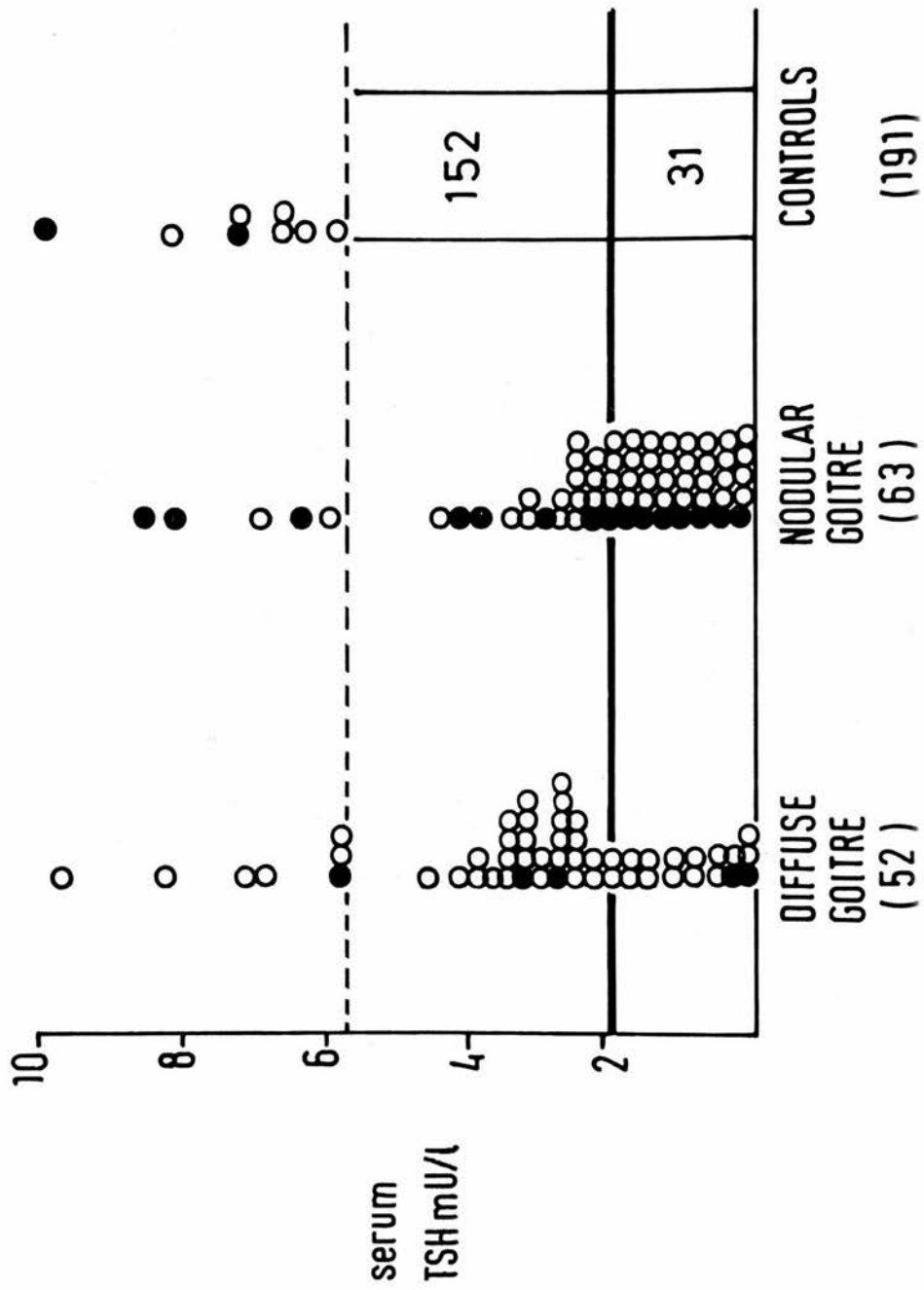


Fig. 1.2

Serum TSH (mU/l) levels in 52 patients with simple diffuse goitre, 63 patients with simple nodular goitre, and 191 euthyroid non-goitrous patients. The upper limit of normal for the assay (5.7 mU/l) is indicated by the broken line and the lower limit of sensitivity of the assay (1.8 mU/l) by the continuous line. The solid symbols represent patients in whom circulating thyroid autoantibodies were detected. The serum TSH level was undetectable in 29% of the patients with diffuse goitre, in 57% of the patients with nodular goitre, and in 16% of the control patients. { (from Journal of Clinical Endocrinology and Metabolism 42, 973-976, (1976) }



Type of goitre	No. of patients	Mean serum TSH mU/l (95% tolerance limits)
Diffuse	52	2.8 (undetectable - 7.0)
Nodular	63	2.3 (undetectable - 5.2)
No goitre	191	2.7 (undetectable - 5.7)

Table 1.1 Serum TSH levels in goitrous and non-goitrous patients, The levels in the patients with nodular goitre were significantly lower than those recorded either in the patients with diffuse goitre ($P < 0.01$) or in the patients without goitre ($P < 0.0001$).

{(from Journal of Clinical Endocrinology and Metabolism, 42, 973-976 (1976) }

CHAPTER 2 . A comparison of the serum TSH level and the TSH stimulation test in patients with suspected hypothyroidism.

The use of a TSH stimulation test to differentiate between primary and secondary hypothyroidism was suggested almost forty years ago (Thompson et al., 1936: Scowen 1937). The report of an increase in the radioiodine uptake by the thyroid gland after the intramuscular administration of bovine TSH (BTSH) to normal subjects (Stanley and Astwood, 1949) formed the basis of the present-day TSH stimulation test. Such a test has been widely used in clinical practice, not only to separate the euthyroid patient with a normal reserve of thyroid function from the euthyroid patient with an impaired reserve of thyroid function and from the patient with primary hypothyroidism, but also to identify the occasional patient with hypothyroidism secondary to disease of the anterior pituitary gland or hypothalamus. The procedure for the TSH stimulation test has varied both in regard to the form of radioiodine uptake and to the dose and duration of administration of BTSH. Most centres have employed a single dose TSH stimulation test (Jefferies et al., 1953: Bishopric et al., 1955: Fletcher and Besford, 1957: Friis et al., 1959) or a test utilising three daily injections of BTSH (Querido and Stånbury 1950: Perloff et al., 1951: Schneeberg et al., 1954). In all series the tracer dose of radioiodine has been administered some eighteen hours after the last or sole dose of BTSH when the effect on the radioiodine uptake by the thyroid gland is at a maximum, although the doses of BTSH given have exceeded that required for a maximal increase in uptake (Einhorn and Larssen, 1959). More recent studies comparing various dosage regimens of BTSH to determine which gives the most effective stimulation for the clinical evaluation of thyroid function indicated that a single dose test of 5 USP units BTSH would differentiate in most instances the normal subject from the patient with primary hypothyroidism or the euthyroid patient with impaired

reserve of thyroid function observed most commonly after iodine-131 treatment of thyrotoxicosis (Jefferies et al., 1956). The identification of the patient with thyroid failure due to disordered pituitary or hypothalamic function may require a three day stimulation test to be performed (Taunton et al., 1965; Burke, 1968).

The availability of a sensitive radioimmunoassay for TSH (Odell et al., 1965; Utiger, 1965) and the demonstration of raised levels of TSH in the serum of patients with primary hypothyroidism or in euthyroid patients with impaired reserve of thyroid function and of low or normal levels of serum TSH in patients with secondary hypothyroidism (Odell et al., 1967b; Hedley et al., 1971a; Hershman and Pittman, 1971; Mayberry et al., 1971; Slingerland et al., 1972) should allow the distinction to be made between primary thyroid failure and secondary hypothyroidism without recourse to the TSH stimulation test.

The purpose of the present study was to test this hypothesis by estimating the serum TSH level and performing the TSH stimulation test in patients referred to a thyroid clinic with suspected hypothyroidism. Since the TSH stimulation test is time-consuming for both patients and technical staff and is not without side-effects, although minor (Einhorn 1958), it would be a distinct advantage to replace the stimulation test by the measurement of a single serum TSH level.

In addition, by estimating serum TSH levels before and after the administration of BTSH in patients with primary hypothyroidism, it is possible to test whether a "short-feedback" of TSH on the hypothalamus exists in man. Several studies have indicated that

pituitary hormones may control their own secretion by regulating at the hypothalamic level the synthesis and release of their hypothalamic factors (Motta et al., 1969). If a negative "short-feedback" of TSH is present in man, the raised serum TSH levels of untreated primary hypothyroidism should fall markedly after the administration of BTSH which shares the biological, but not the immunological, properties of TSH.

PATIENTS AND METHODS

The subjects were one hundred and twenty-seven consecutive patients seen at the Endocrine Clinic, Royal Infirmary, Edinburgh, in whom it was necessary to confirm or exclude a diagnosis of hypothyroidism. The final diagnosis was made from clinical examination and from estimations of serum protein-bound iodine (Simpson, 1967) and total serum thyroxine by competitive protein-binding analysis (Seth, 1973), augmented when necessary by serum cholesterol, electrocardiograph and ankle reflex time, as well as the patient's response to replacement therapy with thyroxine. Patients on thyroid replacement therapy were excluded.

There were fifty-one euthyroid patients. Thirty-three were referred by their general practitioners with suspected hypothyroidism and five of these had a goitre. The other eighteen patients had previously attended the Endocrine Clinic; eight had received iodine-131 therapy and two had been treated by subtotal thyroidectomy for thyrotoxicosis; four had idiopathic Addison's disease, two had hypopituitarism and two had pernicious anaemia with thyroid antibodies in the serum. There were seventy-six patients with primary

hypothyroidism, of whom thirteen had spontaneous hypothyroidism and had been referred by their general practitioners; fifty-six had been previously treated with iodine-131 and seven had undergone subtotal thyroidectomy for thyrotoxicosis.

Blood was withdrawn from each patient for the estimation of serum TSH by a sensitive double antibody radioimmunoassay as previously described in which the upper limit of normal is 5.7 mU/l. The 4 hour uptake of iodine-132 by the thyroid gland was then measured before the administration of BTSH (Thyropar) 10 international units intramuscularly at 16.00 hours on three consecutive days, and was repeated on the day following the last injection. In twenty-four of the patients with primary hypothyroidism the serum TSH level was also estimated eighteen hours after the last injection of BTSH and in three of the patients with primary hypothyroidism the serum TSH level was estimated at 7, 15, 25, 30 (two patients only), 45, 60, 90 (two patients only), 120 and 180 minutes after the first intramuscular injection of BTSH.

Antibodies to thyroid cytoplasm were detected by the indirect immunofluorescence technique using sections of human thyroid tissue and by complement fixation using a saline extract of human thyroid (Doniach and Roitt, 1975).

RESULTS

The levels of serum TSH correlated with the final diagnosis and the results of the TSH stimulation test are shown in Fig. 2.1. Combining all the euthyroid patients in the present series, an

attempt was made to define more precisely the limits of normal in the TSH stimulation test by determining the figure which correlated best with the serum TSH levels i.e. that as few patients as possible were defined as having a normal serum TSH level and an abnormal TSH stimulation test. On this basis, the normal absolute increase in the thyroid gland uptake of iodine-132 at 4 hours, following 10 i.u. BTSH i.m. on each of three consecutive days, was 13% or more.

All seventy-six patients with primary hypothyroidism must by definition be considered to have an abnormal TSH stimulation test, and the greatest absolute increase in the 4 hour iodine-132 uptake by the thyroid gland after TSH stimulation was 8% i.e. 22-30%. The serum TSH level was markedly raised in all the patients with primary hypothyroidism, ranging from 26-537mU/l.

The euthyroid patients could be subdivided into four groups on the basis of the result of the serum TSH estimation and the TSH stimulation test.

(i) Normal TSH stimulation test and normal serum TSH level:

There were twenty-eight patients in this category, of whom only one, who had been treated with iodine-131 for thyrotoxicosis, had a previous history of thyroid disease. A simple non-toxic goitre was present in four of the patients and one patient had partial hypopituitarism.

(ii) Abnormal TSH stimulation test and elevated serum TSH level:

The eight patients in this group had serum TSH levels of 6.4-93.5mU/l. With the exception of the patient with partial hypopituitarism, the patients had antibodies to thyroid

microsomes. Six of the patients had been treated with iodine-131 or subtotal thyroidectomy for thyrotoxicosis.

(iii) Normal TSH stimulation test but elevated serum TSH level:

This group comprised eleven patients. The two highest serum TSH levels of 48.4 and 25.3 mU/l respectively, were found in a patient who had been treated with iodine-131 for thyrotoxicosis and in a patient considered to have Hashimoto's thyroiditis. Circulating thyroid antibodies were present in five of the other nine patients with elevated serum TSH levels.

(iv) Abnormal TSH stimulation test but normal serum TSH level:

There were only four patients in this category, of whom two had previously been treated with radioactive iodine for thyrotoxicosis (15-19%; 24-30%). The remaining two patients with TSH stimulation test results of 13-21% and 19-27% respectively, had not received previous therapy directed at the thyroid gland.

The results of the 4 hour iodine-132 uptake tests by the thyroid gland and the serum TSH levels before and after BTSH 10 i.u. i.m. daily for three consecutive days in the twenty-four patients with primary hypothyroidism are shown in table 2.1. The mean serum TSH level \pm S.E. before the TSH stimulation test was 87.3 ± 11.2 mU/l and 84.7 ± 11.4 mU/l after the TSH stimulation test. The serum TSH level fell in thirteen of the patients, the maximum percentage decrease being 33% (69-45 mU/l), but rose in the other eleven patients,

the maximum percentage increase being 31% (27-36mU/l).

The serum TSH levels before and for three hours after the administration of 10 i.u. i.m. BTSH to three patients with primary hypothyroidism are illustrated in Fig 2.2. None of the three patients showed a fall in the level of serum TSH after exogenous BTSH injection.

DISCUSSION

The TSH stimulation test and the serum TSH level are both employed as tests of reserve of thyroid function. Whereas the TSH stimulation test measures the capacity of the thyroid gland to respond to the stimulus of exogenous BTSH by an increase in the uptake of iodine, the serum TSH level is related to the concentration of thyroid hormones presented to the thyrotrophs of the anterior pituitary gland. Although the two tests therefore assess different aspects of thyroid function there was a correlation between the tests in one hundred and twenty-two of the one hundred and thirty-seven patients in the present series, in that a normal TSH stimulation test was associated with a normal serum TSH level or an abnormal TSH stimulation test with an elevated serum TSH level whether the patient was euthyroid or had primary hypothyroidism. It has long been recognised that an abnormal TSH stimulation test can occur in euthyroid patients, usually after destructive therapy to the thyroid gland for thyrotoxicosis, and can persist for many years without the development of hypothyroidism (Jefferies et al., 1956). Six of the eight euthyroid patients with an abnormal TSH stimulation test and a raised serum TSH level in the present series had been treated in the past with iodine-131 or sub-total thyroidectomy, and it is of interest that raised serum TSH levels,

like abnormal TSH stimulation tests, have been shown to remain elevated in euthyroid patients for some years without the development of hypothyroidism (Slingerland et al., 1972; Toft et al., 1975).

The demonstration of eleven euthyroid patients with normal reserve of thyroid function on the basis of the TSH stimulation test, but with some degree of thyroid failure as indicated by a raised serum TSH level is presumably explained by the pharmacological stimulus of BTSH used in this study, masking a minor degree of impaired thyroid function. If such a hypothesis is true, the measurement of serum TSH is a more sensitive index of thyroid failure than the TSH stimulation test.

The remaining four patients in the series, all of whom were euthyroid, had a TSH stimulation test result and a serum TSH level which were at variance, in that an abnormal TSH stimulation test indicative of thyroid failure, was associated with a normal serum TSH level which in the absence of pituitary or hypothalamic disease is an indication of normal thyroid function. Two of these four patients had been previously treated with iodine-131 for thyrotoxicosis and it is possible that the thyroid remnant was functioning autonomously and was therefore unresponsive to BTSH. If such an explanation is valid, the measurement of serum TSH is a more meaningful expression of thyroid status than the TSH stimulation test in patients who have been previously treated with iodine-131 and presumably subtotal thyroidectomy for thyrotoxicosis in the past. In the two remaining patients no explanation can be offered for the anomalous combination of an abnormal TSH stimulation test and a normal serum TSH level, but it is of interest that Nelson et al., (1972)

described a similar group of patients all of whom had either a simple non-toxic goitre or who had been treated with iodine-131 for thyrotoxicosis.

The present study has shown that the estimation of a single serum TSH level is a better index of reserve of thyroid function than the time-consuming TSH stimulation test, and the sole use of the TSH stimulation test must be to assess whether a patient, empirically started on thyroxine replacement therapy in the past, requires to continue taking such treatment on a life-long basis.

The lack of reduction in the high serum TSH levels in patients with untreated primary hypothyroidism despite the presence of high BTSH levels in the serum lasting twenty-four hours in such patients after the administration of exogenous BTSH (Hershman and Edwards, 1972) is evidence against the negative "short-feedback" of TSH on the hypothalamus in man.

Fig. 2.1

Serum TSH levels (mU/l) correlated with diagnosis and results of TSH stimulation tests in 127 consecutive patients investigated for suspected hypothyroidism. The horizontal line represents the upper limit of normal for the TSH assay (5.7mU/l).

O - post iodine-131; □ - post thyroidectomy; ▽ - spontaneous primary hypothyroidism; Δ - untreated euthyroid; + - hypopituitarism without antibodies in the serum. Solid symbols indicate that thyroid cytoplasmic antibodies were present in the serum.

{adapted from Clinical Endocrinology, 2, 135-139 (1973)}

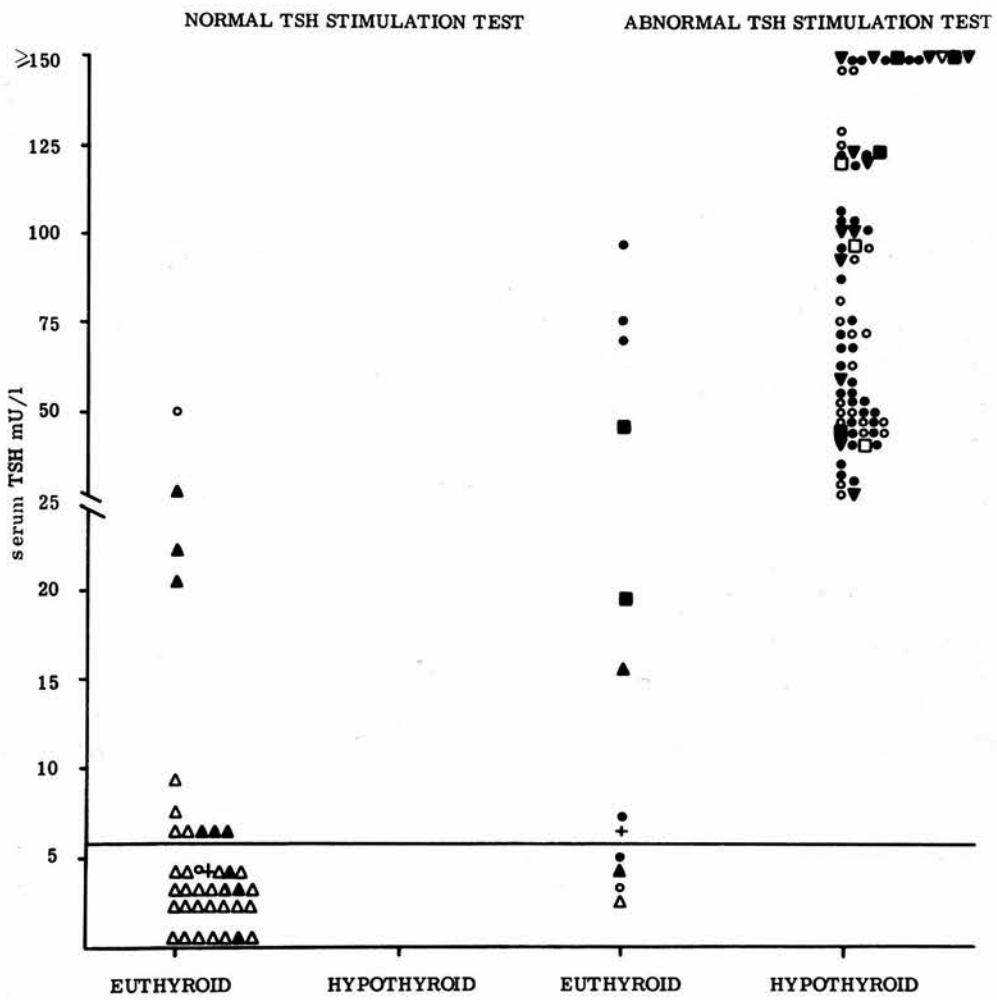
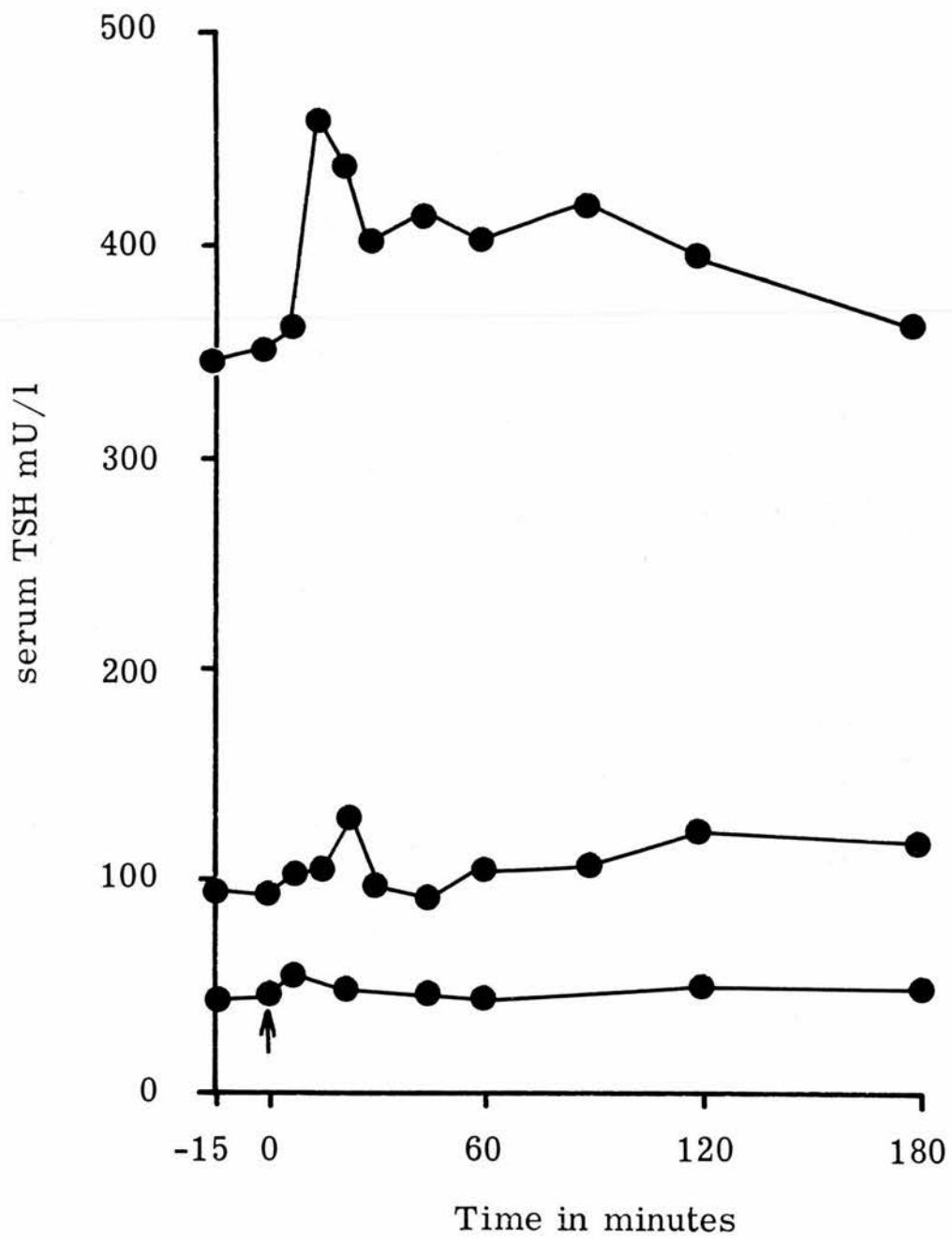


Fig. 2.2

Human serum TSH levels in three patients with untreated primary hypothyroidism in response to 10 i.u. bovine TSH intramuscularly; the arrow indicates the time of injection.

{from Journal of Endocrinology, 59, 189-190 (1973)}



Category and case	4 hour iodine-132 uptake by thyroid gland (%)		HTSH mU/l	
	pre BTSH	post BTSH	pre BTSH	post BTSH
Idiopathic				
1	14	22	210	221
2	5	3	167	184
Post subtotal thyroid- ectomy				
3	7	9	122	138
4	11	14	96	112
5	14	9	203	197
6	10	11	43	50
Post-iodine-131				
7	11	9	41	36
8	22	30	74	75
9	12	9	195	168
10	16	15	44	42
11	16	16	76	63
12	17	16	115	83
13	8	11	74	64
14	7	7	44	47
15	12	7	70	45
16	7	8	93	86
17	16	16	44	45
18	7	7	101	87
19	24	10	44	38
20	11	11	27	36
21	5	4	62	61
22	13	14	37	46
23	9	8	51	53
24	14	9	65	58

Table 2.1 Results of 4 hour iodine-132 uptake tests by the thyroid gland and human serum TSH (HTSH) levels before and after bovine TSH (BTSH) daily for 3 days in twenty-four patients with primary hypothyroidism.

{from Journal of Endocrinology, 59, 189-190 (1973)}

CHAPTER 3

Serum TSH response to TRH in euthyroid patients and
in patients with thyroid disease.

It has been established for many years that the hypothalamus controls the release of TSH from the anterior pituitary gland by means of neurohumoral substances (Harris, 1955), but the first unequivocal demonstration of the presence of a factor in hypothalamic tissue with TSH-releasing activity was not reported until the early 1960's (Guillemin et al., 1962; Schreiber et al., 1962; Guillemin et al., 1963). The TSH-releasing factor (TRF) was purified from hypothalamic tissue from a number of sources including sheep, pig, cow and man and its biological activity demonstrated by means of both in vitro and in vivo studies (Guillemin et al., 1965; Schally et al., 1966a and 1966b; Schally et al., 1967). Schally and his colleagues (1966a) also demonstrated that the peptide fragment of porcine TRF contained three amino-acids, histidine, glutamic acid, and proline, and suggested that TRF be renamed thyrotrophin-releasing hormone (TRH) (Schally et al., 1968). It was subsequently established by the same group of workers (Schally et al., 1969) that the amino acid sequence was glutamic acid-histidine-proline although the simple tripeptide had no biological activity. Various synthetic sequences of the three amino acids were studied and it was found that L-pyroglutamyl-L-histidyl-L-proline-amide had the full biological activity of the isolated TRH (Burgus et al., 1969; Folkers et al., 1969; Gillessen et al., 1970) and was chemically identical (Burgus et al., 1970; Nair et al., 1970)

The rise in serum TSH in response to intravenous TRH in normal man (Bowers et al., 1970; Fleischer et al., 1970; Hall et al., 1970b; Hershman and Pittman, 1970; Ormston et al., 1971a) was anticipated from the previous observation that serum TSH levels increased when a highly purified porcine preparation of the releasing hormone was given to cretins (Bowers et al., 1968a). It was Ormston et al., (1971b)

however, who defined the serum TSH response to intravenous synthetic TRH in a large number of euthyroid subjects and patients with thyrotoxicosis and primary hypothyroidism. The measurement of serum TSH before and at twenty and sixty minutes after 200 μ g TRH is now widely used in the United Kingdom as a thyroid function test. TRH has since been shown to cause the release of prolactin (Bowers et al., 1971; Jacobs et al., 1971; L'Hermite et al., 1972; Toft et al., 1973b) follicle stimulating hormone in the male (Mortimer et al., 1973) and growth hormone in patients with acromegaly (Irie and Tsushima, 1972), but the physiological significance of these findings is in some doubt.

The purpose of the present study was to establish the normal range for the serum TSH response to TRH in patients with no evidence of thyroid disease, and to measure the response in patients with primary hypothyroidism, in euthyroid patients with serum TSH levels close to the upper limit of normal of 5.7mU/l, and in patients with thyrotoxicosis.

PATIENTS AND METHODS

Serum TSH was estimated before and at twenty and sixty minutes after the single administration of 200 μ g TRH as a rapid intravenous injection in the following groups of patients.

- (i) Seventy-four new patients (59 females, 15 males) referred to the Endocrine Clinic with suspected thyroid disease, but in whom no evidence of thyroid dysfunction could be found. The mean age of the patients was thirty-nine years (range 16-77 years). The serum TSH level lay within the normal range of <1.8-5.7mU/l in each patient. The normal range of

the response of serum TSH to 200 µg TRH intravenously was calculated from the results obtained in this group of patients.

- (ii) Forty-nine patients (44 females, 15 males) with a mean age of fifty-three years (range 21-79 years) in whom a diagnosis of primary hypothyroidism was made. The diagnosis in each case was made clinically and on the basis of a low total serum T₄ measured by competitive protein-binding analysis (Seth, 1973), a low ETR (Thorson et al., 1972; Toft et al., 1973a), a lack of response of the 4 hour iodine-132 uptake by the thyroid gland following the intramuscular injection of 10 i.u. bovine TSH for three consecutive days, and a raised serum TSH level. Fifteen of the patients had spontaneous primary hypothyroidism, thirty-one had been treated with iodine-131 and three by subtotal thyroidectomy for thyrotoxicosis.
- (iii) Ten patients (4 females, 6 males) with a mean age of forty-two years (range 15-55 years) who were clinically and biochemically euthyroid but in whom the serum TSH level was found to be at the upper limit of normal or minimally elevated. In three of these patients there was no evidence, past or present, of thyroid disease, although circulating autoantibodies against thyroid microsomes were detected by immunofluorescence in one patient. Two patients had Hashimoto's thyroiditis, two had been treated by subtotal thyroidectomy and two with iodine-131 for thyrotoxicosis. The remaining patient in this group had received radiotherapy to the head and neck for

reticulum cell sarcoma three years earlier.

- (iv) Sixty-three patients (46 females, 17 males) with a mean age of forty-eight years (range 21-77 years) who had thyrotoxicosis. The diagnosis of thyrotoxicosis was made clinically and on the basis of a raised total serum thyroxine and ETR and an increased 4 hour uptake of iodine-132 by the thyroid gland which was repeated in some cases after the oral administration of T_3 120 μ g daily for seven days.

RESULTS

(i) Patients with no evidence of thyroid disease:

The mean serum TSH level (range) before and at twenty and sixty minutes after 200 μ g TRH intravenously in the fifty-nine female patients with no evidence of thyroid disease was 2.7 (<1.8-5.6); 12.0 (3.9-25.3) and 9.3 (3.0-24.4) mU/l respectively, and in the fifteen male patients in the same category, 2.8 (<1.8-5.0); 10.5 (6.6-22.5) and 8.2 (4.7-19.0) mU/l respectively. Although the mean serum TSH level at twenty and sixty minutes after the administration of TRH in the females was greater than in the males, the differences were not significant ($P > 0.05$ in each case). There was no apparent relationship between serum TSH response to TRH and the age of the patient. The mean serum TSH (range) before and at twenty and sixty minutes after TRH in the total seventy-four patients was 2.7 (< 1.8-5.6); 11.7 (3.9-25.3)

and 9.1 (3.0-24.4) mU/l. The range of response in these total seventy-four patients, referred to the Endocrine Clinic with suspected thyroid disease but in whom no evidence of thyroid dysfunction was found, was considered as the normal range and is represented graphically in Fig. 3.1.

(ii) Patients with primary hypothyroidism:

The mean basal serum TSH level (range) in the forty-nine patients with untreated primary hypothyroidism of 82.3 (23.2-614) increased to 177.8 (45.6-830) and 174.4 (27.6-1175) mU/l respectively at twenty and sixty minutes after the injection of TRH, and is represented graphically in Fig. 3.2 in relation to the normal range. There was no overlap of the serum TSH response to TRH with a normal range in any patient with primary hypothyroidism. In all but fourteen of the patients the serum TSH level was higher at twenty minutes than the level at sixty minutes after TRH.

(iii) Euthyroid patients with serum TSH levels at the upper limit or minimally elevated:

The serum TSH responses to TRH in the ten euthyroid patients with basal serum TSH levels at the upper limit of normal of 5.7mU/l or slightly elevated are shown in Table 3.1. The normal response of serum TSH to TRH in patients 1-3 suggests that these three patients have a normal brain-thyroid axis and that the basal serum TSH levels of 5.7, 6.7 and 6.9mU/l should be regarded as normal. In patients 4-10 there was an enhanced response to serum TSH to TRH similar to that

seen in the patients with primary hypothyroidism. The serum TSH levels of 5.9-8.8mU/l in these patients are presumably an indication of impaired reserve of thyroid function, and it is of interest that an aetiological factor existed to account for the raised basal serum TSH level in each case.

(iv) Patients with thyrotoxicosis:

The basal serum TSH level was undetectable at less than 1.8mU/l in fifty-six (89%) of the sixty-three patients with thyrotoxicosis and remained undetectable in fifty-five of the patients. In four patients the basal serum TSH levels of 2.0, 2.1, 2.2 and 2.3mU/l respectively, either fell or remained unchanged after TRH administration. In a further four patients with basal serum TSH levels of <1.8, 1.9, 1.9 and 2.0mU/l there was a slight rise in serum TSH levels to 2.2, 2.1, 2.4 and 2.5 mU/l at twenty minutes and to 2.0, 2.0, 2.2 and 2.1mU/l at sixty minutes after the injection of TRH. The maximum response of serum TSH to TRH, therefore, in a patient with thyrotoxicosis was from 1.9 to 2.4mU/l, an increase of 0.5mU/l.

If the serum TSH level had been measured only before and at twenty minutes after TRH each patient in the present study would have remained in the same TSH response category, and therefore in the absence of pituitary or hypothalamic disease, sampling of the serum TSH level at sixty minutes after the injection of TRH in patients with suspected thyroid disease is probably of little value.

DISCUSSION

The normal range of serum TSH response to TRH in the present series was calculated from the results obtained in patients referred to an Endocrine clinic with suspected thyroid disease but in whom no evidence of thyroid dysfunction was found. Applying the epidemiological arguments expressed in Chapter 1 for the calculation of the normal range for basal serum TSH levels, it is felt that a normal range determined on this basis is more acceptable than one based on results obtained in healthy volunteers or hospital in-patients. The mean serum TSH levels at twenty and sixty minutes after TRH were lower in the female patients than in the male patients, but unlike the report of Ormston et al., (1971b) the differences were not significant which may be a consequence of the small number of male patients. On the other hand, Snyder and Utiger (1972b) were unable to demonstrate a greater magnitude of serum TSH response to 400µg TRH in females aged 20-39 years than in males when matched for age, height and weight, but it is possible that the larger dose of TRH used in this study masked any sex difference. There are similarly conflicting views of the effect of exogenous oestrogen in males on the serum TSH response to TRH. Faglia et al., (1973) found that oestrogens caused an increased response of serum TSH to 100µg TRH, but Gual et al., (1972) were unable to show any augmentation of the serum TSH response to 500µg TRH in males treated with ethinyl oestradiol. A diminishing serum TSH response to TRH with increasing age in man has been reported (Snyder and Utiger, 1972b) but this was not apparent in the present study.

Serum TSH levels in patients with untreated primary hypothyroidism have been shown to be in excess of 20.0mU/l using the current

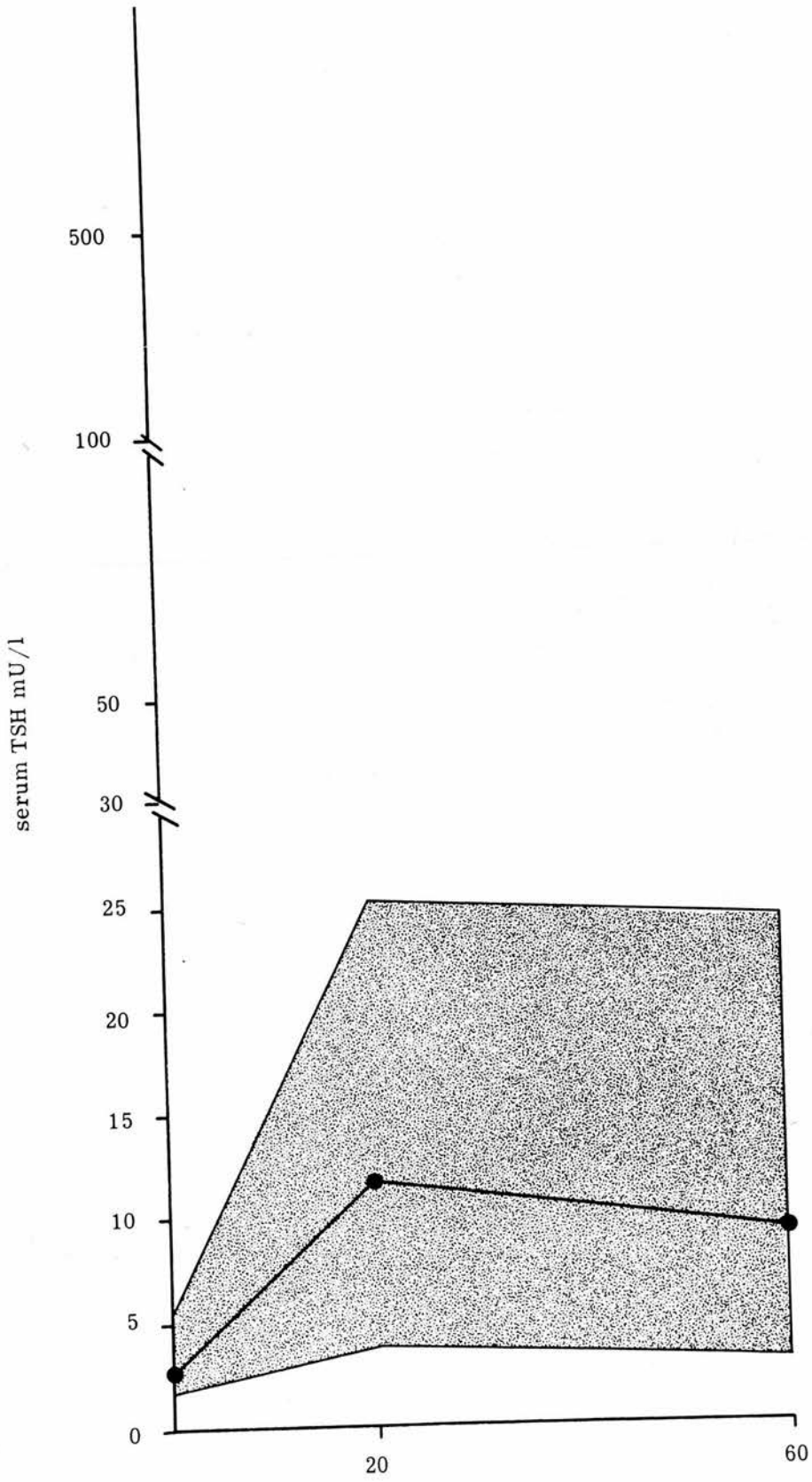
radioimmunoassay system, and since a single estimation of serum TSH will differentiate the euthyroid patient from the patient with primary hypothyroidism, the TRH test is of no added value in the investigation of suspected primary hypothyroidism. It should be noted, in addition, that a raised serum TSH level will be associated with an enhanced response to TRH in euthyroid patients with impaired reserve of thyroid function. The TRH test would appear to be of value, however, in determining whether a serum TSH level, which approximates to the upper limit of normal for the assay, is normal or elevated. If it can be assumed that a normal serum TSH response to TRH, despite a slightly raised basal serum TSH level, is indicative of a normal brain-thyroid axis, the TRH test will identify patients with minor degrees of thyroid failure. Such patients may develop hypothyroidism in the future and are certainly at an increased risk of hypothyroidism after iodine-131 therapy for thyrotoxicosis than patients with a normal serum TSH level (Toft et al., 1975). The seven patients with borderline raised levels of serum TSH in the present study and augmented responses to TRH each had an aetiological factor on which to explain the minor degree of thyroid failure such as surgical or radioiodine treatment of thyrotoxicosis, autoimmune thyroid disease, or the more recently recognised external irradiation of the neck for malignant disease (Glatstein et al., 1971).

A single estimation of serum TSH, in contrast to its value in the diagnosis of primary hypothyroidism, does not differentiate between the euthyroid and hyperthyroid patient. The serum TSH level does not rise, however, after the intravenous administration of TRH, unless very large doses of TRH are given (Hershman and Pittman, 1970).

On account of the sensitivity of the thyrotrophs of the anterior pituitary gland to changes in circulating thyroid hormone levels within the normal range, a lack of response of serum TSH to TRH may occur in euthyroid patients in whom levels of total serum T_3 and T_4 are elevated for the individual but still within the accepted normal range, as in many of the patients with exophthalmic Graves' disease, solitary autonomous thyroid nodules and in those patients on long-term suppressive or replacement therapy with thyroxine. Like the T_3 suppression test, therefore, the major role of the TRH test is in the investigation of patients with suspected thyrotoxicosis in whom clinical examination and biochemical results are equivocal. A normal serum TSH response to TRH excludes the diagnosis of thyrotoxicosis, whereas an absent response is compatible with such a diagnosis. With the possible exception of the investigation of patients with secondary hypothyroidism, the estimation of the serum TSH level sixty minutes after TRH appears unnecessary and it is suggested that serum TSH levels are only measured before and at twenty minutes after 200 μ g TRH intravenously and as such this valuable additional test of thyroid function can be performed readily at an out-patient clinic attendance.

Fig. 3.1

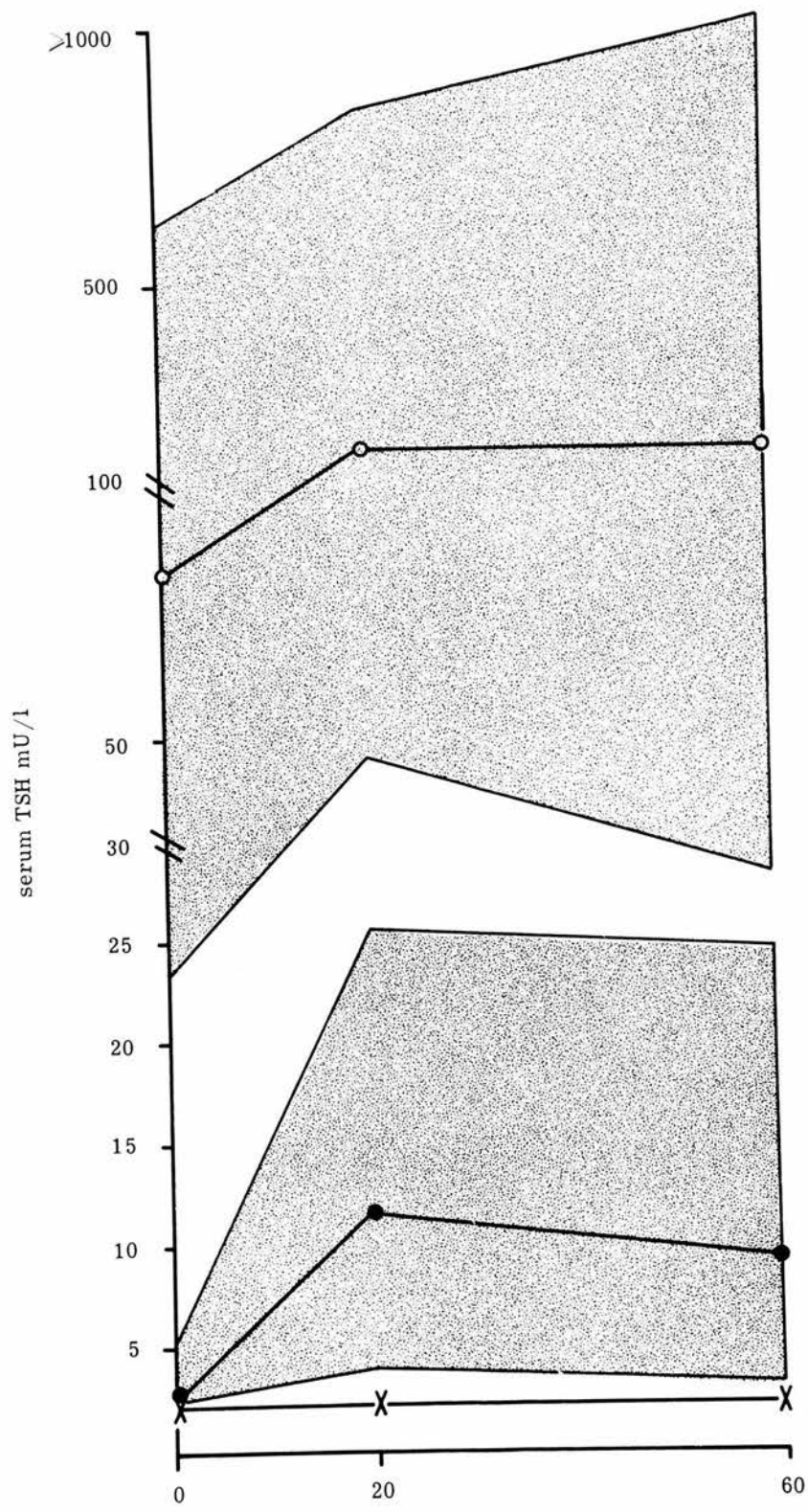
Mean and range of serum TSH levels before and at twenty and sixty minutes after 200 μ g TRH intravenously in seventy-four patients (59 females, 15 males) referred to the Endocrine Clinic, Royal Infirmary, Edinburgh with suspected thyroid disease but in whom no evidence of thyroid dysfunction could be found.



Time in minutes after 200 µg TRH i.v.

Fig. 3.2

Mean and range serum TSH levels before and at twenty and sixty minutes after 200 μ g TRH intravenously in forty-nine patients with untreated primary hypothyroidism and mean serum TSH levels before and at twenty and sixty minutes after 200 μ g TRH intravenously in sixty-three patients with thyrotoxicosis. The normal range is shown for comparison.



Time in minutes after 200 µg TRH i.v.

PATIENT	AGE	SEX	SERUM TSH mU/l			CLINICAL INFORMATION
			0'	20'	60'	
1	61	F	5.7	8.6	2.0	No history of thyroid disease.
2	50	F	6.7	25.0	18.4	Subtotal thyroidectomy for thyrotoxicosis, 1964.
3	36	F	6.9	11.4	8.3	No history of thyroid disease.
4	16	F	5.9	48.0	25.6	Hashimoto's thyroiditis.
5	55	F	6.5	37.0	26.0	Thyroid autoantibodies.
6	51	F	6.9	52.4	40.3	Iodine-131 for thyrotoxicosis, 1957.
7	42	F	7.7	38.2	31.1	Hashimoto's thyroiditis.
8	55	F	8.6	61.0	55.7	Irradiation to head and neck for reticulum cell sarcoma, 1971.
9	39	M	8.7	55.8	35.6	Subtotal thyroidectomy for thyrotoxicosis, 1958.
10	61	F	8.8	63.5	58.0	Iodine-131 for thyrotoxicosis, 1970

Table 3.1 Serum TSH response to 200µg TRH intravenously in ten patients with basal serum TSH levels at the upper limit of normal or minimally elevated. The upper limit of normal for serum TSH before, and at twenty and sixty minutes after TRH is 5.7; 25.3 and 24.4mU/l respectively.

CHAPTER 4

A comparison of the serum TSH response to TRH and the T₃ suppression test in patients with suspected thyrotoxicosis.

The demonstration that thyroid extract or thyroxine reduced the radioiodine uptake by the thyroid gland in normal subjects (Stanley and Astwood, 1949; Greer, 1951; Morgans et al., 1951) but not in patients with thyrotoxicosis (Werner et al., 1952; Greer and Smith, 1954) led to the development of the T_3 suppression test (Werner and Spooner, 1955). Subsequently, the T_3 suppression test became widely used in attempting to differentiate between the patient with thyrotoxicosis and the euthyroid patient with equivocal tests of thyroid function. Although the conditions of the test varied from centre to centre, with respect to form of radioiodine uptake, dosage and duration of administration of T_3 , it became apparent that it effectively discriminated between the euthyroid and thyrotoxic patient in most instances (Perlmutter and Slater, 1955; Dresner and Schneeberg, 1958; Hobbs et al., 1963; Kristensen et al., 1963; Friis, 1963; Burke, 1967; Bayliss, 1967). Lack of suppression of radioiodine uptake by T_3 did not invariably indicate thyrotoxicosis, however, and was noted in a proportion of euthyroid patients with multinodular goitre (Werner and Spooner, 1955) and with exophthalmic Graves' disease (Werner, 1955; Bowden and Rose, 1969; Hall et al., 1970a) and following successful treatment of thyrotoxicosis with radioiodine or surgery (Werner 1956). Despite its undoubted value, the T_3 suppression test has the disadvantage of being time-consuming for patients and technical staff, of involving two radioisotope tests and of possibly precipitating a cardiac dysrhythmia in the older patient with ischaemic heart disease.

The demonstration that a rise in serum TSH occurs following the intravenous injection of TRH in euthyroid individuals (Hall et al., 1970b; Bowers et al., 1970; Fleischer et al., 1970; Hershman and

Pittman, 1970) but not in patients with thyrotoxicosis (Ormston et al., 1971b) introduced a further test of thyroid function which could be used in the differentiation of the euthyroid from the hyperthyroid state.

There are two factors which are common to all cases of thyrotoxicosis; namely, that the thyroid gland is outwith the control of pituitary TSH, and that the levels of T_4 and/or T_3 are invariably raised. The T_3 suppression test indicates dependence or independence of the thyroid gland upon pituitary TSH, whereas the serum TSH response to TRH is a measure of whether excess thyroid hormone is present in the circulation. It is, therefore, conceivable that the T_3 suppression test which has been widely used for almost twenty years could be replaced by the less inconvenient TRH test as a test of thyroid function in patients with suspected thyrotoxicosis, and the purpose of the present study was to test this hypothesis.

PATIENTS AND METHODS

Forty-one consecutive patients (30 females, 11 males) were studied who had been referred to the Endocrine Clinic with suspected thyrotoxicosis and in whom there was no past history of thyroid disease. The mean age was 45 years (range 20-70 years). Thyroid status was determined by clinical examination and by the estimation of the total serum T_4 by competitive protein-binding analysis (Seth, 1973), the ETR (Toft et al., 1973a) and by the measurement of the 4 hour uptake of iodine-132 by the thyroid gland. Nineteen of the patients were thyrotoxic, and the remaining 22 patients euthyroid. In 3 of these euthyroid patients a diffusely enlarged simple goitre



was present, and a further 4 patients had exophthalmic Graves' disease.

Immediately after the initial 4 hour uptake of iodine-132 by the thyroid gland had been measured, the serum TSH level was estimated before and at twenty and sixty minutes after the intravenous administration of 200 μ g TRH. Oral T₃ in a dose of 40 μ g eight-hourly was then given for seven days and the radioiodine uptake by the thyroid gland repeated.

RESULTS

The percentage fall in the initial 4 hour uptake of iodine-132 by the thyroid gland after oral T₃ 120 μ g daily for seven days is expressed in relation to the serum TSH response to TRH in fig. 4.1. All 19 patients with thyrotoxicosis and 3 of the 4 patients with exophthalmic Graves' disease had either no response or a rise of serum TSH of less than 0.5mU/l after TRH. In 8 of these patients there was either no suppression of the radioiodine uptake or the second uptake was greater than the first, whereas in the remaining 14 patients with a lack of response of serum TSH to TRH the suppression of the initial radioiodine uptake ranged from 2-32%.

In the 19 patients in whom there was a rise of more than 0.5mU/l in the serum TSH level in response to TRH, there was a fall of between 30-82% of the initial 4 hour uptake of iodine-132 by the thyroid gland following T₃ suppression. There was no apparent relationship between the degree of thyroidal suppression and the rise in serum TSH in response to TRH.

DISCUSSION

The present study has demonstrated that a lack of response of the serum TSH level to TRH is associated with suppression of the initial radioiodine uptake by the thyroid gland by oral T_3 of < 32%, whereas a rise in serum TSH level in response to TRH is associated with suppression of the radioiodine uptake of > 30%. It would appear, therefore, that the TRH test which is convenient to doctor and patient and is free of major side-effects can replace the time-consuming and potentially dangerous T_3 suppression test in the investigation of patients with thyrotoxicosis. It should be borne in mind that a lack of response of the serum TSH level to TRH or a failure to demonstrate thyroid suppressibility with oral T_3 is not necessarily an indication of the presence of hyperthyroidism. In three of the four patients with exophthalmic Graves' disease an absent serum TSH response to TRH was associated with a lack of suppression of the radioiodine uptake by the thyroid gland after T_3 , confirming the earlier observations by Lawton et al., (1971) and Ormston et al., (1973). The authors detected total serum T_3 levels in such patients to be at the upper limit of normal or frankly elevated, although not in the range usually encountered in thyrotoxicosis. The lack of response of the serum TSH level to TRH in a proportion of patients with exophthalmic Graves' disease, who are by definition euthyroid (Rundle and Wilson, 1945), is an indication of the sensitivity of the pituitary thyrotroph to minor changes in the levels of circulating thyroid hormones (Snyder and Utiger, 1972a). The thyroid autonomy, if present, in patients with exophthalmic Graves' disease may in the future be shown to be related to the presence in the serum of TSH receptor antibodies.

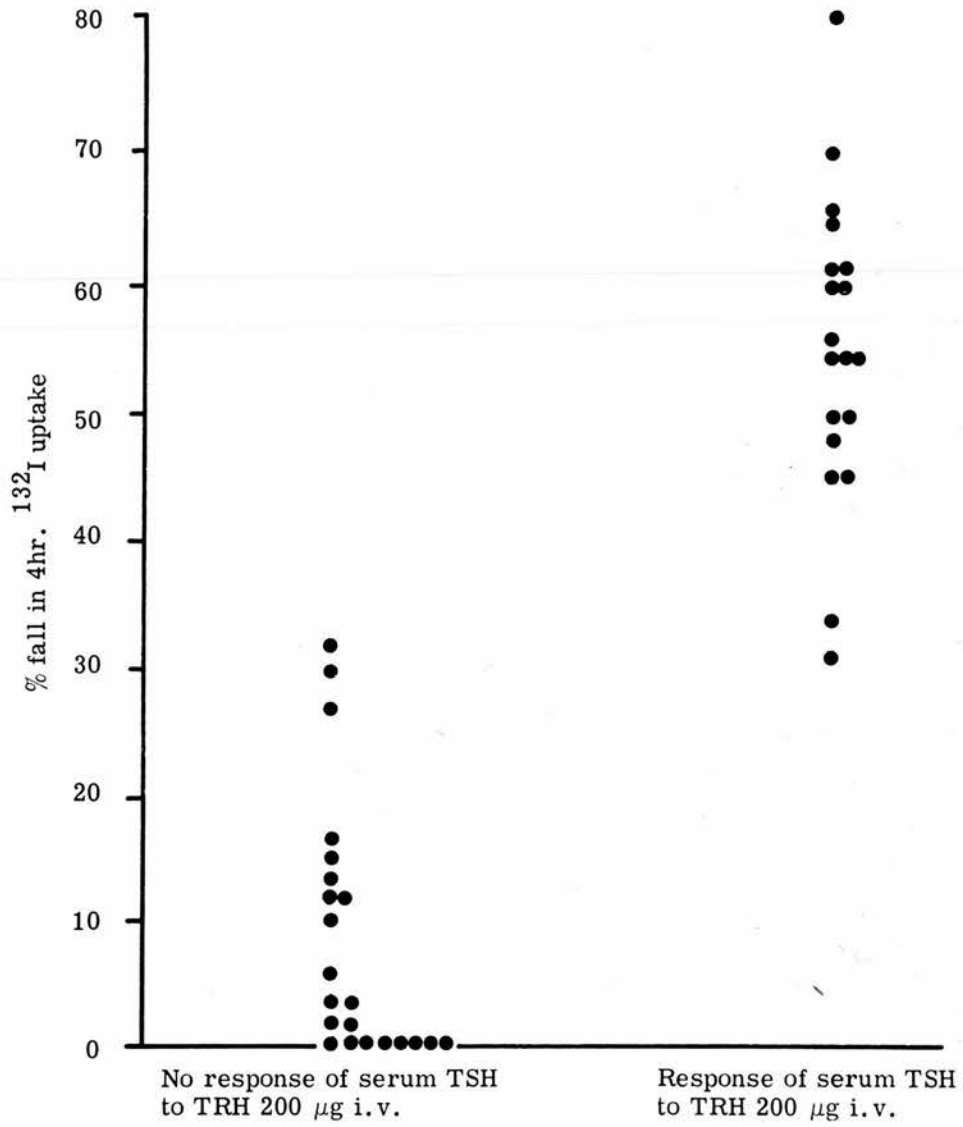
Since the TRH test is a measure of the effect of circulating levels of thyroid hormones at the level of the anterior pituitary gland and the T_3 suppression test is a measure of thyroid autonomy, it is possible that in certain circumstances the correlation between the two tests of thyroid function demonstrated in the present study will not hold. Thyroid autonomy as assessed by the effect of oral T_3 on the uptake of radioiodine has been shown to be present in 50% or more of euthyroid patients previously treated with iodine-131 for thyrotoxicosis, and in a lesser proportion of those rendered euthyroid by subtotal thyroidectomy (Werner, 1956; Hedley et al., 1971b). The ratio of normal to abnormal suppression tests depends on the time which has elapsed since treatment of the thyrotoxicosis (Werner, 1956). The frequency with which detectable TSH receptor antibodies have been found in patients with thyrotoxicosis treated by iodine-131 or subtotal thyroidectomy is similar to the frequency with which thyroid autonomy of the thyroid remnant has been demonstrated by the T_3 suppression test (Mukhtar et al., 1975). It is likely that lack of suppression of the radioiodine uptake by the thyroid gland is a function of the presence of TSH receptor antibodies in the serum which may be found in euthyroid patients with no history of thyroid disease or in those who have been previously treated for thyrotoxicosis. The total serum T_3 and T_4 levels in such patients will be normal and therefore the serum TSH response to TRH will be normal or even exaggerated, despite the demonstration of thyroid autonomy. It is well recognised that a lack of suppression of the radioiodine uptake by T_3 may occur in euthyroid patients with multinodular goitre (Werner and Spooner, 1955; Kristensen et al., 1963; Friis, 1963) due to autonomous function of one or more of the thyroid nodules. Although serum TSH levels have been shown to be significantly lower in

patients with multinodular goitre than in patients with diffusely enlarged simple goitre of euthyroid controls (Chaper 1), there does not appear to be a published study of the correlation of the TRH test and the T_3 suppression test in patients with multinodular goitre. It is possible that a lack of correlation may exist in some patients, in whom the autonomous thyroid tissue is not secreting sufficient thyroid hormones to suppress the pituitary thyrotrophs.

In conclusion, with the exception of patients in the early weeks after iodine-131 or subtotal thyroidectomy for thyrotoxicosis when the pituitary thyrotrophs are still suppressed (Sanchez-Franco et al., 1974; Toft et al., 1974b), a lack of response of the serum TSH level to TRH implies that the patient is thyrotoxic or that the levels of T_4 and/or T_3 in the serum are inappropriately high for the individual despite being in the accepted normal ranges. The euthyroid patient with a lack of serum TSH response to TRH may be at risk of developing thyrotoxicosis in the future, and if this proves to be the case, valuable information has been gained from performing the test. The disadvantages of the T_3 suppression test are numerous and have been stated and as a test of thyroid function in patients with suspected thyrotoxicosis it should be abandoned in favour of the TRH test. The loss of a test of thyroid autonomy is of little clinical significance and it is conceivable that the detection of TSH receptor antibodies in the serum will correlate with thyroid autonomy and might prove to be of some predictive value as regards relapse of thyrotoxicosis especially in the patient being treated with antithyroid drugs.

Fig. 4.1

The percentage fall in initial 4 hour uptake of iodine-132 by the thyroid gland after oral T₃ 120µg daily for seven days in relation to the result of the serum TSH response to TRH.



CHAPTER 5

Thyroid function in patients treated with iodine-131
for thyrotoxicosis.

Radioactive iodine has been widely used in the treatment of thyrotoxicosis for the last twenty-five years. The initial concern was that the irradiation might cause malignant disease, but there is no evidence of an increased incidence of leukaemia (Pochin, 1960; Saenger et al., 1968) or thyroid carcinoma (McDougall et al., 1971b; Dobyns et al., 1974). Furthermore, the radiation dose to the ovaries is small, and the incidence of congenital abnormalities does not seem to be increased in children of parents treated with iodine-131 for thyrotoxicosis during childhood or adolescence (Starr et al., 1969; Hayek et al., 1970; Safa et al., 1975). Radioactive iodine is therefore a safe form of therapy for thyrotoxicosis and is the most common form of treatment in patients over the age of forty years in the United Kingdom. Its main disadvantage is the increasing incidence of hypothyroidism with the passage of time which was originally stressed by Beling and Einhorn (1961) and confirmed by other workers (Dunn and Chapman, 1964; Green and Wilson, 1964; Nofal et al., 1966). The incidence is greatest in the first post-treatment year at 7-22% and continues at 2-5% thereafter (Hagen, 1968) with a cumulative incidence of 80% fifteen years after therapy in some centres (Greig, 1973). In an attempt to reduce the complication of hypothyroidism low dose regimens of iodine-131 were employed (Smith and Wilson, 1967; Goolden and Fraser, 1969) which reduced the incidence of hypothyroidism to 4-5% in the first year and to 7% after five years, but only at the expense of a delay in controlling the symptoms of thyrotoxicosis, necessitating further radioiodine treatment or a prolonged course of antithyroid drugs in approximately half of the patients. More recently, Glennon et al., (1972) showed that the low initial incidence of hypothyroidism after low doses of iodine-131 had increased to 48% at seventeen years after therapy, which is a similar

incidence to that reported after larger doses of radioiodine.

In a further attempt to reduce the high post-therapy incidence of hypothyroidism, the use of iodine-125 was proposed in the treatment of thyrotoxicosis (Greig et al., 1969; Werner et al., 1970). The rationale behind such a proposal was that iodine-125, unlike iodine-131, produced low energy electrons capable of penetrating a short distance only within the thyroid cell. Gillespie et al., (1970) calculated that iodine-125 would irradiate the apex of the thyroid follicular cell three times as much as the nucleus. It was hoped that thyroid hormone synthesis, which takes place at the apex of the cell would be affected to a greater extent than cell division by iodine-125 irradiation, and if so, control of the thyrotoxicosis without risk of permanent cell destruction and hypothyroidism might have been possible. Although it was shown that iodine-125 was effective in controlling thyrotoxicosis, it became apparent that the incidence of hypothyroidism was similar to that which occurred after treatment with iodine-131 (McDougall et al., 1971a; Bremner et al., 1973) and iodine-131 remains the isotope of choice in the treatment of hyperthyroidism. The difficulties in reducing the incidence of hypothyroidism after radioiodine are highlighted by Skillman et al., (1969) who found that the incidence of hypothyroidism was similar in each of three groups of patients treated randomly with 6, 9 or 12 mCi iodine-131. The predictability of permanent hypothyroidism occurring in the majority of patients has led to some workers adopting the policy of intentional ablation of the thyroid gland with radioiodine (Wise et al., 1975), but such a form of treatment for thyrotoxicosis has not yet been widely accepted.

At least three thousand patients are treated with radioiodine for

thyrotoxicosis in the United Kingdom each year, but it has not proved possible, using conventional tests of thyroid function, to predict when or in whom hypothyroidism will develop, resulting in the follow-up of large numbers of patients. The present study was carried out in an attempt to define the value of the estimation of serum TSH in predicting thyroid failure in the early months after iodine-131 therapy for thyrotoxicosis when the incidence of hypothyroidism is greatest, and in patients treated some years previously in whom there is a lower but significant annual incidence of thyroid failure.

PATIENTS AND METHODS

(i) Early follow-up after iodine-131 therapy for thyrotoxicosis

Seventy-two patients with a mean age of fifty-three years (range 37-74 years) were studied, who had been treated with iodine-131 (4-50 mCi: mode 7 mCi) for thyrotoxicosis between August 1972 and October 1973 in the Royal Infirmary, Edinburgh. The thyroid status of each patient was assessed clinically by one observer (ADT) at four to eight weekly intervals after treatment and blood withdrawn on each occasion for the estimation of total serum T_4 , total serum T_3 and serum TSH. The prospective period of follow-up was two to eighteen months. A diagnosis of hypothyroidism was made on clinical grounds and on the basis of a low total serum T_4 and a raised serum TSH level. Total serum T_4 was measured by competitive protein-binding analysis (normal range 60-150 nmol/l) (Seth, 1973), total serum T_3 by radioimmunoassay (normal range 1.0-3.0 nmol/l) (Challand et al., 1975) and serum TSH by the radioimmunoassay

method described in Chapter 1. The upper limit of normal for the serum TSH level for the present study was 7.4mU/l based on an earlier calculated normal range (Irvine et al., 1973) than the normal range of <1.8-5.7mU/l now established for the assay.

(ii) Late follow-up after iodine-131 therapy for thyrotoxicosis

In February, 1972 the total serum T_4 and serum TSH levels were estimated in two hundred and thirty-three euthyroid patients who had been treated with iodine-131 for thyrotoxicosis in the Royal Infirmary, Edinburgh, between 1954 and 1966. A group of sixty-nine of these euthyroid patients with a raised serum TSH level was studied again each year for three years, and a further group of sixty-one euthyroid patients with a normal serum TSH level was restudied at two and three years. The mean age of each group in 1975 was sixty-three years. The number of patients chosen for this follow-up study was arbitrarily determined as adequate for the purpose of the present study. Each patient was examined clinically by one observer (ADT) and blood was withdrawn for the estimation of total serum T_4 , total serum T_3 (1975 only) and serum TSH. In addition, in 1975, the patients fasted overnight for thirteen hours prior to venepuncture, for the estimation of serum cholesterol and triglycerides. Hypothyroidism was diagnosed on clinical grounds and on the basis of a low total serum T_4 and a raised serum TSH level. For the present purpose the euthyroid state is defined as when the patient is euthyroid clinically and when the total serum T_4 level is within the normal range, irrespective of the level of serum TSH.

Total serum T_4 was measured by competitive protein-binding analysis (Seth, 1973) in 1972-1974 and by radioimmunoassay (Seth et al., 1975) in 1975. Values obtained by these two methods showed no statistically significant difference and the normal range for each method was 60-150 nmol/l. Total serum T_3 was measured by radioimmunoassay (normal range 1.1-2.2 nmol/l) (Seth et al., 1976). Serum TSH was measured as described in Chapter 1, but as in the study of the patients in the early follow-up after iodine-131 for thyrotoxicosis, the upper limit of normal was 7.4mU/l. Serum cholesterol and triglycerides were measured by "Autoanalyser" (Technicon Instruments Co.) methods (Kessler and Lederer, 1965; Levine and Zak, 1964).

RESULTS

(i) Early follow-up after iodine-131 therapy for thyrotoxicosis

Forty-one patients were clinically euthyroid at intervals of four to eighteen months after treatment, of whom thirty-two had a normal serum TSH level and a normal total serum T_4 level. In three of these thirty-two patients, each followed up for over twelve months, a transient fall in total serum T_4 to below 60 nmol/l was observed in the early weeks after treatment and was associated with serum TSH levels of <1.8, <1.8 and 8.9mU/l. In the other nine patients remaining clinically euthyroid, normal total serum T_4 levels were associated with serum TSH values in excess of 7.4mU/l.

Clinical hypothyroidism developed in thirty-one patients two to eight months (mean 4.3 months) after treatment. In

seventeen of these patients a low total serum T_4 and a high serum TSH level preceded the clinical features of hypothyroidism by one to four months, and in six patients both indices of thyroid function were normal at the clinic visit one to two months before hypothyroidism was diagnosed. A rise in the serum TSH level preceded a fall in the total serum T_4 level to below the lower limit of the normal range in only one of the thirty-one patients. In seven patients a low total serum T_4 level in the presence of a normal serum TSH level was the first indication of thyroid failure, suggesting that a low total serum T_4 level is a more sensitive index of impending hypothyroidism than the serum TSH level.

Serial total serum T_3 levels were estimated in the seven patients in whom a low total serum T_4 level was the first sign of developing hypothyroidism. In three of these patients the low total serum T_4 and normal serum TSH levels were associated with total serum T_3 levels of 3.5, 1.9 and 1.4 nmol/l, one to two months after therapy with iodine-131. Pituitary TSH secretion was presumably suppressed, albeit temporarily, by the high or normal total serum T_3 concentrations, but as the total serum T_3 levels fell in subsequent weeks, not necessarily into the hypothyroid range, the serum TSH levels rose and clinical hypothyroidism developed. In the remaining four patients a low total serum T_3 , low total serum T_4 and normal serum TSH level were observed while the patient was clinically euthyroid (Fig. 5.1). This phenomenon was temporary and in each case not only was the serum TSH level elevated one month later but hyperthyroidism had developed in three of the four patients.

The fourth patient remained clinically euthyroid despite low total serum T_3 and T_4 levels and a high serum TSH level for a period of two months.

(ii) Late follow-up after iodine-131 therapy for thyrotoxicosis

In February, 1972, the serum TSH level was raised in one hundred and thirty-six (58%) of the two hundred and thirty-three patients euthyroid after iodine-131 therapy and normal in the remaining ninety-seven patients (42%).

The mean \pm SE total serum T_4 , T_3 and serum TSH levels in the sixty-nine euthyroid patients with a high serum TSH level in 1972 and in those remaining euthyroid and available for study in 1973, 1974 and 1975 are shown in Table 5.1. Only three of these sixty-nine patients developed overt hypothyroidism in the first year of follow-up; the serum TSH level had risen in one patient (from 34.6 to 67.3mU/l), had fallen in the second (from 45.6 to 28.2mU/l) and had remained virtually unchanged in the third (90.4 and 92.8mU/l). At two years sixty-four of the sixty-six patients remaining euthyroid in 1973 were available for study, and overt hypothyroidism had developed in a further three patients in whom the serum TSH level remained essentially unchanged (32.8 and 32.0; 23.5 and 26.1; 27.5 and 31.2mU/l). At three years, fifty-eight of the sixty-one patients remaining euthyroid in 1974 were available for study and overt hypothyroidism had developed in one further patient in whom the serum TSH level rose from 39.0 to 64.0mU/l.

The mean \pm SE total serum T_4 , T_3 and serum TSH levels in the sixty-

one patients with a normal serum TSH level in 1972 and in those remaining with a normal serum TSH level and available for study in 1974 and 1975 are shown in Table 5.2. None of the sixty-one euthyroid patients with a normal serum TSH level in 1972 developed clinical hypothyroidism over the period 1972-1975. Between 1972 and 1974 serum TSH levels became slightly raised in three patients (9.4, 9.7 and 12.6mU/l), and between 1974 and 1975 became elevated in a further six patients (8.1, 8.3, 9.2, 10.7, 12.8 and 13.2mU/l). Five patients were lost to follow-up.

The mean total serum T_4 level in the euthyroid patients with a raised serum TSH level was significantly lower than that in the euthyroid patients with a normal serum TSH level in 1972, 1974 and 1975 ($P < 0.001$ on each occasion). In addition, the mean total serum T_3 level was significantly lower in the euthyroid patients with a raised serum TSH level than in the euthyroid patients with a normal serum TSH level ($P < 0.001$). Mean total serum T_3 and T_4 levels in the patients with normal serum TSH levels did not differ significantly from the mean values observed for a normal population (1.70 and 107 nmol/l respectively).

The mean \pm SE serum cholesterol and triglyceride levels in forty euthyroid patients (33 females, 7 males) with normal serum TSH levels and in forty euthyroid patients with high serum TSH levels, matched for age and sex are shown in Table 5.3. There was no significant difference either in mean serum cholesterol or triglyceride concentrations or in their distribution frequencies between the two groups.

DISCUSSION

Although a raised serum TSH level is a sensitive index of thyroid failure, the present study has shown that a low total serum T_4 level is more indicative of impending hypothyroidism in the early months after radioiodine treatment of hyperthyroidism than the serum TSH level. A low total serum T_4 level is a well recognised finding in euthyroid patients many years after iodine-131 treatment, but is invariably associated with high circulating levels of TSH and normal or raised levels of total serum T_3 (Sterling et al., 1969; Sterling et al., 1971; Bellabarba et al., 1972). In such patients the thyroid remnant presumably fails to meet secretory demands, pituitary TSH output rises and increases the T_3/T_4 ratio in the serum and the euthyroid state is maintained. In contrast, a low total serum T_4 , which may be associated with a normal serum TSH level, occurring in the early months after iodine-131 therapy for thyrotoxicosis usually indicates the onset of clinical hypothyroidism within weeks. Of the seven patients in whom a low total serum T_4 and a normal serum TSH level were found before the onset of clinical hypothyroidism, a normal or raised total serum T_3 concentration was present in three patients which may simply reflect the ability of the thyroid gland, damaged by irradiation, to maintain T_3 synthesis and secretion longer than that of T_4 , as has been shown to occur in the thyroid gland damaged by immune mechanisms (McConnon et al., 1971). In the other four patients the transient phenomena of a low total serum T_4 and normal serum TSH level was associated with a low total serum T_3 level for up to two months before the onset of clinical hypothyroidism. A possible explanation of this phenomenon is that the metabolic effects of T_3 and T_4 at the thyrotroph level persist for some time after an alteration in circulating thyroid

hormone concentration, and the serum TSH is slow to rise despite low levels of total serum T_3 and T_4 . Indeed, if T_3 replacement therapy is withdrawn from athyreotic patients serum TSH levels remain suppressed for some days (Hershman and Edwards, 1972) and in humans administration of thyroid hormone for seventy-two hours results in a marked decrease in pituitary TSH content (Bakke et al., 1964). Furthermore, there is a reduced number of thyrotrophs in the pituitary glands of patients with thyrotoxicosis (Murray and Ezrin, 1966). The transient lack of serum TSH response to TRH which is observed despite normal or low levels of circulating thyroid hormones after subtotal thyroidectomy for thyrotoxicosis (Sanchez-Franco et al., 1974; Toft et al., 1976b), during antithyroid drug therapy (Muhlen et al., 1975), and following withdrawal of chronic suppressive therapy with thyroxine (Krugman et al., 1975; Vagenakis et al., 1975) is further evidence for suppression of the brain-thyroid axis previously exposed to high circulating levels of total T_3 and T_4 . Recovery of the axis, which takes four to eight weeks in the majority of patients (see Chapter 6), presumably requires the atrophied thyrotrophs of the anterior pituitary gland to undergo hypertrophy and hyperplasia in order to attain normal capacity for TSH synthesis and secretion. There is an obvious analogy to the suppression of the hypothalamo-pituitary-adrenal axis in patients exposed to prolonged high levels of circulating corticosteroids (Treadwell et al., 1963; Landon et al., 1965; Livanou et al., 1967; Jasani et al., 1967). A sluggish response of the pituitary thyrotroph to the presence of low serum thyroid hormone levels in patients recently treated with iodine-131 for thyrotoxicosis might therefore be expected and explains why the measurement of total serum T_4 is a more valuable test of thyroid function than the serum TSH in

predicting the onset of hypothyroidism in the early weeks after radioiodine therapy.

The late follow-up study has confirmed that, in the majority of euthyroid patients with a raised serum TSH level following iodine-131 treatment of thyrotoxicosis, the serum TSH level will remain unchanged for long periods (Slingerland et al., 1972; Toft et al., 1973c; Toft et al., 1974a; Tunbridge et al., 1974; Toft et al., 1975), although hypothyroidism will continue to develop in a small proportion. On the other hand, in no patient with a normal serum TSH level six to eighteen years after radioiodine therapy did hypothyroidism develop over a three year period of review, although the serum TSH level became elevated in 5% of these patients each year. These findings are highly relevant to the organisation of the long-term follow-up of radioiodine treated thyrotoxic patients. In the Endocrine Clinic, 20% of patients who remain euthyroid one year after radioiodine therapy for thyrotoxicosis have a raised serum TSH level, and from the present study this figure increases to 58% at a mean twelve years after treatment. If an annual rate of hypothyroidism of 2% is assumed between one and twelve years after therapy, the calculated annual rate of transfer of patients from a normal to a high serum TSH level is 5.5%, which is very similar to that of 5% per year observed between 1972 and 1975 in the euthyroid patients with normal serum TSH levels after radioiodine treatment six to eighteen years earlier. It would appear, therefore, that serum TSH levels are of the same significance in patients from one to eighteen years after radioiodine therapy. Serum TSH levels should be estimated at one year after treatment, when the early high incidence of hypothyroidism is over, and patients grouped into (1) those with a high serum TSH level who require annual review

and (2) those with a normal serum TSH level who require to be reviewed at most every three years. Such a policy would reduce considerably the follow-up of the ever-increasing numbers of patients who have been treated with iodine-131 and who have all been reviewed at least on an annual basis in the past either in an endocrine clinic or by means of a computerised follow-up programme (Hedley et al., 1970; Boyle, 1974).

It is important to consider whether a raised serum TSH level following radioiodine therapy is simply an indication for annual review of the patients known to be at risk of developing hypothyroidism in the future, or whether it is a sign of existing thyroid failure albeit subclinical. Previous studies of serum TSH levels after treatment of thyrotoxicosis by iodine-131 or partial thyroidectomy have shown total serum T_4 levels to be significantly lower in patients with raised serum TSH levels than in those with normal serum TSH levels (Toft et al., 1974a; Tunbridge et al., 1974; Evered et al., 1975; Toft et al., 1975). No difference, however, was observed in the total serum T_3 levels between the two groups (Tunbridge et al., 1974; Evered et al., 1975). The maintenance of clinical euthyroidism by T_3 in patients with high serum TSH levels was considered to reflect a compensatory mechanism which is probably TSH dependent. In contrast, the present study has shown, not only total serum T_4 levels, but also total serum T_3 levels in patients with high serum TSH levels to be significantly lower than the thyroid hormone levels of the patients with normal TSH levels after radioiodine treatment. The falling T_3 and T_4 secreted by the irradiated thyroid gland will result in a raised serum TSH level, but, unlike the situation following subtotal thyroidectomy for thyrotoxicosis (Toft et al., 1976b), for example, the irradiated thyroid may be unable to

respond to a high circulating level of TSH with a compensatory increase in thyroid hormone secretion. According to the dose of irradiation, which will vary from follicle to follicle, there may occur delay in mitosis followed by normal mitosis, delayed mitosis followed by cell death in mitosis, inhibition of mitosis or cell sterilisation, reduced cell life-span, and cell death (Doniach, 1971). It is possible that the irradiated thyroid cell, unlike the normal cell, is unable to hypertrophy in response to TSH or TSH receptor antibodies, and thyroid stimulators, by inducing mitosis, may paradoxically increase the rate of cell death within the gland. A raised serum TSH level may, therefore, simply reflect the reduced output of both T_3 and T_4 by the failing thyroid gland which is incapable of compensatory increase in thyroid hormone secretion as a result of irradiation damage.

It is not possible to determine at present whether the suboptimal total serum T_3 and T_4 levels in these patients with raised serum TSH levels after iodine-131 treatment of thyrotoxicosis indicate existing significant hypothyroidism. It is well established that the pituitary thyrotroph is very sensitive to minor changes in the serum levels of total T_3 and T_4 (Snyder and Utiger, 1972a; Snyder and Utiger 1973), but other organs and tissues may be less sensitive to changes in circulating thyroid hormone levels. Indeed, no difference could be demonstrated in serum cholesterol or triglyceride levels between the high and normal serum TSH patients matched for age and sex, although hypercholesterolaemia is well recognised in overt hypothyroidism (Mason et al., 1930; Boyd and Connell, 1937; Wayne, 1960; Furman et al., 1961). It is clear that any increase in morbidity or mortality in the patients with raised serum TSH levels and suboptimal total T_3

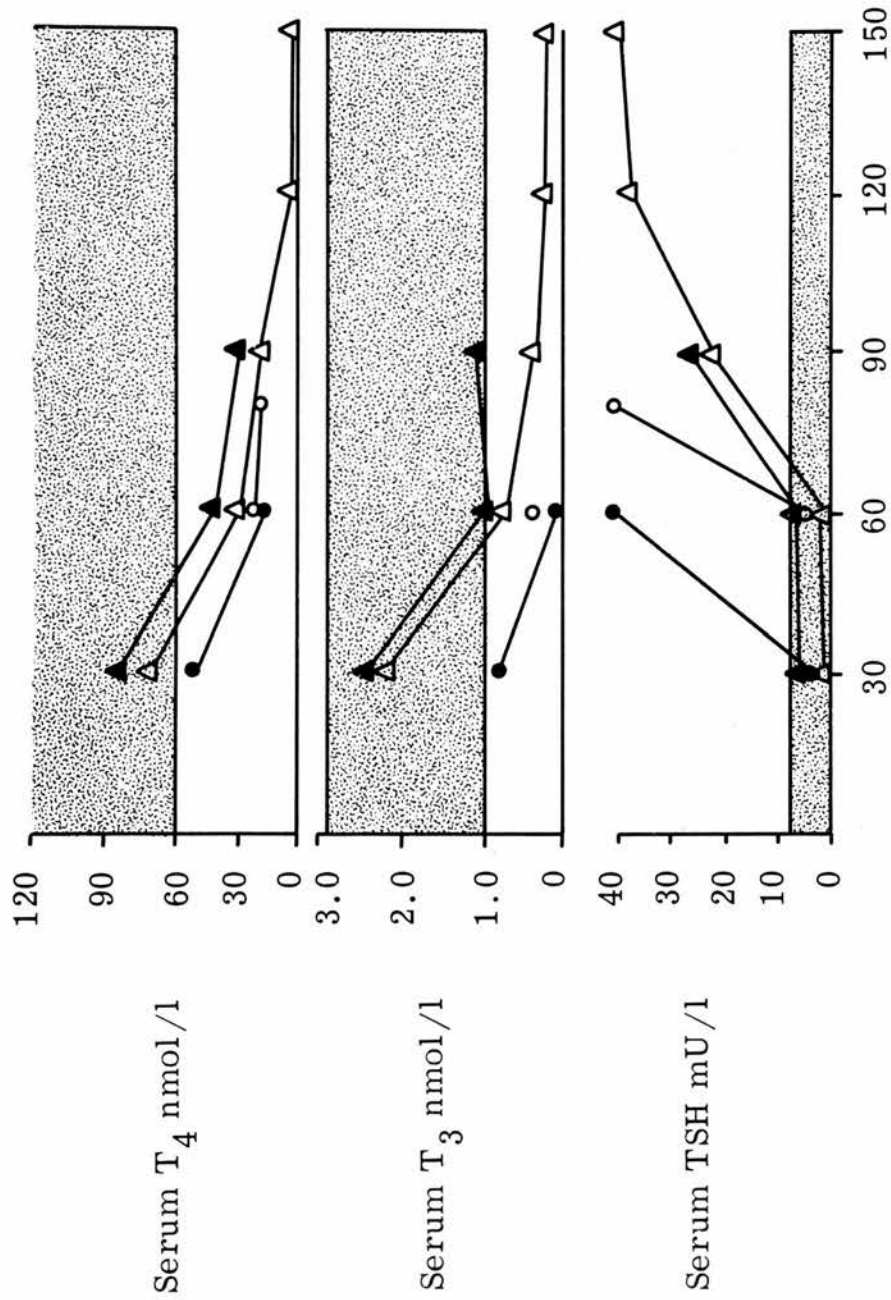
and T_4 concentrations in the serum will only become apparent on long-term follow-up.

If the patients with suboptimal thyroid hormone levels and raised serum TSH levels are considered to be hypothyroid, it is important to recognise the possibility of inducing thyrotoxicosis in some of the patients if the usual thyroxine replacement dosage of between 0.1 and 0.2 mg daily is employed (Evered et al., 1973b). The thyroid remnant may be autonomous due to circulating TSH receptor antibodies, and evidence for autonomous function is provided by the observation that the iodine uptake of the gland is uninfluenced by pharmacological doses of exogenous TSH despite normal levels of endogenous serum TSH in some patients previously treated with radioiodine (Irvine et al., 1973). If clinically euthyroid patients with suboptimal total serum T_3 and T_4 levels and elevated serum TSH levels are to be treated with thyroxine, it would be ideal if the replacement therapy could be adjusted such that the levels of serum TSH in response to TRH lay within the normal range.

Fig. 5.1

Total serum T_4 , T_3 (nmol/l) and serum TSH (mU/l) levels in the four patients in whom a low total serum T_4 and T_3 level was observed in the presence of a normal serum TSH level prior to the development of hypothyroidism.

{from Journal of Clinical Endocrinology and Metabolism, 39, 607-609, (1974)}



Days post iodine - 131 therapy

Year	No. of patients	Serum T-4 (nmol/l)	Serum T-3 (nmol/l)	Serum T.S.H. (mU/l)	No. developing overt hypothyroidism	No. lost to follow-up
1972	69	88.0±1.0	-	25.0±2.0	-	-
1973	66	84.0±1.0	-	22.6±1.8	3	0
1974	61	84.0±1.0	-	21.6±2.0	3	2
1975	57	75.0±3.0	1.52 ± 0.05	26.6±2.6	1	3

Table 5.1 Mean serum T₄, T₃ and TSH levels (±SE) in patients with high serum TSH levels in 1972 and in patients remaining euthyroid and available for study over the following three years (all treated with iodine-131 for thyrotoxicosis between 1954 and 1966).
 {from Lancet, *ii*, 576-578 (1975)}

Year	No. of patients	Serum T-4 (nmol/l)	Serum T-3 (nmol/l)	Serum T.S.H. (mU/l)	No. developing overt hyperthyroidism	No. developing raised serum T.S.H.	No. lost to follow-up
1972	61	113.0±4.0	-	4.0±0.2	-	-	-
1974	58	105.0±3.0	-	4.1±0.3	0	3	0
1975	47	105.0±4.0	1.73±0.05	3.9±0.3	0	6	5

Table 5.2 Mean serum T₄, T₃ and TSH (±SE) in patients with normal serum TSH levels in 1972 and in patients remaining euthyroid and available for study over the following three years (all treated with iodine-131 for thyrotoxicosis between 1954 and 1966).
 {from Lancet, ii, 576-578 (1975)}

T.S.H. level	Serum-cholesterol (nmol/l)	Serum-triglyceride (nmol/l)
Normal	6.36±0.17	1.24±0.07
High	6.53±0.19	1.41±0.12

Table 5.3 Mean serum cholesterol and triglyceride levels (\pm SE) in 40 euthyroid patients with normal serum TSH levels and in 40 euthyroid patients with high serum TSH matched for age and sex (all treated with iodine-131 for thyrotoxicosis between 1954 and 1966) { from Lancet ii, 576-578 (1975)}.

CHAPTER 6

Propranolol in the treatment of thyrotoxicosis by
subtotal thyroidectomy.

The beta-adrenergic blocking drug propranolol is effective in alleviating many of the signs and symptoms of thyrotoxicosis such as tachycardia, tremor, sweating, heat intolerance and anxiety (Shanks et al., 1969) and has been shown to be of value in the treatment of the less common accompaniments of thyrotoxicosis such as myopathy (Pimstone et al., 1968; Kammer and Hamilton, 1974), steatorrhoea (Thomas et al., 1973), and periodic paralysis (Yeung and Tse, 1974). It is used to control symptoms while patients with suspected thyrotoxicosis are undergoing investigation, and has been used successfully in the treatment of thyrotoxic crisis (Das and Kreiger, 1969). It is also a useful adjunct to iodine-131 in the treatment of thyrotoxicosis, alleviating symptoms until the radioiodine has a therapeutic effect (Hadden et al., 1968; Franco et al., 1970). Propranolol does not totally reverse the signs and symptoms of hyperthyroidism and has no effect upon some of the metabolic sequelae such as the increased urinary excretion of calcium and hydroxyproline (Georges et al., 1975) and is therefore considered to be inferior to carbimazole in the long-term treatment of thyrotoxicosis (McLarty et al., 1973; Mazzaferri et al., 1976).

Recently there have been reports of patients undergoing partial thyroidectomy for thyrotoxicosis prepared solely with propranolol (Lee et al., 1973; Michie et al., 1974). The successful treatment at the Endocrine Clinic of a patient with thyrotoxicosis, who was sensitive to antithyroid drugs, by subtotal thyroidectomy under cover of propranolol and the advantages claimed for the procedure such as reduced preparation time, more flexible timing of operation and reduced operative blood loss, led to a change in policy with regard to the treatment of thyrotoxicosis. Since early 1975 the majority of

patients under the age of forty-five years presenting to the Endocrine Clinic with thyrotoxicosis have been treated by subtotal thyroidectomy under cover of propranolol, and carbimazole has only been used in exceptional circumstances such as in patients with asthma or in patients unwilling to accept thyroid surgery. In view of this change in policy in the management of patients with thyrotoxicosis it was important not only to investigate the rate of effect of propranolol in rendering a patient suitable for surgery, but also to establish the surgical efficacy of the procedure, to measure thyroid function postoperatively, and to attempt to determine an appropriate follow-up policy for patients treated in this manner.

The only readily measurable objective sign of response of the thyrotoxic patient to propranolol is the reduction in heart rate, and it was therefore proposed to assess the heart rate response to propranolol by continuous ECG monitoring of patients with thyrotoxicosis in an attempt to define the minimum preoperative period of treatment.

It is apparent that there is a suppression of the brain-thyroid axis in patients who have been exposed to high circulating levels of thyroid hormones (Sanchez-Franco et al., 1974; Toft et al., 1974b; Krugman et al., 1975; Mühlen et al., 1975; Vagenakis et al., 1975; Demeester et al., 1976) analogous to the suppression of the brain-adrenal axis in patients treated with pharmacological doses of steroids over a prolonged period (Treadwell et al., 1963; Landon et al., 1965; Jasani et al., 1967; Livanou et al., 1967). The preparation of patients with thyrotoxicosis for subtotal thyroidectomy with propranolol allowed an assessment of the delayed recovery of the brain-thyroid axis following the sudden withdrawal of excess circulating thyroid hormones, by means

of measuring the serum TSH response to TRH at various intervals after the euthyroid state had been achieved. The period during which a lack of response or a subnormal response of serum TSH to TRH occurs is presumably an index of the delayed recovery of the suppressed brain-thyroid axis.

In many clinics a diagnosis of permanent hypothyroidism is made within three to four months of surgical treatment of thyrotoxicosis (Nofal et al., 1966; Olsen al., 1970). Bartels (1953) found that the majority of patients who developed clinical hypothyroidism after subtotal thyroidectomy for thyrotoxicosis did so within three months of surgery, but it was possible to discontinue thyroid replacement therapy in 20% of these patients within twelve months, indicating that in some patients there is a period of transient hypothyroidism in the early stages after operation. In contrast to the thyroid gland damaged by iodine-131 irradiation, the thyroid remnant after surgical treatment of thyrotoxicosis should be capable of hypertrophy in response to endogenous TSH, in the absence of TSH receptor antibodies. In the present study a positive decision was made not to diagnose permanent hypothyroidism, and if possible, not to start thyroxine replacement therapy before six months after operation. It was hoped that such a policy would allow the behaviour of the thyroid remnant to be monitored in terms of thyroid function and preempt the need for thyroxine replacement therapy in a proportion of patients.

PATIENTS AND METHODS

(i) Continuous cardiac monitoring study:

Six patients were studied (4 females, 2 males) aged twenty-six

to sixty-three years. The diagnosis of thyrotoxicosis was made on clinical grounds and on the basis of the total serum T_4 and T_3 measured by radioimmunoassay (Seth et al., 1975; Seth et al., 1976), and the 4 hour uptake of iodine-132 by the thyroid gland. In addition, there was no rise in the serum TSH level following the intravenous injection of 200 μ g TRH. One patient was studied as an out-patient and five as in-patients. The in-patients were allowed at least twenty-four hours to acclimatise to the hospital environment before starting continuous monitoring. The heart rate monitoring was carried out with miniature tape recording equipment (Oxford Instruments) using a modified V.5 chest electrode. The light weight and portability of these instruments allowed the patients to undertake normal activity during the recording periods. The C.120 'Memorex' tape cassettes were turned over at the end of twenty-four hours and the batteries and tape cassettes were changed every forty-eight hours. Care was taken to ensure that tape recorder speed variations were minimised by using the same recorder for each patient over the taping period. The first day of monitoring was the control day and thereafter propranolol was administered orally in a dose of 40 mg six-hourly and monitoring continued for a further three to four days. The completed tapes were replayed at sixty times real-speed and were checked by two independent observers. The signal was also processed by a Neilson Arrhythmia Computer (Neilson, 1974) which provided continuous heart rate measurements. These rates were stored in a solid state memory device with two hundred and forty individual stores. Each store therefore contained heart rate information for a six minute period of the twenty-four hour

tape recording. In the final analysis the number of six minute periods during which more than six hundred sinus beats had been detected was expressed as a percentage of the total number of six minute periods. This was effectively the proportion of time during which the heart rate was over one hundred beats per minute.

(ii) Subtotal thyroidectomy study

Subtotal thyroidectomy was performed in a total of forty patients (37 females, 3 males) of whom nine had recurrent thyrotoxicosis and had been treated previously with carbimazole. The mean age of the patients was thirty-four years (range 20-63 years). The diagnosis of thyrotoxicosis was made on clinical grounds and on the basis of the total serum T_3 and T_4 levels measured by radioimmunoassay (Seth et al., 1975; Seth et al., 1976) and the serum TSH response to 200 μ g TRH intravenously. The thyroid gland was diffusely enlarged in thirty-three patients and a multinodular goitre was present in six patients. In the remaining patient, the thyrotoxicosis was due to a hyperfunctioning thyroid adenoma. An electrocardiograph was performed on each patient preoperatively and atrial fibrillation demonstrated in three. Propranolol was given in a dose of 40 mg six-hourly orally for a mean preoperative period of seventeen days (range 4-60 days) and was continued throughout the day of operation and for seven days after operation. Patients were admitted to hospital four days prior to surgery and were discharged on the seventh post-operative day. The vocal cords were inspected before and after surgery by

indirect laryngoscopy. Preoperative medication was with diamorphine, cyclizine and atropine, and anaesthesia was induced with an intravenous barbiturate and was maintained with halothane, nitrous oxide and oxygen.

The operative blood loss was estimated by weighing the gauze swabs used at operation. The weight of the thyroid remnant was calculated by weighing a part of the removed thyroid tissue considered to be of equal size to the thyroid remnant.

In all patients serum calcium (Gitelman, 1967), total serum T_3 , total serum T_4 levels, and serum TSH response to 200 μ g TRH intravenously were measured before and at one week after surgery. Serum calcium was also estimated at forty-eight hours postoperatively. The thyroid function tests were repeated, in addition to clinical examination by one observer (ADT) at one, two, three, four, six and nine months depending upon the length of follow-up. In order to measure the acute rate of fall of thyroid hormone levels following subtotal thyroidectomy the total serum T_3 and T_4 levels were estimated daily for seven days in fourteen patients.

RESULTS

(i) Continuous cardiac monitoring study

The effect of oral propranolol in a dose of 40 mg every six hours for three to four days on the continuously recorded heart rate of six patients with untreated thyrotoxicosis is shown in Fig. 6.1.

The greatest reduction in heart rate occurred during the first day of treatment with propranolol in the five patients in whom data was available for this period. In the sixth patient there was a failure of the recording system on the first day of therapy. In three of the patients there was only a small further fall in heart rate despite continued propranolol administration, but in the remaining patients there was a more apparent reduction in heart rate with each successive day of treatment. The effect of propranolol was not related to the severity of the thyrotoxicosis. The out-patient showed as good a response as the in-patients.

(ii) Subtotal thyroidectomy study

The clinical impression was that the operative and postoperative course of the patients compared favourably with that of patients prepared for subtotal thyroidectomy with carbimazole and potassium iodide.

The mean preoperative period of treatment with propranolol was seventeen days. The mean \pm SE operative blood loss was 160 ± 20 ml and the mean \pm SE thyroid remnant was estimated at 7.5 ± 0.6 gm or $18 \pm 1\%$ of the total gland weight. Two patients developed a transient recurrent laryngeal nerve palsy. With the exception of one patient in whom transient hypocalcaemia developed requiring treatment with calciferol for a period of four weeks, the serum calcium has remained in the normal range in all patients throughout the period of follow-up. Two patients have developed permanent hypothyroidism and thyrotoxicosis has not persisted in any patient. In the three patients with

atrial fibrillation before subtotal thyroidectomy, normal sinus rhythm was demonstrated electrocardiographically within four weeks of operation.

The mean \pm SE total serum T_3 and T_4 levels in the forty patients before surgery were 6.9 ± 0.4 and 255 ± 11 nmol/l, and on the seventh postoperative day were 1.0 ± 0.1 and 89.0 ± 6.3 nmol/l respectively. The mean \pm SE total serum T_3 and T_4 levels in fourteen of these patients before and for seven days after thyroidectomy are shown in Fig. 6.2. Four weeks after subtotal thyroidectomy the mean \pm SE total serum T_3 and T_4 levels were recorded at 1.30 ± 0.1 and 66.0 ± 6.3 nmol/l.

There was no rise in the serum TSH levels following TRH in any of the forty patients prior to surgery. Despite normal or low levels of total serum T_3 and T_4 , there was an absent or subnormal response of serum TSH to TRH in 100% of patients at one week, and in 65% of patients at four weeks after thyroidectomy. The serum TSH response to TRH was considered subnormal if the serum TSH level at twenty minutes after the administration of TRH was less than the lower limit of response in control subjects of 3.9mU/l, or as occurred in three of the patients four weeks postoperatively the basal serum TSH level was raised, but at twenty minutes after TRH did not exceed the upper limit of normal in control subjects of 25.3mU/l. The serum TSH response to TRH remained absent in seven (18%) of the patients at eight, twelve and sixteen weeks after operation. In these seven patients who were clinically euthyroid with total serum T_4 levels well within the normal range, the total serum T_3

levels at eight weeks after operation were 1.8, 1.8, 2.1, 2.2, 2.2, 2.3, and 2.6 nmol/l respectively. Similar levels of total serum T_3 towards the upper limit of normal for the assay of 2.2 nmol/l or slightly elevated, although not in the range usually encountered in thyrotoxicosis, were recorded at twelve and sixteen weeks postoperatively. The pattern of changing responsiveness of serum TSH to TRH in the total forty patients after subtotal thyroidectomy is illustrated in Fig. 6.3

In eighteen of the patients low levels of total serum T_3 and T_4 have been observed in the early weeks after surgery and have been associated with symptoms of mild hypothyroidism. Seven of these patients have now been followed up for at least six months, and in five patients the levels of total serum T_3 and T_4 have returned to the normal range in the presence of a raised serum TSH level within six months of operation. The sequential levels of total serum T_3 and T_4 and serum TSH in these five patients with transient hypothyroidism are shown in Fig. 6.4 and 6.5. A diagnosis of permanent hypothyroidism has been made in the two other patients at follow-up at six months after surgery on the basis of clinical examination and persisting low levels of total serum T_3 and T_4 and raised levels of serum TSH. The ultimate thyroid status of the remaining eleven patients with evidence of mild clinical hypothyroidism in the early weeks after subtotal thyroidectomy will be decided at the review six months after operation. In the other twenty-two patients in the study the total serum T_4 levels have remained within the normal range and the total serum T_3 levels within the normal range or slightly elevated throughout the period of out-patient follow-up of from

three to nine months. The serum TSH levels are either elevated or have been transiently elevated in 50% of this group of patients at follow-up.

DISCUSSION

The time course of action of intravenous propranolol on the heart rate of patients with thyrotoxicosis has been well documented (Howitt and Rowlands, 1966; Weiner et al., 1969), but the rate of response following oral therapy has not been fully evaluated. Vinik et al. (1968) demonstrated a significant fall in pulse rate in thyrotoxic patients forty-eight hours after starting treatment with oral propranolol, but more detailed studies do not appear to exist. By continuously monitoring the heart rate of patients with thyrotoxicosis it is apparent that the maximum effect of propranolol in reducing the tachycardia of such patients is present within three to four days. Propranolol does not, however, reduce the heart rate of patients with thyrotoxicosis to normal levels (Howitt and Rowlands, 1966) and it is likely that the tachycardia of hyperthyroidism is the result not only of increased beta-adrenergic activity, but also of a direct action of thyroid hormones on the myocardium which will be uninfluenced by beta-blockade. The decision regarding when a patient with thyrotoxicosis, prepared with propranolol, is suitable for surgery is arbitrary, but the policy applied at present is to achieve a resting pulse rate of less than ninety beats per minute. Heart rates of less than ninety per minute have been attained using propranolol in a dose of 40 mg six-hourly orally in all of the forty patients treated by subtotal thyroidectomy under cover of propranolol in the present series. If propranolol is started as soon as the decision is made to treat the patient by surgical

means, the preoperative period with propranolol depends upon the availability of the surgeon and the domestic arrangements of the patient. It is unlikely that the mean preparation time with propranolol in the present series of seventeen days could be reduced, even although the patients were suitable for surgery some days earlier. It is evident, however, that patients with thyrotoxicosis can be rendered euthyroid by subtotal thyroidectomy under cover of propranolol in a shorter time than that required using established antithyroid drugs, such as carbimazole. A further advantage of propranolol over carbimazole in the preparation of thyrotoxic patients for subtotal thyroidectomy is the more flexible timing of operation, which is to the advantage of both patient and doctor.

It is the impression that the thyrotoxic gland prepared with propranolol is smaller and less vascular than the gland prepared with carbimazole. The mean operative blood loss in the present study of 160 ml is small, and is less than that recorded by the same surgeon during subtotal thyroidectomy for thyrotoxicosis in patients prepared with carbimazole and potassium iodide (McIntosh, 1976). It is probable that many patients are overtreated with carbimazole with a subsequent increase in size and vascularity of the gland under the added stimulus of endogenous TSH.

The rates of fall of the total serum T_3 and T_4 levels during the immediate postoperative period reflect in part the respective half-lives of the thyroid hormones of twenty-four hours and six days. However, within twenty-four hours of any surgical procedure there is a fall in the level of total serum T_3 due to the monodeiodination of T_4 by an alternative pathway to form 3, 3', 5', triiodothyronine (reverse T_3)

(Burr et al., 1975), and a proportion of the fall in the total serum T_3 following subtotal thyroidectomy may be due to this mechanism. The decision to stop propranolol therapy on the seventh postoperative day is based on the finding of normal levels of total serum T_3 and T_4 at that time.

The acute effects of raised levels of thyroid hormones on the adenohypophysis to prevent the release of TSH by TRH is thought to be achieved by a protein inhibitor of TRH action (Bowers et al., 1967; Bowers et al., 1968b) and presumably the effect of prolonged inappropriately high levels of total serum T_3 and T_4 is to cause atrophy of the TSH producing cells, or thyrotrophs, described by Murray and Ezrin (1966) in patients with untreated thyrotoxicosis. The study of serial levels of thyroid hormones and of the serum TSH response to TRH in patients rendered euthyroid by subtotal thyroidectomy under cover of propranolol has enabled the rate of recovery of the thyrotroph to be determined. Although total serum T_3 and T_4 levels were in the lower range of normal or frankly low in the majority of patients one and four weeks after surgery, the serum TSH response to TRH was absent in 100% of patients at one week, and absent or subnormal in 65% of patients at four weeks after subtotal thyroidectomy. The subnormal serum TSH response to TRH indicates partial recovery of the thyrotroph and is intermediate between no response of serum TSH to TRH and the augmented response characteristic of a raised basal serum TSH level (Chapter 3). The lack of response of serum TSH to TRH which persisted in 17% of the patients for longer than eight weeks after surgery is not due to a delayed recovery of the thyrotrophs, but due to a continued suppression of these cells by levels of total serum T_3 and/or T_4 which were either in the upper part

of the normal range or slightly elevated and reflects the sensitivity of the anterior pituitary gland to minor changes of circulating total T_3 and T_4 even within the normal range (Snyder and Utiger, 1972a; Snyder and Utiger, 1973). It is evident therefore that the thyrotroph of the anterior pituitary gland does not regain its capacity to respond either to normal or low levels of thyroid hormones or to pharmacological doses of TRH for four to eight weeks after subtotal thyroidectomy in the majority of patients. Although the suppression of the brain-thyroid axis is not so prolonged or of the same clinical significance as the suppression of the brain-adrenal axis in patients previously exposed to high doses of corticosteroids, the resultant anomalies which may occur in thyroid function tests in the early weeks after operative treatment for thyrotoxicosis should be appreciated.

The incidence of hypothyroidism after subtotal thyroidectomy for thyrotoxicosis depends upon many factors among which are the size of the thyroid remnant (Crile and McCullagh, 1951; Michie et al., 1972), the degree of lymphocytic infiltration of the gland (Whitesell and Black, 1949; Greene, 1950), the presence of complement fixing thyroid antibody in the serum (Irvine et al., 1962; Buchanan et al, 1962; Irvine and Stewart, 1967) the length of follow-up (Nofal et al., 1966) and the progression of thyrotoxicosis to spontaneous hypothyroidism in some patients (Baldwin, 1895; Gowan, 1895). It is apparent from the present study that a condition of mild hypothyroidism associated with low levels of total serum T_3 and T_4 may occur in some patients in the early weeks after operation. However, thyroid hormone levels may return to the normal range as a result of a raised serum TSH level and permanent hypothyroidism should not be diagnosed with confidence

before six months have elapsed. If, as reported by Bartels (1953) and Nofal et al., (1966), over 50% of patients ultimately developing hypothyroidism after thyroidectomy do so within six months of operation, the review policy must be an important additional factor in determining the incidence of hypothyroidism. Although there have been many retrospective studies of the incidence of hypothyroidism following surgical treatment of thyrotoxicosis (Green and Wilson, 1964; Roy et al., 1967; Beahrs and Sakulsky, 1968; McNeill and Thomson, 1968; Olsen et al., 1970; Evered et al., 1975) with figures of between 6% at ten years and 43% at five years of follow-up, there is little information available about the stage at which the diagnosis of permanent hypothyroidism was made postoperatively. It is possible, therefore, that some of the variation from centre to centre in the incidence of hypothyroidism may be accounted for by the review policy of the clinic.

The efficacy of subtotal thyroidectomy for thyrotoxicosis under cover of propranolol has been established. Consideration should therefore be given to the preoperative preparation of patients with propranolol in whom there is an indication for thyroidectomy and in whom there is no history of asthma or cardiac failure. Diabetes mellitus may be a relative contradiction since propranolol has been shown to directly cause hypoglycaemia (Kotler et al., 1966) and may mask the signs and symptoms of hypoglycaemia which are mediated by beta-adrenergic receptors. It should also be stressed, however, that the short half-life of propranolol of 3.2 hours (Shand et al., 1970) makes the administration of the drug on the morning of operation, and every six hours postoperatively, mandatory.

The present study has also defined the patterns of total serum T_3 , T_4 and TSH which occur in the early months after surgery. Although the period of follow-up has been short, it is unlikely that the incidence of recurrent thyrotoxicosis or permanent hypothyroidism will be significantly different in the long-term than in patients prepared for surgery with carbimazole and potassium iodide.

Fig. 6.1

The effect of oral propranolol 40 mg six-hourly on the continuously monitored heart rate of six patients with untreated thyrotoxicosis.

{from *Clinical Endocrinology*, 5, 195-198 (1976)}

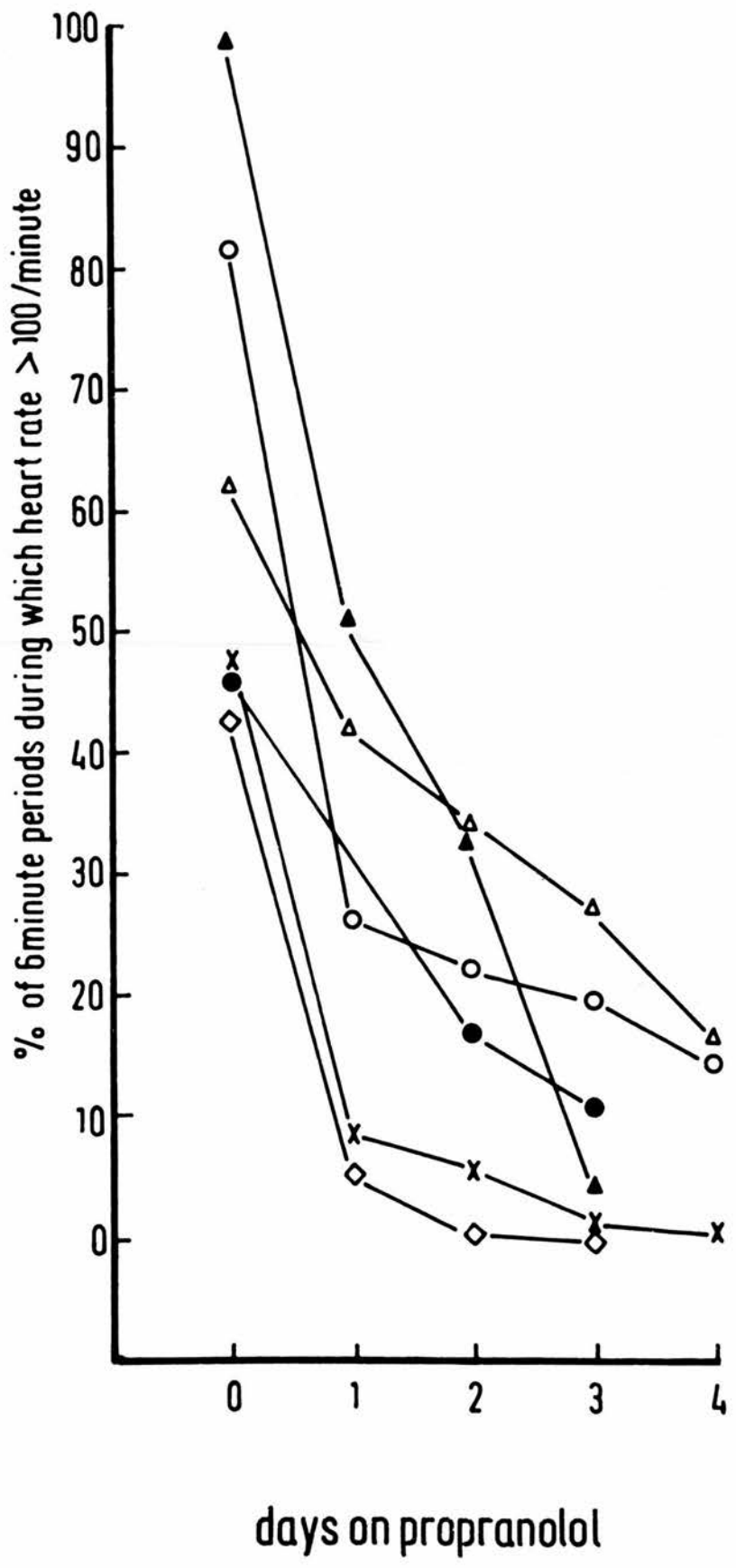


Fig. 6.2

Mean \pm SE total serum T₃ and T₄ levels in fourteen patients before and for seven days after subtotal thyroidectomy for thyrotoxicosis under cover of propranolol.

{from Journal of Clinical Endocrinology and Metabolism (1976) (In press)}

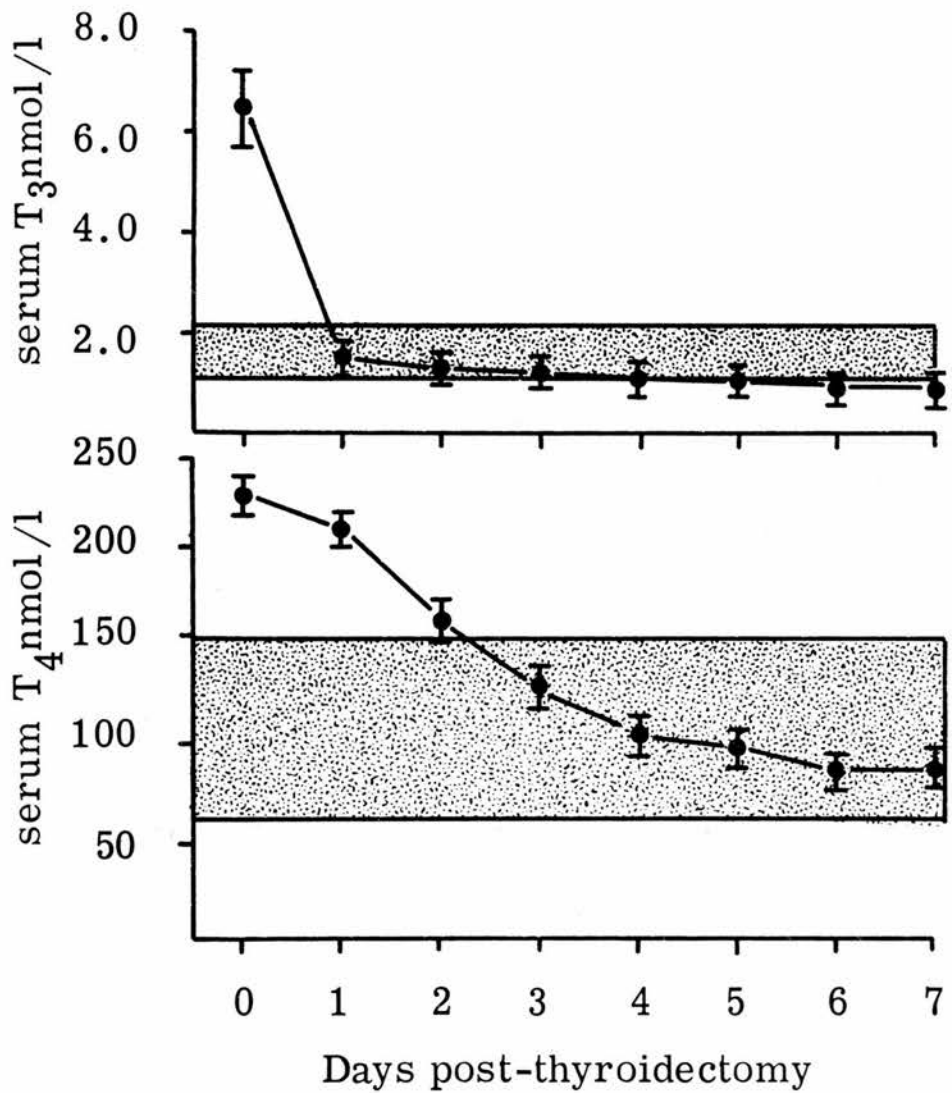


Fig. 6.3

The percentage of patients with absent or subnormal response of serum TSH to 200 μ g TRH i.v. at one, four, eight, twelve and sixteen weeks after subtotal thyroidectomy for thyrotoxicosis under cover of propranolol.

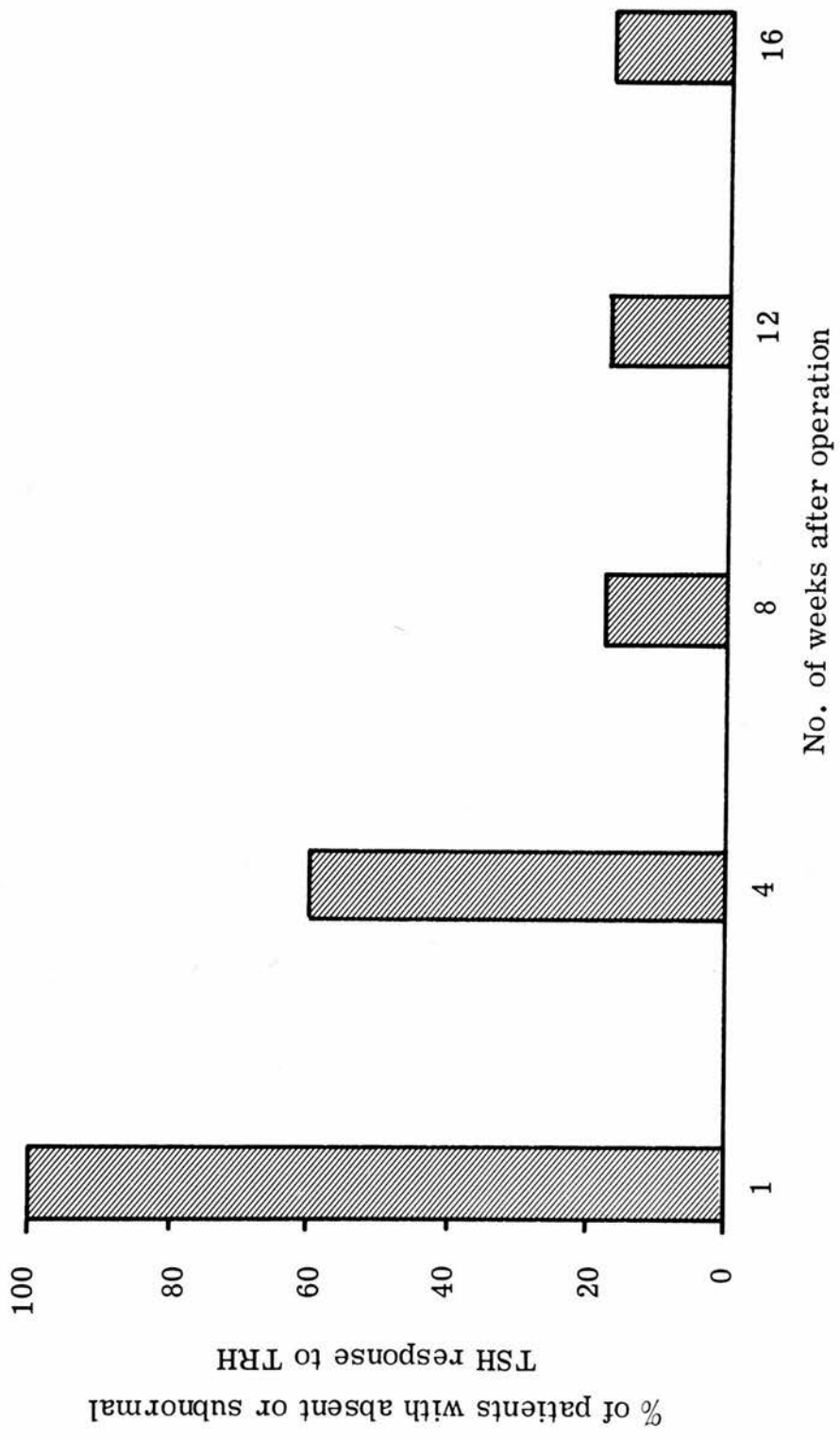


Fig. 6.4

Total serum T_3 , T_4 and TSH levels before and for six months after subtotal thyroidectomy for thyrotoxicosis under cover of propranolol in three patients in whom transient clinical hypothyroidism was observed.

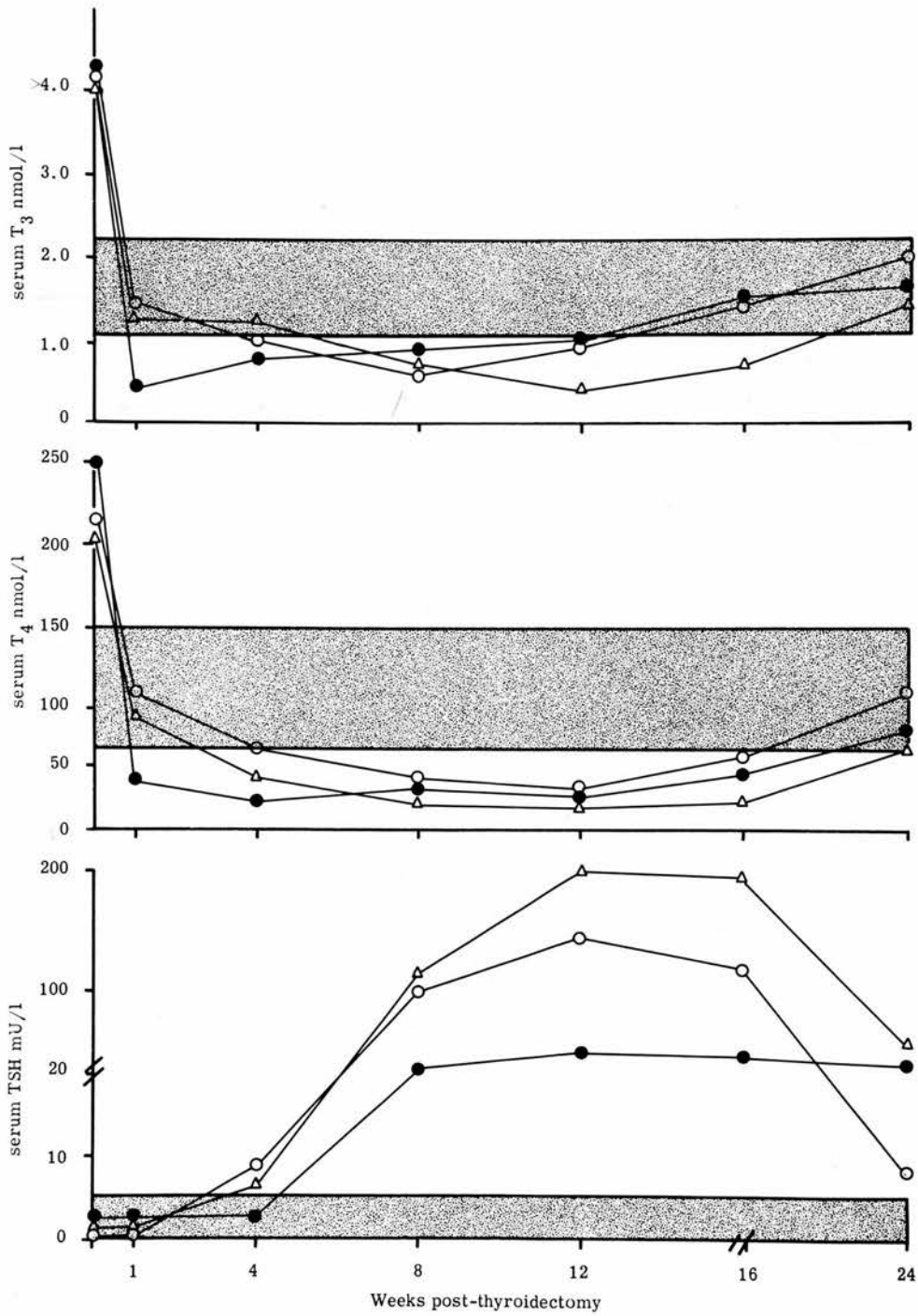
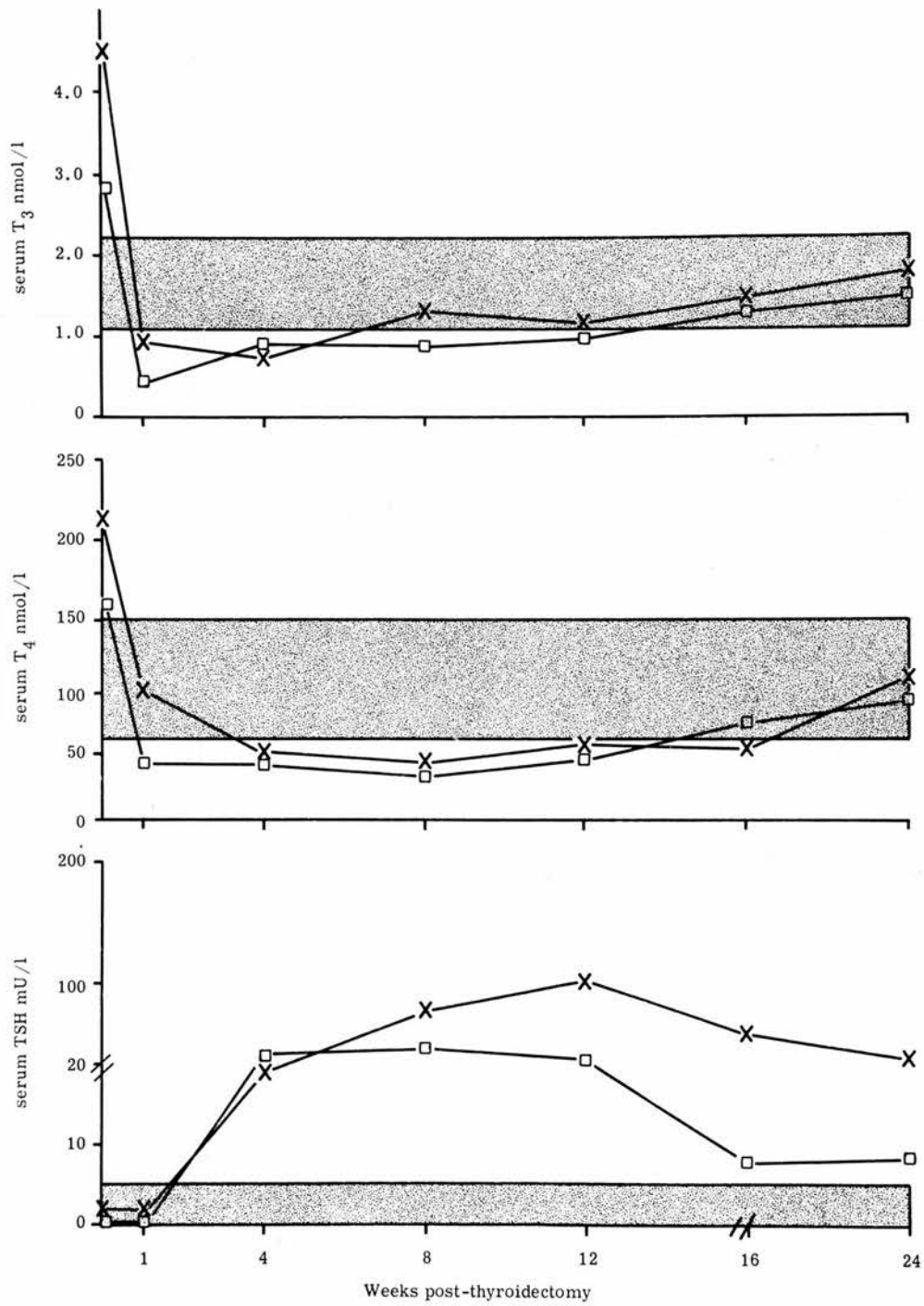


Fig. 6.5

Total serum T_3 , T_4 and TSH levels before and for six months after subtotal thyroidectomy for thyrotoxicosis under cover of propranolol in a further two patients in whom transient clinical hypothyroidism was observed.



REFERENCES

- Anderson, J.R., Goudie, R.B., Gray, K.G. The 'thyrotoxic' complement fixation reaction. *Scottish Medical Journal*, 4, 64-74 (1959).
- Anderson, M.S., Bowers, C.Y., Kastin, A.J., Schalch, D.S., Schally, A.V., Snyder, P.J., Utiger, R.D., Wilber, J.F., Wise, A.T. Synthetic thyrotrophin-releasing hormone. *New England Journal of Medicine*, 285, 1279-1283 (1971).
- Astwood, E.B., Cassidy, C.E., Auerbach, G.D. Treatment of goiter and thyroid nodules with thyroid. *Journal of the American Medical Association*, 174, 459-464 (1960).
- Bakke, J.L., Kammer, H., Lawrence, N. Effect of thyroid hormone on human pituitary thyroid-stimulating hormone content. *Journal of Clinical Endocrinology and Metabolism*, 24, 281-284 (1964).
- Baldwin, W.W. Some cases of Graves' disease, succeeded by thyroid atrophy. *Lancet* i, 145-146 (1895).
- Bartels, E.C. Post-thyroidectomy myxoedema after preoperative use of antithyroid drugs. *Journal of Clinical Endocrinology and Metabolism*, 13, 95-106 (1953).
- Bastenie, P.A., Neve P., Bonnyns, M., Vanhaelst, L., Chailly, M. Clinical and pathological significance of asymptomatic atrophic thyroiditis. *Lancet*, i, 915-919 (1967a).
- Bastenie, P.A., Vanhaelst, L., Neve, P. Coronary-artery disease in hypothyroidism: observations in preclinical myxoedema. *Lancet*, ii, 1221-1222 (1967b).
- Bastenie, P.A., Vanhaelst, L., Bonnyns, M., Neve, P., Staquet, M. Preclinical hypothyroidism: a risk factor for coronary heart disease. *Lancet*, i, 203-204 (1971).
- Bayliss, R.I.S. Stimulation and suppression test of thyroid function. *Proceedings of the Royal Society of Medicine*, 60, 303-306 (1967).
- Beahrs, O.H., Sakulsky, S.B. Surgical thyroidectomy in the management of exophthalmic goiter. *Archives of Surgery*, 96, 512-515, (1968).
- Beckers, C., Cornette, C. TSH production rate in non-toxic goiter. *Journal of Clinical Endocrinology and Metabolism*, 32, 852-854 (1971).
- Beling, U., EINHORN, J. Incidence of hypothyroidism and recurrences following I^{131} treatment of hyperthyroidism. *Acta Radiologica*, 56, 275-288 (1961).
- Bellarbarba, D., Benard, B., Langlois, M. Pattern of serum thyroxine, triiodothyronine and thyrotrophin after treatment of thyrotoxicosis. *Clinical Endocrinology*, 1, 345-353 (1972).
- Bishopric, G.A., Garrett, N.H., Nicholson, W.M. Clinical value of the TSH test in the diagnosis of thyroid diseases. *American Journal of Medicine*, 18, 15-19 (1955).

- Bottazzo, G.F., Pouplard, A., Florin-Christensen, A., Doniach D. Autoantibodies to prolactin-secreting cells of human pituitary. *Lancet*, ii, 97-101 (1975).
- Bowden, A.N., Rose, F.C. Investigation of endocrine exophthalmos. *Proceedings of the Royal Society of Medicine*, 62, 13-15 (1969).
- Bowers, C.Y., Schally, A.V., Reynolds, G.A., Hawley, W.D. Interactions of L-thyroxine or L-triiodothyronine and thyrotropin-releasing factor on the release and synthesis of thyrotropin from the anterior pituitary gland in mice. *Endocrinology*, 81, 741-747 (1967).
- Bowers, C.Y., Schally, A.V., Hawley, W.D., Gual, C., Parlow, A. Effect of thyrotropin-releasing factor in man. *Journal of Clinical Endocrinology and Metabolism*, 28, 978-982 (1968a).
- Bowers, C.Y., Lee, K-L., Schally, A.V. Effect of actinomycin D on hormones that control the release of thyrotropin from the anterior pituitary glands in mice. *Endocrinology*, 82, 303-310 (1968b).
- Bowers, C.Y., Schally, A.V., Schalch, D.S., Gual, C., Kastin, A.J., Folkers, K. Activity and specificity of synthetic thyrotropin-releasing hormone in man. *Biochemical and Biophysical Research Communications*, 39, 352-355 (1970).
- Bowers, C.Y., Friesen, H.G., Hwang, P., Guyda, H.J., Folkers, K. Prolactin and thyrotropin release in man by synthetic pyroglutamyl-histidyl-prolinamide. *Biochemical and Biophysical Research Communications*, 45, 1033-1041 (1971).
- Boyd, E.M., Connell, W.F. Plasma lipids in the diagnosis of mild hypothyroidism. *Quarterly Journal of Medicine*, 30, 467-471 (1937).
- Boyle, C.M. Scottish automated follow-up register for thyroid disease: four years' experience in Glasgow. *British Medical Journal*, 2, 490-492 (1974).
- Bray, G.A. Increased sensitivity of the thyroid in iodine-depleted rats to the goitrogenic effects of thyrotropin. *Journal of Clinical Investigation*, 47, 1640-1647 (1968).
- Bremner, W.F., McDougall, I.R., Greig, W.R. Results of treating 297 thyrotoxic patients with ¹²⁵I. *Lancet*, ii, 281-282 (1973).
- Buchanan, W.W., Koutras, D.A., Crooks, J., Alexander W.D., Brass, W., Anderson, J.R., Goudie, R.B., Gray, K.G. The clinical significance of the complement-fixation test in thyrotoxicosis. *Journal of Endocrinology*, 24, 115-125 (1962).
- Burgus, R., Dunn, T.F., Ward, D.N., Vale, W., Amoss, A., Guillemin, R. Dérivés polypeptidiques de synthèse doués d'activité hypophysiotrope TRF. *Comptes Rendus Hebdomadaires des Seances de l'Academie des Sciences (Paris)*, 268, 2116-2118 (1969).
- Burgus, R., Dunn, T.F., Desiderio, D., Ward, D.N., Vale, W., Guillemin, R. Characterisation of bovine hypothalamic hypophysiotropic TSH-releasing factor. *Nature*, 226, 321-325 (1970).

- Burke, G. The triiodothyronine suppression test. *American Journal of Medicine*, 42, 600-608 (1967).
- Burke, G. The thyrotrophin stimulation test. *Annals of Internal Medicine*, 69, 1127-1139 (1968).
- Burr, W.A., Griffiths, R.S., Black, R., Hoffenberg, R., Meinhold, H., Wenzel, K.W. Serum triiodothyronine concentrations after surgical operation. *Lancet*, ii, 1277-1279 (1975).
- Buttfield, I.H., Black, M.L., Hoffman, J.J., Mason E., Welby, M.L., Good, B.F. Studies on the control of thyroid function in endemic goiter in Eastern New Guinea. *Journal of Clinical Endocrinology and Metabolism*, 26, 1201-1207 (1966).
- Challand, G.S., Ratcliffe, W.A., Ratcliffe, J.G. Semiautomated radioimmunoassays for total serum thyroxine and triiodothyronine. *Clinica Chimica Acta*, 60, 25-32 (1975).
- Cole, E.N., Boyns, A.R. Radioimmunoassay for human pituitary prolactin using antiserum against an extract of human amniotic fluid. *Hormone Research*, 4, 261-273 (1973).
- Costom, B.H., Grumbach, M.M., Kaplan, S.L. Effect of thyrotropin-releasing factor on serum thyroid-stimulating hormone: an approach to distinguishing hypothalamic from pituitary forms of idiopathic hypopituitary dwarfism. *Journal of Clinical Investigation*, 50, 2219-2225 (1971).
- Crile, G., McCullagh, E.P. The treatment of hyperthyroidism. *Annals of Surgery*, 134, 18-28 (1951).
- Das, G., Kreiger, M. Treatment of thyrotoxic storm with intravenous propranolol. *Annals of Internal Medicine*, 70, 985-988 (1969).
- Delange, F.M. Hershman, J.M., Ermans, A.M. Relationship between the serum thyrotropin level, the prevalence of goiter and the pattern of iodine metabolism in Idjwi Island. *Journal of Clinical Endocrinology and Metabolism*, 33, 261-268 (1971).
- Demeester-Mirkine, N., Brauman, H., Corvilain, J. Delayed adjustment of the pituitary response to variations in circulating thyroid hormones in a case of subacute thyroiditis. *Clinical Endocrinology*, 5, 9-13 (1976).
- Dobyns, B.M., Sheline, G.E., Workman, J.B., Tomkins, E.A., McConahey, W.M., Becker, D.V. Malignant and benign neoplasms of the thyroid in patients treated for hyperthyroidism: a report of the Cooperative Thyrotoxicosis Follow-up study. *Journal of Clinical Endocrinology and Metabolism*, 38, 976-998 (1974).
- Doniach, D., Roitt, I.M. Thyroid auto-allergic disease. In: *Clinical Aspects of Immunology*, 3rd ed. pp 1355-1386. Eds. P.G.H. Gell, R.R.A. Coombs, P.J. Lachmann. Oxford, Blackwell Scientific Publications (1975).

- Doniach, I. In: *The Thyroid*. 3rd ed. pp 185-192. Eds. S. Werner and S. Ingbar. New York, Harper & Row (1971).
- Dresner, S., Schneeberg, N.G. Rapid radioiodine suppression test using triiodothyronine. *Journal of Clinical Endocrinology and Metabolism*, 18, 797-799 (1958).
- Dunn, J.T., Chapman, E.M. Rising incidence of hypothyroidism after radioactive iodine therapy in thyrotoxicosis. *New England Journal of Medicine*, 271, 1037-1042 (1964).
- Einhorn, J. Studies on the effect of thyrotropic hormone on the thyroid function in man. *Acta Radiologica: Supplement* 160 (1958).
- Einhorn, J., Larssen, L-G. Studies on the effect of thyrotropin on human thyroid function. *Journal of Clinical Endocrinology and Metabolism*, 19, 28-34 (1959).
- Evered, D., Hall, R. Hypothyroidism. *British Medical Journal*, 1, 290-293 (1972).
- Evered, D., Ormston, B.J., Smith, P.A., Hall, R., Bird, T. Grades of hypothyroidism. *British Medical Journal*, 1, 657-662 (1973a).
- Evered, D., Young, E.T., Ormston, B.J., Menzies, R., Smith, P.A., Hall, R. Treatment of hypothyroidism: a reappraisal of thyroxine therapy. *British Medical Journal*, 3, 131-134 (1973b).
- Evered, D.C., Clark, F., Petersen, V.B. Thyroid function in euthyroid subjects with autonomous thyroid nodules. *Clinical Endocrinology*, 3, 149-154 (1974).
- Evered, D., Young, E.T., Tunbridge, W.M.G., Ormston, B.J., Green, E., Petersen, V.B., Dickinson, P.H. Thyroid function after subtotal thyroidectomy for hyperthyroidism. *British Medical Journal*, 1, 25-27 (1975).
- Faglia, G., Beck-Peccoz, P., Ambrosi, B., Ferrari, C., Travaglini, P. The effects of a synthetic thyrotropin-releasing hormone in normal and endocrinopathic subjects. *Acta Endocrinologica*, 71, 209-225 (1972).
- Faglia, G., Beck-Peccoz, P., Ferrari, C., Ambrosi B., Spada, A., Travaglini, P. Enhanced plasma thyrotrophin response to thyrotrophin-releasing hormone following oestradiol administration in man. *Clinical Endocrinology*, 2, 207-210 (1973).
- Fleischer, N., Burgus, R., Vale, W., Dunn, T.F., Guilleman, R. Preliminary observations on the effect of synthetic thyrotropin-releasing factor on plasma thyrotropin levels in man. *Journal of Clinical Endocrinology and Metabolism*, 31, 109-112 (1970).
- Fletcher, R.F., Besford, H. A test of thyroid and pituitary function using thyrotrophin. *Clinical Science*, 17, 113-120 (1957).
- Foley, T.P., Owings, J., Hayford, J.T., Blizzard, R.M. Serum thyrotropin responses to synthetic thyrotropin-releasing hormone in normal children and hypopituitary patients. *Journal of Clinical Investigation*, 51, 431-437 (1972).

- Folkers, K., Enzmann, F., Boler, J., Bowers, C.Y., Schally, A.V. Discovery of modification of the synthetic tripeptide sequence of the thyrotropin releasing hormone having activity. *Biochemical and Biophysical Research Communications*, 37, 123-126 (1969).
- Fowler, P.B.S., Swale, J. Premyxoedema and coronary-artery disease. *Lancet*, i, 1077-1079 (1967).
- Fowler, P.B.S., Swale, J., Andrews, H. Hypercholesterolaemia in borderline hypothyroidism: stage of premyxoedema. *Lancet*, ii, 488-491 (1970).
- Franco, J., Coppler, M., Kovalski, B. Propranolol and ¹³¹I in the treatment of diffuse thyroid hyperplasia with hyperthyroidism. *Journal of Nuclear Medicine*, 11, 219-220 (1970).
- Friis, T., Christensen, L.K., Andersen, M.S. The value of the thyrotropin stimulation test in the diagnosis of myxoedema. *Acta Medica Scandinavica*, 163, 507-514 (1959).
- Friis, T. On the effect of l-triiodothyronine on the thyroid gland and its clinical application. *Acta Medica Scandinavica*, 173, 569-587 (1963).
- Furman, R.H., Howard, R.P., Lakshmi, K., Norcia, L.N. The serum lipids and lipoproteins in normal and hyperlipidaemic subjects as determined by preparative ultracentrifugation. *American Journal of Clinical Nutrition*, 9, 73-102 (1961).
- Georges, L.P., Santangelo, R.P., Mackin, J.F., Canary, J.J. Metabolic effects of propranolol in thyrotoxicosis I. Nitrogen, Calcium and Hydroxyproline. *Metabolism*, 24, 11-21 (1975).
- Gillespie, F.C., Orr, J.S., Greig, W.R. Microscopic dose distribution from ¹²⁵I in the toxic thyroid gland and its relation to therapy. *British Journal of Radiology*, 43, 40-47 (1970).
- Gillessen, D., Felix, A.M., Lergier, W., Studer, R.O. Synthese des "Thyrotropin-releasing" Hormons (TRH) (Schaf) und Verwandter peptide. *Helvetica Chimica Acta*, 53, 63-72 (1970).
- Gitelman, H.J. An improved automated procedure for the determination of calcium in biological specimens. *Annals of Biochemistry*, 18, 520-531 (1967).
- Glatstein, E., McHardy-Young, S., Brast, N., Eltringham, J., Kriss, J.P. Alterations in serum thyrotropin (TSH) and thyroid function following radiotherapy in patients with malignant lymphoma. *Journal of Clinical Endocrinology and Metabolism*, 32, 833-841 (1971).
- Glennon, J.A., Gordon, E.S., Sawin, C. Hypothyroidism after low-dose ¹³¹I treatment of hyperthyroidism. *Annals of Internal Medicine*, 76, 721-723 (1972).
- Goolden, A.W.G., Fraser, T.R. Treatment of thyrotoxicosis with low doses of radioactive iodine. *British Medical Journal*, 3, 442-443 (1969).
- Gordin, A., Heinonen, O.P., Saarinen, P., Lamberg, B-A. Serum-thyrotrophin in symptomless autoimmune thyroiditis. *Lancet*, i, 551-554 (1972).

- Gordin, A., Saarinen, P., Pelkonen, R., Lamberg, B-A. Serum thyrotrophin and the response to thyrotrophin-releasing hormone in symptomless autoimmune thyroiditis and in borderline and overt hypothyroidism. *Acta Endocrinologica*, 75, 274-285 (1974).
- Gowan, B.C. Myxoedema and its relation to Graves' disease. *Lancet* i, 478-480 (1895).
- Green, M., Wilson, G.M. Thyrotoxicosis treated by surgery or iodine ¹³¹I: with special reference to development of hypothyroidism. *British Medical Journal*, 1, 1005-1010 (1964).
- Greenberg, A.H., Czernichow, P., Hung, W., Shelley, W., Winship, T., Blizzard, R.M. Juvenile chronic lymphocytic thyroiditis: clinical laboratory and histological correlations. *Journal of Clinical Endocrinology and Metabolism*, 30, 293-301 (1970).
- Greene, R. The significance of lymphadenoid changes in the thyroid gland. *Journal of Endocrinology*, 7, 1-6 (1950-51).
- Greer, M.A. The effect on endogenous thyroid activity of feeding dessicated thyroid to normal human subjects. *New England Journal of Medicine*, 244, 385-390 (1951).
- Greer, M.A., Astwood, E.B. Treatment of simple goiter with thyroid. *Journal of Clinical Endocrinology and Metabolism*, 13, 1312-1331 (1953).
- Greer, M.A., Smith, G.E. Method for increasing the accuracy of the radioiodine uptake as a test for thyroid function by the use of dessicated thyroid. *Journal of Clinical Endocrinology and Metabolism*, 14, 1374-1384 (1954).
- Greig, W.R., Smith, J.F.B., Gillespie, F.C., Thomson, J.A., McGirr, E.M. Iodine-125 treatment for thyrotoxicosis. *Lancet*, i, 755-757 (1969).
- Greig, W.R. Radioactive iodine therapy for thyrotoxicosis. *British Journal of Surgery*, 60, 758-765 (1973).
- Gual, C., Wilber, J.F., Tello, C., Rios, E. Administration of synthetic thyrotrophin-releasing hormone (TRH) as a clinical test for pituitary thyrotrophin reserve. *Revista de Investigacion Clinica*, 24, 35-55 (1972).
- Guillemin, R., Yamakazi, E., Jutisz, M., Sakiz, E. Presence dans un extrait de tissus hypothalamiques d'une substance stimulant la secretion de l'hormone hypophysaire thyreotrope (TSH). Premiere purification par filtration sur gel Sephadex. *Comptes Rendus Hebdomadaires des Seances de l'Academie des Sciences (Paris)*, 255, 1018-1020 (1962).
- Guillemin, R., Yamakazi, E., Gard, D., Jutisz, M., Sakiz, E. In vitro secretion of thyrotrophin (TSH): stimulation by a hypothalamic peptide (TRF). *Endocrinology*, 73, 564-572 (1963).
- Guillemin, R., Sakiz, E., Ward, D.N. Further purification of TSH-releasing factor (TRF) from sheep hypothalamic tissues, with observations on the amino-acid composition. *Proceedings of the Society for Experimental Biology and Medicine*, 118, 1132-1137 (1965).

Hadden, D.R., Montgomery, D.A.D., Shanks, R.G., Weaver, J.A. Propranolol and iodine-131 in the management of thyrotoxicosis. *Lancet*, ii, 852-854 (1968).

Hagen, G.A. Treatment of thyrotoxicosis with ¹³¹I and post therapy hypothyroidism. *Medical Clinics of North America*, 52, 417-429 (1968).

Haigler, D.E., Pittman, J.A., Hershman, J.M., Baugh, C.M. Direct evaluation of pituitary thyrotropin reserve utilising synthetic thyrotropin-releasing hormone. *Journal of Clinical Endocrinology and Metabolism*, 33, 573-581 (1971).

Hall, R., Kirkham, K., Doniach, D., El Kabir, D. Ophthalmic Graves' disease. *Lancet*, i, 375-378 (1970a).

Hall, R., Amos, J., Garry, R., Buxton, R.L. Thyroid stimulating hormone response to synthetic thyrotropin-releasing hormone in man. *British Medical Journal*, ii, 274-277 (1970b).

Hall, R., Amos, J., Ormston, B. Radioimmunoassay of human serum thyrotrophin. *British Medical Journal*, 1, 582-585 (1971).

Hall, R., Ormston, B.J., Besser, G.M., Cryer, R.J., McKendrick, M. The thyrotrophin-releasing hormone test in diseases of the pituitary and hypothalamus. *Lancet*, i, 759-763 (1972).

Harris, G.W. Neural control of the pituitary gland. Arnold; London 1955.

Hayek, A., Chapman, E.M., Crawford, J.D. Long-term results of treatment of thyrotoxicosis in children and adolescents with radioactive iodine. *New England Journal of Medicine*, 283, 949-953 (1970).

Hedley, A.J., Scott, A.M., Weir, R.D., Crooks, J. Computer-assisted follow-up Register for the North-east of Scotland. *British Medical Journal*, 1, 556-558 (1970).

Hedley, A.J., Hall, R., Amos, J., Michie, W., Crooks, J. Serum thyrotropin levels after subtotal thyroidectomy for Graves' disease. *Lancet*, i, 455-458 (1971a).

Hedley, A.J., Ross, I.P., Beck, J.S., Donald, D., Albert-Recht, F., Michie, W., Crooks, J. Recurrent thyrotoxicosis after subtotal thyroidectomy. *British Medical Journal*, iv, 258-261 (1971b).

Hershman, J.M., Pittman, J.A. Response to synthetic thyrotropin-releasing hormone in man. *Journal of Clinical Endocrinology and Metabolism*, 31, 457-460 (1970).

Hershman, J.M., Pittman, J.A. Utility of the radioimmunoassay of serum thyrotrophin in man. *Annals of Internal Medicine*, 74, 481-490 (1971).

Hershman, J.M., Edwards, C.L. Serum thyrotropin (TSH) levels after thyroid ablation compared with TSH levels after exogenous bovine TSH: implications for ¹³¹I treatment of thyroid carcinoma. *Journal of Clinical Endocrinology and Metabolism*, 34, 814-818 (1972).

- Hobbs, J.R., Bayliss, R.I.S., MacLagan, N.F. The routine use of iodine-132 in the diagnosis of thyroid disease. *Lancet*, i, 8-10, (1963).
- Howitt, G., Rowlands, D.J. Beta-sympathetic blockade in hyperthyroidism. *Lancet*, i, 628-631 (1966).
- Irie, M., Tsushima, T. Increase of serum growth hormone concentration following the thyrotropin-releasing hormone injection in patients with acromegaly or gigantism. *Journal of Clinical Endocrinology and Metabolism*, 35, 97-100 (1972).
- Irvine, W.J., MacGregor, A.G., Stuart, A.E. The prognostic significance of thyroid antibodies in the management of thyrotoxicosis. *Lancet*, ii, 843-847 (1962).
- Irvine, W.J., Stewart, A.G. Prognostic significance of thyroid antibodies in the management of thyrotoxicosis. In "Thyrotoxicosis" pp. 111-120 (Ed. Irvine, W.J.) Livingstone, Edinburgh (1967).
- Irvine, W.J., Toft, A.D., Hunter, W.M., Kirkham, K.E. An assessment of plasma TSH radioimmunoassay and of the TSH stimulation test in the diagnosis of 100 consecutive patients with suspected hypothyroidism. *Clinical Endocrinology*, 2, 135-139 (1973).
- Jacobs, L.S., Snyder, P.J., Wilber, J.F., Utiger, R.D., Daughaday, W.A. Increased serum prolactin after administration of synthetic thyrotropin-releasing hormone (TRH) in man. *Journal of Clinical Endocrinology and Metabolism*, 33, 996-998 (1971).
- Jasani, M.K., Boyle, J.A., Greig, W.R., Dalakos, T.G., Browning, M.C.K., Thompson, A., Buchanan, W.W. Corticosteroid-induced suppression of the hypothalamo-pituitary-adrenal axis; observations on patients given oral corticosteroids for rheumatoid arthritis. *Quarterly Journal of Medicine*, 36, 261-276 (1967).
- Jefferies, W. McK., Levy, R.P., Palmer, W.G., Storaasli, J.P., Kelly, L.W. The value of a single injection of thyrotropin in the diagnosis of obscure hypothyroidism. *New England Journal of Medicine*, 249, 876-884 (1953).
- Jefferies, W. McK., Kelly, L.W., Levy, R.P., Cooper, G.W., Prouty, R.L. The significance of low thyroid reserve. *Journal of Clinical Endocrinology and Metabolism*, 16, 1438-1455 (1956).
- Kajubi, S.K. Thyroid-stimulating hormone and endemic goitre. *Lancet*, ii, 83-84 (1975).
- Kammer, G.M., Hamilton, C.R. Acute bulbar muscle dysfunction and hyperthyroidism. *American Journal of Medicine*, 56, 464-470 (1974).
- Kessler, G., Lederer, H. In: Automation in analytical chemistry (Ed. L.T. Skeggs) pp. 341-356. New York (1965).
- Kochupillai, N., Deo, M.G., Karmarkar, M.G., McKendrick, M., Weightman, D., Evered, D.C., Hall, R., Ramalingaswami, V. Pituitary-thyroid axis in Himalayan endemic goitre. *Lancet*, i, 1021-1024 (1973).

- Kotler, M.N., Berman, L., Rubenstein, A.H. Hypoglycaemia precipitated by propranolol. *Lancet* ii, 1389-1390 (1966).
- Kristensen, H.P.O., Dyrbye, M., Christensen, L.K., The triiodothyronine suppression test. *Acta Medica Scandinavica*, 173, 411-422 (1963).
- Krugman, L.G., Hersman, J.M., Chopra, I.J., Levine, G.A., Pékary, A.E., Geffner, D.L., Chua Teco, G.N. Patterns of recovery of the hypothalamic-pituitary-thyroid axis in patients taken off chronic thyroid therapy. *Journal of Clinical Endocrinology and Metabolism*, 41, 70-80 (1975).
- Lamberg, B-A., Hernberg, C.A., Hakmila, R. Treatment of non-toxic goitre with thyroid preparations. *Acta Endocrinologica*, 33, 584-592 (1960).
- Landon, J., Wynn, V., James, V.H.T., Wood, J.B. Adrenal response to infused corticotropin in subjects receiving glucocorticoids. *Journal of Clinical Endocrinology and Metabolism*, 25, 602-611 (1965).
- Lawton, N.F., Ekins, R.P., Nabarro, J.D.N. Failure of pituitary-response to thyrotrophin-releasing hormone in euthyroid Graves' disease. *Lancet*, ii, 14-16 (1971).
- Lee, T.C., Coffey, R.J., Mackin, J., Cobb, M., Routon, J., Canary, J.J. The use of propranolol in the surgical treatment of thyrotoxic patients. *Annals of Surgery*, 177, 643-646 (1973).
- Levine, J., Zak, B. Automated determination of serum total cholesterol. *Clinica Chimica Acta* 10, 381-384 (1964).
- L'Hermite, M., Vanhaelst, L., Copinschi, G., Leclercq, R., Golstein, J., Bruno, O.D., Robyn, C. Prolactin release after injection of thyrotrophin-releasing hormone in man. *Lancet*, i, 763-765 (1972).
- Livanou, T., Ferriman, D., James, V.H.T. Recovery of hypothalamo-pituitary-adrenal function after corticosteroid therapy. *Lancet*, ii, 856-859 (1967).
- McConnon, J., Row, V.V., Volpe, R. Simultaneous comparative studies of thyroxine and triiodothyronine distribution and disposal rates. *Journal of Endocrinology*, 51, 17-30 (1971).
- McDougall, I.R., Greig, W.R., Gillespie, F.C. Radioactive iodine (¹²⁵I) therapy for thyrotoxicosis. *New England Journal of Medicine*, 285, 1099-1104 (1971a).
- McDougall, I.R., Kennedy, J.S., Thomson, J.A. Thyroid carcinoma following iodine-131 therapy. Report of a case and review of the literature. *Journal of Clinical Endocrinology and Metabolism*, 33, 287-292 (1971b).
- McIntosh, D. Surgery of the thyroid gland. *Journal of the Royal College of Surgeons of Edinburgh*. (1976) (In press).
- McLaren, E.H., Hendricks, S., Pimstone, B.L. thyrotrophin responses to intravenous thyrotrophin-releasing hormone in patients with hypothalamic and pituitary disease. *Clinical Endocrinology*, 3, 113-122 (1974).

- McLarty, D.G., Brownlie, B.E.W., Alexander, W.D., Papapetrou, P.D., Horton, P. Remission of thyrotoxicosis during treatment with propranolol. *British Medical Journal*, 2, 332-334 (1973).
- McNeill, A.D., Thomson, J.A. Long-term follow-up of surgically treated thyrotoxic patients. *British Medical Journal*, 3, 643-646 (1968).
- Masi, A.T. Potential uses and limitations of hospital data in epidemiologic research. *American Journal of Public Health*, 55, 658-667 (1965).
- Mason, R.L., Hunt, H.M., Hurxthal, L. Blood cholesterol values in hyperthyroidism and hypothyroidism - their significance. *New England Journal of Medicine*, 203, 1273-1278 (1930).
- Mattingly, D. A simple fluorimetric method for the estimation of free 11-hydroxycorticoids in human plasma. *Journal of Clinical Pathology*, 15, 374-379 (1962).
- Mayberry, W.E., Gharib, H., Bilstad, J.M., Sizemore, G.W. Radio-immunoassay for human thyrotrophin. *Annals of Internal Medicine*, 74, 471-480 (1971).
- Mazzaferri, E.L., Reynolds, J.C., Young, R.L., Thomas, C.N., Parisi, A. Propranolol as primary therapy for thyrotoxicosis. *Archives of Internal Medicine*, 136, 50-56 (1976).
- Michie, W., Pegg, C.A.S., Bewsher, P.D. Prediction of hypothyroidism after partial thyroidectomy for thyrotoxicosis. *British Medical Journal*, 1, 13-17 (1972).
- Michie, W., Pegg, C.A.S., Hamer-Hodges, D.W., Orr, F.G.G., Bewsher, P.D. Beta-blockade and partial thyroidectomy for thyrotoxicosis. *Lancet*, i, 1009-1011 (1974).
- Morgans, M.E., Oldham, A.K., Trotter, W.R. The effect of exogenous thyroxine on radioiodine uptake in normal subjects and in cases of thyrotoxicosis remission. *Journal of Endocrinology*, 8, 250-253 (1951-52).
- Mortimer, C.H., Besser, G.M., McNeilly, A.S., Tunbridge, W.M.G., Gomez-Pan, A., Hall, R. Interaction between secretion of the gonadotrophins, prolactin, growth hormone, thyrotrophin and corticosteroids in man: the effects of LH/FSH-RH, TRH and hypoglycaemia alone and in combination. *Clinical Endocrinology*, 2, 317-326 (1973).
- Motta, M., Fraschini, F., Martini, L. 'Short' feedback mechanisms in the control of anterior pituitary function. In: *Frontiers in Neuroendocrinology*, pp 211-253. Eds. L. Martini and W.F. Ganong. New York. Oxford University Press (1969).
- "
Muhlen, A., Hesch, R.D., Kobberling, J. The TRH test in the course of treatment of hyperthyroidism. *Clinical Endocrinology*, 4, 165-172 (1975).
- Mukhtar, E.D., Smith, B.R., Pyle, G.A., Hall, R., Vice, P. Relation of thyroid-stimulating immunoglobulins to thyroid function and effects of surgery, radioiodine and antithyroid drugs. *Lancet*, i, 713-715 (1975)

- Murray, S., Ezrin, C. Effect of Graves' disease on the 'thyrotroph' of the adenohypophysis. *Journal of Clinical Endocrinology and Metabolism*, 26, 287-293 (1966).
- Nair, R.M.G., Barrett, J.F., Bowers, C.Y., Schally, A.V. Structure of porcine thyrotropin releasing hormone. *Biochemistry*, 9, 1103-1106, (1970).
- Neilson, J.M.M. High speed analysis of ventricular arrhythmias from 24 hour recordings. In 'Computers in Cardiology' pp. 55-61 Institution of Electrical and Electronic Engineers, Chicago (1974).
- Nelson, J.C., Johnson, D.E., Odell, W. Serum TSH levels and the thyroidal response to TSH stimulation in patients with thyroid disease. *Annals of Internal Medicine*, 76, 47-52 (1972).
- Nofal, M.M., Beierwaltes, W.H., Patno, M.E. Treatment of hyperthyroidism with sodium iodide 131 . *Journal of the American Medical Association*, 197, 605-610 (1966).
- Odell, W.D., Wilber, J.F., Paul, W.E. Radioimmunoassay of thyrotropin in human serum. *Journal of Clinical Endocrinology and Metabolism*, 25, 1179-1188 (1965).
- Odell, W.D., Rayford, P.L., Ross, G.T. Simplified, partially automated method for radioimmunoassay of human thyroid-stimulating, growth, luteinizing and follicle-stimulating hormones. *Journal of Laboratory and Clinical Medicine*, 70, 973-980 (1967a).
- Odell, W.D., Wilber, J.F., Utiger, R.D. Studies of thyrotropin physiology by means of radioimmunoassay. *Recent Progress in Hormone Research*, 23, 47-85 (1967b).
- Ogihara, T., Yamamoto, T., Fukuchi, M., Oki, K. Serum thyrotropin levels of natives in Sarawak, Borneo Island. *Journal of Clinical Endocrinology and Metabolism*, 35, 711-715 (1972).
- Olsen, W.R., Nishiyama, R.H., Graber, L.W. Thyroidectomy for hyperthyroidism. *Archives of Surgery*, 101, 175-180 (1970).
- Ormston, B.J., Kilborn, J.R., Garry, R., Amos, J., Hall, R. Further observations on the effect of synthetic thyrotropin-releasing hormone in man. *British Medical Journal*, 2, 199-202 (1971a).
- Ormston, B.J., Garry, R., Cryer, R.J., Besser, G.M., Hall, R. Thyrotrophin-releasing hormone as a thyroid function test. *Lancet*, ii, 10-14 (1971b).
- Ormston, B.J., Alexander, L., Evered, D.C., Clarke, F., Bird, T., Appleton, D., Hall, R. Thyrotrophin response to thyrotrophin-releasing hormone in ophthalmic Graves' disease: correlation with other aspects of thyroid function, thyroid suppressibility and activity of eye signs. *Clinical Endocrinology*, 2, 369-376 (1973).
- Patel, Y.C., Burger, H.G., Hudson, B. Radioimmunoassay of serum thyrotropin: sensitivity and specificity. *Journal of Clinical Endocrinology and Metabolism*, 33, 768-774 (1971).

- Patel, Y.C., Burger, H.G. Serum thyrotropin in pituitary and/or hypothalamic hypothyroidism; normal or elevated basal levels and paradoxical responses to thyrotropin-releasing hormone. *Journal of Clinical Endocrinology and Metabolism*, 37, 190-196 (1973).
- Perlmutter, M., Slater, S. Use of thyroid hormone to differentiate between hyperthyroidism and euthyroidism. *Journal of the American Medical Association*, 158, 718-720 (1955).
- Perloff, W.H., Levy, L.M., Despopoulos, A. The use of thyrotropic hormone (TSH) in the diagnosis of myxoedema. *Journal of Clinical Endocrinology and Metabolism*, 11, 1495-1502 (1951).
- Pimstone, N., Marine, M., Pimstone, B. Beta-adrenergic blockade in thyrotoxic myopathy. *Lancet* ii, 1219-1220 (1968).
- Pisarev, M.A., Utiger, R.D., Salvaneschi, J.P., Altschuler, N., DeGroot, L.J. Serum TSH and thyroxine in goitrous subjects in Argentina. *Journal of Clinical Endocrinology and Metabolism*, 30, 680-681 (1970).
- Pochin, E.E. Leukaemia following radioiodine treatment of thyrotoxicosis. *British Medical Journal*, 2, 1545-1550 (1960).
- Querido, A., Stanbury, J.B. The response of the thyroid gland to thyrotropic hormone as an aid in the differential diagnosis of primary and secondary hypothyroidism. *Journal of Clinical Endocrinology and Metabolism*, 10, 1192-1201 (1950).
- Roy, A.D., Allan, J., Harden, R.McG. A follow-up of thyrotoxic patients treated by partial thyroidectomy. *Lancet*, ii, 684-688 (1967).
- Rundle, F.F., Wilson, C.W. Assymetry of exophthalmos in orbital tumour and Graves' disease. *Lancet*, i, 51-52 (1945).
- Saenger, E.L., Thomas, G.E., Tomkins, E.A. Incidence of leukaemia following treatment of hyperthyroidism. *Journal of the American Medical Association*, 205, 855-862 (1968).
- Safa, M., Schumacher, P., Rodriguez-Antunez, A. Long-term follow-up results in children and adolescents treated with radioactive iodine (^{131}I) for hyperthyroidism. *New England Journal of Medicine*, 292, 167-171 (1975).
- Sanchez-Franco, F., Garcia, M.D., Cacicedo, L., Martin-Zurro, A., Escobar Del Rey, F., Morreale De Escobar, G. Transient lack of thyrotropin response to thyrotropin-releasing hormone in treated hyperthyroid patients with normal or low serum thyroxine and triiodothyronine. *Journal of Clinical Endocrinology and Metabolism*, 38, 1098-1102 (1974).
- Schalch, D.S., Gonzalez-Barcena, D., Kastin, A.J., Schally, A.V., Lee, L.A. Abnormalities in the release of TSH in response to thyrotrophin-releasing hormone (TRH) in patients with disorders of the pituitary, hypothalamus and basal ganglia. *Journal of Clinical Endocrinology and Metabolism*, 35, 609-615 (1972).
- Schally, A.V., Bowers, C.Y., Redding, T.W., Barret, J.F. Isolation of thyrotropin releasing factor (TRF) from porcine hypothalamus. *Biochemical and Biophysical Research Communications*, 25, 165-169 (1966a).

- Schally, A.V., Bowers, C.Y., Redding, T.W. Purification of thyrotropic-hormone-releasing factor from bovine hypothalamus. *Endocrinology*, 78, 726-732 (1966b).
- Schally, A.V., Muller, E.E., Arimura, A., Bowers, C.Y., Saito, T., Redding, T., Sawano, S., Pizzolato, P. Releasing factors in human hypothalamic and neurohypophysial extracts. *Journal of Clinical Endocrinology and Metabolism*, 27, 755-762 (1967).
- Schally, A.V., Arimura, A., Bowers, C.Y., Kastin, A.J., Sawano, S., Redding, T.W. Hypothalamic neurohormones regulating anterior pituitary function. *Recent Progress in Hormone Research*, 24, 497-588 (1968).
- Schally, A.V., Redding, T.W., Bowers, C.Y., Barrett, J.F. Isolation and properties of porcine thyrotropin-releasing hormone. *Journal of Biological Chemistry*, 244, 4077-4088 (1969).
- Schneeberg, N.G., Perloff, W.H., Levy, L.M. Diagnosis of equivocal hypothyroidism, using thyrotropic hormone (TSH). *Journal of Clinical Endocrinology and Metabolism*, 14, 223-231 (1954).
- Schreiber, V., Rybák, M., Eckertová, A., Jirgl, V., Kočí, J., Franc, Z., Kmentová, V. Isolation of a hypothalamic peptide with TRF activity in vitro. *Experientia*, 18, 338-340 (1962).
- Scowen, E.F. Effects of the thyrotropic hormone of the anterior pituitary in man. *Lancet* ii, 799-802 (1937).
- Seth, J. Work simplification of a competitive protein binding analysis for serum thyroxine, and a study of some laboratory factors affecting assay results. *Clinica Chimica Acta*, 46, 431-441 (1973).
- Seth J., Rutherford, F., McKenzie, I. Solid-phase radioimmunoassay of thyroxine in untreated serum. *Clinical Chemistry*, 21, 1406-1413 (1975).
- Seth, J., Toft, A.D., Irvine, W.J. Simple solid-phase radioimmunoassays for total tri-iodothyronine and thyroxine in serum and their clinical evaluation. *Clinica Chimica Acta*, 68, 291-301 (1976).
- Shand, D.G., Nuckolls, E.M., Oates, J.A. Plasma propranolol levels in adults with observations in four children. *Clinical Pharmacology and Therapeutics*, 11, 112-120 (1970).
- Shanks, R.G., Hadden, D.R., Lowe, D.C., McDevitt, D.G., Montgomery, D.A.D. Controlled trial of propranolol in thyrotoxicosis. *Lancet*, i, 993-994 (1969).
- Shimaoka, K., Sokal, J.E. Suppressive therapy of non-toxic goiter. *American Journal of Medicine*, 57, 576-583 (1974).
- Siegel, S. In: *Non-parametric statistics for the behavioural sciences*. p. 116, McGraw, Hill. New York. 1956.
- Simpson, D. An automated method for the determination of serum organic iodine. *Clinical Chemistry*, 13, 890-899 (1967).
- Skillman, T.G., Mazzaferri, E.L., Gwinup, G. Random dosage of ^{131}I in the treatment of hyperthyroidism: results of a prospective study. *American Journal of Medical Science*, 257, 382-387 (1969).

- Slingerland, D.W., Hershman, J.M., Dell, E.S., Burrows, B.A. Thyrotropin and PBI in radioiodine-treated hyperthyroid patients. *Journal of Clinical Endocrinology and Metabolism*, 35, 912-917 (1972).
- Smith, R.N., Wilson, G.M. Clinical trial of different doses of ^{131}I in treatment of thyrotoxicosis. *British Medical Journal* 1, 129-132 (1967).
- Snyder, P.J., Utiger, R.D. Inhibition of thyrotropin response to thyrotropin-releasing hormone by small quantities of thyroid hormones. *Journal of Clinical Investigation*, 51, 2077-2084 (1972a).
- Snyder, P.J., Utiger, R.D. Response of thyrotropin releasing hormone (TRH) in normal man. *Journal of Clinical Endocrinology and Metabolism*, 34, 380-385 (1972b).
- Snyder, P.J., Utiger, R.D. Repetitive administration of thyrotropin-releasing hormone results in small elevations of serum thyroid hormones and in marked inhibition of thyrotropin response. *Journal of Clinical Investigation*, 52, 2305-2312 (1973).
- Snyder, P.J., Jacobs, L.S., Rabello, M.M., Sterling, F.H., Shore, R.N., Utiger, R.D., Daughaday, W.H. Diagnostic value of thyrotrophin-releasing hormone in pituitary and hypothalamic disease. *Annals of Internal Medicine*, 81, 751-757 (1974).
- Stanley, M.M., Astwood, E.B. The response of the thyroid gland in normal human subjects to the administration of thyrotropin, as shown with studies with iodine-131. *Endocrinology*, 44, 49-60 (1949).
- Starr, P., Jaffe, H.L., Oettinger, L. Later results of ^{131}I treatment of hyperthyroidism in 73 children and adolescents: 1967 follow-up. *Journal of Nuclear Medicine*, 10, 586-590 (1969).
- Sterling, K., Bellabarba, D., Newman, E.S., Brenner, M.A. Determination of triiodothyronine concentration in human serum. *Journal of Clinical Investigation*, 48, 1150-1158 (1969).
- Sterling, K., Brenner, M.A., Newman, E.S., Odell, W.D., Bellabarba, D. The significance of triiodothyronine (T_3) in maintenance of euthyroid status after treatment of hyperthyroidism. *Journal of Clinical Endocrinology and Metabolism*, 33, 729-731 (1971).
- Taunton, O.D., McDaniel, H.G., Pittman, J.A. Standardisation of TSH testing. *Journal of Clinical Endocrinology and Metabolism*, 25, 266-277 (1965).
- Taylor, S. The evolution of nodular goiter. *Journal of Clinical Endocrinology and Metabolism*, 13, 1232-1247 (1953).
- Taylor, S. Physiologic considerations in the genesis and management of nodular goiter. *American Journal of Medicine*, 20, 698-709 (1956).
- Taylor, S. The nodularity of nodular goitre. *Acta Endocrinologica. Supplement* 179, 59-60 (1973).
- Thomas, F.B., Caldwell, J.H., Greenberger, N.J. Steatorrhea in thyrotoxicosis. *Annals of Internal Medicine*, 78, 669-675 (1973).

- Thompson, W.O., Taylor, S.G., Thompson, P.K., Nadler, S.B., Dickie, L.F.N. The calorogenic action of extracts of the anterior lobe of the pituitary in man. *Endocrinology*, 20, 55-63 (1936).
- Thorson, S.C., Mincey, E.K., McIntosh, H.W., Morrison, R.T. Evaluation of a new in-vitro blood test for determining thyroid status: the effective thyroxine ratio. *British Medical Journal*, 2, 67-71 (1972).
- Toft, A.D., Seth, J., Kirkham, K.E., Marshall, A., Irvine, W.J. Assessment of in vitro thyroid function tests in 100 consecutive patients referred to a thyroid clinic. *Clinical Endocrinology*, 2, 127-134 (1973a).
- Toft, A.D., Boyns, A.R., Cole, E.N., Groom, G.V., Hunter, W.M., Irvine, W.J. The effect of thyrotrophin-releasing hormone on plasma prolactin and thyrotrophin levels in primary hypothyroidism. *Clinical Endocrinology*, 2, 289-295 (1973b).
- Toft, A.D., Barnes, E.W., Hunter, W.M., Seth, J., Irvine, W.J. Raised plasma thyroid stimulating hormone levels in thyrotoxic patients treated with iodine ¹³¹. *Lancet*, ii, 644-645 (1973c).
- Toft, A.D., Irvine, W.J., Hunter, W.M., Seth, J. Plasma TSH and serum T₄ levels in long-term follow-up of patients treated with ¹³¹I for thyrotoxicosis. *British Medical Journal*, 3, 152-153 (1974a).
- Toft, A.D., Irvine, W.J., Hunter, W.M., Ratcliffe, J.G., Seth, J. Anomalous plasma TSH levels in patients developing hypothyroidism in the early months after iodine-131 therapy for thyrotoxicosis. *Journal of Clinical Endocrinology and Metabolism*, 39, 607-609 (1974b).
- Toft, A.D., Irvine, W.J., Seth, J., Hunter, W.M., Cameron, E.H.D. Thyroid function in the long-term follow-up of patients treated with iodine-131 for thyrotoxicosis. *Lancet*, ii, 576-577 (1975).
- Toft, A.D., Irvine, W.J., Hunter, W.M. A comparison of plasma TSH levels in patients with diffuse and nodular non-toxic goiter. *Journal of Clinical Endocrinology and Metabolism*, 42, 973-976 (1976a).
- Toft, A.D., Irvine, W.J., McIntosh, D., Macleod, D.A.D., Seth, J., Cameron, E.H.D., Lidgard, G.P. Thyrotoxicosis treated by sub-total thyroidectomy under cover of Propranolol. (In press) (1976b).
- Treadwell, B.L.J., Savage, O., Sever, E.D., Copeman, W.S.C. Pituitary-adrenal function during corticosteroid therapy. *Lancet*, i, 355-358, (1963).
- Tunbridge, W.M.G., Harsoulis, P., Goolden, A.W.G. Thyroid function in patients treated with radioactive iodine for thyrotoxicosis. *British Medical Journal*, 2, 89-92 (1974).
- Utiger, R.D. Radioimmunoassay of human plasma thyrotropin. *Journal of Clinical Investigation*, 44, 1277-1286 (1965).
- Vagenakis, A.G., Braverman, L.E., Azizi, F., Portnay, G.I., Ingbar, S.H. Recovery of pituitary thyrotropic function after withdrawal of prolonged thyroid-suppression therapy. *New England Journal of Medicine*, 293, 681-684 (1975).

- Vanhaelst, L., Neve, P., Chailly, M., Bastenie, P.A. Coronary-artery disease in hypothyroidism: observations in clinical myxoedema. *Lancet*, ii, 800-802 (1967).
- Vinik, A.I., Pimstone, B.L., Hoffenberg, R. Sympathetic nervous system blocking in hyperthyroidism. *Journal of Clinical Endocrinology and Metabolism*, 28, 725-727 (1968).
- Wahner, H.W., Mayberry, W.E., Gaitan, E., Gaitan, J.E. Endemic goiter in the Cauca Valley. iii Role of serum TSH in goitrogenesis. *Journal of Clinical Endocrinology and Metabolism*, 32, 491-496 (1971).
- Wayne, E.J. Clinical and metabolic studies in thyroid disease. *British Medical Journal*, 1, 1-11 (1960).
- Weiner, L., Stout, B., Cox, J.W. Influence of beta sympathetic blockade (propranolol) on the haemodynamics of hypothyroidism. *American Journal of Medicine*, 46, 227-233 (1969).
- Werner, S.C., Hamilton, H., Nemeth, M. Graves' disease: hyperthyroidism or hyperpituitarism. *Journal of Clinical Endocrinology and Metabolism*, 12, 1561-1571 (1952).
- Werner, S.C. Euthyroid patients with early eye signs of Graves' disease. *American Journal of Medicine*, 18, 608-612 (1955).
- Werner, S.C., Spooner, M. A new and simple test for hyperthyroidism employing l-triiodothyronine and the twenty-four hour iodine-131 uptake method. *Bulletin of the New York Academy of Medicine*, 31, 137-145 (1955).
- Werner, S.C. Response to triiodothyronine as index of persistence of disease in the thyroid remnant of patients in remission from hyperthyroidism. *Journal of Clinical Investigation*, 35, 57-61 (1956).
- Werner, S.C., Johnson, P.M., Goodwin, P.N., Weiner, J.D., Lindeboom, G.A. Long-term results with iodine-125 treatment for toxic diffuse goitre. *Lancet*, ii, 681-685 (1970).
- Whitesell, F.B., Black, B.M. A statistical study of the clinical significance of lymphocytic and fibrocytic replacements in the hyperplastic thyroid gland. *Journal of Clinical Endocrinology and Metabolism*, 9, 1202-1215 (1949).
- Wise, P.H., Ahmad, A., Burnet, R.B., Harding, P.E. Intentional radioiodine ablation in Graves' disease. *Lancet*, ii, 1231-1233 (1975).
- Yeung, R.T., Tse, T.F. Thyrotoxic periodic paralysis. Effect of propranolol. *American Journal of Medicine*, 57, 584-590 (1974).
- Young, R.L., Harvey, W.C., Mazzaferri, E.L., Reynolds, J.C., Hamilton, C.R. Thyroid-stimulating hormone levels in idiopathic euthyroid goiter. *Journal of Clinical Endocrinology and Metabolism*, 41, 21-26 (1975).

AN ASSESSMENT OF PLASMA TSH
RADIOIMMUNOASSAY AND OF THE TSH
STIMULATION TEST IN THE DIAGNOSIS OF
100 CONSECUTIVE PATIENTS WITH
SUSPECTED HYPOTHYROIDISM

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SUMMARY

A plasma TSH estimation and a TSH stimulation test were performed on each of 100 consecutive patients seen at a thyroid clinic in whom it was necessary to exclude a diagnosis of hypothyroidism. None of the patients had received replacement therapy. The normal response to 10 i.u. bovine TSH administered intramuscularly on three consecutive days was shown to be an absolute increment in the 4 hr uptake of ^{132}I by the thyroid gland of at least 13%. The mean plasma TSH in twenty-five untreated euthyroid patients, who had neither goitres nor thyroid antibodies, whose TSH stimulation tests were normal and in whom there was no evidence of hypopituitarism, was $3.8 \mu\text{U/ml} + 3.6$ (2 S.D.). All forty-nine patients with primary hypothyroidism had plasma TSH levels in excess of $25 \mu\text{U/ml}$. In eighty-nine of the 100 patients, the radioimmunoassay of plasma TSH and the TSH stimulation test gave similar information about the reserve of thyroid function and in five euthyroid patients the plasma TSH was $>7.4 \mu\text{U/ml}$ while the TSH stimulation test was normal. The remaining six subjects (including one patient with hypopituitarism and three who had been treated with radioiodine for thyrotoxicosis) were euthyroid with an abnormal TSH stimulation test and a plasma TSH of $<7.4 \mu\text{U/ml}$.

For clinical purposes a plasma TSH of $<7.4 \mu\text{U/ml}$ indicates a normal reserve of thyroid function, a plasma TSH between 7.4 and $25 \mu\text{U/ml}$ is equivocal, and a plasma TSH $>25 \mu\text{U/ml}$ indicates an impaired or absent reserve of thyroid function with or without hypothyroidism. It is concluded that a single plasma TSH estimation should replace the time-consuming TSH stimulation test in the assessment of thyroid reserve.

INTRODUCTION

The TSH stimulation test demonstrates the reserve capacity of the thyroid gland and is most widely used in the diagnosis of primary hypothyroidism. It has the disadvantage of being time-consuming for the patient and supplying to the thyroid gland a pharmacological stimulus in terms of normal pituitary output of TSH (Bakke *et al.*, 1962). The test procedure varies (Hall *et al.*, 1969; McHardy-Young *et al.*, 1972) and there appears to be little agreement as to what is the definition of a normal response.

The purpose of the present study was to correlate the plasma TSH measured by radioimmunoassay with the result of the TSH stimulation test.

PATIENTS

The subjects were 100 consecutive patients seen at the Endocrine Clinic, Royal Infirmary, Edinburgh, in whom it was necessary to confirm or exclude a diagnosis of primary hypothyroidism. The final diagnosis was made from clinical examination and from estimations of serum protein-bound iodine and total serum thyroxine (Toft *et al.*, 1973), augmented when necessary by serum cholesterol, electrocardiograph and ankle reflex time, as well as the patient's response to replacement therapy with thyroxine. Patients on thyroid replacement therapy were excluded.

There were fifty-one euthyroid patients. Thirty-three were referred by their general practitioners with suspected hypothyroidism and five of these had goitre. The other eighteen patients had previously attended the Endocrine Clinic; eight had received ^{131}I and two had undergone surgery for thyrotoxicosis, four had idiopathic Addison's disease, two had hypopituitarism and two had pernicious anaemia with thyroid antibodies in the serum. There were forty-nine hypothyroid patients, of whom ten had spontaneous hypothyroidism and had been referred by their general practitioners; thirty-six had been previously treated with ^{131}I and three had undergone subtotal thyroidectomy for thyrotoxicosis.

The present study was done following that reported in the adjoining paper (Toft *et al.*, 1973) involving different patients.

METHODS

TSH stimulation test. After measurement of the 4 hr uptake of ^{132}I by the thyroid 10 i.u. bovine TSH (thytropar) was administered intramuscularly at 16.00 hours on three consecutive days. The uptake measurement was then repeated on the day following the last injection. The potency of each batch of bovine TSH was verified.

Plasma TSH. The radioimmunoassay of plasma TSH was carried out using a modification of the double antibody method of Odell *et al.* (1967) as described in the adjoining paper (Toft *et al.*, 1973).

Thyroid antibody studies. Antibodies to thyroid cytoplasm were detected by the indirect immunofluorescence technique using sections of human thyroid tissue and by complement fixation using a saline extract of human thyroid.

RESULTS

Among the forty-nine patients with untreated hypothyroidism the largest increase in the

thyroid gland uptake of ^{132}I at 4 hr, relative to the dose of isotope given to the patient, was 8% following TSH stimulation (e.g. a 4 hr thyroid gland uptake of ^{132}I increasing from 7% to 15%). Therefore the increment in the thyroid gland uptake in normal subjects in response to exogenous TSH must be greater than 8%.

Estimations of plasma TSH in the forty-nine patients with primary hypothyroidism ranged from 26 to 537 $\mu\text{U}/\text{ml}$. The mean plasma TSH in the twenty-five euthyroid patients without goitre, without thyroid antibodies in the serum, who had not previously undergone thyroid surgery or therapy with ^{131}I , who had no evidence of hypopituitarism and whose

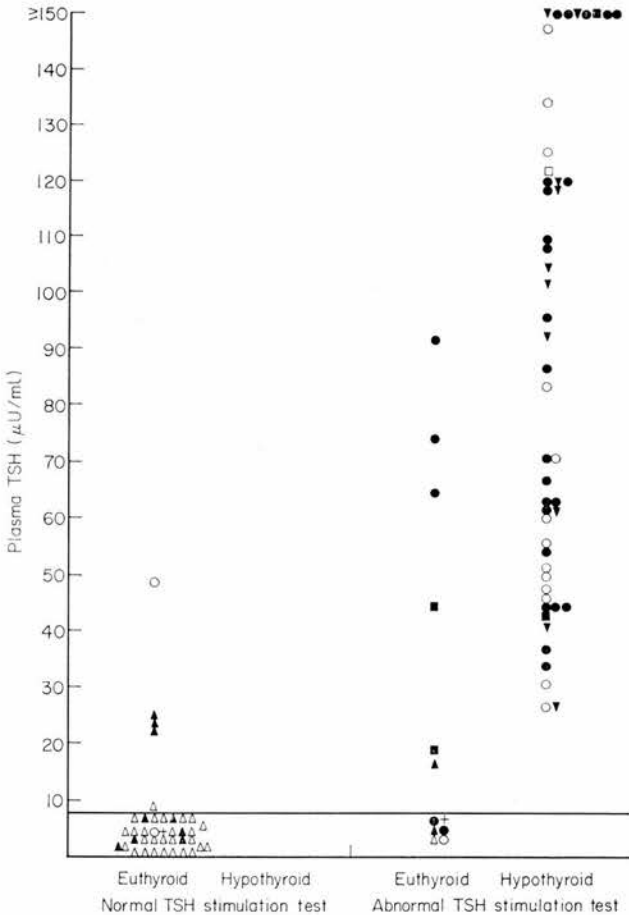


FIG. 1. Plasma TSH levels ($\mu\text{U}/\text{ml}$) correlated with diagnosis and results of TSH stimulation tests in 100 consecutive patients investigated for suspected hypothyroidism. The horizontal line at 7.4 $\mu\text{U}/\text{ml}$ represents the mean (3.8) + 2 S.D. of the plasma TSH levels in twenty-five euthyroid patients who had no goitres, who had not previously been treated by ^{131}I or thyroid surgery, whose serum was negative for thyroid antibodies, who had no evidence of hypopituitarism and who had normal TSH stimulation tests (an absolute increment of $\geq 13\%$ in the 4 hr thyroid gland uptake of ^{132}I following 10 i.u. bovine TSH on each of 3 days). \circ , Post ^{131}I ; \square , post thyroidectomy; ∇ , spontaneous primary hypothyroidism; \triangle , untreated euthyroid; $+$, hypopituitary without thyroid antibodies in the serum. Solid symbols indicate that thyroid cytoplasmic antibodies were present in the serum.

4 hr thyroid gland uptake of ^{132}I increased by at least 8% with exogenous TSH was $3.8 \mu\text{U/ml} \pm 3.6$ (2 S.D.). On this basis the clinic normal range for plasma TSH in patients with no evidence of thyroid dysfunction is estimated to be between 0 and $7.4 \mu\text{U/ml}$ (mean + 2 S.D.).

Combining all the euthyroid patients in the present series, an attempt was made to define more precisely the limits of normal in the TSH stimulation test by determining the figure which correlated best with the plasma TSH levels, i.e. that as few patients as possible were defined as having a normal plasma TSH and an abnormal TSH stimulation test. On this basis, the normal absolute increase in the thyroid gland uptake of ^{132}I at 4 hr following 10 i.u. bovine TSH i.m. on each of three consecutive days, was 13% or more.

In the five euthyroid patients with plasma TSH levels within the range encountered in primary hypothyroidism (i.e. $>25 \mu\text{U/ml}$), the TSH stimulation test was abnormal in four. In the six euthyroid patients with plasma TSH values between 7.4 and $25 \mu\text{U/ml}$ the TSH stimulation test was normal in four and abnormal in two (14–18% and 18–15%, respectively). Plasma TSH measurements in this range were therefore regarded as equivocal. Three of the five euthyroid patients with plasma TSH levels $>7.4 \mu\text{U/ml}$ and a normal TSH stimulation test had thyroid antibodies in the serum; a further patient had had ^{131}I therapy, leaving only one patient with a slightly elevated plasma TSH of $8.8 \mu\text{U/ml}$ for which no explanation could be offered. There was no correlation between the titre of thyroid antibodies and the plasma TSH levels in the euthyroid patients with a normal TSH stimulation test. Of the six patients with an abnormal TSH stimulation test and normal plasma TSH levels, three had received therapy with ^{131}I (15–19%; 24–30%; 14–16%) and one was suffering from hypopituitarism (7–18%), leaving only two patients who had not received previous therapy directed at the thyroid gland (13–21%; 19–27%).

DISCUSSION

Plasma TSH levels were in excess of $25 \mu\text{U/ml}$ in all of the forty-nine patients with primary hypothyroidism included in the present paper as well as in an additional twelve patients with primary hypothyroidism reported in the adjoining paper (Toft *et al.*, 1973), making a total of sixty-one patients. In contrast, the plasma TSH levels in the twenty-five patients with no definite history of thyroid disease or without any demonstrable abnormality of the thyroid gland was 0 – $7.4 \mu\text{U/ml}$ (95% confidence limits). This indicates that for clinical purposes a markedly elevated plasma TSH level is diagnostically important in relation to primary hypothyroidism. In keeping with this is the observation that four of the five euthyroid patients with a plasma TSH $>25 \mu\text{U/ml}$ (45 – $93 \mu\text{U/ml}$) had impaired reserve of thyroid function as evidenced by a low increment in the uptake of ^{132}I by the thyroid gland at 4 hr following prolonged stimulation by a large dose of exogenous TSH. Therefore a high plasma TSH level, although always present in primary hypothyroidism, may also indicate a preclinical condition of impaired reserve of thyroid function without any significant fall in the secretion of thyroxine. A plasma TSH level of between 7.4 and $25.0 \mu\text{U/ml}$ should be regarded as equivocal; four of six patients with levels within this range having a normal TSH stimulation test. However, the use of a large dose of exogenous TSH as employed in the present study in the stimulation test might have masked a minor degree of impaired reserve of thyroid function.

Of the six euthyroid patients with an abnormal TSH stimulation test but with normal plasma TSH levels, three had previously had thyrotoxicosis and had been treated with ^{131}I

and one patient had hypopituitarism. It is conceivable that after therapy with ^{131}I thyrotoxic patients may go through a phase in which they are euthyroid by virtue of the autonomous function of the remaining thyroid tissue and are therefore unable to respond to exogenous TSH stimulation. Presumably this is particularly likely to occur in patients with diffuse goitre. Thus out of the total 100 patients, in eighty-nine the radioimmunoassay of plasma TSH and the TSH stimulation test gave similar information about the reserve of thyroid function. Taking into consideration the arguments just discussed, there were only two patients in whom false negative results were apparently obtained in euthyroid subjects who had an abnormal TSH stimulation test but a normal plasma TSH level.

Previous studies on plasma TSH levels in hypothyroidism and in healthy subjects have not correlated the findings with TSH stimulation tests, nor have they defined a clinical euthyroid range for plasma TSH in patients with a normal reserve of thyroid function. Hershman & Pittman (1971) found the plasma TSH levels to range from 24 to 800 $\mu\text{U}/\text{ml}$ in sixty-one patients with untreated primary hypothyroidism and Mayberry *et al.* (1971) in a series of 156 patients with primary hypothyroidism reported serum TSH measurements in 154 to be $\geq 15 \mu\text{U}/\text{ml}$. Ormston *et al.* (1971) described five patients with 'definite' hypothyroidism with a serum TSH of 3.4–14.8 $\mu\text{U}/\text{ml}$ but all these five patients had serum PBI values of $\geq 4.0 \mu\text{g}\%$. The seventeen patients with adequate evidence of hypothyroidism in the latter series all had serum TSH levels $\geq 19.0 \mu\text{U}/\text{ml}$. The serum or plasma TSH levels in healthy subjects have been variously reported in recent years as being between ≤ 1.0 – $19.0 \mu\text{U}/\text{ml}$ as reviewed by Hall (1972), but in the majority of reports the normal range is $\leq 10 \mu\text{U}/\text{ml}$.

Although we have been able to define a normal response by the thyroid to exogenous TSH more precisely than hitherto, this form of test is time-consuming for the patients compared to venepuncture for measurement of the plasma TSH level. The evidence in this paper indicates that the TSH stimulation test is no longer necessary if there is access to a reliable radioimmunoassay for plasma or serum TSH on a routine basis.

REFERENCES

- BAKKE, J., LAWRENCE, N. & ROY, S. (1962) Disappearance rate of exogenous thyroid-stimulating hormone (TSH) in man. *Journal of Clinical Endocrinology and Metabolism*, **22**, 352.
- HALL, R. (1972) The immunoassay of thyroid-stimulating hormone and its clinical applications. *Clinical Endocrinology*, **1**, 115.
- HALL, R., ANDERSON, J. & SMART, G.A. (1969) In: *Fundamentals of Clinical Endocrinology*, p. 380. Pitman, London.
- HERSHMAN, J.M. & PITTMAN, J.A. (1971) Utility of the radio-immunoassay of serum thyrotrophin in man. *Annals of Internal Medicine*, **74**, 481.
- MCHARDY-YOUNG, S., LESSOF, M.H. & MAISEY, M.N. (1972) Serum TSH and thyroid antibody studies in Addison's disease. *Clinical Endocrinology*, **1**, 45.
- MAYBERRY, W.E., GHARIB, H., BILSTAD, J.M. & SIZEMORE, G.W. (1971) Radioimmunoassay for human thyrotrophin. Clinical value in patients with normal and abnormal thyroid function. *Annals of Internal Medicine*, **74**, 471.
- ODELL, W.D., RAYFORD, P.L. & ROSS, G.T. (1967) Simplified partially automated method for radioimmunoassay of human thyroid-stimulating, growth, luteinizing and follicle stimulating hormones. *Journal of Laboratory and Clinical Medicine*, **70**, 973.
- ORMSTON, B.J., GARRY, R., CRYER, R.J., BESSER, G.M. & HALL, R. (1971) Thyrotrophin-releasing hormone as a thyroid-function test. *Lancet*, **ii**, 10.
- TOFT, A.D., SETH, J., KIRKHAM, K.E., MARSHALL, A. & IRVINE, W.J. (1973) Assessment of *in vitro* thyroid function tests in 100 consecutive patients referred to a thyroid clinic. *Clinical Endocrinology*, **2**, 127.

EFFECT OF BOVINE THYROID-STIMULATING HORMONE (TSH) ON HUMAN PLASMA TSH LEVELS IN PRIMARY HYPOTHYROIDISM: EVIDENCE AGAINST THE 'SHORT-FEEDBACK' OF TSH IN MAN

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It has been established in animals that anterior pituitary hormones control their own secretion by regulating at a hypothalamic level the release of their hypothalamic factors (Motta, Fraschini & Martini, 1969). If a negative 'short-feedback' of thyroid-stimulating hormone (TSH) on the hypothalamus exists in man, the high plasma TSH levels of untreated primary hypothyroidism should fall markedly after the administration of bovine TSH which shares the biological, but not the immunological, properties of human TSH. This report describes the effects of bovine TSH on human plasma TSH (H-TSH) levels in patients with primary hypothyroidism.

Twenty-seven patients with untreated primary hypothyroidism were studied, of whom 20 had been treated with ^{131}I and four by subtotal thyroidectomy for thyrotoxicosis. The remaining three patients had spontaneous primary hypothyroidism. The diagnosis of primary hypothyroidism was made on clinical grounds and on the basis of a low serum protein-bound iodine ($< 3.8 \mu\text{g}/100 \text{ ml}$), a low total serum thyroxine ($< 4.5 \mu\text{g}/100 \text{ ml}$) and a high H-TSH ($> 25 \mu\text{u./ml}$) measured by radioimmunoassay using a double antibody method (Irvine, Toft, Hunter & Kirkham, 1973). There was no significant increase in the 4-h ^{132}I uptake by the thyroid gland after the intramuscular administration of 10 i.u. bovine TSH ('Thyropar') on each of 3 successive days in any patient.

In three patients H-TSH was estimated before and 7, 15, 25, 30 (two patients only), 45, 60, 90 (two patients only), 120 and 180 min after the intramuscular injection of 10 i.u. bovine TSH (Fig. 1). None of the three patients showed a fall in the level of H-TSH after exogenous bovine TSH injection.

A TSH stimulation test employing 10 i.u. bovine TSH intramuscularly at 16.00 h daily for 3 days was carried out in the remaining 24 patients. Human plasma TSH was estimated before the first and 18 h after the last injection of bovine TSH. The mean H-TSH level \pm s.e.m. before the TSH stimulation test was $87.3 \pm 11.2 \mu\text{u./ml}$ (range 27.2–210.3 $\mu\text{u./ml}$) and $84.7 \pm 11.4 \mu\text{u./ml}$ (range 35.5–221.3 $\mu\text{u./ml}$) after the TSH stimulation test. The H-TSH level after exogenous bovine TSH injection fell in 13 patients, the maximum percentage decrease being 33% ($69.5 \rightarrow 44.5 \mu\text{u./ml}$),

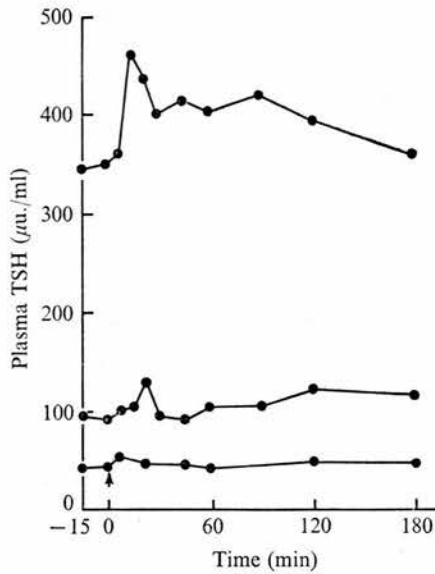


Fig. 1. Human plasma thyroid-stimulating hormone (TSH) levels in three patients with untreated primary hypothyroidism in response to 10 i.u. bovine TSH intramuscularly; arrow indicates time of injection.

but rose in the other 11 patients, the maximum percentage increase being 30.5% ($27.2 \rightarrow 35.5 \mu\text{u./ml}$).

We have been unable to show a fall in the high H-TSH levels in patients with untreated primary hypothyroidism despite the presence of high bovine plasma TSH levels lasting 24 h, achieved in such patients after the administration of exogenous bovine TSH (Hershman & Edwards, 1972). There is, therefore, no evidence for the existence of a negative 'short-feedback' of TSH on the hypothalamus in man.

REFERENCES

- Hershman, J. M. & Edwards, C. L. (1972). *J. clin. Endocr. Metab.* **34**, 814-818.
 Irvine, W. J., Toft, A. D., Hunter, W. M. & Kirkham, K. E. (1973). *Clin. Endocr.* **2**, 135-139.
 Motta, M., Fraschini, F. & Martini, L. (1969). In: *Frontiers in neuroendocrinology*, pp. 211-253. Eds L. Martini & W. F. Ganong. New York: Oxford University Press.

RAISED PLASMA-THYROID-STIMULATING-HORMONE LEVELS IN THYROTOXIC PATIENTS TREATED WITH IODINE-131

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Summary 69 euthyroid patients who had raised plasma - thyroid - stimulating - hormone (T.S.H.) levels ($>7.4 \mu\text{U. per ml.}$) in February, 1972, after ^{131}I therapy for thyrotoxicosis between 1954-66 were reassessed fifteen months later. The initial mean plasma-T.S.H. level \pm S.E. in the 66 patients who remained euthyroid ($25.0 \pm 2.0 \mu\text{U. per ml.}$) was unchanged ($22.6 \pm 1.8 \mu\text{U. per ml.}$) at the end of the study. Overt hypothyroidism developed in only 3 patients with initial plasma-T.S.H. levels of 34.6, 45.6, and 90.4 $\mu\text{U. per ml.}$ At follow-up these patients had plasma-T.S.H. levels of 67.3, 28.2, and 92.8 $\mu\text{U. per ml.}$, respectively. Since raised plasma-T.S.H. concentration occurring after radioiodine treatment of thyrotoxicosis does not alter for a considerable period, it cannot be used as an indication of impending overt hypothyroidism.

Introduction

A RAISED plasma-thyroid-stimulating-hormone (T.S.H.) level is now regarded as the most sensitive index of thyroid failure. Evered and Hall¹ judged euthyroid people with raised plasma-T.S.H. but no symptoms of thyroid dysfunction to have preclinical hypothyroidism. The natural history of such a condition is not known. The present prospective study was designed to observe the clinical and biochemical progress of a large group of euthyroid patients with raised plasma-T.S.H. levels induced by ^{131}I treatment of thyrotoxicosis.

Patients and Methods

69 patients (52 females and 17 males), aged thirty-eight to eighty, who had been treated with ^{131}I for thyrotoxicosis between 1954 and 1966 in the Royal Infirmary, Edinburgh, were studied. In February, 1972, and May, 1973, the thyroid status of each patient was assessed clinically and blood was withdrawn to estimate serum-protein-bound-iodine (P.B.I.), total serum-thyroxine (T4), and plasma-T.S.H. Serum-P.B.I. was estimated by a modification of the Technicon N-56 method,² serum-T4 by a modification of the competitive-protein-binding method of Maclagan and Howorth,^{3,4} and plasma-T.S.H. by a sensitive double-antibody radioimmunoassay.⁵

Results

The mean (\pm S.E.) serum-P.B.I., serum-T4, and plasma-T.S.H. for the 66 patients who remained euthyroid are shown in the accompanying table.

SERUM-P.B.I., SERUM-T4, AND PLASMA-T.S.H. IN FEBRUARY, 1972, AND MAY, 1973, IN 66 PATIENTS WHO REMAINED EUTHYROID

Time	Serum-P.B.I. ($\mu\text{g. per}$ 100 ml.) (mean \pm S.E.)	Serum-T4 ($\mu\text{g. per}$ 100 ml.) (mean \pm S.E.)	Plasma-T.S.H. ($\mu\text{U. per}$ ml.) (mean \pm S.E.)
February, 1972 ..	5.7 \pm 0.2	6.8 \pm 0.1	25.0 \pm 2.0
May, 1973 ..	5.6 \pm 0.2	6.5 \pm 0.1	22.6 \pm 1.8

There was no apparent change in any measurement of thyroid function at the end of the fifteen-month period. The ranges of plasma-T.S.H. levels in February, 1972, and in May, 1973, were 8.7–60 $\mu\text{U. per ml.}$ and 7.5–50 $\mu\text{U. per ml.}$, respectively. The greatest relative increase in plasma-T.S.H. over fifteen months in any patient remaining euthyroid was from 10.2 to 22.3 $\mu\text{U. per ml.}$, and the greatest relative fall was from 26.4 to 11.3 $\mu\text{U. per ml.}$ Overt hypothyroidism had developed in 3 of the initial 69 patients after fifteen months. The plasma-T.S.H. level had risen in 1 (from 34.6 to 67.3 $\mu\text{U. per ml.}$), had fallen in the second (from 45.6 to 28.2 $\mu\text{U. per ml.}$), and had remained unchanged in the third (i.e., 90.4 and 92.8 $\mu\text{U. per ml.}$).

Discussion

In many centres radioiodine is the treatment of choice for thyrotoxicosis in patients over forty. The incidence of subsequent hypothyroidism is highest

during the first post-treatment year (7-22%) and continues at 2-4% per year thereafter.⁶ The ability to forecast not only which patients were at risk of developing hypothyroidism but also when it would develop would be very valuable. Conventional tests of thyroid function cannot identify such patients, and this has resulted in the follow-up of large numbers of patients. Indeed, the interpretation of thyroid-function tests after ¹³¹I therapy for thyrotoxicosis may be difficult. The T.S.H. stimulation test, which indicates the reserve capacity of the thyroid gland, is often abnormal,^{7,8} and an abnormal result may be associated with a normal plasma-T.S.H. level.⁵ Patients may be clinically euthyroid, with normal serum-triiodothyronine but low serum-T4 concentrations.⁹⁻¹¹ Furthermore, Slingerland et al.¹² have found high serum-T.S.H. levels in about 50% of euthyroid patients treated with radioiodine for thyrotoxicosis five to twenty-two years earlier, and they described 7 patients who had remained euthyroid despite raised serum-T.S.H. levels for nineteen to forty-one months.

In the present study, not only did 66 of 69 patients (94%) with high plasma-T.S.H. levels remain euthyroid over fifteen months, but the plasma-T.S.H. levels were essentially unchanged. It was not possible to predict from the plasma-T.S.H. concentration which patients would later have overt hypothyroidism. Raised plasma-T.S.H. levels, which result from a resetting of the brain-thyroid axis, are relatively stable, at least after radioiodine therapy, and are not a sign of the imminent development of frank hypothyroidism. Serial measurements of plasma-T.S.H. are therefore unlikely to be of value in the long-term follow-up of patients treated with ¹³¹I for thyrotoxicosis, unless raised plasma-T.S.H. itself can be shown to be detrimental.

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REFERENCES

1. Evered, D., Hall, R. *Br. med. J.* 1972, *i*, 290.
2. Simpson, D. *Clin. Chem.* 1967, **13**, 890.
3. MacLagan, N. F., Howorth, B. J. N. *Clin. Sci.* 1969, **37**, 45.
4. Toft, A. D., Seth, J., Kirkham, K. E., Marshall, A., Irvine, W. J. *Clin. Endocr.* 1973, **2**, 127.
5. Irvine, W. J., Toft, A. D., Hunter, W. M., Kirkham, K. E. *ibid.* 1973, **2**, 135.
6. Hagen, G. A. *Med. Clin. N. Am.* 1968, **52**, 417.

7. Eckert, H., Green, M., Kilpatrick, R., Wilson, G. M. *Clin. Sci.* 1960, **20**, 87.
8. Slingerland, D. W., Dell, E. S., Burrows, B. A. in 6th International Thyroid Conference (edited by K. Fellinger and R. Hoefler). Vienna, 1970.
9. Sterling, K., Bellabarba, D., Newman, E. S., Brenner, M. A. *J. clin. Invest.* 1969, **48**, 1150.
10. Sterling, K., Brenner, M. A., Newman, E. S., Odell, W. D., Bellabarba, D. *J. clin. Endocr. Metab.* 1971, **33**, 729.
11. Bellabarba, D., Benard, B., Langlois, M. *Clin. Endocr.* 1972, **1**, 345.
12. Slingerland, D. W., Hershman, J. M., Dell, E. S., Burrows, B. A. *J. clin. Endocr. Metab.* 1972, **35**, 912.

**PLASMA-THYROTROPHIN AND SERUM-
THYROXINE IN PATIENTS BECOMING
HYPOTHYROID IN THE EARLY
MONTHS AFTER IODINE-131**

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Summary Clinical examination and measurements of plasma-thyrotrophin (T.S.H.) and total serum-thyroxine (T₄) were made at 1-2-monthly intervals in seventy-two patients treated with iodine-131 for thyrotoxicosis. The period of prospective follow-up was 2-18 months. Forty-one patients were euthyroid with normal serum-T₄ levels (4.5-11.5 µg. per 100 ml.), of whom thirty-two had a normal and nine a high plasma-T.S.H. level (>7.4 µU per ml.). Hypothyroidism developed in thirty-one patients (43%). In seventeen, a low serum-T₄ and a high plasma-T.S.H. preceded the symptoms of hypothyroidism by 1-4 months, but in seven patients a low serum-T₄ in the presence of a normal plasma-T.S.H. level was the first indication of developing hypothyroidism. In six patients both indices of thyroid function were normal at the clinic visit 1-2 months before hypothyroidism was diagnosed, and in only one patient did the plasma-T.S.H. rise precede the fall in serum-T₄. It is concluded that the serum-T₄ may be a more sensitive index of thyroid failure than the plasma-T.S.H. in the early months after iodine-131 treatment of thyrotoxicosis.

Introduction

ALTHOUGH a raised plasma-T.S.H. level is a sensitive index of thyroid failure, Toft et al.¹ demonstrated that high circulating levels of T.S.H. may persist for many months in euthyroid patients treated 7-19 years earlier with iodine-131 for thyrotoxicosis. The present study was designed to determine whether the routine measurement of plasma-T.S.H. is of value in predicting the onset of hypothyroidism in the early months after iodine-131 treatment of thyrotoxicosis when the incidence of hypothyroidism is greatest.²

Patients and Methods

We studied seventy-two patients (sixty-two females and ten males), aged 37-74 years, who had been treated with iodine-131 (4-50 mCi, mode 7 mCi) for thyrotoxicosis between August, 1972, and October, 1973, in the Royal Infirmary, Edinburgh. The thyroid status of each patient was assessed clinically by one observer (A. D. T.), and blood was withdrawn for the estimation of serum-T4 and plasma-T.S.H. at 1-2-monthly intervals after treatment. Hypothyroidism was diagnosed clinically and in the presence of a serum-T4 of $<4.5 \mu\text{g. per } 100 \text{ ml.}$ and a plasma-T.S.H. of $>7.4 \mu\text{U per ml.}$ The prospective period of follow-up was 2-18 months. Serum-T4 was estimated by a modification of the competitive-protein-binding method of Maclagan and Howorth,^{3,4} and plasma-T.S.H. by a sensitive double-antibody radioimmunoassay.⁵

Results

Three patterns of plasma-T.S.H. and serum-T4 levels were observed after iodine-131 treatment of thyrotoxicosis.

1. Thirty-two patients were clinically euthyroid at intervals varying from 4 to 18 months after therapy, with normal plasma-T.S.H. and normal serum-T4 levels. Three of this group, followed up for over 12 months, had a transient fall in serum-T4 to below $4.5 \mu\text{g. per } 100 \text{ ml.}$ in the early weeks after treatment, which was associated with plasma-T.S.H. values of 1.7, <1.5 , and $8.9 \mu\text{U per ml.}$

2. Nine clinically euthyroid patients were found to have normal serum-T4 levels associated with plasma-T.S.H. levels in excess of $7.4 \mu\text{U per ml.}$ 6-18 months after treatment.

3. Clinical hypothyroidism developed in thirty-one patients 2-8 months (mean 4.3 months) after iodine-

¹³¹I treatment. In seventeen of these patients a low serum-T₄ and a high plasma-T.S.H. level preceded the clinical features of hypothyroidism by 1-4 months, and in six patients both indices of thyroid function were normal at the clinic visit 1-2 months before hypothyroidism was diagnosed. In a further seven patients a low serum-T₄ level in the presence of a normal plasma-T.S.H. level was the first indication of developing hypothyroidism. A rise in plasma-T.S.H. preceded a fall in serum-T₄ in only one out of thirty-one patients developing clinical hypothyroidism.

Discussion

The treatment of thyrotoxicosis with iodine-¹³¹I may either make patients euthyroid with normal or high plasma-T.S.H. levels or induce hypothyroidism. The incidence of hypothyroidism after radioiodine is highest during the first post-treatment year and continues at a lower rate thereafter.² The high incidence of hypothyroidism in the present study may reflect the high dose of isotope given in this centre, especially to patients with the cardiac complications of thyrotoxicosis. An increased plasma-T.S.H. level in euthyroid patients after iodine-¹³¹I treatment of thyrotoxicosis may persist for many months,^{1,6} and Toft et al.¹ felt that the routine measurement of plasma-T.S.H. was not of value in predicting the occurrence of late hypothyroidism in a group of patients treated with iodine-¹³¹I, 7-19 years previously. However, in patients in whom hypothyroidism developed within a few months of treatment, an increased plasma-T.S.H. level might be expected to predict impending hypothyroidism. In 55% of patients in whom hypothyroidism developed, both a low serum-T₄ and a high plasma-T.S.H. level were found when the patient was clinically euthyroid 1-4 months earlier. Although the serum-triiodothyronine (T₃) levels were not estimated, these patients presumably fall into the category of patients maintained temporarily euthyroid by normal or high levels of circulating T₃.⁷⁻⁹ The occurrence of low serum-T₄ levels and normal plasma-T.S.H. levels before the onset of hypothyroidism and in the absence of thyroxine-binding-globulin abnormalities demands that serum-T₃ levels are appropriately raised in such patients. In patients in whom hypothyroidism develops in the early months after iodine-¹³¹I treat-

ment of thyrotoxicosis, thyroxine synthesis probably declines more rapidly than T3 synthesis, and T3 is able to maintain euthyroidism for a period. Furthermore the altered T3/T4 ratio is such in some patients that the serum-T4 may be low with a normal plasma-T.S.H. Such a state is also temporary and eventually the secretion of T3 by the damaged gland falls, the plasma-T.S.H. level rises, and the symptoms of hypothyroidism develop. With the exception of 10% of patients who remain euthyroid and in whom a transient fall in serum-T4 was observed in the first weeks after iodine-131 therapy, this study has shown a low serum-T4 level to be a more sensitive index of impending hypothyroidism than the plasma-T.S.H.

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REFERENCES

1. Toft, A. D., Barnes, E. W., Hunter, W. M., Seth, J., Irvine, W. J. *Lancet*, 1973, ii, 644.
2. Hagen, G. A. *Med. Clin. N. Am.* 1968, 52, 417.
3. Maclagan, N. F., Howorth, B. J. N. *Clin. Sci.* 1969, 37, 45.
4. Toft, A. D., Seth, J., Kirkham, K. E., Marshall, A., Irvine, W. J. *Clin. Endocr.* 1973, 2, 127.
5. Irvine, W. J., Toft, A. D., Hunter, W. M., Kirkham, K. E. *ibid.* p. 135.
6. Slingerland, D. W., Hershman, J. M., Dell, E. S., Burrows, B. A. *J. clin. Endocr. Metab.* 1972, 35, 912.
7. Sterling, K., Bellabarba, D., Newman, E. S., Brenner, M. A. *J. clin. Invest.* 1969, 48, 1150.
8. Sterling, K., Brenner, M. A., Newman, E. S., Odell, W. D., Bellabarba, D. *J. clin. Endocr. Metab.* 1971, 33, 729.
9. Bellabarba, D., Bernard, B., Langlois, M. *Clin. Endocr.* 1972, 1, 345.

Plasma TSH and Serum T-4 Levels in Long-term Follow-up of Patients Treated with ^{131}I for Thyrotoxicosis

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Summary

In February 1972 58% of patients euthyroid after iodine-131 therapy given for thyrotoxicosis between 1954 and 1966 had a high plasma TSH ($>7.4 \mu\text{U/ml}$) and 42% a normal plasma TSH level. A group of 69 of the euthyroid patients with high plasma TSH levels ($25.0 \pm 2.0 \mu\text{U/ml}$) in 1972 were re-examined 15 and 24 months later. The mean plasma TSH in the 66 patients remaining euthyroid at 15 months was $22.6 \pm 1.8 \mu\text{U/ml}$, while three patients had become hypothyroid. At 24 months 64 of the patients were still available for study, of whom 61 remained euthyroid with a mean plasma TSH of $21.6 \pm 2.0 \mu\text{U/ml}$, and a further three had become hypothyroid.

All of a group of 61 of the euthyroid patients with normal plasma TSH levels ($4.0 \pm 0.2 \mu\text{U/ml}$) in 1972 remained euthyroid at 24 months with a mean plasma TSH of

$4.1 \pm 0.3 \mu\text{U/ml}$, though the plasma TSH level had become slightly raised in three.

The mean serum T-4 level in the euthyroid patients with a high plasma TSH was significantly lower, though still in the normal range, than that in the euthyroid patients with a normal plasma TSH both in 1972 and in 1974.

Since no patient with a normal plasma TSH level after iodine-131 treatment six to 18 years earlier for thyrotoxicosis developed hypothyroidism over a two-year period, the follow-up of such patients need not be so rigorous as that of similarly treated euthyroid patients with raised plasma TSH levels in whom hypothyroidism developed at the rate of 5% per year.

Introduction

The incidence of hypothyroidism after ^{131}I treatment of thyrotoxicosis is greatest in the first year (7-22%) and continues at 2-4% a year (Hagen, 1968). Toft *et al.* (1974) found a low serum thyroxine (T-4) level to be a sensitive index of developing hypothyroidism in the early months after radioiodine therapy but it has not yet proved possible, using conventional tests of thyroid function, to predict when or in whom hypothyroidism will occur in later years. This results in the follow-up of large numbers of patients. A high plasma thyrotrophin (TSH) level is considered to be a good index of thyroid failure but is not uncommon after ^{131}I treatment of thyrotoxicosis and may persist in euthyroid patients for many months (Slingerland *et al.*, 1972; Toft *et al.*, 1973). The present paper reports the clinical and biochemical

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progress over two years of a group of euthyroid patients with high plasma TSH levels and of a group of euthyroid patients with normal plasma TSH levels who were treated with ^{131}I for thyrotoxicosis between 1954 and 1966. On the basis of the plasma TSH level a rational follow-up policy is suggested for the ever-increasing number of patients who are being treated with radioiodine.

Patients and Methods

In February 1972 the plasma TSH and serum T-4 were estimated in 233 euthyroid patients who had been treated with ^{131}I for thyrotoxicosis in the endocrine clinic of the Royal Infirmary, Edinburgh, between 1954 and 1966. A group of 69 of these euthyroid patients with raised plasma TSH levels were studied again 15 and 24 months later, and a further group of 61 euthyroid patients with normal plasma TSH levels were studied again at 24 months. Each patient was examined clinically by one observer (A.D.T.) and blood was withdrawn for the estimation of serum T-4 and plasma TSH. A diagnosis of hypothyroidism was made on clinical grounds and on the basis of a low serum T-4 ($<4.5 \mu\text{g}/100 \text{ ml}$) and a high plasma TSH ($>7.4 \mu\text{U}/\text{ml}$). Serum T-4 was measured by competitive protein-binding analysis (Seth, 1973) and plasma TSH by a sensitive double-antibody radioimmunoassay (Irvine *et al.*, 1973).

Results

The plasma TSH level was raised in 136 (58%) of the 233 patients euthyroid after ^{131}I therapy for thyrotoxicosis between 1954 and 1966 and normal in 97 (42%) when estimated in February 1972.

The mean (\pm S.E.) serum T-4 and plasma TSH levels in the 69 euthyroid patients with high plasma TSH levels in 1972 and in those remaining euthyroid in 1973 and 1974, 15 and 24 months later, are shown in table I. Only three of the 69 patients developed hypothyroidism over the 15-month period; the plasma TSH had risen in one (from 34.6 to 67.3 $\mu\text{U}/\text{ml}$), had fallen in the second (from 45.6 to 28.2 $\mu\text{U}/\text{ml}$), and had remained virtually unchanged in the third (90.4 and 92.8 $\mu\text{U}/\text{ml}$). At 24 months 64 of the 66 patients remaining euthyroid in 1973 were available for study. Hypothyroidism had developed in a further three patients in whom the plasma TSH levels remained essentially unchanged (32.8 and 32.0, 23.5 and 26.1, and 27.5 and 31.2 $\mu\text{U}/\text{ml}$).

TABLE I—Mean Serum T-4 and Plasma TSH Levels (\pm S.E.) in 69 Patients with High Plasma TSH Levels in 1972 and in 66 and 61 Patients Remaining Euthyroid in 1973 and 1974. All were Treated with ^{131}I for Thyrotoxicosis between 1954 and 1966

	Serum T-4 ($\mu\text{g}/100 \text{ ml}$)	Plasma TSH ($\mu\text{U}/\text{ml}$)
February 1972	6.8 \pm 0.1	25.0 \pm 2.0
May 1973	6.5 \pm 0.1	22.6 \pm 1.8
February 1974	6.5 \pm 0.1	21.6 \pm 2.0

All 61 euthyroid patients with normal plasma TSH levels in 1972 remained euthyroid over a 24-month period and the mean serum T-4 and plasma TSH levels in 1972 and 1974 are shown in table II. In three of these 61 patients, however, the plasma TSH became slightly raised—9.4, 9.7, and 12.6 $\mu\text{U}/\text{ml}$ respectively.

TABLE II—Mean Serum T-4 and Plasma TSH Levels (\pm S.E.) in 61 Patients with Low Plasma TSH Levels in 1972 and 1974. All were Treated with ^{131}I for Thyrotoxicosis between 1954 and 1966

	Serum T-4 ($\mu\text{g}/100 \text{ ml}$)	Plasma TSH ($\mu\text{U}/\text{ml}$)
February 1972	8.7 \pm 0.3	4.0 \pm 0.2
February 1974	8.1 \pm 0.2	4.1 \pm 0.3

The mean serum T-4 level in the euthyroid patients with a high plasma TSH was significantly lower than that in the euthyroid patients with a normal plasma TSH both in 1972 ($P < 0.001$) and in 1974 ($P < 0.001$).

Discussion

The high incidence of hypothyroidism after ^{131}I treatment of thyrotoxicosis necessitates the follow-up of large numbers of patients. In most centres patients are seen frequently in the first post-therapy year, when the incidence of hypothyroidism is highest, and at intervals of six to 12 months thereafter on a lifelong basis or until hypothyroidism develops. Though a low serum T-4 is a good index of impending hypothyroidism in the early months after radioiodine treatment (Toft *et al.*, 1974) it has not proved possible to predict the onset of hypothyroidism in patients treated in earlier years. A low serum T-4 does not have the same significance in such patients as it may persist indefinitely while the euthyroid state is maintained by high or normal levels of circulating triiodothyronine (Sterling *et al.*, 1971; Bellabarba *et al.*, 1972). Over half (58%) of the patients treated with ^{131}I for thyrotoxicosis between 1954 and 1966 had high plasma TSH levels in February 1972 when euthyroid. These high levels, considered to be a sensitive index of thyroid failure, remained unchanged over 24 months in most of the patients but hypothyroidism occurred at a rate of 5% a year. On the other hand, no patient in whom a normal plasma TSH level was found in February 1972, six to 18 years after radioiodine treatment, developed hypothyroidism over the same 24-month period.

It is suggested that in the long-term follow-up of patients treated with ^{131}I for thyrotoxicosis those with a high plasma TSH level should be examined at yearly intervals as they are at risk of developing hypothyroidism, whereas those with a low plasma TSH level should be seen at intervals of two years or longer.

One possible interpretation of the significantly lower mean serum T-4 levels in the euthyroid patients with high plasma TSH levels compared with the euthyroid patients with normal plasma TSH levels after ^{131}I therapy is that the serum T-4 levels in the former group were suboptimal. Any increase in morbidity, such as ischaemic heart disease, in these patients will become apparent only in future years, and at present no thyroxine replacement therapy has been instituted.

References

- Bellabarba, B., Bernard, B., and Langlois, M. (1972). *Clinical Endocrinology*, 1, 345.
- Hagen, G. A. (1968). *Medical Clinics of North America*, 52, 417.
- Irvine, W. J., *et al.* (1973). *Clinical Endocrinology*, 2, 135.
- Seth, J. (1973). *Clinica Chimica Acta*, 46, 43.
- Slingerland, D. W., *et al.* (1972). *Journal of Clinical Endocrinology and Metabolism*, 35, 912.
- Sterling, K., *et al.* (1971). *Journal of Clinical Endocrinology and Metabolism*, 33, 729.
- Toft, A. D., *et al.* (1973). *Lancet*, 2, 640.
- Toft, A. D., *et al.* (1974). *Lancet*, 1, 704.

ANOMALOUS PLASMA TSH LEVELS IN PATIENTS DEVELOPING HYPOTHYROIDISM IN THE EARLY MONTHS AFTER ^{131}I THERAPY FOR THYROTOXICOSIS

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Abstract: Serial measurements of serum T3, T4 and plasma TSH were made in seven patients developing hypothyroidism in the early months after ^{131}I therapy for thyrotoxicosis. In each patient a low serum T4 was found in the presence of a normal plasma TSH before the onset of clinical hypothyroidism. In three of the patients the normal plasma TSH was associated with normal or high serum T3, but in the other four patients both serum T3 and T4 were low in association with a normal plasma TSH. Such a situation may reflect the slow response of the brain-thyroid axis recently exposed to high circulating levels of thyroid hormone, analogous to the suppression of the brain-adrenal axis after prolonged exposure to high circulating levels of corticosteroids.

It has recently been reported that a low serum T4 may be associated with a normal plasma TSH in patients developing hypothyroidism in the early months after ^{131}I treatment for thyrotoxicosis (1). Although serum T3 was not measured, it was suggested that both the euthyroid state and the suppression of plasma TSH were temporarily maintained by normal or high levels of serum T3. The present paper reports serial serum T3, T4 and plasma TSH levels in seven such patients.

Patients and Methods

Seven of thirty-one consecutive patients developing hypothyroidism in the early months following ^{131}I treatment of thyrotoxicosis were found to have a low serum T4 ($< 4.5 \mu\text{g}/100\text{ml}$) in association with a normal plasma TSH ($< 7.4 \mu\text{u}/\text{ml}$) when euthyroid. Each patient had been

examined clinically by one observer (A. D. T.) at 3-8 weekly intervals after therapy and blood withdrawn for the estimation of serum T3, T4 and plasma TSH. The diagnosis of hypothyroidism was made clinically and on the basis of a low serum T4 and a high plasma TSH.

Serum T4 was estimated by competitive protein-binding analysis (normal range $4.5-11.5 \mu\text{g}/100\text{ml}$) (2), serum T3 by radioimmunoassay (normal range $0.6-1.8 \text{ng}/\text{ml}$) (3), and plasma TSH by radioimmunoassay (4).

Results

In three of the patients a low serum T4 and a normal plasma TSH were associated with serum T3 levels of 2.24, 1.2 and $0.88 \text{ng}/\text{ml}$ 1-2 months after therapy with ^{131}I . Pituitary TSH secretion was pres-

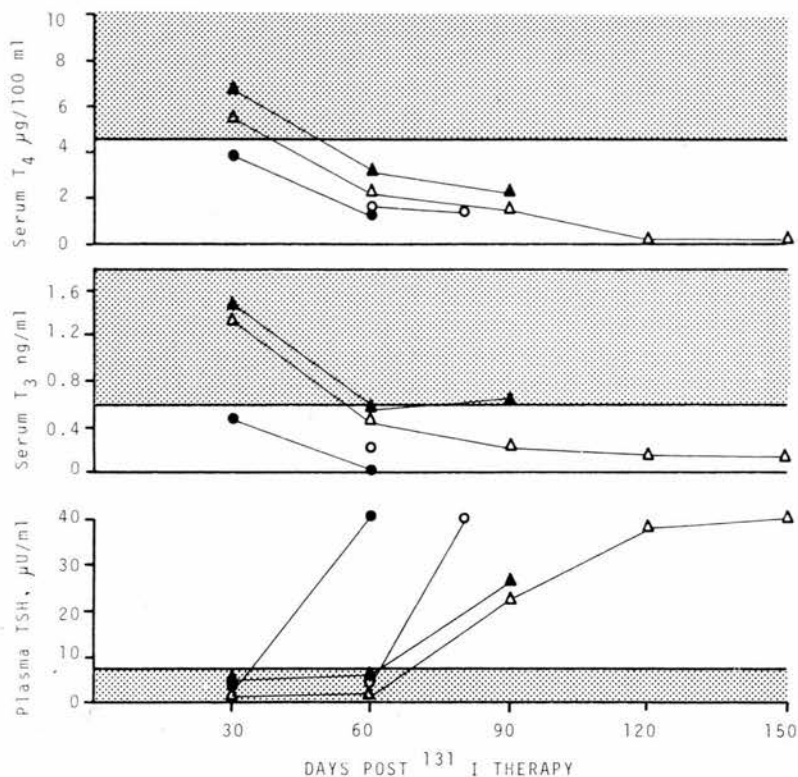


Figure 1. Serum T₄, T₃ and plasma TSH levels in the four patients in whom a low serum T₄ and T₃ level was observed in the presence of a normal plasma TSH prior to the development of hypothyroidism.

umably suppressed albeit temporarily, by the high or normal serum T₃ concentrations, but as the serum T₃ fell in subsequent weeks, not necessarily into the hypothyroid range, the plasma TSH rose and clinical hypothyroidism developed.

In the remaining four patients a low serum T₃, low serum T₄ and a normal plasma TSH were observed while the patient was clinically euthyroid (Fig. 1). Again this phenomenon was temporary and in each case not only was the plasma TSH elevated one month later, but hypothyroidism had developed in three of the four patients. The fourth patient remained clinically euthyroid

despite low serum T₃ and T₄ levels and a high plasma TSH for two months.

Discussion.

It is well recognised that patients may be euthyroid many years after ¹³¹I therapy for thyrotoxicosis despite low serum T₄ and high plasma TSH concentrations. The serum T₃ is normal or high in such a group(5). The thyroid remnant presumably fails to meet secretory demands, pituitary TSH output is no longer suppressed, and the resulting rise in the level of the plasma TSH increases the T₃/T₄ ratio and the euthyroid state may be maintained indef-

initely.

In the present study four patients developing hypothyroidism in the early months after ^{131}I treatment were noted to have the transient phenomenon of low serum T3 and T4 in the presence of a normal TSH which became elevated in the subsequent month. It is possible that the metabolic effects of T3 and T4 at the hypothalamic and/or thyrotroph level persist for some time after an alteration in circulating thyroid hormone concentration, and the plasma TSH remains suppressed despite low levels of serum T3 and T4. Indeed if T3 replacement therapy is withdrawn from athyreotic patients plasma TSH levels remain suppressed for some days (6). An alternative explanation may be suppression of the brain-thyroid axis by excess circulating thyroid hormone in thyrotoxic patients; an analogous situation occurs in the suppression of the brain-adrenal axis in patients

exposed to prolonged high levels of circulating corticosteroids. A sluggish response of the pituitary thyrotrophs to the presence of low serum thyroid hormone levels in patients recently treated with ^{131}I for thyrotoxicosis might therefore be expected.

References

1. Toft, A.D., W.M. Hunter, J. Seth and W.J. Irvine, *Lancet* 1, 704, 1974.
2. Seth, J., *Clin. Chim. Acta.*, 46, 43, 1973.
3. Ratcliffe, W.A., G.S. Challand, J.G. Ratcliffe (in preparation).
4. Irvine, W.J., A.D. Toft, W.M. Hunter and K.E. Kirkham, *Clin. Endocrinol.*, 2, 135, 1973.
5. Sterling, K., M.A. Brenner, E.S. Newman, W.D. Odell and D. Bellabarba, *J. Clin. Endocr. Metab.*, 33, 729, 1971.
6. Hershman, J.M. and C.L. Edwards, *ibid* 34, 814, 1972.

THYROID FUNCTION IN THE LONG-TERM FOLLOW-UP OF PATIENTS TREATED WITH IODINE-131 FOR THYROTOXICOSIS

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Summary In February, 1972, 58% of patients euthyroid after iodine-131 therapy for thyrotoxicosis between 1954 and 1966 had a raised plasma thyroid-stimulating-hormone (T.S.H.) (>7.4 mU/l) and 42% a normal T.S.H. level. A group of 69 of the euthyroid patients with a raised plasma T.S.H. (25.0 ± 2.0 mU/l) in 1972 was re-examined annually for three years. There was no apparent change in the mean plasma T.S.H. level between 1972 and 1975 in the patients remaining euthyroid, but overt hypothyroidism developed in 3 patients in 1973, in a further 3 patients in 1974, and in 1 patient in 1975. In contrast, none of a group of 61 patients, euthyroid with a normal plasma T.S.H. (4.0 ± 0.2 mU/l) in 1972, developed overt hypothyroidism over the next three years, although slightly raised T.S.H. levels were recorded in 3 patients in 1974 and in a further 6 patients in 1975. Both the mean serum T-4 and T-3 in the euthyroid patients with a raised plasma T.S.H. were significantly lower, but still in the respective normal ranges, than those in the euthyroid patients with a normal plasma T.S.H. No significant difference in the fasting serum-cholesterol or triglyceride levels could be demonstrated between the two groups. Since no patient with a normal plasma T.S.H. after iodine-131 treatment for thyrotoxicosis six to eighteen years earlier developed overt hypothyroidism over a three-year period, the follow-up of such patients need not be so frequent as that of similarly treated euthyroid patients with a raised plasma T.S.H. in whom overt hypothyroidism develops at the rate of 2-5% per year.

Introduction

THE treatment of thyrotoxicosis with radio-iodine results in a high incidence of hypothyroidism—

greatest in the first post-treatment year at 7-22%, and continuing at 2-5% per annum thereafter,¹ with a cumulative incidence of 80% fifteen years after therapy in some centres.² Thyroid failure developing in the early months after iodine-131 treatment is not difficult to diagnose, and a low serum-thyroxine (T-4) is the most sensitive index of impending hypothyroidism.³ On the other hand, the diagnosis of hypothyroidism which develops insidiously many years later is more difficult. Since at least 3000 patients are treated with radio-iodine for thyrotoxicosis in the United Kingdom each year, it would be of value to identify those patients at risk of developing thyroid failure. Although a raised circulating level of thyrotrophin (thyroid-stimulating hormone, T.S.H.) is generally a good index of impaired thyroid function, it is not uncommonly observed after radio-iodine treatment and may persist for many months in patients euthyroid by all other criteria.⁴⁻⁷ It is, therefore, of no value in predicting when hypothyroidism will develop. However, Toft et al.^{5,7} studied patients with normal T.S.H. levels over a period of two years who had been treated with radio-iodine for thyrotoxicosis between 1954 and 1966 and similarly treated patients with raised T.S.H. levels, and found that all the patients who developed overt hypothyroidism over the two-year period were derived from the high-T.S.H. group. Such a finding raises the possibility of predicting patients in whom hypothyroidism may develop as a late complication of radio-iodine therapy by estimating the plasma T.S.H., and thereby reducing the long-term follow-up commitment of endocrine units.

The present report is an extension to three years of the study of these patients treated with iodine-131. On the basis of the plasma T.S.H. level a more rational follow-up policy is suggested for the ever-increasing number of patients who have been treated with radio-iodine for thyrotoxicosis. Furthermore, by estimating the circulating triiodothyronine (T-3) and T-4 levels in addition to plasma T.S.H., it becomes necessary to re-evaluate the effect of altered function of the brain/thyroid axis in patients treated with radio-iodine for thyrotoxicosis.

Patients and Methods

In February, 1972, the serum T-4 and plasma T.S.H. were estimated in 233 euthyroid patients who had been treated with iodine-131 for thyrotoxicosis in the endocrine clinic of the Royal Infirmary, Edinburgh, between 1954

TABLE I—MEAN SERUM T-4, T-3, AND T.S.H. LEVELS (\pm S.E.) IN PATIENTS WITH HIGH SERUM T.S.H. LEVELS IN 1972 AND IN PATIENTS REMAINING EUTHYROID AND AVAILABLE FOR STUDY OVER THE FOLLOWING THREE YEARS (ALL TREATED WITH IODINE-131 FOR THYROTOXICOSIS BETWEEN 1954 AND 1966)

Year	No. of patients	Serum T-4 (nmol/l)	Serum T-3 (nmol/l)	Plasma T.s.H. (mU/l)	No. developing overt hypothyroidism	No. lost to follow-up
1972	69	88.0 \pm 1.0	—	25.0 \pm 2.0	—	—
1973	66	84.0 \pm 1.0	—	22.6 \pm 1.8	3	0
1974	61	84.0 \pm 1.0	—	21.6 \pm 2.0	3	2
1975	57	75.0 \pm 3.0	1.52 \pm 0.05	26.6 \pm 2.6	1	3

TABLE II—MEAN SERUM T-4, T-3, AND T.S.H. (\pm S.E.) IN PATIENTS WITH NORMAL PLASMA T.S.H. LEVELS IN 1972 AND IN PATIENTS REMAINING WITH NORMAL PLASMA T.S.H. LEVELS AND AVAILABLE FOR STUDY OVER THE FOLLOWING THREE YEARS (ALL TREATED WITH IODINE-131 FOR THYROTOXICOSIS BETWEEN 1954 AND 1966)

Year	No. of patients	Serum T-4 (nmol/l)	Serum T-3 (nmol/l)	Plasma T.s.H. (mU/l)	No. developing overt hypothyroidism	No. developing raised plasma T.S.H.	No. lost to follow-up
1972	61	113.0 \pm 4.0	—	4.0 \pm 0.2	—	—	—
1974	58	105.0 \pm 3.0	—	4.1 \pm 0.3	0	3	0
1975	47	105.0 \pm 4.0	1.73 \pm 0.05	3.9 \pm 0.3	0	6	5

and 1966. A group of 69 of these euthyroid patients with a raised plasma T.S.H. was studied again each year for three years, and a further group of 61 euthyroid patients with a normal plasma T.S.H. was studied again at two and at three years. The mean age of each group in 1975 was 63 years. The number of patients chosen for this follow-up study was arbitrarily determined as adequate for the purpose of the present study. Each patient was examined clinically by one observer (A. D. T.) and blood was withdrawn for the estimation of serum T-4, T-3 (1975 only), and plasma T.S.H. In addition, in 1975, the patients fasted overnight for thirteen hours prior to venepuncture, for the estimation of serum cholesterol and triglycerides. Hypothyroidism was diagnosed on clinical grounds and on the basis of a low serum T-4 (< 58 nmol/l) and a raised plasma T.S.H. (> 7.4 mU/l). For the present purpose the euthyroid state is defined as being when the patient is euthyroid clinically and when the serum T-4 level is within the normal range, irrespective of the level of plasma T.S.H.

Serum T-4 was measured by competitive protein-binding analysis⁸ in 1972-74 and by radioimmunoassay⁹ in 1975. Values obtained by these two methods showed no statistically significant difference. Serum T-3 was only measured in 1975, by radioimmunoassay under conditions essentially identical to those described for T-4. The sensitivity of the T-3 assay was 0.25 nmol/l, and interassay precision in the euthyroid range was 9.0% as coefficient of variation. Plasma T.S.H. was estimated, as previously described.¹⁰ Serum cholesterol and triglycerides were measured by 'AutoAnalyzer' (Technicon Instruments Co.) methods.^{11,12}

Results

In February, 1972, the plasma T.S.H. was raised in 136 (58%) of the 233 patients euthyroid after iodine-131 therapy and normal in 97 (42%).

The mean (\pm S.E.) serum T-4, T-3, and plasma T.S.H. levels in the 69 euthyroid patients with a high plasma T.S.H. in 1972 and in those remaining euthyroid and available for study in 1973, 1974, and 1975 are shown in table 1. Only 3 of these 69 patients developed overt hypothyroidism in the first year of follow-up; the plasma T.S.H. had risen in 1 (from 34.6 to 67.3 mU/l), had fallen in the 2nd (from 45.6 to 28.2 mU/l), and had remained virtually unchanged in the 3rd (90.4 and 92.8 mU/l). At two years 64 of the 66 remaining euthyroid in 1973 were available for study, and overt hypothyroidism had developed in a further 3 patients in whom the plasma T.S.H. remained essentially unchanged (32.8 and 32.0, 23.5 and 26.1, 27.5 and 31.2 mU/l). At three years, 58 of the 61 patients remaining euthyroid in 1974 were available for study,

and overt hypothyroidism had developed in 1 further patient in whom the plasma T.S.H. level rose from 39.0 to 64.0 mU/l. The mean (\pm S.E.) serum T-4, T-3, and T.S.H. levels in the 61 patients with a normal plasma T.S.H. in 1972 and in those remaining with a normal plasma T.S.H. and available for study in 1974 and 1975 are shown in table II. None of the 61 euthyroid patients with a normal plasma T.S.H. in 1972 developed hypothyroidism over the period 1972-75. Between 1972 and 1974 plasma T.S.H. became slightly raised in 3 patients (9.4, 9.7, and 12.6 mU/l), and between 1974 and 1975 it became elevated in a further 6 patients (8.1, 8.3, 9.2, 10.7, 12.8, and 13.2 mU/l). 5 patients were lost to follow-up.

The mean serum T-4 in the euthyroid patients with a raised plasma T.S.H. was significantly lower than that in the euthyroid patients with a normal plasma T.S.H. in 1972, 1974, and 1975 ($P < 0.001$ on each occasion). In addition, the mean serum T-3 was significantly lower in the euthyroid patients with a raised plasma T.S.H. than in the euthyroid patients with a normal plasma T.S.H. ($P < 0.001$). Mean serum T-3 and T-4 levels in the patients with normal T.S.H. levels did not differ significantly from the mean values observed for a normal population (1.70 and 107 nmol/l, respectively).

The mean (\pm S.E.) serum cholesterol and triglyceride levels in 40 euthyroid patients (33 female, 7 male) with normal T.S.H. levels and in 40 euthyroid patients with high T.S.H. levels matched for age and sex are shown in table III. There was no significant difference either in mean serum cholesterol or triglyceride concentrations or in their distribution frequencies between the two groups.

Discussion

The present study has confirmed that, in the majority of euthyroid patients with a raised plasma

TABLE III—MEAN SERUM CHOLESTEROL AND TRIGLYCERIDE LEVELS (\pm S.E.) IN 40 EUTHYROID PATIENTS WITH NORMAL PLASMA T.S.H. LEVELS AND IN 40 EUTHYROID PATIENTS WITH HIGH PLASMA T.S.H. MATCHED FOR AGE AND SEX (ALL TREATED WITH IODINE-131 FOR THYROTOXICOSIS BETWEEN 1954 AND 1966)

T.S.H. level	Serum-cholesterol (nmol/l)	Serum-triglyceride (nmol/l)
Normal	6.36 \pm 0.17	1.24 \pm 0.07
High	6.53 \pm 0.19	1.41 \pm 0.12

T.S.H. following iodine-131 treatment of thyrotoxicosis, the T.S.H. level will remain unchanged for long periods, although hypothyroidism will continue to develop in a small proportion. On the other hand, in no patient with a normal plasma T.S.H. six to eighteen years after radio-iodine therapy did hypothyroidism develop over a three-year period of review, although the plasma T.S.H. became elevated in 5% of these patients each year. These findings are highly relevant to the organisation of the long-term follow-up of radio-iodine-treated thyrotoxic patients. In our clinic, 20% of patients who remain euthyroid one year after radio-iodine therapy for thyrotoxicosis have a raised plasma T.S.H., and from the present study this figure increases to 58% at a mean twelve years after treatment. If an annual rate of hypothyroidism of 2% is assumed between one and twelve years after therapy, the calculated annual rate of transfer of patients from a normal to a high plasma T.S.H. is 5.5%, which is very similar to that of 5% per year observed between 1972 and 1975 in the euthyroid patients with normal plasma T.S.H. levels after radio-iodine treatment six to eighteen years earlier. It would appear, therefore, that plasma T.S.H. levels are of the same significance in patients from one to eighteen years after radio-iodine therapy. Plasma T.S.H. should be estimated at one year after treatment, when the early high incidence of hypothyroidism is over, and patients grouped into (1) those with a high plasma T.S.H. who require annual review and (2) those with a normal plasma T.S.H. who require to be reviewed at most every three years. Such a policy would reduce considerably the follow-up of the ever-increasing numbers of patients who have been treated with iodine-131 and who have all been reviewed at least on an annual basis in the past either in an endocrine clinic or by means of a computerised follow-up programme.

It is important to consider whether a raised plasma T.S.H. following radio-iodine is simply an indication for annual review of the patients known to be at risk of developing hypothyroidism in future years, or whether it is a sign of existing thyroid failure albeit subclinical. Previous studies of T.S.H. levels after treatment of thyrotoxicosis by iodine-131 or partial thyroidectomy have shown serum T-4 levels to be significantly lower in patients with a raised plasma T.S.H. than in those with a normal plasma T.S.H.^{6,7,13} No difference, however, was observed in the serum T-3 between the two groups.^{6,13} The maintenance of clinical euthyroidism by T-3 in patients with a high plasma T.S.H. level

was considered to reflect a compensatory mechanism which is probably T.S.H.-dependent. In contrast, the present study has shown, not only serum T-4, but also serum T-3 levels in patients with a high plasma T.S.H. to be significantly lower than the thyroid-hormone levels of the patients with a normal plasma T.S.H. after radio-iodine treatment. The falling T-3 and T-4 secreted by the irradiated thyroid gland will result in a raised plasma T.S.H. but, unlike the situation in iodine-deficiency goitre, for example, the irradiated thyroid may be unable to respond to a high circulating T.S.H. level with a compensatory increase in thyroid-hormone secretion. According to the dose of irradiation, which will vary from follicle to follicle, there may occur delay in mitosis followed by normal mitosis, delayed mitosis followed by cell death in mitosis, inhibition of mitosis or cell sterilisation, reduced cell life-span, and cell death.¹⁴ It is possible that the irradiated thyroid cell, unlike the normal cells, is unable to hypertrophy in response to T.S.H. or thyroid-stimulating antibodies, and thyroid stimulators, by inducing mitosis, may paradoxically increase the rate of cell death within the gland. Raised plasma T.S.H. may, therefore, simply reflect the reduced output of both T-3 and T-4 by the failing thyroid gland which is incapable of compensatory increase in thyroid-hormone secretion as a result of irradiation damage.

It is not possible at present to determine whether the suboptimal serum T-3 and T-4 levels in these patients with elevated plasma T.S.H. after iodine-131 treatment indicate existing significant hypothyroidism. It is well established that the pituitary thyrotroph is very sensitive to minor changes in the serum levels of T-3 and T-4,¹⁵ but other organs and tissue may be less sensitive to changes in circulating thyroid-hormone levels. Indeed, no difference could be demonstrated in serum cholesterol or triglyceride levels between the high and normal T.S.H. patients matched for age and sex, although hypercholesterolaemia is well recognised in overt hypothyroidism.¹⁶⁻¹⁹ It is clear that any increase in morbidity or mortality in the patients with raised T.S.H. levels and suboptimal T-3 and T-4 concentrations in the serum will only become apparent on long-term follow-up, and such a study is in progress.

If the patients with suboptimal thyroid-hormone levels and a raised plasma T.S.H. are considered to be hypothyroid, it is important to recognise the possibility of inducing thyrotoxicosis in some of the patients if the usual thyroxine replacement dosage of 0.1 to 0.2 mg is employed. The thyroid remnant may be auto-

mous due to circulating thyroid-stimulating antibodies, and evidence for autonomous function is provided by the observation that the iodine uptake of the gland is uninfluenced by pharmacological doses of exogenous T.S.H. despite normal levels of endogenous plasma T.S.H. in some patients previously treated with radio-iodine.¹⁰ If clinically euthyroid patients with suboptimal T-3 and T-4 levels and raised plasma T.S.H. are to be treated with thyroxine, it would be ideal if the replacement therapy could be adjusted such that the levels of plasma T.S.H. in response to intravenous thyrotrophin-releasing hormone lie within the normal range.

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REFERENCES

- Hagen, G. A. *Medical Clinics N. Am.* 1968, **52**, 417.
- Greig, W. R. *Br. J. Surg.* 1973, **60**, 758.
- Toft, A. D., Hunter, W. M., Seth, J., Irvine, W. J. *Lancet*, 1974, **i**, 704.
- Slingerland, D. W., Hershman, J. M., Dell, E. S., Burrows, B. A. *J. clin. Endocr.* 1972, **35**, 912.
- Toft, A. D., Barnes, E. W., Hunter, W. M., Seth, J., Irvine, W. J. *Lancet*, 1973, **ii**, 644.
- Tunbridge, W. M. G., Harsoulis, P., Goolden, A. W. G. *Br. med. J.* 1974, **iii**, 89.
- Toft, A. D., Irvine, W. J., Hunter, W. M., Seth, J. *ibid.* p. 152.
- Seth, J. *Clinica chim. Acta*, 1973, **46**, 43.
- Seth, J., Rutherford, F., McKenzie, I. *Clin. Chem.* (in the press).
- Irvine, W. J., Toft, A. D., Hunter, W. M., Kirkham, K. E. *Clin. Endocr.* 1973, **2**, 135.
- Kessler, G., Lederer, H. in *Automation in Analytical Chemistry* (edited by L. T. Skeggs); p. 341. New York, 1965.
- Levine, J., Zak, B. *Clinica chim. Acta*, 1964, **10**, 381.
- Evered, D., Young, E. T., Tunbridge, W. M. G., Ormston, B. J., Green, E., Petersen, V. B., Dickinson, P. H. *Br. med. J.* 1975, **i**, 25.
- Doniach, I. in *The Thyroid* (edited by S. Werner and S. Ingbar); p. 185. New York, 1971.
- Snyder, P. J., Utiger, R. D. *J. clin. Invest.* 1972, **51**, 2077.
- Mason, R. L., Hunt, H. M., Huxthal, L. M. *New Engl. J. Med.* 1930, **203**, 1273.
- Boyd, E. M., Connell, W. F. *Q. Jl Med.* 1937, **30**, 467.
- Wayne, E. J. *Br. med. J.* 1960, **i**, 1.
- Furman, R. H., Howard, R. P., Lakshmic, K., Narcia, L. N. *Am. J. clin. Nutr.* 1961, **9**, 73.

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PARTIAL FAILURE OF ANTERIOR PITUITARY AND THYROID PRESENTING AS MYXOEDEMA

By

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ABSTRACT

The development of a sensitive radioimmunoassay of plasma thyrotrophin (TSH) and the isolation and synthesis of thyrotrophin-releasing hormone (TRH) allows a precise evaluation of the disordered brain-thyroid axis. The present report describes a patient who presented with myxoedema due to partial failure of both the anterior pituitary and the thyroid gland. The degree of impaired function of either gland alone would not have caused her clinical presentation.

CASE REPORT

A 58 year old female school teacher presented in July 1973 to the Endocrine Clinic of the Royal Infirmary, Edinburgh, with the features of myxoedema. There was no goitre. The total serum thyroxine (serum T₄) measured by competitive protein binding (*Seth 1973*) was 1.0 µg/100 ml (normal 4.5-11.5 µg/100 ml), plasma TSH measured by radioimmunoassay (*Irvine et al. 1973*) 30 µU/ml (normal < 7.4 µU/ml) and antibodies were detected to thyroglobulin in a titre of 1:2500 by the tanned cell haemagglutination method. Antibodies against thyroid cytoplasm were negative by the complement fixation and the indirect immunofluorescence tests. The 4 h ¹³²I uptake by the thyroid gland increased normally from 13-26 % in response to bovine TSH ("Thytropar") 10 IU im daily for three successive days (*Irvine et al. 1973*), suggesting a diagnosis of pituitary hypothyroidism. Tomography of the pituitary fossa was normal and

the visual fields were intact on formal testing. Urinary luteinising hormone (LH) measured by haemagglutination inhibition was low for a post-menopausal female at 23.3 IU/24 h (normal > 36 IU/24 h). A standard insulin tolerance test was performed using 0.1 units soluble insulin/kg - body weight. The blood glucose (glucose oxidase method) fell to 8 mg/100 ml, but the plasma growth hormone (GH) level measured by radioimmunoassay (HGH-125 Imusay, Abbott Laboratories) was undetectable throughout the test. The plasma 11-hydroxycorticosteroids (11-OHCS) (Mattingly 1962) and the plasma prolactin measured by radioimmunoassay (Cole & Boyns 1973) increased normally from 21 to 45 $\mu\text{g}/100$ ml and from 0.19 to 0.59 mU/ml respectively. The elevated basal plasma TSH level of 30 $\mu\text{U}/\text{ml}$ was unchanged at 20 and 60 min after the rapid iv injection of 200 μg TRH.

When the patient had been taking L-thyroxine 0.15 mg daily for five months the brain-thyroid axis was re-investigated. She was clinically euthyroid, with a serum T_4 of 8.0 $\mu\text{g}/100$ ml and a plasma TSH of < 1.2 $\mu\text{U}/\text{ml}$ which remained undetectable following 200 μg TRH iv. Urinary LH remained low at 26.2 IU/24 h. Plasma GH increased on this occasion to 8.0 ng/ml during insulin-induced hypoglycaemia, the blood glucose falling to 10 mg/100 ml. Plasma 11-OHCS and prolactin levels rose normally during the test. The patient has been followed up for 18 months and remains well. There is no clinical or radiological evidence of pituitary tumour.

COMMENT

We have not observed a patient with a primary hypothyroidism in whom the absolute increase in the 4 h ^{132}I uptake by the thyroid gland was more than 8% following exogenous bovine TSH (Irvine *et al.* 1973). Unless an intrathyroidal enzyme defect was present, which is unlikely in the absence of either a goitre or a high radioiodine uptake, the demonstration of a raised plasma TSH, a high titre of circulating thyroid antibodies but a normal TSH stimulation test indicates an impaired thyroid reserve which in the presence of a normal anterior pituitary gland would not be associated with clinical evidence of hypothyroidism. The low urinary gonadotrophins before and after thyroxine replacement therapy suggest an element of pituitary failure. A lack of growth hormone response to insulin hypoglycaemia is well described in primary hypothyroidism (Iwatsubo *et al.* 1967), but the response in our patient was blunted after five months of adequate thyroxine replacement therapy. Furthermore the elevated plasma TSH level of 30 $\mu\text{U}/\text{ml}$ did not rise following TRH, implying that the thyrotrophs were already secreting TSH to their maximum capacity. In the presence of a normal thyroid gland such a degree of anterior pituitary failure would not cause myxoedema, but in the present case the elevated plasma

TSH was insufficient to maintain a failing thyroid gland and the combination of partial anterior pituitary and partial thyroid failure led to the development of clinical hypothyroidism. We believe this to be the first such case described but with the widespread clinical use of TRH and the radioimmunoassay of TSH more examples may be reported. Although it is tempting to postulate an autoimmune basis for both the thyroid and anterior pituitary dysfunction, circulating antibodies to anterior pituitary tissue were not detected by indirect immunofluorescence.

REFERENCES

- Cole E. N. & Boyns A. R.:* Hormone Research 4 (1973) 261.
Irvine W. J., Toft A. D., Hunter W. M. & Kirkham K. E.: Clin. Endocr. 2 (1973) 135.
Iwatsubo H., Omori K., Okada Y., Fukuchi M., Miyai K., Abe H. & Kumabara Y.:
J. clin. Endocr. 27 (1967) 1751.
Mattingly D.: J. clin. Path. 15 (1962) 374.
Seth J.: Clin. chim. Acta 46 (1973) 431.

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SHORT COMMUNICATION

ASSESSMENT BY CONTINUOUS CARDIAC
MONITORING OF MINIMUM DURATION OF
PREOPERATIVE PROPRANOLOL TREATMENT
IN THYROTOXIC PATIENTS

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SUMMARY

The effect of the beta-blocker, propranolol (40 mg 6-hourly orally) has been studied on the tachycardia of six patients with untreated thyrotoxicosis. Heart rate was monitored continuously using a light portable ECG recorder which allowed the patients to undertake normal activities during the recording periods. The most marked reduction in heart rate was evident at 24 h after starting propranolol treatment. In three of the patients there was only a minor further fall in heart rate despite continued propranolol administration, but in the remaining patients the reduction in heart rate with each successive day of treatment was more marked. These results suggest that if propranolol were to be used alone in the preparation of patients before partial thyroidectomy for thyrotoxicosis, a dose of 40 mg 6-hourly for 3-4 days might be sufficient.

The beta-adrenergic blocking drug, propranolol, is effective in relieving many of the peripheral manifestations of thyrotoxicosis (Shanks *et al.*, 1969). It has been used successfully in the treatment of thyrotoxic crisis (Das & Kreiger, 1969), and is a useful adjunct to iodine-131 in the treatment of thyrotoxicosis, controlling symptoms until the radioactive iodine has a therapeutic effect (Hadden *et al.*, 1968). It has the considerable added advantage in the post-irradiation period of not causing any change in the levels of circulating thyroid hormone and therefore allowing the response to therapy to be more readily assessed. However, propranolol is considered to be inferior to carbimazole as a long-term treatment of thyrotoxicosis (McLarty *et al.*, 1973), and the metabolic consequences of prolonged adrenergic blockade in thyrotoxicosis, such as osteoporosis, have not yet been fully elucidated. Recently, Lee *et al.* (1973) and Michie *et al.* (1974) have reported their experience with propranolol as the sole preoperative agent in patients undergoing partial thyroidectomy for thyrotoxicosis. Such a regime would appear to have certain advantages over the conventional form of pre-operative preparation with carbimazole and iodine and it is therefore

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important to establish the rate of effect of propranolol in rendering a patient with thyrotoxicosis suitable for surgery. The present paper assesses the response of heart rate to propranolol by continuous ECG monitoring of patients with thyrotoxicosis in an attempt to define the minimum pre-operative period of treatment.

Patients and methods

Six patients were studied (four females, two males) aged 26–63 years. The diagnosis of thyrotoxicosis was made on clinical grounds and on the basis of the effective thyroxine ratio (Toft *et al.*, 1973), the total serum thyroxine measured by radioimmunoassay (Seth *et al.*, 1975), and the 4 h uptake of iodine-132 by the thyroid gland. In addition, there was no rise in the plasma TSH level, following the intravenous injection of 200 μ g thyrotrophin releasing hormone. One patient was studied as an out-patient and five as in-patients. The in-patients were allowed at least 24 h to acclimatize to the hospital environment before starting continuous monitoring. The heart rate monitoring was carried out with miniature tape recording equipment (Oxford Instruments) using a modified V.5 chest electrode. The light weight and portability of these instruments allowed the patients to undertake normal activity during the recording periods. The C.120 'Memorex' tape cassettes were turned over at the end of 24 h and the batteries and tape cassettes were changed every 48 h. Care

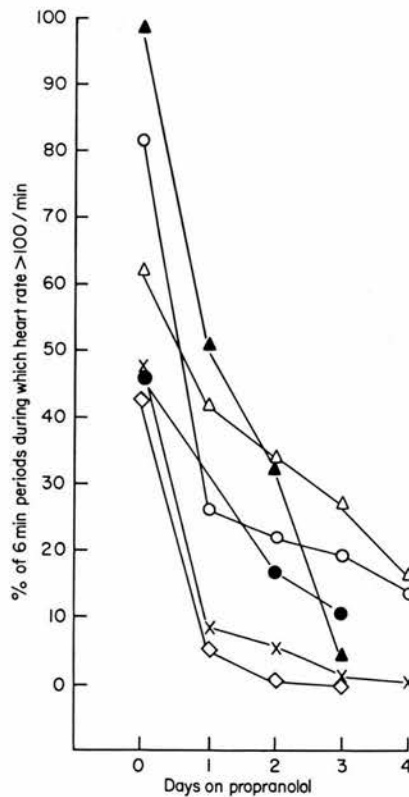


FIG. 1. The effect of oral propranolol 40 mg 6-hourly on the continuously monitored heart rate of six patients with untreated thyrotoxicosis.

was taken to ensure that tape recorder speed variations were minimized by using the same recorder for each patient over the taping period. The first day of monitoring was the control day and thereafter propranolol was administered orally in a dose of 40 mg 6-hourly and monitoring continued for a further 3–4 days. The completed tapes were replayed at 60 times real-speed and were checked by two independent observers. The signal was also processed by a Neilson Arrhythmia Computer (Neilson, 1974), which provided continuous heart rate measurements. These rates were stored in a solid state memory device with 240 individual stores. Each store therefore contained heart rate information for a 6 min period of the 24 h tape recording. In the final analysis the number of 6 min periods during which more than 600 sinus beats had been detected was expressed as a percentage of the total number of 6 min periods. This was effectively the proportion of time during which the heart rate was over 100 beats per minute.

Results

The effect of oral propranolol in a dose of 40 mg every 6 h for 3–4 days on the continuously recorded heart rate of six patients with untreated thyrotoxicosis is shown in Fig. 1. The greatest reduction in heart rate occurred during the first day of treatment with propranolol in the five patients in whom data was available for this period. In the sixth patient there was a failure of the recording system on the first day of therapy. In three of the patients there was only a small further fall in heart rate despite continued propranolol administration, but in the remaining patients there was a more apparent reduction in heart rate with each successive day of treatment. The effect of propranolol was not related to the severity of the thyrotoxicosis. The out-patient showed as good a response as the in-patients.

Discussion

Although the time course of action of intravenous propranolol on the heart rate, cardiac output and tremor of patients with thyrotoxicosis has been well documented (Howitt & Rowlands, 1966; Marsden *et al.*, 1968) the rate of response of these variables following oral therapy has not been fully evaluated. Vinik *et al.* (1968) demonstrated a significant fall in pulse rate in thyrotoxic patients 48 h after starting treatment with oral propranolol, but we are unaware of any more detailed studies.

In view of the demonstration that partial thyroidectomy may be safely performed in thyrotoxic patients prepared solely with propranolol (Lee *et al.*, 1973; Michie *et al.*, 1974), it is important that the minimum time of preparation of patients for surgery is established if such a form of therapy is to become more widely practised. A disadvantage of carbimazole therapy for thyrotoxicosis is the relapse rate of more than 50% after 18 months of treatment. The treatment of thyrotoxicosis primarily by partial thyroidectomy after preparation with propranolol is therefore an attractive proposition. The present study suggests that the pre-operative period of preparation with propranolol 40 mg 6-hourly orally could be 3–4 days.

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References

- DAS, G. & KREIGER, M. (1969) Treatment of thyrotoxic storm with intravenous propranolol. *Annals of Internal Medicine*, **70**, 985-988.
- HADDEN, D.R., MONTGOMERY, D.A.D., SHANKS, R.G. & WEAVER, J.A. (1968) Propranolol and iodine-131 in the management of thyrotoxicosis. *Lancet*, **ii**, 852-854.
- HOWITT, G. & ROWLANDS, D.J. (1966) Beta-sympathetic blockade in hyperthyroidism. *Lancet*, **i**, 628-631.
- LEE, T.C., COFFEY, R.J., MACKIN, J., COBB, M., ROUTON, J. & CANARY, J.J. (1973) The use of propranolol in the surgical treatment of thyrotoxic patients. *Annals of Surgery*, **177**, 643-646.
- MCLARTY, D.G., BROWNLIE, B.E.W., ALEXANDER, W.D., PAPAPETROU, P.D. & HORTON, P. (1973) Remission of thyrotoxicosis during treatment with propranolol. *British Medical Journal*, **ii**, 332-334.
- MARSDEN, C.D., GIMLETTE, T.M.D., MCALLISTER, R.G., OWEN, D.A.L. & MILLER, T.N. (1968) Effect of B-adrenergic blockade on finger tremor and Achilles reflex time in anxious and thyrotoxic patients. *Acta Endocrinologica*, **57**, 353-362.
- MICHIE, W., PEGG, C.A.S., HAMER-HODGES, D.W., ORR, F.G.G. & BEWSHER, P.D. (1974) Beta-blockade and partial thyroidectomy for thyrotoxicosis. *Lancet*, **i**, 1009-1011.
- NEILSON, J.M.M. (1974) High speed analysis of ventricular arrhythmias from 24 hour recordings. *Computers in Cardiology*, pp. 55-61. Institution of Electrical and Electronic Engineers, Chicago.
- SETH, J., RUTHERFORD, F. & MCKENZIE, I. (1975) Solid-phase radio immunoassay of thyroxine in untreated serum. *Clinical Chemistry*, **21**, 1406-1413.
- SHANKS, R.G., LOWE, D.C., HADDEN, D.R., MCDEVITT, D.G. & MONTGOMERY, D.A.D. (1969) Controlled trial of propranolol in thyrotoxicosis. *Lancet*, **i**, 993-994.
- TOFT, A.D., SETH, J., KIRKHAM, K.E., MARSHALL, A. & IRVINE, W.J. (1973) Assessment of *in vitro* thyroid function tests in 100 consecutive patients referred to a thyroid clinic. *Clinical Endocrinology*, **2**, 127-134.
- VINIK, A.I., PIMSTONE, B.L. & HOFFENBERG, R. (1968) Sympathetic nervous system blocking in hyperthyroidism. *Journal of Clinical Endocrinology and Metabolism*, **28**, 725-727.