Section of Endocrinology

President R I S Bayliss FRCP

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President's Address

Stimulation and Suppression Tests of Thyroid Function [*Abridged*]

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The symptoms of thyroidal disease in many patients depend upon the amount of thyroxine (T-4) and triiodothyronine (T-3) circulating in their blood stream; and the successful management of these cases depends upon deciding whether they are hyperthyroid, euthyroid or hypothyroid. Of the many tests of thyroidal function, the uptake of ^{132}I has proved particularly satisfactory (Hobbs 1962*a*, *b*, Hobbs *et al.* 1963) with its normal range (i.e. ± 2 S.D.) at four hours of 11–31% of the dose. With this technique an unequivocally correct diagnosis can be made in at least 85% of patients suffering from hyper- or hypo-thyroidism.

The T-3 suppression test for hyperthyroidism and the thyrotrophin (TSH) stimulation test for hypothyroidism are of particular value in elucidating the 15% of border-line cases in which the clinical and ^{132}I uptake studies are equivocal. In these difficult cases in which the usefulness of these tests has been assessed the ultimate diagnosis has been based on the serum protein-bound ^{127}I level, the clinical diagnostic index of Wayne (1960), the basal metabolic rate, prolonged clinical follow up, and the objective response to treatment with carbimazole or T-4.

Triiodothyronine Suppression Test

Thyroid extract, T-4 or T-3 will suppress pituitary TSH secretion and hence thyroidal activity in normal subjects (Greer 1951) but not in hyperthyroid patients (Werner *et al.* 1952, Greer & Smith 1954, Werner & Spooner 1955). It is upon this fact that the T-3 suppression test is based. Thyroid extract and T-4 are not used because in the dosage required to induce suppression they may provide after metabolic degradation sufficient iodide to influence directly thyroidal function. In normal subjects T-3 suppresses thyroid function in six days or less when given in a dose of 40 µg six-hourly. In this dosage we have induced no undesirable side-effects in hyperthyroid patients although Werner (1962) recommends a daily dose of only 50 µg because of the possible risk of inducing heart failure, anginal pain or cardiac arrhythmia. Occasional euthyroid patients, usually with anxiety states, experience increased sweating, cardiac consciousness and insomnia.

This test has proved useful in elucidating the diagnosis when (1) the uptake of ^{132}I is at the upper limit of normal but clinical evidence of hyperthyroidism is equivocal, (2) the clinical suspicion is high but ^{132}I uptake is in the normal range, (3) a high ^{132}I uptake could be due to hyperthyroidism or iodine deficiency, (4) the correctness of the diagnosis of hyperthyroidism is in doubt in a patient already started on antithyroid drugs, (5) endocrine exophthalmos, particularly affecting only one eye, has to be differentiated from other causes of proptosis, and (6) the thyroidal state and the prognosis is being assessed after treatment of thyrotoxicosis.

Normal suppression: The degree of suppression obtained in 51 euthyroid patients, 13 of whom had long-standing diffuse goitres, is shown in Fig 1. With the exception of 2 who failed to take the T-3 as instructed, all suppressed the ^{132}I four-hour uptake to 16 % or less of the dose and most to a level of 11% or lower.

Abnormal suppression: In 45 patients who gave equivocal clinical or ^{132}I uptake results but were ultimately proven to be thyrotoxic, T-3 failed to suppress ^{132}I uptake below 21% (Fig 2). In some patients the radioiodine uptake actually increased, a phenomenon noted previously by others (Shizume *et al.* 1960, Oddie *et al.* 1960). By this test there was a clear-cut distinction between euthyroid and hyperthyroid patients (Oddie *et al.* 1960, Kristensen *et al.* 1963, Friis

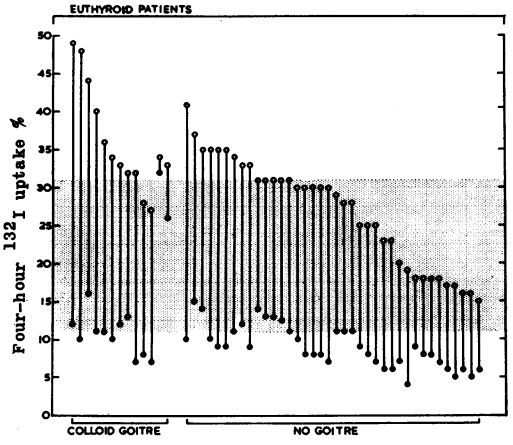

Fig 1 *The triiodothyronine suppression test (40 μg eight-hourly for six days) in 51 patients subsequently found to be euthyroid. Thirteen had diffuse goitres. The 2 who failed to respond did not take the triiodothyronine. ○ before T-3. ● after T-3*

1963). Thus when the problem is to distinguish goitrous or nongoitrous patients with an anxiety state from those with thyrotoxicosis, the T-3 suppression test is of great value. Suppression of the ^{132}I uptake to 16% or less excludes hyperthyroidism (with the single exception of that short phase when rare patients with Hashimoto's thyroiditis may exhibit manifestations of thyroidal overactivity). The converse is not necessarily true because failure to suppress does not mean that the patient is hyperthyroid since in addition to hyperthyroidism there are a number of circumstances in which T-3 suppression does not occur and yet the patient is euthyroid.

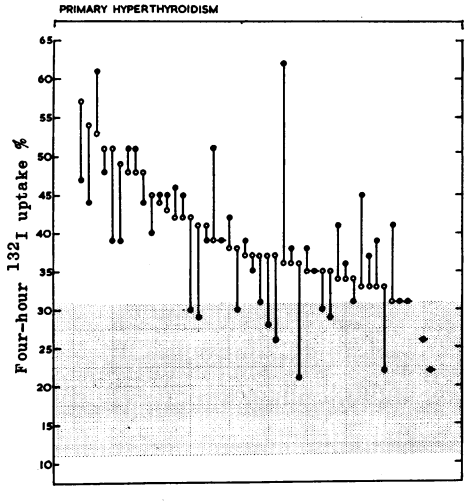

Fig 2 *The triiodothyronine suppression test in 45 hyperthyroid patients. ○ before T-3. ● after T-3*

Hyperthyroid patients who have been rendered euthyroid by antithyroid drugs, radioiodine therapy or thyroidectomy may or may not suppress with T-3 even though the ^{132}I uptake is in the normal range. This failure to suppress, despite euthyroidism, may persist for as long as thirty years after successful treatment, but a return to normal suppressibility seems to occur more quickly after thyroidectomy than after ^{131}I treatment (Werner 1956). This continued failure to suppress despite euthyroidism suggests that the abnormality responsible for the initial hyperthyroidism still persists and that the relief of the hyperthyroid symptoms is a consequence of mechanical or irradiational reduction in the mass of functioning thyroid tissue, an observation in keeping with our current views on the ætiology of thyrotoxicosis (Kriss *et al.* 1964, Adams 1965). Those patients who after treatment show T-3 suppression are certainly euthyroid but those who do not are often also euthyroid, and in our experience one cannot predict which group will later show the higher incidence of a recurrence of hyperthyroidism.

Whereas patients with diffuse non-nodular goitres show normal T-3 suppression, about a quarter of those with nodular goitres do not even though they are euthyroid. In these cases a 'scintiscan' will usually show an autonomous 'hot' nodule.

Patients with exophthalmos preceding manifestations of hyperthyroidism may pose a difficult problem in differential diagnosis. Early in the course of the syndrome, about one-quarter are reported as responding normally to T-3 (Guinet & Descour 1962). The differential diagnosis becomes particularly difficult when the eye signs are unilateral. In 12 consecutive cases (Fig 3) only one of our patients showed a normal response; the remainder, despite being euthyroid, showed the lack of suppression seen in hyperthyroidism.

TSH-stimulation Test

The use of TSH stimulation greatly enhances the diagnostic value of the radioiodine uptake test in hypothyroid states. It has proved of particular value in: (1) Distinguishing euthyroid patients with a low ^{132}I uptake from those suffering from hypothyroidism. (2) Diagnosing hypothyroidism in an early stage when radioiodine uptake and the PBI are in the normal range. (3) Confirming a diagnosis of thyroid deficiency in a patient already started on substitution therapy without prior scientific confirmation of the diagnosis. (4) Distinguishing primary hypothyroidism from that secondary to pituitary failure.

An optimal dose of TSH is 2·5 units intramuscularly and the maximum response obtained

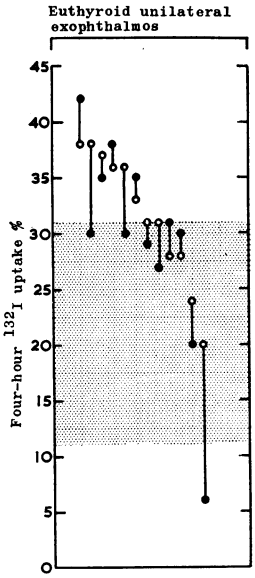

Fig 3 *The triiodothyronine suppression test in 12 euthyroid patients with unilateral exophthalmos. Only one suppressed and he was studied early in the course of the syndrome.* ○ *before T-3.* ● *after T-3*

eighteen to twenty-four hours later (Einhorn 1958). Thus we have measured the thyroidal uptake of ^{132}I before and twenty-two hours after TSH, and when an equivocal response is obtained after one injection of TSH a second or a third injection is given. In normal control subjects one injection increases the ^{132}I uptake to 35–56% of the dose (mean 45·7, S.D. 5·3) irrespective of the pre-stimulation uptake. The result of the TSH-stimulation test may be classified as: (1) Normal when the ^{132}I uptake increases to more than 35%. (2) No response when the uptake does not increase significantly (i.e. more than 5%). (3) Subnormal when the increase is significant but does not reach 35%.

Subnormal response: A subnormal response was observed in many patients singled out for the TSH test because they had a low initial uptake of ^{132}I or because there was clinical suspicion of hypothyroidism (Fig 4). Despite other tests of thyroid function and prolonged follow up it was not possible to establish an ultimate diagnosis of hypothyroidism in any of these patients. A subnormal but definite response to TSH was observed in patients who had already been started on substitution therapy, sometimes for as long as forty years, in the erroneous belief that they were hypothyroid, and also in patients given iodide for a diffuse nontoxic goitre. One patient with severe self-induced diarrhœa showed a decrease in ^{132}I uptake after TSH, doubtless due

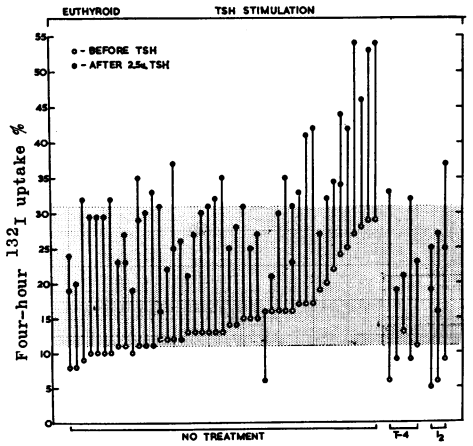

Fig 4 *The response to TSH (2·5 units I.M.) in euthyroid patients with a low initial uptake of ^{132}I or suspected clinically of hypothyroidism. Responses are also shown in euthyroid patients treated with thyroxine (T-4) or iodide (I_2)*

to failure to absorb the orally administered isotope.

A subnormal response was found in euthyroid thyroidectomized patients and in some patients with hypothyroidism secondary to pituitary failure (Fig 5). In the latter group the response to TSH was in part related to the severity of the pituitary insufficiency and in part to its duration. Repeated injections of TSH induce a step-wise increase in ^{132}I uptake which distinguishes these hypopituitary patients from those with primary thyroid failure, although some euthyroid patients with a low initial ^{132}I uptake showed a similar response.

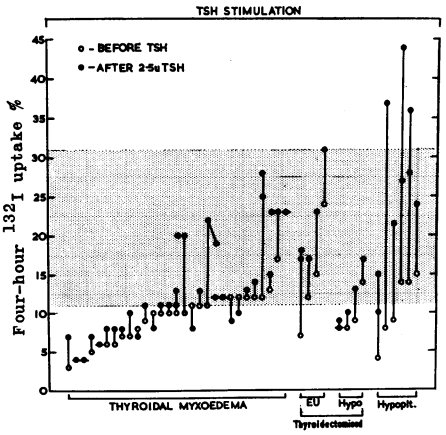

Fig 5 *The response to TSH in patients with primary hypothyroidism, hypopituitary* (hypopit) *patients and thyroidectomized patients who were either euthyroid* (eu) *or hypothyroid* (hypo)

No response: Most patients, who subsequently proved to be hypothyroid, due either to primary thyroid failure or after thyroidectomy, showed no significant response to TSH (Fig 5). A few showed some response to the first injection, but no significant increase with subsequent ones, in contrast to patients with hypopituitarism. One might anticipate that in primary thyroid deficiency a gland persistently secreting a subnormal amount of hormone would, if the pituitary-thyroid axis were normal, be stimulated to the limits of its capacity by endogenous TSH and be incapable of further response to exogenous TSH. The subnormal responses to TSH in euthyroid thyroidectomized patients, some definitely hypothyroid patients and some apparently euthyroid patients may be related to the two separate and distinct functions of the thyroid gland that are influenced by the thyrotrophic hormone, namely the trapping of iodide and the release of stored hormone. When thyroidal function is barely sufficient to maintain euthyroidism, there may be a stage when the amount of thyroid hormone secreted is near normal (as reflected by a low normal PBI level). This is sufficient to regulate the release of endogenous TSH, and although the thyroidal iodide trapping mechanism is working near its maximum, it is still capable of a modest though subnormal response to exogenous TSH. In some instances this low thyroid 'reserve' may be associated with mild and intermittent symptoms of hypothyroidism suggesting that from time to time the secretion of thyroid hormone is inadequate. Such patients cannot readily be recognized as hypothyroid because they have a low normal radioiodine uptake and PBI. None the less their sense of well-being may be improved and a substantial reduction in the serum cholesterol level be achieved by treatment with thyroxine (Jefferies *et al.* 1956).

Thus a negative response to repeated injections of TSH confirms primary thyroid failure, whether or not substitution therapy has already been started. A step-wise increase is very suggestive of hypopituitarism but may also occur in early and mild hypothyroidism and in some seemingly euthyroid patients. The significance of this response requires further study.

Summary

Simple studies with ^{132}I are of finite diagnostic value in 85% of patients with hyperthyroidism or hypothyroidism. In the 15% of border-line cases the T-3 suppression test or the TSH-stimulation test respectively provide useful additional diagnostic information.

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