

Joint Meeting No. 2

Section of Endocrinology with Section of Ophthalmology

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(President of the Section of Ophthalmology)

Meeting February 8 1968

Dysthyroid Exophthalmos

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Investigation of Endocrine Exophthalmos

In the first five years of the Unit, 50 patients with ocular symptoms were referred who were found to have the eye signs of Graves' disease. The results of investigation of thyroid function in this selected series are reported.

Subjects and Methods of Study

Table 1 shows the presenting ocular symptoms and signs. The commonest symptoms were stare and eye protrusion. The commonest signs were lid retraction, exophthalmos and lid lag, with limitation of external ocular movements in half the patients. The ocular signs were unilateral in two-thirds of the patients.

The following methods were used to assess thyroid function:

(1) The Wayne (1960) index is a clinical method of determining whether or not a patient is hyperthyroid.

(2) (a) The ^{131}I tests were chosen to provide accurate and relatively simple methods of determining hyperthyroidism. The T factor provides an indirect measure of thyroid uptake based on the proportion of a test dose of ^{131}I in three collections of urine (Fraser *et al.* 1953). The serum PB^{131}I reflects release of radioiodine from thyroid into blood. (b) The triiodothyronine

(T_3) suppression test is based on the fact that in normal people administration of thyroid hormone results in reduction or suppression of radioiodine uptake by the thyroid, presumably by inhibition of thyroid stimulating hormone (TSH) production by the pituitary. The T_3 suppression test was performed by measuring thyroid four-hour ^{132}I uptake before and after 120 μg of T_3 orally daily for three days. The normal four-hour uptake is 11–31%. Criteria for normal suppression were a second uptake (after T_3) less than 15% of the dose, or less than 85% of first uptake. There are other ways of performing the test, so that criteria for normal suppression vary. This suppressibility of thyroid radioiodine uptake is lost either partially or completely in patients with hyperthyroidism, or in euthyroid patients with the eye signs of Graves' disease (Werner 1955). The T_3 suppression test can thus be used to detect the abnormal pituitary-thyroid relationship of Graves' disease.

Table 1

Eye symptoms and signs in 50 patients

Symptoms	No. of patients
Stare	46
Protrusion	41
Soreness	25
Watering	22
Puffiness	21
Redness	11
Blurring	11
Double vision	10
<i>Signs</i>	
Lid retraction	46
Exophthalmos	46
Lid lag	45
Limitation of external ocular movements	24
Conjunctivitis	17
Corneal lesions	5

Table 2

Wayne clinical index and radioiodine tests in 50 patients

Wayne index	Total No. of patients	Nos. of patients with:		
		Hyperthyroid T factor (> 13)	Hyperthyroid PB ¹³¹ I (> 0.13%) ●	Subnormal ■ T ₃ suppression
< 11 (euthyroid)	24	1 (21)	5 (18)	15 (23)
11-19 (equivocal)	12	3 (12)	6 (8)	8 (11)
> 19 (hyperthyroid)	14	9 (10)	9 (9)	9 (10)

Figures in brackets indicate total number of patients in each group on whom the test was performed

● at 48 hours

■ 4 hour ¹³²I uptake after T₃ greater than 15% of dose, or greater than 85% of first uptake

Table 3T₃ suppression test in euthyroid patients with eye signs of Graves' disease

Series	Uptake	Daily T ₃ dose	No. of patients	T ₃ suppression	
				Normal	Abnormal
Werner (1955)	24 h ¹³¹ I	75 µg 8 days	10	0	10
Guinet & Descour (1962)	24 h ¹³¹ I	200 µg 8 days	13	4	9
Hobbs (1963)	4 h ¹³² I	120 µg 6 days	16	1	15
Burke (1967)	24 h ¹³¹ I	75 µg 8 days	8	4	4
Bayliss (1967)	4 h ¹³² I	120 µg 6 days	12	1	11
Hall <i>et al.</i> (1967)	6 h ¹³² I	100 µg 7 days	19	9	10
Present series	4 h ¹³² I	120 µg 3 days	23	8	15

(3) Circulating antibodies to thyroid antigens were sought as other evidence of thyroid disease. Two methods were used to detect circulating antibody to thyroid colloid antigen thyroglobulin – the sensitive tanned red cell (TRC) method and the less sensitive latex agglutination method.

(4) Bioassay of serum for long-acting thyroid stimulator (LATS), the factor found in the sera of most hyperthyroid patients and believed responsible for this thyroid disease, was performed in several patients.

Results

Table 2 shows that by the Wayne clinical score half the patients fell into the euthyroid range.

(1) *Thyroid tests* (Dr T McK Robb and Dr R Parfitt): As shown in Table 2, by thyroid uptake (T factor) few (13/43) were hyperthyroid, but by PB¹³¹I rather more (20/35), while the majority (32/44) were subnormally suppressible by T₃. Among those 'clinically euthyroid' (by Wayne index), whose other ¹³¹I tests were usually but not always normal, this subnormal suppression by T₃ was almost as frequently found, so confirming the usefulness of this test with euthyroid subjects with exophthalmos.

As indicated in Table 3, other authors have also found this T₃ suppression test usually abnormal in euthyroid patients with eye signs of Graves' disease. None, however, except Werner (1955), have found it always abnormal – Hall *et al.* (1967) at the other extreme found it normal in half such patients.

(2) *Thyroid antibodies*: The results of antibody studies are shown in Table 4. The thyroglobulin TRC test was positive at titres of 1/250 in 2 patients and at 1/25 in a further 2 patients – a total of 4 positives in the 8 patients in whom it was performed. The less sensitive latex test was negative in the 30 patients in whom it was performed, and so is not sufficiently sensitive for use in this context. The TRC test and other sensitive tests for thyroid antibodies such as the fluorescent and complement fixation tests for microsomal antigen, have been found positive in over 50% of patients with the eye signs of Graves' disease, whether or not hyperthyroidism is present, and in up to 10% of normal women (Roitt & Doniach 1960, Buchanan *et al.* 1962, Hales *et al.* 1961, Kriss *et al.* 1967).

(3) *LATS assays* (Professor D S Munro): LATS bioassay was done on unconcentrated sera in 23 patients (Table 4), but not one positive was obtained. This is in accord with the findings of other studies in euthyroid patients with eye signs, though positive LATS titres are usually found in the presence of untreated or treated hyperthyroidism (Munro 1967, Kriss *et al.* 1967, Lipman *et al.* 1967).

Table 4

Antibody and LATS studies

Wayne index	Nos. of patients with:		
	TRC 1/250	Positive latex	Positive LATS
< 11	0 (2)	0 (13)	0 (10)
11-19	1 (2)	0 (9)	0 (7)
> 19	1 (4)	0 (8)	0 (6)

Figures in brackets indicate total number of patients in each group on whom tests were performed

In summary, the T_3 suppression test was usually (32/44) but not always abnormal in these patients with eye signs of Graves' disease, in contrast with the fact that many were clinically euthyroid and showed normal ^{131}I tests; a few (4/8) also showed circulating thyroid antibodies.

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Observations on the Course of Exophthalmos after ^{131}I Therapy

Several observers have stressed that misleading impressions result if studies on the course of exophthalmos rely solely upon changes in the appearance of the eyes (Soley 1942, Rundle & Wilson 1945, Hales & Rundle 1960, Hamilton *et al.* 1960). Lid retraction may lead to an impression of forward protrusion of the eye and any subsequent reduction in width of the palpebral fissure may be mistakenly interpreted as lessening of ocular protrusion. In this paper repeated clinical assessments and measurements of exophthalmos have been made at regular intervals in a large series of patients treated with radioiodine. A clear distinction has been made

between the clinical impression of exophthalmos (apparent exophthalmos) and measurements of ocular protrusion (measured exophthalmos).

Patients and Methods

All the patients were treated for thyrotoxicosis with ^{131}I at the Royal Infirmary, Sheffield, between January 1961 and December 1967. The diagnosis was confirmed by a ^{131}I tracer study and in most cases by a chemical protein-bound iodine (PB ^{127}I) estimation. The majority of the patients were included in a clinical trial of different doses of ^{131}I (Smith & Wilson 1967) and received doses of between 3,500 and 14,000 rads. Twenty patients had previously undergone thyroidectomy for thyrotoxicosis. Antithyroid drugs were used routinely to control troublesome symptoms of thyrotoxicosis persisting after ^{131}I therapy. Women accounted for 84.4% and men for 15.6% of the patients. The mean age (54.6 years) and age distribution (26–84 years) was similar for both sexes.

Before treatment, the incidence of the eye signs listed in Table 1 was noted, and exophthalmos was measured. Early measurements were made by a group of not less than 4 independent observers with a Luedde perspex bar and the mean value calculated. Since September 1965, readings have also been taken with a Hertel exophthalmometer by a single observer (D I R J). A mean value for the degree of exophthalmos in each patient has been obtained by adding the readings from the right and the left eye and dividing by two. It was established that there was good agreement between the two methods of measurement ($r=0.93$). In follow-up studies a single remeasurement with the Hertel instrument has been taken to follow change in measured exophthalmos.

Table 1

Incidence of eye signs in thyrotoxicosis (694 patients)

Lid lag	43.0%
Lid retraction	37.2%
Periorbital oedema	32.1%
Apparent exophthalmos	28.0%
Diplopia	10.4%
Ophthalmoplegia	6.0%
None of the above	31.4%

Accordingly, all patients treated prior to September 1965 were recalled in mid 1967; the degree of exophthalmos was remeasured and ocular signs recorded. Since September 1965 serial measurements with the Hertel instrument are available. Of the 866 patients treated adequate initial data were available in 825. Of these 801 are still living and 749 (93.5%) have been reviewed.