GRAVES'S DISEASE: THE CLINICAL TYPES AND THEIR MANAGEMENT*

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In thyrotoxicosis we consider one of the key problems of internal medicine. On one side classical Graves's disease overlaps the toxic nodular goitres (see Table I).

In both there is overproduction of thyroid hormone, but in other respects there are important differences. The precise aetiological relationship, for example, between secondary toxic goitre and classic Graves's disease is still not clear.

On another side Graves's disease merges into the anxiety states, autonomic imbalance, and neurocirculatory asthenia. On still another there are the gross and intriguing conditions of exophthalmos and ophthalmoplegia that still baffle our comprehension. Beyond are even more obscure linkages with other endocrinopathies, conditions with thymic enlargement, and myopathies.

Classification

Therefore a working classification of Graves's disease such as that given in Table II inevitably presents us

TABLE II.—Classification of Thyrotoxicosis

Group 1.—Classical Graves's disease, exophthalmic goitre, toxic diffuse goitre, primary toxic goitre.
Group 2.—Toxic nodular goitre:
(a) toxic adenoma, hyperfunctioning single nodule (3% of thyrotoxicosis)
(b) toxic multinodular goitre
sporadic endemic
(c) functioning (glandular) thyroid carcinoma with metastases
Group 3.—Ophthalmic types of Graves's disease including exophthalmic ophthalmoplegia
Group 4.—Thyrotoxicosis factitia

with rather a hotchpotch. All the first group of terms are of course synonymous, and the clinical picture is too well known to require description.

Among the toxic nodular goitres, the toxic single nodule is almost certainly a true benign new growth,

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growing and functioning autonomously. In this case thyrotoxicosis is truly thyrogenic, and therefore it is fundamentally different, aetiological, from classic Graves's disease, the origin of which is almost certainly extrathyroid.

The nodules in many toxic multinodular goitres, occurring sporadically, result from previous waves of thyrotoxic hyperplasia. These patients have a long history of low-grade or remittent thyrotoxicosis, and the nodules develop at foci of excessive hyperplasia in the gland substance. But in the endemic type the nodules are due to previous simple hyperplasia, thyrotoxicosis being only a late secondary development. In fact, radio-iodine studies have shown that in the endemic types the nodules are less actively secreting than the internodular tissue (Leblond *et al.*, 1946).

With regard to thyroid cancer, only a very small proportion of patients ever manifest thyrotoxicosis. The hormone-forming ability of the malignant cells parallels their degree of cellular differentiation. Thus it is in the highly differentiated adenocarcinoma with follicles and colloid that thyrotoxicosis may occur. The cancer tissue is never as actively secreting as the normal follicles, but by virtue of its bulk, especially if there are metastases, a marked excess of hormone may be produced (Seidlin *et al.*, 1946; Fitzgerald and Foote, 1949).

The essential lesion in all the cases in Groups 1 and 2 is some degree of thyroid hyperplasia and hypersecretion. But in the ophthalmic types (Group 3) the emphasis is on the ocular changes. The patient may be hyperthyroid; but she may also be euthyroid or even hypothyroid, as in the post-operative subgroup.

In thyrotoxicosis factitia the same systemic manifestations as in natural thyrotoxicosis result from excessive ingestion of thyroid extract. The patient may be overdoing a treatment for obesity or, more often, there is a psychopathic desire to escape into illness or even a suicidal intent.

It is remarkable that such extraneous overdosage with thyroid extract causes inactivity and actual atrophy of the patient's own gland. Thus in two such patients studied by Skanse and Riggs (1948), after a tracer dose of radio-iodine, virtually no radioactivity was demonstrable over the thyroid gland, and in 48 hours 97% of the tracer dose was excreted in the urine, showing that they had no functioning thyroid tissue whatever.

The Pituitary-Thyroid Axis

If we try to understand the thyrotoxic hotchpotch we soon come down to a diagrammatic concept of what has been termed the pituitary-thyroid axis (Fig. 1). There tends to be a physiological balance between thyroid-stimulating hormone (T.S.H.) from the anterior pituitary, and the resulting thyroid secretion (T.H.), which, getting into the blood, circulates back and tends to reduce T.S.H. Administer thyroid extract in excess as in thyrotoxicosis factitia and there is complete suppression of pituitary T.S.H. The patient's own thyroid then shrinks and atrophies.

This concept has a practical bearing on the treatment of toxic adenoma. Using radio-iodine we can compare the iodine uptake and secretory activity of the adenoma with those of the surrounding thyroid tissue. The radio-iodine, undergoing synthesis into hormone, will expose a photographic plate when a thin slice of gland is laid on it.

FIG. 1.—Diagram of the pituitary-thyroid axis. T.S.H.=Thyroid stimulating hormone. T.H.=Thyroid secretion.

Thus, in Fig. 2, modified from Cope *et al.* (1947), the degree of shading indicates the secretory activity. For example, the normal gland is moderately shaded, but the diffusely enlarged gland of Graves's disease, which is of course secreting more hormone, is jet black.

The interesting point is that the gland tissue surrounding the toxic adenoma is shown as shrunken and pale and therefore inactive compared with the normal. Thus, excessive thyroid secretion from the adenoma, inhibiting

FIG. 2.—1. Normal gland. 2. Diffuse hyperplasia. 3. Hyperfunctioning single adenoma with atrophic uninvolved gland. (Cope *et al.*, 1947.)

the anterior pituitary, causes inactivity and shrinkage of such gland tissue as still remains under physiological control. The treatment of toxic adenomata should clearly be surgical, the neoplastic nodule being resected with a layer of the surrounding tissue. But a radical bilateral operation is obviously unnecessary and inadvisable.

Quite recently, also, there has been a rather exciting approach, on the basis of this pituitary-thyroid axis, to the treatment of classic thyrotoxicosis. We cannot give thyrotoxic patients more thyroid hormone, but it is hoped that closely related compounds, such as tetrabromthyronine and tetrachlorthyronine, which do not stimulate the metabolism much, may yet retain the particular chemical linkage which inactivates the anterior pituitary. These are now being tried in large doses by Lerman and Harington (1949).

Eye Signs

It is known that injections of pituitary T.S.H. cause exophthalmos in guinea-pigs, but what part, if any, T.S.H. plays in the eye signs of human thyrotoxicosis

can still only be guessed at. I shall not go into these eye signs in detail, but one or two points may be mentioned.

The first is that, though we talk about the "eye" signs, the eye itself is normal. The clinical appearances all depend on changes in the orbital tissues behind the eyeball.

There are three categories of eye signs, which, with the related orbital tissue changes, are shown in Table III.

TABLE III.—Table of Eye Signs and Related Orbital Tissue Changes

Eye Sign	Orbital Tissue Changes
1. Lid retraction (retraction of the upper lid)	Spasm of the striated levator palpebrae superioris
2. Protrusion of the eyeball (exophthalmos) and lids	Enlargement of the orbital tissues due to deposition of fat in classic Graves's disease. ? Oedema in "malignant exophthalmos"
3. Ophthalmoplegia	Fatty and round-cell degeneration in extrinsic eye muscles

Lid retraction, or, more precisely, retraction of the upper lid, depends on spasm of the striated levator palpebrae superioris; exophthalmos and bulging of the lids depend on overcrowding of the orbital cavity by the enlarged orbital tissue. The enlarged contents cannot escape backwards out of the closed bony orbit, so they push the eyeball and lids forwards. Ophthalmoplegia, which is much more common than is generally recognized, seems to be related to the fatty and lymphocytic degeneration found in the extrinsic eye muscles in Graves's disease.

The only ocular change to benefit much from controlling hyperthyroidism is lid retraction. Where lid retraction is the dominant eye sign there is good cosmetic improvement after thyroidectomy or thiouracil. But it is different with exophthalmos and ophthalmoplegia. These are both aggravated if anything by controlling hyperthyroidism.

Fig. 3 shows the average effect of thyroidectomy on ocular prominence in nearly 40 consecutive thyrotoxic patients (Rundle, 1945). In each case pre-operative readings of ocular prominence were subtracted from post-operative readings and the results averaged. It is clear that the eye becomes about 1 mm. more prominent

FIG. 3.—Showing average effect of thyroidectomy on ocular prominence.

than previously during the year following thyroidectomy; so, where exophthalmos and ophthalmoplegia predominate, the prognosis for cosmetic benefit should be guarded. Of course the central lesion in thyrotoxicosis is hyperactivity of the thyroid, and control of this thyroid hyperactivity transcends all else in therapeutic importance.

Systemic Pathology

The pathology of uncomplicated and complicated cases of thyrotoxicosis is summarized in Table IV, which takes into account the intensity of thyrotoxicosis and

TABLE IV.—*Systemic Pathology of Thyrotoxicosis*

System	Thyrotoxicosis slight—→severe, prolonged	Thyrotoxicosis plus local or associated diseases
Cardiovascular	Auricular fibrillation Tachycardia—→congestive failure Anasarca	Early cardiac breakdown or "masked hyperthyroidism," e.g., angina pectoris
Central nervous	Hyperexcitability—→Acute thyrotoxic delirium	Organic reaction types of psychosis, if predisposition
Endocrine	Low sugar tolerance	Diabetes, if diabetic anlage
Muscular	Weakness—→Thyrotoxic myopathy	Relation to myasthenia gravis and periodic paralysis
Bone	Decalcification—→spontaneous fracture	
Alimentary	G.I. hypermotility—→G.I. crises with vomiting and diarrhoea	
Lymphatic	Lymphoid hyperplasia, thymic enlargement	
Cutaneous		Localized pretibial myxoedema

the state of the end organ. In essence, thyrotoxicosis causes cellular exhaustion in all the systems. It is a chemical disorder; there is remarkably little structural damage. So, if we can eradicate the chemical intoxication, recovery is immediate and gratifying. Of course any local or associated disease will remain and must be taken into account in the prognosis.

In the cardiovascular system, for instance, poisoning of the myocardium produces effects ranging from simple tachycardia to auricular fibrillation and congestive failure with oedema, even where the heart was previously healthy (Kepler, 1932). No distinctive histological lesions are found in the myocardium (McEachern and Rake, 1931). And if there is associated cardiac disease (for example, mitral stenosis or coronary sclerosis) failure may be precipitated by relatively minor degrees of thyrotoxicosis. In fact, thyrotoxicosis may be overlooked as in "masked hyperthyroidism."

Similarly, in the nervous system there is every manifestation from hyperexcitability to acute thyrotoxic delirium, which is a true chemical toxic confusional state. And if there be a psychopathic personality even slight or moderate thyrotoxicosis may precipitate one of the organic reaction types of psychosis. Similarly, in the endocrine system, diabetes may develop if the patient has a diabetic anlage. With this approach we can work out interesting correlations between the intensity of the thyroid intoxication, the functional reserves of the various systems, and the total clinical state of the patient.

Management of Thyrotoxicosis

Now what is the management of the ordinary patient who presents herself with thyrotoxicosis? Should we, or should we not, use the antithyroid drugs? I believe the answer is emphatically yes, that we should use the thiouracils in every case of thyrotoxicosis: with the thiouracils the toxic goitre can be quickly converted into a non-toxic goitre.

In fact, at the present time the practical management of thyrotoxicosis should proceed by the following steps.

First, all toxic goitres should be converted into non-toxic goitres by antithyroid therapy. Secondly, time should be allowed in the euthyroid state for full physical rehabilitation to occur. Thirdly, depending on the individual, a decision should be made for thyroidectomy or for antithyroid therapy as the definitive treatment. The chief considerations here are the patient's psychological, social, and economic backgrounds and how likely is recurrence at some time after the cessation of the drug.

The ideal is to admit the patient to hospital for three or four days right at the beginning unless she is bordering on crisis and therefore should not be moved. Table V summarizes what is done during this initial short stay in hospital.

TABLE V.—*Management of Thyrotoxicosis*

1. Careful history taking—especially social, economic, and psychological factors.
2. Examination—characters of goitre, evidence of systemic damage or of local or associated disease.
3. Measurement of lid retraction, ocular prominence, eye movements.
4. Metabolic rate, haematological examination, etc.

By daily conversations we can establish psychological rapport and get to know the patient as an individual, which counts for so much in treatment. We can also get a fairly accurate assessment of the severity of the thyrotoxicosis at the outset. The patient is then discharged on a daily dose of about 200 mg. of methylthiouracil or the equivalent dose of an allied agent.

Studies by Stanley and Astwood (1947) have shown that the methylthiouracil is about twice as potent as thiouracil, and more than two and one half times as potent as propylthiouracil. But, curiously enough, all three have generally been given in the same dosage. In other words, the dosage of methylthiouracil has been unnecessarily heavy; when used in amounts of 200 mg. daily the response to it is quite adequate and the risk of toxicity is minimal. Nevertheless the patient is told to omit the tablets and report at once if there be sore throat, malaise, temperature, or rash. However, there is certainly no need to dilate on these occasional effects or to intimidate the patient: she reports weekly for observation of subjective improvement, change in the character of the goitre, improvement in the weight and pulse rate. In addition it is useful to check the metabolic rate every fortnight and to measure the ocular changes monthly.

When the patient is euthyroid she is switched to a maintenance dose of 100 mg. of methylthiouracil daily. She is kept on this maintenance dose in a euthyroid state until she recovers all her lost weight and strength. Usually such ambulatory treatment lasts at least two months.

Definitive Treatment

A decision on the definitive line of treatment has usually been made during the initial period in hospital.

In considering thyroidectomy it should be emphasized that preparation with the thiouracils has changed the whole complexion of thyroidectomy and its results. Since we are removing a non-toxic goitre from a physically fit and rehabilitated subject there is no need whatever for haste. Perfect anatomical exposure and perfect haemostasis are the watchwords. We can then identify the parathyroids and recurrent nerves and preserve them. The amount of gland to be left behind can be assessed deliberately. The mortality rate should be virtually *nil*, and the patient need stay in hospital only eight to nine days altogether.

The decision for definitive antithyroid therapy or thyroidectomy depends on the individual patient and the therapeutic facilities available. So far as the individual patient goes, I do not believe that any rule of thumb such as, "Operate on nodular goitres, treat the diffuse ones with thiouracils," will give us the best results. Whatever the characteristics of the goitre, thyroidectomy is the better treatment for what might be called the chronic psychosomatic patient. We may recognize this chronic psychosomatic patient from details of the personal and social histories. There are excessive anxiety, nervous tension, domestic and economic difficulties, and previous evidence of maladaptation or physical disintegration. Thyroidectomy is especially indicated if the goitre be large and thyrotoxicosis severe, or if it is aggravating some associated disease, such as mitral stenosis, or diabetes.

At the other end of the spectrum no one would wish to urge surgery on the young patient with a short history, a small goitre, and mild thyrotoxicosis, especially if its onset was associated with some epochal or other self-limited stress, and especially, too, if the other personal factors are favourable. It is also obviously necessary to employ the antithyroid agents definitively in the patient who refuses operation, or if thyrotoxicosis is only a minor factor in the total clinical picture, or where organic mental disorder looms large.

Medical or Surgical Management?

So far as the available therapeutic facilities are concerned it must be admitted that there is little to choose between really expert medical and really expert surgical management. So that, if we only have the choice between expert medical management and inept surgery, our choice is clear. But medical management, to give its best results, must be individual and indefinitely prolonged. Too often, after a gratifying preliminary response to thiouracil, the patient becomes "lost," as illustrated in the following case.

A married woman aged 26 developed symptoms of thyrotoxicosis shortly after the birth of her second child. The first child had died during the pregnancy and she had also lost her father shortly before. She was treated in the medical department of a big metropolitan hospital and responded well to methylthiouracil. When she again became pregnant she was transferred to the obstetric department. Though antithyroid therapy was omitted during most of her pregnancy, she remained fairly well. After her confinement she was so occupied with the household and her children that she stopped attending hospital altogether.

Finally, in January, 1950, nearly three years after its first onset, she again presented with full-blown Graves's disease. She was shaky, irritable, easily tired, and had lost 14 lb. (6.4 kg.) in the six weeks prior to attending.

On physical examination she presented all the signs of severe thyrotoxicosis, including a diffuse pulsatile goitre,

marked tachycardia, tremor, muscular wasting, and hyper-excitability.

After preparation with methylthiouracil and iodine, bilateral subtotal thyroidectomy was done. She is now relieved of her symptoms and the need for continued treatment.

It is precisely because of such patients that many of us think that surgery is the most practical, expeditious, and sure method of controlling hyperthyroidism in the majority of cases. In his recent presidential address to the American Goiter Association, Haines (1950) also reaches this conclusion after research into the results of modern treatment.

When physical rehabilitation is complete the thiouracils are discontinued and the patient is put on Lugol's iodine 5 min. (0.3 ml.) thrice daily. On the twelfth day, 48 hours before operation, she is readmitted. The haemoglobin, white cells, and metabolic rate are checked the day before operation and, if satisfactory, thyroidectomy is done. It must be emphasized that really conscientious and prolonged medical treatment gives such a high percentage of excellent results that we, as surgeons, must raise our sights to the target of perfection if we are to justify and maintain our dominant place in treatment. Our aims should therefore be: (a) no tetany, no nerve lesions, and a minimum incidence of post-operative hypothyroidism or recurrent thyrotoxicosis; (b) the patient should not need to stay in hospital more than nine days in an uncomplicated case; and (c) the scar should be at necklace level and scarcely visible.

Radio-iodine Therapy

Finally, we may say a word about radio-iodine therapy. Such therapy, though at present largely limited to special centres in the United States, may be expected to become more generally available in the next decade, and, unless unforeseen objections arise, it should prove an extremely simple, safe, and cheap method of controlling hyperthyroidism. Moreover, the goitre usually undergoes fibrosis and disappears. The greatest difficulty is to estimate the dose required. Overdosage leads to irrevocable myxoedema. Present indications are that it is an easy and effective method of treating the patient with severe cardiac or other complication, especially if elderly. Furthermore, toxic diffuse goitres are distinctly more responsive than toxic nodular goitres (Haines, 1950; Moe *et al.*, 1950; Richards *et al.*, 1950).

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