MEDICAL PRACTICE

Occasional Survey

Aetiology of Hyperthyroidism—I*

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Hyperthyroidism is not a single entity but at least 99% of cases are associated either with diffuse enlargement of the thyroid gland (Graves's disease) or with nodular goitre (Plummer's disease). Before considering the former, I should like to mention that some of the rare but no less interesting causes of hyperthyroidism are listed in table I.

TABLE I—Type of Hyperthyroidism

Graves's disease (diffuse toxic goitre)	} 99%
Toxic nodular goitre	
Multinodular (Plummer's disease)	
Uninodular (toxic adenoma)	
Nodular goitre with Graves's disease	
Excess thyroid stimulating hormone	
Pituitary tumour	
Choriocarcinoma and hydatidiform mole	
Embryonal testicular carcinoma	
Other malignancy (?)	
Extraneous thyroid hormone	
Exogenous: Intentional factitious	
Overenthusiastic therapy	
During T—3 suppression test	
Thyroid hormone induced	
Endogenous: Metastatic thyroid carcinoma	
Struma ovarii	
Jod-Basedow (exogenous iodide)	
Transient, associated with thyroiditis	
Subacute	
Hashimoto's	
Irradiation (D.X.R. or ¹³¹ I)	
TSH administration	
Hypothalamic (?)	

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Excessive Production of TSH (or "TSH")

For roughly 25 years overproduction of pituitary thyrotrophic hormone was thought to be responsible for hyperthyroidism. This concept evolved naturally from the finding that the anterior pituitary gland elaborated a hormone which specifically induced hypertrophy and hyperplasia of the thyroid gland.¹ Harington himself² warned against too ready acceptance of this theory in the absence of any objective evidence, and his caution was vindicated many years later when techniques for assaying TSH improved and immeasurably low levels were uniformly reported in hyperthyroidism. It is now accepted that pituitary TSH has no direct role in the development or maintenance of the hyperthyroid state—except in a few isolated cases of functioning tumour of that gland. The first acceptable case of this syndrome was described by Jailer and Holub,³ whose patient had a pituitary tumour with hyperthyroidism and high serum TSH as measured by bioassay in the tadpole; after deep x-irradiation to the pituitary gland the hyperthyroidism remitted and serum TSH levels returned to normal. Other well-documented cases with increased circulating immunoassayable TSH have been described by Faglia *et al.*,⁴ Hamilton *et al.*,⁵ and O'Donnell *et al.*⁶ The occurrence of hyperthyroidism with acromegaly has been reported but the association remains obscure.⁷

Of similar rarity but equal interest are cases of hyperthyroidism due to excessive production of thyroid-stimulating hormone by tumour tissue elsewhere in the body. Normal human placenta produces chorionic TSH, which is thought to play a part in the development of the hyperthyroid features sometimes found in pregnancy.⁸⁻⁹ It is not altogether surprising to find reports of hyperthyroidism due to hydatidiform mole,⁹⁻¹⁰ choriocarcinoma,¹¹ or even embryonal testicular carcinoma.¹² In almost all cases a circulating thyrotrophin has been demonstrated and treatment of the primary condition has resulted in amelioration of the hyperthyroid features. It should be emphasized that neither molar nor chorionic TSH has been shown to cross-react with human pituitary TSH in radioimmunoassay systems. There is no convincing evidence that other secreting tumours of non-endocrine origin produce hyperthyroidism.⁷

Excessive Extraneous Thyroid Hormones

Hyperthyroidism may follow intentional overdosage with thyroid hormones, either misguidedly as part of attempted weight-reducing regimens or as an addiction.^{13 14} Over-enthusiastic treatment of hypothyroidism may result in hyperthyroidism, especially when the original diagnosis is incorrect and increasing amounts of thyroid hormone are administered in an attempt to relieve symptoms erroneously attributed to thyroid deficiency. Unbelievably large doses of thyroid hormone may be tolerated by some euthyroid subjects; my personal record is a patient who took 15-20 grains of thyroid sicca daily for years without trouble, until a lack of resolution of her problem caused her to increase her dose to 28 grains a day and she was subsequently admitted in severe hypermetabolic heart failure. In her case—and in others we have studied—the major part of the ingested hormone passed through the intestine unabsorbed, which probably accounts for the apparent tolerance.¹⁵

During T-3 (tri-iodothyronine) suppression tests transient hyperthyroidism may be induced in some marginal thyrotoxicos owing to the additive effect of the T-3 superimposed on the non-suppressible release of hormone by the thyroid gland.

Apart from these examples of hypermetabolism resulting from clear-cut overdosage, thyroid hormones occasionally seem able to induce hyperthyroidism even when given in normal replacement amounts.¹⁶⁻²⁰

It is difficult to exclude a coincidental occurrence of hyperthyroidism in these subjects but the evidence for an inductive role of thyroid hormone is suggestive. Direct stimulation by thyroxine (or T-3) of hypothalamic TRH synthetase has been shown *in vitro*;²¹ a similar mechanism *in vivo* could account for these reported cases of thyroid-hormone induced hyperthyroidism.

Excessive thyroid hormone may rarely be secreted by functioning metastatic thyroid carcinoma. Uptake of radioactive iodine by metastases is usually limited and hypersecretion of a degree sufficient to produce hyperthyroidism is probably related to large tumour bulk.^{22 23} In one published case,²⁴ and in one of my own, hyperthyroidism was associated with excessive production of T-3, not T-4 (thyroxine)—that is, T-3 toxicosis due to functioning metastatic thyroid carcinoma.

Struma ovarii (teratoma of the ovary with predominant thyroid tissue) is another rare source of ectopic thyroid hormone production. Kempers *et al.*²⁵ reviewed 25 patients with this disorder, eight of whom had hyperthyroidism; five had coexistent adenomatous or colloid goitre. In struma ovarii malignancy is often low grade and hyperthyroidism is treatable with ¹³¹I. Reporting a case of their own, Brown *et al.*²⁶ stated that nine of 23 published hyperthyroid cases of struma ovarii had cervical goitre; the absence of LATS or TSH from the serum of Brown's patient suggested that the hyperthyroidism did not result from a circulating thyrotrophin but from hypersecretion of thyroid hormone(s) by teratomatous thyroid tissue within the ovary. The cervical goitre in 40% of cases is not readily explained.

Iodide-induced Hyperthyroidism

Jod-Basedow (iodide-induced) hyperthyroidism has been recognized for very many years. Coindet,²⁷ who introduced iodine as a treatment for goitre, drew attention to the onset of tachycardia, palpitation, insomnia, and loss of weight and strength in some of his cases—which he attributed to overdosage of iodide, and he therefore urged caution in its use. As a result of the debate that took place at that time, iodide administration fell into disrepute and about 100 years were to elapse before its use was again popularized. In the United States its reintroduction in the 1920's and 1930's in the form of iodized salt was questioned by many workers concerned by the consequent rising incidence of hyperthyroidism,^{28 29} though this was generally attributed to overdosage or to the pre-existence of nodular or adenomatous goitres. Ek *et al.*³⁰ described the development of indisputable hyperthyroidism in seven of 100 previously euthyroid subjects who were given 10 mg potassium iodide daily for two weeks; the authors suggested that pre-

existing hyperfunction of the thyroid gland might have been masked by iodine deficiency, to be brought out when an adequate supply of iodine induced synthesis of extra, excessive amounts of thyroid hormone.

The most striking and well-documented example of iodide-induced hyperthyroidism has been provided by the Tasmanian experience.³¹⁻³³ To combat goitre on the island, potassium iodate was added to the bread supply, 2 p.p.m. calculated on dry weight to provide a mean intake of 80-270 µg per day. Within four months an increase in thyrotoxicosis on the island had been noted, which persisted for several years. Those affected were predominantly of an older age-group (>50 years) with multinodular goitres and did not develop ophthalmopathy. The close association between iodide prophylaxis for goitre and the development of hyperthyroidism seems incontrovertible, but iodide can probably induce hyperthyroidism even in non-goitrous areas: Ermans³⁴ reported hyperthyroidism in four patients with "hot nodules" of the thyroid gland given 500 µg potassium iodide daily for three to nine months; Vagenakis *et al.*³⁵ were forced to abandon a study of the effects of potassium iodide when four of eight goitrous subjects developed thyrotoxicosis; these subjects did not have "hot nodules" and lived in or near Boston—that is, they were not from a low-iodine area.

How iodide induces hyperthyroidism is not understood. It appears somehow to expose an underlying thyroid abnormality, perhaps providing more substrate for thyroid hormone formation by a gland already under increased stimulation by TSH. In this case one would expect hyperthyroidism of limited duration as the extra hormone released should shut off TSH secretion. Continued intracellular iodide deficiency might itself act as a stimulus without the mediation of TSH³⁶ and might help to perpetuate the hyperthyroid state.

Transient Thyroiditis

Transient hyperthyroidism is occasionally seen in association with thyroiditis (subacute or Hashimoto's), after ¹³¹I or deep x-irradiation of the thyroid gland, or after TSH administration. Sudden release of preformed thyroid hormone from the damaged or stressed gland would account for most cases.

Hypothalamic Hyperthyroidism?

I said earlier that hypersecretion of TSH could not be held responsible for the pathogenesis of hyperthyroidism; by inference, a role for thyrotrophin releasing hormone (TRH) is ruled out. A single case reported by Emerson and Utiger³⁷ is of interest in this respect. Their patient presented originally with typical hyperthyroidism and low circulating TSH; treatment with ¹³¹I and carbimazole was followed by biochemical, if not clinical, hypothyroidism. A recurrence of her hyperthyroidism after carbimazole had been stopped was associated with high serum concentration of T-3 and T-4 and, surprisingly, persistent abnormally high serum TSH values; TRH failed to stimulate further TSH secretion. The case is made for thyrotoxicosis resulting from TRH over-production and it is perhaps noteworthy that recurrence of disease was preceded by a stroke, which raises the possibility of cerebral and, more specifically, hypothalamic damage. While this case is of considerable interest it cannot be said to throw any light on the usual form of hyperthyroidism in which serum TSH is low and TRH unresponsiveness is invariably found.³⁸

About toxic nodular goitre there is very little to say. Genuine single toxic nodules usually prove to be follicular adenomas of autonomous function and unknown aetiology; in multinodular toxic glands one or more nodules usually appear dominant on thyroid scanning. The clinical picture differs in some respects

from that found in Graves's disease (less florid, later age of onset, absent exophthalmos) and long acting thyroid stimulator (LATS) is not found in the serum; the role of this stimulator will be discussed more fully below.

T-3 Toxicosis

Before finally approaching the problem of the aetiology of Graves's disease, I should like to mention the condition known as T-3 toxicosis, the criteria of which have been outlined by Hollander *et al.*: signs and symptoms of hyperthyroidism; normal levels of serum PBI or T-4 concentration; normal levels of serum free T-4; normal or raised thyroidal uptake of radioactive iodine, not suppressible by adequate doses of T-3; raised total serum T-3 concentration.³⁹ To these one would probably now add failure of response to exogenous TRH.

The first recorded instance of this syndrome appears in an article by MacLagen *et al.*,⁴⁰ who, using paper chromatographic methods of resolving the thyroid hormones, detected a hyperthyroid patient with normal levels of serum T-4, but high levels of T-3. Little attention was paid to the entity until more specific techniques for T-3 assay were developed;⁴¹ since then several large series have been reported.³⁹⁻⁴² It must be emphasized that T-3 toxicosis is simply a variant of hyperthyroidism, found in patients with Graves's disease, autonomous adenomas, or multinodular glands⁴³ and its existence sheds little, if any, light on the aetiology of hyperthyroidism.

Graves's Disease

My main concern in this lecture is with the aetiology of Graves's disease, which I confessed at the outset is not known. Yet the evidence is accumulating—some circumstantial, much collateral or presumptive—and one feels the answer is not too far away. It is perhaps not inappropriate today to review the factors that seem central to the problem and I intend to do this under three headings: who develops Graves's disease? What precipitates Graves's disease? What causes Graves's disease?

Who Develops Graves's Disease?

Hard facts about the prevalence of hyperthyroidism are not easy to ascertain. A U.K. survey covering 106 general practices (171 doctors) in England and Wales between May 1955 and April 1956 suggested a prevalence of hyperthyroidism of 25-30 per 10⁴ female population; figures for males were less.⁴⁴ A hospital inpatient inquiry in 1967 calculated 3.1 cases of hyperthyroidism per 10⁴ hospital discharges. In neither survey are diagnostic criteria specified. Perhaps the most complete and carefully compiled data are those from Olmsted County, U.S.A.,^{45, 46} which suggest an incidence of 5-6 per 10⁴ females per year.

Comparable statistics from other parts of the world are difficult to find. Maruchi *et al.*,⁴⁷ surveyed 59,106 Japanese people, 2,098 of whom had goitres and 47 were hyperthyroid, to give a prevalence rate of about 8 per 10⁴ subjects examined. Two recent publications have drawn attention to the increased prevalence of hyperthyroidism in the elderly.^{48, 49} A three-year survey in Denmark disclosed a yearly incidence of thyrotoxicosis in people aged 60 years and over which was seven times greater than in a younger age-group (0.98 and 0.14 per 1,000 individuals, respectively).⁴⁹

THYROTOXICOSIS IN UNDERDEVELOPED COUNTRIES

In underdeveloped countries thyrotoxicosis has been considered to be rare.

Trowell⁵⁰ and Gelfand,⁵¹ clinicians with extensive experience of disease patterns in Africa, believed it to be almost non-existent among blacks. Kihn⁵² found thyrotoxicosis to account for 1 in 501 of all white admissions to Groote Schuur Hospital, Cape Town, between 1952 and 1955; the corresponding figures for coloured (mixed ethnic origins) and black admissions were 1 in 812 and 1 in 3,561, respectively. Patel⁵³ reported that only five black thyrotoxic women were seen at Mulago Hospital, Kampala, from 1955 to 1962 out of a total of 33,196 admissions; during the same period 20 white thyrotoxic patients were included in a total of 9,062 admissions. Dancaster⁵⁴ found 18 thyrotoxic blacks out of 74,000 hospital admissions in Natal (incidence 0.024%), whereas Indian thyrotoxics constituted 0.7% of their hospital admissions. Hyperthyroidism in black Africans certainly seems to have been uncommon. But the picture is changing: in Nairobi at the Kenyatta National Hospital five thyroidectomies were performed for hyperthyroidism in the seven-year period, 1956-62; for three years from 1966 to 1968 the figures was 17; and McGill⁵⁵ was able to report his experience of no fewer than 25 Kenya Africans with thyrotoxicosis.

TABLE II—Incidence of Hyperthyroidism at Groote Schuur Hospital (1959-65)

Race	Hyperthyroid	In-patients		Out-patients	
		Total	% Hyperthyroid	Total	% Hyperthyroid
White	290	78,699	0.37	1,270,990	0.023
Coloured	212	79,508	0.27	1,497,855	0.014
African	9	18,572	0.05	250,354	0.004

Caution must be exercised in the interpretation of these data as some selection and bias might easily have been present: this is most evident when the populations at risk are examined more closely. Table II presents the number of thyrotoxics seen at Groote Schuur Hospital during the period 1959 to 1965, broken up into three major ethnic groups. The apparent racial discrepancy is largely explained by the nature of the African population living in Cape Town at this time—in 1965 there were 25,000 African families—that is, 25,000 African women with their husbands—there were 130,000 young men employed as contract short-term labourers.⁵⁶ This male preponderance ($\pm 6:1$) in the population at risk must partially explain the relative infrequency of a disease which is normally predominant in the female. Probably, however, this is not the whole explanation and a real increase has occurred in the prevalence of hyperthyroidism in the African. Socio-economic factors may play a part in this changing picture, raising such questions as the effects of urbanization, of the adoption of more stressful life-styles and, not least, of dietary influences.

Remarkably little has been said of the nutritional status of different population groups in studies of the epidemiology of hyperthyroidism. Trowell⁵⁰ speculated that dietary deficiency might render the endocrine system generally more resistant to the emergence of disease. Underfeeding, especially in respect of protein, can effect depression of thyroid function in laboratory animals possibly through reduced responsiveness to thyrotrophin⁵⁷⁻⁶⁰ and a minor impairment of thyroid function has been shown in human malnutrition.^{61, 62} "Protection" against the development of hyperthyroidism might also be provided by ingestion of goitrogens in natural foodstuffs or by specific dietary deficiencies. The antithyroid action of cassava⁶³ might be significant in some African communities, but it is not a dietary constituent of Southern Africa.

PSYCHOSOMATIC ASPECTS

Much has been written about the psychosomatic aspects of hyperthyroidism, and Trowell,⁵⁰ Patel,⁵³ and others have debated whether the African life pattern might in some way protect against developments of the disease. Charcot⁶⁴ considered it to be a neurosis and influenced generations of physicians

to accept this basis for the disease, but many studies of behavioural and emotional aspects of hyperthyroidism⁶⁵⁻⁶⁸ have delineated no clear-cut pattern of pre-existing personality or emotional experience and one is led to agree with the conclusions that mental attitudes in hyperthyroidism are "a concomitant of the disease state" rather than a predisposing cause.

It has often been said that Africans do not share the Caucasian susceptibility to some diseases previously classed as "psychosomatic"—for example, duodenal ulcer⁶⁹ or ulcerative colitis⁷⁰—but the significance of this observation in relation to hyperthyroidism in particular and to our increasing comprehension of immune responses and autoimmune diseases in general must remain conjectural. It has, for instance, been postulated that malarial infection might confer protection against the development of autoimmune diseases in some exposed populations,⁷¹ but this factor cannot obtain in most parts of Southern Africa from which the disease has been eradicated. Probably other infections may similarly suppress humoral or cellular immunity.⁷²

GENETIC FACTORS

In considering the existence of a population predisposed to hyperthyroidism, genetic factors are clearly important. It has long been known that thyrotoxicosis tends to run in families: Bartels⁷³ found a 60% familial disposition in a study of 70 patients with Graves's disease, an observation which has been confirmed by many authors, and numerous thyroid abnormalities have since been listed in relatives of thyrotoxic patients⁷⁴⁻⁷⁸ (table III). Studies of twins have provided good evidence for a genetic predisposition, and the incidence of Graves's disease has been calculated to lie between 30 and 60% of monozygotic twins and 3 to 9% of dizygotic.⁷⁹ Toxic diffuse goitre was reported in four monozygotic twin pairs by Hassan *et al.*⁸⁰ all four pairs had circulating antibody to thyroidal microsomal antigen, three of four pairs to gastric mucosal-cell antigen. A genetically transmitted predisposition seems highly likely, acting perhaps through immunological homeostatic instability.

TABLE III—Abnormalities Reported in Relatives of Patients with Graves's Disease

- (1) Goitre, hyperthyroidism, hypothyroidism.
- (2) Hashimoto's thyroiditis, circulating antithyroid antibodies.
- (3) Other autoantibodies or autoimmune diseases.
- (4) Abnormal thyroid function tests and increased turnover of radioactive T₄.
- (5) Abnormal non-butanol extractable iodine.
- (6) High circulating LATS.

In this survey of possible predisposing factors a positive family history of hyperthyroidism (or an associated autoimmune disorder) emerges as the strongest marker for the disease. A psychosomatic factor seems unlikely but it is suggested that dietary (or other environmental) influences may help to explain the apparent rarity of the disease in underdeveloped countries; in those classed as "emergent" racial differences seem to be diminishing. While the existence of a genetically predisposed population must be favoured, environmental factors must not be ignored.

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Contemporary Themes

Social Effects of Fractures of the Neck of the Femur

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Summary

One-hundred-and-five patients were visited at home one year or more after they had been treated for proximal femoral fractures to assess the extent to which their social independence had been affected by the incident. Since the accident 25% had become more dependent. The principal factors contributing to this outcome included established dependence, great age at the time of injury, and a poor clinical result. The implications for social services and community care of preventing social impairment justify a more comprehensive investigation. The need for close co-operation between orthopaedic surgeons and geriatricians, already widely acknowledged, is further emphasized.

Introduction

Fractures of the proximal part of the femur, essentially a disease of old age, have been studied jointly by orthopaedic surgeons and geriatricians,^{1, 2} and the epidemiology of fractures of the femoral neck has recently been reviewed.³ In Malmö the incidence was almost doubled for each five-year increment of age over 60 years.⁴ The total female population of the U.S.A. trebled from 1900 to 1960 but the numbers of fractures increased twice as quickly—from 11,000 to 62,000—because of the rapid increase in the older age groups.⁵ Thus these fractures constitute a special and increasing problem in many parts of the world and a "team" approach is the correct one.⁶ Where a joint approach does not exist the least that can happen is serious interruption of the flow of patients through orthopaedic wards.⁷ There are numerous descriptions of survival and morbidity rates after these fractures.^{8, 9}

The impact of the problem on society now and in the future has not been studied before. We therefore pursued a joint inquiry into the social consequences of this accident in elderly patients in a part of England where 19.7% of the population is over 65.

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Patients and Methods

The hospital records of 205 consecutive cases of fractures of the proximal end of the femur were reviewed at least one year after the injury. Twenty-five patients had died in hospital, 39 died after discharge, another 24 patients could not be traced, and 12 known survivors had left the district.

Beals's study⁸ of survival after hip fractures suggests that a hospital mortality of 12.5% and a one-year survival rate of 50% is normal for this condition. The corresponding figures in our group were 12.2% and 54.6%. Examination of the other basic data showed that this group did not deviate appreciably from other published series in any important clinical respect.

Of the 105 patients who were visited one was not included because no surgical operation had been necessary, and the four youngest patients (aged less than 57 years) were omitted. The age and sex of the remaining 100 patients are shown in table I.

TABLE I—Age and Sex of 100 Patients followed up One Year after Fracture of Neck of Femur

Age (Years):	57-64	65-74	75-84	≥85	Total
Men	2	7	6	15	15
Women	10	24	33	85	85
Total	12	31	39	18	100

TABLE II—Length of Interval between Fracture and Operation in 86 Patients

No. of days	-1	-2	-3	-4	-5	-6	-7	-8	-9	-10	>10
No. of patients	18	29	20	12	2	1	2	1	1	1	1

The fracture was attributed to an "accident" in 62 cases, and there was no history of accident in 35 and no record in 3, but such a retrospective analysis is unreliable. Significant medical disability which contributed to or complicated the fracture was found in 82 cases.

Most of the fractures were trochanteric (40 cases) or subcapital stage III or IV (49).¹⁰ Another five cases were subcapital stage I or II, four were subtrochanteric, one was of another type, and in one case there was no record of the type of fracture.

PREOPERATIVE INTERVAL

The preoperative interval, which varied for several reasons—for example, delay in admission, the policy of the hospital—is