MEDICAL PRACTICE

Clinical Endocrinology

Hypothyroidism

DAVID EVERED, REGINALD HALL

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The clinical syndrome of hypothyroidism was first described by Gull in 1874.[1] The term myxoedema was coined by Ord four years later[2] and, though Haliburton pointed out in 1893 that "myxoedema" was not a constant feature of hypothyroidism[3], the terms were considered to be synonymous for many years. It was also widely accepted during the early years of this century that hypothyroidism was an "all or none" phenomenon. Nevertheless, the advent of more precise diagnostic techniques, which enable different aspects of thyroid function to be measured, have shown that hypothyroidism is a graded phenomenon. Hypothyroidism may, therefore, be defined as those conditions which result from suboptimal circulating levels of one or both thyroid hormones. The term "myxoedema" should be reserved for the particular presentation of advanced hypothyroidism in which there is undue swelling of the skin and subcutaneous tissue. The definition of hypothyroidism given is conceptually satisfactory but does pose problems in the practical definition of the various stages of thyroid failure. The problems arise in defining suboptimal levels of circulating thyroid hormone. The laboratory techniques available for assessing thyroid function fall naturally into three groups and the use of each group of techniques allows the definition of different aspects of impaired thyroid function.

Defining Impaired Thyroid Function

TESTS OF THYROID FUNCTION

The available techniques include measurement of circulating thyroid hormone concentrations and radioactive iodine studies. These tests are relatively crude and will generally identify only major degrees of thyroid failure. The most sensitive index of hypothyroidism among this group of tests is the demonstration of an impaired thyroid reserve by measuring the thyroidal uptake of ^{131}I after the administration of a pharmacological dose of thyroid-stimulating hormone (TSH).

TESTS OF PERIPHERAL TISSUE FUNCTION

The tests of function of the peripheral tissues are based on the demonstration of the cellular effects of suboptimal levels of circulating thyroid hormone. These tests include measuring the duration of the ankle tendon reflex, the serum cholesterol, and finding electrocardiographic changes consistent with hypothyroidism. These tests lack specificity and precision, however, but they frequently show abnormalities before measurements of circulating thyroid hormone concentration fall below an arbitrarily defined level.

TESTS OF HYPOTHALAMIC-PITUITARY FUNCTION

Impairment of thyroid function may be assessed by measuring the adaptive changes in hypothalamic-pituitary function, assuming that the hypothalamic-pituitary-thyroid axis remains intact. Now that the range of serum TSH concentrations in normal people has been defined[4] it may be assumed that increased TSH levels are a sensitive index of any deviation from the optimum level of circulating hormone and, to some extent give an indication of the magnitude of this deviation.[5] A rise in serum TSH concentration may be observed, with a prolonged and exaggerated rise after administration of thyrotrophin-releasing hormone (TRH) before there is any other measurable disturbance of thyroid function.[6] The hypothalamus and pituitary may therefore be considered to be the most sensitive "peripheral" tissues in terms of a reduced circulating thyroid hormone level.

Clearly, therefore, hypothyroidism may be defined clinically and in terms of measurable disturbances of thyroid function,

Department of Medicine, University of Newcastle upon Tyne
DAVID EVERED, B.SC., M.R.C.P.

Royal Victoria Infirmary, Newcastle upon Tyne
REGINALD HALL, M.D., F.R.C.P., Professor

Clinical and Laboratory Features of the Various Grades of Hypothyroidism

Grade	Clinical Features	Serum TSH	Thyroid Reserve	Thyroid Antibodies	PBI	Serum Cholesterol Level	Electro-cardiographic Changes
Overt	++	++	++	+ or 0	++	++	++
Mild	+	+	+	+ or 0	+ or 0	+	+
Preclinical	0	+	+	+ or 0	0	+ or 0	+ or 0
Thyroid antibodies without measurable change in function	0	0	0	+	0	0	0

Key: 0—Normal; ++—definite abnormality; +—slight abnormality.

peripheral tissue function, or hypothalamic-pituitary function. The range of diagnostic techniques available vary in their sensitivity and thus allow the identification of the various grades of thyroid failure (see Table).

Epidemiology

Little precise information is available relating to the prevalence or incidence of hypothyroidism in the community, although preliminary evidence suggests that myxoedema is more common than is generally supposed. On the basis of serum protein-bound iodine measurements Lowrey and Starr[7] have suggested a hypothyroidism prevalence of 7·1% in over 5,000 subjects, though this figure seems surprisingly high. It is certainly far above the prevalence of diagnosed hypothyroidism which from a preliminary survey in the North-east of England, occurs in about 0·2% of the adult population; a similar figure has been reported by Gordin *et al.*[8] from a community survey in North Finland. Hence probably there is a substantial pool of undiagnosed hypothyroidism in the community and many of these people will have minimal or non-specific symptoms. There almost certainly exists an additional pool of people with true preclinical hypothyroidism. The frequency of the various grades of thyroid failure in the community remains to be ascertained.

Aetiology

The causes of thyroid failure are numerous. Hypothyroidism is most commonly associated with autoimmune thyroid disease, though circulating thyroid antibodies may be detected in some people without clinical or laboratory evidence of thyroid failure. The presence of thyroid antibodies is useful to define this group of diseases, though it in no way implies a causal relationship. Thyroid damage induced by radioactive iodine therapy or thyroid surgery is a frequent cause of hypothyroidism. Failure of thyroid hormone synthesis is rarely due to genetic defects of various intrathyroidal enzymes.

Goitrogens may interfere with thyroid hormone production or release by several mechanisms. Iodides in excess may cause goitre with or without hypothyroidism in some people. Iodide deficiency never causes hypothyroidism in the United Kingdom, though severe iodide deficiency may cause hypothyroidism, in some areas, leading to the syndrome of endemic cretinism (hypothyroidism, goitre, deafness, and mental retardation). Failure of TSH production as a result of hypothalamic-pituitary disease may also result in hypothyroidism.

Overt Hypothyroidism

The clinical features of overt hypothyroidism are well known and include lack of energy, intolerance to cold, acroparaesthesiae, dryness of the skin and hair, weight gain, constipation, hoarseness of the voice, typical facial appearance, and prolongation of the relaxation phase of the tendon reflexes. Confirmation of the diagnosis by laboratory investigation rarely presents any problem since all the conventional tests of thyroid function are abnormal. This state is the result of a major degree of thyroid failure.

Myxoedema coma, as its name implies, refers to an impaired level of consciousness usually developing in a patient with severe thyroid failure. The condition should be suspected in any patient with hypothermia, though spontaneous hypothermia is not often due to hypothyroidism. The patient generally has the characteristic appearance of myxoedema and the skin feels "icy cold". A low-reading rectal thermometer should be used to show that the temperature of the body core is reduced. Hypoventilation may occur leading to carbon dioxide retention and hypoxia. Respiratory and other infections are not uncommon. Arrhythmias and cardiac failure are common terminal events, particularly after over-vigorous treatment. The mortality rate is high in patients with established myxoedema coma.

Mild Hypothyroidism

The identification of patients with overt hypothyroidism rarely causes any problems. The recognition of lesser degrees of thyroid failure, however, presents many difficulties, since people with mild hypothyroidism frequently have minor or non-specific symptoms. Complaints of lack of energy and facial puffiness should always raise the possibilility of thyroid failure, particularly in those at risk—such as those with a family history of thyroid disease, particularly hyperthyroidism or hypothyroidism, or of pernicious anaemia, and in those previously subjected to destructive therapy to the thyroid.

Conventional tests of thyroid function may give equivocal results, though minor abnormalities of the electrocardiogram may be detected and the serum cholesterol concentration may be raised. Previously the only method of confirming the diagnosis was to show an impaired response of the thyroidal ^{131}I uptake to administered TSH. The diagnosis of mild hypothyroidism can now be confidently excluded by finding a normal serum TSH concentration and a raised level suggests that thyroid failure is likely to be the cause of the patient's symptoms.

Preclinical Hypothyroidism

Preclinical hypothyroidism may be defined as an asymptomatic state in which a reduction in thyroid activity has been compensated for by an increased TSH output to maintain a euthyroid state. Some aspects of preclinical hypothyroidism have previously been described by Bastenie and his colleagues,[9-12] who have defined this stage in terms of circulating thyroid antibodies, and by Fowler and his colleagues,[13 14] who have based their definition largely on raised serum cholesterol concentrations. It is certainly true that many people with preclinical hypothyroidism will have circulating thyroid antibodies or an elevated serum cholesterol concentration or both these phenomena, but neither of these findings is diagnostic of preclinical hypothyroidism. The diagnosis is made by demonstrating an elevated basal serum TSH level and a prolonged and exaggerated rise in serum TSH after administration of TRH in an asymptomatic person.[15] These subjects have a reduced thyroid reserve, which may be shown by a TSH stimulation test. The

abnormalities of thyroid function can be restored to normal by administration of thyroid hormone, though whether these asymptomatic people need hormone treatment remains to be proved.

Autoimmune Thyroid Disease

Circulating antibodies to various thyroid components can be found in hypothyroidism, preclinical hypothyroidism, and Hashimoto's disease, and these conditions show a variable degree of lymphocytic infiltration of the thyroid. The presence of thyroid antibodies correlates with the finding of lymphocytic infiltration of the thyroid and the titre of antibodies is also related to the extent of the lymphocytic infiltration. Many asymptomatic people with circulating thyroid antibodies show some impairment of thyroid function, similar to that seen in Hashimoto's disease, though this is usually of lesser degree (for example, lowered serum protein-bound iodine—PBI—reduced intrathyroidal iodine pool, raised plasma PB ^{131}I, and a raised serum TSH). There is, however, a group of people with circulating thyroid antibodies who have no measurable disturbance of thyroid function. These cannot therefore be classified as having preclinical hypothyroidism, but they must be regarded as being at risk for the development of hypothyroidism.

Thyroid antibodies are found in a substantial proportion of apparently normal people. Dingle *et al.*[16] examined and performed serological tests on a one in ten sample of the adult population, drawn from a general practice in the North-east of England. Antibodies to thyroglobulin in a titre of 1/25 or more were found in 16·2% of women and 4·3% of men and very high antibody titres of 1/80,000 or more were present in 4·6% of women and 1·6% of men. These findings are consistent with the proposition that a significant proportion of the population has undetected hypothyroidism or preclinical hypothyroidism, or is at risk for developing these conditions.

Classification of Hypothyroidism

Hence we propose that the stages of thyroid failure can be defined in the manner described. The clinical and laboratory features of overt hypothyroidism, mild hypothyroidism, preclinical hypothyroidism, and autoimmune thyroid disease not associated with thyroid failure are summarized in the Table. The prevalence of the various grades of hypothyroidism in the community is unknown and the natural history and biological significance of each of these stages of thyroid failure remains to be defined.

Relationship between Hypothyroidism, Lipid Disorders, and Ischaemic Heart Disease

Evidence has been presented suggesting that in a hospital population: (1) People with hypothyroidism have an increased incidence of ischaemic heart disease[10]; (2) Subjects with positive thyroid antibodies and lymphocytic infiltration of the thyroid, but without overt thyroid disease, have an increased incidence of ischaemic heart disease and a raised serum cholesterol concentration.[9 10 13 14]

There is a recognized association between hyperlipoproteinaemia (Fredrickson Types II and IV) and hypothyroidism.[9 10 17 18] The nature and frequency of this association are uncertain since workers in the lipid field have excluded hypothyroidism from further consideration if conventional thyroid function tests are normal. It is, however, clear that mild hypothyroidism and preclinical hypothyroidism cannot be excluded on this basis alone. The hypothesis that preclinical hypothyroidism is a significant risk factor for coronary artery disease remains to be tested in the general population.

Tests of Thyroid Function

The tests of thyroid function which are of value in the diagnosis of hypothyroidism are listed below. Clearly it is not necessary to carry out all, or even most, of these investigations in every patient with suspected hypothyroidism. The investigations which are of greatest value in identifying people with different degrees of thyroid failure has been indicated in the earlier discussion. The patient with gross hypothyroidism requires no more than a single test to confirm the diagnosis and provide objective evidence that the diagnosis was correct for future reference.

Tests of Thyroid Function
P.B.I.
T_3 resin uptake.
Serum thyroxine concentration.[19]*
Serum triiodothyronine concentration.[20]*
Thyroidal ^{131}I uptake at 24 hours (with PB ^{131}I measurements).
Thyroidal ^{131}I uptake after exogenous TSH.

Tests of Peripheral Tissues
Ankle tendon reflex duration.
Serum cholesterol.
E.C.G.

Tests of Hypothalamic Pituitary Function
Serum TSH.[4]
TRH test.[15]*

Thyroid Antibodies
Thyroglobulin antibodies
  Agar diffusion
  Tanned red cell agglutination
  Immunofluorescence.
Thyroid cytoplasmic antibody
  Complement fixation
  Immunofluorescence.

* Tests not generally available at present. For details of other tests see Hall *et al.*[21]

Treatment

All patients with symptomatic hypothyroidism (overt or mild) require treatment. The need for thyroid hormone medication in asymptomatic subjects with preclinical hypothyroidism remains to be proved. L-thyroxine should be used to treat almost all patients with hypothyroidism. The initial dose should not exceed 0·05 mg daily in patients over 40 years of age; an initial dose of 0·1 mg daily may be employed in younger patients. The dose should be increased by increments until the patient is euthyroid. The optimal dose varies between 0·1 and 0·3 mg daily. Recent work[22] strongly suggests that conventional replacement therapy with 0·3 mg daily is frequently too high and that most patients with hypothyroidism are maintained in a euthyroid state on 0·2 mg daily. This dose should rarely, if ever, be exceeded in the elderly. Caution is necessary in patients with ischaemic heart disease, in whom it may not be possible to give full replacement doses.

The addition of a β-adrenergic blocker (for example, propranolol), which can be increased incrementally with the thyroxine, may allow patients with angina pectoris to tolerate a larger dose of thyroxine than would otherwise be possible. There is no indication for triiodothyronine, or tablets combining thyroxine and triiodothyronine, in the routine management of hypothyroidism since these confer no additional symptomatic benefit and there is some suggestion that side-effects may be more frequent.[23] There is only one particular indication for the long-term maintenance of a patient on triiodothyronine in preference to thyroxine—in patients who have had total thyroid ablation for thyroid carcinoma, often it is desirable to stop therapy at regular intervals so that scanning procedures may be carried out. The replacement therapy can be discontinued for a considerably shorter time if triiodothyronine is used.

There is no general agreement about the best therapy of myxoedema coma. It is common practice to give thyroxine in doses of 0·05 mg daily by mouth combined with triiodothyronine 20 μg twice daily by intramuscular injection together with hydrocortisone hemisuccinate 50 mg twice daily (in case of adrenal failure). Assisted respiration may be required if there is carbon-dioxide retention or hypoxaemia. Infections, cardiac failure, or arrhythmias should be treated vigorously and cardiac monitoring is desirable. The body temperature should be slowly raised to normal, using a "space blanket" and heating pads if necessary, in a warm room.

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Scientific Basis of Clinical Practice

The Red Cell

G. W. G. BIRD

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Almost everyone knows that the human red blood cell is a circular biconcave disc consisting of a solution of haemoglobin contained within a membrane, and that its function is to give oxygen to and remove carbon dioxide from the tissues. Not everyone knows that this oddly shaped cell is the site of considerable dynamic activity. The red cell is a veritable microcosm, with surprisingly many enzymes, proteins, lipids, carbohydrates, and electrolytes all vigorously taking part in maintaining its integrity, shape, and function.

In man and many other animals the red cell has no nucleus and therefore does not conform to the strict definition of a biological cell. Nevertheless, the red cell is accepted not only as a cell but as a model cell which has been studied in considerable depth.

During its life span of about 120 days, the red cell travels 175 miles in its prodigious task of delivering oxygen to the tissues.[1] In the average person in the resting state about 250 ml of oxygen is inspired every minute, taken up by the red cells, and given up to the tissues. A red cell spends only 780 milliseconds in a pulmonary capillary in a resting person, yet complete oxygenation takes place in the first third of that time. During activity the rate of oxygen transfer is greatly increased. The process is aided by the vast surface area of the total red cell mass, which has been estimated at about 3,000 square miles.

The biconcave discoidal shape of the mature red cell is adapted to this function of gas transfer. The surface area of the red cell is larger than the minimal area needed to enclose its volume, which would be provided if the red cell were a simple sphere. In the narrow channels of the microcirculation, where oxygen is given up, more red cells can be accommodated in a given volume of blood than would be possible if the cells were spherical. The cell membrane is elastic and therefore distortable; this property aids the movement of the red cell in the microcirculation.

The presence of haemoglobin within rather than outside the red cell is advantageous for various reasons. By providing bolus flow rather than laminar flow it avoids a stagnant layer of flow along the capillary wall. Haemoglobin is isolated from the general metabolic pool, preventing rapid turnover; the half-life of intracellular haemoglobin is 120 days, as against 3 hours and 20 minutes for free haemoglobin. Furthermore, intracellular haemoglobin is kept in close proximity to the red cell enzymes involved in oxygen transport.

Measurements of red cells *in isotonic media* show that the average red cell is 8·4μ in diameter, 2·4μ thick at the periphery, and 1μ thick at its narrowest part.

Red Cell Membrane

The red cell membrane is not just an inert barrier between the plasma and the red cell contents; it is a dynamic structure of some depth (70-80 Å) and intricate organization. It consists of an outer hydrophilic layer of proteins, glycoproteins, and glycolipids; a central hydrophobic layer of α-helical protein, cholesterol and phospholipids; and an inner hydrophilic layer of proteins and glycolipids. The lipid molecules of the central layer are radially orientated, with their polar (hydrophobic) groups facing outwards and their hydrocarbon chains inwards.

According to Zahler[2] the membrane is not a continuous structure but is an aggregate of a number of cylindrical sub-

Regional Blood Transfusion Service, Birmingham B15 2SG
G. W. G. BIRD, M.B., F.R.C.PATH.