reduced—for example, after thyroidectomy or radiiodine therapy and in the presence of thyroiditis.

Further tests for solving difficult problems include estimating the absolute iodine uptake rate by the thyroid; the triiodothyronine suppression test is helpful in distinguishing those raised thyroid radiiodine uptakes which are caused by iodine deficiency or early autoimmune thyroiditis. If the radiiodine uptake is found to be suppressed, this virtually excludes a diagnosis of hyperthyroidism; nevertheless, failure of suppression is also seen in ophthalmic Graves's disease, in some euthyroid patients with Graves's disease, and in the presence of one or more autonomous nodules in the thyroid. Thyroid antibody tests are also useful since they give a clue to the presence and extent of autoimmune thyroiditis. Subclinical thyroiditis is not infrequent in the general population—high thyroglobulin antibody titres were found in 4-6% of women and 1-6% of men in a general practice in the north-east of England.  

Special Diagnostic Problems

During Antithyroid Therapy.—The level of thyroid function during a course of antithyroid drugs is best assessed clinically. Radiiodine uptake measurements 2½ hours or more after the tracer dose are not helpful, though those done 20 minutes after intravenous tracer doses of 131I give a measure of thyroid iodide trapping which is independent of drugs. Measurements of P.B.I. may be misleadingly low, since the thyroid depleted of iodine produces more triiodothyronine than normal during antithyroid therapy and this is less well bound to thyroxine-binding globulin.

After Antithyroid Therapy.—Tests of thyroid function may also give misleading results. The uptake of radiiodine by the thyroid may be raised as a result of the iodine deficiency which follows antithyroid drugs. Usually, however, the results of the P.B.I. or the T-3 resin uptake tests are satisfactory indicators of thyroid abnormality.

Pregnancy.—During pregnancy there are complex alterations in iodine metabolism and thyroid function. The renal loss of iodine is increased, the plasma inorganic iodide falls, and the thyroid clearance of iodide increases maintaining the absolute iodide uptake within the normal range. Thyroxine-binding globulin levels rise in response to the high levels of circulating oestrogens causing a rise in the P.B.I. The nature of the pituitary T.S.H. response and the role of placental-produced T.S.H.-like material is not yet well understood. It is best to avoid administering radiiodine, even 131I, to the pregnant woman. Estimating the free thyroxine index, which is the product of the P.B.I. (raised) and the T-3 resin uptake (lowered), indicates the true level of thyroid function.

Renal Failure.—This, with the characteristic pallor, lea-argy, and fluid retention, may simulate hypothyroidism. Moreover, it may itself complicate tests of thyroid function; there may be retention of iodide, an increase in plasma inorganic iodide, and (because of isotope dilution) the thyroid uptake of radiiodine tends to be reduced, though this may be balanced by failure of excretion of the isotope, which tends to increase uptake. The actual uptake recorded will depend on the balance of these and many other factors. In the nephrotic syndrome the loss of thyroxine-binding globulin (T.B.G.) will lower the P.B.I., though thyroid function remains normal because the free thyroxine level is maintained.

Toxic Adenomas of the Thyroid.—These cause about 5% of cases of hyperthyroidism in the United Kingdom. Nodules may be single or multiple, their secretory capacity depending on their size and on the iodine content of the diet. Some autonomous nodules may produce sufficient thyroid hormone to suppress the output of T.S.H. by the pituitary—and hence the uptake of iodine by the rest of the thyroid—without causing hyperthyroidism. Surface counting of the thyroid after giving radiiodine (a thyroid scan) is helpful since a “hot” nodule is very rarely malignant whereas a “cold” nodule may represent a non-functioning adenoma, a thyroid cyst, a thyroid carcinoma, or even a localized enlargement of a gland affected by thyroiditis. Many apparently single nodules are found at operation to be the largest nodule in a multinodular gland.

Management

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Several developments in the management of thyroid disorders have been discussed in recent articles in the British Medical Journal—concerning radiiodine therapy, antithyroid drug treatment, and thyroid hormones. To enable him to make the correct choice of treatment and subsequent management of a patient the doctor should be familiar with recent therapeutic studies.

Thyrotoxicosis

Antithyroid Drugs

Blocking iodine metabolism in the thyroid gland reduces the output of iodinated thyroid hormones and relieves both the symptoms and some of the signs of thyrotoxicosis. Nevertheless, it is doubtful whether antithyroid drugs alter the underlying mechanism of thyrotoxicosis. Spontaneous remission of thyrotoxicosis does occur, and prolonged treatment with anti-

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thyroid drugs may only control the patient's symptoms until normal thyroid function recovers spontaneously.

Thyrotoxicosis frequently recurs after antithyroid medica-
tion, the percentage of recurrences varying from 50 to 70 in different studies, and the relapse can be hastened by iodide repletion. The fact that triiodothyronine (T-3) suppresses the uptake of radiiodine (131I) by the thyroid suggests that the autonomous metabolism characteristic of thyrotoxicosis is absent. Moreover, the development of T-3 suppression in a previously thyrotoxic patient while receiving antithyroid drugs may indicate that normal thyroid function has been re-established.

Antithyroid drugs are often used inadequately, the common errors being to allow long intervals between doses or to produce hyperplasia of the thyroid with unduly large doses of these goitrogenic compounds. The metabolism of commonly used antithyroid drugs, carbimazole and propylthiouracil, differs, and several factors—including renal function—determine their therapeutic efficacy. The dosage of these compounds must be adjusted according to the patient's response to therapy, and the doses divided, not according to mealtimes,
but at equally spaced intervals of about eight hours three times each day. Any instructions should make allowance for the patient’s work and sleeping habits.

Adverse reactions to antithyroid drugs are relatively uncommon, and interactions with other drugs and food are unlikely. Hypoplasia of the bone marrow and aplastic anaemia may be induced by antithyroid drugs and any untoward feature, such as a rash or severe sore throat, is an indication for stopping the drug. Such patients may tolerate an alternative drug, but marrow hypoplasia cannot be anticipated by regular blood counts.

Subtotal Thyroidectomy

Removing much of the thyroid might be expected to reduce the secretion of thyroid hormone; more surprisingly, thyroid surgery also appears to restore normal thyroid function and histology. Before it is undertaken, however, the thyrotoxicosis should have been controlled with antithyroid drugs, ideally supervised by a physician and surgeon in joint consultation. Hyperplasia of the gland due to excessive medication should be avoided, and once the patient is euthyroid the operation should be arranged as soon as convenient.

Though iodides have been used in the immediate postoperative period over the past 50 years, there is little evidence of the effect of iodide medication on morbidity; it is thought that it reduces the vascularity of the thyroid after antithyroid drug treatment. Thyroxine is often preferred for the immediate postoperative treatment as it will not produce iodism and has no adverse effects. If iodides are prescribed potassium iodide offers accurate dosage and is certainly more convenient than the traditional Lugol’s iodine.

The complications of subtotal thyroidectomy include damage to the recurrent laryngeal nerve, postoperative tetany, and hypothyroidism. In the past few years the incidence of these last two complications has been studied more carefully. Overt tetany is relatively uncommon—but partial parathyroid insufficiency associated with symptoms probably occurs more frequently, though the incidence is generally not as high as reported initially. With time, parathyroid function recovers, and in the meantime symptoms can be relieved by calcium supplements and calciferol.

Hypothyroidism after thyroid surgery has usually been assessed retrospectively, the reported incidence being 3-40%. Nevertheless, this is probably underestimated where follow-up is incomplete or too short. Thus prospective studies have shown an incidence of 30% five years after operation in patients treated for thyrotoxicosis. In both instances replacement therapy was withheld for a few months to ensure that the hypothyroidism was permanent; transient hypothyroidism occurs quite frequently after thyroid surgery, but recovery of function is usually seen within six months.

Undoubtedly the incidence of hypothyroidism reflects the extent of the thyroid resection, though in some cases an autoimmune process is responsible. Nevertheless, a less radical operation may result in a recurrence of the thyrotoxicosis, which is a less desirable and less easily managed complication.

A low incidence of hypothyroidism and no recurrence of thyrotoxicosis are mutually exclusive.

Radiiodine Therapy

Treatment of thyrotoxicosis with radioactive iodine, usually \(^{131}I\), has been available for over 20 years. The advantages for elderly people include ease of administration, often on an outpatient basis, and a negligible risk of any recurrence of the disease. There is no damage to the recurrent laryngeal nerves, tetany never supervenes, and the general hazards of surgery are avoided. The clinical response to radiiodine, however, is very variable, and in the past repeated doses were given to control the patient’s symptoms as quickly as possible.

Experience has shown that hypothyroidism may develop insidiously many years after \(^{131}I\) therapy and that the incidence reaches 40% after ten years and even then is still rising. Unlike postoperative hypothyroidism there is no evidence of autoimmune thyroiditis being associated with this high incidence. Experimental and clinical evidence show that hypothyroidism is related to the radiation dose to the thyroid. Lowering the dose of radiiodine reduces the incidence of hypothyroidism from 40 to 12% after eight years. These results were achieved with a single dose of radiiodine and have been confirmed.

The use of lower doses of radiiodine increases the delay in controlling the patient’s symptoms. Nevertheless, symptoms can be controlled by antithyroid drugs given as well, the mean duration of treatment needed being less than two years; this is similar to the time when antithyroid drugs are used alone, but the results of combined therapy are better than those after antithyroid medication alone. Other workers have used potassium iodide after radiiodine therapy, and propranolol has also been advocated.

Previous treatment with antithyroid drugs has been claimed to improve the response to a single dose of radiiodine, but subsequent studies have refuted this idea. Fractionation of radiiodine therapy is still advocated, but no comparative studies have been published. The actual distribution of radiiodine in the thyroid gland has also been claimed to influence response, but no evidence of this was found in over 300 patients studied in Sheffield, and problems of dosimetry probably explain many anomalous features. A graded scale of thyroid irradiation dosage has been proposed recently.

Other variations in radiiodine therapy have been attempted, including suppression of one lobe by external irradiation before \(^{131}I\) therapy and \(^{131}I\) irradiation of the whole gland, but the former has not been popular and the latter unsuccessful. More recently, \(^{131}I\) has been advocated because it is claimed that, compared with \(^{131}I\), the radiation to the thyroid cell nucleus is less, thus limiting nuclear damage and subsequent failure of cell replication, which is the cause of hypothyroidism after several years. Such studies raise further problems of dosage, solved only recently for \(^{131}I\), but the results of therapy with this longer-life isotope will be of interest.

Choice of Treatment

The choice of therapy is mainly dictated by the age of the patient. Antithyroid drugs are chosen for young adults, but if there is substantial enlargement of the thyroid surgery is preferable. If the patient relapses after a course of antithyroid drugs surgery is indicated. Subtotal thyroidectomy is usually selected for nodular glands with associated thyrotoxicosis. The solitary nodule with thyrotoxicosis (“toxic adenoma”) is treated by hemithyroidectomy in all age groups; the autonomous nodule is removed with little morbidity. Radioiodine is still restricted to patients over 40 years of age, and for these patients thyroid surgery and radiiodine therapy offer definite control of thyrotoxicosis. Propranolol has been shown to control the symptoms of thyrotoxicosis by a peripheral action.

Patients with thyrotoxicosis or hypothyroidism conceive less readily but frequently become pregnant once thyrotoxicosis is controlled or hypothyroidism corrected. When antithyroid drugs are given, the dose is progressively reduced and the drugs stopped altogether before the last trimester, because after then the fetal thyroid can be suppressed by transfer of the drugs from the maternal circulation. Most patients manage thereafter without antithyroid drugs; but those who first develop thyrotoxicosis during pregnancy present a more difficult problem often managed by a combination of antithyroid drugs and thyroid hormones during the last trimester or by thyroid surgery in the second trimester. Full consultation between the doctors concerned and hospital assistance in management is recommended for all pregnant patients with thyrotoxicosis.
The ocular features of thyrotoxicosis may be distressing, though malignant exophthalmos is infrequent. Attempts at controlling exophthalmos have included the use of metronidazole, but the claimed benefit has not been confirmed. Guanethidin (5%) eye-drops relieve lid retraction, but superficial punctate keratitis may be produced. A study of 649 patients treated with radioiodine in Sheffield showed that measured exophthalmos increased after therapy, though lid retraction became less evident. Total ablation of the thyroid has been advocated for malignant exophthalmos but has not been widely adopted; a combination of systemic steroid therapy in high dosage with local surgery is more commonly employed.

The discovery of calcitonin in human thyroid tissue had obvious relevance to possible changes after treatment. Though challenging patients with a calcium load after radioiodine therapy or thyroid surgery suggests that the secretion of calcitonin is impaired, the discovery that calcitonin is also present in human thymic tissue and the parathyroids suggested that complete deficiency is unlikely after treatment of thyroid disorders. Chronic deficiency of calcitonin may produce bone changes, but these considerations do not influence the choice of treatment, though their implications warrant further investigation.

Simple Goitre

The cause of goitre in Britain is not fully understood. In some localities iodine deficiency may be responsible, but genetic factors also play a part. In adolescent children and young adults thyroxine therapy often produces complete and permanent regression of the thyroid enlargement, but in adults the results are less satisfactory, especially if the goitre is nodular. Surgery is the alternative treatment, being indicated if there is enlargement with tracheal and/or oesophageal deviation or compression, haemorrhage into the gland substance, an area which fails to take up the isotope (“cold nodule”) on a thyroid scintiscan, and if the patient develops thyrotoxicosis.

Thyroiditis

Subacute (De Quervain’s) thyroiditis, which is thought to be caused by a viral infection, is characterized by tender enlargement of the thyroid and fever, reduction of the serum P.B.I. level, and a variable, changing isotope uptake in the thyroid on scintiscanning. Usually the condition resolves spontaneously, but rarely permanent hypothyroidism may supervene; therapy with steroids and thyroxine has been advocated. Autoimmune (Hashimoto’s) thyroiditis is a more frequent type of thyroiditis, and may rarely present with a phase of thyrotoxicosis; ultimately hypothyroidism ensues. More commonly the patient is seen in middle age with a firm thyroid swelling and hypothyroidism. The association with macrocystic goitre (Addisonian) anaemia is well established. Invasive fibrous thyroiditis (Riedel’s struma) is very rare, and because of its characteristic hardness surgical exploration is almost always undertaken to exclude cancer of the thyroid.

Hypothyroidism

Hypothyroidism may be spontaneous or the consequence of thyroid surgery or radioiodine therapy. Previously the treatment of hypothyroidism with thyroid hormones has been limited to preparations of animal thyroid which have a variable content of thyroxine and triiodothyronine. With the availability of synthetic thyroxine, with a constant potency, replacement therapy with this single hormone has been widely adopted. In patients taking thyroxine the serum P.B.I. level is disproportionately high compared with their clinical status. This finding coupled with a hesitation in accepting that one hormone can be the physiological equivalent of two naturally occurring thyroid hormones prompted the introduction of combinations of synthetic thyroxine and triiodothyronine.

It has been claimed that a 4:1 ratio of thyroxine and triiodothyronine mimics the action of natural thyroid secretion and at the same time produces a normal serum P.B.I. level. Recent studies have shown an unduly high incidence of untoward symptoms in patients taking the combination without any overall benefit as compared with thyroxine alone. It has never been shown that patients suffer ill-effects from lack of triiodothyronine, which has no unique action making its inclusion with thyroxine essential. There are no combined tablets available commercially in Britain, and thyroxine alone is generally used in the management of hypothyroidism; triiodothyronine may, however, be indicated in the management of myxoedema coma.

Conclusions

Recent progress in the management of thyroid disorders has centred on minimizing the complications of established methods of treatment. Hypothyroidism after thyroid surgery or radioiodine therapy has been more fully recognized by long-term follow-up. The incidence of hypothyroidism can be lowered after radioiodine therapy if the dose is reduced. Hypothyroidism occurring after surgery is usually due to the loss of thyroid tissue, though in some instances an autoimmune thyroiditis contributes. On the other hand, a less radical operation is more likely to be associated with recurrent thyrotoxicosis. It is impossible to foretell which patients will develop hypothyroidism after surgery or radioiodine therapy, and long-term follow-up of patients at risk is necessary. Two schemes for doing this have been described recently. One uses information supplied by the family doctor, who also takes a blood sample for a serum P.B.I. estimation; and the other uses data derived from a postal questionnaire. It is desirable to ensure a follow-up of patients with treated hypothyroidism because many fail to take the prescribed dose of replacement therapy or they have stopped treatment on medical advice.

The selection of treatment for an individual patient depends also on local facilities and experience. Often treatment is determined by the family doctor, who refers the patient either to a surgeon or to a physician. In several centres patients are seen jointly by a physician and surgeon in the preoperative period but the physician undertakes after-care of patients, irrespective of their treatment; furthermore, radioiodine therapy is arranged by the physician. Such arrangements have been successful but are dependent on the co-operation of everyone concerned, supported by an efficient biochemical and isotope service.

References

From the window of his home Mr. Quiggin can see the mountains just across the estuary. Even so, though he and his wife used to be enthusiastic, he has had little opportunity for walking in the hills since he got his consultant post five years ago. "I find myself on call every week for a longer period than my housemen," he said, "and, though I'm in favour of their being paid well, I'd be quite against any new scheme which gave them a basic wage together with a large bonus for overtime work. The important thing is that this would reduce the differential between junior staff and consultants to a ridiculously low amount." 

Mr. Quiggin, who is now in his early forties, shares the orthopaedic work at two hospitals with a consultant colleague. One, the district general hospital, has a new orthopaedic block, with an accident and emergency department on the ground floor, and wards and an operating suite on the first floor. The other, fifteen miles away over the mountains, was built just after the first world war, though its wards and theatre suites have recently been modernized. If anything, Quiggin prefers working in the latter because it is cosier and he sees more of his colleagues in the other specialties. "Another thing," he continued, "our new orthopaedic block was a complete Diktat, and neither my colleague nor I had any say in its design at all. The result is that there are corridors which go nowhere, and rooms which are always empty. We have two operating theatres downstairs in Casualty which are never used, and yet upstairs (where all the operations are done) the theatre suite is far too small. I've seen a large number of new accident and emergency departments up and down the country, and almost all of them are more sensibly planned than this one. What's more, this department