South African Medical Journal : Suid-Afrikaanse Tydskrif vir Geneeskunde

Cape Town, 20 June 1959 Volume 33 No. 25 Deel 33 Kaapstad, 20 Junie 1959

General Practice Series

RECENT ADVANCES AND NEWER CONCEPTS IN THYROID DISORDERS

R. HOFFENBERG, M.D., M.R.C.P., *Department of Medicine, Groote Schuur Hospital and the University of Cape Town*

In a review of thyroid disease published in this series[1] in 1957 some of the basic clinical concepts were discussed. It is the intention of this article to comment on some newer aspects. Many of these will appear to be of academic interest only, but they have important practical implications which will be considered.

PHYSIOLOGY

Ingested iodine is rapidly absorbed into the blood-stream, whence it is trapped by the thyroid gland or excreted into the urine (apart from small quantities which may be lost in the sweat or the faeces). In the thyroid gland the iodine is converted into thyroid hormone by a series of complex and incompletely understood reactions. The hormone is thought to leave the gland as free thyroxine which, when it re-enters the circulation, becomes attached to specific plasma proteins. Much interest has been taken recently in a substance called tri-iodothyronine which some people believe to be the compound responsible for the peripheral activity of thyroid hormone. It is thought to be derived from thyroxine, which possesses an extra iodine atom. While many claims have been made for the added therapeutic efficiency of tri-iodothyronine, there is as yet no real proof that its action is superior to that of thyroxine.

The release of hormone from the thyroid gland is controlled by the anterior pituitary secretion of TSH (thyroid stimulating hormone or thyrotropin). By the familiar feed-back mechanism the pituitary responds to low levels of circulating thyroid hormone by extra secretion of TSH, which stimulates the thyroid gland to extra activity; conversely, high circulating levels damp down pituitary action until it is needed again. In this way a balance is maintained between the utilization and production of thyroid hormone.

THE PATHOGENESIS OF GOITRE

Under certain circumstances the synthesis of thyroid hormone can be blocked or slowed down so that the blood levels fall. If the block persists, pituitary stimulation continues in a vain effort to restore these levels to normal. In such a case hyperplasia of the thyroid gland may result without corresponding increase in its output. This concept of hyperplasia with hypofunction is a most important one, the counterpart of which may be seen in the condition of congenital adrenal hyperplasia.

The *antithyroid drugs* (thiouracil compounds and methimazole) act in the manner considered above, i.e. by interfering with the normal synthesis of thyroid hormone. If their blocking action is prolonged and complete, hyperplasia of the thyroid gland results—hence the term 'goitrogen' applied to substances which impede the production of thyroid hormone. If the thyroid gland increases in size during the administration of antithyroid drugs, the dosage is probably excessive and should be reduced. Alternatively, thyroid sicca (or equivalent thyroxine or tri-iodothyronine) may be added with the object of restoring the blood hormonal levels to normal and abolishing the overactivity of the pituitary gland.

The same mechanism seems to prevail in the pathogenesis of spontaneous non-endemic *cretinism* or *hypothyroidism with goitre*. In many of these patients a similar block in thyroxine synthesis appears to exist—perhaps through deficiency of an essential enzyme. While the precise nature of the defect appears to differ from case to case, the end-result is the same in all, namely hyperplasia of the thyroid gland with low blood levels of thyroid hormone. Administration of thyroid sicca or thyroxine restores the latter to normal, combats the hypothyroidism and damps down the pituitary activity. Naturally in these goitrous hypothyroid subjects therapy must be continued for life.

While iodine deficiency is fundamentally the cause of *endemic goitre*, interest has been aroused in the role of naturally-occurring goitrogens in some areas. An early report described an 'outbreak' of goitre amongst war-time internees. Turnip was identified as the agent responsible. A mild antithyroid action has long been attributed to this vegetable; when it became a staple food, this action was magnified to the point at which it interfered with thyroxine synthesis and goitre resulted. The seeds of cabbage, which is also a member of the brassica family, have been incriminated and from Tasmania has come a report of goitre occurring amongst schoolchildren who had ingested milk from cattle fed on thousand-headed kale.

An interesting sidelight on the pathogenesis of endemic goitre has been the realization that goitre does not occur in all inhabitants of an endemic area, but tends to concentrate in certain families. This suggests that a genetic factor might exist with regard to adaptation to iodine deficiency.

HASHIMOTO'S THYROIDITIS

A similar but more involved mechanism seems to account for the development of this condition. Recent work has given rise to an entirely new concept of auto-immunization, which may prove important in the pathogenesis of many

other unrelated disorders. Normally after birth the body forms antibodies only to foreign substances introduced into the blood-stream from without. Certain body proteins do not normally enter the blood-stream, e.g. spermatozoa, lens protein and thyroglobulin (the protein to which thyroxine and other iodinated compounds are attached in the thyroid gland). If these substances do reach the circulation, they may stimulate the production of antibodies in the manner of foreign proteins. This process of antibody reaction to the host's own proteins is known as auto-immunization.

In Hashimoto's disease this mechanism has been postulated. Under certain circumstances thyroglobulin escapes into the blood-stream and antibodies develop. These not only destroy the circulating thyroglobulin, but attack that which is still contained within the thyroid gland. This leads to gradual loss of thyroid function, with reduced formation of thyroid hormone. Again the pituitary exerts its stimulatory effect; hyperplasia with hypofunction results. Clinically the hypothyroidism may not be marked until a late stage of the disease, but it is important to consider this condition in cases of non-toxic goitre. Since operation will aggravate the hypothyroidism, it is only indicated where there is evidence of considerable compression of surrounding structures. The correct treatment is administration of thyroid hormone, which restores the blood levels and allows the thyroid to involute. Therapy must be permanent.

HYPOTHYROIDISM IN CHILDREN

Far too many errors are still made in the diagnosis of this condition. Thyroid hormone is still being used widely in the treatment of obesity in children whose only fault is gluttony. At times these preparations are used as non-specific slimming agents—a course that cannot be justified on scientific grounds; otherwise they are administered in the mistaken belief that obesity (perhaps with somnolence) is the result of thyroid underactivity. A plea must be made for accurate diagnosis in these cases. Thyroid hormone is a potentially dangerous drug and its indiscriminate use must be deplored.

Of greater consequence are the numbers of truly hypothyroid children whose disease is not recognized, where the correct use of thyroid hormone might be crucial to their proper development. Even with the full range of modern techniques the correct diagnosis may not be easy, but every effort should be made to substantiate it at the earliest possible age.

While the thyroid gland is generally atrophic and therefore impalpable, an enlarged gland does not exclude the diagnosis and may, in fact, be a point in its favour. In early post-natal life clues may lie in such complaints as lethargy, constipation, feeding problems, and respiratory difficulty. Laboratory tests may be misleading although, as a rule, the serum cholesterol is raised and the serum alkaline phosphatase lowered. Bone age is probably invariably retarded—a finding more specific for hypothyroidism in the younger patients. Stable protein-bound iodine estimations and radio-iodine tests may prove valuable, but many observers feel that the latter should not be employed in small children because of risks of carcinogenesis. This objection may be overcome by the use of small doses of shortlived isotopes, e.g. ^{132}I in preference to ^{131}I.

The therapy of childhood hypothyroidism has also come under recent review, there being many who believe that under-treatment is prevalent and who urge the use of thyroid hormone in doses which approach the patient's limit of tolerance. Certainly there can be no rule-of-thumb guide to dosage and adequacy must be measured by definite indices. Serum cholesterol and protein-bound iodine levels are helpful guides. Bone age should be assayed regularly and should approach chronological age. This cannot take place until the height of the serum alkaline phosphatase overshoots the adult range and enters that of the normal growing child. About a month of therapy is required before this effect is noted. Average doses for infants would range from 2-3 grains of thyroid sicca (approximately 0·2-0·3 mg. of thyroxine or 50-75 micrograms of tri-iodothyronine); larger children may need higher doses. Perhaps with these larger doses we may see fewer of those therapeutic failures which we have previously attributed to 'irreversible damage due to long-continued thyroid deficiency'.

TESTS OF THYROID FUNCTION

Determination of the *serum-cholesterol* level remains a useful test for hypothyroidism, but not for hyperthyroidism. It is, however, probably the least reliable of the many tests of thyroid function.

The *basal metabolic rate* requires skill in performance and in interpretation. In proper hands it is a valuable guide—greater importance being attached to low than to high readings.

Estimation of the level of *protein-bound iodine* in the serum can only be done at certain specialized centres, but serum can be sent to these when necessary. This is probably the most valuable single parameter of thyroid function, since it is in effect a direct measure of the level of circulating thyroid hormone. Unfortunately many artefacts may contribute to false readings, amongst these being recent use of mercurial diuretics or of organic iodine-containing radiographic contrast media or inorganic iodides. The normal range for adults is 4·0 to 8·0 μg per 100 ml, and is somewhat higher during pregnancy and in the first few weeks of life.

Tests employing *radio-active iodine* depend upon the introduction into the body of minute amounts of iodine bearing a 'label' of radio-activity which allows reasonably accurate assay of infinitesimal amounts. The patient drinks a colourless, odourless, tasteless liquid which contains the iodine and reports back at specified times for 'counting' over the thyroid region. This procedure takes only a few minutes. In some centres urine studies are done (since renal excretion varies inversely with thyroid activity) and blood analysis. In this way measurements can be made of the rates at which the thyroid concentrates and discharges the iodine. The major drawbacks to this procedure are the necessity of trained staff and specialized equipment and, again, invalidation of the results by previous drugs and therapy. Any iodine-containing compound—even iodized salt and cough preparations with potassium iodide, any antithyroid agent or thyroid substance, will interfere with the test, which may also be of least value where it is most needed, e.g. after previous thyroidectomy, in mild cases of hyperthyroidism and in some cases of nodular goitre.

Used intelligently these tests can be of immense help in the diagnosis of thyroid dysfunction; knowledge of their deficiencies can only increase their value.

THERAPY IN THYROID DISEASE

Other than the introduction of radio-iodine—which can no longer be considered new—there have been no major advances in this sphere. For *hyperthyroidism* there remain 3 methods of treatment:

1. *Prolonged medical treatment*, i.e. the use of antithyroid drugs for periods of at least a year. Success with this regime is more likely with careful selection of patients, the most suitable being young females with small goitres of a diffuse type and mild or moderate hyperthyroidism. If medical treatment is confined to this group there is a cure rate of about 70%, but high relapse rates after cessation of therapy hardly justify its use in other cases.

2. *Surgery*. Despite the illogicality of this sort of operation sub-total thyroidectomy still offers most chance of permanent cure and is probably the treatment of choice for most types of hyperthyroidism.

3. *Radio-iodine*. The results of more than 16 years' experience have helped to clarify its indications. Suitable patients include those with recurrent thyrotoxicosis following operation and those in whom medical treatment has failed and where there is a contra-indication to operation, but it may be preferred in many other hyperthyroid patients who lack these indications and who are over the age of 45 years. Pregnancy is a complete contra-indication to its use, and younger patients should preferably be treated by other means in view of the theoretical risks of carcinoma. The treatment is exceedingly simple and cure can almost be guaranteed, although probably not more than about 60% of patients respond to the first dose. For this reason and the high incidence of post-therapy hypothyroidism (10-15%) regular follow-up visits are essential. It should be noted that while hypothyroidism generally occurs within 6 months, it may appear slowly and insiduously 5 years or more after treatment. This must be borne in mind by practitioners attending patients who have received this form of therapy.

The *eye-signs of thyrotoxicosis* generally consist of lid-lag and lid-retraction with minimal exophthalmos. Occasional hyperthyroid patients show more extensive eye-signs, including more severe degrees of exophthalmos, diplopia, ophthalmoplegia and oedema. In others the eyes deteriorate during anti-thyroid drug administration or following surgical or ^{131}I therapy. Great care must be taken to ensure that these patients do not become hypothyroid as a result of excessive treatment, since this state seems to aggravate existing eye signs. In all such patients small amounts of thyroid hormone or thyroxine (2-3 grains of the former or 0·1-0·3 mg. of the latter per day) should be given with the antithyroid drug. Many people contend that similar thyroid therapy should follow all surgical or radio-iodine treatment of hyperthyroidism. This approach seems perfectly reasonable, since it may prevent the development of severe eye complications.

In the treatment of adult *hypothyroidism* 3 grains of thyroid sicca (or equivalent) generally suffices. When this dosage appears ineffective the validity of the diagnosis should be reconsidered. A point worth noting here is that occasional batches of thyroid sicca have proved to be inactive. We have certainly experienced this with locally produced hormone. Replacement with thyroxine in equivalent dosage has resulted in therapeutic response. The extra cost of thyroxine is so slight that we use it as a routine in preference to thyroid sicca.

No ready solution exists for the problem of *non-toxic nodular goitre*. Single nodules are usually removed because of a greater risk of carcinoma, although selection may be made on the grounds of radio-iodine tests. Those nodules which concentrate iodine readily are less likely to be carcinomatous, while those that are 'cold' should certainly be removed. 'Hot' nodules may be treated with thyroid hormone with a fair chance of shrinkage. Goitres which are very large may be removed for cosmetic reasons of for pressure effects on neighbouring structures.

Small non-toxic multinodular or diffuse goitres are probably best left alone or at most treated with thyroid hormone. Reassurance is often necessary, since many patients are afraid that the goitre will either grow inwards and choke them, or will turn into cancer. Final decision often depends on the skill and availability of the surgeon and on the possibilities of follow-up from the social and economic points of view.

REFERENCE

1. Hoffenberg, R. and Jackson, W. P. U. (1957): S. Afr. Med. J., 31, 737.