REFRESHER COURSE FOR GENERAL PRACTITIONERS

MYXOEDEMA

BY

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Myxoedema is caused by hypothyroidism, but most patients with hypothyroidism are not myxoedematous. This statement probably needs an explanation. The term "myxoedema" was proposed in 1878 by W. M. Ord, physician to St. Thomas's Hospital, because a deposition of a mucinoid substance was observed in the skin of one of his patients on whom a necropsy had been performed. Subsequent analyses of the skin of a number of patients with myxoedema showed that their skin contained no more mucin than that of normal subjects. In fact, true myxoedema is uncommon; most cases thus termed should, strictly speaking, be referred to as suffering from hypothyroidism, but common usage for so many years has universally established the term myxoedema, irrespective of whether the skin contains an excess of mucin or not. Hypothyroidism which arises secondarily to hypopituitarism should not be called myxoedema.

Aetiology

The usual cause of spontaneous myxoedema in Britain is an idiopathic degeneration and fibrosis of the thyroid gland, a disturbance which arises more often in women than in men, and most commonly at the time of the menopause. Juvenile myxoedema is due to a similar cause operating in childhood. Hypothyroidism occurs in about 4% of patients subjected to subtotal thyroidectomy for toxic goitre, but sometimes it persists for only a few months. It not uncommonly arises as a result of the treatment of toxic goitre with radioactive iodine, on account of the difficulty in determining the correct dosage. Chronic fibrosis of the thyroid gland (Riedel's or Hashimoto's disease) is usually accompanied by hypothyroidism, but malignant disease of the gland only rarely gives rise to it. In regions of endemic goitre myxoedema may be the end-result of simple goitre, and is then caused by exhaustion atrophy of the glandular epithelium.

Overdosage with antithyroid compounds—for example, methylthiouracil—in the treatment of toxic goitre may result in myxoedema; their action is to inhibit the synthesis of the thyroid hormone. Myxoedema has been reported as arising through the use of resorcinol ointment for ulcers of the legs, and occasionally during the treatment of pulmonary tuberculosis with *p*-aminosalicylic acid. Both of these substances seem to act similarly to the derivatives of thiouracil. The disorder was occasionally observed when potassium thiocyanate was used in the treatment of essential hypertension, a method of therapy, however, which has now been generally discarded. Thiocyanate causes hypothyroidism by preventing the accumulation of iodine in the thyroid gland, thus reducing the amount of thyroid hormone synthesized. In all instances of myxoedema caused by antithyroid drugs the condition gradually subsides when their administration is stopped.

Diagnosis

The clinical picture of myxoedema is well known and its description needs no repetition here. The complaints of the myxoedematous patient are often vague on account of the slowness of the mental processes, and information of greater value may be obtained from relatives who are aware of the change in the patient's appearance and demeanour. Early cases do not present the typical facies,

while some patients have a heaviness of the features and a slowness of thought which are part of their natural make-up and are not due to hypothyroidism.

It is commonly thought that thinning of the hair of the eyebrows, especially of the outer third, is almost pathognomonic of myxoedema, but this is erroneous, for it may occur in normal subjects of middle age. Another fallacy is that patients with obesity are suffering from hypothyroidism; analysis of large numbers of patients with proved hypothyroidism have demonstrated that only a small proportion of them are fat, while in the experimental field thyroidectomy performed on laboratory animals results in a decrease, not an increase, of body fat.

Myxoedema may present itself in a variety of ways. A clue to the diagnosis in the case of one patient attending hospital for some other condition was the large amount of clothing that she was wearing. Puffiness of the face may suggest nephritis, and evidence of impairment of renal function may of course be found in a myxoedematous patient as a fortuitous accompaniment. At the time of the menopause it may be difficult to decide whether the symptoms complained of are those of the climacteric or are due to hypothyroidism, or the clinical picture may be complicated by the presence of symptoms of both conditions. The possible existence of hypothyroidism should be borne in mind in women presenting with menorrhagia for which no local cause can be found and in sterility in both sexes. Rarely, anginal symptoms may be the presenting feature, and there may be no other clinical evidence of myxoedema apart from the typical changes in the basal metabolic rate and blood cholesterol.

Anaemia.—Anaemia may be a prominent feature of myxoedema and may mask the underlying disturbance. The anaemia of myxoedema is a simple hyperchromic anaemia in which the colour index is slightly above 1 and the haemoglobin rarely below 60%. It may or may not be associated with achlorhydria. It is thought to be caused by the increased oxygen tension in the tissues which arises as a result of the low metabolic turnover and which leads to decreased erythropoiesis; it is thus analogous to the anaemia which may be produced by exposing animals to atmospheres with a tension of oxygen greater than normal. Not being caused by a deficiency of iron or of vitamin B₁₂, it does not respond to the administration of either of these substances, but it improves slowly on prolonged treatment with dried thyroid. Two other types of anaemia occur less frequently: (1) hypochromic anaemia, which resembles an iron-deficiency anaemia, may be associated with a glazed tongue, brittleness of the nails, splenomegaly, and achlorhydria, and the administration of iron as well as thyroid is necessary to procure a complete remission; and (2) Addisonian hyperchromic anaemia, which is rare in combination with myxoedema, responds rapidly to combined treatment with thyroid and liver extract (or vitamin B₁₂), but not to thyroid alone.

Psychoses.—It is important to recognize that psychological disturbances may be so severe in myxoedema that they may dominate the clinical picture to such an extent that the underlying cause—hypothyroidism—may be overlooked. Failure to appreciate this may have unfortunate results. The psychoses which may arise consist in a wide variety of mental changes, and include disorientation, hallucinations, dementia, acute or chronic mania, melancholia, and paranoid and schizophrenic states.

Hypopituitarism.—Hypothyroidism which is secondary to hypopituitarism may closely resemble myxoedema: there are the same lethargy, dryness of the skin, thinning of the hair, increased sensitivity to cold, bradycardia, subnormal temperature, and decreased basal metabolic rate; amenorrhoea and anaemia may be present in both conditions. The differentiating points are as follows: in hypopituitarism the skin of the face may be finely wrinkled and it has a slightly yellowish tinge more often than in myxoedema; the malar flush which is often seen in myxoedema does not occur; there is loss of body hair due to reduced secretion of adrenal and (in men) testicular androgens; the blood pressure is low as a result of diminished adrenal cortical secretion, whereas in myxoedema it is normal or raised; hypothyroidism arises usually late in the course of the disease; there is often evidence of a pituitary lesion, such as a pituitary tumour, or a past history suggestive of a post-partum necrosis of the anterior lobe; there may be hypoglycaemia, whereas in myxoedema the fasting blood sugar is generally normal; and there is increased sensitivity to the injection of insulin, whereas this test is normal in myxoedema.

Laboratory Investigations.—In all cases in which myxoedema is suspected it is advisable, if possible, to have the basal metabolic rate and the blood cholesterol estimated before treatment with thyroid is begun. The basal metabolic rate is typically lowered in myxoedema; in the completely thyroidless person it is minus 40%, which may be termed the myxoedema level. The basal metabolic rate, however, is not always a reliable guide in the diagnosis of myxoedema. For instance, healthy persons may normally have a very low basal metabolic rate and, on the other hand, sometimes in undoubted cases of myxoedema the reading is normal. This latter finding may be because basal conditions were not obtained or because of the considerable variation which is found in the basal metabolic rate of normal persons, though this statement is denied by some authorities. The blood cholesterol (normal: 150 to 200 mg. per 100 ml.) is a more reliable index of the presence and severity of hypothyroidism than is the basal metabolic rate. It is invariably raised in myxoedema, an average figure being between 300 and 400 mg. per 100 ml.

Treatment

The treatment of myxoedema with thyroid substance affords a perfect example of effective replacement therapy. As there may be some variation in the potency of different brands of dried thyroid on the market, it is advisable to adhere to one particular preparation, for changing from one brand to another of different strength may lead to difficulties. Tablets of thyroid, B.P., contain 0.1% of iodine combined as thyroxine. Since the disorder is solely due to deficiency of thyroid hormone, no advantage is obtained by using preparations in which thyroid is combined with other substances.

With regard to the frequency of administration of thyroid, it is a tenet of therapeutics that those drugs which are rapidly destroyed in the body or are rapidly excreted should be given at frequent intervals, whereas in the case of those which exert a prolonged action this is unnecessary. As the action of thyroid hormone is prolonged, the preparation need be given only once daily, preferably after breakfast.

It is customary to begin treatment with small doses of thyroid and gradually to increase the amount until the optimal maintenance dose is reached. Starting treatment with a full dose of 3 to 5 gr. (200 to 320 mg.) daily may

FIG. A
FIG. B
Myxoedema: (A) Before treatment, (B) after six months' treatment with thyroid.

cause precordial discomfort, or even anginal pain, and muscular pain, and cramps. This is because the oxygen requirements of the tissues are increased beyond the capabilities of the heart and circulation at this stage to supply them: this relative inefficiency is caused by the hypotonicity of the myocardium, the anaemia, and the narrowing of the capillaries which has been observed in hypothyroid subjects. The daily dose of thyroid should initially be $\frac{1}{2}$ gr. (32 mg.), and should be increased each week by $\frac{1}{2}$ gr. (32 mg.) until signs of overdosage, such as tachycardia and irritability, begin to appear. Treatment should then be stopped for two weeks, and should be resumed in doses of 1 gr. (65 mg.) a day less than the overdose. The maintenance dose of tablets of thyroid, B.P., varies from 3 to 5 gr. (200 to 320 mg.) daily.

In patients with coronary sclerosis anginal symptoms may arise before the full dose of thyroid is reached as a result of the increased oxygen requirements of the myocardium. Such patients should be kept slightly hypothyroid, at a level at which angina does not arise. In the rare case in which angina is present before treatment is begun it disappears with thyroid therapy, but it may recur when the larger doses are reached. Striking the correct balance may be difficult.

Adequate treatment with thyroid causes the myxoedematous symptoms to regress. As mentioned above, the simple hyperchromic anaemia of myxoedema gradually disappears with thyroid alone, but the hypochromic type requires a preparation of iron in addition, and the Addisonian type requires liver extract or vitamin B₁₂. Another feature which disappears with thyroid therapy is the cardiac enlargement which is sometimes found in myxoedema and which may be due to myxoedematous changes in the myocardium and to generalized dilatation. If reduction in the degree of cardiac enlargement is not obtained the condition is due to some other cause.

Laevo-thyroxine Sodium.—Laevo-thyroxine is the form in which thyroxine exists in the thyroid gland. It was synthesized a few years ago and was found to be highly active when given by mouth. Before the synthesis of laevo-thyroxine, the thyroxine available on the market was the racemic form, which being relatively insoluble is much less active than dried thyroid when given by mouth; it had, therefore, to be administered by intravenous injection and consequently was not adopted as a method of therapy. Laevo-thyroxine sodium is as effective in the treatment of myxoedema as dried thyroid substance, and the principles of its use are the same. For practical purposes 0.1 mg. of

laevo-thyroxine sodium is equivalent in effect to approximately 1 gr. (65 mg.) of tablets of thyroid, *B.P.* As it is a pure substance there is no variation in its potency.

Juvenile Myxoedema

The term "juvenile myxoedema" is applied to hypothyroidism when it arises during childhood. It differs from cretinism in that the causative factor is not present at birth. When the condition arises during infancy the clinical features resemble those of cretinism, in later childhood those of adult myxoedema.

The treatment of juvenile myxoedema is the same as in the adult type; the dose of thyroid should be small at first and should be gradually increased. For a child aged 4 years the daily dose of tablets of thyroid, *B.P.*, should initially be $\frac{1}{4}$ gr. (16 mg.) and should be increased each week by $\frac{1}{4}$ gr. (16 mg.) until the maintenance dose is reached; this is about 2 gr. (130 mg.) daily for a child of this age. Children require in proportion rather more thyroid than adults on account of their growth, and as growth proceeds the dose should be slightly increased each year. If evidence of hyperthyroidism is seen the administration of thyroid should be stopped for three or four days and should be resumed in smaller dosage. For no other reason should treatment be interrupted.

The prognosis of treatment in respect of juvenile myxoedema is better than in cretinism, because in the latter disease the disturbance arises *in utero* at a vital period of growth and development, when some of the damage inflicted may be irreparable. From the point of view of prognosis, therefore, it is important to differentiate juvenile myxoedema from cretinism, but this may be impossible when the disorder arises in infancy. The two conditions are distinguished by inquiring carefully into the early development of the child and by observing the degree of mental deficiency, dwarfing, and bone development.

Localized Pretibial Myxoedema

Localized pretibial myxoedema is characterized by irregular indurated swellings of the skin occurring symmetrically over the antero-lateral aspect of the lower half of the legs. The skin itself is erythematous or yellowish white, and the dilated dimpled hair follicles produce an appearance resembling pigskin. The swellings are due to deposits of mucin. The condition may be a complication of toxic goitre, and occasionally it disappears after subtotal thyroidectomy, but more often it develops after this operation. Treatment so far has on the whole been ineffective.

The cause of the disorder is unknown; it has been suggested that it is due to excessive secretion of the thyrotrophic hormone of the anterior pituitary lobe, and that it is thus analogous to exophthalmos, which is caused by oedema of the orbital tissues presumed to be due to the same factor.

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The report of the Regius Professor of Physic, Cambridge University, for the year 1951-2 includes attendance figures for the monthly symposia for medical practitioners held during the year. The symposia, which took the form of lecture-discussions and case demonstrations, were attended by practitioners from a wide area. The total attendance for the year was 241, as against 209 the previous year, and of the individual symposia the most popular were those on diseases of the lung (41), obstetrics and gynaecology and cardiovascular diseases (38 each).

ROYAL MEDICAL BENEVOLENT FUND

The annual meeting of the Royal Medical Benevolent Fund was held on June 9, with Lord Webb-Johnson in the chair. The annual report, presented by the hon. secretary, Dr. R. Cove-Smith, stated that almost £12,000 had been received during the year by way of legacies. A similar figure had once again come in from the Medical Insurance Agency, whose generous donation of £6,420, being given by deeds of covenant, ensured a regular income of £12,000 until the covenants expired. Dr. Cove-Smith recalled that 20 years ago the maximum annuity that the Fund was able to provide was limited by lack of money to £40 per annum, which was often woefully inadequate; to-day the maximum annuity in payment was £200. At present there were 221 beneficiaries on the books to whom annuities were paid. In addition there were 418 beneficiaries who received gifts or yearly allowances; of these 97 were new applicants. The total number of individuals benefited, however, was considerably in excess of these figures, for in some cases the beneficiaries were married couples, others were widows with families, and money had been given towards children's education and support. The amount distributed as a result of the Christmas gifts appeal was £2,368. The total charitable distribution made during the year on all accounts, including the various trust funds, amounted to £44,410. This extensive work had been carried out within a working expense figure of 7½%.

Lord Webb-Johnson was re-elected president of the Fund, Mr. F. A. Juler honorary treasurer, and Dr. R. Cove-Smith honorary secretary, and the retiring members of the committee of management were re-elected as follows: Dr. H. A. Clegg, Sir Zachary Cope, Dr. D. F. Hutchinson, Mr. F. A. Juler, Miss E. C. Lewis, Sir Arthur MacNalty, Mr. W. H. C. Romanis, and Dr. P. Montague Smith.

In a brief address Lord Webb-Johnson said that the Fund deserved more general support from the profession, and this could only be secured by personal approach. He spoke with gratitude of the service of the auditors, Messrs. Deloitte, Plender, Griffiths and Co., who for 50 years had served the Fund in an honorary capacity. Others to be thanked were the Medical Insurance Agency, the Charities Committee of the British Medical Association, and the medical press, which, he said, always gave space to the Fund's appeals. He also paid a tribute to the Ladies' Guild, through which it was possible to give material assistance in the way of clothing, domestic and nursing help, and educational training.

CENTENARY OF WARLEY HOSPITAL

The Minister of Health, Mr. Iain Macleod, spoke at an Open Day at Warley Hospital, Brentwood, on June 9, held to celebrate the hospital's centenary. The hospital was opened in 1853 as the "Essex County Lunatic Asylum"; later it became the "Brentwood Mental Hospital." Mr. Macleod said that he regarded the mental health service as having first call on the increased capital expenditure which he hoped to see available in the near future. The Ministry was already allocating substantially larger sums to the mental health service. He had called urgently on regional boards for their plans. The first thing he did on becoming Minister was to ask the architects and administrators to find methods of building the accommodation needed. Overcrowding existed in practically every mental hospital in the country. Speaking of the waiting-list of nearly 9,000 mental defectives, Mr. Macleod said that it must never be forgotten how much mental distress was caused to families, particularly mothers, if they had to care for a mentally defective child.

The Minister was welcomed by Alderman C. E. S. Blackmore, chairman of the hospital management committee, who said that during the last five years the regional board had done all in its power to help the hospital. Alderman G. H. Spackman, the vice-chairman, thanking the Minister, said that, although the Essex County Council's scheme in 1939