ETIOLOGY, DIAGNOSIS AND TREATMENT OF THYROID FAILURE

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THYROID failure may be defined as the failure of the thyroid gland to secrete an adequate amount of hormone necessary to maintain a normal rate of body metabolism, thereby resulting in a characteristic group of symptoms and signs. The terms hypothyroidism and myxedema have been defined respectively to indicate mild and severe thyroid failure, but here they shall be used synonymously. The purpose of this paper is to present a review of our experience with the causation, differential diagnosis and treatment of thyroid failure.

The mildest degree of thyroid failure is asymptomatic and may be characterized only by a lowered basal metabolic rate. Actually, this stage is rarely diagnosed and in our experience is usually seen in those patients who have gradual enlargement of the thyroid gland due to struma lymphomatosa (Hashimoto's struma). Treatment with thyroid extract will elevate the basal metabolic rate 20 to 30 per cent, but clinically these patients may feel just the same. It is probably not of great importance to diagnose the disease at this stage.

The early stage of symptomatic thyroid failure is characterized by cold intolerance, dryness of the skin and fatigue, as well as a low basal metabolic rate, but there are no symptoms or signs of the deposition of myxedematous fluid in the intercellular tissues. The patients in this stage of the disease are difficult to diagnose and are equally difficult to separate from that large group of patients with normal thyroid function who have similar symptoms.

Most important is the diagnosis of advanced thyroid failure which disables the patient. Not only are the mild symptoms of hypothyroidism present but, in addition, all the symptoms and signs due to the accumulation of myxedematous fluid. These will be described later.

ETIOLOGY

Hypothyroidism may be due to intrinsic disease of the thyroid or extrinsic causes (Table 1).

Hypothyroidism as a result of extrinsic causes is probably more common than that due to intrinsic disease. However, the latter often contributes to so-called extrinsic hypothyroidism as will be shown.

Total thyroidectomy for any reason whatsoever could be expected to cause thyroid failure. Actually, most surgeons will agree that it is difficult to do a total thyroidectomy. In our own experience myxedema is seen after total thyroidectomy performed for alveolar or papillary carcinoma involving both lobes.

Table 1

Causes of Thyroid Failure

Extrinsic

1. Surgical
   a. Total thyroidectomy
   b. Partial thyroidectomy (for Graves' disease, struma lymphomatosa)
2. Radiation therapy
   a. Radioactive iodine (Graves' disease)
   b. X-ray therapy (struma lymphomatosa)
3. Antithyroid drugs
   a. Thiouracil derivatives
   b. Thiocyanates

Intrinsic

1. Chronic thyroiditis
   a. Struma lymphomatosa (Hashimoto)
   b. Struma fibrosa (Riedel)
2. Spontaneous atrophy
   a. Primary
   b. Secondary to anterior pituitary failure
3. Congenital
   a. Atrophy
   b. Iodine deficient diet

Partial thyroidectomy per se does not usually result in immediate postoperative hypothyroidism unless the patient has Hashimoto's struma or hyperplastic goiter of Graves' disease extensively infiltrated with a fibrolymphocytic type of thyroiditis.

Hypothyroidism has been frequently observed in our experience in patients who have had a partial thyroidectomy for Hashimoto's goiter. The surgery definitely accelerates this development. Therefore, we believe all such patients should be routinely placed on permanent thyroid medication postoperatively even if they present no evidence of thyroid failure at the time of surgery.

Whitesell and Black[1] in a pathologic study of 86 resected hyperplastic thyroid glands of Graves' disease with lymphocytic and fibrolymphocytic replacement noted that the incidence of postoperative myxedema was directly proportional to the degree of replacement of the thyroid tissue. In patients whose partially resected thyroid glands showed 40 to 50 per cent replacement or more, the incidence of postoperative myxedema was 70 per cent according to these authors. Therefore, we believe postoperative thyroid medication should also be prescribed routinely in this group of patients. In our experience most patients who are found to have myxedema have undergone partial thyroidectomy for Graves' disease anywhere from 2 months to 30 years earlier.

Thyroid failure rarely occurs after partial thyroidectomy for toxic or nontoxic adenomatous goiter.

The increasingly widespread use of radioactive iodine especially in treating Graves' disease is making this agent an important cause of thyroid failure. The incidence of myxedema has been about 10 per cent of all patients with Graves' disease who were so treated. However, a small number of these patients have been found to have only temporary myxedema. External roentgen therapy to the thyroid gland usually will not cause thyroid failure unless the patient has Hashimoto's goiter.

Two important causes of reversible thyroid failure are the thiouracil and thiocyanate drugs. The use of thiouracil derivatives, especially in treating Graves' disease, may result in an occasional case of myxedema which will disappear when the drug is withdrawn. A less well recognized cause of myxedema is the thiocyanate group of drugs used especially in the treatment of hypertension. The myxedema may or may not be accompanied by thyroid enlargement. Both will disappear if the thiocyanate is stopped without using thyroid extract.

In cases of thyroid failure attributable to intrinsic disease it is becoming increasingly apparent to us that most spontaneous thyroid failure is probably due to a lymphocytic infiltration into the thyroid gland with secondary atrophy of the thyroid secretory cells. This type of thyroiditis may or may not be different from Hashimoto's struma. The use of the Vim-Silverman needle for biopsy of the thyroid gland has led us to earlier diagnoses of lymphocytic thyroiditis whether in the presence or absence of thyroid failure. When the diagnosis is confirmed by biopsy, the patient is given thyroid extract permanently as prophylactic therapy for the development of hypothyroidism. If the thyroid is enlarged it often shrinks considerably when 2 or 3 gr. of U.S.P. thyroid extract per day is administered.[2]

Since Riedel's type of thyroiditis is so rare in contrast to Hashimoto's thyroiditis, it is not an important cause of thyroid failure.

Spontaneous atrophy of the thyroid gland with fibrosis and no lymphocytic infiltration is seldom observed as a primary process but is more usually secondary to failure of the anterior lobe of the pituitary gland. The degree of secondary thyroid failure depends upon the extent of the failure of the anterior pituitary gland. Severe thyroid failure is rare in patients with anterior pituitary failure.

Cretinism in this country is usually due to intra-uterine athyreosis or atrophy of the thyroid of the fetus. In other countries, such as Switzerland, it may be a result of iodine deficiency in the diet and, furthermore, is characterized by the presence of a goiter.

DIAGNOSIS

Symptoms and Signs

It is well known that the onset of the symptoms and signs of thyroid failure is usually so insidious that many patients will not describe many of the classic

symptoms when the original history is recorded. If the condition is suspected, direct questioning will usually elicit most of the classic symptoms. For this reason it has been our experience that the history is of less value than the physical findings. The important symptoms and signs of thyroid failure as we have encountered them are summarized as follows:

Cold Tolerance. This is a symptom which is difficult to evaluate because many euthyroid patients especially women are sensitive to cold. However, the latter have a long history of cold intolerance while that of the hypothyroid patient is usually of recent onset. The patient should be carefully questioned about cold intolerance. For example: When outside, do you wear more clothes than formerly? Were you comfortable in the extreme heat of the summer while everyone else sweltered? and finally, Do you want the temperature of the house unreasonably hot and do you need more covers on your bed at night than formerly? Occasionally, we have seen a patient with obvious myxedema who denies ever having any cold intolerance.

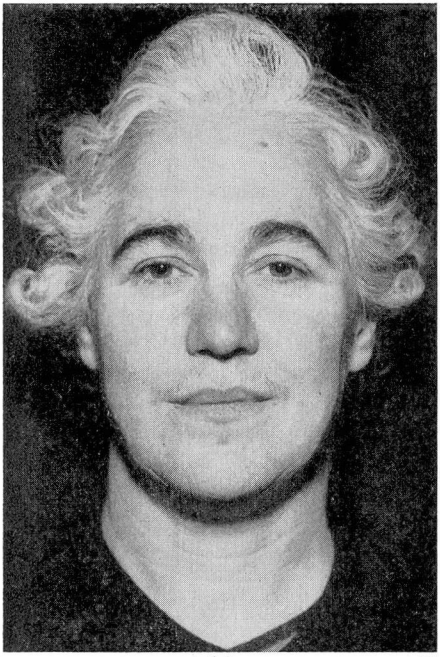
Fatigue. Unfortunately this symptom is not too indicative of thyroid failure since it is nonspecific and present in most other organic diseases as well as functional syndromes.

Dryness of Skin. This symptom and sign must be carefully evaluated before it will be of much help in the diagnosis of the hypothyroid patient. First, the dryness of the skin must have begun fairly recently. Second, the dryness of the skin is general. The degree of dryness may vary, but most patients with myxedema have a "sandpaper-like" skin especially evident over the back and often with excessive flaking. It must be kept in mind that there are other causes of dry skin such as sensitivity to soap and detergents which may be localized to the forearms and hands. Since dryness and loss of hair are not limited to the hypothyroid patient, they are of little aid to the diagnosis. Nail changes are not very helpful either.

Myxedema Facies. The characteristic facies of the myxedematous patient has been the outstanding diagnostic aid in our experience. Once the characteristics of this facies are mentally recorded the diagnosis will almost invariably be made by the alert clinician before the history is taken.

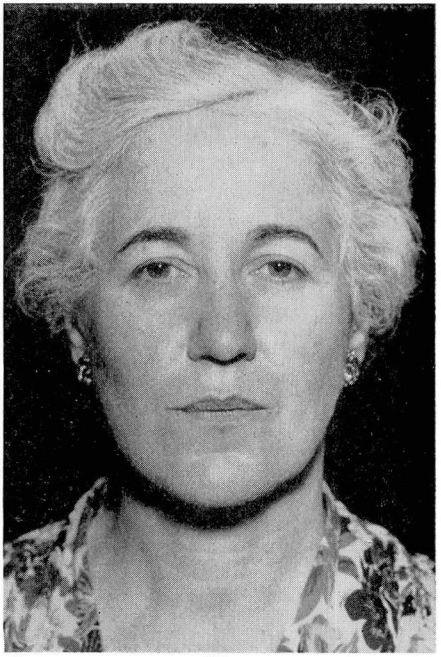
This type of facies is characterized by a pale yellowish-tinged color, puffiness of the entire face, especially of the upper eyelids and portion of the cheeks above the angle of the jaw, and usually an apathetic or listless expression, well-illustrated by lusterless eyes. The lips and the tongue are thickened and coarse. Figures 1 and 2 illustrate the facies of myxedematous patients before and after treatment with thyroid extract.

Mental and Physical Lethargy. The patient will usually be aware of a definite slowing of mental and physical activities. Excessive drowsiness may well be present. The patient will often volunteer that he or she takes twice as long to get any work done either on the job or around the house. The speech is often slowed, husky, and slurred, occasionally simulating that of an inebriated person.



(a)

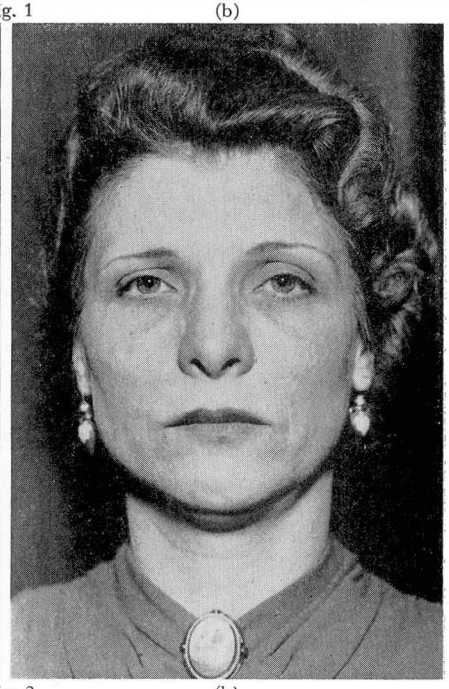
Fig. 1



(b)

(a)

Fig. 2



(b)

Fig. 1 and 2. (a) Facies of myxedematous patient before treatment with thyroid extract. (b) Same patient after treatment with thyroid extract.

The most specific sign of thyroid failure is the slowing of the tendon reflex responses, particularly those of the biceps and Achilles tendons. Characteristically, both phases of this reflex response are delayed, but the delay in the duration of the relaxation phase is most obvious. Lambert, Underdahl, Beckett and Mederos[3] reported that the reflex was present in 77 per cent of patients with myxedema and its incidence was directly proportional to the decrease in the basal metabolic rate. This group also showed that the slow response of the tendon reflex in myxedema was due to an abnormality of the contractile mechanism of the muscle rather than due to abnormal activity of the neural elements of the reflex or the mechanism of excitation of the muscle.

Laboratory Tests

Laboratory tests are not only important to document obvious cases of thyroid failure, but also to help differentiate the hypothyroid from the euthyroid patient. It is our opinion that the basal metabolic rate and plasma cholesterol remain the most useful tests for the diagnosis of hypothyroidism. The protein bound iodine is a good test for diagnosis of thyroid failure, but the procedure itself has certain limitations which preclude its widespread use. The radioactive iodine tracer has certain limitations in its interpretation in patients with thyroid failure.

The basal metabolic rate when properly done and interpreted is still the most satisfactory test available for the diagnosis of thyroid failure because of its ready availability and low cost. In an excellent recent review Kyle[4] discussed the pitfalls encountered in the determination and interpretation of this test. In our patients with thyroid failure the basal metabolic rate usually varies from —20 to —40 per cent. Occasionally, the basal metabolic rate will be normal in the presence of obvious thyroid failure. This is probably due to an extra thyroid factor or disease which tends to elevate the metabolic rate.

Many patients with normal thyroid function have low basal metabolic rates. The fact that most euthyroid patients have a basal metabolic rate between —15 and +15 per cent should not obscure the fact that many patients normally have basal metabolic rates above or below this range, as determined by Boothby.[5] Therefore, patients with low basal metabolic rates are not necessarily hypothyroid and should be carefully differentiated from patients with true hypothyroidism before prescribing thyroid extract.

Just as important as the initial determination of the basal metabolic rate is the repeat basal metabolic rate done after a two months therapeutic trial with thyroid extract. If the basal metabolic rate is elevated 20 or more per cent by treatment, thyroid failure is almost certain. If there is little or no change, the patient probably does not have hypothyroidism.

The plasma cholesterol is also a helpful, readily available, inexpensive aid to the diagnosis of thyroid failure. In almost all patients with thyroid failure the plasma cholesterol will be above 250 mg. per cent. Occasionally,

a value lower than this will be seen in a patient who has proved thyroid failure. One of our patients recently had a plasma cholesterol of 220 mg. per cent which dropped to 110 mg. per cent after treatment with thyroid extract. Another one of our patients with proved myxedema had a plasma cholesterol of 164 mg. per cent initially. In this case a chronic mastoiditis was responsible for the low value; low cholesterol levels are sometimes found with other infections.

It is therefore important not only to determine the initial plasma cholesterol, but also to determine the degree of fall after two months treatment with thyroid extract. As a rule the cholesterol should fall more than 100 mg. per cent if thyroid failure is present. Occasionally an initial normal cholesterol in a patient with myxedema will show little or no decrease after treatment despite the remission of the clinical signs and symptoms and definite elevation of the basal metabolic rate. The reason for this is not known and the plasma cholesterol as an aid to diagnosis is limited in cases such as these. One of our patients with myxedema had a blood cholesterol of 229 mg. per cent and a basal metabolic rate of —30 per cent. Treatment with thyroid extract resulted in an elevation of the rate to —5 per cent, but the plasma cholesterol showed only a small decrease, being 186 mg. per cent.

The protein bound iodine is the most specific test available for evaluating thyroid function since it measures protein bound organic iodine of the thyroid hormone in the circulating blood. When it is correctly performed and carefully interpreted it may be of great help. Unfortunately, it remains an extremely difficult test to perform, consequently expensive and not readily available. Furthermore, the administration of any x-ray contrast media containing organic iodine prior to the determination will result in falsely elevated values. Starr et al.[6] in a study of 39 untreated patients with myxedema found that 32 of these patients had initial protein bound iodine values below 3 micrograms per cent, generally regarded as the lowest limit of normal thyroid function. Perhaps in the future an easier method of performing the determination may be devised, making this test of much more help to the physician in private practice.

The radioactive iodine tracer test is also of limited value in the diagnosis of thyroid failure. It is a simple test to do, but the facilities are not readily available. We have found the normal range of radioactive iodine uptake in 24 hours as measured over the thyroid is 10 to 60 per cent when 100 microcuries is given. A radioactive iodine tracer uptake of less than 10 per cent is usually compatible with thyroid failure in the absence of known iodine blocking agents. However, uptakes as high as 30 per cent in 24 hours may be seen in obviously hypothyroid patients. Therefore, a normal radioactive iodine uptake does not rule out thyroid failure.

The electrocardiogram may be of some help in patients with severe myxedema by showing generalized low voltage changes especially in the T-waves. However, in many patients, the electrocardiogram may be within normal limits, and therefore the test has not been of too much help to us.

Differential Diagnosis

The important conditions to be differentiated from primary thyroid failure are hypometabolism without hypothyroidism, anterior pituitary failure, and nephrosis due to any cause.

The typical patient with hypometabolism without hypothyroidism is usually a nervous woman with or without some intolerance to cold, dryness of the skin, and fatigue, who has a lowered basal metabolic rate varying from —10 to —30 per cent. No characteristic findings of myxedema are present and the plasma cholesterol is almost always normal. The radioactive iodine tracer uptake and protein bound iodine determination are within normal range. A two month therapeutic trial with 2 gr. of U.S.P. thyroid extract will not produce any significant elevation of the basal metabolic rate or any decrease in the plasma cholesterol in such a patient, despite the observation that the patient may feel better due to the nonspecific effect of the treatment.

Most patients with anterior pituitary failure do not show any clinical signs or symptoms of thyroid failure. This is true because the degree of anterior pituitary failure may be mild to moderate. Furthermore, if the anterior pituitary deficiency is moderate to severe the thyroid gland may function independently at a lowered level sufficient to prevent most of the symptoms or signs of thyroid failure from appearing.

Younghusband, Horrax, Hurxthal, Hare and Poppen[7] have noted that in 86 patients with anterior pituitary failure due to tumor the average basal metabolic rate was —20 per cent and 27 of these 86 patients had a basal metabolic rate above —10 per cent. These authors also noted that the average plasma cholesterol was 230 mg. per cent which is slightly above the normal average.

On rare occasions a patient who has anterior pituitary failure will present all the classic features of myxedema. This type of patient may be differentiated from one with primary thyroid failure by investigation for failure of the other endocrine glands, roentgenologic examination of the sella turcica for tumor and examination of the visual fields. It has been advocated that all patients with myxedema should have a roentgenologic examination of the sella turcica. In our opinion this is not necessary if the patient has had a previous thyroidectomy for Graves' disease or struma lymphomatosa, but should be done in those patients with associated amenorrhea or loss of libido and potency.

The patient with a nephrotic syndrome due to any cause may offer initial difficulty in differential diagnosis especially when the basal metabolic rate and plasma cholesterol are determined. However, a careful history, presence of anemia, albuminuria and reversal of the albumin-globulin ratio should easily differentiate the disease from thyroid failure.

TREATMENT

After the diagnosis has been well substantiated the nature of the disease and the necessity of taking thyroid extract permanently should be explained to

the patient. Despite the many new types of thyroid preparations we still find uncoated U.S.P. thyroid extract to be the best standardized preparation so far. Enteric coated or enseal coated thyroid tablets should not be used. We have repeatedly seen patients on liberal doses of coated thyroid tablets who still exhibit all the signs of myxedema.

In the absence of a history of cardiac failure or angina pectoris a daily dose of 1 gr. of U.S.P. thyroid extract is prescribed for one month. If at the end of one month the patient has noted no signs or symptoms of cardiac failure or angina pectoris, the thyroid medication is permanently increased to 2 gr. per day. If angina pectoris occurs, the dose of thyroid is reduced to ¼ or ½ gr. per day. Such a small dose of thyroid will usually cause most of the signs and symptoms of myxedema to disappear although the patient may continue to have evidence of thyroid failure.

The symptoms and signs will usually be resolved within a month. To substantiate the diagnosis further, the basal metabolic rate and blood cholesterol should again be determined after two months. In addition, it is our practice to give the patient after the two month return visit, a letter certifying that a diagnosis of thyroid failure has been made on the basis of clinical signs and symptoms, laboratory tests, and response to treatment. We reemphasize the importance of permanently taking thyroid extract. The certifying letter is given so that the patient will not have the thyroid extract stopped in the future by another physician, as we have done, to prove or disprove a diagnosis of thyroid failure.

SUMMARY

Thyroid failure may be due to extrinsic causes or intrinsic disease. In some instances, extrinsic cause and intrinsic disease combine to produce thyroid failure. Hypothyroidism is likely to occur postoperatively in those patients with Graves' disease who have an abnormal degree of lymphocytic infiltration in their partially resected hyperplastic thyroid glands and also in those patients who have had a partial resection of a Hashimoto's goiter. Both of these groups of patients should be given thyroid extract postoperatively and the administration should continue for the rest of their lives. The cause of most spontaneous myxedema is probably some form of lymphocytic thyroiditis rather than simple atrophy.

The diagnosis of thyroid failure will probably be missed unless the clinician can keep in mind the characteristic features of the "myxedema facies." This type of facies is characterized by a pale yellowish-tinged color, puffiness of the entire face, especially over the upper eyelids and portion of the cheek above the angle of the jaw, and also the presence of an apathetic or listless expression with thickened lips. The delayed biceps or ankle jerk reflexes are specific for myxedema and when present are a valuable aid to diagnosis.

In our experience the determinations of the basal metabolic rate and plasma cholesterol before and after treatment with thyroid extract are still the best and most practical aids for the diagnosis of thyroid failure.

Such conditions as low metabolism without hypothyroidism, anterior pituitary failure, and nephrosis must be carefully differentiated from thyroid failure.

Treatment of thyroid failure should be administered in the form of uncoated U.S.P. thyroid extract for the rest of the patient's life.

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