CLINICAL ASPECTS OF HYPOTHYROIDISM

C. L. HARTSOCK, M.D.

The secretion of the thyroid gland must be maintained at a fairly constant level of production if the human organism is to remain in a state of well-being. For a number of reasons, some known and some unknown, many individuals are unable to maintain an adequate production of thyroxin and this results in various states of disability. The degree of thyroid insufficiency and the age and rapidity of onset are variable factors which serve to produce so wide a range of clinical pictures simulating other conditions that frequently the primary source is not readily apparent.

To suspect the presence of hypothyroidism is all that is necessary to make a correct diagnosis and eventually entirely relieve all the symptoms that result from such a deficiency. However, because of the remarkably negative and unimpressive character of most of the signs and symptoms of hypothyroidism, this condition frequently escapes detection. In view of this peculiar lack of identifying characteristics and the failure of this disease to be impressive in nature, it seems justifiable to present a subject that offers no new features, purely with the object of keeping before you the possibility of a much overlooked cause of many morbid conditions.

The following simple classification will serve as an outline for the further discussion of the problem.

1. Myxedema—severe hypothyroidism of adults.
2. Cretinism—severe hypothyroidism of children.
3. Postoperative or postradiation hypothyroidism and hypothyroidism due to exhaustion of the thyroid by untreated hyperthyroidism. Patients in whom this latter condition occurs may show symptoms of both hypothyroidism and hyperthyroidism so that the condition is frequently called "dysthyroidism."
4. Incipient hypothyroidism—mild and atypical cases in patients of any age.

MYXEDEMA

The most obvious physical sign of severe hypothyroidism in adults is a characteristic thickening of the skin, especially of the face, eyelids, and the supraclavicular region of the neck. This swelling or edema formerly was thought to be due to deposits of mucin in the tissue, and for this reason the term "myxedema" was introduced and still continues to designate the clinical picture which results from marked diminution of thyroid function in adults. Following the introduction of methods for the measurement of the metabolic rate, it was found that in many

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cases in which low metabolism was due to thyroid deficiency, this characteristic condition of the skin was very slight or was completely absent. For this reason it is better to confine the term "myxedema" to the classical syndrome in which a group of other characteritic signs and symptoms is practically always present and to use another term to describe those cases in which this sign is absent, especially as cases in the latter group show such marked variations in the clinical picture that they are all too frequently overlooked. It is better to describe such cases under the separate classification of *incipient hypothyroidism*. I realize that these two types apparently differ only in degree and that many of the incipient cases, if unrecognized, would go on to the myxedematous stage. It is for this very reason that I consider it advisable to present the clinical picture of the premyxedematous stage more definitely, in order that these cases may be recognized earlier. The early cases are more likely to be overlooked than is any other definite clinical entity and this is due in part to the unfortunate choice of the word *myxedema* to describe a condition in which the symptom which gives it its name does not appear in the early stages. When myxedema is present the thyroid deficiency is marked and frequently of long standing. The onset of symptoms has often been so gradual that the patient has been entirely unconscious of the fact that his health has been far from normal; consequently, he does not consult a doctor until the beginning of rather marked mental changes.

In the advanced stage of the disease the patient may complain of almost any symptom which can result from low metabolism. A summary of the literature discloses that symptoms referable to every organ in the body have been attributed to thyroid deficiency and have been relieved by the administration of thyroid extract. It is obviously impossible, therefore, to describe all the symptoms which may be present in myxedema so I shall discuss only those signs and symptoms which are generally present. In the section on incipient hypothyroidism I shall describe the more unusual signs which, of course, may also be present in cases of true myxedema.

Patients with myxedema present a characteristic appearance of the face which should practically always be considered as diagnostic. The features are coarse, the eyes are puffy, the hair is dry and coarse, and frequently very sparse. The speech may be slow, and the patient gives the impression of slow cerebration, the memory being especially poor for recent happenings. If left alone for a short time the patient may fall asleep. The mood is usually quiet and placid but melancholia and depression with marked anxiety may be present.

The patient is always physically tired and frequently complains of soreness and stiffness in the muscles and joints. In spite of being over-

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weight these patients suffer from the cold and require heavy clothing and heavy bed covering. Digestive symptoms are common; constipation is practically always present.

Physical examination reveals a low temperature, a dry skin which feels thick and edematous, especially in the face, hands, feet, and supraclavicular fossae. The nails are brittle and ridged. The pulse is slow and the blood pressure is low, the pulse pressure being especially low. Albumin is frequently present in the urine and there is nearly always some anemia which occasionally is marked enough to suggest pernicious anemia. Free hydrochloric acid often is absent.

Cretinism

Cretinism is the term applied to the marked retardation of physical and mental development produced in children by severe thyroid deficiency. This condition is frequently congenital and the retardation of development begins at birth, but rarely, except in the most marked cases, is it discovered until the child is found to be slow in the development of activities and of normal functions, such as teething, talking, and walking. Even then, recognition of the condition is often delayed because the characteristic appearance usually does not develop clearly until about the second year. It is then noted that the growth is stunted as the result of a general disturbance of the nutrition of the osseous system. The skin is rough and dry. The hair is coarse, often giving the appearance of tow. The features are bloated. The tongue is thick and protrudes, giving a beastlike expression in very severe cases. The teeth appear very slowly and are prone to decay. The bridge of the nose is low and in typical cases the entire picture is unmistakable. In milder cases cretinism must be differentiated from rickets, birth injury, mongolianism, dwarfism, and achondroplasia. Careful study will easily differentiate these conditions but, except for rickets, it is better to treat any of them with thyroid extract until the diagnosis is definitely determined, than to leave a case of cretinism untreated. The results of the deficiency during the period of rapid growth are permanent so that the earlier cretinism is treated, the more nearly will the patient approach the normal. In these cases treatment is often very inadequate even though the condition is recognized early. I believe it is advisable to administer thyroid extract to the point of toxicity in order to determine the appropriate dosage.

Cretinism is not common in the goiter districts in North America but sporadic cases do occur with sufficient frequency to indicate the necessity for vigilance on the part of physicians and especially of pediatricians in order that this condition may be recognized early. Moreover, in goiter districts there are very large numbers of children whose physical

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and mental condition is retarded by a low grade cretinism which is not pronounced enough to produce the characteristic symptoms. These cases are similar to cases of incipient hypothyroidism without myxedema. The prophylactic treatment of goiter by the administration of iodine to children and to expectant mothers should greatly lessen the incidence of this condition. Better standards for determining the basal metabolic rate in juveniles also would give a great impetus toward the correction of these mild insufficiencies of the thyroid gland in children.

In severe cases of cretinism, the prognosis is poor on account of the marked retardation which usually has occurred before the condition is recognized by the physician. The remarkable physical changes which do occur even after a short period in patients subjected to adequate treatment are almost unbelievable.

Postoperative Hypothyroidism

Every patient who has previously had hyperthyroidism, but who after spontaneous cure, operative intervention, radiation therapy, or any other form of treatment, should be suspected of having hypothyroidism, if at any time following the changed state he again complains of ill health.

Hypothyroidism that follows in the wake of hyperthyroidism fundamentally does not differ from the spontaneous type except that it has always appeared to me to present a somewhat more bizarre picture that seems best explained by the adjustment of the organism to the rapidly varying states of metabolism. For example, it is very misleading when exophthalmos persists from a previous hyperthyroidism but in other ways the patient presents many signs of myxedema.

The chief difficulty with patients of this type is their reticence to take adequate and prolonged treatment because of their fear of bringing back their original disease.

Incipient Hypothyroidism

Cretinism, myxedema, and postoperative hypothyroidism are of relatively rare occurrence compared to the milder degrees of the disease. Incipient hypothyroidism is by far the most prevalent and most difficult to recognize of all the types. If one keeps a mental picture of myxedema before him as a guide to the diagnosis of hypothyroidism, he will entirely overlook 75 per cent of the patients who have very mild symptoms of great variation but who require specific thyroid substance for the relief of these symptoms. In its mildest states, the hypometabolism tends to exert a selective action on only one or possibly several of the organs and systems. In other words, no constant group of signs and symptoms are present. Some of the more common ones in

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the various systems will be presented briefly and if these are kept in mind and associated with thyroid deficiency the incipient case of hypothyroidism can be easily diagnosed.

Central Nervous System: Somnolence is a symptom of severe thyroid insufficiency and when it is present the patient is usually in a myxedematous condition. Forgetfulness, lack of concentration, and a tendency to procrastinate are also symptoms which appear in the late stages of the disease. Restlessness, nervousness, and insomnia are more common in the mild cases. Chronic headache which recurs frequently is also a common symptom. These early symptoms are more the result of the general fatigue and hypotension than the direct results of the metabolic disturbance.

Ocular System: Muscle errors which are due to fatigue of the ocular muscles are very common and these, in turn, may cause a host of vague secondary symptoms such as dizziness, headache, neuralgia, and many others that we frequently ascribe to neurasthenia. Exophoria which occurs toward the end of the day is the most frequent type of muscle imbalance.

Ear, Nose, and Throat: A slight edema of the membranes of the nose and throat may be secondary to hypothyroidism. Allergy, another cause for boggy membranes, usually is more pronounced when it is associated with hypothyroidism. We have observed a very interesting symptom complex which is a result of this edematous condition of the membranes. When the membranes near the orifice of the eustachian tube are swollen, there is a tendency for the tube to close and the patient complains of the very annoying sensation in the ear which results from this closure. Rather typical of this type of closure of the tube is its tendency to occur and disappear, sometimes several times in the same day. The use of ephedrine and air inflation of the tube gives only temporary relief, but adequate treatment with thyroid gives quick and permanent relief. Tinnitus is sometimes due to the same cause. Degeneration of the eighth nerve should be suspected of being due to a thyroid disorder. Swelling of the tongue and chronic hoarseness are late symptoms of myxedema.

Cardiovascular System: Bradycardia should always suggest the presence of hypothyroidism but the pulse rate is an unreliable guide because in many cases it is normal or increased. Thyroid insufficiency is occasionally the sole explanation for myocardial weakness. A clue to this etiological factor is found in the low amplitude of the electrocardiographic tracing. Due to the increased cholesterol content of the blood in the presence of hypothyroidism, it may also be a factor in the production of arteriosclerosis, but no improvement is noted following

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treatment with thyroid, although in early cases it is possible that the progress might be arrested.

Dyspnea is entirely a secondary symptom, but that very peculiar type of dyspnea which is best described as sighing respiration is occasionally due to hypothyroidism; more frequently, however, it is due to an anxiety state.

Gastro-Intestinal System: Obstinate constipation as a result of an atonic colon is a characteristic symptom, but all types of indigestion due to fatigue of the gastro-intestinal tract may be caused or aggravated by hypothyroidism. I observed one very interesting case of sudden periodic vomiting in a young woman. No other explanation for her symptoms was ever found and because of other distinct signs of hypothyroidism and a very low basal metabolic rate, she was treated solely from this angle with complete relief from the vomiting. The explanation for this is not clear.

Achlorhydria seems to occur somewhat more frequently in hypothyroidism but this is such a common finding in patients past middle age that coincidence would lessen the value of such statistics. Adequate therapy certainly does not cause a return of the hydrochloric acid.

Genito-Urinary System: One of the classical errors in diagnosis is mistaking a case of myxedema for nephritis because of large amounts of albumin in the urine. I observed such a case recently. The patient's symptoms had been present for twelve years and she had been consulting doctors almost continuously up until five years before our examination. At that time, her physicians made a diagnosis of nephritis, gave up all hope for her cure, and sent her home from the hospital to die. The patient ceased all medical aid or advice and peculiarly enough, her condition improved, but it was still the most advanced case of myxedema I ever saw. The basal metabolic rate was minus 41 per cent. Improvement on thyroid medication was, of course, startling.

Impotence and sterility both in the male and female should cause one to suspect hypothyroidism. In one case a woman was unable to carry pregnancies to full term, but after the institution of thyroid therapy, she had two full-term, normal pregnancies.

Glandular System: Polyglandular disturbances associated with hypothyroidism as a minor or secondary feature are very commonly found, but in many cases the entire glandular syndrome is improved by the use of thyroid therapy alone, and this is especially true in ovarian types of menstrual disorders. Great advances have been made in specific glandular substitution therapy but thyroid therapy still remains the

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most potent and specific. It is of great value in the treatment of pituitary, thyroid, and ovarian types of polyglandular disorders in conjunction with other indicated hormonal therapy.

Skeletal and Muscular System: Vague muscular aches and pains frequently have their origin in thyroid deficiency. Any tendency toward degenerative arthritis is hastened by a low metabolic state. The disturbance of skeletal growth is well exemplified in the cretin.

Hematopoietic System: A mild hypochromic anemia without any other satisfactory explanation should excite a suspicion of thyroid insufficiency. The marked anemias which were thought to be due to myxedema and which simulate pernicious anemia probably also have some deficiency of the extrinsic or intrinsic factor of pernicious anemia.

Hair, Nails, and Skin: Dryness of the hair and skin, brittle and thick, coarse nails, falling hair, and premature greying of the hair are very suggestive symptoms of this disease and sometimes give the earliest clues.

General Symptoms: Obesity, both generalized and that localized around the pelvic and shoulder regions, is the classical sign which usually directs attention to hypothyroidism; however, a fact which is not so generally known is that many thin individuals who never could gain weight begin to do so immediately when they follow well-regulated and observed treatment for mild thyroid insufficiency.

Localized and circumscribed swellings are frequently of myxedematous origin. Swelling of the extremities with changes of temperature or prolonged dependency suggest an early myxedema.

Intolerance of cold and a subnormal temperature is usually found, but several cases of chronic pyrexia have been reported that responded to no therapy other than thyroid. Lack of thirst and hypohidrosis are further suggestive general symptoms.

Many other vague symptoms could be cited that are secondary to the chronic fatigue, decreased cellular function, and inadequate oxidation of thyroid insufficiency, but this would only serve to make the picture confusing. If the more important symptoms mentioned above are kept in mind, one or more will stand out prominently enough to cause the condition to be suspected and recognized.

The variation in the picture of hypothyroidism in patients in the different age groups—children, young adults, and mature adults—is also confusing. Severe hypothyroidism in the child causes the typical cretinism which presents such a classical picture and has been described. Very little is known, however, about mild degrees of hypothydroidism in children. The difficulty of obtaining satisfactory metabolic studies,

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the normal variability of children's weight, growth, development, and intelligence, and the fear of using thyroid preparations in the growing child have presented many obstacles to the investigation of this problem. Undoubtedly, many of the subnormal conditions of childhood about which the mother is much more concerned than the physician eventually will be shown to be due to thyroid deficiency. Diagnostic criteria are still so limited in this group that we must wait for further studies before we can attempt to recognize and treat the incipient states of hypothyroidism in children.

Severe hypothyroidism can be present in middle-aged patients with surprisingly few of the classical symptoms. It is in this group that the more bizarre symptoms of thyroid insufficiency which were mentioned previously are seen. Patients in the older group usually present at least a few of the symptoms suggestive of the clinical picture of myxedema; rarely do they show all of them.

Differential Diagnosis: The symptomatology of the clinical syndrome, achlorhydric anemia or idiopathic hypochromic anemia, frequently suggests hypothyroidism and, unless laboratory studies clearly differentiate the two, it is sometimes necessary to determine whether iron or thyroid replacement therapy is the more specific before the true diagnosis can be determined. Some cases are apparently a combination of both conditions and these do better when both medications are used.

Any asthenic state may be confused with the hypothyroid state until a therapeutic trial proves or disproves the relation of the asthenia to a deficiency of thyroid. Only by a therapeutic trial can many such conditions be differentiated. There is, however, one very common clinical syndrome that is mistaken most frequently for hypothyroidism. I refer to the depressed emotional states that are described under various terms such as melancholia, nervous exhaustion, manic depressive-cyclothymia, involutional melancholia, cerebral arteriosclerosis, and many others. In such depressed states many symptoms are very suggestive of hypometabolism and hypometabolism is present; usually the basal metabolic rate is from minus 15 to minus 30 per cent but it is not due to thyroid insufficiency and does not respond to thyroid medication. The lowered basal metabolic rate is probably the result of the depressed function of the entire body, secondary to the depressed emotional state. Even if thyroid is administered to the point of causing symptoms of toxemia the basal rate, curiously enough, still remains low. One should be alert to sense the emotional tone of the patient and be extremely careful to avoid overstimulating the depressed patient with thyroid extract. It is in this type of patient that I have seen the very few harmful effects of the use of thyroid extract.

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Obesity more than any other sign is suggestive of hypothyroidism and, owing to the difficulties of calculating accurate basal metabolic rates, some types of obesities are falsely treated for hypothyroidism.

Other than obesity and the depressed mental states, the errors of diagnosis are usually sins of omission rather than sins of commission.

Treatment

The greatest handicap to the proper treatment of thyroid deficiency is a widespread fear of the use of thyroid medication. It is true that symptoms of hyperthyroidism can quickly be induced in a patient with excessive doses of thyroid substance but they quickly subside when the medication is withdrawn. If a patient is observed frequently until a maintained dose is established, there need be no fear in the use of this drug. The best method is to gradually increase the dose of thyroid until mild symptoms of toxemia are produced, and then establish the maintenance dose at a level just below this where there were no such symptoms.

The treatment of hypothryroidism of any type consists merely in the substitution of thyroid extract for the deficient secretion. Any form of prepared gland or the active principle, thyroxin, may be used. The gland extracts are satisfactory but the products of the manufacturing companies vary greatly in their relative potency. One should select one or two extracts and become familiar with the results that may be expected from each and then be sure that the patient uses the one that is prescribed. Only in this way can satisfactory results be obtained. One should also be familiar with the action of thyroxin, for some patients in whom gland extracts are ineffective respond to this, and at times the reverse is true.

No matter how mild or severe the case, I prefer to begin with small doses and to increase the dosage gradually until the replacement is sufficient to bring the metabolism to normal, although many prefer to start immediately with doses sufficient to restore the patient to normal, this dosage being calculated on the basis of the metabolic rate. There are two criticisms of this method. First, the patient will not always tolerate large doses immediately and in consequence becomes frightened. These individuals are often familiar with the warnings in regard to the use of thyroid extract for reducing so that any untoward symptoms may dissuade them from giving any further trial to this medication. Patients who have previously had hyperthyroidism are also fearful of a return of their former trouble and must be handled cautiously. The second criticism is that any method of calculation is unreliable. Some patients with a very low metabolic rate will become normal following

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dosage with very small amounts of thyroid extract and others whose basal metabolic rate is only slightly below normal will tolerate large doses.

A very important point in the treatment of hypothyroidism, which for some reason is almost universally disregarded, is that the patient should continue to receive maintenance doses after the metabolic rate has reached the normal level. Very frequently I have seen patients in whom marvelous results followed thyroid medication but who have been advised to discontinue medication completely for awhile. It seems to be the opinion that the thyroid function is restored to normal by the thyroid extract while, in truth, it is only a substitution for a deficiency which will probably continue as long as the patient lives.

I have found that there is a seasonal variation in the amount of thyroid extract required, a larger amount being required in cold weather. Patients who travel should be warned that it may be necessary to vary the dosage with their geographical location. It seems to be especially true that distinctly less amounts are necessary when patients sojourn for any length of time along the seashore. Whether or not it has any beneficial effects, I advise the use of as much fresh sea food as possible, but usually do not prescribe iodine together with thyroid extract. Early in the course of treatment, a determination of the basal metabolic rate should be made every month until the normal level is reached and the proper maintenance dosage determined. A check of the patient's pulse and inquiry concerning the symptoms of palpitation, tremor, and insomnia are made weekly to check overdosage. A very good point to remember is that it is well to administer the thyroid extract early in the day and to avoid giving it late in the afternoon or in the evening. If thyroid extract has been taken as recently as five or six hours before bedtime, even when the metabolism is well below normal, very unpleasant palpitation is often experienced when the patient assumes the recumbent position. In any case one commonly finds that the subnormal symptoms are more pronounced in the morning and, therefore, the dose should be given at this time. I do not think it makes much difference whether it is taken on a full or an empty stomach or whether it is given in enteric coated capsules.

I have mentioned the therapeutic test in doubtful cases, that is, the administration of small doses of thyroid extract for short periods. This can do no harm if the patient is carefully observed and it will often yield brilliant diagnostic and therapeutic results in an otherwise puzzling case.

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