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Non myxedematous hypothyroidism

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-Senior Thesis-

Non-Myxedematous Hypothyroidism

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-Introduction-

The condition hypothyroidism of a non-myxedematous nature is not mentioned as such in the modern textbooks of medicine. Rather, hypothyroidism is mentioned as a condition which occurs either early in life, as cretinism, or in adult life as myxedema. These two subdivisions represent the inadequate discussion of hypothyroidism, as it is usually presented.

In this treatise, an attempt will be made to present that condition reported in the literature as non-myxedematous hypothyroidism or mild hypothyroidism. It is that condition reported in the varying degrees of severity between the conventional normal and clinical entity of true myxedema or absolute thyroid failure. This condition is recognized with relative frequency not only where goiter is endemic, but also in districts where this is not the case. This condition presents symptoms which are vague and indefinite, as first presented, but with a careful history and adequate laboratory facilities diagnosis becomes relatively simple.

Early recognition and treatment of this condition will remove a class of chronic sufferers from those groups which are known as neurasthenia, sufferers from auto-intoxication, myasthenia, constitutional inferiority and menopausal disturbance.

It is with the hope that a better understanding of this group might be obtained, that this paper is written and presented.

-Definition-

Non-Myxedematous hypothyroidism (Synonyms: Mild hypothyroidism, masked hypothyroidism, larval hypothyroidism, or incomplete hypothyroidism) is a condition with deficient thyroid secretion, either of quantity or quality, of unknown etiology which is characterized clinically by chronic fatigue, dryness of the skin and hair, hypersensitivity to cold, increased nervousness, headache, subnormal temperature, and usually menopausal disturbances in the female, of less severity than true myxedema; pathologically, by atrophy and fibrosis of the thyroid gland; and in the laboratory, by a lowering of the basal metabolic rate.

-History-

The clinical picture of hypothyroidism, as recognized in this treatise, developed with the progress of medicine. The first reports of hypothyroidism in the adult are necessarily of the more severe grades and known as myxedema. Cretinism in children was recognized much earlier than adult thyroid deficiency by many observers.

In 1848, Dr. Hugh Norris reported a high incidence of undoubted cretinism in a goitrous village of Somersetshire. So goitrous indeed was the district that "the offspring of strangers acquire bronchocoele, if they become residents at an early age" (46). Fagge (15), discussing "On Sporadic Cretinism Occurring in England" speculates as to what characters would be present should the disease (if that be possible) arise still later in the course of adult life. The development of the skeleton being unalterable when once complete, he feels that the peculiarities of the form in the cranial and facial bones and in the bony framework in general, noted in children would, in the adult, be absent. He believed that the most marked features in such a case, in the adult, "would be a coarseness and thickness of the soft parts of the face (especially the lips), and perhaps of the subcutaneous tissues of the hands and feet, besides the presence of the supraclavicular fatty tumors, and possibly a wasting of the thyroid body, if that should prove to be a constant character of the disease". Thus, this man, who had never seen a case of thyroid deficiency in the adult, gives a good description of this type of case as we now know them.

Sir William Gull (22) is believed to have reported the first cases of adult myxedema. In his paper, "On a Cretinoid State Supervening in Adult Life in Women"

he reports two cases of morbid state of which he has seen five. He states: "I am not able to give any explanation of the cause which leads to the state I have described ----- and having begun appears to continue uninfluenced by remedies." In connection with this, he goes on by saying that it is characterized by languidity, increase in bulk, roundness of face, very smooth skin of fine texture, and a delicate rose purple color to the cheeks, The cellular tissue under the eyes is loose and folded, that under the jaws thick and folded, the lips are large, the alae nasi thick. The nose is so deformed to make the face look flat. The eyes appear wide apart. The hair is soft and flaxen, the expression remarkably placed. The tongue is broad and thick, the voice guttural, the pronunciation is as though the tongue were too big for the mouth; the hands are broad, thick and spade like. The integuments of the chest and abdomen are loaded with subcutaneous fat. The upper and lower extremities are also large and fat with traces of edema which pits doubtfully. He even mentions the slowing of the mental processes and mentions in that regard "No doubt, under the stimulus of external circumstances, there is a response of mental activity which seems to prove that the mind requires but an exertion of the will to work up to the normal level." The description of this condition may be correlated to

that of hypothyroidism in that is of a more severe degree and no mention is made of hypersensitivity to cold and a decrease in perspiration.

This syndrome of symptoms was named myxedema in 1878 by Dr. W. M. Ord, but has been frequently referred to as Gull's disease after the original report. Ord (50) reported a case which came to autopsy and is no doubt the first to be reported. He found the first thing, that the arteries were everywhere greatly thickened; there was much atheroma in the larger vessels and the heart was much hypertrophied on the left side. Section of the thyroid body showed almost complete replacement of its vesicular structure by connective tissue with cell-crowded patches. In giving the syndrome the name of myxedema he states: "As regards the class of cases immediately in question, my suggestion is that the whole collection of symptoms are related as effects to a jelly-like swelling of the connective tissue, chiefly if not entirely consisting in an overgrowth of the mucus yielding cement by which fibrils of the whole element are held together. Accordingly I propose to give the name of myxedema to the affection." Thus it was that myxedema became known as a disease entity.

In 1882 and 1883, Reverdin and Kocker respectively reported cases describing symptoms closely resembling Gull's disease, which in their experience came on in patients upon which they had performed complete thyroid-

ectomy. Means and Richardson.(46)

Sir Victor Horsley (28) in 1892 reviewed the theories of function of the thyroid gland. He presented ten theories as to the foundation of the gland. Some of these theories seem ludicrous with our knowledge of anatomy we read of them today, such as "It acts mechanically to support the larynx and improve the voice." Horsley, however, sums up the theories by saying that, to sum up the indirect facts, we see that they afford very weighty evidence in favor of the view that the thyroid is in truth the important origin of metabolic influence that the general results of thyroidectomy would lead us to believe. So at that time the relationship which the thyroid bears to metabolism was realized.

Following these men substitution therapy came in use as a means of prevention of myxedema. In 1890 Bitteneourt and Serrano reported the relief of symptoms by grafting of half a sheep's thyroid under each breast, Means and Richardson (46). Murray (48) in 1891 was the first to hypodermically inject a patient with the extract from the sheep's thyroid. He states in regards to his results in the myxedematous patient, "She has menstruated normally during the last six weeks at regular intervals. For the last four weeks the skin has been much less dry and she perspires when walking. The hair

remains as before. She is no longer so sensitive to cold." At this time he realized that there is a maintenance dose for patients since he states that after a time the injections need not be made so frequently. At the same time Fenwick (16) injected thyroid extract in a patient suffering from a disease of the kidney. He states, "We find that the thyroid juice possesses a distinct diuretic action in diseases of the kidney, though apparently it is negative in healthy persons." He found no disturbing effects from hypodermic injection of the thyroid extract in this report.

A year later Mackenzie (37) 1892, reported a case treated "with great benefit by feeding with fresh thyroid gland." He commenced his treatment with two whole sheep's thyroids per dose. He found that this was dangerous and not advisable, and that smaller doses, one sheep's thyroid gland every other day or half of sheep's thyroid gland daily was more satisfactory. In his report, he notes that a remedy easily obtained, taken by mouth should produce marked improvement in a disease hitherto intractable except by hypodermic and somewhat risky injections. Fox (18) in the same year as Mackenzie (37) prepared a glycerine extract according to Murray's (48) method and gave one-half sheep's thyroid per day. His patient took an overdose and showed symptoms pertaining to hyperthyroid but showed marked improvement when dis-

continued use of the gland for a few days. At this time it must be mentioned that Hume (29) notes that the Chinese knew of its use before this period. He states, "Organotherapy is described as early as the sixth century when sheep's thyroids were used for cretinism. The practice is familiar to house-wives throughout the land."

This interesting development in the treatment of Gull's disease brought about investigation of the extract of the thyroid gland. Baumann in 1896, discovered that iodine is a normal constituent of the gland and that the iodine content and concentration rapidly increase if iodine is ingested. Means and Richardson (46). Murine (38) in 1907 followed this progress by demonstrating that iodine is essential for normal thyroid activity. He also noted that the commercial dessicated thyroid contains a mixture of normal and abnormal thyroids which explains a part of its varied action clinically.

The next forward step regarding hypothyroidism did not develop in connection with the thyroid but in regard to body metabolism and calorimetry. Benedict (4) in 1912 developed a method of determining the normal metabolism of the body expressed in calories. It was early, only a short time, until Gephart and Dubois (21) in 1916 developed a simplified method of computing metabolism from the body surface area with the aid of Benedict's apparatus. It was soon learned by various investigation

that hypothyroidism was noted as having a negative basal metabolic rate and hyperthyroidism had a positive basal metabolic rate. With this advancement, the distinction between non-myxedematous hypothyroidism with its lessened symptoms and true myxedema became apparent. Non-myxedematous hypothyroidism seldom shows a lower basal metabolic rate than 20%. True myxedema on the other hand, has a rate which is usually below 20% according to Swann (58). With this important development diagnosis can be made of patients before they develop true myxedema and also of those who are on the borderline and show symptoms of hypothyroidism but are not necessarily precursors of myxedema.

Kendall (30) in 1915, succeeding in isolating in crystalline form the compound containing iodine which occurs in the thyroid. He found that administration of the acid-soluble substance which he called **H** produces in the dog and in the human changes, being a rapid increase in pulse rate and vigor, and increase in metabolism and nervous irritability. The physiologic activity is produced by the compound containing iodine in all stages of purity up to and including its crystalline form. He also noted that when given in excess, toxic symptoms were produced, and that the amount of the compound required to produce toxic effects was exceedingly small. He makes no

mention of its use in connection with thyroid deficiency diseases but it is reasonable to suppose that he at once recognized its therapeutic value.

-Incidence-

In regard to the incidence of hypothyroidism it is found everywhere. Crotti (12) states however that it is far more frequent in regions where goitre is endemic, and in individuals whose thyroid is congenitally insufficient on account of their goitrous parentage. No statistics are available, yet as to the comparison of areas in which goitre is endemic and where it is not. Warfield (59). All classes of people are affected; a considerable proportion are professional men and women. Both underweight and overweight as well as normal are found among the patients. Warfield (60). Hensel (25) states in this regard that of fifty-six cases which he collected, twenty-four were of the definitely slender and below normal weight, twenty-two were of normal weight, and ten were overweight. In this condition it is found that women are more definitely predisposed to the condition than men. Minot (47). In a group of fifty cases that Harvel (23) observed there were forty females and ten males. The ages ranged from thirteen to sixty-eight years. Kurten

(33) states that the sex ratio is definitely one of ~~fe~~ female preponderance with the ratio in various series of cases ranging from four to one, in one series, as high as seven to one in another series. In his report of one hundred and eighteen cases, Marsh (39) found that there were ninety-nine females to nineteen males, a ratio of five to one. The ages of this group of cases ranged from fourteen to sixty-six years. He gives the following classification according to age groups:

| | | |
|----------------|-------------|-------------|
| 14 Years ----- | 20 Years -- | 6 patients |
| 21 Years ----- | 30 Years -- | 21 patients |
| 31 Years ----- | 40 Years -- | 39 patients |
| 41 Years ----- | 50 Years -- | 34 patients |
| 51 Years ----- | 60 Years -- | 14 patients |
| 61 Years ----- | 70 Years -- | 4 patients |

The preponderance of patients are found present in the age group from 30 to 50 years or the middle-age group. The most prominent time for hypothyroidism to develop is according to Strong (55), after puberty, during or after pregnancy, and after the menopause. The reason for this can be accounted for because at this time in the life of the female a change in the amount of function of the endocrine system takes place. The thyroid being an endocrine is involved and unless it is able to readjust itself to normal body metabolism after this disturbance, this condition of hypothyroidism may present itself.

-Etiology-

The fact that hypothyroidism tends to develop after puberty, during or after pregnancy or after the menopause would lead one to feel that this is the etiology of the condition. This is a possible explanation for Brandon (7) states that deficiency of iodine may be due to:

- 1) Factors which bring about an abnormally low intake of iodine.
- 2) Factors which interfere with the absorption or utilization of an otherwise adequate intake.
- 3) Factors which increase the needs of the body for the iodine containing hormone.

In this latter group, the processes of puberty, pregnancy, lactation and the menopause probably play a part. However, the peculiar situation arises that cases of hypothyroidism do not respond to iodine therapy. This is probably due to the fact that the gland has become fibrosed and in most instances atrophied to such an extent that it is capable of utilization of the organic iodine therapy.

Hypothyroidism occasionally follows acute infectious, particularly influenza, diseases. This has been noted by Brandon (7), Hensel (25), Kimball (31), Jurten (33), and Strong (55). Focal infection may also be a factor in depleting the thyroid as noted by the above authors. Infection has its chief effects upon the secretive portion of the gland and this after a period of stimulation leading

to hyperthyroid symptoms may injure the gland and might eventually produce a more or less functional inhibition - hence hypothyroidism, according to Hensel (25).

Kimball (31) feels that hypothyroidism may be either chronic extending over many years or come on rather abruptly, and that either type may be the result of infection, malnutrition or exhaustion.

In Kurten's (33) contribution, he states that heredity is concerned as shown by series wherein cretinism, childhood myxedema and adult myxedema have resulted in the offspring of parents where thyroid insufficiencies have been present. Strong (55) feels that certain people apparently operate on a very narrow margin of thyroid reserve and may be easily made hypothyroid if this is not hereditary, it is considered a constitutional diathesis.

Pregnancies, especially frequent ones or repeatedly interrupted ones, plus infectious diseases of a mild degree following abortions, stand out rather prominently as an etiological factor in Kurten's opinion (33). He goes on to state that toxemias, lead and alcoholic, have been mentioned as factors. The persistence of the colloid goitres of adolescence leads to the hypothyroid state in adults which is undoubtedly the reason for its higher incidence in endemic goitrous regions. Crotti (12).

During menopause, the psychic states which develop as a result of the severe endocrine disturbances are al-

ways apparent. These states range from anxiety, grief and mental strain to insanity. This condition with the endocrine disturbance has been noted by Kurten (33) as a possible etiological factor of thyroid insufficiency. However, the question arises whether the psychic states are due to the hypothyroidism or the hypothyroidism is due to the psychic states. The balance seems to be that hypothyroidism causes the psychogenic reactions, for Alexander (1) has noted the clearing of the factors under treatment.

Another etiological factor which has been known since operation on the thyroid with complete removal or partial removal is following operations where apparently too much gland has been removed. Strong (55), states that it is unfortunately true that some cases follow operation on the thyroid. This is not always a result of removing too much gland. We have no means of estimating the functional capacity of what is left after operation, nor have we means of predicting the patient's thyroid needs. An amount of gland that may serve adequately for one proves insufficient for the next.

In regard to all of these theories and hypotheses concerning the etiology of hypothyroidism, it can only be said that they are too indefinite and varied to be specific factors. Kurten (33) states, that the etiology of hypothyroidism is unknown. No theory regarding

its etiology has been definitely proved and accepted except that of iodine deficiency. Alexander (1) states that iodine deficiency does not explain the incidence of thyroid disfunction in these cases on the Virginia peninsula, for there is an abundance of iodine. This leaves the etiological factor as one which probably pertains to the function of the gland its utilization of iodine. This being unknown, the etiology is unknown and can be discussed only according to the above mentioned factors.

-Symptomatology-

As the etiological factor of hypothyroidism is unknown, the symptoms presented by a case of hypothyroidism are vague and indefinite. There is no definite group of symptoms that characterize hypofunction of the gland according to Brandon (7). In this regard, Marsh (39) states that the symptoms of hypothyroidism are numerous. The signs are associated with nearly every physiological and anatomical system of the body. Because of insufficiency of thyroid secretion there is a faulty nutrition of all the cells of the body and a deranged metabolism resulting in the infiltration of the various tissues with the products of faulty catabolism. Blumgarten (6) agrees with this when he writes that hypothyroidism directly or indirectly affects nearly every organ of the body. In considering the symptomatology of hypothyroidism, Alexander (1), discusses it generally in these words: "The symptomatology of mild states of thyroid dysfunction is often vague and elusive, so much so, that physicians are often thrown entirely off their guard. This is not because the physicians lack clinical judgment or diagnostic acumen, but first because the classical signs of major hypothyroidism are not present such as described by Osler (51) as, "marked increase in the general bulk of the body, a firm, inelastic swelling of the skin, which does not

pit on pressure, dryness and roughness, which tend with the swelling to obliterate the facial lines of expression, imperfect nutrition of the hair, decreased perspiration, overweight and slow pulse." Second because they do not avail themselves of basal metabolimetry, which to my mind, is one of the most important methods of diagnostic precision that is available to the clinician today."

"Symptoms depend upon alteration of normal function, therefore, let us consider the etiology of symptoms resulting from mild states of thyroid dysfunction in the light of altered physiology of the thyroid gland. De Quervain (13) mentions four principal functions of the thyroid as follows: "First, control and stimulation of tissue growth in general; second, control and stimulation of the functional processes of tissues; third, neutralization of toxic substances produced in the normal metabolism of the tissues. Fourth, assistance in the defensive actions of the organisms against bacterial toxins." Removal of the thyroid gland from animals results, it is said, in a forty percent reduction of the metabolism. Palmer (52) defines metabolism as follows: "By metabolism is meant the chemical changes which substances undergo when brought in contact with the living cells of the body." Two factors are involved, catabolism or reduction of higher to lower compounds, and anabolism, the building of complex substances from simple ones as the result of these chemical

changes. Heat, Mechanical energy, electric current, all of which may be measured as heat, are produced and life is sustained. Therefore, if so much of normal body function is dependent upon metabolism and so much of normal metabolism is dependent upon thyroid function, it is easy to conceive of the vast complexity of symptoms arising from such an altered state."

Warfield (60) states that the most important single symptom is an undue sense of fatigue, a physical exhaustion which often ends in a neurasthenic state. This is accentuated by Strong (55) who writes that exhaustion or fatiguability is probably the most common symptom, and, while it is by no means pathognomonic, it is always of importance. Bridges (9) also reports the finding of fatigue of a high degree as a characteristic symptom. Hoge (27) mentions this condition as a result of the general "Sub-efficiency of the body machine". There is a variance in the finding of this symptom. Watkins (61) found it in 54% of his cases; Harrel (23) in 64%; Marsh (39) in 99 patients out of 118 or 83.9%; McKean⁽⁴²⁾ states that it was marked in 90%; and Lawrence (34) found it present in 93% of his cases. In his series, Alexander (1) states that it was the most outstanding symptom and occurred in all of the thirty cases. He goes on to write that there is something characteristic about this fatigue. The patient will usually tell you that he or she awakens in the

morning feeling refreshed and rested from the night's sleep but as the day wears on, fatigue and exhaustion overtake them.

Certain symptoms are found which are referable to the gastro-intestinal tract. Constipation is a usual finding in these patients in the opinion of Warfield (20) and he says that one of the bright spots in the management of this group is to be found in the relief of previously intractable constipation by thyroid therapy. Brown (10), Blumgarten (6), Brandon (7) and Alexander (1) all mention this symptom as being present in their respective series. Watkins (61) found it in 44% of his cases, Harrel (23) noted it in 36% and Marsh noted it in 58% of his cases. Alexander (1) explains this symptom as the result of sluggish peristalsis probably due to disturbances of the automatic nervous system giving rise to intestinal atony. There is very often an associated hypoacidity.

McKean (42), Hage (27) and Warfield (60) have noted anorexia, with the characteristic picture being one in which the patient rarely cares for more than one meal a day and seldom eating breakfast. Harrel (23) found that 36% of his cases gave a history of digestive disturbance of some sort. Brandon (7) and Warfield (60) also noted vague abdominal pain which was usually found over the colon. Watkins (61) also noted gaseous eructations in

50% of his cases. Loranger (36) notes it in relation to gall bladder symptoms, and believes that the production of gall stones may be caused by the hypercholesteremia which is present in hypothyroid patients.

Another symptom which is frequently encountered is that of myalgia and arthralgia. Warfield (59) finds that rheumatic pains are also complained^{of} and focal infection may be blamed for the condition. In atypical forms of hypothyroidism, Blumgarten (6) states that this is one of the most common complaints. Backache in the lower lumbar region and right adnexal pains of a vague and dissociated type are a frequent complaint particularly in young females as noted by Kurten (33). Mc Kean (42) also noted this complaint as a frequent symptom. Harrel (33) noted that twenty-six per cent complained of this in his series. Watkins (61) has a higher finding of fifty-six per cent in which loss of muscle strength and myalgia were noted. Swain (57) in a series of 312 cases of chronic arthritis of all types of duration and activity found that thirty-nine per cent of the metabolic rates were abnormal; plus or minus ten being used as normal. Of these, fourteen per cent were plus and 25 per cent were minus. With zero as the dividing line, 63% or two-thirds minus; thirty-four per cent, or one-third were plus. This emphasizes the tendency to low metabolic rates in chronic arthritis irrespective of the type of

arthritis present. No one type of arthritis irrespective of age seems to stand out as having characteristic variations in metabolic rates from the other types. Abnormal metabolism with a tendency to a minus rates is characteristic of arthritis, especially, in the early years, having a tendency to return to normal as the duration of the disease lengthens. The figures suggest that a low metabolic rate may be a prearthritic sign or that patients in the low metabolic group are those in whom arthritis develops.

Thyroid administration in these cases of arthritis with low metabolic rates does not raise the rates in four-fifths of the cases; but if it is carefully given, beneficial results are obtained in spite of the fact that in doses which can be tolerated, it may not change the metabolic rate. The chief improvement is in circulation, muscle tone, weight and vitality. It acts as a stimulant and stabilizes the affected joints.

Numerous symptoms referable to the *cardium* are noted. Strong (55) and Mc Kean (42) noted dyspnea in mild exertion and palpitation. Christian (11) noticed frequent symptoms of circulatory insufficiency as exhaustion and fatigue. Minot (47) notes that a myocarditis is frequently found evidence of which is shown by symptoms of incompetency of the heart, together with its slight enlargement and sounds that are weak in character.

Shortness of breath and vertigo were observed by Swann (58). Dyspnea was present in 26% per cent of Laurence's (34) cases; palpitation in 26% per cent and vertigo in 20%. Kurten (33) observed that heart trouble is a frequent complaint which on analysis usually turns out to be gaseous distension of the stomach. Swann (58) states that the patient's feeling of improvement is the only reliable evidence in proof of benefit from thyroid medication but even this may be psychic.

Headache seems to be a fairly constant symptom of-ten migrainous in character. Watkins (61) observed it in 20% of his cases; Marsh (39) noted it in 25%, Lawrence (34) in 26 per cent, Harrel (43) noted it in 50% while Mc Kean (42) observed it in 60%. The headaches are usually frontal or occipital in nature, which Bridges (9) has also noted. Alexander (1) states that he believes he has noticed a relationship between allergic disease and thyroid deficiency. Thyroid therapy, he found contributed to the relief of migraine in cases with low basal metabolic rates.

These patients also present symptoms relative to the central nervous system. Paresthesias of one kind or another have been noted by Alexander (1), Brandon (7), Kurten (33) and Mc Kean (42). Brandon (17) observed that there was numbness and tingling of the extremities which Strong (55) also describes. Mc Kean (42) describes

a creeping sensation over the back of the neck and arms. There is also a sense of choking, or fullness in the neck when excited, a rather typical globus hystericus picture, and difficulty in swallowing is complained of frequently. Harrel (23) observed this in 14% of his cases. Nervousness and poor emotional control are present. Watkins (61) reports 86% per cent of his cases giving this complaint; Marsh (39) observes it in 77% and Harrel (23) in 52%. Lawrence (34) notes memory loss in 6% while Mc Kean (42) classifies it as memory loss and poor concentration in 54% and Watkins (61) has mental apathy in 40%. Ziegler (64) has reported three cases with psychic manifestations which improved under therapy. A case reported by Mc Kinlay (43) is one with narcolepsy and persistent and repeated somnolence without regard to the appropriateness of the procedure, making effective work impossible. This also improved with thyroid therapy. Beilin (3) reports two cases which had neuritis symptoms which were present with hypothyroidism and in which he believes the thyroid deficiency was the etiological factor. Certain ill-defined, yet important personality changes are frequently noted by the intimate associates of patients, reports Strong (55). He also states unusual irritability, apathy to all things, loss of memory, or loss of ability to concentrate are common.

The patients are usually depressed in spirits. Latent psychotic states may be intensified by the onset of hypothyroidism. Lawrence (34) notes mental depression and irritability in 40% of his cases. With this evidence regarding central nervous system disturbances, it is important to remember that hypothyroidism may be a factor when they are presented.

Symptoms which relate directly to the integument are also present in a high percentage of cases. The most marked condition regarding the integument is undoubtedly the very dry skin. Alexander (1), Bridges (9), Mc Kinlay (43) and Strong (55) report this symptom. Marsh (39) reports it in 75 cases out of 118; Mc Kean (42) finds it in 75% of his cases; and Watkins (61) found it in 56% of his series. Marsh (39) also notes that 54 cases out of 118 present dry or thin hair. This clinical symptom is also noted by Watkins (61), Strong (55) and Mc Kean (42). The next most important symptom related to the integument is that of susceptibility to cold. This is also noted by the above authors. The extremities are usually cold and clammy. Harrel (23) reports that these patients need covers in the summer time and require two and three pair of blankets in the winter time to sleep comfortably. Lawrence (34) noted this susceptibility in 23% of his series. Mc Kean (42) has observed there is a tendency to dental caries which is more pronounced in these cases.

Various pathological manifestations of the skin have been noted by various authors. Bridges (9) reports a case in which localized pigmentation is present. Mc Kean (42) notes that urticaria, furunculosis and eczema are not uncommon. Mc Kinlay (43) reports a series of manifestations of hypothyroidism in which there is a case of chloasmic pigmentation of the face; scant perspiration is also a rather constant symptom as reported by Strong (55) and Alexander (1) although it is not constant. Hensel (29) does not agree with these authors; however, he states that none complain of dry skin or thinning of the hair. In fact, in some of the most outstanding cases the skin is very fine, white and elastic. This, however, cannot be accepted when so many authors report dry skin and thinning of the hair in such a high percentage of cases.

Strong (55) states changes in weight are also important in the patient's initial story. The weight is usually over the estimated normal though underweight is not uncommon. Brandon (7) states that the weight may be increased, or decreased or normal which is in agreement with Warfield (60) and Alexander (1). Hensel (25) in a series of 56 cases found 24 below normal weight, 22 of normal weight, and 10 above normal weight. Lawrence (34) found abnormal weight in 66% of his cases, 33% of the cases were of normal weight, 23% over weight, and 43% underweight. In his series, Watkins (61) states that

16.1% were overweight in 54% of the cases; 12.8% were underweight in 26% of the cases, and 20% were of normal weight. Bridges (9) writes that there is a loss of weight in his report, while Blumgarten (6) states that obesity is a common complaint in atypical cases. Strong (55) states that in spite of the extra weight these patients are obviously in a poor state of nutrition. With this symptom showing such a variance, it is important when it is presented to use care in eliciting the other complaints from the patient and to have the symptom complex of hypothyroidism in mind.

The symptoms referable to the genito-urinary system are significant. Alexander (1) stated that he was unable to find any constant urinary symptoms. Kurten (33) does not state that he has found characteristic symptoms but notes the presence of a diminution of renal function with nocturia, pyuria, dysuria, oliguria, and incontinence in certain patients. Symptoms referring to the menstrual history are prevalent. Strong (55) observed that menstrual irregularity is very common, not, as is so generally believed, complete amenorrhea, but a disturbance characterized by prolonged menstrual intervals, with a complete arrhythmia of the cycle. Brandon (7) has also noted this symptom and Bridges (9) has mentioned the symptom of nearly menopause. In his series, Kimball (31) stated that prac-

tically every type of amenorrhea and dysmenorrhea which was eventually proven to be secondary to hypothyroidism was seen. Lawrence (34) has noted the presence of sterility of married women in 41% of his cases. Delayed puberty up to 15 years was noted in 15% of his cases. Mc Kean (42) reports that he observed that the menses were regular but scant in 66% of his series. Watkins (61) stated that menstrual disturbances were evidenced in 37.5% of his cases, of these about half had passed through the menopause and the rest had a menstrual flow scantier than normal, one patient having menorrhagia. Severe menorrhagia is noted by Blumgarten (6) as a common symptom. Twenty-five cases are presented in a series by Breckenridge (8) which he has divided into obstetric and a gynecologic group. In the gynecologic group of seventeen cases, menorrhagia was predominantly the presenting complaint. This was frequently accompanied by shortening of the intermenstrual interval. In some of the patients there was lengthening of the intermenstrual interval. In all of these patients a careful search was made for local cause before the taking of a basal rate. During the period in which these patients were seen, only one patient was seen in whom the picture of menorrhagia, with shortening of the intermenstrual interval was accompanied by hyperthyroidism.

In 79% of the patients that remained under observation for a sufficient period to justify conclusions, com-

plete relief of symptoms followed thyroid medication. The obstetric group of eight cases he paired as follows: two of missed abortion, two of habitual abortion, two of psuedocyesis, and two of subinvolution. He stated that these cases show that slight to moderate degrees of hypothyroidism may be very important causal factors in a number of gynecologic and obstetric conditions. These include amenorrhea, and more frequently menorrhagia and probably include abortion, miscarriage, premature labor, and death of fetus. Furthermore, hypothyroidism is one of the more frequent causes of menorrhagia and metorrhagia and should be excluded before resort is had to the curette, radium, x-ray or abdominal section.

In the male, Blumgarten (6) observed that impotence occurs. Brandon (7) agrees with this finding and notes loss of sexual power and sterility. Mc Kean (42) also states that loss of libido is common. Forman (17) notes that spermatorrhea may be an early expression of hypothyroidism. This evidence indicates that the normal function of the thyroid gland may be of importance in those cases in which abnormalities of the reproductive system are presented.

The relationship of infections, especially of the upper respiratory tract, are noted by various authors. These people quite frequently show a preponderance of upper respiratory infections according to Alexander (1).

Kurten (33) states that there is a lowered resistance to infections accordingly manifested by frequency of colds, coryza, rhinitis and respiratory infection. Harrel (23) observed that on examination a definite source of infection, either acute or chronic, was found in 80% of the entire group. These infections included diseased teeth and gums, chronic sinusitis, pelvic inflammatory disease, prostate, and influenza of recent date. Watkins (61) observed the same complaints in 52% of his cases. In this regard, Forman (17) states that here the history must not be accepted at its face value, but the examiner must assure himself that these symptoms are not a part of the atopy underlying the coryza rather than true infections of the nasal mucous membranes. The symptoms of susceptibility to infections is summed up by Warfield (59) who states that if there is a lack of the thyroid hormone there is greater susceptibility to infections of various kinds, for the hormone has a decided influence upon bodily resistance and upon antibody production.

In going over the symptoms presented in cases of hypothyroidism it is noted that nearly every system of the body may be involved. This presents a very vague and indefinite symptomatology which is not conducive to diagnosis of the disease from the symptom syndrome alone. The skin manifestations and menstrual disturbance should

place the clinician on his guard.

-Physical Findings-

The physical findings in hypothyroidism in which non-pitting edema is not present are not highly typical. Mc Kean (42) states that the thyroid may or may not be palpated. This finding is mentioned constantly in the literature. Watkins (61) in his series found that the thyroid gland was not enlarged in 76% of his patients. Colloid goiter was present in 14% and adenomatous goiters were present in 6%. The thyroid gland had been resected in 4% of his series. Warfield (59) states in this regard that the thyroid gland may be visible as a swelling at the root of the neck or there may be no evidence of the gland on inspection.

In regard to the vascular system no typical findings are presented. There is considerable controversy in the literature regarding this. Bridges (9) reports that there is generally a slow pulse, subnormal temperature and low blood pressure. Brandon (7) agrees with Bridges (9) regarding the low blood pressure but states that the pulse may be slow or fast. Hensel (25) found the pulse usually slow - 56 to 72 - and the heart tones frequently feeble or faint. Mc Kean (42) also mentions the predominating bradycardia. He reports a hypothermia composite of 97.7 degrees and a hypotension of 111/70. Lawrence (34) ob-

served a pulse of 67 in his series and a hypotension of 111/69. Herrel (23) states that in his series of fifty cases the pulse rate was of no special significance; 8 cases had a pulse rate of 90 or above, the fastest being 124 and the lowest was 64. He goes on to state that some writers claim that hypothyroid cases run a slow pulse, low blood pressure, and subnormal temperature. He did not find it so in this series. The temperature ranged from 97 to 99.1; the blood pressure, systolic, the highest 160, the lowest 90. Twenty-five had a systolic pressure of 110 or lower; these might be classified as hypotensive. He also states that there was not a real obese patient in the group, although a few were slightly overweight.

In regard to obesity, Kurten (33) observed a padding of the dorsum of the hands and feet around the wrists and ankles, fingers and toes; in the dorsal cervical area and the supraclavicular space. Loewenberg (35) agrees with Kurten (33) when he states that hypothyroid obesity is characterized by fat pads in the supraclavicular region and general distribution of fat over the entire body associated with a rather inelastic skin.

Other findings, include a paleness of the mucous membrane observed by Bridges (9). Brandon (7) has observed that in some cases there is a relaxation of Achilles reflex and a thinning of the outer half of the eyebrow.

Loss of distribution of hair over the outer one-third or one-half has also been observed by Strong (55). In relation to the eyes, Weiss and King (62) state that in a series of 26 patients, there has been one common physical finding, that is, the swelling of the eyelids, notably the upper eyelid. Forman (17) reports that the fingers and the nails sometime show an increased brittleness. Warfield (59) sums up the physical findings by stating that so far as known there is no one type of bodily structure which seems particularly prone to develop lack of thyroid secretion.

-Laboratory Findings-

The laboratory findings in hypothyroidism relate chiefly to the basal metabolic rate. Strong (55) states that there is always a lowered basal metabolic rate. He states that the ordinary case of hypothyroidism falls normally between minus 15 to minus 25 per cent, although instances are recorded of minus 50% or lower. Lawrence (34) found in his series the basal metabolic rate was an average of minus 24%. Hensel (25) also states that the one constant finding is a lowered basal metabolic rate. There is a wide range of variability in the degree of reduction of metabolic rates, the readings ranging from minus thirteen to thirty-three percent, but showing no correlation between the degree of reduction and the intensity of symptoms. Harrel's (23) group had a basal metabolic rate of

minus ten or lower. He had a number of cases that had a basal rate between minus five and minus ten whose symptoms were just as pronounced or more so as those with lower readings and responded just as readily to treatment. Hoge (27) is convinced that readings of minus five to ten are more significant than those showing plus ten to plus fifteen because any mechanical error in the reading is always made on the positive side. According to Blumgarten (6) the basal metabolic rate is reduced in proportion to the severity of the disease and this is the diagnostic feature of the disease. Means and Burgess (45) state that sub-normal metabolism in disease other than those of the endocrine glands is distinctly infrequent. Eighty-four per cent of their cases with subnormal rate were either definitely endocrine or presented some suggestion of endocrine. Those cases with definite clinical pictures of hypothyroidism invariably show decreased metabolism. Swann (58) states that the determination of the basal metabolic rate is almost essential in the diagnosis of mild grades of hypothyroidism and in following the response to treatment. However, Strong (55) states that one point worth emphasis is, that, while it is generally recognized that the basal metabolism rate should be based on more than one estimation when dealing with hyperthyroidism, the same, necessity, when dealing with hypothyroidism is frequently over-looked. From the above evidence it is essential that the basal metabolic rates of

all patients suspected of hypothyroidism be determined.

In regard to the blood changes, Warfield (60) states that there are no specific changes and lymphocytosis is not always present. Swann (58) states that the blood counts showed a relative lymphocytosis in his cases. On the other hand, Blumgarten (6) states that blood changes are not constant, the leukocytosis being normal with a relative increase of lymphocytes, monocytes, eosinophiles. Mc Cullagh and Dunlap (41) found the hemoglobin in hypothyroidism is reduced slightly. The degree of relative lymphocytosis in hypothyroidism is about as high as in hyperthyroidism which is 30% or above, in 60% of their cases. Strong (55) and Forman (17) mention an anemia of the secondary type. Stone (54) observed this in 13 of 23 cases. He contributes it to a depression of function in the hematopoietic system due to hypothyroidism. Most authors feel that this condition occurs only in the more severe grades of hypothyroidism. Lawrence (34) found the following results in his series of 30 cases; alveolar carbon-dioxide, 37%; red blood cell count, 4,8000,000; Hemoglobin, 87%; lymphocytes, 39.6%; non-protein nitrogen, 33 mg per cent; urea nitrogen, 14.7% mg; uric acid, 315 mg per cent; and the blood sugar, 99.6 mg per cent which are within normal limits.

The blood cholesterol values are the most specific and constant findings in relation to hypothyroidism.

Mason, Hunt and Hurxthal (40) found that in animals deprived of the thyroid gland, the cholesterol value was much higher than normal but became markedly decreased when thyroid was fed. They found that only in the very severe cases could any direct correlation between the basal metabolic rate and cholesterol value be found. They believed that the blood cholesterol level in hypothyroidism reflects the patient's true condition more accurately than the basal metabolic rate. Epstein and Lande (14) agree with the above authors in that they believe that repeated cholesterol determinations are of value in judging the effects of thyroid therapy and allied conditions of hypothyroidism and allied conditions of hypothyroidism. Blumgart (5) and Blumgarten (6) also mention the finding of increased blood cholesterol values in hypothyroidism. Gardner (20) states that as regards the cases of hypothyroidism there does appear to be some such relationship (that the blood cholesterol is inversely proportional to the basal metabolism rate) and the cholesterol of the plasma is certainly above normal in untreated cases of myxedema. Laranger (36) states in regard to this hypercholesteremia that there is a great need of studying the thyroid function in gallstone cases with an idea of preventing lithiasis by adequate control of hypothyroidism. He feels that this is possibly a preventive treatment which would remove the underlying biochemical

cause. Mason, Hunt and Hurxthal (40) also make this hypothesis in their original work and state further that cholesterol values are important aids in diagnosis and prognosis and in estimating response to treatment in patients with hypothyroidism.

Nickolls and Perlzeweig (49) have noted that after operation involving the partial removal of the thyroid gland there is a tendency for the surface tension of the blood stream to rise even more so than after iodine. They hypothesize that there may be an increase of surface tension of the serum in myxedema and thyroid deficiency. Aub, Bauer, Heath and Ropes (2) demonstrated that in six cases of thyroid deficiency that there was a diminished calcium output. Mason, Hunt and Hurxthal (40) state in this connection that in hypothyroidism the calcium excretion is markedly reduced. Then if arterio-sclerosis is associated with an abnormal cholesterol retention together with a decreased output of calcium, then one would expect a high incidence of arterio-sclerosis in the hypothyroid patient.

The urine findings in hypothyroidism are essentially negative. Harrel (23) states that in his series the urine was negative for the entire group except four cases which showed some pus. According to Strong (55) the urine is ordinarily normal but albumin and casts occur in a sufficient number of cases to give rise to the term pseudo-

nephritis. Lawrence (34) found in his series of 30 cases the 24 hour output to be 1176 cc with a specific gravity of 1.014.

The gastric analysis reveals normal or low acid values, occasionally achlorhydria occurs, according to Strong (55). Brown (10) states that as regards gastric secretory condition in those cases with relatively slight basal reductions, that is, with readings between minus ten and minus twenty, the readings are quite normal, and there is no difference between these readings and those obtained in normal individuals; that is those with readings from minus ten to plus ten. On the other hand, in the cases with very low readings, minus twenty and below, there was a marked tendency to gastric subacidity, a considerable portion of the cases presenting achlorhydria. In 70% of the cases on which the test was done, Harrel (23) found a hypochlorhydria in his series.

X-ray examination, according to Forman (17) shows a consequent retention of the barium meal in the descending colon and sigmoid for 56 to 72 hours, in a high percentage of cases. Strong (55) states that this examination is valuable to eliminate the possibility of organic disease, and will often reveal the atony so characteristic and so commonly the cause of the obstinate constipation. Hoge (27) has found that X-ray studies, made upon these

patients, have without exception shown some degree of gastric distention after six hours. Brown (10) states that there is no characteristic gastro-intestinal picture presented by this group of cases, the digestive symptoms, gastric or intestinal being purely functional in nature not at all different from that encountered in a variety of other conditions.

In this connection, however, Hinton (26) finds that patients giving negative roentgen evidence of changes in the gastro-intestinal tract, the gall bladder and genito-urinary region as well as negative results in the other laboratory procedures, may in a small percentage of cases be suffering from hypothyroidism. In this group with negative roentgen observations a metabolic determination should be done before any treatment is instituted or before the patients are submitted to an exploratory laparotomy, as occasionally a diagnosis will be established and the symptoms relieved with thyroxine and thyroid extract, the patient being saved a needless operation.

X-ray examination of the heart by Mc Lester (44) shows a frequency of the bottle-shaped heart. He states that it is in no sense peculiar to thyroid deficiency, but that it is interesting that so many of his patients with thyroid deficiency have hearts of this shape. Swann (58) has noted that X-ray examination of the heart in mild hypothyroid cases does not as a rule show any marked enlargement in the first examination, but after the patient has been on treatment for

a few weeks a second film of the heart will usually show a reduction in the size of the heart. This authority states that the electrocardiographic changes in this group of cases are lowered voltage and inversion or a flattening of the T wave. Some patients have shown a marked improvement and some a return to normal electrocardiograms after thyroid treatment. Strong (55) states that the electrocardiogram may show a very typical picture in which, while the waves are of normal configuration, the low voltage present in each lead shows reduction in cardiac activity which bears out Swann's findings.

-Diagnosis-

Osler (51) states that the diagnosis of hypothyroidism should be considered in women who have symptoms suggesting a premature menopause, in obesity and in those with constipation the cause for which is obscure. In this regard, Warfield (60) states that diagnosis cannot be made without evidence of a low basal metabolic rate, as there are no pathognomonic symptoms or signs for the mild hypothyroid state. Mc Kean (42) states that a thorough clinical and laboratory survey is of permanent importance before a diagnosis is made. A diagnosis should not be made from one basal metabolic rate alone unless symptoms correspond according to Harrel (23). Mason, Hunt, and Hurxthal (23) feel that blood

cholesterol values are of importance before diagnosis is made. The response to treatment is an important factor according to Strong (55). The therapeutic test as given by Forman (17) is: When it has been determined with a reasonable certainty that the patient does have hypothyroidism will respond definitely and promptly to the administration of iodine, and the other cases presenting somewhat the same picture will not be influenced favorably. Instead, such medication may produce in these patients the symptoms of an overdose, such as a fast pulse, weakness, tremors. Strong (55) states that when a case fails to respond to adequate thyroid treatment which has been continued a sufficient time, it is definite evidence that we are not dealing with a hypothyroidism.

-Differential Diagnosis-

Differential diagnosis must be made from endocrine gland failures, especially suprarenal, posterior pituitary and ovary. From such chronic diseases as (1) occult or incipient tuberculosis, (2) diabetes, (3) chronic nephritis, (4) pernicious anemia, and other blood diseases according to Warfield (60). Koehler (32) states that the differential diagnosis between hypothyroidism and hyposuprarenalism is particularly difficult because of the similarity of the two groups. The patient with hyposuprarenalism, as well as the

one with hypothyroidism usually suffers from a deficiency in the energy metabolism, and consequently experiences languor, fatigability, asthenia, often somnolence, or restlessness and nervous instability.

He states that in hypothyroidism it is customary to see this difficulty occur either as a familial, often with onset at puberty or later at the menopause, or else following colloidal degeneration or thyroidectomy. Hyposuprarenalism, on the other hand, usually has its onset in one of two ways, either concurrent with or following infections or toxic states, or due to exhaustion as a result of great stress or strain.

In hypothyroidism the onset is usually gradual and continues with moderate constancy, the functional symptoms of energy deficiency slowly becoming augmented with the secondary structural changes. In hyposuprarenalism, however, there is considerable variation in the course of the disease; the onset is often sudden and there may be temporary periods of remission, rest or a variation is usually associated with considerable improvement. The patient with hypothyroidism is commonly overweight, the skin and hair dry and an early tendency to loss of hair. In hyposuprarenalism the patient is usually underweight. There frequently was vasomotor instability with flushing and the hands and feet perspired freely.

The blood pressure averages lower in both of these

groups, although it is distinctly lower in the hyposuprarenal group. In this report, Koehler (32) finds the average for the hyposuprarenal group was 102 systolic while the average for the hypothyroid group was 115 systolic. The temperature is low in both groups. Hyposuprarenalism is not affected by thyroid medication. Hyposuprarenalism shows a marked instability of body temperature, as affected by exercise, excitement or variation in external temperature. The basal pulse rate is low both conditions, but here too, the rate in hyposuprarenalism showed the characteristic lability of this disease, and a little excitement frequently developed a rapid rate. Nervous instability is not unusual in hypothyroidism, the average person suffering from this deficiency was commonly phlegmatic, often a victim of somnolence. The hyposuprarenal patient, on the other hand, was particularly unstable nervously, especially when somewhat fatigued.

In this series of Koehler's (32) the average basal metabolic rate for the hypothyroid individuals was a minus twenty-six. The average rate for the hyposuprarenal cases was minus seventeen. The respirations in pure hypothyroidism are uniform and decreased both in amplitude and in rate. In hyposuprarenalism the respiratory movements were found to be very erratic in graphic readings. The hypothyroid patient shows unusual insensitiveness to oxygen. In contradistinction the author found that the hyposuprarenal pat-

ient is very sensitive to lack of oxygen. The hyposuprarenal patient is very sensitive to epinephrine while the hypothyroid patient is not. The same condition was noted with the histamine test.

The therapeutic test was given by Koehler (32) to these cases. He found that the response in the hypothyroid case is very definite. In hyposuprarenalism if there is any improvement, it is slight, and does not compare to that shown by the hypothyroid case.

The differential diagnosis of hypopituitarism and hypothyroid is difficult. Loewenberg (35) states that the most frequent conditions caused by hypofunction of the anterior lobe of the pituitary body and also such conditions of pleuriglandular disturbance in which the anterior pituitary lobe plays the more conspicuous role are:

- 1) Amenorrhea of the type characterized by prolonged interval and scanty flow.
- 2) Sterility, particularly in women who present the girdle-type of obesity. It has been proved beyond doubt by many observers that the anterior pituitary lobe exerts the motive power which stimulates the ovary, causing menstruation, ovulation and estrus.
- 3) Obesity. This may be caused by hypofunction of the pituitary gland, the thyroid gland or the gonads. While sharp lines of obesity cannot always be made, the following distinctions are fairly common.

Obesity of the pituitary type, in addition to other symptoms, is characterized by deposits of fat around the waist line and the hips; the abdominal wall often hangs down like an apron covering the pubis.

Obesity of gonad origin usually causes general distribution of body fat, though the extremities are often thin, thus causing a thick body and thin legs.

Hypothyroid obesity is characterized by "fat pads" in the supraclavicular regions and general distribution of fat over the entire body associated with a rather inelastic skin.

The common findings noted in one and two above, are also found in hypothyroidism. Kurten (33) states that the skin is soft, hair is oily and bitemporal headaches are complained of, as noted previously in this discussion of hypothyroidism. Kurten goes on to state that there is an abnormal distribution of hair on the face, between the breasts, on the abdomen, and arms. He finds that the sugar tolerance is increased; the blood pressure, pulse and temperature are normal, or only slightly subnormal. Sexual frigidity of the acquired type and sterility are frequent. The basal metabolism is low.

In hypothyroidism, no abnormal distribution of hair is noted except the characteristic thinning at the outer one-third of the eyebrow. Hypothyroidism presents the same findings as regards the sugar tolerance, blood pressure, pulse and temperature. The same is true of sexual frigidity of the acquired type and sterility.

Kurten (33) states that it is an interesting observation of long standing that pituitary disturbances almost invariably follow prolonged hypothyroidism and vice versa, so that in late cases we often have to contend with thyropituitarism or pituitary thyroidism, so designated depend-

ing on which preceded the other. Warfield (60) states that careful thyroid finding under rigid observation is of help in differentiation if doubt exists in the mind of the physician.

In ovarian dysfunction, Frank, Goldberger and Spielman (19) find that the majority of obese patients show a normal metabolic rate. Many of their patients would not tolerate thyroid in any form. In this condition, Warfield (60) again states that the therapeutic test is the important one.

In the above author's experience, the most common disease that has to be differentiated from mild hypothyroidism is occult tuberculosis. Unless there is malnutrition, the normal basal metabolic rate in tuberculosis and the presence of a very positive intradermal old tuberculin test are helpful differential points. A careful history, physical examination, and sputum examination should also be determining factors in the differential diagnosis of these two diseases.

Pernicious anemia often suggests hypothyroidism due to the pallor, the dry skin, the absence of weight loss, and the physical and mental apathy according to Strong (55). He continues that paraesthesias may be common in both conditions. The blood picture in thyroid failure may simulate the pernicious type, though as is well known, there is no constant blood picture in pernicious anemia. The two di-

seases may coexist. The basal metabolic rate proves the distinguishing feature. It may be added here that the response of the blood picture to liver therapy would be of value.

In chronic nephritis, the question of a differential diagnosis arises. The pseudo-nephritis of hypothyroidism with albumin and casts in the urine may cause confusion reports Strong (55). He continues that the adequacy of renal function, as judged by concentrations and dilution tests and the absence of retention of nitrogenous products, serves to distinguish hypothyroidism from chronic nephritis. The lower basal metabolic rate in the former and the prompt response to thyroid therapy are of value. A detailed history and symptomatology are also of much value.

"Starvation profoundly affects the basal metabolism," reports Mc Kinlay (43). He has observed a very low basal metabolism of approximately minus 40%, in a dispensary patient markedly underweight who was starved on account of a gastro-intestinal condition. This condition is classified by Strong (55) as a nutritional disturbance. In this group there may occur conditions frequently associated with such reduction in vitality as above noted. This nutritional disorder may result from an insufficient caloric intake or, what is more common, the trouble may arise as a result of a qualitative deficiency. Protein inanition will produce a lowered basal metabolic rate. It is essential, therefore,

to question the patient about his diet preceding the onset of symptoms. Where doubt remains the therapeutic test will settle the question. A diet of adequate caloric value, with sufficient protien, must be included in the treatment of either condition.

From the above evidence, it is important that a differential diagnosis depends upon a careful history, the symptoms and physical findings, the metabolic rate and the response to the therapeutic test.

-Treatment-

If the diagnosis is correct, the treatment is specific, Warfield (60).

According to Strong (55) thyroxin is, no doubt, the most accurate preparation with which to treat these patients. Heurékson and Platou (24) state that in the usual case the dosage of thyroxin varies from 0.1 to 0.8 milligrams daily. When a rapid effect is desired, thyroxin may be given intravenously states Warfield (59). Mc Kean (42) states that the chief advantage in using thyroxin lies in the increased accuracy of dosage possible, and in the fact that it may be given hypodermatically, making administration possible when there is failure of absorption of thyroid substance given by mouth. Its disadvantage is its added cost over the gland substance proper which is in most cases perfectly satisfactory. In the

use of thyroxin, Warfield (60) sums the situation up by saying that there seems to be no valid reason for giving thyroxin, which has to be administered hypodermically or intravenously when administration of the gland substance by mouth will produce the desired result.

The dried gland - official in this country - is four to five times the strength of the fresh gland, official in England, (which, however, is stocked as prepared by Burroughs, Welcome and Company, in many of our local drug stores) states Mc Kean (42). He continues that either may be very satisfactory, providing the relation between them be born in mind. Thyroid gland substance varies in iodine content as regards its potency. The author states that in the last two years, thanks to an immense amount of pharmacological investigation, a definite standard of potency for thyroid gland substance has been laid out, namely, that to conform to pharmacopoeal standard, it shall contain 0.17 to 0.23 % of iodine in thyroid combination. This agrees with the U.S.P. requirements according to Forman (17). Mc Kean⁽⁴²⁾ continues that however, even with this distinct advance, variations in clinical effect still exist. It is well, therefore to choose some one preparation of proved pharmacologic activity and to use this for clinical work. If its results on known cases are satisfactory, this preparation should be continuously used on all individuals of this type. Only in this way may definite conclusions be drawn from any results ob-

tained. Kurten (33) states in this regard that since the pharmacological action of thyroid depends upon its iodine content, it is well to remember that the products of different manufacturers vary, for instance, the product of Burroughs, Welcome and Company, contains 0.08% of iodine; Armour and Co. and the Lilley product, 0.2%; Parke Davis and Company, 0.3%.

The dosage of thyroid extract varies widely according to Warfield (59). He states that some patients have taken as high as fifteen grams daily, and that six to nine grams daily in an average dose. He has found that there is no relationship between the depression of basal metabolism and the amount of thyroid which will normalize the patient. Kurten (33) has also found that it takes varying oral dosages to bring about restitution. His dosages varied from one-half grain to six to eight grains per day. The average dose he found to be one grain three times per day. Mc Kean (42) gauges his initial dosage roughly by the degree of depression of the metabolic level, and begins cautiously with a dosage of one-half to one and one-half grains daily, preferably on an empty stomach and when possible twice a day, to lessen the number of missed doses. Hoge (27) treats his cases a little differently. He believes that all cases should be given, at the beginning one-tenth to one-half grain of thyroid extract increased as deemed necessary, thereby avoiding the danger of converting a long-standing hypothy-

roid suddenly to a marked hyperthyroid, with embarrassing and at times, very disastrous results. He believes that most hypothyroids have been such since early childhood, and are unprepared for a sudden change in their body metabolism. The time of administration, he believe, to be of very great importance. He states that he gives routinely the amount of thyroid gland required for twenty-four hours at one dose, from one to two hours before breakfast. His reason for adopting the above routine, which so far as he knows, is original, was based upon the belief that certain individuals secreted a substance in their gastro-intestinal tract during digestion capable of destroying almost any amount of thyroid gland taken. Gastro-intestinal X-rays made upon these patients have without exception shown some degree of gastric retention after six hours. It should therefore, be obvious, that the usual method of giving the dose shortly before each meal had just as well be given during or afterwards. To further substantiate this, he has found in his patients who had been taking their thyroid in the usual manner before the adoption of the above routine, are getting along just as well under this plan on about one-half the amount they had been formerly taking. Brandon (7) also believes that dosage should be started slowly and gradually increased. He has found that the dosage required to raise the metabolism to normal is usually greater than that required to maintain the normal level of metabolism.

Mc Kean (42) makes repeated tests at one to two week intervals until a normal metabolic level is reached. The dosage required to keep this level is made routine. He then makes checks monthly and adjusts the dosage until the maintenance dose is determined. He then checks his patients semi-annually. He states that the medication has become a food and must be taken indefinitely, and possibly always, in all but a few children and young adults. Brandon (7) states that the duration of treatment depends upon the extent of thyroid failure. He gives his patients regular intervals of intermission in taking the gland thereby lessening the danger of producing hyperthyroidism. Swann (52) continues his medication for a period of at least one year and says that the treatment is indefinite. He also uses the basal metabolic rates in determining treatment and feels that they are only accurate when three or more are taken on different days. Warfield (60) does not have this attitude. He states that it is neither necessary nor desirable to bring the metabolic rate to normal. He finds that it is not the figure of the basal metabolic rate but the well-being of the patient which is the criterion for dosage.

Spingler (53) reports that the tolerance varies in the same individual. This is agreed to by Strong (55) who find that during an acute illness, an increased amount of thyroid substance may be necessary to carry these patients. He has found that occasionally the eradication of foci will permit

reduction in the maintenance dose of thyroid. Brandon (7) has noted that functional activity of the thyroid fluctuates considerably under the influence of fatigue, infection or nervous strain. He finds that if pregnancy supervenes during treatment it usually requires more thyroid to carry the patient at a normal level. Youmans and Riven (63) have also noted that the amount administered will vary in individual patients, as will the level of metabolism at which maximum relief of symptoms is obtained and both must be determined by trial for each individual over various intervals of time.

The use of thyroid implantations has been attempted since the disease was first recognized as noted in the history. Hendrickson and Platou (24) state in this regard that while thyroid implantation has been attempted, no lasting results have been obtained.

Sturgis (56) has found that the earliest symptoms of overdosage consist of a sensation of excessive warmth, palpitation, headache, dizziness and slight tachycardia. Hendrickson and Platou (24) find that in children overdosage prevents growth quickly, and this may be the only sign of overdosage. Other signs of over dosage are rise of temperature, flushed face, tremor, and nausea and vomiting. Sturgis (56) reports that if the drug is discontinued for a few days and then commenced in smaller doses these symptoms rapidly disappear. If, however, the excessive dosage is continued, vomiting, marked tachycardia, severe diarrhea, fibrillary

tremor, and insomnia occur and collapse may supervene.

In cases of circulatory insufficiency with hypothyroidism, Christian (11) reports that the giving of thyroid medication throws an increased amount of work upon the heart to elevate the metabolic level. The heart must be able to respond to this by increasing its work, and he finds that frequently digitalis and other cardiac therapy prior to and during the giving of thyroid medication are advisable.

Alexander (1) adequately sums up the treatment by saying: "If the patient is considerably overweight, put her on low caloric diet along with thyroid. If she is nervous, give her a little sedative. If she is undernourished, boost up her calories. If she is constipated, prescribe an oily laxative. If she is allergic, study her from an allergic standpoint. If there is psychoneurosis, give her mental tonics. All in all, consider the patient in general."

-Summary-

Non-myxedematous hypothyroidism is a condition which is a result of deficient thyroid secretion presenting symptoms of a less severe grade than myxedema.

The condition occurs more frequently in women than in men and is not localized to any country.

The etiology of the condition is unknown.

The symptomatology is vague and indefinite with the characteristic symptoms being fatigue.

The physical examination is essentially negative, with the exception of dry skin and characteristic swelling of the upper eyelids. The thyroid may or may not be palpable.

The laboratory findings are characteristic in that they show a lowered basal metabolic rate and an increased blood cholesterol value.

The diagnosis is based on the history, symptoms and physical findings, confirmed by the basal metabolism and blood cholesterol determinations, and made positive by the therapeutic test.

The differential diagnosis consists in ruling out other endocrine disorders and chronic debilitating diseases.

The treatment is specific.

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