Non myxedematous hypothyroidism in adults

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SENIOR THESIS

NON-MYXEDEMATOUS HYPOTHYROIDISM IN ADULTS

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INTRODUCTORY STATEMENT

Although hypothyroidism, as myxedema, has been recognized as a clinical entity since 1873, it has only in recent years been realized that hypothyroidism may exist without the clinical signs of myxedema. Moreover, since Osler, in his 16 years at Johns Hopkins, saw but ten cases of true myxedema and McKean (60) has seen seventy-two cases of non-myxedematous hypothyroidism in two years of ordinary office practice, it is self evident that the latter condition must be very much more common than myxedema.

It is then, in an effort to clarify and delineate the syndrome of non-myxedematous hypothyroidism that this thesis is written. The reader must, however, keep in mind that myxedema, minimal hypothyroidism, and the "hannal metabolic state are integral and interdigitating parts of a continuum and their separation must necessarily be arbitrary and perhaps not very clear cut at the borderlines."
DEFINITION

Non-myxedematous hypothyroidism is a metabolic disturbance due to "insufficient thyroid incretion" and is characterized by a lowered basal metabolic rate, easy fatiguability, both mental and physical, mild sluggishness, vague gastro-intestinal disturbances, absence of non-pitting edema, and shows a specific beneficial response to proper thyroid medication. It has been variously called non-myxedematous hypothyroidism, mild hypothyroidism, small hypothyroidism, incipient hypothyroidism, larval hypothyroidism, masked hypothyroidism, occult hypothyroidism and hypothyroidism forma frustre.
3.

HISTORY

The knowledge of the presence of goiter and cretinism is very old; Pliny in his Natural History mentions the presence of goiter in pigs, and Hume (21) states "that the ancient Chinese as early as 600 A.D. used the thyroid gland of the sheep to treat cretinism and that the practice was so well established as to be familiar even to the housewives". Marco Polo in his "Travels" says of the people of one of the countries he visited, "they are in general afflicted with tumors of the throat occasioned by the nature of the water they drink"--a remarkably shrewd guess. The literature on cretinism and goiter had already become extensive when it was realized that such states might occur spontaneously in the adult. (Foss, 27).

However, it was not until 1873, when Sir William Gull (32) read his paper "On a Cretinoid State supervening in Adult Life in Women", that any clear mention of the condition, now called myxedema, was made. In this paper Gull described two cases, both middle aged women, characterized by obesity, alteration in facial features, placidity, dry skin, swollen
tongue and edema, about which he says, "the upper and lower extremities are also large and fat, with slight traces of edema over the tibia, pitting doubtfully on pressure". Regarding the relation of this state to cretinism, he states, "It will be noted that I have designated this state as cretinoid... and that it is allied to the cretin state would appear from the form of the features, the changes in the lips and tongue, the character of the hands, the alterations in the conditions of locomotion, and the peculiarities though slight, of the mental state ....".

That these changes might be due to absence of the thyroid was noted by Curling (21) in 1850, who reported the absence of thyroid tissue in two cretins seen at autopsy. Concerning this he wrote, "...for it is highly probable that this abnormal secretion of fat was dependent on the absence of those changes which result from the action of the thyroid...consequent on the want of this gland."

Ord (72) in 1877, reporting on six cases of "cretinoid" states "and on observations begun as far back as 1861, fir proposed the name myxoedema. Of this he says, "...there have come under my notice in St. Thomas Hospital six cases of the disease origin-
ally described by Sir William Gull as "cretinoid" states, "... a disease for which I have since proposed the term 'Myxoedema' expressive of the morbid changes mainly characteristic of the disease."

In 1882, Reverdin (74) read a paper before the Société Médicale de Genève in which he communicated the results of a number of cases of total extirpation of goiterous thyroid glands, and drew the attention of the profession to a series of symptoms following such extirpation, and resembling in their entirety the symptoms of myxoedema. At about the same time Kocher (53) reported a series of 115 thyroid ablations. Of these twenty-four show definite symptoms of myxoedema. In his report these symptoms were quite evidently confused with those of removal of the parathyroid glands. Since the presence of the parathyroid was not known until 1882, when found by Sändigstrom (Richardson (75)), and their function was not discovered until 1891, by Gley, this confusion is not remarkable and appears in much of the early literature.

Schiff (78), in 1884, showed that thyroid ablation in dogs lead to their death. Horsley (39) (40), working with monkeys, records the fall in tem-
perature, slight anemia, relative lymphocytosis, and sluggishness, subsequent to thyroidectomy.

From these experiments he concludes, "that the thyroid is a structure essentially connected with the metabolism of the blood and tissues... and that it forms from the blood a colloidal substance which is transmitted via the lymphatics from the acini of the gland to the circulation."

Bettencourt and Serrano (12), in 1890, transplanted half a sheep's thyroid under the breast of a myxedematous woman and noted the immediate, albeit, temporary clinical improvement. Perhaps influenced by this and Vessalet's intravenous injection of an extract into a thyroidectomized dog, Murray (70), using a glycerine extract of fresh sheep's thyroid injected subcutaneously, had marked success in the treatment of a myxedematous woman. It is interesting to note (71) that this woman, the first successfully treated hypothyroid case, died in 1920 after twenty-nine years of normal life.

One year later, in 1892, Fox (28) reported the successful treatment of a woman by oral administration of "half a sheep thyroid, lightly fried and minced, to be taken with currant jelly twice a week."
MacKenzie (62) also in 1892, and by similar therapy showed a very nice record of the return of the patients pulse, temperature, and respiration to normal.

Bauman (7) found that hydrolysis of thyroid extracts with mineral acids led to an iodin compound which he called thyroidin. Bugnow (15) in 1894, isolated an iodin containing compound which appeared to be a globulin and which had potent though decidedly toxic effects. It was Kendall, (48), however, who in December 1914 succeeded in isolating a crystalline compound containing iodine which later was named thyroxine, the first of the hormones to be obtained in a pure form. By 1926 Harrington had worked out the structural formula tetra iodo-parahydroxyphenyl ether of tyrosine

\[
\begin{align*}
\text{HO} & \\
\text{I} & \text{O} \quad \text{CH}_3\text{CH}_2\text{NH}_2 \text{COOH} \\
\text{I} & \text{I} \\
\end{align*}
\]

and later in 1926 Harrington and Barger had succeeded in synthesizing the compound, thyroxine. Between 1914 and 1917 Kendall working in conjunction with the Mayo Clinic had shown the potent and very specific effects of this hormone.
It was not, however, until the advent of basal metabolic rate determinations that a diagnosis of non-myxedematous hypothyroidism could possibly be made. The first study of the effects of the thyroid on basal metabolism was made by Magnus-Levy in 1895 (64). He made studies on the oxygen consumption of dogs and found that dogs in whom the thyroid had been removed showed a markedly lowered oxygen consumption. He also noted that the administration of thyroid to these dogs caused an increase of oxygen consumption varying from 17 to 72 percent, thus establishing the relation of the thyroid to basal metabolism.

DuBois (59) in 1915, working with several others at the Russel Sage Institute, worked out, by actual measurement the body surface, a formula for surface area accurate to ±1.5 percent. This made possible the determination of large numbers of basal metabolic rates and so led to the establishment of the normal range by Lusk, Benedict, DuBois, Harris, Aub and many others. With the development of a small portable respiration calorimeter by Benedict, in 1918, as a modification of his more cumbersome original universal apparatus (9), the determination of basal metabolic rates became a practical clinical procedure.
Although Hertoghe (36) in 1899, first called attention to the possibility of what he called mild myxedema, it was not until 1924, that Gardner (29) reported the first cases of non-myxedematous hypothyroidism as such. Since that time many cases have been recorded and the condition accepted as a clinical entity.

**ETIOLOGY**

This disease is, as may be anticipated, apparently more common in those regions where goiter prevails although is by no means limited to those areas. As it is a chronic type of ailment and a metabolic disturbance there appears, logically enough, to be no seasonal variation.

Watkins (87) in his series of fifty cases gives the following statistics on age and sex: the average age of the women was 33.4 years and of the men 35.4, of these fifty patients 84 percent were women. Brown (14) says of his 159 cases the majority were women.
between 40 and 60 years of age. Gardner (29) in a series of 275 cases says the females predominate in a ratio of 6 to 1, and that only thirty-four cases were under twenty years of age and only fourteen were over sixty years. Thus it appears that females present 60 to 80 percent of the cases and that age range of maximum occurrence is from 30 to 50 years of age.

The disease is in all probability not invariably caused by any single factor; so that the following discussion will in most instances be of probable or possible inciting agents.

1. Post-surgical

Here, certainly, one can say that many cases, who have undergone a too thorough thyroidectomy, subsequently have a negative B.M.R. and probably in many instances masked hypothyroidism.

2. Intoxication

Hensel (34) believes that the toxins of infections play an important part in the production of hypothyroidism. He quotes the work of Roger and Garnier, in 1900, who examined the thyroids in forty patients dead from measles, smallpox, scarlet fever, diphtheria, typhoid, epidemic meningitis, peritonitis and acute gastro-enteritis. In these they
II.

found in nearly every cases histological changes such as diffuse hemorrhage, epithelial proliferation, swollen cellular protoplasms and desquamation, diminished acinar colloids, and little or no change in the interstitial tissues. He (Hensel) believes that in individuals who have what might be called a "low reserve thyroid" this pathology may lead to permanent insufficiency of hormonal elaboration.

Callison (16), quoting McCarrison, says that hypothyroidism may be caused by the effects of toxins such as alcohol, lead, intestinal toxins, helminthic toxins, and the toxins of the infectious diseases.

3. **Nutritional**

It is obvious that a deficiency in iodine intake may lead both to goiterous hyperplasia and hypothyroidism, and this would probably be in most cases of the non-myxedematous type.

That simple non-specific malnutrition leads to a lowered basal metabolic rate has often been noted. (83) (80) (85) (12). Whether or not this plays any part in the production of hypothyroidism or whether it is one of the effects of hypothyroidism is not known.

4. **Hereditary**
Barret (6) in following the history of a mother and seven children with dystrophies of the hair and nails found that the mother and six of the children had definitely low B.M.R.'s and evident clinical signs of hypothyroidism.

Tebbutt, Woodhill and Hansman (82) quote a case of Jauney's in which a father and three children were definite hypothyroids.

5. Pluriglandular

That the thyroid is at least partially under the control of the pituitary has been definitely shown. The question as to whether or not other glands may influence the thyroid is a subject of spirited and, indeed, often acrimonious dispute. What relation this bears to "hypothyroidism" is an unsettled question.

6. Miscellaneous factors

That acute thyroiditis, x-ray, and destructive metastatic neoplasms may lead to hypothyroidism is self evident. Psychic disturbances such as prolonged fright or anxiety are said by Hensel (34) and McCarrison to be factors in the production of non-myxedematous hypothyroidism, particularly so in those with "low reserve" thyroids. Lastly, it may
be stated that in many, if not most, of the cases the etiology may be truthfully said to be unknown.

It seems to me that the term here is a "Hypometabolic" state which may be

**SYMPTOMATOLOGY**

The symptomatology of non-myxedematous hypothyroidism is in general of a vague character such as one might find accompanying any minor ailment. These indefinite symptoms may appear in any or all systems of the body and taken separately means little; however, this very fact, of their lack of predilection for any one system, should in itself suggest a possible endocrine or enuro-psychiatric cause.

The most constant symptom is easy fatiguability both mental and physical, which according to Watkins (87) is present in 84 percent, McKean (60) says 90 percent, Dowden (23) 94 percent, in fact every investigator reporting on this condition gives
similar figures as to the frequency of this marked fatiguability. This characteristic is not constantly present in any one individual, who may often show periods of normal even increased activity but following this is usually markedly exhausted. This exhaustion is not confined to the physical sphere but also manifests itself in the mental reactions by drowsiness, inability to concentrate, poor memory, and increased number of errors. In brief, they appear to be normally in a somewhat lethargic state and to be conserving their energy, expending it only in spurts. According to Hensel (34) they go to bed tired, sleep but poorly, and seem even more tired in the morning than in the evening. He considers this morning tiredness as one of the salient features of this type of hypothyroidism.

Accompanying this lethargy and easy fatiguability many of the cases, peculiarly enough, are markedly nervous, show poor emotional control and complain bitterly of insomnia. (Watkins (87)). McKean (61) also states that on exertion they may have a mild dyspnea, tachycardia and palpitation, and may in fact be easily confused with neurocirculatory asthenia.
Constipation is another symptom often complained of. It was found by Watkins (87) in 44 percent of his cases, Dowden (23) in 48 percent, and Brown (14) believes it to be one of the most common causes of the atonic type. He quotes a series of 156 cases in whom constipation was the chief complaint; of these 41 percent showed a basal metabolic rate within normal limits (+10 to -10), 6.4 percent were above +10, and in 52.6 percent the B.M.R. was -11 or less. This latter group studied fluoroscopically showed in the majority of instances delayed gastric emptying time, colonic atonicity, and diminished peristalsis. The administration of thyroid to this group resulted in marked clinical improvement in all but a few cases. Deusch (22), making a very careful clinical and experimental study radiographic study of this type of constipation, came to the conclusion that the chief difficulty seemed to lie in the atonicity of the intestinal musculature, particularly in the colon. He further showed that administration of thyroid extract increased intestinal tonus and lowered the threshold for stimulation of peristalsis. Rogers (76) believes that thyroxine acts through the vague and parasympathetics and showed experimentally
that the delayed emptying time of the stomach is not benefitted by thyroxine administered after section of the vague or heavy doses of atroxine.

Other symptoms referable to the gastro-intestinal tract are eructation, indigestion, and anorexia. Brown(14). The anorexia is probably due partially to the gastro-intestinal tract and partially to the lowered B.M.R. It may on the other hand, by leading to malnutrition, be in part responsible for the lowered basal metabolic rate. (McLester (63)).

Another very common complaint of these patients is menstrual disturbance. Watkins (87) noted it in 37 percent of his cases, McKean (61) in 66 percent of his, and Warfield (86), Hensel (34), Seward (78), and other state it to be a common complaint. These disturbances may take the form menorrhagia or amenorrhea but the usual form is scanty menses. An associated complaint is infertility or sterility. Litzenberg (58) in a large series of cases studied comes to the following conclusions: (1) The thyroid-gonad relationship is well established, (2) Myxedema is certainly one of the causes of sterility, (3) Lesser degrees of hypothyroidism
are, by result of investigation, apparently also a cause (or an index of cause) of sterility, (4) A normal B.M.R. is apparently necessary to conception and normal continuance of pregnancy, (5) Properly supervised thyroid medication will restore B.M.R. to normal and will in some cases result in pregnancy, (6) Women who habitually abort should have their B.M.R. taken. Watkins (87) in his series of fifty cases says that the married women averaged 1.67 children, which is well below the general average. Taylor (81) quotes Englebach as stating that hypothyroid mothers who do become pregnant and reach term have a tendency to large babies and dystocia. He further states that 70 percent of all babies weighing over eight pounds at birth are hypothyroid and continue so.

The skin and hair, while not showing the induration and thickening characteristic of myxedema, frequently show changes. Watkins (87) states that 56 percent of his cases showed abnormal dryness of skin and hair. McKean (60) says that 76 percent of his cases have dry or scaly skin and a tendency towards thinning hair, and Hertoghe (36) believes a thinning of the outer third of the eyebrows is a frequent
finding. Chang (18) experimenting with rats, proved that hair growth was deficient in thyroidectomized rats and that administration of thyroid markedly improved this growth of hair both in quality and quantity. Howard (41) found that the nails in 86 percent of his cases showed abnormal riding, pitting or thickening, and Barret (6) quotes a family of hypothyroids with dystrophies of hair and nails. The tendencies toward exzemas, acne, usticaria, and other skin lesions has been noted by many.

Headache is another symptom noted by many, it is usually generalized and of a dull nagging character although it may in some individuals simulate mi-graine. Brown (14) finds it a most common accom­paniment of constipation.

Mclester (63), Hensel (34), Watkins (87), and Gardner (29) all remark on the susceptibility to infection and disease in these patients. Watkins found that in his series of fifty patients 60 percent early serious diseases such as pneumonia and that 70 percent had already undergone major surgery. Gardner (29) states that many convalescents, especially those recuperating from infectious diseases, show a lowered basal metabolic rate, this
being especially true in those whose convalescence is slow. Those whose convalescence was rapid almost invariably had either a normal B.M.R. or a rapid return to it. This observation in conjunction with that of Roger and Garnier (Hensel, 34) suggests that thyroid administration might prove of benefit in treatment of convalescents. Gardner quotes the experimental work of Branchi, Jacobi, Wasserman and others, who showed that the blood serum of thyroidectomized animals had a lessened bactericidal action, as a partial explanation of this increased susceptibility to disease. He also states that Houssay, Sardelli, Clevers, and others have shown that thyroidectomized animals have a lessened ability to form antitoxins.

Many patients because of the dyspnoea on exertion, and palpitation suggest cardiac pathology and McLester (63) commented on the frequency with which a bottle shaped heart is noted in these hypothyroids. Lawrence (57) says that Thatcher and Paul White, after a careful electrocardiographic study of myoedematous hearts, feel that the condition of the heart is similar to that found in myocardial exhaustion. But he (Lawrence) believes that this is
only true of those having a marked myxedema, as most mild myothyroids show a perfectly normal EKG. He points out the fact that the first effect on the heart, with the administration of thyroid, is to increase its work so that there is a primary accentuation of cardiac symptoms, but that later with increased nutrition of the individual, and so his heart, all symptoms referable to the heart not due to organic lesions disappear. He thus feels that even cardiac insufficiency in these individuals may be benefitted by proper administration of thyroid.

Beck (8) believes that urological pathology is common in these hypothyroids and in one hundred cases, of which only sixteen were males, states that the symptoms in order of their frequency are: nocturia, pollakyuria, dysuria, oliguria, and incontinence. In the urine of these patients he found bladder epithelium in excess in sixty-nine, pyuria in twenty-eight, albumen in eight, casts in seven and red blood cells in eight. Several of his male patients complained of loss of libido and some of them cleared upon thyroid medication alone.

Jelliffe (46) writes of a few cases of his presenting all the symptoms of tabes such as shooting
pains, loss of knee and ankle jerks, incoordination; sluggish pupils, slowed mental reactions, gastric crises, in short everything but the positive serology. These cases were all diagnosed by competent neurologists as incipient tabes; all, however, showed a lowered B.M.R. and cleared up immediately with the administration of thyroid.

In summary then it can be said that the chief symptoms are easy fatiguability, menstrual disturbances, constipation, and dryness of skin. These may be accompanied by lethargy, nervousness, insomnia, susceptibility to infection, anorexia, eructation, vague abdominal complaints, headache, indefinite myalgias and arthralgias, cardiac complaints, dyspnea on exertion, urologic, and neurologic complaints.

PHYSICAL FINDINGS

As with the symptomatology, there are no characteristic physical findings. All are varied and rather vague in their nature.
The thyroid gland shows, according to Watkins (87) the following variations: no enlargement in 76 percent, colloid goiter in 14 percent, adenomatous goiter in 6 percent and previous sub-total resection in 4 percent. Dowden (23) on the other hand finds enlargement in 56 percent of his 37 cases. The other authors merely state that the gland may be enlarged, normal, or small.

The dryness of the skin, falling or scanty hair, nail pathology, and tendency towards skin lesions has already been discussed under symptomatology.

The weight may also vary considerably. Hensel (34) finds in 56 cases that 24 were underweight, 22 were of average weight, and 10 were overweight. Gardner (29) in a series of 275 cases, found that 40 percent were 10 or more pounds underweight and believed that this malnutrition may have had some part in lowering the basal metabolic rate. McKeen (60) states that 52 percent of his fifty cases were of normal weight. So in general it may be stated that many have a normal weight, a few are overweight, and a marked percentage are underweight.

The heart is apparently normal in most cases although Mc Lester (63) has pointed out the tendency
to a bottle shaped heart.

The pulse rate may be normal, depressed, or accelerated. Dowden (23) says that the pulse ranged between 50 and 70 in 78 percent of his cases, and between 70 and 90 in 21 percent. Austin (4) says that the pulse was slowed in the majority of his cases and accelerated in a few; he also notes the interesting fact that thyroid therapy tends to accelerate the slowed hearts and decrease the rate of those which were rapid. Hensel (34) says that the pulse is usually slow and often soft. Watkins (87) however disagrees and states that 52 percent of his fifty cases showed an abnormally high pulse rate, 4 percent showed a slow rate and that 44 percent were normal. Quite obviously then the pulse rate is a quite undependable guide in hypothyroidism.

The blood pressure is likewise quite variable. McKean (60), Hensel (34) and Kochler (52) state that the blood pressure is usually somewhat low, commonly between 116/80 to 95/60, but may be normal or high. Watkins (87) again disagrees stating that it was low in 10 percent, normal in 86 percent, and high in 4 percent. This confusion may be
in some measure due to confusion in what is meant by low and normal. Austin (6) reports forty cases of hypothyroidism (B.M.R.'s ranging from -12 to -38) whose blood pressure was increased and showed that the systolic pressure was lowered from 15 to 55 points and the diastolic from 5 to 20 points by proper administration of thyroid. McKean and Koebler state that administration of thyroid to those whose blood pressure is low tends to raise it to the normal.

The body temperature tends to be somewhat lowered, although in many is normal, McKean (60) stating that in his fifty cases the average temperature was 97.7 degrees.

Other physical signs occasionally noted are the presence of mild aches and pains in joints and muscles, and according to Watkins (87) 52 percent showed associated disease such as sinusitis, tonsillitis, dental caries, colitis, arthritis, and cardio-renal-vascular disease.
LABORATORY FINDINGS

One of the most important points in the diagnosis of non-myxedematous hypothyroidism is the lowered basal metabolic rate. Without this finding accurate diagnosis is difficult if not impossible. On the other hand a lowered basal metabolic rate is not pathognomonic of hypothyroidism. Thus it appears that some discussion of the normal standards and their clinical interpretation is necessary.

As has been stated in the history discussion DuBois (59) and others working out their height-weight to surface area formula made possible clinical calorimetry. Gephart and DuBois (30) obtained an average of 39.7 calories per square metre per hour for men and 37.0 for women. Studying a number of individuals of various ages and weights they reached the conclusion that "if a given subject's basal metabolism is more than ± 10 percent from the average they may be regarded as abnormal, but they cannot be proved abnormal unless the departure from the average is at least ± 15 percent". Harris and Benedict (33) in a very careful study of 102 normal
patients found no cases lower than -10 percent. From the data of these very dependable workers it may be seen that a statistical endpoint for the average may be set at -10 percent, the upper limit of normal and upper limit of hypothyroidism. That there may be individuals who are exceptions to this arbitrary statistical rule cannot be doubted.

Boothby and Sandiford (12) in a summary of 25,000 basal metabolic determinations on 8,614 patients at the Mayo Clinic reach the following conclusions:

(1) 77 percent of those patients, other than those with known thyroid disease, fall within the strict DuBois standards of ± 10 percent, and 90 percent are within ± 15 percent.

(2) In 102 cases of known myxedema, 20 percent are in the range of -11 to -20 percent and 80 percent are from -20 percent on.

(3) In 41 cases of post operative (thyroid) hypothyroidism, 46 percent are from -11 percent to 20 percent and 54 percent are below -20.

(4) In 86 cases of questionable clinical hypothyroidism 9 percent are from -10 to 10, 61 percent are from -11 to -20, 30 percent are lower
than -20.

(5) A few cases of colloid goiter, recurrent adenoma without hyperthyroidism and 21 percent of the cases of thyroiditis were below -11.

(6) Other diseases in which 20 percent or more were below -11 are epilepsy 22 percent, hypopituitarism 53 percent (12 percent below -20), Addisons disease 23 percent (15 percent below -20), diabetes 35 percent (18 percent below -20).

Thus in summary all cases of hypothyroidism except a very small percent are below -11 and of diseases which might be clinically confused with hypothyroidism and which give a B.M.R. of -11 or lower there are only hypopituitarism, hyposuprasenalism, and diabetes mellitus. Sturgis (80), Means and Aub (66) and Means and Burgess (67) state that the only other factors which may lower the B.M.R. are profound sleep, malnutrition or starvation, oopherectomy (only if the thyroid is intact). The finding then of a B.M.R. below -15 excludes in itself all diseases and conditions other than hypothyroidism, hypopituitarism, hyposuprarensalism, diabetes mellitus, epilepsy, oopherectomy, and malnutrition.

Myxoedema and masked hypothyroidism cannot be
differentiated by the basal metabolism alone (see the above quoted figures). Means and Burgess (67) state that 100 percent of their cases of myxoedema were below -15 and the average was -23. In all the cases of masked hypothyroidism quoted by the various authors the range was between -11 and -33. However, Thurmon and Thompson (83) in analysis of 1255 patients with one or more readings below -11 found that the B.M.R. was below -20 in 84 percent of the patients with myxedema and in only 29 percent of hypothyroids without myxedema. In conclusion, then, the most probable B.M.R. range for non-myxedematous hypothyroidism is -11 to -20 with a few going as low as -33.

The blood cell findings in non-myxedematous hypothyroidism are suggestive but not conclusive. Mackenzie (62) shows that experimental thyroidectomy in dogs is followed by a decrease in red blood cells and hemoglobin amounting to about 30 percent and that regeneration in experimental anemia is retarded by thyroidectomy. He also shows three cases of anemia of the primary type in humans that showed an excellent response to thyroid therapy. Warfield and Green (86) show eight cases of anemia, of the achlorotic type, and in whom the average B.M.R. was below
-15 who showed a marked improvement with thyroid medication. Mackenzie (62) however found the red blood count normal in 13 patients with myxedema. McKean (60) however states that a mild secondary anemia is often seen. Thus it seems anemia may or may not be present.

More often there is a relative lymphosytosis but this is not invariably present. Hutton (43) in a series of sixteen cases whose B.M.R. was -10 or lower showed that in only one case was the polymorphonuclear count over 65 percent and the general average was 57 percent. This finding was noted also by many of the other authors.

Mason, Hunt, and Hurxthal (65) showed that the blood cholesterol in those whose B.M.R. was below -20 was definitely higher than normal more markedly so in those whose basal rate was lower. Furthermore the high cholesterol returns to normal with the basal rate under thyroid therapy, and when the administration of thyroid is stopped, it precedes the B.M.R. in returning to its original state. The work of Hess (35) shows similar results.

Hess (35) shows that the normal creatinuria of childhood is decreased or about in hypothyroids of
any marked degree, and that administration of thyroid causes this to return to normal even before the B.M.R. is altered.

Janney (45) and others have emphasized the nitrogen retention in hypothyroids and have shown that this is restored to normal by thyroid administration.

Aub, Bauer, Heath, and Rapes (2) have shown in a series of cases, whose B.M.R. averaged -32, that the calcium excretion was 40 percent below normal. Furthermore, they have shown by X-Ray studies that there is a decreased bone density in hyperthyroids and an increased bone density in hypothyroids.

Brown (14), Hage (38), and Rogers (76) have shown that the emptying time of the stomach may be five or six hours in hypothyroids. Brown found the following facts about gastric acidity in hypothyroidism: 45 patients with normal basal rates but gastro-intestinal disturbance showed an averaged free acid of 35.5 and an average total acid of 53.5 whereas 41 patients with a basal rate of -11 to -20 showed free acid of 36 and a total of 55 which essentially the same as the normals. However, ten patients showing a B.M.R. of -20 or lower averaged 15.4 free acid and a total of 32, a significant
difference, moreover four of the ten showed an achlorhydria and none were hyperacid.

Campbell (17) in an analysis of a few cases whose BMR's averaged -30 states that there is a definite decrease in blood sugar fasting level and a marked increase in sugar tolerance. Thyroid administration caused these to return to normal.

Gilligan and Edsall (31) find that there is a marked increase in the insensible water loss of hypothyroid patients and that this returns to normal levels with proper thyroid medication.

PATHOLOGY

The references to the pathology of the thyroid gland in this condition are but few and those chiefly of a speculative nature.

The work of Roger and Garnier, quoted by Hensel (34), showing the cloudy swelling, hemorrhage, loss of acinar colloidal material, and lack of interstitial damage subsequent to infectious diseases and infections has already been stated. Tebbutt, Woodhill and Hansman (82) point out three with basal rates of -18, -21, and -8, in whom a definite diffuse or nodular
hyperplasia of interstitial tissue was present, and believe this to be a result of pathology described by Roger and Garnier. Williamson and Pearce (89) have described in more detail. They show the stages of epithelial degeneration or necrosis, connective tissue replacement, and regard the end stage as a diffuse or nodular cirrhosis, which in its more pronounced form appears as Riedls' struma - the woody thyroid. This is probably an accurate picture in some types of hypothyroidism.

That this is not the only type of pathology is indicated by Tebbutt and co-workers who quote Simmond's cases of nearly complete aplasia with no evidence of hypothyroidism. Williamson and Pearse also state that myxedema can arise in the earliest phase, long before any actual atrophy occurs, and believe that in these cases the deficiency is due to disturbed or underfunction of the gland, and this latter view although hypothetical seems a likely explanation of many cases. In this same category comes the "low reserve thyroid hypothesis of Hensel (34).

It is obvious then that there remains a great deal of work to be done on the patho-physiology of this condition before any very satisfactory explanations can be set forth.
DIAGNOSIS

Diagnosis, it is agreed by all of the authors, depends on three main factors: (1) Lowered basal metabolic rate, usually between -10 to -20 but may be lower (2) Specific response to proper thyroid medication and (3) Clinical findings such as easy fatiguability, lethargy and nervousness, constipation, dry skin, menstrual disturbances, headache, and vague aches and pains.

DIFFERENTIAL DIAGNOSIS

The conditions from which non-myxedematous hypothyroidism must be differentiated are chronic debilitating diseases such as tuberculosis; focal infection; anemias of various types; malnutrition; neurasthenia and related psychic manifestations; epilepsy; true myxedema; hypopituitarism; hyposuprarenalism; and diabetes mellitus.

As has been previously shown by Boothby and Sandiford (12), Thurman and Thompson (83) and Means and co-workers (66) (67), once properly taken the basal metabolic rate rules out all but epilepsy, diabetes, myxedema, hypopituitarism, hyposuprarenalism
and malnutrition.

Epilepsy is easily ruled out by seizures.

Diabetes is likewise easy to rule out by blood and urinary sugar determinations, increased rather than decreased sugar tolerance, and the lack of diabetic improvement with thyroid therapy.

Myxedema can be ruled out by the presence of non-pitting edema, thickened wrinkled desquamating skin, enlarged tongue, short thick fingers, facial changes, narrow lid slits, retarded boney growth and deformities, and clumsiness. In the masked hypothyroid these findings are absent. The very mild cases of myxedema may be very difficult to differentiate; however such differentiation would only be of academic interest for both show a specific response to thyroid administration, namely return to normal. (McKean)(60).

The differentiation of the hypopituitary in the more advanced forms presents no difficulty according to Eidelsberg (25). Anterior hypopituitarism presents the following symptoms; slow or arrested growth, small and shortened extremities, slender fingers, small genitals and breasts, amenorrhea, absence of body hair and secondary sex characteristics. The cases of posterior hypopituitarism show a girdle type of obesity and increased sugar tolerance. Both may show decreased
size of the sella turcica, and both show only slight or complete absence of response to thyroid administration.

The differentiation of hyposuprarenalism is more difficult. Koehler (52) presents the following points of difference:

<table>
<thead>
<tr>
<th>HYPOTHYROIDISM</th>
<th>HYPOSUPRARENALISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Temperature lowered but tends to be steady.</td>
<td>1. Temperature may be lowered but more labile.</td>
</tr>
<tr>
<td>2. Pulse rate often slowed.</td>
<td>2. Pulse rate may be slowed but it is much more labile.</td>
</tr>
<tr>
<td>3. Average BMR -26 with steady respiration.</td>
<td>3. Average BMR -17 with uneven respiration.</td>
</tr>
<tr>
<td>4. Epinephrine reaction -05 cc. of 1:10000 solution blanches an area of 1-1.5 cm. in diameter.</td>
<td>4. In most the blanched area is larger, more irregular and tends to streak along the lymphatics.</td>
</tr>
<tr>
<td>5. Histamine reaction -.05cc 5. of 1:1000 solution gives a wheal 0.5-1mm high, 0.8-1.2 cm. in diameter and lasting 30-45 minutes.</td>
<td>5. Gives a more marked and larger wheal often with pseudopods and lasting 45 minutes to several hours.</td>
</tr>
</tbody>
</table>

Furthermore therapeutic test differentiates the two very nicely; hypothyroidism shows marked
clinical improvement with thyroid therapy and no response to cortical extracts, whereas hyposuprarenalism shows just the reverse.

Malnutrition is differentiated from masked hypothyroidism with some difficulty and Barr (5) and Seward (78) believe it to be a factor in the underweight hypothyroids. In general the malnourished individual presents nearly the same salient clinical features as the hypothyroid case, but lacks the satellite findings such as dry skin, constipation, high blood cholesterol, decreased calcium excretion, relative lymphocytosis, and increased insensible water loss.

**TREATMENT**

The specific response of cases of masked hypothyroidism, as well as myxedema, to the administration of fresh thyroid gland, dried or dessicated gland, or thyroxinosis one of the characteristic features of the disease. In general it may be stated that all bodily functions, either elevated or depressed, tend to return to the normal levels, and the patient feels much better.
Many criteria for the determination of proper therapeutic dosage, among these are pulse rate, temperature, blood sugar level, pulse pressure, blood cholesterol, creatine excretion (in children) the patients feelings, and basal metabolic rate determinations. Of these Youmans and Riven (90), Dowden (23), Gardner (29), Lawrence (57), and Hensel (34) believe that only the basal metabolic rate checked against the patients feelings and clinical findings are of any value. Youmans and Riven (90) and Wade (85) noted that basal rate of patients, who had been given thyroid and then taken of it, showed a lower reading than before thyroid administration, and they suggest that is may have diagnostic value and should be considered in therapy.

The toxic symptoms subsequent to overdosage are, according to McKean (69), headache, muscle and joint pain, palpitation, dizziness, diarrhea, and nausea and vomiting. Should these appear the administration of thyroid must be stopped at once, discontinued for a few days, and then started again with a smaller dose.

Thyroid for practical purposes is administered in two forms, dried gland and thyroxine. Of the two thyroxine is by far the most potent but for this reason more dangerous to use. Sollman states that the dosage
of thyroxine administered hypodermically lies between 0.2 to 2 mgm. of thyroxine per day and that the daily total need of the body is between 0.2 - 0.4 mgm. per day. Thyroxin is rarely used clinically because of its high cost and potency.

The usual method of thyroid is the dried whole gland, and in its use it should be remembered that the American U.S.P. Standard (0.17-0.23 percent iodine) is five times as strong as the English variety (Burroughs Wellcome). According to McKean, the safest and best means of administration is 1/3 to 1 1/2 grains daily, taken on an empty stomach, for ten days, then check the basal metabolic rate, increase or decrease the dose as necessary and in ten days recheck repeating this process until the optimum dosage for maintenance is reached. Following this occasional recheck of BMR and patient to be sure of continued good results. He found that an average of 3.2 grains daily to change the average low BMR of -22 to an average of optimum of -1. Hensel (34) found that needed from 3-5 grains daily of the dried fresh gland or from 1-2 grains of the desiccated. McLester (63) feels that a large initial dose of from 30 to 60 grains of the dried fresh gland, followed in a few days by beginning low daily doses gives more rapid and better results. Lawrence (57) could discover no
relationship between the amount of depression of BMR and the amount of thyroid necessary to return the basal rate to normal, one patient with an initial BMR of -34 required but three grains daily and another needed eight grains daily to reduce the BMR from -14 to normal.

The use of iodides has been little discussed in relation to thyroid deficiency other than in endemic goiter. Barr (5), the only reference found on this subject considered iodides as his "sheet anchor." of therapy but unfortunately says nothing of dosage.

Watkins (87), Taylor (81), and McLester (63) emphasize the importance of correlative indication of foci of infection and treatment of associated disease. They also believe that careful scrutiny of patients diet, to assure a balanced diet and one of sufficient caloric value, is a highly important part of proper therapy.

**SUMMARY**

1. Non-myxedematous hypothyroidism is a common and important metabolic disease.

2. The chief symptoms are easy fatiguability, dry skin, lethargy or nervousness, constipation, vague
digestive disturbances, mild aches and pains, and a lowered basal metabolic rate.

3. Diagnosis depends on clinical findings, a lowered basal metabolic rate, and response to thyroid therapy.

4. Response of this disease to thyroid administration is specific and of diagnostic importance.
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