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Mild hypothyroidism

Frank A. Stewart
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MILD HYPOTHYROIDISM

by Frank A. Stewart

Senior Thesis
Presented to the
College of Medicine
University of Nebraska
Omaha, 1940
TABLE OF CONTENTS

INTRODUCTION 1
CLASSIFICATION 3
PHYSIOLOGY 6
PATHOLOGY 9
HISTORY 11
INCIDENCE 14

<table>
<thead>
<tr>
<th>Subject</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>15</td>
</tr>
<tr>
<td>Sex</td>
<td>15</td>
</tr>
<tr>
<td>Distribution</td>
<td>16</td>
</tr>
<tr>
<td>Relative Incidence</td>
<td>17</td>
</tr>
</tbody>
</table>

ETIOLOGY 18

<table>
<thead>
<tr>
<th>Subject</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>18</td>
</tr>
<tr>
<td>In Women</td>
<td>20</td>
</tr>
<tr>
<td>Heredity</td>
<td>21</td>
</tr>
<tr>
<td>Thyroidectomy</td>
<td>21</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>22</td>
</tr>
<tr>
<td>Other Endocrines</td>
<td>22</td>
</tr>
<tr>
<td>Iodine Deficiency</td>
<td>22</td>
</tr>
<tr>
<td>Iodine Excess</td>
<td>23</td>
</tr>
<tr>
<td>Protein Metabolism</td>
<td>24</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>25</td>
</tr>
</tbody>
</table>

SYMPTOMS 26

<table>
<thead>
<tr>
<th>Subject</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>27</td>
</tr>
<tr>
<td>Nervousness</td>
<td>29</td>
</tr>
<tr>
<td>Mentality</td>
<td>30</td>
</tr>
<tr>
<td>Psychoses</td>
<td>31</td>
</tr>
<tr>
<td>Constipation</td>
<td>31</td>
</tr>
<tr>
<td>Other G-I Symptoms</td>
<td>33</td>
</tr>
<tr>
<td>Headache</td>
<td>34</td>
</tr>
<tr>
<td>Neuralgia</td>
<td>35</td>
</tr>
<tr>
<td>Feeling of Coldness</td>
<td>36</td>
</tr>
<tr>
<td>Menstrual Disturbances</td>
<td>37</td>
</tr>
<tr>
<td>Sexual Disturbances</td>
<td>39</td>
</tr>
<tr>
<td>Weight Variations</td>
<td>40</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>42</td>
</tr>
<tr>
<td>Symptoms</td>
<td>44</td>
</tr>
</tbody>
</table>
# PHYSICAL FINDINGS

- The Skin
- The Hair
- The Nails
- Edema
- The Pulse
- The Blood Pressure
- The Heart
- Arteriosclerosis
- Temperature
- Tendon Reflexes

# LABORATORY FINDINGS

- The Red Blood Count
- The White Blood Count
- The Blood Cholesterol
- Glucose Tolerance and Blood Sugar
- Iodine Tolerance
- Gastric Acidity
- The Urine
- Blood Calcium
- Blood Oestrogen
- Blood Proteins
- Resistance to Direct Current

# DIAGNOSIS

- The Basal Metabolic Rate
- Interpretation of the B.M.R.
- Other Conditions Causing Low B.M.R.
- Further Differential Diagnosis
- Hypothyroidism and Hyperthyroidism
- Diagnosis in Children by X-ray
- Response to Thyroid Extract

# TREATMENT

- Thyroid Extract
- Methods of Administration
- Establishing the Maintenance Dose
- Length of Treatment
- Results of Thyroid Treatment
- Danger of Thyroid in Coronary Disease
- Toxic Effects
- Thyroxine
Iodine 90
Hydrochloric Acid 90
General Measures 91
Polyglandular Glandular 91
Other Medications for Increasing Metabolism 93
Miscellaneous Observations on Thyroid Therapy 94

CONCLUSIONS 96

BIBLIOGRAPHY 98
INTRODUCTION

During recent years considerable evidence has accumulated to emphasize the importance of hypothyroidism without myxedema as a separate clinical entity. The literature on the subject has grown up mostly within the last two decades, but on the whole it has been presented and accepted with ever increasing enthusiasm.

In 1931 Vis (119) was of the opinion that the medical world in general knew little about hypothyroidism and scarcely recognized the word or the clinical picture which it represents. Although the condition has gained more and more recognition in the last decade, it still seems to Bryan (17) that the possibility of the disease is not kept in mind by the average physician and that difficulty in recognizing mild hypothyroidism is largely due to this fact.

Most authors on the subject are agreed with Frosch (32) who said a few years ago, "Hypothyroidism to my mind is a very common condition and one overlooked altogether too often." Whereas myxedema was long recognized before mild hypothyroid states were even suspected to exist, it is now generally accepted that hypothyroidism without myxedema is more prevalent than hypothyroidism with myxedema. Youmans and Hiven (131) concluded that hypothyroidism is more common than is generally appreciated and
that it has a wide distribution, and this fact is generally conceded by those who have made a study of its incidence.

Englebach (27) called mild hypothyroidism "non-myxedematous hypothyroidism" and defined it as "hypometabolism in which no non-endocrine or endocrine etiology other than the thyroid is presented." The definition is stretched, however, by most authors to include all states of lowered metabolism in which there is thyroid deficiency as the predominating factor and an absence of the characteristic signs and symptoms of myxedema. Thus it includes many subthyroid states in which there may be also limited involvement of other endocrine factors.

Clinically, mild hypothyroidism presents a bizarre picture and a multiplicity of symptoms, according to most writers, and no definite physical findings. It is the variability in the condition which makes its recognition so difficult. The diagnosis must rest on the basal metabolic determination and the response of the patient to thyroid therapy in most instances. And many cases of hypothyroidism are diagnosed as other conditions because, as Seward (105) says, there is often a similarity of the symptoms to those either of organic or functional disturbances in different organs and systems throughout the body.
CLASSIFICATION

Warfield (121) makes a simple classification of hypothyroid states as follows:

(a) Cretinism - severe hypothyroidism in children
(b) Myxedema - severe hypothyroidism of adults
(c) Masked or occult hypothyroidism - mild and atypical cases of any age

It is with this last group, mild hypothyroidism as it is most commonly called, that this thesis will chiefly concern itself. Other terms by which the condition is known are non-myxedematous hypothyroidism, subthyroidism, latent hypothyroidism, incipient hypothyroidism, thyroid deficiency, and so forth. Myxedema and cretinism are generally referred to by their specific names, and in this thesis whenever "hypothyroidism" is mentioned it will be understood to mean "mild hypothyroidism".

Harstock (43) in his simple classification includes with mild hypothyroidism, myxedema, and cretinism a fourth class - post-operative or post-radiation hypothyroidism and hypothyroidism due to exhaustion of the thyroid by untreated hyperthyroidism. Patients in whom this condition occurs may show symptoms of hypothyroidism and hyperthyroidism both, so that the condition is frequently called "dysthyroidism" according to Harstock.

Lawrence (62) believes that the reason for the
clinical dissimilarity of cretinism, myxedema, and hypothyroidism without myxedema lies in the age periods in which the thyroid failure occurs. Failure in adult life, after growth has ceased, produces myxedema. Congenital or intra-uterine failure causes cretinism. And it is failure during childhood or adolescence, according to Lawrence, that produces hypothyroidism without myxedema. It is the general consensus of opinion among the writers, however, that mild hypothyroidism may develop at any age.

Vis (119) feels that mild hypothyroidism, simple goiter, and myxedema are all different gradations of the same process, and Thompson (115) says that myxedema usually does not develop until the B.M.R. has dropped to at least -25%. And McLester (80) agrees that disabilities of mild hypothyroidism are probably identical with those of myxedema and differ only in degree, myxedema being always permanent, and mild thyroid disorder being transient in many cases. Youmans and Riven (131) say that mild cases of hypothyroidism may be the forerunner of myxedema or on the other hand may be a specific syndrome. Mc Kean (77) agrees with Lawrence (62) on this latter view, and says that mild hypothyroidism is a clinical entity, differing not so much quantitatively as qualitatively, and suggests the two are due to some different process in the thyroid gland. Lawrence says that thyroid failure of marked
degree may exist without causing myxedema as evidence that it is a definite clinical type, but most authors side in with those cited above who believe that mild hypothyroidism and myxedema are different degrees of the same process. Kocher differentiates the two clinically (77).

Thompson (115) classifies hypothyroidism as either (a) primary or (b) secondary, stating that the primary type is caused largely by destruction of the thyroid tissue and that the syndrome which results is completely cured by the administration of desiccated thyroid. The secondary type, he says, is caused by lack of adequate stimulation of the thyroid, notably by the anterior lobe of the pituitary gland and possibly also by the adrenal cortex. Correction of the hypothyroidism in this instance relieves only a part of the symptom complex because the hypothyroidism constitutes only a part of the pathological disturbance.

Mild hypothyroidism is divided further by Lathrope (60) into (a) temporary and (b) permanent. (a) It may be merely an exhaustion state of the gland capable to restitution to the proper level with adequate rest. (b) It may be a fundamental limitation or shortage of the gland's power to function due to defective heredity, to acquired injury, or both.
PHYSIOLOGY

All modern authors seem agreed with Wharton (126) that the chief function of the thyroid is to regulate the speed of metabolic processes of the body. He goes on to say that the thyroid hormone acts as a catalyst, sensitizing the body cells to sympathetic stimulation - the thyroid, adrenal, and sympathetic nervous system thus working in synergism, antagonistic to the parasympathetics. It increases oxygen consumption, provides the skin with adequate amount of water, fat and blood, regulates activity of the sweat glands, stimulates the heart rate, regulates secretion and motility of the gut, and so forth. Mental activity is improved by the thyroid secretion. Metabolism of proteins, fats, and carbohydrates, gaseous exchange, and water balance, all are increased by the thyroid hormone.

Midelberg (25) adds that with other endocrine glands the thyroid controls the sex development and characteristics, controls sugar metabolism, detoxifies the end products of metabolism and of infectious toxins, controls development of osseous and nervous tissue to some extent, and so on.

Gardner (35) mentions that the thyroid is an important indirect factor in resistance to infection, and is thought by some authors to increase the bacteriocidal action and antibody formation of the blood. Many authors
have observed that hypothyroid patients are more susceptible to infections.

Wharton (126) stated that the thyroid hormone also produced an increased rate of cell differentiation, and Hertoghe (46) told in 1915 that the secretion of the thyroid plays a part in both (a) cell growth and (b) cell destruction. (a) He stated that the thyroid governs the building up of cells and growth of tissues, and the thyroid hormone is essential to the morphological completeness of cells necessary for the perfect accomplishment of their functions. He noted by way of demonstration that a child with thyroid insufficiency ceases to grow but commences to grow again if thyroid extract is given in adequate amounts. (b) The thyroid aids in cell destruction by regulating the destruction of the albumin molecule and governing the processes by which waste material is eliminated. Supposedly, if the activity of the thyroid is impaired, the products of decomposition are not carried off at the required rate - and accumulation in situ of mucin, fat, and other bye-products is his way of explaining the non-pitting edema of myxedema.

Harstock (44) says that thyroid insufficiency causes incomplete oxidation in the metabolic processes of almost all the cells of the body. Inadequate oxidation results in decreased cellular function and chronic fatigue. The
first affects are usually manifest by symptoms referable to any particular system, accounting for multiplicity of symptoms encountered in different cases.

Wharton (126) discussed briefly the inter-relation of the thyroid gland and other endocrines, and so did vis (119) and Higgins (48). Wharton says that the pituitary produces a thyrotropic hormone which causes hyperplasia of the thyroid, increased metabolism, excretion of calcium and creatinine, and increased blood iodine. Any influence of the anterior pituitary on the metabolism, according to Higgins, is probably through the thyroid. Wharton says the thyroid has a reciprocal influence on the adrenals and gonads; Higgins found that suprarenal insufficiency may lower basal metabolism and that the gonads also may influence the thyroid. Experimental evidence, he said, seemed to support the view that castration tends to lower the metabolism, probably through suppression of thyroid activity.

Wharton stated also that the thyroid supplements thymic action, that the action of insulin is antagonistic to the thyroid hormone, and that the thyroid and parathyroids have an antagonistic action (thyroid increases the calcium and phosphorus loss from the bones without increasing the blood content as appears in hyperparathyroidism).
PATHOLOGY

Most authors do not mention any change in the pathology of the thyroid gland in hypothyroidism, but Seward (105), Kimball (57), Warfield (121), and many others report the frequent association of simple goiter with hypothyroidism. Vis (119) and Russell (99) say that simple goiter is due to hypothyroidism - it seems that the gland, unable to secrete sufficient thyroxine, becomes hypertrophied in an effort to compensate for the deficit.

Barr (5) thought that in the fibro-cystic goiter the thyroid became the storehouse for calcium rather than iodine, and that the parenchyma degenerated and was replaced by fibrous tissue.

In 1883 the committee of the London Clinical Society (96) appointed to investigate myxedema reported that the disease is caused by changes in the thyroid gland of a destructive nature, the most common form of destructive change being substitution of a delicate fibrous tissue for the proper glandular structure. William and Pearce (129) believed that the functional strain incident to long continued hypofunction is important in causing structural changes in the thyroid gland itself, but that the specific pathological changes of the gland in myxedema are not found in non-myxedematous hypothyroidism.

Wharton (126) said that hyperplasia and finally
exhaustion atrophy occur in simple goiter. Thompson (115) found that primary hypothyroidism produces replacement of the normal gland tissue by "scar tissue", but that in secondary hypothyroidism the gland may be of variable size, the epithelium flat or cuboidal, and the acini filled with colloid.

In spite of these reports, many writers feel that there is no specific change in the thyroid gland itself in mild hypothyroidism, and no specific change elsewhere in the body. Some mention localized deposits of fat and edema. Others speak of association of arthritic changes, arteriosclerotic changes which Harstock (44) says is due to the increased blood cholesterol, and nephrotic changes in the kidney. Brown (15) emphasized the effect of long-continued hypothyroidism on the gastro-intestinal tract and Barrett (6) called attention to the effect on the nervous system, but from more of a functional relationship than organic.
The earliest description of thyroid deficiency was in 1850 when Curling (21) described the features of two children with no thyroid gland at autopsy.

In 1871 Fagge described sporadic cretinism in England. He suggested wasting of the thyroid as the probable cause of cretinism and predicted with remarkable accuracy some of the symptoms that might result from a deficiency of thyroid in adults.

Two years later Sir William Gull (38) reported two cases of the "cretinoid state" supervening in adults, and expressed the hope that "once the attention of the profession is called to these cases our clinical knowledge of them will improve". In 1875 he made a report on five cases.

urd (88) in 1878 was much impressed with mucin deposits in the subcutaneous tissue in adults and named the disease "myxedema".

According to Seward (105), Reverdino and Kocher in Switzerland made some of the earliest observations pointing to insufficient secretions of the thyroid as the cause of the disease, and Simmond (109) made similar observations about 1883.

In 1883 a committee was nominated by the London Clinical Society (96) to investigate the subject of
myxedema. The committee recognized myxedema as a well-defined clinical entity and stated that myxedema in adults is practically the same disease as cretinism in children. They did not recognize the possibility of a mild hypothyroid state.

History of treatment of thyroid deficiencies began about 1890 when Victor Horsley (52) suggested implantation of thyroid tissue in treatment of severe hypothyroidism. Murray (85) made extracts of sheep's thyroid for subcutaneous injections and in 1891 began treating a patient with myxedema.

Oral administration of thyroid preparations in treatment of thyroid deficiencies is frequently credited to the work of two men working independently in 1892, Fox (31) and MacKenzie (69). However, Hoge (51) gives the credit to Schiff who he says transplanted thyroid gland into the abdominal wall and initiated treatment by feeding the dessicated glands in 1885.

According to Hoge (51), Magnus-Levy reported in 1895 that administration of thyroid preparations raised the rate of both oxygen and carbon dioxide exchange through the lungs. And in 1904 he pointed out the principles of interrelationship between thyroid activity and basal metabolism. Hoge says that all recent work has verified the findings of Magnus-Levy that metabolism is always
elevated by thyroid therapy.

According to Warfield (121), Koch called attention to the possibility of minor decreases in thyroid secretion in 1904. He felt that such cases would not present a true myxedema but was unable to do anything but speculate on their occurrence. As Marr (72) has said, interest in thyroid deficiencies has been limited to myxedema and cretinism until recent years. There has been a considerable amount of literature on mild hypothyroid states in the past two decades but previously this condition was scarcely recognized.

The active principle of the thyroid secretion was isolated in 1915 by Kendall (55) and named "thyroxin". In 1927 Harrington and Burge (41) synthesized thyroxin from tyrosine. However thyroxin has never gained the popularity for clinical use that the dessicated gland has enjoyed.
INCIDENCE

According to Musser (87) moderate degrees of deficient thyroid secretion are extremely common, particularly in the female. Likewise Lathrope (60) says that minor degrees of thyroid deficiency are very common and responsible for a considerable amount of chronic ill health. All classes of people are affected, and a considerable proportion are professional men and women. Warfield (121) says. General figures on the incidence of hypothyroidism are probably low; Wharton (126) feels that many patients who could be helped by thyroid therapy are never recognized as hypothyroids.

Dr. Cecil Barlow (4) in England, who had his attention focused on hypothyroidism when he discovered that he was himself "on the highroad to myxedema", was immensely impressed with the large number of persons to be seen going about with obvious thyroid deficiencies which had probably been unrecognized and untreated. He concluded that the average medical man is not nearly sufficiently alive to the condition.

Thus the incidence of hypothyroidism is probably greater than generally appreciated. Rosch (32) says that he has seen all too many patients treated as psychoneurotics, neurasthenics, or "nervous breakdown", when the real cause was a hypofunction of the thyroid. All
too many patients are treated with diet for constipation, iron for anemia, and strychnine for weakness when they should be getting thyroid extract.

AGE: Musser (87) says that hypothyroidism may occur at any age of life. Youmans and Kiven (131) also say that hypothyroidism may occur at any age, but frequently in young and adolescent. General consensus is that the condition is more common after maturity. More than half the cases in Higgins' (48) experience fell between the ages of thirty and fifty, and Seward (105) reported it more common in this same age group. Incidence in Lathrope's (60) series showed 4/5 of the cases to occur between the ages of 21 and 50. In women Bryan (17) says that hypothyroidism is more likely to occur at three periods of life - at puberty, pregnancy, and the menopause, especially the latter. And Higgins (48) found incipient hypothyroidism more frequently near the menopause. Average age in Watkins' (123) series was 34.

SEX: Gull (38) originally described myxedema as a condition of females, and the committee of the London Clinical Society (96) recognized as early as 1883 that the condition affects women much more frequently than men. According to Bryan (17) and Higgins (48) hypothyroidism is a condition of both sexes, but more common in the female. Seward (105) and Lathrope (60) place
the ratio of females to males in their experience at
four to one. Watkins (123) in his series reported 84%
females and 16% males.

**DISTRIBUTION:** Hypothyroidism seems to be somewhat more commonly reported in regions where goiter is
most prevalent. Sturgis was convinced of this (17).
Warfield (121) reports comparatively common occurrence
of mild hypothyroidism among persons living in goiter
regions such as the Great Lake basin, and Seward (105)
speaks of the relative frequent occurrence at Roanoke,
Virginia in a section of the country where goiter is
commonly seen. Vis (119) studied thousands of children
in the primary grades and high school in the state of
Michigan and reported in 1931 that 25% to 45% had simple
goiter, and concluded in his report that a mild state
of hypothyroidism is a common clinical entity in Michigan,
probably the most common of all chronic diseases in that
state. Baskett (7) reported mild hypothyroidism comparatively common in the Mississippi river basin. Thus we
have many reports on mild hypothyroidism from regions where
goiter is common, but the reports of Thompson and Thompson
(118) from New England, King (58) from Baltimore, Higgins
(48) from Virginia, and Youmans and Kiven (131) in Nash-
ville, Tennessee show that the condition is not confined
to such areas, but may occur where incidence of goiter is
ETIOLOGY

Old writers discussed "psychic trauma", childbirth, and so forth as the cause of hypothyroidism. Today the etiology is still rather indefinite, but there are a number of factors which seem to play a part - such as infection, pregnancy, the menopause, heredity, thyroidectomy, thyroiditis, effect of other endocrines on the thyroid, iodine deficiency, protein metabolism, and so forth.

INFECTION: McLester (80) believes that the infection theory is quite reasonable, and Vis (119) says that systemic infection increases the load on the thyroid and in turn predisposes to thyroid deficiency. Russell (99) feels that any infection may be the contributing factor in depleting the thyroid, but particularly influenza. Hertoghe (46) frequently saw enlarged tonsils and adenoids in sub-thyroidism, and propounded the theory that infection in the nasopharynx affects the thyroid, causing inflammation and destructive changes followed by atrophy. Barr (5) noted the enlarged adenoids and curiously thought this to be an "imperfect natural attempt to compensate for defective action of the thyroid. Seward (105) mentions influenza, and also toxemia of pregnancy, puerperal infection, and other illnesses producing toxemia as possible causes of damage to the thyroid resulting in hypothyroidism.
Focal infections and hypothyroidism are frequently associated, according to Core (51) and others, and often focal infections show improvement of thyroid medication when other treatment has failed. McKean (77) noted an increasing tendency to dental caries in hypothyroidism and cited a case in which development of dental caries was definitely inhibited by thyroid therapy. Lathrope (60) believes that foci of infection have much to do with deterioration of the thyroid function in subthyroidism, and found that in his series 75% not only had well established foci of infection but had a history of repeated infective incidents since childhood. Watkins (123) reported that 60% of the subthyroids in his series of 50 had suffered some potentially serious disease earlier in life (10 had had tonsillitis, 5 pneumonia, 5 typhoid fever, 2 pulmonary tuberculosis, and so on), and a strikingly large proportion of these had been operated for various conditions. Seward (105) reported a high incidence of focal infections in a series of 50 hypothyroids also (infected tonsils in 19, ethmoiditis in 4, pyorrhea in 4, cholecystitis in 7, cervicitis in 3, etc.), and he reported no satisfactory improvement in these or the usual methods of treatment, but that on thyroid therapy the B.M.R. returned to normal and all symptoms subsided. This brings up of course the question of whether the
foci of infection are actually an etiological factor in hypothyroidism, or whether they are predisposed by an already existing hypothyroid state. All that can be definitely stated is that the two conditions are frequently associated, but most authors seem to feel that each has a direct influence on the other. Harrell (40) in his series of mild hypothyroids found 80% suffering from focal infections.

Connor (19) and many others have recognized that many patients with a thyroid deficiency suffer from chronic arthritis. Krosch (32) stated that hypothyroidism is a frequent symptom of the associated debility of chronic arthritis, but that this is not the causative factor in the condition.

IN WOMEN: The tendency for hypothyroidism to develop during pregnancy and at the menopause has already been mentioned (see incidence). These seem to be definite etiological factors in some cases. King and Herring (59) feel that hypothyroidism of moderate degree is a fairly common complication of pregnancy, and that it seems logical to determine the B.M.R. as a routine early in pregnancy and institute proper treatment if the rate is low to prevent abortion.

Hertoghe (46) on the other hand feels that pregnancy is a factor in modifying symptoms of already existing
hypothyroidism. He is of the opinion that pregnancy is accompanied by stimulation of the thyroid secretion. "Some of these hypothyroid women," he says, "never feel so well as when they are pregnant, and when the periods of gestation and lactation have passed they again fall into their former state of lassitude and torpor, accompanied by general infiltration."

HEREDITY: Lathrope (60) named heredity first among the etiological factors of hypothyroidism. Shelton (107) also called attention to the familial tendency to hypothyroidism, and Frosch (32) cited a case of hypothyroidism with a definite family history of thyroid disturbance. Sloan (110) mentioned that there is sometimes evident a family history where hypothyroidism is associated with simple goiter, and it is possible that the family history is frequently on the basis of dwelling in a region of endemic goiter rather than on a true hereditary character of the condition.

THYROIDECTOMY: Crile's book mentions that if cases in which thyroidectomy has been performed or radiation used are studied 10 to 15 years later, a moderate to severe grade of hypothyroidism will be found in a large percentage (17). But most authors seem to minimize this danger. Russell (99) says that some cases of hypothyroidism develop following thyroidectomy but that
these cases are rare

**THYROIDITIS:** Plummer attributed hypothyroidism to atrophy of the thyroid as the result of thyroiditis (105). And according to Bryan (17) acute thyroiditis is often followed by hypothyroidism, and arteriosclerosis and senile changes are causative factors too, due to decreased blood supply of the gland. However, this is not mentioned by most authors.

**OTHER ENDOCRINES:** While Vis (119) links thyroid deficiency with disturbances of other endocrine glands, and a few others hint at this factor, it seems to be impossible to demonstrate any definite etiological interrelationship. McLester (80) says it is futile to discuss the interrelationship of the various endocrines as a possible factor in hypothyroidism.

**IODINE DEFICIENCY:** Wharton (126) says that simple goiter is a response to an absolute or relative iodine deficiency, and Russell (99) says that simple goiter is in reality mild hypothyroidism. Likewise Vis (119) associated simple goiter with hypothyroidism, and stated that it occurred where iodine is lacking and may be prevented by administration of iodine. We have seen that incidence of hypothyroidism is reported higher in regions of endemic goiter where the iodine supplied is
inadequate. Kimball (57) reported the incidence of goiter in Michigan in 1924 to be 38.6%, before iodized salt was used there. After four years during which iodized salt was used in that state, incidence of goiter there fell to 9.9%.

Maine and Lenhart (70) say that the iodine content of the thyroid gland is inversely proportionate to the epithelial hyperplasia, decreased in exophthalmic goiter and increased in colloid goiter. They also demonstrated that iodine administration to dogs produced rapid involution of the thyroid gland. With this in mind, Hinton (49) says that thyroid disfunction whether hyperactive or hypoactive is due to imperfect iodine metabolism - that the bizarre types of hypothyroidism are apparently due to the inability of the individual to metabolize iodine, rather than to a true iodine deficiency.

**IODINE EXCESS:** There is little evidence to support the theory that hypothyroidism may be caused by an excess of iodine. Thompson mentions that in rare instances the ingestion of an excess of iodine may cause a slight lowering in the basal metabolism in normal individuals and occasionally marked lowering and the development of myxedema in patients with exophthalmic goiter who have only a slightly elevated metabolism or
who have a normal rate of metabolism following a subtotal thyroidectomy. With this in mind, that individuals with unstable thyroid glands sometimes go from the plus to the minus side of metabolism with prolonged Lugol's, McKean (77) offers the theory that hypothyroidism may be precipitated by excess ingestion of iodide in the form of the sodium iodide now added to common table salts. This is contrary to common belief.

PROTEIN METABOLISM: Hinton (49) reasons that since iodine ultimately unites with tyrosine, the end product of protein metabolism, to form the active principle of the gland, a disturbance in protein metabolism may be the important factor in producing disfunction of the thyroid rather than an iodine disturbance. Excess tyrosine and decreased iodine produces thyroxine with less than the normal amount of iodine (hyperthyroidism), and not enough tyrosine to mobilize the iodine produces colloid goiter or hypothyroidism with goiter. Such disturbances he says may result from intestinal disorders, dietary irregularities, scarcity of iodine in the diet, or dysfunction of tissue normally responsible for oxidizing the excess of tyrosine. McCarrison (75) has claimed that thyroid disturbances are at least partly intestinal in origin. Sweet and Ellis (112) ligated the external ducts of the pancreas and produced colloid goiter in
dogs and found the iodine content increased. Hinton (49) explains this reaction on the basis that a lack of trypsin in the gut produced incomplete hydrolysis of peptones and proteases, and hence a normal supply of tyrosine was not available in the thyroid for the formation of thyroxin.

**MISCELLANEOUS:** Russell (99) and Lathrope (60) have mentioned that worry, anxiety, overwork, and the hurry and strain of modern life may play a part in the etiology of hypothyroidism. And Russell says that poverty and unhygienic surroundings and especially incomplete or unbalanced diets may contribute. Lathrope finds excessive use of coffee common in hypothyroids, and while he doubts that this has any causal role he feels that it acts as an irritant to the nervous system and intensifies symptoms already existant.

Seward (105) believes that there is a constitutional factor, since some people with hypothyroidism do not have symptoms. McLester (80) feels that hypothyroidism is usually due to unknown influences which "damage the structural integrity of the functional capacity," and Marine (71) is likewise of the opinion that the essential cause is unknown.
SYMPTOMS

Russell (99) and Warfield (121) have called attention to the multiplicity and bizarre nature of the symptoms of mild hypothyroidism, and Harstock (44) has said that in the middle aged group symptoms are especially bizarre and seldom typical. Barksdale (3) explains the bizarreness of symptoms by reasoning that if one is inherently weak in one or more organs or systems, in the absence of adequate thyroid extract that weakened organ or system will be the first to register complaint, and thus a variety of symptoms is possible.

Watkins (123) and many others feel that there are no clear cut, specific symptoms or signs, but Hoge (50) believes that all of these cases show definite and positive symptoms if we look for them. And McLester (80) thinks that hypothyroidism is a well-defined clinical entity.

Onset according to Harstock (43) and others is insidious. McLester (80) is impressed with the distinctive lowering of the sense of well-being and says that the patients "do not feel well". Barlow (4) says that these patients resign themselves to being "not so young as they were" because they feel sluggish physically and mentally, their keenness for their favorite amusements is not what it was, they feel that they have to drive themselves to do things they formerly did with zest.
We have mentioned the multiplicity of symptoms encountered by most authors. Easy fatiguability and lack of energy are probably the outstanding, and nervousness is quite commonly mentioned. Craddock (20), Hoge (50), and McKean (77) include many symptoms: apathy, senile expression, dry skin and hair, obesity, slow pulse, slow digestion and excretion, feeling of coldness, stiffness and pain in extremities, mental depression, fatiguability, menstrual disturbances, biliousness, feeling of inertia in the morning and of stimulation in the evening, sluggish memory, difficulty in concentration, headache, slight dyspnea, loss of libido, lowered temperature and blood pressure, a tendency for dental caries to develop, susceptibility to eczema and furuncles, falling hair, obesity in early life, susceptibility to intercurrent infections, nervousness, at times loss of weight, tinnitus, relative sterility, narrowness of the lid slits, lack of appetite, poverty of thought, lack of feeling, and clumsiness. Any one, or a few, or a number of these symptoms may occur in the hypothyroid patient presumably. Of course all authors are not agreed on some of these symptoms, and we will attempt to discuss the different views on each group of symptoms.

FATIGUE: Wharton (126) found fatigue the most common symptom in hypothyroidism. Hoge (51) felt that
weakness and chronic fatigue are the most common presenting symptoms, and Warfield (121) said that the most important single symptom is physical exhaustion which leads to a neurasthenic state.

Lathrope (60) found undue fatigue in 64%, White (127) found fatigue out of all proportion to activity and usually associated with nervousness in 57%, and Watkins (123) encountered weakness and abnormal fatigue in 54%, while McKean (77) described distinctive mental and physical fatigue in 90%, with pronounced inertia.

Bryan (17), Lawrence (61), Youmans and Riven (131), Marr (72), Connor (19), and others speak of abnormal fatiguability, weakness, and drowsiness too. Ravin (92), and Vis (119) add shortness of breath and Harstock (45) speaks of "sighing respiration" occasionally due to hypothyroidism.

White (127) found that the patients commonly lacked ambition and the ability to start doing things, and Watkins (123) encountered a loss of energy and initiative in 82%.

Musser (87) reported that sleepiness was a frequent complaint, and Hertoghe (46) describes somnolence in hypothyroids, saying that they sleep any place, any time, and never feel rested or refreshed. Watkins (123) found an abnormal desire for sleep in 28%, and unusual
wakefulness in 6%, while Seward (105) encountered insomnia more often than drowsiness. 15.5% in White's (127) series complained of sleepiness during the day, but on the other hand 25% of the remainder slept poorly at night.

Lathrope (60) and Hinton (44) describe the usual finding of intense fatigue and lassitude in these patients on rising, gaining of vigor until mid-afternoon, and returning fatigue in late afternoon. McKean (77) described a feeling of inertia in the morning but of stimulation in the evening. Gardner (35) encountered fatigue particularly in the latter part of the day, and Russell (99) said that the hypothyroid may awaken feeling refreshed, but easily grows tired during the day and has no reserve to fall back on.

NERVOUSNESS: Seward (105) found nervousness and irritability in varying degrees to be the chief complaint in half of his patients, and Youmans and Hiven (131) cited several cases in which nervousness and insomnia and lack of emotional control were the outstanding complaints. Watkins (123) discovered nervousness in 86% in his series, Lathrope (60) in 56%, and White (127) in 76%. In White's experience the nervousness was usually associated with fatigue, and he described it as being "like that which one experiences when one is extremely sleepy"
and has forced one's self to stay awake". Harstock (44) says that the nervousness results from chronic fatigue. Hoge (51) and Higgins (48) found some patients nervous, but they did not consider this a major symptom.

Wharton (126), Marr (72), White (127), and Russell (99) associated emotional instability with the nervousness. Wharton noted undue alertness and excitability in some instead of drowsiness. Marr encountered depression and emotional instability. White noticed marked instability in some, as crying, quick anger, and marked despondency at times. He said that increased nervousness and fatigue was noted by many patients in higher altitudes.

Lathrope (60) speaks of palpitation frequently under excitement and Connor (19) mentions palpitation and precordial pain in some of these patients.

MENTALITY: Probably most authors agree with Wis (119) that there is a varying degree of mental retardation. Watkins (123) found mental apathy in 40%, and McKean (77) reported a sluggish memory and inability to concentrate in 54%. Gardener (35) and Connor (19) also mentioned the loss of the power to concentrate in these subthyroids. And Russell (99) spoke of listless mental states, slow thought and movement, and mental depression.

Lumans and Hiven (131) on the other hand say that mental lethargy is lacking. Russer (87) says that the
mentality may be normal or sluggish. He says these patients reason well, but that the memory is poor and attention is wandering, and their speech is usually slow. Ravin (92) also speaks of the impairment of memory and slow speech.

PSYCHOSES: Ziegler (132) reported three cases in which he showed latent psychotic and hereditary disposition brought out by hypothyroidism which disappeared when the hypothyroidism passed away.

Jacobi (54) says that hypothyroidism may stir up latent schizophrenia; and Wiltrakis and Partipilo (130) report a case of psychosis of schizophrenic nature, associated with a B.M.R. of minus 45% in the absence of myxedema, which improved to normal on thyroid therapy.

Haywood and Woods (45) described mental derangements in one group of hypothyroids with symptoms resembling those of a depression psychosis, and another group with symptoms like dementia praecox.

Frosch (32) reported a case of "idiopathic epilepsy" which was brought into action by the precipitating condition of hypothyroidism.

The consensus of opinion is that psychotic states resulting from hypothyroidism are not common.

CONSTIPATION: Youmans and Hiven (131) feel that constipation is perhaps the most frequent symptom of
hypothyroidism and that it is often very intractable.
Havir (92), Higgins (48), McLester (80), Marr (72),
Connor (19), and others mention frequent constipation
among their patients, and Watkins (123) met it as a
complaint in 44% of his patients.

Seward (105) and Higgins (48) say that constipation
is quite common but scarcely more so in mild hypothyroid-
ism than in other conditions. Lathrope (60) says that
constipation is the rule, but that some of these patients
have an achylic type of looseness, with 2 or 3 loose
stools daily, after ingestion of food.

Wharton (126) says that the constipation is usually
spastic, but Harstock (44) and Russell (99) found that
obstinate constipation as a result of an atonic colon
is characteristic.

Brown (15) reported hypothyroidism a factor in
chronic constipation of middle age, especially in women.
Russell (99) noted that constipation may be a severe
and striking symptom in women around the menopause. He
says to consider the possibility of hypothyroidism when
you see intractable constipation in women from 40 to
50 years of age.

Brown (15) relates an interesting story of a woman
who was sent to John Hopkins for a resection for relief
of an intestinal obstruction. She had other symptoms
of hypothyroidism too, and when placed on thyroid medication, her bowels returned to normal and she was saved from the operation.

Musser (87) occasionally found patients who were entirely normal except for constipation which was relieved by thyroid administration.

OTHER G-I SYMPTOMS: Most authors are agreed that poor appetite and indigestion are fairly common symptoms among these patients. Lathrope (60) estimated that 73% of his hypothyroid patients complained of indigestion in some form, 47% complained of impaired appetite. Russell (99) said that these patients rarely eat breakfast.

Seward (105) commented on the vagueness of the gastro-intestinal complaints and the multiplicity which he encountered - anorexia, fullness, gas, distention, nausea, dull pain, and so forth. Harstock (44) said that all types of indigestion may be caused or aggravated by hypothyroidism. Watkins (123) found abnormal gaseous eructation in 50%.

Connor (19) commented on abdominal pain and distress in hypothyroidism. Hinton (49) said that the abdominal pain may simulate that of ulcers, but that there is no evidence of ulcers by X-ray and no relief with the Sippy diet.
Most authors mention that headache is a symptom of which these hypothyroid patients frequently complain. McKean (77) found headache to be one of the complaints in 60% of his series; Lathrope (60) in 49% of his; Watkins (123) in 20%; and White (127) in 20%. Higgins (48) on the other said that headache is probably no more common in mild hypothyroidism than in other conditions.

Hertoghe (46) stated that the headache assumes two forms: "(a) It sometimes originates in the frontal sinuses and extends over the orbits, remaining frontal. (b) Sometimes it originates at the occiput and a painful center in the neighborhood of the occipital nerve lends to it the character of a neuralgia; from the occiput it may invade the corresponding part of the brain, and the patient describes the attack as one of migraine."

Seward (105) found headache extending from the vertex to the suboccipital region in 18 subthyroid patients in a series of 53.

Harstock (44) says that the headache of hypothyroidism is a chronic headache which recurs frequently. Hertoghe (46) says that it is more intense in the mornings and usually disappears in the evening after a good dinner. He says that it is precipitated by the least fatigue, slight perspiration, faint draught, and so forth.
Wharton (126) mentioned the occurrence of migraine headaches in hypothyroidism, and Seward (105) recognized 2 of this type in his series of 53 patients with mild hypothyroidism. Parhon (89) believes that thyroid deficiency is the main cause of migraine, acting through the sympathetic nervous system. And Rubenstone (98) recently reported the case of a woman with migraine and epilepsy who had two daughters with migraine, all of whom were hypothyroid and responded well to thyroid therapy.

NEURALGIA: Higgins (48), Marr (72), Connor (19), and others mention that some of these hypothyroid patients complain of vague, indefinite pains in the muscles and joints. Seward (105) found this to be a complaint in 4 of his series of 53 hypothyroid patients; 13% in White's (127) series complained of general aches and pains. According to McLester (80) these patients complain especially of numbness and vague pains in the legs and arms occurring after exercise. Russell (99) mentions backache in hypothyroids.

Joint pains in the hypothyroid patient may be arthritic in nature rather than neuralgic. Wharton (126) suggested that thyroid deficiency is in the background in some cases of arthritis, and Harstock (44) said that any tendency to degenerative arthritis is hastened by
a low metabolism. Swain and Spear (111) found 39% of 200 cases of arthritis had abnormal, usually low, basal metabolisms.

Paresthesiae are also sometimes complained of by these patients. Ravin (92) and McKean (77) said that some hypothyroids complain of numbness and tingling of the hands and feet. Alexander (1) mentioned the occasional complaint of a tingling or burning sensation over the body. Vis (119) thinks that the numbness and tingling is possibly associated with impairment of the parathyroid function.

FEELING OF COLDNESS: An inability of many hypothyroid patients to stand cold was noted by Ravin (92), Bryan (17), McKean (77), Morr (72), and others. Lathrope (60) says these patients don't like cold weather as a rule, and Musser (87) says that they are cold when others are comfortable and do not perspire freely in warm weather.

Seward (105) reported that 12 of the 53 patients in his series were susceptible to cold, and 8 complained of cold hands and feet. Russell (99) says that subthyroid persons occasionally complain of cold hands and feet, and Hoge (51) that they always complain of cold extremities.

Youmans and Hiven (131) found in their experience
that patients with mild thyroid deficiency are not unduly sensitive to cold however. And while Harstock (44) noted an intolerance to cold usually, he says that several cases of chronic pyrexia have been reported on the other hand, which responded to no therapy other than thyroid extract.

**MENSTRUAL DISTURBANCES:** Menstrual disturbances, including amenorrhea, dysmenorrhea, menorrhagia, and metrorrhagia, seem to be quite common in women suffering from a thyroid insufficiency. According to Vis (119) and most authors these disturbances are probably due to the relation of the thyroid to the ovaries, but the actual mechanism is obscure. Pertoghe (46) offered a theory concerning the effect of the thyroid secretion on the plasticity of the blood in an attempt to explain the relation of hypothyroidism to menstrual disturbances.

Tharton (126) says that menstrual disturbances are among the most common symptoms in subthyroid women. He noted that the menses were usually profuse and often irregular. 37\% of the women in Watkins' (123) series complained of menstrual disturbances. Of 16 girls in Gordon's (36) series, 9 gave histories of menstrual disturbances. Seward (105) found a history of irregular menses in 3 patients in a series of 53. White (127) observed a large group of subthyroid women and found the
menstruation normal in 23% and abnormal in 77%, scanty or excessive or irregular. 33% in his series complained of pain at the time of the menstrual flow.

There seem to be slightly more reports in the literature of excessive menstrual flow associated with hypothyroidism than of amenorrhea, but reports of both are quite common. Shute (108) has urged more attention to the relation of hypothyroidism to menorrhagia. Thommen (114) reported relief of menorrhagia with thyroid extract, and Salzman (100) reported some cases of uterine hemorrhage controlled by thyroid extract. Marr (72) and Breckenridge (12) reported both menorrhagia and metrorrhagia occurring in hypothyroid women.

Amenorrhea and dysmenorrhea are not uncommonly found complaints. McKean (77) reported the menstruation scanty in 66% of the women in his series. Musser (87) and Vis (119) reported hypothyroidism as a cause of amenorrhea and dysmenorrhea, and Dodds and Robertson (23) restored normal menstruation to several women with amenorrhea by administration of adequate doses of thyroid extract. Russell (99) noticed an early menopause in several women with a thyroid deficiency.

According to Hoge (51) and Hertoghe (46) the symptoms of hypothyroidism are generally in women at the time of menstruation, and Hertoghe has observed spontaneous.
amelioration of symptoms in certain cases of slight thyroid deficiency after the menopause.

SEXUAL DISTURBANCES: In women sterility, habitual abortion, and miscarriage are often suggestive of hypothyroidism, according to Wharton (126) and Musser (87). Litzenberger (67) says that hypothyroidism is a certain cause of sterility. A normal B.M.R. is apparently necessary to conception and normal continuance of pregnancy. He says that women who habitually abort should have their basal metabolism determined and that thyroid will often restore the B.M.R. to normal if it is low and result in conception and full term pregnancy. Hertoghe (46) reported that many sterile women have become pregnant after taking thyroid extract.

In White's (127) large group of hypothyroid women, he found that 27.4% had never been pregnant, 15.7% had a history of abortion or still birth, and 56.9% had a history of 1 to 7 full term pregnancies. Litzenberger and Carey (68) reported on a group of 78 married women with a low basal metabolism; 35 were absolutely sterile; 6 had had abortions or still births but no living children; and 9 with one or more living children had also had one or more abortions or still births. They also reported that of 52 sterile women with a low basal metabolism who were given thyroid treatment 17 later
conceived.

McKean (77) observed loss of libido in some of his hypothyroid patients, and McLester (80) said that this was occasionally the chief complaint in men. Sanders (101) and Harstock (44) noticed impotence and sterility in both men and women with hypothyroidism. Gordon (36) observed 29 boys in his series and reported that only 2 showed normal sexual development; 27 had evidences of hypogonadism, such as unilateral or bilateral cryptorchism.

WEIGHT VARIATIONS: Harstock (44) says that classically the hypothyroid picture is supposed to be one of obesity, both general and local around the pelvic and shoulder regions, but he observed many thin individuals with hypothyroidism. Actually most authors seem to agree with Warfield (121) and Frosch (32), who say that these patients may be overweight, underweight, or of normal weight.

Ravin (92) said that there is frequently a weight increase in the hypothyroid individual, with a fat increase both general and supraclavicular. McLester (80) stated that these patients are often overweight and have flabby, poorly developed muscles in many cases. Weight changes are particularly noticeable in young women, who are more likely to be short and dumpy and overweight, according to Musser (87). Marr (72), however, said that hypothyroidism
is seldom the cause of obesity, but may result in fat pads. In McKean's (77) experience, when there was increased adiposity, it had a predilection for supraclavicular and upper dorsal areas and upper arms and legs.

While we noted above that Musser (87) and McKean (77) observed increased adiposity in many hypothyroid patients, they both also noticed that a number were underweight and undernourished and had poor appetites; and these patients gained weight on adequate doses of dessicated thyroid. Lawrence (62) found a weight loss in many subthyroids instead of a weight gain; Wharton (126) said that they are underweight as commonly as obese; and Lee (64) said that actually most patients in his observation were thin. Lathrope (60) reported that half of his hypothyroid patients were 10 pounds or more underweight. Watkins (123) found that about a third of his patients with hypometabolism were underweight, and if they were over 30% overweight they were invariably victims of hypopituitarism rather than a primary hypothyroidism.

The weight variation of the patient with hypothyroidism may be influenced by his age. Seward reviewed a series of 53 patients in which he demonstrated that 16 under the age of 35 were underweight and 2 were
overweight, and 12 over the age of 40 were overweight and 2 were underweight. He reasoned that during the period when nutritive requirements are at a maximum, any impairment of oxidative processes results in a weight loss. Hoge (51) on the other hand noted that the tendency in hypothyroidism was more inclined to obesity in early life and to subnormal weight in adults, according to his observations.

**MISCELLANEOUS:** Hoge (51), Gordon (37), and others have noticed a lowered resistance in these hypothyroid patients to infections, especially of the nose and throat. Mayo (74) observed more complications following surgery.

Lee (65) and Alexander (1) observed the relatively high incidence of vasomotor rhinitis in hypothyroid patients, in both the young and the adults, and found that it was usually relieved by thyroid extract. Seward (105) reported vasomotor rhinitis in four patients in whom a low basal metabolism was the only significant finding, and tests with allergens were negative. Thyroid extract gave complete relief in all four cases. Harstock (44) said that slight edema of the nose and throat may be secondary to hypothyroidism, and that allergy is more prominent when associated with hypothyroidism.

Gardner (35) mentioned tinnitus and deafness occurring in patients with thyroid insufficiency. According
to Harstock (44) there are frequently annoying sensations in the ears due to swelling of the tissues about the Eustachian tube orifices and tinnitus sometimes occurs, and these are usually relieved by thyroid medication. Ravin (92) says impairment of hearing is occasionally associated with hypothyroidism. And Hertoghe (46) speaks of noises and buzzing in the ears which disappear under thyroid treatment.

Ocular muscle errors are common, according to Harstock (44), and may cause secondary dizziness, headache, neuralgia, and many symptoms frequently ascribed to neurasthenia. Most frequent muscle imbalance, he says, is that of exophoria toward the end of the day. Giddiness, says Hertoghe (46), is one of the most constant and distressing features and may cause falls, but most authors do not mention this symptom.

Murray (86) pointed out in 1898 that certain hallucinations of sight are not uncommon in a condition which he described as "early thyroid fibrosis". Hertoghe (46) says that hypothyroid patients sometimes see objects or mice which move rapidly across the floor, and that bright points of light may appear in the field of vision. There is little or no mention of this symptom elsewhere in the literature.

Hertoghe (46) also mentioned slight hoarseness occurring
in subthyroid individuals, but most authors do not recognize this as a symptom. Youmans and Riven (131) say that hoarseness is lacking. Russell (99) remarks that sometimes the voice of the hypothyroid patient is high pitched.

Connor (19) mentions water retention and oliguria, and also diuresis, in hypothyroid states.

**SYMPTOMS IN CHILDREN:** Very little is known of mild hypothyroidism in children, according to Harstock (44), due to the difficulty in obtaining satisfactory metabolic tests, variability of the child's weight, growth, development and intelligence, and the fear of using thyroid medication in the growing child. He thinks that many subnormal childhood conditions will probably eventually be shown to be due to thyroid insufficiency.

Most authors are agreed that children deficient in thyroid secretion are below par in physical and mental development. Musser (87) speaks of growth disturbances and sluggish physical actions in children with mild hypothyroidism. Sloan (110) noticed mental subnormality in children following moderate lack of thyroid secretion in fetal life.

Connor (19) found delayed dentition and delayed bone development, especially of the flat bones, in hypothyroid children. He described the so-called "adenoid
type" as the hypothyroid child, saying that they have dry skin, are underweight, undergrown, catch cold easily, have a poor appetite, are irritable, do not play well with other children, have leg aches and headache, and occasionally have enuresis.

Wharton (126) reported lack of growth and sex development in hypothyroid children, and acceleration of growth and development by thyroid extract. Kerley (55) recently reported a case of subthyroidism with defective and absence of secondary sex characteristics, dental development in a young girl, who proceeded to develop normally in both respects when thyroid extract was administered.

Bernard and Miller (48) recently reported on the occurrence of disease of the hip associated with hypothyroidism in children - slipping of the epiphysis and osteochondrosis of the head of the femur.

Englebach made the statement in 1922 that 70% of all babies born weighing over 8 pounds are hypothyroid, and that if these babies do not walk, talk, or have teeth at the end of one year, the percentage may be increased to 90%. He made the statement that these individuals develop into subnormal men and women unless properly treated and suggested the benefit of recognition and treatment early in life, during the first year (113).
PHYSICAL FINDINGS

Many authors agree with Schutz (104) that there are no constant physical findings. Others have noted changes in the integument, such as dry skin and coarse hair, and in the cardiovascular system, such as a slow heart rate and low blood pressure, which they consider characteristic.

Youmans and Riven (131) remarked about the absence of physical findings, and White (127) observed a large number of patients and said that the physical examination was usually essentially negative. White observed in a series of 90 hypothyroid patients that 21 had slight enlargement of the thyroid, and several had small adenomas. Russell (99) said the thyroid gland may or may not be slightly enlarged. We have already noted the relation of hypothyroidism to colloid goiter. Watkins (123) found no enlargement of the thyroid in 76% of his subthyroid patients, colloid goiter in 14%, adenomatous goiter in 6%, and in 4% the gland had been resected.

As to general appearance most authors are agreed that there is no characteristic picture in mild hypothyroidism like there is in myxedema. Connor (19) says there are no special types; Some are sthenic and some are asthenic. Seward (105) agrees that hypothyroidism occurs in both types, but says that it is seen more
w wrinkling of the forehead may have some diagnostic bearing in hypothyroid states.

McKean (77) noted dry skin in 75% of his hypothyroid patients; Watkins (123) noticed abnormal dryness in 56%; and the skin was dry in 19 of the 90 hypothyroid patients in White's (127). Seward (105) observed 53 subthyroid individuals and noted dryness of the skin in 20 of them, and thickening of the skin in 9.

Youmans and Riven (131) stated that the skin is usually not dry, harsh, or thick, and Musser (87) was of the same opinion. Lathrope (60) says that the skin is dry, but may be thin and translucent as likely as thick and coarse. And McLester (80) hasn't seen the thickened skin in individuals with non-myxedematous hypothyroidism.

McKean (77) spoke of the relative high incidence of eczema and urticaria in hypothyroid individuals. Wharton (126) mentioned eczema and acne occurring relatively frequently in his group, and Vis (119) spoke of acne. Marr (72) mentioned frequent "dermatological conditions" occurring in hypothyroidism and the retarded healing of skin lesions.

Wharton (126) reported some cases of acne vulgaris which were improved on thyroid therapy. Thommen (114) reported a few obscure cases in which chronic eczema
and alopecia areata were relieved by use of thyroid extract.

Bregman (13) considered hyperactivity of the parasympathetic nervous system with resultant hypersecretion of the sebaceous glands to be the basis of acne vulgaris. This may explain the frequency of acne in hypothyroidism, in which there is also a dominance of the parasympathetics.

**THE HAIR:** Many writers have observed that the hair is abnormally dry. Several speak of falling of the hair. Bryan (17) said to think of hypothyroidism in cases of alopecia. Havin (92) and Musser (137) mention coarseness of the hair. In White's (127) series of 90 patients, 20 had dry and scanty hair.

Youmans and Riven (131) and McLester (80) on the other hand say that loss of hair seldom occurs. And Seward (105) states that he has seen thinning of the hair in several hypothyroid patients, middle-aged or past, but no more than the average at that age. Still Harstock (44) says that falling hair and premature graying are very suggestive symptoms of thyroid deficiency.

Barlow (4) and Wharton (126) noticed that in many of these patients the outer third of the eyebrow is gone or scanty, with the remainder of the eyebrow coarse or fan-shaped.

-49-
THE NAILS: Ravin (92) observed brittle nails in patients with hypothyroidism. Farstock (44) says they are brittle and thick and coarse. Bryan (17) stated that they are often brittle and have transverse ridges.

EDEMA: Most of the authors do not mention edema in mild hypothyroid states. Higgins (48) speaks of localized edema in a few of these patients, with slight pitting of the ankles, tightness of the fingers, and fullness of the eyelids. Ravin (92) mentioned edema of the eyelids, face and cheeks, and non-pitting edema of the ankles. Russell (99) observed puffiness of the face in some subthyroid individuals, and Weiss and King (125) stated that swelling of the eyelids is a comparatively common finding in hypothyroidism and may be the only obvious abnormality in a casual examination.

THE PULSE: The various authors are not in agreement as to whether the pulse is slow, rapid, or variable in hypothyroidism. Ravin (92), McKean (77), Higgins (48), McLester (80), and Marr (72) found the rate to be slow as a rule. Hoge (51) said that the pulse is as likely to be rapid as slow; Youmans and Riven (131) say that the rate is not slow, but may be rapid; and Lee (64) says that tachycardia is common. Harstock (44) states that bradycardia suggests hypothyroidism, but that the pulse may be normal or rapid. And Seward (105)
says that the heart rate is variable. He cited a case of hypothyroidism with precordial pain and a heart rate of 104 which did not respond to digitalis but returned to normal on thyroid therapy. Watkins (123) in his hypothyroid series found the pulse rate rapid in 52%, slow in 4%, and normal in 44%.

Lathrope (60) observed in his hypothyroid patients that the pulse rate on standing was rapid, but slowed to 70 or below when the patient was lying down. White (127) said that the pulse rate as taken at his office was 10 to 15 beats more rapid as a rule than at the time the B.M.R. was tested, when it was 60 to 70 in most cases. Higgins (48) counted the pulse during basal metabolism tests with the patient at complete rest and found, contrary to Lathrope and White, that the rate was below 70 in only a few instances and was definitely above normal in some.

THE BLOOD PRESSURE: Apparently there is no uniform effect of hypothyroidism on the blood pressure. There have been several reports of both hypotension and of hypertension occurring with thyroid deficiency.

Russell (99) said that low blood pressure was common in these patients. Vis (119) reported likewise. McLester (80) said that the blood pressure was usually low with a systolic pressure of 100 or less. In Lathrope's (60) experience the systolic blood pressure
formula: 3/4 Pulse Pressure plus 3/4 Pulse Rate minus 72 equals the B.M.R. Gale (33) proposed a similar formula for calculating the basal metabolism: The B.M.R. equals the Pulse Rate plus the Pulse Pressure minus 111.

Wharton (126) mentions the pulse rate and the pulse pressure as a valuable means of estimating the B.M.R. at the bedside, but says that they should be backed up by other procedures. Even if basal precautions are taken, the results are open to 10% error in half the cases he says. Higgins (48) found no true relation between the pulse pressure and metabolic readings in his series, by use of Read's (93) correlation coefficient.

**THE HEART:** Most authors seem to feel that there is no influence of hypothyroidism on the heart as regards physical findings. Ravin (92) spoke of the poor quality of the heart sounds and dilation of the heart in hypothyroidism. Marr (72) observed enlargement of the heart in some cases, and McLester (80) frequently found a bottle shaped heart (probably on X-ray examination of the chest).

Electrocardiogram reports by some authors showed positive findings in hypothyroidism. Harstock (44) reported a low amplitude of the electrocardiogram sometimes, which he said was due to myocardial weakness. Raven (92) noted a low voltage especially in the T waves.
in leads I and II. Marr (72) reported an E.K.G. with low voltage in most cases of hypothyroidism, frequently with T wave changes and conduction disorders, occasionally with disturbance of the conduction and mechanism of the heart to the extent that complete heart block might result. Seward (105) on the contrary says that the E.K.G. is normal in hypothyroidism.

**ARTERIOSCLEROSIS:** Most authors do not recognize any relation between hypothyroidism and arteriosclerosis. However, Malta (30) pointed out the frequency with which arteriosclerosis and hypothyroidism are found coexisting. And Barr (5) stated that arteriosclerotic changes were facilitated by hypothyroidism.

Harstock (44) thought that hypothyroidism may be a factor in arteriosclerosis due to the increased blood cholesteros. Wharton (126) seemed to think that the parasympathetic dominance of hypothyroidism might have some relation to the arteriosclerotic changes of later life, since Hall (39) had demonstrated that arteriosclerosis develops after long continued administration of acetyl-choline.

**TEMPERATURE:** In hypothyroidism the body temperature is slightly but quite constantly below normal, according to Foge (51) and Connor (19). Lathrope (60) also says that the temperature by mouth is often below
normal, and in White's (127) hypothyroid group the
temperature was below 98 degrees in 13 of the 90 cases.
McKean (77) usually observed a low buccal temperature,
about 97.7 degrees, but he saw one young lady with a
high temperature which returned to normal on thyroid
therapy and rose again when the thyroid extract was
discontinued.

**Tendon Reflexes:** Most writers make no mention of
the tendon reflexes in mild hypothyroidism. Kavin (92)
observed prolongations of tendon reflexes. Wharton (126)
says that reflexes with slow extension are characteristic
but are seldom elicited. Higgins (48) found that the
patellar reflexes showed no demonstrable delayed response
in mild hypothyroidism, but mentioned that this response
had been pointed out in more advanced types of thyroid
deficiency.
LABORATORY FINDINGS

There are several laboratory procedures which have been employed as an aid to diagnosis in hypothyroidism, and some fairly consistent findings have been reported by most authors - including a moderate secondary anemia, increased blood cholesterol, increased glucose tolerance, a tendency to hypochlorhydria, and sometimes a mild albuminuria.

THE RED BLOOD COUNT: Ravin (92), McKean (77), McLester (80), Russell (99) Gardner (35), and others report a mild or moderate secondary anemia occurring quite commonly in mild hypothyroidism without any other satisfactory explanation. Wharton (126) explains that anemia occurs in hypothyroidism because of the decreased oxygen consumption and the decreased need for red blood cells to carry this gas.

Seward (105) reported a moderate decrease in the red blood cell count and the hemoglobin in one third of his cases. Lathrope (60) observed anemia in 85% of his hypothyroid group, with a red blood cell count of from 3 to 4.4 million and a hemoglobin of 65% to 80%. White found a slight anemia in 19 of his series of 90 hypothyroid individuals.

As to the type of anemia, most authors agreed that it was a moderate secondary anemia, as we mentioned above.
Warfield and Greene (122) described a secondary anemia of a "chlorotic type" in these patients. Connor (19) described a hyperchromic type of anemia in hypothyroidism, with a color index above one, and comparable to pernicious anemia; but the red blood cells are large and stain well and megalocytes and nucleated red cells are absent he says. On the other hand Harstock (44) found a mild hypochromic anemia frequently associated with thyroid deficiency. He said that when marked anemia simulating pernicious anemia occurs, there is probably also some deficiency of the extrinsic or intrinsic factors of pernicious anemia.

Youmans and Riven (131) say that anemia in hypothyroidism is not of diagnostic importance. Higgins (48) claims that in his experience, anemia was not a complicating factor in hypothyroid states.

Experimental evidence in behalf of the relation of hypothyroidism to anemia is furnished by Sharpe and Bisgard (106), who reported that complete removal of the thyroid gland in rabbits produces a macrocytic anemia.

THE WHITE BLOOD COUNT: Lawrence (62) and Frosch (32) have reported an increase in the number of lymphocytes in hypothyroidism. McKean (77) found a moderate leukopenia in many cases, but not uncommonly a relative mononucleosis.
Higgins (48) stated that in his experience there was no change in the differential of the white blood cell count associated with hypothyroidism.

**THE BLOOD CHOLESTEROL:** Hypercholesteremia is common in hypothyroidism according to Kavin (92), Schutz (104), and many others. Marr (72) thinks that blood cholesterol studies are a useful laboratory aid to diagnosis, and Harstock (44) says that they should be done routinely. A high blood cholesterol in children too young for a satisfactory basal metabolism test is especially of diagnostic value, according to Sanders (101).

Mason (73), Bronstein (14), Hess (47), and Pouncher (91) et al suggest the level of the blood cholesterol as a useful check on the severity of the hypothyroidism and a guide to the efficacy of the thyroid therapy, since the B.M.R. is not always dependable.

Wharton (126) says that the normal blood cholesterol is 150 to 180 mg.%, and that this is increased in hypothyroidism, but that he has not found blood cholesterol studies of particular value in this condition.

Moellig and Ainslie (84) believe that cholesterol metabolism is controlled through the pituitary, and that the blood cholesterol indicates pituitary and not thyroid function. But Connor (19) reasons that thyroid deficiency is actually at fault in the disturbance of
lipoid metabolism, since thyroid extract given in cases of hypercholesteremia decreases the blood cholesterol.

GLUCOSE TOLERANCE AND BLOOD SUGAR LEVELS: Hypoglycemia and increased glucose tolerance seem to be the rule in hypothyroidism according to most authors. Connor (19) says that hypothyroidism is one of the commonest causes of hypoglycemia. He thinks that the mechanism is often associated with disturbed liver function and decreased storage of glycogen, and also infers decreased sympathetic tonus, which is another factor in depression of blood sugar level.

Lawrence and Rowe (61) noted a hypoglycemic tendency and Lathrope (60) found that the blood sugar (non-fasting) was 100 mg.% or lower in 72% of his hypothyroid group.

Lawrence (62) feels that in doubtful cases of hypothyroidism with a basal metabolic rate of minus 10% to minus 20%, an elevation of the sugar tolerance is the most useful diagnostic aid. But he is of the opinion that slight thyroid failure may not affect the sugar tolerance. Bryan (17) and Frosch (32) also reported an increased glucose tolerance in mild hypothyroidism, and Frosch found that it was decreased after thyroid therapy.

Frosch (32) reported a case of hypoglycemic shock in a patient with a basal metabolic rate of -36, in which
he theorizes as to the cause as follows: thyroid inhibits insulin function, and with the thyroid depressed in hypothyroidism the pancreas excreted an excess of insulin which led to the attack. Other reports of hyperinsulinism associated with hypothyroidism include two cases reported recently by Carmichael (18), and a recent case report by Mendelson (83) in which the B.M.R. was -19 and the fasting blood sugar was 40 mg.%, and both increased to normal on thyroid medication. Mendelson feels that many cases of hyperinsulinism would also reveal hypothyroidism if carefully worked out.

Marr (72) on the other hand reported a case of diabetes in which the blood sugar was originally 500 mg.% and was finally controlled on 20 units of insulin a day, in whom a B.M.R. of -40 was discovered and thyroid therapy instituted. A maintenance dose of one grain of thyroid extract daily restored the glucose tolerance test to normal and the insulin was discontinued. Marr believed that the diabetes was secondary to the hypothyroidism. Similarly, Thommen (114) reported a case of glycosuria which was relieved by thyroid extract.

IODINE TOLERANCE: Wharton (126) said that the iodine tolerance test is analogous to the glucose test. It seems to be quite consistently altered in hypothyroidism, but Wharton says that it is impractical as a clinical
routine. Schutz (104) says that the iodine tolerance test is still a time consuming test and not suitable for clinical use, but may eventually be simplified.

Elmer (26) reported that in hypothyroidism the tissues do not fix iodine as they do in euthyroidism or hyperthyroidism. Iodine is injected intravenously and the percentage eliminated in the urine in six hours is measured. In hypothyroidism this is about 23-40%; in euthyroidism 12-20%; and in hyperthyroidism it is usually below 12%, but may be as high as 20%.

Watson (124) has a technique a little different from Elmer's on the iodine tolerance test. He gives 250 grams of iodine per kilogram of body weight in 15 cc. of 0.85% sodium chloride. Blood iodine estimations are made before the test, after 5 minutes, 2 hours, 4 hours, and 6 hours. No food is allowed during the test. Normally he found 9-23% retention of the iodine after 6 hours, in thyrotoxicosis none, and in hypothyroidism an increased retention.

GASTRIC ACIDITY: The frequent finding of gastric hypoacidity has been reported by several authors. Brown (16) observed diminished secretion of hydrochloric acid if the basal metabolic rate was -20% or lower. Russell (99) observed anacidity sometimes associated with hypothyroid states. In 20 patients with gastro-intestinal
complaints, Sewqrd (105) found a normal gastric acidity in 4, hypoacidity in 12, and hyperacidity in 1.

Harstock (43) says that achlorhydria seems to occur somewhat more frequently in hypothyroidism than average, but that it is so common in patients past middle age that coincidence lessens the value of statistics. He found that adequate thyroid treatment in these patients produced no return of hydrochloric acid.

There appears to be some relation between hypo­cholorhydria and anemia in these hypothyroid patients. Lathrope (60), who reported hypochlorhydria in many cases of thyroid deficiency, said that it was usually associated with a definite secondary anemia. Lerman and Means (66) reported that in myxedema there is an unusual tendency to anemia among patients with achlorhydria. And Lerman, Pierce, and Brognan (65) found that the red blood cell count and the hemoglobin tend to vary directly with the level of gastric acidity.

Instead of the test meal (of doubtful value in lesser cases of hypochlorhydria) Lathrope (60) adopted the therapeutic test. He gave hydrochloric acid to all of those hypothyroid patients with impaired appetite or flatulence indigestion. Most of them would take 10 to 20 drops of dilute hydrochloric acid with marked improvement in appetite and relief of indigestion. A few were made more uncomfortable on the hydrochloric acid and it
had to be stopped, but the majority proved to be hypochloric on this test.

Lathrope (60) believe that infection has much to do with the lowered gastric acidity in these patients, since Faber (28) has pointed out the high incidence of infectious conditions in the past history of patients with achyla gastrica.

THE URINE: The urinalysis is negative except for a frequent trace of albumin, according to Seward (105). McLester (80) and Harstock (44) say that the albumin in the urine frequently causes hypothyroidism to be mistaken for nephritis. In addition to the albuminuria which Gardner (35) sometimes observed in subthyroid patients, he occasionally found even casts in the urine without satisfactory explanation. Thommen (114) reported albuminuria relieved by thyroid extract. The active mechanism here is still obscure.

Bronstein (14), Hess (47), and Pouncher (91) have reported a partial or complete cessation of creatinine excretion in hypothyroid states. Incidentally Seward (105) found the blood urea normal.

BLOOD CALCIUM: Seward (105) tested the blood calcium in 8 of his hypothyroid patients and found it normal in every case. Connor (19) said that many hypothyroid people, especially children, have a low blood calcium,
feeding. With Grant she later showed it to be influenced by thyroid or thyroxin alone, and to be more specific than the basal metabolic rate (126).

But Robertson and Wilson (97) and Horton (53) et al say that this test has no clinical value as yet.
DIAGNOSIS

Most writers base their diagnosis of hypothyroidism on a correlation of clinical symptoms and signs with laboratory procedures, the basal metabolism determination, and the response to thyroid medication wherever possible. The B.M.R. and the response to thyroid are considered most essential as a rule.

Harstock (44) says, "The only satisfactory method for detecting the disease is to suspect it, as one suspects focal infections, as a possible explanation of vague disturbances, especially when these are related to the neurasthenic or exhaustive syndrome."

The clinical picture of hypothyroidism is so variable that many atypical cases go undiagnosed, according to Marr (72). He has reported many atypical cases which responded to thyroid treatment, and believes that improvement on thyroid therapy is one of the criteria for diagnosis.

Seward (105) feels that there are no pathognomonic signs or symptoms. Diagnosis can be made only after prolonged observation, and is justified only when the symptoms are associated with a low basal metabolic rate. Most writers are of a similar opinion.

However Lathrope (60) says, "A very just suspicion of the disease may be easily engendered solely from the
clinical evidence, and the general practitioner who has once recognized the condition may often diagnose it correctly without recourse to laboratory procedures." He goes on to say that "clinical evidence is the all important factor in evaluation of the condition," and rates that more essential than the basal metabolic rate, contrary to the views of most authors.

THE BASAL METABOLIC RATE: Diagnosis of hypothyroidism is usually made on the finding of a lowered basal metabolic rate. This is the principle means of diagnosis and is quite a valuable procedure.

The basal metabolic rate in hypothyroidism is always low according to McKean (77). And McLester (80) says that in a small group of hypothyroids in "poor health" the decreased B.M.R. is the only finding.

Marr (72) thinks that the diagnosis depends more on the B.M.R. than on the clinical picture. And Lathrope (60) feels that even slight minus readings are of significance provided symptoms and signs offer a fair suggestion of thyroid deficiency. But Hoge (51) says that the diagnosis of hypothyroidism on the basis of a low metabolic rate (even as low as -20) is questionable unless there are also definite physical findings and complaints.

McLester (80) considered the B.M.R. the final
10% is more significant than plus 10% to plus 15% in the opinion of Hoge (51) and Harrell (40). The common errors, according to Youman and Riven (131) give falsely high rather than low figures, and with rare exceptions falsely low rates can not be obtained.

Schutz (104) warns that repeated basal metabolic tests may be necessary to get the true low level in some cases. And Thompson (115) also mentioned that a single determination may not be reliable. He said that at least two tests on different occasions are essential, and that the second test may show a drop of as much as twenty five per cent.

The level of the B.M.R. can not always be correlated with the symptoms according to Seward (105), for many patients with a moderately low rate have more pronounced symptoms than those with a lower rate. And Barksdale (3) is also of the opinion that the severity of symptoms does not parallel the basal metabolic rate.

The question of when to give thyroid medication in terms of the basal metabolic rate is still in some dispute. Warfield is of the opinion that patients with a -8% metabolic rate should be given thyroid, and Bridges believes that it should be given in the presence of a rate of -5% with symptoms (40). And Vis (119) says that a definitely low B.M.R. is rare, even in hypothyroidism,
to the individual case and must be worked out by trial and error in each case, according to most authors. Harstock (44) says that the original B.M.R. is not a very good indication of the amount of thyroid necessary to bring the metabolic rate up to normal; and Marr (72) found that those having a very low B.M.R. required the smaller doses.

Most authors report that they begin cautiously with small doses of thyroid extract daily, and that they gradually increase the dose as necessary to establish a normal basal metabolic rate and a feeling of well-being. Then they establish a maintenance dose. All during this time the patient must be kept under close observation. Clinical observations, laboratory, and metabolic tests serve as a guide to the regulation of the treatment. And even after the patient is established on a maintenance dose, observation of the patient is necessary from time to time as it may be necessary to increase or decrease the dose.

METHODS OF ADMINISTRATION: There are various methods of prescribing thyroid administration. It may be well to review a few of the methods which various authors have employed:

Thompson (115) says that the ideal method is to raise the basal metabolic rate gradually to normal with
slowly increasing doses of dessicated thyroid to avoid any unpleasant symptoms and the danger of coronary accidents. He begins with a small dose, 1 grain per day, and increases gradually after several weeks. The dose must be raised slowly, he says, because two months is required for adjustment to any dose. He attempts to maintain the B.M.R. at normal with a minimal dosage, which averages in his experience from $1\frac{1}{2}$ to 2 grains of U.S.P. thyroid extract daily.

McKean (77) begins cautiously with a dosage of $\frac{1}{2}$ to $1\frac{1}{2}$ grains on an empty stomach two times a day. The maintenance dose is established by check-up at intervals on the basal metabolic rate.

Seward (105) uses larger doses to start. He usually prescribes 2 to 6 grains daily for 2 weeks, then rechecks the B.M.R. and establishes the dosage according to the B.M.R. and the intensity of the symptoms. Usually he got a maximum response only after the B.M.R. was normal for a few weeks.

McLester uses a large dose, about 4 grains, of dessicated thyroid daily for about 2 weeks, then cuts the dosage to $1\frac{1}{2}$ to 2 grains, and after 2 to 3 weeks more cuts it to 1 grain a day.

Nevertheless most authors seem to feel that the
original dosage should never be more than 1 grain, and
Gardner (35) says that one grain of dessicated thyroid
per day is often sufficient in minor cases. He has
used both Armour's and Park, Davis and Co.'s prepara-
tions. Russell (99) begins with one grain and increases
gradually as necessary.

Harstock (44) says that the original dose should
never be less than 1 grain a day. If the patient does
not tolerate this dosage, he says that hypothyroidism
doesn't play much part in the symptoms.

Larr (72) begins with small doses and gradually
increases, being governed by the patient's condition.
He has found that it takes 6 to 8 weeks for the patient
to realize material benefit. He likes to keep his
patients on the minus side of the metabolic scale.

Lathrone (60) observed a more rapid response to
treatment than did Larr. If the treatment doesn't meet
with improvement in a relatively short time (3 to 4
weeks let us say), he suspects (a) incorrect diagnosis,
(b) improper thyroid dosage, or (c) complicating fac-
tors. Incidentally, he says that these patients do
not require as much thyroid in summer as in winter or
in Florida as in the northern states.

Variable response to thyroid administration is
due to variable efficacy of the preparations and variable
absorption of the drug, according to Mc Lester (80).

**TIME OF ADMINISTRATION:** Hose (14) says the dose must be at a regular time each day. He starts with \\( \frac{1}{2} \) grain doses, increasing as necessary, one dose daily 1 to 2 hours after breakfast. He believes that many clinicians who claim to get little results with thyroid by mouth would find their results improved if the dosage were given at a regular time each day.

Harstock (44) feels that the time of administration of thyroid should never be after mid-afternoon, as it causes difficulty in going to sleep and palpitation of the heart when the patient first lies down.

**ESTABLISHING THE MAINTENANCE DOSE:** Barksdale (3) states that treatment can not be regulated by any means other than the basal metabolic rate. Most authors suggest that the maintenance dose be established so as to maintain the B.M.R. at a normal level.

Harstock (44) and Frosch (32) suggest that due to mild symptoms of excitement, and so forth, it may be necessary to maintain the patient at a metabolic rate slightly below normal. The patient's own normal metabolic rate may be below standard figures. They suggest that the patient's sense of well-being is a better guide than trying to maintain a normal basal
metabolic rate.

Slight overstimulation, occurring for an hour or so after the thyroid is taken, is an indication that the patient is approaching the normal metabolic rate, according to Harstock (44).

Lathrope (60) is accustomed, he says, to employ the mouth temperature as one of the indices to variation of the dosage of thyroid, since the basal metabolic rate is not an entirely reliable guide.

In younger patients, where the basal metabolic determination is impracticable, Eidelsberg (25) increases the dosage of thyroid until the rectal temperature is above 99.6 degrees.

In older patients, Eidelsberg (25) establishes the maintenance dose so that the pulse rate at rest is 96 or above, or the basal metabolic rate is at least plus 6%.

LENGTH OF TREATMENT: Patients must be advised that they will have to take thyroid medication for a long time, according to Musser (87). And in McKean's (77) opinion, thyroid therapy must be continued indefinitely, except in a few children and very young adults.

Harstock (44) says, "Once a hypothyroid always a hypothyroid," and he agrees that constant maintenance thyroid therapy is required after it is once begun, except in some cases of hypothyroidism after thyroidectomy,
when the condition may last only a short time. Even this is permanent and requires constant treatment if persistent over five years.

On the other hand McLeater (80) found that after taking thyroid for a few months many of his patients no longer needed it. And Seward (105) reported that about half of his patients were able to discontinue the thyroid medication for intervals of a few weeks to months at a time.

Youmans and Riven (131) reported that if thyroid therapy is withdrawn the basal metabolic rate falls to a much lower level than before treatment and return of symptoms characteristically occurs, explaining that administration of thyroid allows a decreased function and atrophy of the thyroid gland.

RESULTS OF THYROID TREATMENT: In true primary hypo-thyroidism relief of symptoms is strikingly quick and complete if the proper amount of thyroid extract is supplied, according to Youmans and Riven (131). They say that the amount of thyroid necessary, however, is often larger than generally appreciated.

In cases of low metabolic rate due to causes other than hypothyroidism, thyroid medication is ineffective and may even make the symptoms worse (131).
DANGER OF THYROID ADMINISTRATION IN CORONARY DISEASE:

In patients with arteriosclerosis or coronary disease, large doses of thyroid should be avoided because of the increased danger of coronary thrombosis, according to Thompson (115). He says that it may be necessary to maintain the metabolic rate at a slightly subnormal level due to inability of the heart to meet the demands of a normal level. Marr (72) feels that coronary disease is a contraindication to thyroid therapy.

TOXIC EFFECTS: There is danger of administering thyroid medication with over enthusiasm, according to McLester (60). He feels that because thyroid substance benefits in a graphic manner a few patients who are deficient in thyroxin, there is a temptation to prescribe it with too little discrimination. He warns us to beware of toxic effects, saying that "there are few therapeutic measures which when needed bring more satisfactory results, and there are few which when improperly used are more clearly capable of harm."

Frosch (32) and Lathrope (60) caution us never to give thyroid without a basal metabolic determination, and to observe the patient closely until the effect of the treatment has been observed and established.

Harstock (44) stated that a hyperthyroid state may be produced by over dosage, but disappears always when
thyroid is withdrawn. He has never seen permanent hypothyroidism produced by use of the active hormone.

McKeen (77) likewise states that toxic effects are of brief duration and cause no harm if the thyroid extract is discontinued temporarily and then resumed in smaller doses. Among the toxic effects of overdosage he includes headache, muscle and joint pains, palpitation, dizziness, diarrhea, and occasionally nausea and vomiting. Russell (99) adds nervousness, restlessness, irritation of the skin, rapid pulse, and less frequently mild delirium.

Thompson (117) and his associates describe a period of intoxication which lasts from 1 to 3 weeks, beginning about 24 to 48 hours after the initial administration of a large dose of thyroid—characterized by aching and marked tenderness of the muscles, falling out of the hair, peeling of the skin, often fever, and occasionally nausea.

**THYROXIN:** The general consensus of opinion seems to be in agreement with McLester (80) that thyroxin is not as satisfactory for use clinically as is thyroid extract, although the former is used extensively experimentally.

McKeen (77) thinks that thyroxin has some advantages over thyroid extract in that increased accuracy of dosage
is possible and that it may be given hypodermically when there is failure of absorption when given by mouth. He reported in 1929 that thyroxin had been used to some extent in Mayo's clinic.

Thompson (115) said that thyroxin in alkaline solution works well by mouth, but that it has no advantage over the dessicated thyroid. And Musser (87) observed that thyroxin is by no means definite in its action, nor regular in its effect, since it is absorbed from the intestines in varying degrees.

**Intravenous administration** of thyroxin, according to Thompson (115) is rarely necessary or desirable, and Musser (87) stated that thyroxine should be given intravenously only in exceptional circumstances.

Most authors do not seem to feel that there would be any particular disadvantages to use of thyroxine in treatment of these cases, but actually it is seldom used clinically. Hope (51), for example, feels that thyroxin can be given satisfactorily by mouth or intravenously, but he uses thyroid extract. Thyroid extract seems to be the more convenient and more economical preparation.

Bryan (17) reported a reaction from thyroxin, consisting of fever, severe cramp-like pains, tenderness of all muscles (which may last several weeks), nausea for 3 to 4 days, vomiting, and tachycardia.
Finton (49) combines thyroxin with thyroid therapy. He gives 1 mg. of thyroxine intravenously once a week for 8 to 10 weeks, with thyroid extract 1 gr. orally 2 to 3 times a day. The thyroxine is discontinued as soon as the metabolism is elevated to normal. He feels that better and prompter results are obtained by this method of treatment. In patients who will not tolerate dessicated thyroid by mouth, he says thyroxin tablets, 1/80 gr. or 1/60 gr., twice a day may be beneficial.

**IODINE**: If the hypothyroid patient can't take enough thyroid to relieve his symptoms, on account of increased pulse rate or toxic reaction, he can often be helped by the addition of iodine in the form of Lugol's solution, according to White (127).

However, in Hoge's (51) experience iodine does no good and makes some cases worse. He has, he says, seen a mild myxedema converted to an atypical hyperthyroidism by use of iodine.

Kimball (57) recently stated that iodized salt is an efficient and safe method of preventing simple goiter, but stresses that it must have one part of potassium iodide to 5000 parts of the salt.

**HYDROCHLORIC ACID**: In view of the frequent association of hypochlorhydria with hypothyroidism, Lathrope (60) administered hydrochloric acid to these patients to
correct digestive disturbances and poor appetites. He began with ten drops of dilute acid in one half glass of water with each meal. Seward (105) also mentioned that he gave hydrochloric acid for relief of indigestion in these cases.

**GENERAL MEASURES:** Seward (105) also prescribed mild sedatives, mild laxatives, and mild analgesics as necessary. He advised rest regularly during the day and early retirement at night. Optimism and encouragement are essential in the treatment, he says.

And Gardner (35) thinks that all other methods for improving the general health, such as hygienic, dietary, and corrective measures should be employed. But Hinton (49) feels that dietary regulations are not necessary and that other medicines, such as sedatives, should be rarely administered.

**POLYGLANDULAR THERAPY:** According to Harstock (44), polyglandular disturbances associated with hypothyroidism are common, and often the entire glandular syndrome is improved by thyroid alone, especially in the ovarian types of menstrual disorder. Gardiner (34) says that thyroid extract is specific for primary hypothyroidism, but that an auxiliary agent must be used in secondary hypothyroidism.

In treatment of hypothyroidism secondary to hypo-
pituitarism, Thompson (115) says that we must combine administration of desiccated thyroid with other forms of therapy. In treatment of Fröhlich's syndrome and some patients with Simmond's disease, he found that marked improvement may be produced by combining the anterior pituitary-like principle from the urine of pregnant women and suitable dietary measures with the thyroid therapy.

Gardiner (34) in treatment of Fröhlich's syndrome combines a weight reducing diet with thyroid extract and sexhormone therapy (either the male sex hormone or prolan B). In Simmond's disease he administered thyroid extract plus prolan A and B and a hypernutrition diet.

Hypothyroidism associated with Addison's disease may be marked, according to Thompson (115), and thyroid administration often constitutes an important part of the treatment in conjunction with adrenal cortex extract. Means, however, says that thyroid extract is contraindicated in treatment of Addison's disease (34).

Harrison (42) mentions that, while the thyrotronic hormone of the anterior pituitary is valueless in treating true primary hypothyroidism, it serves in some instances to differentiate the primary insufficiency from that secondary to pituitary deficiency, since the former does not respond with an increase in the basal metabolic rate and the latter does.
Whereas most authors seem to feel that thyroid alone is usually sufficient in treating hypometabolic states, and McLester (90) says that we should avoid all polyglandular preparations, Eidelsberg (25) emphasizes the need of polyglandular treatment and not monoglandular.

Eidelsberg (25) supplements thyroid therapy with pituitary treatment for pituitary deficiency complicating hypothyroidism. He gives anterior lobe substance 12 to 40 grains daily, orally, and extract of the anterior lobe substance 1 cc. hypodermically 2 to 3 times a week, and posterior lobe extract ½ cc. 2 to 3 times a week.

Pituitary extracts have not yet gained favorable recognition with most clinicians in treating these conditions, however, and Thompson (115) recently said that there is as yet no pituitary extract which is fully suitable for clinical use.

OTHER MEDICATIONS FOR INCREASING METABOLISM: Thompson (115) mentions that epinephrine, dinitrophenol, dinitro-orthocresol, and diiodothyronine increase oxygen consumption and increase metabolism, each presumably by a different mechanism, but says that they do not influence thyroid function. He does not advise their use for treatment of hypothyroidism. Gardiner (34) also
relative hypothyroidism leads to the changes which produce the late toxemias of pregnancy. They were clinically able by administration of thyroid extract to produce marked improvement after toxemia had developed, and feel that prophylactic administration of thyroid extract will prevent occurrence of most late toxemias of pregnancy.

In treatment of a large colloid goiter which may show a low basal metabolism, Hoge (51) says that we shouldn't give iodine, but should do a partial thyroidectomy and enable the remaining gland to function properly. It may then be necessary to give dessicated thyroid or the gland may again enlarge.

There were 8 cases out of the 80 in White's (127) hypothyroid series which didn't respond to dessicated thyroid. Of these 8, one improved on thyroxin; one improved after addition of thelin; two cases treated with thyroid and Lugol's solution improved; and one case improved on Lugol's solution alone.

In spite of any supplementary measures which may be employed, all authors are agreed that dessicated thyroid extract is the main essential in treatment of hypothyroid states.
CONCLUSIONS

1. Mild hypothyroidism is a clinical entity of wide distribution, occurring more frequently in regions of endemic goiter possibly, but more common in all localities than is generally appreciated.

2. Mild hypothyroidism is more common in females than in males.

3. The etiology of hypothyroidism is still rather indefinite and in all probability it is influenced by a number of factors.

4. Mild hypothyroidism is characterized by a multiplicity of symptoms of a bizarre nature, and presents no distinct clinical picture. Easy fatigability and lack of energy are probably the outstanding complaints.

5. There are no constant physical findings in mild hypothyroidism. Dry skin, coarse hair, and low body temperature are frequent findings.

6. Increased blood cholesterol is the most useful laboratory aid to the diagnosis of mild hypothyroidism. Moderate secondary anemia, hypochlorhydria, and increased glucose tolerance are also observed in many cases.

7. The basal metabolic rate is always decreased in mild hypothyroidism.

8. The final diagnosis is based on the correlation of the vague symptom complex, the low basal metabolism,
and the response to thyroid administration.

9. Thyroid extract is the specific treatment for primary hypothyroidism. An auxiliary agent must sometimes be used in treating secondary hypothyroidism.

10. The physician should become familiar with one standard preparation of desiccated thyroid extract and use only that one preparation in his practice.

11. Treatment should be begun cautiously and increased slowly until an adequate maintenance dose is established. The patient should be observed closely until the maintenance dose is established.

12. Treatment must be continued for long periods of time, usually throughout life.

13. Patients on thyroid treatment should be observed from time to time by their physician. It may occasionally be necessary to increase or decrease the maintenance dose. Toxic reactions may result from overdosage.

14. The basal metabolic rate and the patient's feeling of well-being are the best guides to the regulation of the treatment.
BIBLIOGRAPHY

1. Alexander, E.L.
Hypothyroid State

2. Aub, J.C. and DuBois, E.F.
Clinical Calorimetry. Nineteenth Paper. The Basal Metabolism of Old Men
Arch. Int. Med. 19: 823, 1917

3. Barkdale, G.H.
Mild Hypothyroidism

4. Barlow, H.C.
Plea for Earlier Recognition of Thyroid Deficiency
Practitioner 127: 648-658, 1931

5. Barr, Sir James
Hyper- and Hypo-Thyroidism, Causation, Prevention, and Treatment
Practitioner 106: 381-399, 1921

6. Barrett, A.M.
Hereditary Occurrence of Hypothyroidism with Dystrophies of the Nails
Arch. Neur. and Psych. 2: 628-637, 1919

7. Baskett, E.D.
Hypothyroidism in Young Women

8. Bernard, B. and Miller, P.R.
Hypothyroidism as a Cause of Disease of the Hip

9. Boothby, W.M., Berkson, J., and Dunn, H.L.
Studies of the Energy of Metabolism of Normal Individuals: A Standard for Basal Metabolism, with a Monogram for Clinical Application
Amer. Jour. Physiol. 116: 468, 1936

10. Boothby, W.M. and Sandiford, I.
Summary of Basal Metabolism Data on 8,614 Subjects with Special Reference to the Normal Standards for the Estimation of the Basal Metabolic Rate
Jour. Biol. Chem. 54: 783-803, 1922
11. Brazier, M.A.B.
   An Electrical Method for Use in Diagnosis of Diseases of
   the Thyroid Gland
   The Lancet 2: 742, 1933

12. Brekenridge, J.D.
   Some Practical Aspects of Hypothyroidism
   Amer. Jour. Obst. and Gynec. 23: 871-875, 1932

13. Bragman, A.
   New Conceptions of the Etiology and Pathogenesis of Acne Vulgaris
   Arch. Derm. and Syph. 36: 758, 1937

14. Bronstein, I.F.
   Studies in Cretinism and Hypothyroidism in Childhood
   Jour. Amer. Med. Ass. 100: 1661-1663, 1933

15. Brown, T.R.
   Hypothyroidism as a Cause of Intractable Constipation

16. Brown, T.R.
   The Effect of Hypothyroidism on Gastric and Intestinal Function
   Jour. Amer. Med. Ass. 97: 511-513, 1931

17. Bryan, N.C.
   Hypothyroidism

18. Carmichael, J.L.
   Hyperinsulinism Associated with Hypothyroidism

19. Connor, P.J. and Maier, F.J.
   Hypothyroidism
   Color. Med. 34: 385-389, 1937

20. Craddock, A.B.
   Hypothyroidism of Adults
   South Med. Jour. 22: 141-143, 1929

21. Curling, T.B.
   Two Cases of Absence of the Thyroid Body, and Symmetrical
   Swelling of Fat Tissue at the Sides of the Neck, Connected
   with Defective Cerebral Development
   Med.-Chir. Trans., Lond. 33: 303, 1850
22. Davis, A.C.
The Clinical Significance of Low Basal Metabolic Rate
Jour. Laus. 54: 329-332, 1934

23. Dodds, E.C., and Robertson, J.D.
Masked Hypothyroidism as a Cause of Amenorrhea

24. DuBois, E.F.
Basal Metabolism in Health and Disease, 3rd ed.,
Lea and Febiger, Philadelphia, 1937

25. Eidelberg, J.
Endocrinopathies: the Thyro-pituitary Syndrome. Diagnosis and Treatment

26. Elmer, A.J.
Iodine Tolerance Test for Thyroid Insufficiency
Endocrin. 18: 487-496, 1934

27. Englebach, W.
Textbook of Endocrine Medicine, vol. 3

28. Faber, K.
Lectures on Internal Medicine
Paul B. Hoeber, New York, 1929

29. Fazge, C. H.
On Sporadic Cretinism Occuring in England
Med.-Chir. Trans., Lond., 54:150, 1871

30. Falta, W.
The Ductless Glandular Diseases, 3rd ed.

31. Fox, E.L.
A Case of Myxedema Treated by Taking Extract of Thyroid by Mouth

32. Frosch, H.I.
Hypothyroidism
New York St. Jour Med. 36: 785-790, 1936

33. Gale, A.M., and Gale, C.H.
Estimation of the Basal Metabolic Rate
The Lancet 1: 1287, 1931
34. Gardiner, J.F.
Clinical Recognition and Treatment of Thyroid Deficiency
States and Other Disorders of Hypometabolism

35. Gardiner, E.L.
Hypothyroidism with Special Reference to Minor Thyroid
Deficiencies
Jour. Endo. 44: 10-18, 1934

36. Gordon, M.D.
Endocrine Obesity in Children
Jour. Pediat. 10: 204, 1937

37. Gordon, A.H.
Some Clinical Aspects of Hypothyroidism

38. Gull, Sir W.W.
On a Cretinoid State Supervening in Adult Life in Women
Trans. Clin. Soc., Lond. 7: 130, 1873

39. Hall, G.E.
Experimental Heart Disease

40. Harrell, C.L.
Thyroid Deficiency; Clinical States
Virginia Med. Monthly 57: 71-81, 1930

41. Harrington, C.R. and Barger, G.
Constitution and Synthesis of Thyroxine

42. Harrison, K.S.
Clinical Application of Thryotropic Hormone

43. Harstock, C.L.
Clinical Aspects of Hypothyroidism
Cleveland Clin. Quart. 6: 53-62, 1939

44. Harstock, C.L.
Diagnosis and Treatment of Hypothyroidism

45. Hayward, E.P. and Woods, A.H.
Mental Derangements in Hypothyroidism, Their Misleading
Effects in Diagnosis
Jour. Amer. Med. Assoc. 97: 164-165, 1931
46. Hertoghe, E.
Thyroid Insufficiency
Practitioner 94: 26-69, 1915

47. Hess, J.H.
Blood Cholesterol and Creatinine Excretion in the Urine as
Aids to Diagnosis and Treatment of Hypothyroidism
Ann. Int. Med. 8: 607-611, 1934

48. Higgins, W.H.
Incipient Hypothyroidism: Clinical Study
Jour. Amer. Med. Assoc. 85: 1015-1017, 1925

49. Hinton, J.W.
Iodine Metabolism and the Hypothyroid State

50. Hoge, A.G.
Hypothyroidism; Diagnosis and Treatment
West Virg. Med Jour. 25: 87-89, 1929

51. Hoge, A.G.
The Mild Hypothyroid

52. Horsley, V.
Not on Possible Means of Arresting the Progress of Myxedema
Brit. Med. Jour. 1: 257, 1890

53. Horton, J.W., Vanravenswaay, A.C., Hertz, S., and Thorn, G.W.
The Clinical Significance of Electrical Impedance Determinations
in Thyroid Disorders
Endocrin. 20: 72, 1936

54. Jacobi, E.
Myxedema und Psychose.
Arch. f. Psychiat. 86: 426-441, 1939

55. Kendall, E.C.
Isolation of the Compound Containing Iodine, from the Thyroid
Jour. Amer. Med. Assoc. 64: 2042-2043, 1915

56. Kerley, C.G.
Subthyroidism with Defective Dental Development
Arch. Pediat. 55: 540-552, 1938

57. Kimball, Q.S.
Prevention of Goiter in Michigan and Ohio
Jour. Amer. Med. Assoc. 64: 2042, 1915
58. King, J.T.
Hypothyroidism
South Med. Jour. 17:662-669, 1924

59. King, E.L. and Herring, J.S.
Hypothyroidism in the Causation of Abortion, Especially of the "Missed Variety"
Jour. Amer. Med. Assoc. 113: 1300-1302, 1939

60. Lithropes, J.H.
Thyroid Deficiency
Int. Clin. 47th series 1: 72-83, 1937

61. Lawrence, C.H.
Physiological Background for Symptoms of Thyroid Failure, with Consideration of Results of Treatment

62. Lawrence, C.H.
Thyroid Failure without Myxedema

63. Lawrence, C.H. and Rowe, A.W.

64. Lee, R.L.
Hypothyroidism: A Common Symptom

65. Lerman, J. and Means, J.H.
Gastric Secretion in Exophthalmic Goiter and Myxedema

66. Lerman, J., Pierce, F.D. and Brogan, A.J.
Gastric Acidity in Normal Individuals

67. Litzwemerger, J.C.
Relation of Basal Metabolism to Sterility
Amer. Jour. Obst. and Gynec. 12: 766, 1926

68. Litzwemerger, J.C. and Carey, J.B.
The Relation of Basal Metabolism to Feculation
Amer. Jour. Obst. and Gynec. 17: 550-552, 1929

"-103-"
59. Mackenzie, J.W.G.  
A Case of Myxedema Treated with Great Benefit by Feeding  
with Fresh Thyroid Glands  

60. Maine, T. and Bement, C.H.  
Further Observations on the Relations of Iodine to the  
Structure of the Thyroid Gland in the Sheep, Dog, Dog,  
and Cat.  
Arch. Inst. Med. 3: 65, 1:09

61. Marin, Tice, Friedenwald, and Warren, eds.  
Practice of Medicine  
W. F. Prior Co., Hagerstown, Md., 1932

62. Marr, A.M.  
Hypothyroidism  

Blood Cholesterol Values in Hypothyroidism and Hypertrophy  

64. Mayo, C.H.  
Thyroid Deficiency, a Commonly unrecognized Disorder  
Post Jour. Surg. 41: 427-430, 1933

65. McCarrison, R.  
Researches on Gastric Produced by Cabbage  
Indian Jour. Med. Research, 18: 1311-1334, 1931

66. McCullough, T.P.  
Some Clinical Considerations of Basal Metabolism  

67. McKeen, R.M.  
Hypothyroidism without Myxedema; its Recognition and Treatment  

68. McKinlay, C.A.  
Concerning Limitation of Clinical Significance of Low  
Basal Metabolic Rate  
Minn. Med. 14: 713-714, 1931

69. McKinlay, C.A.  
Manifestations of Hypothyroidism in United Fields of Medical Practice  
Minn. Med. 13: 281-284, 1930
80. McLester, J.S.
Thyroid Deficiency as a Cause of Poor Health

81. Means, J.H.
Thyroid and Its Diseases
T. J. Lippincott, Phil., 1937

82. Means, J.H., and Burgess, H.W.
The Basal Metabolism in Non-Toxic Goiter and in Borderline Thyroid Cases
Arch. Int. Med. 30: 507-516, 1922

83. Mendelson, R.W.
Hyperinsulinism Associated with Hypothyroidism
Southwest Med. 23: 135-137, 1939

84. Moelling and Ainslie --- Wolf, W., ed.
Endocrinology in Modern Practice
Saunders, Philadelphia, 1937

85. Murray, G.R.
Note on Treatment of Myxedema by Myxedema Injection of an Extract of Thyroid Gland of a Sheep

86. Murray, G.R.
The Diagnosis of Early Thyroidal Fibrosis

87. Russer, J.J.
Latent Hypothyroidism
Tri-State Med. Jour. 10: 2115-2118, 1938

88. Ord, W.M.
On Myxedema, a Term Proposed to be Applied to an Essential Condition in the "cretinoid" affection Occasionally Observed in Middle Aged Women
Med. Chi. Trans., 61: 57, 1878

89. Parhon, C.I.
Sur le Traitement de la Migraine
Paris Med. 150: 412, 1936

90. Patterson, J.B., Nicodemus, R.E., and Hunt, H.F.
Hypothyroidism, An Etiological Factor in Eileapsia
Creatine Metabolism in Children with Hypothyroidism
Jour. Amer. Med. Assoc. 102: 1132-1135, 1934

92. Ravin, A.
Myxedema; Cases Illustrating Phases Receiving Recent Attention

93. Read, J.M.
Basal Pulse Rate and Pulse Pressure Changes Accompanying
Variations in Basal Metabolic Rate
Am. J. Med. 34: 533-535, 1924

94. Read, J.M.
Correlation of Basal Metabolic Rate with Pulse Rate and
Pulse Pressure
Jour. Amer. Med. Assoc. 73: 1867, 1922

95. Reilly, W.A. and Smyth, F.S.
Stippled Epiphyses with Congenital Hypothyroidism

to investigate the Subject of Myxedema

97. Robertson, J.D. and Wilson, A.T.
A Combined Study of the Basal Metabolism and Impedance Angle
in Thyrotoxicosis and Myxedema
The Lancet 2: 1158, 1934

98. Rubenstone, A.O.
Migraine; Epilepsy Their Association with Hypothyroidism

99. Russell, R.O.
Mild Hypothyroidism with Report of Cases

100. Salzman, S.
Hypothyroidism a Factor in Certain Types of Uterine Hemorrhage
Amer. Jour. Obst. 74: 612-613, 1951

101. Saunders, L.C.
Incipient Hypothyroidism
Mississippi Doctor 13: Febr., 1935
102. Schaeffer, R.L., Strickroot, F.L., and Purcell, F.W.
The Endocrine Implications of Juvenile Chondro-Epiphysitis

103. Schick, B. and Topper, Anne
Low Basal Metabolism

104. Schutz, H.E.
Non-Myxedematous Hypothyroidism

105. Seward, F.P.
A Clinical Study of Mild Grades of Hypothyroidism

106. Sharpe, J.C. and Bisgard, J.D.
The Relation of the Thyroid Gland to Hematopoiesis

107. Shelton, E.K.
Familial Hypothyroidism; Clinical Study,
Endocrin. 15:297, 1931

108. Shute, E.V.
Resistance to Proteolysis Found in the Blood Serum of
Aborting Women

109. Simon, F.
Discussion of Myxedema

110. Sloan, E.V.
Diseases and Disfunction of the Thyroid Gland
Color. Med. 33: 22-13, 1938

111. Sloan, L.T. and Spear, L.M.
Studies of Basal Metabolism in Chronic Arthritis

112. Sweet, J.E. and Ellis, J.W.
Influence on Spleen and Thyroid of the Complete Removal of the
External Function of the Thyroid
113. Taylor, W.A.
Hypothyroidism
Northwest Med. 24: 429-430, 1928

114. Thommen, A.A.
Obscure Forms of Thyroid Insufficiency
Med. Jour. and Rec. 131: 603-608, 1930

115. Thompson, W.C.
The Hypothyroid States

116. Thompson, W.C. and Thompson, P.K.
Low Basal Metabolism Following Thyrotoxicosis; Permanent Type without Myxedema

117. Thompson, W.C., Thompson, P.K., Taylor, S.G., Nailer, S.B.,
and Dickie, L.F.M.
The Pharmacology of the Thyroid in Man

118. Thomson, F.M. and Thompson, W.O.
Low Basal Metabolism without Myxedema
Arch. Int. Med. 46: 879-897, 1930

119. Vis, W.R.
Diagnosis of Mild Hypothyroidism
Jour. Miss. State Med. Soc. 30: 829-830, 1931

120. Wahl, E.
Hypothyroidism with Special Reference to Types

121. Turfield, E.S.
Hypothyroidism

122. Turfield, E.S. and Greene, E.L.
Hypothyroidism and Its Relationship to Cerebrospinal Fluid

123. Watkins, R.M.
Mild Hypothyroidism
Ann. Int. Med. 7: 1534-1539, 1934
124. Watson, E.M.
An Iodine Tolerance Test for Investigation of Thyroid Function
Endocrin. 20: 356, 1936

125. Weiss, H.B. and King, C.
Swelling of Thyroid in Patients with Myxedema
Ohio State Med. Jour. 23: 341-343, 1932

126. Tharton, G.K.
Unrecognized Hypothyroidism

127. White, J.W.
Hypothyroidism without Myxedema
Color. Med. 34: 382-384, 1937

128. Wilkins, L.
Some Problems and Methods of Diagnosis of Cretinism and
Juvenile Hypothyroidism
Delaware State Med Jour. 13: 183-194, 1932

129. Williamson, G.C. and Pearce, I.H.
The Pathological Classification of Cretin
Jour. Path. and Bact. 20:361-387, 1925

130. Wiltrakis, G.A. and Partipilo, A.V.
Non-Myxedematous Hypothyroidism, Case Reported with Psychosis

131. Youmans, J.B. and Riven, S.S.
Hypothyroidism without Myxedema

132. Ziegler, L.H.
Psychoses Associated with Myxedema
Jour. Neurol. and Psycho-path. 11(41): 20-27, 1930