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Review of hypothyroidism

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A REVIEW OF HYPOTHYROIDISM

BY

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INTRODUCTION

The usual method of guaging thyroid activity in adults and children over ten years of age has been the determination of the basal metabolic rate. This procedure has been in vogue since 1900, when it was first used in myxedema and severe hypothyroidism. But often times we find individuals with basal rates in the myxedema range who are symptom free. Are we, then, able to rely on basal metabolism as being pathognomonic of thyroid activity? It will, therefore, be the purpose of this paper to not only give a review of hypothyroidism but to also try and show that the estimation of the basal metabolic rate has been overrated in thyroid diseases and especially in the milder grades of hypothyroidism. If such a hypothesis can be proven, it shall be attempted to find some procedure which will be more specific than the determination of the basal metabolic rate.

HISTORY

T; B. Curling, (20) in 1850, first described the features of two children in whom no thyroid gland was found at autopsy. Twenty years later, 1871, C. H. Fagge (28) again described cretinism and he regarded atrophy of the thyroid gland as the probable cause of this condition. Because a child of eight years of age developed the condition following a case of measles, Fagge concluded that such a condition could develop in an adult and need not be congenital. Though never having seen such a case he predicted with accuracy the changes in the soft tissues which are characteristic of myxedema.

Sir William Gull, (35) in 1873, reported two cases of thyroid deficiency developing in adults but it was not until 1878 that the condition received its name of myxedema from W. M. Ord, (73) because of the mucin deposits in the sub-cutaneous tissues of adults. This has since been proven untrue. F. Semon, (84) in 1883, pointed to an insufficient secretion of the thyroid as the cause of myxedema. During this same year, The Clinical Society of London appointed a committee for the stu-

dy of myxedema and they proved that the disease was caused by destructive changes in the gland.

G. R. Murray, (70) in 1891, developed an extract from the thyroid gland of sheep and in the same year successfully treated a patient with myxedema by sub-cutaneous injection. In 1892, E. L. Fox, (30) and H. W. G. MacKenzie,(63) independently of each other, began the oral administration of a thyroid preparation with very good results.

Although mild grades of hypothyroidism were known to exist and were treated by thyroid substances, there is very little in the literature regarding this subject until 1925. Probably the first mention of mild hypothyroidism was by S. Salzman, (82) who,in 1916, reported cases of uterine hemorrhage due to thyroid deficiency. The hemorrhage was relieved by desiccated thyroid. In 1924, C. H. Lawerence (58) wrote on hypothyroidism without myxedema and in 1925, W. H. Higgens (42) wrote on incipient hypothyroidism and described the symptoms and signs that we now use

in diagnosis.

Since 1925, more and more articles have been written on the subject of mild hypothyroidism. R. I. Lee, (60) in 1925, described rhinitis occuring with a thyroid deficiency. In 1926, T. R. Brown (12) associated constipation with thyroid deficiency. J. S. McLester, (68) in 1929, wrote on mild hypothyroidism as a cause of poor health. J. W. Hinton, (43) in 1932, described indefinate abdominal pains which were relieved by treatment with thyroid substance and, in 1933, C. H. Mayo (67) described mild hypothyroidism as a common unrecognized disorder.

Epstein and Lande, (26) in 1922, found high cholesterol values in hypothyroidism and, in 1930, Mason, Hunt, and Hurxthal (65) described low cholesterol levels in hyperthyroidism and elevated levels in hypothyroidism. In 1934, Hess (41) described serum cholesterol and creatine excretion as possible aids in diagnosis of mild hypothyroidism in children. In the same year, Poncher, Visscher and Woodward (75) described creatine metabolism in children with hypothyroidism and they

suggested that creatine excretion and blood cholesterol might serve as a useful check on the severity of hypothyroidism since basal metabolism does not always give a true picture of the severity of the condition.

CLASSIFICATION

Several methods of classification have been advocated. Soloman and Weiss(81)base their classification as to age, whether monoglandular or polyglandular and whether primary or secondary. Pope (76) uses age periods in one's life for his classification. Fravel (31) uses severity of symptoms in his classification. Although that of Soloman and Weiss is probably the most thorough, for ease of discussion a modified form of that advocated by Fravel will be used as follows.

1. Myxedema.
    (a) Spontaneous.
    (b) Postoperative.
2. Cretinism.
    (a) Sporadic.
    (b) Endemic.
3. Severe Hypothyroidism.
    (a) Adult.
    (b) Child.
4. Mild Hypothyroidism.
    (a) Adult.
    (b) Child.

PHYSIOLOGY

To date, three chemical compounds have been isolated from the thyroid gland, iodothyroglobin, diiodotyrosine and thyroxine. Thyroxine, itself, is optically inactive but dextro and laevo forms have been demonstrated. By clinical observations, thyroxine has been found to differ from desiccated thyroid which is more complex and produces more bodily changes. (111)

It is thought that cells lining the acini absorb iodine from the blood and convert the iodine into diiodotyrosine and protein combinations. Diiodotyrosine probably represents a stage in the synthesis of thyroxine by the gland. (64)

The chief function of the thyroid gland is to regulate the speed of metabolic processes of the body. This is accomplished largely by the thyroid hormone acting as a catalyst, sensitizing the body cells to sympathetic stimulation. The thyroid, adrenals and sympathetic nervous system act together. Increased thyroid activity accelerates the sympathetic system. The converse is also true in that the parasympathetic system is

predominate in hypothyroidism. Thus in hyperthyroidism there is a tachycardia caused by sympathetic sensitization in the cardiac center in the medulla as well as in the muscle fibers of the heart. The hormone provides the skin with adequate amounts of water, fat, blood and also regulates the activity of the sweat glands. This is why we see skin changes in hypothyroidism. Hyposecretion of the thyroid results in hypersecretion aand hypermotility of the intestine which accounts for the symptoms of spastic colon, mueus in the stool, flatulence and constipation. Mental activity is slowed due to the slowing of metabolic processes in the brain.

The anemia which often occurs in hypothyroidism is probably on the basis of decreased oxygen consumption and consequently a decreased need for red cells to carry oxygen. (111)

The interrelation of the thyroid gland and other endocrine glands has been demonstrated. Evans (27) has shown that the anterior pituitary produces a thyrotropic fraction which if not present causes atrophy of the thyroid gland. But he also maintains that the growth promoting function of the pituitary is dependent upon a nor-

mally functioning thyroid. The thyroid has a reciprocal influence upon the adrenals and gonads which is probably indirect through the pituitary gland. The adrenal cortex inhibits the thyroid and the thyroid supplements thymic activity. Insulin is antagonistic to the thyroid hormone which may be due to sympathetic stimulation or to increased glycogenolysis. The relation of the thyroid to the parathyroid is antagonistic because of the opposite action on the sympathetic nervous system. The thyroid hormone increases calcium and phosphorus loss from the bones without producing increased amounts in the blood such as occurs in hyperparathyroidism. (64)

MYXEDEMA

Definition.

Myxedema is a slowly progressive, constitutional disease occuring in adults between the ages of thirty and sixty, and is the result of atrophy, disturbed function or removal of the thyroid gland. It is characterized by mental impairment, physical changes, alteration in blood chemestry and almost always by a low basal metabolic rate. (10) (85)

Etiology.

The general consensus of opinion is that spontaneous myxedema is the end result of a functionless thyroid gland. This idea has prevailed since Murray, (70) Fox (30) and MacKenzie (63) successfully treated myxedema with preparations of the gland tissue. But why there is a lack of secretion has been impossible to discover. Several theories have been proposed but they have never been proven. Conklin (17) believes that myxedema may be due to a relative or absolute insufficiency of iodine necessary for the production of thyroxine or an instability of acinar cells, through various injuries, to pro-

duce this hormone.

Because the condition is more frequent in the female, it is thought that one factor in its production is the strain on the thyroid gland during pregnancy and child birth. (17) (32) (68)

Psychic trauma, shell shock, operative shock, and prolonged nervous strain have been advocated and cases have developed following such episodes (4) but it would have been interesting to have examined those patients previous to the receiving of such psychic stimulation. It is more probable that they were just candidates for myxedema because of a pre-existing mild hypothyroidism which was aggravated by the stimulation to become more severe.

C. H. Lawerence (59) writes that the presence of myxedema as determined by inspection is not essential to the existence of marked thyroid failure and that there is considerable evidence that myxedema is fully as dependent upon vascular pathology as on diminished thyroid function per se. It is agreed that vascular pathology is pre-

sent but does it precede the thyroid failure or is it the result of thyroid dysfunction. The latter appears to be the more correct as coronary sclerosis, arteriosclerosis, angina pectoris, dilatation and cardiac decompensation have been proven to follow myxedema.

Hertzler (40) maintains that myxedema is not synonomous with deficient thyroid secretion. He states that, "There can be a deficiency or an absence of thyroid secretion without any of the clinical signs of myxedema as total thyroidectomies have shown". He finds that when symptoms of hypothyroidism develop after thyroidectomy, that the tissue which was not removed was responsible for myxedema and not the removal of too much tissue. His treatment of myxedema is entire removal of the thyroid gland and his conclusion is that what we considered a "negative state" was in reality the gland producing a substance which was deleterious to the patient. But we ask ourselves, why do most patients respond to thyroid

medication? The most obvious reason is that the thyroid is not producing thyroxine but Hertzler believes that thyroid medication neutralizes the harmful substance which the gland is producing. This idea appears radical and is far removed from our general concept of the physiology of the thyroid gland but because much of our knowledge of medicine has come from such radical ideas more research should be done along this line.

The most widely accepted theory as a cause of spontaneous myxedema is that of infection. Many patients date the onset of their symptoms shortly after an acute infection or they give a history of a severe infection. Infections described have been influenza, acute tonsillitis, typhoid fever, pneumonia, tuberculosis, malaria, gout and encephalitis. Probably these infections produced an acute thyroiditis with subsequent atrophy. (17) Roger and Garnier, (39) in 1900, examined critically the thyroid gland in patients who died of measles, scarlet fever, diphtheria, small pox, typhoid fever, meningitis and peri-

tonitis. In every case they found histological changes as diffuse hemorrhage, epithelial proliferation, swollen cellular protoplasm, cellular desquamation and colloid either thin or absent but no change in the interstitial connective tissue. The infectious process had its chief effect on the secretory part of the gland. They concluded that infectious processes first brought about a period of functional stimulation with hyperthyroid symptoms but that enough injury was produced so that eventually there could be a more or less complete functional inhibition which could result in myxedema.

Kent (52) has noted frank cases of exophthalmic goiter become myxedematous during a recession of the disease. He has also found that those doomed to myxedema following operation show a more or less degree of chronic inflamation and that even if gland tissue remained these patients would develop hypothyroidism.

Blumgart and Davis (9) find that in every case of total removal of the thyroid a hypothy-

roid state has occured.

Else (25) finds that if the gland is kept saturated with Lugol's solution by mouth for several months after radical operation, hypothyroidism does not develop and if it does, it is only transitory. The iodine apparently aids the gland in regeneration.

Scott (83) finds that in all total thyroidectomies it is impossible to remove all of the thyroid tissue due to the presence of retro-tracheal gland tissue and that this is the reason that hypothyroidism seldom develops after radical operation. Hertzler says that the gland may be removed in its entirety without producing myxedema but Scott says that Hertzler always leaves some tissue behind.

Several viewpoints on the etiology of myxedema have been reviewed. At the present time lack of secretion appears to be the most plausible and has the most evidence to substantiate it. But because we have different ideas, it should stimulate more research on the thyroid gland.

Pathology.

Because myxedema is treated by replacement with thyroid substance there is no report in the literature regarding this subject. Hertzler (40) is probably the only man to use surgery in the treatment of myxedema and he has, therefore, ample material for study. The following will be a review of his findings.

The gland may be atrophic, small and fibrous and contain little or no thyroid tissue. There may be no acini. But he says that these are extremes and one usually finds a small fibrous gland containing a few insignificant acini which seem functionless.

Another group, those who previously had a goiter which was once useful but which has gone back on the patient, furnishes the most common source of material. The gland is fibrous and has the same picture as the previous description.

In some cases, part of the gland has the appearance of an old goiter and another part shows a degenerated state which is difficult to differentiate from that found in goiters in subcretin-

oid states.

Histology.

The typical gland of spontaneous myxedema shows large areas of fibrous tissue infiltrated with round cells. Enclosed are small acini lined with degenerated epithelium or none at all. Also present are large, pale staining, acidophilic, foamy cells resembling those of adrenal tumors. It is these cells, according to Hertzler, which are associated with myxedema and which if present in the gland in which a subtotal thyroidectomy was done, that patient will need thyroid medication.

Symptoms.

Symptoms and signs first described by Ord (73) are characteristic of myxedema. He described it as a progressive and insidious disease. The patient first lounges around, leading an inactive life and becomes disinterested in those things which previously occupied his time. He becomes forgetful and prefers solitude. Sensitivity to cold is noticed early and the patient will be observed to

be wearing more and warmer clothes even in temperatures when one would not expect it. There is a gradual increase in weight with specific localization of fat pads, a peculiar non-pitting edema of dough like consistancy, over the dorsa of the hands and feet, about the wrists and snkles, in the supraclavicular fossa and about the face.

The skin becomes dry, scaley and harsh to the touch. It is thick and puffy and has an edema like appearance. Frequently a yellow color is observed and it is thought that this is due to a lessened conversion of carotine to vitamin A in the liver because of the depressing effect of lowered metabolism.

Expression is masklike, features become coarse and the face and eyelids become puffy giving the patient a mongoloid appearance.

As the disease progresses, mental sluggishness becomes more marked and memory becomes poorer. There is somnolence. Concentration is diminished. He shirks responsibility.

Later the lips and tongue thicken, and the speech becomes slow and monotonous due to the thickening of the tongue and slowing of mental processes. The voice is coarse and low pitched because of edema of the vocal cords. Movements become clumsy and the patient tires with the slightest exertion. (85)

Numbness and parathesias may be present especially in the extremities. They are usually associated with chilliness. Joint pains are common.

The hair thins and becomes sparse and dry. Oftentimes the earliest sign is a thinning of eyelashes and eyebrows.

Anorexia and vague abdominal pains are common complaints. Constipation of a more or less degree is invariably present.

As a rule the pulse rate is slow and blood pressure and temperature are below normal. If the condition has existed for any length of time albumin will be found in the urine and there may be a slight impairment of renal function.

should be remembered that there are va-

rious modifications of the preceding description especially in severity of symptoms and physical appearance. It is only in the well developed case of long duration that the typical findings are found to be present.

Labratory.

It is in the well developed case that we find the most characteristic labratory findings, although even here our findings may be within normal range.

Thurman and Thompson (100) report that if the basal rate is lower than minus twenty five anunder functioning thyroid is present but if the basal rate is less than minus twenty one an under functioning gland is usually not present. Boothby (10) considers anything greater than minus fifteen as indicative of thyroid failure. This in general is the opinion of DuBois (23) and Lawerence.(59)

In contrast to this White (112) reports ninety cases with basal levels between minus ten and minus forty without any of the clinical signs

of myxedema. Palmer (74) reports a case of classical myxedema in a woman with a basal rate of minus eleven. Seward, (86) Lee, (60) Watkins (106) and Barksdale (3) are of the opinion that there is no constant parallelism between basal metabolic rate and clinical symptoms. They consider the basal rate as an approximation and not a test. However, they do agree that persistant low rates should be taken roughly as evidence of hypothyroidism.

Thyroid activity influences blood cholesterol so that the latter is elevated in myxedema . Many writers consider that cholesterol reflects the severity of hypothyroidism better than does the basal rate. Conklin (17) considers normal levels as between one hundred and thirty and two hundred and thirty milligrams percent. Anything above the latter number is significant of hypothyroidism. He finds values as high a six hundred milligrams percent. Wharton (111) says that cholesterol metabolism may be controlled by the pituitary and that study of blood cholesterol pro-

bably reveals pituitary activity and not thyroid function. He says that blood cholesterol has not been useful in his studies of thyroid conditions. Mason (65) finds an inverse ratio between cholesterol values and basal metabolic rate but only in the severe forms and not in mild hypothyroidism. He says that the most striking feature of the study of blood cholesterol in myxedema is the manner in which high cholesterol levels return to normal following treatment. Through his studies he concluded that there could be no myxedema in patients who had a low basal rate with a normal serum cholesterol,

We see that in both basal metabolism and serum cholesterol there are differences of opinion between different authors as to the value of these two procedures. So far, we could not state with certainty that either of these procedures were pathognomonic of myxedema but we could state that low basal rates and high cholesterol values are more apt to be present than they are to be absent. This question will be considered in more detail in our study of the milder forms of hypothyroidism.

Complications.

Conklin (17) finds that the myxedema heart is a clinical entity. There is a generalized enlargement of the heart, it becomes flabby and the rate becomes slower. Blood pressure tends to remain nearly normal. These factors tend to lead to myocardial degeneration.

Bartels and Bell (52) describe coronary sclerosis as representing a direct complicating factor in myxedema. It is usually found in patients over forty years of age.

Anemia of a secondary type is usually present and is probably on the basis of decreased oxygen consumption.

A renal insufficiency may be present which may confuse one with a nephritic syndrome. However, the microscopic findings so characteristic of nephritis are usually not present unless the condition co-exists with myxedema. (17)

Treatment.

There are two methods of treating myxedema, Hertzlers and the rest of the medical profession.

Hertzler is probably the only surgeon in the world who treats myxedema by total thyroidectomy and he maintains that myxedema is markedly relieved, even more so than by the use of thyroid medication. He states, "patients on thyroid medication still realize they are carrying a burden and their improvement seldom approaches a state of complete well being as when they undergo complete thyroidectomy". He does complete thyroidectomies for myxedema whether or not goiter is present, for patients who have had Basedow's disease and subsequently develop myxedema, and in fact, for all conditions of the thyroid gland. He does say that in atrophic goiter the results are less brilliant because there are likely to be complicating factors in which there is a polyglandular condition. Hertzler also says he does not use thyroid medication after his operation and he apparently has the necessary proof to back up his statements. He also makes the statement, "the function of the thyroid gland in the adult has been overrated as total thyroidecto-

mies have shown". As this work has never been repeated by other surgeons we will have to pass it by until some surgeon with more nerve than sense will take it upon himself to either prove or disprove this method of treatment. But, supposing Hertzler were right. Maybe we would be doing our patients a greater service by subjecting them to surgery rather than feeding them pills. This work should do much toward stimulating more research on the thyroid gland.

The accepted form of treatment is, of course, thyroid medication. There are two methods. McLester (68) begins by giving large doses of desiccated thyroid, three grains or more daily for two weeks, then reducing the dosage to two grains daily for another two weeks and then maintain on one grain daily from then on. But supposing a patient had an enlarged and weakened heart and was subjected to large doses. It would seem natural then, that the heart could be stimulated to such a point that failure might occur. In fact many patients have died from large doses of thyroid. This method, therefore, appears to be dangerous and should not

be used.

The other method is known as the French method. (37) One and one-half grains of desiccated thyroid per day is given in three or more doses for one week. Medication is then stopped for one week. The next week a slightly larger dose is given and the week following, the medication is again stopped. This method is followed until a maintainence level is found. In this manner there is no strain on the heart.

Perhaps even a better method would be to begin with one-half grain or less per day and gradually increase the dose once each week until a maintainence level is found.

Pope (76) finds that iodine often helps if there is no response to thyroid alone. He also advocates cold hydrotherapy, mechanotherapy and static wave currents.

How are we to tell when we have reached a maintainence level? Many physicians use basal metabolic determinations as a guide and when the rate has been elevated to within normal levels, the patient is maintained on that dosage. Others find that the basal rate does not help them in

any way and they, therefore, use clinical improvement to determine the correct dosage. Still other men increase the dosage until some symptoms of hyperthyroidism appear and then reduce the dosage so as to maintain the patient at a level just below the point where symptoms appeared. Toxic symptoms consist most commonly of headaches, muscle or joint pains, palpitation, dizziness, diarrhea and occasionally nausea and vomiting.

CRETINISM

In order to clearly understand the milder grades of hypothyroidism in children, it is necessary to have a clear cut picture of cretinism in our minds.

Definition.

Cretinism is a disease of infancy and childhood and is due to a more or less complete lack of thyroid secretion. It is characterized by stunted physical development, retarded mental development and a characteristic appearance.

Distribution.

Cretinism occurs endemically and sporadically. The endemic form occurs in regions where goiter is endemic as in the valleys of the Alps, Pyranees and Himalayas but it is relative rare in this country. It is common in parents who have goiter. It has been estimated that one out of every twenty goiterous mothers give birth to mentally defective or imbecile children.(77) Goiter may or may not be present in this form of cretinism. The sporadic form occurs in any region and usually of non-goiterous parents. The thyroid gland is usually absent in this form. There is apparently no heriditary or environmental causes.(56)

Etiology.

Because of its presence at birth, cretinism is described as being of congenital origin. It may also appear in several members of one family which points to heredity as a cause. In regions of endemic goiter, a lack of iodine in the maternal organism may cause a failure of thyroid development during fetal life or shortly after with subsequent cretinism. (97) Thyroiditis probably plays an important role in those cases developing after the first or second year of life. Abnormal function of the pituitary with loss or insufficiency of the thyrotropic hormone is probably of some importance but there has been no mention of such as a cause of cretinism.

Pathology.

There may be no gland present as first described by Curling (20) or the gland may be small and atrophic in which fibrous tissue has replaced normal acinar tissue. (28) Herman, (39) on an autopsy on one cretin, found the thyroid present but in an atrophied condition and infiltrated by a growth of new connective tissue.

Typical Cretin.

Cretinism is seldom noticed by the parents until the child is ten or twelve months of age, when they observe that the child is not gaining in stature, intelligence and physical activity as a normal child should. By this time the typical picture of the condition is present.

The typical cretin is short of stature and of stocky build. He is dull, listless and apathetic. (113) The hair is coarse and dry with a tendency to sparsity which often is shown only in the eyebrows. Fontanels and sutures close late.

The cretinoid facies is characterized by coarse, heavy features. The eyes are widely spaced, small and pig-like, giving an idiotic expression. The lids are puffy and swollen. The nose is broad and short and the root is flattened and undeveloped while the tip is wide and flaring. The mouth is broad and gaping and the lips are pale, dusky and thick. The tongue is thick, broad and protuberant. Drooling is characteristic. The cheeks are pale and may have a yellowish tinge due to presence of carotine which has not been transformed to vitamin A. (113)

The skin is thick, wrinkled, cool and shows circulatory mottling. The extremities are cold and bluish in color. There is a lack of muscle tone. The hands are broad and short.

The abdomen is protuberant and frequently an umbilical hernia is present. (78)

On the outer sides of the sterno-clavicular muscle are usually symetrical swellings which have a doughy, inelastic feel. Often similar swellings are on the buttocks, back of the shoulders, over the dorsa of hands and feet and around the wrists and ankles.

In taking the history we find that the baby was late in holding up its head, late in sitting, late in standing and late in walking, or in the severe case he may not be able to do any of these. Eruption of the first tooth occurs later than the seventh month. Birth weight is usually over eight and one-half pounds. (85) Mentally the child appears dull and listless. He refuses the breast. He seldom cries and when he does the sounds are hoarse and gutteral. The child does not play with toys and he does not pay attention to his surroundings.

Suggestive signs may be listed as follows,

1. Birth weight of eight and one-half pounds or over.
2. Failure to nurse.
3. Delay beyond the fifteenth day in separation of the umbilical cord.
4. Delay beyond the fifth month in holding up the head.
5. Delay beyond the seventh month in recognizing immediate attendents.
6. Delay beyond the eighth month in the appearance of lower central incisor teeth.
7. Delay beyond the eleventh month in sitting up.
8. Delay beyond the fourteenth month in talking with monosyllables.
9. Delay beyond the fourteenth month in standing or walking a few steps.
10. Delay beyond the twentyth month in closure of the anterior fontanel.

Any delay in one or more of the preceding should arouse suspicion of hypothyroidism. (85)

Wilkens(113) says that the above description is not the usual type of cretin seen in this country. He says that diagnosis is not easy during the first years of life because frequently the classical syndrome is not present. On general inspection the baby looks like a fairly normal infant, younger than the actual age due to the fact that absence of thyroid activity causes a retardation in all developmental processes as growth, bone development, dentition and mental development. The study of the osseous development is the most essential procedure in the diagnosis of cretinism.

Labratory.

The basal metabolic rate is the commonly accepted method of guaging thyroid activity in adults but the method is of questionable value in the diagnosis of hypothyroidism during childhood because the patients are too young or to unintelligent to cooperate in the use of the respirator. There is also difficulty in selecting standards from which to calculate the deviation. The influence of even slight emotional disturbance is marked and of long duration. In thirty three patients with unquestionable hypothyroidism, Wilkens

and Fleischman, (113) in their special apparatus, could only make satisfactory determinations in ten children. They find wide variations both in the hypothyroid and in the normal child. In comparison with the Boothby-Sandiford surface area rates, they find that the hypothyroid child and the obese child have similar low rates. (115) However with the heighth standards of Talbot, (97) the child with hypothyroidism shows definate low rates while the obese child has normal or elevated rates. They occasionally see children with low rates who have neither symptoms or signs. Wilkens (117) states that, "Hypometabolism is not synonomous with hypothyroidism." Therefore, we can conclude that the determination of the basal rate in the child is of no importance and is not practible.

Wilkens, Fleischmann and Block(114) in determining the cholesterol values on normal and hypothyroid children find that in fifty seven normal children the serum cholesterol ranged between ninety six milligrams percent and three hundred and eight milligrams percent with an average of one hundred and eighty eight milligrams per cent.

In the cretin the range was between one hundred and forty five milligrams percent and six hundred and sixty milligrams percent with an average of three hundred and eight milligrams percent. These figures show that there is a tendency for serum cholesterol to be higher in the cretin than in the normal child. They conclude that a serum cholesterol value below three hundred milligrams percent does not exclude thyroid deficiency but that a concentration above three hundred milligrams percent is highly suggestive if diabetes, nephrosis and hepatic disease are ruled out. They find that the normal child will show a serum cholesterol which will vary by as much as eighty milligrams percent while the cretin as much as two hundred milligrams percent. In a later paper Wilkens and Fleischmann(118) review the findings after therapy has been started. In those cases in which a high serum cholesterol was present, there was an immediate drop in the value. They further found that the injection of five milligrams of thyroxine in the cretin caused the serum cholesterol to reduce by on hundred and twenty to two hundred and thirty milligrams percent and the

effect lasted thirty to sixty days while in the normal child the same dose of thyroxine caused only a slight and transient effect ranging from zero to sixty four milligrams percent and returned to its previous level within ten days. In another article, they describe the effect of withdrawal of thyroid medication upon the serum cholesterol.(118) In this case the serum cholesterol increased greatly in the course of four to twenty weeks, reaching levels ninety eight to four hundred and eleven milligrams percent above the level of the treated period. In the normal child there was an increase of only ten to fifty five milligrams percent. The increase of serum cholesterol was usually greater than that which existed before treatment was begun. Rapidity and regularity of cholesterol rise showed individual differences in the hypothyroid children. This work has also been done by Goodkind and Higgens.(33) All these writers conclude that determination of blood cholesterol level following the withdrawal of thyroid therapy is of diagnostic significance in the doubtful cases of treated cretinism. Chuen Fan(16) finds that the level of blood cholesterol gives a general

indication of the therapeutic effect of thyroid therapy.

We have, so far, two diagnostic aids, the response of cholesterol to a therapeutic dose of thyroxine and the measurement of serum cholesterol after the withdrawal of therapy.

W. C. Rose (79) was the first person to discover that creatine excretion is physiologic up to the time of puberty. Hess (41) found that in children with hypothyroidism creatine is absent in the urine and that it is restored to normal by thyroid therapy. He also noticed that as thyroid therapy was reduced, the creatine excretion reduced. He therefore concluded that hypofunction of the thyroid gland causes a decrease or a complete cessation of creatine excretion which is restored to normal after the administration of thyroid extract.This work corresponds to that of Poncher, Visscher and Woodward (75) who say that the metabolism of creatine appears to be definately influenced by thyroid activity in childhood. They find that a change in creatine metabolism is an important finding and is useful in diagnosis and in the control of therapy.

Wilkens and Fleischmann, (114) (117) (118) in 1941, repeated the work on creatine and they find that there is a tendency for creatine excretion to be low in the hypothyroid child but that it can be just as low in the normal child. The creatine tolerance test was of no value in their cases. The increase of creatine in the urine is their most sensitive indicator of thyroid response in children but they find three types of response, a negative in which there was no effect from thyroid hormone but marked with thyroxine, a positive in which there was an increased creatinuria with thyroid hormone and thyroxine and a false negative in which there was no increase with either the hormone or thyroxine. Creatine excretion was found to average four and two tenths milligrams per kilo body weight per day in the normal and one and seven tenths milligrams in the hypothyroid. From their work they conclude that it is impossible to differentiate the untreated hypothyroid child from the normal child on the basis of the excretion of creatine. They do say that a low creatinuria is very suggestive of hypothyroidism in the absence of other conditions but the absence of this finding does not exclude hypothyroidism.

They further find that the oral administration of thyroid or the injection of a single dose of thyroxine shows that the effect upon the serum cholesterol serves better to differentiate the hypothyroid from the normal child than does change in creatinuria. Cholesterol determination is carried out easily without hospitalization while the patient must be in the hospital for the determination of creatine in the urine. Of the two procedures the determination of the serum cholesterol appears to be the most advantageous.

Recent work by Talbot (98) reveals that serum phosphatase may be of aid in the diagnosis of hypothyroidism. He finds that the level of serum phosphatase of infants and children with untreated hypothyroidism is abnormally low and that it is restored to normal by adequate therapy. Normal has been found to be over four and one-half units while the hypothyroid is lower than four and one-half. His conclusion is that serum phosphatase provides a simple and reliable index of thyroid deficiency during childhood and infancy.

The labratory procedures just described find their most usefulness in the early diagnosis of hypothyroidism of short duration and before skeletal changes have made their appearance.

It is generally agreed that in the advanced case a roentgen study of the osseous system is of greater importance than the determination of serum cholesterol, urinary creatine or basal metabolic rate. Stockard,(95) in 1923, showed conclusively that the amount of thyroid secretion present in the developing individual is an important factor in determining the rate of growth. Dorff (22) regards any retardation as confirmatory evidence of mild hypothyroidism and pathognomonic of cretinism providing that rickets, mongolism, celiac disease, congenital syphillis or Cooley's erythroblastic anemia were eliminated.

In a series of cases studied by Signorelli, Hosen and Miles, (92) it was found that neither rickets, scurvy or congenital syphilis presented any retardation of appearance of epiphyses

and centers of ossification. The majority showed normal or early appearance. They concluded that the late appearance of the epiphyses or centers of ossification cannot be attributed to syphilis, scurvy or rickets but they clearly indicate and are diagnostic of thyroid deficiency.

Connor and Maier (18)say that the diagnosis in the new born may be made during the first week of life by x-ray of the elbow or knee, one nucleus is missing where two are normally.

Wilkens (119) finds that epiphyseal dysgenesis associated with hypothyroidism is manefested in roentgenograms by the appearance of multiple irregular islets of ossification in the cartilages scattered over a large area. These enlarge and coalesce to form irregular, spongy, porous masses. All centers of endochondral ossification may be affected. This abnormality is found in all hypothyroid children in whom x-rays were made at frequent intervals after treatment was begun. It was found not only in cartilage which already was ossified prior to thyroid treatment but also in those which be-

gan to ossify during the course of treatment. Only those centers showed dysgenesis in which the appearance of ossification had been delayed as a result of hypothyroidism. With continued treatment, ossification took place normally in those centers which ordinarily would not have been ossified at the age when therapy was begun. These observations suggest that in hypothyroidism a disturbance occurs in the cartilage in a stage just prior to the begining of calcification. He has never found unquestionable epiphyseal dysgenesis in any condition except hypothyroidism. It was not found in dwarfs who did not have hypothyroidism even when they had delayed osseous development.

Diagnosis.

Diagnosis is comparatively simple when the typical picture of cretinism is present but in order to procure the best results with thyroid therapy diagnosis must be made early, within the first few months is most desirable. In the case of the infant, special attention should be paid to a birth weight of eight and one-half pounds or over and refusal of the breast. If such finding be found present, roentgenograms of ossifi-

cation centers is indicated and should be done at once. In order to further confirm the diagnosis, serum cholesterol and phosphatase can be measured. The former, before and after a trial injection of thyroxine.

Treatment.

In the adult it is the usual practice to carry along on whatever dosage of thyroid the patient feels best but in the infant this is not the case. We have to give as large a dose of thyroid as the infant can tolerate. Each infant is a special problem as no two react alike to thyroid medication. We must find a daily dose which produces slight but unpleasant toxic effects and then maintain a therapeutic level slightly below this point. The rate of growth can be checked by frequent x-rays which are compared with the standards. For the cretin the following dasage is suggested.

age	dosage
Two to four months	one tenth grain daily
Four to eight months	two tenth grain daily
Eight to twelve months	three tenths grain daily
One to two years	one half grain daily
Two to four years	One half to one grain
Four to Twelve years	one to two grains daily

End Results of the Cretin.

There appears to be a difference of opinion as to the end results of thyroid therapy in the cretin. Kerley (53) reports that he has had nine cretins who are all now apparently normal. Several of them have gone through college. Gordon (34) finds that the best results are obtained in the cretin seen before the end of the first year of life and that delay after this time, the response is less marked. Holt and McIntosh (46) have not seen normal mental development even in cases in which treatment was started first year of life. Herman (39) maint ins that the improvement of mental development as great as improvement in physical d velopment, although he does say that if treatmen is started before the first year of life and ment is adequate, regular and continu that these patients may attain normal phys and mantal development. Brown, Bronstein d Kraines (14) find that cretins, if treated, predistined to a final low mental de that a small proportion may develop n Most of their cases remained with an below seventy.

Prophylaxis.

All women should have ample iodine in their intake during the entire period of pregnancy and if she is found to be suffering from hypothyroidism she should have thyroid medication. This has reduced goiter in Switzerland from eighty per cent to twenty per cent.

MILD HYPOTHYROIDISM IN ADULTS

We have seen, so far, that myxedema is the end result of hypothyroidism but we still have yet to discuss those types of mild, moderate and severe hypothyroidism which precede the development of myxedema. The distinction between the three is made evident by the severity of symptoms. For this reason the following discussion will deal mainly with mild hypothyroidism but it should be kept in mind that the following discussion also applies to the more severe grades of hypothyroidism, the only difference being in the severity and number of symptoms present.

Definition.

By mild hypothyroidism we mean a fractional loss of function of the thyroid gland which causes a wide varity of symptoms which in most instances are confusing and often lead to wrong diagnoses. One, several or all the body organs may give rise to symptoms which often makes diagnosis impossible unless the problem is clearly understood.

Etiology.

Etiology is still in doubt. Although we all consider a partial thyroid deficiency as the cause, we only have unproven theories as to why there should be only a partial loss.

Because the condition is more frequent in the female sex, it is generally believed that one factor which may promote the condition is strain on the thyroid during pregnancy (32) and child birth. (68) If this were true we would expect to see more cases. However, the condition may be such that the patients do not feel bad enough to seek medical aid and the symptoms are explained to themselves as being due to advancing age.

Psychic trauma, shell shock, operative shock and prolonged nervous strain have been advocated and cases have been found after such episodes. (4) We are misled in such instances as people have the bad habit of dating the onset of symptoms in any disease to some episode as above, Inall probability the condition was present before such happenings but it may have been made worse by the incident.

Another condition which has frequently been noted in thyroid deficiency is hypertrophied tonsils and adenoids. Here again, we come into contact with foci of infection but if diseased tonsils can give rise to joint symptoms there is no reason to believe that they could not affect the thyroid gland and cause a partial destruction or atrophy. Probably in the earlier stages of atrophy, the gland is able to secrete sufficient thyroxine to maintain the individual for many years but as stress and strain of life increases, the supply of thyroxine diminishes and the individual sooner or later becomes concious of sense of ill being.

Some authors are inclined to believe a constitutional factor is operative in many patients. Barrett,(7)in 1919, reports a family which for six generations had sixty one of its members who showed a peculiar trophic disorder of the nails and hair and various abnormalities of a mental or nervous character. On thyroid therapy the nails and hair showed marked improvement and he theorized that hypothyroidism was the main trouble. In reviewing the family history, he came to the

conclusion that hypothyroidism was a mendelian dominate character. Shelton(89) studied a family of six with proven hypothyroidism and he also concluded that heridity plays some part in the development of mild hypothyroidism.

The most widely accepted theory is that of infection. Most patients have a history of a previous acute infection or the condition has become apparent shortly after an acute infection. It has developed following typhoid fever, whooping cough, influenza, pneumonia and toxemia of pregnancy.(4) (86)

From the foregoing, we can conclude that several factors are contributing to the production of mild hypothyroidism. Probably some people are endowed with a thyroid gland which will not stand up under the stress of life or infections and which sooner or later will give rise to poor health Pathology.

Here again we have to refer to the work of Hertzler(40) who treats these conditions by total thyroidectomy and who is the only one to report on the pathology and histology in these conditions.

He finds that the pathology varies greatly, It may be that of a cretinoid gland, of a maldeveloped gland without functional acini, of a gland with imperfect acini or the gland may be only a spongy mass with few acini present.

Histology.

There are imperfect acini, cells may be flat or they may be absent. Hertzler finds that the earliest stage is represented by an area of round cell infiltration which surrounds the acini. Later the colloid becomes a clumpy irregular mass lying in the center of the lumen. The acinal cells then swell and ultimately fill the lumen. These cells are pale staining and foamy in appearance and represent his socalled "myxedema cells". There is no tendency to form fibrous tissue.

Symptoms.

The symptoms of mild hypothyroidism can only be understood when it is recalled that a lack of thyroxine affect, directly or indirectly, the normal functions of nearly every organ in the body. Barksdale (3) says that if one be inherently weak in one or more organs or anatomic system either through heridity or by virtue of disease, then in the absence of an adequate supply

of thyroid extract, that weakened organ or anatomic system will register complaints. Obviously the symptoms must then vary accordingly. We may, therefore, divide the symptoms into several groups as will follow but it is to be remembered that the manifestations may range from mild to severe and that in the milder forms there may be only one or several symptoms which will give a lead as to the trouble.

Neurological: It is generally ageed among physicians that a feeling of tiredness or weakness is foremost among symptoms. (58) The patient does his tasks only by great effort. Once tired, nervousness is apt to appear and may reach such proportions as as to simulate hyperthyroidism. There may be tremor, insomnia, palpitation, tingling in the hands and feet and other symptoms of a neurotic to further complicate the picture. (106) (32) (68)Headache may be present. It usually begins at the vertex and radiates into the suboccipital region. In some cases the head ache may be migrainous in character. (86) It is usually associated with constipation. There is a lack of

endurance and the patient is unable to stand any sort of strain, either physical or mental. Ease of fatigue probably troubles them most. (68)There is no impairment of reasoning powers but the patient is not capable of sustained mental activity.

Gastro-intestinal: Symptoms in this system are often present. Constipation, either mild or obstinate, is probably of most importance especially in obese women of middle life. It is thought to be on the basis of parasympathetic stimulation. (111) When a barium enema is given, there is noticeable retention of the barium in the descending and sigmoid colon. Stone (94) finds that many of these patients have abdominal pains varying from a vague distress to shooting pains which are very easily confused with appendicitis, ruptured ectopic pregnancy, peptic ulcer and gall bladder disease. In fact many of these patients have been subjected to surgery because inadequate histories were taken. Lester (61) finds that there may even be fever, leukocytosis, abdominal tenderness on palpation and rebound tenderness to further complicate the arrival to a diagnosis. Moehlig (69) reports of thirty two cases which simulated eith-

er peptic ulcer, chronic cholecystitis or mucus colitis. He explains this by having the thyroid gland affect the hypothalmus which in turn acts upon the gastro-intestinal tract.

Loranger (62) finds a relation between gall-stones and hypothyroid states especially in women. Lack of thyroxin, so it is thought, aids in the formation of free cholesterol from the cholesterol ester in the liver and the relation between cholesterol and bile salts is altered which allows cholesterol to precipitate. He finds that once cholelithiasis has occured and corrected that there is great need to study the thyroid gland function and prevent the recurrence of stones which happens if a mild hypothyroid state is present.

Genito-urinary: Menstrual disturbances are often the main complaint in many patients. Chief among these is excessive uterine bleeding during menstruation. (82)The periods come at more frequent intervals and are of longer duration.It is thought that lack of coagulation is due to an inhibitory substance and that when the thyroid is deficient such substance is not neutralized by thyroxin. (96) Davis (21) says that miscarriages

and sterility are common in mild hypothyroidism. Fortune (29) says he has seen scanty menses infrequent periods and dysmenorrhea in some cases. Hamblen, Pullen and Cuyler (36) have proven that the thyroid has no direct effect or association with the gonado-pituitary axis but that hypometabolism results in a quantitative slowing down of ovarian activity.

Polyuria and nocturia may be present but this is more common in children. (4) There may be a large number of epithelial cells in the urine which is analogous to the shedding of the cuticle.

Sir James Barr (6) says that if the prostate is enlarged he treats the patient with desiccated thyroid and iodine.

Skin and appendages:: Dryness of the skin, although seldom the presenting complaint, may be present. There may be a desquamation from exposed surfaces. There may be a thinning and falling of hair. (106) Barlow (4) says that one of the most important and distinctive signs is a thinning of the eyebrows on the outer third.

Skin eruptions of all kinds have been found present as various types of eczema, psoriasis, purigo, herpes and dermatitis. They may appear on any body surface and may appear at the same season of the year. It usually starts in the same month of each year and may last from one week to several months. Hubbard and Martin (47) have described several such conditions which rapidly cleared with thyroid medication.

Absence of perspiration and ridging of the nails may be evident.

Eye, ear, nose and throat: Puffiness of eyelids, impairment of hearing, mouth breathing and hoarseness of the voice are all suggestive signs. (32) (109) The swelling is especially seen in the upper lid and is worse in the morning after arising. Weiss and King (109) say that the swelling receded with thyroid therapy and returned when therapy was stopped. Mouth breathing is due to enl rged adenoids and is not directly due to thyroi failure.

Vasomotor rhinitis, hay fever and asthma been associated with hypothyroidism. Lee (60)

says that one of the functions of the thyroid is to protect us against foreign proteins and when the supply of thyroxine is inadequate we are apt to become sensitized to some protien.

Cardio-respiratory: Breathing is usually normal although in come cases it may be somewhat slowed. The pulse is usually slow(21) although rapid rates have been encountered.(106) Heart rythm is regular and blood pressure is usually normal.

Weight: Janey(51) says that obesity is one of the most early, striking and persistant signs of hypothyroid states but Watkins(106) finds that only about fifty percent of the cases are above normal, thirty percent are under weight and twenty percent are normal. Seldom do they have the noticeable supraclavicular, neuchal, bracelet of ankle padding seen in myxedema but often upon palpation a slight thichening in these regions may be found.

Muscular: There may be slowness and clumsiness of muscle action of any degree. There may

be numbness and pains especially noted after exercise. They tire easy and the muscles appear flabby. (68) Rhumatic pains of various types suggesting chronic arthritis are in many instances of hypothyroid origin. (32)

Edema: J. C. Mussio (71) describes a dropsical syndrome found usually in women between ages of twenty five and forty five without any organic affection to explain the existing effusion. Treatment with thyroid substance induces a pronounced diuresis.

Blood: Anemia may be present and may be the most conspicuous clinical fact in many patients with hypothyroidism. The blood picture often resembles a primary anemia or a chlorosis. There may be a relative or absolute lymphocytosis, it may even resemble a leukemia. The red cell count is usually under four million and hemoglobin ranges from forth eight to fifty six percent which differentiates it from pernicious anemia. (50) (103)

We can now begin to understand why many sufferers do not recognize that they are ill. They may admit that they feel more tired than

they used to; that they feel the cold more than they previously did; that they are unduly sleepy after meals; that their hair is getting thinner; that exertion is more of an effort than formerly; and that their memory is becoming faulty. These symptoms are usually attributed to increasing age and not to any abnormal disorder. It is nor suprising that they do not seek medical aid.

Labratory.

Basal metabolism. The estimation of the basal metabolic rate has long been used as the sole criterion for thyroid activity. It is generally considered that rates of minus thirty to minus fourty are myxedema; that if rates of minus twenty to minus thirty occur, there are definate signs of hypothyroidism; and that rates of minus ten to minus twenty are mild hypothyroid states. But are we justified in assuming that such readings indicate true thyroid deficiency? The calculation of surface area from heighth and weighth alone show an error of fifteen percent.(111) Wishart(121) finds that the day to day variability in metabol-

ism, from minimum to maximum, differs by as much as thirty percent. He has also seen many patients with rates as low as minus twenty one who are in perfect health. It is probably well to remember that when doing a basal test we are measuring only oxygen consumption which is only a small part of the entire activity of the thyroid gland.

What is found in the literature on this subject?Boothby (11) at the University of Minnesota, ran over eight thousand tests on apparently normal individuals and he concluded that plus or minus fifteen was normal and that deviation beyond this range separates diseases into increased and decreased thyroid activity. McLester (68) says that basal rate is always low in thyroid deficiency and it furnishes the final criterion by which the patient is judged. C. H. Davis (21) finds that one third of the women in the Milwaukee area have low basal rates. Those with rates of minus ten or lower were treated with small doses of disiccated thyroid and with only few exceptions they reported improvement in

their general physical condition. W. W. Palmer (74) says that the basal metabolic level is now recognized as one of the best indicators of the activity of the thyroid gland but inconsistancies exist as he has seen patients with myxedema with rates of minus eleven. Mason, Hunt and Hurxthal (65) say that a basal rate of minus twenty suggests hypothyroidism but occasionally one is found without any signs or symptoms suggesting dininished thyroid function. They find that low rates are often found in young individuals without complaints but if a low rate is found with asthenia, fatigue or other subjective signs, the diagnosis of hypothyroidism can be made.

Cahoe (15) concludes that a moderate low rate of minus fifteen to minus thirty, in itself, does not establish the diagnosis but in the presence of a number of the symptoms of hypothyroidism, even with only slight depression or normal readings that the administration of thyroid substance is indicated. If the basal rate is minus thirty or lower a diagnosis of hypothyroidism is justifiable.

Ohler and Ullian (72) find that the inclination is to pay attention to all negative readings provided they are associated with the clinical signs of decreased body heat. They find that the basal rate varies directly with the intensity of symptoms. They also say that many people normally have a low basal metabolism.

Watkins (106) finds that in all cases of mild hypothyroidism the basal rate is lowered to a point moderately below normal.

Seward (86) says a basal rate of minus twelve to minus fifteen is significant if associated with clinical evidence of decreased energy production but it is unwise to make a diagnosis on the basal rate alone when it is only moderately decreased but if it is associated with fatigue one is justified.

Hoge and Harrell (45) find that readings of minus five to minus ten are of more significance than readings on the positive side. They say that if any error is made it will always be on the positive side.

Vandenberg (101) says that if he finds a patient who complains of lack of pep and their basal

rate ranges from minus six to positive five, he starts them on one-half grain of thyroid daily and he has obtained good results.

Hinton(84) describes patients who had abdominal discomfort after meals and who had rates from zero to minus ten. They all improved on thyroid medication but their rates remained the same.

From the foregoing, we can conclude that basal metabolism has a definate place in mild hypothyroidism and that the depression of the basal rate varies directly with the intensity of symptoms. We also see that with few exceptions they all pay particular attention to symptoms and most all leave a loop hole for escape when they report normal individuals with low rates who are symptomless. None go so far as to state that a decreased basal rate is pathognomonic of hypothyroidism.

Now let us see if we can find support that moderately low rates are not indicative of hypothyroidism.

Wahl (102) says there is no positive relationship between the intensity of symptoms and

the degree of lowered metabolism. He states, "There is no fixed level for metabolism even for normal and there is no proof that a patient is better off with a rate of minus eight than one with a rate of plus eight". Many people show a rate well below the normal who are healthy in every respect. He has also found myxedema patients who become symptom free with rates of minus eighteen to minus twenty.

Sexton (87) reports on one hundred and thirty six patients. Thirty three of these had rates between minus eleven and minus fifteen and less than one-half of them improved on thyroid. He did find that as the rate became lower the percentage of improvement increased. He states, "The significance of low basal rate in the absence of clinical hypothyroidism has been uncertain and the value of thyroid therapy in these cases has been difficult to foretell". He finds that as a result many clinicians have developed the tendency to consider lightly any rate that does not descend to a level of minus twenty five.

Lawerence (59) finds that if the rate is below minus thirty the diagnosis is thyroid failure but if the rate is between minus fifteen and minus thirty it may be due to any number of causesas pathological fatigue, syphilis of the central nervous system, nitrogen starvation and hypofunction of other endocrine glands. He says that some people with moderate low rates are helped by thyroid and others are not and that is why he regards the basal rate as an insufficient basis for the diagnosis of thyroid failure. He further says that the administration of thyroid is not justifiable with only a low basal rate.He uses symptoms plus the basal reading and makes his diagnosis only after other diseases are ruled out.

Waters and Williams (104) find that the basal rate estimation, subject as it is to various influences is unreliable in determing thyroid insufficiency and that the importance of basal metabolism has been over emphasized in the diagnosis of variations of the thyroid gland activity. They state, "If basal rates be accepted, use it only as one evidence of the disease.

Weiss and King (109) find no direct relation between the degree of depression of the basal rate and the amount of thyroid necessary to bring it back to normal. They say, "Every patient is a law unto humself".

Hubbard and Martin (47) found a patient with a basal rate of minus eleven who had to take two and one-half grains of thyroid daily to raise the basal rate to a positive reading but another with a rate of minus eighteen could not even take one-eighth of a grain.

Higgens (42) find some patients with a low reading who have shown fewer signs of thyroid deficiency than others whose rates are considerably less markedly low.

Barksdale (3) says there is no constant parallelism between basal metabolic rate and clinical symptoms. He studied eleven patients with rates of minus elevev to minus twenty four who had no complaints.

Youmans and Riven (122) say that rates of normal to minus thirty are not pathognomonic of mild hypothyroidism.

White (112) says symptoms occur more often in people who do not have a low basal rate than in those who have a low rate.

Thommen (99) finds no relation between the intensity of symptoms and the basal rate.

Bassler (8) finds many patients with a low basal rate who are symptom free. He finds that if the rate is minus twenty five or lower an under functioning thyroid is present but if less than minus twenty one an under function is usually not present.

Thurman and Thompson (100) report a patient with chronic thyroiditis in which half of the gland was removed. The basal rate was minus twenty before the operation and has ranged from minus fifteen to minus twenty one since without symptoms.

From the findings of these men, one would be compelled to say that the measurement of the basal metabolism does not have the importance that we formerly supposed it to have.

What can be concluded from the foregoing reviews? Because many healthy, symptomless

people have low basal rates we can say that the basal rate is not pathognomonic of decreased thyroid function. We can also conclude that if a rate is below minus twenty five thyroid failure is probably present but that if we have rates between zero and minus twenty, unless symptoms are present, it is not an indication of thyroid failure. All authors apparently lay more stress on symptoms than they do on negative basal readings. It is probably true that sll rates on the negative side are important findings but they should be interpreted in the light of a carefully taken history and physical examination. A basal metabolic reading by itself is of no consequence in the diagnosis of thyroid deficiency.

Cholesterol: In 1922, Epstein and Lande (26) found high cholesterol values in hypothyroidism. They concluded that the relationship was definate in adults but not so definate in children. Hess (41) also finds high cholesterol values in hypothyroidism and he concluded that cholesterol reflected better the severity of hypothyroidism and the true clinical condition than the metabolic rate. He found values above the normal of one hundred and seventy in all cases of hypothy-

roidism. He also found that cholesterol is reduced by thyroid medication and that it may be used as a guide to the efficacy of thyroid treatment.

Wharton(111) says that cholesterol is high in mild hypothyroidism but that it is also influenced by other factors a pregnancy and the ingestion of certain foods. He also brought out an idea that cholesterol metabolism may be controlled by the pituitary and that the study of blood cholesterol probably reveals pituitary activity and not thyroid function. It was not useful in his studies of hypothyroidism.

Mason(64) finds that the most striking feature of a study of blood cholesterol is the manner in which high cholesterol levels return to normal following treatment.

Hurxthal (47) also considers blood cholesterol a more accurate guide than basal rates. He says that if the rate is minus fifteen or lower and if cholesterol is above one hundred and seventy milligrams percent to consider a hypothyroid state.

Westra and Kunde,(110) in their work on cretin rabbits,find that the blood cholesterol is higher than in the normal. The cholesterol level decreased when desiccated thyroid was fed. There was no change in the normal rabbits who were fed thyroid.

Aub and Heath (2) find that cholesterol values are of definate value in estimating the gravity, diagnosis, prognosis and response to treatment in hypothyroidism.

We see that there is some lack of agreement among these authors but in the main they consider an elevated cholesterol a more important finding than a lowered metabolic rate. If both cholesterol and metabolism were indicators of thyroid disease, we would expect to find a correlation between the two. Mason, Hunt, and Hurxthal (65) report that no such correlation is present. Rothbert (80) finds no relation in children in whom he was able to do a satisfactory metabolic determination.

Hurxthal and Simpson (49) find that the significance of cholesterol is enhanced by the response to dessicated thyroid.They report that when

two grains of U. S. P. thyroid is given, the serum cholesterol should be lowered by at least forty percent the original value and should remain lowered longer than ten days. In the normal, the response is less noticeable and returns to normal within one week.

It appears that as far as cholesterol and metabolic determinations are concerned, that neither are pathognomonic of thyroid disease but that they both are important findings when symptoms are present.

Iodine: Watson (107) uses an iodine tolerance test in which iodine is given intravenously and the amount of retention observed. Normal is nine to twenty three percent in six hours but in the hypothyroid the percentage of retention is much greater. The labratory requirements, technical difficulties and the inconvenience to the patient, however, makes this test impracticable as a routine procedure.

Elmer (24) finds that the measurement of the iodine in the urine after giving potassium iodide intravenously is of value in the atypical forms of hypothyroidism. In seventeen cases of

hypothyroidism, he found that after six hours there was a constant and marked increase in elimination which amounted to from twenty three to forty percent while in hyperthyroidism it was decreased or normal. Neither of the iodine tests have found favor among clinicians.

Diagnosis

How, then, shall we procede to establish a diagnosis of mild hypothyroidism?First, we shall take a careful history and try to bring out any of the previously described symptoms. Second, we shall rule out chronic foci of infection, blood dycrasias, cardiac disease, drug habituation, long continued over work, under rest, under nutrition, Addison's disease and tuberculosis. Third, if we are still in doubt, we shall do a basal metabolism and serum cholesterol.Our diagnosis, then, of mild hypothyroidism shall be a diagnosis primarily of exclusion of other conditions and then a careful correlation of symptoms with labratory findings. If labratory findings are within normal range, we are still justified in giving a therapeutic test with thyroid if the

symptoms of mild hypothyroidism are present and if the above named conditions are ruled out.

Treatment.

It is generally understood that treatment should be administered with caution. Large doses should be avoided as many patients have expired as the result of excessive doses. There is no adequate method to determine the initial dose, it is wise, therefore, to begin with doses ranging from one-tenth grain to one grain daily and gradually increase the dose each week by one-tenth grain until some toxic symptom appears. It requires a longer time but it is safe, for signs of mild hyperthyroidism can be recognized before the patient has received enough thyroid substance to cause trouble. When first signs of mild hyperthyroidism appear, the dose is reduced by one-tenth grain and this may be used as a maintainance dose. Toxic effects consist most commonly of headaches, muscle of joint pains, palpitation, dizziness, diarrhea and occasionally nausea and vomiting. Weismann (108) finds that the most reliable method of determining correct dosage is to

increase the dosage to the point of diuresis and then drop back to the dose just previous. Vandenberg (101) recommends the giving of B complex which stimulates tissues to better function and one may be able to lower the dosage. Adequate diet, rest, exercise and psychotherapy are important adjuncts.

MILD HYPOTHYROIDISM IN CHILDREN

There is no uniform opinion as to the symptoms of the mild or borderline cases of hypothyroidism in childhood and the diagnosis has often been made without substantial proof and then later proved by a therapeutic trial of desiccated thyroid. As described in the adult, the symptoms and signs may be refered to any organ or system in the body and as such will be described.

Neurological.

Ashe(1) describes many of these cases as behavior problems. They are unable to get along in school, with their teacher and with other children. They are subject to emotional states varying from depression to excitement. They may be nervous and high strung, irritable and they all show a moderate degree of mental sluggishness. They are usually non-dependable, unattentive and forgetful. Costello (19) says that mentality is not always affected in hypothyroid states. He has seen many children with definate symptoms of hypothyroidism who are of normal mentality and some who are unusually bright. Kerly (54) finds the mild hypothyroid to have loss of interest in sports, home and school. He says that they are indifferent students in school and are unable to con-

centrate on their work. The condition is often familial. Headaches may or may not be present. It has been noticed that those children who are under treatment sleep much better than they did previous to treatment.

Muscular.

One of the main complaints is habitual fatigue, lack of endurance and lack of energy. (54) There is no capacity for sustained effort. Physical inactivity is shown to some degree by all patients. It is hard for them to get out and play the strenuous games that normal children indulge in, they would rather sit around and do nothing which is not a sign of a normal child. Many complain of vague indefinate muscular and joint pains. (1) Spasmophilia and tetany are suggestive signs. (57)

Gastro-intestinal.

Many patients will give a history of constipation, either mild or obstinate, and of vague pains in the abdominal region. In the infant colic and constipation are usually disclosed in the history. Pylorospasm is usually present. (57) Appetite is usually poor. (91)

Skin.

Skin conditions are not the uaual presenting complaints but it may be often shown that there is a tendency toward dryness and scaling. Often there is a history of an alergic reaction manifested by an eruption or eczema. The skin may or may not be cool to the touch. Usually a pallor is noticed about the cheeks. Wilkens (115) says that one should hesitate in making a diagnosis of mild hypothyroidism in children with bright ruddy cheeks and lips.

Cardiac signs.

Pulse rate is usually decreased and pulse pressure is decreased but these are unreliable signs as they are often present in the normal child. Ashe (1) finds in some cases, especially in behavior problems due to hypothyroidism, that there may be a complaint of pain over the cardiac region. The pain is mild and vague and easily differentiated from heart pathology.

Genito-urinary.

Kerly, (55) in his studies of sub-thyoidism among young girls of fifteen years of age,

finds that the appearance of menses is delayed by several years and that when therapy was started the menses appeared in about two weeks. Enuresis may or may not be present. It is most often seen in children between two and seven years of age.(34) Delayed and defective genital development may be present. (53)

Eyes.

Pain in the eyes has been described by Costello,(19)especially in little girls who have a tendency toward obesity. The pain is not severe but just enough to make the child complain. It appears after reading or studying. He also finds that myopia is invariably present. On thyroid therapy the eye symptoms are the first to disappear.

Weight and height.

Costello (19) says that generally speaking, one can say that in the sub-thyroid child there is a tendency toward obesity. Lamb (57) finds these patients may be over weight and under height, under weight and over height, under weight and under height or they may be normal. There

appears to be some relation between obesity and mild hypothyroidism but it is not pathognomonic, it should, however, arouse our suspicion of a possible hypothyroid condition.

Kerley (54) describes a syndrome in children which he call the "fatigue group". They suffer from habitual fatigue and there is absence of capacity for sustained effort. They either are failing in their school work or at the bottom of the class, probably because of their inability to concentrate. They show no interest in home, school or sports. Height and weight are average and there is no retardation in bone age. Treatment with desiccated thyroid brings about a marked improvement in all the findings.

Costello (19) describes another syndrome, that of the bright, alert little girl who gives a history of having been fat all her life. Her developmental history is that of a normal child, she sat up, teethed, walked and talked at the normal age. She is mentally bright and interested in her surroundings. She usually complains of pain in her

eyes after studying. Her appetite is good but her endurance is embarressed by her obesity. Physically, the fat is evenly distributed, myopia is present, tonsils and adenoids are enlarged, the heart rate is slower than normal and the abdomen is enlarged. Genitalia re normal. In those in which basal rate can be determined it is invariably lowered minus fourteen to minus twenty six. On treatment the first sign of improvement is in the eyes.

In summary, we can say that fatigue and lack of endurance and mental sluggishness are the main symptoms in mild hypothyroidism in childhood just as they are the main symptoms of the same condition in the adult.

Labratory.

We have described previously how basal metabolism is unreliable in children because of lack of cooperation and lack of adequate standards. With our present standards all children show lowered metabolic rates.

One thing we shoud be interested in is, what age can we start taking basal readings in the child? Smith (93) says that he is unable to take

adequate metabolic tests on children under fourteen. Ashe (1) finds metabolic determinations satisfactory as young as six but he considers minus twenty as still normal. Hess (41) says that below the age of eight, the basal determination is of no value with the ordinary apparatus. Probable the age of eight should be the lower limit at which we should begin to rely on basal rates but to much importance should not be placed upon a low reading unless supplemented by symptoms and other labratory findings. We should also remember that in all probably hypometabolism is not synonomous with hypothyroidism. (115)

Shelton (90) says that serum cholesterol values are uninformative in the border line group of hypothyroids. Ashe (1) maintains that in mild cases blood cholesterol is an aid in diagnosis. From the later works of Wilkens, Fleischmann and Block (114) (117) (118) we find that although cholesterol values may be within normal levels, the response of cholesterol to a single dose of thyroxine or the daily administration of desiccated thyroid differs in the normal child and in the hypothyroid child.

Although this work was done on the more severe types, the difference between the normal responce and that of the hypothyroid was so great that they conclude that this is the only labratory procedure which will separate the normal from the mild hypothyroid with any degree of certainty. They also say that more research need be done before we are sure that this labratory procedure will hold in the mild cases.

As to creatine, Wilkens and Fleischmann say that the tendency is for creatine excretion to be low in the hypothyroid child but that it may be just as low in the normal child. It is , therefore, impossible to differentiate the untreated case of hypothyroidism from the normal. They find normal excretion of creatine to be four and two-tenths milligrams , per kilo, per day. They say that the increase of creatine in the urine in response to thyroid therapy is the most sensitive indicator of thyroid response in children. Whether this will hold in the mild case remains to be seen .

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Perhaps the most reliable of indices is the

x-ray of the osseous system. Molitch (66) studied five hundred inmates of a home for boys to determine the incidence of mild hypothyroidism. Their average age was fourteen. Roentgenograms were made of the carpal bones of all the boys and fifty four were found to have retarded osseous development. Their conclusion was that sub-clinical types of hypothyroidism may be recognized by osseous retardation and that it is the most consistant finding in hypothyroid children. In their studies they found that mental retardation is not an important manifestation of sub-clinical hypothyroidism. Dorff (22) found that any child who presented any suspicion of hypothyroidism should be subjected to a thorough roentgen ray study of the bony frame work. Any retardation is accepted as confirmatory evidence of hypothyroidism if rickets, scurvy of congenital syphilis were not present. But we have previously shown that there is no osseous retardation in these conditions.(page 39) Signorelli, Hosen and Miles (92) in their roentgenogram study of the osseous system also concluded that the only method of accurately diagnosing mild hypothyroidism is by study of the epiphyses for without exception they

Diagnosis.

Our final diagnosis of mild hypothyroidism should be based on the following:

(10) a carefully taken history to determine any degree of physical or mental retardation or both.

(2) a careful search of signs and symptoms akin to those of cretinism but in a milder degree.

(3) a delay in the unfolding of the osseous framework as revealed by x-ray.

(4) labratory procedures as cholesterol, creatine and basal rate to further confirm our diagnosis.

The latter, as yet, are of questionable value in the mild forms of hypothyroidism. The determination of cholesterol response to therapy or a therapeutic injection of thyroxine or the effect of withdrawal of thyroid medication offers the most likely possibility as an aid in diagnosis.

Treatment.

Wilkens (116) says, "We must find a tolerance for each patient". That is, we must find a daily dose of desiccated thyroid which produces slight but unpleasant toxic effects and maintain a therapeutic level slightly below this point. Each patient offers a special problem in finding

the correct dosage. It is best to begin with a small dose, one-fourth to one-half grain daily, and gradually work up to tolerance. Attention should be paid to diet and exercise, and if any foci of infection found, they should be adequately treated. Teeth and tonsils should receive particular attention as the teeth are invariably carious and the tonsils are usually hypertrophied and infected.

CONCLUSIONS

We have seen in the preceding pages that in the severe grades of hypothyroidism low basal rates and elevated serum cholesterol values are more apt to be present than they are to be absent. It is also stated that unless the serum cholesterol is elevated, even with lowered basal rate, the typical picture of myxedema does not develop. There are also many cases in which the basal rate in myxedema has been as high as minus eighteen to minus ten and cases have been reported of myxedema patients becoming symptom free when the basal rate is elevated to minus eighteen to minus twenty. There are also normal individuals with rates as low as minus twenty five and minus thirty, who are apparently healthy.

In the mild cases of hypothyroidism in adults, we find authors who conclude that the basal rate has a definate place in the mild types while others find no positive relationship between depression of the basal rate and severity of symptoms. In some cases those individuals with low rates show fewer symptoms and signs than those who have rates within the normal range.

From the above findings, we can only conclude that low basal rates are present in conditions in which oxygen consumption is decreased whether it be hypothyroidism, pituitary and other glandular conditions, undernutrition, underrest, syphilis of the central nervous system, tuberculosis or other chronic debilitating diseases. If all but hypothyroidism be ruled out, then we must assume that a lowered rate is characteristic of decreased thyroid activity. The degree of depression, however, may not parallel the severity of symptoms. For those who are symptom free with low rates, we have no explanation except that they are endowed with an organism which enables them to utilize less oxygen than the ordinary individual.

Cholesterol has been advocated as being of more value than the estimation of the basal rate. It has been shown that the significance of cholesterol is enhanced by the response to thyroxine in which the serum cholesterol is lowered by at least forty percent of the original value and remains lowered longer than ten days while in the normal the response is less noticeable and returns to normal within one week.

In the child the basal rate is of no value under the age of eight years but here we have several diagnostic aids. Probably of most importance is the retardation of the appearance of ossification centers and spiphyseal unions. Other aids which will probably be of value are the response of cholesterol to thyroxine and to the withdrawal of thyroid therapy. Urinary creatine and serum phosphatase may also prove to be of value in mild hypothyroidism.

Another question to be raised is concerning the etiology of mild hypothyroidism. Our general belief, based on the fact that all such patients respond to thyroid therapy, is that there is a fractional loss of thyroid tissue. But why can the thyroid gland be removed and only a small portion be allowed to remain and still very few develop symptoms? It has been shown that all these glands show some degree of chronic infection. We can now say that there is a partial loss of secretion from the gland plus another unknown quantity which is either the response of the gland to the infection or the result of the infection on the gland.

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exibit a variable delay in the time of appearance and development. Gardiner (32) says that bone age studies of the various ossification centers and epiphyseal unions determine exactly the degree of thyroid retardation.

Our next question is, what centers to x-ray? At birth an x-ray of the knee should show the distal epiphuses of the femur and the proximal epiphyses of the tibia. At one year, the ossification centers of the capitate, hamate, distal epiphyses of the radius and tibia and the epiphyseal head of the humerus and femur should be present. At three years, the triangularis and epiphyses of the phlanges and the metacarpal centers should appear; at four years the lunate; at five years, the trapezium and scaphoid; at six years, the distal epiphyses of the ulna; and at ten years, the pisaform. Many other such illustrations may be found in any chart on the normal time appearance of ossification centers and epiphyeal unions. We should, therefore, get roentgenograms of the shoulder, hip, knee, hand or foot depending on the age of the child.