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Subclinical hypothyroidism :and its relation to obstetrics and gynecology

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Subclinical Hypothyroidism and Its Relation to Obstetrics and Gynecology

by

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Contents

Introduction

Subclinical hypothyroidism is not a condition which causes death, or even much disability, but it does rob life of much of its zest and makes the preformance of ordinary tasks an almost impossible effort. Therapeutically it is one of the most gratifying conditions in all the practice of medicine according to Fortune (17).

The term subclinical hypothyroidism was chosen because it has came into use the last two or three years. I think it is better term than mild hypothyroidism, thyroid deficiency and hypothyroidism without myxedema. Throughout this thesis I shall use the term hypothyroidism meaning subclinical hypothyroidism.

Having came in contact with numerous people who have been suffering from this syndrome I decided that I would write upon it. In my research of material the outstanding fact found was that the majority of the writers make a plea to recognize this syndrome more often than the physician does.

I have limited my subject to the practice of Obstetrics and Gynecology with symptoms found in other fields as a help to diagnosis, because to me the symptoms in obstetrics and gynecology are the most salient complaints of hypothyroidism. They can give the most serious complaints of the disease. I will of course especially in my signs and symptoms have reference to other fields in medicine which should give opening clues to the practitioner as to symptoms found in obstetrics and gynecology.

I will include the treatment in most cases at the end of the symptoms in each case. The treatment is giving some type of thyroid to the patient whether it is the hormone itself or some form of thyroid extract. It is generally governed according to the patients disappearance of symptoms, heart rate, tremor or restlessness, and until the basal metabolic rate does not exceed normal which some authorities like to have as a plus ten.

The history presented deals mostly with pure thyroid deficiency which later has developed into the discovery and recognization of this syndrome.

I wish to thank Doctor Leon McGoogan for his help and services in letting me use some of his own private patients as examples of the different types of symptoms found in obstetrics and gynecology.

History

Thomas Wharton (74), in 1656, in his "Adenograhia" gave the first real account of the gland as to its anatomy. Wharton seemed to be impressed as to the function of the gland in that his drawings showed extreme vascularity of the organ and he went so far as to say it contributes some substance to the blood: to be sure he thought it was a waste product or superfluous humor, but even so the notion is prophetic. The germ of the idea of internal secretion seems to have been in the mind of Theophile de Bordeu (12), who in 1776, set forth his belief that not only every gland but every organ of the body elaborates a specific substance or secretion which passes into the blood stream, and that upon these secretions the physiological integration of the body as a whole depends. The real knowledge of thyroid insufficiency may said to start with Sir Astely Cooper (9), who did thyroidectomies on two puppies in 1836 without, however, discovering anything of importance except that the animals could survive the operation. Other observations made about the same time by T. W. King (38) of Guy's Hospital who observed that in the thyroid, "like all parts of the same class, its nourishment does not seem to be the main intention of its vascular supply":

again, "Whilist the nourishment of a part is indispensable to its existence, the influence of which it exerts upon the circulatory fluids may be more or less needful for the healthful subsistence of the entire animal", and finally, "We may one day be able to show, that a particular material principle is slowly formed, and partially kept in reserve: and that this principle is also supplementary, when poured into the descending cava to important subsequent functions in the course of the circulation.

In 1847 Hugh Norris (54) noted a high incidence of cretinism in a goiterous village in Somersetshire, and expressed the belief that this certinism "is not only accompanied by but in some measure caused by the presence of goiter". Some three years later, the description of the features of two children in whom no thyroid glands were found at autopsy by Curling (10) in 1850, and of another sporadic certinism in England by Fagge (16) in 1871, stimulated the interest of physicians in a disease hitherto not investigated. Fagge regarded, "Wasting of the thyroid body" as the probable cause of cretinism and he predicted with remarkable accuracy some of the symptoms that might result from a deficiency in the secretion of the thyroid in adults. Two years later Sir William Gull (25) reported two cases of the cretinoid state developing in adults. In discussing these cases he expressed the hope that "once the attention of the profession is called to these cases, our knowledge of them will in proportion improve". Ord (57) in 1878, being impressed with the mucin deposits in the subcutaneous tissues of adults, named the disease Myxedema. Next came the more or less simultaneous discussion by Reverdin (60) 1882 and of Kocher (41) 1883 that a like syndrome follows complete operative removal of the thyroid in human beings, or as Kocher called it, cachexia strumipriva. This led Felix Simon (66) in 1883 to suspect the existence of a common condition probably a causative factor, in myxedema, cachexia and cretinism as being the loss of function of the thyroid whether operable or otherwise. Finally the investigations of the committee appointed in 1883 by the Clinical Society of London (61) showed that the disease is caused by changes of a destructive nature in the thyroid gland.

Immediately after this discovery of the cause, it became obvious that successful treatment depended upon supplying thyroid substance from an external source. Thus substitution therapy followed in short order. Victor Horsley (33) in 1890 suggested the implantation of thyroid tissue, and the same year Bettencourt and Serrano (7) reported the relief of symptoms by the graft of a half a sheep's thyroid under each breast. In 1891 Vassale (69) reported the prevention of cachexia strumpriva in dogs by intravenous injections of an extract of their own thyroids. Murray (49) conceived the idea of making an extract of sheep's thyroids for subcutaneous injections and in 1891 he began treating a patient with myxedema with injections. Fox (18) and MacKenzie (50) independently of each other, in 1892, began the oral administration of thyroid preparations. Both of these last writers, it is interesting to note, describe what clearly were thyrotoxic symptoms when the dosage was to large. Thus the recognition of a syndrome due to thyroid lack bore fruit first, and the cure thereof by the giving of the gland, and second, the crowning achievement twenty years later, in the isolation of the active principle itself, the horomone or antacoid, thyroxine, by Kendall (37) in 1915.

Physiology

According to Wharton (73) the chief function of the thyroid gland is to regulate the speed of the metabolic processes of the body. He continues that this is accomplished largely by the thyroid hormone acting as a catalyst, sensitizing the body cells to the sympathetic stimulation. The thyroid adrenals, and sympathetic nervous system act together. The sympathetic and parasympathetic systems are antagonistic. The activity of an organ, or of even the entire individual, depends upon which is the stronger system. Thyroid activity accelerates the sympathetic system, therefore, most of the symptoms ascribed to the hyperthyroidism are really an expression of hyper-activity of the sympathetic nervous system. Usually the converse is true, in that the parasympathetic system is predominant in hypothyroidism. This is an agreement with majority of authors upon action of thyroid.

Oxygen consumption is increased by the action of thyroid extract on the sympathetics. The thyroid hormone provides the skin with adequate amounts of water, fat and carbohydrates, regulates activity of sweat glands, stimulates the heart rate, regulates secretion and motility of the gut. Hypothyroidism or increased vagus activity results in hypersecretion and hypermotility; these in turn account for symptoms of spastic colon, mucus in the stool, flatulence, and constipation, unless they are counteracted by other influences. Metabolism of proteins, fats and carbohydrates, gaseous exchange and water balance are all increased by the thyroid hormone. Thyroid extract is said to act upon the tissues producing an increased rate of cell differentiation, in contrast to the pituitary which hastens cell multiplication. Anemia, which occurs in hypothyroidism, probably because of decreased oxygen consumption and consequently a decreased need for red cells to carry this gas.

The inter-relation of the thyroid and other endocrine glands is acknowledged. In one association they may be complementary, while in another they may be opposed. Eidelsberg (14) has shown that with other endocrine glands, the thyroid control the sex development and characteristics, controls sugar metabolism, detoxifies the end products of metabolism and of infective toxins, controls the development of osseous and nervous tissues to some extent.

The thyroid has a reciprocal influence upon the adrenals and gonads which may be direct, or, more probably, indirect through the pituitary gland. Enlargement of the thyroid gland and occurs with increased demands made upon it during puberty, menstruation, pregnancy and the menopause.

Wharton (73) stated that the thyroid hormone also produced an increase rate of cell differentiation and Hertoghe (30) wrote in 1915 that the secretion of the thyroid plays a part in both (a) building up of the cells, that is to say, the formation and growth of the tissues, and (b) that it regulates the destruction of the albumen molecule, and governs the processes by which waste material resulting from the incessant regeneration of the organs, is eliminated.

Hertoghe went so far as to say that having once determined the part played by the thyroid gland in normal economy, it should be possible accurately to define the symptoms which would result from diminution of its secretion in varying degrees. Unfortunately, however, that is a point at which we have not as yet arrived. He also noted, as a way of demonstration, that a child with thyroid insufficiency ceases to grow but continues to grow when thyroid is given.

Hartsock (28) says that thyroid insufficiency causes incomplete oxidation in the metabolic processes of almost all the cells of the body. Inadequate oxidation results in disrupted cellular function and chronic fatigue. The first affects usually manifested by symptoms referrable to any particular system accounting for multiplicity of symptoms included in different cases.

Wharton (73) goes on to say that the pituitary gland produces a thyrotropic hormone which stimulates thyroid activity, resulting in hyperplasia of the thyroid, increased metabolism, excretion of calcium and creatinine, and an increased level of the blood iodine. Any influence of anterior pituitary on metabolism, according to Higgins (32) is probably through thyroid, Higgins also, found that suprarenal insuffiency may lower basal metabolism. Experimental evidence, the later authority said, seemed to support the view that castaration tends to lower the metabolism, probably through suppression of thyroid activity.

Finally in relation to the ovaries Glober (23) thinks that the thyroid in some way or another improves the germ plasma of the ova. Thus, if a patient has low metabolism the adequate amount of thyroid is not present to keep the germ plasma of the ova.

Pathology

Simple goiter according to Seward (64), Kimball (40) Warfield (71) and many others is associated with hypothyroidism. Russell (62) and Vis (70) also write that simple goiter is due to hypothyroidism. The later two writers think that the gland, unable to secrete sufficient thyroxine, will eventually become hypertrophied in some sort of an effort to make up for the deficit of thyroxine.

In 1883 the committee of London Clinical Society (61) showed that the disease is caused by a destructive nature in the gland. They were investigating the cause of myxedema. This destruction they thought was the substitution of delicate fibrous tissues for proper glandular structure. Barr (2), in his research on fibro-cystic goiter that the thyroid became the store house for calcium rather than iodine, and that the paraenchyma degenerates and was replaced by fibrous tissue. Pearce (58) in his article believes that the functional strain incident to long continued hypothyroidism is very 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.

Some of the above writers also have observed arthritic changes, arterial-sclerosis, etc. which leads Hartsock (28) to say it is due to the increase blood cholesterol and nephrotic changes in the kidneys. Thompson (67) found that primary hypothyroidism produces replacement of the normal gland tissue by a "scar tissue", but that in secondary hypothyroidism the gland maybe of variable size, the epithilium flat or cuboidal, and the acini filled with colloid. Barret (3) called attention to the effect on the nervous system, but from more of a functional relationship than organic, and Brown (6) emphasized the effect of long continued hypothyroidism on the gastro-intestinal tract.

Signs and Symptoms

The signs and symptoms which form the clinical picture are many and greatly varied. Those of the reproductive organs are as follows: amenorrhea, menorrhagia, or metrorrhagia, oligomenorrhagia, sterility, and disturbances of pregnancy such as miscarriage, abortion, toxemias, hemorrhages and troubles with lactation. There is also a syndrome connected with menopause which the thyroid is at fault.

Some of the symptoms and signs to be noted with reference to subclinical hypothyroidism other than its relation to reproductive organs, according to Marr (46), Vis (70), McLester (53) and others are as follows: dry and thickened skin, slow pulse, dryness and thinning of hair, constipation, gastro-intestinal disturbances, fat pads, narrowing of palpebral fissures, insomnia, pallor, anemia which is secondary, sensitiveness to cold, muscular and rheumatoid pains, headaches, retarding healing of skin lesions, dermatological conditions, disturbance of conduction mechanism to extent that complete heart break may result, tingling and numbness of fingers, breathlessness, and the blood pressure is usually low. The systolic pressure maybe 100 or less. A constant and striking feature is the low pulse pressure. McLester (53) thinks of all these the salient characteristic is the lack of endurance. These people are unable to stand any sort of strain, physical or mental. While they offer all sorts of complaints, to the observant doctor it is evident that easy fatigue troubles them most, and chronic nervous exhaustion is frequent diagnosis when subclinical hypothyroid should be thought of. Of course all of the above will not be present and even one or two may go along with the reproductive symptoms and signs. With any of these signs a basal metabolic rate should be done with the range being below zero found.

Diagnosis

The diagnosis is made in this disease by the signs and symptoms present with the help of laboratory procedures. A low basal rate is very diagnostic. A quick way to estimate the basal metabolic rate according to Gale and Gale (20) is to take the pulse rate plus pulse pressure minus 111 equals estimation of rate. This will give a bedside estimation and the results are open to a ten percent error in about half of the cases. Other laboratory procedures that are of help are; blood cholesterol determinations, glucose tolerance test, and iodine tolerance tests. These will be taken up under laboratory procedures. Another test that will help in the diagnosis is the therapeutic response to thyroid medication.

Differential diagnosis should be made from hypo-ovarianism, hypopituitarism, hyposuprarenalism, and starvation and other diseases. Hypo-ovarianism is usually due to the deficiency of ovarian function. This ovarian function may be caused by the retardation of growth and of secondary sexual development. The fat that is generally present is usually located with dorsal padding of the hands, pelvic girdle obesity, with forearms and legs comparatively free from fat. In hyposuprarenalism the basal will not be so low, the fat will generally be located around the shoulder, neck and trunk. The extremities are free of this fat. The other diseases that may give a low basal will be taken up under interpretation of basal metabolic rate.

Laboratory

The use of the laboratory is of great help in diagnosing this disease. The greatest help is, of course, the Basal Metabolism machine. This machine is usually of the Benedict-Roth variation. This is a closed circuit respiration apparatus. From these readings a calculation of the basal metabolic rate can be estimated. Almost every physician has one of these in his office or has one available. The method depends upon the volumetric measurement of oxygen absorption by the subject, by recording the shrinkage of total volume of gas in a closed system into which the patient breathes, and from which the carbon dioxide which he contributes is removed. The shrinkage in volume, therefore, actually equals the oxygen absorption. Since the gas is measured volumetrically, corrections for temperature and barometric pressure have to be made. Other corrections have all been placed in convenient tables so that all labor of arithmetical calculation has been eliminated and conversion of oxygen into calories becomes very simple. Basal oxygen absorption is what is actually determined and is what we refer to as basal metabolism.

Secondary anemia will be found in a majority of the patients according to Tompkins, Brittingham and Drinker (68). A blood count is generally taken in working up a patient but one is indicated if a patient is found to have anemia. If found it should be corrected by some form of iron.

The blood cholesterol level is markedly elevated in subclinical hypothyroidism according to Hurrthal and Hunt (36), and Gilligan, Volk, Davis and Blumgart (22). In cases where a basal metabolic rate is impossible this procedure should be looked into. In fact Hess (31) thinks the blood cholesterol level is much more important and a better guide than the basal metabolic rate. McGee (51), however, thinks that the first reading is not essentially correct and more readings should be run before a true reading is established.

There is an increase in the glucose tolerance test in subclinical hypothyroidism according to Coggeshall and Greene (8). This is thought to be due to the increase of the carbohydrates in the liver and the thyroid is not depleting and metabolizing them as it normally should.

Hypochlorhydria is a tendency in hypothyroidism and should be checked when the patient presents herself. If present some type of treatment should be followed.

A mild albuminuria according to O'Keefe (56) and other observers may be present and sometimes leads to a diagnosis of nephritis when the subclinical hypothyroidism is at fault.

There is an increase retention of the iodine in the iodine tolerance test of 20 to 40 per cent as was shown by Elmer (15) in 1934. Watson (72) in 1936 developed a technique a little different from Elmer's. He gives 250 gr. of iodine per kilogram of body weight in 15 cc. of .85 per cent sodium chloride solution. Blood iodine estimations are made before the test, after five minutes, two hours, four hours, and six hours. No food is allowed during the test. He found 9 to 23 per cent retention of iodine after six hours in thyrotoxicosis and hypothyroidism an increased retention.

Interpretation of Basal Metabolic Rate

Interpretation of this reading is of importance. The reading should be in the realm of the clinical symptoms in that they should in some way coincide. If the reading is just below zero, say a minus four, the patient should be treated as a mild hypothyroid if the clinical symptoms are present. Litzenberg (42) and a great many of the writers use a minus ten and as the point to call a patient a subclinical hypothyroid, but I think that it depends upon the clinical symptoms present and that no great difference can be made between a minus ten and a minus five.

Some of the following diseases or syndromes according to Gardiner (21) that may give a low basal metabolic rate.

1. Primary hypothyroidism with or without myxedema.

2. Secondary hypothyroidism

   a. Anterior pituitary lobe failure
      (Frohlich's syndrome or Simmonds disease)

   b. Adrenal cortex failure
      (Addison's disease and subclinical states of adrenal insufficiency)

3. Miscellaneous disorders

   a. Mal-nutrition

   b. Nephrosis

   c. Anemia

d. Menstrual disorders

e. Sterility and habitual aborters

f. Vitamin B deficiency

g. Following iodine adminstration

h. Certain diseases of the central nervous system

i. Unclassfied disorders as chilblain, dry skin, and so forth

The majority of the miscellaneous disorders have been taken up in this thesis as symptoms of subclinical hypothyroidism.

Puberty

The thyroid plays a great part in the growth of a child but when that child reaches that period of life called puberty, a sub-clinical hypothyroid patient will find that she will have a great deal of trouble. At this time there is supposed to be an enlargement of the thyroid gland. This was noted by Marine, (45) and many other observers, who states that it is physiological. However this is at times a turning point towards a permanent hypo or hyper-thyroidism. Thus it is possible that the thyroid may be at fault and not enlarged enough as it should, or not enlarged at all.

Some of the most common symptoms noted here are amenorrhea, irregularity and scanty periods. After all other possibilities have been ruled out, a physician should suspect that the thyroid is at fault. The patients may start menstrual peroids but in a period of time have symptoms of amenorrhea, scanty or irregular peroids.

The following is a case showing a patient who started at age 15 to menstruate and was regular every 28 days, flowing moderately for 5 days. When she reached 17 years of age, she went 8 months without having any periods what so ever. Her physical was negative throughout. A basal metabolic rate was done and found to be minus 20. She was placed on thyroid gr. 1 t.i.d. with her next period being in 2 months, with moderate flow and no pain. She has been normal since and is still taking thyroid.

Granger (24) noticed this in 1915 when he treated a girl of 19 years whose flow was rare and over long intervals and then insufficient in amount. She also had an infantile vagina. He treated her with thyroid extract gr. 2½ and she started to menstruate and became regular.

Mid-Life

During a woman's life from puberty to menopause she passes through a great deal of problems which are severe if the patient is a sub-clinical hypothyroid. In relation to reproductive organs she has the following to contend with: amenorrhea, menorrhagia, metrorrhagia, oligomenorrhagia, hemorrhage, sterility, disturbances of pregnancy such as miscarriage, abortion, and toxemias. Also lactation problems can be found in this group.

Amenorrhea

Amenorrhea, absence of menses, is a common symptom in a patient who has sub-clinical hypothyroidism. The usual physical examination shows the patient to be essentially negative; that is no pathology is present that will cause the amenorrhea.

This symptom generally leads the physician to ask for a basal metabolism test. This is generally found to be minus.

Haines and Mussey (27) in fifty cases of sub-clinical hypothyroidism with amenorrhea in which thyroid therapy restored normal catamenia in 29 patients. Thyroid therapy produced slight improvement in 7 patients and thyroid therapy produced no result in fourteen patients. The average basal metabolic rate in this group was minus 18, with maximum minus 11 and minimum minus 30.

Haines and Mussey (26) had 27 patients with amenorrhea. Twenty-two had amenorrhea from two months to four years. Four patients had abnormal profuse menstural bleeding when it occurred. Basal metabolic rates had a distribution in six, from minus 11 to minus 15, in 16 from minus 16 to minus 20, in 4 from minus 21 to minus 25, and one case minus 27. They reported a 59 per cent cure with thyroid treatment.

Dodds and Robertson (13) in England, had five cases of what they called secondary amenorrhea. The patient presented none of the usual features of generalized disorders known to cause amenorrhea. In all the patients the basal rate was greatly diminished. Treatment with thyroid extract raised the basal rate to normal and menstruation at same time reappeared. The same authors go so far as to say that the condition may not be recognized until the basal metabolic rate is measured.

Meissner (48) reports 9 cases in which amenorrhea was the chief symptom and upon having basal metabolic rates run they were found to be low. With this finding they were put on treatment with disappearance of symptoms.

The following are some case histories that help to show how the treatment of amenorrhea in the subclinical hypothyroid patient may help that patient. The patient, age 36, came in with amenorrhea for 10 months. Her periods before were regular with 28 days and lasting six. Her blood pressure 110/60.

She was loggy, tired easily and wanted to sleep as much as possible. The basal metabolic rate was found to be minus 12. She was put on thyroid extract gr. $\frac{1}{2}$ t.i.d. with regular period coming at the normal time. She is normal now with the taking of the thyroid.

The patient's last menstruation was three months ago. Her uterus is small. Her menses started at 13 and regular every 34 to 35 days lasting 5 to 6 days. One month later she had some spotting for two days.

Two months later no menses. Three months later spotting again. At this time the patient was tired and unable to be as active as she formerly was. A basal metabolic rate was done and found to be minus $10\frac{1}{2}$. She is now on thyroid extract gr. $\frac{1}{2}$ b.i.d. with relief of symptoms.

Menorrhagia

Menorrhagia, abnormal profuse menses, is also a common symptom that the physician will contact in this clinical entity. Breckenridge (5) reports 17 cases of menorrhagia. Thirteen had menorrhagia, with two of irregular menstruation which was shortened and two of irregular menstruation which was lengthened. He had 100 per cent cure of the cases under thyroid extract treatment. He also pleas that subclinical hypothyroidism should be excluded before resort is made to cureete, radium, X-ray or abdominal section.

Haines and Mussey (27) reported 15 cases of menorrhagia. They produced no result with thyroid therapy in 4 cases, slight improvement in 3 cases and restored normal catamenia in 8 cases. Twelve of these patients noted improvement in general health. The average basal metabolic rate was minus 17.3 in those who improved and minus 27 in those who did not improve.

Wharton (73) had six cases in which menorrhagia was the important and prominent symptom. He even goes so far as to say that this symptom alone should suggest lack of thyroid to the alert physician. Under treatment all of these 6 cases improved and eventually became normal. Winkelstein (76) also had three cases of menorrhagia in women who were sterile and these eventually became normal with treatment and the patients also became pregnant. Shute (63) strongly urges more attention to this relationship of thyroid lack to menorrhagia.

The case to be presented is common to the symptom of menorrhagia. The patient, age 31, had always had irregular periods. They come from 4 to 6 weeks and lasted 6 to 7 days and were quite profuse. She had a baby in January with next period following in 9 weeks, then 5 weeks, lasting 5 days, then 5 weeks lasting 6 days and now none seven weeks later. She was quite nervous and perspired easily. Her appetite has been good but she could not gain. Pelvic examination proved to show no pathology. A basal metabolic rate was done on two occasions. The first was minus 8 and the second minus 13. She was placed on thyroid extract gr. 1 t.i.d. with period coming every 28 days and no spotting present. The nervousness and perspiration also disappeared. She is now on thyroid gr. 3 every other day.

Another case of a patient who had taken thyroid extract but stopped with returning of menorrhagia. Patient was put on thyroid 6 years before, due to low basal metabolic rate. She was put on thyroid gr. 1 t.i.d., periods became regular and the patient also lost 50 pounds over 3 years. She stopped the thyroid 3 years later with return of symptoms. The patient had a basal metabolic rate of minus 10, and with the above symptoms was put on thyroid extract gr. 1 t.i.d. with removal of menorrhagia and regularity established.

Fortune (17) reports two patients with convulsive siezures resembling epilepsy which were associated with each menstrual period.

Bell (4) reports cases of mastidynia, or pain in the breasts, which have been severe that it incapacitates the patient is often associated with menorrhagia. Upon treating the menorrhagia the severe mastidynia was helped. In some of his cases he did not have the menorrhagia but upon giving treatment in the form of thyroid extract at about the twenty-first day of her cycle the pain was greatly relieved.

Hemorrhage

Salzman (63) was the first to write about this subject in this country. He quotes an article by Sehrt (Müchen Med. Wochensehr, 19, vol Lx, p. 661). Sehrt demonstrated that marked alteration of the coagulability of the blood in cases of hypothyroidism. He stated his conviction that in certain cases of hemophilia were in reality cases of hypothroidism. In twenty cases of pure hemorrhagic disease of the uterus he found that thyroid deficiency was present in thirteen.

Salzman reports a case in which the patient had bled continuously from the uterus for six months. The patient refused operations and everything else. The patient was given thyroid and the bleeding stopped in two days. The patient later stopped the thyroid with bleeding starting again, and upon resumation of the thyroid the bleeding stopped. He later had some cases of bleeding which thyroid helped. Salzman concluded his article by stating that there is a type of hemorrhage from the uterus not caused by a discernable pelvis pathology, nor related to any of so-called hemorrhage states, but due to alteration or lack of one or more of the hormones which control the normal flow of blood from the uterus. This alteration is due to deficiency in the secretion of the thyroid gland and such hemorrhage therefore can be controlled by a judicious exhibition of dried glandular thyroid substance.

Hayd (29) reports a case of fibroids of the uterus in which the patient bled profusely. He gave the patient thyroid and the bleeding stopped. After this the patient had this fibroid removed.

This may be considered a type of metrorrhagia or menorrhagia, but believe that this type of hemorrhage is much more serious than the latter two so have put hemorrhage under a separate heading.

Sterility

Sterility is a common cause for the patients to come to the physician and this sterility in some of the cases can be traced to subclinical hypothyroidism. Litzenberg, (42) in 1926, was the first to mention sterility in women with subclinical hypothyroidism. He opens his article in saying that "it has been known for years that marked disturbances of the function of the thyroid gland cause sterility, but the possibility that milder alterations of that function may also affect fecundity has been given scant attention." He approached the question from two angles: first, what proportion of sterile women have a low basal metabolic rate and can any of them be relieved by treatment, and second, what proportion of women with a low basal metabolic rate are sterile. He reports 69 consecutive cases of sterility of which twenty-two had a basal metabolic rate of minus ten or below. Of these twenty-two, eighteen received carefully supervised thyroid medication of whom six, or 33 1/3 per cent became pregnant with in a short time after beginning treatment, usually within two months.

Litzenberg's conclusions are interesting. 1.--

The relation between the thyroid gland and the ovary is well known. 2.--Myxedema is certainly a cause of sterility. 3.--Lesser degrees of hypothyroidism are also a cause of sterility. 4.--A normal basal rate is apparently necessary to conception and to a normal continuance of pregnancy. 5.--Properly supervised thyroid medication will restore the basal metabolic rate to normal and in some cases result in conception.

In 1929, Litzenberg and Carey (43) ran a series of 2,500 consecutive determinations of the basal metabolic rate in all types of patients, of whom 758 had a rate of minus ten or lower. In this group of patients, he had 52 sterile women who had low basal readings. Seventeen, or 30 per cent, conceived under treatment, one woman becoming pregnant four times and another twice, one woman had twins and two aborted (the treatment having been discontinued after conception), giving them a result of their treatment sixteen babies. Thus, they come to the conclusion that the basal metabolic rate should be taken in all cases when no other causes of sterility can be found, either in the wife or her husband. They conclude their article in that if the statement be true that the reproductive cells are more subject to deleterious influences than any other cells in the body, that their findings are not difficult to understand.

Mays (44) says that the patients with thyroid sterility may present either hypo or hyperthyroidism. However, the majority of these cases present mild subclinical pictures of hypothyroidism. He warns that we must not look for frank cases of dysfunction of the thyroid in sterility, but to investigate our cases more thoroughly before giving them up for lost. Novak (55) also makes the same plea for sterility in that a thorough study of any case of sterility must embrace a study of thyroid, especially by basal metabolic rate determinations, in both the wife and her husband. Novak also thinks the thyroid may have its effect upon the germ plasma, thus the maldevelopment of the ova and in the male sperm.

Winkelstein (76) reports sixteen selected cases out of seventy-one. No patient was considered sterile until at least one full year had elapsed after marriage, during which time, notwithstanding frequent sex relations and absence of contraceptive devices, pregnancy had not occurred. Of the sixteen cases, nine conceived, eight becoming pregnant within six months, and seven remained sterile. Of the seven remaining sterile their basal metabolic rates averaged plus nine, with the lowest being plus three and the highest plus 14 per cent. In this group their was no evidence of thyroid dysfunction. He concludes his study with saying that the effect of thyroid, as an adjuvant or curative measure for sterility, was only demonstrable where a definite lack of thyroid was present. Likewise, where no deficiency in thyroid metabolism existed the addition of this drug was of no apparent value.

The following is a case to illustrate the main complaints of a patient that is sterile. The patient age 26, has been married for three years with the result of no pregnancies. She in the past has had irregular menses, sometimes going six months before a period. Pelvic examination showed no pathology. The basal metabolic rate was found to be a minus 18. She was put on treatment of thyroid extract gr. $\frac{1}{2}$ t.i.d. with conception about seven months later and delivery of a child.

Pregnancy

Hertoghe (30), in 1915, said "many women who have taken thyroid extract with view to reduce their obesity have been surprised by becoming pregnant in the course of this medication and this unexpected result is due to the thyroid inhibition of menstruation." This statement is very true in pregnancy and sterility and has proved over and over again in the literature up to the present date.

During pregnancy the normal increase of the basal rate is between fifteen and thirty per cent with the greatest increase in the latter months. This has been shown by Wilts (75), Davis (11), Frazier and Ulrich (19), and Brown (6). Brown (6) and Purdy (59) go so far as to say that any case not showing this physiological increase is at least one of potential subclinical hypothyroidism. If this does not occur normally one should give thyroid to insure the continuance of the pregnancy and also to insure a normal child without cretinism. Brown has proved this to be true by ossification centers of certain bones. They go so far as to say that cretins have hypothyroid mothers.

O'Keefe (56) believes pregnancy and its results undoubtedly play an important part in the life of the thyroid. He goes so far as to say that the physiological enlargement of the thyroid in normal pregnancy may go the way of the hyperthyroid of puberty. However, if there is an interruption of pregnancy before maturity, there is a tendency toward hypothyroidism. This in turn is even more marked if the interruption is complicated by infection. Conversely there is a greater tendency toward miscarriage among hypothyroid patients. So many cases have dated their hypothyroidism symptoms from pregnancy and its complications that it makes O'Keefe believe that repeated pregnancies, septic abortion, uncomplicated miscarriages, regardless of the course, will result in decrease function of the thyroid.

Miscarriage and Abortion

Miscarriage and abortions are a very common disturbance complicating pregnancy in patients suffering from subclinical hypothyroidism. Some of the symptoms that may bring the patient to the physician along with these are menorrhagia and metrorrhagia and all of the authors and investigators mention this association. The etiology of miscarriage and abortion is thought to be the germ plasma. Huntington (35) believes this to be true. He came to this conclusion after a review of 104 consecutive cases of miscarriage and he says that the deficient thyroid plays an important role.

King and Herring (39) had 150 cases of "missed" variety of abortions in which 61 or forty per cent were subclinical hypothyroids. Of these 61 patients, eleven were multiparas who had had thirteen previous miscarriages. In this group of hypothyroids they had eight abortions, two of these women had adequate treatment, while in six cases the subclinical hypothyroidism was not detected promptly because the patient was not seen sufficiently early and there was little or no treatment and abortion occurred. For the other patients of this group the diagnosis was made early and treatment initiated early with the pregnancy going to term. They, however, had eleven cases of threatened abortion in this group. In their study they felt that the fetal loss would have been greater, especially in some instances where the basal metabolic rate was low. They concluded their article in making a plea that it is logical to determine the basal metabolic rate as a routine in early pregnancy and to institute proper treatment when the rate is found to be low.

Litzenberg (42) in his articles on sterility mention abortions and miscarriages as a problem of pregnancy. Of those who were sterile twenty-eight per cent had abortions. Fortune (17) and Novak (55) called attention to the habitual aborter in subclinical hypothyroidism. They had numerous cases where they were found to be subclinical and upon treatment delivered viable children. Breckenridge (5) also reports four cases, two abortions and two miscarriages, who when properly treated delivered viable children.

The following is one of Fortune's cases. The patient, age 30, had a history of two previous abortions. The physical examination and laboratory procedures were negative except for a minus 22 basal metabolic rate. These abortions seemed to always come at the beginning of the sixth month. She was placed on treatment at the beginning of the third month with delivery of a normal full term baby.

Toxemia in Pregnancy

There is some evidence that hypothyroidism may have a place in toxemia of pregnancy. Bartholonew and Colven (1) thinks that hypothyroidism undoubtedly plays a part in causing excess hypercholesteremia and that if this is treated by thyroid extract or iodine when indicated may control the excessive hypercholesteremia. They believe that in pregnant women of this particular endocrine type caused by the thyroid, hypercholesteremia renders them potential victims of toxemia. Hypercholesteremia, which most authorities agree is present in subclinical hypothyroidism, to their way of thinking causes a narrowing of lumen of the smaller placental arteries thus rendering these arteries to infarction which in turn causes the toxemia.

Hughes (34) in his study of toxemias has come to the conclusion that pre-eclampsia develops more often in the following types of patients. 1- When the basal metabolic rate was abnormally low during the first trimester and failed to increase during the duration of the pregnancy. 2- When the basal metabolic rate dropped appreciably to a low value and remained at this level throughout the pregnancy. The first series of patients, 550 patients, the prenatal care was thorough and adequate, but the metabolism was allowed to take its own course. In this series pre-eclampsia occurred in 5.2 per cent of the cases. In the second series of private ~~private~~ patients, 558 patients, the same amount of prenatal care was given, but all of the patients with basal metabolism rates below zero were given treatment with thyroid in order to maintain a constant level which was on the plus side. The incidence of per-eclampsia in this group was 2.5 per cent. From these results he felt that it is important to follow the basal metabolic rate from the onset of pregnancy. His conclusions were as follows: 1- That basal metabolic rates indicates that pregnancy has an effect on the glands controlling metabolism and that this is indicated and shown in the first and third trimesters. 2- That giving treatment to those with low rates in the first trimester reduces the incidence of late toxemia fifty per cent, but must be given early in pregnancy.

Lactation

Purdy (59) presents a case of a woman who was carried through her pregnancy on thyroid extract and after delivery lactation came in normal, but when she stopped taking her thyroid extract her milk supply diminished. When she was put back on her former treatment the milk supply was soon back to normal.

Menopause

During the menopause some very interesting changes have been observed. So many women go through menopause without any disturbing symptoms that it is reasonable to conclude that the so-called menopausal symptoms are not due to the dying ovary alone. It is O'Keefe (56) idea that a woman with an otherwise normal glandular equilibrium will pass through the menopause without any disagreeable symptoms, however, if there is a pre-existing subclinical hypothyroidism that woman will have a stormy menopause ranging from severe nervousness to absolute insanity. O'Keefe goes on to say that to explain this belief is purely theory. However, it seems plausible that if a normal glandular equilibrium is maintained to natural menopause the endocrine hormones are able to bridge the gradual break and adjust themselves. Undoubtedly endocrine function does not play the part in a woman past the menopause that it does during the child-bearing age. In a pre-existing hypothyroidism the the thyroid is unable to stand the additional strain, and the already damaged thyroid is aggravated beyond control. Therefore, in severe menopausal changes you will, in his experience, invariably elicit a history of pre-existing glandular disturbances.

Hertoghe (30) also believes that if a person has been suffering from the symptoms of subclinical hypothyroidism before menopause she will have a stormy and intensified menopause.

Bell (4) in his article sums up the menopausal syndrome in that the woman frequently becomes adipose, and with this adiposity are often associated mental apathy and lassitude. These are signs of alterations in the general metabolism, especially in regard to the carbohydrates. He says that this state of affairs is probably brought on in part by the pituitary; but the thyroid also maybe undergoing atrophic changes. In the treatment of this condition thyroid gland appears to have a better effect than that of the pituitary. The scanty flow or the profuse flow associated in these cases are helped by the administration of thyroid treatment.

Hayd (29) in certain pelvic conditions where congestions are common gives thyroid extract with disappearance of the following. Where the parts have a distinctly blue color, the cervix deeply ingested with blood, and the veins of the broad ligament distended and varicosed, with a general sagging of the pelvic contents.

The following is a case taken from O'Keefe's (56) article. The patient, age 44, has scanty periods are very irregular and associated with extreme nervousness. She had an abortion about ten years ago. Up till the time of her abortion her menses were regular and lasted 3 to 4 days. After that they began to diminish and the patient became depressed and went so far as to have hallucinations. Her skin was dry and the pelvis was essentially negative. A basal metabolic rate was determined and found to be a minus 14 per cent. On treatment of thyroid extract the patient improved and went on with her menopause.

McKean (52) had an individual in the late menopausal zone which presented a moderate hypertensive state and upon a basal metabolic rate was found to have thyroid lack. She was placed upon therapy and the pressure fell within normal limits and remained there so long as the therapy was continued, but was found to rise when the therapy was discontinued.

Conclusions

The following are the conclusions to this thesis:

1. That subclinical hypothyroidism is very prevalent today.

2. That subclinical hypothyroidism is not recognized as often as it should be.

3. That subclinical hypothyroidism is much more common than myxedema and cretinism.

4. That subclinical hypothyroidism can assume symptoms of almost any disease.

5. In the female subclinical hypothyroidism plays an important role as to her comfort and well being.

6. That mensturel disturbances, hemorrhage, sterility, maintenance of pregnancy, abortions, toxemias and other female disorders can be traced to subclinical hypothyroidism.

7. That the main diagnosis in this disease is a balance between the symptoms and signs and the laboratory procedures.

8. That the main laboratory procedure is the use of the basal metabolism machine.

9. That the treatment in subclinical hypothy-

roidism is the giving of thyroid in some form or other in order that the patient will have a plus metabolic rate.

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