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Thyroid disease and pregnancy

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INTRODUCTION

It was recognized by the ancients that there is a relationship between the thyroid gland and the sex epochs of the female. The thyroid has been known for centuries to undergo hypertrophy during pregnancy. The Romans were familiar with this phenomenon and there are references to it in all the later literature.

It was not, however, until the appearance in 1874 of Sir William Gull's paper "On a Cretinoid State Supervening in Adult Life in Women" that we began to really learn something of the function of this gland and it's relation to the female. All will agree that much progress has been made during the fifty years that have followed it's publication. While today, we can speak with pride of the fact that we can prevent endemic goiter and cretinism, yet it must still be admitted that our knowledge of the role of the thyroid gland in human physiology is still quite meager.

We are, at this time, apparently entering into an era of endocrine medicine. Medicine, as all other things, has advanced in waves. Just as in the past we have passed through a so-called period of focal infections, now we are finding ourselves in the midst of a great deal of research on the glands of internal secretion. As is to be expected, the pendulum of activity will swing from one extreme to the other before a happy medium will be discovered.

Since the female sex mechanism is thought to be the scene of greatest hormonal activity when it passes through it's various cycles and especially during pregnancy, and since the thyroid gland is probably the one internal secreting gland of which we

know the most, hence it was thought fitting and proper that a review of the more recent work on the dysfunction of that gland as related to pregnancy be made. We have, accordingly, attempted to review the most of the more recent work published especially in the past fifteen years. This must of necessity be limited in general to the English journals. It is not our purpose to summarize all that has been written on this subject during this period, but instead to give a comprehensive survey of the subject.

In this paper we propose to consider thyroid disease under two great headings of 1) hypothyroidism and 2) hyperthyroidism. A great deal more has been written on the latter phase than on the former. This is perhaps due to the fact that the more serious emergencies are associated with the latter. There will be, no doubt, more to be said on the relation of hypothyroidism to pregnancy than we suspect at this time. Some excellent reports have already been made on this condition.

Much of the generalities connected with the thyroid must be omitted since a paper of this kind must of necessity be limited in its scope. Hence the anatomy of the thyroid gland and the microscopic pathology is omitted and only the physiology and pathological changes incident to pregnancy are given.

PHYSIOLOGY OF THE THYROID

According to Mayo (33) the function of the thyroid gland comes under four great headings. Its first function is morphogenic which is shared with the pituitary, the thymus, the suprarenal cortex and the testicle. This action is not exerted to the same extent on all tissues or on all organs. This action also has an effect on the development of the nervous system. Insufficient thyroid secretion interferes with the proper development of the nervous system much more than inadequacy of any of the other glands mentioned.

The second function of the thyroid gland is to regulate the normal processes of the various physiologic mechanisms. This action is exerted by a stimulating substance which is the most powerful excitant of nitrogenous and respiratory exchanges. This action is essentially catabolic and is therefore antagonistic to the first action which is essentially anabolic.

The next function of the thyroid is to neutralize certain toxic products of normal metabolism. It is believed that this action may be due to its stimulant action, but is probable that both processes, stimulation and neutralization, go on together.

The fourth function of the thyroid is that of defense against bacterial invasion. This view is regarded by Mayo (33) as being theoretical, but of course the thyroid plays an indirect part in the struggle against infection because its secretion participates in most of the vital functions.

According to Marine (32) who has done extensive work on the thyroid gland, the major function of the thyroid is to provide

a means through its iodine containing hormone for maintaining a higher rate of metabolism than would otherwise exist and for varying this rate. The gland is not essential for the vegetative life of adult animals. In the young it is necessary for growth and differentiation. Thyroid removal in animals causes a lowering of metabolism (measured as heat production) as much as 40 per cent, which is comparable to the maximum decrease seen in the severest forms of human myxedema.

That the thyroid gland provides the means for varying the rate of heat production can be shown in several ways. (32) First it has been shown in animals that sufficient but sublethal injury to the suprarenal glands causes a marked chronic increase in heat production, provided the thyroid gland is intact, but thyroid removal prior to injuring the suprarenal glands greatly reduces or abolishes the increase. Secondly in all animals there is a marked rise in heat production during pregnancy and lactation. Thyroidectomy in the rabbit abolishes or greatly reduces this normal rise in metabolism. (Marine) This relation of the thyroid to the increased heat production of pregnancy and lactation probably has an important bearing on thyroid enlargements (goiters) occurring during pregnancy and lactation and will be discussed in greater detail later. Thirdly the administration of thyroid glands causes a striking increase in heat production. Fourthly thyroid removal causes a decrease in heat production. These facts constitute sufficient evidence that the thyroid plays an important part not only in the maintainence of a given basal rate of metabolism but also in providing a means, through fluctuation in its activity, for varying this rate.

The functional activity of the gland is controlled chemically mainly through the blood stream but perhaps also indirectly through the sympathetic nervous system. The functional capacity of the gland is not impaired by sectioning of the nerves running in the adventitial coats of the vessels and encasing the gland in paraffine. (32) Marine has transplanted thyroid tissue to other parts of the body and showed that the autotransplanted gland has the same capacity for hyperplasia, involution and storage of iodine as is exhibited by the normal gland.

Prior to birth the fetal thyroid is dependant on the thyroid of the mother. The thyroid of the fetus contains little or no iodine. At this period of life the thyroid is more cellular and the vesicles smaller and fewer, containing less colloid than in later years. Apparently the fetal organ does not function to perfection until some months after birth. This is due to the fact that the maternal thyroid continues in a state of heightened activity throughout the earlier months of lactation, during which time the infant derives from its mothers milk, part at least, of the thyroid secretion which it needs. (33)

With the cessation of suckling, according to Mayo, and with the commencement of taking more solid food, the thyroid apparatus of the child begins to act for itself, elaborating it's secretion from the raw materials of the food and responding to every call made on it by the processes of increasing growth and the maturation of the bodily functions.

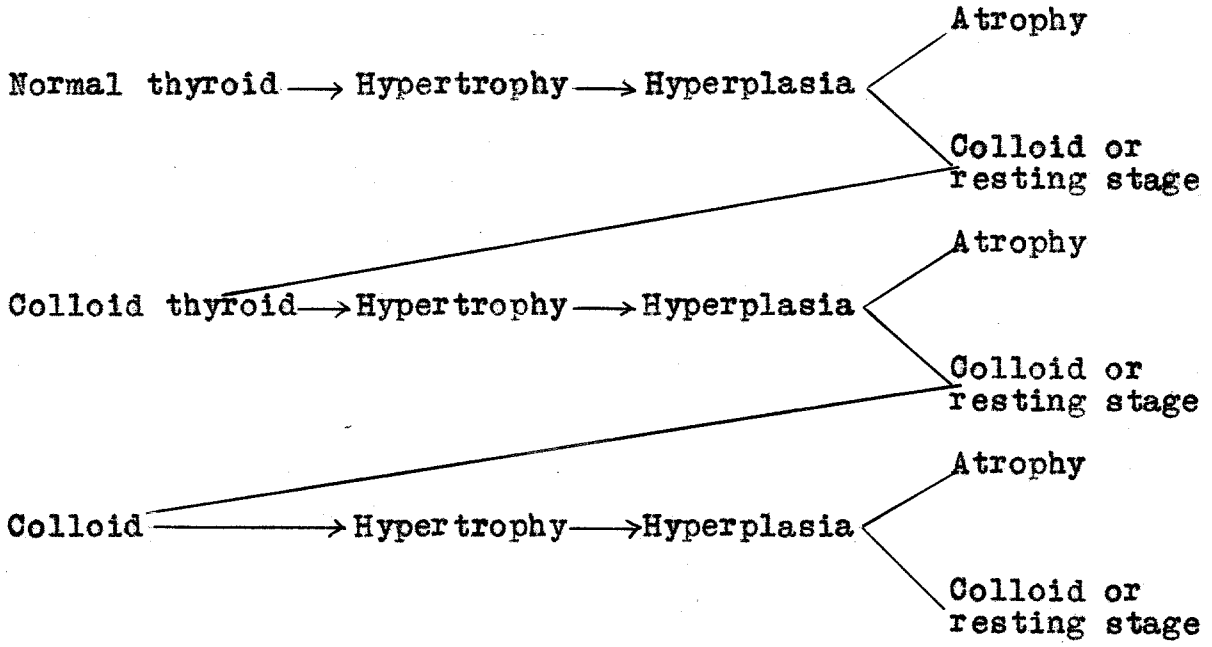
Throughout child life the thyroid is in a state of constant activity which may manifest itself, especially under slight toxic

provocation, in hypertrophy of the organ at about the period of the second dentition. At puberty, also, and with the onset of menstruation, the physiologic capacity of the organ is strained to the utmost, and hypertrophy is likely to occur.

The thyroid gland exhibits great variations in functional activity to meet wide variations in metabolism occurring during the life of the animal, particularly in the female. For example there are variations in season. An increase in the iodine content has been found in the summer and a decrease during the late winter and early spring months. The periods at which enlargement of the thyroid are likely to appear, namely at puberty, during pregnancy and lactation, during the menopause and during protracted febrile reactions, are the periods in which thyroid activity is known to be increased. Marine's (32) classical work has shown that increased thyroid activity is associated with a decrease in iodine store in the gland, provided the intake of iodine at such times is not correspondingly increased, and if the iodine store falls below 0.1 per cent thyroid enlargement begins. This fact is a point to be borne in mind in the matter of thyroid enlargement during pregnancy and lactation. Further consideration of this factor will be discussed in a later section. The morphologically normal thyroid contains on an average 0.2 per cent iodine. The maximum store is between 0.5 and 0.6 per cent and the minimum store associated with normal gland structure is 0.1 per cent. The thyroid gland is endowed with an enormous capacity for growth, which provides a factor of safety and a compensatory mechanism to meet functional demands. These enlargements of the

thyroid are familiar to all of us as ordinary goiter.

By a series of experiments with dogs, Marine (32) worked out the physiologic cycle of the thyroid on an anatomic basis. This is reproduced below.



This cycle he declares to be the same for all animals including man. The thyroid begins to hypertrophy when the iodine store falls below a given level, and continues this hypertrophy and hyperplasia until exhaustion atrophy or recovery supervenes. By recovery is meant the return to the colloid or resting stage, and not the disappearance of the thyroid enlargement. The colloid gland is the condition nearest to normal both anatomically and chemically that a gland can assume which has once been in the state of active hyperplasia, and such colloid glands are capable of all the reactions of a normal gland. They can repeat the cycle many times. Marine has produced this in dogs experimentally These cell changes are not specific for any clinical disease, but

occur in response to any stimulus for increased thyroid activity. This may be a relative or absolute lack of iodine, or the increased needs of the animal for thyroid activity during the various physiologic periods.

Thus we see that the thyroid gland has a multiplicity of functions and goes through a definite order of changes when conditions are such that the nutrition of the gland is altered. We are now ready to consider the activity of the gland in normal pregnancy. Obviously the scope must be broad.

THE THYROID IN NORMAL PREGNANCY

This phase of the paper is most difficult to discuss since it is a matter of controversy as to what constitutes the normal and what is the abnormal. Fall (17) says that a woman on becoming pregnant usually will give evidence of a mild hyperthyroidism if the signs and symptoms are carefully looked for. Nervousness, tremor, vomiting, nausea, weight loss, sweating, enlargement of the gland and sometimes slight exophthalmos are frequently noted. In fact, many of these signs and symptoms have been pointed out by the obstetricians as signs of pregnancy without attempting to explain their fundamental significance.

According to Davis thyroid hypertrophy in women either starts as a congenital defect or begins at puberty or during pregnancy. 41 per cent of 520 pregnant women examined early in pregnancy had some hypertrophy of the gland. He regards this enlargement as usually being slight and transient in pregnancy.

To further substantiate this contention of thyroid enlargement in pregnancy we have the work of Marine. He regards the enlargement as in the nature of a work hypertrophy to stimulate metabolism identical in appearance and so far as we know, different only in degree from that seen in simple goiter. Both of these reactions can be controlled and prevented either indirectly by giving iodine or directly by giving the iodine-containing hormone in physiologic doses. (30)

The basal metabolic rate during pregnancy is a matter of contention also. Plass and Yoakam (39) have conducted a large series of basal metabolic determinations in normal pregnant women with

normal and pathologic thyroid glands. Their findings indicate that the metabolic rate shows an increase during normal uncomplicated pregnancy of approximately 15 per cent, with a fall to normal in the first few days after delivery. They believe that a greater rise with a slower fall to normal suggests increased thyroid activity incident to pregnancy. A small percentage of their cases (20 per cent) with normal thyroids had a metabolic rate which rose above plus 20 per cent. Patients with palpable thyroid disease show a greater tendency toward such high rates, the incidence rising to 35 per cent with small colloid and adenomatous goiters and to 50 per cent in the larger colloid type. This is taken to indicate that pathologic thyroid glands are less able to respond normally to the demands of gestation, but tend to function abnormally and so to produce symptoms of hyperthyroidism.

From their results Plass and Yoakam (39) declare that iodine given prophylactically during pregnancy is apparently unable uniformly to prevent gestational hypertrophy of the normal thyroid gland, but seems to be quite effective in preventing such a change in glands which are pathologically altered when pregnancy begins, and they actually lead to a reduction in the size in certain colloid goiters. It acts very effectively when given to pregnant women to prevent the appearance of congenital goiter in the newborn.

Falls (16) regards the mild hyperthyroidism as judged by the clinical manifestations and basal metabolic rate, as being a not uncommon complication of pregnancy and requires no special treatment. He does regard many of the nervous symptoms seen in preg-

nancy as being probably due to an abnormal activity of the thyroid gland induced by the pregnant state.

In line with these investigations we have the work of Sandiford and Wheeler (42). They conducted a series of metabolic studies on women during pregnancy and menstruation. They also declare that there is a gradual increase in the total heat production during pregnancy but they report a higher figure as the normal rate at term. Plus 25 per cent was set as the normal figure Increase in heat production could be accounted for by the added metabolism of the fetus, placenta and accessory structures and there was no evidence to suggest that there is a change in the actual rate or the intensity of heat production of a unit mass of maternal tissue. Sloan (44) regards a pregnant woman with a normal basal metabolic rate as probably being subnormal.

Stewart and Menne (43) investigated the action of iodine on normal pregnant rabbits. 13 healthy female rabbits were selected, fed with standard prepared rabbit food and housed under careful conditions. They were given varying doses of iodine in the form of Lugol's solution. These doses were calculated according to the physiologic optimum.(0.045 mgm. for human adult in 24 hours) The rabbits were given amounts varying from 0.00065 mgm to 0.00305 mgm or one, two, three and four times the physiologic requirements of iodine. These dosages were maintained throughout pregnancy and lactation. Three of the rabbits (controls) had no iodine. Seven of the 10 became pregnant. Two developed infection and one proved sterile. Two of the controls became pregnant. From 8 to 25 basal metabolic rate determinations on each rabbit were performed. These indicated that those rabbits given additional

iodine developed a smaller (3.6-2.9 per cent) increase in the basal metabolic rate than did the controls. (39.2-45 per cent increase)

The study of microscopic sections of the thyroid glands revealed degrees of activity that corresponded with the basal metabolic rate variation. In those rabbits receiving an increased amount of iodine there was less evidence of functional activity than in the glands of the controls. The inactivity was most pronounced in the thyroid glands of those rabbits receiving four times the physiologic iodine requirement. There was no striking difference in the lobes of the thyroid at the time of the delivery of the young and at the end of lactation. There is evidence, therfore, that the increase of the physiologic doses of iodine tends to compensate the metabolic demands of pregnancy and thus protects the thyroid gland from overfunctioning. (43)

The increased function of the thyroid during pregnancy is further emphasized by Soule (45) who has studied oxygen consumption in pregnancy and hyperthyroidism. In both pregnancy and hyperthyroid conditions a decreased oxygen consumption was noted. With an increased minute volume of cardiac output, the amount of oxygen given off in the tissues per unit of circulating blood is decreased. Whereas in the non-pregnant state the blood gives up 30 to 40 per cent of its oxygen in the tissues, in pregnancy, and Basedow's disease only 20 to 30 per cent of the oxygen content is released per unit of circulating blood.

A general consideration of symptoms and finding per se makes pregnancy a "hyperthyroid state". As mentioned previously, Fall holds the same contention. Soule believes that the pregnant

woman, as distinguished from a Basedow, is in a physiologic condition in which there is hyper-function of the thyroid. Anselmino and Hoffman in their extensive and thorough study throw new light on the question as to whether the increased metabolism of pregnancy is due to the fetus alone or whether it is due to an increase in the mother's metabolism per se. They have demonstrated an increased amount of thyroid hormone during pregnancy. Also evidence that the level of this hormone is higher in the mother's circulation than in the fetus. (45)

In contradistinction to the foregoing workers who maintain that the increase in metabolic rate is normal, we have the work of Davis (8) who declares that if a women with a normal thyroid takes sufficient iodine during the course of a normal pregnancy, her basal metabolic rate will remain within normal limits, although it may show a gradual increase during the last weeks of pregnancy. The average rate of seven women with simple hypertrophy was plus 22.1 per cent before term, with a later drop to plus 3.1 per cent. The average rate of nine women believed to be of the hyperthyroid type was plus 32.2 per cent before delivery with a drop 11 days post partum to plus 8.9 per cent. The average metabolic rate of nine women with normal thyroids at term was plus 2.4 per cent. Their average after delivery was 1.3 per cent. With the exception of two patients in the last group, these patients took small doses of iodine during the last months of pregnancy.

Marine (31) studied the influence of pregnancy on heat production in rabbits with and without thyroidectomy. He concluded that there was a greater increase in heat production during

pregnancy than some workers believe and that the increase is in part dependant upon the maternal thyroid and that the enlargement which may occur at this time is essentially a compensatory or work hypertrophy.

Yoakam (49) found that the incidence of goiter was 60 per cent in his series of pregnant women in Detroit which compared closely with results obtained in goiter surveys made upon the general population of Michigan. There was a corresponding high incidence of congenital goiter. He concluded that endemic goiter may have its origin in intrauterine life. He found that measurement of the neck during pregnancy, as a means of determining enlargement of the thyroid gland, was less accurate than palpation of the isthmus and estimation of its thickness in centimeters. Iodine salt was found to be an ideal prophylactic agent in patients with normal or only slightly enlarged thyroid glands, but it was thought that additional iodine was advisable when visible symetrical enlargements of the thyroid exist.

This brings us to the consideration of the prevention of congenital goiter. Undoubtedly the prevention of thyroid enlargement in the newborn lies within the pregnant state and is closely allied with the diet and therapy which is directed toward the maternal thyroid. As stated before the fetal thyroid is relatively inactive at birth and remains so for some months after birth so that the fetus and newborn infant are dependant upon the mother's thyroid for it's metabolic hormone. As Marine (31) has pointed out, the enlargement of the fetal thyroid which is so directly dependant upon the maternal thyroid insufficiency is also a purely physiological or compensatory reaction. As stated in the previous

section on physiology, when the iodine store of the thyroid becomes lower than 0.1 per cent a hyperplasia begins and a hypertrophy results. The end result is always the colloid goiter. The gland newer goes back to its original state. Yoakam (49) has shown that before the introduction of iodine salt into Michigan and with 64 per cent of a group of mothers receiving sodium iodide phrophylactically during pregnancy, 35 per cent of the newborn infants had congenital goiter, while where no iodine was given the incidence of congenital goiter increased to 60 per cent. He concluded that iodine given prophylactically only during the last trimester of pregnancy is of little value in the prevention of congenital goiter. Following the introduction of iodine salt the incidence of congenital goiter was reduced to 4 per cent. This reduction he believes, is due to the use of prophylactic iodine earlier in pregnancy. The incidence of maternal goiter, found to be 25 per cent on the eastern sea coast, with 11 per cent congenital goiter, shows that even in regions where goiter is not endemic careful observation of the thyroid and rational prophylactic iodine administration during pregnancy would decrease the general incidence of goiter in these regions. (49)

Dean (12) reports a case in a goiter district in Canada in which both parents had simple goiters of moderate size. The husband was less marked than the wife. Six years previous the woman had given birth to an anencephalic monster. Four and one half years later a similar child was born. Shortly after this iodine was prescribed for both husband and wife and in both cases after several months the goiter nearly disappeared. A year and a half after the last pregnancy a normal, healthy boy was born with

no deformity. This finding may be related to the morphogenic function of the thyroid secretion as related by Mayo. (33) It was noticed that a number of simple goiter cases were present in that district and that a certain percentage of births had infants with a slight enlargement of the thyroid. Older children in those families had well developed goiters. Iodine therapy was begun during the last three to four months of pregnancy (the first time seen for prenatal care) and the author has not seen a single case of congenital goiter where this treatment was had.

Davis and Urdan advocate the administration of adequate amounts of iodine during pregnancy and lactation to every woman who lives in a goiter district. They believe that the use of iodized salt has generally decreased the incidence of goiter. A pregnant woman should have one tablet of iodostarin three times a week or ten drops of syrup of hydriodic acid twice a week. (10) Davis feels that this prophylaxis will lessen to a great extent the incidence of congenital goiter. The severest effects of thyroid insufficiency occur during fetal life when irreparable damage may be done to the nervous system if the thyroid insufficiency is great enough.

Hence we would conclude that pregnancy is definitely a period of thyroid strain and in the event that insufficient iodine is supplied, hyperplasia and hypertrophy of the gland results. Whether the increased metabolic rate during pregnancy is due to the increased protoplasmic mass or to the hyperfunctioning of the thyroid gland or to both is still somewhat in debate but the evidence points strongly to the latter theory. That the prophylactic treatment of simple goiter in pregnancy is important is

recognized by all. The prevention of congenital goiter lies in the management of the pregnancy. Most observers are agreed that in cases of definite thyroid enlargement during pregnancy, iodine is indicated; also where goiter is endemic the concensus of opinion is that iodine is again indicated. All are in unison in affirming the fact that the introduction of iodized salt has reduced the incidence of congenital goiter and some believe that it is sufficient prophylaxis in the average pregnancy where a simple goiter is not already present.

HYPOTHYROIDISM IN PREGNANCY

It has been the observation of O'Keefe (38) that any hypofunction in the endocrine chain results in a hypothyroidism within a period of six months or a year. The relationship of hypothyroidism to pregnancy is certainly of great importance. There are five distinct hypothyroid hazards in a womans life: 1) puberty 2) pregnancy 3) menopause 4) operations 5) infection. Puberty is probably the least important of the five. There is usually a hypertrophy of the thyroid gland which is termed physiologic. However, this is at times a turning point towards a permanent hypo or hyperthyroidism. Pregnancy and its results undoubtedly play an important part in the life of the thyroid. The so-called physiological enlargement of the thyroid in a normal pregnancy may go the way of hypertrophy 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 hypothyroid symptoms from pregnancy and it's complications that O'Keefe believes that repeated pregnancies, one septic abortion, two or more uncomplicated miscarriages, regardless of the cause, will result in a decreased function of the thyroid gland. (38)

Thyroid deficiency is manifest by several syndromes the chief of which are simple goiter, masked hypothyroidism, myxedema and cretinism. Most authors agree with Marine (32) that simple goiter and myxedema are but stages of the same process. In as much as we have already considered simple goiter in pregnancy

we will limit our discussion of that condition here. Simple goiter is a compensatory hypertrophy and hyperplasia of the thyroid gland occurring endemically, sporadically and epidemically, developing during the course of a nutritional disturbance of unknown nature but depending immediately upon a relative or absolute deficiency of iodine. (10) The principle point to remember is that it is a real deficiency disease and must be treated as such during pregnancy by the administration of iodine.

Brown (4) states that thyroid deficiency occurs most frequently in women of 30 to 50 years of age. The frequency is five to six women to one man. He believes that masked hypothyroidism, short of true myxedema is quite important in pregnancy. He lists a large number of symptoms which he calls symptoms of mild hypothyroidism. A gain in weight of from 15 to 50 pounds over a period of a few years, without any change in habits of eating and exercise to account for it, is significant. Irregularity of menses, both in periodic appearance and amount of flow, with ammenorrhea the most frequent finding is mentioned. Other symptoms are changes in the skin-a dry, scaly, itching skin with a thinning or absence of axillary or pubic hair and an annoying seborrheic dermatitis of the scalp, with loss of lustre, increasing brittleness and thinning of the hair of the head; frequent attacks of respiratory infection; an extreme sensitveness to cold requiring added covers and clothing to keep the individual comfortable; a tendency to be sluggish, especially in the early morning after an undisturbed night's rest; various neuralgic or neuritic pains may be constantly present in one area or may be shifting from one region to another; obstinate constipation

without anatomical abnormalities and not relieved by ordinary methods of treatment by changes in diet, intestinal flora or exercise; mental symptoms accompanied by melancholia, delusions or hallucinations of a peculiar type usually associated with smaller animals as mice, rats, cats and dogs. A patient may complain of only a single one of these symptoms or of several, and only a careful history will obtain the information that may point to a hypothyroid state. Brown thinks that many cases in pregnant women are missed. The severity or multiplicity of symptoms has very little relation to the basal metabolic rate. A frank myxedematous person may be a minus 15 or 20 and another showing very few symptoms will have a minus 30 or 40. The signigicant feature is that the reading be a minus one. The author recommends the administration of thyroid extract sufficient to maintain a plus reading if possible-with frequent checks of the basal metabolic rate. This assures the development of a normal child. According to Engelbach, at birth a normal child should have one nucleus of ossification at the upper end of the tibia and two in the ankle. Absence is proof of insufficient thyroid dosage and such a child should have one grain daily at two weeks of age, increasing 1/8 grain per month until proper dosage is reached (usually one to two grains), such being determined by elevation of the rectal temperature to 100 degrees F. Brown has given thyroid to a hypothyroid mother during pregnancy and for one year following, during which time 8,880 grains of thyroid extract were given without symptoms of overdosage. The child showed no signs of thyroid deficiency during it's first year of life. (4)

O'Keefe (38) has devoted a great deal of work to the study

of masked hypothyroidism as related to obstetrics and gynecology. His symptoms agree in general with those given by Brown. He says that nervousness is very characteristic; it is not the excitable type but a depressive, irritable, melancholic type. There may be crying without cause, tiredness, laziness, forgetfulness and an inability to sleep at the right time and a tendency to fall asleep at the wrong time. They may imagine creeping sensations over the back, neck and arms, with a quivering sensation of the abdominal muscles. Often reflex stimulation of the throat occurs causing frequent swallowing without relief of irritation. The patient often complains of a fast heart - which is due to gas formation in the stomach - in reality the heart is abnormally slow. The distention of the stomach creates a discomfort in the heart region, a sensation of increased heart rate, shortness of breath, a throbbing in the ears, and a distress over the precordial area. Headaches, constipation and gas pains are practically always present and the hands and feet are always cold he states. Hot flashes without perspiration except for scanty and cold amounts on the forehead are frequently noted. Very commonly there is a history of pre-existing infection.

Most people have believed heretofore that hypothyroid people were sterile. This is the case in the true myxedematous individual, but patients may have large families in spite of a hypothyroidism that has existed for years. Many are unable to conceive while having a focus of infection and become pregnant after it's removal. Their children are overweight at birth and throughout early life. They are backward in school and prone to infection.

Married women show a decreased sex desire. Unmarried girls avoid company - especially males. (38)

The author finds that 80 per cent of the hypothyroid women are fat, equally distributed over the body. The thyroid may or may not be enlarged - but in his experience 50 per cent of enlarged thyroids show hypothyroidism. This is in line with the previous mentioned contention that thyroid hypertrophy is a deficiency manifestation. O'Keefe also states, in unison with Brown that the basal metabolic rate is significant only if the reading is minus. It is also an important check on medication. The picture just given is so designated hypothyroidism because in the author's experience good results were obtained by thyroid medication. He declares that thyroid medication is both palliative and curative depending not so much on the severity of the case as on the duration. A cure can be expected if treated within the first six months of the disease. If in the one to two year period, the response is excellent, but cures are smaller. If the condition is of long standing, treatment is purely palliative. He feels that all hypothyroids should have thyroid extract during pregnancy. (38)

Many interesting corallaries may be found in the literature. Harvey, Covey and Andrews (22) reported a case of toxemia of pregnancy which gave a history of therapeutic abortion for toxemia, spontaneous abortion and a known basal metabolic rate of minus 26 per cent. The findings on entry to the hospital were a dry skin and hair, marked mental and physical fatigue, toxemia of pregnancy, low temperature and blood pressure and a slow pulse

and a basal metabolic rate of minus 24 per cent. A diagnosis of a longstanding hypothyroidism without myxedema, complicated by pregnancy, was made. Thyroid extract and calcium gluconate in normal saline were given. Labor was induced medically and recovery was slow. Hence we see that hypothyroidism may be a factor in toxemias.

Mudaliar et al investigated a case of thyroid deficiency in pregnancy and demonstrated experimentally that there is a check relationship between the posterior pituitary hormone and the thyroid hormone. They demonstrated that the thyroid is one of the main factors in the maintainence of pregnancy to term. Hypertrophy progresses from the seventh to the ninth month, then regresses to the end of pregnancy. When it is hypertrophying, the posterior pituitary seems to be held in check; if not, the posterior pituitary, by itself, is capable of decreasing the basal metabolic rate. Lack of hypertrophy is manifest in some women by shedding of superfluous hair and escape of small amounts of posterior pituitary hormone causing small pains the last months of pregnancy. At the end of pregnancy regression of the thyroid removes the check so far exercised on the posterior pituitary which, as it were, bursts out of control in the circulation and produces labor pains. The case in point gave rise to symptoms of hypothyroidism, to repeated abortions, to spontaneous flow of milk in the mother and to vesical troubles in the baby. These symptoms were relieved by thyroid administration to the mother. It was found, in the milk of the hypothyroid mother, that a hormone was present which was identical with pituitrin. This was also

found in the milk of normal women for a few days after delivery, probably to help involution.(35)

The fact that hypothyroidism can be inherited is illustrated by a case reported by Witts (48). The mother developed myxedema at fifty after having had eight children. The daughter was a mild cretin and was greatly improved by thyroid medication. Eight months after the onset of thyroid medication diabetes was discovered and then she became pregnant. After going into coma for lack of insulin a seven to eight month macerated fetus was delivered. Before thyroid she was troubled with irregular periods and menorrhagia. Following therapy her periods became regular. She is now on insulin and thyroid extract.

It becomes very obvious that the obstetrician has a great deal of responsiblity in the proper management of a pregnancy. It is generally recognized that colloid goiter, cretinism, deaf-mutism and retarded differential development are obvious defects from thyroid deficiency. Sloan (44) declares that much of the subnormality as seen among the criminal classes and mental defectives in general is due to a faulty thyroid, the etiology of which goes back to intrauterine life. He agrees with O'Keefe and Brown that the diagnosis of thyroid insufficiency is little aided by the basal metabolic rate since we have no standards for normal pregnancy. As stated before he regards a woman with a normal basal metabolic rate in pregnancy as probably being subnormal. Dependance must be placed upon physical examination, personal family history and clinical judgment. The treatment resolves itself into simple thyroid medication. The basal metabolic determination is the best means of control for dosage that we have.

HYPERTHYROIDISM IN PREGNANCY

It is only within recent years that very much attention has been paid to the association of thyrotoxicosis and pregnancy. At the outset one is impressed by the rarity of the condition. Lahey (27) found that pregnancy occurred with hyperthyroidism in only 0.41 per cent of the cases. This comprised a total of fifteen patients who were pregnant out of 3,678 patients operated for toxic thyroid at the Mayo clinic (36) from January 1923 to January 1930 there were only 29 cases of hyperthyroidism and pregnancy, an incidence of only 0.60 per cent. Yoakam (49) found that the incidence of hyperthyroidism in pregnant women was 3.7 per cent. These latter statistics are taken from the obstetrical angle and not from the surgical angle, hence the findings are a little different - but essentially alike in this - that the association of the two conditions is quite uncommon.

Despite the rarity of the association of these two conditions it is a subject of interest to both the obstetrician and the surgeon. As it is human nature for every man to view the situation through the colored glasses of his own specialty so we shall see that the management of this condition varies somewhat depending on whether the author discussing it is a surgeon or an obstetrician.

Exophthalmic goiter may be described as a constitutional disease apparently due to an excessive, probably an abnormal secretion of an enlarged thyroid gland showing diffuse parenchymatous hypertrophy; it is characterized by a high basal metabolic rate with the resulting associated manifestations, with a peculiar nervous syndrome and usually exophthalmos, and with a tendency toward the

gastro-intestinal crises of vomiting and diarrhoea. In contrast, the symptoms of adenomatous goiter are those essentially due to prolonged elevation of the basal metabolic rate caused by the presence in the tissues of an excess of a normal thyroid secretion; exophthalmos does not occur and the symptoms are not associated with typical diffuse parenchymatous hypertrophy but with the occurrence of adenomatous tissue in the thyroid gland. A confusing factor in differential diagnosis (according to Mussey et al) is the fact that approximately one third of the cases of exophthalmic goiter occurring in this country are superimposed on a preexisting adenomatous goiter; a causal relationship between the two conditions has not, however, been demonstrated. (37)

Lahey (38) considers exophthalmic goiter and toxic adenoma to be one and the same disease. He has always viewed pregnancy as a serious complication of hyperthyroidism and says that if permitted to go full term, labor is difficult, prolonged and necessitates the employment of a general anesthetic during a very active stage of hyperthyroidism and does definitely represent a very serious mortality factor in the management of hyperthyroidism. His views are not shared by all as we shall see.

In general there are two theories of toxic goiter. The first theory advanced by Möbius and Ganthier is that the disease is of thyroid origin. The other theory is that the thyroid, while it plays an important role, is secondary to and depends upon some neuroconstitutional defect or anomaly which renders the individual anatomic control over various visceral functions susceptible of injury by a great variety of non-specific influences such as fright, worry, physical and mental strain, trauma and the under-

mining of nutrition by focal and systemic infection.(Marine) It is apparent that an exophthalmic goiter may occasionally develope in pregnancy where the psychic background is unfavorable or in association with a toxemia. According to Davis and Urdan (10) it is more usual for the disease to develope some months after delivery. The observations of Falls and Davis indicate that this group of patients should be treated by rest in bed, iodine and sedatives. Most of them make satisfactory recovery without surgery and it has been observed by these men that a relative hypofunction may be expected after the period of hyperfunction.

Hinton (23) declares that Grave's disease usually develops in the early months of pregnancy and more frequently in primiparae. The management will depend entirely upon the condition of the patient when first seen. He believes that unless she is critically ill it is not necessary to interrupt the pregnancy but a thyroidectomy can be performed and the patient carried through a normal delivery. If the case is very mild it may be possible to carry the patient through her pregnancy on medical management and defer more radical measures until later. He groups the cases needing interruption into two classes: 1) chronic hyperthyroidism associated with the adenomatous goiter in which there is a definite myocaridal degeneration, 2) cases of exophthalmic goiter which are of a fulminating type whichendangers the life of the mother by allowing pregnancy to continue. He further asserts that 90 per cent of cases can be carried to a normal delivery if properly managed.

Falls (16) regards a mild hyperthyroidism as a not uncommon complication of pregnancy for which no treatment is necessary.

His findings indicate that symptoms of exophthalmic goiter may manifest themselves first during pregnancy and if present before conception usually are aggravated but may be ameliorated. The vomiting and toxic symptoms of an exophthalmic goiter during pregnancy are apt to be wrongly diagnosed as hyperemesis gravidarum Falls declares that Lugol's solution administered orally, intravenously or intramuscularly apparently has been of value both as a prophylactic and as a curative remedy in many cases of hyperemesis. In his series of cases he has not had to resort to abortion since beginning the use of Lugol's solution. He is convinced that there may be a thyrotoxic element in most cases of hyperemesis.

Harvey, Covey and Andrews (22) report a case of hyperemesis gravidarum associated with exophthalmic goiter. They state that hyperemesis is often caused by thyrotoxicosis. In their case they controlled the hyperemesis medically and a thyroidectomy was performed in the fifth month of pregnancy. The pre-operative and post-operative response was in no way different than in a non-pregnant woman and pregnancy progressed to a normal termination at term. They declare that thyroidectomy if performed before the sixth month of pregnancy is no different from any other case and in no way influences the pregnancy. That finding agrees with those of many other men.

A case reported by Polowe (40) developed acute symptoms of hyperthyroidism in the seventh month of pregnancy. A subtotal thyroidectomy was performed in the eighth month of gestation and she was delivered normally of a normal baby twelve days after the estimated term.

Mussey and Plummer (36) found that since the use of compound

solution of iodine internally in cases of exophthalmic goiter, begun in 1922, followed by partial thyroidectomy when this procedure was indicated, the pregnant woman was able to carry through pregnancy with resonable expectancy of health and of normal living offspring. Formerly, interruption of pregnancy was usually advised in severe cases of hyperthyroidism complicating pregnancy, and miscarriages were prone to occur spontaneously if treatment was not given. From January 1923 to January 1930 at the Mayo clinic they treated 41 cases of hyperthyroidism complicating pregnancy. 29 cases were of exophthalmic goiter and 12 of toxic adenomata. Four of the 29 gave the onset as during pregnancy as did 2 of the 12. The symptoms were aggravated by the pregnancy in 5 of the 29 (17%) and 6 of the 12 (50%). One case of exophthalmic goiter spontaneously improved during pregnancy. 22 of the 29 had a partial thyroidectomy during pregnancy. 20 of the 22 had iodine; the other two were prior to 1922. The other seven were carried through on compound iodine solution. Of the seven, exophthalmos recurred in three, three were controlled by iodine post-partum and one required partial thyroidectomy one month post-partum.

In eleven of the twelve adenomata operation was advised; two refused and nine were operated. One with mild symptoms was carried on medical treatment without iodine. All patients reported relief or improvement. There were no miscarriages and no maternal deaths. 36 babies were born to 37 mothers. These men recommend compound solution of iodine, ten drops three times daily. It should cause distinct improvement and a lowered basal metabolic rate within two weeks in exophthalmic goiter. (36)

Davidson (7) reports a case of sterility for ten years, which,

shortly after an attack of acute tonsillitis, began having toxic symptoms of Grave's disease. Soon afterward she became pregnant and miscarried. This was repeated not long afterward. Finally at the fourth to fifth month of a third pregnancy there was an exaggeration of the disease. Lugol's solution was given and the patient improved to a certain point, then thyroidectomy was done. She had an uneventful recovery.

In a report of 73 cases of pregnancy associated with hyperthyroidism or following thyroidectomy, Fahrni (14) concluded that thyroidectomy during pregnancy was preferable to interruption in hyperthyroidism. He declared that interruption was definitely more dangerous than surgery. He also found that after the operation the pregnant women were is such physical condition as to be able to go through confinement in a comparatively normal manner. Thyroidectomy was the procedure of choice up to six months of pregnancy, conservative treatment being indicated after that. While he advised against pregnancy for two years post-operatively, nevertheless he saw no justification for advising interruption of pregnancy. He noted an absence in congenital deformities in the babies. In his group, 14 were pregnant at the time of operation, 22 became pregnant within one year and 37 became pregnant the second year after operation. In all there were 85 babies born to the 73 women in the series.

Frazier and Ulrich (19) found that 3.2 per cent of the cases operated for thyrotoxicosis, developed the toxic thyroid during pregnancy. Seven patients with toxic goiter, upon whom thyroidectomy was performed during their pregnancy, were reported. All of the pregnancies went to term and all the mothers were delivered

of normal babies. They also declare that pregnancy should not be voluntarily terminated because of the development of thyrotoxicosis. Mild degrees of hyperthyroidism during pregnancy were controlled by iodine. They recommend immediate thyroidectomy in cases where severe degrees of thyrotoxicosis complicate pregnancy or in milder degrees of toxicity not controlled by iodine. Furthermore they state that the recurrence of hyperthyroidism during pregnancy subsequent to thyroidectomy may be prevented by the administration of iodine. (19)

Gibbons (21) agrees that iodine should be given a pregnant woman who has previously been operated for toxic goiter. He warns, however, against the use of iodine in non-toxic adenoma in pregnancy because of the danger of an iodine hyperthyroidism. He declares that it is hazardous to give iodine to any pregnant woman over 25 with diffuse colloid goiter because of the possibility of deep seated adenomata. This stand is not in accord with the position of Davis (9) who declares that there is no evidence that the use of small amounts of iodine has been harmful for patients with adenomatous goiter.

The dangers of iodine administration to individuals with adenomatous glands has been greatly exaggerated according to Hyman and Kessel. (25) They declare it occurs at most in a fractional percentage of cases and is a temporary phenomenon. It should not deter the physician from the routine administration of an iodide in the non-symptomatic goiters that occur synchronous with the epochs in the female sex life.

Hyman and Kessel regard true exophthalmic goiter as a relatively uncommon disease. They declare that the majority of the cases

sent to them with the diagnosis of exophthalmic goiter do not have the disease. They maintain that the diagnosis of exophthalmic goiter should not be made without the presence of tachycardia and increased basal metabolic rate - these being the only symptoms constantly present. The dangers of so-called iodine hyperthyroidism has created an anxiety neurosis in physicians, they declare, a state that has seriously interfered with the prophylactic and curative use of iodides. Between the fears of the patient and the fears of the physician, the whole subject has become unnecessarily complicated and obscured in their estimation. They found that the effect of labor and the puerperium on the exophthalmic goiter was usually an amelioration of the symptoms and the test of pregnancy was well met at all times by the circulatory system. In a series of 50 consecutive patients of exophthalmic goiter, 40 were women; 20 of these were married and nine had twelve children - about the average expectancy. Like so many others they do not think that therapeutic abortion is indicated because of exophthalmic goiter per se. On the other hand, rapid loss of weight, increasing tachycardia, nervousness and elevation of the basal metabolic rate may force the attendant to induce abortion, they believe. (25)

What then, we may ask, is the effect of hyperthyroidism on pregnancy? Kunde et al (26) experimentally produced severe hyperthyroidism in rabbits and observed that the processes of oestrus, ovulation, fertilization, migration and implantation took place, but in most instances the young were never born, resorption occurring instead. Resorption of all or many of the fetuses occurred during the latter two thirds of pregnancy. An exact analogy cannot be drawn in human pregnancy. The incidence

of pregnancy in hyperthyroidism is believed by some (Day, Falls, Gardner-Hill, et al) to be low while others (Hyman and Kessel, Mussey, Plummer and Boothby) believe it is the average expectancy. Most all agree that miscarriages occur more frequently in the associated conditions.

Clute and Daniels (6) concluded from their series of patients with hyperthyroidism during pregnancy that hyperthyroidism does not cause an unnatural termination of the pregnancy in the majority of cases when it is properly treated. Bothe (2) found that a high percentage of patients with hyperthyroidism either pregnant or not, gave a history of prolonged nausea and vomiting during previous pregnancies. Falls (17) found that thyrotoxicosis caused hyperemesis gravidarum in a certain percentage of cases. Other investigators corroborate this claim.

Deutschman (13) declared that a pathological condition of the thyroid gland seems to be one of the etiological factors of placenta praevia. He reports a case in which he regards hyperthyroidism as the indirect etiological factor. His theory is that this is brought about by a disturbance of physiologic hormonal balance through toxic hormones affecting the ovarian hormones, which predispose to the formation of a few uterine fibroids which in turn prevent a normal decidual reaction with subsequent abnormal implantation of the fertilized ovum. The patient presented had a fibrotic uterus and had had placental trouble in each of three pregnancies (two placenta praevia and one ablatio placenta). Deutschman also states adversely that in his opinion a woman suffering from toxic adnomata or from exophthalmic goiter, should not be permitted to go through with the pregnancy, lest her life

be jeoparidized by unforeseen and unexpected fatal complications which may arise during the process of labor. (13) The general concensus of opinion does not agree with this view.

Frazier and Ulrich (19) did not think that pregnancy was affected by toxic goiter if properly controlled. Gardner-Hill (20) found that 54.5 per cent of pregnancies with primary Grave's disease were unsuccessful. Miscarriage was the chief finding. Gibbon found that in most instances pregnancy could be completed normally at term if the proper treatment is used. Harvey et al (22) agrees that abortion may be avoided if correct measures are used. Hinton (23), while granting that some cases may require interruption, declared that 90 per cent of the cases may be carried normally to term. Mussey and Plummer (36) found that since the use of Lugol's solution there is reasonable expectancy of health and living babies in pregnancy associated with hyperthyroidism.

Hence we see that the majority of men believe that while formerly thyrotoxicosis endangered the pregnancy greatly, since the use of Lugol's solution the situation is greatly improved. Uncontrolled hyperthyroidism in pregnancy is thought by many to be disastrous leading to abortion in some cases, hyperemesis gravidarum in others. In general the belief is that pregnancy may proceed with reasonable normality if properly controlled.

What is the effect of pregnancy on the hyperthyroidism? In some degree we have answered this but there are reports yet to be mentioned that are worthy of comment. Luker (28) reports a case in which a patient suffering from exophthalmic goiter became pregnant and improved to such an extent that she was almost well at the time of labor. The labor was free from complications and

resulted in the birth of a living male child and there was no recurrence of symptoms following confinement. All of which goes to show that we do not yet completely understand the physiology of the thyroid gland. Wallace (47) found that a fair percentage of cases were improved. Mussey, Plummer and Boothby (37) found that the control of toxic goiter was not appreciably affected by the presence of pregnancy. Strouse and Daly also found that they were able to control hyperthyroidism regardless of the pregnancy. Lahey found, in studying thyroid mortality factors, that pregnancy was always a serious complication of hyperthyroidism. He pointed out that if permitted to go full term and labor is prolonged and necessitates the employment of a general anesthetic during a very active stage of hyperthyroidism, it does definitely represent a very serious mortality factor in the management of hyperthyroidism. He gives two methods of treatment: 1) by interruption of pregnancy or 2) by operation on the thyroid - and thinks the latter course is by far the more satisfactory to pursue. Clute and Daniels (6) did not see anything occur in pregnancy with hyperthyroidism which did not also occur in non-pregnant women. Falls, however, declares that the pregnant woman reacts differently to the syndrome which we call thyrotoxicosis.

Here again we see that the effect of pregnancy on hyperthyroidism may be quite serious if attention is not given to both conditions. It becomes a problem for both the obstetrician and the surgeon to consider together. In a certain number of cases thyrotoxicosis is improved; another group is neither ameliorated or aggravated; a third group is found in which the thyrotoxicosis is markedly increased. (47) All will agree that pregnancy is an added burden

to hyperthyroidism and should be avoided if possible. Pregnancy does not appear to be a cause of primary hyperthyroidism.

As regards pregnancy after thyroidectomy for primary hyperthyroidism, Clute and Daniels (6) found that it did not cause a recurrence of thyroid toxicity. Fahrni's (14) findings agreed with these men. These are the findings in general. The general opinion is that these women should have iodine during subsequent pregnancies however. (Gibbon, Davis) Thyrotoxicosis in a cured patient seldom recurs as a result of pregnancy and the fact that the condition once existed should not contraindicate future childbearing. Fahrni (14) advised against pregnancy for two years post-operatively - but - should they become pregnant in the interval, then he sees no justification for advising interruption of the pregnancy.

Babies born of thyrotoxic mothers are generally normal. (6) Aside from the fact that some reported more frequent miscarriages, if the babies were born alive at term, they were normal in every respect. Congenital goiter was not found.

In summarizing the treatment of hyperthyroidism in pregnancy we note a clear division in the methods used before and after 1922 when the use of iodine was introduced in the treatment of exophthalmic goiter. Prior to 1922 interruption of pregnancy was usually advised in severe cases of hyperthyroidism complicating pregnancy. Miscarriages were prone to occur spontaneously if treatment was not given. Preliminary ligation was practised in the milder cases, followed by thyroidectomy after delivery if the pregnancy went to term.

Since 1922 treatment has changed so much that most men regard

interruption of pregnancy as definitely not indicated except in extreme cases of sudden onset. The concensus of opinion is that a thyroid crisis is apt to be precipitated by interruption. When symptoms of thyrotoxicosis are definitely established the procedure depends on two factors: first, the severity of the thyroid intoxication and secondly, the period of gestation. When symptoms are mild and do not progress iodine is indicated in the form of Lugol's solution, ten drops three times daily. If severe, progressive exophthalmic goiter is present and pregnancy is not further than six months, subtotal thyroidectomy may be performed in the usual manner with pre-and post-operative preparation with Lugol's solution. The pregnancy may be disregarded as far as the thyroid is concerned. If however, the toxic goiter develops in the latter months of pregnancy medical management is the treatment of choice. An adequate regime of rest and sedation, iodine therapy with careful observation and study by clinical and laboratory methods throughout gestation is the procedure of choice. Labor should be shortened as much as possible. Occasionally vaginal or abdominal caesarian section may have to be resorted to. Induction of labor before term is sometimes indicated. Thyroidectomy is best performed about two weeks after delivery. Iodine therapy is indicated in subsequent pregnancies.

CASE HISTORIES

(Obtained from the literature and from the files of the University Hospital)

CASE ONE*.- Mrs. R. D. Admitted to the hospital Oct. 3, 1932 because of continuous vomiting, progressive loss of weight and weakness.

Onset: Last menstrual period began Jan. 30, 1932. Vomiting began between the 5th and 6th week of gestation. She was put to bed by her family physician, given sedatives, intravenous glucose and frequent feedings with complete relief from vomiting for two weeks. She was in bed for 8 weeks, during which time, moderate vomiting returned; headache was constant. Weight declined from 140 lbs to 125 lbs and the edema which appeared in the early weeks of pregnancy disappeared. The urine was reported normal. Blood pressure was 125/70. A severe herpetiform rash appeared on the dorsum of the arms and legs while in bed, progressing 4 to 5 days, remained stationary 5 days and gradually subsided leaving a pigmentation of the skin. Throughout this time she was on a regime of frequent feedings, calcium lactate 0.65 gm Bid and Haliver Oil. From the 15th to the 23rd week she was up and about some each day and vomited only occasionally. In spite of gradual recurrence of edema, weight fell to 110 lbs (as it was on entrance to the hospital). The pulse fell from 60 and 70 to about 50. From the 23rd week to Oct. 3rd the condition remained the same except she was unable to go about because of weakness.

Past History: Appendectomy at 12 with removal of a tumor of the ovary. Pneumonia at 9. Three months previous to last mentrual period the basal metabolic rate was minus 26 per cent and from then on and throughout pregnancy 0.13 gm of thyroid was administered daily.

Menses and Marital History: Menses began at 14. Regular every 28 days lasting 4 to 5 days. Married 4 years. Therapeutic abortion in 1929 after 8 weeks of severe vomiting. Spontaneous abortion in 1931 at 5th or 6th week - no vomiting; 6 to 7 weeks required for recovery. A rash similar to the above described appeared in this pregnancy.

Family History: Not significant.

Physical: Poor nutrition, skin loose - without subcutaneous fat. Skin and hair dry. Eyes sunken, mucous membrane pale. Mentality clear but thought and speech slow. Concentration was difficult. Moderate edema of face, feet, legs and sacral region. Pulse 44, respirations 15, temperature 97.8, B.P. 100/76, weight 120 lbs. Regional examination (abdomen) negative. Knee jerks sluggish and at times absent; achilles, wrist, plantar and biceps not obtained on repeated trials. All other reflexes negative.

Urine, specific gravity 1.030, other findings normal.

Hemoglobin 100%, RBC 4,110,000, WBC 5,600. Basal metabolic rate minus 24 per cent. Blood sugar 106 mgm%, blood calcium 6 mgm.

On these findings a diagnosis of long standing hypothyroidism without myxedema, complicated by pregnancy, was made.

The patient was placed on sedatives, small frequent feedings and vitamine D. Thyroid extract 0.2 gm was given daily; also calcium

gluconate in normal salt solution. Food was poorly tolerated and the retained caloric intake never exceeded 1,500 calories. During the next two weeks the urine output exceeded the fluid intake and apparent edema disappeared, weight fell to 103 lbs, pulse rose to 56, blood pressure rose to 114/78 with slight improvement in strength. At this point the condition seemed stationary and so labor was induced medically. At the end of the first stage, marked by periods of inertia, labor was terminated by a mid-forceps delivery of a normal male child.

The lying-in period was uncomplicated. On the 12th day post-partum the weight was 85 lbs. One month post-partum slight dependant edema was still present. The urine diluted from 1.010 to 1.020 and was normal in all respects. The weight was 83 lbs, pulse 64, B.P. 90/68, Hb 70%.

Subsequent recovery wqs slow. At 7 months post-partum the physical condition was good but emotional instability was still present.

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CASE TWO.- A white female, age 37 years. A miscarriage in 1923. Subsequent menorrhagia and metrorrhagia. Basal metabolic rate minus 19.6 per cent. Treatment with thyroid extract began Dec. 19, 1923 with amelioration of symptoms. Subsequently carried to full term pregnancy and delivered of living child in November, 1924, under thyroid medication.

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CASE THREE.- A white female, 35 years of age. Gave a history of habitual abortion, miscarriage, or death of fetus. History of empiric, incomplete antisyphilitic treatment based on martial history. Blood wassermann negative. About 3 months pregnant when first seen. Basal metabolism minus 10 per cent. Carried successfully to term on thyroid medication.

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CASE FOUR.- Mrs. R. C. #20848. Age 38, white, farmer's wife. Past history: Had 5 normal full term pregnancies and 3 miscarriages at 14, 6 and 20 weeks. Following the last miscarriage 1½ years ago recovery of the strength of leg muscles was slow. Family and Menstrual History: Not significant.

The patient was first seen on April 21. She complained of extreme weakness for 8 weeks and vomiting 6 weeks; she was admitted to the hospital at once. She was well previously except for a severe pyelitis lasting for 2 weeks, 2 years ago. She had noticed an irregularity of the heart at times for the past 2 to 3 years. Her last menstrual period was Jan. 28. On March 1st she noticed weakness. Weight was then 176 lbs (5 to 10 lbs under usual weight) Nausea and vomiting began 2 weeks later. It was unrelieved by simple measures. Nine days later she was sent to a local hospital by her family physician and given intravenous glucose, sedatives and frequent feedings with temporary good results. Nine days later she went home. Weakness and loss of weight was progressive. Vomiting returned in two weeks.

Physical Examination (April 21): A picture of extreme prostration and restlessness. Body movements were poorly coordinated and purposeless. Eyes were staring, skin dry and loose. Weight was 131 lbs, pulse 140, temperature 99.2, respirations 20, B.P. 148/84. Uterus was the size of a 3 to 3½ month pregnancy.
Treatment: Absolute rest in bed, food withheld, icebag to the epigastrium, and liquids by teaspoon amounts. 25 grams of glucose in 500 cc of normal salt solution every 8 hours by vein. Sodium bromide in 90 cc of solution twice daily be rectum and 0.13 gm sodium luminal intramuscularly twice daily. The next morning the blood sugar was 92 mgm%, the BMR plus 82% and weight 126 lbs. Because of poor veins 5% glucose in salt solution was given by hypodermoclysis. She was placed on Titus' feeding schedule and Lugols as recommended by Falls in the treatment of toxic vomiting of pregnancy. Under sedation and divided feedings, vomiting subsided and parenteral fluids were discontinued after the first 36 hours. On the second day the medical consultant was called and he noted a positive von Graeffe sign and Stellwag sign, tremor of the lips, tongue, hands and feet; slight smooth and symmetrical enlargement of the thyroid, heart enlarged to the left, systolic murmur (mitral) transmitted to the neck.

Twelve days later the surgical consultant advised thyroidectomy whenever condition permitted.

Basal metabolic rate determinations were: April 22 plus 83%, April 24 plus 59%, May 2 plus 30%, may 16 plus 12%.

Subtotal thyroidectomy was performed on May 20. The lobes of the gland were 3 to 4 times the normal size and the isthmus was large. The gland had a typical beefy red appearance. The pathological diagnosis of exophthalmic goiter in involutionary stage was made. Ninth day post-operative the patient was up, the pulse 80 and the B.P. 122/56. She was dismissed on the tenth day.

The weight increased to 176 lbs, the B.P. 126/80 and the pulse 80. Nov. 1, 1933 the patient went into spontaneous labor lasting 6½ hours at the end of which a normal child was born. On Nov. 11 the BMR was a minus 3%, the weight was 152, pulse 80. She was dismissed on Nov. 12. On Feb. 1, 1934 the patients weight was 178 lbs, her pulse 88 and Hb 71%. Her general physical condition was good.

CASE FIVE.- Mrs. A. J. #45970, age 32 years, entered the University Hospital on 1/9/34, complaining of nervousness, palpitation and shortness of breath.
Present Illness: The patient states that she was well until 8 years ago with the exception of a chronic appendix which was removed at age of 15 years. 8 years ago she developed a swelling of the thyroid which was symptom-free except from pressure of the mass in the neck. After her first pregnancy 7 years ago, the goiter began to give rise to symptoms; she became quite nervous, had palpitation and was very short of breath. She had an enormous appetite. The symptoms progressed until 6 years ago when she had the goiter removed. She felt fine for one month after the operation - then there was a recurrence of the mass and the symptoms.

She refused a second operation so radium was tried. She says that the goiter has been decreasing in size ever since. She has been quite well since except for some nervousness and palpitation. She has a good appetite but not excessive. The heat bothers her - she likes the winter best. Last menstrual period began June 28. She felt life the middle of November. There has been an increase of nervousness with the pregnancy. Her feet began to swell in September. This disappeared on resting. Later they began to swell again. She saw a physician on Dec. 9, who told her she had high blood pressure.

Past History: Appendectomy at 15, tonsillectomy at 18. Usual childhood diseases.

Family History: Mother has "high blood pressure and kidney trouble" Otherwise negative.

Martial History: Husband living and well; one child 7½ years. Menses began at 13, always irregular since marriage, dysmenorrhea before the first child.

Physical Examination: Exophthalmos and staring expression. Thyroid - large nodular masses on either side. Heart enlarged to left, systolic murmur. P2 accentuated. B.P. 200/100. Pulse, Corrigan type. Abdomen enlarged to size of 6 to 7 months pregnancy. Slight edema of feet and ankles. BMR was plus 76 and 78. Urine showed 1 plus albumin.

Diagnosis of pregnancy with hyperthyroidism was made.

Course and Treatment: The albumin in the urine increased during the stay in the hospital to 4 plus. She was immediately placed on absolute rest, sedation and Lugol's solution. She developed a left sided hemianopsia which eye consultation found to be due to pressure on the veins of the retina caused by spasm of the arteries and not due to hemorrhage. This soon cleared up. On 2/14/34 she delivered spontaneously. Her weight dropped post-partum from 160 lbs to 115½. The B.P. dropped from 200/100 to 170/80. Her general condition was improved. Lugol's solution was continued. The BMR dropped to plus 35 and 34. Thyroidectomy was performed and the right lobe only removed. It was decided to leave the left lobe until later. She was dismissed after an uneventful post-operative course.

She reentered the hospital on 4/26/34. She had had occasional attacks of tachycardia and excitement and some tremor. The BMR was plus 60 and B.P. was 190/80. The left lobe of the thyroid was removed. She was given Lugol's post-operatively. On 5/4/34 the BMR was plus 17 and 19. She was dismissed 5/8/34 in good condition.

CASE SIX.- Mrs. V. N. #48762, white female, age 24, para III, gravida IV, entered the University Hospital complaining of palpitation, nervousness, profuse perspiration and some swelling of the ankles.

Present Illness: Patient states that she first noted the neck enlargement at 17 to 18 years of age. No symptoms were present. Three months ago she noticed an increasing of the enlargement of the neck. No other symptoms were present - but she requires fewer

covers at night than her husband and her feet are uncovered when asleep; her hands and feet sweat easily; her ankles swell about noon, but this is gone in the morning upon arising.
Past History: Scarlet fever at 4 without complications. Measles at 7. Had severe swelling of the ankles with the first child. Urinary frequency every 2 hours, occasionally nocturia once a night. Menses began at 14, regular. Has been always rather phlegmatic.
Pregnancies: 1st - 18 years - severe swelling ankles last month. Noted neck enlargement. Normal labor.
2nd - 20 years - premature, 7 month. Thyroid increased
3rd - 23 years - normal - thyroid increased.
4th - 24 years - see P. I.
No miscarriages.
Family History: Mother had goiter at 30, which went away under medical treatment.
Physical Examination: Anxious facies, dilated pupils, visible precordial pulsation, excess perspiration palms and soles and below the breasts and slight, fine tremor of the hands. No exophthalmos. Thyroid enlarged, especially the left lobe. Moist coarse rales posteriorly. Pulse 140, heart beat forceful, rythm regular, and systolic murmur transmitted to the axilla. Abdomen - fundus 37 cm above symphysis - floating head. Edema over the ankles and feet. B.P. 160/90.
Diagnosis of pregnancy with hyperthyroidism.
Course and Treatment: On 11/28/34 the BMR was plus 25 per cent, pulse 80 to 120. Was put on Lugol's. Subjective improvement noted On 12/5/34 the BMR was plus 19 and 16. She delivered prematurely on 12/14. Labor was normal.

Surgery was considered but delivery rendered it unnecessary. Was dismissed on 12/24 to return later for thyroidectomy.

Reentered 12/27/34 to surgery complaining of nervousness, tremor and tachycardia. She was placed on Lugol's solution. The BMR determinations were 12/28 plus 59 and 56, on 1/8/35 plus 31 and 35, on 1/10 plus 30 and 31, on 1/22 plus 41, on 1/29 plus 25 and 24, on 2/6 plus 20 and 21 and on 2/18 plus 27 and 28. Infected tonsils and teeth were found so on 1/24/35 a tonsillectomy was done. Thyroidectomy was done on 2/20. The pathological report was nodular goiter. On 3/1/35 there was considerable bleeding from the wound. Transfusions were considered but have not yet been performed. Alveolectomy is still to be done. At the present time the patient is still in the hospital. Her general condition is not yet satisfactory.

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*Reported by Harvey, Covey and Andrews (22).
**Reported by Breckinridge (3).

CONCLUSIONS

I. Pregnancy is a definite period of thyroid strain and unless sufficient iodine is supplied hyperplasia and hypertrophy of the gland results.

II. All women living in goiter areas should have prophylactic iodine during pregnancy and lactation.

III. The prevention of congenital goiter rests in the management of pregnancy.

IV. Simple goiter, whether existing before pregnancy or occurring after that condition is instituted is quite amenable to small doses of thyroid substance or iodine preparations.

V. Hyperthyroid states are often unrecognized because of inattention to minor complaints and signs.

VI. The basal metabolic rate is of little aid in the diagnosis of thyroid insufficiencies.

VII. The incidence of pregnancy associated with hyperthyroidism is low.

VIII. Spontaneous abortion and premature labor frequently occur in Grave's disease.

IX. A diagnosis of hyperemesis gravidarum should not be made until hyperthyroidism has been ruled out.

X. The babies born to mothers with toxic goiters begin life quite as normally as other infants.

XI. All milder forms of toxic goiter in pregnancy should be treated conservatively and the pregnancy carried to term.

XII. In the event of surgical interference, conservative thyroid surgery is preferred to abortion, as the risk to life is less, and as the pregnancy often remains undisturbed. Medical management is preferable after six months of gestation, followed by thyroidectomy during the puerperium.

XIII. Pregnancy is not contraindicated in a cured case of thyrotoxicosis.

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