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Relation of the thyroid to ovarian function

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INTRODUCTION

The thyroid gland has long been considered to have a rather intimate functional relationship with the female gonads. Clinically the importance of the thyroid in reproduction has been known for many years. Thyroid deficiency as well as hyperthyroid conditions are often associated with menstrual disorders and other phenomena of the female sexual cycle.

This paper represents a consideration of this assumed relationship and an attempt to explain the mechanism by which the thyroid might exert an influence on ovarian function. The very nature of the endocrine system and the important functions of the thyroid in general physiology and body economy complicate this problem. It is considered necessary to include a discussion of general thyroid physiology as well as the role played by the anterior pituitary and adrenals. However, a definite attempt has been made to limit the discussion as strictly as possible to the two glands involved in the primary question.

HISTORY

"From our present knowledge of thyroid function, it is evident that the thyroid gland has always been a necessary unit of human anatomic structure, and that thyroid disfunction has been a scourge of mankind since the beginning of time."(1)

The pre-Christian era reveals no definite description of goitre as a distinct clinical condition. This may be explained, at least in part, by the fact that only a few fragments of ancient literature have been discovered, and that even these are not always too clearly interpreted. Some passages in the Hippocratic writings seem to refer to goitre, but there is quite evident confusion between this disease,scrofula and other tumor conditions in the neck. While the Greeks of the Hippocratic age seemed unable to differentiate goitre from other tumors, in some way they became aware of the curative properties of iodine without realizing the nature of the curative agent, and they were accustomed to the use of sea water and seaweed products for treating certain tumors and swellings. (2)

The first seven centuries of the early Christian era encompass the times and the works from Celsus to Paul of Aegina. We are indebted to the early writ-

ings of Celsus for the first definition of bronchocele. To Celsus a bronchocele wasa "tumor under the skin between the skin and the larynx, which is fleshy only or may contain a sort of honey-like substance, sometimes even containing small bones and hairs mixed together."(1) He recommended, in the way of operative measures, a midline incision, evacuation of the fluid, if there were any, or, if the tumor were solid, he advised that it be drawn out of the wound and treated with liniments. It was reported by Celsus to have been easier to remove the tumor mass with a scalpel. It would seem to indicate that the surgeons of that day had some success with goitre extirpations. If such were the case, it is more than can be said of any age again until the nineteenth century. (3)

The fabled Galen wrote a book on tumors but did not definitely refer to goitre. He did speak of tumors pressing on the windpipe and causing aphonia. He further showed familiarity with the recurrent laryngeal nerve and warned of the danger of injuring this nerve in operative procedures. Galen believed the thyroid to be part of the vocal apparatus. (4)

For several centuries following the death of Galen, little advance was made in the study of the thyroid. During the Renaissance Period the story of the thyroid was associated with some of the most illustrious names in

the history of medicine. Such famous men as Vesalius, Paracelsus and Wharton made note of the presence of this gland(5) It was Wharton who gave the name of thyroid to the gland. It is a term derived from the Greek language signifying shield. The name was undoubtedly influenced by the shield-like appearance of the gland on the surface of the trachea. Wharton believed the gland was merely a cosmetic organ whose function was to produce a nice soft roundness in the neck. (6)

There were numerous early theories regarding the function of the thyroid, many of which seemed to be influenced by its anatomic position in relation to the trachea and vocal cords. A few of these theories are mentioned as a matter of historical interest. Among the various functions ascribed to the thyroid were: a mechanical support to the larynx protecting it from the cold; a cushion whose pressure modulated the voice; the possession of an excretory canal for the secretion which acted as a lubricant for the vocal cords; an arterial reservoir between the cephalic and carotico-subclavian systems to control the amount of blood in the cerebral circulation. Still other theories were advanced invariably based on little or no experimental evidence. The belief ultimately became prevalent that the gland served no important physiological role. (7)

Perhaps much of the early confusion can be blamed on the fact that for many years there was a controversy concerning the presence or absence of an excretory canal. Vater, early in the eighteenth century, believed the thyroid to be a gland of external secretion but was unable to locate an outlet. Haller, towards the end of the same century, was perhaps the first to decide that the thyroid was a gland of internal secretion. After careful search had failed to reveal a duct, he classed the gland with the spleen and assumed that the secretion was taken up directly by the blood stream. The conception of the thyroid as a ductless gland was not placed on a firm basis until the middle of the nineteenth century when the prolonged investigations and minute dissections of Cruveilhier demonstrated beyond a doubt that there was no duct. (1) As late as 1870 some men still believed in the existence of an excretory canal. They felt that the thyroid communicated directly with the esophagus and considered the foramen cecum to be the point of outlet for the canal. (5)

Once the question as to the presence or absence of an excretory duct had been settled, investigators became absorbed in the task of trying to explain the function of the thyroid secretion. Early in the second half of the nineteenth century, two of the greatest physiologists

of their time helped to crystallize the first definite conceptions of internal secretions. Claude Bernard was conducting his epochal studies of glycogen and pancreatic functions. At about the same time Brown-Sequard was carrying out his investigation of the adrenals. (1) Schiff of Geneva by performing thyroidectomies on dogs contributed some of the first experimental work on thyroid secretion and demonstrated its importance to body function. (7) It was not until 1874 that Gull first associated atrophy of the gland with the symptoms now known to be characteristic of thyroid deficiency. (8) Hypofunction of the thyroid in adults is still known as Gull's disease, while the term myxedema was applied to the clinical syndrome by Ord in 1878. (4) Murray in 1891 was the first to treat a case of hypothyroidism by injecting an extract of the thyroid gland and the following year other men demonstrated the clinical efficacy of the oral ingestion of thyroid tissue. (2) Magnus-Levy in 1895 made the epochal discovery of the effect of the thyroid on metabolic rate. He demonstrated that Gull's disease was characterized by a low basal metabolic rate, and that the administration of thyroid to hypothyroid or normal individuals increased the rate of oxygen consumption. (9)

It would seem appropriate to mention the work of Kocher in connection with the investigations done on

the thyroid gland in the closing years of the nineteenth century. His observations on total thyroidectomy for the cure of goitre in man established the first experimental confirmation of Gull's clinicopathologic observations. He designated the symptom-complex following total thyroidectomy in man as cachexia strumipriva. (8) Horsley at the same time showed that cretinism, myxedema and cachexia strumipriva were all due to thyroid deficiency and susceptible to treatment with thyroid extract. (2)

The discovery of the curative effect of thyroid gland substance in myxedema initiated biochemical investigations which led to the discovery of iodine as a normal constituent of the thyroid gland by Baumann in 1895. (10) It was not until 1915 that the physiologically active iodine was isolated in crystalline form. This epochal work was done by Kendall and he gave the name of thyroxine to this active principle. (11) In 1926-27 Harington succeeded in determining the empiric formula of thyroxine and effected its synthesis. (12) The groundwork had been completed for more exhaustive and scientific investigation of the thyroid function.

EMBRYOLOGY

The thyroid, parathyroids and thymus are derived from the entodermal pouches of the embryonic pharynx. The thyroid originates from the second and third bronchial clefts as an outpouching of the foregut, the end of which gradually expands while the stalk of attachment narrows to form the thyroglossal duct. The lower end of this duct forms the pyramidal lobe. The lingual connection becomes thinner as it develops and finally disappears. The original attachment leaves the foramen cecum which may be seen at the junction of the posterior and middle thirds of the tongue in the midline. Occasionally the thyroglossal duct persists producing a so-called "thyroglossal cyst". The embryonic relationship between the thyroid, parathyroids and thymus glands must be kept in mind because it explains the frequent occurrence of misplaced gland tissue of one within the substance of another. (8)

HISTOLOGY

Microscopically the thyroid gland consists of numerous lobules separated from one another by connective tissue partitions. Each lobule is again subdivided into tiny follicles, bags or acini, lined with one layer of cuboidal epithelium. These cells pour into the acini a gluey substance called colloid, which contains thyroxine, the active principle of the thyroid. On section there are circles of cuboidal cells within which there is the homogeneously pinkish,acid staining colloid. Around each circle is a small amount of connective tissue, which carries the blood vessels, nerves and lymphatics.

Each lobule consists of a fibro-elastic capsule lined with a pavement epithelium which continues directly into the intralobular lymphatics, so that the whole cavity of the gland unit is a lymphatic space or sinusoid into which the intralobular lymphatic vessels open. These lymphatics in turn form minute blood vessels which cannot be distinguished as arteries or veins because they possess no muscular coat. These vessels penetrate the walls of the lymphatic sinusoids, continue inward and break up into a network of capillaries surrounded by epithelial cells. No connective tissue surrounds the intrasinusoidal capillaries. They are separated from both the lymphatics of the sinusoid and the gland cells by their epithelial cells

only. Colloid material can always be found in the lymph vessels and spaces. This shows that the colloid material is distributed by that route.

The essential gland epithelium is arranged in cellular columns which consist of a syncytium with its nuclei placed toward the center of the column. Within the nuclei are channels forming an intricate network. As colloid is formed it collects first in the center of the cellular column, and, as the amount of colloid increases, it distends and distorts the gland units, so that the essential structure is then difficult to distinguish. As a result the cuboidal cells lining the follicle become flattened by the colloid material into squamous epithelia. (5)

ANATOMY

The thyroid gland is located on the anterior surfaces of the larynx and trachea, its lobes extending outward for a distance of one to one and a half inches. There are two lateral lobes which are usually, though not always, connected by a crossbar known as the isthmus. In the majority of instances a projection, known as the pyramidal process, extends from this isthmus and runs upward between the two lateral lobes toward the hyoid bone. The entire gland has the shape of an "H" with the crossbar below the middle of the parallel bars and a central process running upward from the horizontal portion.

Its size varies considerably in different races and in different individuals of the same race. It may be considered that a width of six to seven centimeters and a weight of twenty to forty grams is the average. The gland is somewhat larger in women than in men. Ordinarily it is not palpable or can be only faintly outlined by palpation. When it can be too easily demonstrated and shows prominently on swallowing it is definitely enlarged.

The gland is completely surrounded by a capsule with partitions extending into its substances thus dividing it into lobules. Occasionally masses of thyroid tissue

may be found distributed in the vicinity of the main body. An example of this is the not too uncommon occurrence of a lingual thyroid buried in the tissues of the tongue.

The thyroid is the most highly vascular organ in the body, being richly supplied with vessels through branches of the innominate, external carotids and the thyrocervical trunk. The superior and inferior thyroid arteries are quite large and form a complete network permeating the entire gland substance. The nerve supply is derived from the sympathetic system exclusively, receiving fibers from the inferior and middle ganglia of the cervical sympathetic chain. (10)

PHYSIOLOGY

A brief consideration of the general physiology and function of the thyroid seems indicated before the more specific study of its relation to the ovary is discussed. No attempt will be made to prove or to elaborate upon generally accepted theories concerning the function of the thyroid in body economy unless they are specifically related to ovarian function. There will be no elaboration on any of the systemic effects of thyroid malfunction unless it is considered essential to the discussion of the primary question.

It is generally accepted that the principle purpose of the thyroid in body economy is to regulate the speed with which chemical processes occur during life. (13) This fact is utilized clinically in measuring thyroid function by means of the basal metabolic rate estimation. An overactive thyroid will increase the activity of the heat regulating center and cause a greater heat production. Such an increase requires a greater amount of oxygen which is the basis of the standard metabolism rate determination.

Thyroid substance has been definitely shown to exert a dominating influence upon the rate of tissue differentiation. This is in contradistinction to the

role of the anterior lobe of the pituitary which governs the growth as far as mass is concerned. The biologist, Gudernatsch, proved this difference when he found that feeding thyroid substance to tadpoles greatly accelerated the process of differentiation of tissues while the rate of increase in actual size was not influenced. Normally tadpoles require from eighteen to thirty days to develop hind legs and from fifty to seventy days to metamorphose into frogs. Gudernatsch caused the hind legs to develop as early as three to four days and the metamorphosis into frogs to be completed in from twelve to twenty-one days by feeding thyroid substance to the tadpoles. (14) The resulting frogs were perfectly formed but transformation into "adult" animals occurred so rapidly that the pituitary gland, acting at its normal rate,failed to cause adequate growth in size. The end result was the production of a frog perfectly formed but no larger than many insects.

The maintenance of proper functioning of the skin and ectodermal derivatives is at least partially dependent upon normal thyroid function. In hyperthyroidism the hair is fine and silky while the skin is warm and moist. This is in contrast to hypothyroidism where the hair is brittle and the skin is cold and dry. (8)

The heart rate is increased by an overactive thyroid while hypofunction is often associated with a bradycardia.

The effect on mentality is self evident as shown by a comparison of the alert, quick, intelligent hyperthyroid to the dull, apathetic cretin. (15)

The thyroid affects food metabolism by its action of increasing heat production. Hyperthyroidism is associated with hyperglycemia and glycosuria. (9)

By stimulation of the sympathetic nerves supplying the kidney, thyroid substance produces an increase in the elimination of fluids. Infiltration of the skin seen in myxedema may be considered as a specialized disturbance in water metabolism. (16)

There is a great increase in calcium and phosphorus excretion in hyperfunction of the thyroid. There is an even closer relationship between the amount of cholesterol in the blood and the function of the thyroid. In general the higher the rate of thyroid function the lower the degree of cholesteremia. This knowledge is utilized as a confirmatory thyroid function test where increased cholesteremia indicates hypofunction of the thyroid if other factors influencing blood cholesterol can be excluded. (10)

Because both the thyroid and ovary are members of the endocrine family, a brief discussion of the relationship existing between the thyroid and some of the other endocrine glands seems appropriate.

That the pituitary influences thyroid function has been known for many years. (15) Only since the investigation and discovery of the various fractional hormones of the anterior lobe has that relation been fairly definitely classified. A thyrotropic fraction has been isolated and its effects noted. An excess results in a loss of iodine. Active hyperplasia of the gland occurs along with an increase in the excretion of calcium and creatinine, and a rise in the basal metabolic rate. This cycle of events may be produced in experimental animals by the injection of the thyrotropic hormone. In man it is seen after the thyroid gland becomes inadequate in its secretion of thyroxine. Such an insufficiency of thyroxine may occur if the iodine supply is deficient, if the body's demands are exceptionally great, or in the presence of an actual deficiency of thyroid tissue such as would follow thyroidectomy. In the absence of a sufficient amount of thyroxine, the anterior lobe of the pituitary becomes enlarged and by the overactivity of this anterior lobe a compensatory hypertrophy of the thyroid occurs. Thyroidectomy or a parenchymatous goitre produces pituitary hypertrophy while hypophysectomy produces an atrophy of the thyroid. (13)

The interaction of the thyroid and adrenal medulla is based upon their common relationship to the

sympathetic nervous system, as well as upon their interaction by way of the pituitary. The thyroid hormone increases the irritability of the sympathetic system and sensitizes the tissues. This is the basis for the adrenalin test in exophthalmic goitre. (10)

The relationship of the thyroid to the adrenal cortex is less well-known than the connection with the medulla. Apparently the cortex exerts an inhibiting or regulatory effect upon the thyroid, since with the ablation of the cortex and the absence of its effects, there is a temporary increase in heat production. (16)

The effect of the thyroid on the thymus is evidently synergistic. Removal of the thyroid gland hastens the involution of the thymus, while thyroid feeding brings about regeneration of an atrophied thymus. Thymic hypertrophy has accordingly been noted in cases of increased thyroid activity, as for example in acromegaly and goitre. (13)

The action of insulin is opposed by the thyroid hormone so that removal of the thyroid renders an individual more sensitive to insulin and more susceptible to hypoglycemic shock. Thyroid feeding diminishes the hypoglycemic effect, possibly through the promotion of glycogenolysis and possibly through the additional stimulation of the sympathetic system which is brought about by the thyroid. (15)

The relation of the parathyroids to the thyroid

is, at least in part, antagonistic. Parathyroid excess reduces the sensitivity of the structures enervated by the sympathetic nerves while thyroid excess increases it. On the other hand, calcium loss from the bones is accomplished by an excess of either the parathyroids or the thyroid. But in the former the blood calcium is increased, acting thus as a sympathetic sedative, while in the latter it is eliminated as quickly as it is mobilized, thus avoiding hypercalcemia. (16)

EMBRYOLOGY AND HISTOLOGY

The ovaries are derived from the coelomic epithelium as the genital ridge. The germinal epithelium, composed of the cells which later differentiate into the ova is recognizable as early as the sixth week of intra-uterine life. The actual ovarian development is preceded by the appearance of an indifferent organ which does not become recognizable as the ovary until the beginning of the fourth month. For about two months thereafter the cells assume the role of a germinal epithelium, acting as the originators of the primordial sex cells. The wolffian and mullerian ducts develop equally until a predominance of one causes a lag in the development of the other. Only a vestige of the latter finally remains. It is probable that all the primordial ova which are going to be formed have appeared by the end of the fifth intra-uterine month. (17)

The germinal epithelium of the infant is composed of simple cuboidal cells, but in the adult the cells flatten and become more squamous. Directly underneath the general epithelium lies a dense layer of connective tissue, the tunica albuginea. The ovary is composed of two layers, one a superficial cortex and the other a deep medulla. The medulla has a highly vascular

and very cellular stroma of connective tissue in which the follicles are embedded with the products of their maturation and degeneration. It is not considered necessary to describe the growth and maturation of the follicles amd development of the corpus luteum. During the period of sexual life only one ovum a month is discharged, accounting for the loss of perhaps 360 sex cells. By far the greatest majority of the estimated original 400,000 sex cells undergo atresia, a process which may occur in the graafian follicle at any stage of its development. (18)

ANATOMY

The ovary is a paired, flat, ovoid organ measuring approximately one half by one by one and a half inches. Each ovary is so small and so high in the pelvis that it is not generally felt on bimanual examination unless it is definitely ptosed or enlarged. The right ovary is frequently slightly larger than the left. Each presents a whitish surface, which becomes corrugated after puberty due to the scars which form after the rupture of each matured follicle.

Each ovary reposes in what is known as the fossa ovarica, a depression in the lateral wall of the pelvis. The posterior border of the organ is directed backward and medially toward the rectum, while the upper pole is attached to the pelvic brim by the suspensory ligament. The hilus is attached by its mesovarium to the posterior surface of the broad ligament. A layer of germinal epithelium, so called because it is the source of the ova and follicles during embryonic life, envelops the organ completely.

Each ovary is divided into a cortex and a medulla. The outer cortical portion is composed of interstitial connective tissue in which the follicles are embedded. This is the structure in which the ova later develop. The inner or medullary portion is composed of

connective tissue, lymph capillaries, blood vessels and a few strands of smooth muscle and elastic fibers.

The blood supply is derived from the uterine and ovarian arteries which eventually lose their identity by forming a plexus in the medulla. From this plexus smaller branches run into the cortex and finally break up into fine capillaries. The veins are rather large and tortuous in the medulla, gathering in the hilus to form a venous plexus. The nerve supply is derived from the ovarian and uterine nerves. It is also believed that sympathetic nerve cells are present in the ovary, but this has never been definitely proved. (8)

PHYSIOLOGY

In addition to its oogenic function, the ovary elaborates internal secretions which are responsible for certain developmental features. The most important of which are: growth and development of the uterus, vagina and mammary glands at puberty; the appearance and maintenance of the secondary sex characteristics; initiation and maintenance of the menstrual cycle; certain of the bodily changes that take place during pregnancy, especially the embedding of the ovum in the uterus, and the development of the placenta, relaxation of the symphysis pubis, and, together with the anterior pituitary, promotion of lactation. (19)

The principle specific hormone of the ovary is estrin, also known as oestrin, theelin, progynon or female sex hormone. Numerous commercial preparations all prepared in more or less crystalline form and containing this hormone have been placed upon the market under such names as theelin, folliculin and amniotin. (18)

Estrin is produced mainly by the graafian follicle and the corpus luteum. The corpus luteum is believed to produce the greatest quantity of estrin, since the hormone is normally present in maximum amounts in the blood about three days before the menstrual flow.

This is the time when the corpus luteum functions most actively. (20)

In the premenstrual period the presence of estrin leads to endometrial hyperplasia and enlargement of the uterine glands. The uterine and vaginal mucosa increase in thickness and vascularity, a process which is driven to its final stages by progestrin, the secretion of the corpus luteum. Estrin is also responsible for the growth and maintenance of the secondary sex characteristics and together with the products of the anterior lobe of the pituitary, promotes lactation. (18)

Following the preparatory changes in the endometrium brought about by the action of estrin, the next hormone progestin, secreted by the corpus luteum, brings about the changes in the uterine mucosa occurring during the last three or four days of the premenstrual period. The uterine glands enlarge, become tortuous, and extend in a branching fashion. The mucous membrane proliferates greatly and becomes more or less ready to receive the fertilized ovum if fertilization has occurred. If no fertilized ovum arrives, as always happens, except when pregnancy occurs, most of the prepared endometrium is thrown off en masse with concomitant bleeding lasting for a period of three to five days. In other words,

changes take place throughout the month, in preparation for the menstrual period. Every day the system makes further preparation until, after twenty-eight days, the reaction of menstruation occurs. If there is an amenorrhea aside from pregnancy, or if the menstrual periods are too far apart, it may be explained by the fact that the accelerator or hormone responsible for the menstrual preparation was either insufficient or inefficient being deficient either in quantity or quality. That the estrin rather than progestin is chiefly responsible for the menstrual flow is conclusively shown by the demonstration of instances of anovulatory menstruation, where no corpus luteum and consequently no progestin is present. (21)

If fertilization occurs the corpus luteum continues to secrete progestin, not only preparing the uterine mucosa for the reception of the ovum, but helping in its nidation and the formation of the decidua. At the same time the continued presence of the hormone inhibits further ovulation and renders the uterine mucosa refractory to estrin, which otherwise would cause contraction of the uterine muscles with the likelihood of abortion. As it is the uterine mucosa remains quiet and leaves the embedded ovum undisturbed. Once placentation occurs the presence of the corpus luteum is not so essential and pregnancy may continue following

an ovariectomy. Both ovulation and uterine bleeding are inhibited by progestin, best demonstrated in a pregnancy where the persistent corpus luteum and placenta continue to pour out this hormone. The withdrawal of the corpus luteum either by reason of nonfertilization of the ovum or by surgical removal, causes the onset of menstruation. If such removal occurs in the early part of pregnancy, abortion is the inevitable result but this need not occur if pregnancy is well on the way. (22)

Estrin and progestin both complement and antagonize one another. Their complementary nature is demonstrated by the fact that progestin can act only after generative organs have been primed by estrin, while conversely, if estrin persists the action of progestin is neutralized for it is necessary that estrin produce its effect, withdraw and allow progestin to act. (18)

THE RELATION OF THE THYROID TO THE OVARY

The relation of the thyroid to the sex organs in the female is the most ancient and classical illustration of the interrelation of the function of glands of internal secretion. Known to the ancients in its crudest external manifestation, a subject of their daily gossip, it has passed down through the ages. (25) According to Hoskins (10) the Romans made a practise of measuring the necks of brides as a test for prenuptial virginity. This is perhaps the earliest record suggesting the possible relationship between the thyroid and ovarian function. An intimate thyroid-ovarian association is suggested by the transient thyroid enlargement which frequently accompanies puberty, menstruation, sexual excitement, pregnancy and lactation. The high incidence of thyroid disease during adolescence and at the menopause would also seem suggestive of some relationship. This association is further emphasized by the observation that menstrual and reproductive disorders are often encountered in thyroid disease and are frequently benefited by the administration of thyroid. (26) According to Crotti (4) thyroid hyperplasia is six to eight times more common in women during and after adolescence than in the male. Until this period, sex makes no difference in the relative incidence.

Three main methods are available for the study

of an endocrine function. An extract of the gland tissue may be prepared which may then be injected into animals and a study made of its effects; a particular gland may be removed from an animal and its subsequent development, growth and actions noted; studies may be made upon human subjects in whom one or other gland is known to be deficient or overactive. (23)

The rat has proven to be the most easily adaptable experimental animal for this particular problem. The speed with which they proliferate, relatively rapid growth to maturity and the ease with which they may be handled are three factors which make the rat so appropriate for this use. The female rat is a particularly suitable animal for the study of the effects of thyroid on the sexual cycle as the vaginal smear method enables the experimentor to follow the oestrus cycle with ease. Having ascertained the normal cyclic rhythm, it is a relatively simple matter to study the effects of increased or decreased thyroid function by use of the vaginal smear method. (24) At the risk of seeming sacrilegious one might say, in reference to menstruation, that it is "an outward and visible manifestation of an inward, hormonal change". Certainly this phenomenon of ovarian function has played an important part clinically as well as experimentally in the study of this question.

Removal of the thyroid in the immature animal usually delays the time of the onset of puberty. This assumption is based on the work of Marine (25), Hoffman (26) and Goldzieher (13) and others. In contradiction to these results, Lee (27), Evans and Long (28) concluded that thyroidectomy before the establishment of oestrus resulted in no postponement of puberty. It is felt that the work of Evans and Long should be largely discounted. Many of the experimental animals used in their work were found to have some regeneration of the thyroid tissue on post-mortem study. Lee did not consider any animal which showed the slightest sign of thyroid regeneration in the compilation of his results. He also discarded any of the rats which did not seem to be in good health following recovery from the operation. Similar careful technique on the part of Ross (24) failed to corroborate the results obtained by Lee. Her results upheld the assumption of the majority group that thyroidectomy in immature female rats leads to retarded sexual development in keeping with the generally disturbed body growth.

Much more work has been done on the effect of thyroidectomy on the mature female than on the immature animal. Here again the results and conclusions are by no means unanimous. The work of Lee (27) again merits close attention because of his carefully controlled

experiments. He studied the oestrus cycle of the experimental animals and ascertained the lengths of the various phases of the cycle before removing the thyroid. In order to estimate the effects of surgical shock he subjected a group of control animals to sham operations consisting of exposure of the thyroid without actually removing the gland. The oestral rhythm was followed by the smear method and daily determinations of the stage of the cycle were made. Many of the animals, including those subjected to the sham operation, exhibited a disturbance of the regular rhythm for one or two cycles following operation. This could be explained on the basis of surgical trauma or intercurrent infection. In all of the thyroidectomized animals reported on, the rhythm was re-established but the cycles did not return to normal length. In each case the cycles became longer on the average and less regular. The dioestrum or rest interval was the period involved in the lengthening process, occupying from three to fifteen days as compared to two days in the average normal cycle. None of the other stages of the cycle showed any abnormalities.

On the basis of his experimental work, Lee concluded that the thyroid exercises a stimulating action on those cells of the ovary that elaborate the hormone responsible for the cyclic changes of the reproductive tract. Thyroidectomy, in removing the stimulus to the ovarian cells,

causes the time between the production of successive physiologic doses of ovarian hormone to be increased and the dioestrum of the cycle to be correspondingly lengthened.

Many experimental workers have substantiated Lee's results in regard to the effects of thyroidectomy on the oestral cycle. Marine (25) is convinced that removal of the thyroid in young animals will cause arrested sexual development and decreased function in the adult animal. Mazer (20) feels that an inadequate supply of the thyroid hormone will profoundly depress sex function. Kunde (29), Sherwood (30), Van Horn (31) and Hammett are but a few of the investigators who have shown similar results of thyroid ablation on ovarian function. Evans and Long (28) were of the opinion that thyroidectomy affected neither the onset of pregnancy nor the length of the oestrus cycle. Smith and Engle (32) also found that thyroid ablation does not cause any severe upset to the reproductive system of the rat.

Hoffman (26) decided that the effects in the sexual sphere observed following thyroidectomy have been too varied to permit any definite conclusions. According to some workers, thyroid ablation in the immature animal usually delays the time of maturity and materially retards genital development. In the mature animal lengthening

or absence of the estrual cycles, involuntary changes in the secondary sex organs, retardation of follicular maturation, and marked depression of reproductive functions have been reported following this operation. On the other hand, several competent investigators (26) found that thyroid ablation did not delay the onset of estrual cycles or appreciably disturb gonadal and reproductive function of the mature animal.

A great deal of research has been carried out in an attempt to ascertain the effects of gonadectomy on the thyroid gland. Anderson and Kennedy (33) found that the weight of the thyroid tended to decrease following gonadectomy and regressive changes of a histological nature took place. Crotti (4) also reported involution and regressive changes in the thyroid following removal of the ovaries. Sherwood (30) found marked structural changes in the thyroid but no appreciable change in the basal metabolic rate. Marine (25) merely states that removal of the ovaries in animals probably tends to decrease thyroid activity. Loeb (34) found similar results in his work on guinea pigs. This work on the same laboratory animal with similar results was done six years earlier by Chouke (35). There seems to be a general unanimity of opinion that there is some depression of thyroid function following removal of the ovaries. This is characterized more by histologic

signs than by any decrease in basal metabolic rates.

Experimental hyperthyroidism can be readily produced and serves as one method of studying the effects of the thyroid on ovarian function. Weichert (36) found that feeding desiccated thyroid to normal and pregnant rats profoundly affected reproductive processes. The pregnant rats either died, resorbed the fetuses, or delivered themselves after a prolonged gestation. If the fetuses were delivered, they were either born dead or perished shortly after birth. In nonpregnant rats with normal oestrus cycles, desiccated thyroid inhibited oestrus. After the feedings were begun, the rats showed a regular oestrus for about two cycles after which vaginal smears showed a typical dioestrus picture which persisted as long as thyroid was being fed. About six days after the feedings were stopped the regular rhythmic cycle recommenced. Weichert believed that the inhibition of the oestrus could be explained as a result of the response of the pituitary to excessive stimulation by thyroxine.

Van Horn (37) found that it required excessive amounts of injected theelin in order to produce oestrus in experimentally hyperthyroid rats. Kunde (29) in working with rabbits has shown that thyroid feeding is not incompatible with oestrus, ovulation and fertilization but the fetuses are resorbed later in gestation. Crotti (4)

believes that hyperthyroidism inhibits oestrus in rats. When prolan is given in conjunction with thyroxine, oestrus is no longer inhibited. This would seem to show that the pituitary does activate the ovary. An interesting sidelight on this question is the fact that small doses of thyroxine act as a stimulant to rather than a depressant of ovarian function. This may conceivably be explained as one manifestation of the generally increased basal metabolic rate resulting from thyroxine stimulation. If the amount of thyroxine is increased, or if it is continued over a long period, it will result in marked interference with sexual function. This conclusion was reached by Da Costa (38) in his experimental work on female rats, and is essentially corroborated by Marine (39), Kunde (29), Cameron (40) and Ross (24).

A corollary to this phase of investigation is the study of the thyroid and its function following the injection of estrogenic substances. Experiments were carried out on normal, ovariectomized, hyperthyroid and hypothyroid test animals. Pincus and Werthessen (41) showed that the injection of estrogenic substances over a prolonged period of time will result in atrophy of the thyroid gland, flattening of the epithelium and an increase in colloid. During the first few days following instigation of the injections they found an increase in the size

of the thyroid. This result of early stimulation followed by regressive changes in accordance with the work of Da Costa (38) studying the effects of thyroxine on the ovaries. Sherwood (30) studied this question in relation to basal metabolic rate changes. His control animals were subjected to thyroidectomy and the hypothyroid levels were determined. Desiccated thyroid was then administered, maximum levels established, the feeding discontinued and the time interval necessary to reach the previous hypothyroid level determined. It required a period of thirty-four days to reestablish the previous hypothyroid levels. The test animals were subjected to the same procedure and similar levels of hypothyroid and hyperthyroid basal rates were recorded. When the thyroid feedings were discontinued, these animals were injected with solutions of amniotin or theelin. The return to the original hypothyroid level averaged sixteen days for this group. This would seem to show that a direct tissue effect was obtained inasmuch as the principal gland related to metabolism had been removed. Certainly it shows that estrogenic substances in excess can reduce the rate of metabolism which has been previously accelerated by thyroid feedings. This ability to affect thyroid function has also been reported by Hoffman (26) and Crotti (4). Loewenberg (22) found a decrease in the metabolic rate, as well as the previously discussed thyroid involution, following castration of experimental

animals. Thus it would appear that either an excess or a decreased amount of estrogenic substance will reduce thyroid function as manifested by metabolic rates.

It has already been demonstrated that variations in the concentration of thyroxine will materially affect ovarian function. From a consideration of the experimental results so far discussed, it is apparent that the problem of thyroid-ovarian relations is not a simple question of one gland stimulating or depressing the function of the other. Rather it evolves itself into a consideration of finely balanced causes and effects influenced by the pituitary. The anterior pituitary has been firmly established as the principal governing body in the entire endocrine system. (8) The most powerful known stimulant of thyroid activity is the thyrotropic hormone elaborated by the anterior pituitary. (39) The thyroid and pituitary are delicately balanced so that a deficiency of thyroid stimulates the latter to produce more thyrotropic hormone as shown by the hypertrophy of the pituitary which follows thyroidectomy. This compensatory hypertrophy would appear to be entirely an attempt to compensate for the decreased level of thyroxine because one of the effects of thyroidectomy is a decrease in the concentration of the ovulation producing hormone of the pituitary. (42) Moderate thyroid feeding will produce an increase in the gonadotropic fraction elaborated by the

anterior pituitary. (37) This specific fraction represents the chief source of stimulation of ovarian function. (13) Test animals in which experimental hyperthyroidism has suppressed oestrus will again show cyclic manifestations upon administration of anterior pituitary extract. (4) The action of the thyroid on the sex glands is probably neither direct nor specific for the striking sexual precocity which can be elicited with anterior pituitary hormone cannot be duplicated with thyroid substance (26) nor can the complete suppression of gonadal function which is invariably a sequel to hypophysectomy be produced by thyroid ablation. (43) It would appear in the light of the evidence presented that the seemingly contradictory conclusion of Crotti (4) that the thyroid inhibits the ovary and the ovary stimulates the thyroid in normal physiologic conditions is not without some merit.

The clinical approach to this problem is complicated, or rather handicapped, in certain respects. Our civilization is either too far advanced or not enough advanced to allow experimental procedures to be practised on humans. The controlled experiments carried out on animals as exemplified by the work of Lee (27), Ross (24), Van Horn (37) and other competent research workers cannot be duplicated on human subjects. Nor is it possible to assume that results obtained from animal experimentation presuppose similar results in the human. The clinician is limited to the study of individuals in whom one of the two glands is proven to be either overactive or underactive. The best example of this situation is in the case of the thyroid. Basal metabolic rate determinations enable the clinician to estimate with reasonable assurance whether he is dealing with a hyperactive or hypoactive thyroid. In a like manner the study of vaginal smears or curetted materal will enable the pathologist to ascertain, at least to a certain degree, the functional activity of the ovaries. The psychological element which further complicates this problem when it deals with the human subject, must remain as the unknown factor in the equation.

Hypothyroidism in the female is often accompanied by irregularities in the menstrual cycle. In extreme cases of thyroid deficiency, such as frank cretinism or myxedema,

sex function is profoundly depressed. (22) Menstruation in the female cretin is generally delayed and in some cases never occurs. Genital hypoplasia, so common in this particular manifestation of decreased thyroid function, is natually concomitant with the suppression of ovarian function. When ovarian function is not completely lacking, the menstrual periods are characterized by irregularity in the cycle as well as in the quantity of the flow. The same holds true for cases of myxedema when it develops before the menopause. The absence of thyroid hormone will result in abnormalities of menstruation if not complete cessation. (26)

Milder forms of hypothyroidism with a diminished or insufficient thyroid secretion result in hypoplasia of the genital organs leading to deficient sexual function in the young and regression of sex organs in the adult. Thyroid removal does not totally abolish sex function nor can injections of its active principal evoke maturity. (13) However, menstrual disturbances are a usual accompaniment of deficient secretory activity of the thyroid and range from total loss of the cyclical function to menorrhagia. Complete amenorrhea so common in pituitary and primary ovarian hypofunction is relatively rare. The intermenstrual interval is either shortened or lengthened, but the quantity and duration of the flow are usually increased. (20)

Bram (44) concludes that menstruation in thyroid

deficiency may be at times regular in rhythm, but it is usually excessive in quantity and characterized by menorrhagia. He is supported by the work of Lawrence and Rowe (45)who found that menstrual disorders not dependent on pelvic disease represented a prominent symptom in cases of hypothyroidism and were characterized by an irregularity of flow and menorrhagia. McGarrison (46) considers menorrhagia as a definite symptom of thyroid deficiency. Warfield (47) is of the opposite opinion and stresses the infrequency of menstrual disorders seen in cases of hypothyroidism. Hamblen, Pullen and Cuyler (48) feel that the thyroid has no direct association with the gonadopituitary axis. The hypometabolism of thyroid failure results in a quantitative slowing down of ovarian activity and faulty maturation of the ova. The alterations in the local oxygen metabolism of the ovary are largely concerned with its responsiveness or sensitivity to the gonadotropic influences of the pituitary. This work would appear to be in contradiction to the conclusions of Bryant (49). He has shown that thyroidectomy is followed by hypertrophy of the anterior pituitary. This hypertrophy does not necessarily imply an increase in function because Bryant found many of the cells were subject to vacuolization and degenerative changes indicating a depression of the specific secretion of these cells. This degeneration would seem to suggest that some

of the results of thyroid deficiency may be produced indirectly through depression of the pituitary gland.

Although sterility is a noticeable accompaniment of hypothyroidism, pregnancy is not incompatible with moderate grades of thyroid deficiency. In regions where goitre is endemic, women with colloid or adenomatous goitre may give birth to infants also with colloid goitre or frank cretinism. The development of colloid goitre during pregnancy usually does not affect the course of the gestation, unless the degree of hypothyroidism is so intense as to bring about abortion or miscarriage. Litzenburg and Carey (50) have observed that women with hypothyroidism showing a history of previous miscarriages, could be carried to full term pregnancies by the use of thyroid tissue. Mazer (20) contends that women suffering from habitual abortion without an ascertainable cause, will respond favorably to small doses of thyroid even when the basal metabolic determination is normal. This conception is in agreement with the findings of Foster and Thornton (51) who also found thyroid therapy of value in menstrual irregularities of unknown etiology. Winkelstein (52), as a result of his study on the effect of thyroid on sterility in normal and hypothyroid females, takes issue with Mazer's conclusions in the use of thyroid in the absence of definite evidence of thyroid hypofunction. He found that the effect of

thyroid as an adjuvant or a curative measure for sterility was demonstrable only when a definite lack of thyroid function was present, and was of little or no value when normal function existed. In this he is substantiated by the findings of Severinghaus (53) who decries the tendency of clinicians to give thyroid in the absence of any signs of decreased thyroid function in the treatment of sterility or other abnormalities of the sexual sphere including habitual abortion. King and Herring (54) have shown that abortion, especially of the "missed variety" is often associated with hypothyroidism and is amenable to thyroid therapy. Means (6) also substantiates these findings.

Hypothyroidism may be seen in gynecologic practise in a very frank form with such symptoms as obesity, mental sluggishness, somnolence, puffiness and dryness of the skin, coarseness of the hair, and with the characteristic dull, stupid facies. In such cases the patient may suffer with either menstrual deficiency or menstrual excess, more commonly the latter. The basal metabolic rate will show marked lowering while the blood cholesterol will be very high. In milder or masked forms of hypothyroidism there is often a complete absence of the symptoms mentioned above although the thyroid factor may be indicated by a decreased metabolic rate and a relatively high blood cholesterol level. The

menstrual picture in this milder form is not so definite, but in the majority of cases it seems to take the form of an excessive flow.

The clinical investigators seem to have placed less emphasis on hyperthyroidism in relation to irregularities of ovarian function than on hypothroidism. It has been shown in the discussion on animal experimentation that hyperthryoidism does exert definite effects upon the sexual cycle. The conclusions drawn were that increased thyroid action will stimulate ovarian function at first, but, if long continued or excessive, it will inhibit the manifestations of ovarian activity. Reports in clinical literature seem to bear out these same results in the human. The characteristic menstrual pattern seen in thyrotoxicosis is that of oligomenorrhea or amenorrhea as contrasted to the menorrhagia commonly associated with hypothyroidism. (55)

This particular phase of the problem is complicated by the difference in effect upon ovarian function exerted by hyperthyroidism in exophthalmic goiter as compared to hyperthyroidism in connection with adenomatous goiter. The former manifestation of thyroid hyperactivity is almost without exception associated with marked concomitant irregularities in the menstrual cycle while the adenomatous form is seldom accompanied by such abnormalities. (20) This difference in reaction can be explained by the two different disease processes involved. In exophthalmic goiter the clinician is dealing with a systemic condition profoundly affecting the generative organs as well as other

glands of internal secretion. On the other hand, in the hyperthyroidism of adenomatous goiter, a single gland is seriously affected, whereas the other ductless glands including the ovaries are only slightly involved, if at all. (21)

In the preadolescent woman suffering from exophthalmic goiter, menstruation is either delayed or totally absent until recovery is effected. (26) In the adult the irregularities in the sexual cycle may vary from total absence to marked excess of flow. Bram (44) states that fully fifty percent of cases of typical Grave's disease present varying degrees of amenorrhea depending upon the duration and severity of the illness, the age of the patient, and somewhat upon her sexual history. Smith (56) avers that women with toxic goiter occasionally have short periods of amenorrhea, otherwise their pelvic organs seem to behave in a normal manner. Hamblen (17) states that menstrual disorders are commonly associated with hyperthyroidism. Menorrhagia may occur, but more frequently there is hypomenorrhea, oligomenorrhea and eventually amenorrhea. Regressive changes may occur in the internal and external genitals, due primarily to the general emaciation and exhaustion rather than to secondary ovarian deficiency. (19)

Sterility is a common corollary to hyperthyroidism but pregnancy may occur in some patients with severe

hyperthyroidism and they may even proceed to term without untoward circumstances. (10) Moderate hypertrophy of the thyroid has been generally accepted as incident to pregnancy. Davis (57) has reported that approximately forty percent of his patients examined early in pregnancy had some enlargement of the thyroid gland, and Reycraft (58) found that over half of his patients showed appreciable enlargement. Marine (25) is of the opinion that the iodine content of this gland is decreased during pregnancy. In a large percentage of cases, definite enlargement of the gland can be recognized clinically, and in a small number of cases symptoms of hyperthyroidism may supervene. (20) Davis (57) advocates the administration of small doses of iodine during the course of pregnancy even when the thyroid is not enlarged. The studies of Baer (59), Cornell (60), and Rowe and his associates (61) indicate that the metabolic rate is increased in most women at the end of pregnancy. Sandiford and Wheeler (62) have shown that the rapid increase in the metabolic rate occurring in the last three months of pregnancy is not due to the presence of an excess of thyroxine in the tissues, but is caused by an increase in the amount of protoplasmic tissue brought about by the growing fetus. Accordingly a basal metabolic rate of plus twenty to thirty is not necessarily an indication of hyperthyroidism in the latter months of pregnancy. In the absence of pregnancy the basal

metabolic rate is at its highest point during the premenstrual stage and reaches its low ebb at the time of the flow according to Hoskins.(10) He further believes that the thyroid hypertrophies to the point of palpation in about one-half of the cases of pregnancy.

The literature which has been reviewed indicates beyond any reasonable doubt that the thyroid exerts a potent effect upon ovarian function. Variations in the amount of thyroxine elaborated may result in diverse irregularities in the menstrual pattern (63), sterility, abortion or the production of abnormal offspring. (64)

SUMMARY AND CONCLUSIONS

There can be no reasonable doubt that the thyroid exerts a definite influence upon the function of the ovaries. Experimental and clinical evidence has clearly shown abnormalities in thyroid function are generally accompanied by variations in the sexual sphere. A review of the literature reveals no complete unanimity of opinion regarding the exact nature of ovarian response to increased or diminished thyroid activity. In general hypothyroidism results in a delay in the onset of puberty and a suppression of ovarian function after puberty. The characteristic menstrual abnormality is menorrhagia although dysmenorrhea, oligomenorrhea and amenorrhea have been noted. In the presence of an overactive thyroid, the menstrual disorder is more apt to be amenorrhea although variations up to and including menorrhagia have been noted.

Neither hypothyroidism nor hyperthyroidism is completely incompatible with pregnancy unless the condition involving the thyroid gland is extreme. Any marked variation from normal thyroid function has a deleterious effect on a pregnancy ranging from long, difficult labor as seen in hypothyroidism to resorbtion, abortion or stillborn young as seen in hyperthyroidism. It has been shown

that the administration of thyroid will spectacularly alleviate menstrual disorders which have been manifest in the presence of decreased thyroid activity. Also by treating hyperthyroidism the clinician has been able to control concomitant abnormalities in the sexual sphere.

Having shown a definite thyroid-ovarian relationship, the next step is to attempt to ascertain the mechanics of this relationship. The main function of the thyroid, in the eyes of many investigators, is to control the rate of oxygen consumption. It is conceivable that the effect on sexual activity springs directly from this power to regulate metabolism. By increasing ovarian metabolism, the thyroid may be considered as directly increasing ovarian function. The administration of thyroid to a normal person or experimental animal will cause an increase in ovarian function. If long continued or given in excess, the early stimulation will be followed by a depressant action and regressive changes in the ovary will take place. This phenomenon is compatible with the belief held by many men that the thyroid-ovarian relationship is a direct one. The ensuing regression may be due to toxicity associated with hyperthyroidism or merely the fact that any stimulation, mechanical or chemical, will lead to a depressing action if long continued.

The concept of a direct relationship is not

weakened by a consideration of ovarian function in hypothyroidism. A decrease in metabolism might very well explain ovarian dysfunction. The hormones contributing to the maintenance of the sexual cycles may not be present in sufficient concentration for normal function.

There is a strong probability that the mode of action is indirect rather than direct; the action being mediated through the anterior pituitary. This gland, reputedly the key figure in the entire endocrine system, is known to possess a thyrotropic and a gonadotropic fraction within its hormonal secretion. It has been shown to exert powerful influences on both the thyroid and the ovary. Pituitary transplants from an animal made experimentally hyperthyroid have been shown to cause marked stimulation to ovarian function in the recipient animal. This would appear to be positive evidence that any thyroid stimulatory effect upon the ovary is mediated, at least in part, through the anterior pituitary.

An interesting hypothesis to account for the thyroid effect on ovarian function involves the concentrations of theelin and thyroxine. Before the pituitary can complete the cycle culminating in menstruation by elaborating prolan, a certain level of theelin must be attained. In the presence of a normally functioning thyroid, pituitary and ovary, the sexual cycle is completed. The ovary

elaborates a sufficient amount of estrogenic hormones, the pituitary,properly stimulated by the thyroid and in the absence of a pregnancy,drives the cycle to its normal end in the menstrual flow. Menstrual irregularities based on abnormality in thyroid function can be explained as the result of failure to stimulate the pituitary in the case of hypothyroidism. In overactivity of the thyroid with its concurrent increase in general metabolism, elimination of theelin by the kidney may be increased or its production inhibited by overstimulation or by the toxic effects associated with hyperthyroidism. This is merely a theory and is not meant to be represented as a factual reality.

There is only one conclusion to be drawn. The thyroid exerts a definite influence upon ovarian function, and the effect seems to be depressive. The mechanism through which this effect takes place is unknown. It is felt that it may be predominantly through the mediation of the anterior pituitary although a direct action through the thyroid's influence on metabolism may be a contributing factor. The actual mechanism is yet to be ascertained.

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