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Interrelationships of the anterior pituitary and thyroid glands

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INTERRELATIONSHIPS OF THE ANTERIOR PITUITARY
AND THYROID GLANDS

Senior Thesis
1935

Orlo K. Behr
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Introduction:

This thesis is not an attempt at a discussion of the pituitary gland in its many relationships to physiology and disease. Neither is it intended as a discussion of the thyroid gland in its entirety. It will, however, attempt to correlate the experimental evidence which points to a functional relationship between the two glands, and with this in mind, will present certain clinical conditions in which the two glands are involved.

Embryologically the relation between the anterior pituitary and the thyroid is very close, both structures being formed from a mass of epithelium split off from the pharynx. (50) A certain resemblance between the two glands histologically has long been recognized, (52, 53) more particularly the fact that there is present in the normal pituitary a substance similar in appearance to the colloid material of the thyroid.

Experimental Work

Thyroid Ablation in its Relation to the Anterior Pituitary Gland:

The first work setting up any sort of a hypothesis as to a relation between the thyroid and the anterior pituitary was that of Rogowitsch in 1888. (59) He found enlargement of the pituitary following thyroidectomy in rabbits and dogs. He also reported an increased production of colloid by the cells of the anterior lobe with indications of its passage into the blood vessels. He was induced by these results to formulate the theory that after thyroidectomy the pituitary takes over the
function of the thyroid gland and endeavors to compensate for the loss of thyroid secretion through increased activity.

Following Rogowitsch's work, evidence began to accumulate substantiating his results. Hofmeister in 1892 found hypertrophy of the hypophysis in thyroidectomized rabbits, with the gland doubling its weight in twelve weeks. (37) Steida, 1890, found hypertrophy of the hypophysis in thyroidectomized animals to be due to an increase in the number of "Hauptzellen" or chromophobe cells with the formation of vacuoles in them. (74) He was unable to find any changes in the chromophil cells or an increase in colloids.

Gley found that at the end of a year in a thyroidectomized rabbit, the pituitary had increased to five times its normal weight. (33)

In most of these early experiments, the weights of the animals were not given, and the results were generally very loosely presented. In 1912, Degener carried out a carefully controlled series of experiments with accurate weights. The anterior lobes of the pituitaries of the thyroidectomized animals were found to be distinctly heavier than in the control animals, and the increase appeared to run parallel to the time elapsing between thyroidectomy and death, the longer the interval, the greater the size of the pituitary. (21)

Others in the years following, have reported similar results, the enlargement being chiefly in the anterior lobe. To interpret this enlargement as an increase in function, however, seems to be a mistake, as shown by recent work of Bryant's (11)
In his experiments on thyroidectomized rabbits, he finds the anterior lobe profoundly changed while no other changes could be detected in the other lobes. The pars anterior, however, showed a striking decrease in the number of eosinophile cells amounting to an almost complete disappearance in cases of long standing. Those cells that remain have less granules and do not stain so intensely. It is the chromophobe cells that are mainly responsible for the increase in weight and size of the organ following thyroidectomy. The basophile cells are no longer recognizable. The chromophobe cells, however, were markedly hypertrophied. Many evidences of degeneration are to be found in these cells, some going to a complete breakdown and resulting in punched out spaces containing cellular debris.

In evaluating his findings, the author says, "There is no justification for interpreting these results as indicating increased secretory activity of the pituitary gland in cases of thyroid deficiency--quite the contrary. The disappearance or reduction of the alpha cells indicates rather a depression of the specific secretion of these cells, and the tendency of the enlarged chromophobe cells to degenerate is an indication of the tendency of functionally depressed cells to complete their cytomorphosis and disappear rather than to de-differentiate and reproduce. The profound modification of both alpha cells and chromophobes under these conditions, suggests that some of the results of thyroid deficiency may be produced indirectly through depression of the pituitary gland."
Interrelationships in Metamorphosis and Body Growth:

The spark, so to speak, which ignited the long train of research into the relations of the anterior pituitary and thyroid glands to metamorphosis and body growth, was the work of Gudernatsch (1912-1914) concerning the effect of thyroid feeding on anuran tadpoles. (35) In the feeding of different animal extracts of various glands he found that the most striking results could be obtained with thyroid feeding. The influence was such that it stopped any further growth while simultaneously accelerating the differentiation of the body immensely and bringing it to a premature end. It was not of much importance in what stage of differentiation the thyroid was started, for within three to five days a change in the features could be noticed. Gudernatsch was of the impression that the suppression of growth was only incidental since rapid differentiation does not allow growth.

Shortly following Gudernatsch's experiments on thyroid feeding, Adler made the first attempt to remove the pituitary in anuran tadpoles. (1) Out of 1200 specimens in which the hypophysis was destroyed by cautery at a late stage, three individuals survived. In none of these tadpoles did the hind limbs develop beyond a bud, transformation did not take place, and they remained neotenous tadpoles.

In 1916, Bennett Allen and P. E. Smith working independently, simultaneously devised a method for removing the anlage of the hypophysis in three to four m.m. tadpoles. (2, 67) The results they reported were similar, each showing contraction of
the pigment cells of the epidermis producing loss of pigmentation, retardation of growth, retardation of metamorphosis, and atrophy of the thyroid. In the light of Gudernatsch's experiments, Smith suggests that the non-development is due to atrophy of the thyroid and not directly to the hypophysis. In describing the appearance of the thyroid in his hypophysectomized tadpoles, he notes that they are one-third normal size and show few vesicles and little colloid.

Many workers now began to experiment in this field and much work, some contradictory, began to be reported. To record all the findings could not be done within the scope of this thesis, but some of the more pertinent evidence will be considered.

In 1917 Allen removed the thyroid in anuran tadpoles. (3) For three months no changes were noticed, then when metamorphosis began in the controls, there was no change in the thyroidectomized animals. The only organs which showed any development from then on were the gonads, the brain, alimentary tract, and other organs failing to develop. However, thyroid administration brought about resumption of development even four months after it had ceased.

Swingle in 1918 reported some striking results when he was able to produce complete metamorphosis in tadpoles in three weeks when it ordinarily took two to three seasons, by thyroid feeding, thus producing miniature but otherwise normal frogs. (75)

The above work seems to establish unquestionably the relation of the thyroid to metamorphosis. All observers were also
agreed that the active principle was an Iodine compound.

Swingle found that when iodine or its inorganic compounds were administered either in the food or dissolved in the medium, that metamorphosis was greatly stimulated. (76) He also found that it would induce metamorphosis in thyroidless larvae and that a certain small amount was necessary in the water for even normal tadpoles to metamorphose. This view harmonizes with that expressed by Kendall. (39) Thyroxine affects the mammal's basal metabolic rate in a manner quantitatively related to the dose. Injection of a derivative, however, had no effect upon the basal metabolism. On the other hand, Kendall found that both thyroxine and his inert derivative were active when tested in regard to amphibian metamorphosis. From this he concludes that thyroxine has two modes of action, one a specific one in virtue of its construction and the other a non-specific one in virtue of its iodine content.

An intimate connection with the work of Allen and Smith on hypophysectomized tadpoles was made by Allen when he showed the possibility of inducing metamorphosis in hypophysectomized tadpoles with thyroid administration. (3) Furthermore, he showed that whereas tadpoles endowed with both these glands can complete their metamorphosis with the intake of very minute quantities of iodine, the addition of large quantities of inorganic iodine will also induce metamorphosis in tadpoles in which the thyroid, the pituitary, or both glands are absent. The exact action of the Iodine is unknown, and as Uhlenhuth has pointed out, the form in which it is acted on in the tissues is ob-
scure, and it may be that the animal tissues have the power of transforming the iodine into thyroxine. With this view, the primary function of the thyroid would be not so much that of manufacturing as of storing the thyroxin. (78)

P. E. Smith in a series of experiments in which various lobes were either injected or transplanted in hypophysectomized tadpoles found that the individual into which the pars anterior had been grafted underwent precocious development and that the thyroid in these tadpoles was hyperplastic. Replacement with the other lobes had no effect upon development or the thyroid. (70) From these experiments it appears that the anterior lobe is the part concerned with metamorphic changes and that it operates by stimulating the activity of the thyroid. That the metamorphosis is not referable to a direct action of the anterior lobe on the body tissues, is shown by the fact that the thyroidectomized tadpoles to which it is given do not metamorphose. (72) Furthermore, it is shown by Uhlenhuth that at the time of metamorphosis when the growth of the organs is interrupted that the thyroid is more active structurally. (79) Therefore it seems definitely established that in relation to tadpole metamorphosis that the thyroid gland is essential, but that the anterior pituitary also influences it by stimulating the thyroid.

The relation to body growth is somewhat different and here the anterior pituitary with its growth hormone is the most important. However deficiencies in thyroid, clinically at least, are also blamed for growth deficiencies, witness cretinism. It is a moot question, however, how much of this deficiency may be
due to secondary pituitary involvement with decrease of the
growth hormone from the anterior pituitary. Evans & Long have
isolated the growth hormone and proven it to come from the
anterior lobe, more specifically, the eosinophilic cells of
this lobe. (26) They have produced dwarfed rats by hypophy-
sectomy and acromegalic giants by injection of the anterior
pituitary growth stimulating substance. Putnam, Teel, and
Benedict have produced classic acromegaly in different strains
of dogs through anterior pituitary injections. (55)

It has been shown that injection of beef anterior pit-
uitary growth preparations or the implantation of gland substa-
ance causes resumption of growth in animals dwarfed by hypo-
physectomy. (71) It has also been shown that thyroidectomy pro-
duces a dwarfing of experimental animals. However, thyroid
administration does not cause growth in the absence of the
anterior pituitary, while anterior pituitary growth hormone
induces growth in rats dwarfed by thyroidectomy. (73, 27)
Therefore, of these two glands the anterior pituitary is the
only essential one for growth. However, this does not preclude
that the thyroid is not normally an aid to the growth action
of the pituitary. In experiments on thyroidectomized and hyp-
ophysectomized rats with feeding of anterior pituitary growth
hormone, with and without thyroid, the skeletal growth was in-
creased in those animals receiving thyroid in addition to the
anterior pituitary preparation. (69) Clinically, also, the
results of replacement therapy in cases of pituitary dwarfism
seem to be better if the two are given together. (31) This in-
dicates either a stimulating effect on the pituitary by the
thyroid or a synergistic effect of the two.

Relation of Anterior Pituitary to Thyroid Gland Structure:

The first evidence that pituitary ablation caused definite and invariable changes in the structure of the thyroid gland came with the work of Allen and Smith previously cited. They found that if the ectodermal bud going to form the anterior, intermediate, and tuberal lobes of the hypophysis was removed in the early stages of tadpole life, that the thyroid failed to undergo normal development. The follicles were much reduced in number and size, contained little colloid, and were lined by flattened epithelium. These experiments, while showing that normal development did not take place in the absence of the pituitary, did not show whether this was due to the absence of the whole gland or one of its parts. In a series of later experiments, however, it was shown that the administration of anterior lobe para- enterally, but not of the other lobes, produced reparative effects. This shows that the thyroid atrophy is due to a loss of the anterior pituitary secretion alone.

Further interesting results have been shown. While the paraenteral administration of anterior lobe substance restored the thyroid to normal it did not bring about any hyperplastic or abnormally large glands. However, extracts made from the central portion of the anterior pituitary produced pronounced enlargement and hyperplasia, while an extract made from the peripheral portions did not even restore the gland to normal. However this latter extract gave a greater stim-
ulus to body growth than did the extract made from the central portion of the gland. Since identical procedures, the same dosage, and the same dilutions were used, the quantitative difference in the response of the two points to a different concentration of the two hormones, one which stimulated body growth and the other which stimulates the thyroid.

This difference of activity was further supported by a histological study of the gland, which showed that the central part of the gland which supplied the thyroid hyperplasia was more plentifully supplied with basophiles, while in the peripheral portion, the acidophiles were more plentiful. This is in accord with experimental findings which regard the acidophiles as supplying the growth hormone and the basophiles as supplying the gonad hormone. In isolating the thyrotropic or thyroid stimulating hormone, certain workers have claimed it to be the same as the gonadotropic hormones that are derived from the basophilic cells. (56)

The above experiments have shown that by varying the amount of anterior pituitary secretion available, any type of structure from extreme atrophy to pronounced hyperplasia could be produced in tadpoles.

The effects of hypophysectomy in mammals upon the thyroid structure is essentially that produced in tadpoles, with the exception that the operation must be done at a later stage when the thyroid has had a chance to develop, and the results are those of atrophy or involution rather than failure of development.

In rats, a very good animal for this sort of work since
they possess a tough diaphragm separating the pituitary from the brain substance, the pituitary can be removed without injury to the hypothalamus. In these animals, within ten days after hypophysectomy, the thyroid begins to show a decrease in size which reaches its maximum within a month. Accompanying this is a pronounced structural change. There is a decrease in colloid and a marked flattening of the follicular epithelium with a loss of much of its cytoplasm. The thyroid also loses its capacity to undergo compensatory hypertrophy, and no hypertrophy will take place following partial thyroidectomy as occurs in normal animals. Evidently the stimulus for hypertrophy is lacking.

Houssay describing the picture of the thyroid in hypophysectomized dogs says, "The thyroid of hypophysectomized dogs shows morphological and functional signs of hypothyroidism. The weight of the gland is decreased, the epithelium low and flattened, almost endothelial, the cells are small, the vesicles of normal width appear dilated, and the colloid is dense with no central vacuoles and few at the periphery. There are no zones of functional activity as in normal thyroids. After subtotal thyroidectomy, compensatory hypertrophy is not produced. Sometimes the walls of the acini break down and large vesicles are produced." (38)

Replacement therapy, on the other hand, in the form of fresh hypophyseal implants, produces marked reparative changes in the form of increased size of the thyroid and a return to normal appearance of the follicular epithelium. (38, 68) The picture of involution can again be restored by stopping the
implants. This has been shown by the taking of biopsys at various stages in the course of the experiment. (70)

That the injections of anterior pituitary extract will produce a hypertrophy and hyperplasia of the thyroid of normal guinea pigs was first reported by Loeb and his co-workers. (45) Previous to this they had been working with the feeding of anterior pituitary extract by mouth and had come to the conclusion that this substance acted as a depressant on the thyroid, as shown by the failure for compensatory hypertrophy to occur when it was given. The finding, however, that the injection of anterior pituitary extract had a stimulating effect on the thyroid led them to the conclusion that there was both a depressant and a stimulating hormone in the anterior pituitary. (45) This will be discussed in more detail later.

While they found that thyroid substance was effective in preventing the hypertrophy caused by potassium iodide feeding or compensatory hypertrophy, they found that it was much less potent in preventing the effects of anterior pituitary injections. (51)

Let us compare a description of experimentally produced hyperplasia as given by Loeb, with a description of the hyperfunctioning phase of hyperthyroidism as given by Rienhoff in a recent article on thyroid pathology. (56)

Loeb(44), in giving a resume of the histological changes seen with experimental hypertrophy of the thyroid, describes the complex as follows, "1. Acini which are larger than medium
sized and often irregular, 2. higher epithelium, 3. an increase in the number of mitoses, 4. softening of the colloid, 5. an increase in the number, size, and activity of the phagocytes, and 6. probably an increase in lymphocytes and in the number of spurs and papillae reaching into the cavity of the acini."

Reinhoff in a description of the hyperfunctioning phase of hyperthyroidism in the human, says, "At the height of the activity of the disease, the gland in the gross or macroscopically was soft and of a reddish brown color and very vascular. Microscopically, the follicles were quite irregular in shape and size, having a lace like appearance, with a pronounced diminution in the colloid, that which was present staining very slightly. The colloid did not abut upon the apices of the epithelial cells but was separated from them by non-staining chromophobic vacuoles. The parenchyma of the gland was markedly increased in comparison to the equally pronounced decrease in the amount of colloid. The hypertrophy of the epithelial cells resulted in the elongation of the cells from a cuboidal to a columnar type and the hyperplasia caused an infolding of the epithelium lining the follicles."

The similarity between these two descriptions is quite apparent.

Other observers have shown similar results in ducks, rabbits, pigeons, and other experimental animals, although various animals seem to vary in the thyroid response to anterior pituitary injections. (4, 12, 16, 23, 32, 36, 38, 58, 62)
Rats are particularly resistant, and hyperplasia could be produced only by pituitary transplants in the case of Smith's experiments(71), and Anderson was able to produce it only with the simultaneous injection of killed staphylococcus cultures along with the anterior pituitary extract.(4)

Crew and Wiesner were the first to suggest the term "Thyreotropic hormone" for the thyroid stimulating substance of the anterior pituitary.(16) Since then, several workers have reported isolation of this hormone by various means.(5, 40, 58) It has been shown to be free of both the growth and gonadotropic hormones, since neither increased growth or maturity could be produced by the continuous injection of the hormone, while on the other hand, quite typical thyroid hyperplasia could be produced with it.

Recent work has shown that this effect of hyperplasia is only temporary and that after two to four weeks the thyroid begins to show involutional changes which progress to such a degree that the gland comes to resemble that of an untreated hypophysectomized animal.(32, 15, 36) There is a corresponding fall in the basal metabolism after an initial rise that may go to a minus rate. This picture parallels that seen in the human with Grave's disease to a certain degree. Marine brought out the cycle of change in the human from normal to hyperplasia to "Exhaustion atrophy after spontaneous prolonged hyperplasia", (48) and Rienhof gives a good summary of the involutional changes occurring the thyroid both after potassium iodide administration and spontaneously.(56)
Collip and Anderson explain this exhaustion phenomenon on the basis of an antithyrotropic substance which apparently is manufactured through repeated administration of thyrotropic substance. (15) This antithyrotropic substance is present in the animals blood and can be demonstrated by the fact that if blood serum taken from animals to which thyrotropic hormone has been administered for a long period of time is injected into normal or hypophysectomized animals, that these animals are resistant to thyrotropic hormone of the anterior pituitary of known, tested strength. The method of manufacture of this antithyrotropic substance is not understood.

Collip and Anderson claim that they have also found anti-hormones for the adrenals, gonads, and pancreas, and have recently postulated a theory for anti-hormones, which is, to quote from them, "1. The responsiveness of an individual to an administered hormone varies inversely with the hormone content or production of the subject's own gland. 2. For each hormone, there is an opposite, an antagonistic or anti-hormone substance. 3. The absolute amount of a hormone and its respective antagonist determines the degree of stability of the subject so far as this particular endocrine function is concerned." (14) In other words, the two opposed activators function similar to a buffer system, and a hyperfunctioning state of an endocrine gland may not be due to an over secretion but rather to a lack of inhibitory substance, and v. v.

To summarize the experimental changes in the thyroid gland structure in relation to the anterior pituitary, we find that
hypophysectomy results in atrophy, replacement therapy restores it to normal, and anterior pituitary injections produces a temporary hyperplasia of the gland in normal animals, varying in its response according to the species, with a subsequent regression due to the development of some antithyrotropic substance.

Relation of Anterior Pituitary to Basal Metabolism:

Various observers have shown that ablation of the pituitary gland causes a decrease in the basal metabolism in experimental animals. (7, 29, 38) The first to record this were Benedict and Homans in 1912. (7) They produced a definite fall in pulse, respiration, and total metabolism in dogs in which they performed the hypophysectomy. They also reported a retardation of growth, abnormal deposits of fat, and non-development of sex organs. The results of their experiments are objected to on the grounds that in their operation they also produced injury to the tuber cinereum and brain substance.

Foster and Smith in 1926 determined the basal metabolism of hypophysectomized rats before and after implants of the anterior pituitary were made. (29) Their experiments showed that the hypophysectomized animals were thirty-five percent below the average of a series of normal animals. Their body weight was also invariably lower than the controls, and they had to be kept at a temperature above that of normal rats to prevent death by chilling. They were able to restore the basal rate to normal by daily anterior pituitary implantations or by daily injections of thyroid extract, but not by daily injections of posterior lobe extract.
Some quite conclusive work has been reported by Houssay and his associates regarding the basal metabolism in hypophysectomized and thyroidectomized dogs. (38) They found that hypophysectomy resulted in a lowering of the basal rate between thirteen and sixteen percent from the controls. They interpret this lowering to be due either to an alteration of thyroid function or a suppression of a pituitary hormone acting directly on the basal metabolism. The decrease in metabolism noted in the hypophysectomized animals is not as low as that in athyroidism, and if the thyroid is removed in hypophysectomized animals, the metabolism is further lowered. However, if the pituitary is removed in thyroidectomized animals, additional diminution does not occur. Therefore, they conclude that the pituitary does not have any direct effect of its own on the metabolism, but that hypophysectomy produces a partial suppression of thyroid function. With the use of anterior pituitary extract, they are able to raise the basal metabolism in normal and hypophysectomized dogs but not in thyroidectomized dogs.

Lee and Gagnon report contradictory results in their experiments. (42) They found a decrease in the basal rate starting several days after the injections were started and continuing eight to ten days after they were stopped. The majority of the evidence, however, is in favor of an initial rise at least.

Siebert and Smith, working with guinea pigs which were normal, partially, and completely thyroidectomized, found that the daily injection of one cc. of acid extract from bovine ant-
terior pituitary gland causes a marked and rapid rise in the basal rate which does not occur after thyroidectomy.\((63, 64)\) With these injections, the top figure, approximately plus sixty percent increase, is reached within ten days, and then it gradually falls to a level of plus fifteen percent. The injection of the same amount of extract in partially thyroidectomized animals causes a slight but definite rise in basal metabolism. In further work, Siebert reported that this rise could be prevented by the addition of .05 Grams of potassium iodide daily or decreased after it had become elevated.\((65)\)

Friedgood has recently presented a detailed paper in which he has studied the individual variations of guinea pigs in their response to the injection of various anterior pituitary preparations, and has compared their basal rates with the histological appearance of the gland. He divides the behavior of the basal metabolic rate following daily uninterrupted injections of some anterior pituitary extract into three periods. In the first period he obtains a sharp rise in basal metabolic rate reaching a maximum of plus twenty-six to plus sixty percent between the seventh and fourteenth day.\((32)\) There are individual variations not dependent on the daily dose, so that in some cases the response is sharply curtailed from the start. During this period there is an increase in pulse and body temperature with a loss of weight.

The second period is characterized by a remission which develops when the peak has been reached. During this period, the basal metabolism returns to normal within one to three weeks. After the remission, the rate may show a transient in-
crease or may even fall below its normal value.

The third period is characterized by another elevation of basal rate in those animals in which the injections are continued over a period of a month or more.

During the first ten days he finds a definite correlation between the advanced hypertrophy and hyperplasia produced in the gland and the increased basal metabolism. During the second period when the basal metabolism begins to drop, however, he does not find a corresponding involution of the gland. On the other hand, Hertz and Kranes working with rabbits found evidence of involution as early as the third week and definite atrophy by the end of a month of treatment. (35) This discrepancy may be explained on the basis of the different species of animals the two were working with. Friedgood offers two explanations for his findings.

If one assumes that cellular hypertrophy or hyperplasia always represents hyperfunction, then one must assume that the effects of the calorigenic hormone are neutralized by a protective compensatory mechanism. The explanation which he favors is that there is a stage of relative insufficiency in which the thyroid is no longer able to manufacture the calorigenic hormone as rapidly as necessary due to injury to the protoplasm or exhaustion of raw products. In all probability, Collip's theory of the production of an antithyrotropic hormone is the correct one, and the basal metabolism is affected before the gland shows any structural change.

Eventually, with uninterrupted injections of anterior pit-
uitary extract, the thyroid approaches normal and becomes comparable to those of the normal controls. One of the glands which had been intermittently stimulated over a period of time, showed extensive scarring indicating parenchymal injury.

In Friedgood's discussion of his findings, he says, "The clinical course of the basal metabolic rate in exophthalmic goitre is also similar to that of the experimental syndrome in guinea pigs. Both these conditions are characterized by a progressive intensification of the metabolic disturbance until a peak or crisis is reached, after which there is a period of sustained activity which spontaneously subsides over a variable length of time. Since the guinea pig lives his span of life in a small fraction of time allotted to the human being, it is not surprising that the clinical course of the experimental syndrome is expressed in terms of weeks, rather than in terms of months or years as in man. It is also interesting that recrudescences can occur under certain conditions in both instances. ................. Although this study has recorded a remarkable similarity between exophthalmic goiter in man and this experimental syndrome in animals, it is obviously hazardous at the present state of our knowledge, to identify the pathogenesis of these two conditions with each other."

We have seen in the thyroid hyperplasia and the increased basal metabolism produced by the injection of thyrotropic hormone in experimental animals a similarity between this condition and that of clinical hyperthyroidism. Besides these findings, there are other similarities to be pointed out.
Relation of Anterior Pituitary to Exophthalmos:

Exophthalmos, one of the cardinal signs of Grave's disease, has recently been reported as being produced experimentally by several workers in guinea pigs, rabbits, and young ducks.(32, 47, 49, 62) Most of those who have observed its production are of the opinion that it takes several weeks for it to develop, although Loeb(47) reports that he can observe it within four to six days. The fact that it is not prominent until the state of involution atrophy is under way makes it difficult to explain on the basis of hyperthyroidism. In fact, Marine has even been able to produce it in thyroidectomized guinea pigs. (49) His conclusions are that it is due to a stimulation of the centers in the mid brain controlling the sympathetic innervation of the eye (pupillo-dilator muscle and muscle of Muller). He feels that the exophthalmos is an independent effect of the thyrotropic hormone and that it does not act through the thyroid. The common occurrence of the symptom with Grave's disease, however, makes it difficult to separate its production from some abnormal state of the thyroid.

Relation of Anterior Pituitary to Iodine Content of Thyroid and Blood:

Another similarity between the experimental syndrome produced by anterior pituitary injections and Grave's disease is the iodine content of the gland and blood stream. Closs, Loeb, and MacKay first reported their work on the iodine content of the thyroid gland and of the blood stream following the administration of anterior pituitary hormone in 1931.(12, 13) It had previously been shown that there was a decrease in the
acetone-insoluble or globulin iodine fraction of the thyroid gland of toxic goiter, while the total blood iodine was increased, these findings indicating that Grave's disease was concerned with an increased outpouring of thyroxin. These workers, therefore, decided to determine whether a similar distribution of iodine could be produced in the guinea pig under experimental conditions, with the injection of thyrotropic hormone of the anterior pituitary.

Reporting their results, they found: 1. the thyroid gland larger grossly than in the controls; 2. a loss of weight in the injected animals while the controls gained; 3. an increase in the blood iodine (controls sixteen gamma percent and the injected forty-one gamma percent); and 4. a consistent decrease in the concentration of the alcohol insoluble or organic iodine of the gland in every case. The organic iodine content of the control glands averaged 28.5 mgm. % while that of the injected animals averaged 7.2 mgm%. The alcohol soluble or inorganic iodine did not show any appreciable change in either gland or blood.

These findings harmonize with the histological findings under anterior pituitary administration. As has been shown the colloid undergoes softening and liquifaction. Inasmuch as the iodine is chiefly stored in the colloid, the diminishing of this justifies the conclusion that the iodine has been depleted in spite of the marked proliferation of acinar epithelium and increase in weight of the gland.

Loeb, Closs, and MacKay conclude by saying that these experiments strongly suggest that the injection of anterior
pituitary extract not only causes the changes in gland histology, the increase in basal metabolic rate, but also reproduces in the organism of the guinea pig the changes in organic iodine distribution which are characteristic of Grave's disease in man.

Foster, Gutman, and Gutman have also reported on this question. (28) They used sheep as their experimental animals so that they could make their estimations on one of the lobes of the thyroid before treatment and use this for a control on the other lobe removed after treatment. They found in every case a decided drop in the organic and total iodine of the thyroid following treatment, presumably due to an increased liberation of thyroxine into the blood stream, although they did not make any blood determinations. Hyperplasia of the remaining lobes was present in direct proportion to the degree of chemical change.

Other workers have substantiated these findings, so that it is quite well established that anterior pituitary injection or the thyrotropic hormone affects the thyroid gland and blood stream in relation to their iodine content in a similar manner in which they are affected in the human Grave's disease.

Relation of Anterior Pituitary to the Glycogen Content of the Liver:

In carrying out the parallelism between Grave's disease and its experimental counterpart, the functional alteration of the thyroid produced by anterior pituitary injections, we can look at the liver and study its reaction to the anterior pituitary hormone. That this organ is concerned with
the elimination of the toxic elements of the thyroid, is shown by the well known glycogen, fat, creatin, and creatinin depletion of this organ in Graves disease. In this condition it is unable to store fat or glycogen in direct proportion to the severity of the disease. Eitel and Loeser have reported on this problem in recent months. (23) Assuming that the injection of anterior pituitary extract produces effects analogous to those of hyperthyroidism, they found it necessary to prove, 1. that the injection of anterior lobe substance will decrease the glycogen content of the liver just as thyroid gland substance and thyromin, and 2. that the glycogen reduction is brought about by the action of the thyroid gland. In their experiments they injected anterior pituitary extract and measured the liver glycogen, muscle glycogen, blood sugar, and appearance of the thyroid gland, with the following results:

1. Characteristic hyperplasia of the thyroid

2. General effects not marked. All showed an increase of appetite and some showed exophthalmos.

3. An initial reduction of liver glycogen in the first few hours following injection which is replaced in twenty-four hours. The content then remains constant for about four days when a decrease in the liver glycogen content begins to show. From then on the decrease is continuous until on the seventh to eleventh day the liver is glycogen free.

4. The glycogen depletion is a direct result of the hypertrophy of the thyroid caused by the injection of anterior lobe substance, since the effect occurs only when the thyroid
is present and does not occur in thyroidectomized animals.

5. These changes are reversible, so that after discontinuance of the injections, within seven days the glycogen content is normal and the signs of hyperthyroidism have disappeared.

Other Effects of the Anterior Pituitary in Relation to the Thyroid:

Other similarities have been observed between experimental animals under the influence of the thyreotropic hormone and patients with Grave's disease. These include increased restlessness of the animals and tachycardia. Other animals respond much more vigorously than others and die in an apparent state of acute thyrotoxicosis with rapid pulse and an increased Basal metabolism up to plus 100%.

It is obviously premature to connect the pathogenesis of hyperthyroidism with the thyreotropic hormone, but the similarity between the two conditions can not be denied. No more can the fact that the anterior pituitary secretes a hormone which accelerates the thyroid activity of experimental animals to a marked degree. With the above experimental findings in mind, namely that the anterior pituitary does secrete a thyrotropic hormone which when injected into experimental animals produces changes in the thyroid which result in stimulated metamorphosis, hyperplasia and hypertrophy of the gland, increased basal metabolism, and other changes characteristic of Grave's disease, and the fact that the thyroid ex-
erts an influence upon the anterior pituitary so that thyroidectomy results in changes in the anterior pituitary that are interpreted as decreased function, let us turn to what clinical evidence that may be found of an interrelationship between the anterior pituitary and the thyroid.

**Clinical Evidence:**

It is surprising in the light of such conclusive experimental evidence presented above that the interrelationship of the thyroid and anterior pituitary is not more generally recognized clinically. There are probably several factors to account for this. In the first place, it has been shown that up to one-half of the anterior lobe may be destroyed without any untoward effects being noticed in relation to the thyroid. Secondly, while obesity has been considered to be the cardinal symptom of dyspituitarism, recent work has shown that it is probably not related to the anterior lobe at all. The most acceptable concept of the obesity of pituitarism is that it is concerned with the posterior lobe, tuber cinerum, hypothalamus mechanism as proposed by Cushing.(17) Therefore, probably many of the pituitary obesities do not have any actual anterior lobe deficiency as far as the thyrotropic hormone is concerned. Lastly, there are probably many instances in which the thyroid is involved in pituitary disease or vice versa, in which the dysfunction of one of the glands is not recognized and the condition is called a uniglandular disorder. Much of the experimental work reported above has been done in the last five years, so it is not remarkable that significance of the effect of the
two glands on each other is not generally recognized.

The dearth of medical literature on the clinical relationships of the two glands is not so great, however, as one might be led to believe from the above statement. English literature contains numerous examples of secondary involvement of one gland due to primary disease in the other, although it is only until recently that the significance of this has been understood. Foreign literature has not been covered here very extensively, but even more work has been done on the continent in correlating the two glands clinically than has been done in this country.

In the following pages, certain clinical conditions will be discussed in which a primary disease of one gland shows a secondary involvement of the other, and these findings will be correlated with the experimental evidence that has been presented in the preceding pages.

Cretinism and Myxedema and Their Effects upon the Anterior Pituitary:

In conjunction with the experimental finding of enlargement of the hypophysis in animals in which thyroidectomy had been performed, medical literature contains numerous references to enlargement of the hypophysis with various hypothyroid conditions in the human. Eichorst found the pituitary gland large and hyperemic in cretinism and myxedema. (22) There were often hemorrhages and later a growth of connective tissue and cyst formation. Finally, the pituitary became smaller and smaller. Boyce and Beadles report two cases of
myxedema and one of cretinism in which they found the hypophysis to be enlarged, the enlargement being entirely in the anterior lobe. (10) In all their cases, the thyroid was either atrophied or entirely absent. Wells reports that in a case of scleroderma where the thyroid was greatly atrophied, the hypophysis was found to be twice the normal size and there was a large accumulation of colloid material. (80)

Fournier and Helguera have reviewed an extensive literature on cases of myxedema in which the enlarged hypophysis has produced optic atrophy and hemianopsia through pressure on the optic chiasm. (30)

Does this mean that the pituitary has enlarged in an effort to take over a vicarious function for the diseased thyroid, or does it mean that the enlargement is a representation of the effort of the pituitary to stimulate the failing thyroid to function? In the light of Bryant's work, (11) it would seem that neither of these hypotheses are correct.

You will recall that in his experiments on thyroidectomy, he did find an increase in the size of the hypophysis, but that on histological examination the change was found to be only a pseudo-hypertrophy and did not represent increased function, but rather that there was a diminution in the number and size of the chromophiles. As the acidophiles have been shown to be the cells concerned with the secretion of the growth hormone and the basophiles concerned with the sex hormones, it is interesting to theorize as to how much of the dwarfism and disturbances in sex characteristics in cretinism may not be due to secondary hypophyseal damage.
The thyrotropic substance has been isolated. Perhaps further work will show a similar substance secreted by the thyroid which stimulates the anterior pituitary to activity, the absence of which leads to a deficiency of the anterior lobe.

The Biglandular Deficiencies:

In the following pages the work of Englebach (25) on biglandular disorders will be discussed. As will be shown most of these represent a hypofunction of one gland initially with hypofunction of the other gland superimposed, presumably through a deficient supply of some stimulating substance derived from the other gland.

In the early periods of life, namely up to adulthood, the simultaneous involvement of both the thyroid and the pituitary gland is more common than uniglandular involvement. These biglandular disorders go under the name of thyro-pituitarism and pituitaro-thyroidism, depending on which gland the blame may be placed as being the initial offender. Comparatively few uniglandular deficiencies do not progress into biglandular disorders in the early age groups, so that after a few years it may be difficult to determine which gland was initially at fault. In the light of the experimental work we have discussed previously, it is not surprising that we should find syndromes in which the symptoms are those of involvement of both the thyroid and the pituitary and in which the symptoms will clear up under combined replacement but will not respond to uniglandular treatment. You will recall the various experiments
on hypophysectomy in which the thyroid atrophied and lost its function and vice versa the experiments on thyroidectomy in which the animals ceased growth and in which the chromophil cells of the anterior pituitary or those responsible for the growth and sex hormones practically disappeared. It is not surprising, therefore, to see clinically signs of pituitary insufficiency implanted upon those of hypothyroidism or vice versa.

Before being able to interpret the symptomatology of these biglandular disorders, it is essential to understand the part which each gland plays in the symptom complex of the two disorders. Therefore, the symptomatology of hypothyroidism and hypopituitarism will be discussed briefly in the following pages.

**Symptomatology of Hypothyroidism:**

The symptomatology of hypothyroidism will be discussed in relation to the four periods of life, namely infancy, juvenility, adolescence, and adulthood. This division and the discussion of the same has been taken entirely from Englebach's volumes on "Endocrine Medicine". (25)

A deficiency of thyroid secretion shows itself prenatally in the production of congenital hypothyroidism. One of the important functions of thyroxin is the embryonal differentiation of primitive tissues which develop into the different organs and systems of the body. This has been shown experimentally under the chapter on "Interrelationships in Metamorphosis and Body Growth". Clinically this deficiency is shown in the re-
tarded development of the osseous and nervous systems and faulty tooth development. The most important diagnostic sign of congenital hypothyroidism is delayed development of the ossification centers, and if this is found, one should look for other signs of thyroid deficiency. Overweight at birth, provided other causes can be ruled out, should make one suspect hypothyroidism. However, this overweight rarely persists beyond the first year, since the gastro-intestinal upsets with atony and constipation which accompany this disorder lead to malnutrition. The infant is generally less resistant to infections, especially of the upper respiratory tract. This may be due to a poor development of the sinuses resulting in poor aeration. The deficient development of the mastoid cells may account for the high incidence of mastoiditis in these children. There is also a hyperplasia of the lymphoid tissue of the upper respiratory tract which might account for their increased susceptibility.

Thyroid deficiency retards the laying down of the tooth buds in prenatal life and the eruption of them in post-natal life. It is difficult for the permanent teeth to erupt, resulting in the characteristic malposition and overcrowding. Ocular deficiencies are manifest by the common incidence of internal strabismus in hypothyroidism. Mental development and walking are quite delayed in this condition and may be accounted for by the delayed development of the nervous and osseous systems. The child is slow in learning to eat and perform other routine motions. Other signs of mental deficiency are shown by the per-
formance of purposeless movements, uncouth sounds, and habitual crying. Unbilical hernia is usual and inguinal hernia not infrequent. In relation to this, undescended testicle is quite common in the male infant.

The skin is thick, hair coarse, and nails furrowed and brittle. A secondary anemia is often present which gives the skin a lardaceous alabaster color. Associated with this is a leucopenia and reduction in the polymorphonuclear cells. Poor development of the skull and face bones results in a brachycephalic head, broad face, and high saddle nose. The nostrils are flat and broad, the lips thickened and open, and the tongue thick and protruding. The temperature may be subnormal and extreme sensitiveness to the cold present. The determination of the basal metabolism is generally unsatisfactory in infants. Of course, all degrees of this condition may be present from mild hypothyroidism to typical cretinism.

During juvenility, two types of pure hypothyroidism are recognized by Englebach, namely congenital hypothyroidism and acquired juvenile myxedema. The symptoms of congenital hypothyroidism are very similar to those discussed under infancy. In order to establish the diagnosis certain things should be found. These are namely, 1. history of myxedema in mother and retardation of development since birth, 2. history of arrested physical growth and mentality throughout infancy and juvenility, 3. hormonal signs and symptoms of congenital hypothyroidism, 4. disturbance in other systems previously discussed which are characteristic of the disease, and 5. an improvement under thy-
roid therapy.

The acquired form of hypothyroidism or juvenile myxedema is a relatively rare disease. There is a history of normal development up until the time that the deficiency becomes manifest, then there is an arrest of physical development and regression of mentality associated with the characteristic signs referable to other systems such as the classic facies, enlarged tongue, generalized mucin infiltration with subdermal edema and characteristic fat padding in the supraclavicular region and the dorsum of the hands and feet. In both the acquired and congenital forms the basal metabolism rate is an important adjunct to diagnosis.

The hypothyroidisms of the adolescent period have the same general characteristics of those discussed above. In addition, the onset of menstruation in girls and the development of secondary sex characteristics in both sexes alters the picture somewhat. With inactivity of the thyroid there is generally a tendency for an early onset of menses and the amount of flow is generally increased. Thyroxin is considered an inhibitory hormone to gonadal activity, consequently the early onset and increased flow in hypothyroidism. As a rule the menstrual rhythm is not modified and there is no dysmenorrhea.

In the adult myxedema is the most common form of hypothyroidism, although there may be a non-myxedematous form and some congenital hypothyroidisms may be carried over. In the myxedematous adult normal development has taken place, so that the thyroxin deficiency here pertains more to a decreased cel-
lular activity of tissues which have properly developed and differentiated, therefore the changes are chiefly functional. Marked reduction in irritability of both the central and autonomic nervous systems resulting in diminished perception, impaired memory, and decreased reflexes along with lessened secretory secretory and motor function as shown in the decreased peristalsis and cardiac action is present. The decreased cardiac action results in a decreased oxidation and consequently a lowered basal metabolism. Respiration is also decreased. The general slowing up of body metabolism results in a subnormal temperature and a sensitiveness to cold. The effects on the gastrointestinal tract are a reduction in motility of the intestine and a relaxation resulting in chronic constipation. The general infiltration of mucin effects all the organs so that for example, the kidneys produce a decreased amount of concentrated urine in which albumin and casts are often present. The subdermal infiltration of the skin with consequent changes in the sweat glands and hair follicles accounts for the thickness and dryness of the skin and the coarse, dry, and scanty hair. The mucoid accumulation probably has similar inhibiting effects on the other endocrine glands.

Although the osseous system has reached its full growth by the time of the development of the deficiency, the muscular system shows the effects by decreased tone and energy. The inhibiting effect on the genitals is manifest in sterility and onset and prolongation of the climacteric. In addition to these changes there is the anemia and lardaceous color, general obesity
with characteristic fat pads, and the typical facies. The voice has a low guttural character and the articulation is poor. The special senses are also involved with the general infiltration resulting in retinal changes similar to albumin-uric retinitis and varying degrees of deafness and tinnitus.

Positive diagnosis of adult myxedema depends upon: 1. exclusion of other simulating diseases such as chronic nephritis, pernicious anemia, thyro-pituitarism, and chronic heart disease, 2. demonstration of positive clinical characteristics of myxedema, and 3. a relief of its symptoms by thyroid therapy.

Symptomatology of Hypo-pituitarism:

The symptomatology of deficient pituitary disorders is much more complicated than those of hypothyroidism. Symptoms related to the anterior lobe can be traced to the loss of the growth hormone and the sex hormones primarily. However the majority of cases have symptoms associated with both the anterior and posterior lobes together with symptoms attributable to disturbances in the contiguous mid-brain. The pars intermedia of the posterior lobe besides secreting pituitrin has connections with the hypothalamus through the tuber cinerum and so influences or is influenced by those primitive centers in the diencephalon which control the important processes of metabolism, water balance, thermogenesis, and emotion. (17) It is disturbance of this neuro-hypophyseal mechanism which results in the nutritional states of adiposity or emaciation, polyuria, oliguria, diabetes insipidus, modifications in body
temperature, states of wakefulness or somnolence, and disturbances in carbohydrate metabolism. The interrelationship between the pituitary and other endocrine glands besides the thyroid and the gonads also complicates the syndromes which may be produced. For example, hypophysectomy also results in atrophy of the suprarenal cortex (71) and clinically both these glands are related to gonad function. Also the hypertrichosis seen with acromegaly and late pituitarisms in the female is one of the cardinal signs of suprarenal disorders. (25) Likewise, the pituitary acts as a relative governor of the islands of Langerhans in the pancreas. Whether this is a direct action or an indirect one through its action on the suprarenals and the secretion of adrenalin is not determined. It is only necessary to consider Collip and Anderson's work on inhibitory hormones (14) to see how complex the clinical syndromes of dyspituitarism may become. It is not possible in the realm of this thesis to discuss the various syndromes which may be produced by pituitary deficiency, but some of the more classical symptoms as related to the different age periods will be related in order to interpret the findings in the biglandular disorders. The work of Englebach (25) will be drawn upon for this information.

Pure infantile pituitarism during infancy is rare according to the literature, although Englebach in his series of endocrinopathies collected eight cases, one of which was a hyperactivity. Since the sex hormones do not become active until puberty the signs are that of abnormal growth with or without adiposity. In contrast to the hypothyroidisms, the hypopituitarisms are apt
to have a birth weight lower than normal. There is apt to be a precocious eruption of teeth and they are widely spaced and small concurrent with the deficient supply of the growth hormone. There is no retardation in appearance of the ossification centers and mental development is not affected. To repeat, the chief findings are those of a general diminution of growth.

During juvenility the most common pituitary disturbance is that of adiposogenital dystrophy or Frohlich's syndrome. The symptomatology of this disorder is principally that of a sudden abnormal increase in weight and failure of development of the genital system with statural measurements indicating either an increase or a decrease of the growth hormone. The adiposity is typical showing a girdle type, enlargement of the breasts, and marked padding over the mons pubis. The hands are broad and the fingers short and tapering with dorsal padding of the dorsum and wrist. Genital hypoplasia together with this typical adiposity should make the diagnosis. Anterior lobe hypopituitarism without the adiposogenital syndrome produces statural underdevelopment with under weight. Children of this type often have precocious mental development as contrasted with the retardation seen in the hypothyroids.

The majority of pituitary disturbances discovered during adolescence are those that have progressed from juvenility or infancy. The same general findings are present here that have been discussed previously but in addition there is the effects which the deficient pituitary secretion exerts upon the gonads and secondary
sex characteristics. The two types of hypopituitarism found in this period are the adiposogenital dystrophy syndrome and the anterior pituitary dwarfism or Lorain-Levi disorder. In the hypopituitarisms there is a delay of menstruation generally to after fifteen years, and the flow when it starts is decreased and irregular. More or less severe dysmenorrhea accompanies these disorders. In the complete hypopituitarisms menstruation fails to appear owing to the lack of the ovulation hormone which produces maturity. Secondary sex characteristics are slow in developing and the genitals are infantile in appearance.

During the adult period there are many more reported cases of anterior lobe deficiencies than in the other periods. The symptomatology is chiefly confined to growth disturbances, there being a general decrease of the body and its organs to about one-third normal size and to the disturbances of the genital function. Amenorrhea and dysmenorrhea is common as is underdevelopment of the sex organs. Sterility and early loss of libido is often present. There are few complaints referable to other organs although the physical strength is below par and there may be a mental instability.

Adiposogenital pituitarism in the adult is a relatively common syndrome. In those in which the onset occurs after the genital and osseous systems have developed the only changes are those associated with the typical girdle-mammary-mons obesity and functional gonadal disturbances. The adiposity does not run into the extremities and there is neither dorsal padding
or supraclavicular fat pads, differentiating it from that of myxedema. The lower girdle adiposity is the most pronounced and extends from the level of the navel to the junction of the middle and lower one-third's of the thigh. In severe cases the abdomen is pendulous and the mons pubis forms an apron hanging between the thighs. The mammae are enormous and pendulous. Later in the course of the disease there is an adiposity of the shoulder region limited to the deltoid area. In the cases in which the adiposity dates from juvenility marked infantility of the genitals is present. In the others in which the onset is during adult life amenorrhea or dysmenorrhea is prominent. Loss of libido and sterility is also found in some cases. Chloasmic pigmentation is present in about one-half the cases, and hypotrichosis is relatively common. The peculiar separation of the incisors is found in many of these cases and other regional signs such as tapering of the fingers and smallness of the hands are present.

*Symptomatology of Thyropituitarism and Pituitarothyroidism:*

From the above resume of the hypofunctions of the thyroid and anterior pituitary glands in the various age periods it can be seen that in many instances their symptomatology does not coincide, so that with the concurrent hypofunctioning of both glands one could expect some rather bizarre syndromes.

Englebach (25) in his series on "Endocrine Medicine" presents 2,098 cases of endocrinopathies of which 342 were diagnosed as biglandular disorders in which both the pituitary and the thyroid were involved. He divides the cases according to
the different age groups corresponding to the infantile, juvenile, adolescent, and adult periods. He subdivides these cases into thyropituitarism and pituitarothyroidism depending on which gland was initially involved and in addition separates each group as to whether they are adipose or non-adipose. There is no other work that contains anywhere near the volume of cases that his does, and therefore, a review of his analysis of symptomatology will be given in the discussion of these bi-glandular disorders.

During infancy thyropituitarism in which pituitarism is superimposed upon a congenital hypothyroidism with a hypofunctioning of both glands is more common in his series than are uniglandular involvements. Heredity seems to play the most important part etiologically with infectious diseases playing the chief role as far as exogenous causes are concerned. As a rule the birth weight is relatively normal which helps to distinguish the condition from both the uncomplicated uniglandular disorders. Dentition in most cases occurred late, illustrating the thyroid element. Also there was a considerable delay in walking and talking. Other signs of defective mental and physical processes were observed. In the non adipose cases most of them showed a retardation in height illustrating the pituitary deficiency. As a rule the centers of ossification were delayed and less dense than normal. In some cases the osseous development was normal or advanced with the stature diminished. This variability of findings can be explained by the varying degrees of preponderance of one deficiency over the other.
The facies is generally that of cretinism with squinting, crossed eyes, high saddle nose, and thick lips though not so pronounced as in the pure hypothyroidisms. Some of the cases show an overcrowding of teeth characteristic of hypothyroidism, while others show a marked separation characteristic of hypopituitarism. Internal strabismus and cryptorchism were found in some cases showing the thyroid element, and a characteristic pituitary adiposity was found in some cases. The differentiation of this syndrome from pure hypothyroidism can be made on the premature or normal birth weight, less typical facies, greater retardation of growth, separation of teeth in some cases, and finally the failure to react to thyroid medication alone.

During juvenility the biglandular disorders again predominate over the uniglandular according to Englebach's series. The adipose thyropituitarisms are the most common type and differ from the non-adipose in that there is apparently no deficiency in the growth hormone since they have normal or increased stature. The pituitary involvement is shown in these cases by the typical adiposity and genital hypoplasia. Other pituitary signs are infrequent in the adipose thyropituitarisms although the non-adipose type shows a marked diminution in stature characteristic of deficiency of the anterior lobe growth hormone. However, certain regional signs may be found such as spacing of the teeth, tapering fingers, and genital hypoplasia which incriminate the pituitary. The thyroid element is seen in the delayed dentition, delayed physical and mental development, delayed ossification, and lowered basal metabolism.
These thyropituitary disorders frequently give a history of constipation which is evidently a thyroid factor since it is not found in uncomplicated pituitary deficiencies. In certain of these cases polydypsia and polyuria was present and indicated hypophyseal involvement.

The pituitarothyroidisms of this period and the adolescent period will be discussed under the adult period since they occur in much greater numbers in that period.

During adolescence the biglandular disorders in this particular series still outnumber the uniglandular two to one. Many of these adolescent disorders had their beginning in the juvenile or infantile periods but it is only when the genital abnormalities become recognizable that they are apparent. In a review of 44 cases Englebach (25) gives an analysis of the symptomatology as follows;

The thyroid symptomatology was largely contained in the personal history and consisted of overweight at birth, delayed dentition, walking, and talking, and signs of mental deficiency during infancy. The general hormonic signs of thyroid involvement were insignificant, supraclavicular padding being present in only a few cases. The regional signs referable to decreased thyroid function were largely facial, ocular, dental, and genital. Of the forty-four cases, seven showed malposition and overcrowding of the teeth while others were still wearing braces or gave a history of correction. Two cases showed a strabismus and cryptorchism was present in one. Sixteen showed precocious menstruation which, however, in the course of a year became ir-
regular and increased in the amount and duration of flow. Twenty cases showed a basal metabolism below normal. The osseous development was delayed in but nine cases.

The symptomatology referable to pituitarism is as follows. Statural abnormality was not noted in the adipose type, while in the non-adipose type the majority were underdeveloped. The classic obesity is the most important general sign incriminating the pituitary. It is much more characteristic than that seen in the juvenile periods, being of the girdle, mons, and mammary type. Unusually large, miniature, or separated teeth were present in thirteen cases. The hands and feet in a large majority of cases were typically short and broad with tapering fingers. Menstrual disturbances such as delay in onset, amenorrhea, dysmenorrhea, and metrorrhagia were present in many. In the male hypoplasia of the genitals was present in most instances.

As in the other periods, the final test is a therapeutic one, and these cases will react to combined replacement therapy where uniglandular therapy will do little if any good.

Of the adult endocrinopathies the biglandular disorders hold a rather minor place in comparison with the other age periods. In this period there is considerably less evidence of mental deficiency and statural deviations than in the earlier periods. Hypoactivity of the pituitary and thyroid in this period does not have a marked effect on the nervous and osseous systems since these have largely developed. In most cases the pituitary involvement is more marked than that of the thyroid,
the adiposity and functional derangement of the genital system being the chief findings. The adiposity is of the typical pituitary type described under adiposogenital pituitarism. However, when a marked hypothyroidism is associated the regional distribution is not so marked and it is more general. In these cases there is sometimes added supraclavicular and dorsal hand padding. Chloasmic pigmentation indicative of pituitary disturbance is often found. Abnormal hair distribution may be seen in some cases, presumably due to secondary involvement of the suprarenal cortex. In the male the genital signs are mostly decrease of libido and potency and in the female abnormal menstruation, frigidity, and sterility is found. Infantile genitalia is not common in the adipose type, but in the non-adipose type due to early deficiency of the pituitary and thyroid there was decreased stature and lack of genital development in about one-third of the cases. The teeth were either separated or crowded indicative of either a thyroid or a pituitary deficiency. The thyroid was incriminated mostly through the lowered basal rate, the family and personal history, the mental defects, and the regional abnormalities of teeth and skin.

Pituitarothyroidism which has not been discussed consists of an initial hypophyseal disorder upon which thyroidism has been engrafted. In adult life these conditions are often so intermingled that it is difficult to determine which one predominates, although in most cases the pituitary element is the most pronounced. This condition is essentially the same as the
thyropituitary syndromes previously discussed except in the time of appearance of the glandular deficiencies. The signs of pituitarism are characteristically the menstrual disorders accompanied by a rapidly increasing adiposity unrelieved by diet and exercise of the characteristic type. The onset of the thyroid symptomatology is manifest by varying degrees of mental change from stupor to extreme somnolence along with a lowering of the basal metabolism. In addition to these changes regional signs previously discussed are present. According to Englebach the degree of extreme somnolence known as pituitary hibernation is not possible in either uniglandular myxedema or hypopituitarism but is a summation of the two disorders and is always associated with either pituitarothyroidism or thyropituitarism.

The most conclusive evidence in all of these biglandular disorders is the therapeutic reaction. In most of the cases reported in Englebach's series these biglandular disorders had been pronounced either hypothyroidism or hypopituitarism and treated as such with no avail. With a correct diagnosis, however, of a biglandular disorder and the instituting of biglandular therapy all showed improvement of varying degrees but in all cases marked enough to show clearly the biglandular deficiency. Frazier (31) feels that he obtains better results in all his pituitary insufficiencies, regardless of whether or not a thyroid deficiency is demonstrable, if he uses thyroid extract along with the anterior pituitary extract. Rony (60) believes that thyroid disease may be divided into that due to a primary disturbance of the gland and that secondary to either
an oversupply or an under supply of the thyrotropic hormone of the anterior pituitary. To support his view he presents three cases, one of adult myxedema, one of cretinism, and another of juvenile hyperthyroidism, which showed no response to thyroid therapy but gave rapid improvement with the instituting of pituitary therapy. The effects of anterior pituitary therapy upon cases of exophthalmic goiter and hyperthyroidism are not entirely conclusive. Some men (8, 19, 57) have reported a marked diminution in the basal rate in several cases of Grave's disease following treatment with anterior pituitary extract. The effects were not obtained until after a few weeks of continuous treatment, but the lowering of basal metabolism amounted to as much as fifty percent in some cases. The explanation of this delayed action is possibly to be found in Collip's theory of an antithyrotropic substance developing after prolonged anterior pituitary stimulation. (15) On the other hand, Thompson et al. (77) found that anterior pituitary injections gave an increase in severity in exophthalmic goiter. This would be expected at first according to the experimental findings, but possibly continued administration would have given a fall in basal metabolism as it did in the other cases reported. It is not the aim of this thesis to advocate anterior pituitary injections in the treatment of hyperthyroidism as the reported results are entirely to few to come to any conclusions in the matter. It is my contention, however, that this field is far from exhausted and that the future holds much in the way of more satisfactory treatment
in both thyroid and pituitary disorders and more cases will be
brought to light in which the primary disturbance may be placed
on the other gland and treated accordingly.

There are two other conditions of the pituitary gland which
I wish to discuss in their relation to the thyroid. One rep­
resents a hyperfunction and the other a hypofunction. These are
respectively, acromegaly and Simmond's disease.

Acromegaly and Its Effects upon the Thyroid:

That there is a definite relationship between goiter and
acromegaly is an established fact. The mechanism of the relation­
ship has not been so well understood, however. Acromegaly is
the same thing to pituitary disease that hyperthyroidism is to
thyroid disease, a hyperfunctioning of the pituitary due to an
eosinophilic adenoma of the gland. The etiology has been est­
ablished and most of the symptomatology in relation to skeletal
growth explained through the work of Evans and Long in the pro­
duction of experimental gigantism with the use of the growth
hormone of the anterior pituitary. (26) However, there are
certain disturbing factors that are not so easily explained un­
less one takes into account the experimental work previously
discussed on the thyrotropic hormone of the anterior pituitary.
These findings are the increased basal metabolic rate which is
so often present and the presence of an enlarged thyroid, pres­
ent much more often than to be coincidence.

Cushing and Davidoff's (18) on the basal metabolism in
acromegaly show 45.8 percent of 72 cases above plus ten per­
cent, the highest being plus sixty percent and the average be­
ing plus twenty-six percent. There were only six patients below
minus ten percent. Boothby's (9) figures on thirty cases show fifty percent above plus ten percent. Davidoff (20) reports a definitely enlarged thyroid in twenty-five of one-hundred cases of acromegaly. Of these twenty-five there were seventeen that had had a basal metabolic rate determination and of these fifteen showed an increased basal metabolism, three of whom had had a thyroidectomy with reoccurrence of the goiter in two out of the three.

Cushing proposes the view that the anterior pituitary exerts a direct calorigenic effect in the production of the increased basal metabolism, his objections to the theory that the increased basal metabolic rate is due to the thyroid being stimulated by the overactivity of the anterior pituitary being,

1. Seventy-five percent of the cases with increased basal metabolism showed no enlargement of the thyroid.

2. The three excised goiters were of the colloid adenoma type and not characteristic of Grave's disease.

3. The basal rate while lowered in these three cases by thyroidectomy was not permanently.

The problem of heat production and the control of metabolism is of course far from solved, but in the light of recent experiments previously discussed in this thesis under "Relation of Anterior Pituitary to Basal Metabolism" it seems more logical to place the increased basal metabolism at the fault of the thyroid stimulated to increased activity by the anterior pituitary adenoma. It seems feasible that there may have been an increased function of the thyroid which produced the mild
increase in basal metabolism without any definite enlargement being felt. As to the histological study of the three glands removed, this is not a large enough number to draw any conclusions from, and as Cushing says, the gland may have been removed in a resting stage without showing any characteristic changes of hyperthyroidism which may have been present at another time. As to the last, that is that following thyroidectomy the decrease in basal metabolism was only transitory, it could hardly be expected that the gland would not undergo another hypertrophy if the source of the trouble still remained active.

In the light of the experimental work previously discussed on the thyrotropic hormone the most logical explanation of these changes of the thyroid and basal metabolism in acromegaly that it is due to an increased production of this thyrotropic hormone by the hyperactive anterior pituitary gland.

Simmond's Disease and its Effects upon the Thyroid:

The syndrome known as Simmond's disease or hypophyseal cachexia offers a striking example of anterior pituitary deficiency. The disease is most frequently found in women, and is characterized by striking emaciation, premature aging, wrinkling of the facial skin, loss of pubic and axillary hair, dental caries, loss of libido and sexual function, and accompanied by hypothermia and depression of the basal rate. Most of the reports of this disease have been in foreign literature there being relatively few cases reported in this country.

The mechanism for the production of the syndrome is any
condition which destroys the anterior lobe of the pituitary, either embolic, inflammatory, or neoplastic. With the destruction of this lobe we should expect changes in the other endocrine glands for which the anterior pituitary is the motor. Evidence of this is present both clinically and pathologically. Clinically the loss of libido and sexual power with retrogression of the secondary sex characteristics is evidence of gonad atrophy and this is supported pathologically by the finding of demonstrable atrophy of these organs. Graubner (34) in reviewing the reports of thirty-three cases of pituitary cachexia found that in each instance the thyroid was small, atrophic, and frequently sclerotic. This finding fits quite well with the lowered temperature and decreased basal metabolic rate found so constantly with this condition. Thus, in the light of the experimental evidence that has been presented concerning the thyrotropic hormone of the anterior pituitary, we may conclude quite logically that the destruction of the source of this hormone has resulted in an atrophy and deficient functioning of the thyroid just as surely as experimental hypophysectomy does so.

Conclusion:

I believe that sufficient evidence, both experimental and clinical, has been presented here to show that there is a definite interrelationship between the anterior pituitary and thyroid glands. The ablation of one gland results in changes in the other, both anatomically and physiologically, indicative of decreased function. This has been shown experimentally in
the various hypophysectomy and thyroidectomy experiments, and clinically in the biglandular disorders, hypothyroid conditions, and Simmond's disease. In the case of the anterior pituitary, extracts have been made containing the thyrotropic hormone, which produce definite changes in the thyroid even to the point of creating a state of experimental hyperthyroidism. The closest correlation with this clinically is the condition of acromegaly, in which increased basal metabolism and thyroid hypertrophy has been found in a significant percentage of cases. In brief, therefore, we may say that the anterior pituitary controls the functional state of the thyroid to an undetermined degree probably through a specific hormone manufactured by its own cells and that in turn the thyroid probably has a similar effect upon the anterior pituitary although it has not been so definitely shown experimentally.

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