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The Interrelationships of the Pituitary and Thyroid Glands to Preadolescent Growth

By

Karl F. Stefan

Senior Thesis

University of Nebraska College of Medicine

1934
Introduction

Endocrinology is now in a stage of rapid transition. In the past very little was known, definitely, about the endocrine system. The result was that innumerable articles were written upon the possible functions of these glands and the action of their secretions. To attempt to review all these articles in this paper would not only be quite impossible, but of little value. Let us suffice to say that knowledge of the endocrines has increased by leaps and bounds within the generation, and even more rapidly in the last five years.

To be more specific one might say that we are still feeling around in the dark about many of the endocrine reactions, but that recent laboratory and clinical investigations have been more scientific, more dependable, and hence more fruitful. The result is that there is knowledge now on hand from which very definite conclusions can be drawn. The difficulty is in correlating the works of the various authors so that the end result will appear as logical as each single bit of work.

It is to this end that I have chosen preadolescent growth as my topic. In this field there have been many and varied theories upon the exact mechanism and control of growth. To be sure a large percentage is
still theoretical, however the purpose of the correlations to be made herewithin are to clarify the present beliefs, and to present to the reader the conclusions of the various laboratory and clinical men.
GROWTH

Growth per se is highly complex and not a little fantastic. The process in relation to a composite, finely balanced mechanism, such as the human body, becomes a subject akin to the prehistoric monsters in size, and as intricate as the finest watch of the present generation. It is not only gigantic in its facts, but also has so many variables that hypothetical explanations of its various reactions are fields in themselves.

Growth is unsatisfactorily defined from many angles: Anatomically speaking, it is said to consist of an increase either in the number, or the size of cells in the living body; chemically it is defined as the transformation of food stuffs, salts, fats, carbohydrates, proteins, etc., and water, into new chemical entities which form the organized protoplasm of living tissue (this is essentially a definition of life); and speaking from a physiological standpoint, growth is a process and the resultant effect of this process (24). No one
of these definitions is satisfactory; especially as they do not convey in any sense the process of growing old or young, large or small. Hence one must regard the definition as being as complex as the subject.

Cause of growth.—The reason for or causation is highly theoretical. Of all the theories expounded by various authors it is sufficient to say that the autocatalytic theory is most anniversally accepted. That is, the accelerative factor in the process of growth is either a chemical substance, or substances, or a chemical condition which is strictly analogous to the accelerative factor in the less complex autocatalyzed reactions. i.e., Bacteria, uni-cellular organisms, etc. (16a)

In considering growth from a normal standpoint practically all authors agree that there are three distinct periods of growth. Abt (16a); Robertson (16b); Talbot (10); and Howe (24). Many others describe the process as three "cycles" (Fig. 2) while the English and German authors describe it as a "springing up" period followed by a "filling-out period". (Fig. 3)

Talbots' summary is brief and enlightening.—

1) Growth is the characteristic feature of childhood which is often the only index of the state of health.
Fig. 2.—Graph representing three growth cycles (Robertson), from Alt's Pediatrics, Philadelphia, 1923, W. B. Saunders Company, Vol. I.

Fig. 3.—Growth curves for height and weight showing three springing-up periods followed by three filling-out periods. (After Strutz, 'Der Körper des Kindes und Seine Pflege, Stuttgart.) Boys continuous line; girls, dotted line.

Fig. 4

Change in body proportions with growth. Showing the length of different portions of the body as compared with the head at different periods of life.
2) It is most rapid at three different periods in the life of every individual.

a) 1st cycle. -

During the first six months of infancy.
Here the rate of growth is most rapid of all cycles, as the body must suddenly adjust itself to a varying environment and acquire muscle and vigor.

b) 2nd cycle. -

When the child is five to seven years of age all strictly infantile characteristics are last and the individual enters childhood.

c) 3rd cycle. -

Here the child is passing through the stage of puberty or adolescence, and rapidly acquires adult proportions and secondary sexual characteristics.

Fig. 4 serves very well to show the difference in proportion of the various parts of the body at these periods. It is well to keep these characteristics in mind to correlate physical findings in cases of abnormal growth, for the normal development may be interrupted at any stage.

Abt summarizes growth as follows:

1) Growth of man and animals takes place in periods
or cycles in which slow growth and rapid growth alternate, there being three main cycles.

2) Each of these cycles in the expression of an underlying self-accelerated process.

3) The accelerating factor is some substance or group of substances produced during growth.

4) The inhibitive factor which alternately brings growth in any given cycle to a standstill is the accumulation of the products of growth.

5) Removal of these products, as by local death, injury or inanition, reinaugurates the process of growth until equilibrium is reattained.

6) The sum of the process constituting growth are governed and determined in rate and magnitude by the specifically slowest essential process.

7) Cell multiplication and cellular growth by intussusception are manifestations of and are the same underlying process. The former phenomenon being dependent upon the latter and occurring as a rule whenever the rate of growth by intussusception exceeds certain critical limits.

From all this it is possible to see that there is only one basic factor of growth, but there are many complicating factors which act as variables and effect
the extent type of growth. As long as these variables
are in harmony, growth is normal, a shift of one effects
them all. C.A. Aldrich (24) names quite a number of
factors which have an influence upon growth. Of the
variables he names the effect of the endocrine as a
central of growth is the one with which this paper is
concerned. Goldstein (28) and Engelhart (26) say, con-
cerning this variable that the conditions of abnormal
growth and development in children, requiring special
attention constitute a very serious and difficult pro-
blem in medicine." Laboratory investigations and clin-
ical experience have shown that disturbances of the in-
ternal secretions are responsible for the anomalies of
growth and morphogenesis. The difficulty in the diag-
nosis, as well as the treatment, lies in one's ability
to recognize these abnormalities early, when one's eff-
orts are more likely to be effective.

It is very interesting to note that true juvin-
ile cases of endocrine growth syndromes have been recog-
nized and treated early only within the last few years.
Before this tumor cases were not recognized until they
were far advanced, or at post mortem. The recent rapid
advances in endocrinology are enabling the physician to
diagnose his case early and obtain satisfactory therap-
entic results before the damage is beyond reach. (26)
Of all the endocrines having influence upon growth, and not one can be ignored, the pituitary and thyroid are the most important. Hence it is the interrelationship of these two glands to growth that shall be discussed here. This shall be done first through correlation of their embryology and histology; second through discussion of their physiology (normal physiology, abnormal physiology, and experimental physiology); third by a discussion of the growth disturbances, due to abnormal physiology encountered in preadversent; and fourth by citing a few reported cases illustrating this interrelationship.

EMBRYOLOGY (33-15-16-5-17)

Thyroid.- This gland develops from an outpocketing of the mid-ventral floor of pharynx at the level of the first pharyngeal pouches. (Entoderm) As the gland migrates caudad it remains connected to the pharyngeal floor by the thyroglossal duct. This duct may remain patent or demonstrable throughout life, but usually atrophies clearing the sixth week of intrauterine life.

Simultaneously, the thyroid loses its lumen and is converted into solid epithelial plates. The gland then becomes crescentic in shape and settles to a transverse position with a lobe on each side of the trachea.
Pituitary.—The glandular portion of this gland (anterior lobe) develops from an endodermal pocket located just in front of the pharyngeal membrane. This sac, known as Rathke's pouch is a diverticulum of the stomad- leum. This elongates and by the third month is not only in approximation with the posterior lobe (neural lobe), but organization into the hypophysis as such is already taken place.

The apex of the diverticulum becomes thin and constitutes the Pars Intermedia. A glandular portion, stretching along the infundibulum is the Pars Tuberalis.

The neural lobe (Posterior lobe) develops by an outpocketing from the hypothalamic floor in the region of the third ventricle. The stalk of tissue which permanently attaches the posterior lobe to the diencephalon is termed the infundibulum.

It is to be noted here that both the thyroid and anterior lobe are derived from the same type of epithelium—that is, entoderm. This embryological relationship will be of value subsequently in attempting to correlate the function of these two glands.

Histology (16-18-42)

Thyroid.—During early intrauterine life the thy-
roid is developing vesicles from solid epithelial cell masses, through the intermediary stage of branching tubules. In the latter one-half of fetal life the epithelial cells become more active, colloid is secreted and stored in vesicles, this continues until birth. Then for the first few weeks the gland rests and uses up the colloid previously secreted.

Throughout infancy and childhood the secretory activity is marked, and so is absorption, but the gland always maintains a reserve of colloid in its small vesicles. At puberty the demand for this colloid is at its highest and the gland, though secreting its greatest extent, is unable to store up any appreciable amount of colloid as it is absorbed as quickly as is secreted. After adolescence, when requirements are diminished, the gland continues to secrete until large amounts of colloid are stored up in its large vesicles. Then follows a period of comparative inactivity throughout adult life. Toward the fiftieth year the thyroid again attempts further activity but this is not marked. In old age the necessity for thyroid secretion does not warrant great activity of the gland, so that it retrogresses.

**Pituitary.**

1. Anterior Lobe.

As in all entodermal structures, the pituitary,
at first, is a mass of undifferentiated, non-granular, epithelial cells. These are the only cells present in the fetus at eight weeks, and are predominant to the end of fetal life. During the third month other cell types begin to differentiate.

1. Chromophile cells with granules taking stain.

   A. The first of these to differentiate are the Ox-yphil or eosinophilic cell type. They gradually increase during fetal life, rapidly increase during childhood, and at puberty constitute 50% of the total number of cells in the gland, being located dorso-posteriorly. The number is constant until later life when they begin to decrease.

   B. A little later the Basophilic cells are noted. They are confined to the periphery (anterior-ventrally) close to the blood supply. They increase very slowly in both intra and extrauterine life, but multiply progressively into old age, when they become predominant.

2. About the seventh month unstable granular cells differentiate. They are:

   I. Chromophobe cells--with granules that are neutral staining--i.e. neutrophiles. They occur in all parts of the anterior lobe, are richest among the
basophile cells, are practically the only cell seen in the infundibulum and are in the ventral posterior part of the Posterior lobe. These cells also become more abundant in later years.

II. Posterior Lobe.- This is composed entirely of neuroglial tissue, with insignificant cell bodies and interlacing fibers. It is a theory of cell function that the products of the cells are either extruded from the cell (cast out) or the cell completely evacuates its contents (as in a mucous cell) or that the cell entirely breaks up. Whatever the mechanism, the Hyaline like bodies and granular bodies are said to be cellular in origin. The former are absent in fetal life, but present in the second year of life and increase in size and number until puberty from which time on they decrease. (Hence an association with eosinophilic cells.) The former are always noticed near pars intermedia between neuroglial fibers. They increase in size and number in later life being located near the posterior part.

III. The Infundibulum.- This is mostly neuroglial tissue and contains only a few scattered neutrophilic cells. No vesicles granular, hyaline bodies, etc., are present.

IV. Pars Intermedia.- Early in fetal life this is a mass of undifferentiated cells. By term it consists
of two to three rows of solid cells which go to form vesicles in the (fifth month) the cells being neutrophilic, the colloid in the lumen basophilic. Later in childhood some of the vesicular wells take a basophilic stain.

Thus we see a gland, primarily undifferentiated at birth, childhood, and at puberty predominately eosinophilic cells and Hyalin like bodies. In adult life and old age basophilic cells and granules become more predominant. It is well to note that the eosinophilic cell differentiations is sequel to the growth cycle and it is mainly to this cell and to the anterior lobe that partial regulation of growth is assigned. (17)

Physiology

(1,3,4,5,11,16,17,23,56,57)

These glands not only develop from the same parent tissue, and start developing early in fetal life, but further they enlarge or differentiate with equal rapidity. This is well depicted in the various curves of Fertik, Majong, and Monossohn (29). These curves show by actual weight the increase in size of the glands to puberty. Graphs, 1, 2, & 3 all are of the thyroid--both sexes, female and male curves respectively. Graph 4 shows the hypophysis and epiphysis. Although the Graphs are on different scales they all extend from birth to thirteen
Weight curve - Thyroid - both sexes


Thyroid - wt. curve γ

2. Gewichtskurve der Schilddrüse (weibl.).

Thyroid - wt. curve α

3. Gewichtskurve der Schilddrüse ( männl.).

Thyroid - wt. curve α

4. Gewichtskurven der Hypophyse & Epiphysen

S. Gewicht in gr.

17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
years of age with the exception of No. 2 which is from birth to eleven years.

Note in the thyroid curves an increase in weight from five to eight years, a small drop, then an increase again. In the hypophysis this is more evident, and the birth weight is high in proportion. If this were to be interpreted as function one would say that function was progressive from birth on, but was more marked from ages five to seven and again at eleven to thirteen (beginning puberty). Thus we encounter the physiological relationship.

Thyroid.—To this gland has been assigned the function of acceleration of metabolism. That is increasing body temperature and acceleration of the growth of all tissue.—i.e. metamorphosis. Marine (19) states—"The fact that only higher chordates have a true thyroid and that animals will survive its removal indefinitely indicates that the gland is not essential for vegetative life in adult mammals, but is indirectly essential in young animals in that it is necessary for growth in maturation." Hence one might explain the histological changes of the gland as being a reaction to physiological demands in the body and not mere development. This means that the thyroid is a necessary factor in normal development, but in an indirect manner as it furnishes the driv-
ing force for all metabolic activities.

It is a known and accepted fact that the thyroid secretions have a direct influence on the B.M.R. The lack of which cause a lowering and the overproduction of which cause a rise in metabolic rate. (34) (12). The B.M.R. is lowered in diseases of other glands, but only through their effect in the thyroid. Although all tissues are effected by thyroid metabolism, some tissues tend to display their reactions more than others, further these reactions appear to be controlled by the thyroid, but only through stimulation of the latter from some other force, namely the pituitary. These reactions are:

1. Mental functions.
2. Development of bone centers and ossification of epiphyseal junction.
3. Function of sex glands, (especially in female.)

Thyresan, a thyroid albumin preparation is used therapeutically to test for hypothyroids, backward children and mongolian imbeciles. Since the extract is harmless to normal children, K. Rupitius, (13), considers that the outward disturbances shown, in the noted conditions, by large doses indicates a definite thyroid disturbance.

The Physiological variations of the thyroid, either hyper or hypo function. The latter alone, has no demonstrable effect upon growth, but is present in cases
of hyperpituitarism. The former is very essential—both in itself and conjointly with other growth disturbances.

The etiology of thyroid insufficiency may be either primary or secondary, and is of several types.

a. Primary.—

1. That which follows faulty prenatal development or destruction of the thyroid—i.e. Cretinism.

2. That which follows postnatal destruction of the thyroid—i.e. Childhood myxedema.

3. Transitory states of functional disability which have no effect upon growth.

b. Secondary.—

This is a hypothetical condition conceived of as existing when the physiological relationships of the body do not demand the maintenance of the normal level of thyroxin. Starvation, psychoses, pituitary disorders, etc. (56)

The Pituitary.—

I. Anterior lobe.— The normal functions of this
part of the gland are to control and regulate skeletal growth, and function and development of the genitals and secondary sex characteristics. It is evident then that this lobe is the most important part of the gland—especially in view of the subject of this paper.

It has been definitely proven (14, 25, 26) that the cytological source of the growth hormone is the eosinophilic cell. This hormone is called antuitrin-G to distinguish it from the sex hormone, antuitrin-S. The latter is said to be more a product of the basophilic cells. The neutrophile cells are claimed to be non-secretory, the symptoms present in chromophobe adenomas are due to pressure and impaired function of other cells. Evans (3a); Riddle, Bates, and Dykshorn (36); Anderson and Collip (37), and many others have shown that the anterior pituitary produces a thyroid stimulating hormone, which is separate from the growth hormone. These hormones have not been separated before, but recently methods have been devised to make this possible. By some men this is called the Calarogenic Hormone. (55)

Other hormones are the "Master Sex" hormones (Prolan-a and Prolan b- basophilic in origin, Diuretic Hormone, Lactation Hormone, etc.

II. Posterior Lobe.— The functions of the secret-
ions of this lobe are many and varied. The composit pictures that they present immediately places one on guard as to the authenticity of the numerous ascribed functions. The reason for this statement is the fact that the neural lobe is not disconnected from the hypothalamus, and that this region of the brain apparently has control over many of the function accredited to the posterior lobe. Further this region of the brain is quite inaccessible for satisfactory tests and is still a field of hypothesis.

However, the main recognized functions are controls of:-

1. The contraction of Involuntary muscle.
2. In part, of the blood pressure.
3. Carbohydrate metabolism (19), glycosurea, hyperglycemia, sugar tolerance, and obesity.
4. Polyurea and renal secretion.
5. Body temperature (17).
6. Specific dynamic action of food substances (23).

The true source of this hormone is not known, but has been attributed to both lobes of the pituitary. However, the experimental results indicate that it is primarily formed in the posterior lobe. (56)

The abnormal physiology of the pituitary is essentially responsible for growth syndromes. Like the thy-
roid hypo-secretion and hyper-secretion may take place. But unlike thyroid metabolism both variations cause im-
proper growth.

The etiology of hypo-secretory states can be summed up under five main headings. (57)

1. There may be primary under-function resulting from bio-chemical or metabolic changes within the individual.

2. It may be secondary to the anatomical changes in the gland produced by the recession from a state of previous hyperactivity.

3. It may be due to direct pressure of a local tumor.

4. It may be due to indirect pressure from a distant tumor, or from conditions elevating the intracranial pressure.

5. It may be due to trauma---i.e., gun shot wounds, fractures or internal hemorrhages.

Hypersecretory states are due to:

1. Tumors of the cells of the gland--mainly eosinophilic or basophilic.

2. Theoretically to abnormal types of secretion. This is not considered plausible, but only a blind explanation submitted before the physiology was better understood.
3. Loss of thyroid secretions.

Thus we see that, as far as growth is concerned, the pituitary is the gland of primary importance. The anterior lobe controlling osseous or skeletal growth, the posterior lobe carbohydrate metabolism body temperature, and obesity. The thyroid, on the other hand, is a gland secreting a substance which is more universally utilized in the body, and is necessary in all growth processes as a calylitic agent, if not a part of the reaction itself. It is through the variations in secretion of these endorphines that growth abnormalities take place. With the pituitary both hypop and hyper function give definite clinical syndromes. On the other hand hypersecretion of the thyroid does not seem to give any clinical growth response, but a lack of thyroid secretion causes a restriction of growth, mental functions, maturation, etc. Consequently as we formerly noted, we are not concerned with hyper and hyperthyroidism.

Refering back to the growth cycles one is again confronted with the fact that both the pituitary and thyroid are functioning with maximum efficiency at the peak of each cycle, a fact which more firmly links the activity of the two glands.
Experimental Physiology

For quite some time there has been a dispute about the interrelationship of these two glands in disease. As post mortem examination is the only true means of comparison, data from older reported cases and papers on the subject is not of great value. There are two main reasons for this.

1. Not enough complete post mortem were conducted.

2. When complete examinations were permitted the average report only contained a summary of the external appearance of the gland, i.e., there was seldom, if ever, a microscopic examination made of both glands on the same case. In fact, the former autopsy reports were concerned only with the gland apparently at fault—hence any relationship was passed over as an insignificant detail.

In order to prove the interrelated mechanism of these glands, many experiments have been completed. The astounding part of them all is the singular results obtained by the more careful observers.

Aron J., Benait, (53) in 1932 injected over forty young guinea pigs with anterior lobe extract and folliculin. The pigs receiving the former above showed marked increase of activity in the thyroid. Those receiving both
hormones showed no action. This was primarily done to show the relation of thyroid, pituitary and gonads and also serves to illustrate the relations of the first two organs.

Meagher and Hewer (42) report a number of interesting facts.

(a) Hypophysectomized rats show thyroid atrophy and reduced B.M.R. as low as 35%. The true relation is proven when pituitary therapy corrects this condition in the younger animals. The failure of the thyroid to react to therapy in older rats was attributed to senile changes in the gland.

(b) If in preadolescent rats, the pituitary is renewed the result is animal with sparse, fine hair, thin skin, unstable temperature, reactions, etc. The fine hair and thin skin are quiet evidences of hyper-thyroidism. The appearance of the hair and the instability of the temperature reaction are anterior and posterior lobe signs respectively.

(c) Overdoses of anterior lobe to a dog causes acromegaly (post-adolescent hyper-pituitarism) and polyphagia, asthenia, lactation etc., (marked evidences of thryo-tropic activity).

(d) Decreased pituitary function due to pressure causes a lowering of B.M.R. and blood pressure, also polydypsia and
polyurea. Here progeria is usually evidenced in pre-nature senescence—wrinkled skin, fine scant hair, etc. All of these apparently inconsistent symptoms are definitely the result of hypo functioning of the pituitary and thyroid.

(e) In chromophobe adenomas the hypo-function of the thyroid is more marked, the skin being dry, think, wrinkled, and hair scant etc. This being the case, production of the thyro-stimulating hormone by the neutrophile cell seems quite impossible. This is even more evident when the B.M.R. is lowered, often as low as forty.

3. Buena & Barnes. (35)

Collaborate Meagher and Hewers work, but added a bit more to it. They found that feeding pituitary extract to normal dogs caused an increase in the B.M.R. as high as 30%. Sequel with the raise in metabolic rate was an increase in other metabolic processes—in poly urea, poly dypsia, increased heart rate, increased body temperature, etc.

The added work was to repeat this experiment on thyroidectomized dogs, the results here being nil compared to the former reactions. These men believed this conclusive proof of the evidence of a thyro-stimulating hormone in the pituitary body.

4. Riddle, Bates and DyKshorn (36) not only
found that the thyroid enlarges with pituitary therapy but also found that some extracts failed to cause this hyperplasia and hypertrophy. There reason was that some extracts contain a thyro-stimulating hormone, while in other it has been destroyed.

5. Anderson and Collip (37) were able to make a highly purified extract of the anterior pituitary—a thyreotropic hormone. The injection of this extract caused increase in the B.M.R. If used in hypophysectomized rats and guinea pigs it is found that the replacement is not only complete, but that the thyroid is then over sensitive to the hormone and hyper-thyroidism may result.

6. Using the Iodine content of the blood and thyroid gland as indicators investigators (13-b-5, 13-b-7) have shown that pituitary extract injections cause an increase in the I₂ content of the blood and a decrease in I₂ content of the thyroid. This is accompanied by hypertrophy and hyperplasia of the thyroid in an attempt to produce more colloidal material.

7. Rielly (34), working on the accepted theory that retarded bone age is the result of hypothyroidism, studied twenty two cases of young girls in whom early ossification had taken place. In these cases there were
evidences of pituitary disorder, in that the characteristic type of girdle obesity and overgrowth was present. The only sign of hypothyroidism was a constantly low B.M.R. in all cases ranging from ten to thirty-two. Aron (41) states that the basal metabolic rate (B.M.R.) is a good criterion of the activity of the thyroid, and that is--"often effected by the pituitary." Hence in these cases there may have been an eosinophilic hyper-pituitarism giving the increase in growth, while the posterior lobe gave rise to the metabolic upset--causing the obesity. Later there was a decrease in the thyreo-tropic hormone causing retarded ossification and decreased B.M.R.

8. Houssay, Noveill, and Sammatrino (39) summarize the experimental interrelations thus:

a.- Hypophysectomy produces hypoplasia, atrophy and hypofunction of the thyroid.

b.- Anterior Pituitary extract provoke hyperactivity and hyperfunction of the thyroid.

c.- Thyroidectomy causes hypertrophy of the hypophysis.

Therefore, experimentally, we have definite proof that the pituitary and thyroid functions are closely related. It is now necessary to correlate these laboratory findings with the clinical problems found in human subjects. In
### Characteristics of Various Endocrine Disturbances

(From Talbot-10)

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<th>Anterior Pituitary</th>
<th>Thyroid</th>
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<td>Hyper (↑)</td>
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<td>Scanty</td>
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<tr>
<td>1. Hair</td>
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<td>2. Sexual development.</td>
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<td>loss of desire.</td>
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<td>4. Growth</td>
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<td>5. Metabolism</td>
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<td>acromegaly</td>
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<td>6. Blood</td>
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<td>Diminished sugar and calcium.</td>
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<td>7. Carbohydrate</td>
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<td>tolerance</td>
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<td>8. Other Features.</td>
<td>Pressure symptoms</td>
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order to do this the pituitary and thyroid deficiencies will be discussed first, then the hyper secretory state of the pituitary. As the symptoms will be discussed under types of growth syndromes, a chart of the characteristics of thyroid and Pituitary disturbances is submitted here.

**Growth Disturbances**

A classification of this subject which could be adaptable to any purpose concerning growth deficiencies is not available, also symptoms expressed in patients, besides the evidences of the glandular disturbances, namely neighborhood symptoms, are not to be considered here. Engelbach, Schaefer, and Brausius (24) prefer to consider them from three angles.

I. Hypopituitarism.
   a. Aneolastic.
   b. Neoplastic
      1. Intrasellar.
      2. Extrasellar.

II. Polyglandular
   a. Hypo-pituitaro-thyroidum
      (Pituitary primary, thyroid secondary)
   b. Hypo-thyreotpituitarism
      (Thyroid primary, pituitary secondary)

III. Hypergenitatism, parathyroidism, supra renalism, etc.
An attempt to use such a classification of growth deficiencies, even though the subjects under discussion are the pituitary and thyroid, is found to be rather awkward in this case. This is due to the fact that there are so few strictly uniglandular syndromes recognized, hence some more general means of classification is necessary. Engelbach (26) would not agree to the last statement as, in his conception uniglandular endocrine disorders are not so uncommon, but that their frequency varies directly with the practitioners ability to recognize and recognize the various cases. He concedes however, that biglandularisms are much more common than uniglandularisms. (45)

Goldstein, (58) states however, "At autopsy we always find more than one gland pathologically effected. It may be hypoplasia, congestion, degeneration, cystic degeneration, tumors of the gland, or of neighboring structures, hyperplasia, or hemorrhage in the gland substance. Regardless of this the main symptoms are caused by the affected gland primarily envolved in the patient."

The classification to be used here is one of composite nature, altered to suit the presenting problems and taken mainly from the article of H. Goldstein (28) P. Bassoe (20b) on infantilism and dwarfism, and other authors on giantism and eunichoidism.
I. Growth Deficiencies--(Hyposecretory syndromes)

A. Infantilism:

1. Psychic infantilism.
2. Corporeal infantilism.
   a. Brissaud's Syndrome (Cretin type, or myxedematous dwarf)
   b. Frolich's Syndromes (Dystrophia-adiposo-genitalis)
   c. Laurence-Biedl syndrome.
   d. Paltafu's syndrome.
   e. Bramwell's syndrome.
   f. Simmond's syndrome.

B. Dwarfism:

1. Proportionate or true dwarfs. (ateliosi of Goldstein)
   a. Primordial dwarfs. (essential microsomia)
   b. Hypophyseal dwarfs (Miniature men)
2. Disproportionate Dwarfs.
   a. Christian's syndromes and Osteopovesis.
   b. Achrondroplasia
   c. Falta's Syndromes.
   d. Nutritional Stunting (Ricketts & Potts' disease)
   e. Congenital syphilis.

C. Mongolism.

II. Hypersecretory States (Overgrowth)
a. Giantism.

b. Euchnoidism.

Infantilism and dwarfism, both as terms and as diagnosis, are often confused and misused synonymously. The two have clear lines of difference, and should not be confounded. Infantilism is a syndrome of retardation or detention of development of the entire organism, or in parts of it, dating from infancy or early childhood, in the persistence of morphological characteristics proper to infants or preadolescents. It implies a pathological condition and abnormal functioning in the ductles glands responsible for somatic and physical changes in the child. On the other hand dwarfism is considered to be a hypophysiological state in which the stature of the child is much below normal for its age and race. It may retain the body proportions (proportionate dwarfs) or may loose them (disproportionate dwarfs).

A.-Infantilism.- Here the child is diminutive in size and infantile in form. The head is relatively large while the extremities are much shorter than the trunks. See Fig. 4) These cases have been considered as "miserable physiological constitutional specimens" by Cavengt of Spain, and Bauer and Chauvet. That is they have a weak constitution with a pathological background. Krabbe (50) Edelstein (47) Engelbach (26) Golstein (28) and many
FOR COMPARATIVE DIFFERENTIATION THE FOLLOWING CHART MAY BE USED.

<table>
<thead>
<tr>
<th></th>
<th>INFANTILISM</th>
<th>DWARFISM</th>
<th>DISPROPORTIONATE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stature</strong></td>
<td>Small</td>
<td>Small</td>
<td>Small</td>
</tr>
<tr>
<td><strong>Body Proportions</strong></td>
<td>Infantile</td>
<td>Relevant to age.</td>
<td>Relatively large</td>
</tr>
<tr>
<td><strong>Head</strong></td>
<td>Large Prop. short</td>
<td>Relevant to age.</td>
<td>Extreme micromelia</td>
</tr>
<tr>
<td><strong>Extremities</strong></td>
<td></td>
<td>Proportionate</td>
<td>often crooked.</td>
</tr>
<tr>
<td><strong>Assesus</strong></td>
<td>a. Delay in epiphyseal development.</td>
<td>a. May have delayed epiphyseal development.</td>
<td>a. No delay in epiphyseal development.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>e. Lime salts may be present in cartilage.</td>
<td></td>
</tr>
<tr>
<td><strong>Dentition</strong></td>
<td>Delayed</td>
<td>Delayed - improper sequence</td>
<td>May be normal or delayed.</td>
</tr>
<tr>
<td><strong>Muscular Develop-</strong></td>
<td>Muscular weak-ness</td>
<td>Usually weak, may be normal</td>
<td>Usually strong.</td>
</tr>
<tr>
<td><strong>ment</strong></td>
<td>Retarded</td>
<td>Aplastic</td>
<td>Fairly well de-veloped.</td>
</tr>
<tr>
<td><strong>Secondary Sexual Character-</strong></td>
<td>Poorly developed or absent.</td>
<td>Usually absent</td>
<td>Well developed.</td>
</tr>
<tr>
<td><strong>istics.</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td>Varied. From thin infantile type</td>
<td>Normal</td>
<td>Normal to Swarthy</td>
</tr>
<tr>
<td><strong>Vascular and Lymphatic System</strong></td>
<td>May be hypoplastic or bus-involute.</td>
<td>Normal</td>
<td>Often have early arteria-schrasi.</td>
</tr>
<tr>
<td><strong>Mentality</strong></td>
<td>Usually accompanied by psycho-infantilism or Puerilism</td>
<td>Normal</td>
<td>Puerile in proportion to the micromelia, but usually mentally sound.</td>
</tr>
<tr>
<td><strong>Life Expectancy</strong></td>
<td>Often die early of intercurrent infections.</td>
<td>Seldom live to old age.</td>
<td>Age fast, often accompanied by progeria</td>
</tr>
</tbody>
</table>
others consider disease of the pituitary and thyroid as the essential pathological feature. This will be brought out in the various types of infantilism.

The psychic type of infantilism does occur as a singular syndrome and is attributed to thyroid disorders—both as to amount and type of secretion. However this usually exists as one of the symptoms in somatic or corporeal infantilism.

A.-Brissaud's Syndrome (Infantile myxedema or childhood) This is the true cretin type. Many authors classify it under disproportionate dwarfs, and it is often referred to as myxedematous dwarfism. However, it is a definite pathological condition that responds to therapy and is therefore truly an infantile type.

Cretinism is a chronic constitutional deficiency disease due either to an absence or a deficiency of the thyroid secretion. (Thyroxin or diiodo-tyrosine). This includes all cases originating prenatally, during infancy or childhood, or at any time before puberty. The symptoms depend upon the age at which the disease originated. In the past much confusion was caused in referring to prenatal and infancy cases as Cretinism and those developing after specific fevers and later in life as childhood myxedema. As a matter of fact they both give the same symptoms, differing only in degree, the most marked difference be-
ing in the myxedematous infiltration of the skin which
occurs later in the disease and gives rise to the name of
childhood myxedema.

Boothby (56) Oster (5) and others divide this into
sporadic and endemic types. The former is due to con-
genital absence, atrophy due to a specific fever, or to
development of goiter. The latter occurs wherever goiter
is very prevalent. Although the definite cause is not
known it is attributed to Iodine deficiency of several
generations, as the goiter is found in 60% of the mothers
and 40% of the fathers of Certins. Also the latter form
is not quite as severe as the former.

The typical symptoms are delayed growth (usually
bone development), mental retardation, sparse hair, dry
skin, and there may be loss of weight from malnutrition.
By the end of the first year the myxedematous signs
show up—i.e. Puffy eyelids and bloated face, non-pit-
ting edema of skin and mucous membrane, large protruding
tongue, delayed dentition, underdeveloped pudgy ex-
terminities, etc. The child may die early of intercurrent
infection, or go on to develop subnormally both mentally,
physically, and sexually.

Here the situation presented does not suggest the
lack of pituitary hormones in any way. The trouble here
is that there is no thyroid tissue capable of being
stimulated by the thyro-stimulating hormone of the
pituitary. Also the interaction of the thyroid is here
shown that without thyroxin, autuitrin-G cannot function
in the former is the control or the catylist of the
latter. This is further proven in clinical practice
in that thyroid therapy yields almost miraculous re-
results showing that this is essentially a thyroid de-
fiency.

Contradictory to this some French authors—Aron,
Van Coulaert, and Stahl (41) attempt to connect myxedema
with the anterior lobe of the pituitary. They report
three cases of "congenital myxedema" in which thyro-
stimulating anterior pituitary hormone from urine was
superior therapeutically to thyroxin and thyroid extract.
Further they interpret this as a primary pituitary de-
fiency of the thyro-stimulatory hormone. With all due
respect to these men their interpretation appears to be
a bit prejudiced. They record no tests of pituitary fun-
ton nor do they include in their discussion the poss-
ibility of a co-existing pituitary and thyroid deficiency.
One must recognize that the interaction of these two
glands begins before birth, and that these cases may have
been polyglandular syndromes especially as hypopituitaro-
thyrodism is considered common and treated in a similar
manner (25) see cases.

B.- Frolich's Syndrome.- This occurs in certain
diseases of pituitary, but may also occur in certain les-
ions of the hypothalamas which involve the pituitary. Its
presence is attributed to the absence of the Specific
dynamic Acting hormone (55). The thyroid relation here
is shown in that thyroid ectomy also causes a hypoactivity
of this hormone.(3) This syndrome may occur at any age,
the symptoms depending on the maturity of the individual.

The symptoms here can be summarized under four
heads:

1. Pituitary adiposity (esp. feminine distribution in males), subnormal temperature, and in-
creased carbohydrate metabolism.

2. Sexual retardation or genital infantilism.


4. Neighborhood symptoms—especially in pre-
sence of tumor.

Obesity is an interesting problem and is encountered
in many children. Goldstein (21) accredits it to the pos-
terior pituitary, associated with thyroid deficiency.
Engelbach (22) has a much clearer conception of the juvinile
type of adiposity. He gives the cause of overweight to be
anterior lobe hypopituitarism at birth, posterior lobe
hypopituitarism during the juvinile stage, and thyreo
gonadal in puberty and post puberty cases. From this and
from other articles, it is my belief that this syndrome should be considered primarily a pituitary problem with the thyroid involved later on. For example, Weber (52) reports a case of pituitary obesity which, on autopsy, showed a relatively normal pituitary, but with increased colloid in the thyroid. One would be inclined to believe that this is one of Engelbach's precocious puberty cases in which there was a thyreo-gonadal syndrome.

In the treatment of most types of Juvenile Obesity many authors advocate a high fat diet, (13, b, 6) claiming that the fat decreases the use of glycogen in the body by stimulating the hypophysis. It is well known that both the pituitary and thyroid are important in carbohydrate metabolism and as cases of obesity usually show upset carbohydrate metabolism, thyroxin and anterior pituitary extract was fed to afflicted patients. The result was very beneficial when both endocrine extracts were given at the same time, more so than when either one was used alone. (13, b, 2)

C.-Laurence-Biedl Syndrome.- This is a familial syndrome of composite nature. The etiology is unknown, but is suggested to be a congenital deficiency of the secretions of the posterior hypophysis, plus a congenital defect in the genito-tropic centers of the hypothalamus. It is of interest here because it consists of Frolich's
Syn-drome, mental deficiency, polydactylyism, and Retinitis Pigmentosa. Hence besides the suggested connection in Frolich's Syndrome the mental deficiency strengthens the contention of thyroid-pituitary intract-ion growth syndromes.


F.- Simmond's Syndrome are not of concern here, being related to other endocrines and post adolescent cases.

B.--Dwarfism.--

1. Proportionate dwarfs, (206, 26, 28, 29, 31, 55) This is the true dwarf or atelioses. This means a child not arriving at perfection in which the stature of the child is much below the normal for its age and race, but in which it retains the body proportions. Of this there were two types:-Primordeal and hypophyseal.

a. Primordeal dwarfs.- So far as the primordeal dwarfs are concerned, there seems to be no explanation of the etiology. The condition is usually heredity and present at birth, an essential microsemia if you please. No endocrine or other abnormality has so far been demonstrated. Meig describes them as adults in small mould.

b. Hypophyseal dwarfs.- These dwarfs are the "Minature Men" of Lorraine-Levi. They are a form of preadolescent
hypo pituitarism which results in skeletal undergrowth involving all the bones of the body. The skeleton is delicate and graceful, i.e. truly proportional in every respect. The mentality is normal and there is no obesity. The patients are just small with aplastic genitalis and assees development. The connection here may again be in this sequence—Hypo-pituitarism—no thyro-stimulating hormone—no thyroxin to activate the antil-trim-G. of the anterior lobe.

2. Disproportionate dwarfs.—Under this classification falls the dwarfed cases in which the body proportions are lost. The cause of the achondroplastic dwarf is unknown, but must be the same in all cases, as they are all alike. Christian's Mydrome is a type founded on theoretical etiology. The three others listed are also etiological types, i.e. Falta's, Ricketts and Patts disease and congenital syphilis, but will not be discussed here.

a. Achondroplastic dwarf.—(Chondrodystrophica-Fetalis)

Here the micromelia is extreme, the extremeties being not only short, but crooked. The heads are relatively large, the body muscular and strong, and the patient imbibed with excessive appetities and lusts. It is this type of a dwarf that usually constitutes the circus dwarf. Quite frequently these "little people" become prematurely
old, wrinkled and grey, often suffer from progeria. Dock, Craig, and Maxwell (32) state that the diseases of bones of the fetus and infants are definitely a matter of faulty growth. Of these diseases cases of achondroplasia and osteoporosis are the only ones to which the pituitary and thyroid can be definitely connected.

b. - Christian's Syndrome (55)

This is a disease of childhood in which bone symptoms appear early, and are later complicated by diabetes insipidus. The characteristics here are decalcification of the skull and jaw. This is not essentially either pituitary or thyroid, but there is a definite connection through the endocrine chain. This is shown by Stattner (43) who reports a case of hypo-pituitary-thyroidism in which thyroid extract was stated as the cause of this "Selective osteoporosis" of childhood.

c.-Monogolism-

This condition was originally described by Landgon-Dawn (59) in 1866, and, although it has been recognized as a fairly common disease since that time, little or nothing of importance has been discovered about it.

The etiology is as much a mooted point today as it was in 1866. But, as it is considered to have some endocrine genesis, it has come to be classified by some observers with endocrine disturbances. This is due to the
fact that it seems to resemble cretinism in many ways and is always associated with a peculiar cast of counten­
cance as are acromegaly, Frolich's syndrome and exophthal­
amic goitre. (10)

Sajous, (17); Moore, (14); Talbot, (10) Gorden, (49), and many others have observed that there are a number of constant factors present which may not be the primary cause of this condition, but may accentuate the primary factor. Briefly they are:

a. Parental weakness—i.e. offspring of old parents, or parents of markedly different ages.

b. 50% are found to be the last-born in large families.

c. Prenatal infections such as syphilis and alcoholism.

d. Improper diet deficient in vitamins of phosphorus containing substances.

In the past these conditions were considered as being true etiological factors. At the present time there are two main theories of causation:

a. That the condition is due to faulty eugen­
icies in a disturbance in chromosome distribution.

b. That the thymus, thyroid, and pituitary are primarily at fault. Talbot (10) believes that some other gland than the thyroid is at fault. Sajous (11) gives preference to the thymus, while Gordon (40) claims
thyroid disturbance as the essential case with the pituitary being involved to a lesser degree. Gordon's report is unbiased and also considers the adrenal and thymus as possible causes. However his survey of post-mortem examination made on Mongolian idiots favors the thyroid-pituitary theory most strongly. Truely the last word has not been said about this subject, and the greater proportion is entirely theoretical. Of one thing I feel certain, and that is that there is definite endocrine envolvement. Whether this is primary or secondary to some pre-existing condition is impossible to state at the present time.

The symptomatology of Mongolians is very characteristic. The physical signs are often considered to be similar to those of the cretin. However the following table by Talbot (10) serves well to give the physical signs of the Mongol, and also to compare with those of the cretinism.

<table>
<thead>
<tr>
<th>Mongolism</th>
<th>Cretinism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Recognizable at birth.</td>
<td>1. Rarely recognized before second or third month of life, but always evident by sixth month.</td>
</tr>
<tr>
<td>2. Eyes almond-shaped, tipped upward and outward. Epicanthic fold marked. Strabismus.</td>
<td>2. Eyes horizontal and piglike.</td>
</tr>
</tbody>
</table>
Mongolism.

3. Skin of cheeks flored red, elsewhere marbled.
4. Tongue fissured, pointed and not thick. Often protrudes.
6. Skin fine and soft.
7. Hair fine and soft.
8. Hands short, little finger shorter than others.
9. Feet short with great toe separated from others.
10. Joints lax and very flexible.

Cretinism.

3. Complexion pale, waxy, with a yellow tint.
4. Tongue thick and square, fills the mouth. Constantly protrudes.
5. Expression dull, stupid.
6. Skin dry and coarse.
7. Hair dry and coarse.
8. Hands square, spade-like.
9. Feet square. Great toe seldom widely separated from others.
10. Joints not abnormally flexible.

The imperfect mentality of these patients is suggested by the name Mongolian idiots. They are easily separated from Morons by the marked defect in mentality the absence of post adolescent hypoplasia of the gonads, and presence of normal time of epiphyseal closure. They also present a perfect picture of constitutional diathesis, in reference to their susceptibility to upper respiratory infections, and as a result usually die young of some intercurrent disease.

Due to non-treatment in early life the average
Mongolian idiot is not benefited by endocrine therapy. However, proper treatment can be instituted and beneficial results obtained. Prophylactic treatment in cases of suggested Mongolian idiocy, or under conditions tending to produce such an infant, is considered unsuccessful. This constitutes feeding the mother described thymus, thyroid, and pituitary, together with a generous varied diet.

In cases of established Mongolian idiocy the same treatment is instituted plus further endocrine therapy to the infant. Good food plenty of fresh air, and removal of all possible foci of infection are essential factors for successful treatment, in this, as in all diseases.

**HYPERSECRETORY STATES**
(Hyperphysiopathies)

**Giantism:** This clinical syndrome is commonly known as preadolescent hyperpituitarism, and has been universally discussed and accepted as a true unglandular disease. In the later years, however, the viewpoint has changed as the subject became more closely studied.

Goldstein (21) states that "the influence of the pituitary, particularly hypersecretion of the anterior portion, thyroid, and gonads of giantism, no
matter what type has been unquestionably demonstrated."
Aron, Van Coulaert, and Stahl (91) connect giantism and
acromegaly with other hormones (than the pituitary).
They stress mostly the thyroid stimulating hormone of the
pituitary and the thyroid hormones.

Cushing (1) states that repeated injections of
anterior lobe extract lead to no special changes. This
is an argument which indirectly favor the view that
giantism is due to some perversion of secretion rather
than to normal excess. He also states that the per­
verted secretion acts abnormally on other endocrine
glands.

Osler (5) in discussing giantism and acromegaly
states that the thyroid is interrelated definatly in
at least one-third of the cases. The association in us­
ually hypothyroidism, but thyreotoxicosis and increased
B.M.R. (which is lowered by Lugols) are also found.
Goitre is frequent, myxedema and flabby obesity may
occur later in the disease.

Thus we see a defineate relationship between
these glands, acting again here in giantism. The diff­
iculty in classification of giantism lies in the fact
that there are again so many variables. Of one thing
one can be certain, and that is that hyper secretion
of perverted secretion of the pitutary is constantly
present. The thyroid may be in a hyper or hypo secretory state and the gonads are usually in a physiological state comparable to the thyroid.

For use in this paper the following simple classification of pre-adolescent gigantism shall be used.

A. True gigantism (proportionate)
B. Pathological gigantism (disproportionate)
   1. Eunichoid gigantism.
   2. Premadolescent acromegalic gigantism.

A. True proportionate giants may be considered quite analogous to the true proportionate "little men" of Lorraine Levi type, in that their body proportions and physiological activities are apparently normal in every respect. In these cases one finds a perfect physical specimen that is unusually large.

B. In pathological gigantism there is a period of marked hyper secretory activity, which is usually followed by a gradual change to exactly the opposite state. Fatla (17) describes pathological gigantism as "a rendering potent of the entire ductless glandular system, that is followed by rapid exhaustion, in which some glands, such as the sexual glands for example even at the beginning of the disease, show signs of loss of function and maldevelopment."
Eunichoid giants are usually confused with true eunichoids. This is probably due to the fact that both dystrophies have a longer lower measurement than upper, and that their span is greater than their height. The difference lies in the development of function of the genitals in eunichoid giants. The genitals are usually well developed and function as well as those of a normal individual; whereas in true eunochoidism in the male, the genitals are objectively small and underdeveloped and there is a complete absence of sexuality. There is little difference between the two as far as secondary sexual characteristics are concerned, with the exception of the voice. In the true eunichoid the voice is of unstable high pitched, often unpleasant quality, while in the eunichoid giant it is well developed and deep-toned. Further, the eunochoid giant may later show symptoms increased intracranial pressure, or neighborhood pressure symptoms.

The preadolescent acromegalics giants are those having the characteristic general over-development of the body and of a hyper secretion of the anterior pituitary, to which has been added the specific changes present in the overgrowth of the short and flat bones, particularly the head, face, hands and feet.
Consequently we view this syndrome of body overgrowth which takes place before epiphyseal closure as an odity which results from abnormal secretions of the endocrine glands. The pituitary is generally considered at fault primarily, while the thyroid, thymus and adrenals come to play more important parts later in the disease. The disease may take one of the four courses:

1. They may remain in a mild hyperactive state for a considerable number of years, or even throughout life.

2. A certain percent have recrudescenses of hypoactivity, occurring for longer or shorter periods.

3. Some cases alternately change into a complete hypo-activity in which both lobes of the pituitary are finally involved. (Complete bilobar hypopituitarism)

4. A certain percentage of these cases change into pathological giants, leaving either local changes in the pituitary gland or distressing hormonal signs, either of eunichoidism or acromegaly.

Also these cases are not strong in comparison to their stature, but are often weaklings. Resultantly they seldom live to old age, although some have lived to be sixty years old, and is commonly observed that proportionate giants and eunichoid giants live much longer than preadolescent acromegalic giants.
CASE REPORTS
CASE NO. I

April 1, 1932. Female. Age, 15 years. Occupation, student, private school.

Diagnosis: Hypothyropituitarism.

History: The patient was adopted at the age of six months and was a very small baby. At that time she had rickets and was given cod liver oil. She talked at 18 months, but did not walk until after two years of age. She was always slow in school. She is now under a private tutor and is doing quite well. Her maturity occurred between 11 and 12 years of age. Her periods were regular and normal.

Family History: Not known.

Physical Examination: This patient showed moderate structural undergrowth. There was a slight but definite lower girdle obesity. Her skin was dry with scaling over the outer aspects of the upper arm. Her teeth were small and misaligned. Her third molar teeth were absent, and there were no unerupted teeth demonstrated by the Roentgen ray examinations. Her secondary sex characteristics were well developed for her age. Her hands and feet were quite small but the fingers were short.

Laboratory Examinations: The results of the urinalysis, blood count, and blood chemical examinations were within the limits of normal. The blood Wassermann reaction was negative. Roentgen ray studies of osseous conditions of the hip, wrist, elbow, and ankle showed a slightly advanced development. Roentgen ray examinations of the sella showed normal outlines.

Course: This patient was under observation for a period of two months before treatment was instituted and showed no growth. Treatment was instituted May 22, 1932, at which time her height was 58.7 inches. On September 10, 1932 her height was 59.7 inches. In a period of three and one-half months this patient showed an increase in height of one inch.
CASE NO. II


Diagnosis: Hypothyropituitarism.

History: The patient is the only child and represents the only conception. The pregnancy was normal, and his weight at birth was 10 pounds, 1 ounce. Dentition, walking, and talking occurred at 12 months. Physical and mental development progressed satisfactorily up to the fifth year. Since then his physical development had been quite stationary.

Family History: His mother was tall and slender, and his father was tall. His mother's sister had an exophthalmic goiter.

Physical Examination: This patient was structurally underdeveloped. His skin was extremely dry, inelastic and thickened. Over the sternum and lower extremities were lesions from scratching. There was a marked alabaster color present. The nose was quite blunt, and there was a pot belly present. The mucous membranes were quite pale. The pulse was relatively slow. There was a slight hypertrophy of the penis.

Laboratory Examinations: The urinalysis showed no evidence of disease. The blood count showed red blood cells, 3,400,000. The results of the blood chemical examinations were within normal limits. Roentgen ray study of the osseous conditions of the knee, elbow, wrist, shoulder, hip, and ankle showed a delay in development of 3 to 5 years. In addition there was a generalized proliferative and degenerative process in most of the epiphyses and chondral margins, most marked in the knees. Roentgenograms of the thymus and sella showed normal outlines. An orthopedic examination was made by Dr. L.C. Wagner. He ascribed the undergrowth and epiphyseal changes to an endocrine cause.

Course: The patient was under observation for a period of three months before the institution of treatment, and during this time he showed no change in height. April 25, 1932, he was placed upon Antuitrin-G. The total height at that time was 47.5 inches. September 16, 1932, his total height was 50.2 inches. This shows an increase in height of 2.7 inches in a period of four and one-half months.
CASE NO. III

April 2, 1932. Female. Age, 9 years 5 months.
Occupation, school girl.

Diagnosis: (1) Hypothyropituitarism. (2) Enlarged thymus.

History: The mother had a severely toxic pregnancy. The patient's weight at birth was 8 pounds. Development during the first year was normal. During her second year it was noted that she was quite clumsy and fell frequently. She did not enter school until the age of 8 years. Up to that time her mother believed that she was mentally retarded. Following the administration of thyroid her mentality improved, but there was no noticeable increase in stature. In June, 1931, her height was 42.2 inches.

Family History: The father was tall and over-developed. One brother, two years of age, showed a marked structural overgrowth.

Physical Examination: Structurally this patient showed moderate undergrowth and was short and stocky. Her skin was extremely dry and inelastic with some subdermal thickening and a generalized pallor of the alabaster type. Her scalp hair was fine but extremely dry. The eyelids were somewhat thickened. The nasal bridge was low and the lips were pouting. There were only two upper central incisors present. Her upper abdomen was quite prominent, and there was a small umbilical hernia.

Laboratory Examination: The results of the urinalysis, blood count, and blood chemical examinations were within normal limits. The blood Wassermann reaction was negative. Roentgen stud of the osseous development of the wrist, elbow, ankle, knee, and hip showed a delay of 3 to 4 years with the same chondroepiphysitis present in Case No. II. Roentgen rays of the thymus showed an enlarged thymic shadow.

Course: This patient was under observation from April 2, 1932 to May 25, 1932, before treatment was instituted and showed no growth. At this time the patient's height was 42.7 inches. September 10, 1932, the patient's height was 44.2 inches. A total increase of 1.5 inches in a period of three and one-half months.
CASE NO. IV.

November 27, 1931. Male. Age, 18 years, 6 months. Occupation, student.

Diagnosis: Hypopituitarothyroidism.

History: The patient's birth weight was 7 1/2 pounds. His growth and mental development were normal during the first and second years. Beginning at the third year his mother noted that he was smaller than other babies of his age, and that growth retardation had continued since that time. During the past year, under the observation of a physician, it was determined that he had grown one inch. His progress through school was satisfactory during his first three grades but since then he had difficulty. He was eighteen years of age and had not graduated from high school. He was somewhat incorrigible, but his mother believed that this was due to his introspection because of his retardation in physical development.

Family History: No endocrine abnormalities were noted.

Physical Examination: This patient was short in stature but stocky. His head was slightly large compared with the rest of his body. His external genitalia were well developed. There was no axillary or pubic hair growth. His nose had a low bridge and his lips were thickened and pouting. His hands and feet were relatively small, and his skin was dry and scaly.

Laboratory Examination: The results of the urinalysis, blood count, and blood chemical examinations were within normal limits. The basal metabolic rates were minus 20, minus 24, and minus 15 per cent. The electrocardiograph showed slight right axis deviation. Roentgen study of osseous development of the wrist, elbow, knee, and ankle showed a delay in development of two to four years. Roentgenograms of the thymus and sella showed normal outlines.

Course: The patient was under observation for a period of five months before treatment was instituted. During this time he showed an increase in growth of one-half inch. On April 23, 1932, he was placed an Antuitrin-G. At that time his height was 53.0 inches. Measurements taken on September 21, 1932 showed his height to be 55.7 inches. This shows a total increase in height during a period of five months of 2.7 inches.
CASE NO. V.

March 29, 1932. Male. Age, 14 years 7 months. Occupation, student, private school.

Diagnosis: Hypopituitarothyroidism.

History: His mother gained about 30 pounds during this pregnancy. The patient walked and talked at two years. At the age of 14, six of his deciduous teeth had to be removed. These should have been lost at the age of 6 or 7. Until the age of 5 he was considered normal in growth. He had numerous infections after this age. When first seen by his physician, two years ago, he had a basal metabolic rate of minus 20 per cent. He was then given thyroid and since that time had grown from 48.7 to 52.0 inches. There was no mental retardation.

Family History: On the paternal side of the family there was a tendency to overgrowth; and on the maternal side to undergrowth, but there were no giants nor dwarfs.

Physical Examination: There was a marked structural underdevelopment. The patient was not obese. His skin was dry with a slight subdermal thickening. His eyebrows were scanty, and there was no axillary or pubic hair. There was a relative hypoplasia of the external genitalia.

Laboratory Examination: The results of the urinalysis, blood count, and blood chemical examinations were within normal limits. The basal metabolic rates were minus 10 and minus 8 per cent. Roentgen ray study of osseous development of the ankle, elbow, and hip showed a delay of 1 to 3 years. Roentgen examination of the thymic area and sella showed normal outlines.

Course: This patient was under observation for two months, from March 29, 1932, to June 1, 1932, without treatment, and showed a stationary growth. At this time his total height was 52 inches. This shows an increase of 2.7 inches in a period of three and one-half months.
Discussion of Cases I-V.

These cases were submitted by Englebach, Schaefer, and Brasius (25) and are of very elementary value in this paper due to their correlation of the interaction of the two glands. In all cases the authors assume one gland or the other as the primary source of the trouble. Following the cases it becomes evident that secondary involvement of other endocrines is inevitable if the disease is allowed to progress. The results obtained by hormonal therapy add to the value of the conclusion drawn by the authors.

Case No. VI from the Uni. Hospital, No. 46346, is included here as an advanced case of hyposecretory activity.
CASE NO. VI.


Diagnosis: Hypopituitarothyroidism.

History: The patient has always been large for her age and when a small girl was heavier than any of her playmates. Due to the fact that her mother died when she was young, she knows nothing about her birth and early childhood. She only attended school to the 4th grade, when her mother died and she stayed home to help keep house.

Recently she has been gaining weight rapidly. At 18 years she weighed 200 lbs., at 21 years 250 lbs., at 31 years 271 lbs., and at 33 years 421 lbs. She also complains of difficult breathing, acral paraesthesiae, palpitation, pain in lower back, etc.

Family History: There is no family history of obesity, nor is the patient any taller than her sisters.

Physical Examination: The patient is a well developed, obese, dry scaly skinned, hirsuitous female of stated age. A definite cardiac syndrome has developed, and the patient is quite uncomfortable.

Laboratory Examination: The blood counts and blood chemical examinations were within normal limits. The B.M.R. varied from 20 to 7 at first, but later trials showed a definite tendency toward lower metabolic rates.

Discussion: This patient is included as an example of what could have been prevented with proper hormonal therapy during the juvenile stages of development. This was probably a case of juvenile adiposity, primarily involving the pituitary and secondary involving the thyroid and ovaries. In such advanced cases, where degenerative changes are beginning to take place, very little can be done along the line of cure.
SUMMARY AND CONCLUSION

The endocrine chain is the complex, delicately balanced, interrelated system of glands of internal secretion. Due to this close association all of the glands are affected when one does not function properly, but some of the glands have strong interrelationships and cause more definite disturbances. It has been found that certain glands have the tendency to govern given activities of the body and the malfunction of one, or an interrelated group, causes a specific clinical syndrome.

Growth is a constant body activity which has been linked with the endocrine chain in general. Of this hormonopoietic system the pituitary and thyroid glands have been considered elementary in the control of growth. Hence the association or interaction of these two glands has developed into a question of increasing importance.

This association seems quite plausible when it is noted that both glands originate (whole or part) from the same embryonic tissue, and when both glands develop equally, in both size and function, comparable to the cycles of growth. It seems possible when carefully regulated physiological experiments show definite effect
of the products, or absence of products of one gland upon the other. It seems probable when any pathological disturbance of either gland causes a digression of body growth from normal, with polyglandular morphological changes demonstrable at post mortem. And it seems inevitable when, in properly diagnosed cases, carefully planned thyro-pituitary therapy corrects, or tends to correct clinical symptoms.

Growth is a factor which is of most importance during preadolescent years, and which is governed in part by the interaction of the pituitary and thyroid. The primary growth hormone is secreted by the eosinophilic cells of the anterior pituitary, but the thyroid gland stimulates all body activity, so without it the pituitary cannot function. Further the pituitary secretes a hormone that activates the thyroid. In primary deficiency diseases, of the pituitary there is not only an absence of growth hormone for the thyroid to act on, but also a lack of thyro-stimulating hormone. In primary thyroid disease the growth hormone is present but not properly activated and there is no normal thyroid tissue to react to the thyro-stimulating hormone. In cases of overproduction of the pituitary, there is an oversupply of the growth hormone and thyroid stimulating hormone, so that the former is completely activated by the latter.
In conclusion, I wish to convey my impression of the subject by briefly summarizing as follows:

I. The pituitary and thyroid glands do have direct interrelationship in preadolescent growth.

II. The thyroid is not directly related to growth per se; but is the driving force behind all metabolic activities, one of which is growth.

III. The pituitary is concerned primarily with osseous growth and fat metabolism. In turn it secretes a thyro-stimulating hormone which activates its products.

IV. Because of this interrelationship growth in pathological states suffers either directly through the pituitary or indirectly through the thyroids.

V. Successful therapeutics in these cases demands, first, early correct diagnosis, and second treatment primarily with the deficient hormone, or removal of the offender if hypersecretion, or a neoplasm, is the etiological factor.
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