THYROID AND GROWTH

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INCREASE in length of an organism takes place in the early part of its life, and depends upon many factors. The harmonious relationship among these factors produces the normal and constant increase in length which is terminated when ossification is completed at the epiphyseal zones of growth. With the cessation of ossification and union of diaphyses and epiphyses the morphological and physiological maturity of the organism is usually reached.

The factors concerned with growth and maturity have been pointed out by many authors (1–11). It is difficult to establish a classification of these factors because there is complex interaction among them. This fundamental 'substrate,' by which is meant the inherent capacity of the cells of the organism to divide and produce new elements, has intrinsic characteristics due to hereditary factors which condition growth to a certain extent; and it is the 'substrate' upon which other factors operate.

Some factors, such as diet, may ultimately accomplish increase in mass by supplying the cells with the material necessary for their growth and division. Vitamins and hormones regulate cell metabolism and are responsible for growth and differentiation. We have to distinguish, therefore, between simple increase in mass such as can be produced by excessive diet and increase in mass resulting from growth and differentiation in which vitamins and hormones are involved.

Alteration of the capacity of the substrate can be illustrated clinically in cases of retardation of growth in the course of chronic disease. This interference with growth can be seen in the so-called zones of cessation of growth in the bones (12) and in the acceleration and retardation of ossification (13–17). The existence of a definite minimum effective dose and of a limit of maximum stimulation beyond which there is no further growth effect emphasizes the impor of the substrate.

The experiments of Smith (11) demonstrated sation of growth after hypophysectomy wit sumption of growth following administration tive growth factor of anterior pituitary origin secondary cessation of growth on discontinuan such treatment. Also, in accordance with the wo Smith, when thyroid is given together with pitu growth hormone, growth is fostered more tha pituitary alone.

It is our purpose, in this paper, to show sta changes, in individuals of 20 years and under, ically manifested as a function of the thyroid.

In the clinical field, the early descriptions of tinism stressed the retardation of growth as an e tial feature of the syndrome; and as time has pa we have come to appreciate the relationship of fa of growth to thyroid deficiency. This explana has been borne out further by the study of bon velopment in acquired hypothyroidism of the juv type in which it has been shown that there is reta tion of epiphyseal closure and of development in bones of the wrist.

The opposite phase of the question—namely, possibility of clinical overgrowth as the result of peractivity of the thyroid—primarily concerns u this study (18–23).

CLINICAL MATERIAL

We selected all the cases of definitely proved ophthalmic goiter in our juvenile group, that is all s patients of 20 years or under. There were 121 ca 13 boys and 108 girls. For comparison we have serted a few cases of juvenile hypothyroidism wh we have had occasion to observe, 1 boy and 7 g From the 121 cases we exclude the boys for simpli in graphic representation and 3 cases with indepe ent chronic disease, thus leaving 104 cases with

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complicated toxic goiter in girls. In figure 1 the height for age of this group is compared with that of normal girls; and it is apparent that the thyrotoxic are consistently taller for their age.

In figure 1 also is shown the average deviation from the normal height, in centimeters, of our juvenile patients with Graves' disease. (Benedict, Talbot and Crum-Wood tables were used to obtain normal average heights.)

It is clearly seen that up to the age of 18 when closure of epiphyses normally occurs and growth of normal individuals has usually ceased, as indicated by the plateau in the normal growth curve, there is a preponderance of over-height in hyperthyroid individuals.

From 18 to 20 years the tendency to over-height is less striking. Isolated examples of over-height in these latter age groups were investigated; and it was found that in these cases the disease had been present for a long time according to their histories, and at the onset of their illness the over-height individuals were in the 'open epiphyses' group. It is to be noted that the two maximum deviations in the hyperthyroid group

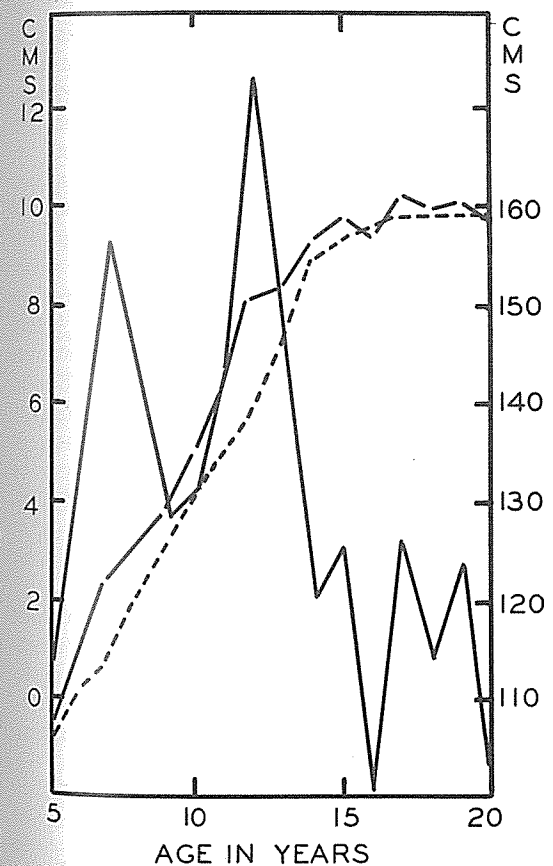


Fig. 1. Height referred to age for 104 thyrotoxic girls (broken line), compared with Talbot's curve for normal girls (dotted line). Scale on right. Average deviation in cm. of our juvenile patients with Graves' disease from normal height (solid line). Scale on left.

coincide with the two normal accelerated growth periods, that is during the 6th to the 8th years and the 12th to the 14th years.

In considering excessive final stature we have to consider three different factors, any one of which may produce this condition.

(*a*) Growth at a normal rate, but prolonged beyond normal time limits (e.g., lack of inhibitory action of gonadal factors).

(*b*) Growth at an abnormally rapid rate for the normal period of time (acceleration of annual rate of growth, e.g., our group of thyrotoxic juveniles).

(*c*) Rapid rate of growth during an abnormally long period (e.g., pituitary overactivity in juvenile gigantism).

As indicated in figure 1, the cases of hyperthyroidism at the time of epiphyseal union, 18 to 20 years show no further excess in growth. This would indicate, as in the work of Smith, that the role of the thyroid is to speed up growth, but that the opposite processes, those that stop growth, take place at the correct time. Hence the largest deviations are observed in those cases in which the age of the patient allows the possibility of greatest growth.

In figures 2, 3 and 4 is represented, in reference to age, the growth of some of our patients. Normal growth is represented by heavy broken lines; and growth during the period of the disease of our patients is represented by dotted lines. The cross indicates the stature of the patients when first seen in the clinic; the arrow, the time when treatment was begun. The lower horizontal heavy line represents the normal rate of growth referred to the normal expected annual growth; the broken line represents, in centimeters, the excess over normally expected annual growth of the hyperthyroid patients. As can be seen in these graphs, the higher stature of the patients when first seen in the clinic indicates that previous growth has been acclerated as compared with the normal expected growth. When adequate treatment is given, the rate decreases, and comes to lie within normal limits. To compare, we show in figures 5, 6 and 7 the growth curves of 3 myxedematous patients with retarded rate of growth when first seen in the clinic, and accleration produced in them when treatment is given. The results are similar to those of other authors (38–41). They serve to stress the fact that thyroid feeding does not cause premature cessation of growth.

Dorothy B. (fig. 2) was admitted to the Massachusetts General Hospital at the age of 12 years, 10 months, with a classical picture of thyrotoxicosis of about 11 months' duration. Goiter, exophthalmus, weight loss of about 10 lb. were characteristically present. B.M.R. was between +50 and +60 before iodides were administered. Subtotal thyroidectomy was performed after a short preliminary period of observation on iodine. She was 11.8 cm. overheight for her age at the age of 12 years, this rapid rate of

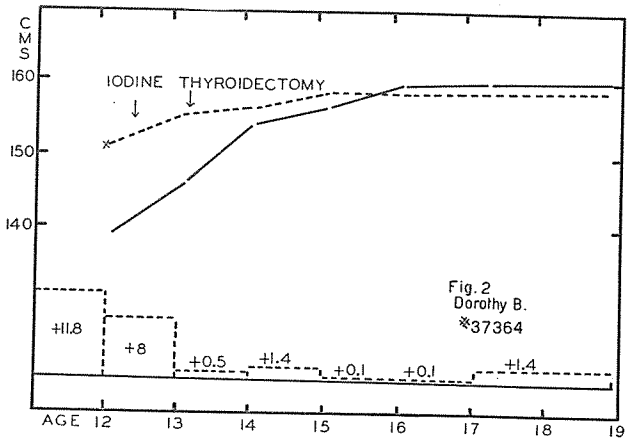


Fig. 2. GROWTH OF *Dorothy B.* IN CM. AT VARIOUS AGES DURING OBSERVATION ON IODINE AND AFTER SUBTOTAL THYROIDECTOMY (dotted line) AS COMPARED WITH AVERAGE NORMAL GROWTH CURVE (broken line). Below is given the deviation from annually expected growth during the same period, in cm.

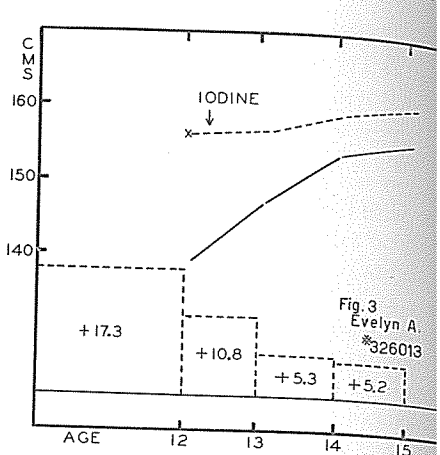


Fig. 3. GROWTH OF *Evelyn A.* IN CM. AT VARIOUS AGES I TREATMENT OF TYPICAL GRAVES' DISEASE.

growth continued while she was observed on iodine, and her growth approximated the normal after subtotal thyroidectomy.

Figure 3 shows the accelerated growth in *Evelyn A.* which occurred despite iodine treatment. This patient was 17.3 cm. overheight for her age at admission to the hospital at the age of 12.

Figure 5 shows the growth of *Dorothy M.* a myxedematous patient on thyroid therapy. Her chief complaint on admission was failure to grow. Characteristic facies of myxedema were present; and moderate obesity was associated with the other classic findings. B.M.R. was −25 to −32. Thyroid, 1.5 grains daily, was administered. Observation has continued in this case through the entire adolescent period. She was 12.2 cm. below average normal height at entry; and at the age of 17 was approximately 2 cm. overheight for her age. No evidence of premature closure of the epiphyses occurred in this case.

Florence McK. (fig. 6), aged 14, was 16 cm. underheight on admission. She was given 1.5 grains of U.S.P. thyroid daily. The growth rate approached normal thereafter.

Mary C. (fig. 7) was a typical case of myxedema at the age of 10½ years. Her primary complaint was failure to grow; she was 7.4 cm. underheight when started on thyroid therapy. In the next 3 years under thyroid therapy she grew 2.1 cm., 4 cm., and 2.8 cm. so that at the age of 13 she approximated normal height for her age.

DISCUSSION

We have shown in our material that an increase in height has to be included among the symptoms of thyrotoxicosis in young patients (17–23). The experimental work of Smith (11) indicates that the excess of thyroid is the basis of this acceleration of growth. Which comes first, the overgrowth of the individual or the hyperplastic state of the gland? Smith's work would indicate that the latter resulted in overgrowth because of the addition of extra thyroid hormo the patient's normal production of growth horr Webster (37) would explain the acceleratic growth caused by thyroid as due to a stimulati production of growth hormone, better utilizati foods, or some other, unknown mechanism. It i conceivable that the thyroid hyperplasia is a resu increased growth and increased demand. Of ou perthyroid patients 29 show an increase in st that cannot be considered due to the disease, be the overgrowth could not have taken place durin short duration of the disease, or because the s toms began when no further growth was expecte dicating that excess of growth had taken place b the onset of the disease. Such hyperplasia, how does not occur in the cases of overgrowth du gonadal insufficiency; the eunuchoidal type us has a normal or lowered metabolism. These case contrast to the above hyperthyroid cases, have t included in the first type of overgrowth, tha growth at a normal rate but over a longer perio time. There is no true acceleration of growth in t cases.

In the bibliography of juvenile thyrotoxi there is a considerable amount of literature (28) w summarizes the statistics. The cases presented in last 10 years (24–36) do not give emphasis to sta as an important factor to be considered in determ tion of therapy.

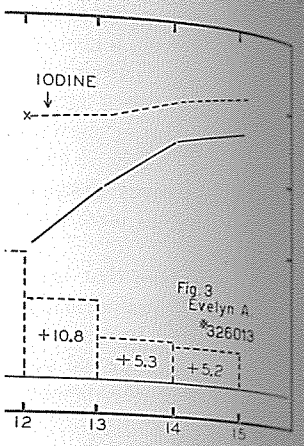
We would like to emphasize the importance of serving the two factors, actual stature and rat growth of the young patients, in deciding a whether the treatment should be more or less rad A subject with a stature above normal, i.e., wi high rate of growth, should be submitted to a n

radical or more rapid cure than a subject with normal or lower than normal stature, whose disease it would be rational to treat with less interference with the growth stimulus, i.e. by non-surgical means, if other factors permit.

C. O. C. (M. G. H. 245155) was first seen in August of 1937 with a classic picture of Graves' disease in a boy of 14. Symptoms had been present for over 2 months. He was treated by the administration of Lugol's solution and given x-ray treatment, which improved his condition but did not cure it entirely. He grew 7 in. in the space of 22 months, and at the age of 28 (1940) presented the picture of 'thyrotoxic gigantism' shown in figure 8. According to our present knowledge of the relation of thyroid to growth we would (if we had this boy today) advise radical surgical treatment of his goiter because of the rapid speed of growth displayed during the period of partially uncontrolled thyrotoxicosis. This case illustrates most strikingly the fact that the excess of thyroid hormone did not produce an early or premature closure of the epiphyses. Had the latter occurred, gigantism would not have ensued. X-rays of the sella turcica of this boy were normal (1940).

SUMMARY

Factors governing the rate of growth of the human organism are discussed in relation to clinical evidence that the thyroid hormone is a synergist to the anterior pituitary hormone, which promotes growth. The animal experimental evidences of Smith are discussed in this connection. The growth promoting effect of thyroid therapy in juvenile myxedema is reviewed; and examples of such growth stimulation in our own clinic are cited. A study of the heights at various ages of 121 thyrotoxic patients in the juvenile



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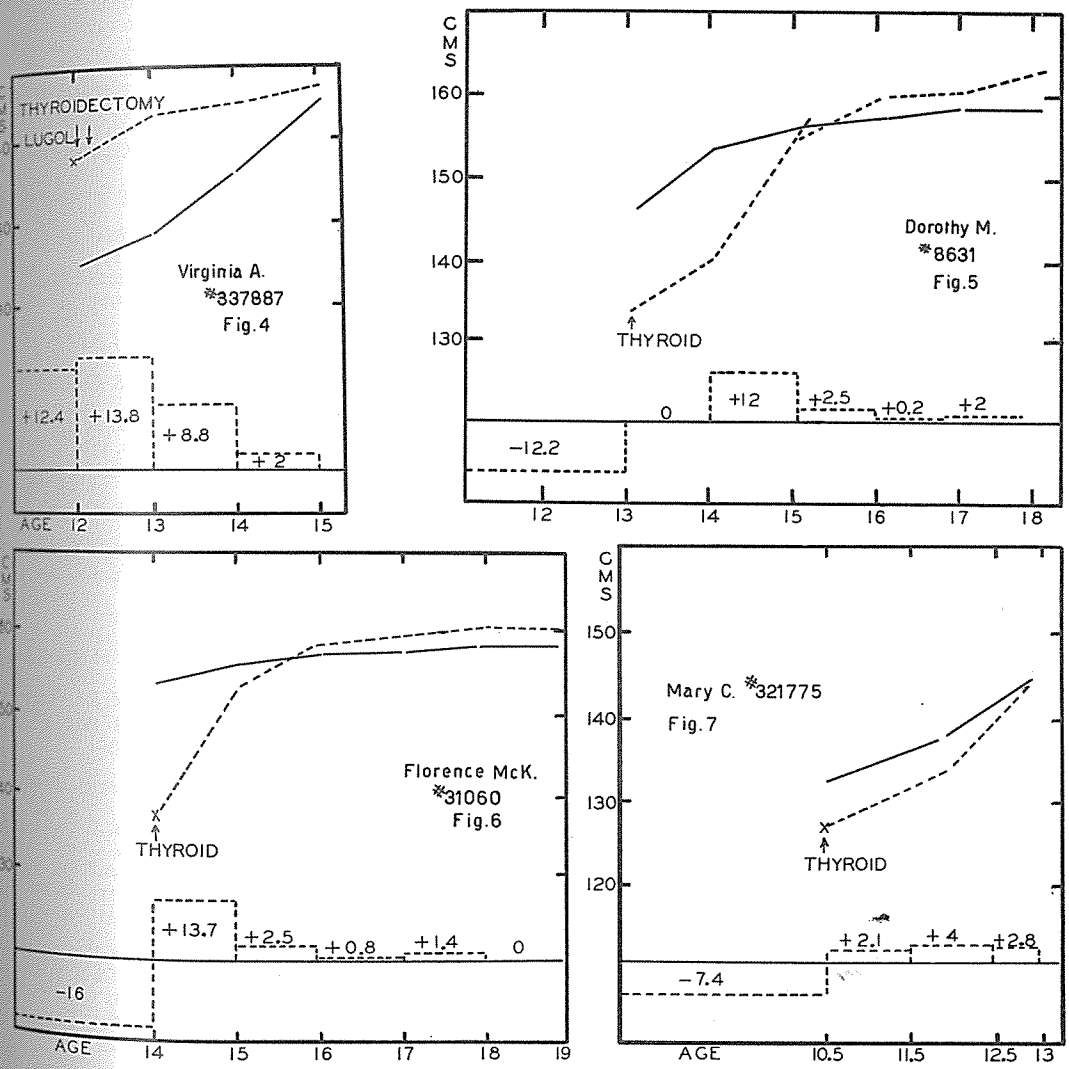

Fig. 4. GROWTH OF *Virginia A.* AT VARIOUS AGES DURING TREATMENT OF TYPICAL GRAVES' DISEASE.

Fig. 5. GROWTH AND ANNUAL STATURAL INCREASE OF A PATIENT WITH MYXEDEMA ON THYROID THERAPY.

Fig. 6. GROWTH OF *Florence McK.* TYPICAL MYXEDEMA.

Fig. 7. GROWTH OF *Mary C.* TYPICAL MYXEDEMA.

group was made. Annual speed of growth was considered, as well as total growth as related to age and stage of treatment of the disease. The following conclusions were reached.

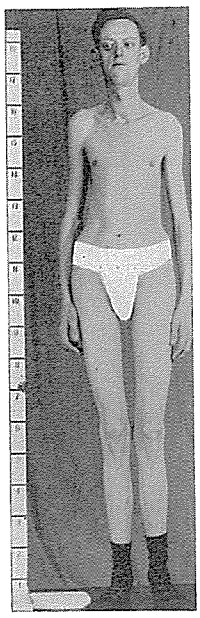

Fig. 8. An example of overgrowth due to uncontrolled thyrotoxicosis in a juvenile exophthalmic goiter patient. Acceleration of growth is due mainly to long bone stimulation.

Overgrowth takes place in juvenile thyrotoxic patients with such remarkable regularity that it can be considered one of the cardinal symptomatic manifestations of the disease in this age group. In our experience the speed of growth during the thyrotoxic period of individual cases is an even more striking feature than their actual degree of over-height for age. The excessive thyroid hormone present in such cases accentuates the peaks in the normal growth curves, and modifies the speed of growth according to the normally expected speed of growth at any given period of life of the juvenile patient with this disease. This is strikingly shown by the cessation of growth stimulation past the age of 16 years, at which time the epiphyses normally begin to close. It appears that thyroid hormone in excess does not produce premature or late closure of the epiphyses. Its growth effect can, therefore, be considered as truly synergistic to the normally existing factors for structural increase ('substrate').

A case of 'thyroid gigantism' in our clinic is presented as an example of the importance of applying the conclusions derived from this study in the clinical management of individual cases of juvenile thyrotoxicosis. In the determination of a therapeutic program for both the thyrotoxic and the myxedematous juvenile patient speed of growth must be regarded, as well as the actual height on presentation to the physician.

On the basis of this study we are at present studying the growth promoting effects of thyroid feeding on underheight individuals and pituitary dwarves.

We are indebted to Professor J. H. Means, Chief of the Medical Staff of the Massachusetts General Hospital, for valuable advice and stimulation in the course of this work.

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