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# CURRENT PROGRESS

## Growth Hormone Deficiencies in Childhood

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I AM greatly honoured by the invitation of The Canadian Medical Association to deliver the third Tisdall Lecture.

Dr. Frederick Tisdall died 18 years ago at the age of 55, on the day after he had attended the ceremony of laying the cornerstone of the great Hospital for Sick Children in Toronto. He was the Director of the Research Laboratories at that hospital. He was one of the foremost nutritionists in the world and his research work on vitamin D is still highly regarded. In World War II he did good service, both for Canada and for England, by conducting diet and nutrition surveys among Canadian servicemen overseas and British civilians. The President of the University of Toronto described him as "a generous colleague, a loyal friend, a lover of his fellowmen and a fine citizen". You will easily understand then why I am proud to have been asked to deliver this lecture named in his honour. My talk today relates to defective growth in childhood, a subject in which he had a consuming interest.

The clinical picture of children suffering from a suspected deficiency of growth hormone was built up by many observers over many years. The diagnosis remained presumptive until growth hormone was isolated from human pituitary glands and became available for investigation and treatment.[1-3] Subsequent scientific studies[4] have shown that the earlier descriptions of growth hormone deficiency were substantially accurate. The elaboration of a reliable growth hormone assay and of other diagnostic tests has now permitted considerable precision in diagnosis. However, these tests are not easy to perform, and their use is still limited to endocrine clinics.

In our clinic 21 hypopituitary patients have been investigated by these modern techniques. It is on this group that the present paper is based, though I shall draw largely on the experience of other workers.

The Third Frederick Tisdall Memorial Lecture, presented at the One Hundredth Annual Meeting of The Canadian Medical Association, Quebec, P.Q., June 9-17, 1967.

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### ETIOLOGY

Until more is known of the pathogenesis of these conditions, classification will continue to be unsatisfactory. A provisional etiological classification of our patients is given in Table I.

TABLE I.—ETIOLOGICAL CLASSIFICATION OF GROWTH HORMONE DEFICIENCIES IN CHILDHOOD

| | | *No. of patients* |
|---|---|---|
| I *Idiopathic* | | 13 |
| a. Including possible perinatal injury | 5 | |
| b. Calcified infarct | 1 | |
| II. *Secondary* | | 6 |
| a. Neoplasm | 1 | |
| b. Healed tuberculous meningitis | 2 | |
| c. Trauma | 3 | |
| III. *Genetic* | | 2 |
| Total | | 21 |

Thirteen of the patients fall into the "idiopathic" category; nine of these are boys and four are girls. It is unlikely that the growth hormone deficiency in these patients is due to a single cause. Idiopathic hypopituitarism in children has frequently been ascribed to perinatal injury. Only 5 of these 13 patients had a history of difficult delivery or neonatal illness —two boys and three girls. It is, of course, possible that localized damage might have occurred at birth without any relevant perinatal or neonatal history. One patient (Case 8) with calcification in the sella turcica had no suspicious perinatal or neonatal history, and no history of later trauma. This lesion may be attributed to hemorrhagic infarction of the pituitary at the time of birth. Bailey *et al.*[5] in Toronto have described a similar patient. This idiopathic group may also include patients with a genetic defect that has not revealed itself in the collateral family history.

The "secondary" group embraces a broad range of causes such as neoplasms, inflammations and infiltrative lesions. The causes are many but the cases are few. There is only one neoplasm in this small series of six cases. Craniopharyngiomas betray themselves by the presence of calcification; they are usually suprasellar, but may be intrasellar. Chromo-

phobe adenomas rarely give rise to symptoms in childhood. Healed tuberculous meningitis was the cause in two patients—a legacy from the unhappy past. In one of the three cases which I have attributed to trauma, there was no diagnostic doubt. This boy had an accident at the age of 5 years, which was followed by a severe illness, and there is tell-tale calcification in the sella turcica. In the other two patients, a circumstantial story was told of an accident at the ages of 4 and 5 years, without succeeding illness, but with subsequent retardation of growth. Possibly these two patients could have been more appropriately included in the idiopathic group.

*Genetic causes.*—Familial cases of growth hormone deficiency have now been described by Trygstad and Seip,[6] by Rimoin, Merimee and McKusick,[7] by Bailey *et al.*,[5] and by Sheikholislam and Stempfel.[8] The mechanism of inheritance appears to be autosomal recessive. In this series, a father and son were proved to have an isolated growth hormone deficiency.

### *Hormonal Grouping*

Among our 21 patients (Table II) there were six examples of an isolated growth hormone deficiency. Two of these occurred in one family. Many examples of this condition have now been described: 7 by Brasel *et al.*,[9] 16 by Goodman, Grumbach and Kaplan[10] and 5 (familial) by Sheikholislam and Stempfel.[8]

TABLE II.—HORMONAL GROUPING OF GROWTH HORMONE DEFICIENCIES IN CHILDHOOD

| | | *No. of patients* |
|---|---|---|
| I. Isolated GH deficiency | | 6 |
| II. With TSH deficiency | | 11 |
| III. With ACTH deficiency | | 2 |
| IV. With TSH and ACTH deficiency | | 2 |
| Total | | 21 |
| V. With sex hormone deficiency (over 15 years) | | |
| *Sexual failure* | 2 | |
| *Sexual retardation* | 8 | |

Strictly speaking, these patients cannot be said to have an isolated growth hormone deficiency until adult life is reached and associated sexual failure can be more confidently excluded. The report of Sheikholislam and Stempfel that the administration of human growth hormone to a sexually infantile female of 18 years produced sexual maturation raises the possibility that sexual retardation in these patients may be the consequence of deficiency of growth hormone.

### *Growth Hormone and Thyroid Stimulating Hormone*

In our series, 11 patients had an associated thyroid stimulating hormone deficiency as indicated by the serum protein-bound iodine and in some, by radioiodine uptake. However, the degree of the defect in thyroid function is very variable. One of our patients was a frank cretin (Case 6) and one was grossly thyroid-deficient in the second year of life. The majority, however, had no gross clinical evidence of hypothyroidism and had no clinical improvement after thyroxine therapy. The reduction in serum protein-bound iodine levels was gradual in some of them, occurring towards the end of the first decade or early in the second decade. A curious and unexplained feature in some of these patients is that the level of serum protein-bound iodine measured over several years may vary—sometimes lying within the normal range, sometimes outside it. The same observation has been made by Goodman, Grumbach and Kaplan[10] in 6 of their 15 patients with thyroid stimulating hormone deficiency. It seems possible that, in some patients, partial failure of the thyroid gland may be dependent on the growth hormone deficiency. I attempted to test this hypothesis in three patients during the short-term administration of human growth hormone, but it had no effect on the serum protein-bound iodine level or radioiodine uptake.[15]

### *ACTH Deficiency*

There was evidence of associated adrenocorticotropin (ACTH) deficiency in four of our patients. In only two was the deficiency sufficient to warrant steroid therapy. Both of these were in the secondary group.

### *Sexual Failure*

All our patients who are over 15 years of age have shown retardation of puberty. Two, who are now adult, have shown no sexual development. Only one patient has demonstrated his reproductive capacity (Case 2).

## CLINICAL PICTURE

### *Physical Appearance*

The features of these children are immature for their age. Their appearance is babyish, which contrasts strongly with their intelligence, which is average for their age (except in the brain-damaged children). This facial immaturity is assumed to depend on a poorly developed facial bony structure. Their complexions are pink, except if hypothyroidism supervenes, when the

skin is obviously pale. The children often develop some truncal obesity. Although their caloric intake is small, in these obese children it must be greater than their caloric output.

*Growth*

Children who suffer from growth hormone deficiency are of average weight and length at birth. When adequate growth records are available, it can be seen that growth velocity falls away during the first year of life and retardation of growth is well established in the second and third years. In our children of the idiopathic type, the parents observed growth retardation between the ages of 1 and 4 years. This variability may reflect defective parental observation but more probably represents varying rates of growth failure.

When growth is charted, it will be seen that the curve falls away increasingly from the third percentile. This widening gap is very suggestive of growth hormone deficiency and, taken with the degree of growth failure, provides the best clinical guide to the diagnosis.

*Skeletal Maturation*

Skeletal maturation is always retarded, though in isolated growth hormone deficiency to a lesser degree than is linear growth, so that the height age/bone age ratio is usually less than 1. Goodman, Grumbach and Kaplan[10] point out that this dissociation does not occur in the presence of multiple hormonal deficiencies where in their 18 patients in this group the height age/bone ratio was 1.28. This presumably reflects the essential part that thyroxine plays in skeletal maturation. Growth hormone probably has no specific effect on skeletal maturation, although when human growth hormone is administered to children with growth hormone deficiency skeletal maturation is advanced, but never to a degree beyond that of the height age.

*Spontaneous Hypoglycemia*

Of the eight children who had biochemical evidence of hypoglycemia, five had attacks of spontaneous hypoglycemia in earlier life. As in other forms of spontaneous hypoglycemia in childhood, the attacks disappeared in later childhood, presumably owing to the development of corrective homeostatic mechanisms. It is surprising that a boy aged 2 (Case 3) with a fasting glucose level of 16 mg. per 100 ml. shows no clinical evidence of spontaneous hypoglycemia. Moreover his appetite is very poor, quite unlike the adult patients with an insulin adenoma.

*Other Investigations*

Before coming to the specific investigations, I should mention two other investigations in which we have been interested—the measurement of the sella turcica and the blood cholesterol.

Riach[11] has devised a sellar index relating the lateral area of the sella turcica to skull size. The range of the sellar index is 1.4 to 2.8. Of the 13 children with idiopathic growth hormone deficiency 8 had a sellar index below this range.

The blood cholesterol may be raised above 250 mg. per 100 ml. in the absence of evidence of hypothyroidism. Of the eight patients with growth hormone deficiency unaccompanied by signs of thyroid stimulating hormone deficiency, four showed levels of cholesterol above 250 mg. per 100 ml. This may be the direct consequence of growth-hormone deficiency.

SPECIFIC DIAGNOSTIC TESTS

*The Radioimmunoassay and Insulin-Induced Hypoglycemia*

Unfortunately the radioimmunoassay cannot be used as an unaided test to identify growth hormone deficiency. At some times in the 24 hours, the levels of growth hormone in normal children may be undetectable. Growth hormone secretion is stimulated by activity and apprehension, but these physical and emotional states are not appropriate to provide a test stimulus for children. Hypoglycemia provides a more certain and measurable stimulus, and insulin-induced hypoglycemia was used by Frantz and Rabkin[12] and Kaplan *et al.*[13] to identify hypopituitary subjects. We have used this method for the last three years in the diagnosis of hypopituitarism in childhood.[14] We have now applied this test in 47 children and confirmed the diagnosis of growth hormone deficiency in 14 of them (Fig. 1).

The radioimmunoassay used is a modification of that described by Hartog *et al.*[15, 16] in 1964. In our patients we have accepted 10 μmg. per ml. as the top level for hypopituitary patients after an adequate hypoglycemia stimulus (and in Case 1, 11 μmg. per ml.). The failure of the growth hormone values to rise appreciably in response to hypoglycemia is an important diagnostic feature in hypopituitary patients.

The intravenous insulin tolerance test has been described elsewhere.[14] It is an exacting method both for the patient and the investigator. We use 0.1 unit of insulin per kg. body weight for children over 6 years of age and 0.05 unit of insulin per kg. for younger children, for brain-damaged children and for those who

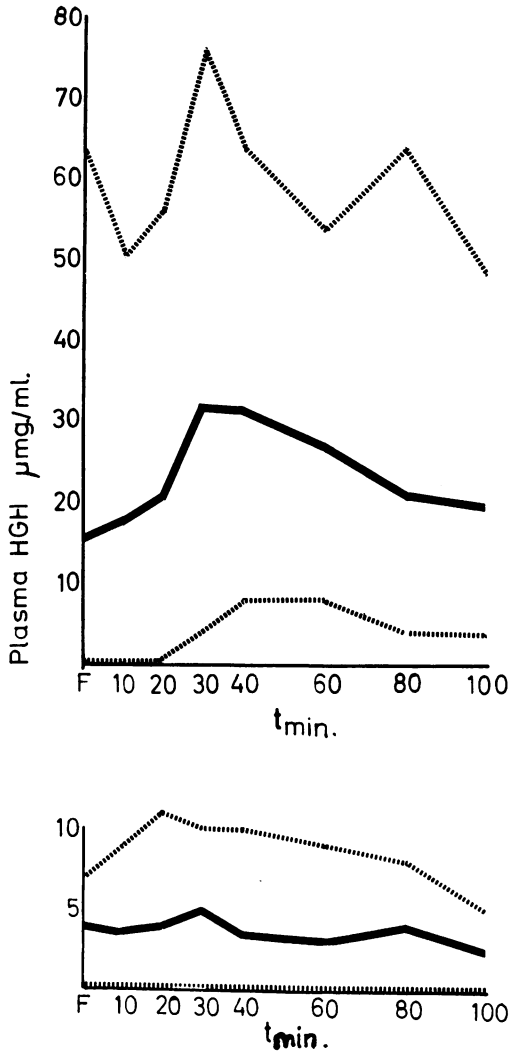


Fig. 1.—Mean and range of plasma human growth hormone (HGH) in the insulin hypoglycemia test. Non-hypopituitary (top) n=33; hypopituitary (bottom) n=14. tmin.=time in minutes. Scale for HGH is different in the two graphs.

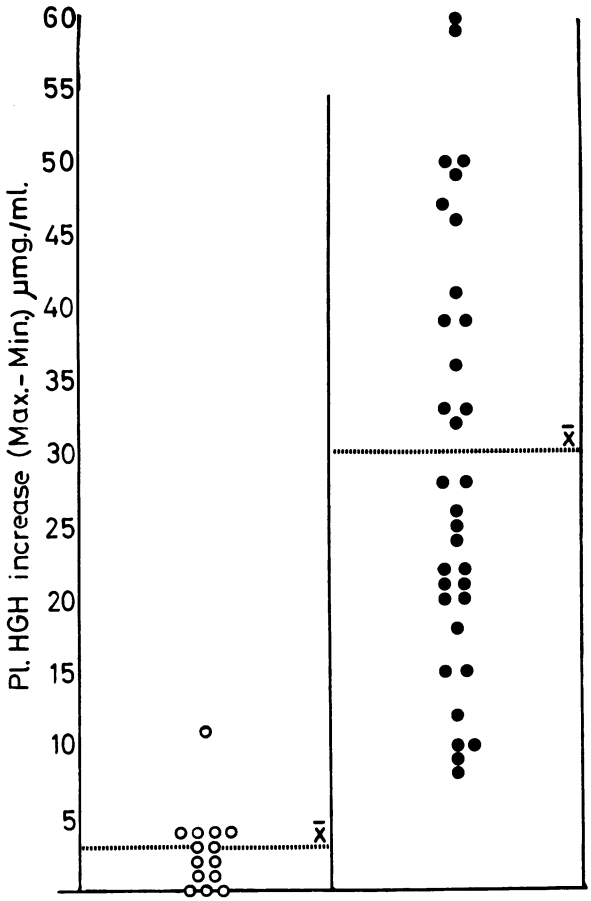


Fig. 2.—Plasma HGH response in the insulin hypoglycemia test. Hypopituitary=open circles; non-hypopituitary=closed circles. Mean increment for the hypopituitary patient is 3 µmg. per ml. (including Case 1, 11 µmg. per ml.). Mean increment for the non-hypopituitary patient is 30 µmg. per ml.

suffer from convulsions. The technique requires scrupulous care to avoid the hazards related to hypoglycemia.

Fig. 2 shows the plasma growth hormone results in increments from the lowest level to the highest. The hypopituitary children, diagnosed by other methods, showed a complete separation from the non-hypopituitary children except for one patient (Case 1). Disregarding this boy, the increments in the hypopituitary children range from 0 to 4 µmg. per ml. with a mean of 2, while the increments in the non-hypopituitary children range from 8 to 60 µmg. per ml. with a mean of 30.

In order to avoid the necessity of using the insulin tolerance test in the diagnosis of all children of short stature, we employ a screening test—a glucose tolerance test prolonged to five hours. In about half of these children we are able to exclude the diagnosis by these means.

Although the insulin tolerance test, together with the radioimmunoassay of growth hormone, have taken us a long way toward the definitive diagnosis of growth hormone deficiency—some observers would say the whole way—we have vigorously pursued a second diagnostic enquiry —the human growth hormone nitrogen retention test.[17-20] In the endocrine field few tests will give complete diagnostic certainty, and a second test does clarify doubtful or borderline results obtained in the first test. With the help of a second test, we may eventually be able to elucidate the problems of a partial deficiency of growth hormone or of a low pituitary growth hormone reserve.

### *The Human Growth Hormone Nitrogen Retention Test*

This test was first described by Prader *et al.*[21] and we have used it with some modification

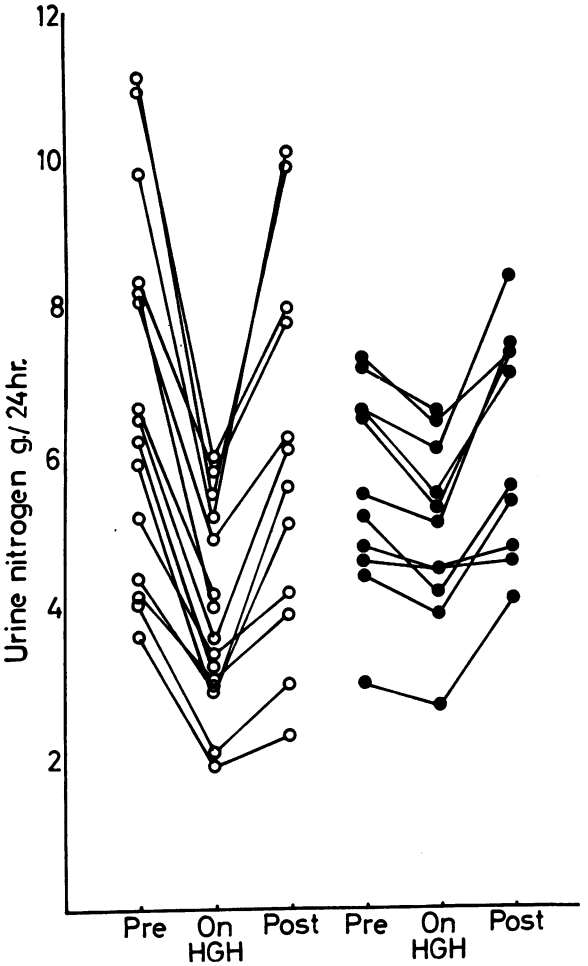


Fig. 3.—The HGH nitrogen retention test: 17 hypopituitary children (open circles) and 12 non-hypopituitary children (closed circles).

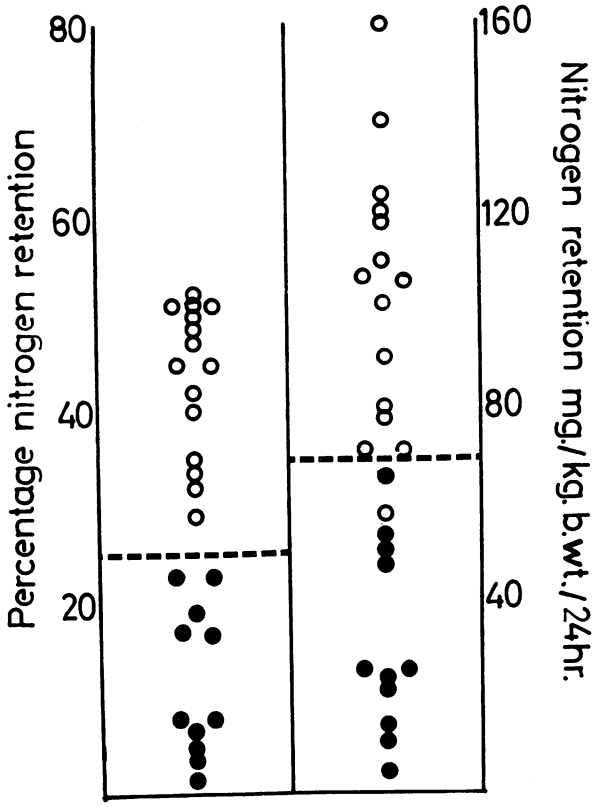


Fig. 4.—HGH nitrogen retention expressed as a percentage nitrogen retention (left column), and in mg. per kg. body weight (right column). Hypopituitary=open circles; non-hypopituitary=closed circles.

since its first publication in 1964. We have applied the test to 29 patients and it has supported a diagnosis of hypopituitarism in 17 of them.

The test depends on the fact that, in hypopituitary patients, the administration of human growth hormone produces a greater degree of nitrogen retention than it does in non-hypopituitary patients of short stature.

The children are placed on a diet of their own choosing which contains a fixed amount of protein during the whole test period. There are a preliminary five-day baseline period, a five-day period of daily human growth hormone injections and a final five-day period of human growth hormone withdrawal. The daily urinary nitrogen excretion is estimated throughout the test.

We give 10 mg. of human growth hormone at 10 a.m. This is a much larger dose than that used by Prader *et al.*,[21] but it may give us a slightly better separation between the two groups. As in the insulin tolerance test, we have not used this method in normal children but only in children of short stature who act as controls.

Fig. 3 demonstrates the difference in nitrogen excretion between the two groups. The fall in urinary nitrogen excretion is much steeper in those on the left—i.e. they have a greater nitrogen retention. In general, by the completion of the test, the hypopituitary children do not return to pre-human growth hormone levels in the withdrawal period. The non-hypopituitary children often have increased nitrogen excretion (a rebound phenomenon) in the withdrawal period.

Fig. 4 analyzes these results in a less graphic but more quickly intelligible way. As in Fig. 3, there are 17 hypopituitary children (open circles) and 12 non-hypopituitary children of short stature (closed circles). The results are expressed in two ways. In the left-hand column they are shown as percentage nitrogen excretion—that is, the decrease in average nitrogen excretion measured in g. per 24 hours expressed as a percentage of the baseline excretion. In the right-hand column the results are expressed in

mg. nitrogen retained per kg. body weight per 24 hours.

All the hypopituitary children (open circles) have more than a 25% retention of nitrogen. All the control children (closed circles) have less than 25%. In the right-hand column, all the hypopituitary children retain more than 70 mg. per kg. per 24 hours of nitrogen, and all the control children except one retain less than 70 mg. per kg.

The test as outlined above is long and entails a good deal of ward and laboratory endeavour. The final phase of human growth hormone withdrawal is not essential for diagnosis, and our results show that a three-day pre-human growth hormone period and a three-day human growth hormone period will give the same results with only slight loss of diagnostic certainty.

These two tests have made it possible both to diagnose growth hormone deficiency and to exclude the diagnosis in other children of short stature. They have brought diagnostic precision to the assessment of a large group of short children in whom classification has been difficult.

Special attention should therefore be paid to Case 1 whose increment in the growth hormone assay, 11 μmg. per ml., brought him into the lower ranges of the non-hypopituitary children of short stature (Fig. 2).

CASE 1.—"C.D." This boy was investigated at the age of 14½ years. He was delivered by cesarean section but his neonatal history was normal. His parents first became aware of his short stature when he was 2 years of age. His height was then ½ inch below the third percentile and although his height has remained thus, the gap has widened but little. At the age of 14 years his height was 3 inches below the third percentile (height age 10 years). There is no history of short stature in the family.

He is of good intelligence. No abnormality was discovered on physical examination. Genitalia were prepubertal.

*Investigations*

*Radiographs:* The skeletal maturation is retarded. The bone age is 10 years. The sella turcica is very small with a lateral area of 28 sq. mm. (average area for his age: 74½ sq mm.). The sellar index is 0.85 (normal range: 1.4 to 2.8).

*Serum cholesterol:* 293, 259 and 268 mg. per 100 ml.

*Serum protein-bound iodine:* 4.0 and 4.5 μg. per 100 ml.

*HGH nitrogen retention test:* Decrease in urine urea nitrogen excretion on human growth hormone administration = 50%.

*Intravenous insulin test:* 0.1 unit per kg. body weight.

| *Time* (min.) | *Fasting* | *10* | *20* | *30* | *40* | *50* | *60* | *80* | *100* |
|---|---|---|---|---|---|---|---|---|---|
| *Blood glucose* mg. per 100 ml. | 59 | 39 | 15 | 14 | 18 | 19 | 19 | 26 | 30 |
| *Plasma growth hormone* μmg. per ml. | 0 | 5 | 11 | 10 | 4 | 3 | 1 | 2 | 4 |

*Diagnostic Summary*

This boy's growth chart showed less than the expected falling away from the third percentile as usually seen in hypopituitarism. His height age was 11 and his bone age 10 years. The sella turcica was very small. He had hypercholesterolemia in the absence of hypothyroidism.

The human growth hormone nitrogen retention test was strongly positive. The intravenous insulin tolerance test showed hypoglycemic unresponsiveness. The plasma growth hormone reached a level of 11 μmg. per ml.; the highest level we have accepted in hypopituitarism has been 10 μmg. per ml. The rise was from 0 to 11 μmg. per ml. The highest rise in 13 other hypopituitary children was 4 μmg. and the mean rise was 2 μmg. per ml.

Taking all these facts together, we suggest that this boy is suffering from a growth hormone deficiency which may be only partial. In the face of a strong hypoglycemic stimulus, he is only capable of a low output of growth hormone.

In the last six months his genitalia have increased in size and he has gained 6.3 cm. in height. He is entering puberty and therefore he has an isolated growth hormone deficiency.

Further brief case histories follow.

1. *Genetic Growth Hormone Deficiency*

CASES 2 AND 3.—Case 2 is now aged 23 years. I first knew him at the age of 7½ years (Fig. 5). With thyroid and testosterone therapy, his growth curve was kept approximately parallel to the third percentile but well below it (Fig. 6). His final height is 138 cm. (54½ inches). At 16½ years he required a small dose of prednisone for chronic asthma. His growth velocity is portrayed in cm. per year on the admirable velocity charts prepared by Tanner and Whitehouse[22] in 1967 (Fig. 7) and all the charts are reproduced here by their kind permission. The first spurt was associated with testosterone and thyroid therapy and the second was the pubertal growth spurt. He had only 1 μmg. per ml. growth hormone in his blood on hypoglycemic stimulation. He married a girl whose height was 152 cm. (59 inches). Fig. 8 shows the couple with their first two children. The first child, a boy, aged 2 years is 65.5 cm. (26 inches) in height and the second, a girl, at the age of 8 months is already 8 cm. taller than her brother. Like his father, the son's growth hormone level rose no higher than 1 μmg. per ml. despite severe hypoglycemia. His fasting blood glucose level is 16 mg. per 100 ml. Both the mother and the sister have

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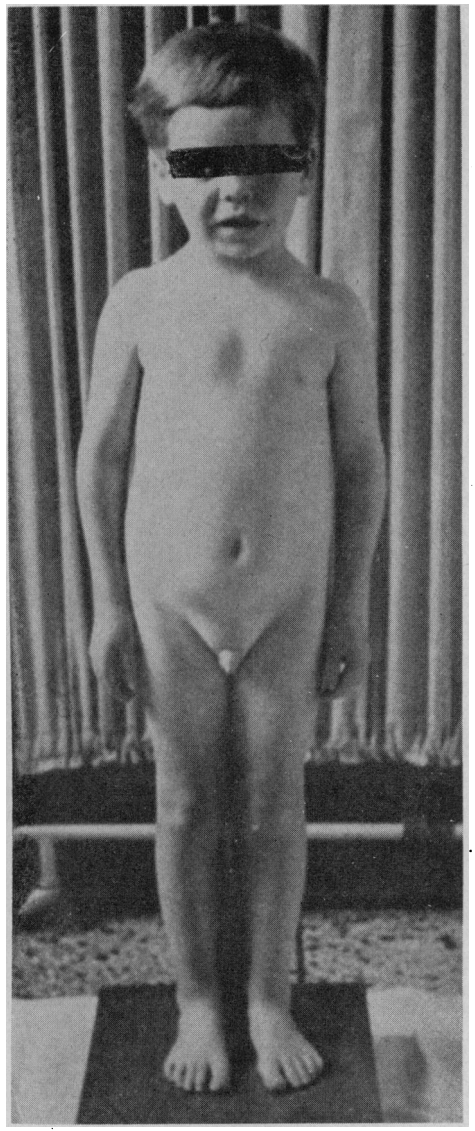

Fig. 5.—Case 2, aged 7½ years. Height, 94 cm. (37 in.); height age, 2¾ years.

normal levels of circulating growth hormone (52 μmg. and 13 μmg. per ml. respectively).

*Isolated Growth Hormone Deficiency*

CASE 4.—This boy is now aged 10½ years and his growth chart shows the widening gap between his growth and the third percentile. His present height is 103 cm. (40½ inches) (Fig. 9). The growth velocity chart shows his rate of growth—3.5 cm. per year increased to 8 cm. per year by his first course of methandrostenolone (Dianabol) and 6 cm. per year by the second course. His growth rate then settled again at 3 cm. per year (Fig. 10). The human growth hormone nitrogen retention test showed a 36% fall in nitrogen excretion. The growth hormone level was 0 μmg. per ml. on hypoglycemic stimulation. There is no evidence of any specific etiological factor.

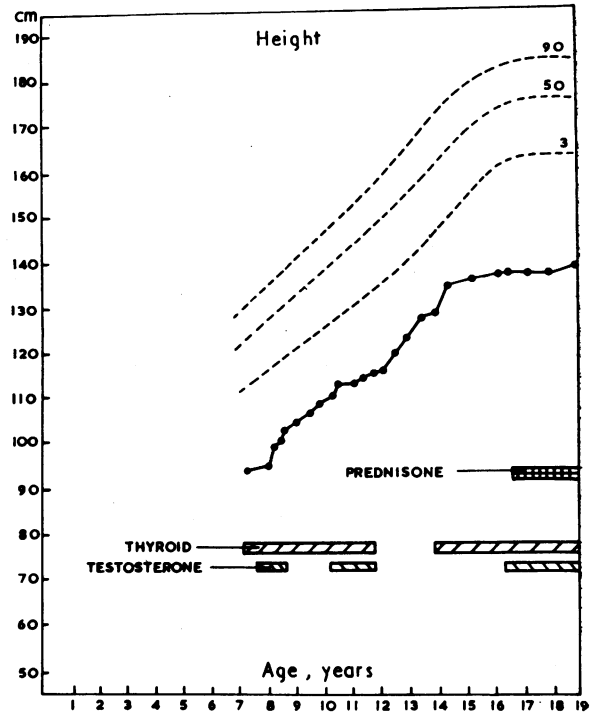


Fig. 6.—Case 2—longitudinal growth chart.

*Growth Hormone Deficiency with Gradual Depression of Thyroid Function*

CASE 5.—This boy is now 18 years of age and the genitalia have been enlarging during the past

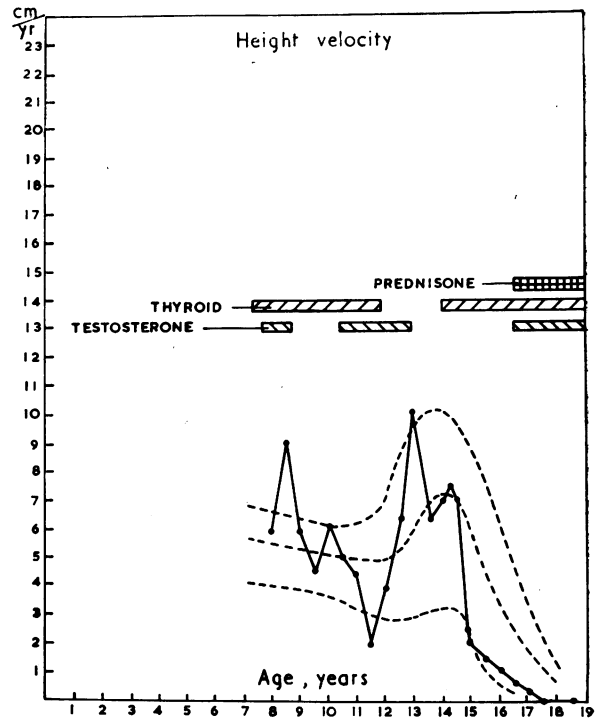


Fig. 7.—Case 2—growth velocity chart.

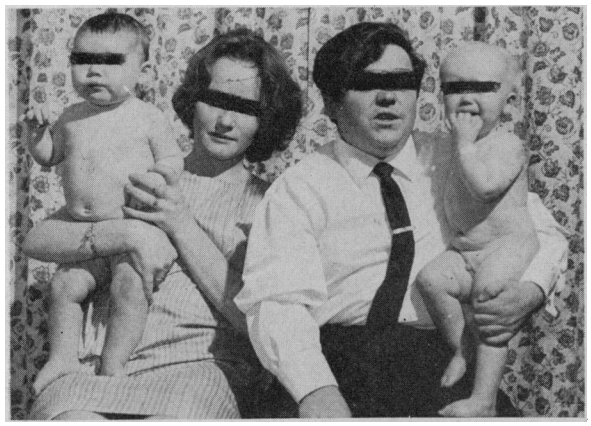

Fig. 8.—Genetic isolated growth hormone deficiency in father and son (aged 2 years). Sister in mother's arms aged 8 months.

two years and his pubic hair has been growing. His present height is 140 cm. (55½ inches). His highest growth hormone level was 7 μmg. per ml. during profound and persistent hypoglycemia. The nitrogen retention test showed 36% retention of nitrogen.

The serum protein-bound iodine levels have fluctuated over the years, the lowest being 3.3 μg. per 100 ml., and several other results have been in the normal range. Thyroxine therapy did not stimulate his growth. There was no typical falling away in his longitudinal growth chart, but his growth curve has been kept approximately parallel to the third percentile by testosterone and protein anabolic therapy in the early years (Fig. 11). The height velocity chart demonstrates this effect, but the ultimate spurt was presumably associated with a pubertal growth spurt as pubertal changes developed (Fig. 12).

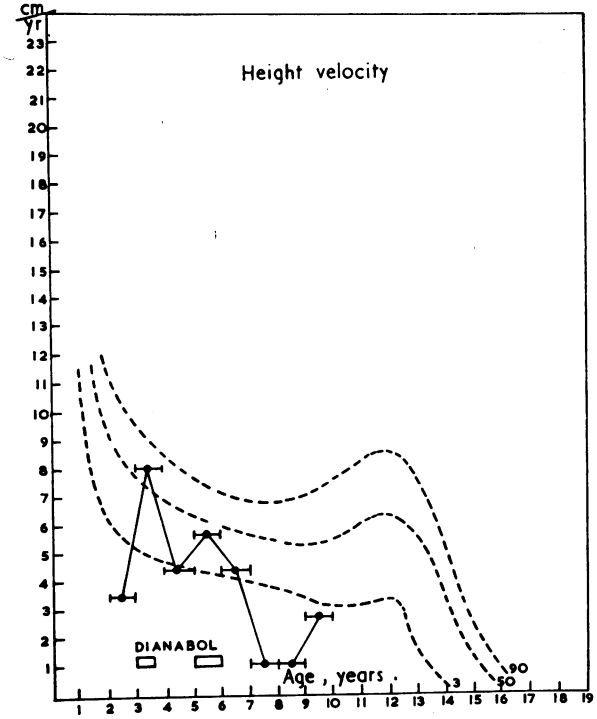


Fig. 10.—Case 4—growth velocity chart.

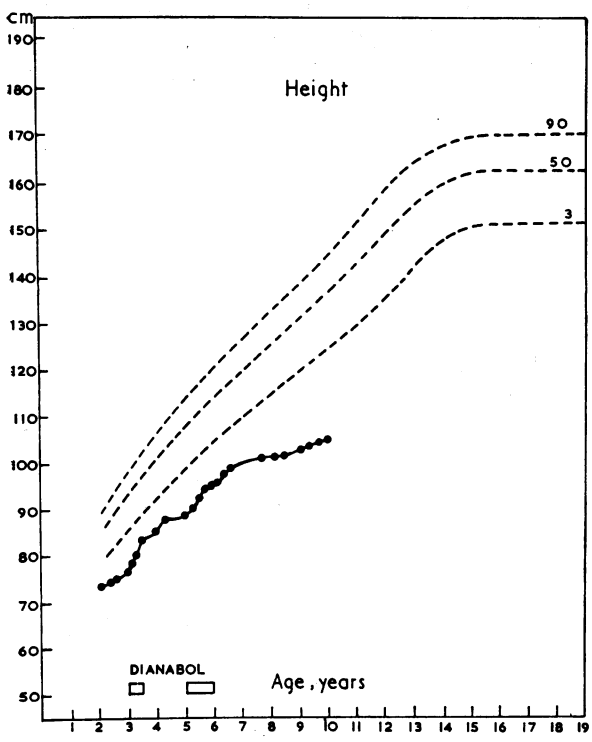


Fig. 9.—Case 4—longitudinal growth chart.

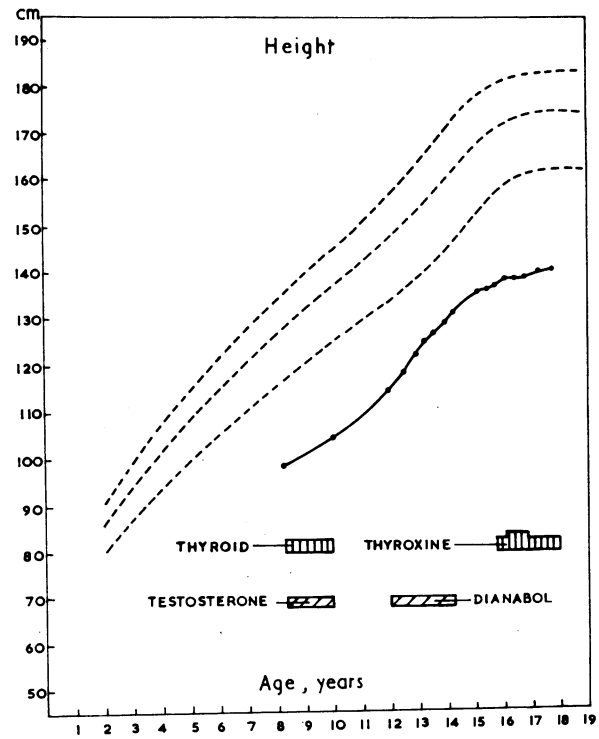


Fig. 11.—Case 5—longitudinal growth chart.

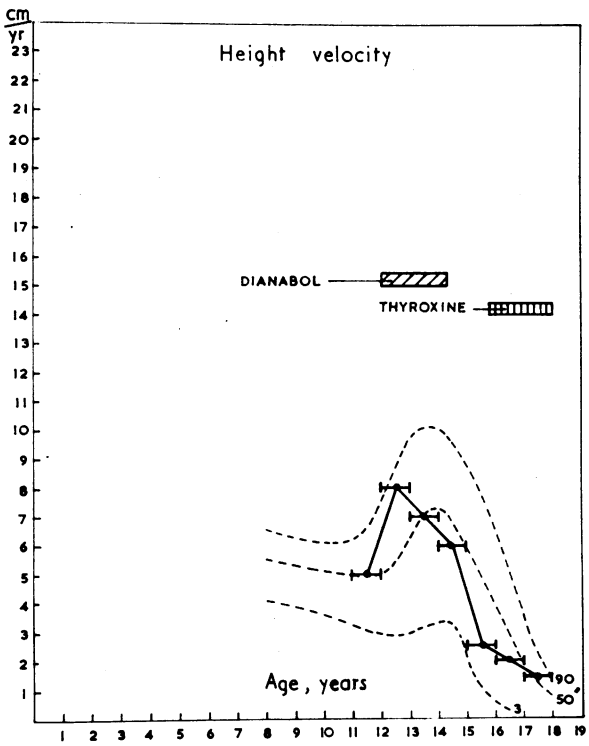


Fig. 12.—Case 5—growth velocity chart.

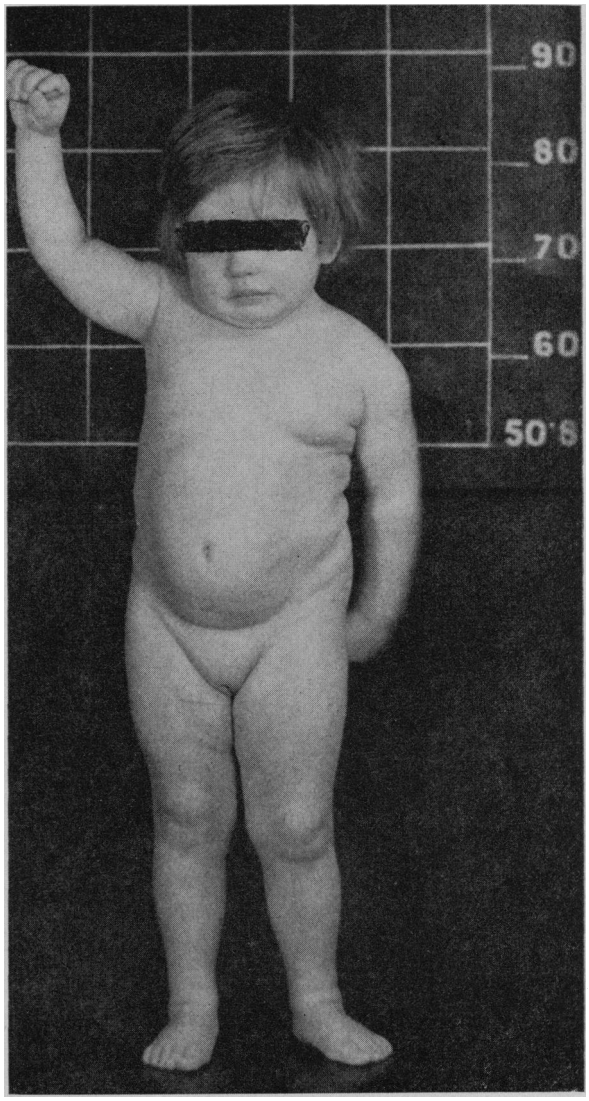

Fig. 13.—Case 6, aged 4½ years. Height, 85 cm. (33½ ins.); height age, 2 years.

*GH Deficiency with Neonatal Cretinism*

CASE 6.—This girl is now aged 10½ years. She was accurately diagnosed as a cretin in the first few weeks of life. Fig. 13 shows her at the age of 4½ years at a time when thyroxine therapy was stopped to confirm the diagnosis—she was then frankly myxedematous.

Her growth curve shows the characteristic widening gap and the failure to reach anywhere near the third percentile despite adequate thyroxine therapy (Fig. 14). The velocity curve is interesting (Fig. 15). She grew only 10.5 cm. in the initial year of thyroxine therapy. She advanced by only 6 cm. in the second year. Anabolic steroid therapy gave her 9 cm. of growth in a year, and after this her annual grow rate gradually fell to 3.6 cm.

An associated growth hormone deficiency had long been suspected. When a growth hormone assay became available, this test showed that her growth hormone levels in a prolonged glucose tolerance test did not rise above 3 μmg. per ml. (blood glucose levels at 2, 3, 4 and 5 hours were 27, 33, 34 and 42 mg. per 100 ml.), which was the fasting level. She had 35% of nitrogen retention in the human growth hormone test. There is no discoverable etiological factor. Presumably this girl had a total failure of thyroid stimulating hormone production from birth, in addition to growth hormone deficiency. This is a rare presentation, but growth hormone deficiency should be suspected when cretins and hypothyroid children fail to get the expected "catch-up" growth on thyroxine therapy.

*GH and ACTH Deficiency*

CASE 7.—This girl is now aged 15½ years. Her present height is 173 cm. (44 inches). She had spontaneous hypoglycemia. She has no sexual development. The degree of nitrogen retention was 52%. The growth hormone level did not rise above 4 μmg. despite glucose levels ranging from 17 to 12 mg. per 100 ml.

In the water load test the excretion was poor (45%) but became normal after ACTH stimulation. The 17 - hydroxycorticosteroids (OHCS) urinary excretion was very low, 0.5 to 1 mg. per 24 hrs. The plasma cortisol was at a low normal level (5 μg. per 100 ml.), but responded normally to ACTH (44 μg. per 100 ml. at 4 hours). There is no evidence of thyroid deficiency. The growth chart shows

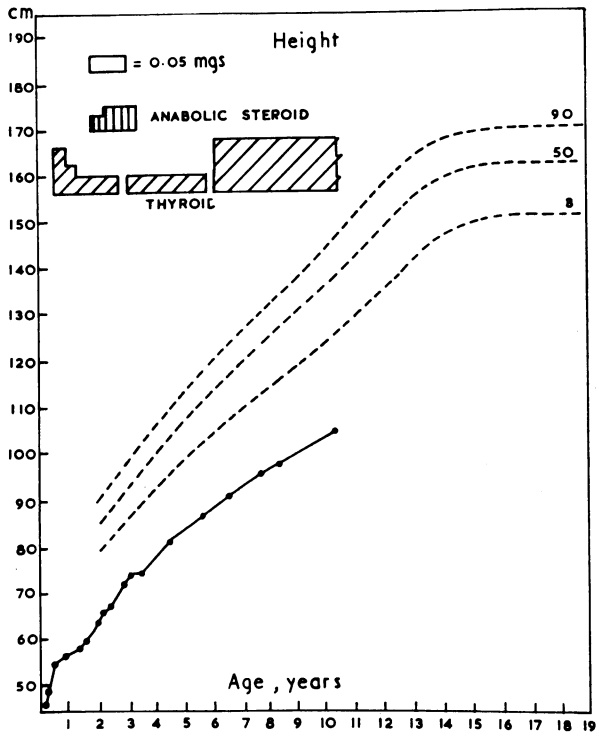


Fig. 14.—Case 6—longitudinal growth chart.

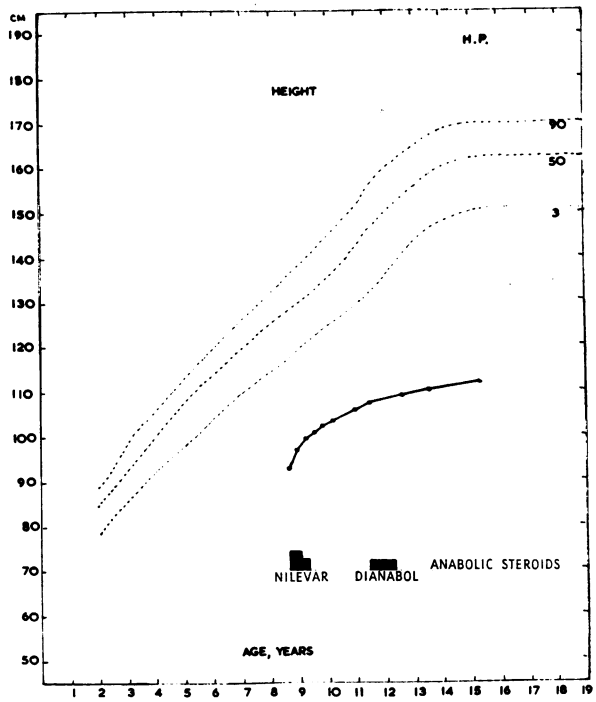


Fig. 16.—Case 7—longitudinal growth chart.

the widening gap (Fig. 16) and the velocity chart shows a steadily diminishing growth rate down to an annual increment of 1.5 cm. or below in the last three years (Fig. 17). A growth spurt of 8 cm. was achieved in one year by virilizing doses of an anabolic steroid.

There is no evidence suggesting perinatal brain damage, but her intelligence quotient is said to be 80%.

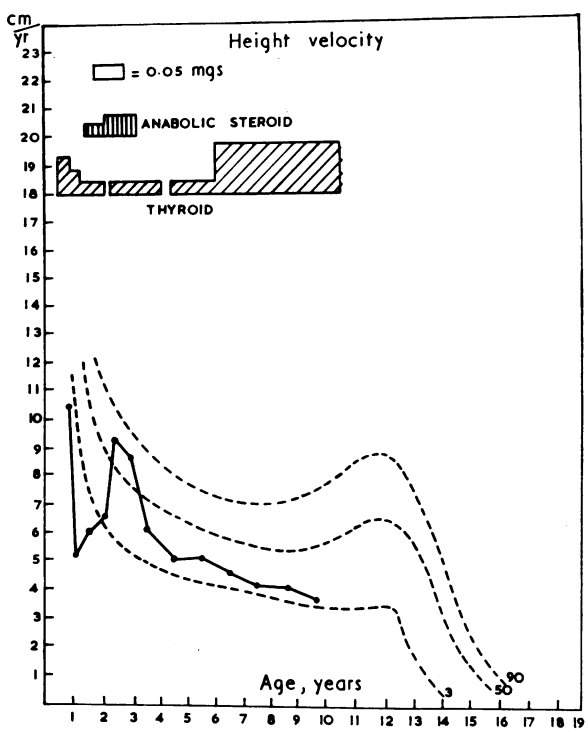


Fig. 15.—Case 6—growth velocity chart.

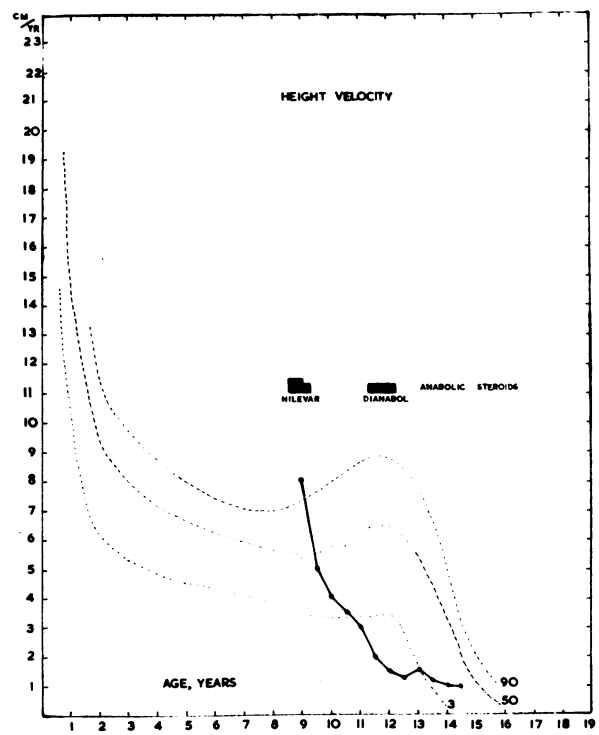


Fig. 17.—Case 7—growth velocity chart.

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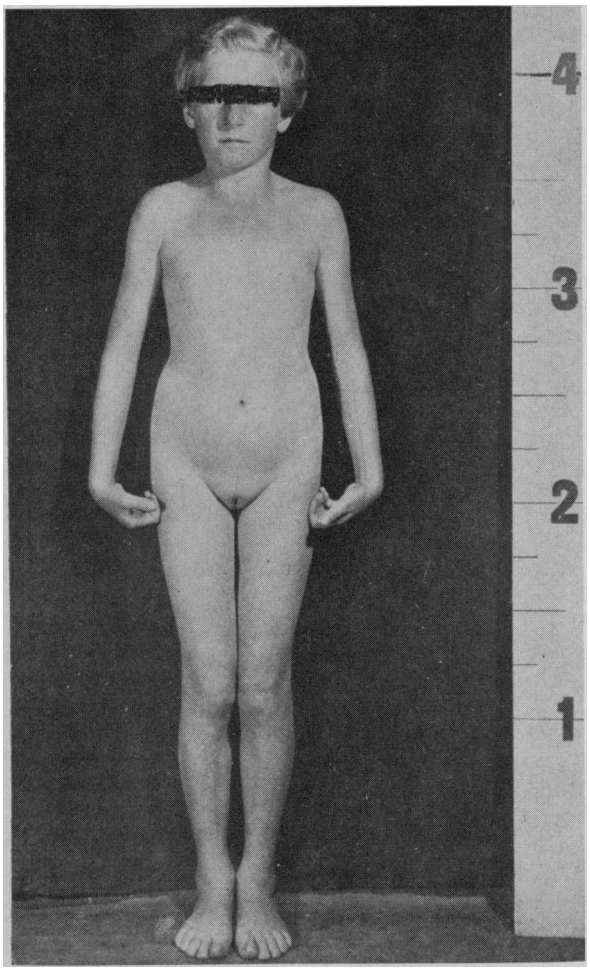

Fig. 18.—Case 8, aged 16 years. Height, 140 cm. (55 ins.); height age, 10 years.

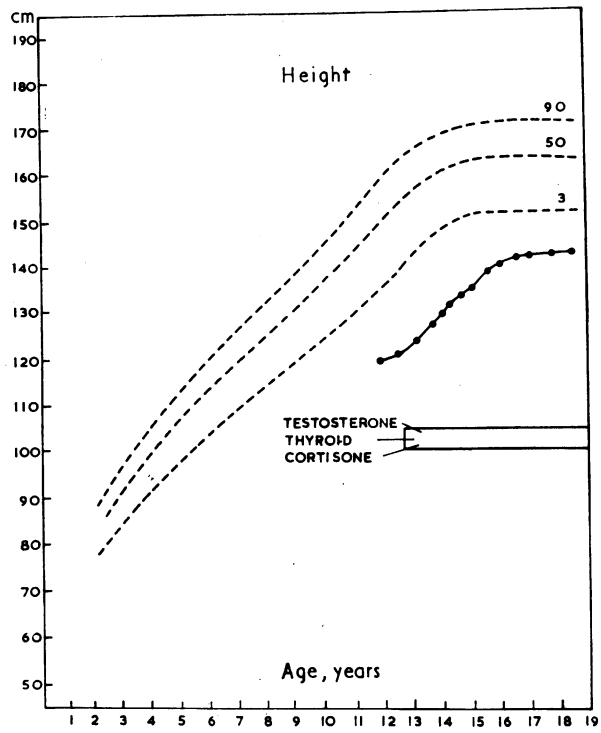


Fig. 19.—Case 8—longitudinal growth chart.

*Intrasellar Calcification*

CASE 8.—This girl is now aged 23 years (Fig. 18). She has evidence of growth hormone deficiency. The nitrogen test showed 51% of nitrogen retention. Her final height is 145 cm. (56 inches) (Fig. 19). She has had no sexual development. She has mild thyroid and adrenocortical deficiency. At age 12 years it was discovered that she had intrasellar calcification (Fig. 20). There has been no advancement of the lesion in 11 years. The pathological diagnosis is in doubt, but since there is no history of trauma and the retarded growth was noticed in the second year of life, a tentative diagnosis of perinatal hemorrhagic infarction of the anterior lobe of the pituitary has been made.

*Intrasellar Tumour*

CASE 9.—The girl was 13 years at the time this photograph (Fig. 21) was taken. Growth retardation was observed from the age of 8 years. Enlargement of the sella turcica was recognized at the age of 10½ years (Fig. 22). She had no growth hormone secretion following hypoglycemic stimulation, and the degree of nitrogen retention is 53%. She has severe thyroid failure but her adrenocortical function is normal. There has been no sexual development. Thyroxine therapy has brought her growth velocity parallel to the third percentile and she now grows at

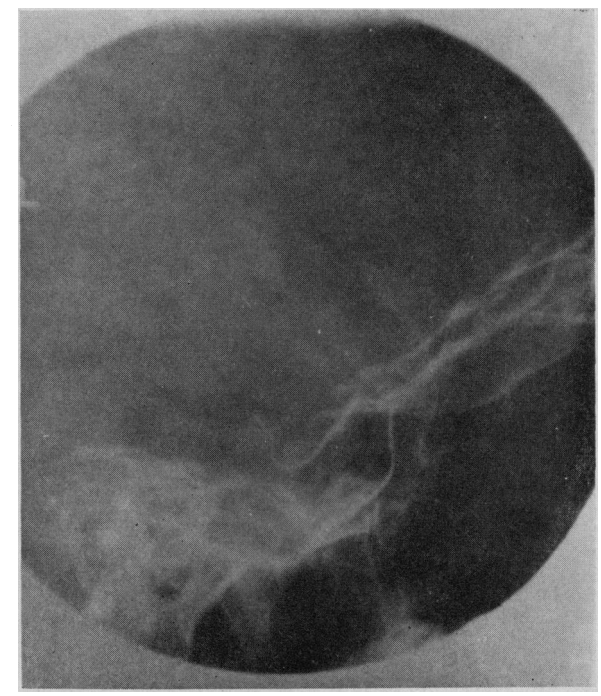

Fig. 20.—Case 8—radiograph of skull showing calcification in sella turcica.

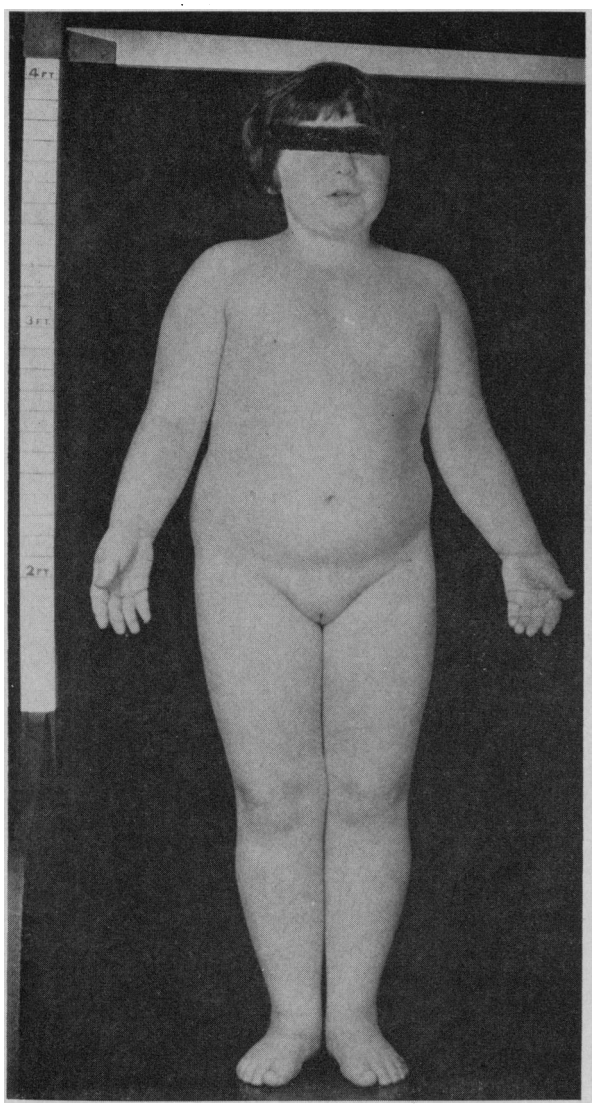

Fig. 21.—Case 9. Height, 124 cm. (49 ins.); height age, 7 years. Obesity (overnutrition) does not advance linear growth in the presence of GH deficiency.

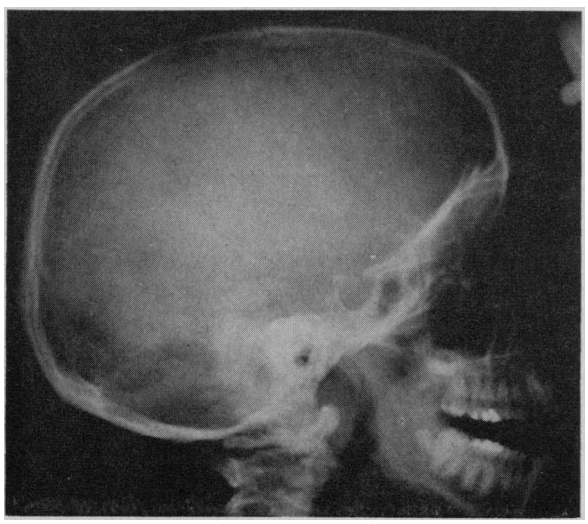

Fig. 22.—Case 9—skull radiograph shows enlarged sella turcica.

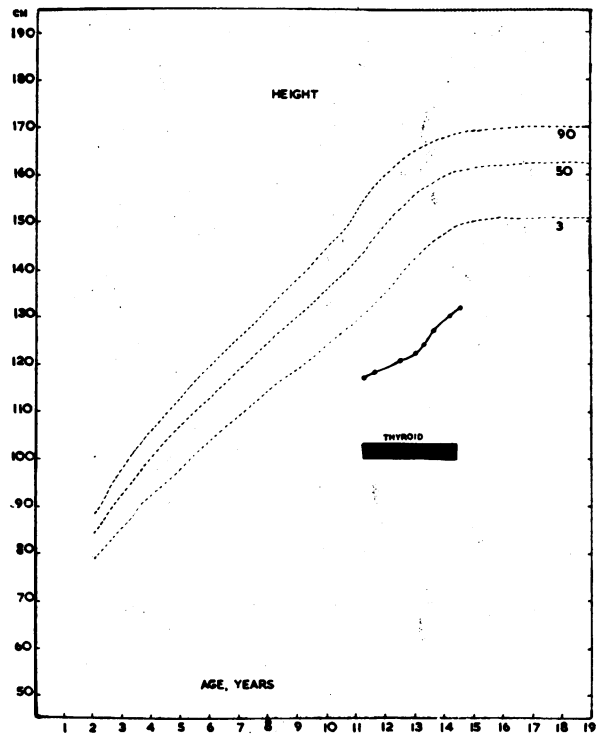


Fig. 23.—Case 9—longitudinal growth chart.

the rate of 6 cm. a year (average for a prepubertal girl). She has not had the "catch-up" growth expected in thyroxine-treated hypothyroidism in childhood (Figs. 23 and 24). The nature of the intrasellar lesion is unknown.

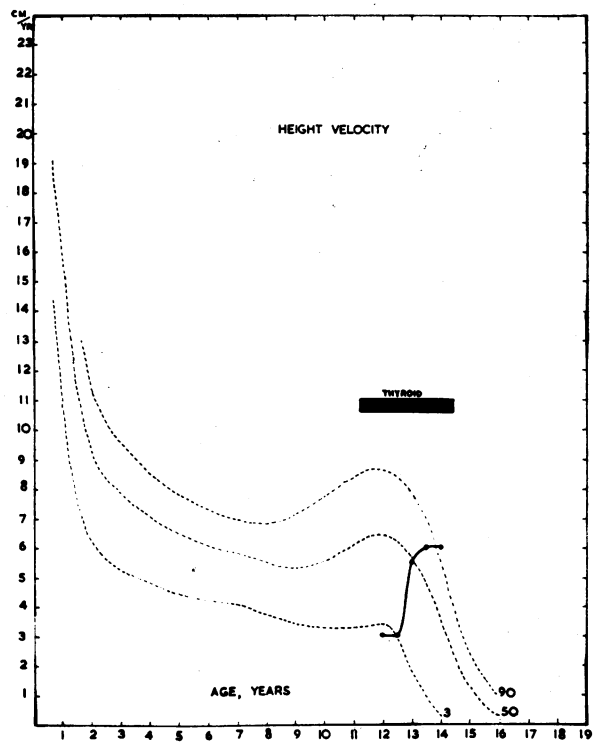


Fig. 24.—Case 9—growth velocity chart.

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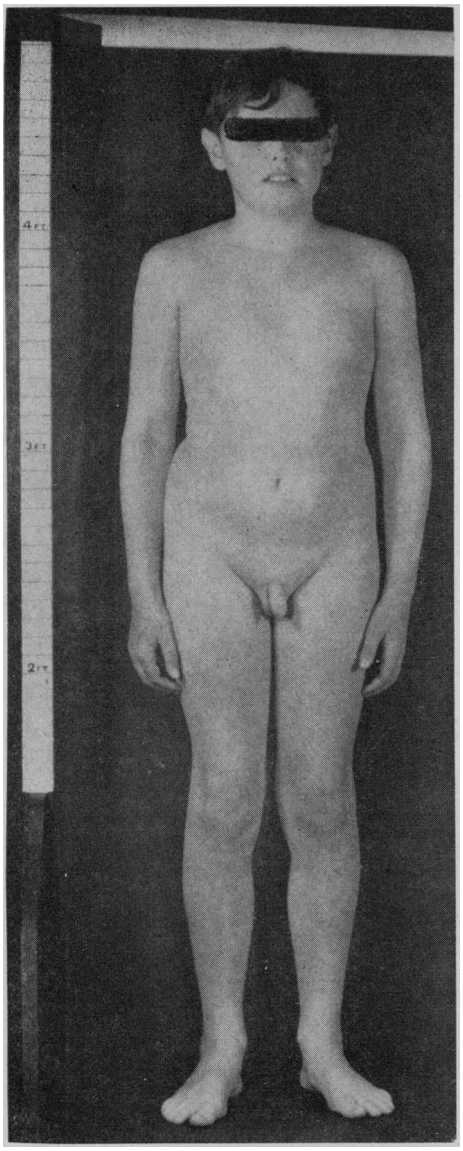

Fig. 25.—Case 10, at age 15 years. Height, 145 cm. (57 ins.): height age, 11 years, Prepubertal.

*Calcified Tuberculoma*

CASE 10.—This boy is now aged 20 years. He had tuberculous meningitis at the age of 6 and growth failure was noticed at 10 years. The photograph in Fig. 25 was taken at 15 years. He did not enter puberty until his twentieth year. He has a large calcified lump above his sella turcica (Fig. 26). The maximal level of growth hormone in response to hypoglycemia was 5 μmg. per ml. and his nitrogen retention was 44%. He has no evidence of thyroid or adrenocortical failure. His height at 19 years was 160 cm. (Fig. 27), and since his bone age then was 14½ years he still has some growth potential remaining. On the velocity chart the penultimate spurt was due to androgen therapy and the last was probably due to a pubertal growth spurt (Fig. 28).

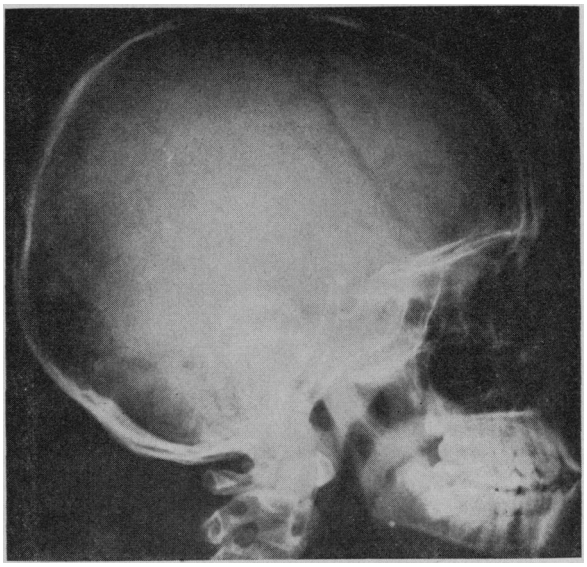

Fig. 26.—Skull radiograph of Case 10—illustrating a calcified lump above the sella turcica.

TREATMENT

Growth hormone deficiency is treated with growth hormone prepared from human pituitaries. Man does not respond to growth hormone prepared from animal pituitaries. Results from the treatment of growth hormone deficiency over periods up to two years or more have been reported by several authors.[21-25]

The doses used varied from 6 to 18 mg. weekly, and various dosage schedules have been

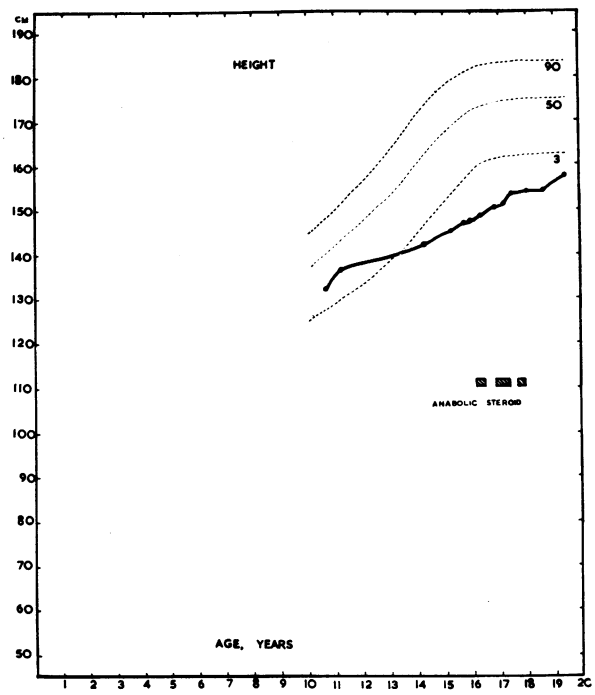


Fig. 27.—Case 10—longitudinal growth chart.

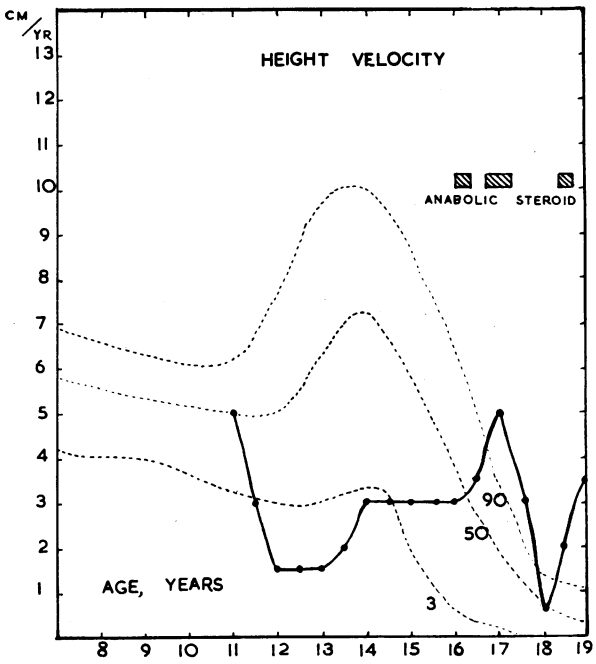


Fig. 28.—Case 10—growth velocity chart.

followed. The results obtained in all series are similar. There is a greatly accelerated velocity of growth in the first year of treatment, which may be regarded as the period of "catch-up" growth. The mean growth rate in six patients treated by Prader *et al.*[21] was 3.4 cm. per year before human growth hormone treatment, 8 cm. per year during the first year of treatment and 5.5 cm. during the second year of treatment. In 12 patients treated by Seip and Trygstad,[25] the mean growth before treatment was 2.2 cm. and in the first year of treatment it was 10 cm. Five of the 12 patients treated for a second year gained an average of 6 cm.

Normal growth rates can therefore be achieved by prolonged therapy, but growth in the "catch-up" period does not make up the stature lost in the early years. Most of the 40 cm. of rapid growth that occurs in the first three years of life is never recovered. However, when the hypopituitary short stature has its origin in later childhood or adolescence, average adult height may be attained. Raben[26] in 1964 described three such patients. One patient grew from 125 cm. to a height of 165 cm. in five and one-half years of treatment.

The record for growth promotion is held by Nadler, Neumann and Gershberg,[27] who treated a baby aged 1 year (length 18 inches) with 1 mg. of human growth hormone three times a week and produced a growth of 7 inches in three months.

If the child has hypothyroidism of any degree, thyroxine should be given in addition to growth hormone. The effects of these two hormones are synergistic in regard to linear growth. As we have already seen, when growth hormone is deficient, thyroxine cannot replace growth hormone as a growth stimulant.

### *Human Growth Hormone Antibodies*

As a rule, the slowing down of growth velocity in the second and third years of treatment is due not to the formation of human growth hormone antibodies but to a natural slowing down after the brief period of "catch-up" growth. When antibodies are produced in high titre, the resistance to human growth hormone may be absolute, as in three of nine children reported by Prader *et al.*[21] When the titre of antibodies is low, they may not suppress the effect of human growth hormone on metabolism and growth.[28] If slowing down of growth occurs from this cause, it may be overcome by increasing the dose.

In the 12 patients reported by Seip and Trygstad,[25] no antibodies were formed. Their human growth hormone was prepared by the method described by Roos, Fevold and Gemzell[29] in 1963. The Zurich and London human growth hormone is prepared by Raben's method.

### *Alternative Treatment*

No synthetic preparation of growth hormone is available and there is no substitute for it. The protein anabolic steroids, of whatever variety, seem to be effective in patients with growth hormone deficiency only when used in virilizing doses. When virilization occurs, skeletal maturation will be disproportionately advanced and no ultimate benefit will be achieved.

If sexual failure is definitely established, testosterone must be administered to the men, and estrogen and progesterone to the women.

### *The Future*

All children suffering from growth hormone deficiency should be treated with human growth hormone. If 300-500 mg. a year is the minimum requirement for treatment and if 3-4 mg. of HGH can be extracted from one pituitary, then about 150 pituitaries a year are required to treat one patient. The incidence of growth hormone deficiency in childhood is not known. If the incidence is one in every 100,000 of the population, the requirement for Canada would be 30,000 and the requirement for Great Britain 75,000 pituitaries annually. Some observers

would put the incidence much higher than this. My experience in Great Britain inclines me to guess that it is lower, probably no more than 1 in every 250,000 of the population. There should obviously be a few pituitary collecting agencies in every large country.

Many problems still remain to be elucidated, but the rapid advances in our knowledge in the last 10 years encourage us to be hopeful about the future.

The investigations reported in this paper have been the work of the following members of my staff, G. A. Brown, P. H. W. Rayner and L. Stimmler, and I am grateful to them for their help. The human growth hormone used in these investigations was provided by the Medical Research Council.

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