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HORMONAL INFLUENCE ON GROWTH*

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Growth depends on the anabolism of protein, and its measurable *chemical* index is the retention of nitrogen and its measurable *clinical* index is the growth in length of the skeleton. If, for the sake of convenience and simplicity, we limit ourselves to the consideration of deviations of height as we discuss hormonal influences on growth we shall not forget that the growth of certain organs and certain cells is dependent on a specific stimulus, so that, for example, even in the presence of dwarfism due to athyroidism or hypothyroidism, enlargement of the anterior pituitary (Hubble, 1956), increased growth of hair (Perloff, 1955), and genital hyperplasia may all be observed (Hubble, 1955). Again, some growth occurs in all organs, even in the total absence of hormonal influences, for, while the hormones stimulate or inhibit growth processes, cellular growth is not entirely dependent on hormonal action.

The hormones which support growth are those which assist in the anabolism of protein, and those which inhibit growth are the hormones which are catabolic or anti-anabolic.

Childhood is the predominantly protein-anabolic phase, and the infant adds 10 in. (25 cm.) to its stature in the first year and 4 in. (10 cm.) in the second year ;

FIG. 1.—Average annual increments in height in boys, expressed as a percentage increase.

annual growth increments continue to occur at a diminished rate, expressed as a percentage increase of skeletal length, until the puberty growth spurt, when the rate temporarily increases, to fall away quickly until the time of epiphyseal closure occurs. In Fig. 1 these average annual increments in boys are shown as a percentage increase of height. In the first year it is 50%,

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in the second year 13%, and it falls to 3% in the thirteenth year, to rise again to 4.4% with the onset of puberty. This annual percentage increase in height offers us, disease and malnutrition apart, an approximate clinical index of the activity of the protein-anabolic hormones.

Protein Anabolism

What are the hormones which influence growth in man? The most powerful of the protein-anabolic hormones is the *growth hormone*—and it is unfortunate that we know less about its function in man than we do of any other hormone. No preparation of it which is potent in man has yet been produced, and, unlike all other pituitary hormones, it has no endocrine target-organ by whose function we might indirectly assess its activity. We can only assume its presence in man, and we have to be content with applying to man the considerable knowledge of its action in experimental animals. The experimental evidence is that growth hormone acts by directly stimulating tissue synthesis from amino-acids (Russell, 1951). It has also an effect on fat and carbohydrate metabolism, to which I refer later.

Thyroxine is necessary for the complete action of the growth hormone, and these two hormones have a synergistic action on protein anabolism—neither achieves its full effect without the help of the other. The effects of thyroxine-lack and thyroxine-excess on growth in both man and animals are so well documented that it is unnecessary to consider them further here.

Insulin also has a synergistic action with the growth hormone in its effect on protein anabolism in animals (Gaunt, 1954). Lawrence, Salter, and Best (1954) showed that insulin is a protein anabolizer in its own right and that growth in hypophysectomized animals can be maintained by insulin. In its action on protein anabolism, and therefore on growth, it is probably less important quantitatively than thyroxine and certainly less so than the growth hormone ; but for our clinical purposes, and certainly until we have available chemical assays of these hormones, we should regard them as an integrated group of protein-anabolic hormones—growth hormone, thyroxine, and insulin. At puberty new and powerful protein anabolizers are introduced in the adrenal androgens in both girls and boys, and in boys by the testicular androgens. The effect of these androgens on protein anabolism and growth is well seen at puberty (the evidence has been reviewed by Tanner, 1955) and in diseases such as the adrenogenital syndrome, in

virilizing tumours of the adrenal and the ovary, and in interstitial-cell tumours of the testis. Except for one patient with congenital virilism I shall not refer again to this interesting group of children. In the estimation of the urinary 17-ketosteroids we have a well-established and sufficiently accurate method of assaying these androgens.

Protein Catabolism

In the group of protein anabolizers it has been necessary to include hormones from five organs: the anterior pituitary, the thyroid, the pancreas, the adrenal cortex, and the testis. For the protein catabolizers, the growth inhibitors, it is necessary to consider only the adrenal cortex, and for practical purposes we may regard this protein catabolism as the work of one hormone, cortisol (compound F). Its action is directly opposed to the action of the growth hormone, since it inhibits the incorporation of amino-acids into protein, particularly in connective and lymphoid tissue.

Cortisol and cortisone (compound E), prednisone and prednisolone, will inhibit, partially or completely, the growth of children, as you will see if you watch the growth of children who are having continued steroid therapy for diseases such as chronic asthma, nephrosis, rheumatoid arthritis, and collagen diseases. It is unusual for cortisone to depress the rate of growth if it is used in doses of less than 35 to 60 mg. per square metre of body surface (this is an average surface area for a child of 10 years) (Blodgett *et al.*, 1956). Sensitivity of children to this inhibition of growth by glucocorticoids shows, however, an individual variation. The amino-acids which are not being used for protein synthesis are then converted to glucose by the action of cortisol, a process known as gluconeogenesis. This is one of the homeostatic mechanisms by which the body corrects hypoglycaemia.

Protein Metabolism

I want now to introduce a concept which I have found useful in considering these problems of growth and protein metabolism; although it is not possible to provide proof for all the steps in this hypothesis it gives a ready explanation of well-established clinical facts, and I shall use it throughout this paper when dealing with various disorders of growth. Hypotheses, in medicine as in physics, should be regarded as valid for as long as they provide a useful explanation of the known facts.

Protein metabolism provides the site for a contest between the anabolic and the catabolic hormones. During the phases of active growth the anabolic hormones are in the ascendant. If you look again at Fig. 1, depicting the rapid growth of children in the first two years of life, you may correctly conclude that I assume either that children at this age are making a large amount of growth hormone or that their tissues are very sensitive to its action. This hypothesis is summarized as follows:

Competition for Protein in Childhood

A (Protein-Anabolizers)	K (Protein-Catabolizers)
G (Growth Hormones)	
+	} C (Glucocorticoids)
T (Thyroxine)	
+	
I (Insulin)	

In normal growth the protein-anabolizers are more powerful than the protein-catabolizers. $A > K$.

In infancy the *anabolic* hormones (growth hormone, thyroid, and insulin) are much more powerful than the *catabolic* hormones from the adrenal cortex (the glucocorticoids), and rapid growth occurs. Growth hormone not only spares protein for growth, as I have already said, but it also inhibits the oxidation of carbohydrate. This means

that fat has to be used in large amounts by the growing child for its daily requirements of energy (Gaunt, 1954), and explains the clinical observation that ketosis is more common in young children than in older children and adults. Hypoglycaemia is difficult to deal with in young children and sometimes is disastrous in its consequences. This is explained by the fact that the action of the growth hormone allows little protein for gluconeogenesis and, in addition, it tends to suppress the utilization of carbohydrate by the tissues.

These are common clinical observations, but this formula also explains a rarer observation made by Blodgett *et al.* (1956): children with hypopituitarism are sensitive to the action of cortisone, so that as little as 5 to 20 mg. of cortisone per square metre of body surface daily will, in them, produce Cushing's syndrome and total cessation of growth. In hypopituitarism there is a disappearance of the protein-anabolic hormones (with the exception of insulin, which is itself reduced in amount since its output is regulated by the height of the blood sugar), so that when these contenders for protein are removed a small dose of cortisone is sufficient to claim all the protein in the metabolic pool.

These hormonal influences on the female skeleton are summarized as follows:

The Four Skeletal Ages of Woman

G + T + I	>C	Growth in infancy and childhood
G + T + I + A	>C	Growth in adolescence
g + T + I + A	≈C	Arrest or retardation of growth
g + T + I + a	<C	Post-menopausal osteoporosis

I have assumed that the quantitative effects of thyroid, insulin, and cortisol remain constant throughout life. In infancy the growth hormone (represented by a large G) captures the protein; in adolescence a diminishing amount of G is reinforced by the androgens (A); in adult life the anabolic hormones are in equilibrium—disease, disaster, and pregnancy apart—with the catabolic hormones, and the bones hold their protein; after the menopause the catabolism of decrecence arrives, with the protein anabolizers in decline (small g and small a) and the unhappy bones yield up their protein.

Disorders of Growth in Childhood

I will now consider some of the disorders of growth in children which illustrate this concept of growth as a competition for protein which is won by the anabolizers. The first two patients suffer from *primary hypopituitary dwarfism*; which can now be firmly differentiated from all other forms of dwarfism; the third child is a boy aged 8 years suffering from *Cushing's syndrome*, due to adrenocortical hyperplasia, with total arrest of growth; the fourth child is suffering from *congenital virilism*, despite her average growth and average bone-age; the fifth child suffers from *glycogen-storage disease* which induces catabolic consequences and defective growth; and the sixth child is an example of the catabolic phase with impaired growth which may occur in childhood in the course of a disease, *diabetes*, which is associated with a deficiency of one of the anabolic hormones, insulin.

Primary Hypopituitary Dwarfism

I have seen five examples of this constitutional disorder—which, let me emphasize, is quite unrelated to disease of the pituitary—three patients under my care and two by the courtesy of colleagues (Professor N. B. Capon and Dr. Cedric Harvey). Two are boys and three are girls. The appearances in all the cases are identical, so I will limit myself to the description of two of my own patients who have had a long follow-up and who have been carefully investigated by modern techniques.

P. T. B., aged 19½, weighed 7 lb. (3.2 kg.) at birth and his mother stated that his growth was normal up to the age of 2 years. I first knew him when he was 7½ years, but lost sight of him after six months; his height was then 39 in. (99 cm.). He

came under my care again at the age of 16½, when the photograph shown in Fig. 2 was taken and his height was 49 in. (124.5 cm.)—an average height increment without treatment of a little more than 1 in. (2.5 cm.) a year. At 19½ years his height was 56½ in. (143.5 cm.), an average annual increment of 2½ in. (6.3 cm.)—after much treatment—which gives him a height-age of 11 years;

FIG. 2.—Primary hypopituitary dwarfism: P. T. B., aged 16½ years.

his bone-age is 14 to 15 years. His facial appearance at 16 years was immature, related to retarded development of the facial bones, and his personality was a happy, childlike, timorous, and immature. His intelligence was good. At 17, before testosterone therapy was begun, there was no evidence of puberty—pubic and axillary hair had not appeared, the length of the flaccid stretched penis was 2 in. (5 cm.), and the length of the testes was less than 1 in. (2.5 cm.).

T. B., aged 13½, was first seen at the age of 7½ when his height was 36 in. (91.5 cm.) height-age 2 to 3 years and his bone-age was 5 years. His birth weight was said to have been 7 lb. (3.2 kg.) and his growth was not thought to have been abnormal until he was 2 years old. The development of his facial bones was retarded, giving him a babyish appearance. He has had various treatments (see below). At 13½ years his height is 50 in. (127 cm.) (height-age about 7 years) and his bone-age 10 to 11 years. His maternal first-cousin, now aged 26, suffers from hypopituitary hypogonadism (Hubble, 1951) but has no deficiency of the growth hormone. After I published this description of the family hypopituitarism I discovered that his cousin had a double dose of the maternal grandfather's genes, for it was alleged that his grandfather was also his father.

The clinical criteria, then, in these cases are: normal birth weights, and growth that appears to have been normal for an indefinite period after birth; great retardation in height; a bone-age which although retarded is much less retarded than the height-age; a height increment, without treatment, of approximately 1 in. (2.5 cm.) a year; babyish facies; failure of sexual development as a rule; rarely, as in T. B., pituitary failure may be seen in another member of the family.

There is no clinical evidence of hypothyroidism, and the diagnosis of the "Tom Thumb" (proportionate) dwarf is easily excluded by the normal development of facial bones, by the average bone-age, and by a maturing personality which corresponds to the chronological age, all of which occur in the latter condition. Investigations have confirmed and extended the diagnosis of primary hypopituitarism in both these patients.

The *pituitary fossa* was of normal dimension in both boys. The *blood cholesterol* was high in both: in P. T. B. at the age of 16½–17 years the average of three values before treatment was 391 mg. per 100 ml., and in T. B., at the age of 7½ to 8 years, the average of three estimations before treatment was 270 mg. per 100 ml. The *insulin-sensitivity* test was normal in T. B., but in P. T. B., after 3.5 units intravenously, the fasting blood sugar of 78 mg. per 100 ml. fell to 11 mg. per 100 ml. in 30 minutes, but in a further half-hour had returned to 66 mg. per 100 ml. (increased insulin sensitivity but no hypoglycaemic unresponsiveness). The *response to water load* (Kepler 1) was normal in P. T. B.

Adrenocortical Urinary Assays.—17-Ketosteroids: In P. T. B. (aged 16–19 years) the average of four estimations was 2.7 mg./24 hours, and in T. B. (aged 10–13 years) 3.5 mg./24 hours. **17-Ketogenic steroids:** In P. T. B. (aged 16–19 years) the average of four estimations was 2.2 mg./24 hours and in T. B. (aged 10–13 years) 2.2 mg./24 hours. All these values are low, but the 17-ketogenic steroids are relatively much lower than the 17-ketosteroids (aged 6–10 years: average excretion of 17-ketosteroids 1–4 mg./24 hours and of 17-ketogenic steroids 2–8 mg./24 hours).

Response to intramuscular corticotrophin gel, 20 units daily for four days (Fig. 3): the 17-ketogenic steroids per 24 hours in P. T. B. reached 36.4 mg. on the third day of treatment and in T. B. reached 27.8 mg. on the fourth day of treatment. This is a good response to corticotrophin, despite the low initial values. The basal metabolic rate in P. T. B. was +5%.

FIG. 3.—Response of 17-ketogenic steroids to intramuscular corticotrophin (20 units twice daily for four days).

¹³¹I Uptake.—P. T. B. (aged 16½ and 19½ years) had a normal uptake curve over 48

hours, a normal plasma activity, and a normal response to T.S.H., 10 mg., given eight hours before the second uptake.

Gonadotrophins.—None present in P. T. B. (assayed five times between 16½ and 19½ years).

We may now add to the clinical criteria for primary hypopituitary dwarfism already cited the following metabolic and endocrinological data: hypercholesterolaemia of varying degree, increased insulin sensitivity (not invariable); normal thyroid function; reduced adrenocortical function responding normally to corticotrophin, and therefore itself dependent on deficient corticotrophin production by the pituitary.

If we now return to the formula for growth at puberty we see that these children with *primary hypopituitary dwarfism* lack G and A.

Competition for Protein in Primary Hypopituitary Dwarfism

$G + T + I + A > C$ Normal adolescent growth
 $G + T + I + A \equiv$ or $< C$ Protein equilibrium in primary hypopituitary dwarfism

If G and A are absent there is a situation in which the protein anabolic hormones are represented by thyroid and insulin alone, and these are general rather than specific protein anabolizers. Cortisol should therefore be supreme—and the child would be in a state of Cushing-like catabolism were it not, as I have shown, that cortisol itself is also deficiently produced. It would have been possible to forecast from this formula that there must be reduced adrenocortical function in primary hypopituitary dwarfism, since these children do not present the picture of Cushing's syndrome.

Treatment of Primary Hypopituitary Dwarfism

These children are short of growth hormone and androgens so that treatment by methyltestosterone, combined with thyroid therapy, is reasonable. Nor, as I have shown, is much opposition to be expected from the glucocorticoids, whose urinary output has not been increased by androgen therapy. The results of treatment are good and one can achieve average annual height increments of 3 to 4%. The ultimate height depends, of course, on the age at which epiphyseal fusion occurs.

P. T. B. was 56½ in. (143.5 cm.) at 19½ years, and he had grown 2 in. (5 cm.) a year for the last three years. His bone-age was still no more than 15 years, so we may hope

that his ultimate height will exceed 5 ft. (152.5 cm.), which is what I promised him when he started treatment three years ago, at 49 in. (124.5 cm.) (Fig. 4). The development of his personality has been just as striking as the development of his facial bones, the increase in his height and musculature, and the disappearance of his puppy-fat. The

FIG. 4.—P. T. B., aged 19½ years, after treatment.

absence of axillary hair and the growth of hair limited to the female escutcheon is dependent on the continued deficiency of adrenal androgens.

Treatment by testosterone and thyroid should be continued until the bone-age matches the chronological age; then thyroid treatment may be continued alone, but no addition to ultimate height can then be expected. An obvious enlargement of the clitoris in girls requires cessation of testosterone therapy, at least for a year or two; but no fear of inhibition of pituitary sex hormones

should be allowed to interfere with therapy, for, once the diagnosis is established, hope of sexual development may be abandoned. There is, I believe, only one case reported in the literature (Hewer, 1944) in which failure of the growth hormone has not been accompanied by failure of the sex hormones.

I have used other reputed growth factors in treatment—anterior pituitary hormones, GF4, androstenediol, 19-nortestosterone (a weak androgen), and insulin—but none of these is to be recommended. Insulin is the only one of these in which I have been much interested, and I was able to show in T.B.'s case, in an eight-day nitrogen balance, that a good nitrogen retention was achieved. Obesity was the result of therapy, however, and not a gain in height (Fig. 5)—for his height curve flattened out and he gained 14 lb. (6.4 kg.) in three months—a tolerable adiposity.

My last remark about therapy is that the response to treatment provides a further diagnostic criterion between hypopituitary dwarfism and the primordial "Tom Thumb" dwarf.

M. B., aged 9 years, has a weight-age of 2 years and a height-age of 2½ years. His genital hyperplasia was caused by over-enthusiastic testosterone therapy between the ages of 2 and 3 years, and this was the only period during which his height increment paralleled the average height curve (Fig. 6). Otherwise the gap in both his height and weight curves is gradually widening. He has for the last three years been treated by a long-acting insulin without benefit. The very slow growth in the "Tom Thumb" dwarf resists all forms of therapy.

Catabolic or Anti-anabolic Mechanisms

Robert (Fig. 7), aged 9 years, is suffering from Cushing's syndrome. He had ruddy cheeks, great fat deposits, especially in his buffalo hump, and hirsuties. His father told me that there had been no growth in height in the preceding two years. The boy was 43½ in. (110.5 cm.) at 6½ years, and he was still 43½ in. when I saw him at the age of 8½ years. This arrest of growth never occurs in simple obesity, and it was not difficult, despite his youth and his sex, to make the diagnosis of Cushing's syndrome.

Up to 1950 there were 26 authentic reported cases of Cushing's syndrome in childhood under the age of 10 years, only four of them in boys (Lawson Wilkins, 1950). The usual investigations made it improbable that there was a tumour of the adrenal cortex, despite the fact that all the reported cases of Cushing's syndrome under the age of 10 years had been due to an adrenal tumour.

In Table I is set out the supporting evidence from urinary endocrine assays that Robert is indeed suffering from Cushing's syndrome, that a neoplasm of the adrenal cortex is highly improbable, and that the excessive output of the adrenocortical steroids is dependent on pituitary stimulation. In the third and fourth columns the 17-ketosteroid and 17-hydroxycorticosteroid urinary output in mg. a day are given. The 17-ketogenic steroids have been omitted,

FIG. 5.—Case T.B. Treatment by protamine zinc insulin (16 units daily for three months, from age 9½ to 10 years) flattened out his height curve and increased his weight by 14 lb. (6.4 kg.).

FIG. 6.—M. B., "Tom Thumb" dwarf. Treatment by testosterone from the age of 2 to 3 years produced an average height increment, but was discontinued on account of genital hyperplasia. Insulin used for three years has not accelerated either his weight or height gain.

Fig. 7.—Robert, aged 8½ years. Cushing's syndrome due to adrenocortical hyperplasia.

TABLE I.—Robert. Creatinine, 17-Ketosteroid, 17-Hydroxycorticosteroid in Urinary Assays per 24 Hours, Together with the Response to 9- α -Fluorohydrocortisone (Dr. J. K. Norymberski)

Day	Creatinine	17-KS	17-OH CS	Treatment by 9- α -Fluorohydrocortisone
1	0.51 g.	6.8 mg.	21.7 mg.	
2	0.56 „	7.1 „	20.9 „	2 mg.
3	0.54 „	7.7 „	17.4 „	2 „
4	0.58 „	9.3 „	16.2 „	5 „
5	0.54 „	6.8 „	16.4 „	5 „
6	0.33 „	3.5 „	8.0 „	5 „
7	0.28 „	3.6 „	9.1 „	

but their level, always a little less than the 17-hydroxycorticosteroids, followed closely their changes.

It will be seen that the 17-hydroxycorticosteroids are three to four times as high as would be expected in a boy of his age, and the 17-ketosteroid output is approximately doubled. In the last column of Table I is set out the administered dose of 9- α -fluorohydrocortisone. Now, 9- α -fluorohydrocortisone is a very effective depressant of corticotrophin in these small doses—compared with cortisone—and it has the added advantage that its degradation products do not interfere with the urinary assays of 17-ketogenic steroids and 17-hydroxycorticosteroids (Cope and Harrison, 1955). During this five-day course of 9- α -fluorohydrocortisone the output of 17-ketosteroids was halved and the output of 17-hydroxycorticosteroids was reduced by more than half. Neoplasms of the adrenal cortex are not as a rule pituitary-dependent, so that this result assists in the exclusion of a tumour.

It is assumed that in Cushing's syndrome the adrenal cortex is hypersensitive to corticotrophin stimulation. This was so in the case of Robert, in whom 30 units of intramuscular corticotrophin gel twice daily raised the 17-ketosteroid excretion to 30 mg./24 hours and the 17-hydroxycorticosteroid excretion to 189 mg./24 hours. The excess of adrenal glucocorticoids has been sufficient in Robert's case to prevent the allocation of any protein to skeletal growth. This protein wastage is nicely demonstrated by an unpremeditated observation in the second column of Table I. Urinary creatinine output is used in many laboratories as a rough check on the accuracy of the 24-hour urinary collections. It will be seen that when the 17-hydroxycorticosteroid output was reduced to normal levels the creatinine urinary output is halved—from 560 to 280 mg. daily. Ex-

cessive protein wastage has been arrested and the catabolic hormones are once more held in check by the anabolic hormones.

It will be recalled that the characteristic striae of Cushing's syndrome are less common in children suffering with this disease than in adults (Lawson Wilkins, 1950) and they are absent in Robert. Also, striae occur rarely in children treated by steroids. The explanation is not clear. Fuller Albright (that great master of metabolism) in the Harvey Lectures for 1942-3 provided the classical account of the changes in Cushing's syndrome—a brilliant contribution to medical thinking—and related the "thin skin" to the defect in protein synthesis. It is tempting to say that the anabolizers of protein—the growth hormone and possibly the adrenal androgens—may be adequate in Cushing's syndrome of childhood to prevent protein wastage in the skin. It would be impossible to advance this explanation in the face of the complete arrest of growth which occurred in Robert.

Professor Illingworth, of Sheffield, has generously allowed me to discuss the next patient. Helen was 2 years and 2 months old when the photograph (Fig. 8) was taken, and when I saw her she was 2 years and 8 months. The enlargement of the clitoris which can be seen in Fig. 8 was present at birth. Her height at the age of 2 years 2 months was 36 in. (91.5 cm.)—on the 50 percentile—and her growth in the subsequent eight months has been 1 in. (2.5 cm.). Growth in one year at this age, on the fifty percentile, is 2.8 in. (7.1 cm.), so that Helen's growth is now less than average. Her bone-age, on the other hand, is a little in advance of her chronological age—perhaps by 2 years. In Table II are set out the values for the urinary steroid metabolites—and for these estimations and for those in the last patient with Cushing's syndrome Professor Illingworth and I are indebted to Dr. J. K. Norymberski, of Sheffield.

In the second and third columns the values are approximately the same as for Robert, the boy with Cushing's syndrome, and yet Helen is obviously not suffering from Cushing's syndrome. The fifth column is headed 21-deoxyketols. The urine of normal men and women contains less than 0.5 mg. of 21-deoxyketols/24 hours (Norymberski), and therefore the excretion of these substances is greatly raised in Helen. This finding is now regarded as characteristic of virilizing adrenal hyperplasia, in which there is assumed to be a block in the formation of cortisol from progesterone which normally occurs in four stages: this arrest is held to occur at the second of the four stages by an enzymic defect which blocks the synthesis at 17- α -hydroxyprogesterone; this substance and some of its urinary metabolites, such as pregnanetriol, are 21-deoxyketols, and in congenital adrenal hyperplasia large quantities appear in the urine (Bongiovanni *et al.*, 1956). This girl may then be assumed to be suffering from congenital adrenocortical hyperplasia.

Fig. 8.—Helen, aged 2 years 2 months, suffering from congenital virilism but with normal height and bone-age. (Professor R. Illingworth's patient.)

TABLE II.—17-Ketosteroids, 17-Hydroxycorticosteroids, Iso-dehydroandrosterone, and 21-Deoxyketols in Urinary Assays per 24 Hours, Together with Response to 9- α -Fluorohydrocortisone (Dr. J. K. Norymberki)

Day	17-KS	17-OH CS	SDHA	21-Deoxyketols	Treatment by 9- α -fluorohydrocortisone
1	7.6	19.5	3.8	3.0	
2	7.0	19.3	2.2	2.4	
3	6.7	14.3	1.5	1.7	1 mg.
4	—	—	—	—	1 "
5	2.3	6.1	0.9	0.7	1 "
6	3.8	11.1	1.6	2.1	
7	6.5	12.4	2.2	2.0	

Before considering still further difficulties let us take refuge, while looking at the last column, in some facts which are crystal clear. Helen was given 1 mg. of 9- α -fluorohydrocortisone daily for three days, and, with the consequent depression of corticotrophin output from the anterior pituitary, the output in the urinary steroids was reduced to one-third to one-quarter of their previous level. Therefore we may conclude, as in the case of Robert, that the excessive output of steroids is pituitary-dependent and the adrenal cortex in Helen is either exceptionally sensitive to corticotrophin or there is an excessive output of that hormone. The usual explanation of the elevated 17-ketosteroid excretion in congenital adrenocortical hyperplasia is that the production of cortisol is insufficient to hold in check the corticotrophic activity of the pituitary; but in Helen the output of 17-hydroxycorticosteroids is high—let us say three to four times the average output. Dr. Norymberki tells me that the metabolites of 17- α -hydroxyprogesterone—both pregnanetriol and 21-deoxyketols—together with the metabolites of cortisol—both the dihydroxyacetones and the triols—contribute to the assay of the urinary 17-hydroxycorticosteroids.

The brilliant investigations of the steroid chemists have not yet fully explained the biological consequences of adrenocortical hyperplasia: it has not yet been established, for example, what is the androgenic substance circulating in excess, nor is it known whether 17- α -hydroxyprogesterone itself has any androgenic effect (Reifenstein, 1956). Without further analysis of the urinary steroids, can clinical observation and deduction make any contribution in the case of Helen? I believe they can. We may conclude from the enlargement of the clitoris, which has been present since birth, and from the moderate advancement of her epiphyseal development, that there is excessive androgenic activity. Despite this excess of androgens there has been no acceleration of growth, and we may conclude from a consideration of the hormonal growth formula that the anabolic effect of the androgens has been held in check by the catabolic effect of a high output of cortisol. In fact, the struggle for protein in Helen is won by the anabolizers only in the same degree as in the normal child.

Why, then, does this high output of cortisol not suppress pituitary activity in the output of corticotrophin? This is still a problem in many cases of Cushing's syndrome, and I cannot debate it here (see Jailer *et al.*, 1956). I may advance, then, a final clinical conclusion that in Helen there are two separate abnormalities: (1) a partial but not a complete arrest at stage II in the formation of cortisol from progesterone, and (2) an unspecified derangement of the normal corticotrophin-cortisol homeostasis.

A full description of these two children, Robert and Helen, is to be published elsewhere (Hubble and Illingworth, 1957).

The Catabolic Mechanisms in Two Diseases

During the last ten years we have become accustomed, in dealing with acute illness, accidents, and operations, to the notion that in these stressful situations the catabolic side of the equation temporarily dominates the anabolic. There are two chronic diseases in childhood in which growth failure may occur because the competition for protein is lost by the anabolizers, and I will conclude this address

by a discussion of them. The first is *glycogen-storage disease*. Dwarfism is one of the features of glycogen-storage disease, and here the interference with growth is associated with the same metabolic effect on protein as is seen in Cushing's syndrome. The basic difficulty is the non-availability of hepatic glycogen, and the metabolic consequences of this were worked out in a classic paper by Bridge and Holt (1945).

D. W. was proved to be suffering from glycogen-storage disease by the failure of his blood sugar to rise after injections of adrenaline and glucagon, and by a liver biopsy which demonstrated an excess of glycogen in his liver. His height at 6 years was 4 in. (10 cm.) below the 10 percentile, and he was moderately obese, with a weight 10 lb. (4.5 kg.) above the average for his height. With the addition of protein to his diet, as recommended by Bridge and Holt (1945), he has grown 14 in. (35.5 cm.) in five years, so that his height has achieved the 50 percentile, as is shown in Fig. 9. His liver is smaller but still much enlarged. Gluconeogenesis from protein allows the correction of hypoglycaemia in this disorder, and the addition of protein, particularly at the night feed, gives enough substrate for the anabolic hormones to ensure normal growth.

The homeostatic correction of chronic hypoglycaemia by gluconeogenesis, presumably brought about by an increased secretion of corticotrophin, is one of the fundamental biological mechanisms (Long, 1952) and obviously in glycogen-storage disease it takes precedence of the growth hormone in the competition for protein.

Van Creveld (1952)—who, at the same time, but independently of Von Gierke, described glycogen-storage disease in 1928, and has therefore had the opportunity of watching his cases for 25 years—reported that two of his patients had not only achieved average growth but had exercised their reproductive functions. Having regard to the formula, this need not surprise us. As age advances there is a diminishing requirement of protein for growth, so that more protein is available for gluconeogenesis; and as the anabolic factors are increasingly counterbalanced by the catabolic hormones the conversion of protein to glucose is more easily achieved, with a correspondingly diminished dependence on hepatic glycogen and on the fat depots for the daily metabolic needs.

There is in diabetes a shortage of available carbohydrate, and the wastage of protein and fat which occurs in consequence in the untreated diabetic is well recognized. However, an interesting syndrome (Mauriac, 1930; Houet, 1949; Guest, 1953) which occurs in the imperfectly treated child diabetic has features in common both with Cushing's syndrome and with glycogen-storage disease. Its diagnostic features are dwarfism, obesity, florid facies, hypercholesterolaemia, greatly increased glycogen and fat deposit in the enlarged liver, and sexual retardation. Fig. 10 is a photograph of a child who died at the age of 15 years in consequence of this metabolic abnormality. Fig. 11 shows the progressive retardation of height from a 6-in. (15-cm.) to an 11-in. (28-cm.) deficiency in the space of four years. Fig. 10 shows the Cushing-like cheeks, the hepatomegaly sketched in, the obesity, and the absence of sexual development. At necropsy greatly increased glycogen and fat deposits in the liver were demonstrated.

Fig. 9.—Better-than-average height increments in D.W., a boy with glycogen-storage disease given additional protein.

Such children are uncontrolled diabetics who are without insulin for long periods of the 24 hours. Clearly not all uncontrolled diabetic children develop this syndrome—but I have for the last five years watched the growth of two other diabetic children who showed less severe examples of the same syndrome. With adequate treatment with long-

FIG. 10.—Mauriac syndrome in a diabetic aged 15 years. The shading shows the area of hepatomegaly.

FIG. 11.—Progressive retardation of growth in patient shown in Fig. 10.

the excretion of 11-oxosteroids in their urine was three times the average amounts. These children are insulin-sensitive and run easily into hypoglycaemia; McArthur and her colleagues (1952) showed that there was a greatly increased corticosteroid excretion in a diabetic male mongol aged 19 years who had frequent daily insulin reactions. Children with the Mauriac syndrome have long periods of ketosis, and it has been shown that in diabetic ketosis increased adrenocortical activity occurs (Stowers, 1951; McArthur *et al.*, 1952). All the features of this syndrome—the moon-face, the obesity, the glycogen and fat deposits in the liver, and the failure of growth and of sexual development—are adequately explained by a deficiency of insulin and by an excess of cortisol.

Competition for Protein in the Mauriac Syndrome (Childhood Diabetes)

G + T + I > C Normal growth
G + T + i ≡ or < C Arrest or retardation of growth

acting insulin and without any change in diet, their growth has been better than average and all the other evidences of the syndrome have been removed. Insulin alone has caused the disappearance of this catabolic mechanism. Salter and Best (1953) showed that insulin was an effective protein anabolizer and would produce growth in hypophysectomized rats. In diabetic children treated with insufficient insulin throughout the 24 hours there will then be a serious deficiency on the anabolic side of the formula for growth.

In addition to this there is, I believe, an increase of adrenocortical steroid output, so that there is also an enhancement of the catabolic side of the formula. Five years ago the assay of urinary steroids was not as reliable as it is today, but in two of my children with the Mauriac syndrome it was shown, by the courtesy of Dr. Wilfred Payne, that

Summary and Conclusions

In childhood there is a competition for protein which is won by the protein anabolizers, and normal growth results.

The protein anabolizers are the growth hormone, thyroxine, insulin, and the androgens; the protein catabolizers are the glucocorticoids, of which the chief is cortisol.

To the classical picture of primary hypopituitary dwarfism these features are added—hypercholesterolaemia, adrenal hypocorticism, and deficient production of corticotrophin.

The treatment of primary hypopituitary dwarfism by methyltestosterone and thyroid is described, and its differentiation from primordial dwarfism is indicated.

Two examples of adrenocortical hyperplasia in childhood are described. In the first, a boy with Cushing's syndrome, arrest of growth resulted; and in the second, a girl with congenital virilism, average growth has occurred.

Two examples of catabolic diseases are discussed—glycogen-storage disease and the Mauriac syndrome in child diabetes.

The construction of a simple hormonal formula for growth explains many features of endocrine and metabolic disease in childhood.

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