

# Studies with Human Growth Hormone\*

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Let me tell you at the outset of my appreciation of the great honour you have done me in asking me to deliver the first Lawson Wilkins Memorial Lecture. I accepted this invitation with eagerness because I cherish any link that binds Lawson Wilkins' life and work to mine.

I often turn to the page in the second edition of his great textbook in which he proudly listed the 31 Associates and Fellows who had worked with him from 1938 onwards. Between 1957 and his retirement other names were added to this published list. Nearly all of them are here this evening and all of them would have been here had it been possible. As I read these distinguished names, I recognize that it is in their achievement, present and promised, that Lawson Wilkins' true immortality lies. I count no man a great scientist who has not founded a school, who has not handed on his torch to a host of eager disciples. This was part of Rudyard Kipling's meaning when he wrote,

'Let us now praise famous men . . .  
For their work continueth  
And their work continueth  
Broad and deep continueth  
Greater than their knowing.'

I wrote of Lawson Wilkins on his retirement that 'he found the subject of paediatric endocrinology a murky backwater. He widened its banks, dredged its bed, cut down the weeds, and linked its stream with the main current of endocrinology whose waters have been freshened and invigorated by their youthful tributary' (Hubble, 1960). He left behind him a *corps d'élite*, composed of men and women whom he had trained, to continue and extend these splendid labours.

## Metabolic Studies with Human Growth Hormone

We have studied the effect of human growth hormone (HGH) on lipid metabolism, its influence

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on adrenocortical and thyroid function, and its effect on the urinary excretion of nitrogen. Ten dwarfed patients were selected for study. They were kept on a constant diet, previously determined by the consideration of the patient's appetite and taste and maintained throughout the period of the experiment. Any endocrine, or anticonvulsive therapy, was either given throughout the investigation or had been stopped at least two months before the experiment began. The pre-treatment period lasted from 5 to 9 days, the HGH period from 5 to 9 days, and in 7 patients the observations were continued for 2 to 7 days after HGH had been withdrawn. The HGH was supplied by the Medical Research Council\* and had been prepared by the Raben method of extraction from human pituitaries.

Details of the methods are given in Appendix I.

The 10 patients who entered this study were all of short stature and all of them had been under observation for many years. They had been submitted to various endocrine investigations. The diagnoses in the 10 patients together with a brief clinical summary are given in Appendix II. (All measurements of maturation refer to the time of the trial and insulin was administered intravenously in a dose of 0.1 unit/kg. body weight except in Case 2.)

**Organic hypopituitarism** (Cases 1, 2, and 3). The hypopituitarism in these three patients was the result of tuberculous meningitis, perinatal brain damage (presumed), and intrasellar craniopharyngioma (presumed) respectively.

**Idiopathic hypopituitarism** (Cases 4, 5, and 6). These three patients were all grouped together since their hypopituitarism was of unknown aetiology. It appeared improbable that they shared a common pathogenesis. Case 4 presented as a cretin in infancy but her growth failed to respond to

\* Cases 1-4 were treated with MRC Batch No. R6: biological activity 1.19 i.u./mg. 10 mg. were used  $\equiv$  12 i.u. Cases 5-8 were treated with MRC Batch No. R7: biological activity 0.63 i.u./mg., and 20 mg. were used  $\equiv$  12.6 i.u. Cases 9 and 10 were treated with Batch No. R8: biological activity 0.64 i.u./mg., and 20 mg. were used  $\equiv$  12.8 i.u.

adequate thyroid, thyroxine, and triiodothyronine therapy. She had mild spontaneous hypoglycaemic attacks. The sella turcica was tiny (12.5 sq.mm.). There was some defect of adrenocortical function. *Case 5* presented with hypoglycaemic attacks at the age of 3 years when his short stature and slow velocity of growth were observed. *Case 6* had the clinical features of idiopathic hypopituitarism. He had no hypercholesterolaemia. During the past two years he has shown evidence of mild deficiency of thyroid and adrenocortical function. If it were not for this partial deficiency of other target glands, the diagnosis of hypopituitarism in this boy would be open to doubt. The hypoglycaemic response of growth hormone has not yet been tested.

**Suspected idiopathic hypopituitarism** (Cases 7, 8, and 9). These three patients had all been suspected of idiopathic hypopituitarism. All were severely retarded in growth. Two of them (Cases 7 and 8) had hypercholesterolaemia. Two (Cases 8 and 9) showed an inadequate response to the metyrapone test indicative of a low corticotrophin reserve. Thyroid function was normal in all three. Cases 7 and 8 were regarded as non-hypopituitary dwarfs when they entered the trial, but there was doubt about Case 9, later confirmed by the failure of his growth hormone level to rise during insulin-induced hypoglycaemia.

**Primordial dwarf** (Case 10).

#### Diagnosis of Hypopituitarism

The diagnosis of hypopituitarism is still a matter of some difficulty. In those dwarfed patients whose growth and bone maturation are severely retarded, who show hypoglycaemic unresponsiveness in the insulin tolerance test, and who display some deficiency of thyroid or adrenocortical function or of both—the presumptive diagnosis can easily be accepted. There appear to be patients, however, who probably have some deficiency of growth hormone production and yet who do not show all these features. On the other hand, many dwarfed patients show both increased insulin sensitivity and hypoglycaemic unresponsiveness in the insulin tolerance test and yet fail to show the other features of hypopituitarism. Certainly our experience of the insulin tolerance test makes us unwilling to accept this as a diagnostic test for hypopituitarism.

The straight radio-immuno-assay of growth hormone (GH) appears unlikely to be of great help either in the diagnosis of hypopituitarism or in the differential diagnosis of short stature. The response of GH to insulin-induced hypoglycaemia (Hunter and Greenwood, 1964) promises to be of greater

diagnostic value. Our experience with this investigation is increasing and will be the subject of a separate report. There are obvious difficulties in its application to young children and doubtful results may be obtained (Kaplan, Abrams, Bell, Conte, and Grumbach, 1965). Where hypoglycaemia produces an unequivocal rise of GH or an undoubted failure of GH stimulation, the test is a valuable one in the differential diagnosis of short stature.

#### Effect of Human Growth Hormone on Lipid Metabolism

Hubble (1957) suggested that some children with hypopituitarism showed hypercholesterolaemia in the absence of frank hypothyroidism, and Lawson Wilkins came to agree with this. When HGH became available its effect on lipid metabolism was investigated.

The physiological effects of growth hormone on lipid metabolism have not yet been fully elucidated. Growth hormone is a specific agent of fat katabolism and produces both increased mobilization and utilization of fat. As has been shown by Rabinowitz, Klassen, and Zierler (1965) growth hormone produces an immediate increased uptake of fatty acids by muscle, and judging from the changes in the respiratory quotient these fatty acids are katabolized. Coincidentally the amount of glucose entering the muscle is reduced by one-third. These authors showed that after about 30 minutes there was an increased output of free fatty acids (FFA's) from adipose tissue, again with an earlier diminished entry of glucose into the fat. These changes presumably account for the depletion of fat in the carcasses of animals that have been chronically treated with growth hormone. It is probable that there is deficient lipogenesis in addition to increased lipolysis, but the evidence for this is more equivocal, and there have been differing reports in different environmental conditions.

Of these 10 children, 7 showed a depression of the levels of the serum cholesterol on HGH with a rebound on withdrawal (Table I). The five children who had levels above 200 mg. in the resting fasting state showed an average reduction of 57 mg./100 ml. in the HGH period and an average rise of 52 mg./100 ml. during the withdrawal period (Fig. 1). The children who showed this fall and rebound in cholesterol included both hypopituitary and non-hypopituitary dwarfs. 3 children showed a rise in cholesterol levels during the HGH period; and of these 2 were on thyroxine therapy (Cases 2 and 4). The third was the boy (Case 6) who had been confidently diagnosed as suffering from idiopathic

TABLE I  
Changes in Serum Cholesterol on HGH Administration  
(mean fasting levels in mg./100 ml.)

	Pre-HGH	HGH	Post-HGH	Δ HGH	Δ Post-HGH
Case 1	294	236	250	- 58	+ 4
Case 2	191	200	197	+ 9	- 3
Case 3	370	267	346*	- 103	+ 79
Case 4	168	193	187*	+ 25	- 6
Case 5	212	148	197*	- 64	+ 49
Case 6	136	158	161*	+ 22	+ 3
Case 7	279	230	280	- 49	+ 50
Case 8	272	259	336	- 13	+ 77
Case 9	178	156	226	- 22	+ 70
Case 10	184	166	207*	- 18	+ 41

\* Single estimation.

hypopituitarism but who never showed any hypercholesterolaemia: during the past two years there has been some evidence of depressed thyroid and adrenocortical function (see later).

It may be concluded that in the majority of our patients and in the doses used HGH depresses the level of blood cholesterol with a rebound after withdrawal of HGH. While this fall in the blood cholesterol is a specific effect of HGH, it is not specific for hypopituitarism. Indeed it occurred in a cretin who was given 10 mg. of HGH for 4 days. The cholesterol was 705 mg./100 ml. before HGH was given and it fell to 412 mg./100 ml. by the end of the HGH period. In a further month of thyroxine therapy the cholesterol had returned to

normal levels. Although we have not explained the hypercholesterolaemia which may occur in deficiency of GH we have demonstrated that exogenous HGH will regularly reduce the raised blood cholesterol to a normal level. It may also be concluded that while hypercholesterolaemia occurs in some hypopituitary patients, even in the absence of hypothyroidism, it may also occur in dwarfed patients not suffering from hypopituitarism, as in 2 of these 10 patients (Cases 7 and 8).

### Fasting Free Fatty Acids

None of our 10 patients—including those with hypopituitarism—had fasting resting FFA's below normal levels. After a fast prolonged to 16 hours in 6 patients, the level of fasting FFA's increased in all of them. The normal fasting resting levels of FFA's in our 6 hypopituitary patients can be held to confirm the observations of Dole, Bierman, and Roberts (1957) that control of the blood concentration of fatty acids proceeds normally in man even in the presence of hypopituitarism.

### Response to a Fat Load

In 6 of the 9 patients who were given a fat meal of 2 g. animal fat per kg. body weight the blood was cleared of fat more slowly (9 hours and beyond) during the HGH period. This effect was also shown in non-hypopituitary as well as in hypopituitary patients.

### Production of Pre-β Lipid

Pre-β lipoprotein, as detected by paper electrophoresis, appeared in the fasting state in our 10 patients during the 6-9 days of HGH treatment. It had not been present in sufficient quantity to be detected by this method in the control period. Earlier studies in our laboratory revealed that the presence of a marked pre-β band on paper electrophoresis corresponded to a very low density fraction (Sf 15-100) in excess of 125 mg. lipid/100 ml. serum, as measured by the ultracentrifuge (Pantelakis, Fosbrooke, Lloyd, and Wolff, 1964).

### Hypothesis for Effects on Lipid Metabolism

These three changes—the reduction in serum cholesterol, the delayed clearing of fat, the production of pre-β lipid—may all be a consequence of fatty acid mobilization by HGH. Pre-β-lipoprotein (Sf 15-100) contains about 50% triglyceride and 20% cholesterol, while β-lipoprotein (Sf 3-9) contains about 20% triglyceride and 40% cholesterol. Cornwell, Kruger, Hamwi, and Brown (1961) suggested that the relative quantities of these β-

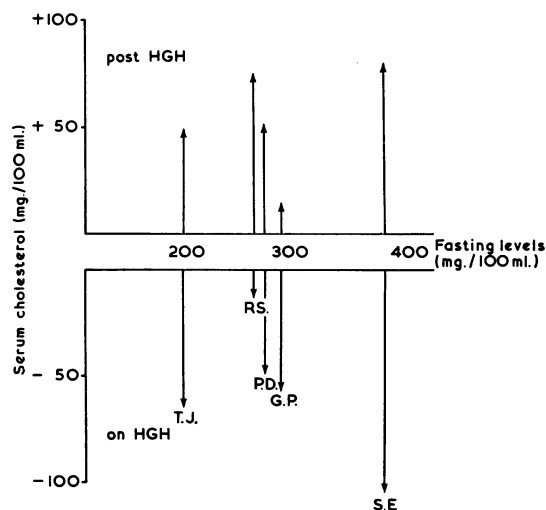


FIG. 1.—Changes in serum cholesterol levels before and after HGH administration in 5 patients whose fasting values were above 200 mg./100 ml.

lipoprotein fractions produced by the liver were, in part, influenced by the amount of FFA's circulating. High FFA levels result in increased hepatic uptake and, by conversion to triglyceride, stimulate the production of pre- $\beta$ -lipoprotein. This is apparently formed at the expense of 'true'  $\beta$ -lipoprotein.

These lipid studies will be the subject of a report by the investigators concerned in the research (Fosbrooke, Wolff, Lloyd, Chance, and Albutt). Our present objective is further to define by ultracentrifuge studies the quantitative and qualitative changes in lipid metabolism of HGH given in short term, high dosage.

#### Effect of HGH on Pituitary Target Hormones

There are some hypopituitary patients in whom failure of thyroid or adrenocortical function can be detected in the first few years of life: these include children suffering from perinatal brain damage (as in Case 2) and also children of the idiopathic type who show no evidence of brain damage (as in Case 4). In some patients who have been diagnosed with fair confidence as suffering from idiopathic hypopituitarism, there is in the second decade of life evidence of partial failure of thyroid or adrenocortical function or of both. This is evidenced by Case 6, a boy now aged 15 years, who, in the past two years, has shown some defect in the function of thyroid and adrenal cortex. The serum PBI has on several occasions been below 3.5  $\mu\text{g.}/100$  ml. and the  $^{132}\text{I}$  uptake is 12% at 60 and 90 minutes. Both values have demonstrated a normal response to TSH. Thyroxine therapy has produced no increased velocity of linear growth. The plasma cortisol was 4.4  $\mu\text{g.}/100$  ml. and showed a delayed response to corticotrophin stimulation. There was no increase of urinary 17-hydroxycorticosteroids on the second day of the metyrapone test, but the degree of inhibition (25%) of 11- $\beta$ -hydroxylase activity was below our required standard (30%), as estimated by the ratio of tetrahydro-S (THS) to 17-hydroxycorticosteroid (17HCS) output in the urine.

This sort of partial failure of target hormones could be the direct consequence of HGH deficiency, and it was interesting to see whether HGH in short-term high dosage had any recognizable effect on either thyroid or adrenocortical function. 3 patients were tested for thyroid function by serum PBI and radioiodine uptake tests before and during HGH therapy, and no significant difference was detected. Neither were significant differences observed in the urinary steroid patterns nor in the level of the plasma cortisol during HGH administration.

The possibility that a deficiency of endogenous

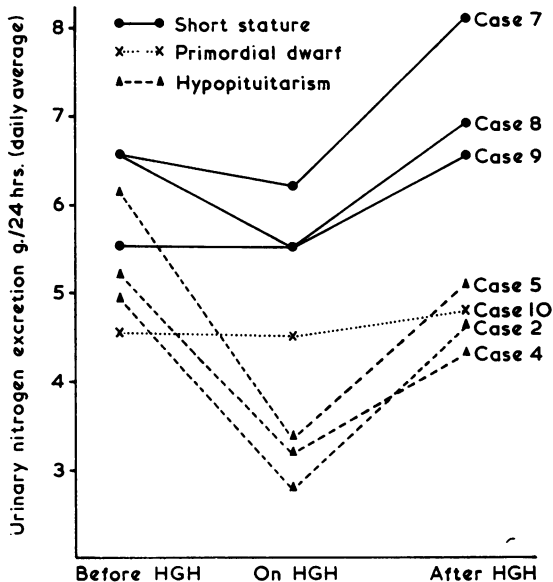


FIG. 2.—Urinary nitrogen excretion in 7 patients.

HGH does indeed slowly impair the function of the target organs is not necessarily denied by these short-term experiments.

#### HGH Nitrogen Retention Test

Estimations of urinary nitrogen were made throughout the control and HGH periods in 10 patients and in the withdrawal period in 7 patients. The nitrogen in each day's urine was separately estimated and the results averaged for each period. These results are given in Table II and Fig. 2.

The results are also given in terms of nitrogen retention, expressed as a percentage increase or decrease of the pre-HGH nitrogen excretion in the

TABLE II

Urinary Nitrogen Excretion Results  
(g./24 hr. daily average, number of  
days in brackets)

Case No.	Pre-HGH	HGH	Post-HGH
1	10.9 (6)	6.1 (9)	—
2	5.9 (6)	2.8 (9)	4.7 (5)
3	8.2 (7)	4.6 (5)	—
4	5.2 (8)	3.2 (5)	4.2 (4)
5	6.2 (6)	3.3 (7)	4.9 (2)
6	6.6 (9)	4.6 (7)	—
7	6.5 (8)	6.2 (7)	8.0 (7)
8	5.5 (8)	5.4 (6)	6.9 (7)
9	6.6 (5)	5.4 (8)	6.6 (5)
10	4.6 (5)	4.5 (6)	4.8 (3)

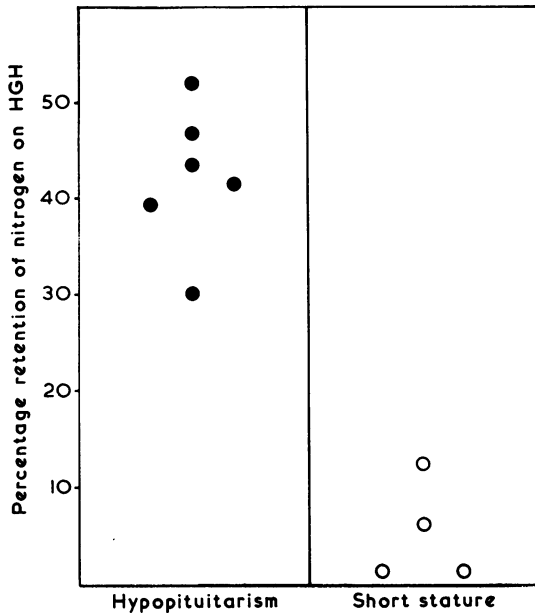


FIG. 3.—Percentage retention of nitrogen on HGH.

HGH and withdrawal periods. These percentages are given in Table III and graphically in Fig. 3.

The 6 hypopituitary children (Cases 1-6) showed a sharp fall in nitrogen excretion in the HGH period which, estimated as increased nitrogen retention, showed a percentage increase varying from 30 to 47%. The 3 non-hypopituitary dwarfs (Cases 7, 8, 10) showed very little diminution of nitrogen excretion. One patient (Case 9) in whom the diagnosis of hypopituitarism is still uncertain showed

TABLE III  
Nitrogen Retention in HGH Period and in Withdrawal Period (expressed as percentage of average daily pre-HGH excretion)

	On HGH (% retention)	After HGH (% retention)
<i>Hypopituitary Dwarfs</i>		
Case 1 .. .. .	+ 44	
Case 2 .. .. .	+ 47	- 20 (5)
Case 3 .. .. .	+ 44	
Case 4 .. .. .	+ 38	- 20 (4)
Case 5 .. .. .	+ 47	- 22 (2)
Case 6 .. .. .	+ 30	
<i>Uncertain Hypopituitary Dwarf</i>		
Case 9 .. .. .	+ 18	+ 0 (5)
<i>Non-hypopituitary Dwarfs</i>		
Case 7 .. .. .	+ 5	+ 23 (7)
Case 8 .. .. .	+ 2	+ 25 (7)
<i>Primordial Dwarf</i>		
Case 10 .. .. .	+ 2	+ 4 (3)

a degree of nitrogen retention intermediate between these two groups (18%).

The results in the HGH withdrawal period are of considerable interest. The 3 hypopituitary children had not returned to their pre-HGH level of nitrogen excretion in 2, 4, and 5 days, respectively—they were still retaining an increased amount of nitrogen as compared with their control period. The 2 non-hypopituitary dwarfs were excreting more nitrogen in the withdrawal period than in either the pre-HGH or the HGH periods. Case 7 lost 12.6 g. and Case 8 15.9 g. more nitrogen in the 7 days after HGH than they retained in the HGH period.

Case 9, the doubtful hypopituitary patient, had the same output of nitrogen in the post-HGH period of 5 days as in the pre-HGH period of 5 days.

The urinary nitrogen excretion in Case 10, the primordial dwarf, did not change significantly in either period.

The percentage nitrogen retention results in the HGH period, as set out in Table III and Fig. 3, may be compared with the results of Prader, Illig, Széký, and Wagner (1964). Their 12 hypopituitary patients showed an increased nitrogen retention ranging from 27 to 50%; in their 3 children of normal height it ranged from 12 to 29%; and in their 3 children of short stature it ranged from 8 to 15%. If the results in these 12 hypopituitary children are added to our 6 hypopituitary children the increased nitrogen retention ranged from 27 to 50% of the pre-HGH nitrogen excretion. Only one of their control children overlapped this hypopituitary range, and none of ours did. The nitrogen retention test is then a useful diagnostic test for hypopituitarism.

In considering the nitrogen retention in the withdrawal period in our 7 patients, it appears that the hypopituitary children take several days to return to their pre-HGH level of nitrogen excretion. In them it may be assumed that the administered HGH is still actively causing nitrogen retention.

The two children who showed a large increase in nitrogen excretion in the withdrawal period, despite little nitrogen retention during HGH administration, may be assumed to have experienced a suppression of endogenous GH which lasted for more than a week after withdrawing exogenous HGH. The same 'rebound' phenomenon was observed in two adult 'normals' as described in a Medical Research Council report (1959).

The primordial dwarf on whom exogenous HGH had little effect on nitrogen excretion may have a resistance to its normal action on nitrogen metabolism. Lipsett, Bergenstal, and Dhyse (1961) investigated 4 primordial dwarfs who all failed to

respond to HGH by nitrogen retention, though they showed increased urinary calcium excretion, as did our patient. (All our 10 patients showed increased urinary calcium excretion on HGH.)

The HGH nitrogen retention test requires further application in the investigation of children of short stature. Although it may not sharply differentiate children with partial growth hormone deficiency from children whose short stature is due to other causes, these preliminary results suggest that it will be very useful in doing so, especially when the results are considered in conjunction with the response of GH to hypoglycaemia. The effects on nitrogen excretion following the withdrawal of HGH may be as useful diagnostically as the degree of nitrogen retention in the period of HGH administration.

Prader and his colleagues used HGH in a dose of 2 mg./m.<sup>2</sup> body surface—a much smaller dose than our 10 mg. daily. Their dose was sufficient to differentiate hypopituitary children, but it may be that our larger dose is required to produce the suppressive consequences of endogenous hormone, which became evident in the withdrawal period.

We are now standardizing the test in 3 periods of 5 days each.

### Summary

Ten dwarfed patients whose short stature was of varying aetiology were studied by investigation of some of the metabolic effects of human growth hormone, 10 mg. being administered daily for a period of 5 to 9 days. The patients were maintained on a constant diet during a preliminary control period, while receiving HGH, and in 7 patients from 2 to 7 days in the post-HGH period. HGH produced a reduction in serum cholesterol, with a rebound on withdrawal, in 7; a delayed clearance of fat from the blood after a fat load in 9; and the appearance of pre- $\beta$  lipoprotein in the fasting state, as measured by paper electrophoresis, in all of them. The fall in serum cholesterol and the rebound on withdrawal of HGH has some relevance to the observation that hypercholesterolaemia occurs in some hypopituitary patients even in the absence of hypothyroidism.

No change was observed in tests of thyroid and adrenocortical function during the short-term high dosage administration of HGH.

Hypopituitary patients show a considerable retention of nitrogen on HGH administration, and we have confirmed the work of Prader and his colleagues that this provides a valuable diagnostic test for growth hormone deficiency. The measurement of urinary nitrogen excretion after the with-

drawal of HGH also promises to be a useful investigation in the differential diagnosis of short stature. Nitrogen excretion in the withdrawal phase in hypopituitary children returns slowly to its pre-HGH levels; two non-hypopituitary dwarfed children excreted much more nitrogen in the withdrawal period than they retained in the HGH period. One primordial dwarf showed a negligible change in urinary nitrogen excretion both in the HGH and in the post-HGH periods.

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## Appendix 1

### Methods

#### Lipid studies

- (1) *Serum total lipids*: Turbidimetric method of De la Huerga, Yesinick, and Popper (1953).
- (2) *Serum lipoprotein fractionation*: The paper electrophoretic method described by Salt and Wolff (1957).
- (3) *Serum total cholesterol*: Estimation essentially according to the method described by Sackett (1925).
- (4) *Plasma free fatty acids*: The titration method of Dole (1956) as modified by Trout, Estes, and Friedberg (1960).

#### Adrenocortical investigations

- (1) *Corticotrophin stimulation* (20 mg. b.d. for 3 days):
  - (a) Urinary 17-hydroxycorticosteroids as Silber-Porter chromogens (Silber and Porter, 1954). Method improved and modified by B. T. Rudd.
  - (b) Plasma cortisol measured by the fluorimetric method described by Rudd, Sampson, and Brooke (1963).
- (2) *Metyrapone test* (metyrapone 250 mg. b.d. for 1 day):
  - (a) Urinary 17-hydroxycorticosteroids as above.
  - (b) Tetrahydro-S estimated by the method of Henke, Doe, and Jacobson (1960). Method improved and modified by B. T. Rudd.

#### Growth hormone assay

- (1) Hartog, Gaafar, Meisser, and Fraser (1964).
- (2) Hypoglycaemic stimulation of growth hormone (Hunter and Greenwood, 1964).

**Glucose oxidase estimation of glucose.** Discombe (1963).

**Measurement of sella turcica.** Riach (1965). Modification of a method described by Haas (1954).

## Appendix II

### Case Reports

**Case 1.** A boy aged 17½ years. He suffered from tuberculous meningitis from 6 to 8 years of age and his growth failure was first noticed at the age of 12 years. The skull radiograph showed suprasellar calcification. He had epilepsy. His height was 60 in. (152 cm.) (height-age 13 years 4 months). He was pre-pubertal, and there were no secondary sexual characters. The bone-age was approximately 13 years. The area of the sella turcica was 71 sq. mm. (average for height 73.5 sq. mm.). There was no growth in sellar size in 3 years. There was no evidence of thyroid or adrenocortical failure. There was neither fasting nor non-fasting hypercholesterolaemia. The fasting growth hormone level was 4 µmg./ml., and there was no response to insulin-induced hypoglycaemia (blood glucose levels 29, 20, 33 mg./100 ml. at 15, 23, and 30 minutes, respectively).

**Case 2.** Aged 12½ years. The obstetric history suggested that this girl might have suffered perinatal brain damage. Epilepsy began at the age of 15 months. IQ 60. There was no evidence of adrenocortical failure but some evidence of hypothyroidism. There was neither fasting nor non-fasting hypercholesterolaemia. She had a severe degree of hypoglycaemia in the insulin tolerance test. Her height was 49.5 in. (125 cm.) (height-age 8 years 4 months). The bone-age was 9 years. The size of the sella turcica was 31.25 sq. mm. (the average for height 63.9 sq. mm.). She was on thyroxine therapy during the test period. The fasting level of growth hormone was 1 µmg./ml., and there was no rise following insulin (0.1 unit/kg. subcutaneously) induced hypoglycaemia.

**Case 3.** Aged 19½ years. Her slow growth and short stature were first recognized at the age of 4 years. At the age of 11 years she had intrasellar calcification, presumably due to a craniopharyngioma. There was some evidence of both adrenocortical and thyroid failure. There was no development of secondary sexual characters. Consistent and severe hypercholesterolaemia was present, which was not reduced by thyroxine therapy. During the trial she was maintained on thyroxine, cortisone, and methandienone. Her height was 48 in. (121 cm.), and there was nearly complete fusion of the skeleton. The area of the sella turcica was 88.75 sq. mm. (average for height 64.6 sq. mm.). The fasting growth hormone level was 0 µmg./ml.

**Case 4.** Aged 8 years. Cretinism was diagnosed on adequate clinical and biochemical evidence at the age of 9 weeks. Despite thyroid, thyroxine, and triiodothyro-

nine therapy, she failed to achieve the expected velocity of growth, though the metabolic consequences of hypothyroidism were corrected. She had mild hypoglycaemic attacks. There was neither fasting nor non-fasting hypercholesterolaemia. Her height was 38.5 in. (98 cm.) (height-age 3 years 6 months), and her bone-age was between 6 years 10 months and 7 years 10 months. The sella turcica was 12 sq. mm. (average for height 52.5 sq. mm.). The fasting growth hormone level was 1  $\mu$ mg./ml.

**Case 5.** Aged 11 years 10 months. This boy presented with spontaneous hypoglycaemia in his fourth year. At the age of 6½ years, his height-age was 3½ years, and his bone-age was 3½ years. His skeletal maturation was unduly accelerated by the use of a protein anabolic drug, and at the time he entered the study his height-age was 8 years and his bone-age 11 years. His adrenocortical function was normal, but he had evidence of a mild deficiency of thyroid function. There was non-fasting hypercholesterolaemia, but the levels of fasting cholesterol were within normal limits, i.e. below 250 mg./100 ml. There was increased sensitivity to insulin. The area of the sella turcica was 39 sq. mm. (average for height 67.8 sq. mm.). The fasting growth hormone level was 2  $\mu$ mg./ml., and there was no response to insulin-induced hypoglycaemia (blood glucose level was 15 mg./100 ml. at 20 minutes and 33 mg./100 ml. at 40 minutes).

**Case 6.** Aged 15 years 2 months. The impairment of growth velocity and his short stature were noticed by his parents at the age of 3 years. He had intermittent treatment with thyroid and with a protein anabolic drug without effect on his stature. He presented the typical appearance of idiopathic hypopituitarism and during the last two years he showed partial defect of thyroid and adrenocortical function. He had no hypercholesterolaemia. During the past year he showed commencing pubertal changes. His height was 53 in. (135 cm.) (height-age 9½ years). The area of the sella turcica was 55.5 sq. mm. (average for height 67.8 sq. mm.). The fasting growth hormone level was 7  $\mu$ mg./ml.

**Case 7.** Aged 10½ years. This boy was born at 32 weeks' gestation by breech delivery with extended legs. His birth weight was 5 lb. 6 oz. (2,409 g.). His mother first noticed his retarded growth at the age of 3 years. He had a good response to methandienone therapy given intermittently over 9 months. There was a family history of short stature. His height was 46.5 in. (118 cm.) (height age 6 years 9 months). There was no increased insulin sensitivity. Thyroid and adrenocortical function were normal. The non-fasting levels of cholesterol ranged from 237-333 mg./100 ml. and the fasting level was 278 mg./100 ml. The area of the sella turcica was 51.25 sq. mm. (average for height 64.1 sq. mm.).

The fasting growth hormone level was 3  $\mu$ mg./ml. and

rose during insulin-induced hypoglycaemia to 21  $\mu$ mg./ml.

**Case 8.** This boy, age 9½ years, was born weighing 3.5 lb. (1,586 g.) at 34 weeks' gestation. He had always appeared small from infancy. There was a family history of short stature. He had a moderate response in linear growth to methandienone, given intermittently for 9 months. His height was 45.75 in. (116 cm.) (height-age 6 years). There was no increased insulin sensitivity. He had non-fasting hypercholesterolaemia (average 333 mg./100 ml.) and fasting levels ranging from 248 to 296 mg./100 ml. The thyroid function was normal. The response to a water load was normal, the resting levels of urinary steroids and plasma cortisol were normal, the response to corticotrophin was normal, but the metyrapone test indicated a defective corticotrophin response. The sella turcica measured 70 sq. mm. (average for height 64.1 sq. mm.). The fasting growth hormone level was 8  $\mu$ mg./ml. and rose during insulin-induced hypoglycaemia to 17  $\mu$ mg./ml.

**Case 9.** He presented at 10½ years. His birth weight had been 9 lb. (4,082 g.), and there was no evidence of perinatal damage. His short stature was not noticed till he was 3 years of age. There was no family history of short stature. His response in linear growth to methandienone given daily for one year was only moderate.

His height was 47 in. (119 cm.) (height-age 6 years). There was no increased insulin sensitivity and no hypercholesterolaemia, non-fasting or fasting. Thyroid function was normal and the only abnormal result in adrenocortical function was to the metyrapone test which indicated a low adrenocortical reserve. The area of the sella turcica was 50.5 sq. mm. (average for height 65.7 sq. mm.).

The fasting growth hormone level was 7  $\mu$ mg./ml. and there was no rise during insulin-induced hypoglycaemia (blood glucose 22 mg./100 ml. at 20 minutes and 48 mg./100 ml. at 30 minutes).

**Case 10.** This boy presented at 8½ years. His birth weight had been 8 lb. 7 oz. (3,826 g.). There was no history of perinatal damage. When he was 6 months old he weighed only 11 lb. 8 oz. (5,216 g.). There was no family history of short stature, neither were there associated physical stigmata, or any evidence of endocrine abnormality. His facies had been described as 'pekinese', but he showed no characteristics of recognized syndromes associated with short stature. His growth curve travelled still further away from the third percentile from the age of 2 to 5 years despite thyroid therapy. Methandienone given for 1 year 9 months produced an acceleration of linear growth and greater increase of skeletal maturation. His height was 45 in. (114 cm.) (height-age 6 years). The area of the sella turcica was 61.5 sq. mm. (average for height 63.2 sq. mm.). The fasting growth hormone level was 12  $\mu$ mg./ml.