Papers and Originals

Growth Response of 26 Children with Short Stature given Human Growth Hormone*

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Human growth hormone (H.G.H.) causes some, but not all, dwarfed children to grow at a normal or greater than normal rate. In the most favourable circumstances children given the hormone may catch up so effectively that in the end they reach normal adult size. The precise sorts of small children who benefit and the amount and nature of the growth produced are still matters for research. During the past five years the Medical Research Council has obtained contributions of human pituitary glands from departments of pathology throughout the United Kingdom and has made available a limited supply of H.G.H. for clinical trials. This paper reports the first results, so far as growth in small children is concerned, of this co-operative venture. The number of glands received permits the treatment of only about 40 children at present dosage; there are undoubtedly far more children in the country than this who would benefit from treatment. In the light of the findings reported in this paper, therefore, we would urge pathologists and others to send still more pituitaries for extraction (the details of the procedure are given in Appendix I).

Patients

Table I gives particulars of the 26 patients whose growth has been assessed at regular three-monthly intervals. All were followed for at least a year before treatment, and all had at least one full year of treatment. One patient who developed antibodies to H.G.H. and ceased to grow was taken off at nine months. All measurements and all skeletal maturity ratings were done by a single anthropometrist (R. H. W.).

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The patients are arranged according to diagnosis and by increasing age within each diagnostic category. The three patients with postoperative craniopharyngioma had had their operations several years before H.G.H. treatment. They had evidence of failure of secretion of thyroid-stimulating hormone and A.C.T.H. as well as of H.G.H. All were on maintenance doses of thyroxine and cortisone, which were continued throughout H.G.H. treatment. It is possible that Case 21 should also be classified in this first section instead of where he is; he has not had a craniopharyngioma, but does have evidence of thyroid-stimulating hormone and A.C.T.H. failure.

The second section of Table I lists 16 patients with short stature of origin, strictly speaking, unknown. These are variously known as "idiopathic dwarfs," or, more recently, as "hyposomatotropic dwarfs" (Mason and Tanner, 1967), since we think their short stature is due to lack of secretion or of action of growth hormone, not necessarily combined with lack of other pituitary functions. The criteria according to which this diagnosis was made have been fully discussed by Clayton, Tanner, Newns, Whitehouse, and Renwick (1967). Briefly, such patients have no evidence of a gross lesion of the nervous system or of chromosomal defect, are more than 3.5 standard deviations below the mean height for their age, and have a bone age 65% or less of their chronological age. Cases 18 and 19 had bone ages a little less retarded than this, and Case 16 had had his bone age increased by anabolic steroids before entry to the trial. All except Cases 12, 18, and 19 had a lower than normal response to A.C.T.H., as measured by excretion of 17-hydroxycorticoids. Thyroid function, as assessed by protein-bound iodine or ¹³²I uptake, was normal in all except Cases 7 and 21. Growth hormone levels are not available for most of these patients, though since 1965 determinations of plasma H.G.H. in response to fasting and insulin have been a condition of entry to the trial, together with a short metabolic test of response to three days of H.G.H. administration.

In the third section of Table I are two probably small normal children who were treated early in the trial in the belief that they were hyposomatotropic dwarfs; we changed the diagnosis as we gained more experience of this type of patient. In the fourth section are two children with rheumatoid arthritis on high doses of corticosteroids; they were consequently stunted, and H.G.H. was given to see if it would overcome this. In the last section is a child with renal dwarfism, a child with gonadal dysgenesis, and a child who was originally thought to be a hyposomatotropic dwarf but who developed signs of an intracranial lesion during the period of the trial.

Table I gives the chronological age at the time of investigation and the bone age determined from a radiograph of the left hand and wrist.

In column 5 of Table I the dose of H.G.H. each successive year is given, and, under the dose, the total increment of stature in centimetres during that year. Thus Case 1 (0-24)

reads as follows: a first control year without H.G.H., then in the second year a dosage of 24 i.u. H.G.H. per week. This boy grew 4.1 cm. in the pretreatment year, and 7.1 cm. in the treatment year. Some patients have been treated continuously—for example, Case 10 had doses of 0-40-60-24-24—and some intermittently, such as Case 16, with doses of 0-45-0-12-0. The dose of H.G.H. varied from year to year, partly because the trial was planned that way, but partly also because different batches of H.G.H. turned out to have different strengths, and these strengths were not known in advance of treatment; hence 30 mg. of one batch amounted to 24 i.u./wk., while 30 mg. of another was only 12 i.u./wk. Where there was a change of batch during a given treatment the average dose over the year has been recorded. The figures in parentheses (10) refer to

a dose of unknown strength believed to be between 10 and 20 i.u. In all cases treatment was given by intramuscular injection of H.G.H. suspended in saline on two days each week; the dosages refer to international units received per week. Periods of less than a full year are indicated; in these the height response is recorded in centimetres per year, not as the increment during the actual time.

In the last column are further remarks. Though no systematic study of the occurrence of antibodies to H.G.H. was made, Dr. J. Székely kindly determined the level according to her haemagglutination technique (Székely, Hässig, and Prader, 1962) in a number of cases, and Dr. Barbara Clayton by the immuno-electrophoretic technique in others. In four cases of idiopathic dwarfism antibodies were found at a time when the rate of

TABLE I.—Patients Treated with Human Growth Hormone and Regularly Measured Each Three Months

Case No.	Sex	Chron. Age when Treatment Began*	Bone Age (T.W.) when Treatment Began	Dose of H.G.H. (i.u./wk. in Each Successive Year) and Height Gain in or per Year (cm.)	Remarks
<i>Craniopharyngioma (Postoperative)</i>					
1	M	14.3	10.4	0—24 4.1 7.1	0.1 mg. thyroxine and 5 mg. cortisone daily
2	F	16.7	11.8	0†—(10)—0†—30—0 2.1 4.0 2.0 6.7 0.9	0.2 mg. thyroxine and 10 mg. cortisone daily
3	F	17.8	10.1	0†—(10)—0†—30—0 2.9 4.3 0.2 6.7 1.4	0.2 mg. thyroxine and 10 mg. cortisone daily
<i>"Idiopathic" or Presumed Hyposomatotropic Dwarfism</i>					
4	M	2.1	1.0	0—18—18†—24† 5.2 19.3 15.1 2.8	Antibodies (haem.) 1 : 4,000 at ↓
5	M	2.1	<1.0	0—24—18—24 3.1 12.6 9.0 9.3	Brother of Case 10. 2.5 mg. cortisone daily
6	M	3.4	1.3	0—24 6.8 9.0	
7	F	3.4	1.6	0—18 3.0 15.3	0.1 mg. thyroxine daily
8	M	4.7	2.3	0—24—24 3.2 12.7 10.1	
9	M	4.7	2.2	0—12 3.1 11.2	
10	M	6.2	2.7	0—40—60—24—24 3.0 15.7 11.4 7.2 7.2	Brother of Case 5
11	M	8.6	5.1	0—12—24 4.6 8.4 7.9	
12	M	10.3	6.6	0—24†—24†—0 3.4 10.0 0.6 2.7	Antibodies (imm.) 1 : 80 at ↓; 1 : 2,560 at ↓
14	M	11.1	7.2	0—(10)—0†—30—0—12—0† 4.8 5.7 3.0 5.7 1.4 6.7 5.9	
15	F	11.7	5.3	0—24—12—24 1.4 12.9 8.6 8.9	
16	M	11.8	10.7	0—45—0—12—0† 2.9 3.9 2.2 4.2 3.3	
17	M	13.9	8.8	0—12—24† 0.7 8.6 7.8	
18	M	14.4	10.0	0↓—18†—24†—0† 2.0 8.9 3.4 7.1	Antibodies (haem.) 1 : 200 at ↓; (imm.) 1 : 3 at ↓
19	M	15.1	11.4	0↓—24†—0†—0† 2.4 3.2 1.0 2.4	Antibodies (haem.) 1 : 1,000 at ↓; nil at ↑
21	M	19.4	12.9	0—12—12† 4.9 10.4 8.7	0.3 mg. thyroxine and 5 mg. cortisone daily
<i>Probably Small Normal</i>					
22	M	6.4	4.5	0—24—0 5.5 5.4 4.6	
23	M	11.3	7.9	0—(10)—0†—30†—0 4.7 5.5 5.5 6.4 5.9	Twin
<i>On Corticosteroids for Rheumatoid Arthritis</i>					
24	F	9.8	Not rateable	0—12—48†—0† 4.4 6.2 3.3	
25	F	10.5	5.9	0—12—0 0.26	
<i>Miscellaneous</i>					
13	F	11.0	9.1	0—18—0 3.3 4.2 3.3	Gonadal dysgenesis XO/XXI
20	F	16.2	10.9	0—24—0 0.4 3.4 1.3	Pinealoma found after H.G.H. treatment
26	M	12.7	12.7	0—10—30—0 4.1 4.0 5.5 2.9	Renal dwarfism

* Refers to first full year's treatment—some early cases were previously treated for shorter periods.

† 6 months.

‡ 9 months.

growth sharply diminished, in conformity with the results of Prader, Wagner, Széky, Illig, Touber, and Maingay (1964). Case 4, for example, had successive quarterly rates of growth (cm./yr.) of 19.8, 20.8, 19.9, 16.5, 18.1, 13.7, and then 5.6. Serum taken at the end of this last quarter showed antibodies in high titre (1/4,000; haemagglutination). Growth in the two subsequent quarters was 0.0, 0.0. In Case 12 no antibodies were demonstrated by the haemagglutination technique, but a titre of 1:2,560 was obtained by the more sensitive immunoelectrophoretic technique at the time when growth dropped from about 10 cm./yr. to nearly zero. Case 10 had low-titre antibodies by the sensitive technique, which may have slowed down his response. Antibodies were looked for and not found in Cases 1, 7, and 15, who responded well throughout treatment, and in Cases 6, 13, 14, 16, 20, and 22, who never responded well. Since mid-1966 antibody levels have been estimated by this technique every three months in all patients in the trial. Each of the six batches of hormone chiefly used was associated with the production of antibodies in one or more cases, so little difference seems to exist between batches.

Methods

Growth Hormone.—The H.G.H. was prepared by a slight modification of the Raben method (Raben, 1959; Hartree, 1966). The yield is about 1 g. of powder per 350 pituitaries, the powder being some 40% growth hormone and 60% other material. It is free of measureable amounts of thyroid-stimulating hormone or gonadotrophic activity. The powder was ampouled in 10- or 5-mg. amounts, and the contents of one ampoule in normal saline were injected intramuscularly twice weekly. The potency was assayed by increase of body weight during 10 days in hypophysectomized rats compared with that caused by the international standard preparation. Apart from a few early doses, six batches of hormone were used in the trial, which within the limits of error could be regarded as of two different potencies—1.2 i.u./mg. (R5, 6, and 9) and 0.6 i.u./mg. (R4, 7, and 8). The i.u./wk. given in Table I have been calculated accordingly. The details of the potencies, as determined by Dr. Bangham and his staff, are given in Appendix II.

Growth Response.—The anthropometric methods used have been fully detailed and illustrated (Tanner, 1964); stature was measured with the child fully stretched on a counterbalanced digital read-out stadiometer, sitting height with the Harpenden anthropometer, and skinfolds with the Harpenden skinfold calliper (Tanner and Whitehouse, 1955). Only a selection of the anthropometric results are given here.

Skeletal maturity ratings, and hence bone age, were made by the Tanner-Whitehouse method, the standards for British children (Tanner, Whitehouse, and Healy, 1962) being used.

Results

Height Growth

The absolute rates of growth in stature on and off treatment are given in Table I. Because the growth rate of children varies with season of the year (see Tanner, 1962) periods of less than a year are in general unsatisfactory for determining a response, though of course a change of rate from, say, 2 to 20 cm./yr. is highly significant even if the periods concerned are only of three months. This is provided that the measurements have been made by a skilled anthropometrist; in the hands of unskilled personnel errors alone can generate these figures (see Mason and Tanner, 1967).

An example of a successful response to treatment is shown in Fig. 1. On the left-hand graph is plotted the height attained at successive ages, and on the right-hand graph the rate of growth, both in three-monthly periods (dotted lines) and averaged over successive whole years (solid lines). The details of such plots, and the method of construction of these standard charts for height attained and velocity of growth have been described elsewhere (Tanner, Whitehouse, and Takaishi, 1966).

The results in all the patients are displayed in Fig. 2 A-D. We wish to know whether the treatment has caused an acceleration in growth, and, if it has, whether the new velocity is high enough for the child to catch up to his normal fellows, either rapidly or in the long run. Accordingly we have plotted for

FIG. 1.—Case 10. Presumed hyposomatotropic dwarf. Left: height attained plotted against chronological age (solid joined dots) and against skeletal age (crosses). Right: rate of growth at three-monthly intervals (dotted line) and averaged over successive years (solid lines). Hatching indicates H.G.H. dosage in i.u./wk.

each child the velocity of growth in stature before and during treatment relative to the velocity expected for the chronological age of the child—that is, to the 50th percentile velocity at the child's age. As these children are nearly all retarded in bone age, one might argue that the "expected" velocity should really be the 50th percentile for their bone age rather than their chronological age. This makes no very substantial difference, however, except at puberty. At adolescence normal children have a spurt in growth (seen in Fig. 1). But only one of our patients enters adolescence, even of those with chronological ages 15 to 19. In consequence we have taken as the expected velocities the preadolescent figures of 5 cm./yr. for our boys over 12 years old and 5.5 cm./yr. for our girls over 10. This conforms well with their bone ages.

Fig. 2 is divided into four panels to make it easier to follow the individual patients. The children bear the same numbers as in Table I. Fig. 2, A and B, shows the children who have been on continuous H.G.H. treatment: Fig. 2 A shows younger children (2.1 to 4.7 years), Fig. 2 B older children (6.2 to 19.4 years). All have the diagnosis of hyposomatotrophic dwarf. The heavy vertical line marks the beginning of treatment, and the yearly velocities are plotted at the mid-year. Years in which treatment was given are plotted as open circles (O), and years without treatment as solid circles (●). Taking the 10 children in Fig. 2 A and B together, the average pretreatment velocity was 0.52 times that expected; in the first year of treatment it was 1.92 times expected, in the second year (7 cases) 1.62 times expected, in the third year (3 cases) 1.44 times expected. There was no obvious difference in response between the younger and older children. The individual curves show that the velocity response usually becomes a little less as treatment proceeds. This probably represents the usual diminution of catch-up growth seen when a child or animal reapproaches its normal growth curve (Tanner, 1963; Prader, Tanner, and von Harnack, 1963; Prader, Illig, Székely, and Wagner, 1964). None of these children, it must be added, has yet quite reached the 3rd percentile for height attained; but several are approaching it—for example, Case 10 in Fig. 1, left.

In Fig. 2 C the hyposomatotrophic patients treated intermittently are shown. Four (Cases 4, 12, 18, and 19—shown by broken lines in Fig. 2 C) were taken off treatment because they developed antibodies. The others were taken off treatment largely because it seemed of doubtful value. These cases are the failures, relative or absolute. Case 4 was a striking success for nearly two years and had actually reached the 25th percentile when he developed antibodies and ceased entirely to grow. Case 12 grew well during the first six months but then slowed right down as he developed antibodies. Case 18 also grew well for six months before developing antibodies; Case 19 developed (or already had) antibodies when treatment began and responded little.

Case 14 is interesting in that he responded to H.G.H., but only slightly. In each of his three years of treatment he grew faster than in the adjacent years off treatment; but the effect was too small to have practical importance; he remains a very small boy indeed. Case 16 is similar. It may be significant that these two boys resembled each other physically and were short but sturdy and muscled, in contrast with most of our hyposomatotrophic dwarfs.

Cases 13 and 20 are also illustrated in Fig. 2 C. Case 13 simply failed to respond to H.G.H. She was originally thought to be a hyposomatotrophic dwarf, but further investigation showed her to have the rare chromosome mosaic XO/XX₁, with a female-type buccal smear. Case 20 clearly responded to H.G.H., but only to the clinically useless extent of raising her velocity ratio from 0.1 to 0.6 of expected; off treatment it returned to 0.2. An unsuspected pinealoma was then demonstrated in the area of the pituitary, but whether this was responsible for the decreased growth and the lack of useful response to exogenous H.G.H. we do not know.

In Fig. 2 D are shown the three postoperative craniopharyngioma patients (solid lines). All responded. The dose of about 10 i.u./wk. was insufficient in Cases 2 and 3 to restore normal prepubertal velocity, but 30 i.u./wk. in both cases produced a velocity of 6.7 cm./yr. Case 2 reached the 40th

FIG. 2.—Ratio of velocity in stature to expected velocity of stature at the child's chronological age (if <10 in girls, <12 in boys, or to figure of 5 cm./yr. (boys) or 5.5 cm./yr. (girls) if beyond these ages). A and B: Hyposomatotrophic dwarfs on continuous H.G.H. treatment. C: Hyposomatotrophic dwarfs on intermittent treatment (solid lines) or developing antibodies (broken lines). D: Normal small children (broken lines), children with craniopharyngiomas (solid lines), or children on corticosteroid therapy (dotted line and Case 25). ●=No treatment. O=Treatment.

percentile for height and Case 3 the 10th before H.G.H. was stopped and sex hormone administration begun. Also in Fig. 2 D (broken lines) are the two patients we think are probably small normals. Neither showed any response to H.G.H. Case 23 was a twin separated at birth from his mother, who had active tuberculosis. Both he and his co-twin were very small when first seen at age 11, but both steadily caught up from this age onwards and the untreated twin had just as great a velocity as the treated.

Lastly, in Fig. 2 D are the two children (Cases 24 and 25) on heavy doses of corticosteroids. Neither showed much increase in velocity, though one (Case 24) did respond a little. Evidently the most important thing to do in such cases is to reduce the corticosteroid dose so far as possible.

Skinfolds

It seems that a good height velocity response to H.G.H. is nearly always accompanied in hyposomatotrophic dwarfs by an initial fall in the amount of subcutaneous fat measured over the triceps and under the angle of the scapula. This fall is usually lacking in those who fail to increase their growth rate. All 11 hyposomatotrophic dwarfs who had a good initial height response were above average in skinfolds before treatment. Their average percentile of triceps and subscapular folds combined was the 75th before treatment, and fell to the 50th at the end of the first three months of treatment. Thereafter the skinfolds tended to rise again, and this was particularly marked in those who developed antibodies and stopped growing. Of the four hyposomatotrophic dwarfs who did not respond to H.G.H. in height growth two were fat also, but two lean. None showed a significant drop in skinfolds on treatment. The two small normal children and the child with gonadal dysgenesis showed neither a height response nor a drop in skinfolds. A fuller account is appearing elsewhere (Tanner and Whitehouse, 1967).

Limb-Trunk Proportions

The proportions of limb-to-trunk length, and changes during treatment, were followed by plotting sitting height against stature on the standard charts in use at the Hospital for Sick Children Growth Clinic (Tanner and Whitehouse, unpublished). These charts give percentiles for sitting height at given stature irrespective of age. As a rule children stay at approximately the same percentile position as they grow, at least up to adolescence.

The hyposomatotrophic dwarfs appear to have a low sitting height for their stature; all 16 were at or below the 50th percentile, and nine were at or below the 25th. Furthermore, most of those who responded to H.G.H. did so relatively more in trunk length than in leg length. Of the 10 patients included in Fig. 2 A and B seven increased their percentile position during treatment and none decreased. Case 10, who for several years before treatment was between the 10th and 25th percentiles, increased steadily on treatment and by the end of four years was at the 60th percentile. Another (Case 21) increased from the 3rd to the 50th percentile in two years (he was on thyroxine and cortisone as well as H.G.H.). The craniopharyngioma patients, however, showed no change in position; their growth was fairly evenly distributed between trunk and legs, if anything with a tendency to greater leg growth—that is, in the opposite direction to the others.

Measurements of trunk length are by no means simple to take, and the standards available are not so well based as simple height standards. It seems clear, however, that this is an area which should be further explored in the H.G.H. trial, in relation to both differential diagnosis and response to treatment. A fuller report is in preparation.

Skeletal Maturity

One of the chief criteria for the diagnosis of hyposomatotrophic dwarfism is a delay in bone age, which in most cases is less than 65% of chronological age (Clayton *et al.*, 1967). The third column in Table I gives an indication of this.

When successful treatment with H.G.H. is begun the bone age begins to catch up just as does the height. We may consider the ratio of bone age velocity to the expected bone age velocity, just as for the height equivalent in Fig. 2. In the case of bone age, however, the expected velocity is always 1 "year" per chronological year, since bone age is defined this way. Thus a graph of simple bone age velocity in "years" per year resembles exactly Fig. 2. In the 10 hyposomatotrophic dwarfs with sustained good height responses illustrated in Fig. 2 A and B the average bone age velocity for the year before treatment was 0.66 "year" per year. In the first year of treatment it averaged 1.4 "years" per year.

The patients in Fig. 2 C are less uniform. Case 4 increased from a pretreatment figure of 0.0 to figures of 1.15 and 1.35 in the first two years, and fell to 0.40 when growth ceased as antibodies developed. Case 14, who consistently accelerated slightly in height growth each time he was given H.G.H., also consistently increased his bone age velocity; during three treatment periods it averaged 1.54, as against 0.37 in the corresponding three pretreatment periods. Case 16 showed no consistent acceleration on treatment either in height or in bone age, and neither did the two small normals nor the patient with gonadal dysgenesis.

It is important to know whether height growth or skeletal maturity increases faster under treatment. If skeletal maturity increased faster (as it may with certain anabolic steroids) then we would be in danger of stunting the child ultimately; if skeletal maturity increased less fast we would have nothing to fear from such an effect. Many investigators have dealt with this by calculating a "height age" and plotting this against bone age. There are, however, considerable objections to this, and we have proceeded more directly by comparing the velocity of each measure in terms of the expected increment of each in a normal child of the same chronological age. Thus we have calculated the ratio:

$$\frac{\text{bone age velocity/expected bone age velocity}}{\text{height velocity/expected height velocity}}$$

In seven out of the 10 sustained good responders this ratio was above 1 in the year preceding treatment, indicating that the height growth was being more affected than bone maturation by the lack of H.G.H. When H.G.H. was given the ratio dropped to below 1. Thus, although H.G.H. caused a catch-up in bone maturity as well as in height, the bone maturity catch-up was less intense. In the three youngest children, however, the reverse occurred, the bone age advancing less fast than height before treatment, and faster than height during treatment. Only a study of more cases will show whether this age difference represents something endocrinologically important or is simply due to sampling error. The poor responders again show rather diverse results, as do the normal small children.

The two girls with operated craniopharyngiomas showed very little gain in skeletal maturity during H.G.H. treatment, despite a good height response. The boy, on the other hand, returned to a normal rate of skeletal development during treatment. It seems likely that the interaction of growth hormone with other hormones, especially thyroxine, controls what happens to bone age when H.G.H. is given. But evidently there is no danger of premature epiphyseal closure in any of our cases.

Dose of Human Growth Hormone

We are not at present able to say much about the effect of different dose levels of H.G.H. on rate of height growth. The

basic data are given in Table I. Only nine children have been treated at two or more different dose levels for a full year. Three of these were children who responded very poorly if at all to any of our levels of dosage. Of the remaining six two (Cases 2 and 3) were craniopharyngioma cases, and both grew faster (6.7 cm./yr.) on 30 i.u./wk. than on a dose that was probably about 10 i.u./wk. (about 4.0 cm./yr.). Of the other four children two (Cases 11 and 15) responded a little more to 24 i.u./wk. than to 15 i.u./wk. when the natural decrease of catch-up is allowed for; and the other two, brothers, provide little evidence one way or the other. Compared with most other reports in the literature the growth rates we have obtained with 24 i.u./wk. are high, and we suspect that this may be somewhere near the optimal dose, at least in cases uncomplicated by corticosteroid administration. But this question clearly needs much more thorough investigation.

Discussion

All three patients with operated craniopharyngiomas grew well in response to H.G.H., and the two of them who have been treated for long enough reached normal height. Neither of the two normal small children responded. The two children on large doses of corticosteroids and the case of renal dwarfism also failed to respond to any significant degree.

The remaining 18 children were diagnosed as presumed growth-hormone-lacking dwarfs. Ten of these responded well to H.G.H. administration and continued to do so during uninterrupted treatment over periods of one to four years. But we have a further eight who benefited little if at all, and we need to inquire why. Four of these eight developed antibodies to H.G.H., three of them after a good initial response. Of the remaining four one was shown towards the end of treatment to have a pinealoma and another was a case of gonadal dysgenesis with chromosome mosaic and a normal buccal smear.

There remain two boys who simply failed to respond, and we think the diagnosis in these must be something other than hypsomatotropic dwarfism. They had normal birth weights and normal buccal smears. But their bone ages were not as much retarded as those of the responders, they were sturdier and more muscular in build, and they were the only ones whose sitting height was at the 50th percentile for stature. Clearly, further studies are needed to see whether a truly separate group of non-responding dwarfs exists.

Our results on growth in height in the operated craniopharyngioma patients are comparable with those reported by Raben (1965). Prader, Illig, Széky, and Wagner (1964) treated two operated craniopharyngioma patients and four children who corresponded closely with our "good-response" hypsomatotropic dwarfs. The dose used was between 10 and 15 mg. a week, which is likely to be a little below our dose, and the velocities reported over the first year of treatment are also somewhat below ours, though in general the two sets of results are very comparable. The same applies to the patients treated by Seip and Trygstad (1966). The results of Wright *et al.* (1965) on height growth are also generally similar to ours. Soyka, Ziskind, and Crawford (1964) gave small doses and obtained rather low velocities in their cases of hypopituitarism. So far as we know there are no critical studies on the effect of H.G.H. on bone age, and no previous reports on skinfolds or trunk/limb proportions.

Choice of Patients

The present series does not permit us yet to make firm recommendations about choice of patients, and the trial continues, with special emphasis at present on gonadal dysgenesis, dwarfs of low birth weight, and children with short stature of less degree than those so far investigated, as well as on cranio-

pharyngioma cases and presumed hypsomatotropic dwarfs of all varieties. It does seem clear that operated craniopharyngioma cases, if their growth is affected, will usually or always benefit from H.G.H., combined with any other necessary hormones, and may be expected ultimately to attain normal height, unless antibody formation should supervene. It seems fairly clear, too, that normal small children do not benefit from H.G.H. Cases of idiopathic dwarfism or hypsomatotropic dwarfs are in our present state of differential diagnosis still a mixed lot. Many respond well, and if caught early could perhaps be brought ultimately to normal stature. Some fail to respond for reasons we do not yet understand, and some develop antibodies and cease responding. Only further studies will clarify these questions.

Summary

We have studied the growth response of 26 children and adolescents with short stature or hypopituitarism treated with human growth hormone (H.G.H.). Each child was measured three-monthly for at least a year before treatment and for between one and four years of treatment, always by the same anthropometrist. Sixteen of the patients were presumed hypsomatotropic dwarfs—that is, children we suppose lack growth hormone but not other anterior pituitary secretions—aged 2.1 to 19.4 years. Three patients aged 14.3 to 17.8 had had craniopharyngiomas removed. Two patients we think, in retrospect, were normal small children. Two were cases of rheumatoid arthritis on large doses of steroids. There was one case of renal dwarfism, one of gonadal dysgenesis, and one of a pinealoma. Growth hormone was given by intramuscular injection of the Raben preparation in saline twice weekly at an average dosage in most instances of approximately 20 i.u./wk.

Of the hypsomatotropic dwarfs the 10 who responded well were growing in height at 0.52 times their expected velocity during the year before treatment, and accelerated to an average of 1.92 times expected during the first year of treatment. Seven of these cases had an average velocity of 1.62 times expected in the second treatment year. Four hypsomatotropic dwarfs developed antibodies to H.G.H.; three of them after six months of treatment, and one after responding very well for 18 months and reaching the 25th percentile for height. Two other supposed dwarfs responded poorly or not at all for reasons which are at present not clear.

The two normal small children did not respond to H.G.H.; neither did the patients on large doses of corticosteroids, nor the child with gonadal dysgenesis. The child with a pinealoma increased her velocity on treatment, but not to normal levels.

The three craniopharyngioma patients responded well, growing at a velocity of about 7 cm./yr. on treatment, in contrast with a pretreatment velocity of between 1 and 3 cm./yr. One was taken off treatment on reaching the 40th percentile for height, another the 10th percentile; the third continues.

A good height velocity response is nearly always accompanied by an initial fall in the amount of subcutaneous fat as measured by skinfold callipers.

All our hypsomatotropic dwarfs had below-average trunk lengths for their stature; and there is a distinct tendency for the H.G.H. growth response to be greater in the trunk than in the limbs.

These patients have a delayed bone age before treatment. Patients who have a good height response also show a marked increase in velocity of bone age. However, the acceleration of bone age is in most cases not so marked as the acceleration in height. There is accordingly no fear of closing the epiphyses before full growth in height has been attained.

At present pathologists in all parts of the U.K. contribute pituitary glands from necropsies. Enough H.G.H. is extracted to treat 40 patients a year. The number who might benefit from treatment is certainly much greater than this, and we

appeal to all pathologists to increase their contributions so far as they are able.

Note on Patients.—A number of these cases are described by Clayton *et al.* (1967). The reference numbers relate as follows:

This Paper	Clayton <i>et al.</i>	This Paper	Clayton <i>et al.</i>	This Paper	Clayton <i>et al.</i>
4 .. 3-1		10 .. 3-12		16 .. 3-17	
5 .. 3-2		11 .. 3-13		17 .. 3-24	
7 .. 3-3		12 .. 3-14		18 .. 3-21	
8 .. 3-7		14 .. 3-18		19 .. 3-25	
9 .. 3-11		15 .. 3-16		22 .. 1-10	

Appendix I

Pituitary glands should be stored in acetone and sent direct to Dr. Anne Hartree, Department of Biochemistry, Cambridge. A small sum plus the postage may be reclaimed by application to the Medical Research Council, 20 Park Crescent, London W.1, from whom further details of procedure may be obtained if required. Glands from persons of all ages are suitable.

Appendix II

Collectors of glands were instructed to put them in 20 ml. of acetone, which could subsequently be replaced by a smaller volume of acetone. Batches of glands were pooled and fractionated. The extract containing growth hormone was put in 20- to 60-g. batches, and then dissolved in 0.05 N NaOH, adjusted to pH 7.5 to 8.5 with 0.1 N HCl, and diluted to 10 mg./ml. After sterilization by filtration through a membrane of average pore diameter 0.45 μ the solution was freeze-dried in 1-ml. amounts in ampoules, which were then sealed. Each batch of ampoules passed the B.P. 1963 tests for bacterial sterility and freedom from pyrogens (at 5 i.u./kg. rabbit body weight).

The potency of each batch, compared with the international standard, is shown in Table II. The estimate of prolactin

activity is also given. Batches R5 to R9 were also assayed for antidiuretic activity, and, with the use of rats under a constant water load, found to have some 0.05 to 0.15 i.u./mg.

TABLE II

Batch	Growth Activity*		Prolactin Activity† (i.u. per Nominal 10 mg. of Growth Hormone‡)
	i.u. per Nominal 10-mg. Ampoule‡	i.u. per mg. (Specific Activity)	
R4	7.2 (5.2-10.2)	0.63	17.7 (10.8-29.1)
R5	11.0 (8.0-15.2)	?	22.9 (17.0-30.7)
R6	11.9 (8.8-16.9)	1.14	15.4 (0.76-186.2)
R7	5.6 (4.3-7.3)	0.83	11.5 (6.4-15.6)
R8	6.2 (4.0-9.4)	0.68	25.7 (14.9-44.4)
R9	12.1 (10.3-14.2)	1.23	74.8 (39.2-210.9)

* Increase over 10 days in body weight of hypophysectomized rats, compared with International Standard for Growth Hormone (bovine).

† Pigeon crop sac method using systemic injection, compared with 2nd International Standard for Prolactin (bovine).

‡ Confidence limits $P = 0.95$.

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Modification by Monoamine Oxidase Inhibitors of the Effect of Some Sympathomimetics on Blood Pressure

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The importance to clinicians of knowledge of interactions between sympathomimetics, whether taken as drugs or in food, and monoamine oxidase inhibitors has been self-evident since the accidental discovery in clinical practice that these interactions can cause not merely an unpleasant experience but even death. It is salutary to reflect that, though the interactions were predictable on theoretical grounds, and can be induced in animals, they were not in fact predicted, so that no warnings were given when the drugs went into clinical use.

Little formal experimentation in man has been done, probably because of the drama of the initial clinical experiences, and therefore little is known of the size of the risks of ordinary dosage of sympathomimetics.

The experiments reported here were undertaken to provide some knowledge of the magnitude of this risk from different kinds of sympathomimetic and different kinds of monoamine

oxidase inhibitor. They are few in number, not because they were thought to be particularly dangerous—careful observation in a clinical pharmacological laboratory with the ready availability of the α -adrenergic receptor blocking drug, phentolamine, was thought to render the experiments safe enough to be justified—but because it is not easy to find people willing to spend the necessary time in the laboratory as well as to take a monoamine oxidase inhibitor for one or more weeks.

It was thought unethical to attempt to perform the experiments on patients taking monoamine oxidase inhibitors for mental disorder.

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