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Catch-up growth induced by growth hormone in the craniofacial skeleton of the Snell strain of the hypopituitary dwarf mouse

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SUMMARY Immature Snell strain dwarf mice were treated with human growth hormone for 20 and 40 days, between the ages of 22 and 41 days and 22 and 61 days, respectively. Mature dwarfs were similarly treated for 20 and 40 days between the ages of 62 and 81 days and 62 and 101 days, respectively. These groups of treated mice were compared with untreated dwarfs and normal mice reared under the same conditions. The catch-up growth effected by human growth hormone on the craniofacial and somatic development of the Snell strain dwarf mouse at both immature and mature ages was considerable, overall being approximately 14 per cent.

Neurocranial parameters tended toward the values of normal mice achieving 89–98 per cent of normal growth. Viscerocranial parameters showed greater catch-up, from a lower start point, reaching 81–93 per cent of the control. This catch-up growth in mature mice (aged 82–102 days) was at a time when any substantial growth in either dwarf or normal mice has usually ceased.

Introduction

Patients with growth hormone deficiency have aberrant facial development with a saddled nose and protuberant frontal bones (Scharf and Laron, 1972); the maxilla and mandible exhibit retrognathism, which is more marked in the maxilla (Edler, 1979); the clivus is short and facial width is reduced, although the calvarium is of normal size and shape (Pirinen *et al*., 1994); and facial height, in particular posterior facial height, is reduced (Spiegel *et al*., 1971; Pirinen *et al*., 1994).

Restoration of growth by replacement therapy with manufactured growth hormone is an accepted part of clinical practice in children of short stature (Buchanan, 1988). Little is known about the effects of this growth hormone replacement therapy on the craniofacial region.

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For practical and ethical reasons it is not possible to perform a prospective longitudinal study of growth hormone-induced catch-up growth in the skulls of humans. The genetic defect of the Snell strain of mouse causes deficiency of all anterior pituitary hormones, including growth hormone (Snell, 1929). This results in dwarfism and has widespread inhibitory effects on the axial, appendicular and craniofacial skeleton (van Buul-Offers and van den Brande, 1985). Daily injections of growth hormone bring about catch-up in growth which approaches that of normal mice (Wallis and Dew, 1973; van Buul and van den Brande, 1978; van Buul-Offers and van den Brande, 1985). The term 'catch-up growth' was introduced to describe the increased growth velocity that occurs in children after a period of growth retardation when the cause of the retardation is removed (Prader *et al*., 1963). The potential for catch-up is a feature of animals that are immature in their skeletal development; mature animals lose the potential. Catch-up may

be achieved either by a rapid increase of growth velocity to supranormal levels or by a normal velocity prolonged beyond the time when growth has usually ceased.

The aim of this study was to investigate the catch-up growth induced by human growth hormone on the craniofacial skeleton of the Snell strain of hypopituitary dwarf mouse in immature and mature animals.

Materials and methods

Animal stock and management

The mice were from the colony at The Institute of Child Health, London. Dwarfs were bred from heterozygous phenotypically normal mice, to produce offspring at a ratio of one dwarf (dw/dw) to three normal mice in each litter. The animals were housed in a constant environment of 26°C; a relative humidity of 60 per cent, and light/dark cycles of 12 hours (Roberts and Blackwood, 1983). Normal and dwarf mice were reared together in mixed litters. After 10 days the animals were marked by ear punching. Food and water was available *ad libitum*. They were weaned and separated from the dams at 22 days. Subcutaneous injections of human growth hormone (hGH) Somatonorm (KabiVitrum Ltd, Uxbridge UB8 2YF, UK), 20 μg/g body weight, were administered daily in the scruff of the neck. Additional animals were reared so that mice dying prematurely could easily be replaced.

Experimental groups

Twelve groups of six animals were formed—a total of 72 mice. Normal mice were killed at days 22, 42, 62 and 102; dwarf mice were killed at days 22, 42 and 62.

Dwarf mice were treated when immature with daily injections of hGH (a) injected for 20 days from day 22 to day 41 and killed at day 42; (b) injected for 40 days from day 22 to day 61 and killed at day 62. Dwarf mice when mature were treated with daily injections of hGH (a) injected for 20 days from day 62 to day 81 and killed at day 82; (b) injected for 40 days from day 62 to day 101 and killed at day 102.

Saline injected dwarf mice were injected for 20 days with saline, from day 22 to day 41 and killed at day 42.

Specimen preparation and radiography

The mice were killed by asphyxiation in a carbon dioxide chamber, then decapitated and fixed in formaldehyde solution. Radiographs were taken with a Hilger micro focal unit (Watson and Sons, London, UK). The machine settings were 2.5 mA, at 23 kV for 50 seconds. The anode to film distance was 1 m. A 1 cm steel calibration rod was incorporated into the clear acrylic table on which the specimens were positioned for the taking of the radiographs. Dorso-ventral and lateral skull views were taken at a magnification of ×5. This magnification was achieved by adjusting the ratio of the anode–object and object–film distance to 83.3 and 16.7 cm, respectively. For each view the skull was orientated and held in position with Sellotape, so that for the dorso-ventral view the maxillary plane was parallel to the film plane. For the lateral view, to avoid superimposition and aid specimen positioning, the skulls were sectioned with an air rotor in the parasagittal plane and the smaller fragment of the skull discarded. The sagittal plane was then aligned parallel to the film plane. The whole body, minus the skull, was placed on the acrylic table and radiographed at ×1 magnification with the axial skeleton stretched into a straight line and the limbs orientated so that measurements could easily be made (Hughes and Tanner, 1970).

Digitization and analysis of radiographs

The computer software used was '3-D Comp version 6' (P.J. Scott and Co., London UK) with the computer linked to a Metrograph digitizer. The apparatus was calibrated by digitizing a metal ruler of known length. The cephalometric landmarks were derived from previous studies on rodents (Kiliaridis *et al.*, 1985; Engström *et al.*, 1988; Vilmann *et al.*, 1989). The cephalometric points and measurements used are defined below and illustrated in Figures 1 and 2.

Lateral skull radiograph

Rh rhinion—the most anterior margin of the nasal bones (ignore ossicles).

Na nasion—the midpoint of the external surface of the frontonasal suture.

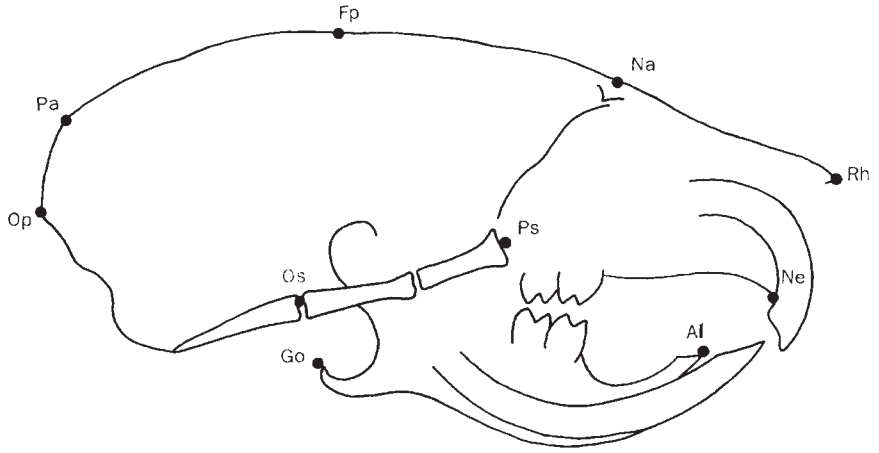

Figure 1 Cephalometric points used on lateral skull radiograph.

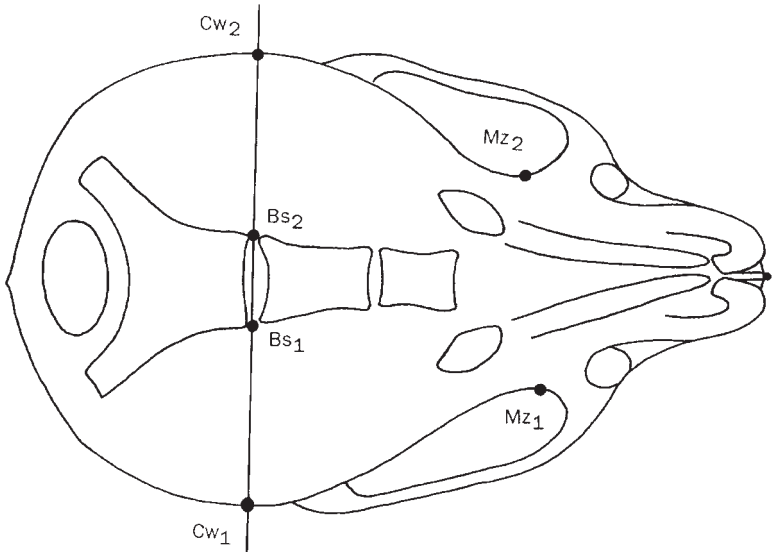

Figure 2 Cephalometric points used on dorso-ventral radiograph.

Fp fronto-parietal suture—the midpoint of the fronto-parietal suture on the ectocranial surface.

Pa parietal–interparietal suture—the midpoint of the ectocranial surface of the suture between the parietal bone and the interparietal bone (lambdoid suture).

Op opisthion—the most ventral point of the image of the dorsal margin of the foramen magnum.

Os occipito-sphenale—the midpoint of the basi-occipital basi-sphenoid synchondrosis midway between the ectocranial and endocranial surfaces.

Ps pre-sphenoid—the rostral edge of the pre-sphenoid bone midway between the dorsal and ventral edges.

Ne nasodentinal—the most anterior, inferior point on the image of the premaxilla lingual to the upper incisor tooth.

Al alveolare—the tip of the alveolar process lingual to the mandibular incisor.
Go gonion—the most posterior superior point of the angular process of the mandible.

Dorso-ventral radiograph

Mz1 maxilla, left—the intersection of the image of the alveolar crest on the buccal side of the left first molar and the image of the root of the malar process.
Mz2 maxilla, right—the intersection of the image of the alveolar crest on the buccal side of the right first molar and the image of the root of the malar process.
Bs1 midpoint of the outermost border (left), of the basi-occipital basi-sphenoid synchondrosis.
Bs2 midpoint of the outermost border (right), of the basi-occipital basi-sphenoid synchondrosis.
Cw1 calvarium, left—the intersection of a line drawn through Bs2 and Bs1 with the left ectocranial surface of the cranium.
Cw2 calvarium, right—the intersection of a line drawn through Bs1 and Bs2 with the right ectocranial surface of the cranium

Axial and appendicular (body) radiograph [not illustrated]

Hd humerus, distal—the middle of the advancing edge of endochondral ossification in the distal end of the humerus.
Hp humerus, proximal—the middle of advancing edge of endochondral ossification in the proximal end of the humerus.

Measurements used

Os–Fp neurocranial height.
Cw1–Cw2 neurocranial width.
Os–Ps section of cranial base length.
Ps–Ne maxillary length.
Mz1–Mz2 maxillary width.
Ps–Na–Ne angle between anterior cranial base and an anterior maxillary point.
Rh–Na nasal length.
Go–Al mandibular length.
Hd–Hp humerus length.

Error evaluation

Intra-operator reproducibility was examined by digitizing 11 randomly selected radiographs of each view on two occasions, at least 8 weeks apart. The data were plotted, and the method of Bland and Altman (1986), a paired *t*-test, and 95 per cent confidence intervals were used to assess differences. The error of the standard deviation was calculated to aid in the assessment of random errors (Houston, 1983).

Statistical treatment of data

The following were performed for the distances measured.

Comparison of all groups. Two sample *t*-tests were performed and an estimation made of 95 per cent confidence intervals on animal groups of the same age. For treated animals a one-way analysis of variance was performed on animal groups of the same age. The mean and 95 per cent confidence intervals were calculated for the following (group numbers are also given in Table 1) (i) young dwarfs treated for 20 days (groups 2, 6 and 8); (ii) young dwarfs treated for 40 days (groups 3, 7 and 9); and (iii) mature dwarfs treated for 40 days (groups 4, 7 and 11).

It is known that very little growth occurs in dwarf mice beyond the age of 42 days (van Buul and van der Brande, 1978; Tracey and Roberts, 1985; Jones and Roberts, 1988). For this reason group 7 (dwarf mice aged 62 days) was compared with controls and mature treated dwarfs at 102 days.

Percentage catch-up. Measurements of untreated and treated dwarfs were compared with normal mice at 102 days of age and the findings presented as a percentage of these normal mice. This was undertaken for each individual and the mean, standard deviation, standard error and 95 per cent confidence intervals calculated for each group. The groups were the same as above, i.e. after 20 days treatment at day 42, and after 40

Table 1 Comparison between normal, dwarf, immature treated dwarfs, mature treated dwarfs and saline treated Snell mice for skull length (Op–Rh).

Section A: Normals versus untreated dwarfs									
Normal	*n*	*x*	SD	Dwarf	*n*	*x*	SD	*P*	CI (95%)
Age 22 days (group 1)	6	96.2	1.3	Age 22 days (group 5)	6	77.2	3.8	<0.0001	15.0–23.0
Age 42 days (group 2)	6	107.3	2.7	Age 42 days (group 6)	6	80.7	1.9	<0.0001	23.5–29.7
Age 62 days (group 3)	6	111.1	2.7	Age 62 days (group 7)	6	80.0	2.9	<0.0001	27.5–34.8
Age 102 days (group 4)	6	112.8	2.0	Age 62 days (group 7)	6	80.0	2.9	<0.0001	27.1–33.6
Section B: 'Growth' control and 'saline' control comparisons									
Dwarf	*n*	*x*	SD	Dwarf (controls)	*n*	*x*	SD	*P*	CI (95%)
Age 42 days (group 6)	6	80.7	1.9	Age 62 days (group 7)	6	80.0	2.9	$P = 0.62$	–2.49–3.90
Age 42 days (group 6)	6	80.7	1.9	Age 42 days (group 12)	6	78.0	2.7	$P = 0.08$	–0.34–5.80
Section C: Untreated dwarfs versus immature treated dwarfs									
Dwarf	*n*	*x*	SD	Dwarf (treated)	*n*	*x*	SD	*P*	CI (95%)
Age 42 days (group 6)	6	80.7	1.9	Age 42 days (group 8) (20 days of hGH)	6	85.3	1.8	<0.002	–6.9– –2.2
Age 62 days (group 7)	6	80.0	2.9	Age 62 days (group 9) (40 days of hGH)	6	96.0	4.5	<0.0001	–21.0– –11.0
Section D: Untreated dwarfs versus mature treated dwarfs									
Dwarf	*n*	*x*	SD	Dwarf (treated)	*n*	*x*	SD	*P*	CI (95%)
Age 62 days (group 7)	6	80.0	2.9	Age 82 days (group 10) (20 days hGH)	6	91.4	2.2	<0.0001	–14.7– –8.0
Age 62 days (group 7)	6	80.0	2.9	Age 102 days (group 11) (40 days hGH)	6	97.5	2.0	<0.0001	–20.87– –14.5
Section E: Normals versus immature treated dwarfs									
Normal	*n*	*x*	SD	Dwarf (treated)	*n*	*x*	SD	*P*	CI (95%)
Age 42 days (group 2)	6	107.3	2.7	Age 42 days (group 8) (20 days hGH)	6	85.3	1.8	<0.0001	19.0–25.1
Age 62 days (group 3)	6	111.1	2.7	Age 62 days (group 9) (40 days hGH)	6	96.0	4.5	<0.0001	10.0–20.0
Section F: Normals versus mature treated dwarfs									
Normal	*n*	*x*	SD	Dwarf (treated)	*n*	*x*	SD	*P*	CI (95%)
Age 102 days (group 4)	6	112.8	2.0	Age 102 days (group 11) (40 days hGH)	6	97.5	2.0	<0.0001	12.7–18.0

days treatment of both immature and mature dwarfs at 62 days and 102 days, respectively.

Results

The comparisons between different groups of animals are shown in Table 1. To illustrate the pattern of differences only the data from one measurement are given, this being Op–Rh, which is the length of the skull (Figure 1). All other linear and angular comparisons gave similar results. These results (Table 1, section A) indicate

Table 2 Effect of 40 days hGH treatment on immature dwarf mice.

	Dwarf day 22	Dwarf day 62	Treated dwarf day 62	Difference between dwarf day 22 and dwarf day 62	Difference between dwarf day 22 and treated dwarf day 62	Net gain between dwarf day 62 and treated dwarf day 62
Distance	G	H	I	J	K	L
Op–Rh	80	72	86	–8	+6	+14
Na–Oi	87	80	92	–7	+5	+12
Os–Fp	94	85	89	–9	–5	+4
Cw1–Cw2	99	95	98	–4	–1	+3
Os–Ps	78	72	85	–6	+7	+13
Ps–Ne	75	64	82	–11	+7	+18
Mz1–Mz2	91	83	93	–8	+2	+10
Rh–Na	74	63	81	–11	+7	+18
Go–Al	85	71	86	–14	+1	+15
Hd–Hp	74	60	82	–14	+8	+22
Ps–Na–Ne	89	89	95	0	+6	+6
Weight	40	22	54	–18	+14	+32
Overall						+14

The values in columns G, H and I are expressed as a percentage of fully grown normal mice.

that at all ages from 22 to 102 days there was a highly significant difference between normal and untreated dwarf animals.

The comparisons between untreated dwarfs at 42 days and untreated dwarfs at 62 days comprise the 'growth' controls (Table 1, section B) and show that there was no growth after 42 days in untreated dwarfs. The effects of daily injections of saline for 20 days comprise the 'saline' controls and show no effect on growth of the animals.

The effects of daily injections of growth hormone on immature treated dwarfs (Table 1, section C) were highly statistically significant for both 20 and 40 days of treatment. In addition, the difference between treatment for 20 and 40 days in the immature treated dwarfs was highly significant ($t = 5.41$, df = 10, $P < 0.0003$).

The highly significant effect of daily injections of growth hormone on mature dwarf mice (Table 1, section D) is shown by the comparison of 62-day-old untreated dwarfs with 102-day-old mature dwarfs treated for 40 days.

The immature treated dwarfs exhibited considerable catch-up growth, but this had not reached normality after 20 days of growth hormone therapy (Table 1, section E) as there was a highly significant difference between normals and immature dwarfs treated for 20 days. Even after 40 days of growth hormone therapy there was still a significant difference between the normal animals and the immature treated dwarfs.

This pattern was repeated for mature treated dwarfs after 40 days of hGH therapy (Table 1, section F), when there was still a significant difference between the two groups. There was also no difference between the immature and mature groups of dwarf mice treated for 40 days with hGH ($t = 0.75$, df = 10, $P < 0.4728$). This is an important finding as it indicates that there is essentially no difference between the immature treated dwarfs and the mature treated dwarfs in the amount of growth after 40 days of growth hormone therapy. The results are also expressed as percentage gain (Table 2). For clarity, only the results of the 40 days of hGH treatment are shown in the table, although similar trends with smaller percentages were achieved with 20 days treatment of hGH. It is clear that the effects of treatment, shown in column L, are to increase growth by 4–32 per cent for different parameters. The greatest increase (32 per cent) was for weight, whilst the greatest linear increase was 22 per cent for humeral length (Hd–Hp). The greatest cranial increase was 18 per cent for nasal length (Rh–Na). These findings for mature

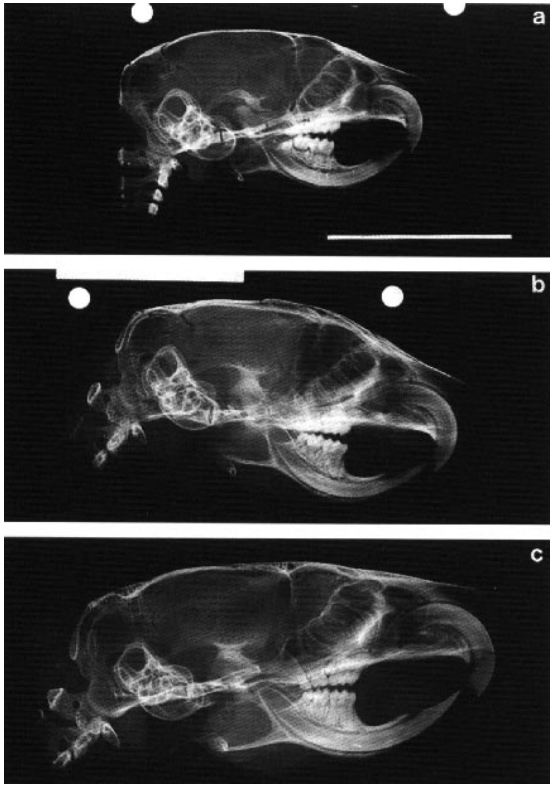

Figure 3 Lateral skull radiographs illustrating the effect on young dwarf mice of 40 days of hGH treatment. (a) Untreated dwarf; (b) immature dwarf treated for 40 days; (c) normal mouse. All animals are at the same magnification and were 62 days old at time of death. The rule bar in (a) is 1 cm.

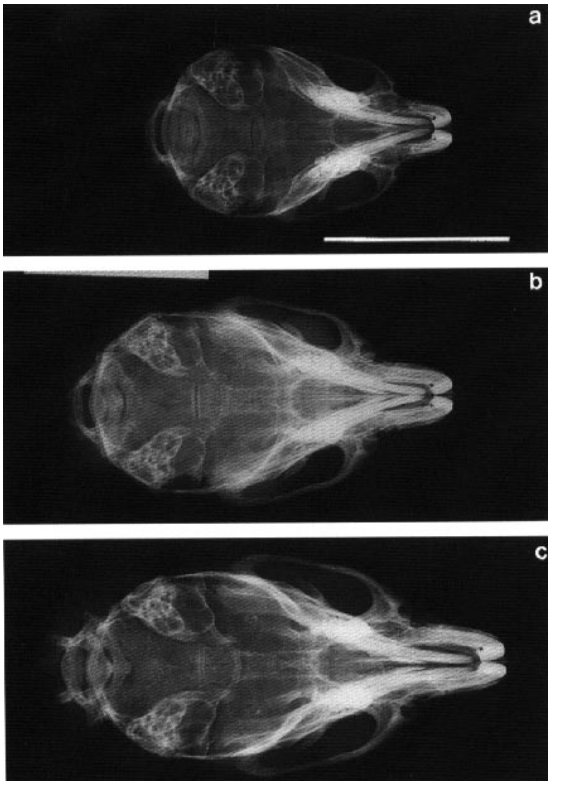

Figure 4 Dorso-ventral skull radiographs illustrating the same points as in Fig. 3 except (b) is a mature dwarf treated for 40 days.

dwarfs were similar for 20 and 40 days of hGH treatment.

The effects of hGH on growth of both immature and mature dwarf mice were highly significant but at no time did the treated dwarfs approach more than 86 per cent of the full growth shown by normal mice. This is illustrated with the data from Table 1, in which the skull length of untreated mice was calculated as 72 per cent of normals and 86 per cent for both immature and mature treated dwarfs. There was no difference in the percentage increase for immature and mature treated dwarfs. An example is given of the lateral skull view of animmature mouse treated for 40 days, an untreated dwarf and a normal mouse skull (Figure 3). A similar pattern was used for the dorso-ventral radiographs (Figure 4), although the dwarf skull in this illustration is a mature treated dwarf. The percentage differences given above are readily apparent.

Error evaluation

The calculated *P*-values were at an acceptable level (all greater than 0.05), all means and standard errors of the mean were close to zero in relation to the distances or angles measured, and the 95 per cent confidence intervals were close to each other and ranged about zero.

Discussion

The data for the normal mice verify the continued growth up to 102 days (van Buul and van den Brande, 1978). Dwarf mice cease growing by 62 days, hence for this study 22-day-old dwarf mice are designated as immature and 62-day-old mice as mature. The

reason for this classification is that linear growth usually ceases when the endochondral growth site(s) of an individual bone is/are obliterated by epiphyseal–metaphyseal fusion (Dawson, 1934). This has been confirmed for normal dwarf mice, in which there is almost no limb growth after 32 days of age (Tracey and Roberts, 1985). In dwarf mice, although growth virtually ceases, the endochondral growth sites remain unfused and capable of further growth provided that the stimulus of circulating growth hormone is re-established (Boettiger and Osborn, 1938).

A further factor to consider is the difference in growth between male and female mice. In the Long Evans strain of rat, skeletal development of males is more rapid and prolonged than that of females (Wright *et al.*, 1966; Roberts and Blackwood, 1983). In the present investigation no attempt was made to study these differences as the main purpose was to demonstrate the phenomenon of catch-up growth. The data illustrated in section A of Table 1 endorse this as the differences between normal and dwarf mice are highly statistically significant. In addition, the differences between treated immature and mature dwarf mice respectively, and the untreated dwarf mice (Table 1, sections C and D) also show highly significant differences. Further work would be justified to separate the male and female mice to estimate the differences in catch-up growth in relation to gender.

The degree of catch-up growth for both immature and mature dwarfs is similar. For this reason, the results from both immature and mature animals will be considered together. This is a unique finding as it is generally regarded that mature animals have much less potential for catch-up growth. The probable reason for the apparent anomaly in this study is that in the dwarf mouse the endochondral growth sites throughout the body do not lose their functional architecture (Jones and Roberts, 1988), and so, under the influence of recrudescent pseudosecretion (daily injections of human growth hormone), the dormant growth activity within the growth cartilages is stimulated into activity. The success of this pseudosecretion can be judged from the very high degree of catch-up growth achieved. As indicated, the similarity in catch-up growth between immature and mature animals demonstrates the remarkable ability for endochondral growth sites throughout the body to respond after a period of dormance, provided that the architectural structure of a functional endochondral growth plate is maintained.

The difference in catch-up growth between neurocranial and viscerocranial growth is clear, with the neurocranial measurements increasing by only 3, 4 or 10 per cent, with viscerocranial measurements increasing by 10–15 per cent (Table 2). This difference is at first perplexing but it is recognized that neurocranial growth is more advanced in very young rodents such as the laboratory rat, with over 75 per cent occurring before weaning (Young, 1959). However, the neurocranium still shows signs of catch-up, either by appositional growth or by renewed sutural growth with a small but statistically significant amount of growth (see Table 2).

The bones of the viscerocranium, largely of intramembranous origin, not only continue to develop into adult life but, as shown here, have a large potential for catch-up growth in response to growth hormone therapy. This may be the influence of intramembranous elements, but it is more likely that this catch-up in the viscerocranium is the result of the influence of cartilaginous elements, including those of the mandible, the nose and especially the cranial base (spheno-occipital synchondrosis). These elements have an important role in the craniofacial development of man as well as the Snell strain of mouse (Roberts and Lucas, 1994).

Endochondral ossification is readily stimulated by human growth hormone, and hormone deficiency is known to affect endochondral ossification more markedly than appositional growth (Urist, 1972). In untreated humans with either deficient or excessive growth hormone, the cartilaginous growth sites of the cranial base and mandible, as well as the sutural and appositional facial growth mechanisms, are affected (Pirinen *et al.*, 1994).

This late catch-up growth is after the time when both normal and dwarf mice do not usually show any substantial growth, and is an example of both re-stimulated and prolonged

growth beyond the time when normal growth has stopped.

In dwarf mice, although growth stops early, the epiphyses of long bones, including the humerus, do not fuse until late in life, if at all (Dawson, 1934). The cranial base synchondroses appear to be more radiolucent in mature dwarfs when compared with mature normal mice, and therefore have not undergone bony fusion. Interestingly, patients with isolated growth hormone deficiency exhibit a delay in puberty, a lack of epiphyseal closure and a continuation of growth into the third decade (Kaplan, 1975).

Conclusions

1. Human growth hormone is effective at stimulating catch-up growth of immature Snell dwarf mice over a 20 day period (between days 22 and 41) and a 40 day period (between days 22 and 61). There is an overall catch-up of 14 per cent.
2. Treatment is particularly effective on nasal, maxillary, mandibular and humerus lengths, elements due largely to endochondral ossification.
3. Human growth hormone is effective at stimulating catch-up growth of mature Snell dwarf mice over a 20 day period (between days 62 and 81) and a 40 day period (between days 62 and 101). There is an overall catch-up of 14 per cent.

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