Facial Growth Response to Human Growth Hormone in Hypopituitary Dwarfs

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Orthodontists are interested in retarded facial growth. When a Class II dental malocclusion patient presents with a retardation of growth, it is a difficult treatment problem if facial growth is slow or in a downward and backward direction. The orthodontist counts heavily on the pubertal growth spurt to speed treatment and enhance the final result. The following study was undertaken to utilize the rare opportunity to document the craniofacial growth occurring during a growth spurt initiated by administration of human growth hormone (HGH) to a group of pituitary dwarfs.

Human growth hormone is a protein which has a single polypeptide chain of 188 amino acids. Its blood level is determined by a radioimmunoassay. The radio-assay for HGH was used by McKusick[1] for dwarfs with sexual ateliosis. He found their blood deficient in growth hormone. He defined sexual ateliosis as a growth hormone deficiency only. He stated that some sexual ateliosics may have inherited their dwarfism as a recessive trait.

Panhypopituitarism, Gilford's asexual ateliosis, is a dwarf condition deficient in pituitary gonadotropins, thyrotropin, and ACTH in addition to a deficiency in growth hormone. Consideration of a genetic etiology in the asexual type is very rare. McKusick stated that panhypopituitarism can be successfully treated at any age with HGH due to the fact that the sutures and epiphyses remain open. The sexual ateliosics have retarded but complete suture closure and treatment is possible only at earlier ages.

In a review of HGH administration studies to children and adults, Ruben[2] and Finkel[3] found that growth hormone affects protein, fat, carbohydrate and electrolyte metabolism. The same effects were seen by Vest et al.[4] when they administered HGH to infants; however, the magnitude of change was much less in their infants than in the children and adults of the earlier studies. The poor response was postulated to be caused by a general lack of end-organ response to the hormone.

It is generally agreed that the slow and retarded development of a hypophyseal asexual dwarf may continue until 40 to 50 years of age.[5] Most asexual dwarfs remain sterile and many have a microanomaly in the region of the anterior lobe of the hypophysis. Dentally, the teeth are of normal size but retarded in eruption by about 25%[5-12] Although the maxilla and mandible are both retarded, the mandible is retarded more due to lack of ramus growth.[9,10] There is a general underdevelopment of the width and depth of the face[9] and the bone age or skeletal development is retarded about 50%[5-13] Markus[6] maintained that dwarfs retain the childlike convexity of the face even in older age and found numerous types of malocclusion present.

Many different types of supplemental therapy have been tried in the past on pituitary dwarfs with little success.

From the Department of Orthodontics, Univ. of Minnesota, and the Mayo Clinic.

Thyroxin, gonadotropins, and animal growth hormone along with impure extracts of the human pituitary, all have had very little effect on altering the retarded growth of a dwarf.

A national study was established to administer and evaluate the effects of various HGH therapies. The agency alotted HGH to those patients who best qualified and therefore would benefit the most from the limited supply of hormone. The Mayo Clinic Pediatric Department administered the HGH and medically evaluated the patients reported in the portion of the national study reported here.

Methods and Materials

Nine hypopituitary dwarfs at the Mayo Clinic pediatric department were accepted in the national study due to significant retardation in growth as evaluated by clinical and laboratory results.

The patients ranged in age from 8 3/12 years to 19 10/12 years at the start of the treatment. The nine patients were part of a group of pituitary dwarfs which were under evaluation for several years. Pretreatment cephalometrics were available on all nine patients over a 3-4 year period. Six implants were placed in each of four patients, three in the maxilla and three in the mandible.[15-18] Models, cephalometric radiographs and panoramic radiographs were taken every six months for a period of 18-24 months from the time treatment was started. Four of the nine patients had a low PBI and received synthetic thyroxin. Three of the four HGH and thyroxin patients were randomly chosen to receive cortisone supplemental therapy. Thyroid hormone replacement was considered adequate as indicated by PBI during therapy. HGH was administered intramuscularly in the amount of two units three times a week. Cortisone was administered in the amount of 5 mg four times a day and synthetic thyroxin (thyroid) 0.1 mg per day. Treatment in all patients was stopped after 18 months for a six-month period of evaluation. Further intermittent treatment was proposed for all nine patients.

Directional facial growth and corresponding soft-tissue changes were evaluated by superimposing serial radiographic tracings on the sella nasion line. In the four implanted patients, maxillary and mandibular growth was evaluated by superimposing each jaw separately on the implants. In those patients without implants, individual jaw growth was estimated by superimposing on landmarks that are known to change very slowly. Implant methods have shown the lingual, periosteal, and endosteal surfaces of the mandibular symphysis are fairly stable. The inferior alveolar canal is also a very stable landmark. Mandibular notch and coronoid process were traced from lateral head X-rays with the mandible wide open and used for serial superposition of the mandible. Maxillary superpositions were done by best fit of the total maxilla in nonimplanted patients. Measurements of arch width and arch length changes were made from plaster models accumulated every six months during treatment. Dental age[12,20] was determined from panoramic radiographs made at six-month intervals. Keller[12] made pretreatment dental age evaluations according to Moorrees[20] on some of the same dwarfs in his study but could not establish a change. This perhaps was due to HGH therapy over too short a period to notice any significant change. A one-year treatment interval is used to determine increment change in the present study. Bone age or skeletal development was obtained from wrist plates[21] taken at yearly intervals during therapy.

TABLE I

Patient	Facial Plane Start	Facial Plane 1 yr	Ang. of Convexity Start	Ang. of Convexity 1 yr	Y Axis Start	Y Axis 1 yr	ANB Start	ANB 1 yr	Mand. Plane to SN Start	Mand. Plane to SN 1 yr	Upper Incisor to N-Po (mm) Start	Upper Incisor to N-Po (mm) 1 yr
#1	85	+4	14	—6	56	—2	2	—1	37	—1	7	—2
#2	81	+2	11	0	60	—2	1	+1	40	—4	8	0
*#3	81	+1	13	—1	60	—1	6	—1	41	—1	9	—2
*#4	85	+3	15	—2	57	—2	8	—3	28	—1	11	0
#5	86	+2	11	—1	55	0	5	—1	27	—3	3	0
*#6	81	+2	13	—2	60	—1	7	0	37	—2	7	+2
#7	86	+2	9	—1	58	—4	4	0	32	—4	6	+1
#8	84	+5	2	+1	57	—2	—1	+2	30	—2	5	—1
*#9	79	0	14	—2	70	+1	6	—1	46	+2	8	—1
$\bar{X}$		+2.33		—1.75		—1.44		— .44		—1.78		— .33
S.E		1.5		1.93		1.42		1.42		1.58		1.75
Prop. Chg.		.89		.78		.78		.56		.89		.44
"p"		.01		.08		.08		.		.01		

*Implants present.

Results

The changes observed in these patients receiving human growth hormone are analyzed as craniofacial changes determined from superimpositions of serial cephalograms on cranial base landmarks. These changes represent the sum total of all dental and facial changes that occurred relative to the cranial base. Local changes of the teeth, pterygomaxillary fissure, and condyle relative to the respective maxillae and mandibles were recorded by superpositions of the maxillae and mandibles on implants or structures within the maxilla and mandible. Implant superpositions also demonstrated absolute growth changes of each maxilla and mandible. Changes in dental arch dimensions and eruption patterns were also evaluated using serial plaster casts and panoramic radiographs.

The cephalometrically measured facial skeletal changes that occurred relative to the cranial base (SN) over a one year period of HGH therapy are shown in Table I. In all patients the magnitude of the anterior component of growth was greater in the mandible than in the maxilla. Statistical analysis of the six cephalometric landmarks after one year of treatment revealed a general decrease in facial convexity; all patients showed changes tending to lessen convexity in four of the six parameters measured (Figs. 1-9). The upper first molar vertical growth coupled with the condylar growth vector created extreme anterior vertical height changes in patient #9. This growth pattern produced a very steep mandibular plane for this patient and, during therapy, Downs' angle of convexity and Y axis decreased, and the facial plane increased.

Measurements of three dental cephalometric landmarks (Table II) showed that the directional dental changes were not as consistent as facial changes. The apparent uprighting of the mandibular incisors over the year of treatment was not significant as measured in relation to the mandibular plane. Larger increments of vertical growth at the mandibular condyle relative to the anterior dentoalveolar region did produce a significant decrease in the mandibular plane. This movement carried the mandibular incisors into a more upright position relative to the maxillary incisors. This change is further substantiated by the significant

TABLE II

Patient	$\overline{1}$ to Mand. Plane		$\frac{1}{\overline{1}}$ Angle		$\underline{1}$ to A-Po (mm)	
	Start	1 yr	Start	1 yr	Start	1 yr
#1	85	+1	139	—3	4	—1
#2	93	0	131	+8	7	0
*#3	95	—2	120	+4	9	—2
*#4	105	+1	118	—2	7	+1
#5	101	+2	126	+1	3	0
*#6	106	—10	126	+2	8	—2
#7	95	—3	133	+2	5	—1
#8	88	—8	130	+15	5	—1
*#9	90	—4	134	+4	4	0
$\overline{X}$		—2.56		+3.44		—.67
S.E.		4.2		5.4		1.0
Prop. Chg.		.56		.78		.56
"p"				.08		

*Implants present.

reduction in the interincisal angle. The upper incisor, as measured to SN, is not included in the tables, but this parameter both increased and decreased.

Individual maxillary and mandibular growth changes as revealed by superimpositions of each jaw independently over a year of therapy were represented by predominantly sutural and condylar growth (serial tracings patients #1 and #9). The implanted patients (#3, 4, 6 and 9) precisely revealed that anterior changes were the result of surface additions on the maxillae and the mandibles plus specific dentoalveolar, sutural, and condylar growth. The vertical displacement of the maxilla seen in the craniofacial tracings shows changes that can only be associated with growth in the facial sutures and nasal septum. The mandible shows some inferior border and sigmoid notch additions but the major

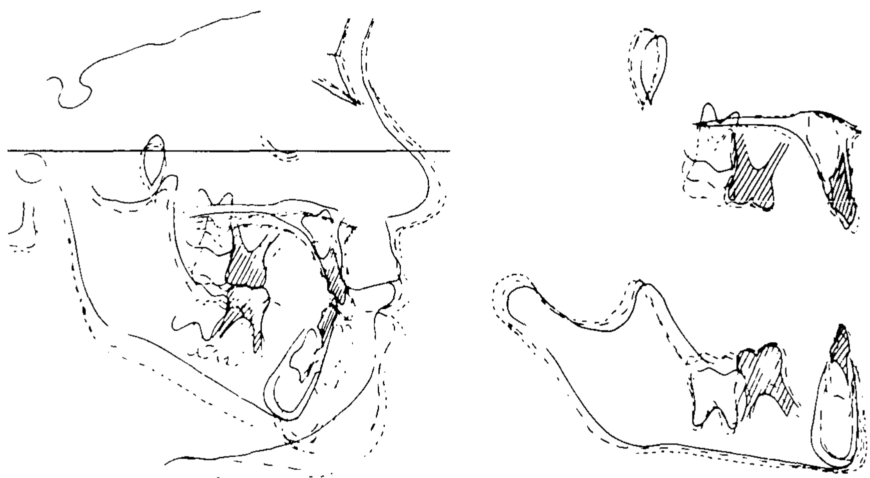

Fig. 1 Male, chron. age 8 3/12 yrs., bone age 2 8/12 yrs., dent. age inc. = 1 yr., height inc. 1 yr. = 4¼", weight inc. 1 yr. = 6 lbs., head circ. 1 yr. = 1.3 cm. HGH administered for 18 months + 6 months after HGH stopped. No other supplement.

Composite tracings during the first 16 months of the 18 month administration of human growth hormone. The subsequent one year and 1.5 year cephalometric tracings are superimposed on SN at S. The individual maxillary tracings show a comparison of tooth movement and pterygomaxillary fissure movement as shown by best-fit superpositions on the maxilla itself. The mandibular composite shows the tooth movement and mandibular growth during administation of human growth hormone by superpositions on the mandibular canal and internal symphyseal line. Strong vertical and anterior components of growth are demonstrated in the individual maxillary and mandibular composite tracings.

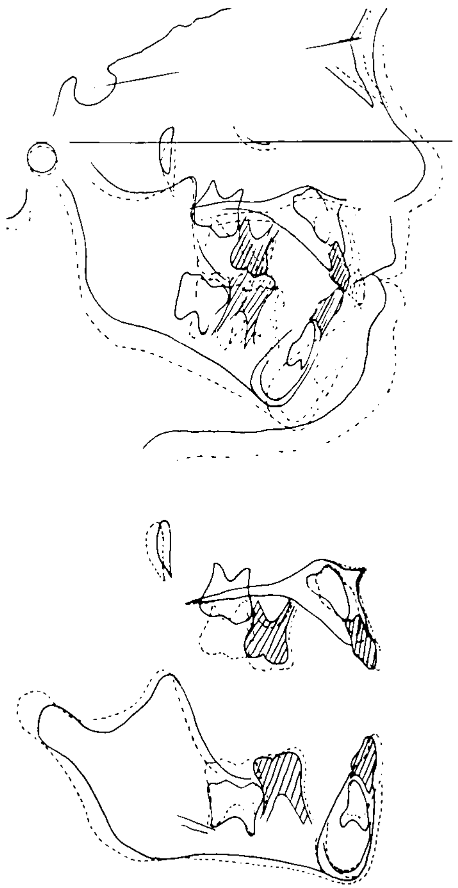

Fig. 2 Male, chron. age 7½ yrs., bone age 3 0/12 yrs., dent. age inc. = 2 yrs., ht. inc. 1 yr. = 5¼″, wt. inc. 1 yr. = 10 lbs., head circ. 1 yr. = 1.4 cm. HGH administered for 18 months + 6 months of no HGH. No other supplement.

Tracings during the first 16 months of the 18 month administration of human growth hormone. Superimposition demonstrates growth during the administration of human growth hormone between 7:6 years and 9:0 years. The upper maxillary tracings show a dentoalveolar movement and pterygomaxillary fissure movement during the mixed dentition stage. The mandibular composite shows the condylar growth in amount and direction as superimposed on mandibular canal and symphysis. Forward mandibular rotation is the result of a posterior vector of large magnitude in the condyle with lesser amounts of vertical components in the dentoalveolar regions.

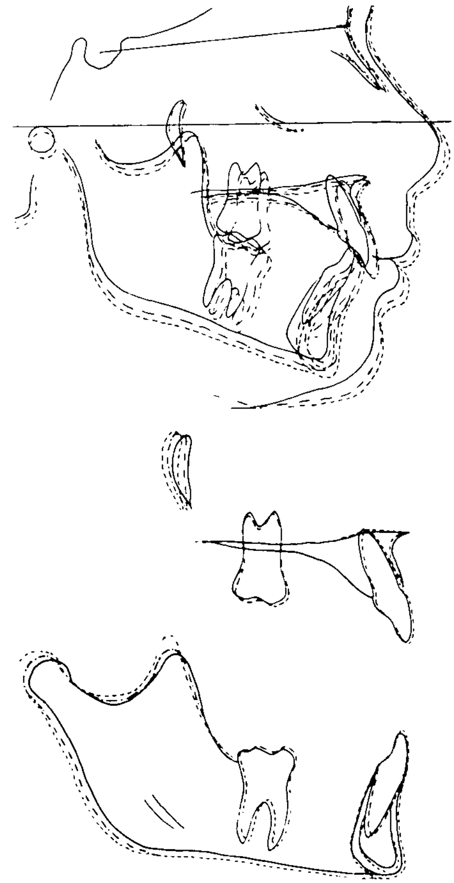

Fig. 3 Male, chron. age 12½, bone age 3 0/12 yrs., dent. age. inc. = 1 yr., ht. inc. 1 yr. = 4½″., wt. inc. 1 yr. = 6½ lbs., head circ. 1 yr. = 1.2 cm. Implants, HGH administered for 12 months—still on hormone. Thyroid trt. was tried for 1 year at 5 yrs. age, no success in growth.

Tracings of patient #3 during the first 13 months of the 18 month administration of the hormone. The tracings of the patient at 12:0 years, 13:0 and 13:6 are superimposed on SN at S to show the growth during treatment with human growth hormone. Maxillary tracings are superimposed on implants according to Björk to demonstrate tooth and pterygomaxillary fissure movement. Mandibular growth as represented in the mandibular superposition on implants depicts condylar and coronoid process growth during the experimental period. The overriding anterior vector of mandibular growth is the result of an anterior vector of condylar growth with a small concomitant vertical dentoalveolar growth.

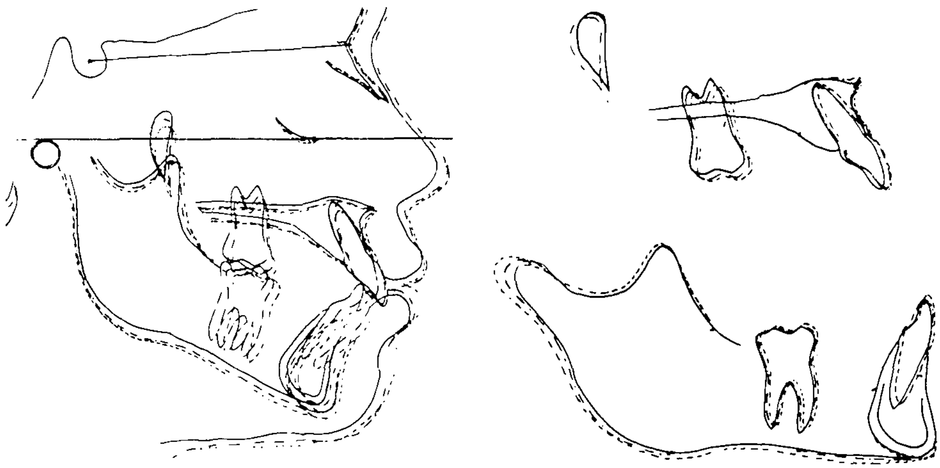

Fig. 4 Male, chron. age 12½ yrs., bone age 6 0/12 yrs., dent. age inc. 0 yr., ht. inc. 1 yr. = 3", wt. inc. 1 yr. = 2 lbs., head circ. 1 yr. = .4 cm. Implant, HGH administered for 1 year, syn-thyroid administered for 1 year.

Cranial base superpositions show equal amounts of growth during the six-month interval periods of 12:1, 12:7 and 13:1 years (one year hormonal treatment). The maxillary tracings demonstrate superposition on implants showing tooth movement during the growth period and also movement in a posterior direction of pterygomandibular fissure. Mandibular growth is demonstrated in the second figure showing superpositions on metallic implants to demonstrate tooth movement and posterior direction of condylar growth. Vector analysis shows an equal amount of vertical and anteroposterior magnitude in the comparisons of the dentoalveolar and condylar areas.

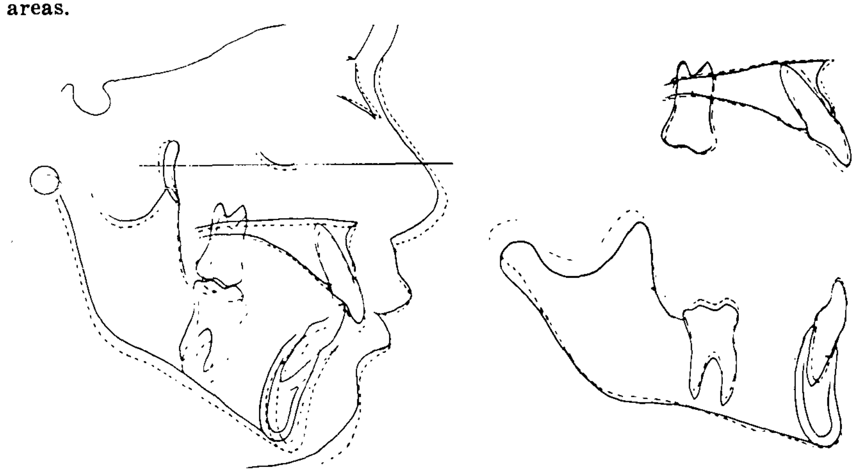

Fig. 5 Male, chron. age 11 11/12 yrs, bone age 6 3/12 yrs., dent. age inc. = 2 yrs., ht. inc. 1 yr. = 2½", wt. inc. 1 yr. = 8 lbs., head cir. 1 yr. = 0 cm. HGH administered for 18 months—off last six months, cortisone administered for 18 months, syn-thyroid for 18 months.

Tracings of patient #5 during the first year of total of 18 month administration of human growth hormone. Cranial base superpositions show the first growth period of one year and the six month subsequent growth in the patient between 13:0 to 13:6 years. The maxillary tracings demonstrate tooth movement and pterygomandibular fissure movement during the 16 month growth period. The lower mandibular superposition is the result of superpositions on mandibular canal and symphysis illustrating tooth movement and posterior vertical movement of the condyle. The anterior component change is one of the largest measured in comparison with the small dentoalveolar changes.

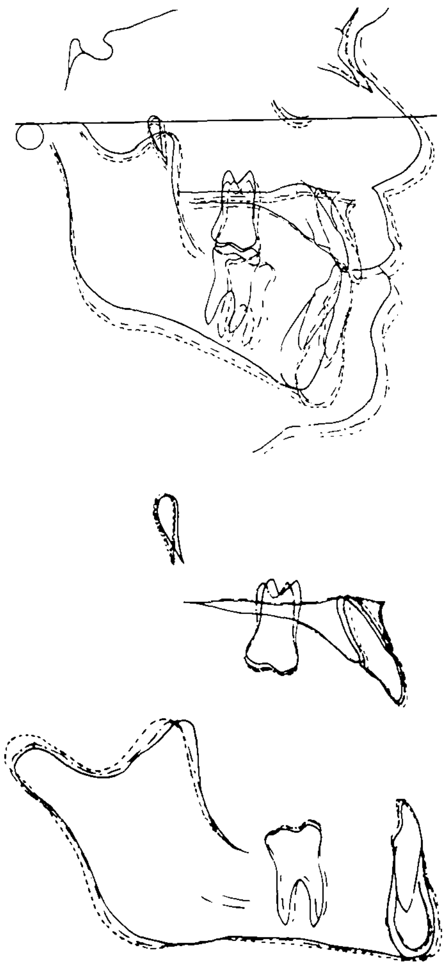

Fig. 6 Male, chron. age 14 9/12, bone age 7½ yrs., dent. age inc. = 5 yrs., ht. inc. 1 yr. = 5", wt. inc. 1 yr. = 6½ lbs., head circ. 1 yr. = .8 cm. Implants HGH administered for 1 year. No other supplement given.

The cephalometric tracings superimposed on SN line demonstrate growth from 7:6 years to 8:0 years and 8:6 years. The anterior growth components seem more significant than the vertical components. Evaluation of the upper maxillary superpositions shows that the pterygomandibular fissure has mostly an anterior component of growth. Mandibular composites superimposed on mandibular canal and tooth bud along with the symphyseal region also depict a greater anterior component of condylar growth than vertical.

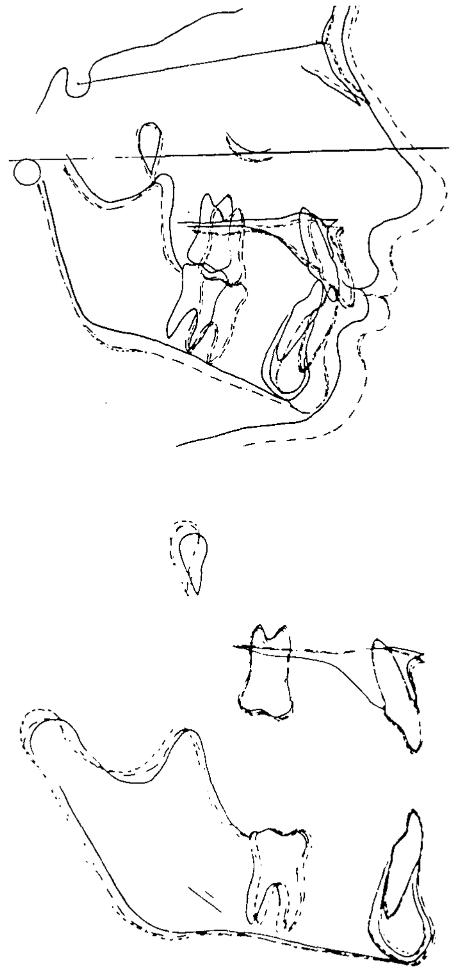

Fig. 7 Female, chron. age 16 5/12 yrs., bone age 2 yrs., dent. age inc. = 1 yr., ht. inc. 1 yr. = 3½", wt. inc. 1 yr. = 7½ lbs., head circ. 1 yr. = 1.0 cm. HGH administered for 18 months—no post 6 month results yet. Receiving no other supplement, possible syn-thyroid in future. Last 6 month during trt.—developed antibody against HGH.

Tracings of patient #7 during the first 16 months of human growth hormone treatment. A clockwise closing rotation of the mandible with significant anterior growth of pogonion is demonstrated on the tracings at 16:5 years, 17:5 and 17:11 years. The maxillary tracings show the pterygomandibular fissure growing vertically. The mandibular tracing superimposed on mandibular canal and mandibular anterior symphysis also shows a significant vertical component greater than the posterior condylar vector.

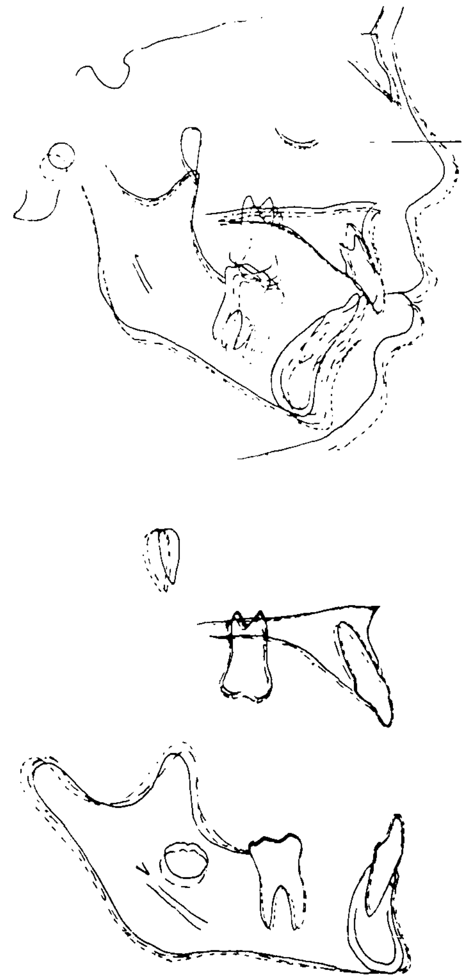

Fig. 8 Male, chron. age 15 10/12 yrs., bone age 9 yrs., dent. age inc. = 2 yrs., ht. inc. 1 yr. = 3½", wt. inc. 1 yr. = 5 lbs., head circ. 1 yr. = .3 cm. HGH administered 18 months—records 6 month after HGH stopped. Cortisone administered 18 months—possibly antibody prod. last 6 months trt. Syn-thyroid administered 18 months.

Tracings of patient #8 during the first 14 months of the 18 month administration of HGH. A clockwise closing rotation with significant anterior magnitude similar to patient #7 is found in comparisons of the first year tracings and one four months later. Maxillary superimpositions demonstrate posterior sutural growth with small amounts of dentoalveolar changes. Mandibular superpositions demonstrate posterior and vertical growth in the ramus and condyle.

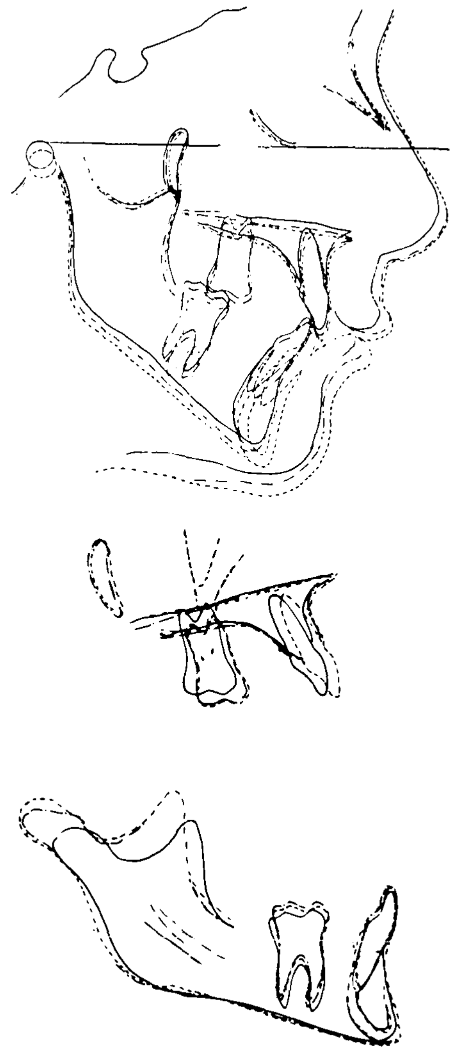

Fig. 9 Male, chron. age 20 0/12 yrs., bone age 11 0/12 yrs., dent. age inc. = 1.5 yrs., ht. inc. 1 yr. = 3¾", wt. inc. 1 yr. = 9 lbs., head circ. 1 yr. = .2 cm. Implants, HGH administered for 1 yr.—still under trt. Syn-thyroid administered for 1 yr.—still receiving it.

Tracings of an implant patient (#9) at 19:10 years, 20:4 years and 20:10 years. Although cranial dimensions did not change appreciably, the maxilla and mandible show a large magnitude displacement for the oldest bone-age dwarf in the study. Maxillary superposition demonstrates more dentoalveolar change than sutural. Mandibular superpositions on implants illustrate condylar changes in both the vertical and posterior direction of seemingly equal magnitudes.

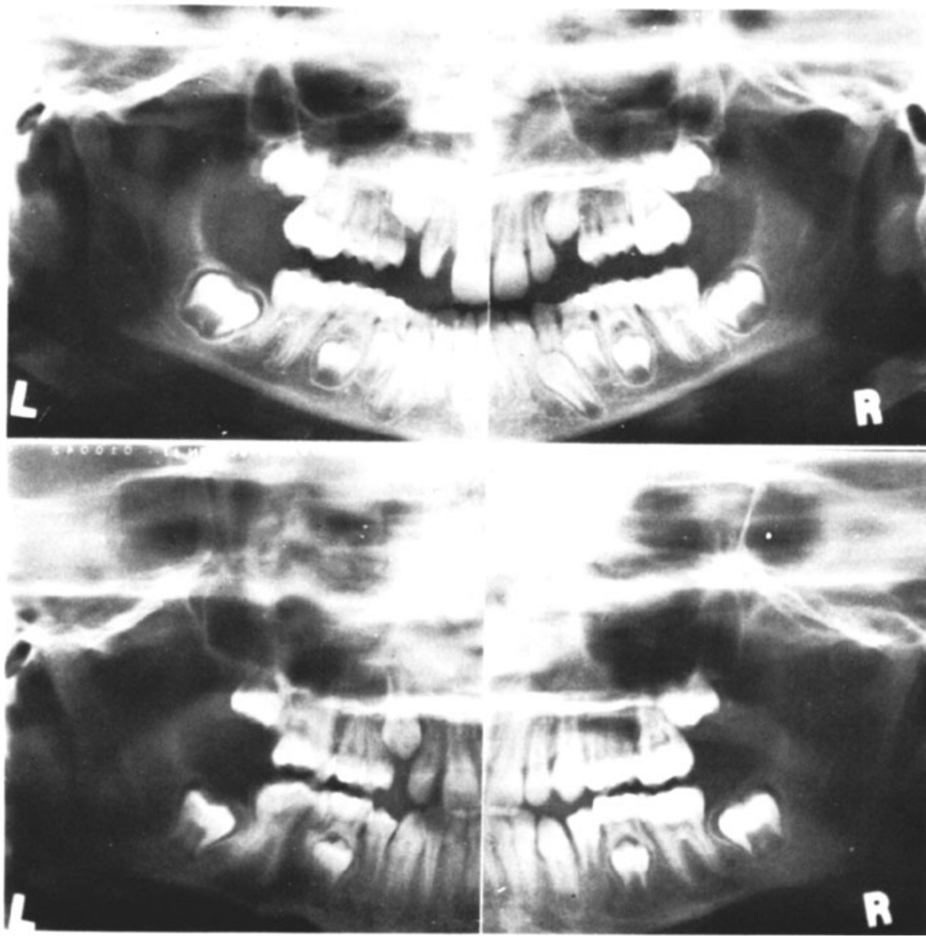

Fig. 10 One year comparisons of panoramic X-rays on patient #5 according to Moorrees. Except for teeth unable to erupt, the patient's original 25% retarded dental age responds normally during HGH administration.

portion of the vertical component is represented by condylar growth in patients #1 through 9. The major portion of the anterior growth in the mandible was also due to condylar growth. The rotation of the mandible during growth converted vertical growth to anteroposterior displacement.[22]

Evaluation of plaster models for changes in arch dimension and maxillary bony width changes demonstrated a minimal change and these measurements are not included in the tables. The arch dimensional changes ranged from 0-1 mm with the majority of values less than 0.5 mm.

Six of the nine patients had maxillary bony width increases of 0-1 mm measured between second molar tooth buds and buccal plate to buccal plate on posteroanterior radiographs. Two patients had a buccal plate increase of 2 mm and one a width increase of 3 mm.

Panoramic radiographs revealed that dental age, according to Moorrees et al.,[19] increased one year or more over the year of therapy in eight of the nine patients (Fig. 10). Because the dental age at the start of treatment was retarded by about 25% in all cases, the HGH administration resulted in a trend toward reducing the retarded dental age.

Discussion

The absolute contributions of various sites to total head changes during adolescent growth cannot be evaluated unless they are known. Enlow[18] stated that the apparent growth is valuable only because "it shows those topographic changes that one actually sees grossly." Speculation on total head changes related to growth studies and orthodontic treatment results have been numerous and varied in the literature. Craniofacial changes must be evaluated according to actual growth and displacement of specific bones and jaws. More useful clinical information can result if the absolute growth is evaluated under a set of conditions where only a few variables are involved. Some investigators have applied serial growth data and implants to evaluate and predict absolute growth.[15-19]

This study has applied the classical techniques for evaluation of hormone administration by utilizing data collection before, during, and after administration of hormone. Absolute growth indexing has been evaluated by utilizing the more accurate recent techniques of superimpositioning serial maxillary and mandibular tracings with and without implants.

Human growth hormone has been shown to be effective in growth stimulation of hypopituitary dwarfs.[1,3,14] The effects of HGH administration on general body metabolism and cartilage growth has been evaluated in normal infants, children, and adults.[3,4] Some data are available on HGH effects on the general skeletal growth of the pituitary dwarf, but longitudinal data on the effects of HGH on facial growth in the normal child and pituitary dwarf are lacking. A single variable of HGH administration was possible in the nine patients, because supplemental therapy with synthetic thyroid and cortisone was made in order that HGH therapy could be evaluated.

In all cases the patients' facial growth had been growing at rates far less than normal. Rapid acceleration and deceleration of growth corresponded to the HGH therapy.

Past investigators have described the dental and facial conditions of hypopituitary dwarfism.[5-10] There is general agreement that the width and depth of the face is severely retarded and, although slow growth may continue on into middle age, the face still maintains a childlike convexity. The mandible is observed to be more retarded than the maxilla and the dental age is retarded by 25% and the bone age by 50%.[5-11] This study revealed that eight of nine patients had various cephalometric analysis measurements which were one or more standard deviations below Downs' mean in relating the convexity of the face. For example, eight out of nine patients had a Downs' angle of convexity measurement which was one or more standard deviations below the mean. Patient #8 measurements, for some unknown reason, fell within Downs' and Riedel's normal ranges. It is interesting that he became more prognathic in all measures during therapy while still staying within normal ranges (Table I, Fig. 8).

The hypopituitary dwarfs in this study, although retarded skeletally for years, responded very quickly to treatment. The face lost some of its convexity by a growth spurt of the mandibular condyles. The mandibular growth and remodelling was more accelerated than similar changes in the maxilla. Dimensional arch changes in

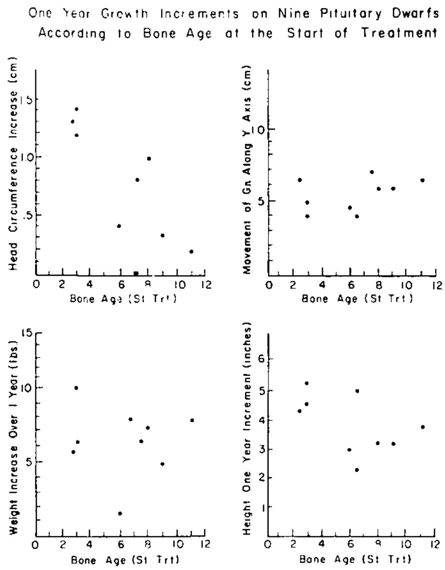

Fig. 11 One year growth increments on nine pituitary dwarfs according to bone age at the start of treatment.

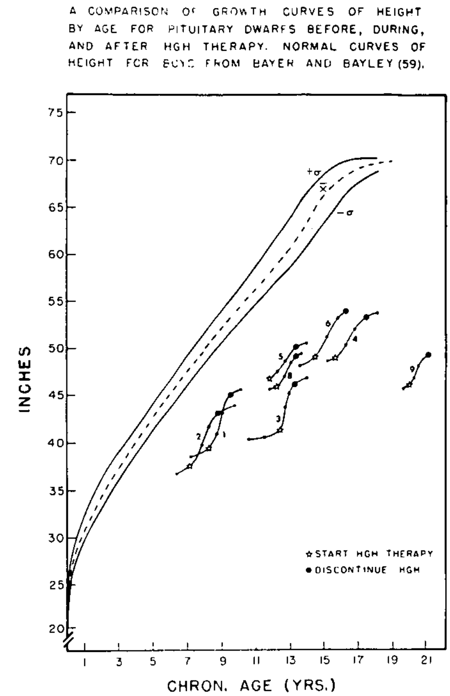

Fig. 12 A comparison of growth curves of height by age for pituitary dwarfs before, during and after HGH therapy. Normal curves of height for boys from Bayer and Bayley.

both jaws did not occur as would be predicted by reports in the literature.[16,19,20] The significance of the changes that did occur were ones of magnitude and directional components. Although these patients were severely retarded and most growth predictions would suggest more mandibular than maxillary growth, no information exists to establish that, under the influence of HGH, one site of facial growth will grow faster than another.

When the patient's individual pattern of growth was manifested in a vertical direction (Fig. 9), the growth hormone administration gave more magnitude to individual vertical growth component. All the other patients in the study responded to HGH in a way suggesting an anteroposterior component of growth. This is more representative of the typical Class II classification if Class II is associated with a growth retardation since administration of HGH resulted in increased magnitude of the anterior growth component.

All mandibular growth was manifested through rotational movement. A further description of rotational mandibular growth is reported elsewhere.[22]

Four different growth variables are compared to the starting bone age of all nine hypopituitary dwarfs by scattergrams in Figure 11. Height curves for the eight boys are represented in Figure 12 (#7 is a female). Although bone age does not appear to correlate with three of the four measures of growth, the head circumference measure does appear to possibly possess a negative correlation to increasing bone age. The three patients with the youngest bone ages demonstrated the greatest cranial suture response.

All the pituitary dwarfs in this study responded to the administration of human growth hormone even though there was a large variability in their original bone age. A pubertal-like growth spurt occurred in all target growth areas. Only some cranial target sites were found to be unresponsive to HGH. These represent more mature sutural areas where further growth may be impossible. Facial growth may continue beyond the 11:0 years bone age demonstrated in this study. However, caution should be exercised with regard to expectations regarding cranial suture changes in older patients.

Summary and Conclusions

The craniofacial growth of nine pituitary dwarfs receiving HGH was evaluated. Total growth was studied in all nine persons by superimpositions of serial cephalometric tracings on SN. Individual maxillary and mandibular growth for each jaw was obtained by serial superpositions of the tracings on implants in four patients and in five patients on structures that have been shown by the implant method to be very stable during growth.

Other dental and facial changes were evaluated in all nine patients by use of serial models and panoramic radiographs. All patients received HGH, three received HGH plus cortisone and thyroid, and one received HGH plus synthetic thyroid. Craniofacial and individual maxillary and mandibular growth was observed and the results recorded. The following conclusions can be drawn from the administration of human growth hormone to hypopituitary dwarfs:

1. The majority of craniofacial changes occurred in the condyles, sutures of the cranium and sutures of the cranial base bordering on the maxilla.

2. Except for apparently normal minor eruptive changes the teeth did not move within the individual jaws in eight of the nine patients. One patient with extreme vertical first molar changes also showed vertical component changes of growth in the condyle.

3. Facial plane changes occurred in the prognathic direction. All ANB changes occurred in the direction of less convex profile. Condylar growth seemed to be the principal growth factor during treatment in the majority. The mandibular growth demonstrated a closing rotation in eight of the nine patients. The ninth patient showed a mandibular opening rotation during hormonal administration. This patient had originally demonstrated a relatively greater anterior facial height as compared with the posterior facial height.

4. Minimal change was noted in the various arch dimensions and in maxillary bony width during treatment.

5. The retarded dental age of the dwarfs improved slightly during therapy.

6. Accelerated and decelerated growth rates occurred during administration and withdrawal of HGH, respectively. Cranial sutural growth was found to slow down with increasing bone age of the pituitary dwarfs. All other measured growth and weight changes showed no relation to bone age during administration of human growth hormone.

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