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Outcome of Growth Hormone Therapy in Children with Growth Hormone Deficiency Showing an Inadequate Response to Growth Hormone–Releasing Hormone

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Saizen® (recombinant growth hormone [GH]), 0.2 mg/(kg·wk), was given in an open-label fashion for an average of 51 mo to 27 children with presumed idiopathic GH deficiency who had withdrawn from a trial of Geref ® (recombinant GH-releasing hormone [GHRH] 1–29) because of inadequate height velocity (HV) (25 children), the onset of puberty (1 child), or injection site reactions (1 child). Measurements were made every 3–12 mo of a number of auxologic variables, including HV, height standard deviation score, and bone age. The children in the study showed excellent responses to Saizen. Moreover, first-year growth during Saizen therapy was inversely correlated with the GH response to provocative GHRH testing carried out 6 and 12 mo after the initiation of Geref treatment. These findings indicate that GH is effective in accelerating growth in GH-deficient children who do not show or maintain a satisfactory response to treatment with GHRH. In addition, they suggest that the initial response to GH therapy used in this way can be predicted by means of provoc-ative testing.

Key Words: Children; Geref; growth hormone; growth hormone–releasing hormone; Saizen.

Introduction

Geref ® (Serono, Geneva) is a recombinant product consisting of the first 19 amino acids of growth hormone–releasing hormone (GHRH)—the shortest fragment to possess the full biologic activity of the natural hormone *(1,2)*. The efficacy and safety of Geref in the treatment of growth failure have been assessed in an international trial involving 110 children with growth hormone deficiency (GHD). Results from the first year of this study showed that, in general, Geref is effective and well tolerated *(3)*. After 6 mo of treatment, 74% of evaluable patients showed a satisfactory response to Geref (defined as an increase in height velocity [HV] over baseline of at least 2 cm/yr); after 12 mo, the corresponding figure was 84%.

In this article, we describe a supplementary study to the international Geref trial involving the children in this trial who were based at centers in the United States. The aim of this study was to assess the long-term efficacy and safety of Saizen® (recombinant human GH; Serono) in children who do not show a satisfactory response to Geref or in whom the response to Geref is initially satisfactory but subsequently decreases to an unsatisfactory level.

Results

Twenty-seven children were enrolled in the Saizen study. Of these, 25 were switched from Geref because of unsatisfactory growth, 1 was switched because of the onset of puberty, and 1 was switched because of a localized injection site reaction. Table 1 summarizes the demographic characteristics.

The mean duration of treatment with Saizen was 51.1 mo. Twelve patients completed 5 yr of treatment, but only three completed 6 yr, and only two completed 7 yr. Therefore, the auxologic data presented are for only the first 5 yr.

During the course of the study, 16 patients were withdrawn when they reached final height. Of the remaining patients, two withdrew when they moved away, six reached satisfactory or predicted height and elected to stop treatment, one was noncompliant and was discontinued, one was lost to follow-up, and one was discontinued by his private physician for reasons unrelated to adverse events.

Annualized HV during Saizen treatment is plotted in Fig. 1. Median HV ranged from 6.9 cm/yr during yr 1 to 5.7 cm/yr during yr 5. HV was significantly improved (compared

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Table 1
Patient Demographic Characteristics (n = 27)[a]

Age (yr)	9.0 ± 2.7 (5.0–15.7)
Gender (male/female)	17/10 (63/37%)
Height (cm)	116.2 ± 15.5 (90.1–152.0)
Weight (kg)	24.0 ± 13.1 (11.4–67.3)
Etiology of GHD	
Idiopathic	25 (92.6%)
Organic	2 (7.4%)
Reason for leaving Geref study	
Lack of growth	24 (88.9%)
Entered puberty	1 (3.7%)
Both reasons	1 (3.7%)
Neither reason	1 (3.7%)
Tanner staging	
Prepubertal	25 (92.6%)
Pubertal	2 (7.4%)

[a]Where appropriate, data are presented as mean ± SD, with ranges in parentheses.

with HV at the time of withdrawal from the Geref study) in the first, second, and third years of Saizen therapy ($p < 0.05$ for all 3 yr).

Height standard deviation score (HSDS) was significantly improved, compared with baseline, after each year of Saizen treatment ($p < 0.001$ for all 5 yr) (Fig. 2). Median HSDS at baseline was –2.9, and the median increases from baseline after yr 1–5 were 0.5, 0.8, 1.2, 1.5, and 1.9, respectively. Median HSDS after 5 yr was therefore –1.0.

HV standard deviation scores (HVSDSs) are shown in Fig. 3. The median HVSDSs after yr 1–5 were 2.4, 1.7, 1.0, 2.1, and 0.9, respectively.

Chronologic age exceeded height age (HA) throughout the period of Saizen treatment (Fig. 4). Bone age (BA) was lower than chronologic age during the first years of treatment with Saizen, but increased more rapidly than chronologic age and was similar to this variable in later years (Fig. 5).

Auxologic changes in children treated three times per week (n = 13) were not different from those treated six to seven times per week (n = 14). Significant catch-up growth was present in each of the 5 yr of Saizen treatment and was progressive over these years. All patients in the study reached predicted height, except the five who dropped out.

Table 2 summarizes changes in insulin-like growth factor-1 (IGF-1) concentrations during the study. The mean IGF-1 concentration at baseline was 124.0 ng/mL, and the mean increase during Saizen treatment was 238.3 ng/mL.

No life-threatening adverse events were reported during the study, and only two adverse events were considered severe. One patient had a 7-mo episode of severe anorexia beginning at mo 33, and one patient required hospitalization during the second month of treatment owing to severe abdominal pain. Both events were considered by the investigators to be unrelated to the study drug.

Discussion

The results of this open study show that treatment with GH produces marked improvements in growth rate in GH-deficient children who do not show or do not maintain a satisfactory response to GHRH therapy. The median HV of 6.9 cm/yr observed during the first year of GH therapy compares favorably with yr 2 growth responses seen in children receiving GH as first-line therapy *(4–6)*. Comparison with yr 2 data from such children is appropriate because children in the present study had received growth-promoting therapy for 1 yr before GH treatment was started.

Comparison of HV data from the present study with results from GHRH stimulation tests carried out during the original Geref trial shows that HV after 12 mo of treatment with Saizen correlates inversely with the peak GH concentrations seen in stimulation tests conducted after 6 and 12 mo of Geref therapy (6-mo test [iv GHRH]: $r = –0.420$, $p = 0.03$; 12-mo test [sc GHRH]: $r = –0.506$, $p = 0.046$). This suggests that a diminished GH response to GHRH stimulation testing may be predictive of an augmented response during the first year of GH treatment. The predictive value of stimulation testing has been demonstrated previously by Ranke et al. *(7)*, who have shown that the auxologic response to GH therapy in patients with idiopathic GHD depends on the severity of the deficiency: the worse the deficiency (i.e., the smaller the response to provocative testing), the greater the response to therapy. No significant correlation is seen when responses to GHRH testing during the Geref trial are compared with HV after yr 2, 3, 4, or 5 of Saizen therapy. This is consistent with results from other studies showing that maximum HV is achieved during the first year of GH treatment *(8,9)*.

In conclusion, this study indicates that GH is effective "rescue therapy" for patients in whom the response to GHRH is unsatisfactory. In addition, it suggests that the initial response to GH therapy used in this way can be predicted by means of provocative testing.

Materials and Methods

Patients

The original trial of Geref involved prepubertal children with presumed idiopathic GHD *(3)*. Children were eligible for this trial if they had not received prior treatment with growth-promoting agents and met specific selection criteria prior to beginning a 6-mo pretreatment observation period. They were considered to have GHD if HV was below the 10th percentile for chronologic age, height was 2.5 or more SD below the mean for chronologic age, and peak GH response to provocative stimuli was <10 mg/L. Whenever possible, organic causes of GHD were excluded by means of clinical history taking and high-resolution computed tomography or magnetic resonance imaging.

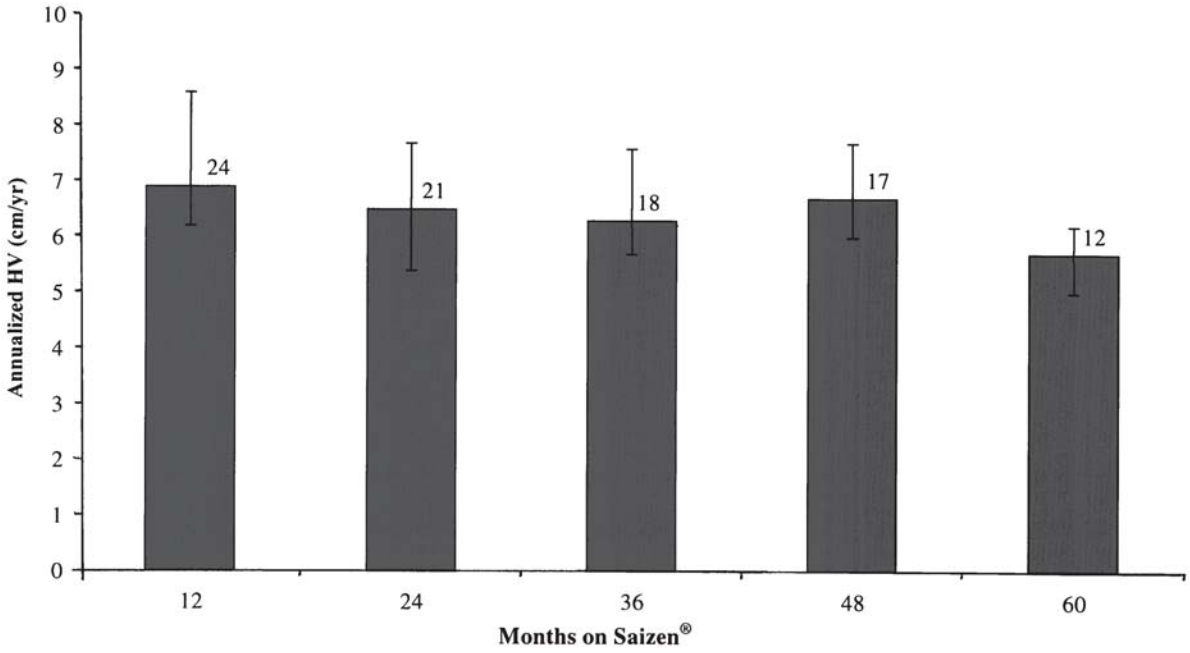

Fig. 1. Change in annual HV during Saizen treatment. All figures show median values with 1st and 3rd quartiles. *n* is shown above each bar here as well as in Figs. 2–5.

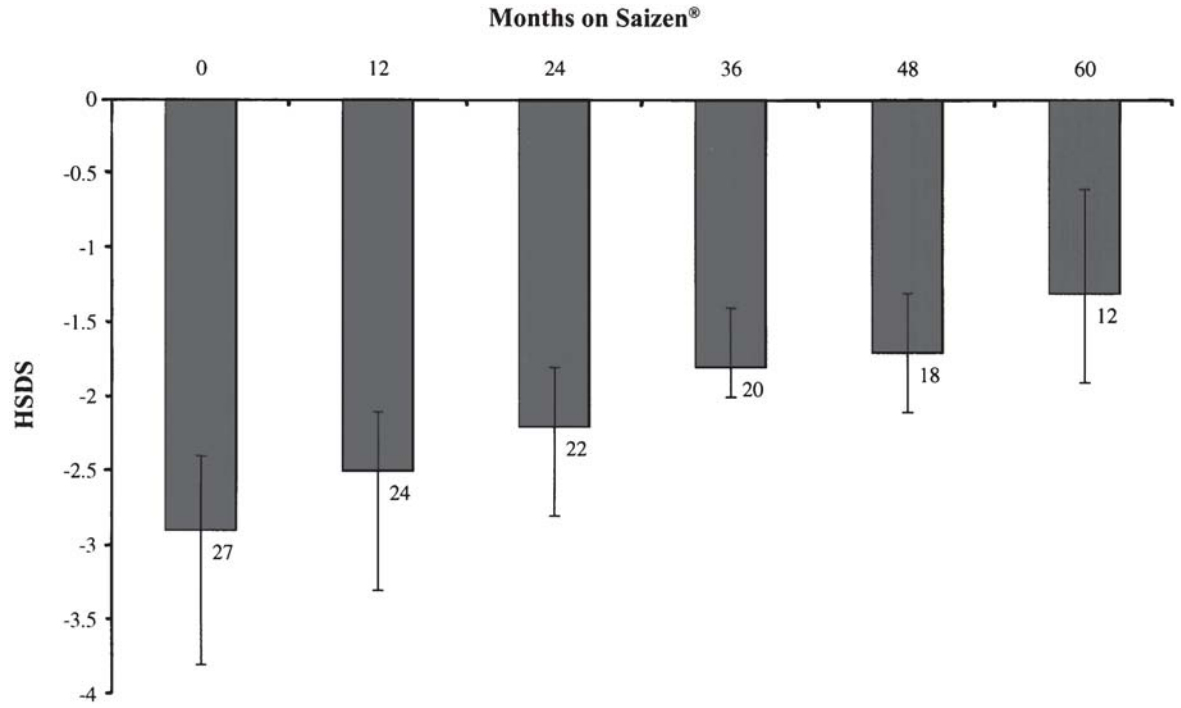

Fig. 2. Change in HSDS during Saizen treatment.

Of the 110 children enrolled in the Geref trial, 33 were based at centers in the United States. Only these American children were eligible for entry into the supplementary Saizen study. The inclusion criteria for this study (i.e., the criteria for discontinuation of Geref treatment and initiation of Saizen treatment) were as follows: unsatisfactory growth, defined as a HV <2 cm/yr above baseline, at any time during treatment with Geref (HV was assessed every 6 mo during the Geref trial); and the onset of puberty during Geref treatment.

Each participating institution received internal ethics committee approval for the original Geref study and the follow-up Saizen study. Written informed consent was obtained from each child's parent or legal guardian prior to enrollment in each study.

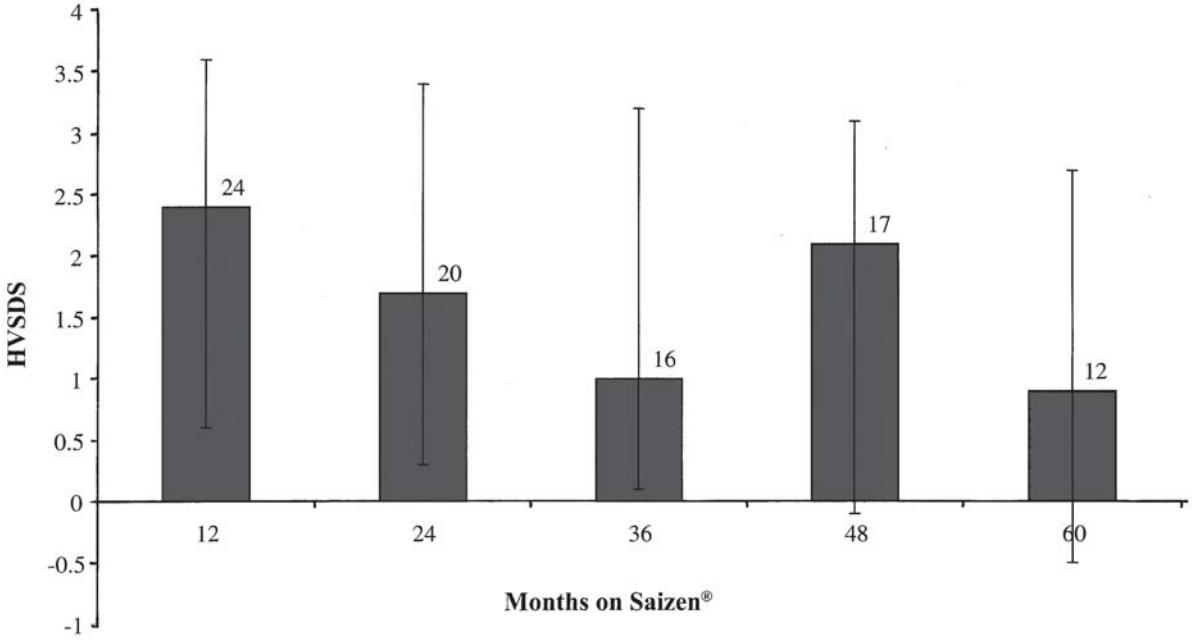

Fig. 3. Change in HVSDS during Saizen treatment.

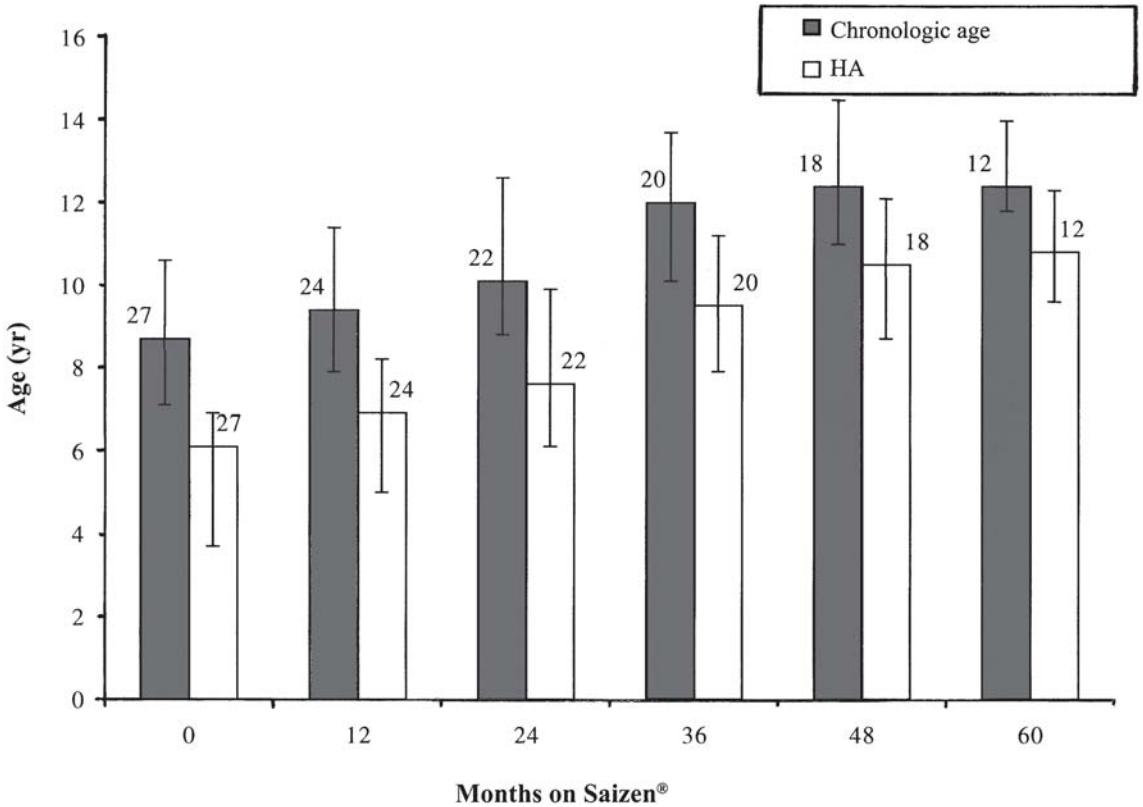

Fig. 4. Chronologic age and HA. Results are expressed as median values with 1st and 3rd quartiles.

Methods

Treatment with Saizen began 30–60 d after the last dose of Geref had been administered. Saizen was given at a dose of 0.2 mg/(kg·wk) until final height was achieved or the patient withdrew for other reasons. It was administered by sc injection between three and seven times per week; dosing frequency was at the discretion of the investigator. Medications that were considered necessary for the patient's welfare, and that did not interfere with the study medication or its evaluation, were permitted at the discretion of the investigator.

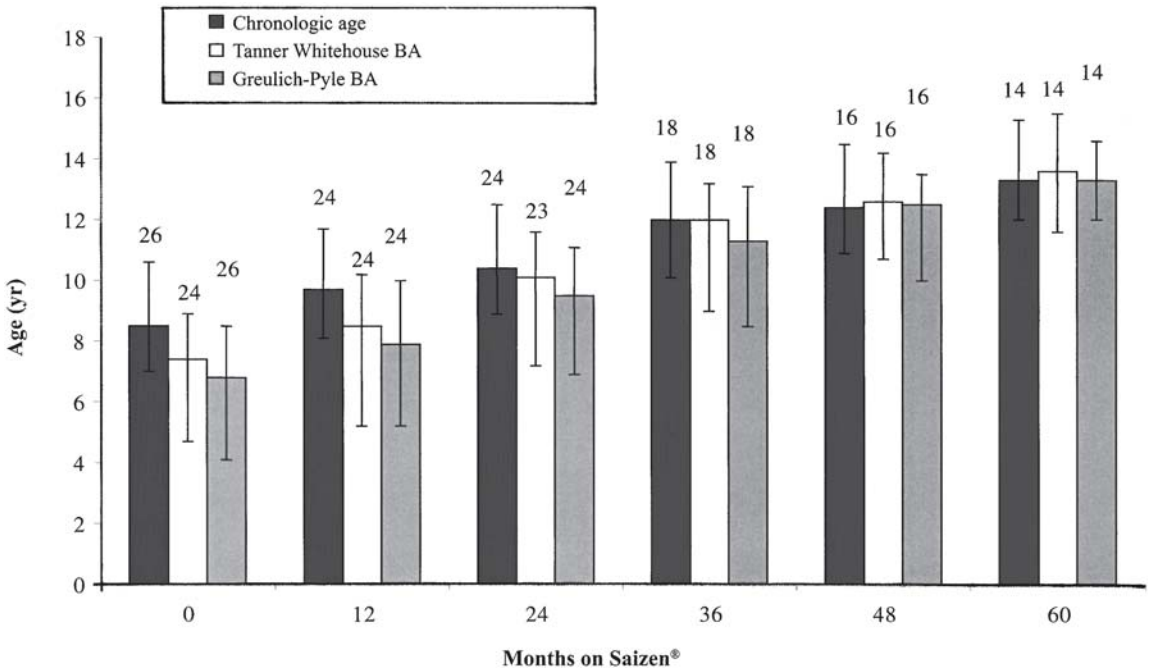

Fig. 5. Chronologic age and BA. Results are expressed as median values with 1st and 3rd quartiles.

Table 2
IGF-1 Concentrations During Saizen Treatment[a]

		Value (ng/mL)				Change from baseline (ng/mL)		
Time point	*n*	Mean (SD)	Median	Range	*n*	Mean (SD)	Median	Range
Baseline	25	124.0 (106.1)	102.0	(5.0, 514.0)				
12 mo	22	206.1 (125.7)	172.5	(5.0, 483.0)	20	86.5 (98.6)	78.0	(–98.0, 381.0)
24 mo	20	275.5 (162.4)	243.5	(39.0, 690.0)	18	173.2 (139.7)	125.5	(34.0, 561.0)
36 mo	16	327.5 (164.0)	287.5	(104.0, 665.0)	15	180.8 (160.2)	139.0	(–50.0, 592.0)
48 mo	16	373.9 (212.2)	319.5	(99.0, 876.0)	15	248.5 (164.9)	229.0	(40.0, 646.0)
60 mo	7	313.4 (186.5)	250.0	(83.0, 585.0)	6	266.3 (111.5)	226.0	(166.0, 462.0)
72 mo	1	187.0	187.0	(187.0, 187.0)	1	169.0	169.0	(169.0, 169.0)
84 mo	1	255.0	255.0	(255.0, 255.0)	1	237.0	237.0	(237.0, 237.0)
Last on treatment	25	358.9 (208.2)	313.0	(39.0, 876.0)	23	238.3 (180.2)	235.0	(–50.0, 646.0)

[a]Last on treatment = last value obtained on treatment.

Height and weight were measured at the initiation of Saizen therapy and every 3 mo thereafter. Blood was drawn for clinical laboratory testing every 6 mo, and the concentration of IGF-1 was measured annually. X-rays of the left hand and wrist were taken yearly for determination of BA; all films were read by a central reader using both the Tanner-Whitehouse and Greulich-Pyle methods of measurement *(3,10)*. HV, HVSDS, and HSDS were calculated yearly; HVSDS and HSDS were derived from the standard height tables of Prader et al. *(11)*. Auxologic data were com-pared with baseline values using Wilcoxon signed rank tests.

References

1. Rivier, J., Spiess, J., Thorner, M., and Vale, W. (1982). *Nature* **300**, 276–278.
2. Guillemin, R., Brazeau, P., Bohlen, P., Esch, F., Ling, N., and Wehrenberg, W. B. (1982). *Science* **218**, 585–587.
3. Thorner, M., Rochiccioli, P., Colle, M., Lanes, R., Grunt, J., Galazka, A., Landy, H., Eengrand, P., and Shah, S. (1996). *J. Clin. Endocrinol. Metab.* **81**, 1189–1196.
4. Blethen, S. L., Baptista, J., Kuntze, J., Foley, T., LaFranchi, S., and Johansen, A. (1997). *J. Clin. Endocrinol. Metab.* **82,** 418–420.
5. Ranke, M. B., Price, D. A., Albertsson-Wikland, K., Maes, M., and Lindberg, A., on behalf of the International Board of the Kabi Pharmacia Growth Study. (1997). *Horm. Res.* **48**, 62–71.

6. August, G. P., Julius, J. R., and Blethen, S. L. (1998). *Pediatrics* **100**, 512–516.
7. Ranke, M. B., Lindberg, A., Chatelain, P., Wilton, P., Cutfield, W., Albertsson-Wikland, K., and Price, D. A. (1999). *J. Clin. Endocrinol. Metab.* **84**, 1174–1183.
8. Frasier, S. D., Rudlin, C. R., Zeisel, H. J., Liu, H. H., Long, P. C., Senior, B., Finegold, D. N., Bercu, B. B., Marks, J. F., and Redmond, G. P. (1992). *Am. J. Dis. Child.* **146**, 582–587.
9. Stubbe, P., Frasier, S. D., Stahnke, N., Cacciari, E., Job, J. C., Preece, M., Frisch, H., Zachmann, M., and Zeisel, H. J. (1992). *Horm. Res.* **37(Suppl. 2),** 28–36.
10. Greulich, W. W. and Pyle, S. I. (1959). *Radiographic atlas of skeletal development of the hand and wrist.* Stanford University Press: Stanford, CA.
11. Prader, A., Largo, R. H., Molinari, L., and Isseler, C. (1989). *Helv. Paediatr. Acta Suppl.* **52**, 1–125.