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Effects of growth hormone in short children after renal transplantation

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Abstract. From 1991 to 1993, 90 children having received a kidney graft with a post-transplantation period of at least 12 months were included in a prospective study carried out in 18 French pediatric centers. After informed consent and randomization, children received recombinant human growth hormone (rhGH) (Genotonorm, Pharmacia peptide hormones) 30 U/m^2 per week, either immediately on enrollment, for the treated group, or after 1 year of follow-up for the group serving as a control. After 1 year both groups were treated and we analyzed data during the subsequent years. Eighty-five children completed the 1-year study. Growth velocity was significantly increased by rhGH: 7.7 cm with a gain of +0.3 standard deviation score in the treated group versus 4.6 cm in the control group (P<0.0001) during the 1st year. Four factors predicted response to therapy: growth velocity prior to GH therapy, glomerular filtration rate (GFR) at the start, mode of corticosteroid administration, and degree of insulin resistance. After 1 year we observed a moderate, significant decrease in GFR in both groups. Biopsy-proven acute rejection episodes were not significantly more frequent during the 1st year in the group of patients who received rhGH: 9 in 44 versus 4 in 46 patients. The patients who rejected did not differ in terms of age, renal function at the start, and type of immunosuppression, but history of rejection before GH treatment was discriminatory: 6 of 17 children with two or more episodes had a new rejection versus 1 of 22 who had no or only one episode (P=0.01). Glucose tolerance was not modified after 1 year of GH therapy. During the subsequent years of treatment a decrease in growth velocity was noted: 5.9 cm at 2 years, 5.5 at 3 years, and 5.2 cm at 4 years. In conclusion, GH is efficient for improving growth velocity in short transplanted children, inducing clear-cut but limited catch-up growth. The risk of rejection was shown only in patients with a prior history of more than one rejection episode.

Key words: Human recombinant growth hormone – Renal transplantation – Rejection

Introduction

Growth retardation remains a major concern in children with chronic renal insufficiency. Despite assiduous management and increasingly effective therapy, many patients are growth retarded at the time of transplantation. After successful transplantation, growth improves in 30% to 50% of children [1–3]. Glucocorticoids, given preventively or for rejection episodes, are the main cause of persistently poor growth in these cases [1, 4]. It has been clearly demonstrated that treatment with glucocorticosteroids interferes with the integrity of the somatotrophic axis by suppression of pituitary growth hormone (GH) release, downregulation of hepatic GH receptors, inhibition of insulin-like growth factor (IGF) bioactivity, and complex alteration of the serum profile of IGF binding proteins (IGFBP) [5–7]. In addition, glucocorticoids have a direct inhibitory effect on cartilage in reducing collagen synthesis and bone formation [8–10]. A moderate decrease in renal graft function is also generally associated with poor growth [1, 4] and experimental studies have shown tissue resistance to recombinant human (rh) GH in uremia [11, 12]. Renal dysfunction may contribute to high immunoreactive IGF BP concentrations. The imbalance between IGF levels and excess IGFBP is likely to play a role in growth failure in these children [13–15]. Since 1989, rhGH has been shown to be effective in improving growth velocity in short children with chronic renal failure, in dialysis patients, and after renal transplantation [16–20]. It was also known, however, that GH may increase the activity of the immune system

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[21], thereby increasing the risk of transplant rejection. In most reports the incidence of rejection following rhGH was no greater than without this treatment [16, 19, 22]. In other reports the use of rhGH was associated with biopsy-proven acute rejection in children with previously stable renal graft function [23, 24]. Therefore, a controlled study was needed to determine whether the administration of rhGH exposes transplanted children to an increased risk of rejection. Such a study was performed in Europe and was published in part [25]. We report here fuller data of the French centers that participated in this European study. These results have been partially reported in abstract form [26–28].

Patients and methods

From 1991 to 1993 Pharmacia conducted a randomized European multicenter controlled study of rhGH in short children having received a kidney graft. The present report concerns the data collected in the 18 participating French centers under the auspices of the Société de Néphrologie Pédiatrique (Angers, Clermont-Ferrand, Dijon, Lille, Lyon, Nancy, Nantes, Paris Enfants-Malades, Paris Robert-Debré, Paris Trousseau, Reims, Rennes, Roscoff, Rouen, Saint-Etienne, Strasbourg, Toulouse, Tours). This study was approved by an ethics commitee (CCPPRB Hôpital Cochin, Paris). Written informed consent was obtained from all parents and from children when possible.

Inclusion criteria for the study were: (1) growth retardation with height standard deviation score (SDS) for chronological age (CA) below –2 SD; (2) a slow growth velocity for CA below –1 SD; (3) post-renal transplantation period of at least 12 months; (4) stable renal function with a glomerular filtration rate (GFR) >20 ml/min per 1.73m^2; (5) normal thyroid function, no diabetes, no history of cancer, and no other visceral disease; (6) prepubertal or early pubertal status. Prepubertal patients had testicular volume <4 ml for boys and breast development <B2 for girls; early pubertal patients had testicular volume between 4 ml and 8 ml for boys and breast development between B2 and B3 for girls at the beginning of treatment. Bone age had to be less than 11 years for boys and less than 9 years for girls in the prepubertal group and less than 14 years for boys and 13 years for girls in the early pubertal group. Immunosuppressive therapy consisted of a combination of prednisone, azathioprine, and cyclosporin, according to the protocol of each center.

After randomization, children were given rhGH (Genotonorm) 30 U/m^2 per week, with daily subcutaneous injection either immediately, for the treated group, or after 1 additional year of follow-up for the group serving as control. When effective, and in the absence of side effects, GH treatment was continued. Patients were examined at enrollment and subsequently every 3 months by one investigator at the outpatient clinic of each participating center. The dose was adjusted to body surface area at the three-monthly visits. Height was measured with a stadiometer.

Growth data were compared with the current French standards [29]. We used the body mass index (BMI) (W/H^2) of Rolland-Cachera et al. [30]. Puberty ratings were determined according to Tanner stages [31]. Bone age was determined according to Greulich and Pyle [32] by the same investigator every 12 months. Annual growth velocity during the 1st year was compared with the predictive growth velocity according to bone age at the start of the study. Inulin clearance was determined at baseline and every 12 months. The GFR was also estimated at baseline and every 3 months using the Schwartz formula [33].

At enrollment, stimulated GH secretion was investigated by a standardized propanolol-glucagon test [34]. Plasma GH levels were determined by commercial radioimmunoassay. Glucose regulation was assessed by a standard oral glucose tolerance test (OGTT) (1.75 g glucose/kg body weight, maximum 75 g), after an overnight fast, at the start of the study and at 12 and 24 months. Plasma glucose and serum insulin concentrations were measured at 0, 15, 30, 60, and 120 min. Impaired glucose tolerance was defined using standards proposed by the National Diabetes Data Group [35]. Control values for fasting plasma glucose and insulin and their response during the OGTT were obtained from the data of Rosenbloom et al. [36].

Statistical analysis. Results are expressed as mean ±SD. Analysis of variance (ANOVA) was used to compare times of treatment (paired ANOVA) or populations (factorial ANOVA). We used multiple regression analysis to define the predictive characteristics of response to rhGH: stepwise regression, backward and forward procedure. To analyze pubertal progression we also used the Mann-Whitney test. Frequencies were compared with the chi-squared test. $P<0.05$ was taken to indicate a significant difference.

Results

Baseline characteristics

Ninety patients were included in the study, 65 boys and 25 girls, who were transplanted between 1982 and 1991. Fifty-nine children (65%) had congenital kidney disease: malformations (12 hypoplasia, 12 dysplasia, 24 obstructive uropathies) or hereditary disorders (8 juvenile nephronophthisis, 3 chronic microcystic interstitial nephritis). The others had acquired disease (24 glomerulopathies, 7 hemolytic uremic syndrome). Forty-four, the treated group, received rhGH immediately, and 46, the control group, 1 year later. Fifty-five were prepubertal and 35 were in early puberty, with the same ratio in the two groups. Patient characteristics at the start of those who completed the 1st year are given in Table 1. Mean CA was 12 years, mean height SDS was –3.5 SD, and mean baseline annual growth velocity was 4.1 cm. Mean bone age was delayed by 3 years. There was no difference in mean height SDS or baseline annual growth velocity between the two groups. However, the mean weight in the control group was slightly less than in the treated group: –1.8 SDS versus –1.3, respectively (P=0.02). The BMI confirmed this small difference: W/H^2 +1.3 SDS in the control group versus +2.1 SDS in the treated group (P=0.04). All children were slightly overweight. The patients were on average 3 years post transplantation. Mean inulin clearance was 52±20 ml/min per 1.73m^2 in the control group and 50±18 ml/min per 1.73m^2 in the treated group. The immunosuppressive regimen was the same in the two groups. At enrollment 66 patients received daily steroids: 34 in the control group and 32 in the treated group. Twenty patients, 10 in each group, received alternate-day prednisone therapy at a mean dosage of 0.20 mg/kg per day. Prednisone had been withdrawn in 2 patients of the control group and 2 treated patients at the start of the trial.

Among the 74 children tested for GH secretion, the mean GH peak in response to the glucagon-propanolol test was 45.5 ng/ml. There was no difference in mean GH peak in either group. Four children had a GH response below 10 ng/ml and only 1 of them had a GH peak below 5 ng/ml. A second test was not performed in

Table 1. Baseline characteristics: patients who completed the 1st year of the study

	Control group (*n*=44)	Treated group (*n*=41)	
Chronological age (years)	11.8±3.3	12.2±3.1	NS
Bone age (years)	8.8±2.6	9.7±3.1	NS
Height (cm)	123.6±13	127.5±15	NS
Height (SDS)	–3.7±1.3	–3.3±1	NS
Growth velocity (cm)	4.2±2.1	4.1±2	NS
Time from grafting (months)	33±21	40±27	NS
GFR-calculated (ml/min per 1.73 m^2)	61±27	67±26	NS
GFR-inulin (ml/min per 1.73 m^2)	52±20	50±18	NS
Daily/alternate-day/no steroids	34/10/2	32/10/2	NS
GH peak (ng/ml)	41.2±37	50±40	NS

SDS, Standard deviation score; GFR, glomerular filtration rate; GH, growth hormone; NS, not significant

Table 2. Growth data at 1 year

	Control group (*n*=44)		Treated group (*n*=41)		
	Baseline	At 12 months	Baseline	At 12 months	
Height velocity (cm)	4.2±2.1	4.6±2.7	4.1±2	7.7±2.5	*P*<0.0001
Height (SDS)	–3.7±1.3	–3.7±1.3	–3.3±1	–3±1.2	*P*=0.005
Weight (SDS)	–1.8±1	–1.8±1	–1.3±1.1	–1.2±1.3	NS
W/H^2	17.65±2.4	18.13±2.8	19.3±3.3	19.3±3	NS
W/H^2 (SDS)	+1.3±1.8	+1.6±2.0	+2.1±2.1	+2.2+2.1	NS
Bone age (years)	8.4±2.7	9.4±2.9	9.1±3.2	10±3.1	NS
HV/BA (SD)		–1.6±3		+1.86±2	*P*<0.0001

HV/BA, Height velocity according to bone age at the start; W/H^2, body mass index

these children. The mean peak GH response was not significantly different between prepubertal and early pubertal children. No correlation was observed between GH peak and growth velocity prior to therapy, weight, and steroid dosage at the beginning of the study.

Growth data

Eighty-five children completed the 1-year study. Growth data are given in Table 2. Growth velocity was significantly increased by rhGH, 7.7 cm in the treated group versus 4.6 cm in the control group, *P*<0.0001 (Fig. 1). A significant improvement in the height SDS occurred in the treated group with a gain of +0.3 SDS. Weight increase was similar in the two groups, but we observed a change in body appearance, with increased muscle bulk and reduced fat mass in the treated group. Progression in bone age was not accelerated by rhGH: +1.0 year in the control group and +0.9 year in the treated group. Mean growth velocity according to bone age at the start was +1.86 SD with GH and –1.60 SD in the control group. The control group was placed on GH therapy after the first 12 months. To analyze growth, data from their first 12 months of therapy were grouped with the 1st-year data from the treated group and so on for the 2nd, 3rd, and 4th years of treatment. During the subsequent years of

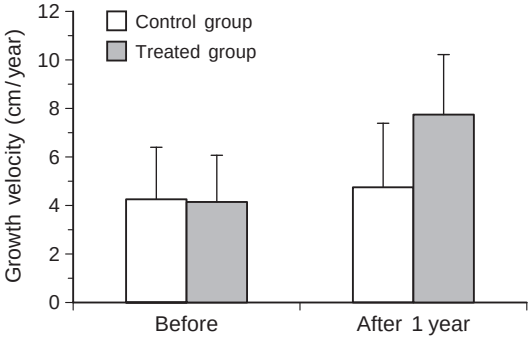

Fig. 1. Growth velocity after the 1st year of the study

treatment, a decrease in growth velocity was noted compared with the 1st-year data, but growth rates remained above the values obtained before treatment: 5.9 cm (56 patients) at 2 years, 5.5 cm (41 patients) at 3 years, and 5.2 cm at 4 years (14 patients). Standardized height increased from –3.5 SD at baseline to –2.5 SD after 3 years of treatment (Table 3).

The response to rhGH was not uniform, with some patients having a remarkable response, some only a minimal change in height velocity, and 8 patients not being affected. The predictive factors for response to GH in these patients were determined by evaluating several factors and treatment modalities at the beginning of the

Table 3. Growth velocity with GH

Patients *n*	Growth velocity (cm/year)				
	Baseline	1 Year	2 Years	3 Years	4 Years
56	4.4	7.8	5.9		
41	4.4	8.4	6.7	5.5	
14	4.6	8.5	6.7	6	5.2

study in a multiple stepwise regression analysis. Three factors were found to be predictive of response to therapy: GFR at the start, growth velocity prior to GH therapy, and mode of corticosteroid administration. Growth velocity during treatment was positively correlated with inulin clearance at the start of treatment, P=0.001. A reduced GFR had a significantly negative influence on growth, but height gain was greater for the children with baseline GFR <50 ml/min per 1.73m^2 whose growth velocity was 3 cm without GH and 6.6 cm with GH, versus 6.7 and 8.4 cm for the children with GFR >50 ml/min per 1.73m^2. Growth velocity with rhGH was positively correlated with growth velocity before therapy (P=0.03), but height gain was minimal (<3 cm) when baseline growth velocity was >7 cm/year. Better responses occurred with alternate-day steroid administration: 8.8 versus 6.6 cm/year with daily administration (P=0.001). However, the GH-induced increment was similar in the two groups: +2.8 versus +2.7 cm. In contrast, GH peak after stimulation, CA, bone age, pubertal state, degree of growth retardation, and time from grafting had no effect on response to GH therapy.

Influence of rhGH on pubertal development

Pubertal development was analyzed after the 1st year of the study in the two groups. In all patients, both prepubertal and pubertal at the start of the study, pubic hair increased more significantly in the treated than in the control group (P=0.04). Again considering all patients, increase in testicular volume from 3.8 ml to 5.6 ml versus 3.0 to 4.2 ml did not reach significance (P=0.10). In girls, because of the small number of patients (10 in each group), breast development was not interpretable. The limited time of observation did not allow investigation of the growth spurt in this study.

Renal function (Table 4)

After the 1st year a moderate but significant decrease in GFR was observed in both the treated and control groups. Mean plasma creatinine level was 110 µmol/l at the start and 121 µmol/l at 1 year in the treated group versus 115 and 134 µmol/l in the control group. Mean inulin clearance was 50 ml/min per 1.73m^2 at the start and 49 ml/min per 1.73m^2 at 1 year in treated patients versus 52 and 45 respectively in control patients. Two patients in each group lost their graft and returned to dialysis. After 1 year the mean urea, bicarbonate, urinary protein excretion, and microalbuminuria were unchanged in the two groups.

Calcium, phosphorus, and vitamin D metabolites

At 1 year, calcium was significantly decreased in the two groups, ionized calcium was unchanged, while phosphate increased in both groups. Urinary calcium excretion was unchanged. Parathyroid hormone tended to increase during the 1st year in all patients. Vitamin D metabolites, 25-hydroxy-vitamin D and 1, 25-dihydroxy-vitamin D were unchanged. There was a marked and statistically significant increase in serum alkaline phosphatase in the treated group (P=0.001).

Table 4. Laboratory data at 1 year

	Control group (n=44)		Treated group (n=41)		P
	Baseline	At 12 months	At start	At 12 months	
Renal function					
Creatinine (µmol/l)	115±49	134±51	110±52	121±57	NS
GRF, Schwartz (ml/min per 1.73 m^2)	61±27	54±23	67±26	64±26	NS
GFR, inulin clearance (ml/min per 1.73 m^2)	52±20	45±21	50±18	49±23	NS
Urea (mmol/l)	12.8±7.7	14±7.8	12.4±6	12.4±5.7	NS
Bicarbonate (mmol/l)	22±3.3	22±3.6	22±3.5	22±3.6	NS
Proteinuria (g/l)	0.6±2.2	0.8±2.8	0.15±0.2	0.22±0.3	NS
Microalbuminuria (mg/l)	95±230	93±235	27±26	51±42	NS
Calcium-vitamin D					
Calcium (mmol/l)	2.44	2.38	2.46	2.42	NS
Ionized calcium (mmol/l)	1.30	1.26	1.31	1.31	NS
Phosphorus (mmol/l)	1.35	1.44	1.41	1.51	NS
Urinary calcium (mmol/l)	1.2±1.3	1±1	0.88	0.62	NS
Parathyroid hormone (pg/ml)	62±51	74±69	59±42	92±94	NS
25-OH-vitamin D (ng/ml)	57	49	51	44	NS
1,25-OH$_2$-vitamin D (pg/ml)	50	62	54	55	NS
Alkaline phosphatase (l/Ul)	216	208	203	267	0.001

25-OH-vitamin D, 25-hydroxyvitamin D; 1,25-OH$_2$-vitamin D, 1,25-dihydroxyvitamin D

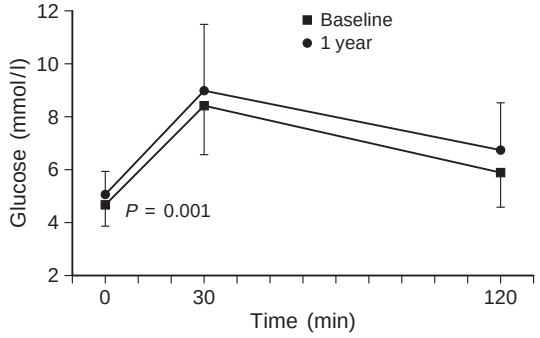

Fig. 2. Glucose concentrations during the oral glucose tolerance test (OGTT)

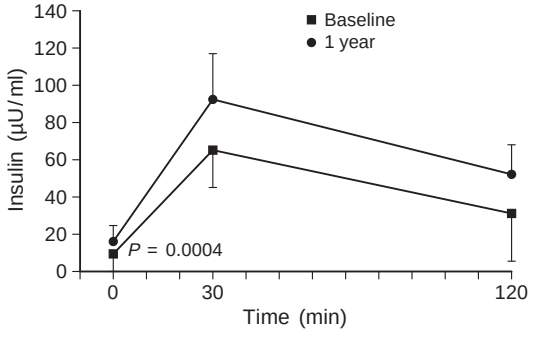

Fig. 3. Insulin concentrations during OGTT

Glucose tolerance (Figs. 2 and 3)

Baseline OGTT. The results of OGTT were analyzed in 49 patients at enrollment. Mean fasting plasma glucose and plasma insulin were normal during the test compared with published control values. Analysis of individual values showed normal plasma glucose values in 44 children; 5 had impaired glucose tolerance and 11 had insulin resistance. Multiple regression analysis showed a significant linear relationship between fasting glucose concentration and fasting insulin concentrations (P=0.04) and also with time after transplantation (P=0.0003).

Effect of GH treatment on OGTT responses. The results of OGTT were compared at the start and at 1 year in 20 treated and 19 control children . Mean fasting glucose concentrations increased slightly but significantly in the two groups (P=0.001); the mean values were not different. Mean glucose concentrations during OGTT were not different after 1 year in control and treated children. Mean fasting plasma insulin and mean values during OGTT increased significantly at 1 year in the two groups (P=0.0004), but again the mean values were not different.

Correlation of OGTT with growth velocity. Correlations were studied between glucose and insulin levels on the one hand and growth velocity, weight SDS, GFR, GH peak, and steroid dosage on the other. A strong, significant negative correlation was found between fasting plasma insulin at baseline and growth velocity after 1 year of therapy (P<0.0001).

Rejection

Acute, biopsy-proven rejection episodes were not significantly more frequent during the 1st year in the group of patients who received rhGH compared with controls: 9 in 44 versus 4 in 46 patients (P=0.11). Nevertheless, rejection episodes occurred more frequently with GH in patients with a history of more than one rejection episode. In children with no or one rejection episode prior to GH, 3 patients in each group, treated (n=27) and control (n=25), had a new rejection episode during the 1st year of the trial. In children with a history of two or more rejections, 6 of the 17 treated patients had a new episode, but only 1 of the 21 control patients (P=0.01). During the 2nd year of the study, a rejection episode occurred in 6 of the patients who had constituted the control group, during their 1st year of GH treatment. Again, this rejection episode occurred in 1 of the 22 children who had a history of no or one rejection episode, but in 5 of the 19 children who had more than two rejections (P=0.01). Adding these patients to the 9 GH-treated patients who underwent a rejection episode during the 1st year of the trial, we compared the total of 15 patients who had a rejection episode during their 1st year of treatment with the patients who did not reject. These two groups did not differ in age (mean 12 years), time since transplantation, renal function at the start, and immunosuppressive regimen. Among them, 4 children were noncompliant. They had been transplanted 34 months previously; 13 children received daily and 2 alternate-day steroids. Their mean creatinine level at start of therapy was 122 μmol/l. The rejection episodes occurred at an average of 4 months after initiation of GH. Rejections were treated with methylprednisolone in 14 patients and with antithymocyte globulin in 1. In 4 cases GH was immediately interrupted; these patients recovered and maintained stable renal function (mean creatinine level at last follow-up 151 μmol/l). Eleven children continued GH despite a first rejection: 5 lost their graft and returned to dialysis, 4 had another episode and stopped GH after a second rejection (mean creatinine level at last follow-up 168 μmol/l), and only 2 recovered and maintained stable renal function (mean creatinine level at least follow-up 135 μmol/l).

Twelve other patients had acute rejection during the 2nd and 3rd years of therapy. GH was assumed to be the cause in some cases, but this was difficult to demonstrate without a control group. However, it seems that increased risk for rejection continued during the 2nd and 3rd years of therapy. In 7 other cases, chronic rejection worsened during treatment, but the role of rhGH was difficult to prove.

Adverse effects

One patient developed papilledema without other symptoms of benign intracranial hypertension. Diagnosis was made by routine ophthalmological examination. Papilledema resolved after discontinuation of rhGH.

Withdrawal from study protocol

GH therapy was continued based on effectiveness, safety, and tolerance. Three patients initially in the control group were not treated after 1 year; 1 had developed diabetes and 2 had improved growth velocity above 7 cm during the first period without GH. A total of 75 children with a functioning graft received treatment over 1 year, 56 completed 2 years, 41 completed 3 years, and 14 4 years. Reasons for withdrawal of GH therapy were: acute rejection in 13 cases, increased serum creatinine level in 7 cases, non-compliance in 2 cases, lack of effectiveness in 4 cases, target height obtained in 9 cases, and patient or parent request without an obvious medical reason in 8 cases. rhGH was discontinued after papilledema in 1 patient, and because of severe viral infection in 2 patients. Ten patients lost their graft and required dialysis: they were withdrawn from the study but continued rhGH therapy on dialysis.

Discussion

Despite advances in therapy and optimal medical care, some children do not achieve appreciable catch-up growth after transplantation [1, 2]. Mehls et al. [37] have shown the possibility of growth improvement in uremia, and in 1989 rhGH was suggested for treating small children with renal failure under conservative treatment or after kidney transplantation. Many studies have demonstrated that rhGH improves growth after kidney transplantation [16–20, 38, 39]. The present study supports these findings, since rhGH induced catch-up growth in the majority of cases. This improvement in growth was, however, less than that in patients with chronic renal failure managed conservatively and given rhGH. In such patients mean growth velocity was about 12 cm/year in the 1st year and 8.3 cm/year the 2nd year, and standardized height progressed from –2.6 SD at baseline to –0.7 SD after 24 months of treatment [40, 41]. In transplanted children the height gain was moderate with GH and tended to decrease in the subsequent years, nevertheless remaining above baseline. This tapering effect has already been observed in patients receiving GH therapy, whatever the indication for treatment, dose, and duration. Despite this relative decrease in growth velocity after 2 years, if no adverse effects occur and treatment is efficient, it appears acceptable to continue GH until target height is obtained.

Weight gain was not modified by rhGH in our study. Treatment with rhGH had no effect on body weight, but could improve muscle bulk and body appearance of children receiving corticosteroids [19]. Cochat et al. [42] showed a significant increase in lean body mass and a decrease in fat mass in seven children who received GH after renal transplantation. Bone maturation appeared unaffected, indicating the possibility of an improvement in adult height.

As in the present report, the first European study [20] showed that pubertal status did not appear to influence the effectiveness of rhGH. The results of Janssen et al. [17] were similar in the prepubertal and early pubertal group, but Benfield et al. [43] reported an improved height SDS which correlated positively with progression in Tanner stage. GH therapy in boys and girls with isolated GH deficiency appears to accelerate the rate of pubertal maturation [44, 45], and it was suggested that GH treatment might induce acceleration of puberty in boys with idiopathic short stature [46]. In the present study many patients had an advancement in Tanner stage with rhGH and faster development of pubic hair, but the data were not conclusive for testicular volume and breast development. Further investigations are required to determine whether pubertal maturation is influenced by GH or interferes with the growth-promoting effect of GH in transplanted children. In this study GH was shown to be effective whatever the CA, bone age, or pubertal status.

Four factors predictive of effectiveness were determined: growth velocity prior to GH, GFR at start, modalities of prednisone therapy, and insulin resistance. The German study group [47] showed that growth velocity was positively correlated with pretreatment growth velocity. Rees and Maxwell [48] confirmed this correlation during treatment. We also observed that growth velocity was positively correlated with pretreatment velocity, but height gain was minimal in patients with normal growth velocity before therapy. The negative influence of a reduced GFR on growth after transplantation is well known. In the reports of Benfield et al. [43] and Janssen et al. [17] a linear correlation was found between growth velocity under GH and creatinine clearance. Our report confirmed a positive correlation between growth velocity with therapy and GFR at the start. But children with GFR below 50 ml/min doubled their growth rate and benefited more from rhGH than children with GFR above 50 ml/min, who had better spontaneous growth and a moderate increment in height gain.

Prednisone dosage is another major factor inhibiting post-transplantation growth. Ingulli et al. [49] showed that the only factor affecting rhGH response was the use of prednisone: all 5 patients not receiving prednisone demonstrated catch-up growth compared with only 1 of the 12 patients receiving prednisone. Only recipients with normal renal function could stop prednisone, and these patients usually exhibited catch-up growth and did not require GH therapy. In the present study, only 4 of the 90 patients included were off prednisone. Rees and Maxwell [48], analyzing growth velocity in 17 prepubertal transplanted children receiving alternate-day prednisone, showed prednisone dose to be an important predictor of response. In contrast, Hokken-Koelega et al. [39], comparing 6 children on daily and 5 on alternate-day prednisone, reported no difference in growth velocity with GH. In the present study growth velocity tended to be better with alternate-day than with daily steroid therapy. However, growth gains were statistically the same with the two modes of treatment.

The present study showed a hitherto unreported negative correlation between fasting plasma insulin levels at start and growth velocity after 1 year of treatment, independent of steroid doses. It is well known that glucocorticoids induce insulin resistance [50, 51]. The reduced

growth response to GH treatment associated with higher insulin resistance might reflect the same adverse effect of glucocorticoids on two different target tissues, hepatic cells for insulin and bone cartilage for GH. This effect is dependent on steroid doses, but it may also depend on individual sensitivity or bioavailability of the drug. Sarna et al. [52] showed that similar methylprednisolone dosages result in greater inhibition of adrenal cortisol production in liver transplant than in renal transplant recipients due to a greater exposure to prednisolone. The same group [53] showed that the area under the time-concentration curve of methylprednisolone, rather than the dose, predicts adrenal suppression and growth in children with liver and renal transplants. Thus the same glucocorticoid dose could inhibit growth in one patient and not in another. As far as exposure to the drug is concerned, it would be important to adjust glucocorticoid dose according to individual glucocorticoid pharmacokinetics.

Interpretation of reports on GFR change with GH treatment is hindered by methodological bias if GFR is based on plasma creatinine, since GH intake increases muscle bulk. Thus in the present study we refer to inulin clearance. GH may affect GFR in several ways. It is well established in animals [54] and humans [55] that GH increases the GFR and renal plasma flow in a parallel manner, an effect mediated by IGF-I [56]. This was not observed in subjects with a reduction of GFR below 50 ml/min [57] and was not expected to occur for that reason in a number of patients included in the present study. GH was also shown to be involved in degradation of renal function, since GH transgenic mice develop renal failure with renal lesions of glomerulosclerosis [58]. A recent study by Kawaguchi et al. [59] in rats showed that prolonged administration of GH dose-dependently induces deterioration in renal function and structure. Increased kidney size and glomerulosclerosis have also been demonstrated in humans with acromegaly [60], but in these situations the circulating concentrations of GH are markedly elevated, far above the level obtained with the dosage used in this study. IGF-I receptors have been located in the mesangium [61] but IGF-I does not seem to play a role in glomerular sclerosis [62]. Finally, if GH promoted rejection, this could also be a factor affecting GFR. In children with chronic renal failure under conservative treatment, the data substantiate the conclusion that rhGH is not associated with an accelerated decline in kidney function. Fine et al. [41] reported a stable GFR with a significant decline from baseline only after 5 years of GH administration, and this was probably related to the natural history of the disease process rather than GH treatment.

Published reports give conflicting results on the effect of rhGH on graft function in transplanted children. Fine et al. [16], Rees et al. [22], and Van Es [20] did not observe deterioration of renal function. Janssen et al. [17] reported no accelerated decline of graft function with GH. Maxwell et al. [18] showed an increase in GFR after 1 week and 6 months of GH therapy, which returned to baseline by 1 year. Tonshoff et al. [19] and Hokken-Koelega et al. [63] showed the same degradation of GFR in the treated group as in the control group. However, Bartosh et al. [64], Benfield et al. [43], Chavers et al. [65], and Van Dop et al. [66] described a reduction in renal function in some patients with rhGH. In our study, involving a greater number of patients, we observed a moderate decline in graft function during the 1st year of the trial, which was not significantly different between the two groups. In the subsequent years we observed a moderate decline in graft function, but it was not possible to ascribe the decrease in GFR to GH.

GH may also affect the immune system [21], improving the immune reaction [67] and thereby theoretically increasing the incidence of transplant rejection. Tyden et al. [23] reported biopsy-proven acute rejection in two recipients with previously stable renal graft function and Schwartz et al. [24] also reported two patients with acute rejection of the nine children treated with GH. In contrast, Fine et al. [16], Laine et al. [68], Rees et al. [22], and Tonshoff et al. [19] reported no significant change in the number of acute rejection episodes following rhGH treatment.

The present study, which included 90 children with a control group, showed clearly that the risk of acute rejection was not increased in children who had no or only one episode prior to commencing GH treatment, while patients with more than one episode were exposed to a significant risk of developing another. We found that rejection episodes occurred in 30% of the patients with this history, but the patients who rejected did not differ in terms of age, renal function at the start, and type of immunosuppression. Non-compliance frequently occurs in children; in this study 4 patients were non-compliant in the treated group versus 1 in the control group (NS). HLA matching and pretransplant cytotoxic antibody were not documented in this study. An important observation was that the continuation of GH after a first rejection episode was associated with a high risk of further episodes and finally of graft loss. Only 2 of the 11 patients who continued GH despite a first crisis maintained stable renal function.

Progression of chronic rejection [43, 66, 69] has been described. In the report of Jabs et al. [69], all seven children with previously diagnosed chronic rejection had an increase in serum creatinine concentration after receiving rhGH. Similar findings were observed in our study, but it is difficult to prove the role of GH treatment since the evolution of chronic graft rejection is variable and unpredictable.

After exclusion of 1 patient with recurrent nephrotic syndrome in the control group, there was no significant change in proteinuria during the study. Other laboratory data were not modified with GH treatment, except for a significant increase in alkaline phosphatases in association with improved growth. This is presumed to be related to new bone formation. GH is known to have numerous effects on the calcium-phosphate/1,25-dihydroxyvitamin D parathyroid hormone axis, including an increase in tubular phosphate reabsorption in normal children [70]. Pretreatment hyperparathyroidism worsened in 2 patients in the treated group. However, we found no effect of GH treatment on calcium, phosphorus, and vita-

min D metabolism with unchanged levels of 25- and 1-25-dihydroxyvitamin D. No increase in urinary calcium excretion was observed in children who received vitamin D.

The mean fasting plasma glucose levels and the OGTT curve were slightly increased at the end of the 1st year and were similar in the treated and the control group. These findings confirm the results of previous studies [39, 71, 72]. The insulin level was high during OGTT in 22% of the patients at the start of the study and increased during the 1st year of treatment, but was again similar in the treated and control group, probably as a consequence of corticosteroids. However, the long-term effects of hyperinsulinemia in association with GH treatment are not yet known.

Femoral head avascular necrosis [73] and intracranial hypertension [74] have been reported in several series of patients receiving rhGH. Few such serious adverse effects were observed in this study. There was no avascular necrosis of the femoral head and only one episode of benign intracranial hypertension, where symptoms resolved after discontinuation of rhGH.

Psychological tolerance must also be considered. Some patients did not tolerate daily GH subcutaneous injections, and 8 of the total of 87 children who started this treatment asked to stop it.

In conclusion, GH effectively improves growth velocity in short transplanted children, with clear-cut but limited catch-up growth. The risk of rejection is not increased in patients with a history of no or only one rejection episode, but this risk is significant in the others. In addition, there is a high risk of further episodes if rhGH is continued after a first rejection during this treatment. These risks must be carefully considered before initiating treatment with rhGH in a transplanted child. In high-risk cases close monitoring is mandatory.

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Workshop

Early renal development: a key to the understanding of adult disease?

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The VIIth Workshop on Developmental Nephrology in association with the XIth Congress of the International Pediatric Nephrology Association (London, 12–16 September 1998) will be held in Stockholm, Sweden, 9–11 September 1998. The workshop will focus on molecular mechanisms regulating early kidney maturation with the hypothesis that some adult diseases may have their roots in fetal or early postnatal life. It will consist of poster sessions and 5 sessions with invited speakers as follows:

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- Nephrogenesis: from stem cell to mature nephron
- Apoptosis: a double-edged sword
- Regulatory systems
- Molecular mechanisms of water and electrolyte homeostasis

Speakers include: G. Germino (Baltimore), K. Tryggvasson (Stockholm), R. Lifton (Yale), R. Thakker (London)

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