0031-3998/92/3104-0406$03.00/0
PEDIATRIC RESEARCH

Vol. 31, No. 4, 1992
Printed in U.S.A.

Effects of Prolonged Growth Hormone Administration in Rats with Chronic Renal Insufficiency

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ABSTRACT. Recombinant hGH (rhGH) augments short-term linear growth in experimental animals and children with chronic renal failure. Significant augmentation of final height, however, requires prolonged growth hormone therapy during years of growth. The effects of prolonged rhGH treatment on linear growth, progression of renal dysfunction, and longevity in the setting of renal insufficiency are unknown. We examined at 9, 15, and 25 wk growth in length and weight, glomerular filtration rate measured by inulin and creatinine clearance, food efficiency (g ingested/weight gained), and survival in treated (U-GH) and untreated (U) 75% nephrectomized uremic rats and in treated (S-GH) and untreated (S) sham-operated rats. We also measured kidney weight to body weight ratios at the time the rats were killed. Treatment was rhGH 1.0 mg s.c. three times a week during wks 4–12 of life. Length of U-GH rats was greater than that of U rats ($p < 0.05$) at 15 and 25 wk (but not at 9 wk) and equal to that of S rats throughout the study. Length of S-GH rats exceeded that of S rats. At 9 wk, weight was diminished in both U and U-GH rats ($p < 0.05$) *versus* S and S-GH rats; by 15 wk, U-GH rat weight was equal to S rat weight. Glomerular filtration rate measured by creatinine was markedly reduced in U and U-GH rats and did not increase in response to prolonged rhGH in either U-GH or S-GH rats. Diminished food efficiency of U rats *versus* S rats ($p < 0.05$) was not improved significantly by rhGH. Mortality from chronic renal failure was eight of 19 (42%) in U-GH rats compared with four of 13 (31%) in U rats. Both mean glomerular area and sclerotic index were increased in U-GH rats *versus* U rats ($p < 0.05$). The growth-promoting effect of rhGH was observed late (rather than early) in the growth period. Prolonged rhGH treatment did result in U-GH rats attaining length and weight comparable to S rats, ameliorating the growth failure due to uremia. Glomerular filtration rate was not adversely affected by prolonged rhGH treatment, and there appeared to be significant renal growth with growth hormone administration as measured by kidney weight/body weight ratio. Survival data, however, suggest that the growth-stimulating effect of rhGH in uremic animals may be accompanied by a trend toward reduced longevity, and histologic evaluation revealed increased glomerular hypertrophy and glomerulosclerosis in both normal and uremic rats treated with rhGH. (*Pediatr Res* 31: 406–410, 1992)

Received February 26, 1991; accepted November 22, 1991.
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Abbreviations

CRF, chronic renal failure
GH, growth hormone
rhGH, recombinant human growth hormone
ANOVA, analysis of variance
GFR, glomerular filtration rate
KW, kidney weight
BW, body weight
C_{CR}, creatinine clearance
C_{IN}, inulin clearance
CRI, chronic renal insufficiency
SI, sclerotic index

Impaired linear growth is an important consequence of CRF during childhood. Each year, the average child with CRF loses 0.3–0.5 SD in height SD scores for chronologic age, resulting in a final adult height more than 2 SD below the mean in 34% of children who receive kidney transplants before age 15 y (1). The pathogenesis of this growth failure is complex; improvement in metabolic status alone by dialysis does not consistently improve growth (2, 3). Several studies suggest that alterations in GH and IGF-1 play an important role. Elevated random and provoked GH levels in uremic patients suggest hypothalamic dysregulation (4) or end-organ resistance to this hormone. High levels of immunoreactive IGF-1 (5) in the midst of depressed IGF-1 bioactivity (6) reflect, in part, elevated concentrations of IGF-1 binding proteins (IGF-1 BP3) found in kidney disease.

These observations have stimulated interest in GH treatment of CRF-associated growth failure. Subtotal nephrectomized rats receiving short-term administration (14–20 d) of rhGH demonstrate accelerated linear growth without elevating IGF-1 levels (7). Recombinant hGH treatment of children with CRF for comparably short periods (6–12 mo) results in accelerated linear growth without detectable alterations in renal function (8–10). Although such shorter-term results are encouraging, significant augmentation of final adult height for rhGH-treated children with CRF will require sustained therapy throughout several years of growth (11). Experimental evidence supporting the efficacy and safety of such long-term GH therapy is lacking.

In addition to stimulating linear growth, GH exerts multiple metabolic and anabolic effects on soft tissues, including kidney. The effects of prolonged rhGH administration not only on growth but also on rate of progression of renal dysfunction and longevity of a recipient with CRF are unknown. This study examines the effects of extended rhGH treatment of partially nephrectomized rats throughout the period of time of rapid growth.

MATERIALS AND METHODS

The study design is depicted in Figure 1. Fifty-seven male, 3-wk-old Sprague-Dawley rats (Harlan Sprague-Dawley, Inc., Indianapolis, IN), weighing 31–55 g, were placed in four experimental groups: *1*) U-GH, chronic renal insufficiency + rhGH (n = 24); *2*) U, chronic renal insufficiency (n = 20); *3*) S-GH, sham operated + rhGH (n = 7); and *4*) S, sham-operated (n = 6). CRI was induced by a one-step uninephrectomy and ligation of ½ to ⅔ of the contralateral kidney, as described previously (12). Excised control kidneys were weighed as total kidney wet weights. Kidney weights were determined by weighing all noninfarcted renal tissue in nephrectomized or sham-operated animals. Sham operation involved the same midline incision without removal or ligation of renal tissue. Nephrectomies and sham operations were performed under general anesthesia (35–50 mg/kg intraperitoneal pentobarbital sodium, USP) at 3 wk of age. Animals were housed in separate cages with free mobility at constant ambient temperature (22–24°C) and had *ad libitum* access to tap water and regular powdered rat food (24% crude protein; Teklad Premier, Madison, WI).

After a 1-wk recovery period, U-GH and S-GH animals received s.c. rhGH (1 mg met-rhGH; Genentech, Inc., South San Francisco, CA) three times per wk during wks 4–12 of life. U and S animals received 0.2 mL of sterile water (placebo) s.c. three times per wk during the same period. For rhGH-treated rats, rhGH was given for 8 wk, discontinued for 12 wk, then reinstituted for 10 d. The reinstitution of GH was performed to examine persistent *versus* acute rhGH effects. At 2-wk intervals, under ether anesthesia, weights and lengths (nose tip to base of tail) were measured. Careful measurements of food and water consumption were made twice weekly.

Tritiated inulin (355.5 μCi/g) NET-314L; New England Nuclear, Wilmington, DE) was delivered via Alzet mini osmotic pumps (Alza Corp., Palo Alto, CA) implanted s.c. in the dorsum of the neck. Using siliconized metabolic cages, 18-h urine collections were obtained for determination of inulin and creatinine clearances at 8–9, 12 (creatinine only), 20–22, and 23 wks of age. Urine samples were collected under oil and stored at −70°C until assayed. Creatinine concentrations were determined on tail vein blood samples using a Beckman Creatinine Analyzer 2 (Beckman Instruments Inc., Brea, CA) as previously described (13). Serum and urine ^{3}H-inulin values were measured as cpm per 20-μL aliquot in 3.5 mL of scintillation cocktail. A Packard Tri Carb 300 (Packard Instrument Co., Downers Grove, IL) determined the counts per sample. At 25 wk of age, animals were killed by overetherization, and necropsy samples were obtained.

Remnant kidneys or kidneys from sham-operated rats were obtained at the time of death and were immersion-fixed in 10% neutral buffered formalin. Coronal sections were routinely processed and embedded in paraffin. Three-mm thick sections were made, stained with periodic acid-Schiff, and examined microscopically (Olympus BH2; Olympus Optical Co. Ltd., Tokyo, Japan).

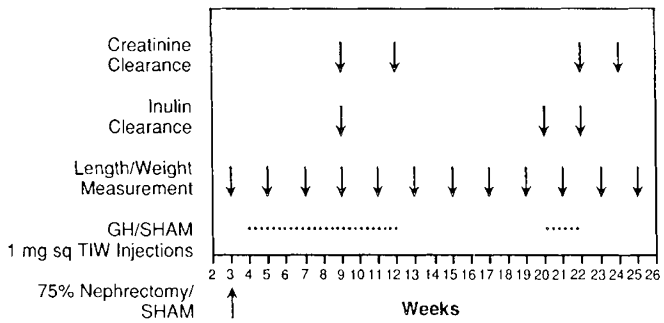

Fig. 1. Depiction of study design indicating timing of procedures and measurements (↓) and intervals of rhGH administration (••••).

Mean glomerular area. Glomeruli were assessed morphometrically on control and treatment group kidney sections at 23 wk. The planar area of each glomerular capillary tuft was determined on these sections using a computerized planimeter (Micro-plan II; Monsanto Corp., Natick, MA). The values of these planar areas, measured in approximately 50 glomeruli, were averaged for each specimen to obtain mean glomerular area for each rat.

Glomerular sclerosis. A semiquantitative score (SI) was used to evaluate the degree of glomerular sclerosis using the scoring system of Raij *et al.* (14). Severity of sclerosis was graded from 0 to 4+ for each glomerulus on the same sections used for morphometric assessments. Thus, a 1+ lesion represented involvement of up to 25% of glomerulus whereas 4+ represented sclerosis of 75–100% of glomerulus. Whole kidney sclerosis index was then calculated by averaging the scores for all glomeruli (on average some 50 glomeruli) present on the single thin section (15–17).

All procedures were performed within the regulation of the Animal Welfare Act and the NIH Guide for the Care and Use of Laboratory Animals.

Results are expressed as the mean ± SD. All growth data was normalized to reflect the percentage of change from baseline, (*i.e.* from 3 wk of age). Data for each growth response and for metabolic parameters were analyzed for wk 9, 15, and 25, using a one-way ANOVA at each time point. The overall type I error rate (α) was 0.05 for each response. The Bonferroni correction for multiple comparisons was used so that α was 0.017 (0.05/3) for each ANOVA at each time point. When the overall F test was significant, pairwise comparisons were made using Fisher's least significant difference method for multiple comparisons. Analysis of survival data was performed using a χ^2 contingency table.

RESULTS

Survival (Table 1). Operative mortality among all four groups was five of 57 (9%; range 0–15%). Acute mortality in nephrectomized rats (occurring within 1 wk of surgery and before rhGH therapy) was eight of 44 (18%). CRI mortality was eight of 19 (42%) in the U-GH group and four of 13 (31%) in the U group (NS, p = 0.52); total survival (including iatrogenic deaths) also did not differ significantly between the two groups ($p > 0.2$). All S and S-GH animals survived to 25 wk except for one iatrogenic mortality.

Growth (Table 2). Compared with control animals, U rats demonstrated linear growth retardation throughout the postoperative study period. Significant differences in lengths of U-GH (22.9 ± 0.8 cm) *versus* U (22.2 ± 0.3 cm) rats ($p < 0.05$) were observed. The overall F test for one-way ANOVA of change in length (from age 3 wk) was not significant at wk 9, but was significant at wk 15 and 25 ($p < 0.017$ at each time point). Pairwise comparisons indicated that S-GH rats had a significantly higher percentage of change than did U rats at 15 wk. At 25 wk, the length of S-GH rats was significantly greater than that of the other three groups. In addition, the length of U-GH rats had also

Table 1. *Survival of U-GH, U, S-GH, and S rats through first 25 wk of life*

Group	n	Iatrogenic mortality	CRF mortality*	Survivors
U-GH	19	4/19 (21.1%)	8/19 (42.1%)	7/19 (36.8%)
U	13	1/13 (7.7%)	4/13 (30.8%)	8/13 (61.5%)
S-GH	6	0/6 (0%)		6/6 (100%)
S	6	1/6 (16.7%)		5/6 (83.3%)

* CRF mortality indicates death during or after treatment with rhGH.

Table 2. *Length of study animals (cm ± SD) at start of study (3 wk of age) and during (9 and 15 wk of age) and 10 wk after (25 wk of age) rhGH administration or sham injection*

	Length (cm)			
Age	U-GH	U	S-GH	S
3 wk	10.4 ± 0.3 (n = 19)	10.4 ± 0.3 (n = 13)	10.6 ± 0.2 (n = 6)	10.6 ± 0.2 (n = 6)
9 wk	19.3 ± 1 (n = 14)	18.9 ± 0.7* (n = 13)	20.1 ± 0.8 (n = 6)	19.8 ± 0.4 (n = 6)
15 wk	22.9 ± 0.8† (n = 10)	22.2 ± 0.3 (n = 10)	23.4 ± 0.2‡ (n = 6)	22.5 ± 0.4 (n = 6)
25 wk	24.4 ± 0.8†§ (n = 7)	23.4 ± 0.4* (n = 8)	25.6 ± 0.2‡ (n = 6)	24.5 ± 0.3 (n = 5)

* $p < 0.05$ U *vs* S.
† $p < 0.05$ U-GH *vs* U.
‡ $p < 0.05$ S-GH *vs* S.
§ $p < 0.05$ U-GH *vs* S-GH.

Table 3. *KW/BW ratios [(KW/BW) × 100] in U-GH, U, S-GH, and S animals at 25 wk of age*

Group	KW/BW ratio
U-GH	0.68 ± 0.16 (n = 15)
U	0.52 ± 0.06* (n = 13)
S-GH	0.66 ± 0.04 (n = 6)
S	0.69 ± 0.06 (n = 6)

* $p < 0.05$ U *vs* all other groups.

increased significantly from baseline compared with that of the U rats.

Weight gain was reduced in both U and U-GH rats compared with both S and S-GH rats ($p < 0.05$) by 7 wk of age and persisted thereafter. The overall F tests for percentage of increase in weight at wk 9, 15, and 25 were all significant. Subsequent pairwise comparisons showed that the S rats' percentage of weight increase was significantly higher than those of U and U-GH rats at all three time points. Similarly, the S-GH rats' increase was significantly higher than those of U and U-GH rats at wk 15 and 25. No significant percentage of weight increase occurred between U and U-GH rats or between S and S-GH rats at any time.

KW/BW ratio [(KW/BW) × 100] (Table 3). U-GH rats demonstrated a KW/BW ratio (0.68 ± 0.16) that was greater than that of U rats (0.52 ± 0.06 [$p < 0.05$]) and comparable to that of the S (0.66 ± 0.04) and the S-GH (0.69 ± 0.06) groups. In the one-way ANOVA of KW/BW ratios, the overall F test was significant ($p < 0.05$). Pairwise comparisons using Fisher's least significant difference method showed that the mean KW/BW ratio of U rats was significantly lower than each of the means of the other three groups.

Food and water use. "Food efficiency" was determined by dividing g of food consumed by g of weight gained. No significant differences in food efficiency were noted between any of the groups during the first 15 wk of growth. Between 15 and 25 wk of age, however, food efficiency in uremic animals declined compared with that in sham-operated animals 0.1 ($p < 0.05$). GH treatment did not augment food use when nephrectomized (*i.e.* U *versus* U-GH) or sham-operated animals (S *versus* S-GH) were compared.

"Water efficiency" was determined by dividing the mL of water consumed by g of weight gained. Nephrectomized animals (both U-GH and U) required more water for growth ($p < 0.005$) during each interval studied (5–9, 9–15, and 15–25 wk).

Renal function. C_{CR} per 100 g BW determinations were made four times during the study period: *1*) after 6 and 8 wk of GH/sham injection therapy (effect of prolonged GH administration); *2*) 8–10 wk after cessation of GH/sham injection therapy (persistence of GH effect); and *3*) after reintroduction of GH therapy for 10 d at 23 wk of age (Fig. 2).

Five wk after 75% nephrectomy, C_{CR} of U (0.155 ± 0.06 mL/min) and U-GH (0.185 ± 0.08 mL/min) rats were markedly reduced ($p < 0.001$) compared with those of S (0.82 ± 0.04 mL/min) and S-GH (0.815 ± 0.07 mL/min) rats by one-way ANOVA at all time points (Fig. 2). C_{CR} did not change with age in any study group. GH therapy did not significantly alter C_{CR} in either nephrectomized or sham-operated animals when compared with untreated control animals.

C_{IN} per 100 g BW determinations were similar in U (0.15 ± 0.07 mL/min) and U-GH (0.14 ± 0.10 mL/min) rats after 5 wk of GH therapy. U-GH rats did demonstrate higher C_{IN} (0.23 ± 0.14 mL/min) than U rats (0.12 ± 0.07 mL/min) 8 wk after cessation of GH therapy. This difference became nonsignificant (0.24 ± 0.14 *versus* 0.19 ± 0.11 mL/min) 10 d after resuming GH therapy at 23 wk of age (Fig. 3).

Histologic analyses. Mean glomerular tuft area, measured morphometrically on a single section of the kidney, was increased by 44% rhGH in U-GH *versus* U rats (13.72 ± 1.36 *versus* 9.53 ± 0.84 $mm^2 \times 10^{-3}$; $p < 0.05$). rhGH also enhanced glomerular growth in rats with intact renal parenchyma (10.42 ± 1.74 *versus* 7.79 ± 1.01 $mm^2 \times 10^{-3}$; $p < 0.05$) (Fig. 4). These increases in glomerular size were accompanied by more severe glomerulosclerosis, assessed on a single thin section by average SI (0–4 scale). SI was 2.15 ± 0.58 in U-GH rats *versus* 1.17 ± 0.61 in U rats. In S-GH rats, SI was comparable to that in U rats (1.13 ± 0.77; p = NS) and in marked contrast to that in S rats (0.15 ± 0.10; $p < 0.05$) (Fig. 5).

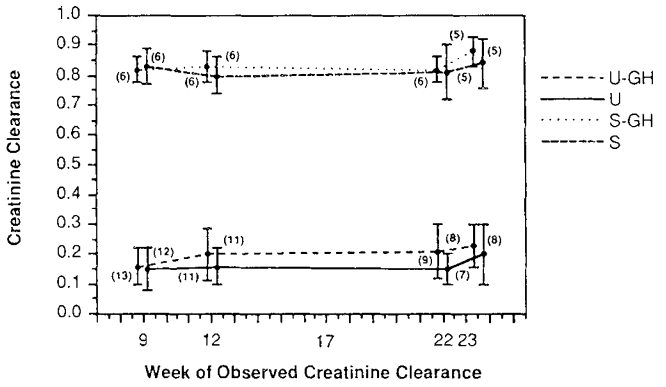

Fig. 2. Mean C_{CR} (±2 SEM) per 100 g BW over time for all study groups.

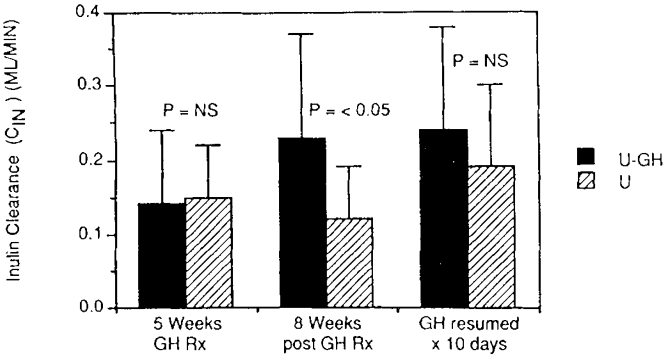

Fig. 3. Inulin clearance per 100 g BW determinations in U and U-GH animals.

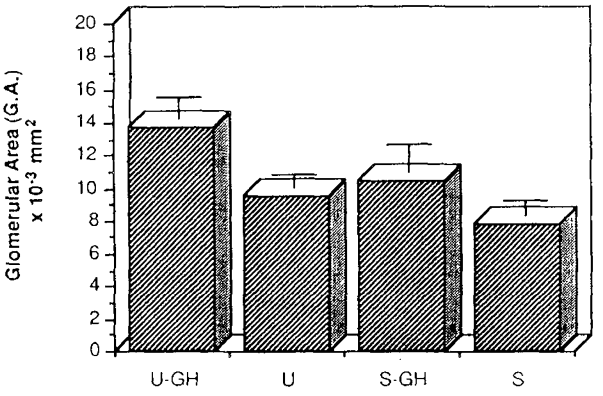

Fig. 4. Glomerular area (10^{-3} mm) plotted for all four groups. U-GH *vs* all other groups, $p < 0.05$.

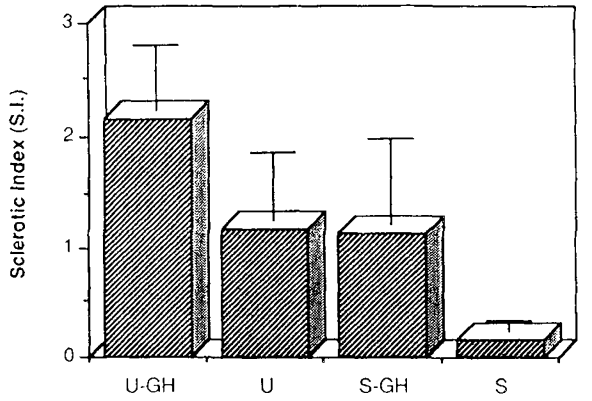

Fig. 5. SI plotted for all four groups. U-GH *vs* U, S-GH, and S, $p < 0.05$. U and S-GH *vs* S, $p < 0.05$.

DISCUSSION

Clinical trials investigating augmentation of linear growth in children with CRF are already underway. Results of shorter term therapy are encouraging, demonstrating increased growth velocity and improvement in eight SD scores for chronologic age and skeletal age (9–11). Investigations of the effect of rhGH on linear growth and renal function using animal models have similarly examined short treatment intervals using varied doses of GH. Significant increments in final adult height, however, will only be achieved with treatment spanning several years of growth. Questions remain not only about the efficacy of prolonged GH therapy in achieving this goal, but also about beneficial or detrimental renal effects in the setting of preexisting CRF. Our study examines the effect of "moderate" dose rhGH administration throughout the period of rapid linear growth (with and without renal insufficiency) on: *1*) final length of rats; *2*) GFR; *3*) renal size; *4*) survival, and 5) renal histology.

Previous investigators have determined the rapid growth period in rats to be between birth and 12 wk of age (12, 13). We specifically chose to study this entire time period to determine the effect of GH supplementation throughout the period of rapid growth.

Treatment with rhGH (1 mg) three times a week augmented linear growth of both uremic and control rats (7). In contrast to previous studies, however, increased linear growth of GH-treated control and nephrectomized rats occurred late rather than early in the treatment period. This difference may reflect our choice of a lower GH dose (3 mg/wk compared with 5 mg/wk), which could be affordably administered over a 56-d interval. Inasmuch as a dose-response relationship for GH use in uremic animals has not been established, selection of a "reasonable" rhGH dose is problematic. Short-term administration of 1.75 mg/wk does not augment growth of nonuremic rats (7). We feel the selection of an intermediate dose more closely approximates the clinical application of prolonged GH treatment of children with CRF.

The degree of CRI was similar between U and U-GH animals; further, little variation was observed between animals within each group as demonstrated by Figure 2. Significant growth retardation occurred relatively early in U rats. The temporary narrowing in the differences in lengths between U and S rats at 15 wk of age was likely related to mortality of the most severely affected uremic rats. Treatment with rhGH corrected uremia-induced growth failure. The discrepancy between U and U-GH animals became progressively larger at 9 wk (0.4 cm), 15 wk (0.7 cm), and 25 wk (1.0 cm), indicating a persistent rhGH effect throughout the growth period. The degree of additional growth observed due to prolonged, moderate-dose rhGH therapy is interesting for two reasons. First, the approximately 4–5% increment in length corresponds roughly to a reasonable expectation for beneficial outcome (3–5 inches) in children with CRF currently treated with rhGH (8, 10). Second, rhGH therapy not only improved the growth of uremic animals, but resulted in growth rates of U-GH rats that were indistinguishable from those of S rats. Thus, our data further support the ability of rhGH therapy to improve uremia-induced growth failure and add new experimental evidence that this growth-promoting effect can be sustained throughout a prolonged growth phase.

The effects of prolonged rhGH treatment on renal function are not well defined. Previous short-term studies (7–14 d) in normal animals have demonstrated an increase in GFR after GH administration (18). Long-term (greater than 14 d) studies have not been reported. It has been speculated that long-term GH administration might deleteriously affect GFR by leading to hyperfiltration (19). The increase in GFR reported in normal animals with 7–14 d of GH administration may demonstrate that hyperfiltration is indeed present. In our study, however, GH administration (for 2 wk) in animals with CRI did not increase GFR.

To our knowledge, this is the first report on the effects of prolonged GH administration (9 wk) on renal function in a growing animal. Our data in sham-operated animals demonstrate that the increase in GFR found with short-term GH administration does not persist over longer periods of GH administration. The mechanisms by which GH alter GFR are unknown (18, 19). Therefore, it is difficult to know why the acute effect of GH on GFR in healthy animals does not persist with prolonged administration.

Animals with CRI who received GH had a somewhat higher GFR 8 wk after stopping GH compared with the control CRI animals. These data may be explained by *1*) sicker animals dying earlier in the GH group, thus leaving the "healthier" animals, or *2*) GH conferring some short-term beneficial effect on renal function in CRI. In light of the histologic data, the first explanation is certainly possible, but the number of animals used and the timing of our measurements does not permit us to definitively determine which of the two explanations is correct. Further study will be needed.

Effects of long-term rhGH treatment on renal morphology are also complex. GH-stimulated IGF-1 appears to function as a paracrine growth factor in the settings of GH-induced hypertrophy and compensatory hypertrophy of the kidney and in proximal tubular regeneration after ischemic injury (20, 21). On the other hand, deleterious effects of continuous GH excess on renal histology are suggested by human autopsy data and animal models of gigantism. Enlargement of renal mass, glomeruli, convoluted tubules, and capillary membrane thickness has been described in the setting of prolonged hGH excess (22). Transgenic animals that express chronically high levels of GH or GH-releasing hormone demonstrate mesangial cell proliferation and glomerulosclerosis in addition to increased renal mass. Sclerosis may be GH-dependent, inasmuch as glomerular hypertrophy observed in IGF-1 transgenic mice is not accompanied by sclerosis, matrix alterations, (23, 24) or increased albumin excretion

(25). GH deficiency, on the contrary, may protect against glomerulosclerosis in partially nephrectomized rats (26). Renal morphologic and histologic changes resulting from prolonged pulsatile rhGH treatment in animals with reduced renal mass and function have not been previously reported.

The larger KW/BW ratio in animals with CRI that received rhGH might imply that rhGH can augment renal function to a near normal level. The compensatory hypertrophy seen with CRI and GH administration returned KW (initially ~25% of normal) to that of normal animals of the same weight with two kidneys. This might explain how GH could maintain CRI over a long period of time after rapid body growth had ceased and after GH administration had stopped. Further, it might suggest that GH could in the short term actually improve function in CRI compared with animals with CRI who did not receive GH. Our data differ from those of Mehls *et al.* (27), who found no effect of GH on KW/BW. The Mehls *et al.* study involved only 7 d of GH administration as opposed to 9 wk in our study.

A concern of using rhGH to stimulate linear growth in children with CRI is that rhGH may superimpose additional undesirable growth stimuli, leading to glomerulosclerosis and accelerated decline in renal function. Our data indicate that compensatory hypertrophy in renal mass is accompanied by glomerulosclerosis in both uremic and sham-operated rhGH-treated animals. Glomerular tuft area was significantly increased in both U-GH and S-GH rats when compared with untreated control animals. Marked alterations in sclerosis, as judged by SI, were also observed. SI of U-GH rats was nearly double that of U rats. Equally disconcerting was an increase of SI in S-GH rats to a degree equal to that in U rats.

Thus, rhGH therapy of rats with CRI was associated in our study with deleterious histologic renal consequences. This finding in the setting of pulsatile rhGH administration is important because this approximates the clinical treatment of CRI children with GH. Previous reports of GH-associated glomerulosclerosis in humans (gigantism) and experimental animals (transgenic mice) reflected nonpulsatile exposure to elevated GH levels. Although the findings of rhGH-associated sclerosis raise concern, their significance vis-à-vis GH therapy of children with CRI is unclear. Exposure of U-GH animals to extremely high relative doses of rhGH throughout the entire period of rapid growth does not mirror current experimental rhGH treatment of children with CRI. In addition, glomerulosclerosis observed in our rhGH-treated animals was not accompanied by detectable diminution in renal function. Nevertheless, our data suggest the possibility that long-term rhGH therapy may impair glomerular function and perhaps accelerate a decline in renal function.

In conclusion, rhGH administered to normal and CRI rats during the rapid growth period (3–12 wk of age) results in improved linear growth in the CRI animals. GFR in CRI animals is not adversely affected by GH. In fact, the improvement in GFR as measured by C_{IN} was coincidental with attaining normal KW/BW ratios in the CRI animals receiving rhGH. However, histologic data indicate that this salutory effect of rhGH on linear and renal growth is accompanied by progressive glomerulosclerosis in both U-GH and S-GH animals. Although rhGH-associated impairment of renal function was not observed, survival data suggest that the growth-stimulating effect of rhGH in uremic animals may be accompanied by a trend toward reduced longevity.

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