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NEPHROLOGY FORUM

Stimulating growth in uremic children

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Case presentation

A 4-year-old white boy presented to Stony Brook University Hospital for the first time at 3 weeks of age with failure to thrive. He was born at 40 weeks gestation by caesarean section (for breech presentation); the birth weight was 3.80 kg. He was discharged at 5 days of age. At 2 weeks of age, he developed loose, watery stools approximately 4 times daily. At that time the infant was receiving Enfamil, 1.0 to 1.5 oz, every 3 to 4 hours. Five days prior to his first admission to the hospital, the patient had been given instead a soy formula; the diarrhea ceased, but formula intake remained at 1.0 to 1.5 oz every 3 to 4 hours. Occasional postprandial vomiting was noted at that time. On the day prior to admission, the patient's weight decreased to 3.66 kg, and he was admitted for evaluation.

Physical examination on admission revealed a temperature of 98°F; respiratory rate, 32 breaths/min; heart rate, 164 beats/min; blood pressure, 79/54 mm Hg; and weight, 3.35 kg. The baby was alert, well hydrated, and in no distress; the remainder of the physical examination was unremarkable. Serum biochemical data on admission showed a sodium of 135 mEq/liter; potassium, 6.9 mEq/liter; chloride, 106 mEq/liter; bicarbonate, 15 mEq/liter; BUN, 74 mg/dl; and creatinine, 2.0 mg/dl. Cultures of urine, blood, and cerebrospinal fluid were negative. The initial serum calcium level was 8.6 mg/dl; serum phosphorus, 6.5 mg/dl; and serum alkaline phosphatase, 292 IU. A renal ultrasound showed bilaterally small, echogenic kidneys, with the right kidney measuring 3 cm in length and the left kidney measuring 4 cm in length (normal length, 5.0 ± 0.4 cm). A DTPA renal scintiscan disclosed 2 small, poorly functioning kidneys. Voiding cystourethrogram revealed a normal bladder and urethra. An MRI scan showed bilateral small kidneys with loss of corticomedullary differentiation.

The clinical diagnosis was renal insufficiency secondary to bilateral renal dysplasia. The formula was changed to PM 60/40, which is low in potassium and phosphorus; sodium bicarbonate also was prescribed at a dose of 2.5 mEq/kg/day in 4 divided doses. Calcium carbonate (1250 mg/day) was added to the formula, and dihydrotachysterol (DHT), 0.25 μg/day, was prescribed. The baby's formula was supplemented with polycose and medium-chain triglycerides to achieve a final caloric concentration of 34 calories/30 cc, and he was given 130–150 calories/kg/day. While in the hospital, the infant gained 0.3 kg, the BUN decreased to 25 mg/dl, and the serum creatinine level decreased to 1.4 mg/dl. The serum calcium level increased to 10.8 mg/dl, and the serum phosphorus decreased to 4.9 mg/dl. Two weeks after discharge (at age 5 weeks), his weight had increased to 4.7 kg (75th centile); his length was 55 cm (50th centile). One month later (at age 9 weeks), he weighed 5.0 kg and was 55.4 cm in length.

At 13 months of age, he was doing well clinically; his weight was 10.6 kg (50th centile), length was 74.3 cm (10th centile), and head circumference was 46 cm (25th centile). The BUN was 80 mg/dl; serum creatinine, 2.1 mg/dl; serum calcium, 10.0 mg/dl; and serum phosphorus, 6.0 mg/dl. The hematocrit was 31%. At 16 months of age, the patient's weight was 10.7 kg, length was 76.5 cm, and head circumference was 47 cm. His weight had declined from the 50th to 30th centile; his centiles for length and head circumference were stable. The BUN at that time was 75 mg/dl, and the serum creatinine level was 1.9 mg/dl. Dietary intake of calories, protein, and fat was well above the recommended daily allowance (RDA) parameters for his age, as assessed by a 3-day home dietary diary. When he was 19 months old, his weight was 11 kg (25th centile), length was 79.7 cm (10th centile), and the BUN and serum creatinine levels were 46 mg/dl and 2.1 mg/dl respectively. At 26 months of age, his weight was 11.6 cm (5th centile); height, 80.4 cm (< 3rd centile); and head circumference, 48 cm (10th centile); the serum creatinine level was 1.8 mg/dl. Thyroid function studies (TSH, T_3RU, T_4, and FTI) were normal. Growth hormone (GH) evaluation at that time included nocturnal sampling (GH increased from 3.9 ng/ml to 33 ng/ml between 2400 hr and 0400 hr) and a propranolol/L-dopa stimulation test, which revealed GH levels of 18 ng/ml and 23.0 ng/ml at 60 and 90 min following stimulation. Blood glucose and insulin levels disclosed no carbohydrate intolerance.

Discussion

DR. RICHARD N. FINE (*Professor and Chairman, Department of Pediatrics, State University of New York at Stony Brook, Stony Brook, New York*): Growth retardation is one of the serious clinical manifestations associated with irreversible renal insufficiency in infants, children, and adolescents. Although the relationship was first noted at the end of the last century [1], the availability of dialysis and renal transplantation, which could prolong the lives of children who developed end-stage renal disease (ESRD), focused attention on the medical and psychosocial consequences of the growth retardation that accompanies chronic renal failure [2, 3].

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Despite extensive investigative efforts (detailed in four international conferences beginning in 1977) [4–7], the precise cause of growth retardation in children with chronic renal failure has not been defined. Multiple factors have been implicated [8]: (*1*) age at onset of chronic renal failure; (*2*) concomitant acidosis; (*3*) progressive renal osteodystrophy; (*4*) inadequate caloric intake; and (*5*) perturbations of various growth factors. In addition, repetitive episodes of electrolyte imbalance in infants with dysplastic renal disease also have been identified as contributing to growth retardation in these children [9].

Correction of acidosis, prevention and/or treatment of renal osteodystrophy, provision of adequate caloric intake, and correction of any electrolyte abnormalities have not uniformly achieved optimal linear growth in children with chronic renal failure, as today's case illustrates. That growth retardation persists despite the presumed correction of these untoward factors is indicated by the recent report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) [10]. Of more than 1500 pediatric recipients of renal allografts (who received a renal transplant since January 1987), the majority manifested significant growth retardation at the time of transplantation (< 5th percentile on the growth curve and/or a standard deviation score (SDS) more negative than minus 2.00). Moreover, 25% of these patients had not previously received dialysis.

Reasoning from these observations, investigators have concluded that perturbations of the various growth factors and their end-organ effects are likely candidates to explain the growth retardation, and much information has been assembled to assess this possibility. Growth hormone levels are elevated in children with chronic renal failure [11]. Measurement of somatomedin-C (insulin-like growth factor, IGF) by bioassay revealed low levels both in adults and children with chronic renal failure [12, 13], whereas radioimmunoassay revealed elevated levels of IGF in children with chronic renal failure [14]. This discrepancy led Phillips et al to conclude that an inhibitor of somatomedin activity is present in uremia [15]. Utilizing newer techniques (radioimmunoassay and radioreceptor assay following acid chromatography), Powell and coworkers demonstrated normal IGF-1 levels, slightly elevated IGF-2 levels, and elevated IGF binding protein (IGF-BP) levels in children with chronic renal failure [16]. A theoretical possibility is that IGF-BP binds circulating free IGF-1 levels and functions as a uremic inhibitor.

The presence of elevated growth hormone levels in growth-retarded children with chronic renal failure dampened interest in the potential therapeutic efficacy of exogenous GH in reversing the defect. However, a report by Mehls and Ritz in the early 1980s utilizing porcine GH in the uremic (5/6 nephrectomy) rat model demonstrated that giving short-term (2 weeks) intraperitoneal porcine GH in supraphysiologic doses increased the animals' linear growth and weight [17]. Treatment did not totally correct the growth retardation associated with uremia in the uremic rat model, but a significant increment was obtained. Therefore, other unidentified factors contributed to the growth retardation in this animal model. Subsequent studies utilizing recombinant human growth hormone (rhGH) and rat GH in the uremic rat model confirmed that a significant increase in growth velocity was obtained [18–20]. The study by Nakano and colleagues was particularly important because it demonstrated that the salutary effects of GH treatment accrued despite the presence of a protein-restricted diet [20]. Consequently, if protein restriction decreases the rate of progression of chronic renal failure, the concomitant use of rhGH with protein restriction in growth-retarded children would be expected to be therapeutically efficacious.

Table 1. rhGH Treatment in children with chronic renal failure

Reference	# of pts	prior 12 months	rhGH 12 months
Koch et al [22]	5	4.9 ± 1.4[a]	8.9 ± 1.2[a]
Tonshoff et al [23]	9	4.4[a]	8.0[a]
Wilson et al[b] [24]	2	—	9.4[a]
Rees et al [25]	6	4.8[a]	10.7[a]

[a] Cm/yr.
[b] Cystinosis.

Stimulated by the results reported in the uremic rat model, we initiated a phase-I study in the latter half of 1986 using supraphysiologic doses of rhGH in 5 growth-retarded children who had chronic renal failure (GFR, 14–30 ml/min/1.73 m^2). We administered the rhGH subcutaneously, 0.125 mg/kg thrice weekly, and observed a significant increase in the annualized growth velocity following 6 months of treatment: 4.9 ± 1.4 cm/yr to 10.1 ± 2.0 cm/yr, ($P < 0.01$) [21]. Subsequent studies reported (*1*) by Koch et al of the actual one-year data from 5 phase-I patients [22], (*2*) by Tonshoff et al of 9 patients, 8 of whom had ESRD and were undergoing continuous ambulatory peritoneal dialysis (CAPD) [23], (*3*) by Wilson et al of 2 patients with cystinosis [24], and (*4*) by Rees et al of 6 patients with chronic renal failure [25] all demonstrated an increased rate of growth following one year of rhGH treatment compared with that achieved during the year prior to treatment (Table 1).

The number of patients enrolled in our phase-I study has increased to 11, and the length of followup has been extended from 18 months to 4 years (Table 2). Following a report that daily injections (but the same weekly dose) of rhGH in children with GH deficiency increased growth velocity over that obtained with the thrice-weekly schedule [26], we gave the patients in our phase-I study a daily dose of rhGH (0.375 mg/kg/week). Let's look at a variety of clinical parameters to assess the success of the daily rhGH schedule.

Growth hormone levels. Prior to receiving rhGH treatment, each patient, save one (Patient 9) had either a 24-hour integrated spontaneous GH test (GH levels obtained every 30 minutes during a 24-hour period, Patients 1 through 5) or an L-dopa/propranolol GH stimulation test (GH levels obtained 60 and 90 minutes following stimulation). In addition, Patients 1 through 5 had the L-dopa/propranolol test after one year of rhGH treatment and after discontinuing treatment for 10 days. The results of the L-dopa/propranolol stimulation tests are shown in Table 3.

Patients 6 and 11 with cystinosis had an abnormal GH stimulation test; that is, they both failed to achieve a GH level greater than 10 ng/dl. Similarly, Patient 3 had an abnormal stimulation test and manifested only one peak between 5 and 7 ng/dl during the 24-hour spontaneous GH secretion test. The remaining patients demonstrated an adequate response to the stimulation test (GH level greater than 10 mg/dl).

Growth velocity. During the year prior to rhGH treatment, the mean ± SD growth velocity of the 11 patients was 5.4 ± 2.2

Table 2. Patient data

Pt.	Age (*yrs*)	Renal disease	Duration of treatment (*months*)	SDS
1	6.6	PUV[a]	18	−3.36
2	4.9	Dysplasia (BOR)[a]	36	−2.18
3	4.1	PUV	48	−2.16
4	2.9	Dysplasia	48	−3.40
5	3.8	Dysplasia	48	−3.38
6	8.1	Cystinosis	36	−2.17
7	5.8	Dysplasia	36	−2.40
8	16.3	Alagille's syndrome[a]	36	−5.93
9	9.4	Dysplasia	24	−3.34
10	2.5	Dysplasia	24	−2.80
11	10.6	Cystinosis	18	−4.14
mean	6.8		30	−3.21
± SD	4.1		12	1.12

[a] PUV, posterior urethral valves; BOR, brachial otorenal syndrome; Alagille's syndrome, arteriohepatic dysplasia.

Table 3. L-dopa/propranolol stimulation test[a]

Pt.	Serum growth hormone levels (*ng/dl*) 60 min	90 min
1	12.6	3.6
2	18.9	15.5
3	6.8	4.5
4	22.2	15.7
5	46.4	19.5
6[b]	5.3	4.1
7	23.6	12.9
8	18.4	10.1
9	—	—
10	24.9	28.4
11[b]	3.7	2.6

[a] Baseline tests were performed before initiation of rhGH in Patients 6–11. Studies in Patients 1–5 were performed following one year of rhGH treatment but after therapy had been discontinued for 10 days.
[b] Cystinosis.

Table 4. rhGH Treatment in chronic renal failure

Pt.	Growth velocity (*cm/yr*) −12 mon	12 mon	24 mon	36 mon	48 mon
1	4.8	8.7			
2	6.3	10.7	7.7	9.5[a]	
3	6.3	7.5	9.8	7.3	7.4
4	3.0	8.6	8.1	9.6	5.9
5	4.3	9.2	5.6	6.0	7.5
6	5.0	7.2	8.2	7.8	
7	5.7	8.9	9.8	7.4	
8	3.0	6.2	4.2	5.2	
9	6.7	9.5	7.2		
10	10.7	11.9	7.1		
11	3.2	9.2			
mean	5.4	8.9	7.5	7.5	6.9
± SD	2.2	1.6	1.8	1.6	0.9
−12 mon versus		P = <0.00005	NS	<.008	NS

[a] Underlined value indicates that the patient received daily rhGH for the previous 12 months.

cm/yr (Table 4). Following rhGH treatment, the mean ± SD growth velocity increased to 8.9 ± 1.6, 7.5 ± 1.8, 7.5 ± 1.6, and 6.9 ± 0.9 cm/yr at 12, 24, 36, and 48 months, respectively. The increment in growth velocity increased significantly at 12 and 36 months following rhGH treatment, compared with that achieved during the year prior to treatment.

The lack of significance at 24 months is attributed to the inclusion of Patient 10. Growth data at 12 to 24 months, when the patient's chronologic age increased from 3.5 to 4.5 years, was compared with data from the year prior to treatment, when the patient's chronologic age increased from 1.5 to 2.5 years. Since the expected increment was much greater during the latter time interval, it is not possible to compare actual growth velocity as an indicator of efficacy, but the improvement in the SDS is a more valid parameter for comparison.

Improvement in growth velocity was verified in Patient 10 by the change in standard deviation score following rhGH treatment (Table 5). The mean SDS decreased significantly at all time intervals following treatment. Of 7 patients treated for 36 months, 5 reached the normal growth centile, defined as above the 5th centile on the growth curve and an SDS more positive than −1.88. Patient 2 actually exceeded the 50th centile on the growth curve at 36 months, as indicated by a positive standard deviation score. This level was at the patient's 50th centile for mid-parental height; therefore rhGH treatment was discontinued at that time because the child's stature was considered normal for chronologic age at the 50th centile (Fig. 1).

Weight gain and anthropometric measurements. The mean ± SD for weight gain following rhGH treatment increased significantly from that achieved during the 12 months prior to treatment: from 1.6 ± 0.6 kg/yr to 3.1 ± 0.6 (P = 0.0001), 3.0 ± 0.8 (P < 0.0002), 3.6 ± 1.5 (P < 0.0009), and 3.4 ± 1.0 kg/yr (P = NS) at 12, 24, 36, and 48 months of rhGH treatment, respectively. The mean ± SD for triceps skinfold thickness (TSF) decreased significantly at all time intervals, the mid-arm circumference (MAC) increased significantly at 24 and 36 months, and the mid-arm muscle circumference (MAMC) increased significantly at all time intervals following rhGH treatment. The patients thus demonstrated an increase in muscle mass; consequently, significant anabolism was attributable to the rhGH treatment in addition to the increment in growth velocity.

Bone age. In general, mean bone age did not increase more than the advancement in chronologic age; in individual patients, however, the increase in bone age exceeded the advancement in chronologic age (Table 6). The ratio of change in height age to change in bone age was greater than 1.0 in each instance; thus the increment in height exceeded the expected advancement in bone age. Therefore, true catch-up growth (defined as an increase in the SDS for height) occurred, and the increased growth velocity was not merely an increment in height consequent to advancement in bone age.

Glucose intolerance. At the initiation of the phase-I study, we were concerned that GH administration would accentuate the glucose intolerance of uremia. Altered glucose homeostasis occurs in 30% to 60% of patients with acromegaly [27]. Of these, 20% develop frank diabetes mellitus [28]. In normal individuals, high-dose GH administration can lead to increased fasting blood glucose levels [29] as well as to an increase in fasting insulin levels [30]. Consequently, we monitored fasting

Table 5. rhGH Treatment in chronic renal failure

Pt.	Height standard deviation score (SDS) 0 mon	12 mon	24 mon	36 mon	48 mon
1	−3.36	−2.18			
2	−2.18	−1.46	−0.69	+0.13[a]	
3	−2.16	−1.89	−1.13	−0.72	−0.29
4	−3.40	−2.71	−2.60	−1.78	−1.64
5	−3.38	−2.99	−2.99	−2.77	−2.12
6	−2.17	−1.68	−1.10	−0.63	
7	−2.40	−1.65	−0.72	−0.30	
8	−5.93	−5.16	−5.29	−4.50	
9	−3.34	−2.44	−2.06		
10	−2.80	−1.94	−1.89		
11	−4.14	−3.35			
mean	−3.21	−2.50	−2.05	−1.51	−1.35
± SD	1.12	1.07	1.46	1.64	.95
0 mo versus P =	<.00005		<.0001	<.0003	<.02

[a] Underlined value indicates that the patient received daily rhGH for the previous 12 months.

Table 6. rhGH Treatment in chronic renal failure

Pt.	Bone age (*years*) 0 months	12 months	24 months	36 months	48 months
1	4.3	5.4			
2	3.3	4.3	4.3	5.5	
3	2.9	3.3	4.5	5.5	7.0
4	1.7	2.2	2.8	4.3	4.5
5	2.7	3.8	4.7	5.5	7.0
6	7.5	8.3	9.4	11.5	
7	3.0	4.2	6.0	7.0	
8	9.8	10.5	14.0	14.5	
9	7.2	8.0	10.5		
10	0.2	2.0	3.0		
11	8.0	10.0			
mean	4.6	5.6	6.6	7.7	6.2
± SD	3.0	3.1	3.9	3.8	1.4
0 months versus P =	<.00005		.0002	.0001	<.02

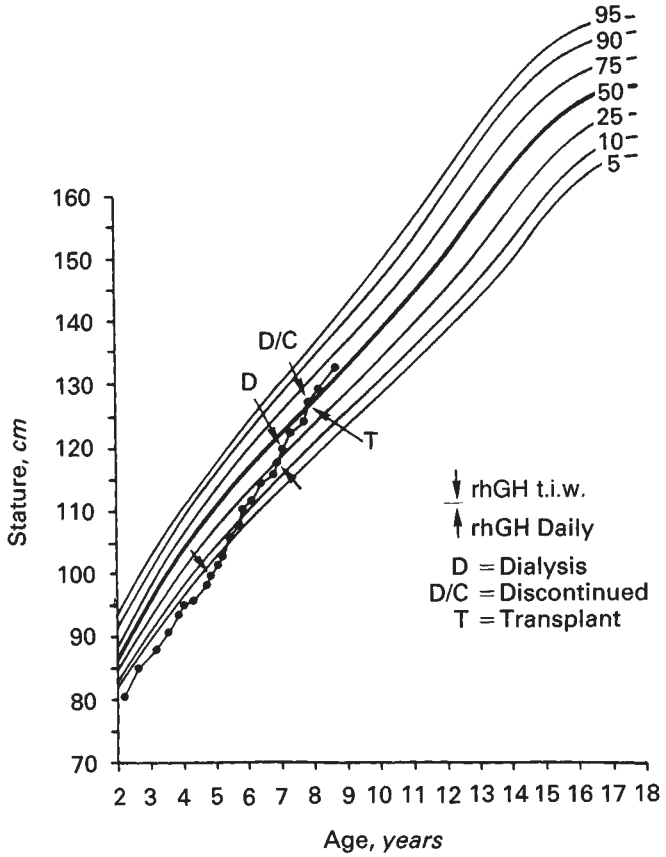

Fig. 1. *Growth curve of Patient 2 before and after treatment with rhGH.* (t.i.w., 3 times weekly.)

and 2-hour postprandial blood glucose and serum insulin levels serially before and after rhGH administration.

We detected no significant increase in the fasting and 2-hour postprandial blood glucose and insulin levels following rhGH treatment. Serial glucose tolerance tests in Patients 1 through 5 during the first year of treatment revealed no significant change in the blood glucose or insulin levels [22]. Similarly, other reports detailing the use of rhGH in children with chronic renal failure and in those undergoing dialysis revealed no adverse effects of rhGH treatment on glucose tolerance [23–25].

Serum calcium, phosphorus, and alkaline phosphatase levels. Exogenous [31] and endogenous [32] growth hormone increases calcium excretion and decreases phosphorus excretion by the normal kidney [31, 32]. We attempted to assess rhGH's potential for producing perturbations in the serum calcium and phosphorus levels. In our serial studies, we observed no significant increase in the serum calcium level (Table 7). The mean serum phosphorus level increased significantly at 36 and 48 months, respectively.

Following initiation of our phase-I study, Foremen et al published a report indicating that the concomitant administration of rat GH and 1,25-dihydroxyvitamin D_3 caused severe hypercalcemia and markedly increased the $U_{Ca^{++}}/U_{Cr}$ in the uremic rat model [33]. These results raised a concern regarding the potential adverse impact of concomitant rhGH and 1,25-dihydroxyvitamin D_3 treatment on the progressive decline of renal function in children with chronic renal failure because of hypercalcemia and increased renal calcium deposition [34]. All the patients in our study were receiving prophylactic 1,25-dihydroxyvitamin D_3, so we serially assessed the $U_{Ca^{++}}/U_{Cr}$ to detect hypercalciuria following rhGH treatment. Except for the 2 patients with cystinosis and Fanconi syndrome who had hypercalciuria prior to rhGH treatment, no patient had a consistent $U_{Ca^{++}}/U_{Cr}$ greater than 0.20 (the upper limit of normal) following rhGH treatment [35]. The dose of rhGH administered to the patients in our study did not produce significant hypercalciuria despite concomitant 1,25-dihydroxyvitamin D_3 administration.

The serum alkaline phosphatase level did increase significantly with rhGH treatment, however (Table 7). This phenomenon also has been noted following rhGH treatment of children with GH deficiency and is thought to reflect GH's effect on osteoclastic activity [36].

Table 7. Biochemical data[a]

Serum levels	0 months	12 months	24 months	36 months
Calcium, *mg/dl*	9.7 ± 0.8	9.7 ± 0.5	9.7 ± 0.5	9.9 ± 0.6
Phosphorus, *mg/dl*	4.7 ± 1.0	5.0 ± 1.0	5.1 ± 0.9	5.2 ± 1.2[b]
Alkaline, phosphatase, *U/liter*	239 ± 104	315 ± 130[b]	381 ± 226[b]	359 ± 156
Cholesterol, *mg/dl*	191 ± 63	201 ± 41	206 ± 35	217 ± 34
Triglyceride, *mg/dl*	176 ± 118	154 ± 62	149 ± 56	186 ± 109

[a] All data reflect the mean ± SD.
[b] $P < 0.05$; all other values NS versus 0 months.

Table 8. Calculated creatinine clearance (*ml/min/1.73 m²*)

Pt.	0 months	12 months	24 months	36 months	48 months
1	14	13			
2	17	18	12		
3	16	14	15	10	11
4	14	19	19	14	14
5	30	25	28	24	20
6	64	56	48	45	
7	37	52	45	42	
8	30	24	22	16	
9	26	18	15		
10	22	15	15		
11	35	27			
mean	28	26	24	25	15
± SD	15	15	14	15	5
0 months versus P =		NS	NS	NS	NS

Serum cholesterol and triglyceride levels. Hyperlipidemia with elevated triglyceride levels occurs in approximately two-thirds of acromegalic patients [37]. This increase has been attributed to reduced activity of hepatic triglyceride lipase and lipoprotein lipase [38]. Because lipoprotein lipase also is decreased in uremia, and because the potential therefore exists for accentuated perturbations in lipid metabolism in uremic patients receiving rhGH, we evaluated lipid metabolism in our patients and, as noted in Table 7, found no significant change in the serial serum cholesterol or triglyceride levels following rhGH treatment. Similarly, Tonshoff and colleagues noted no change in the serum cholesterol, triglyceride, or lipoprotein profiles (HDL, LDL, VLDL cholesterol) after giving rhGH for 12 months to 10 children with chronic renal failure [39].

Renal function. Exogenous [40] and endogenous [41] growth hormone increases glomerular filtration rate (GFR) and renal plasma flow (RPF). Hypophysectomy reverses both phenomena [42]. Because of the concern that rhGH-induced hyperfiltration might accelerate the decline in renal function, we calculated GFR at frequent intervals following initiation of rhGH treatment.

Although 2 patients (Patients 1 and 2) required initiation of dialysis following 18 and 30 months of rhGH treatment respectively, we did not observe a significant decline in the calculated GFR (creatinine clearance) for the group as a whole [44] (Table 8). Similarly, Tonshoff et al observed no change in the slope of the calculated GFR curve for the year prior to rhGH treatment, compared with that observed during the year following rhGH treatment [39]. Utilizing inulin clearance to measure GFR, the same group observed no significant change following 6 weeks of rhGH treatment [45].

Haffner and coworkers measured the GFR by inulin clearance in 7 healthy adult volunteers and 7 adults with chronic renal failure prior to and following 3 days of rhGH administration [46]. Glomerular filtration rate increased significantly in the volunteers but not in the adults with chronic renal failure. This finding was attributed to a lack of renal reserve, which presumably is required for GFR to rise in response to rhGH. Therefore, although the potential for rhGH-induced hyperfiltration with a consequent progressive decline of GFR exists, no data to date demonstrate that such a circumstance has occurred in pediatric patients with chronic renal failure who have been treated with rhGH.

The concern about the potential adverse impact of GH-induced hyperfiltration is supported by data from animal models, however. Doi et al demonstrated that transgenic mice, which chronically express excessive GH and GH-releasing hormone, have large, abnormal glomeruli with mesangial hypercellularity and sclerosis, a triad that progresses to glomerulosclerosis [47]. Similarly, Wanke and coworkers recently observed that GH-transgenic mice had a shortened life expectancy primarily because of renal failure [48]. The renal lesion morphologically was glomerulosclerosis. Consequently, the lack as yet of any definitive data correlating hyperfiltration with rhGH treatment of children with chronic renal failure should not make us complacent; assiduous surveillance for this potential complication is still necessary.

Levels of insulin-like growth factor. In our study, IGF-1 levels significantly increased following rhGH treatment (Table 9). Tonshoff and colleagues reported similar findings, including an increase in somatomedin bioactivity [23]. Although the IGF-BP level increased slightly, the rise was considerably less than the increment in the IGF-1 level. Therefore, there was a substantial net increase in the unbound IGF-1 level. The authors concluded that the IGF-BP was the "uremic inhibitor" and that the mechanism for improvement in growth velocity following exogenous rhGH treatment is attributable to the net increase in the unbound IGF-1 level, as reflected by the increase in bioactivity.

What are the potential short-term and long-term benefits of rhGH treatment in children with chronic renal failure? The potential short-term benefits of rhGH treatment are: (*1*) alleviation of the psychosocial consequences of marked impairment of linear growth and (*2*) delaying renal transplantation by eliminating growth retardation as an indication for "pre-emptive" engraftment, which currently accounts for almost one-quarter of all renal transplants performed in children in the United States [10]. Although precise data regarding the indications for pre-emptive transplantion are not available, it seems likely that persistent growth retardation is among the more common reasons for employing this intervention.

The availability of 1,25-dihydroxyvitamin D_3 for preventing the development of clinical renal osteodystrophy, rhGH to correct the growth retardation, and recombinant human erythropoietin (rHuEpo) to reverse the anemia of chronic renal failure has the combined potential to delay the clinical need for dialysis and transplantation and to prolong the duration of conservative treatment. Patient 3 (Fig. 2) illustrates this; he has

Table 9. rhGH Treatment in chronic renal failure: *IGF-1 levels (U/ml) (Acid chromatography)*

Pt.	0 months	6 months	12 months	18 months	24 months	30 months	36 months	48 months
1	0.49	1.49	1.36	0.72				
2	0.53	1.05	1.49	1.47	1.37	1.07	1.43	
3	0.36	0.48	0.66	1.02	1.54	0.78	2.66	3.36
4	0.14	0.29	0.78	0.70	1.00	0.76	1.95	1.96
5	0.31	0.19	0.36	0.57	0.55	0.56	1.02	1.49
6	0.21	1.02	0.47	1.55	0.79	1.42	1.47	
7	0.40	0.94	1.44	1.33	1.01	1.01	2.75	
8	0.65	1.09	1.80	0.69	1.47	1.56	1.53	
9	—	2.72	2.81	4.48	3.26	3.39		
10	0.64	1.40	0.96	0.83				
11	0.18	0.83	0.81	1.30				
mean	.39	1.5	1.18	1.33	1.37	1.32	1.83	2.27
± SD	0.18	0.69	0.71	1.10	0.84	0.90	0.66	0.97
0 months versus *P*		<.002	<.0006	<.002	<.0006	<.002	<.002	NS

had conservative treatment for more than 18 months following initiation of rHuEpo treatment despite having a GFR comparable to that of Patients 1 and 2, who required therapy for end-stage renal disease (dialysis); rHuEpo was not yet available when these patients could have benefited from it. During this 18-month period, continued rhGH treatment has produced increased height in Patient 3. Perhaps in the future we will be able to significantly prolong the period of conservative management of chronic renal failure by reducing the clinical consequences of uremia in children—renal osteodystrophy, growth retardation, and anemia.

The long-term benefit of rhGH in children with chronic renal failure is that rhGH facilitates achievement of the genetic potential for height by improving the growth velocity to the extent that patients reach the 50th centile on the growth curve for mid-parental height. If this goal is achieved prior to the development of end-stage renal disease, then the possibility of these children obtaining normal adult heights following dialysis and/or transplantation will be enhanced. Long-term followup of the children currently receiving rhGH treatment is required to determine whether we can help these children reach that goal.

Questions and answers

DR. LEONARD KLEINMAN (*Professor of Pediatrics, State University of New York at Stony Brook, Stony Brook, New York*): It appears that all 3 patients who were treated with growth hormone for at least 48 months showed a decline in glomerular filtration rate. Does this make you leery about the very-long-term effects of growth hormone on renal function? Also, if growth hormone has an adverse effect on renal function, do you think it's a direct effect, or might it be mediated by IGF? Has anyone tried to use IGF itself, rather than GH, to stimulate growth?

DR. FINE: The clearances that I showed you were calculated creatinine clearances, which probably are not the optimal method to use to follow patients serially. We did not use inulin clearances from the beginning, so we didn't have baseline data with which to make comparisons when we saw the beneficial effects of rhGH. Calculated creatinine clearances used in a controlled study revealed no difference in the decline of renal function in patients receiving rhGH and the control population

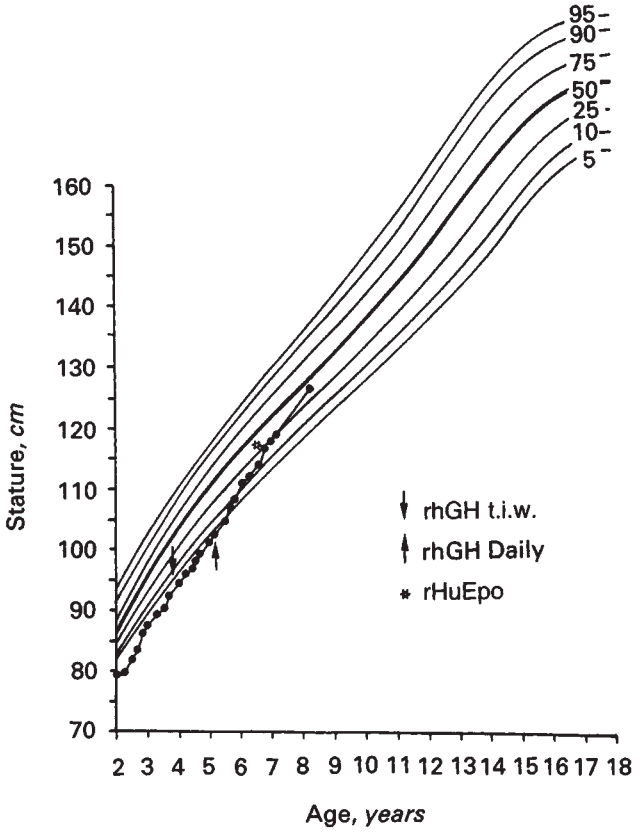

Fig. 2. *Growth curve of Patient 3 before and after treatment with rhGH and rHuEpo.* (t.i.w., 3 times weekly.)

(unpublished data). In our patients treated over 4 years, the calculated creatinine clearance fell from 15 to 10 ml/min/1.73 m^2; we interpreted this change to be the anticipated decline in renal function and not an accelerated decline secondary to rhGH. I think your point is well taken, however, and a controlled study has been initiated in which two-thirds of the children have been treated with rhGH and one-third have been treated with a placebo (unpublished data). No statistically

significant difference was apparent in the calculated creatinine clearance data from the subjects given placebo versus the rhGH-treated group over a 2-year period. To my knowledge, IGF-1 is available for experimental trials in animals but has not yet been approved for use in humans with renal failure. My colleagues in endocrinology might want to comment.

DR. SANDRA BLETHEN (*Associate Professor of Pediatrics, State University of New York at Stony Brook*): Several companies throughout the world are now making IGF-1. Clinical trials are beginning to assess the effects of IGF-1 in patients who have no growth hormone receptors—the so called Laron-type dwarf [49]. IGF-1 also has been used to treat hyperglycemia and growth failure in a patient with Mendenhall's syndrome, which involves a severe defect in the insulin receptor [50]. So IGF-1 presumably could be tried in children with chronic renal failure.

DR. FINE: I think your other point is also very well taken. The data in the transgenic mice suggest that the IGF-1 does not produce the kind of sclerosis that either growth hormone or growth-hormone-releasing hormone does. We are in the process of setting up studies to look at the effects of IGF-1 in the uremic rat model. I think it is important because IGF-1 might have less of an adverse impact on renal function than rhGH does if, indeed, rhGH has any adverse clinical impact.

DR. JORDAN J. COHEN (*Dean, School of Medicine, State University of New York at Stony Brook*): You noted that in rats with chronic renal failure, the administration of growth hormone did not normalize growth, and you cited this result to suggest that factors other than GH deficiency might be involved in the growth retardation seen with chronic renal failure. How do we know that sufficient hormone was given? Has a dose-response curve been established in the rat or, for that matter, in the children that you've treated with rhGH? Also, can you elaborate on how rhGH stimulates growth? Are all of its effects mediated by IGF? And how does IGF work at the level of cartilage and bone to promote growth?

DR. FINE: I think I will defer to my endocrine colleagues to comment on the precise mechanism of action of IGF. Presumably, growth hormone stimulates IGF production. Whether it stimulates circulating IGF or stimulates local paracrine production, and whether growth of cartilage is enhanced only by local stimulation of IGF, I don't know. Perhaps Dr. Blethen could give us an answer.

With regard to the dose-response relationship, a similar dosage was used in all the rat studies, and only short-term studies were performed. In our studies, we have only used one dose. One of the questions that obviously needs to be answered is whether a lower dose will produce the same effect as the higher dose. Studies are planned to address this issue; it is not only important because of the potential for adverse side effects that potentially could be minimized by a lower dose, but also because growth hormone is very expensive. At the moment, however, no dose-response data are available.

DR. COHEN: Based on the current costs and dosage schedule of rhGH, how expensive would it be to treat a child for one year?

DR. FINE: The cost is probably somewhere between $12,000 to $18,000 per year. As a matter of fact, it might even be more than that, because we are using a higher dosage than that used to treat children with GH deficiency. A more accurate estimate might be $20,000 to $25,000 per year.

DR. BLETHEN: I have two comments. First, one of the other things that GH does is regulate the IGF-binding proteins. In particular, growth hormone suppresses the levels of the IGF BP-1, the unsaturated binding protein [51]. So, GH also might increase the bioavailability of IGF by suppressing the binding protein. Second, the role of GH and IGF on bone growth has been studied, and some good animal data suggest that growth hormone promotes growth and cell division of the undifferentiated stem cell, whereas IGF-1 promotes growth and cell division of the differentiated cell [52]. So, in fact, growth hormone has both direct and indirect effects on cartilage growth.

DR. FINE: Tonshoff and colleagues from Heidelberg measured IGF-1 and the binding protein before and after rhGH administration and found that the levels of both IGF-1 and the binding protein increased, but that the net effect was more free IGF-1 [23]. Your hypothesis that net, free IGF might play at least a partial role is reasonable.

DR. ROBERT WEISS (*Director of Pediatric Nephrology, New York Medical College, Valhalla, New York*): I would like to raise a concern about the effects of a rapid increase in growth velocity on the course of metabolic bone disease. Most patients with chronic renal failure experience a modest increment in growth velocity as they approach puberty, and that is when we begin to see the development of slipped capital-femoral epiphysis. I've seen this complication in several pre-pubertal patients with suboptimal control of their renal osteodystrophy. Have you encountered the same thing?

DR. FINE: That is an excellent question. The development of slipped capital-femoral epiphysis has been described in children without chronic renal disease who were given rhGH. One recent report described a child with GH deficiency who was treated with rhGH and who developed a slipped capital-femoral epiphysis [53]. All our patients have been treated with vitamin D and have had no clinical or radiologic evidence of overt renal osteodystrophy when they were treated with rhGH. We followed these children serially with bone radiographs. No data are available on the effect of rhGH on renal osteodystrophy in patients with chronic renal disease; studies will need to be done in the future. Clinically, we have no evidence of progression of the renal bone disease in the children we followed.

DR. YELLESHPUR JAYARAM (*Director, Child Health, Suffolk County Health Department, Hauppauge, New York*): Do patients who respond well to rhGH experience a change in blood pressure?

DR. FINE: None of our patients has developed hypertension subsequent to rhGH treatment. However, none of these patients were hypertensive beforehand and all had some form of renal dysplasia. This group of pediatric patients rarely has hypertension in conjunction with their chronic renal disease, so these children probably are at a lower risk for this potential complication of rhGH treatment. In the patients with renal allografts whom I have treated with growth hormone, I have not encountered an rhGH-related increment in hypertension. I do think hypertension is a concern, however, because sodium retention can occur during treatment with rhGH.

DR. EDWARD NORD (*Associate Professor of Medicine, State University of New York at Stony Brook*): I have a three-part question. First, given that IGF is thought to work at the local level where it is released, what can one learn from measuring

plasma IGF-1 levels? My second question has to do with the possible role of IGF in the absence of growth hormone. In the kidney, cells of the inner medullary collecting duct can make IGF by a process independent of growth hormone. Might this be true of bone? My third question relates to the patients you described who received both erythropoietin (rHuEpo) and rhGH and in whom the need for dialysis appeared to be delayed significantly. Are you suggesting that this treatment retarded the decline in renal function?

DR. FINE: I'll ask Dr. Gelato to answer your first question in a moment. I am not suggesting that rhGH has a salutary effect on GFR, but I am saying that in pediatric patients, the impetus to initiate dialysis typically entails a number of considerations: typical symptoms of uremia, significant renal osteodystrophy that has been unresponsive to treatment, and significant growth retardation in children who are otherwise doing well. When transplantation is undertaken without previous dialysis, it is termed pre-emptive. As a matter of fact, according to the latest report of the North American Pediatric Renal Transplant Cooperative Study, which has enrolled between 1500 and 2000 pediatric renal transplant recipients in this country since 1987, almost one-quarter of all the renal transplants in pediatric patients are pre-emptive. Although we don't know for sure, the presumption is that poor growth is the major reason for pre-emptive transplantation in these children. All other therapeutic maneuvers have failed, and transplantation is seen as the answer to resolving the growth retardation. I am suggesting that treatment with rhGH might offer an alternative to pre-emptive renal transplantation for the growth-retarded child with chronic renal disease. Moreover, experience with rHuEpo suggests that many of the symptoms previously attributable to uremia—for example, nausea, vomiting, lethargy, unwillingness to go to school—in pediatric patients are in fact related to anemia. If we can correct the anemia, prevent the bone disease, and sustain or improve growth, which are the major factors that have precipitated decisions to initiate dialysis in the past, we might be able to obviate the need to initiate dialysis as early as we have been.

DR. MARIE GELATO (*Associate Professor of Medicine, State University of New York at Stony Brook*): Insulin-like growth factors work both by endocrine and autocrine/paracrine mechanisms. Just how circulating levels of IGF-1 relate to tissue levels, however, is not really clear. I don't think anybody knows the exact mechanisms yet, but tissue levels probably are just as important, if not more important, than circulating levels, at least in some respects. It is clear that these growth factors can be made by virtually all tissues of the body because their corresponding mRNA is found in all body tissues. Growth hormone not only stimulates the liver to produce and release IGF-1 into the circulation to act presumably by endocrine mechanisms, but it stimulates other tissues to produce IGF-1 as well. Additional factors, such as retinoic acid, TGF-α, and TGF-β, also can directly stimulate the production of these growth factors at the tissue level. Indeed, the regulation of IGF production in a given organ probably relates to the factors involved in the overall regulation of that organ's function. So I think growth hormone plays an important role in IGF regulation, but it probably does not provide the only explanation for how these factors are stimulated and how they act.

DR. COHEN: Anemia has been thought to participate in growth retardation in children with chronic renal failure. We've now had several years of experience with rHuEpo. Do we have any reliable data on what effect correction of anemia with rHuEpo has had on growth in the absence of exogenous rhGH?

DR. FINE: Preliminary studies utilizing rHuEpo have not substantiated any beneficial effect on growth. More extensive controlled studies in dialysis patients are in progress, and these should help settle the question.

DR. THOMAS WILSON (*Director, Division of Pediatric Endocrinology, State University of New York at Stony Brook*): Could you comment on the doses of rhGH that are being used in the clinical trials? What concentrations of growth hormone are achieved in the serum of these patients relative to what they make on their own?

DR. FINE: The dose used has been 0.375 mg/kg/week. On a daily basis, it is 0.05 mg/kg per dose; if growth hormone is given only 3 times per week, we give 0.125 mg per dose, which is somewhat higher than the dosage used in GH-deficient individuals. In pharmacokinetic studies published by Tonshoff and colleagues, the levels achieved with one dose reached the 60–80 ng/ml range within one or two hours [45]. To my knowledge, no one has compared different dosages or tried to compare the dose achieved with endogenous levels of growth hormone. Dr. Charles Stewart is conducting pharmacologic studies to evaluate serum levels following different methods of growth hormone administration. We don't yet know whether giving rhGH in the morning or the evening, or giving two doses a day rather than one, makes a difference. Obviously, many issues remain to be addressed, and I suspect that one of the reasons investigators are not pursuing these issues more vigorously is that the Federal Food and Drug Administration has yet to approve rhGH for use in children with chronic renal disease.

DR. CHARLES STEWART (*Clinical Assistant Professor, State University of New York at Stony Brook*): You've commented on the potential effect of rhGH on GFR and the resulting potential decline in glomerular function. Have studies been done to assess the effect of rhGH on renal tubular function, in particular on the renal handling of calcium and phosphorus? I wonder whether the bone disease that afflicts these children might be affected by treatment with rhGH.

DR. FINE: I am not aware of any human studies investigating renal tubular function in patients treated with rhGH.

DR. COHEN: I'm still puzzled about how exogenously administered rhGH has these dramatic effects when endogenous levels of the hormone are already elevated. I'm also puzzled about why endogenous levels are not even higher than they are. If, as you noted, IGF exerts negative feedback control on growth hormone, why don't the low levels of bioavailable IGF result in even higher levels of growth hormone? As you showed us, other stimuli can provoke further increases in GH.

DR. FINE: We are operating with the hypothesis that the binding protein is increased relatively less by exogenous rhGH than is free IGF-1. But I agree that we don't have a very good explanation for why rhGH improves growth velocity.

DR. GELATO: I agree with you; I don't think there is a good explanation. It is clear, however, that IGF-binding proteins not only carry these substances but also can alter their function. Binding protein-1, BP-1, which is the binding protein that appears to be increased to the greatest extent in chronic renal failure, actually can inhibit the action of IGF-1. So not only are the levels of bioavailable IGF low, there also might exist a

substance in the circulation that impairs the ability of IGF-1 to function normally. Thus, when rhGH is given, the balance of forces might change. Not only might the amount of IGF-1 be increased, but an inhibitor might be decreased as well, thereby yielding an enhanced effect. It would be interesting to look at the effects of rhGH on the IGF-binding protein in these children.

In addition, these children might be growth hormone resistant. It is possible that the growth hormone they make is not biologically active. For example, the growth hormone might be glycosylated and therefore might not function normally. If this is the case, exogenous rhGH, which is biologically active, could enhance growth.

DR. WILSON: Another possible explanation relates to a putative, short feedback loop by which growth hormone could inhibit the release of GF-releasing factor. Because of this feedback loop, the body could maintain a certain damper on growth hormone secretion, which exogenously administered rhGH could bypass.

DR. WEISS: Dr. Fine, I know you have done some work on the effects of rhGH in overcoming the growth retardation that occurs in children treated with corticosteroids. Would you comment on the use of rhGH in children who receive steroids after renal transplantation or who have steroid-dependent nephrotic syndrome?

DR. FINE: We've done some rat studies with Otto Mehls, and the data will be published shortly in *Kidney International*. But let me summarize our work. When we gave the rats steroids, their growth decreased. When we made them uremic, their growth decreased further. Giving either group rhGH improved growth. Theoretically, then, appropriate doses of rhGH might be able to overcome the effects both of uremia and of steroids. It appears that, in a rat model, rhGH can overcome the growth-suppressing effects of steroids. We have treated pediatric renal transplant recipients, and a similar study of transplant patients was reported from Europe [54]. Indeed, rhGH increases growth velocity in transplant recipients receiving corticosteroids. However, in a patient with renal functional impairment who is receiving steroids and is given rhGH, growth velocity does not accelerate as much as in a patient with chronic renal disease who has the same degree of renal functional impairment but who is not given steroids. One of the issues that needs to be resolved is how to adjust the dosage of rhGH for the additive growth-retarding effects of steroids. With regard to the nephrotic syndrome, I think patients receiving long-term steroids for the nephrotic syndrome and who have short stature could benefit from rhGH therapy. Currently ongoing studies are evaluating the effects of rhGH in asthmatic patients who require chronic steroid therapy and whose growth is retarded (unpublished data).

DR. NORD: Is there any evidence or any reason to believe that either rhGH or IGF would have a therapeutic effect on the metabolic bone disease that occurs in adults with chronic renal failure?

DR. FINE: I can't address the issue of bone disease, but I can address the issue of patients on dialysis who are wasted or are catabolic. There are preliminary studies using rhGH in hemodialysis patients [55]; rhGH was anabolic in these patients. Therefore rhGH could be used in an adult dialysis population with the wasting syndrome to improve anabolism. With regard to bone disease, I'm not aware that this issue has been addressed specifically.

DR. COHEN: Have we learned anything about the mechanism of growth retardation in children with chronic renal failure by studying the dramatic catch-up growth that often occurs after successful renal transplantation?

DR. FINE: Yes, we have: the younger the recipient, the more dramatic the catch-up growth. The patients who are the most growth retarded also have improved growth, but the amount of improvement is not as marked as we would like. Consequently, a significant number of transplant recipients are persistently growth retarded. Sometimes a growth spurt occurs immediately after transplantation, but the growth frequently is not sustained.

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