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Predicted reciprocal serum creatinine at age 10 years as a measure of renal function in children with nephropathic cystinosis treated with oral cysteamine

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Abstract. The predicted reciprocal creatinine at age 10 years (PRC_{10}), a parameter of renal function based upon the linear relationship between reciprocal serum creatinine and age, incorporates age, serum creatinine, and rate of renal deterioration into a single term. PRC_{10} measurements were employed to assess renal function in children with nephropathic cystinosis treated with oral cysteamine, a cystine-depleting agent. In 71 children receiving oral cysteamine for at least 1 year, PRC_{10} decreased linearly with initial serum creatinine concentration. This indicated that, although established renal damage in cystinosis was irreversible, early intervention with cysteamine therapy could favorably alter the rate of glomerular deterioration. In other analyses, mean PRC_{10} was shown to increase with duration of cysteamine therapy and extent of leukocyte cystine depletion. The predicted reciprocal creatinine value at a certain age can be useful in analyzing the effects of therapeutic intervention in a disease with a relatively uniform rate of renal deterioration.

Key words: Reciprocal serum creatinine – Renal function – Nephropathic cystinosis – Cysteamine – Creatinine clearance

Introduction

Creatinine clearance is currently the most widely employed measure of glomerular filtration rate (GFR) in children with progressive renal disease. One particularly useful application of creatinine clearance measurements is to compare values before and after a specific therapy. However, creatinine clearance may not reflect GFR under all conditions [1], and other estimates of GFR require either complete urine collections. or injection of compounds which are filtered but not reabsorbed or secreted. These procedures may be difficult to perform uniformly and reproducibly when many centers are involved in a study protocol. As an alternative, formulas involving height can be employed [2], but height itself may change, independently of renal function, due to the therapy under investigation.

Because of these reservations, we introduced a renal function parameter that incorporates age, initial serum creatinine, and rate of progression of renal disease into a single term, i.e., the predicted reciprocal serum creatinine at a certain age. The use of this determination is based upon the linear relationship between reciprocal serum creatinine and age, which characterizes progressive renal disease of adults [3] and children [4–6]. In children, the age for which the reciprocal serum creatinine is predicted can be the age at which renal failure is generally reached for the particular disease involved.

That age would be 10 years for nephropathic cystinosis [7]. This lysosomal storage disease is a rare autosomal recessive disorder resulting from defective transport of the disulfide amino acid cystine across the lysosomal membrane [8–11]. Intracellular cystine accumulates to 50- to 100-fold normal levels in leukocytes and cultured fibroblasts, and to 1000-fold normal levels in other tissues [12]. This apparently causes the clinical and pathological findings of the disease [12, 13], which include renal Fanconi syndrome in infancy, growth retardation, photophobia, and late findings [14] such as hypothyroidism [15], pancreatic insufficiency [16, 17], corneal erosions and decreased visual acuity [18], and myopathy [19]. The most characteristic manifestation of nephropathic cystinosis is progressive glomerular deterioration requiring dialysis or renal transplantation by approximately 10 years of age [12, 13].

The specific therapy for cystinosis is cysteamine (β-mercaptoethylamine), a free thiol capable of depleting over 90% of the cystine in cystinotic leukocytes in vitro or in vivo [20]. Cysteamine accomplishes this by reacting with intralysosomal cystine to form cysteine, which rapidly leaves cystinotic lysosomes [8], and cysteine-cysteamine mixed disulfide. This compound leaves cystinotic lysosomes much faster than does cystine itself [21], and does so

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via a lysosomal carrier system for lysine which is intact in cystinotic lysosomes [22].

We demonstrated the utility of the predicted reciprocal creatinine at age 10 (PRC_{10}) by applying it to patients with nephropathic cystinosis treated with cysteamine for 0–73 months. A national collaborative study based on creatinine clearance determinations concluded that chronic cysteamine therapy helped preserve renal function in cystinosis [7]. Analysis by PRC_{10} not only confirmed this finding (verifying the validity of the PRC_{10} determination), but also contributed important new information concerning cysteamine therapy in cystinosis which could not be gleaned from creatinine clearance measurements alone.

Methods

Data. The data were taken from the national collaborative cysteamine study, in which 93 children with cystinosis were treated for up to 73 months between 1978 and 1985 with cysteamine hydrochloride (Sigma Chemical, Human Use Division, St. Louis, Mo., USA) at an average dose of 51.3 ± 7.2 mg/kg per day (expressed as cysteamine free base), given every 6 h [7]. The mean leukocyte cystine level prior to treatment was 9.3 nmol $^1/_2$ cystine/mg protein (normal, <0.2), and cysteamine reduced this, on average, by 82%. Fifty-five children with cystinosis treated between 1976 and 1978 [23] with either ascorbic acid (27 patients given 200 mg/kg per day) or placebo (28 patients), but not with cysteamine, served as historical control subjects. A concurrent control group would have been superior, partly because supportive care may have improved between 1976 and 1985. However, it seemed inappropriate to withhold cystine-depleting therapy from a group of patients with a fatal disease whose natural history was well recognized.

Data for the placebo and ascorbic acid subjects were pooled for analyses, since the two groups did not differ significantly from one another in baseline parameters, including initial creatinine (two-sided $P > 0.2$), nor did they differ significantly upon follow-up.

Patients were examined every 4 months at 1 of 53 medical centers, where blood chemistry and parameters of growth and renal function were measured. GFR (expressed in ml/min per 1.73 m^2 body surface area) was estimated by the formula: 0.55 × height (cm)/serum creatinine (mg/dl) [2]. This equation gave values that correlated well with creatinine clearance values determined through 24-h urine collections in 22 children with cystinosis ($r = 0.88$) [7] and 77 children without cystinosis ($r = 0.905$) [2].

Statistical procedures. The PRC_{10} for each subject was calculated by first estimating, by linear regression techniques, the best-fitting straight line that related the subject's reciprocal serum creatinine measurements to the age when each measurement was made; the resulting equation was then evaluated at age 10 to obtain the prediction. In testing the linearity of relationships, the dependent variable was grouped into categories so that a lack of fit statistic could be estimated and tested through analysis of variance [24]; in addition, a runs test [25] and the sign test [26] were applied to residuals to assess their randomness as an indicator of goodness of fit. The observed differences in PRC_{10} (or creatinine clearance) between treatment groups could be attributed to pretreatment differences in other factors (i.e., covariates), such as initial creatinine and age at entry into the study. The effects of these factors were removed by analysis of covariance [27]. In this procedure the linear relationship between the covariate and PRC_{10} was used to estimate the effect of the covariate and to subtract the effect from the observed PRC_{10}, so that the remaining differences were due only to the treatment effect.

Results

Reciprocal serum creatinine as a function of age in cystinosis

The reciprocal of serum creatinine has been shown to decrease approximately linearly with age in individuals with progressive renal disease [3–6]. This relationship was demonstrated for five cystinosis patients in two of these studies [5, 6], as well as for five other cystinosis children in a separate report [28].

We examined the linearity of reciprocal serum creatinine with age in our own patients in two ways. First, the children with progressively increasing serum creatinine values were investigated longitudinally. Thirty patients (14 cysteamine-treated, 16 controls), followed for an average of 29 months, had individual correlation coefficients for reciprocal creatinine versus age ranging from 0.73 to 1.00 (mean ± SD, 0.93 ± 0.09). This compares well with the mean correlation coefficient of 0.93 previously reported for 29 patients with a variety of renal disorders and progressively increasing serum creatinine values [6]. Examples of our patients' individual plots are given in Fig. 1.

Second, the reciprocal creatinine versus age relationship was studied cross-sectionally (Fig. 2). In this analysis, each of 141 subjects with nephropathic cystinosis was represented by a single reciprocal serum creatinine value prior to the initiation of any cystine-depleting therapy. Despite the heterogeneous severity of the cystinosis in these subjects, the data approximately fit a straight line corresponding to the equation $y = -0.013x + 1.72$, where y is reciprocal creatinine in $(mg/dl)^{-1}$ and x is age in months (Fig. 2). This closely resembled the pretreatment line obtained by Yudkoff et al. [28]. In that study, age was expressed in terms of months and a negative sign was omitted from the published slope of the line, described by $y = 0.016x + 1.78$. An examination of the linearity assumption for our analysis verified that a straight line appropriately described the data.

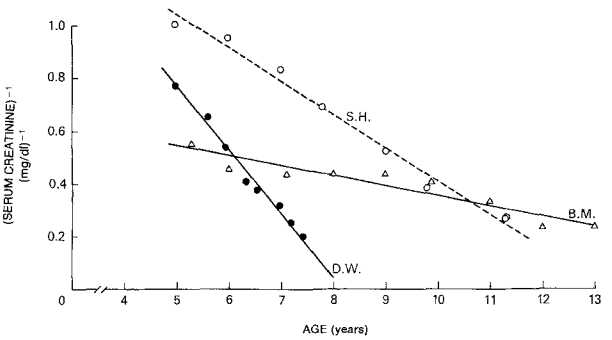

Fig. 1. Longitudinal analysis of reciprocal serum creatinine as a function of age. Reciprocal serum creatinine values in $(mg/dl)^{-1}$ were plotted against age for three children with cystinosis. B.M. (△) and S.H. (○) took suboptimal doses of oral cysteamine starting at 5 years of age. D.W. (●) could not tolerate chronic cysteamine therapy

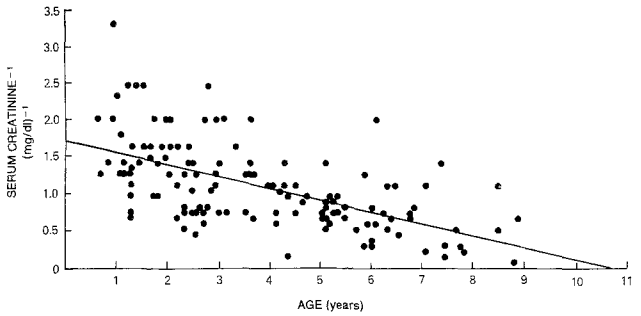

Fig. 2. Cross-sectional analysis of reciprocal serum creatinine as a function of age. Baseline serum creatinine (mg/dl) was determined for each of 141 children with cystinosis referred for possible entry into study as either cysteamine-treated subjects or controls. Twelve observations are superimposed on others. The line was determined by the least-squares method and followed the equation $y = -0.161\ x + 1.72$. The correlation coefficient was 0.62. The slope, whose standard error was 0.018, differed significantly from zero ($P = 0.0001$). Expressing age in terms of months, the equation is $y = -0.013\ x + 1.72$

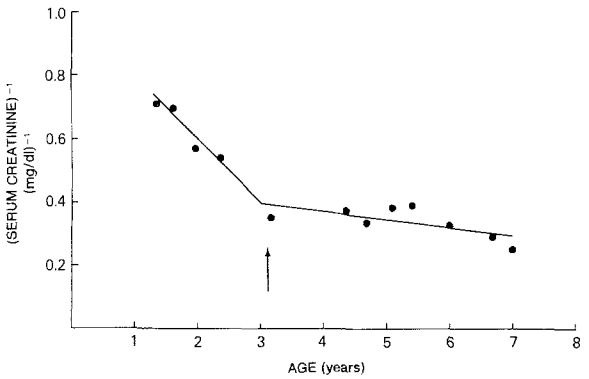

Fig. 3. Reciprocal serum creatinine as a function of age for a cystinosis patient before and after initiation of cysteamine therapy. The *arrow* signifies initiation of effective cystine-depleting therapy. Both lines were constructed by the least-squares method and include the 38-month values. Cysteamine therapy changed the PRC_{10} from −0.99 to +0.21

Determination of PRC_{10}

By analyzing each individual's data longitudinally, a projected value for reciprocal creatinine at age 10 could be determined. This indicated the rate at which renal damage was proceeding; a value above 1 meant that the predicted serum creatinine at age 10 would be less than 1. A value less than 0.1 (or negative) meant that kidney failure (serum creatinine >10 mg/dl) would occur before age 10.

The influence of cysteamine therapy upon PRC_{10} is illustrated in an exceptional patient who did not receive significant amounts of cysteamine until 38 months of age (Fig. 3). This girl's creatinine clearance had fallen from 28.4 to 17.3 ml/min per 1.73 m^2 between 16 and 38 months of age. It fell further to 15.3 ml/min per 1.73 m^2 by 84 months of age. Using PRC_{10} analysis, her value was −0.99 prior to the initiation of substantial cystine depletion, and she was predicted to attain a serum creatinine of 10 mg/dl at age 54 months. After the start of robust cysteamine therapy, her PRC_{10} changed to +0.21, with the prediction that a serum creatinine of 10 mg/dl would be reached at 172 months of age.

PRC_{10} determinations were performed on restricted groups of the cysteamine-treated and control populations. Children were required to be on the study for at least 12 months, to have contributed data to the study on at least three different occasions, and to have had an initial serum creatinine of less than or equal to 2.0 mg/dl. These restrictions served to remove very short-term compliers and children already approaching terminal renal failure at the time they began treatment. The restricted cysteamine group contained 71 children (76% of the total population who received cysteamine), and the restricted control group contained 39 children (71% of the total control population). During the course of investigation, 11 of the 71 cysteamine-treated (15%) and 8 of the 39 control children (21%) withdrew from the study due to non-compliance or renal failure; all data analyses were performed on the entire 110 children in the restricted study groups, regardless of whether they subsequently withdrew from the study.

Table 1. Renal function in restricted treatment groups

	Cysteamine ($n = 71$) $x \pm$ SEM	Control ($n = 39$) $x \pm$ SEM	P
Initial creatinine (mg/dl)	0.97 ± 0.05	1.19 ± 0.06	0.0090
Initial age (years)	3.3 ± 0.2	4.4 ± 0.3	0.0086
Final age (years)	6.7 ± 0.3	6.0 ± 0.3	0.1122
Time on study (years)	3.3 ± 0.2	1.6 ± 0.1	0.0001
Final creatinine clearance (ml/min per 1.73 m^2)			
– unadjusted	43.8 ± 2.4	27.8 ± 3.2	0.0001
– adjusted[a]	41.8 ± 1.7	31.9 ± 2.6	0.0048
PRC_{10} $(mg/dl)^{-1}$			
– unadjusted	0.66 ± 0.08	0.19 ± 0.08	0.0002
– adjusted[b]	0.62 ± 0.07	0.33 ± 0.10	0.0202

[a] For final age, initial age, and initial creatinine by analysis of covariance. (This also adjusts for time on study)
[b] For initial age and creatinine

Occasionally, the regression of reciprocal creatinine versus age gave a positive slope, e.g., when only three creatinine values were available or an infant's initial creatinine was 0.6 mg/dl and fell to 0.4 mg/dl a year later. This type of fluctuation was presumed to reflect laboratory variation or lack of progression of renal disease, and a value of zero was assigned to the slope. This occurred 18 of 71 and 6 of 39 times for the cysteamine and control groups, respectively.

Applications of the PRC_{10}

Mean PRC_{10} values were determined for the restricted cysteamine and control groups, and compared with the mean final creatinine clearance values (Table 1). Both parameters demonstrated the maintenance of renal glomerular function by chronic cysteamine therapy, even after statistical adjustments were made for differences in initial age and serum creatinine between the two study groups. The PRC_{10} data would predict mean serum creatinine levels of 1.51 and 5.26 mg/dl for the cysteamine and control groups, respectively, at age 10 years.

Table 2. Study groups stratified by time on cysteamine

	Duration of cysteamine therapy (months)			
	0[a]	12–24	25–48	49–73
n	20	20	23	28
Mean time on study (months)	19.9	18.8	35.3	57.3
Initial age (years)	4.35 ± 0.43[b]	3.75 ± 0.53	2.94 ± 0.43	3.40 ± 0.32
Initial creatinine (mg/dl)	1.17 ± 0.07	1.12 ± 0.11	0.93 ± 0.10	0.90 ± 0.06
Creatinine clearance (ml/min per 1.73 m^2)				
– initial	43.3 ± 2.9	50.4 ± 6.2	57.62+ ± 5.1	55.6 ± 3.3
– final	37.4 ± 3.3	51.8 ± 8.5	58.8 ± 5.1	56.9 ± 5.3
– (final-initial)	–5.9 ± 3.0	1.4 ± 4.9	1.2 ± 5.6	1.4 ± 4.2
PRC_{10}				
– unadjusted	0.22 ± 0.12	0.49 ± 0.20	0.60 ± 0.13	0.84 ± 0.09
– adjusted for initial age and creatinine	0.40 ± 0.15	0.55 ± 0.13	0.54 ± 0.12	0.79 ± 0.11

[a] Placebo control group
[b] SEM

Table 3. Stratification according to leukocyte cystine levels

	Leukocyte cystine depletion groups[a]			
	1	2	3	4
n	19	18	16	18
Initial age (years)	3.27 ± 0.52[b]	2.98 ± 0.37	2.90 ± 0.55	4.20 ± 0.43
Initial creatinine (mg/dl)	0.87 ± 0.07	0.91 ± 0.09	0.80 ± 0.10	1.29 ± 0.10
Creatinine clearance (ml/min per 1.73 m^2)				
– initial	56.6 ± 4.4	57.8 ± 6.0	62.42+ ± 5.5	43.0 ± 5.1
– final	64.6 ± 6.6	59.2 ± 6.4	63.0 ± 7.0	37.9 ± 6.9
– (final-initial)	8.0 ± 5.8	1.4 ± 4.2	0.5 ± 8.1	–5.0 ± 3.4
*P**		0.374	0.450	0.066
PRC_{10}	0.96 ± 0.11	0.65 ± 0.12	0.68 ± 0.20	0.35 ± 0.18
*P**		0.064	0.203	0.006

[a] Groups 1–3: Two or more leukocyte cystine levels obtained per year
Group 1: Median level <1 nmol $^1/_2$ cystine/mg protein
Group 2: Median level between 1 and 2 nmol $^1/_2$ cystine/mg protein
Group 3: Median level over 2 nmol $^1/_2$ cystine/mg protein
Group 4: Fewer than two levels obtained per year or could not tolerate full recommended dose of cysteamine
[b] SEM
* Two sided *P* value compared with group 1, using Student's *t*-test

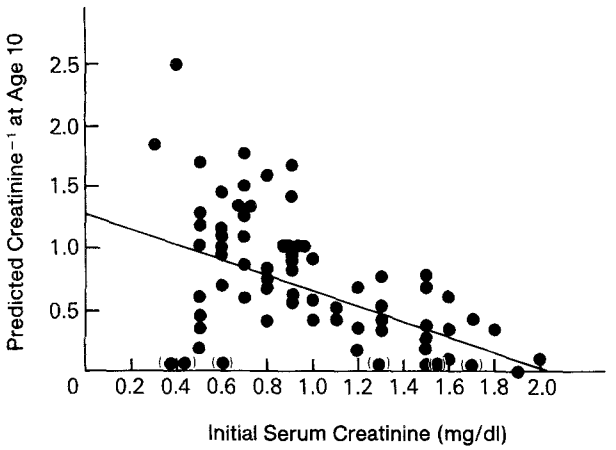

Fig. 4. Predicted reciprocal creatinine at age 10 (PRC_{10}) as a function of initial serum creatinine in children receiving cysteamine. Calculation of the PRC_{10} is described in the text. Points in parentheses have negative values, reflecting the fact that renal failure was predicted to occur well before age 10. The line, whose equation is $y = 0.64\ x + 1.29$, represents the best least-squares fit of the data. Testing of residuals verified the linearity. The correlation coefficient was 0.41. The slope, whose standard error was 0.172, differed significantly from zero ($P = 0.0004$)

The utility of the PRC_{10} value became apparent when renal function was assessed as a function of specific parameters in the restricted subject populations. For example, the PRC_{10} was plotted against initial serum creatinine in the control group, and no trend was apparent (data not shown). This was expected since, without salutary intervention, the PRC_{10} will not be altered by merely "following" the patient; it will be the same for a patient initially examined when his/her serum creatinine is 2.0 mg/dl as for one assessed when his/her serum creatinine is 0.6 mg/dl. The renal damage will progress inexorably, *as predicted.* In contrast, if intervention is beneficial, the PRC_{10} should increase with therapy, and should be greater in patients treated early (e.g., serum creatinine 0.6 mg/dl) than in those already having substantial renal damage (serum creatinine 2.0 mg/dl). This is exactly what was observed for the cysteamine-treated group; the PRC_{10} decreased when plotted against initial serum creatinine concentration (Fig. 4). It is apparent that renal damage already present is irreversible, but cysteamine therapy can favorably alter the PRC_{10}, i.e., preserve remaining renal function.

Subgroups of children stratified according to duration of cysteamine therapy were also analyzed (Table 2). Differences between final and initial creatinine clearance determinations did not reveal any benefit attributable to progressively longer durations of cysteamine therapy. PRC_{10} determinations, however, showed a clear benefit attributable to increasing duration of cysteamine treatment. Although only the zero time and 49–73 months treatment groups differed significantly from one another in adjusted PRC_{10} ($P = 0.042$), there was an obvious trend of increasing PRC_{10} with time on study. In fact, when PRC_{10} was plotted against months on study for each of the 71 cysteamine-treated children (data not shown), the slope was positive (0.017) and significantly different from zero ($P = 0.009$), even after effects of initial age and initial creatinine were adjusted for by analysis of covariance. For the 39 children in the control group, time on study had no effect on PRC_{10} (data not shown).

Table 4. PRC_{10} for cysteamine and control subgroups[a]

Patients over 3 years of age *n*	Cysteamine 31	Controls 30	*P**
Initial age (years)	5.28 ± 0.25	5.05 ± 0.24	0.503
Initial creatinine (mg/dl)	1.22 ± 0.07	1.20 ± 0.07	0.788
PRC_{10}	0.50 ± 0.08	0.21 ± 0.09	0.015

[a] All values are means ± SEM
* Two-sided *P* value using Student's *t*-test

The PRC_{10} determination was also applied to groups stratified according to the extent of leukocyte cystine depletion (Table 3). Reduction of the leukocyte cystine level to less than 1 nmol $^1/_2$ cystine/mg cell protein is considered excellent depletion, and was associated with a high PRC_{10} ($n = 19$, $PRC_{10} = 0.96 \pm 0.11$ SEM, adjusted $PRC_{10} = 0.91$). This group differed from the group of least-compliant patients, who contributed fewer than two cystine levels per year or had leukocyte cystine levels over 3 nmol $^1/_2$ cystine/mg protein because they could not tolerate the recommended dose of cysteamine ($n = 18$, $PRC_{10} = 0.35 \pm 0.18$, adjusted $PRC_{10} = 0.53$). Changes in creatinine clearance values before and after therapy did not differ significantly among the various compliance groups (Table 3).

Finally, we addressed the issue of whether initial age or initial serum creatinine at the start of cysteamine therapy determined ultimate renal outcome. Cysteamine-treated and control subjects were grouped by initial age over 3 years and the mean PRC_{10} value determined (Table 4). Cysteamine therapy proved beneficial even in this group of children over age 3, despite their elevated mean initial serum creatinine level (1.2 mg/dl), indicating that even relatively late intervention can be helpful.

Discussion

Two parameters for assessing renal function in children, the creatinine clearance rate and the PRC_{10}, have their own advantages and disadvantages. Creatinine clearance requires urine collection or else relies upon height measurements, and it varies with age. The PRC_{10} requires only serum creatinine determinations, and represents a single value which incorporates the parameters of initial age, initial serum creatinine and rate of renal deterioration. Moreover, it uses all of the available data points rather than just the final one. In a disease with a constant rate of renal deterioration, the PRC_{10} does not change with age unless some intervention (e.g., therapy) alters that rate. Because a single number denotes each individual's PRC_{10}, this term lends itself to mathematical manipulations much more readily than an age-varying rate such as creatinine clearance. On the other hand, there is no "initial" and "final" PRC_{10}, so that only rarely (e.g., Fig. 3) can a patient be used as his or her own control. In addition, the PRC_{10}

requires follow-up of long enough duration to determine the rate of renal deterioration. Our choice of at least 12 months of follow-up was somewhat arbitrary; it may not be optimal for cystinosis, nor sufficient for other renal diseases.

A final caveat is that, although there is ample evidence that the relationship of reciprocal serum creatinine versus age is just as linear in cystinosis as in other renal diseases, this relationship manifests itself only with progressive renal deterioration. Patients with constant, low creatinine values may make the slope portion of the PRC_{10} determination appear precarious. However, the PRC_{10} also relies upon the actual value of the serum creatinine which, if relatively constant, has been strengthened by being measured repeatedly over the course of follow-up. This offsets the fact that a slope near zero results in a poor correlation coefficient for the reciprocal creatinine versus age curve. One measure of the overall validity of the PRC_{10} calculation is that, for the entire study group of cystinosis patients, it gave results which coincided with the creatinine clearance results (Table 1).

In choosing the PRC_{10} as a parameter to follow in children with cystinosis, several alternatives were discarded. The age at which reciprocal creatinine was predicted to be 0.1 $(mg/dl)^{-1}$ could not be used, because this value would be infinity in patients whose reciprocal creatinine versus age curve had a positive or zero slope. Comparing the slopes themselves was not very useful because slope values do not contain enough information, i.e., there is no consideration of initial age or initial creatinine value. Hence, much of the information inherent in the PRC_{10} would be lacking, and statistical significance would be reduced when comparing data for subgroups of treated patients. Finally, predicting the serum creatinine itself at age 10 for each individual was not helpful because the high values in any group of patients disproportionately weighted the mean for that group.

It also became apparent that the PRC_{10} could be applied to large groups of patients whose rates of renal deterioration were rapid and uniform. These qualifications were met by the group of patients investigated to determine whether chronic oral cysteamine therapy helped preserve renal function in cystinosis [7]. Data from a control group were available [23], patients were followed for a considerable period of time with serum creatinine measurements, and the disease itself had a fairly uniform natural history of renal deterioration. In fact, the data of Fig. 2, which predict that a serum creatinine of 10 mg/dl will be reached at a mean age of 10.1 years, confirmed previous reports of the age at renal failure in cystinosis. In a survey of 205 European children with cystinosis, the median age of renal failure was 9.2 years [29].

The decreasing relationship between PRC_{10} and initial serum creatinine among cysteamine-treated children (Fig. 4) indicates that the greater the renal damage at the start of cysteamine therapy, the less benefit would accrue from subsequent cystine depletion. That is, the renal damage of cystinosis appears irreversible, and cysteamine's effect was not curative. However, cysteamine does alter the course of renal disease in cystinosis to an extent inversely related to the degree of existing renal damage.

Conclusions such as these were difficult to make using creatinine clearance measurements. For example, if final creatinine clearance rather than PRC_{10} were plotted against initial serum creatinine (as for Fig. 4), the results would be inconclusive because the final creatinine clearance depends so heavily upon the final age, which varied extensively among the subjects. Hence, the random variation in the data would obscure the trend apparent in Fig. 4 using the PRC_{10} (which does not vary with age).

Other conclusions drawn from PRC_{10} analyses included the findings that the extent of preservation of renal function increased with duration of cysteamine therapy (Table 2) and with extent of leukocyte cystine depletion (Table 3). These conclusions were difficult or impossible to derive from creatinine clearance measurements before and after treatment (Tables 2, 3). The PRC_{10} findings represent important evidence confirming the efficacy of cysteamine therapy in nephropathic cystinosis, and indicate that more and longer cystine depletion is preferable in treating this disease.

Use of predicted reciprocal creatinine values may be helpful in assessing therapies for other renal diseases besides cystinosis. Extensive longitudinal data would be needed on treated as well as untreated patients, and the renal disease must be shown to be uniformly progressive (see Fig. 1) and reasonably homogeneous with respect to age at renal failure. The appropriate calculation to make would be the predicted reciprocal creatinine for the average age at which renal failure is expected.

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