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NEPHROLOGY FORUM

Measurement of renal function in chronic renal disease

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Case presentations

Patient 1. A 42-year-old woman first was evaluated at the New England Medical Center after an episode of dysuria that resolved following treatment with an antibiotic. Her weight was 55.5 kg and the blood pressure was 150/100 mm Hg. Urinalysis disclosed 3+ protein, 5–15 red blood cells/high-power field, occasional granular casts, and oval fat bodies. A 24-hour urine sample contained 3.9 g protein and 820 mg creatinine. Serum creatinine was 1.1 mg/dl and creatinine clearance was 52 ml/min. Because of the laboratory abnormalities, a mild sensorineural hearing loss bilaterally, and a family history of renal disease, a diagnosis of hereditary nephritis was made. Hypertension was treated with hydrochlorothiazide. During the next 3 years, her blood pressure was usually in the range of 130/95 mm Hg, but occasional values were as high as 180/110 mm Hg. Urinary protein excretion declined to 0.64 g/day. She complained of nocturia but otherwise was asymptomatic.

At age 45 years, her blood pressure was 160/85 mm Hg and serum creatinine was 2.2 mg/dl. Propranolol, 20 mg twice daily, was added to her regimen, and a 40 g protein diet was prescribed. During the next 4 years, her hypertension was treated with hydrochlorothiazide, 50 mg/day; atenolol, 50 mg/day; and captopril, 25 mg/day; her blood pressure was usually in the range of 130–140/80–90 mm Hg. Body weight and serum albumin concentration remained stable. Serum creatinine ranged from 2.2 to 2.5 mg/dl.

At age 49 years, she entered the feasibility phase of the Modification of Diet in Renal Disease (MDRD) Study. She was randomly assigned to follow a very low protein diet (16 g/day, equivalent to 0.28 g of protein/kg ideal body weight/day) supplemented with 12 g/day of an essential amino acid mixture and high-calorie, low-protein nutritional supplements. Her antihypertensive medications were not changed. Dietary protein intake, estimated from measurements of 24-hour urinary urea excretion, ranged from 0.3 to 0.5 g/kg/day. Her weight decreased by 2 kg, and the serum albumin and transferrin concentrations were stable. Table 1 shows detailed renal function measurements during a 9-month interval.

At age 51 years, at the conclusion of the feasibility phase of the MDRD Study, a 40 g protein diet was resumed. During the following year, she remained relatively asymptomatic. Blood pressure has been in the range of 110–130/80–90 mm Hg while she has been taking hydrochlorothiazide, 50 mg/day, and captopril, 25 mg/day. Her weight has declined by an additional 4 kg. At the time of her most recent visit, the serum albumin was 4.1 g/dl; serum creatinine was 2.2 mg/dl, and 24-hour urine protein excretion was 0.12 g/day.

Patient 2. A 55-year-old man was found to have renal disease after an evaluation for urethral burning during ejaculation. Urinalysis disclosed 2+ protein, and the serum creatinine was 1.5 mg/dl. He had had several prolonged hospitalizations 2 years earlier for multiple trauma from a motor vehicle accident and postoperative complications, including acute tubular necrosis.

He was evaluated at New England Medical Center at age 58 because of an elevated serum creatinine. His weight was 106.8 kg and blood pressure was 138/86 mm Hg. Urinalysis revealed 3+ protein, 2–5 red blood cells/high-power field, and 2–3 granular casts/low-power field. A 24-hour urine sample contained 3.1 g protein and 1100 mg creatinine. The serum creatinine was 2.3 mg/dl and creatinine clearance 33 ml/min. Renal biopsy showed focal and segmental glomerulosclerosis. One year later, the patient enrolled in the feasibility phase of the MDRD Study. He was randomly assigned to follow a very low protein diet (22.4 g/day, equivalent to 0.28 g protein/kg ideal body weight/day) supplemented with 22 g/day of a mixture of essential and nonessential ketoacids and high-calorie, low-protein nutritional supplements. His blood pressure was in the range of 130–160/80–90 mm Hg without antihypertensive medications. Dietary protein intake, estimated from measurements of 24-hour urinary urea excretion, averaged 0.5–0.6 g/kg/day. His weight remained stable, as did the serum albumin and transferrin concentrations. Table 1 shows detailed renal function measurements during a 6-month interval.

At the conclusion of the feasibility phase of the MDRD Study, when he was age 61 years, a low-protein diet (52 g/day) was recommended. Over the next 5 months, his blood pressure rose to 160–170/90–100 mm Hg, and the serum creatinine increased to 7.4 mg/dl. He suffered multiple injuries in another motor vehicle accident and required hemodialysis for treatment of severe azotemia. He remains dialysis dependent.

Discussion

DR. ANDREW S. LEVEY (*Director, Nephrology Clinical Research Center, Division of Nephrology, New England Medical Center, and Associate Professor of Medicine, Tufts University School of Medicine, Boston, Massachusetts*): These two case histories illustrate several important points about the assessment of renal function during progressive renal disease. First, during the short period of followup in the MDRD Study, both

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Table 1. Selected renal function data during one year of followup in the MDRD Study[a]

Time from initial visit	P_{cr} *mg/dl*	GFR *ml/min/ 1.73 m²*	C_{cr} *ml/min/ 1.73 m²*	$U_{cr}V$ *mg/day*	TS_{cr} *mg/day*	C_{cr} − GFR *ml/min/ 1.73 m²*	C_{cr}/GFR
Patient 1							
0	2.5	19	18	585	−27	−1	.95
3 mos.	2.5	14	24	801	339	10	1.71
6 mos.	2.6	13	29	987	538	16	2.23
9 mos.	2.5	12	23	759	363	11	1.92
Patient 2							
0	2.4	35	32	1484	−140	−3	.91
3 mos.	2.4	28	31	1438	159	3	1.11
6 mos.	2.7	22	25	1285	157	3	1.14

[a] Abbreviations: P_{cr}, serum creatinine; GFR, glomerular filtration rate; C_{cr}, creatinine clearance; $U_{cr}V$, renal creatinine excretion; TS_{cr}, tubular secretion of creatinine.

patients experienced a progressive decline in renal function as assessed by glomerular filtration rate (GFR) (Table 1). Second, despite similar serum creatinine values (P_{cr}), the level of renal function differed markedly between the two patients. Third, despite a relatively stable P_{cr}, the GFR declined steadily both patients. Fourth, the urinary creatinine excretion differed between the 2 patients and was variable over time. Fifth, tubular secretion of creatinine was variable; hence, the relationship between creatinine clearance and GFR, expressed as either the difference between the measurements or the ratio of the measurements, also was variable.

Unfortunately, these 2 patients are not unusual; many common renal diseases progress to renal failure, often for unclear reasons. In experimental animals with renal diseases, initial renal injury can be self perpetuating by several pathways [1, 2] and can result in progressive renal failure. Additional experimental evidence suggesting that these pathways can be interrupted has raised the hope that someday we will be able to halt or delay the progression of chronic renal disease in humans.

These observations in animals have given rise to numerous clinical trials. Because the decline in renal function in most chronic renal diseases is slow, however, it is not practical to assess the effect of an intervention by determining the time elapsed before renal failure ensues. For this reason, many investigators have evaluated the effectiveness of therapy by measuring the rate of decline in renal function. The most popular method is measurement of the rate of decline in the reciprocal of the serum creatinine concentration ($1/P_{cr}$), assuming that this measure reflects the rate of decline in creatinine clearance and hence in GFR [3, 4]. Using this method, several investigators have concluded that low-protein and low-phosphorus diets can retard the progression of renal disease [5–9]. As a result, many nephrologists have adopted dietary modification as routine therapy for patients with chronic renal disease.

The goal of my discussion is to analyze the utility and limitations of measuring GFR and $1/P_{cr}$ to assess the level of renal function and rate of progression. I will focus on three topics: (*1*) GFR as an index of renal function; (*2*) the relationship between GFR and $1/P_{cr}$; and (*3*) applications of the rate of decline in renal function in studies of the progression of renal disease. I will conclude that P_{cr} and $1/P_{cr}$ provide a rough index of GFR, but that the rate of decline in $1/P_{cr}$ may not accurately reflect the rate of decline in GFR. I will suggest that conclusions from the studies of the effectiveness of low-protein and low-phosphorus diets, in which the rate of decline in $1/P_{cr}$ is the principal measure of the rate of progression, are not definitive. Finally, I will suggest that future studies should include measurements of GFR, and that other features of the design of clinical trials, such as selection of patients, length of followup, and sample size, are equally important in identifying therapies that can retard the progression of renal disease.

GFR as an index of renal function

The usefulness of any diagnostic test is based on its accuracy (comparison to a standard), precision (related inversely to the variability of measurements), and convenience. In clinical practice, physicians use test results to characterize the degree of functional abnormalities in individual patients; tests are repeated to assess changes in individuals over time. In clinical trials, investigators use test results to characterize a study population; repeated evaluations are performed to assess changes in the population over time. The decision to use a particular test depends on features of the test, features of the subjects to be tested, and the setting in which the test is used.

The rate of glomerular filtration generally is believed to be the best overall index of renal function in health and disease. Interestingly, this belief, although widely held, has not been subjected to formal evaluation. Attributes of the GFR as an overall index include the following: (*1*) It is a direct measure of renal function [10]. (*2*) It is reduced prior to the onset of symptoms of renal failure [11]. (*3*) In chronic renal diseases, the reduction in GFR correlates with the severity of some of the structural features of the end-stage kidney, such as the extent of tubulointerstitial sclerosis [12, 13]. (*4*) Signs and symptoms of uremia appear when GFR falls below 5–10 ml/min, even when azotemia, acidosis, hypocalcemia, phosphate retention, and anemia are corrected. But there are pitfalls in using the GFR as an index of renal function. First, the measurements are difficult to perform. Second, estimates of GFR can be imprecise. Third, GFR can be relatively insensitive for detecting early renal disease and for monitoring its progression.

Performance of GFR measurements. Rigorous assessment of GFR requires the measurement of renal clearance, utilizing an

ideal filtration marker. Inulin, a 5200 dalton polymer of fructose, fulfills the criteria for an ideal filtration marker and is the standard against which other markers are compared [14]. The classical method of Homer Smith included continuous intravenous infusion of inulin, urine collection by bladder catheterization, and measurement under standard conditions; subjects were studied while lying down the morning after an overnight fast [10]. However, the classical inulin clearance method is not practical either for clinical practice or clinical research. Inulin currently is in short supply, and it is difficult to measure. As a consequence, alternative filtration markers and clearance methods have been developed and validated. The most widely used alternative filtration markers in the United States are ^{125}I-iothalamate and ^{99m}Tc-diethylenetriaminepenta-acetic acid (DTPA). Both iothalamate and DTPA are excreted almost entirely by glomerular filtration. Radionuclide labeling permits accurate detection of minute doses of the marker in plasma and urine, and little of the radionuclide dissociates from the marker. The ^{125}I-iothalamate is administered as either a subcutaneous or intravenous bolus; ^{99m}Tc-DTPA is administered as an intravenous bolus. Because urine is collected by spontaneous voiding, its flow rate is stimulated by water loading to reduce the possibility of error due to incomplete emptying of the bladder. Simultaneous measurements of renal clearance of ^{125}I-iothalamate and ^{99m}Tc-DTPA by these methods, and of inulin by standard techniques, reveal similar results [15–23].

Although not available in the United States, ^{51}Cr-ethylenediaminetetra-acetic acid (EDTA) is widely used as a filtration marker in Europe. Plasma clearance typically is measured to avoid the need for urine collections. Simultaneous measurements of renal inulin clearance and plasma ^{51}Cr-EDTA clearance yield similar results, but this similarity derives from a coincidence of two errors: underestimation of renal inulin clearance by renal ^{51}Cr-EDTA clearance and overestimation of renal ^{51}Cr-EDTA clearance by plasma ^{51}Cr-EDTA clearance [23–32].

Radiation exposure is minimal with all three isotopes. In general, one chooses a filtration marker according to the ease of obtaining, administering, and counting the radioisotope. In an effort to avoid exposing patients to radiation, some investigators have performed clearance procedures using minute doses of nonradioactive iothalamate (Conray) or diatrizoate meglumine (Hypaque) and high-performance liquid chromatography to measure plasma and urine samples [33, 34]. These methods require expensive and time-consuming laboratory techniques, however.

Precision of estimates of GFR in humans. Clearance measurements can be used to estimate GFR of an individual or of a study population. In an individual, the precision of the estimate is influenced by variability in the assessment of urine and plasma concentrations of the filtration marker, variability in renal function during multiple urine collection periods during a single clearance procedure, and variability in renal function from one clearance procedure to the next. Within a study population, the estimate is influenced additionally by variability in renal function among individuals. I will focus on the variability in renal function from time to time in individuals and on the variability in renal function within a study population. Table 2 compares the variability of measurements of GFR and serum creatinine in humans, expressed as the ratio of the standard deviation to the mean (that is, the coefficient of variation [CV]). Also included is the minimal difference (that is, the critical difference [CD]) between measurements that is necessary for the difference to be statistically significant [35]. For all measurements, the greater the variability, the less precise the estimate of the level of renal function, and the greater the required difference between estimates for statistical significance.

Table 2. Comparison of coefficients of variation (CV) and critical differences (CD) for measurements of GFR and serum creatinine (P_{cr})

Comparison of two measurements in a single individual			
Renal function	Measurement	CV %	CD %
Normal	GFR	7.5	20
Normal	P_{cr}	11.0	31
Reduced[a]	GFR	12.0	33
Reduced	P_{cr}	6.3	18

Comparison of two individuals			
Renal function	Measurement	CV %	CD %
Normal	GFR	15	42
Normal	P_{cr}	15	42

[a] Reduced renal function refers to GFR less than 30–50 ml/min. (From Refs. 16, 36, 37.)

First, consider time-to-time variability in an individual. As the top half of Table 2 shows, the CV of measurements of GFR and serum creatinine depend on the level of renal function [16, 36, 37].* In individuals with normal renal function, the CV is 7.5% for GFR and 11% for serum creatinine, whereas in individuals with reduced renal function (GFR less than 30–50 ml/min), the CV is 12% for GFR, but only 6.3% for serum creatinine. As a result, within the normal range of renal function, the CD for measurements of GFR would be less than that for serum creatinine; hence, in comparing the level of renal function in a normal individual at two separate times, GFR measurements would be more precise than would measurements of the serum creatinine. In patients with reduced renal function, however, the CD for measurements of serum creatinine would be less than that for GFR; that is, measurements of serum creatinine would be more precise.

Second, consider variability among individuals. As shown in the bottom half of Table 2, in the normal population, the CVs for GFR (adjusted for age, gender, and body size) and serum creatinine (adjusted for gender) are both approximately 15% [38, 39]. In comparing two individuals with nearly normal renal function, then, the CD between measurements of either GFR or serum creatinine would be 42%. It is important to note that variability in measurements of renal function among normal

* In the study of individuals with normal renal function, urine was collected by bladder catheterization, with an average CV between collection periods of only 7.5% [36]. In the study of patients with renal disease, urine was collected by spontaneous voiding, with an average CV between collection periods of 20% [16]. Hence, the higher CV between measurements that was observed in patients with renal disease might be due, in part, to the higher CV among collection periods as a result of different methods of urine collection.

Table 3. Effect of variability and hypothesized difference in renal function in two groups on sample size requirement to detect the difference[a]

Variability in renal function in each group	Hypothesized differences in mean level of renal function between two groups		
CV	10%	20%	50%
15%	80	20	<10
25%	200	40	10
50%	600	300	30

[a] Sample size is the total number of patients, divided into two groups, that must be included in a clinical trial to detect a hypothesized difference between the groups. CV is the coefficient of variation among patients included in the trial (assumed to be equal in both groups). Calculations are performed for an alpha error of 0.05 (two-sided) and a beta error of 0.20 (one-sided) [40].

individuals is greater than the variability in repeated measurements in a single individual, irrespective of the renal function parameter that is measured.

Among patients with renal disease, variability in renal function is influenced additionally by criteria used to select the patients. For example, in the studies of low-protein and low-phosphorus diets that I mentioned earlier, the CV of serum creatinine among patients selected ranged from approximately 5% to 30% [5–9]. As shown in Table 3, variability in renal function within a study population has an important effect on the design of a clinical trial to determine the efficacy of therapy for renal disease. The number of patients (sample size) required to detect a difference between two groups depends on the hypothesized difference between the groups, the desired statistical power of the analysis, and the variability among patients [40]. For a given degree of statistical power, the greater the CV among patients or the smaller the hypothesized difference between groups, the greater the required sample size, irrespective of the measure of renal function that is used. These considerations emphasize the importance of variability among individuals and patient selection criteria, as well as the choice of renal function measurements in the design of clinical trials.

Sensitivity of GFR measurements. In principle, GFR is the sum of the filtration rates of all nephrons. The following equation depicts the determinants of single-nephron GFR (SNGFR):

$$SNGFR = K_F \cdot \Delta P$$

$$SNGFR = A \cdot P(\Delta P_H - \Delta P_O)$$

where K_F is the ultrafiltration coefficient, defined as the product of glomerular surface area (A) available for filtration and its hydraulic permeability (P); and ΔP is the net filtration pressure, defined as the difference between the transglomerular hydrostatic (ΔP_H) and oncotic (ΔP_O) pressure gradients. These gradients are affected, in turn, by the level of renal blood flow and afferent and efferent glomerular arteriolar resistances [41].

From this equation, it is clear that a decrease in either glomerular capillary surface area or permeability can reduce the GFR. It is also clear, however, that alterations in arteriolar resistances could lead to a countervailing alteration in filtration pressure that might stabilize SNGFR despite glomerular injury. For example, the earliest alteration in the determinants of SNGFR might be reduced hydraulic permeability due to damage to the glomerular capillary wall; an increase in glomerular capillary surface area (from perfusion of previously unperfused capillary channels or from glomerular hypertrophy) would maintain K_F and thus SNGFR. Once K_F declines, increased ΔP_H and reduced ΔP_O from augmented glomerular perfusion might maintain SNGFR. Once SNGFR declines, these same effects in undamaged nephrons might maintain whole-kidney GFR. These alterations have been observed in experimental animals and likely occur in humans with progressive renal diseases [42]. Hence, measurement of GFR might not reveal the extent of initial or subsequent structural glomerular damage and might not be a sufficiently sensitive index for detecting renal disease or for assessing its progression.

Relationship between GFR and the reciprocal of the serum creatinine concentration

The use of creatinine as an exogenous filtration marker was first reported in 1926 [43]. Within 10 years, sensitive biochemical assays were developed that permitted accurate quantitation of creatinine concentrations in normal serum and measurement of endogenous creatinine clearance [44]. These studies demonstrated that creatinine is not an ideal filtration marker in humans; it is excreted both by glomerular filtration and by tubular secretion. Creatinine clearance thus would be expected to overestimate GFR at all levels of renal function. Moreover, some creatinine is excreted via extrarenal routes, and the rates of renal and extrarenal excretion vary in patients with renal disease. Hence, the relationship between creatinine clearance and serum creatinine level varies; as a result, the relationship between GFR and the serum creatinine level also varies. Figure 1 shows results from a representative study by Shemesh and colleagues, in which simultaneous measurements of GFR by inulin clearance, creatinine clearance, and serum creatinine level were made in patients with glomerular diseases [20]. It is clear from these data that neither the creatinine clearance nor the serum creatinine level accurately estimates GFR. Indeed, the sensitivity (proportion of true positives) of a reduced creatinine clearance or elevated serum creatinine level in detecting a reduced GFR was only 75% and 61%, respectively.

Nonetheless, the serum creatinine concentration remains the most widely used measure of progression of renal disease in clinical practice and in clinical trials. Arguments in favor of using this measure follow:

(*1*) *Accuracy.* In assessing progression, it is necessary to determine accurately the *change* in the level of renal function rather than the exact level of function. Although the serum creatinine level does not provide an accurate assessment of GFR, some have claimed that changes in $1/P_{cr}$ are an accurate reflection of changes in GFR [3, 4].

(*2*) *Precision.* As I said earlier, in patients with reduced renal function, the time-to-time variability for the serum creatinine level is lower than that for GFR. Hence, the serum creatinine level is a more precise estimate of the level of renal function than is GFR, and changes in serum creatinine level are easier to detect than are changes in GFR.

(*3*) *Convenience.* The serum creatinine level is easily measured in all clinical laboratories. No special preparation is necessary on the part of the patient or the laboratory. Measurements thus can be made frequently and in all patients.

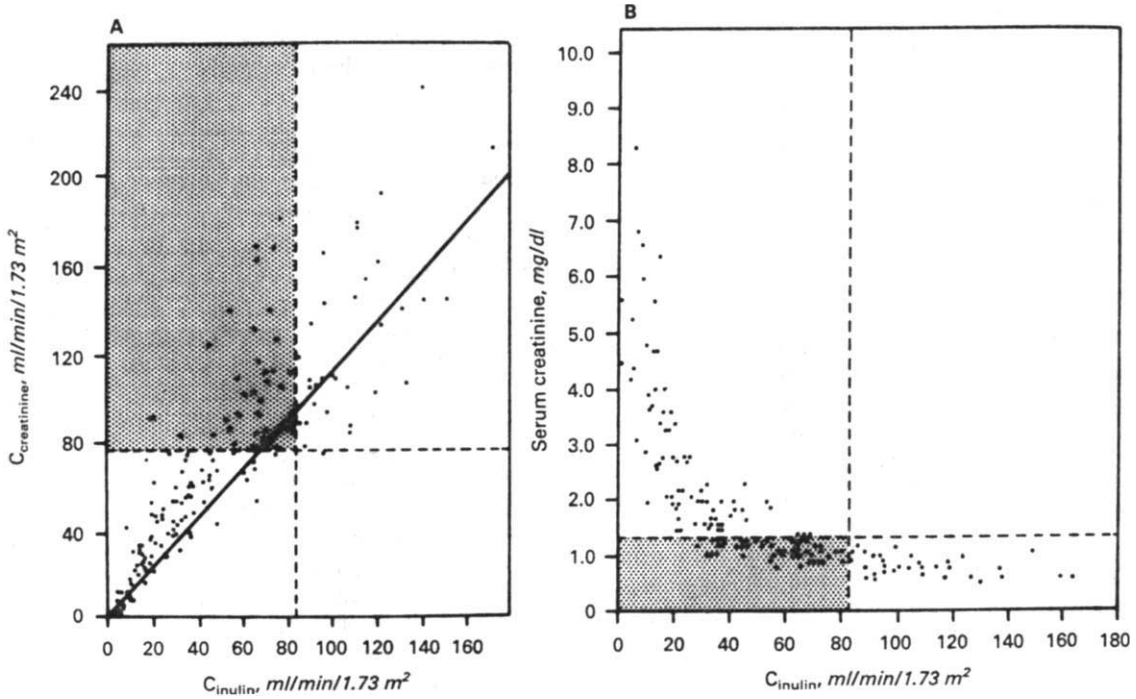

Fig. 1. *Relationships between GFR, C_{cr}, and P_{cr} in patients with glomerular disease.* Vertical dashed lines in **A** and **B** correspond to the lower limit for inulin clearance (82 ml/min/1.73 m²); the horizontal line in **A** corresponds to the lower limit for creatinine clearance (77 ml/min/1.73 m²); the horizontal line in B corresponds to the upper limit for the serum creatinine concentration (1.4 mg/dl). The *shaded areas* include values for patients in whom inulin clearance is reduced but creatinine clearance (**A**) or serum creatinine concentration (**B**) remains normal. (From Refs. 20 and 45.)

Clearly, the key argument is the first one. What follows is a critical evaluation of the assumptions on which it is based.

Theoretical relationship between GFR and the reciprocal of the serum creatinine concentration. Given that renal creatinine excretion occurs by tubular secretion as well as by glomerular filtration, the following equation can be derived:

$$U_{cr}V = GFR \cdot P_{cr} + TS_{cr}$$

where $U_{cr}V$ is the rate of renal excretion and TS_{cr} is the rate of tubular secretion (usually given in mg/day). Creatinine is also lost by extrarenal routes. Thus:

$$U_{cr}V = G_{cr} - E_{cr}$$

where G_{cr} is the rate of generation and E_{cr} is the rate of extrarenal elimination (usually given in mg/day).* If we rearrange these formulas and solve for $1/P_{cr}$:

$$1/P_{cr} = GFR/(G_{cr} - E_{cr} - TS_{cr})$$

Finally, the rate of change in $1/P_{cr}$ is obtained by differentiation with respect to time, as shown in the equation below:

$$d/dt[1/P_{cr}] = [1/(G_{cr} - E_{cr} - TS_{cr})] \cdot d/dt[GFR] + GFR \cdot d/dt[1/(G_{cr} - E_{cr} - TS_{cr})]$$

Implicit in the use of the slope of the linear regression of $1/P_{cr}$ versus time as an estimate of the rate of change in GFR in an individual is the assumption that rates of change in both $1/P_{cr}$ and GFR are constant over time and are related to each other by a proportionality constant. Implicit in its use in a study population is that the proportionality constant is the same for all patients. These assumptions are valid only under certain conditions:

(1) If the term $G_{cr} - E_{cr} - TS_{cr}$ is constant over time and among patients, the following equations apply:

$$G_{cr} - E_{cr} - TS_{cr} = k$$

$$1/P_{cr} = GFR/k$$

$$d/dt[1/P_{cr}] = (1/k) \cdot d/dt[GFR]$$

This condition applies whether or not the individual terms G_{cr}, E_{cr}, and TS_{cr} are constant.

(2) If the terms G_{cr}, E_{cr}/P_{cr}, and TS_{cr}/P_{cr} are constant over time and among patients, the following equations apply:

$$G_{cr} = k', \; E_{cr}/P_{cr} = k'', \; TS_{cr}/P_{cr} = k'''$$

$$1/P_{cr} = (GFR + k'' + k''')/k'$$

$$d/dt[1/P_{cr}] = (1/k') \cdot d/dt[GFR]$$

In the following discussion, I will review previously published studies suggesting that neither of these conditions is met. Instead, the studies suggest that differences exist in tubular secretion, extrarenal elimination, and rate of generation of

* In an earlier publication, the term E_{cr} was used to represent clearance of creatinine due to extrarenal elimination [45]. In this discussion, extrarenal clearance is expressed as E_{cr}/P_{cr}.

Table 4. Effect of level of renal function on tubular secretion of creatinine in glomerular disease[a]

Range of GFR[b]	>80	40–80	<40
Patients (*n*)	42	50	81
GFR (*M* ± *SD*)	113 ± 32	60 ± 7	22 ± 9
C_{cr} (*M* ± *SD*)[b]	134 ± 45	94 ± 23	42 ± 18
C_{cr} − GFR (*M* ± *SD*)	21 ± 45	34 ± 23	20 ± 18
C_{cr}/GFR (*M*)	1.16	1.57	1.92

[a] From Ref. 20.
[b] Values for GFR and C_{cr} are given as ml/min/1.73 m^2.

creatinine among patients with chronic renal disease, and that these parameters change over time. In each of the following sections, I will illustrate the hypothetical effects of such differences among patients and changes over time on the rate of decline in $1/P_{cr}$, despite an assumed constant rate of decline in GFR.

Effects of tubular secretion. Creatinine is secreted in the proximal tubule by an active process that transports organic cations [46]. Drugs that inhibit creatinine secretion include other organic cations, such as cimetidine and trimethoprim [47, 48], and probenecid, an organic anion [49]. Inhibition of creatinine secretion reduces creatinine clearance and increases the serum creatinine level without changing the GFR. Clinically, it is important to distinguish drug-induced alterations in creatinine clearance and serum creatinine level due to an inhibition of creatinine secretion from those due to a reduction in GFR.

Most of the data regarding tubular secretion of creatinine in humans are derived from cross-sectional studies (measurements at one time only) in normal individuals and in patients with chronic renal disease, such as the study by Shemesh and colleagues (Fig. 1) [20]. Additional data from this study (Table 4) demonstrate the marked variability in the magnitude of creatinine secretion among patients. The mean difference between creatinine clearance and GFR (the clearance of creatinine due to tubular secretion, that is, TS_{cr}/P_{cr}) and the mean ratio of creatinine clearance to GFR differ in patients with different levels of GFR. Moreover, at each level of GFR, the variability among patients was high: the coefficient of variation of creatinine clearance due to tubular secretion was 214%, 68%, and 90% among patients with GFR values that were greater than 80, 40–80, and less than 40 ml/min 1.73 m^2, respectively. Longitudinal studies also demonstrate that tubular secretion varies widely in individual patients during the course of renal disease [20, 50].

Figure 2 shows the effects of the tubular secretion of creatinine on the rate of change in $1/P_{cr}$ in 2 hypothetical patients, (*a*) and (*b*), with declining GFR. The effect of differences between patients is shown in the left panel. Values for TS_{cr} are constant in both patients, but lower in (a) than in (b). Despite the same rate of decline in GFR, the rate of decline in $1/P_{cr}$ is greater in the patient with the higher TS_{cr}. The effect of changes over time is shown in the right panel. Both patients have the same initial TS_{cr}; however, in (a) TS_{cr} is constant, but in (b) TS_{cr} increases as GFR declines. Despite the same rate of decline in GFR, the rate of decline in $1/P_{cr}$ is lower in the patient with increasing TS_{cr}.

Effects of extrarenal creatinine elimination. Creatinine is eliminated almost entirely by renal excretion in humans with normal renal function; negligible amounts are excreted in feces and sweat [51, 52]. In patients with renal disease, however, the renal excretion of creatinine is far lower than in normal individuals. Table 5 shows data from Goldman indicating that the renal creatinine excretion is lower at all stages of chronic renal disease, with lowest values occurring in patients with the most severe reductions in renal function [52].

One reason for the reduced renal creatinine excretion is that creatinine is also eliminated by extrarenal routes, probably because of degradation by intestinal microorganisms [53, 54]. As I will mention in a moment, another possible reason is decreased generation of creatinine. Table 6 illustrates the wide range of values for extrarenal creatinine elimination [53, 54]. Despite the variability in E_{cr}, in one study, clearance of creatinine due to extrarenal elimination (E_{cr}/P_{cr}) varied only from 0 to 3.0 ml/min, and E_{cr} significantly correlated with P_{cr} ($r = .69$), indicating that E_{cr}/P_{cr} was relatively constant among this group of patients [54].

Figure 3 shows the effects of the rate of extrarenal elimination of creatinine on the rate of change in $1/P_{cr}$ in 4 hypothetical patients, (*a*) through (*d*), with declining GFR. The effect of differences among patients is shown in the left panel. The rate of extrarenal creatinine elimination is lowest in (*a*) and highest in (*d*). Despite the same rate of decline in GFR, the rate of decline in $1/P_{cr}$ is least in the patient with the lowest extrarenal elimination rate. The right panel shows the effect of changes over time. Extrarenal creatinine elimination is unchanged in (*a*) and increases most in (*d*). Despite the same rate of decline in GFR, the rate of decline in $1/P_{cr}$ is least in the patient with the greatest increase in extrarenal elimination.

Effects of creatinine generation. Creatinine generation is defined as the entry of creatinine into body fluids from endogenous or exogenous sources. Endogenous creatinine is the final breakdown product of creatine metabolism. After synthesis from amino acid precursors or absorption from the gastrointestinal tract, creatine is concentrated in muscle, stored as creatine and phosphocreatine, and converted to creatinine. Exogenous creatinine originates from dietary ingestion. Thus, the rate of creatinine generation is affected by muscle metabolism and diet.

Generation of creatinine from creatine depends on the size of the creatine pool and its rate of turnover to creatinine [55]. Approximately 98% of creatine and phosphocreatine is contained in muscle; the total body creatine pool thus is related to muscle mass. In a healthy 70 kg young man, for example, the total body creatine pool is approximately 100 g to 120 g. Daily creatine turnover has been estimated to be only 1.6% to 1.7% of the total pool. Therefore, in a steady state of creatinine balance, the creatinine generation rate from muscle metabolism would be 1700 to 2000 mg/day.

Muscle mass is related to age, weight, and gender. Accordingly, differences in creatine pool and in creatinine generation rate among individuals are to be expected. Walser recently summarized the data on renal creatinine excretion from 5 reports on 1100 healthy individuals and patients without renal or hepatic disease [56]. (In these subjects, creatinine excretion is expected to equal the creatinine generation rate.) He calculated that the renal creatinine excretion ($U_{cr}V$, mg/kg/day) is related to age (years) as follows:

$$U_{cr}V = 28.2 - 0.172 \times \text{age (men)}$$

$$U_{cr}V = 21.9 - 0.115 \times \text{age (women)}$$

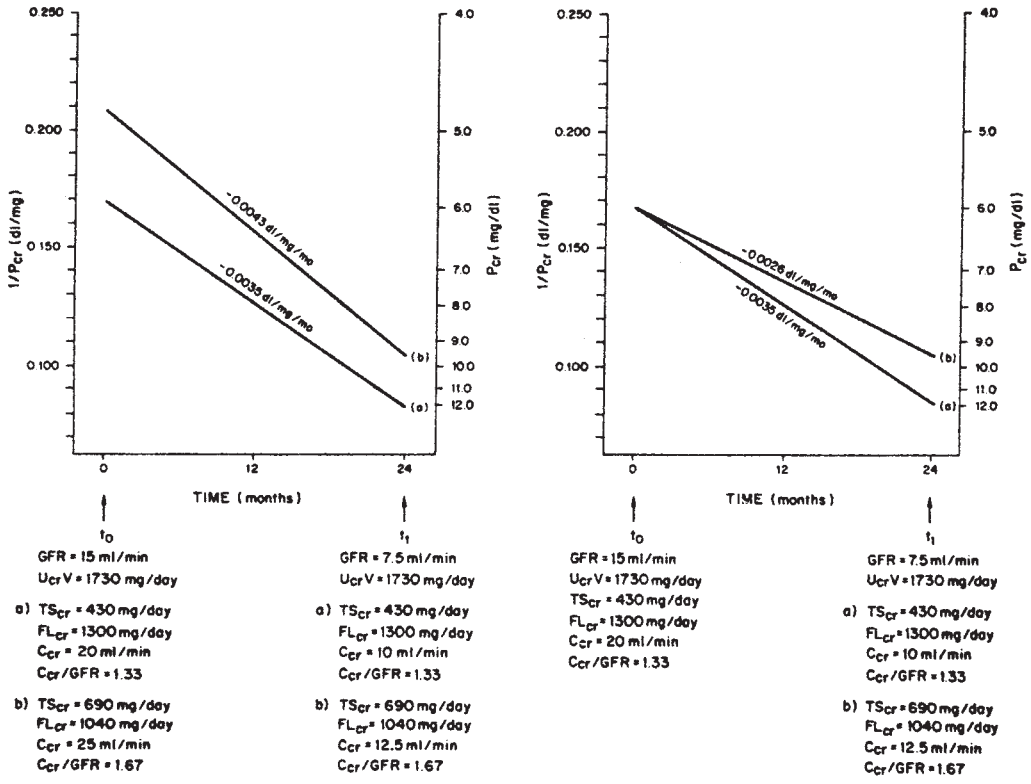

Fig. 2. *Effects of differences between patients and changes over time in TS_{cr} on the rate of decline in $1/P_{cr}$.* Values for initial and final GFR, TS_{cr}, FL_{cr}, (rate of creatinine filtration, defined as GFR · P_{cr}), $U_{cr}V$, C_{cr}, and C_{cr}/GFR are illustrated for two hypothetical patients, (*a*) and (*b*). In both patients, $U_{cr}V$ is constant at 1730 mg/day throughout the 2-year interval. In the *left panel*, values for TS_{cr} are different but constant. In (*a*) TS_{cr} is 430 mg/day, whereas in (*b*) TS_{cr} is 690 mg/day. As a result, the ratio of C_{cr}/GFR is 1.33 in (*a*) and 1.67 in (*b*). Consequently, initial and final values for $1/P_{cr}$ are higher in (*b*) than in (*a*), and the rate of decline in $1/P_{cr}$ is greater in (*b*) than in (*a*). In the *right panel*, the 2 patients have the same initial TS_{cr}, 430 mg/day, resulting in an initial ratio of C_{cr}/GFR of 1.33. In (*a*) the rate is constant, but in (*b*) the rate increases to 690 mg/day as GFR declines, resulting in a final ratio of C_{cr}/GFR of 1.67. Consequently, the final value of $1/P_{cr}$ is higher and the rate of decline in $1/P_{cr}$ is lower in (*b*) than in (*a*).

Table 5. Creatinine excretion in chronic renal disease[a]

P_{cr} range (*mg/dl*)	Patients (*n*)	C_{cr} mean (*ml/min*)	P_{cr} mean (*mg/dl*)	$U_{cr}V$ mean ± SD (*mg/day*)
<2.0	85	85.1	1.16	1320 ± 420
2.0–4.0	29	29.9	2.95	1200 ± 430
4.0–6.0	17	16.5	4.84	1110 ± 470
>6.0	22	6.4	10.37	880 ± 380

[a] From Ref. 52.

Table 6. Extrarenal elimination of creatinine in chronic renal disease[a]

Patients (*n*)	8[b]	9[c]
Range of C_{cr} (*ml/min*)	2.4–8.3[d]	1.90–10
Range of P_{cr} (*mg/dl*)	6.6–18	6.3–24
Range of E_{cr} (*mg/day*)	312–715	0–797
Range of G_{cr} (*mg/day*)	776–1752	1017–1921
Range of E_{cr}/G_{cr} (%)	16–66	0–56
Range of E_{cr}/P_{cr} (*ml/min*)	1.2–7.0[d]	0–3.0

[a] Abbreviations: C_{cr}, creatinine clearance; P_{cr}, serum creatinine level; E_{cr}, rate of extrarenal elimination of creatinine; G_{cr}, rate of generation of creatinine.
[b] From Ref. 53.
[c] From Ref. 54.
[d] Values from 5 patients who were not being dialyzed.

Alterations in the rate of creatinine generation also can arise from changes in the size of the pool or the rate of turnover of creatine. In conditions associated with muscle wasting, such as inflammatory and degenerative diseases, and in malnutrition, creatine turnover can be increased [57–60]; this rise initially can lead to an increased creatinine generation rate, but subsequently to reduced muscle mass and decreased creatinine generation.

Finally, the creatinine generation rate also is affected by dietary intake of exogenous creatine and creatinine, derived largely from ingestion of meat. The creatine content of meat ranges from 3.5 to 5.0 mg/g, of which as much as 65% can be converted to creatinine during cooking [61, 62]. Ingested creatine and creatinine both are absorbed by the gastrointestinal tract. Therefore, in principle, alterations in meat intake affect the creatinine generation rate by altering the total body pool of both creatine and creatinine.

Crim, Calloway, and Margen demonstrated that ingestion of a creatine supplement expands the creatine pool and increases renal creatinine excretion, and conversely, that eliminating creatine from the diet contracts the creatine pool and reduces renal creatinine excretion [63, 64]. These changes in the creatine pool and in renal creatinine excretion occur without

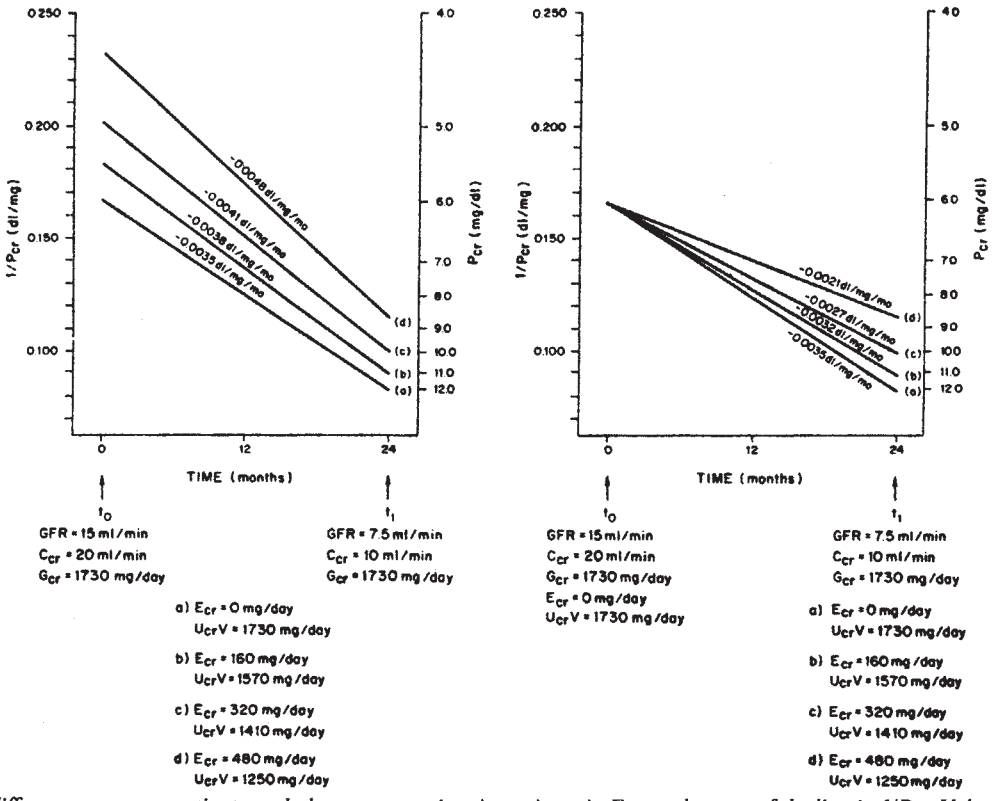

Fig. 3. *Effects of differences among patients and changes over time in patients in E_{cr} on the rate of decline in $1/P_{cr}$.* Values for initial and final GFR, $U_{cr}V$ and E_{cr} are illustrated for 4 hypothetical patients, (*a*) through (*d*). In all 4 patients, G_{cr} is taken to be the same and constant at 1730 mg/day. In the *left panel*, values for E_{cr} vary from 0 to 480 mg/day but are constant throughout the 2-year interval. As a result, $U_{cr}V$ for the 4 patients varies from 1730 to 1250 mg/day. In (*a*) E_{cr} is lowest, as are initial and final values for $1/P_{cr}$ and rate of decline in $1/P_{cr}$. By contrast, E_{cr} is highest in (*d*), as are initial and final values for $1/P_{cr}$ and rate of decline in $1/P_{cr}$. In the *right panel*, initial E_{cr} is 0 mg/day in all 4 patients. However, the final value varies from 0 mg/day in (*a*) to 480 mg/day in (*d*). As a result, initial $U_{cr}V$ is the same in all 4 patients, 1730 mg/day, but final $U_{cr}V$ varies from 1730 to 1250 mg/day. In (*a*) E_{cr} is unchanged, and the rate of change in $1/P_{cr}$ is greatest. By contrast, in (*d*) the final value for E_{cr} is highest, and the rate of change in $1/P_{cr}$ is least.

concurrent alterations in nitrogen balance or total muscle mass. Figure 4, from studies by Bleiler and Schedl [65], shows the decline in renal creatinine excretion and serum creatinine following elimination of meat from the diet and the substitution of a creatine-free protein formula (casein). Because of the low turnover rate of creatine, the changes evolve over weeks following the change in dietary creatine. On the other hand, ingested creatinine rapidly increases serum and urinary creatinine levels [66, 67]. Figure 5 shows the effect of a meat meal on serum creatinine [67]. Given that the creatinine content of cooked beef can be as high as 3 mg/g, ingestion of one quarter-pound hamburger could increase the renal creatinine excretion by 350 mg.

Few data are available on creatinine generation in patients with chronic renal disease. As I mentioned previously, renal creatinine excretion is lower than expected in patients with chronic renal disease, possibly because of decreased creatinine generation. In studies I referred to earlier, creatinine generation was within the expected range for normal individuals, and the increase in extrarenal creatinine elimination accounted for the reduction in its urinary excretion [53, 54]. Indeed, Mitch and Walser hypothesized that creatinine generation is normal throughout the course of chronic renal disease and that increased extrarenal excretion can fully account for the decline in renal excretion [68]. However, dietary protein restriction, anorexia, and weight loss in patients with chronic renal disease are likely associated with reduced meat intake and muscle mass, and these reductions would be expected to decrease creatinine generation.

Figure 6 shows the effect of creatinine generation on the rate of change in $1/P_{cr}$ in hypothetical patients who have declining GFRs. The effect of differences among 4 patients, (*a*) through (*d*), is shown in the left panel. Creatinine generation is highest in (*a*) and lowest in (*d*). Despite the same rate of decline in GFR, the rate of decline in $1/P_{cr}$ is least in the patient with the highest G_{cr}. The effect of changes over time is shown in the middle and right panels. In the middle panel, G_{cr} is constant in (*a*) but declines gradually in (*b*). Despite the same rate of decline in GFR, the rate of decline in $1/P_{cr}$ is lower in the patient with declining G_{cr}. In the right panel, the 2-year followup interval is divided into three 8-month periods. The G_{cr} is again constant in (*a*). In (*b*), however, the G_{cr} is constant during the first period, declines gradually during the second period, and remains constant at a lower value during the third period. The rate of decline in $1/P_{cr}$ is initially the same as in (*a*), but subsequently it is slower and then faster than in (*a*). Thus, despite a constant rate of decline in GFR, the rate of decline in $1/P_{cr}$ changes if creatinine generation changes.

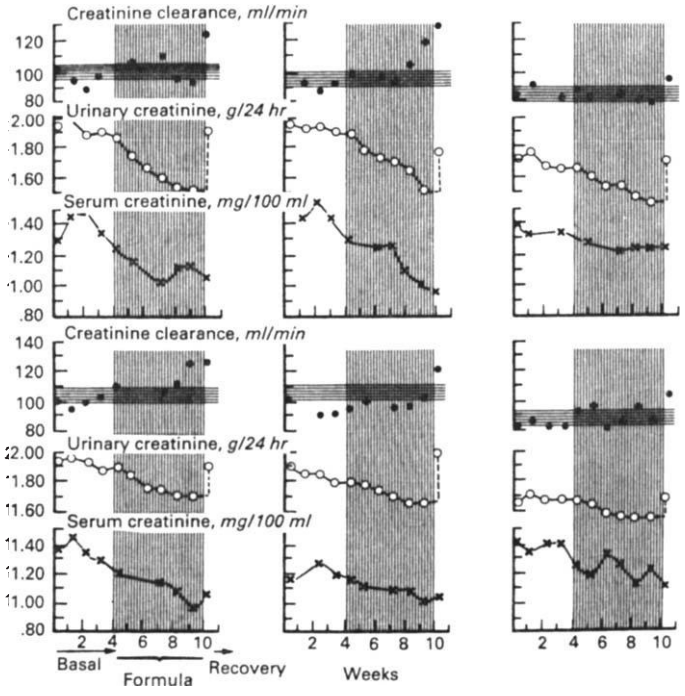

Fig. 4. *Effect of elimination of meat from the diet and substitution of creatine-free protein formula.* Serum and urinary creatinine and creatinine clearance, measured at weekly intervals, are shown in 6 healthy subjects. (From Ref. 65.)

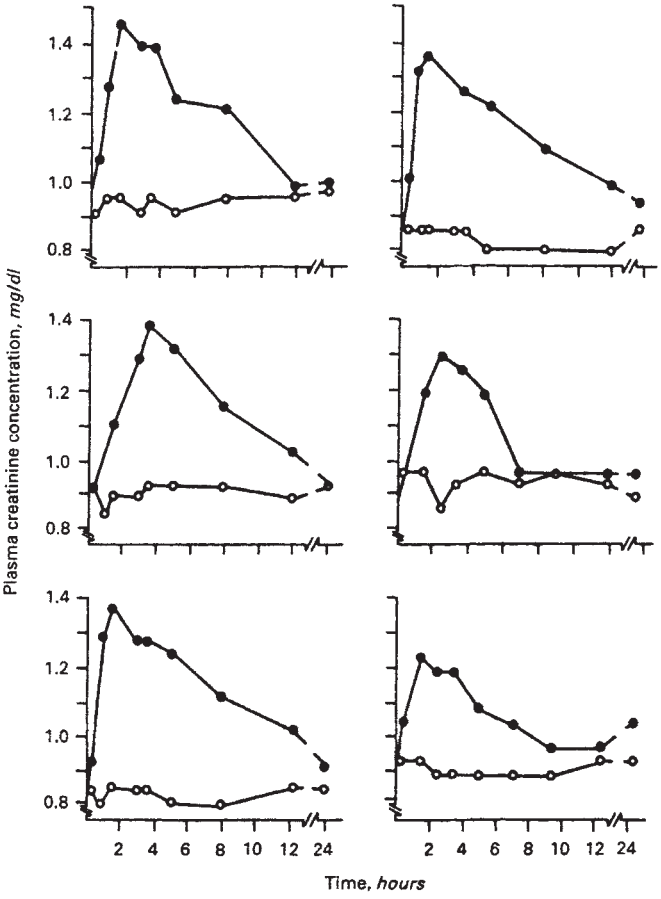

Fig. 5. *Effect of meat intake on plasma creatinine concentration in 6 healthy subjects. Solid circles* represent values after a meal containing cooked meat protein. *Open circles* represent values after a meal devoid of meat protein. (From Ref. 67.)

Observations on the relationship between rates of decline in the reciprocal of the serum creatinine and GFR. Thus far, only limited data are available on the relationship between rates of decline in $1/P_{cr}$ and GFR. In three separate reports, the correlation in groups of patients was relatively weak: the proportion of variability in rates of decline in $1/P_{cr}$ that can be attributed to variability in rates of decline in GFR was only 0.14 to 0.52 [69–71]. These results demonstrate that the rate of decline in $1/P_{cr}$ is not an accurate measure of the rate of decline in GFR during short-term (one- to two-year) studies. One possible explanation for these relatively weak correlations, as I said, is that tubular secretion, extrarenal elimination, and generation of creatinine differ among patients and change over time in a given patient. Other explanations also are possible, however. First, rates of decline in both GFR and $1/P_{cr}$ might not have been constant throughout the followup interval. Indeed, even if the rate of decline in GFR were constant, the studies I have reviewed suggest that the theoretical conditions for a constant decline in $1/P_{cr}$ were not met. Second, the estimates of the rates of decline in GFR and $1/P_{cr}$ may not have been precise. The studies reported so far are characterized by small absolute changes in renal function, a limited number of measurements, and short followup intervals. These factors might result in imprecise estimates of the rates of decline in GFR and $1/P_{cr}$ and therefore might weaken the correlation between them. Longer periods of followup might be necessary for more precise estimates and for satisfactory correlations.

In summary, the theoretical analysis and observed correlations suggest that the rate of decline in $1/P_{cr}$ is affected by several factors other than the rate of decline in GFR, including tubular secretion, extrarenal elimination, and generation of creatinine. These factors are highly variable among patients with renal disease and change as renal disease progresses. As a result, differences among patients in the rate of decline in $1/P_{cr}$ do not necessarily represent differences in the rate of decline in GFR. Similarly, changes over time in the rate of decline in $1/P_{cr}$ in individual patients need not represent changes in the rate of decline in GFR. These conclusions challenge the argument that changes in $1/P_{cr}$ accurately reflect changes in GFR. Furthermore, they raise questions about the validity of the conclusions of the aforementioned studies of low-protein and low-phosphorus diets on the progression of renal disease.

Applications of the rate of decline in renal function in studies of the progression of renal disease

Thus far, I have concentrated on the use of measurements of GFR and $1/P_{cr}$ to estimate the rate of decline in renal function. In this section, I will focus on methodologic limitations in applying this estimate, irrespective of the measure of renal function that is used, to studies of the progression of renal disease. The estimated rate of decline in renal function can be applied in one of two general ways: (*1*) In an individual patient, rates during different periods of time can be compared; changes in the rate are associated with changes in the patient's disease

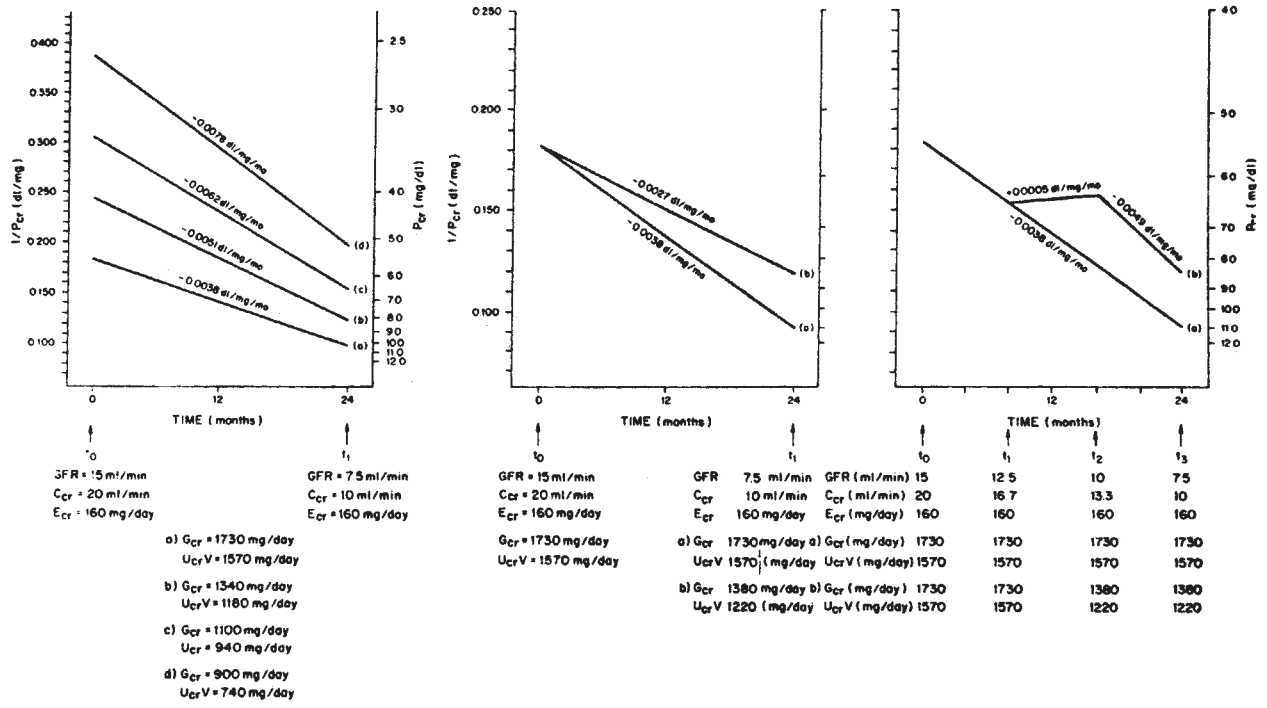

Fig. 6. *Effects of differences among patients and changes over time in patients in G_{cr} on the rate of decline in $1/P_{cr}$.* In all patients, E_{cr} is assumed to be 160 mg/day and constant. Hence, the values for $U_{cr}V$ are 160 mg/day lower than the values for G_{cr}. Values for initial and final GFR, E_{cr}, G_{cr}, and $U_{cr}V$ are illustrated for hypothetical patients. In the *left panel*, values for G_{cr} are different but constant. Values for G_{cr} are derived from the value for E_{cr} and the expected values for $U_{cr}V$ based on age, weight, and gender of 4 hypothetical patients, according to the formulas derived by Walser [56]: (*a*) 42-year-old man weighing 75 kg; (*b*) 72-year-old man weighing 75 kg; (*c*) 42-year-old woman weighing 55 kg; and (*d*) 72-year-old woman weighing 55 kg. In (*a*), G_{cr} is greatest, and initial and final values for $1/P_{cr}$ and rate of decline in $1/P_{cr}$ are least. In (d), G_{cr} is least, and initial and final values for $1/P_{cr}$ and rate of decline in $1/P_{cr}$ are greatest. In the *middle and right panels*, initial values for G_{cr} are 1730 mg/day, but change during followup. In the middle panel, G_{cr} remains constant at 1730 mg/day in (*a*), but declines gradually by 350 mg/day to a final value of 1380 mg/day in (*b*). As a result of declining G_{cr}, final $1/P_{cr}$ is higher and the rate of decline in $1/P_{cr}$ is lower in (*b*). In the *right panel*, the 2-year followup interval is divided into three 8-month periods. The G_{cr} remains constant throughout all three periods in (*a*). However, in (*b*), G_{cr} is constant at 1730 mg/day during the first period (from t0 to t1), but declines gradually from 1730 mg/day to 1380 mg/day during the second period (from t1 to t2), and then remains constant at 1380 mg/day during the third period (from t2 to t3). The rate of decline in $1/P_{cr}$ is initially the same as in (*a*), but subsequently it is slower and then faster than in (*a*).

or treatment. Typically, in this type of study, patients serve as their own controls. (*2*) In groups of patients, the mean rates can be compared; differences in rates are associated with differences in the patients' diseases or treatments. In this type of study, one group serves as the control for another. The principal methodologic limitations of these applications derive from the assumption of a constant rate of decline in renal function in an individual patient and from variability in the rates of decline among patients. In the following discussion, I will explain these limitations as well as the implications on the design of clinical studies.

Assumption of a constant rate of decline in renal function. The use of linear regression analysis to estimate the rate of decline in renal function rests on the assumption that the decline in renal function over time is linear, that is, that the rate of decline is constant. Constancy of the rate of decline in renal function can be assessed, in part, from the correlation of renal function and time. Although no statistical test can prove that the observed relationship is truly linear, a high correlation suggests that the regression line is a reasonable description of the true relationship.

Mitch and colleagues were the first to recognize the strong correlation between $1/P_{cr}$ and time [72]. Since then, numerous other reports have confirmed their findings [73–78]; values for r^2 (the proportion of variability in $1/P_{cr}$ that can be attributed to variability in time) exceeded .70 in approximately 90% of patients [78]. Fewer reports describe the pattern of decline in GFR [71, 79–81]. Although correlations were not as high in some studies, in general the pattern was consistent with a constant rate of decline. Because of these high correlations, Mitch and Walser proposed that the rate of decline in renal function (both GFR and $1/P_{cr}$) is constant and that changes in the rate after initiation of the treatment can be taken to represent the consequences of treatment [3, 4].

The finding of a constant rate of decline during part of the course of renal disease, however, does not indicate that the rate of decline is constant throughout the entire course. For example, consider a hypothetical patient in whom the true decline in renal function follows the pattern of a sigmoid curve. Figure 7 shows three lines with different slopes that closely approximate the true relationship during three time periods. Extrapolating the slope of any of the regression lines to another period, however, would lead to an incorrect estimate of renal function.

For a number of reasons, it is likely that the rates of decline

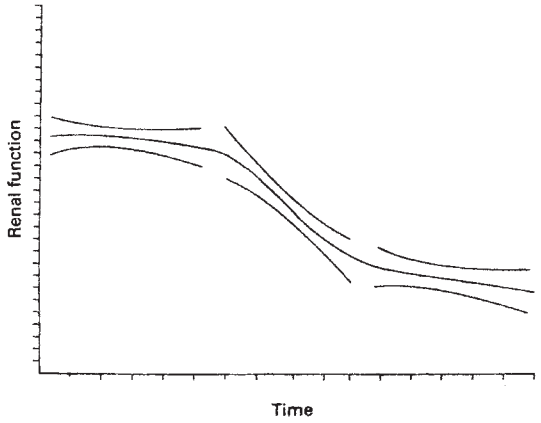

Fig. 7. *Linear approximation to a non-linear decline in renal function over time.* The *solid curved line* represents the true change in renal function over time. The *interrupted curved lines* represent hypothetical 95% confidence intervals for the slopes of straight lines that approximate the curve during three time periods. Note that extrapolations of the straight lines to earlier or later periods would not accurately reflect the true relationship of renal function over time.

in GFR and $1/P_{cr}$ are not constant throughout the entire course of chronic renal disease. Based on possible countervailing alterations in the determinants of SNGFR that I mentioned earlier, it seems likely that the rate of decline in GFR in the initial stages of renal disease is slower than in the later stages. The determinants of $1/P_{cr}$ also appear to vary throughout the course of renal disease. Maximal increases in tubular secretion occur when renal function is minimally impaired, whereas maximal increases in extrarenal elimination occur when renal function is more severely impaired. Indeed, Mitch has called attention to the fact that the rate of decline in $1/P_{cr}$ is not constant if serum creatinine levels less than 2–3 mg/dl are included in the analysis of $1/P_{cr}$ versus time [3]. The possibility that the rate of decline in renal function is not constant throughout the entire course of progressive renal disease is a clear warning that patients should not be their own controls in studies of the effects of treatment on the rate of progression. Instead, if the effect of treatment is to be assessed from a comparison of the rates of decline in renal function before and after treatment is begun, studies should include a concurrent control group that does not receive the treatment.

Variability in the rate of decline among patients. If the rate of decline in renal function (either GFR or $1/P_{cr}$) in an individual truly is constant over a period of time, then the slope of the regression line would provide a precise estimate of the rate during that interval. Because of the observed strong correlations between the level of renal function and time in individuals, the mean of the slopes of the regression lines in a study population has been taken as an estimate of the rate of decline in renal function of the group. However, because the rates of decline among individuals are highly variable, the mean slope is not a precise estimate. In the studies I have mentioned [5–9, 72–77], the mean rate of decline in $1/P_{cr}$ ranged from approximately 0.001–0.003 dl/mg/month, with a coefficient of variation greater than 100%, even among patients with the same type of renal disease. The range in rates of decline in GFR is similarly large [79–81]. As I said earlier, because of the large variability among patients, large sample sizes are required for clinical trials, irrespective of the measure of renal function that is used (Table 3).

Perhaps we can now understand why numerous treatments appear to slow the pace of progressive renal disease in experimental animals, yet none of these treatments has been proven to be effective in humans. First, in the laboratory, variability is reduced to a minimum. A single disease is studied in a genetically homogenous population of experimental animals. Initial renal structure and function are either normal or are altered to a similar extent by an identical experimental maneuver. Because treatment is initiated at the same stage of the disease in all animals, its effect is relatively uniform. Second, it is possible to perform invasive and repetitive assessment of renal structure and function in the laboratory. Because the effect of treatment is assessed by the most accurate and precise methods available, there are few false-positive and false-negative results. Consequently, the required sample size is relatively small.

In contrast, in clinical trials, variability is typically enormous. Diverse renal diseases are studied in a diverse population. Even in patients with the same disease, one finds a wide range of severity of initial alterations in renal structure and function. Furthermore, it is impossible to control rigorously other important variables in the experimental setting. Even if treatment is truly effective, its effectiveness is not likely to be uniform. The type and frequency of assessments are limited to those that are most convenient rather than to those that are most accurate or precise, making it difficult to detect the effect of treatment. As a result, large samples would be required; even then, negative findings can result. The utility of a treatment might be recognized only if it is highly effective in delaying progression; partially effective treatments might be overlooked. On the other hand, positive findings from a well-designed clinical trial should provide relevant clinical and pathophysiologic information; treatments that are effective in diverse patients with diverse renal diseases are likely to interrupt a common pathogenetic mechanism in the progression of renal disease.

Outlook

Future studies should include a longer followup interval and also include measurements of GFR. The use of serum creatinine or $1/P_{cr}$ as the only measure of renal function can result in misinterpretation of the results. In addition, we should focus our attention on individual renal diseases, identify stages in their progression, and identify sensitive methods for assessing the extent of alteration in structure and function at each stage. Several such studies of diabetic nephropathy are underway [82]. Similar efforts are necessary in other relatively common, well-studied diseases, such as polycystic kidney disease, membranous nephropathy, and IgA nephropathy. Obviously, successful clinical trials will require large numbers of patients, cooperation among large numbers of institutions, and expenditures of vast resources. It will be important to establish national priorities for initiating and funding these studies [83].

In the meantime, how should we assess renal function in our patients? Measurements of GFR using the bolus infusion and spontaneous voiding methods, and using radioisotope-labeled filtration markers are accurate, precise, and simple enough for use in clinical practice. However, because the serum creatinine concentration is more convenient to measure, it will remain the

most widely used index of renal function in clinical practice. Nonetheless, a greater appreciation of its limitations is necessary; measurement of the serum creatinine level is an inadequate method for detecting chronic renal disease early and for estimating the rate of progression, at least during short (one- to two-year) intervals. These are serious shortcomings in view of the considerable effort to identify therapies that can delay the progression of chronic renal disease. If effective therapies are found, we will need to employ more accurate measures of renal function in routine clinical practice.

Questions and answers

DR. NICOLAOS E. MADIAS (*Chief, Division of Nephrology, New England Medical Center*): You presented data on creatinine secretion that were mostly based on cross-sectional studies. How much do we know about creatinine secretion from longitudinal studies in patients with progressive renal disease? Also, is there any information about the creatine turnover rate in patients with renal disease as opposed to normals?

DR. LEVEY: The answer to your question about creatinine secretion is complicated for two reasons. First, it is necessary to distinguish between the rate of tubular secretion of creatinine (TS_{cr}, measured in mg/day) and clearance of creatinine due to tubular secretion (C_{cr} − GFR, or TS_{cr}/P_{cr}, measured in ml/min/1.73 m^2). Although tubular secretion rises during chronic renal disease, clearance due to tubular secretion rises only if the increment in secretion is proportionately greater than the increment in the serum level. Second, it is necessary to keep in mind the absolute level of renal function when the rate of secretion and clearance due to secretion are measured.

In two studies that measured the rates of decline in C_{cr} and GFR (assessed from clearances of radioisotope filtration markers) in patients with initial GFRs less than 60 ml/min/1.73 m^2, C_{cr} declined slightly faster than GFR, indicating that clearance of creatinine due to tubular secretion also declined [71, 81]. In both studies, correlations of rates of decline in C_{cr} and GFR were weak. In two other studies, serial values for C_{cr} and GFR (assessed from inulin clearances) were reported in patients with normal initial GFR as well as patients with reduced GFR [50, 84]. In one of these studies, changes in C_{cr} exceeded changes in GFR [84]. In the other study, however, changes in C_{cr} were slightly less than changes in GFR, and were directionally discordant in one-half of measurements [50].

In my view, the most likely sequence of events related to tubular secretion of creatinine is as follows: When GFR first declines, tubular secretion is augmented, stabilizing the serum level. Hence, clearance due to tubular secretion rises; consequently, C_{cr} declines more slowly than GFR, and the ratio of C_{cr} to GFR rises. Thereafter, as GFR declines further, tubular secretion increases further, but not in proportion to the increase in serum level. Hence, clearance due to tubular secretion actually declines slightly, and C_{cr} declines faster than GFR. However, because of the further decline in GFR, the ratio of C_{cr} to GFR increases further. As a result of these complex changes, it is not possible to predict accurately changes in GFR from changes in C_{cr}.

With regard to your question about creatine turnover, I am not aware of studies on this parameter in patients with chronic renal disease. However, an increased turnover rate has been observed in patients with muscle diseases or malnutrition [58, 85] and in rats with infection [86]. In principle, an increased turnover rate would lead to an initial increase in creatinine generation. If the rate of creatine synthesis is unchanged, the creatine pool would decline, leading to a subsequent decrease in creatinine generation. If GFR and tubular secretion were unchanged, the serum creatinine would initially rise and subsequently decline to below the baseline value.

DR. MADIAS: Have potential differences in tubular creatinine secretion and in the relationship between GFR and creatinine clearance been examined between patients with predominantly tubulointerstitial diseases and those with predominantly glomerular diseases?

DR. LEVEY: The data that I presented in today's discussion were derived by Shemesh and colleagues from patients with glomerular diseases [20]. Others have reported similar findings in patients with a variety of renal diseases [20, 25, 49, 84, 87–103]. However, I am not aware of studies that searched for differences among patients with glomerular and tubulointerstitial diseases.

DR. JOHN T. HARRINGTON (*Chief of Medicine, Newton-Wellesley Hospital, Newton, Massachusetts*): First, how do you weigh the three characteristics of an ideal test, either in clinical practice or in clinical research? Second, when we have used changes in serum creatinine as indicators of changes in GFR, have we been too narrow? By that, I mean if one looks at the change in serum creatinine in conjunction with other clinical and laboratory data, such as changes in BUN, blood pressure, urinalysis, urinary protein excretion, etc., could one identify the patients who apparently have had normal serum creatinine levels yet low glomerular filtration rates?

DR. LEVEY: In answer to your first question, let me emphasize that the questions that need to be answered in clinical practice are different from those that need to be answered in clinical trials. In clinical practice, we need to know whether renal function is reduced and whether it is changing. To answer these questions, we need only determine the approximate level of renal function; hence convenience in performing the laboratory test may outweigh limitations in its accuracy and precision. In contrast, in clinical research, we need to know the exact level and rate of change in renal function. Thus in clinical research we need to employ more accurate and precise tests than in clinical practice, even if they are less convenient.

In answer to your second question, let us examine the influence of other clinical or laboratory data on the predictive value of a normal or low serum creatinine level in indicating normal GFR in patients with renal disease. Based on the data presented in Figure 1, an elevated serum creatinine is 100% specific, but only 60% sensitive. Because of the low sensitivity, the predictive value of a normal or low serum creatinine is also low; that is, a low proportion of patients with a normal or low serum creatinine level have a normal GFR. Sensitivity, and therefore predictive value, can be improved by considering factors other than GFR that also affect the serum creatinine level, such as age, gender, and body size, as discussed earlier. These considerations are explicit in various formulas that can be used to predict C_{cr} from P_{cr} [104–112]. These formulas are not useful, however, in patients at the extremes of age and body size, those with edema, and patients in whom the serum creatinine changes from day to day. Another limitation is the inaccuracy of C_{cr} as an index of GFR, as I discussed earlier.

The predictive value of a negative test is also increased if the prevalence of disease in the population to be tested is low. For example, in a patient with normal blood pressure, normal urinalysis, and no family history of renal disease, the likelihood of renal disease is quite low. If the prevalence is as low as 0.5%, then the likelihood that a patient with a normal or low serum creatinine has a normal GFR would be 99.7%; that is, only 0.3% of negative tests would be falsely negative. On the other hand, in a patient with evidence of renal disease, the predictive value of a negative test would be much lower, and more negative tests would be falsely negative. For example, as Figure 1 shows, in patients with glomerular disease, the predictive value of a normal or low serum creatinine was only 40%. Thus 60% of negative tests were falsely negative [20].

I do not doubt that the astute clinician can interpret the serum creatinine concentration in light of considerations of creatinine metabolism and disease prevalence and infer correctly whether GFR is reduced and whether it is changing. It seems quite unlikely, however, that even the most experienced nephrologist can accurately predict the level of GFR and its rate of change from the serum creatinine. Whether practitioners will need more accurate and precise tests of function in the future depends on the results of clinical trials now in progress.

DR. JEROME P. KASSIRER (*Assoc. Physician-in-Chief, Dept. of Medicine, New England Med. Ctr.*): You argue that the sensitivity of the serum creatinine as an index of renal function is low, but of course the sensitivity of the test depends on the cut-off point. In the study by Shemesh et al, the cut-off point for serum creatinine was 1.4 mg/dl [20]. I am uncomfortable with this value because most nephrologists would consider a value this high as normal only for quite muscular people. If the cut-off point were set at a lower value, the sensitivity would be higher.

DR. LEVEY: Your point is well taken. Nonetheless, a cut-off value of only 1.2 mg/dl applied to the data of Shemesh et al [20] is associated with a sensitivity of only 78%, and a predictive value of a normal or low serum creatinine of only 53%. Thus, 47% of negative tests still would be falsely negative. Even though nephrologists might regard a serum creatinine of 1.4 mg/dl as high, I suspect that most physicians regard a slight elevation in serum creatinine as indicating only a minimal reduction in renal function. Clearly, this view is not warranted. When serum creatinine is 1.4 mg/dl, GFR can range from 30 to 80 ml/min/1.73 m^2. The inaccuracy and imprecision are apparent at lower cut-off values as well. More accurate and precise tests are necessary to estimate the true level of renal function.

DR. RONALD PERRONE (*Division of Nephrology, New England Medical Center*): Your analysis of reciprocal creatinine slopes points out the possible pitfalls: the assumption of stability of creatinine generation, extrarenal clearance, and tubular secretion. Yet in published studies, most patients appear to have a constant rate of decline in reciprocal serum creatinine. What do you think might account for this?

DR. LEVEY: It is quite clear that the correlations of reciprocal serum creatinine versus time were very high in these reports [72–78], suggesting that the rate of decline in reciprocal serum creatinine is relatively constant. I suspect that the explanation for the high correlations is as follows: (*1*) Because the period of followup began only after serum creatinine was elevated, GFR already was moderately reduced, and during the period of followup, the further decline in GFR might have proceeded at a relatively constant rate. (*2*) Because the followup interval was relatively long (2–6 years), the effect of the decline in GFR on serum creatinine might be quantitatively greater than the effects of changes in creatinine secretion, extrarenal elimination, and generation.

On the other hand, during the short intervals of followup (1–2 years) in the clinical trials I mentioned [5–9], GFR might have declined only slightly, and serum creatinine might have been affected more by changes in creatinine metabolism than by changes in GFR. Hence the rate of decline in reciprocal serum creatinine might not have been an accurate estimate of the rate of decline in GFR in these studies.

DR. PERRONE: Perhaps selection of patients with creatinine greater than 3 mg/dl to start with reduces the variation due to tubular secretion, and changes in extrarenal clearance and in generation of creatinine are small and opposite.

Let me ask another question. Your discussion concentrated primarily on creatinine and GFR, which are markers of glomerular filtration. We know from renal biopsy studies by Austin et al in patients with lupus nephritis that the degree of tubular interstitial involvement is actually a more important prognosticator for long-term outcome [113]. Do you know of any good measures of tubular interstitial function other than renal biopsy that might have predicted outcomes?

DR. LEVEY: Interestingly, the extent of tubulointerstitial fibrosis correlates with GFR [12, 13]. Moreover, in the study by Austin et al, elevated serum creatinine was also an important predictor [113]. It would have been interesting to compare the predictive value of the GFR and the tubulointerstitial changes observed on renal biopsy. Other tests of tubular function, such as maximal urine concentration and ammonium excretion, also correlate with the extent of tubulointerstitial and glomerular damage [12, 13]. However, these factors have not been thoroughly examined with regard to prediction of the outcome of chronic renal disease.

DR. MICHAEL MADAIO (*Division of Nephrology, New England Medical Center*): If the slopes for GFR versus time are not constant but change over long periods of time, can we accurately predict time to end-stage renal disease? If not, short-term studies might be valuable in determining the effect of therapeutic interventions on rate of decline in GFR over short intervals but might not accurately predict the long-term effect on the course of renal disease. In this regard, many other supervening factors could influence the rate of progression, and it is likely that these factors influence GFR at different times and variably throughout the course of progression in an individual patient.

DR. LEVEY: Your question is an excellent one. It is extremely important that outcome measures used in clinical trials be validated not only for accuracy and precision, but also for clinical significance. For example, demonstration that a dietary intervention slows the rate of decline in GFR for a period of a few years does not prove that the intervention prevents renal failure. To prove that, it would be necessary to follow patients in the trial for a longer interval to determine the frequency of onset of renal failure or to establish the relationship between the rate of decline in GFR and the onset of renal failure in other patients following a similar dietary intervention.

The current NIH-supported studies of diabetic nephropathy provide an example of the use of outcome measurements whose

clinical significance has been extensively studied [82]. Patients in various stages in the evolution of renal disease are being studied, including those without any evidence of renal disease, those with microalbuminuria, and those with clinical proteinuria. The development of these findings in patients who did not have them initially is considered evidence of onset and progression of renal disease. Although each study may take 5 to 10 years to complete, a study of the course to renal failure would have required more than 20 years. Of course, this approach required previous studies to delineate the relationships among the stages of diabetic nephropathy.

DR. KASSIRER: Have rigorous criteria been used in assessing the relationship between progressive renal tubular disease and glomerular function?

DR. LEVEY: In the studies by Striker and colleagues [12, 13], 70 patients underwent renal biopsy and measurement of GFR, renal blood flow, and urinary concentration and acidification. Most patients had glomerular diseases. Correlation coefficients of GFR with tubulointerstitial damage were −0.60 to −0.65, whereas the correlation with glomerular damage was only −0.30. Interestingly, the correlation coefficients of maximal urinary concentration, and ammonium excretion with structural features were even higher: −0.60 to −0.80 with tubulointerstitial disease and −0.35 to −0.60 with glomerular diseases.

DR. HARRINGTON: De Wardener and his colleagues also demonstrated that the major pathologic correlate of renal failure in patients with glomerular disease was, in fact, tubular interstitial disease [114].

DR. PAUL KURTIN (*Chief, Division of Pediatric Nephrology, New England Medical Center*): I have two comments. First, the problems you have outlined in interpreting reciprocal serum creatinine are magnified in infants and young children, who are undergoing developmental and maturational changes in both renal function and body composition. For example, muscle mass increases from 25% to 40% of lean body mass in maturing children. Second, what is the meaning of correcting renal function for surface area, and can we be misled in interpreting renal function by including changes of surface area that are not related to changes in renal function? For example, the first patient presented today lost 6 kg, which would be calculated as a slight decrease in surface area, leading to an increase in surface-area-adjusted GFR. Have you taken into account these changes in surface area, and do they change in any way your interpretation of slopes?

DR. LEVEY: I agree fully with your comments regarding interpretation of the serum creatinine concentration in infants and young children. In adults, small changes in weight do not lead to changes in surface area that are sufficient to alter adjusted values for GFR meaningfully. In the first patient, unadjusted values for GFR were 19, 14, 13, and 12 ml/min during the 9-month observation period. In the second patient, unadjusted values were 35, 28, and 22 ml/min.

The surface area correction was introduced by Taylor, Drury, and Addis [115] and adopted by Moller, McIntosh, and Van Slyke to minimize variability in urea clearance results among normal adults and children [116, 117]. This correction is appropriate, as body surface area is more closely related to metabolic activity and renal size than are weight or height [118]. (The value of 1.73 m^2 represents the mean surface area of men and women 25 years of age.) Despite this adjustment, surface-area-adjusted values for GFR in children are below adult values until the age of 2 years [119, 120]. Hence, the use of surface area correction in infants might not be valid. The same limitation also might apply in populations with different body habitus. This has particular significance in studies of renal function and progression of renal disease in these patients. For example, in cross-sectional studies, the normal range should be defined from measurements of GFR in a comparable population without renal disease. In longitudinal studies, changes should be calculated from changes in unadjusted GFR.

DR. HARRINGTON: I was interested in your comment about the change in serum creatinine following meat feeding. You said that there was approximately a 0.5 mg/dl rise in individuals with normal serum creatinine levels. Do you get a larger or smaller delta serum creatinine with meat feeding in individuals with baseline serum creatinines in the 5–8 mg/dl range?

DR. LEVEY: Because the space of distribution of ingested creatinine (total body water) is not changed, the increment would be expected to be similar. However, because of reduced GFR, ingested creatinine would be excreted more slowly. Hence, the elevation in serum creatinine might persist longer. Because the increment in serum creatinine is proportionately greater in individuals with a low serum creatinine concentration, the error in estimating GFR would be greatest in patients with P_{cr} near the normal range.

DR. MADAIO: After the ingestion of a casein diet, why didn't creatinine clearance fall? I would have expected that eating less meat would have caused the GFR to fall in these subjects.

DR. LEVEY: First, recall that casein is a source of protein, even though it does not contain meat. Studies by Lindheimer and colleagues have demonstrated a rise in GFR in dogs after casein feeding [121]. Second, the effect of dietary protein intake on GFR in normal humans is relatively small. In the study by Hostetter and colleagues, the peak rise in GFR after a large protein load was only 10% [122]. Given the variability in C_{cr} in the study by Bleiler and Schedl [65], it would have been difficult to detect a sustained reduction in C_{cr} of this magnitude after substitution of casein (if it had occurred).

DR. HARRINGTON: One of your arguments for using iothalamate clearance as a measure of GFR clinically was that there might be improved clinical outcomes. One of the settings in which this could be tested would be in patients after renal transplantation. One could test caring for patients using simply the delta serum creatinine in the standard fashion, versus caring for patients with delta iothalamate clearances, and determine whether there were a difference in outcome.

DR. LEVEY: Comparisons also could be made in the outcome of patients receiving drugs whose doses are adjusted according to renal function, such as cis-platinum, methotrexate, and aminoglycoside antibiotics.

DR. MADIAS: Going back to your points on creatinine metabolism, in view of the fact that there is no preformed creatinine in muscle, what might be the reason for the more rapid rise in serum creatinine level following rhabdomyolysis-induced acute renal failure as compared with other types of acute renal failure?

DR. PERRONE: A relatively recent study describes the conversion of phosphocreatinine in muscle to creatinine and creatine phosphate under physiologic conditions [123]. This mechanism might be accelerated in rhabdomyolysis, as this

intermediate is sensitive to changes in pH and body temperature.

DR. AJAY K. SINGH (*Fellow in Nephrology, New England Medical Center*): The observations on extrarenal elimination of creatinine appear to be based on three human studies using a relatively small number of patients [51, 53, 54]. Is there any experimental evidence based on animal models that validates these data?

DR. LEVEY: I am not aware of studies examining extrarenal elimination of creatinine in animals with experimental renal disease. However, extrarenal elimination can be induced in rodents with normal renal function by feeding creatinine [124]. The hypothesized mechanism is the induction in the intestine of bacterial enzymes capable of degrading creatinine. This same effect might occur in patients with chronic renal disease whose intestinal secretions contain high levels of creatinine.

DR. SINGH: It has been proposed that with a progressive decline in GFR, the increase in extrarenal elimination of creatinine accounts for the reduction in renal creatinine excretion, suggesting that creatinine generation is indeed constant [68]. Could you comment on whether any studies have confirmed this hypothesis?

DR. LEVEY: The rate of extrarenal creatinine elimination clearly is greater in patients with reduced renal function. In the studies that I described earlier [53, 54], estimated rates of creatinine generation of patients with renal disease were within the normal range for healthy adults of similar age and gender. The mechanism for this increase might simply be the increased concentration of creatinine in intestinal secretions as serum creatinine rises. This would be consistent with the constant rate of clearance (E_{cr}/P_{cr}) of creatinine due to extrarenal elimination that was observed in the study by Mitch, Collier, and Walser [54].

DR. DEMETRIOS VLAHAKOS (*Fellow in Nephrology, New England Medical Center*): Changes in protein intake influence serum creatinine by two opposing forces, namely, alterations in creatinine and creatine intake as well as parallel changes in GFR. In view of these counteracting mechanisms, would you like to comment further on the relationship between serum creatinine and GFR when employing low-protein diets in patients with chronic renal insufficiency?

DR. LEVEY: Changes in protein intake alter GFR both in normal humans and in patients with renal disease. I already have discussed the effect of a large protein meal on GFR and C_{cr} in normal humans. The same effect is observed in patients with chronic renal disease; a single large meal or a sustained increase in protein intake for one month results in an increase in GFR and C_{cr} [125, 126]. Interestingly, P_{cr} also was increased after protein loading in normal individuals [127], but not in patients with chronic renal disease [126]. The converse effect is observed in individuals consuming low-protein diets; in healthy vegetarians, C_{cr} was lower than normal [128]. Interestingly, their serum creatinine concentrations were not elevated, presumably because of decreased intake of creatine and creatinine. These studies highlight the effects of differences in diet on renal function and on creatinine metabolism and the effects of changes in the diet on these parameters. They demonstrate the pitfalls of attempting to predict either the level, or changes in the level, of renal function on the basis of the serum creatinine concentration in patients with different or changing diets.

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Note added in proof

Since presentation of this Forum, Ihle et al have reported the results of an important, well-designed clinical trial demonstrating the beneficial effect of a low-protein diet to retard the progression of renal disease [129]. In contrast to previous studies, renal function was assessed by glomerular filtration rate (plasma clearance of ^{51}Cr-EDTA), a control group was included, and outcome was measured as final GFR (rather than as rate of decline in GFR). Despite small sample size and wide variability in final GFR within the study groups, demonstration of efficacy was possible because of the large difference in mean final GFR between the study groups. Most patients included in the study had initial GFRs less than 25 ml/min/1.73 m^2. Given the wide range of values for P_{cr} and C_{cr} at a GFR of 25 ml/min/1.73 m^2, it would be appropriate to measure GFR to select patients for implementation of this diet in clinical practice.