Kidney International, Vol. 35 (1989), pp. 670–674

Progression of renal insufficiency: Role of blood pressure

PETER C. BRAZY, WILLIAM W. STEAD, and JAMES F. FITZWILLIAM

Nephrology Division and Department of Medical Information Systems, Duke University Medical Center and Durham VA Medical Center, Durham, North Carolina, USA

Progression of renal insufficiency: Role of blood pressure. The effect of blood pressure on progression of renal insufficiency was examined in a large group of patients who eventually required dialysis. Out of 198 consecutive new chronic dialysis patients, 86 had sufficient data predialysis to determine rates of progression of renal insufficiency by reciprocal creatinine versus time plots. Average plasma creatinine at first contact was 3.8 ± 0.2 mg/dl and at the time of dialysis was 11.4 ± 0.4 mg/dl. Mean duration of follow-up was 33.4 ± 2.5 months and the average rate of decline in reciprocal creatinine was −0.009 ± 0.001 dl/mg month. Patients were stratified by average value of diastolic blood pressure measured in clinic. Patients in the lowest quartile had a rate of decline in reciprocal creatinine of −0.007 ± 0.001 dl/mg month, which was slower than that of patients in the third and fourth quartiles, −0.010 ± 0.001 and −0.011 ± −0.002 dl/mg month, respectively ($P < 0.05$). In individual patients, a mean diastolic BP of <90 mm Hg was associated with a rate of decline in reciprocal creatinine of −0.006 ± 0.001 dl/mg month which was significantly less than the rate of −0.009 ± 0.001 when the diastolic BP was >90 mm Hg. Thus, in a large group of patients who have progressed to ESRD, there is an association between control of diastolic blood pressure and a slower rate of decline in renal function.

The natural course of renal insufficiency from any cause appears to be progression over time to end-stage renal disease (ESRD) [1,2]. In animal models where renal insufficiency progresses to end stage disease in months, the progression can be delayed by therapeutic interventions, such as restriction of dietary protein [3], phosphorus depletion [4] and reduction in systemic and/or intrarenal arterial blood pressure [5,6]. Clinical studies employing a low protein diet with or without supplemental amino acids or their keto acid analogues have confirmed this beneficial effect in patients with renal disease [7,8]. The clinical value of reductions in systemic blood pressure have not been demonstrated in large groups of patients with renal disease from a variety of causes. The purpose of this retrospective, longitudinal study was to determine if there was any appreciable effect of treatment with antihypertensive drugs on the rate of progression of renal insufficiency in a large cohort of patients who ultimately developed ESRD. The data from 86 such patients indicate that control of diastolic blood pressure to an average value of less than 90 mm Hg was associated with a slower rate of decline in renal function.

Received for publication March 2, 1988
and in revised form September 12, 1988

Methods

Data from patients seen and followed by the Nephrology Section of the Durham VAMC have been kept on a computerized medical record since January, 1979 [9]. From this database, we identified all patients who started dialysis therapy at the Durham VA Medical Center between January 1, 1982 and December 31, 1987. The list included patients with acute renal failure (reversible disease or renal failure as a complication of another illness) and chronic renal failure. For the patients with chronic renal failure, we reviewed the computerized medical records to determine when they were first seen by the Nephrology Section, duration of follow-up until dialysis, rate of decline in renal function (a plot of reciprocal plasma creatinine versus time), blood pressure measured at clinic visits, and prescribed medications.

The change in renal function was estimated by the slope of the reciprocal of plasma creatinine versus time plot. The minimum criteria for this plot were four measurements of plasma creatinine during a time period that was at least six months. The average number of data points per patient was 16 (±8 SD). We used the reciprocal creatinine versus time plots in this study because that was the only quantitative measure of renal function available retrospectively on this patient population. To minimize potential problems with this approach, we examined patients' records for changes in dry weight that might affect rates of creatinine production. The dry weight of patients averaged 79.0 ± 16.3 kg (standard deviation) and did not change significantly during the time course of this study.

Results

The patient population

In the six year period between January 1, 1982 and December 31, 1987, 358 patients began dialysis therapy at the Durham VA Medical Center. Patients were considered to have acute renal failure if they recovered renal function or if renal failure was part of a terminal illness associated with the failure of multiple organs. One hundred sixty patients were in this category. These patients were not considered in the remainder of the study.

The remaining 198 patients started maintenance dialysis for chronic renal failure during this time interval. In reviewing their records, we identified 112 patients who were dialyzed within six months of first contact with the VA Nephrology Section. This time period was inadequate for determining the rate of progression of renal disease or the efficacy of a therapeutic intervention. These patients comprise 56% of new chronic dialysis patients in this medical center. This finding suggests that a large

Table 1. Antihypertensive medications

Medication	Use *% of patients*
Furosemide	94
Beta blockers	50
Prazosin	50
Clonidine	34
Hydralazine	26
Minoxidil	19
Calcium channel blockers	12
Methyldopa	3
Guanethidine	2
Captopril[R]	2

percentage of patients who develop ESRD are not referred to a medical center until very late in the course of their disease. Some of these patients did not seek medical care until late in the disease; others were followed by a primary care physician prior to referral.

The remaining 86 patients had sufficient predialysis data to evaluate the effect of blood pressure control on the progression of renal insufficiency. These patients consisted of 84 men and 2 women. Forty-four of them were Black, 40 White, 1 Oriental and 1 Hispanic American. Their average value of plasma creatinine at first contact with the Nephrology Section was 3.8 mg/dl (range of 1.1 to 8.6 mg/dl). The average creatinine value at the start of dialysis was 11.4 mg/dl (range of 5.0 to 22.0 mg/dl). The mean duration of pre-dialysis follow-up was 33.4 months (range 6.8 to 111.2 months). Their age at the time of dialysis was 55.4 years (range 25.0 to 75.5 years). The cause of progressive renal failure was identified from the patient's problem list. The frequency of specific diagnoses were as follows: diabetes mellitus in 30%, glomerulonephritis in 24%, interstitial nephritis associated with urinary tract obstruction, stones or infection in 12%, polycystic kidney disease in 3%, multiple myeloma in 3%, rejection of renal transplant in 3%, systemic diseases with renal involvement in 3%, and unknown in 22%. Hypertension was present on the problem list in 80% of these patients.

In this population 95% of patients were treated with antihypertensives prior to onset of dialysis. The drugs prescribed and the percentage of patients who were given them are indicated on Table 1. The use of angiotensin converting enzyme inhibitors and calcium channel blockers was limited because much of the time course of this study predates their generalized use for the treatment of hypertension. Phosphate binders were prescribed for 73% of the patients prior to dialysis. The usual starting dose of aluminum hydroxide was 500 to 1000 mg with meals. Most of the patients were instructed in a relatively low protein (0.6 g/kg/day plus replacement of losses due to proteinuria), low sodium (2 g/day) diet. Patient compliance with prescribed medications or diet was not assessed directly.

The change in renal function was estimated by the slope of the reciprocal of the plasma creatinine versus time plot. The data from these plots were usually well described by a single line. The R values for linear regression analyses were greater than 0.8 in 90% of the cases and were less than 0.5 in only four cases (5%). The data did not fit a second order function as well as a linear function. As a group the average slope in the reciprocal plasma creatinine plots was -0.0090 ± 0.0007 (SE) ml/mg month. This rate of decline is approximately equivalent to a reduction in glomerular filtration rate of -0.9 ml/min/month, if we assume that the glomerular filtration rate is 100 ml/min when the plasma creatinine is 1.0 mg/dl.

Effect of blood pressure

The systolic and diastolic blood pressures taken in the sitting position in renal clinic were averaged for each patient. To determine if there was an effect of blood pressure on the overall rate of decline of the reciprocal plasma creatinine, we stratified the patients according to their diastolic blood pressures. The average rate of decline in the reciprocal plasma creatinine for each quartile of patients is shown in Figure 1A. The quartile of patients with the lowest diastolic blood pressures had mean diastolic pressure of 80 ± 1 (SE) mm Hg and an average rate of decline of -0.0071 ± 0.0010 dl/mg month. The second quartile had average diastolic blood pressure of 88 ± 1 mm Hg and a rate of decline that was not different from the lowest quartile. The third and fourth quartiles had mean diastolic blood pressures of 93 ± 1 and 101 ± 1 mm Hg, respectively, and had significantly faster rates of decline in reciprocal creatinine, -0.0105 ± 0.0015 and -0.0108 ± 0.0015 dl/mg month, respectively, than that of patients in the lowest quartile ($P < 0.05$ by unpaired t-test). The rate of decline of the second quartile was significantly lower than that of the fourth quartile ($P < 0.05$) but was not significantly different from that of the third quartile ($P < 0.10$). Thus, in this general population of patients with chronic renal failure, higher levels of diastolic blood pressure were associated with a more rapid rate of progression to ESRD.

The data from patients in each quartile was examined to determine if there was a predilection for a specific diagnosis or antihypertensive treatment. The patients with diabetes mellitus or glomerulonephritis were distributed equally among the quartiles of diastolic blood pressure. Antihypertensive medications were prescribed by several physicians according to their preference. The frequency of their use was dispersed among the quartiles of diastolic blood pressure. We examined the slope of the reciprocal creatinine versus time plot for patients on each medication and found no significant differences. Thus, there was no identifiable association of diagnosis or medication with any of the quartiles of diastolic blood pressure.

When the data were stratified for mean systolic blood pressure, there were no significant differences between the rate of decline of reciprocal creatinine between groups (Fig. 1B). The rate of decline averaged -0.0079 ± 0.0012 dl/mg month for the lowest quartile of systolic blood pressure whose average systolic pressure was 132 ± 1 mm Hg. The highest quartile had a mean systolic blood pressure of 181 ± 2 mm Hg and an average rate of decline in renal function of -0.0088 ± 0.0013 dl/mg month.

Characterization of baseline values

Next we asked the question, is the rate of progression of renal insufficiency the same over time or does the rate increase or decrease as renal function deteriorates. To evaluate this possibility we divided the reciprocal creatinine versus time plots into arbitrary one year segments for up to five years of follow-up and compared the slopes of adjacent segments by a paired t-test. In this analysis we found some variation in the slope of the reciprocal creatinine versus time plot year to year in individual

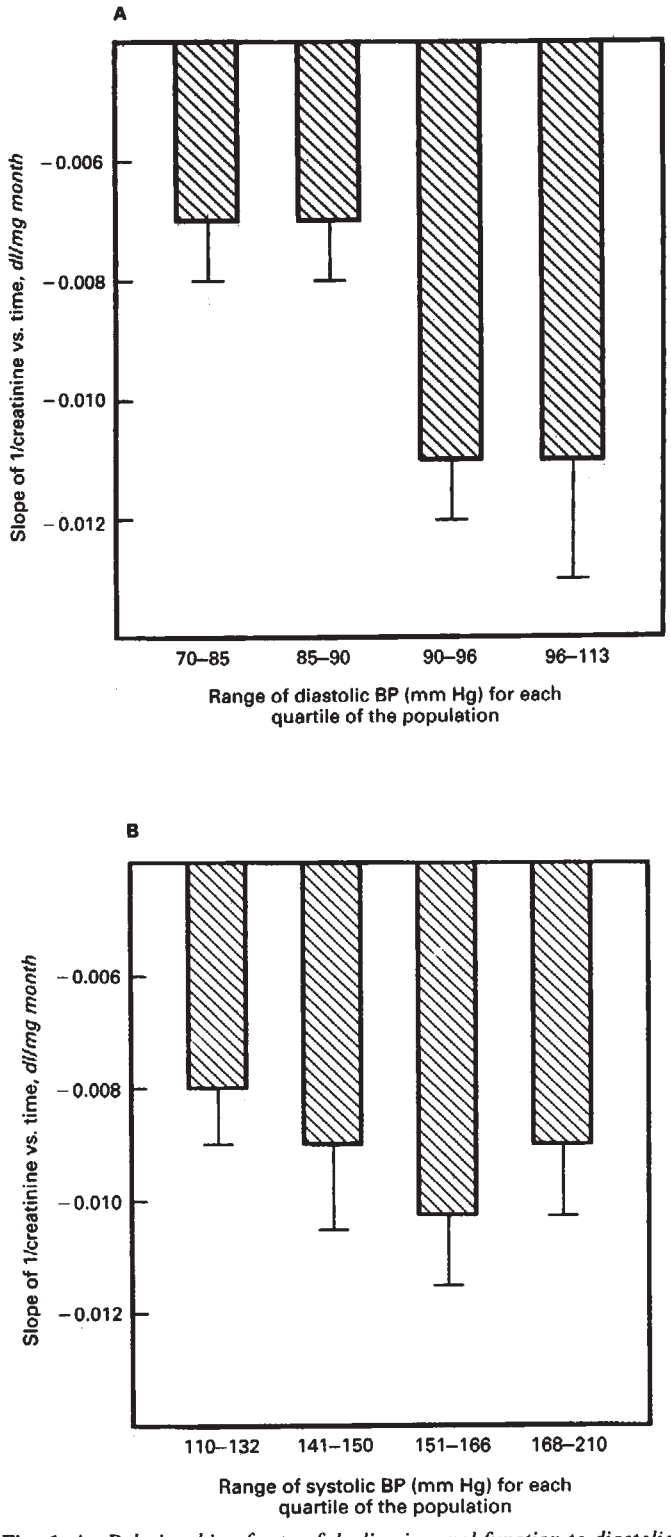

Fig. 1. A. *Relationship of rate of decline in renal function to diastolic blood pressure.* Patients were stratified into quartiles by mean diastolic blood pressure. Range of diastolic blood pressures for each quartile is indicated on X axis. Bars represent mean + SE of slope from reciprocal creatinine versus time plot for 21 patients. Statistical comparisons between quartiles were made using an unpaired *t*-test and are given in the text. **B.** Relationship of rate of decline in renal function to systolic blood pressure. Range of systolic blood pressures for each quartile is indicated on X axis.

patients even though the whole plot closely followed a single line. In these patients as a group, however, there was no significant trend for the slope to become more or less negative during the follow-up time. Thus, in this population of patients, the rate of progression of renal insufficiency did not change during five years of follow-up.

Next we examined the data to determine if the slope of reciprocal creatinine versus time plot changed as the plasma creatinine increased. For each patient, the slope of the reciprocal creatinine versus time plot was calculated for the following three intervals of plasma creatinine: values from 1.5 to 3.0 mg/dl, from 3.1 to 6.0 and from 6.1 to 12. The slopes from subsequent intervals in each patient were compared with a paired *t*-test. Again, there were often changes in the slope of an individual case from one interval to the next, but these changes were just as likely to occur in either direction. The mean paired differences in these slopes indicate no significant difference in the slope as the plasma creatinine increases within the range of 1.5 to 12 mg/dl. Thus, the slope of the reciprocal creatinine versus time plot was not affected by the level of plasma creatinine.

Effect of change in blood pressure in individual patients

The slope of the reciprocal creatinine versus time plot does not change as a function of time or plasma creatinine; does it change with an alteration in the level of diastolic blood pressure? To address this question, we identified nineteen patients (six with diabetes mellitus) who had adjacent time periods when their diastolic blood pressure was consistently above 90 mm Hg and when it was below 90 mm Hg. The slope of the reciprocal creatinine versus time for both time periods was determined in each individual and the data were compared by a paired *t*-test. In 14 cases the direction of the change in blood pressure was a reduction and in five cases an elevation. Figure 2 shows mean values for the slope when diastolic blood pressure was controlled and when it was >90 mm Hg. The average value of the diastolic blood pressure was 97 ± 2 mm Hg for the hypertensive time period and 84 ± 1 mm Hg for the normotensive time interval. The hypertensive time interval was associated with a significantly faster rate of decline in reciprocal creatinine than the normotensive interval ($P < 0.005$). These data indicate that in a single patient an average diastolic blood pressure less than 90 mm Hg is associated with a slower rate of progression to ESRD.

Discussion

The purpose of this retrospective study was to review systematically our previous experience with patients who progressed to ESRD and from that experience to determine those factors which were associated with an amelioration of the rate of progression. The results of this study should provide an hypothesis or a reasonable basis for prospective studies which will determine, more directly, the role of these factors in progressive renal disease. The factor which we examined was control of blood pressure. The data indicate an association between control of diastolic blood pressure to values less than 90 mm Hg and a slower rate of progression to renal failure.

Use of the reciprocal plasma creatinine versus time plot as an indication of changes in glomerular filtration rate (GFR) is controversial. It has been used as a simple method for following

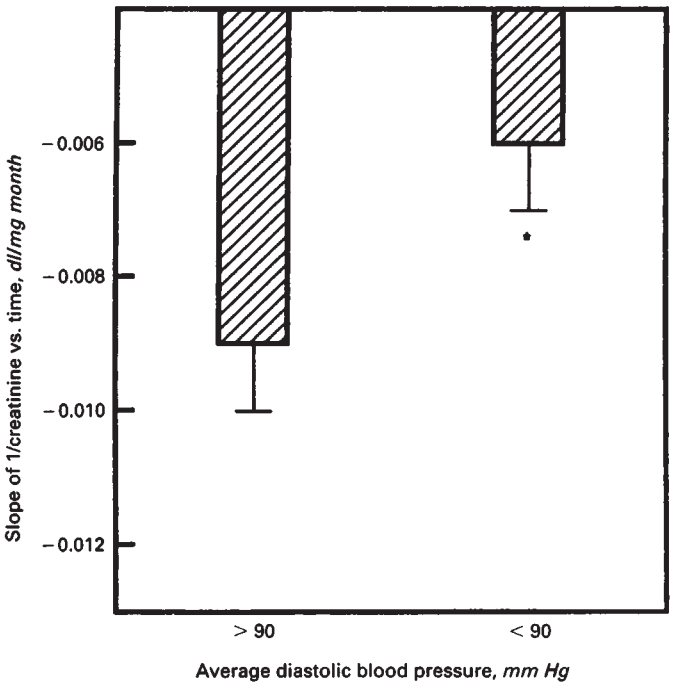

Fig. 2. *Effect of diastolic blood pressure on rates of decline in renal function in individual patients.* Bars represent mean + SE of slope from reciprocal creatinine versus time plot determined at times when their diastolic blood pressure was >90 mm Hg and again when it was <90 mm Hg. *N* equals 19 patients. Statistical comparison between slopes was made using a paired *t*-test and * indicates $P < 0.05$.

or estimating the rate of progression of renal insufficiency [7,10,11]. However, this mathematical transformation has not always been useful. Gretz, Manz and Strauch [12] reported that reciprocal creatinine data from early time points was a poor predictor of when dialysis will occur. In patients with severe renal insufficiency (GFR less than 16 ml/min) the slope of the reciprocal creatinine versus time plot significantly underestimated the change in glomerular filtration rate as measured by radiolabelled EDTA clearances [13]. The inaccuracy of the reciprocal creatinine estimate of GFR is related to the observation that creatinine clearances and inulin clearances differ in patients with renal insufficiency [14]. Creatinine clearances were generally greater than inulin clearances, but there was no constant relationship between these clearances over a wide range of renal function (mild to severe reductions in GFR) [14]. We used the reciprocal creatinine versus time plots in this study because that was the only quantitative measure of renal function available retrospectively on this patient population. To minimize the problems mentioned above, we selected patients who had completed their progression to ESRD and did extensive analyses to identify possible effects of follow-up time or level of plasma creatinine on this plot (**Results**). These analyses confirm the linearity of the slope of the reciprocal creatinine versus time plots for the patient data being studied. With these constraints in mind, we used the slope of the reciprocal plasma creatinine versus time plot as an estimate of changes in renal function.

An association between control of diastolic blood pressure and progression of renal disease has been shown in animal models of renal disease. In the subtotal ablation model of renal disease in rats, the reduction in GFR and incidence of glomerular sclerosis can be ameliorated by a variety of maneuvers such as administration of anticoagulants [15,16], thromboxane synthetase inhibitors [5] or angiotensin converting enzyme inhibitors [6,17]. In each of these maneuvers there was a significant reduction in systemic blood pressure which may have contributed, in part, to preservation of function. Hypertension has also been implicated in the progression of renal disease in the nephrotoxic serum nephritis model of renal injury in rats. Baldwin and coworkers showed that antihypertensive treatment in this disease reduces the glomerular lesions and proteinuria [18] and conversely, that superimposing hypertension with a renal vascular clip enhanced the glomerular lesions [19]. Thus, in two animal models of renal disease, hypertension may be one of the factors causing progression of dysfunction.

In patients with renal disease the role of hypertension in the progression of disease is less clear. Two studies have shown that control of blood pressure reduced the rate of progression of renal insufficiency in a small number of patients with insulin-dependent diabetes mellitus and diabetic nephropathy [20,21]. In these studies with 6 and 10 patients, mean values of blood pressure were reduced from 162/103 and 144/97 mm Hg to 144/95 and 128/84, respectively, and the rate of decline in GFR was reduced to 40% of the baseline value. This positive finding was not confirmed in a larger study by Oldrizzi, Rugiu and Maschio examining the association of hypertension and progression of renal insufficiency in patients on a protein-restricted diet [22]. In their study 113 patients on a low-protein diet for an average of 51 months were stratified by mean arterial pressure. The monthly rate of increase in plasma creatinine was not affected by level of blood pressure. These authors concluded that many factors other than hypertension might have influenced the progression of renal insufficiency in this population. Bergstrom et al [11] reported that control of diastolic blood pressure to an average value of 90 mm Hg in 17 patients with renal insufficiency was associated with a 50% reduction in their rate of decline of the reciprocal plasma creatinine. Thus, studies which report a positive effect of blood pressure control in ameliorating the progression of renal disease are limited in number of patients or type of renal disease, that is insulin-dependent diabetes mellitus. Studies with a large number of patients and a variety of renal diseases have been unable to show a role for hypertension in the progression of clinical renal disease.

In comparison to previous studies, our data examined a relatively large number of patients. We screened data on all patients who started chronic dialysis at our medical center during a six year interval and selected those who were followed long enough prior to dialysis to provide information regarding their rate of decline in function. Our patient population may be somewhat unique in that it is 50% Black and has a very high incidence of hypertension. Data from the entire time of follow-up indicated an association between control of diastolic blood pressure and slower rates of progression to ESRD (Fig. 1). This result is similar to that of Bergstrom et al [11]. The same relationship did not occur for mean values of systolic blood pressure, which may explain negative results of Oldrizzi et al [22], who stratified patients by mean arterial pressure. The relationship between diastolic blood pressure and rate of decline in renal function was confirmed in our study by the

demonstration that in individual patients reduction of mean diastolic blood pressure from hypertensive range to values less than 90 mm Hg was associated with a significant reduction in the rate of progression to ESRD (Fig. 2). The rate of progression was reduced by 33%, a value similar to that observed by Mogensen [20] and Parving et al [21] in patients with diabetic nephropathy. Thus, the present study extends previous observations by showing the association of diastolic hypertension and progression of renal insufficiency in a large population of patients with a variety of renal diseases. Additionally, the data indicate that control of diastolic hypertension may slow the rate of progression of renal insufficiency in a general population of renal patients.

Thus, this retrospective study of all patients who progressed to dialysis at the Durham VA Medical Center indicates that the reciprocal creatinine versus time plot is linear in the majority of patients; that control of diastolic blood pressure to values less than 90 mm Hg is associated with a slower rate of progression toward ESRD. These data indicate that control of diastolic hypertension in patients with renal insufficiency is a potentially effective way to slow the progression toward ESRD. On the basis of these data, future studies should prospectively examine the effectiveness of specific antihypertensive agents like the angiotensin converting enzyme inhibitors.

Acknowledgments

The authors thank Drs. Paul Klotman, Tom Coffman, Laura Svetkey and William Yarger for their help in these studies. Support for these studies was provided by the Research Service of the Veterans Administration. Dr. Brazy is an Established Investigator of the American Heart Association.

Reprint requests to Peter C. Brazy, M.D., Nephrology Section H4/510, University of Wisconsin Clinical Science Center, 600 Highland Avenue, Madison, Wisconsin 53792, USA.

References

1. Brenner BM, Meyer TW, Hostetter TH: Dietary protein intake and the progressive nature of kidney disease: The role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation and intrinsic renal disease. *N Engl J Med* 307:652–659, 1982
2. Klahr S, Purkerson ML, Heifets M: Factors that may retard the progression of renal disease. *Kidney Int* 32(Suppl 22):S35–S39, 1987
3. Mitch WE: The influence of diet on the progression of renal insufficiency. *Ann Rev Med* 35:249–264, 1984
4. Ibels LS, Alfrey AC, Haut L, Huffer WE: Preservation of function in experimental renal disease by dietary restriction of phosphate. *N Engl J Med* 298:122–126, 1978
5. Purkerson ML, Joist JH, Yates J, Valdez A, Morrison A, Klahr S: Inhibition of thromboxane synthesis ameliorates progressive kidney disease of rats with subtotal renal ablation. *Proc Natl Acad Sci USA* 82:193–197, 1985
6. Anderson S, Meyer TW, Rennke HG, Brenner BM: Control of glomerular hypertension limits glomerular injury in rats with reduced renal mass. *J Clin Invest* 76:612–619, 1985
7. Walser M, Mitch WE, Collier VU: The effect of nutritional therapy on the course of chronic renal failure. *Clin Nephrol* 11:66–70, 1979
8. Maschio GL, Oldrizzi L, Tessitore N, D'Angelo A, Valvo E, Lupo A, Loschiavo C, Fabris A, Gammaro L, Rugiu C, Panzetta G: Effects of dietary protein and phosphorus restriction on the progression of early renal failure. *Kidney Int* 22:371–376, 1982
9. Stead WW, Garrett LE Jr, Hammond WE: Practicing nephrology with a computerized medical record. *Kidney Int* 24:446–454, 1983
10. Mitch WE, Walser M, Buffington GA, Lemann J Jr: A simple method for estimating progression of chronic renal failure. *Lancet* 2:1326–1328, 1976
11. Bergstrom J, Alvestrand A, Bucht H, Gutierrez A: Progression of chronic renal failure in man is retarded with more frequent clinical follow-ups and better blood pressure control. *Clin Neph* 25: 1–6, 1985
12. Gretz N, Manz F, Strauch M: Predictability of the progression of chronic renal failure. *Kidney Int* 24:S2–S5, 1983
13. Mathillas O, Attman PO, Aurell M, Delin K, Grauerus G: Conflicting results between glomerular filtration rate and serum creatinine measurements in chronic renal failure. *Contr Nephrol* 53: 71–73, 1986
14. Bauer JH, Brooks CS, Burch RN: Clinical appraisal of creatinine clearance as a measure of glomerular filtration rate. *Am J Kidney Dis* 2:337–346, 1982
15. Purkeson ML, Hoffsten PE, Klahr S: Pathogenesis of glomerulopathy associated with renal infarction in rats. *Kidney Int* 9:407–417, 1976
16. Purkerson ML, Joist JH, Greenberg JM, Kay D, Hoffsten PE, Klahr S: Inhibition by anticoagulant drugs of the progressive hypertension and uremia associated with renal infarction in rats. *Thromb Res* 26:227–240, 1982
17. Jackson B, Debrevi L, Cubela R, Whitly M, Johnston CI: Preservation of renal function in the rat remnant kidney model of chronic renal failure by blood pressure reduction. *Clin Exp Pharm Physiol* 13:319–323, 1986
18. Neugarten J, Kaminetsky B, Feiner H, Schacht RG, Liu DT, Baldwin DS: Nephrotoxic serum nephritis with hypertension: Amelioration by antihypertensive therapy. *Kidney Int* 28:135–139, 1985
19. Neugarten J, Feiner HD, Schacht RG, Gallo GR, Baldwin DS: Aggravation of experimental glomerulonephritis by superimposed clip hypertension. *Kidney Int* 22:257–263, 1982
20. Mogensen CE: Long-term anti-hypertensive treatment inhibiting progression of diabetic nephropathy. *Brit Med J* 285:685–688, 1982
21. Parving HH, Smidt UM, Andersen AR, Svendsen PAA: Early aggressive antihypertensive treatment reduces rate of decline in kidney function in diabetic nephropathy. *Lancet* 1:1175–1177, 1983
22. Oldrizzi L, Rugiu C, Maschio G: Hypertension and progression of renal failure in patients on protein-restricted diet. *Contr Nephrol* 54:134–143, 1987