THE PROGRESSIVE NATURE OF RENAL DISEASE

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BARRY M. BRENNER, M.D.
JAY H. STEIN, M.D.

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Preface

In the 1930s, experimental studies demonstrated that the severity and ultimate outcome of chronic renal failure (CRF) was determined in large part by the diet. The possibility that a similar relationship also occurs in humans with CRF was largely ignored until the late 1970s, when it was noted that the course of renal insufficiency in individual patients was improved after they began therapy with diets restricted in protein and phosphorus. This finding generated intense interest in understanding why CRF, once established, progresses to end-stage renal disease and how the course of CRF can be improved. In this book we assemble the available experimental and clinical data bearing on the pathophysiologic factors that cause progressive renal insufficiency, and examine the impact of therapy on the course of CRF.

Data presented in this book emphasize how results from studies of experimental animals and clinical investigations can be used to understand and treat an important disease process. The book has more chapters than previous volumes in this series because of the multifaceted nature of the experimental methods and dietary regimens used to study the progressive nature of CRF. It is hoped that this in-depth review of pathophysiologic mechanisms in experimental and clinical CRF will provide the impetus for further work to design methods to slow the progression of CRF. Carefully designed, prospective trials will be necessary to establish which patients will benefit, the degree of benefit that can be achieved, and which treatment regimen is preferable in terms of compliance and maintenance of protein nutrition. However, data presented in this book indicate that substantial progress has been made in understanding and treating CRF.

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The contribution of glomerular hemodynamic alterations to progressive renal disease

TIMOTHY W. MEYER
BARRY M. BRENNER

INTRODUCTION

Serious chronic renal insufficiency usually progresses to end-stage renal failure (Mitch et al., 1976). Patients with reductions in the glomerular filtration rate (GFR) to about one-fifth of normal can expect eventually to require dialysis or transplantation, regardless of the original cause of the reduced function. These observations suggest that, after a certain point, a reduction in the number of functioning nephrons causes eventual failure of the remaining nephron units.

CONTRIBUTION OF ELEVATED CAPILLARY PRESSURES AND FLOWS TO GLOMERULAR INJURY FOLLOWING REDUCTION IN NEPHRON NUMBER

The simplest model for studying the consequences of reduced nephron number is provided by surgical ablation of renal tissue. More than 50 years ago, Chanutin and Ferris (1932) showed that removing three-

fourths of the renal mass in rats resulted in a syndrome of hypertension and increasing proteinuria, ultimately leading to uremic death. Collaborative morphologic studies by Wood and Etheridge (1933) demonstrated extensive glomerular sclerosis along with arteriolar sclerosis, tubular atrophy, and interstitial fibrosis in the remnant kidneys of these rats. Shimamura and Morrison (1975) later profiled the development of pathologic changes in remnant glomeruli following renal ablation of approximately 85 percent. Early glomerular hypertrophy was accompanied after 3 months by ultrastructural changes, including vacuolization of epithelial cells and "fusion" of epithelial cell foot processes. By 6 months, there was notable expansion of the mesangium along with focal areas of denudation of endothelial and epithelial cells from the glomerular basement membrane. Progressive mesangial expansion and collapse of capillary lumina eventually resulted in the appearance of focal and segmental glomerular sclerosis in initially normal remnant glomeruli.

The segmental sclerotic lesions which develop in remnant glomeruli of the rat following ablative injury resemble those seen in a variety of human renal diseases. A number of workers, therefore, have employed the rat renal ablation model to identify factors potentially responsible for the progression of human renal insufficiency (Purkerson, Hoffsten, and Klahr, 1976; Ibels et al., 1978; Kleinknecht et al., 1979; Hostetter et al., 1981). One line of evidence suggests that changes in glomerular hemodynamic function following a reduction in nephron number cause progressive injury to the remnant glomeruli (Hostetter et al., 1981). Early workers demonstrated increases in the single nephron glomerular filtration rate (SNGFR) of remnant nephrons following renal ablation. The glomerular hemodynamic basis for this augmentation in SNGFR was delineated by Deen et al. (1974) using micropuncture methodology in rats of the Munich-Wistar strain. These rats have surface glomeruli that are accessible for direct measurement of glomerular capillary hydraulic pressures. In rats studied 2 to 4 weeks following unilateral nephrectomy, Deen et al. (1974) found that the weight of the remaining kidney and its total GFR had increased by about 40 percent over the values in sham-operated control rats. The SNGFR was also strikingly increased, to a mean value of 46 ± 3 nl/min (SEM) in the uninephrectomized rats as compared to 25 ± 1 nl/min in the controls.

In order to dissect the mechanism of this increase, it is useful to recall that the rate of glomerular ultrafiltration may be expressed as

$$\text{SNGFR} = K_f \cdot \overline{P}_{UF} = k \cdot S \cdot \overline{P}_{UF}$$

where $\overline{P}_{UF}$ is the mean net ultrafiltration pressure (P_{UF} averaged along the length of the capillary) and represents the difference between mean hydraulic and oncotic pressures across the glomerular capillary. The ultrafiltration coefficient, K_f, is the product of the effective hydraulic conductivity (k) and total surface area (S) of the glomerular capillaries. It

may be seen from this equation that the increase in SNGFR following uninephrectomy could have resulted from an increase in K_f, $\overline{P}_{UF}$, or both. The first of these possibilities, that an increased SNGFR follows an increase in K_f, was examined by creating an experimental situation in which K_f could be determined in uninephrectomized rats. The necessary condition of filtration pressure disequilibrium was achieved by 2 percent plasma loading, which permitted calculation of unique values of K_f (Deen et al., 1974). The average K_f was 0.078 nl/(sec·mm Hg), a value similar to that previously reported by these authors for non-nephrectomized rats. To the extent that the average value of K_f determined in this study resembles that for non-nephrectomized rats, these data suggest that the adaptive increase in SNGFR following uninephrectomy is primarily the result of an increase in $\overline{P}_{UF}$. For a constant K_f, changes in $\overline{P}_{UF}$ and SNGFR are determined solely by changes in the mean transcapillary hydraulic pressure difference, $\overline{\Delta P}$, systemic protein concentration, C_A, and initial glomerular plasma flow rate, Q_A. Changes in Q_A serve to modify the average transcapillary oncotic pressure difference: increases in Q_A tend to reduce this pressure difference and thereby increase the SNGFR, while the opposite is true for selective decreases in Q_A. In this study, uninephrectomy was associated with no difference in C_A relative to that of non-nephrectomized controls. In contrast, $\overline{\Delta P}$ and Q_A were significantly larger in nephrectomized rats, averaging 40 versus 34 mm Hg and 136 versus 76 nl/min, respectively. The observed increase in SNGFR was, therefore, the combined result of these adaptive increments in $\overline{\Delta P}$ and Q_A. The increments in $\overline{\Delta P}$ and Q_A in turn reflect reductions in both afferent and efferent arteriolar resistance evoked by the reduction in nephron number.

The magnitude of the increase in the SNGFR and of the underlying reductions in arteriolar resistance in rats with more extensive renal ablation rises in proportion to the amount of renal mass ablated (Kaufman et al., 1974). The hemodynamic events which cause marked single nephron hyperfiltration following extensive renal ablation have been assessed by Hostetter et al. (1981). One week after right nephrectomy and infarction of approximately five-sixths of the left kidney in Munich-Wistar rats, the SNGFR and its hemodynamic determinants were assessed in the remnant nephrons of these rats and in nephrons of sham-operated controls. The SNGFR in animals undergoing this extensive degree of renal ablation averaged 62 ± 6 nl/min, more than twice the mean value of 28 ± 3 nl/min of the control rats. This marked increment in the SNGFR 1 week after extreme ablation was ascribable mainly to two factors. First, Q_A was elevated, on average, to 187 ± 20 nl/min as compared to 74 ± 11 nl/min in controls. Second, the mean glomerular transcapillary hydraulic pressure difference, $\overline{\Delta P}$, averaged 44 ± 2 mm Hg, as compared to the control value of 37 ± 1 mm Hg. This greater average value for $\overline{\Delta P}$ occurred despite an increase in proximal tubule hydraulic pressure,

P_T, because the mean glomerular capillary hydraulic pressure, $\overline{P}_{GC}$, increased markedly in the remnant glomeruli. Systemic plasma protein concentration, C_A, was not different in the two groups of animals. Thus, as in the study of Deen et al. (1974), higher average values for $\overline{\Delta P}$ and Q_A were responsible for the augmented driving force for filtration. The marked increase in Q_A in this study by Hostetter et al. (1981) is consistent with the findings of Kaufman, Siegel, and Hayslett (1975), who demonstrated that with graded degrees of ablation, the mean glomerular blood flow varies directly with the extent of ablation.

In rats, the pace of remnant glomerular injury, like the magnitude of remnant glomerular hemodynamic change, is correlated with the portion of renal mass ablated (Shimamura and Morrison, 1975; Purkerson et al., 1976; Hostetter et al., 1981). Evidence that increased capillary pressures and flows actually cause glomerular injury was provided by Hostetter et al. (1981) in studies of rats subjected to 90 to 95 percent nephrectomy as described above. Severe restriction of dietary protein intake, which lowers glomerular filtration rate in intact animals (Ichikawa et al., 1980), was used to blunt adaptive hyperfiltration following reduction of the animals' renal mass. In animals fed a 6 percent protein diet, Q_A and $\overline{\Delta P}$ were maintained at near-normal values following renal ablation, so that the average value of the SNGFR in the remnant kidney was restricted to 38 ± 6 nl/min. This was markedly lower than the average SNGFR of 62 ± 6 nl/min found in rats that had undergone a similar degree of ablation but had been fed standard laboratory chow containing 24 percent protein. Limitation of glomerular hyperfiltration and prevention of glomerular capillary hypertension and hyperperfusion by protein restriction were associated with preservation of glomerular structure. Within 2 weeks after ablation, remnant kidneys of animals fed standard chow showed protein reabsorption droplets in their glomerular epithelial cells, an attenuation of epithelial cell bodies, and focal fusion of foot processes. These epithelial cell changes were associated with lifting of endothelial cells from the inner aspect of the glomerular basement membrane and with an increase in mesangial area. Glomerular morphologic abnormalities were much less extensive in remnant kidneys of protein-restricted rats, and proteinuria was limited in these animals, suggesting preservation of the glomerular permselectivity barrier.

These studies by Hostetter et al. (1981) showed that limitation of capillary pressure and flow prevented early glomerular injury following very extensive renal ablation. More recent studies have shown that dietary protein restriction maintained over 4 to 8 months also lowers the remnant kidney GFR and retards the development of proteinuria and glomerular sclerosis in rats subjected to less extensive renal ablation (Meyer et al., 1983; Madden and Zimmerman, 1983). The 6 percent casein diets used to restrict protein intake in these studies proved to limit body growth. Limitation of the increase in the remnant kidney GFR and of glomerular

injury in protein-restricted rats following extensive renal ablation may thus have reflected a smaller body size, as well as a lower daily protein intake. El-Nahas et al. (1983) have recently shown, however, that lowering the dietary protein content from 20 percent casein to 8 percent casein in Sprague-Dawley rats subjected to 90 percent renal ablation limited the development of glomerular lesions over a 4-month period without restricting body growth. Kleinknecht and coworkers, who initially showed that graded reductions in dietary protein content increased the lifespan of young rats subjected to renal ablation (Kleinknecht et al., 1979; Salusky et al., 1981), have also recently shown that the beneficial effect of protein restriction remains apparent when the caloric intake and body weight are carefully matched following ablation (Kleinknecht, Chapter 2).

CONTRIBUTION OF ELEVATED GLOMERULAR CAPILLARY PRESSURES AND FLOWS TO GLOMERULAR INJURY IN EXPERIMENTAL MODELS OF HYPERTENSION AND DIFFUSE PARENCHYMAL DISEASE

Studies in rats have identified progressive segmental glomerular sclerosis as a key feature of hypertensive renal injury. These studies further suggest that increases in capillary pressure and flow cause glomerular sclerosis in experimental hypertension. Hill and Heptinstall (1968) first suggested that elevated glomerular capillary pressure caused glomerular sclerosis in rats with mineralocorticoid-salt hypertension. Azar et al. (1977, 1978) later demonstrated a direct relation between accelerated glomerular sclerosis and increased glomerular capillary pressure in rats with "post-salt" hypertension. Subsequent studies have supported these workers' contention that glomerular injury would be associated with hypertension only when the increase in systemic pressure was transmitted to the glomerulus. Thus, premature sclerosis is not prominent among superficial glomeruli of spontaneously hypertensive rats (SHRs) whose capillary pressure and flow are near normal (Feld et al., 1977; Arendshorst and Beierwaltes, 1979). Early proteinuria and sclerosis in this strain of rats are confined to juxtamedullary glomeruli, which have higher filtration rates and presumably higher pressures, flows, or both than those of the outer cortex (Bank, Allerman, and Aynedjian, 1983). In contrast, rats with two-kidney, one-clip hypertension exhibit marked elevation of glomerular capillary pressure and rapidly develop glomerular lesions in the unclipped kidney (McQueen and Hodge, 1961; Schweitzer and Gertz, 1979).

Recent studies by Dworkin et al. (1984) have provided more direct evidence that glomerular injury in rats with mineralocorticoid-salt hypertension is hemodynamically mediated. Uninephrectomized Munich-

Wistar rats were given normal saline to drink and weekly injections of desoxycorticosterone, leading to an increase in their mean arterial pressure to 155 mmHg as compared with a value of 115 mmHg obtained in control uninephrectomized rats given water to drink and not injected with mineralocorticoid. The mean SNGFR of 68 ± 5 nl/min in the hypertensive rats was not significantly greater than the mean value of 65 ± 3 nl/min observed in the normotensive controls. Values for the plasma flow rate, Q_A, were likewise similar in the two groups. However, as had been predicted by Hill and Heptinstall (1968), rats with mineralocorticoid-salt hypertension exhibited an increase in $\overline{\Delta P}$ to 44 ± 1 mmHg, a value 7 mmHg greater than observed in the control rats. This increase in $\overline{\Delta P}$ was associated with an increase in proteinuria and a notable prevalence of glomerular sclerotic lesions within 4 weeks after the induction of hypertension. Dworkin et al. (1984) further studied a group of uninephrectomized rats given saline to drink and injected with desoxycorticosterone, but also simultaneously put on a 6 percent casein diet. Protein restriction limited these animals' mean SNGFR to 40 ± 4 nl/min. As in rats subjected to renal ablation, limitation of the SNGFR by dietary protein restriction reflected a restriction of Q_A and $\overline{\Delta P}$ to values similar to those seen in intact, two-kidney rats maintained on standard chow. Normalization of glomerular capillary pressures and flows was associated with marked reduction in proteinuria and in the prevalence of glomerular sclerotic lesions.

Rats subjected to extensive renal ablation, like patients with serious renal insufficiency, usually develop systemic hypertension. The experimental studies described above suggest that antihypertensive therapies aimed at reducing glomerular capillary pressure, flow, or both should limit glomerular injury when nephron number is reduced. In accord with this hypothesis, Anderson et al. (1984) recently found that the angiotensin II converting enzyme inhibitor, enalapril, reduced glomerular capillary pressure as well as systemic blood pressure and preserved glomerular structure in rats subjected to an 85 percent reduction in nephron number. In untreated rats, renal ablation was followed by an increase in mean arterial pressure to approximately 140 mm Hg, and there were striking increases in glomerular capillary pressure and flow that elevated the remnant nephron GFR to values more than twice normal. These glomerular hemodynamic changes were associated with the development of proteinuria and widespread glomerular segmental lesions within 8 weeks after ablation. A dosage of converting enzyme inhibitor sufficient to normalize the animals' systemic blood pressure also normalized their glomerular capillary pressure. Glomerular plasma flow was not reduced by the converting enzyme inhibitor therapy, and net glomerular hydraulic permeability actually increased, so that remnant nephron GFR remained elevated despite the reduction in glomerular capillary pressure. Use of the converting enzyme inhibitor to prevent systemic and