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NEPHROLOGY FORUM

Hemodynamically mediated glomerular injury and the progressive nature of kidney disease

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Case presentation

A 26-year-old woman was transferred to New England Medical Center (NEMC) from another hospital with a diagnosis of acute renal failure complicating antepartum hemorrhage, abruptio placentae, and shock. Emergency Caesarean section delivered a stillborn child 2 days prior to transfer. Postoperatively, the patient developed hypotension, oozing from the surgical site that required multiple transfusions, and acute oliguria. At NEMC, the patient remained oliguric for 16 days and was virtually anuric for the first 10 days; the 24-hr urine volumes averaged less than 50 cc. An abdominal x-ray revealed an 11.5-cm right kidney and a 12.5-cm left kidney. The BUN and serum creatinine levels rose as high as 128 and 18.9 mg/dl. Hemodialysis was performed on three occasions during the period of oligoanuria. The urine output subsequently increased to a high of 1900 ml by the 29th hospital day. The patient was discharged 5 weeks after admission with a serum creatinine of 12.6 mg/dl.

Over the next 6 months, the serum creatinine gradually declined to 4.9 mg/dl. Nine months after the episode of acute renal failure, percutaneous renal biopsy yielded only medullary tissue with nonspecific degenerative changes, a marginal focus of necrosis, and numerous protein casts. At this time, abdominal x-ray showed a 10-cm right kidney and an 11-cm left kidney. Over the next 3 years, the serum creatinine continued to decline gradually and finally reached 4.0 mg/dl. During this period, urinary protein excretion ranged between 0.5 and 2 g/day. During this 3-year period, the patient also developed hypertension and was treated for the next 5 years with 750 mg/day of methyldopa. In addition she had recurrent episodes of right-sided paresthesias and blurred vision that resolved following the discontinuation of oral contraceptives. After she stopped taking the oral contraceptive, she developed amenorrhea and galactorrhea. Evaluation revealed low levels of FSH activity consistent with partial pituitary destruction; this problem presumably was sustained in the immediate postpartum period.

After maintaining stable renal function (the serum creatinine was approximately 4.0 mg/dl) for another 4 years (years 4 through 8 after the episode of acute renal failure), the serum creatinine slowly rose over the ensuing 7 years. Hypertension returned, concomitant with the further decline in renal function, and again was treated with methyldopa. During this period, 24-hr urinary protein excretion varied from 0.5 to 1.2 g. Uremic symptoms developed when the serum creatinine reached 8.7 mg/dl, 15 years after the acute postpartum renal failure, and chronic ambulatory peritoneal dialysis was initiated.

Discussion

DR. BARRY M. BRENNER (*Samuel A. Levine Professor of Medicine, Harvard Medical School, and Director, Renal Division, Brigham and Women's Hospital, Boston, Mass.*): This woman developed severe acute renal failure in the immediate antepartum period in association with abruptio placentae, massive intrauterine hemorrhage, and cardiovascular collapse. She became profoundly oliguric and required several hemodialysis treatments before experiencing partial return of renal function. This pattern of incomplete recovery of renal function after an episode of massive peripartum hemorrhage secondary to abruptio placentae is characteristic of the lesion of acute, bilateral, renal cortical necrosis. Numerous reports emphasizing the association of peripartum hemorrhage with bilateral renal cortical necrosis have appeared since the initial description by Bradford and Lawrence in 1898 [1]. In several of the patients reported, organs other than the kidneys also were injured as a consequence of the severe cardiovascular collapse, including the anterior pituitary, liver, spleen, adrenal glands, and pancreas, with the anterior pituitary and adrenals being particularly susceptible. In the patient under consideration today, amenorrhea and galactorrhea were recognized after a latent period of several years; these sequelae probably reflected a mild form of Sheehan's syndrome.

A number of excellent reviews have considered the well-established clinical and pathologic features of bilateral renal

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cortical necrosis [2–5]. Rather than reiterate this information, I instead would like to devote my discussion to the clinical outcome of this patient's renal failure. Specifically, we are told that renal function improved slowly and incompletely after her acute illness, and that the serum creatinine concentration declined to 4.9 mg/dl at 6 months and reached a nadir of 4.0 mg/dl at 3 years. Renal function remained relatively stable at this compromised level for the next 4 years. Not only does the persistent azotemia connote a marked loss of nephron number, but the presence of proteinuria during this interval indicates that surviving glomeruli were abnormal as well. Not surprisingly, her renal function deteriorated progressively in association with hypertension, and necessitated the initiation of chronic dialysis.

Prior to the availability of dialysis, early death from uremia was the usual outcome in patients with severe bilateral cortical necrosis. In the past three decades, however, control of hyperkalemia, metabolic acidosis, circulatory congestion, and the symptoms of uremia by conservative and dialytic management has enabled such patients to survive the typically protracted oligoanuric period seen in this disorder, which often extends for several weeks beyond that usually noted in patients suffering from the more commonplace entity of acute tubular necrosis. Whereas patients with acute tubular necrosis experience a relatively prompt return of renal function to near-normal levels within days to a few weeks following the onset of diuresis, renal function rarely recovers fully in patients with extensive renal cortical necrosis. This loss of function reflects the permanent nephron destruction that takes place in the areas of necrosis. In the latter cases, creatinine clearances typically rise from extremely low levels during the oligoanuric period to values approaching 10 to 15 ml/min after 3 to 6 months, and peak at 20 to 30 ml/min after 1 to 3 years [4]. It is generally assumed that this slowly progressive improvement in overall renal function results from the functional and structural hypertrophy of the nephrons that escape the initial vascular damage, with juxtamedullary glomeruli and tubules being the least affected. Unfortunately, many patients fail to sustain even these modest levels of glomerular filtration rate; after a variable interval of relative functional stability, GFR again declines, usually in association with overt proteinuria and hypertension [4, 6, 7].

Until recently, no satisfactory explanation was available to account for the eventual deterioration of renal function observed so commonly in this patient population, although factors such as hypertension, subsequent pregnancy, and progressive interstitial fibrosis have been suggested. I believe that the progression to end-stage renal disease in bilateral cortical necrosis is a predictable, long-term hemodynamic consequence of the initial loss of nephron mass induced by widespread and irreversible ischemic renal injury. Indeed, such hemodynamically mediated progression to end-stage renal failure is not unique to this form of renal vascular injury, but may be a final common pathway in a host of renal disorders characterized by irreversible reduction in the number of functioning nephron units.

Evidence for hemodynamically mediated chronic renal injury in animals

Let me develop this hypothesis by citing some relevant experimental evidence obtained in animals. As is well known, when renal mass is reduced, the remaining nephrons undergo functional as well as structural hypertrophy. Adaptations in the microcirculation of remnant glomeruli result in an increased mean driving force for filtration and, therefore, a marked increase in single-nephron glomerular filtration rate (SNGFR) [8, 9]. The magnitude of this increase in SNGFR correlates closely with the amount of renal mass that has been lost; that is, greater degrees of ablation result in greater increases in SNGFR in the residual glomeruli [8–10]. This adaptive hyperfiltration in surviving glomeruli generally is regarded as beneficial because it minimizes the reduction in total GFR that otherwise would ensue.

A growing body of evidence, suggests, however, that single-nephron hyperfiltration—or some hemodynamic determinant(s) thereof—may eventually prove injurious to the structural and functional integrity of residual glomeruli [9, 11–14]. Fifty years ago Chanutin and Ferris recognized that removal of approximately three-fourths of the total renal mass in the rat led to a syndrome of progressive azotemia, proteinuria, and glomerular sclerosis [15]. Shimamura and Morrison documented the progression of glomerular damage in adult rats subjected to surgical resection of approximately 90% of total renal mass [11]. The rats manifested an increase in glomerular size within 3 months, and this increase was accompanied by ultrastructural alterations, which included vacuolization of glomerular epithelial cells and effacement of foot processes. By 6 months, expansion of mesangial matrix and denudation of cells from areas of glomerular basement membrane heralded progressive hyalinization and ultimately sclerosis of these remnant glomeruli. Studies employing unilateral nephrectomy and infarction of approximately three-fifths of the remaining kidney revealed morphologic changes similar to those deriving from extensive surgical ablation [12]. With somewhat more severe reductions in renal mass induced by uninephrectomy and infarction of approximately five-sixths of the remaining kidney, Olson et al observed similar structural disruption but at an accelerated pace; morphologic abnormalities were evident in remnant glomeruli at one week after the ablative procedure [13]. At that time, glomerular endothelial and epithelial cells were detached from the adjacent basement membrane in a focal manner. Protein reabsorption droplets were visible in both glomerular epithelial and mesangial cells, and mesangial volume was increased.

Proteinuria also develops following renal ablation; most rats subjected to high-grade nephrectomy eventually excrete several hundred milligrams of protein per day as compared to less than 10 milligrams per day in control animals [11]. Olson and coworkers documented a fourfold increase in protein excretion in rats only one week after unilateral nephrectomy and infarction of approximately five-sixths of the remaining kidney [13]. This level of protein excretion is especially noteworthy in view of the fact that the total GFR for the remnant kidney was only 15% to 20% of the value for both kidneys in control rats. Thus, factored for GFR, protein excretion was more than 20-fold greater in experimental than in control animals.

In an effort to further characterize this acquired defect in permselectivity, Olson and coworkers evaluated the processing of tracer macromolecules after severe reduction in renal mass [13]. Relative to values in control animals, glomerular filtration of uncharged macromolecules, as assessed by the fractional

clearance of neutral dextrans, was not altered for dextrans with molecular radii in the range between 20 and 38 Å. Fractional clearance values for neutral dextrans larger than 38 Å were increased significantly in remnant glomeruli, however. This finding indicated partial disruption of the size-selective properties of the glomerular capillary wall. Such a defect is in keeping with the findings of Robson and colleagues, who demonstrated an increase in the fractional clearance of another neutral polymer, polyvinylpyrrolidone, in rats subjected either to subtotal nephrectomy or unilateral pyelonephritis [16].

When the charge-selective properties of the glomerular wall were probed using both negatively charged dextrans and variously charged molecules of horseradish peroxidase, a defect in the ability to restrict negatively charged macromolecules also was apparent [13]. In short, remnant glomeruli lose both size- and charge-selectivity, and these alterations account for the progressive proteinuria that occurs after loss of renal mass.

Based on recently acquired data from our laboratory [8, 9, 13, 14, 17–20], we have suggested that the syndrome of progressive azotemia, proteinuria, and glomerular sclerosis occurring with renal ablation is due to sustained elevations in glomerular capillary pressures and flows. In our initial study, SNGFR and its hemodynamic determinants were measured in remnant glomeruli one week following right nephrectomy and infarction of approximately five-sixths of the left kidney in Munich-Wistar rats [9]. Values for SNGFR in partially nephrectomized rats averaged 63 nl/min, more than twice the mean value of 28 nl/min of sham-operated control rats. This marked increment in SNGFR 1 week after ablation was due mainly to significant changes in two factors: (*1*) Glomerular capillary plasma flow rate (Q_A) was elevated on average to 187 nl/min compared to 74 nl/min in controls; and (*2*) Mean glomerular transcapillary hydraulic pressure difference ($\overline{\Delta P}$) averaged 44 mm Hg, as compared to the control value of 37 mm Hg. No meaningful differences in the remaining two determinants of SNGFR, namely, systemic oncotic pressure or glomerular capillary ultrafiltration coefficient, emerged in these studies.

To ascertain whether these increments in pressures and flows constitute the basis for eventual damage to remnant glomeruli, we sought to blunt the adaptive increases in Q_A and $\overline{\Delta P}$ by restricting dietary protein intake [9]. The average value of SNGFR of 38 nl/min in rats on a 6% protein diet was markedly lower than the mean value of 63 nl/min obtained in the rats with a similar degree of ablation but fed a standard, 24% protein, diet. This blunting of the hyperfiltration response was the result of a failure of Q_A (92 nl/min) or $\overline{\Delta P}$ (32 mm Hg) to increase despite the extensive loss of renal mass. Associated with this near-normalization of SNGFR and its hemodynamic determinants was a striking reduction in the structural abnormalities observed in remnant glomeruli [9]. Additionally, protein excretion remained at the same low rate as in normal rats, largely because the defects described earlier in size- and charge-selectivity were, for the most part, prevented [13].

Similar elevations in glomerular pressures and flows occur not only in remnant kidneys following surgical ablation but in other models of renal disease as well [17, 21–23]. Moreover, in these models hyperfunctioning glomeruli eventually deteriorate in the same manner as do remnant glomeruli in rats undergoing extensive renal ablation. Studies by Azar et al in "post-salt" hypertension [24] and by Dworkin and colleagues in "DOCA-salt" hypertension [18] reveal a strong correlation between glomerular pathology and glomerular capillary hypertension and hyperperfusion; these findings lend additional support to the concept that "adaptive" hemodynamic changes contribute to the ultimate destruction of surviving glomeruli in renal diseases of diverse cause. Further support for this view derives from the observation that unilateral nephrectomy hastens the progression of glomerular sclerosis induced by a variety of maneuvers including renal irradiation [25], injection of nephrotoxic serum [26], and repeated administration of puromycin aminonucleoside [27]. Unilateral nephrectomy also hastens the development of azotemia and renal histopathology in the NZB × NZW mouse, an animal model of lupus erythematosus [28]. Presumably, uninephrectomy adds to the hemodynamic burden of glomeruli previously subjected to these various forms of injury.

Graded reductions in dietary protein intake have been shown to prolong survival of young rats subjected to extensive renal ablation [29, 30]. Protein restriction also retards the progression of nephrotoxic serum nephritis in rats [31, 32] and the lupus-like nephropathy of the NZB × NZW mouse [33]. In the "DOCA-salt" hypertensive rats studied in our laboratory, protein restriction was shown to limit the glomerular hemodynamic changes and the associated glomerular structural abnormalities and proteinuria as well [18]. On the other hand, accelerated glomerular sclerosis occurs in uninephrectomized rats either fed high-protein diets [34, 35] or induced to overeat by hypothalamic injury [36].

Collectively, these findings support our view that hemodynamic alterations are responsible for the early morphologic derangements observed in subtotally nephrectomized rats fed a standard diet. Other investigators have suggested that dietary phosphorus restriction and thyroparathyroidectomy limit the progression to uremia that occurs in rats with underlying renal injury [37, 38]. The beneficial effect of these maneuvers originally was attributed to a reduction in circulating parathyroid hormone levels and decreased deposition of calcium and phosphorus in the renal interstitium [37, 38]. Such changes are unlikely to account for the protective effect of low protein feeding, however. Dietary phosphorus content was comparable in the normal (0.99%) and low-protein (0.70%) diets [9]; both levels were well above the 0.04% used in the studies of phosphorus restriction by Alfrey and coworkers [37, 38]. More important, in the study by Hostetter et al, calcium phosphate deposits were not demonstrable in the remnant renal tissue at the conclusion of the study [9].

More recent studies by Alfrey and coworkers suggest that the previously described beneficial effects of dietary phosphate restriction and thyroparathyroidectomy are not related to prevention of interstitial crystalline deposits or to suppression of parathyroid hormone [39]. Indeed, parathyroidectomy alone did not confer the same protective effect as was initially seen with thyroparathyroidectomy. Of note, chronic low phosphate feeding as well as thyroidectomy lead to reductions in GFR in normal animals [40, 41]. In the studies of Alfrey and coworkers, kidney weights were lower in animals given nephrotoxic serum and followed either by severe phosphate restriction or thyroparathyroidectomy, relative to nephritic animals fed a normal diet or with intact thyroid glands [38, 39]. These findings therefore are consistent with the view that phosphate restriction and thyroidectomy limit renal growth; perhaps these maneuvers

also limit compensatory hemodynamic alterations. The possibility thus exists that phosphate deprivation and thyroidectomy are protective by virtue of their inhibition of hemodynamic alterations in remnant glomeruli and not by any direct effect on divalent ion metabolism.

Mechanisms of hemodynamically mediated glomerular injury

If hemodynamic alterations underlie the progressive sclerosis of residual glomeruli, how do such physical alterations exert their effects? The increased mean glomerular transcapillary hydraulic pressure difference, $\overline{\Delta P}$, may injure the capillary network by some process analogous to the effects of systemic hypertension on arterioles; this mechanism presumably involves mechanical disruption of normal vascular integrity. But it seems unlikely that systemic hypertension per se adequately accounts for the progressive glomerulopathy that occurs with renal ablation. For example, Purkerson, Hoffsten, and Klahr reported that rats subjected to only partial infarction of one kidney developed arterial hypertension, with a mean arterial pressure of 153 mm Hg [12]. Despite the hypertension, in these rats with only a small portion of the renal mass removed, glomerular morphologic abnormalities did not develop. Using other animals subjected to a far greater degree of renal ablation (comparable to that employed by Hostetter et al [9]), Purkerson and colleagues were able to reduce systemic blood pressure to near-normal levels with antihypertensive drugs, yet significant glomerular damage ensued [12]. These various findings prompted these authors to suggest that uremia or a critical reduction in renal mass was necessary for development of the progressive glomerular lesion [12]. In addition, the pattern of intrarenal resistances and, consequently, of glomerular pressures and flows observed in subtotally nephrectomized rats differs from that described in several other animal models of chronic hypertension that involve no reduction in renal mass [42, 43]. Such hypertensive rats display no increase in glomerular capillary hydraulic pressures despite systemic arterial hypertension; moreover, glomerular plasma flow rates tend to be reduced, not elevated, because intrarenal resistances typically are increased. In contrast, rats with partial renal ablation exhibit reduced afferent and efferent arteriolar resistances in the presence of mild systemic hypertension, thereby favoring increased glomerular capillary hydraulic pressures and plasma flows [9]. It is interesting to speculate that this failure to autoregulate glomerular capillary hydraulic pressure and plasma flow may underlie the hemodynamic abnormality of pathogenetic importance in this model. In this regard, Azar et al have suggested that reductions in intrarenal resistances might play a key role in the glomerular damage that arises with unilateral nephrectomy in the so-called "post-salt" hypertensive model [24]. Also, in the "DOCA-salt" model of hypertension, Dworkin and coworkers recently demonstrated that elevations in Q_A and $\overline{\Delta P}$ correlate closely with structural damage [18]. Furthermore, as I already have stated, they showed that these hemodynamic changes and their attendant morphologic alterations could be reversed with low-protein feeding. Finally, Feld and colleagues have speculated that a relative inability of the juxtamedullary nephrons to autoregulate is somehow responsible for the greater glomerular injury that this nephron population suffers in the spontaneously hypertensive rat [44].

Whereas systemic arterial hypertension is not a factor common to all the models considered thus far, intrarenal hypertension (increased $\overline{\Delta P}$) and hyperperfusion (increased Q_A) clearly are. As shown in Figure 1, their combined effects lead to an increased transcapillary flux not only of ultrafiltrate (increased SNGFR) but of macromolecules as well (increased albuminuria). Associated changes in the intrinsic permselective properties of the glomerular wall also result in an increased flux of macromolecules through the wall. This increased transglomerular traffic of plasma proteins ultimately might injure a component or components of the glomerulus [27, 45]. Indeed, studies of ferritin localization demonstrate a greatly increased deposition of this electron-dense protein in the mesangial region of glomeruli following surgical ablation as compared to control animals [13]. It is therefore likely that an overloading of this region might be a general mechanism for increasing matrix deposition, the forerunner of glomerular sclerosis [27, 45]. The resulting loss of glomerular units imposes a further hemodynamic burden on less affected glomeruli, and leads to their eventual destruction as well.

Evidence for hemodynamic factors in the initiation and progression of diabetic glomerulopathy

In patients with diabetes mellitus, glomerular hyperfunction occurs prior to loss of nephron units and thus may contribute to the *initiation* as well as to the *progression* of the glomerulopathy commonly encountered in this metabolic disorder [19]. Several investigators have documented overt hyperfiltration in children and young adults with juvenile-onset diabetes [46, 47]. Hostetter et al have shown that similar glomerular hyperfiltration in the rat made diabetic with streptozotocin is due, as is the case with renal ablation, to intrarenal vasodilation and sustained elevations in Q_A and $\overline{\Delta P}$ [17].

The potential importance of intrarenal hemodynamic alterations in the pathogenesis of diabetic glomerulopathy also receives support from a variety of observations over the last decade. Steffes, Brown, and Mauer compared the progression of mesangial expansion in rats with streptozotocin-induced diabetes and with or without unilateral nephrectomy [48]. Mesangial deposition of circulating plasma proteins and mesangial widening were more marked in diabetic animals with superimposed unilateral nephrectomy. Although intrarenal hemodynamics were not measured in this study, we can reasonably assume that values for SNGFR, Q_A and $\overline{\Delta P}$ were elevated above normal in the remnant kidneys of these diabetic rats as a result of contralateral nephrectomy. Further studies by these same investigators using the streptozotocin model of diabetes in rats have defined the effects on the diabetic glomerular lesions of a unilateral renal artery clip, the so-called "two-kidney Goldblatt" hypertensive model [49]. Diabetic as well as normal animals became hypertensive with this maneuver. In unclipped, normotensive diabetic rats, characteristic glomerular lesions developed equally in both kidneys. In diabetic rats with a unilateral renal artery clip, however, a distinct asymmetry of these glomerular lesions was found; the unclipped kidneys, in which glomeruli were likely to be exposed to elevations in Q_A and $\overline{\Delta P}$, showed more severe glomerular injury than did the kidneys of normotensive diabetic rats. Moreover, the clipped kidneys in the same diabetic animals had less glomerular injury than did

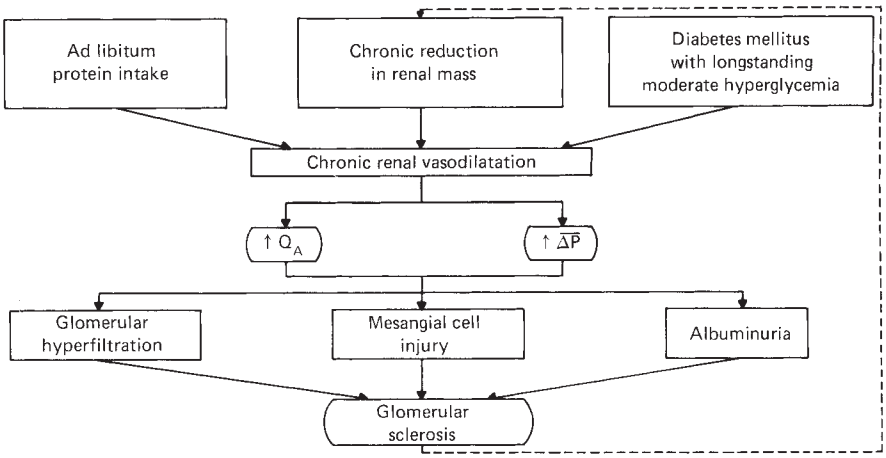

Fig. 1. *Role of sustained increments in glomerular pressures and flows in the initiation and progression of glomerular sclerosis.*

the kidneys of normotensive diabetic rats. This disparity between the two kidneys was present despite identical procedures for producing diabetes in the two diabetic groups, and despite equivalent degrees of hyperglycemia in normotensive and hypertensive animals. These studies clearly indicate that alterations in intrarenal hemodynamics can influence the glomerular structural changes characteristic of experimental diabetes. The clinical counterpart of these findings has also been reported from autopsy findings in a patient with diabetes and unilateral renal artery stenosis [50]. Kimmelstiel-Wilson lesions were confined to the kidney with the patent renal artery; its contralateral partner with the tight stenosis exhibited little glomerular pathology. Finally, diabetic patients with essential hypertension typically progress more rapidly to renal insufficiency than do normotensive diabetic patients, and recent studies by Mogensen indicate that treatment of the hypertension in these patients slows this accelerated rate of progression [51].

Taken together, these experimental studies and clinical observations strongly suggest that renal hemodynamics exert a key influence on the initiation and rate of progression of diabetic glomerulopathy. Indeed, the process leading to overt diabetic glomerulopathy is consistent with the general principle that sustained elevations in Q_A and $\overline{\Delta P}$ are ultimately detrimental to the glomerulus. Such elevations in Q_A and $\overline{\Delta P}$ may result from hyperglycemia-induced extracellular fluid volume expansion and/or from altered glucoregulatory or vasoregulatory hormone action. Whatever their origin, the hemodynamic alterations lead to increased SNGFR which, in turn, augments the glomerular transcapillary convective flux of plasma proteins (Fig. 1). Long-term elevations in glomerular pressures and flows also would be expected to alter the permselective properties of the glomerulus and further increase protein filtration. Such increased transglomerular traffic of plasma proteins leads to their accumulation in the mesangium and thereby stimulates proliferation of mesangial cells and matrix and eventuates in glomerular sclerosis. Thus, the renal hemodynamic alterations associated with less than optimal metabolic control of diabetes could themselves initiate glomerular sclerosis. With loss of the function of sclerotic glomeruli, less severely afflicted glomeruli would undergo compensatory hyperfiltration, thereby closing a positive feedback loop that promotes progressive glomerular injury and eventual loss of renal function.

The progressive nature of human renal disease

Nephrologists know all too well that the vast majority of patients with glomerular filtration rates below approximately 25 ml/min eventually require dialysis or transplantation, regardless of the original cause of reduced renal function. Time plots of the reciprocal of serum creatinine concentration clearly testify to the steady deterioration of nephron function; this decline tends to occur at rates more characteristic of a given patient than of a particular underlying disease [52, 53]. In some patients, the disease responsible for the initial renal injury remains active throughout the course to end-stage renal failure; more often, however, renal failure progresses even when a well-defined initiating process either has remitted spontaneously or has been controlled therapeutically. For example, as Baldwin discussed in a recent Nephrology Forum [54], renal disease following acute poststreptococcal glomerulonephritis can progress in the absence of continued immunologic injury to the kidney. Likewise, as with the woman considered at this conference, patients with bilateral cortical necrosis often enjoy a temporary period of recovery prior to the progression of end-stage renal insufficiency [4]. In these patients, glomerular sclerosis eventually destroys the surviving juxtamedullary units. This pattern of destruction is strikingly reminiscent of the preferential involvement of deeper glomeruli in patients with various forms of renal disease, especially the entity of focal and segmental glomerular sclerosis [55]. Presumably, the higher ambient values for SNGFR in deeper glomeruli which, in all likelihood, are driven by higher local pressures and flows, make them more vulnerable than are more superficial units to the further hemodynamic stresses that occur with widespread renal injury [56]. Patients with vesicoureteral reflux also exhibit a progressive glomerulopathy, despite the absence of hypertension or active urinary tract infection, and often despite surgical correction of the reflux [57]. The hemodynamic and other factors thought to contribute to glomerular sclerosis in reflux nephropathy have been considered in detail by Cotran at another recent Nephrology Forum [58]. Glomerulosclerosis, progressive azotemia, and proteinuria also are common findings in patients with long-

standing abuse of analgesic drugs [59], sickle cell nephropathy [60], segmental hypoplasia [61], congenital nephrotic syndrome [62], massive obesity [63], and, of course, type-I (juvenile onset) diabetes mellitus [17, 19].

Is there a critical number of functioning nephrons below which hemodynamically mediated glomerular injury is inevitable? No firm conclusion is possible yet. When, however, the number of nephrons is reduced by more than 50%, as in oligomeganephronia, remnant glomeruli initially undergo functional and structural hypertrophy, which is followed by proteinuria, glomerular sclerosis, and progressive renal failure [61]. Moreover, evidence has been amassed recently by Kiprov, Colvin, and McCluskey suggesting that unilateral renal agenesis in humans predisposes to focal and segmental glomerular sclerosis and even to end-stage renal failure [64]. Unfortunately, there has been little systematic, long-term follow-up of children and adults who have undergone surgical nephrectomy for grade-I renal cell carcinoma, trauma, or organ donation; such studies clearly are needed to evaluate this issue. I will describe our preliminary findings in follow-up of kidney donors during the question-and-answer period at the end of my discussion. Other, related questions deserve attention: *(1)* Is the entity that we routinely call "chronic transplant rejection" a form of hemodynamically mediated renal injury in allograft recipients? In many instances, graft function deteriorates over several years, usually in association with proteinuria, despite the absence of clinically apparent episodes of acute rejection. *(2)* Is there a spectrum of oligonephron states that spans the extremes of marked hypoplasia, on the one hand, and normal nephron number on the other? *(3)* Is the propensity for young males to be more seriously affected than are females in certain renal diseases (such as hereditary nephritis, IgA nephropathy, and focal and segmental glomerular sclerosis) due in part to the renotrophic effects of androgenic hormones? In rats, the magnitude of proteinuria following unilateral nephrectomy is greater in males than in females [34], as is the incidence of spontaneous glomerular sclerosis associated with aging [65]. *(4)* Does the hyperfiltration of pregnancy contribute to the deterioration of renal function seen in some gravidas with underlying diabetes, lupus nephritis, and other forms of previously mild renal insufficiency? Likewise, since hyperfiltration with repeated pregnancies can have a cumulative effect, are multiparas more prone to hypertension and intrinsic renal disease than are nulliparas? (5) Finally, are some individuals predestined to develop renal insufficiency because of chronic renal vasodilation and sustained elevations in intrarenal pressures and flows that are "physiologic" rather than the consequence of a disease process? For example, we recently have expressed concern that the high-protein diet characteristic of modern Western society might itself induce chronic renal hyperperfusion and thereby predispose to progressive glomerular sclerosis and age-related declines in GFR. In brief, one can argue that a fundamental mismatch exists between the design characteristics of the human kidney and the functional burden imposed by the ad libitum eating habits now regarded as normal in our society. Sustained excesses of protein in the diet impose correspondingly sustained increases in renal blood flow and GFR, and thus require that the "reserve" glomeruli of the outer cortex be utilized more or less continuously. This pattern of continuous hyperfiltration implies that time-averaged glomerular pressures and flows are higher than values that would be expected to prevail with lower protein intakes, as when feeding is intermittent; in turn, the resulting "intrarenal hypertension" could well predispose to age-associated progressive glomerular sclerosis and declining renal blood flow and GFR.

In normal individuals, the decrease in GFR between the third and ninth decades is approximately 40%. This decline may be the biologic price of renal hyperperfusion associated with ad libitum feeding, and might be tolerable in the absence of diabetes, acquired renal disease, or surgical loss of renal mass. An unrestricted protein diet, however, could exaggerate the increments in glomerular pressures and flows associated with an episode of nephron loss, and could accelerate the development of glomerular sclerosis and lead to more rapid loss of renal function.

Current treatment modalities for patients with chronic renal insufficiency unfortunately do little to interrupt the hemodynamic mechanisms of progressive renal failure. If my hypothesis is correct, we will need therapies aimed at preventing excessive glomerular pressures and flows to check the relentless progression of clinical renal disease. An obvious first step, as suggested by Addis more than three decades ago [66], might be a reduction of protein intake, implemented early in the course of intrinsic renal disease. Indeed, Maschio et al [67] and Giordano [68, 69] recently have argued that the rate of progression can be effectively retarded in a variety of renal disorders by prolonged control of dietary protein intake. Likewise, early institution of rigid metabolic control by continuous insulin infusion or other means in patients with juvenile-onset diabetes could prove effective in preventing glomerulopathy in this high-risk population [70]. Given these perspectives, I think we have reason to be optimistic about the clinical and therapeutic possibilities that lie ahead.

Questions and answers

DR. JEROME P. KASSIRER: Your hypothesis to explain progressive renal damage is fresh, provocative, and exciting. If we are going to begin widely recommending protein restriction to prevent progressive renal failure, it would be of considerable advantage to understand the mechanisms by which the damage takes place. What is known about the precise mechanisms that cause the increase in single-nephron GFR in preserved glomeruli when other glomeruli are damaged? Second, how does protein intake affect the GFR?

DR. BRENNER: I guess I would put it a little differently. Whether we understand how protein restriction works, I see little reason not to recommend this dietary modification to patients with renal disease, and a few studies that have been done thus far support this belief [67–70]. These and other studies suggest that by reducing dietary protein intake to approximately 0.7 g/kg/day we can achieve considerable amelioration, if not arrest, of progression of the disease. Based on these preliminary findings, I would also recommend that people who undergo nephrectomy restrict their protein intake to a similar extent.

Not much is known about the mechanisms of this amelioration. We know that there is a hyperemic renal response to a protein meal, and we know that the response can be duplicated with certain amino acids, but not with urea. If one infuses glucagon or growth hormone, hemodynamic changes that occur

with protein or amino acids can be duplicated. And, as you know, both hormones are released when amino acids are infused or when a high-protein meal is ingested.

DR. JORDAN J. COHEN: Is there any evidence that these lesions can be either stabilized or reversed?

DR. BRENNER: You can certainly expect stabilization if you start with serum creatinine levels below about 6 mg/dl. Several investigators have shown stabilization with essential amino acids and their nitrogen-free analogues in patients with advanced renal insufficiency [71, 72]. Maschio and coworkers have been successful in arresting progression when the patients' serum creatinines are below 3 mg/dl [67]; it is harder to arrest progression when serum creatinine values exceed 6 mg/dl, but a halt to the progression has occurred in some of these patients.

DR. NICOLAOS E. MADIAS: Can you prevent the deleterious effect of a high-protein diet in the remnant kidney by keeping the renal artery clipped?

DR. BRENNER: Dr. Lance Dworkin in our laboratory tried unsuccessfully to do this in our renal ablation model. He found it extremely difficult to gauge the constriction when renal mass is reduced so markedly. Furthermore, I don't see this as a practical clinical approach and therefore we have no plans to pursue this direction experimentally. Pharmacologic approaches to reducing renal perfusion seem more promising, perhaps involving long-term diuretic therapy or the use of prostaglandin synthetase inhibitors.

DR. MADIAS: Is there any evidence that chronic renal vasodilation induced by pharmacologic manipulation leads to glomerular sclerosis?

DR. BRENNER: I don't believe that such information is available.

DR. GEETHA NARAYAN *(Renal Fellow, NEMC):* If you attribute renal damage in juvenile-onset diabetics to modest elevations of blood glucose, wouldn't you expect to see renal damage more commonly in adult-onset diabetics who have only modest evaluations of blood glucose most of the time?

DR. BRENNER: Hyperfiltration has not been a consistent finding in adults with type-II diabetes, for reasons not entirely clear, at least to me. There may be something different about renal vascular reactivity in patients with juvenile-onset diabetes that favors the development of renal hyperperfusion and hyperfiltration. Whatever the mechanisms involved, the risk of hyperfiltration exists in the diabetic child, and so does the risk of glomerulopathy; in the adult we typically don't see either effect.

DR. JOHN T. HARRINGTON: Are the rats that received a low-protein diet in nitrogen balance at that level of intake?

DR. BRENNER: We haven't had a chance to quantitate nitrogen balance in our rats, but they look well and are active in the cage.

DR. HARRINGTON: All the experimental data you have shown us today comes from rats. Are there other animal models in different species in which glomerular sclerosis can be provoked by protein feeding?

DR. BRENNER: Very little work has been done. Several researchers, however, have reported progressive glomerulosclerosis in aging dogs [73–78].

DR. COHEN: Gradually progressive renal damage can occur in obese patients who have undergone intestinal bypass. Does the initiation of glomerular damage in that setting fit into your hypothesis?

DR. BRENNER: Once the patient has extensive glomerular damage, I think it unlikely that the process can be arrested. We know from studies in rats with genetic obesity as well as from studies in rats with severe overeating induced by hypothalamic injury that a progressive glomerulopathy is the rule. In both circumstances the glomerular lesions can be ameliorated by restricting food intake [79]. Equivalent studies have been performed in humans, and most of the reported patients with this progressive glomerulopathy have been massively obese; dietary restriction may slow the progression in those patients.

DR. COHEN: You alluded briefly to the observation that phosphate restriction also tends to forestall the development of progressive renal damage. How do you link these findings to your present hypothesis?

DR. BRENNER: We have to scrutinize the papers incriminating phosphate as the culprit in progressive glomerulosclerosis. Alfrey originally showed that phosphate restriction can lead to some arrest of progression. Thyroparathyroidectomy did the same; but when he did selective parathyroidectomy, protection was no longer achieved. Recently he and his colleagues have claimed that thyroidectomy alone confers protection [39]. The protection previously claimed for phosphate restriction thus is now in doubt. Moreover, in a recently published clinical study in which phosphate intake was selectively reduced in patients with various forms of renal disease, no evidence of protection was obtained [80]. Phosphate-binding gels were used, diet was not restricted, and the progressive decline in renal function was not ameliorated. I think the protein, not the phosphate, is the important factor.

DR. HARRINGTON: Dr. Brenner, I'd like to turn from protein intake to protein excretion. Dr. Beldon Idelson and I and our colleagues have reported that all our patients with nephrotic syndrome whose protein excretion fell to between 150 mg/day and 2.0 g/day maintained normal renal function for as long as 15 years [81]. Others have made similar observations [82]. We had no ready explanation for this observation, but it seems to me to be consistent with your hypothesis.

DR. BRENNER: Do you have any information regarding the incidence of hypertension in these patients?

DR. HARRINGTON: We did not analyze the blood pressures in our published report, but that information probably could be obtained from reviewing the patients' charts.

DR. MADIAS: I would suspect that the presence of renal nerves is not required for the vasodilation that develops with ingestion of a high-protein diet. Has this been tested?

DR. BRENNER: To my knowledge, this type of experiment has not been reported. It is interesting though that patients with familial dysautonomia develop a characteristic glomerular lesion. Do you know what it is?

DR. KASSIRER: Focal sclerosis.

DR. BRENNER: Exactly. One could speculate that the vasodilation leads to sustained high glomerular flows and pressure, thereby predisposing the patient to progressive glomerulosclerosis. Some of these patients progress to end-stage renal disease [83].

DR. COHEN: What has been your experience in the follow-up of kidney transplant donors?

DR. BRENNER: Drs. Robert C. Goldszer, Raymond Hakim,

and I have contacted a number of adults who donated kidneys in the Brigham program 10 or more years ago [84]. To date we've studied 25 individuals (13 men and 12 women) with a mean age of 60 years. Of the 19 people who donated kidneys 10 to 14 years ago, 7 are hypertensive (diastolic blood pressure greater than 90 mm Hg), and urine protein excretion averages 130 ± 19 SEM mg/day. None was hypertensive at the time of donation, and protein excretion at that time was always less than 50 mg/day. Six other individuals donated a kidney more than 15 years ago, and of these, 3 are hypertensive; daily protein excretion averages 366 ± 127 mg/day. Similar findings have been reported by others [85]. Clearly, similar follow-up studies are required in other centers for us to obtain a fair and accurate analysis of this potential problem.

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