Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation

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HOSTETTER, T. H., J. L. OLSON, H. G. RENNKE, M. A. VENKATACHALAM, AND B. M. BRENNER. Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. Am. J. Physiol. 241 (Renal Fluid Electrolyte Physiol. 10): F85-F93, 1981.—Micropuncture studies were performed in three groups of male Munich-Wistar rats 1 wk after surgery: group I, eight control rats that underwent laparotomy and were fed a normal diet; group II, nine rats that underwent right nephrectomy and segmental infarction of five-sixths of the left kidney and were fed a normal diet; and group III, seven rats that underwent the same renal ablative procedure and were fed a low protein diet. Single nephron glomerular filtration rate (SNGFR) was higher in the remnant kidney of group II rats compared with group I rats due to higher average values for mean glomerular transcapillary hydraulic pressure difference (AP) and initial glomerular plasma flow rate (QA) in group II. Glomeruli in remnant kidneys of group II showed striking alterations in morphology, including epithelial cell protein reabsorption droplets, foot process fusion, and mesangial expansion. Group III rats demonstrated a mean SNGFR not statistically different from that of group I, but significantly less than that of group II rats. This lack of absolute hyperfiltration in remnant glomeruli of group III rats relative to group I obtained because QA and AP did not increase above values found in group I. The glomerular structural lesions seen in group II were also largely attenuated in group III. These studies demonstrate that alterations in glomerular hemodynamics associated with renal ablation are accompanied by structural lesions and suggest that sustained single nephron hyperfiltration may have maladaptive consequences by damaging remnant glomeruli.

glomerular filtration; hypertrophy; chronic renal failure

WHENrenal mass is reduced, the remaining nephrons undergo functional as well as structural hypertrophy (13). Adaptations in the microcirculation of remnant glomeruli result in an increased mean driving force for filtration and, therefore, a marked increase in filtration rate (8). The magnitude of increase in single nephron glomerular filtration rate (SNGFR) correlates closely with the amount of renal mass that has been lost. That is, greater degrees of ablation result in greater increases of SNGFR in the residual nephrons (17). This functional hypertrophy is generally considered beneficial in the sense that it minimizes the reduction in total glomerular filtration rate that would otherwise occur. However, a number of workers have shown that a pathological process of sclerosis eventually occurs in the glomeruli of these residual nephrons (20, 24, 26, 27). These studies showed that after unilateral nephrectomy and partial ablation of the remaining kidney, eventual sclerotic destruction of remnant glomeruli was accompanied by progressive azotemia, proteinuria, and arterial hypertension (20, 24, 26). With severe reduction in renal mass, alterations in glomerular structure were detected as early as 2 wk. By 7 wk more than 50% of glomeruli exhibited morphological changes, and all animals died by 90 days (24). In an effort to ascertain the mechanisms that underlie this destructive process, we have attempted to correlate the changes in structure and function that occur in remnant glomeruli at an early stage in this process.

METHODS

Glossary

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AP</td>
<td>mean femoral arterial pressure, mmHg</td>
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<tr>
<td>C</td>
<td>protein concentration, g/100 ml</td>
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<tr>
<td>GFR</td>
<td>glomerular filtration rate (whole kidney), ml/min</td>
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<tr>
<td>Hct</td>
<td>blood hematocrit in femoral artery or afferent arteriole, vol/100 ml</td>
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<td>Kt</td>
<td>glomerular capillary ultrafiltration coefficient, nl/(s·mmHg)</td>
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<tr>
<td>ΔP</td>
<td>glomerular transcapillary hydraulic pressure difference, P_GC − P_T, mmHg</td>
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<td>ΔΠ</td>
<td>glomerular transcapillary colloid osmotic pressure difference, Π_GC − Π_T, mmHg</td>
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<tr>
<td>P</td>
<td>hydraulic pressure, mmHg</td>
</tr>
<tr>
<td>Q</td>
<td>plasma volume flow rate, nl/min</td>
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<tr>
<td>R</td>
<td>resistance to blood flow, dyn·s·cm⁻²</td>
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<tr>
<td>R_TA</td>
<td>total arteriolar resistance, R_A + R_E, dyn·s·cm⁻³</td>
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<td>SNFF</td>
<td>single nephron filtration fraction</td>
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<td>SNGFR</td>
<td>single nephron glomerular filtration rate, nl/min</td>
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Superscript

(overbar) mean value

Subscripts

A afferent arteriole
E efferent arteriole
GC glomerular capillary
T proximal tubule
Male Munich-Wistar rats weighing 200–250 g were employed in these studies. Three groups of rats were studied. Group I: control rats (n = 8) underwent laparotomy and manipulation of the renal pedicles and were maintained on standard rat chow consisting of 24% protein (Wayne Lab-Blox, Allied Mills, Chicago). Group II: these rats (n = 9) underwent right nephrectomy and infarction of approximately five-sixths of the left kidney by ligation of two or three branches of the renal artery. They were also maintained on the same standard rat chow. Group III: these rats (n = 7) underwent the same renal ablative procedure as group II but were fed a 6% protein diet replete with electrolytes, trace minerals, and vitamins for 1–2 wk prior to surgery and were continued on this diet to the time of micropuncture study. All animals were studied 7 days after renal ablation or sham surgery.

On the morning of micropuncture study, the rats were anesthetized with Inactin (100 mg/kg body wt i.p.). They were prepared in standard fashion for micropuncture (4) and studied under normal hydropenic conditions. Plasma urea concentration was measured at the beginning of each micropuncture experiment using a Beckman Analyzer 2 (Beckman Instruments, Fullerton, CA). Samples of proximal tubule fluid were obtained by micropuncture for determination of flow rate and inulin concentration, the latter by the method of Vurek and Pegram (32). Efferent arteriolar blood samples were obtained for measurement of total protein concentration (31). Hydraulic pressure measurements were made in cortical tubules and vessels using the servo-null micropipette technique (4). The details of the calculations employed have previously been given (4). Statistical analyses were performed with the unpaired t test. Statistical significance was defined as P < 0.05.

Following micropuncture, the kidneys from each rat were examined morphologically. For light and electron microscopy, the kidneys were fixed by perfusion at the measured arterial pressure with 1.25% glutaraldehyde in 0.1 M cacodylate buffer (pH 7.4); the tissue was rinsed in buffer, postfixed in 1% osmium tetroxide, dehydrated, and embedded in epon 812. Thick sections (1 μm) were stained with 0.5% toluidine blue in 1% aqueous borax. Thin sections (60–90 nm) were stained with uranyl acetate and lead citrate and examined in a Philips 201 electron microscope at 60 kV. For scanning electron microscopy, tissue after postfixation was dehydrated in graded alcohols, critical point dried with carbon dioxide, and coated with gold-palladium. The tissue was then examined with an Advanced Metals Research 1000A scanning electron microscope at 20 kV. Following dehydration in absolute alcohol, additional tissue was frozen in liquid nitrogen, fractured, and critical point dried. The cleaved surfaces were identified with a dissecting microscope, plated with gold-palladium, and examined with a scanning electron microscope.

RESULTS

Micropuncture studies. Mean values for whole kidney GFR, AP, SNGFR, and the pressures, flows, and resistances governing glomerular ultrafiltration are summarized in Table 1. Mean arterial pressure averaged 112 +

![Table 1. Summary of renal cortical micropuncture studies in groups I, II, and III.](http://ajprenal.physiology.org/)

Values are means ± SE. PUN, plasma urea nitrogen. See glossary for other abbreviations.
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2 (SE) and 128 ± 4 mmHg in groups I and II, respectively (P < 0.005). Values for whole kidney GFR averaged 0.72 ± 0.06 in group I and 0.21 ± 0.3 ml/min in the remnant kidneys of rats in group II (P < 0.005). In keeping with this reduced GFR, these group II rats were azotemic, with a plasma urea nitrogen concentration (PUN) averaging 89 ± 6 mg/100 ml as opposed to 20 ± 1 mg/100 ml in control rats (group I) (P < 0.05). Values for whole kidney GFR averaged 0.72 ± 0.06 in group I and 0.21 ± 0.3 ml/min in the remnant kidneys of rats in group II (P < 0.005). In keeping with this reduced GFR, these group II rats were azotemic, with a plasma urea nitrogen concentration (PUN) averaging 89 ± 6 mg/100 ml as opposed to 20 ± 1 mg/100 ml in control rats (group I) (P < 0.05). Values for SNGFR in group II animals averaged 62.5 ± 6.4 nl/min, more than twice the mean value of 27.8 ± 3.2 nl/min of group I (P < 0.005). This marked increment in SNGFR 1 wk after one and five-sixths nephrectomy in group II rats could be ascribed mainly to two factors. First, initial glomerular plasma flow rate, QA, was elevated on average to 187 ± 20 nl/min in group II compared with 74 ± 11 nl/min in group I (P < 0.001). Second, the mean glomerular transcapillary hydraulic pressure difference, AP, averaged 44 ± 2 mmHg in group II as compared with 37 ± 1 mmHg in group I (P < 0.025). This greater average value for AP resulted despite an increase in proximal tubule hydraulic pressure, P_T, since mean glomerular capillary hydraulic pressure, P_GC, increased markedly in the remnant glomeruli (Table 1). Systemic plasma protein concentration, C_A, was not different between these two groups. Thus, the higher average values for AP and QA were responsible for the augmented driving force for filtration.

The glomerular capillary ultrafiltration coefficient, K_t, was calculated as its minimal value for group I rats because these rats were at or near filtration pressure equilibrium, with no statistical difference between measured values for P_E and AP (P > 0.2). Unique values for K_t were calculable for the group II animals, however, since they did not achieve filtration pressure equilibrium, with AP significantly greater than P_E (P < 0.025). Thus, minimal K_t values averaged 0.041 ± 0.007 nl/(s·mmHg) in group I, whereas in remnant glomeruli of group II rats unique K_t values averaged 0.063 ± 0.018 nl/(s·mmHg). Since the group I values were minimal, it is not possible to statistically compare them with the numerically greater unique value calculated for group II.

Afferent and efferent arteriolar resistances as well as total arteriolar resistances also differed markedly between group I and group II (Table 1). Group II rats had average values for all of these resistances that were half or less of those of group I rats. Thus, the elevated glomerular capillary hydraulic pressures found in group II rats may be ascribed not only to the higher values of AP in this group but also to reduced afferent arteriolar resistances, R_A.

Despite comparable reduction in renal mass, the rats maintained on a low protein diet (group III) were not different from average values obtained in group I. Furthermore, the numerically higher minimal mean value of K_t in group III, compared with that in group I, would not account for any substantial change in SNGFR in group III, since this group, like group I, was at or near filtration pressure equilibrium (i.e., no statistical difference between P_E and AP, P > 0.2). Thus, low protein feeding in group III was associated with SNGFR values in remnant glomeruli with little or no hemodynamic change relative to group I animals, despite a degree of ablation equivalent to that of group II.

Mean arterial pressure in group III averaged 117 ± 4 mmHg, a value roughly midway between those found in groups I and II and not significantly different statistically from either of them. Also, the average value of total arteriolar resistance, R_TA, in group III animals was intermediate between values obtained in groups I and II, and not significantly different from both. Although the afferent and efferent arteriolar resistances were also intermediate in group III, they were not consistently statistically distinguishable from those of groups I and II.

Morphological studies. In each animal, from 10 to 42

FIG. 1. Light micrographs of glomeruli from experimental rats 7 days following operation. A: group II rat. Note segmental increase in mesangium and blebs (arrowheads) in epithelial cells. B: group III rat. Glomerulus is normal. (Toluidine blue, ×300.)
glomeruli were examined by light microscopy. Glomeruli from group II animals displayed a wide range of morphological abnormalities. Osmophilic droplets representing lysomes containing reabsorbed protein were present not only in the epithelial cells of glomeruli but also in proximal tubule cells. Attenuation of glomerular epithelial cells resulted in the appearance of blebs, visible by light microscopy in 43% of glomeruli in group II rats. Increased mesangium was also discernible in 16% of these glomeruli (Fig. 1A). These alterations appeared to be more frequent in the outer cortex, although juxtamedullary glomeruli were also involved, so that no clear stratification of the lesions could be found. The renal vasculature was normal, whereas rare hyaline casts were observed in tubules. Group I animals demonstrated none of these abnormalities, and in group III the extent of the glomerular lesions was markedly diminished (Fig. 1B). Though proximal tubule cells in group III showed approximately the same amount of protein reabsorption droplets as in group II, the number of such droplets in the glomerular epithelial cells was markedly reduced. In addition, fewer than 10% of glomeruli in group III demonstrated the blebs of attenuated podocytes and no mesangial enlargement was observable.

Transmission electron microscopy in group II demonstrated focal lifting of endothelial cells from the lamina rara interna, with accumulation of flocculent material beneath them (Fig. 2, inset). Occasional endothelial cells of this group contained whorls of membranous material. These whorls also were noted within capillary lumina. Protein reabsorption droplets were present in the epithelial cells of the glomerulus and the proximal convoluted

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**FIG. 2.** Transmission electron micrograph of glomerulus from group II rat. Vacuolar changes are seen in endothelial cell (V). Protein reabsorption droplets (D), blebs (arrow), microvilli (arrowheads), and focal obliteration of foot processes (F) are demonstrated. (Uranyl acetate and lead citrate, ×4,000.) Inset. Note lifting (arrowheads) of endothelial cell from lamina rara interna. (Uranyl acetate and lead citrate, ×13,350.)
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tubule. In the podocytes these droplets were homogeneous but sometimes contained flocculent material. Similar proteinaceous material was noted in the urinary space. Increased numbers of pinocytotic vesicles were observed at the base of the pedicels. Marked attenuation of the epithelial cell cytoplasm was seen frequently. These attenuations account for the blebs described above by allowing formation of large pockets that communicated with the urinary space. Microvilli and focal foot process obliteration were also noted in podocytes (Fig. 2). The number of mesangial cells and the amount of mesangial matrix were both clearly increased in focal areas, as described elsewhere (22). As with light microscopy, group I animals showed no lesions. Transmission electron microscopy in group III animals showed some of the abnormalities present in group II, although to a lesser extent and involving fewer glomeruli (Fig. 3). Endothelial cells in group III rats were unremarkable. Epithelial cells showed no evidence of foot process fusion and somewhat fewer protein reabsorption droplets than in group II rats. The mesangium of group III animals was not readily distinguishable from that in group I controls.

Changes in the morphology of the glomerular epithelial cells of group II animals were also well demonstrated by scanning electron microscopy (Fig. 4). Microvilli were very prominent in some areas, and focal obliteration of foot processes contrasted with other areas containing normal interdigitating pedicels (Fig. 4). The blebs were also well demonstrated by this technique (Fig. 4). Fractured specimens were used to examine large expanses of the endothelial surface, as this technique reliably opens glomerular capillaries to view (Fig. 5A). In some areas

**Fig. 3.** Transmission electron micrograph of glomerulus from group III rat. Note normal mesangium (M) and capillary walls. (Uranyl acetate and lead citrate, x7,500.)
of normal animals. These values have ranged from 0.048 to 0.107 nl/(s·mmHg), a range that obviously includes the value calculated in group II (21, 29). In addition, the minimal $K_f$ value calculated in group III is not statistically greater than the unique value in group I; nevertheless the SNGFR is significantly less in group III than in group II rats, thus reinforcing the probability that even had some increase in $K_f$ occurred in group II animals, it would not of itself account for the augmented SNGFR in this group (3).

Associated with striking hemodynamic changes, glo-

FIG. 4. Scanning electron micrograph of glomerulus from group II rat. View from urinary space. Cytoplasmic blebs (arrows), numerous microvilli (arrowhead), focal obliteration (O) and coarsening (C) of foot processes are seen (×3,600).

small blebs were present on the surface of endothelial cells (Fig. 5B), probably corresponding to the collections of membranous and vacuolated material observed by transmission electron microscopy (Fig. 2). In other areas the endothelium was unremarkable. The glomeruli of both group I and III animals were entirely normal by scanning electron microscopy.

DISCUSSION

The changes in hemodynamics found in remnant glo-

FIG. 5. Scanning electron micrographs of glomerular capillaries. A: normal endothelial appearance is revealed in group I rat. B: group II rat. Scattered endothelial blebs (arrows) are often present in this group (×18,000).
meruli of group II rats were replete with structural alterations at 1 wk. There were abnormalities of all three glomerular cell types. Endothelial cells showed lifting, membranous whorls, and microvillus formation. Epithelial cell abnormalities were largely those associated with proteinuric states, namely protein droplets, microvilli, and foot process obliteration or “fusion.” Additionally, the epithelial cell blebs, consisting of attenuations of these cells, were noted. These structures have been described in at least two other situations. Eclema and Arends (10) observed this abnormality in the glomerular lesion of senile sclerosis of the rat. Also, Takigawa et al. (28) present views of such changes in a study of chronic Masugi nephritis. The pathogenesis of these blebs is unknown. Last, there is slight mesangial thickening at 1 wk following one and five-sixths nephrectomy.

The possibility of a link between the marked changes in glomerular pressures and flows and these readily apparent structural alterations has been suggested (27). That is, the hyperfiltration (and/or the increased glomerular pressures and flows determining the hyperfiltration) might in itself be the cause of the altered glomerular morphology (27). To test this hypothesis, we studied rats fed a low protein diet. This maneuver was employed in an attempt to vitiate the hyperfiltration of remnant glomeruli observed with ablation in group II rats fed a normal diet. We used this dietary manipulation based on the observations that high protein feeding leads to increased renal hypertrophy after unilateral nephrectomy and that general dietary restriction blunts this process (19, 33). Furthermore, studies by Ichikawa et al. (15) demonstrated that rats fed this diet from soon after weaning to age 5 mo had a mean SNGFR 35% less than rats pair-fed a high protein diet. This method of influencing renal function proved to influence markedly the hemodynamics of the residual nephrons. The average SNGFR value, although numerically slightly higher than in group I rats, was not statistically greater: indeed, this average value was significantly lower than in group II rats. Furthermore, the structural changes seen in association with single nephron hyperfiltration in group II were strikingly reduced in group III rats given this low protein diet. Nevertheless, near normalization of SNGFR and its hemodynamic determinants relative to group I was accompanied by remarkable amelioration of the structural abnormalities seen in remnant glomeruli of group II animals with absolute single nephron hyperfiltration.

These studies are consistent with the possibility that single nephron hyperfiltration (and/or some hemodynamic determinant thereof) is responsible for the early morphological derangements observed in group II rats. However, it is possible that some effect of the low protein feeding other than one relating to glomerular hemodynamics accounted for the lesser glomerular damage in group III rats. Several recent studies have suggested that phosphorus restriction has a beneficial effect on the progressive uremia seen in rats with marked degrees of renal injury (14, 16). We doubt that changes in dietary phosphate account for the difference between groups II and III observed in the present study. Dietary phosphorus content was comparable in the normal and low protein diets, being 0.99 and 0.70%, respectively, both well above the 0.04% level used in the studies of phosphorus restriction cited above. More important, no calcium or phosphorus deposits were demonstrable in the remnant kidneys at this early stage of the hypertrophy process.

If hemodynamic alterations underlie this glomerulopathy, the question arises as to how these alterations exert their effects. The mechanism whereby hyperfiltration and/or its hemodynamic determinants alter glomerular structures is not known; however, several possibilities present themselves. The increased glomerular transcapillary hydraulic pressure difference, ΔP, may injure the capillary network by some mechanism analogous to the effects of hypertension on the systemic arterial vessels, presumably involving mechanical disruption of normal vascular integrity (23). In this regard, the increased systemic arterial pressure demonstrated by the animals in group II could have contributed to the observed glomerular abnormalities. However, it seems unlikely that systemic hypertension adequately accounts for the functional and structural changes observed. For example, Purkerson et al. (24) reported that rats subjected to only partial infarction of one kidney developed arterial hypertension, with a mean arterial pressure of 153 mmHg. But in spite of this hypertension, these rats, with only a minor portion of the renal mass removed, did not exhibit structural changes in their glomeruli (24). These investigators also were able to reduce systemic blood pressure to near normal with antihypertensive drugs in other animals subjected to a degree of renal ablation comparable to that employed in the present study. Nevertheless, a significant degree of glomerular damage ensued. These various findings prompted Purkerson et al. (24) to suggest that uremia or a critical reduction in renal mass was necessary for the progressive glomerular lesion. In addition, the pattern of intrarenal resistances, and consequently glomerular pressures and plasma flows, observed in group II animals was quite different from that described in several other models of chronic hypertension in animals with no reduction in renal mass (1, 9). These other hypertensive models have displayed no increase in glomerular capillary hydraulic pressures despite systemic hypertension and have demonstrated reductions in glomerular plasma flow rate. Both of these findings were associated with increased intrarenal resistances (1, 9). In contrast, the rats in group II had reduced afferent and efferent arteriolar resistances in the face of mild systemic hypertension, and, therefore, had increased glomerular capillary hydraulic pressures and plasma flows. 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. (2) have suggested that reductions in intrarenal resistances may play a key role in the glomerular damage seen with unilateral nephrectomy in the so-called “post-salt” hypertensive model. Also, Feld and co-workers (11) have speculated that a relative inability of the deep cortical nephrons to autoregulate was somehow responsible for the greater glomerular injury that this nephron population suffers in the spontaneously hypertensive rat. In any case, it seems reasonable to conclude that the
changes in glomerular dynamics and structure that we observed in group II rats were probably not a simple consequence of systemic arterial hypertension.

The increased movement of filtrate across the glomerular capillary wall in group II rats would be expected to entail an increased transcapillary convective flux of macromolecules as well as water and crystalloid (7). This increased transglomerular traffic of plasma proteins may ultimately have had an injurious effect on some component or components of the glomerular capillary wall (5, 6, 12, 30). In addition, changes in the intrinsic permeability of the glomerular wall might have occurred and resulted in increased movement of macromolecules through the wall, thereby contributing to the ultimate injury of remnant glomeruli (12, 30). Indeed, proteinuria does occur within 1 wk of renal surgical ablation in this model. The potential significance of this finding is discussed elsewhere (22).

Clinically, chronic renal insufficiency regularly progresses to end-stage renal failure, and several studies indicate that for any given patient the rate of progression is predictable (18, 25). Interestingly, these studies indicate that the predictable rate of decline in renal function is idiosyncratic, varying from patient to patient, and apparently not related to the underlying cause of the chronic renal insufficiency (25). It seems quite plausible that after some critical reduction in nephron mass by an initial disease process, a progressive destruction of remnant glomeruli might proceed in remnant nephrons by one or more final common pathways. For example, evidence has recently accrued demonstrating that calcium deposition in the renal parenchyma may represent one such pathway (14, 16). The present studies indicate that if renal hemodynamic derangements may be another common pathogenetic mechanism leading to renal failure after any of a variety of initial insults have reduced nephron mass below some critical level.

In summary, 1 wk after ablation of approximately eleven-twelfths of the renal mass in the rat, remnant glomeruli exhibit striking structural abnormalities in association with a marked increase in SNGFR, the latter due to greatly augmented glomerular pressures and flows. The level of single nephron hyperfiltration can be largely prevented by a low protein diet, and this restraint on the filtration rate despite loss of renal mass is accompanied by near normal values of glomerular pressures and flows. Under these circumstances, the glomerular structural lesions are also largely prevented. These findings, therefore, suggest that "adaptive" increments in SNGFR may represent a potentially adverse response to severe reduction in functioning renal mass and contribute to the progressive destruction of remaining glomeruli that occurs in humans and animals. The role of these potentially adverse adaptations in other forms of progressive renal insufficiency remains to be determined. However, the possibility exists that such adverse adaptations may constitute a common path for the final destruction of remnant nephrons after any of a variety of initial injuries have reduced renal mass below some critical level.

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