Nephron adaptation to renal injury or ablation

BRENNER, BARRY M. Nephron adaptation to renal injury or ablation. Am. J. Physiol. 249 (Renal Fluid Electrolyte Physiol. 18): F324–F337, 1985.—In early stages of permanent renal injury or extensive ablation, structural and functional adaptations associated with hypertrophy partially compensate for nephron losses. Glomerulotubular balance is maintained in these conditioned nephrons by intrinsic tubule and peritubular capillary adaptations that parallel single nephron glomerular filtration rate (SNGFR). Studies of Na⁺-H⁺ exchange in renal cortical brush border membrane vesicles indicate that tubule functional adaptation is not tied to loss of renal mass per se but rather to factors such as dietary protein content that set the level of SNGFR. Likewise, the structural heterogeneity that follows chronic renal injury or extreme ablation of renal mass is less a consequence of nephron injury than of adaptation linked to dietary protein intake. Indeed, since dietary protein restriction blunts the need for compensatory glomerular hyperfiltration, there is neither a stimulus for nephron hypertrophy nor for enhanced tubule ion and fluid transport. In rats with remnant kidneys, experimentally induced diabetes mellitus, or severe hypertension, increases in glomerular pressures and flows precede proteinuria, glomerular sclerosis, and azotemia. Protein restriction prevents these hemodynamic adaptations as well as the late complications. Similar conclusions appear to be applicable to a wide spectrum of clinical circumstances characterized by reduced nephron number.

glomerulotubular balance; glomerulonephritis; tubule transport; hyperfiltration; renal mass; renal blood flow; dietary protein; glomerular filtration; renal hypertrophy

... I would emphasize particularly the contrast between a low glomerular filtration rate due to conditions imposed upon a kidney of normal size, as in heart failure, and a low glomerular filtration rate due to loss of nephrons. In the first instance the rate of filtration per glomerulus is low, and in the second instance it is high. The total effective renal function is reduced owing to loss of tissue, but the work of each remaining unit is increased. Workers in the field of applied renal physiology have frequently overlooked this essential distinction, and at the risk of overemphasis I will illustrate it by a simile from industry. The total production or output of a factor may fall for one of two reasons. The team of workers may become slack or may not have enough to do, like the nephrons in heart failure; or the team may have been seriously depleted in numbers owing to illness, the few remaining workers actually putting in overtime in an unsuccessful attempt to compensate for the absence of their fellows. The latter is the state of affairs in experimental renal failure, as our obliging rats may have clearly demonstrated, and there is good reason to believe that it is the state of affairs also in chronic renal failure in the human subject. If we only study the total production of the factory, without regard to the output per man, or in the case of the kidney the overall function without regard to structure, we fail to distinguish between these two cases of inadequacy, and since the behaviour of the tubule cells is in a large measure dependent upon the rate at which glomerular filtrate is reaching them, the distinction is of primary importance in the interpretation of the phenomena of renal disease.

—R. Platt (97)

CHRONIC RENAL DISEASE has as its principal pathophysiological derangement the permanent loss of nephron units. In early stages, structural and functional adaptations in surviving nephrons partially compensate for these unit losses, but as renal disease advances these adaptations eventually prove inadequate. Until the studies of Oliver (88–92), Platt (97, 98), Bricker (18–20), and others (14, 35, 38, 68), however, it was generally believed that the surviving nephrons in any form of chronic Bright’s disease underwent progressive structural deterioration, with a given nephron within a diseased kidney no longer looking like or functioning like any other. Jean Oliver, one of the most distinguished pathologists in our discipline’s history, was the first to take exception to the view that a highly chaotic architectural state exists in the chronically diseased kidney. As shown in Fig. 1, a photomicrograph of an end-stage kidney taken from Oliver’s classic treatise (59), the glomerulus and its tubule in the inset on the left are markedly atrophic, whereas the corresponding structures in the inset on the right are clearly hypertrophic. Throughout the remainder of the tissue, other glomeruli and tubules exhibit similar structural heterogeneity. Nephrons microdissected from single diseased kidneys confirmed this striking divergence in glomerular volumes and tubule lengths (38, 89).

Despite these structural extremes, the studies of Bricker, Bank, and Gottschalk and their respective associates (2, 7, 44, 72, 73) beginning in the mid-1960s showed clearly, if not surprisingly, that tubule functions continue to parallel glomerular function as closely in chronic renal disease as they do in health; that is, glom-
Marked dispersion of SNGFR values is not unique to pyelonephritis, but, as shown in 1974 by Allison and co-workers (2), also characterizes the kidney with chronic membranous (Heymann) glomerulopathy. In contrast to the narrow range of SNGFR values obtained in normal kidneys, values in nephrotic kidneys again varied considerably. Despite this marked heterogeneity in SNGFR values in the diseased kidney, the data in the upper panel of Fig. 3 revealed tight coupling to absolute proximal fluid reabsorptive rate (APR). Even with a more severe form of nephritis, that induced by anti-glomerular basement membrane antibody (Fig. 3, lower panel), which served to reduce SNGFR values below normal, the same tight coupling between filtration and APR was observed. Identical conclusions were soon reported by Maddox and co-workers (76).

More recently, Ichikawa et al. (60) sought the basis for this continued close coupling between filtration and reabsorption in diseased kidneys. In glomeruli of rats also with chronic membranous glomerulopathy, whether filtering at subnormal, normal, or supernormal rates, local intracapillary hydraulic pressures were uniformly elevated. Indeed, high intraglomerular hydraulic pressures have been found in nearly all forms of renal injury associated with permanent nephron loss studied in the author's laboratory thus far (28, 34, 56, 57, 60, 77). Furthermore, as shown in Fig. 4, values for glomerular plasma flow rate, QA, and ultrafiltration coefficient, Kr, varied as much as did SNGFR, and both determinants of ultrafiltration proved to be responsible for the observed wide variations in SNGFR (60). Presumably, capillary dropout hinders perfusion when the glomerulus is severely damaged, and this hypoperfusion together with the resulting loss of filtering surface area account for the low QA and Kr values and, in turn, the low SNGFR values that were found. For the hyperfiltering glomeruli, on the other hand, exaggerated perfusion and well-preserved

erulotubular balance is very tightly maintained in both circumstances. Figure 2, taken from a paper by Bank and Aynedjian (7) almost 20 years ago, illustrates the striking heterogeneity of single nephron glomerular filtration rates (SNGFR) measured in kidneys of rats with advanced pyelonephritis, as contrasted with the far narrower range of values found in normal kidneys. Despite this marked dispersion of SNGFR values in diseased kidneys, however, these workers found that tubule fluid-to-plasma inulin concentration ratios, a measure of fractional reabsorption, increased with proximal tubule length in essentially the same proportion as occurred in the normal kidney (7), a conclusion also reached by others contemporaneously (72, 73).

FIG. 1. Low-power view (×24) of renal cortex from a case of chronic Bright's disease (Addis and Oliver, case XV) showing atrophic and hypertrophic nephron units. See text for details. From Ref. 89.

FIG. 2. Frequency histogram of SNGFR values in normal (narrow distribution) and pyelonephritic rats (broad distribution). See text for details. From Ref. 7.

FIG. 3. Preservation of glomerulus-proximal tubule balance despite widely varying SNGFR values in rats with chronic membranous glomerulopathy and anti-GBM-mediated glomerulonephritis. See text for details. Redrawn from Ref. 2.
values of $K_f$ were observed, implying little structural damage, and, hence, as discussed below, the expected hypertrophic response to loss of more seriously affected units. In these studies (60), just as in those of Allison and associates (2), APR varied in parallel with SNGFR irrespective of whether filtration rate per nephron was low or high. Moreover, loop of Henle Na$^+$ reabsorption also remained tightly coupled to loop Na$^+$ delivery rates over the wide range of deliveries encountered in the diseased kidney (60), indicative of well-preserved “tubulo-tubular” balance.

Figure 5 depicts schematically how the renal cortical microcirculation contributes to the preservation of glomerulotubular balance in the circumstance of heterogeneous renal injury (60), just as my colleagues and I had earlier found it to do in normal kidneys (16, 17, 29, 59). The open circle in Fig. 5 depicts typical values for SNGFR and APR in normally hydrated rats. The ratio of APR to SNGFR defines the base level of proximal fractional reabsorption, so that any point along the dashed line denotes perfect glomerulotubular balance. As shown in Fig. 4, variations in $K_f$ and glomerular plasma flow rate $Q_A$, entirely account for the wide range of SNGFR values observed in chronic membranous glomerulopathy. Thus, when values for $K_f$ and $Q_A$ in a given glomerulus are reduced, SNGFR is reduced, as shown in Fig. 5 as a shift in the solid arrow to the right of normal, but also to a concurrent increase in $C_E$ and, in turn, to increases in $P_r$ and APR, accounting for the glomerulotubular balance observed in such hyperfunctioning nephrons as well. Thus, the extent of glomerular damage or lack thereof dictates the microvascular conditions downstream to the glomerulus and in so doing establishes the peritubular capillary Starling forces required to preserve glomerulotubular balance.

We might reasonably ask, at this point in the discussion, why the high values for SNGFR and APR? Why not just reduced values consistent with chronic and sustained injury secondary to the deleterious consequences of disease? And why the structural hypertrophy of some nephrons in chronic renal disease? In fact, such hypertrophy and hyperfunction, although confined only to some of the nephrons in chronic intrinsic renal disease (89, 90), have generally been shown to occur in all remnant nephrons in response to partial nephrectomy (19, 28, 44, 50, 51, 56, 66, 88, 90, 98, 123). Indeed, the more renal tissue removed, the greater the perfusion and filtration in remnant glomeruli (66).

Absolute proximal NaCl and NaHCO$_3$ reabsorption increase in parallel with these adaptive increases in SNGFR after renal ablation (51, 78, 123, 124) and, given the high $Q_A$ (28, 123) and normal $K_f$ (28) values that prevail, would predictably be associated with favorable adaptations in the peritubular capillary Starling forces (Fig. 5). Moreover, adaptations in tubule epithelia also occur after partial renal ablation and these too contribute to maintenance of glomerulotubular balance. Thus, Fine and associates (40, 120) documented increases in fluid absorption ($J_t$) in proximal convoluted and straight tubule segments harvested from rabbits several weeks after partial nephrectomy, when remnant glomeruli would surely have been hyperfiltering. Studies in my laboratory confirmed these increases in glomerular and tubule function after just 24 h of ablative surgery (118). Since these increases in $J_t$ persist in tubule segments perfused in vitro and occur at 24 h when hypertrophy is not yet evident, at least microscopically, true transport adaptations in the epithelium are presumed to have occurred.

FIG. 4. SNGFR correlates closely with prevailing values of glomerular plasma flow rate ($Q_A$) and ultrafiltration coefficient ($K_f$) in rats with chronic membranous glomerulopathy. See text for details. Reproduced from J. Clin. Invest. 69, 185–190, 1982 by copyright permission of The American Society for Clinical Investigation.

FIG. 5. Schematic diagram depicting the role of peritubular capillary Starling forces in preserving glomerulotubular balance for each functional nephron unit in chronic renal disease. See text for details. Reproduced from J. Clin. Invest. 69, 185–190, 1982 by copyright permission of The American Society for Clinical Investigation.
Indeed, renal cortical microvillus membranes also preserve their conditioning to hyperfiltration in vitro as evidenced by enhanced Na\(^+\)-H\(^+\) exchange in membrane vesicles derived from dog (25) and rat (49) kidneys after partial renal ablation. Insight into some of the factors responsible for this membrane conditioning to partial nephrectomy is provided in Fig. 6 (adapted from Ref. 49). Renal cortical brush border microvillus membrane vesicles were prepared from six groups of rats. In three groups (closed circles), kidney mass was left intact (designated sham or S groups) but dietary protein intake was either reduced to 6%, raised to a high level of 40%, or maintained at the standard level of 24%. In three other groups (open circles), these same diets were fed to rats that had undergone uninephrectomy (UNx) 2–3 wk prior to study. For the two-kidney sham animals (closed circles depicted in Fig. 6), inulin clearances varied directly with protein intake, as did Na\(^+\) transport. At any given protein intake, uninephrectomized rats (open circles) exhibited significantly higher values for both GFR and Na\(^+\) transport than did animals with two kidneys. Of particular importance, however, when uninephrectomized rats were fed the lowest protein chow, the expected increases in GFR and Na\(^+\) transport were largely prevented, average values remaining at much the same levels as in sham rats maintained on standard chow. Similarly, Maddox and Gennari (unpublished observations) have shown with micropuncture techniques in vivo that the typically observed augmentation in absolute proximal NaCl and NaHCO\(_3\) reabsorption associated with renal ablation in the rat is largely prevented by concurrent low protein feeding.

Let me recapitulate the main points made thus far. 1) Structural heterogeneity in chronic renal disease is paralleled by functional heterogeneity, the latter expressed in part by marked dispersion in SNGFR values in the diseased kidney. 2) Despite this functional heterogeneity, glomerulotubular balance is maintained by intrinsic tubule and peritubular capillary adaptations that parallel the filtration rate for each nephron unit. 3) Finally, studies in brush border membrane vesicles indicate that tubule functional adaptation is not tied to loss of renal mass per se but rather to factors such as dietary protein content that set the level of SNGFR. Indeed, despite extensive renal ablation, dietary protein restriction effectively prevents both the hyperfiltration and the increased tubule Na\(^+\) transport.

In view of this last finding, is it possible that the hypertrophied nephrons that contribute to the structural heterogeneity of the end-stage kidney are also a function of the animal’s protein intake rather than a direct consequence of the underlying disease process? In fact, this possibility was already suggested in 1939 in an all-but-forgotten paper by Smadel and Farr (116) showing that the marked structural heterogeneity of the chronically diseased kidney could be entirely prevented by concomitant protein restriction. Figure 7 shows gross and microscopic views of typical kidneys from three groups of rats given identical doses of nephrotoxic serum several months previously (116). Panel 3 shows the coarsely granular kidney surface typical of chronic glomerulonephritis and below it in panel 6 the alternating areas of nephron atrophy and hypertrophy that account for the granularity of the cortical surface. The renal tissue in panels 3 and 6 was obtained from two rats fed chow rich in protein. By contrast, the rat whose tissue is shown in panels 1 and 4 was maintained chronically on a much lower protein diet. Despite comparable doses of nephrotoxic serum, the renal cortex in the latter rat remained essentially normal on both gross and microscopic examination. An intermediate protein intake in the two rats represented in the middle panels was associated with an intermediate degree of injury. These instructive findings in nephrotoxic serum nephritis have recently been confirmed (84). As indicated above, conditioning is not limited to spontaneously occurring or experimentally induced chronic renal disease. Following partial nephrectomy in the rat, although compensatory hypertrophy and hyperfunction occur and although renal function may remain stable for a few months, glomerular sclerosis eventually develops and progresses to the point where the animal dies of renal failure. Shown in the right panel of Fig. 8 is the typical appearance of the end-stage kidney occurring in the rat 8 mo after 65% ablation of total renal mass (55), contrasted with the more normal renal architecture seen on the left, photographed at the same magnification. Of note is that the rat whose kidney is depicted on the left also underwent the same 65% ablation of renal mass as was carried out on the right but was fed a low (6%) protein diet chronically rather than the high (40%) protein chow given the rat on the right.

I pointed out above that the familiar enhancement of tubule Na\(^+\) transport that occurs with partial nephrectomy can be prevented by concurrent dietary protein restriction (49). The structural heterogeneity of the kidney in chronic renal disease can likewise be shown (as in Figs. 7 and 8) to be less a consequence of nephron injury than of adaptation linked to dietary protein intake (55, 84, 116). Indeed, since dietary protein restriction blunts the need for compensatory hyperfiltration, there is neither the stimulus for nephron hypertrophy nor the need for enhanced tubule Na\(^+\) transport.

Although normal glomeruli possess a remarkable degree of hemodynamic reserve, a decrease in their number beyond a certain limit may lead to a functional overload of the surviving units irrespective of the nature of the
renal disease. Were this overload to impose morphologic change, then the glomerular lesions in late stages of various chronic renal diseases could represent, at least in part, the response to the increased functional activity. In keeping with this concept of functional overload, I hardly need remind the reader that chronic renal insufficiency invariably progresses to end-stage renal failure in patients, just as it does after ablation in rats. Although in some instances the disease responsible for the initial renal injury may remain active throughout the progression to renal failure, more often total GFR continues to decline despite a well-defined initiating process having either remitted spontaneously or been controlled therapeutically.

How much of a reduction in nephron mass must occur to initiate progressive renal disease in the absence of ongoing injury? We know that glomerular sclerosis develops in children born with reduced numbers of functioning nephrons (39, 80, 108), and focal glomerular sclerosis is now recognized with increasing frequency in patients with unilateral renal agenesis (9, 67, 119). The latter circumstance implies that progressive glomerulosclerosis may be initiated by the loss of only a single kidney. Few long-term follow-up studies of patients undergoing uninephrectomy for trauma, localized tumor, or elective organ donation, circumstances in which the remaining kidney is likely to be normal at the time of surgery, have been reported. In a recent survey (48), a disturbingly high incidence of hypertension and proteinuria was found in donors 10 or more years after uninephrectomy, and these findings, in addition to biopsy-proven focal glomerular sclerosis, have been confirmed in several centers (24, 37, 122, 129). A role for hemodynamic factors in the initiation of focal glomerular sclerosis seen in renal transplant recipients has also been suggested (26, 95, 105, 106).
Rats with remnant kidneys exhibit this same tendency to develop proteinuria and hypertension (23, 100, 115). Hostetter and co-workers (56, 94) found that these abnormalities as well as glomerular sclerosis were preceded by so-called “adaptive” increases in glomerular capillary pressures and flows. Figure 9 depicts the marked increases in SNGFR (middle row), due to the similarly marked increases in plasma flow rate (QA) and mean capillary hydraulic pressure (Pc) in remnant glomeruli compared with glomeruli from sham-operated two-kidney control rats (top row). Although not shown, these increases in function were due to afferent arteriolar vasodilation, which served to transmit more flow and pressure from the systemic circulation to the capillaries of remnant glomeruli (56). Moreover, in studies by Azar, Dworkin, and Anderson and their respective associates (4, 6, 33, 34) in several models of hypertension and by Hostetter and others in experimental diabetes (57, 62, 126), a similarly strong association between glomerular pathology and preceding glomerular capillary hypertension and hyperperfusion has also been found. The results support the concept that so-called adaptive hemodynamic changes contribute to the ultimate destruction of hyperfunctioning glomeruli in renal diseases of diverse origin.

Studies in my laboratory also indicate that high protein intake in the presence of renal injury contributes to the increased perfusion of surviving glomeruli and thus to their eventual destruction (56). As shown in the bottom row of Fig. 9, a reduction of dietary protein content from 24 to 6% blunted the hemodynamic changes associated with ablation of renal mass. Glomerular plasma flows and hydraulic pressures remained nearly normal in rats given a low protein diet despite extensive loss of renal mass. SNGFR values were therefore much lower than in animals subjected to a similar degree of renal ablation but fed a standard (24%) protein diet (middle row).

Restoration of glomerular hemodynamics to normal by protein restriction was associated with preservation of glomerular architecture and lessening of proteinuria (55, 56, 94). Indeed, protein restriction, as discussed above, not only retards the progression of nephrotoxic serum nephritis in rats (84, 116), but also prevents glomerular structural alterations and proteinuria in several forms of hypertension in rats (32, 34) and nullifies the expression of diabetic nephropathy in streptozotocin-treated rats otherwise destined to develop severe renal disease (127). In the latter study, rats with streptozoto-
cin-induced diabetes were maintained for 12 mo on daily insulin to reproduce the moderate hyperglycemia typically achieved in insulin-dependent diabetic patients. During these 12 mo they were fed 6, 12, or 50% protein chow ad libitum. Those on 50% protein chow exhibited pronounced elevations in glomerular capillary hydraulic pressures, and in this group 24 h urinary albumin excretion rates rose markedly and progressively over the 12-mo study. In contrast, in rats fed the lower protein diets, glomerular pressures remained at more normal levels, as did urinary albumin excretion. Moreover, the morphological features of diabetic glomerulopathy developed only in the high protein group and consisted of either pronounced mesangial expansion or the more advanced lesion of glomerular sclerosis.

In 1931, Shannon and co-workers (114) observed that changing the diet of dogs from carbohydrate to meat increased renal blood flow and GFR by as much as 100%. This effect has since been duplicated in a variety of species including human (12, 52, 54, 85, 96). Sustained increases in renal perfusion and filtration occur with long-term protein feeding, whereas after ingestion of individual protein-rich meals the hemodynamic changes are more transient. O'Connor and Summerill (85–87) and others (114) have shown that the rise in GFR that follows ingestion of meat by dogs is not reproduced by feeding equicaloric meals of carbohydrate or fat or quantities of urea, sulfate, or acid in amounts equivalent to those produced by catabolism of the meat meal. On the other hand, increases in renal blood flow and GFR can be achieved by oral or intravenous administration of a variety of amino acids (71, 81). Evidence suggests that a circulating hormone(s) is responsible for the increased renal perfusion and filtration induced by protein-rich meals or amino acids, since their renal effects can be blocked in rats (81) and humans (22) by somatostatin. Establishing the identity and mechanism of action of the specific effector(s) are but two of the many interesting issues awaiting resolution in this area.

I assume that the changes in renal function induced by individual high protein meals reflect an early evolutionary adaptation of the kidney to meet the excretory needs of carnivores whose protein intake was intermittent rather than as nearly continuous as it is with us today (5, 21, 41, 53, 75). In Africa's Great Rift Valley, anthropologists have repeatedly unearthed the bones of large fauna lying in close proximity to primitive stone butchering tools (21, 69, 99). These and other clues have helped shape the view that primitive man and earlier hominids (Homo habilis and Homo erectus) had access to high protein meals only intermittently, since such meals came chiefly from successful hunts (5). Anthropologists have also deduced from several lines of evidence that prehistoric man's diet changed abruptly between 3,000 and 10,000 years ago, coincident with the implementation of newly acquired agricultural and herding techniques (36, 76, 111). The result has been a drastic shift to a more continuous pattern of food intake that now exceeds 3,000 cal and 100 g of protein daily in many developed countries.

Does this transformation in dietary habits create a fundamental mismatch between the evolutionary design characteristics of various body organs and the physiological tasks to which they are now exposed? As Robert Ardrey has stated (5):

For millions of years we survived as hunters. In the few short millennia since our divorce from that necessity there has been no time for significant biological change—anaatomical, physiological, or behavioral. ... For a mere one percent [or less] of the history of true man, we have lived under conditions which we now regard as normal.

As serious students of nephrology we too must consider whether, in animals and humans feeding more or less continuously rather than intermittently, we are creating a mismatch between the design characteristics of the kidney and the tasks now imposed by ad libitum intake of high protein foods. In this regard, my colleagues and I (15) recently proposed a hypothetical schema (Fig. 10) to depict the changes in renal function likely to be associated with the shift from intermittent to ad libitum feeding. Consider first the hunter-savenger consuming large meals of meat but only at infrequent intervals, as depicted by the dashed lines in the bottom panel. Such meals would have been rich not only in protein but also in potassium, hydrogen ions, phosphorus, other mineral solutes, and water. We presume that after ingestion of each large meal, vasodilator mechanisms associated with protein feeding serve to increase total renal blood flow and GFR, as illustrated in the top panel (85, 104). In turn, relatively rapid excretion of water, electrolytes, and nitrogenous wastes would be expected to parallel these increases in GFR. In support of this supposition, it has been shown that shortly after dogs are fed modest meat meals, excretions of water, urea, sodium, potassium, and phosphorus increase by as much as 200% or more (86). In contrast to the hyperemic and hyperexcretory pattern of renal function in the immediate postprandial period, renal blood flow and GFR are considered to fall to low base-line levels in the intervals between meals (top panel), facilitating conservation of water and electrolytes while intake is low.

Alternatively, when food is available ad libitum, eating patterns change, as depicted by the solid line in the

![Figure 10](https://example.com/fig10.png)
Individual meals, although smaller, are more frequent, and the aggregate amounts of food and protein consumed increase substantially, as has been confirmed experimentally (121). In turn, renal blood flow and GFR are sustained at high levels (top panel). The renal hyperperfusion and hyperfiltration seen in animals fed ad libitum must reflect the increased perfusion and filtration occurring in individual glomeruli. These glomerular adaptations, in turn, must reflect higher time-averaged glomerular capillary pressures and flows.

Recent evidence obtained in conscious rats offers considerable support for this hypothesis (42). In this study, rats were maintained on unlimited quantities of standard chow either made available daily or only on alternate days. Clearances of inulin and p-aminohippurate (PAH) were measured repeatedly in these conscious animals after 25 wk on the different diet schedules (Fig. 11). As shown by the left bar in each panel, calculated values for renal blood flow (RBF) and GFR were 30% higher on the daily diet than on the day of feeding in rats fed only on alternate days (center bars). And, as indicated by the right bars, fasting day values in the latter group were even lower than on the fed day.

That diets and feeding schedules impact strongly on renal function is supported by several additional lines of evidence. As noted above, studies in renal brush border membrane vesicles derived from rats fed high protein diets revealed an augmentation of Na⁺-H⁺ exchange that correlated closely with the associated hyperfiltration (49). In addition, Seney and co-workers found a substantial increase in ascending thick limb of Henle NaCl transport in rats fed high protein diets (112) and suggest that such augmented salt absorption serves as a tubuloglomerular feedback signal to induce chronic increases in SNGFR (110, 113). Of related interest, Bouby and co-workers (13) recently described a selective increase in the thickness of the inner stripe of the outer medulla in rats fed high protein diets. This disproportionate zonal increase was shown to reflect selective hypertrophy of ascending thick limbs of Henle and also coincided with significant enhancement of urinary concentrating capacity. Moreover, chronic low (8%) protein feeding in rats led to a smaller lumina of thin descending limbs of Henle of short-looped nephrons and a significant thinning of the epithelium of thin descending limbs in long-looped nephrons (109). The morphological changes in the latter study were associated with reduced urea concentrations in papillary tip tissue as well as lower maximal urine concentrating capacity relative to rats fed 24% protein chow.

Returning to the theme of chronic renal failure, I am intrigued with the possibility that augmented intrarenal pressures and flows associated with ad libitum feeding contribute to the marked structural heterogeneity observed in kidneys of older laboratory animals. Progressive glomerular sclerosis, heralded by proteinuria, involves the majority of glomeruli in old rats, mice, hamsters, and dogs (3, 11, 46, 47, 63). Development of lesions can be delayed by making food available on alternate days or by limiting food intake to one-half to two-thirds that consumed by animals fed ad libitum (3, 10, 63, 121, 125).

Age-related studies of renal function in healthy human beings by Shock and associates (27, 107) also indicate that GFR declines progressively after the third decade; values in young adults are roughly half those measured in young adults. And morphologic studies demonstrate sclerosis of up to 40% of the glomerular population between the fourth and eighth decades (64, 65). By itself, age-related glomerular sclerosis poses no threat to well-being, since renal function is generally not seriously compromised even in octogenarians. If, however, intrinsic renal disease or surgical loss of renal tissue adds to the glomerular burden imposed by chronic dietary excess, the course of glomerular sclerosis may be hastened appreciably. Indeed, Thomas Addis suggested more than 35 years ago that ad libitum feeding may contribute to progression of renal insufficiency in humans (1) just as he and the MacKays had earlier found it to do in rats (74). If he were alive today, Addis would hardly be surprised by the recent findings of Maschio, Giordano, Mitch, Donker, and their respective associates confirming that restriction of dietary protein slows considerably and may even halt the progression of many forms of chronic renal disease (31, 43, 79, 82).

Taken together, the foregoing observations in normal aging and in patients and animals with various forms of renal parenchymal loss are consistent with the hypothesis that sustained hyperfiltration [or some hemodynamic determinant(s) thereof] is ultimately detrimental to glomerular structure and function. One possible schema (Fig. 12) portrays reduction in renal mass, systemic hypertension (whether primary or secondary to renal disease), conventionally treated diabetes mellitus, and ad libitum feeding as leading to unremitting renal vasodilation. The resulting long-term elevations in glomerular capillary pressures and flows promote hyperfiltration, impair the perselective properties of the glomerular wall (94), and very likely also injure the component cells of the glomerulus (45). The ensuing glomerular sclerosis exerts a positive feedback stimulus to compensatory adaptation in less affected glomeruli, contributing in turn to their eventual destruction.
Unfortunately, our current treatments for chronic renal insufficiency do little to interrupt these hemodynamic mechanisms of progressive renal failure. Figure 12 also depicts how therapies aimed at preventing excessive glomerular pressures and flows or subsequent steps in the injury process may retard the otherwise relentless progression of clinical renal disease. An obvious first step (denoted 1) should be a reduction of protein intake. Although therapy to bring diastolic blood pressure to the 85–90 mmHg range (2) hardly needs justification today, our recent demonstration (126) of marked protection against renal injury in normotensive diabetic rats given a potent angiotensin I converting enzyme inhibitor suggests that further lowering of diastolic pressure to the 65 70 mmHg range may afford heretofore unexpected renal-sparing effects, a possibility clearly deserving of prompt clinical testing. Anticoagulant and antiplatelet drugs (3) have also proved beneficial in animal studies (93, 101) and in early clinical trials as well (30, 128) and merit further clinical evaluation, as do drugs (4) that interfere with arachidonate metabolism (8, 102). The latter have been shown to lower blood pressure in rats with reduced renal mass (102) but may have other beneficial effects as well. In diabetics, rigid metabolic control achieved by continuous insulin infusion by other means instituted early in the disorder (5) could likewise prove effective in preventing glomerulosclerosis in this high-risk population (103). Short of such rigid metabolic control, a goal difficult to achieve on a wide scale today, aggressive lowering of blood pressure and avoidance of excessive protein intake, as shown in rats (126, 127), can in themselves reduce the risk of glomerular injury in this metabolic disorder. Whether restricting phosphorus intake (6) proves to be of additional benefit, as Alfrey and co-workers have suggested (58), remains an open question in view of recent evidence to the contrary (70, 117).

When should dietary protein modification or any other potentially beneficial therapy be initiated? To date we have generally relied on the use of the reciprocal of the serum creatinine versus time plot to obtain a near-linear profile of progression (82, 83). However, losses of renal function exert little discernible effect on indirect measures of GFR such as serum creatinine concentration, at least until half or more of total filtration power has been lost, and only beyond this point do serum markers clearly exceed normal limits. Not only do such relatively insensitive measures of renal function provide limited information as to the extent of impairment in total GFR, but they fail to provide insight into the state of function of the surviving nephrons, a point made so effectively by Platt (97) in the opening quotation.

A prognostically more useful approach is suggested in Fig. 13. In this example, I consider the forces acting on glomeruli in the course of the most subtle of all forms of chronic renal disease, graceful aging. The bottom panel depicts the nephron population we may regard as typical of the healthy young rat, and presumably a healthy young human adult as well, with SNGFR values for the entire population bunched in a tight Gaussian distribution and with the mean value depicted by the dashed line. By
eating our modern, hence biologically excessive protein diet, a small fraction of the glomeruli at the upper end of the function scale (the hatched area in the bottom panel) is considered to be burdened, due to the adaptive increases in glomerular pressures and flows that account for their relative hyperfiltration. With the passage of time, these glomeruli develop progressive sclerosis and eventually fail so that, as shown in the middle panel, the population is still largely Gaussian and despite the heterogeneity in SNGFR values shown in the top panel of Fig. 13 conforms exactly to Oliver's description of the end-stage kidney, with an abundance of nonfunctioning glomeruli intermixed with those of moderate and supernormal function and, presumably, structural features also running the gamut from atrophic to hypertrophic.

Another example of how this approach can be used is illustrated by the marked expansion of the nephron population in the middle panel in which half the glomeruli may be considered to have SNGFR values identically equal to zero and the remainder accommodating our customary dietary protein excess by adaptive hyperfiltration. The price of the latter, namely high glomerular pressures and flows, contributes in turn to eventual destruction of remaining glomeruli, as depicted in the top panel. Reduction in protein intake at the time of uninephrectomy would, I feel certain, blunt the adaptive hyperfiltration and slow, if not prevent, the ensuing accelerated nephron damage. Diagrams similar to those shown in Figs. 13 and 14 have been constructed by B. R. Dunn and myself for many forms of chronic renal disease and lend considerable insight not only into the magnitude of functional loss but, more important, into the adaptations that accrue from these losses and the attendant risks that patients incur when these adaptations are permitted. Such schemas and their underlying pathophysiological principles argue for early therapeutic intervention in all cases.

I believe we have come to a point in our thinking about the progressive nature of renal disease at which a new paradigm is in order for clinical nephrology, the premise for which can be succinctly stated:

**GLOMERULAR HYPERTENSION, HYPERPERFUSION, HYPERFILTRATION, AND HYPERTROPHY ARE PERNICIOUS IN THE LONG RUN.**

If such is the case, we might ask whether so-called "normal values of GFR" are optimal or whether such high values reflect an unnecessary and undesirable functional burden. The kidneys of vegetarians and others with more moderate protein intake do all they need do for their owners at much lower GFR values (12). How should such so-called "normal function" be evaluated? Should we confirm a functional reserve capacity, as Bosch and associates have suggested (12), by demonstrating that GFR can rise in response to a large meat..
meal or some other acute renal vasodilatatory challenge? If such a rise does not occur, glomerular pressures and flows may be presumed to be at maximal, and therefore potentially harmful, levels. We might also ask whether our modern high protein diet alters human tubule transport functions, as it does in rats, and thereby influences perhaps even clouds our understanding of physiological mechanisms and set points? As physicians, should we be preventing so-called "compensatory hypertrophy," and if so, how? Once again, should our end point be restoration of a functional reserve capacity or are other methods for evaluating potential risk needed? Similarly, should we be preventing the hyperfiltration seen in early diabetics, and, if so, how? At the very least, the common practice of supplementing the protein intake of young diabetics to offset the calorie loss associated with carbohydrate restriction should be seriously questioned. Finally, when antihypertensive drugs are prescribed, especially in patients with renal insufficiency, should these be selected, as they usually are today, on the basis of their ability to preserve or even raise renal perfusion? Might we not be more successful in preserving renal function in the long run with drugs that lower renal perfusion slightly? These are but a few of the questions that spring to mind. With the coming of answers, if supportive of this new paradigm, as I believe they will be, will also come the responsibility for physicians to see to it not only that patients with renal risk factors be identified but that they be given early access to dietary and other beneficial therapies in the hope that we can obviate, or at least postpone substantially, their eventual need for dialysis and/or transplantation.

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Address reprint requests to the author at Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115.

REFERENCES

HOMER SMITH AWARD LECTURE


85. MOWREY, D. KNUTSON, AND B. M. BRENNER. Control of proximal tubule function by 10.220.33.5 on June 22, 2017 http://ajprenal.physiology.org/ Downloaded from


