THE YALE JOURNAL OF BIOLOGY AND MEDICINE 52 (1979), 271-287

Structural and Functional Adaptation after Reduction of Nephron Population

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Received December 8, 1978

This review of adaptive changes in renal structure and function in subjects with reduced renal mass has two primary goals. One is to provide a description of the remarkable compensatory increases in glomerular filtration rate (GFR), and renal blood flow, at the level of individual nephrons, and the alterations in water and electrolyte transport by tubular epithelium. These processes preserve fluid and electrolyte balance in subjects with progressive renal failure, until whole kidney GFR is reduced to about 20 percent of normal, and provide the basis for conservative clinical medical management. The other aim is an attempt to provide an understanding of the mechanisms involved in compensatory adaptation, since this information, in addition to amplifying our understanding of renal transport processes, helps to elucidate the functional limitations placed on subjects with renal insufficiency. An attempt has been made to analyze both clinical observations and relevant experimental models and an effort has been made to correlate renal function with different patterns of renal injury.

The human kidney maintains a constant volume and composition of body fluids by altering the constituents of the final urine. External balance of water, electrolytes, and non-electrolyte substances is preserved by regulation of the rate of reabsorption of glomerular ultrafiltrate and the rate of renal tubular secretory processes. As renal tissue is destroyed by disease or removed by surgery, the excretory load imposed on surviving nephron units increases markedly. Adaptive changes in renal structure and transport properties of surviving nephron units, however, usually preserve homeostasis of water and solutes until overall glomerular filtration rate (GFR) is substantially reduced. Moreover, even in advanced renal failure, the excretory capacity of the kidney is characterized by marked adaptative changes by the individual functioning nephrons. In the present paper, we shall review the structural and functional adaptations which occur in animals and patients with renal insufficiency to preserve the homeostasis of body fluid composition.

In many studies concerned with the adaptational changes in renal insufficiency there has been a tendency to regard all conditions characterized by reduced overall glomerular filtration rate as being comparable. It seems likely, however, that the type of renal damage and pattern of tissue injury have important implications with respect to the compensatory response. For example, after removal of one kidney or large amounts of renal mass by surgical ablation or partial infarction, surviving nephron units are structurally intact and probably exhibit maximal compensatory adaptation. Furthermore, since the cause of renal insufficiency in that circumstance is not progressive, functional adaptations tend to be stable. In contrast, most types of acquired renal disease are progressive and involve irregular patterns of injury. In

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parenchymal renal disease, intact and damaged segments are found in different portions of individual nephrons [1]. Injury involving predominantly the cortex of the kidney results in a different type of functional impairment from one affecting the medulla. These factors, therefore, should be taken into account in an analysis of the compensatory response associated with a decrease in functioning renal mass.

STRUCTURAL ADAPTATIONS: COMPENSATORY RENAL GROWTH

The occurrence of compensatory renal growth in surviving tissue, after reduction of renal mass, is well established. Initiation of that process appears to be quite rapid. After uninephrectomy in rats, for example, an increase in cell membrane production, reflected by the rate of (^{14}C) choline incorporation into phospholipid, is demonstrable within five minutes [2]. A true increase in kidney weight occurs within 24 hours [3] and within one to two weeks renal mass increases 30 to 40 percent [4]. Similar changes probably occur in man, since, in renal transplant donors, the size of the contralateral kidney increases markedly following organ donation [5].

The stimulus for compensatory renal growth, however, results in a different response among the various segments of the nephron. Although all nephron segments increase in length after removal of one-half the initial nephron population, microdissection studies have shown that the greatest change involves the proximal convolution. The volume of proximal and distal tubular segments has been estimated in control animals and in animals with one surviving kidney [6]. Tubular length was estimated by microdissection, while changes in tubular radii were measured in snap frozen kidneys, to reduce distortions induced by fixation. Luminal surface increased 92 percent in the proximal convolution and 47 percent in distal tubule, indicating that compensatory growth results in marked differences in apparent surface area in those nephron segments. In addition to changes in tubular epithelium, the volume of glomeruli and glomerular capillary surface area also increases markedly after surgical ablation of renal tissue [7]. In contrast to the uniform growth patterns that occur after surgical removal of tissue, microdissection studies have emphasized a diversity of structural changes after acute renal injury [8] and in chronic glomerulonephritis in both patients and in animal models of renal disease [9]. Heterogeneity in size and shape of glomeruli and tubules reflect an irregular pattern of irreversible damage, characterized by atretic zones and hypertrophied segments existing along the same nephrons.

The capacity for adaptive structural change appears to correlate directly with the amount of functioning tissue that has been removed. Within four weeks of surgery, involving progressive ablation of renal tissue in the rat, renal mass increased 81 percent after removal of one-half of renal mass and 168 percent after removal of approximately three-fourths of the initial mass, compared with a growth rate of 30 percent in controls [10]. Although the relative importance of hypertrophy and of hyperplasia in the growth response after severe reduction in nephron population has not been determined, the formation of new cells probably plays an important role. Hyperplasia has been estimated to increase the number of new cells by 87 percent in the cortex and by 79 percent in medulla of the remnant kidney within 10 days of surgery [11]. There is no increase, however, in the number of the basic structural and functional units, the nephrons [12].

The primary stimulus for compensatory renal growth has not been elucidated although humoral and/or retained excretory products are probably important determinants. Recent studies have shown that changes in renal electrolyte transport and associated energy-related processes do not stimulate renal growth [13]. The

biochemical events that characterize renal compensatory growth and the factors that influence that process have been comprehensively reviewed [14].

FUNCTIONAL ADAPTATIONS: RENAL BLOOD FLOW AND GLOMERULAR FILTRATE RATE

Surgical reduction of functioning renal mass produces increased renal blood flow and glomerular filtration rate in surviving nephrons. After removal of one kidney in experimental dogs, total blood flow in the contralateral organ rose 50 to 100 percent within one to two weeks [15,16]. In organ donors for kidney transplantation, the clearance of para-amino-hippurate, an estimate of cortical plasma flow, rose 55 percent above preoperative values of one kidney [17]. Changes in the rate of blood flow to surviving nephrons correlate inversely with the amount of functioning tissue and may result in strikingly elevated rates of flow to individual glomeruli and nephron segments. In studies involving progressive surgical ablation of renal tissue in the rat, mean glomerular blood flow rose twofold above control in remaining renal tissue of uninephrectomized animals and fourfold after 70 percent nephrectomy [18]. In experimental models of parenchymal renal disease, there is evidence that blood flow also rose significantly in viable portions of the kidney. Clearance studies in animals with autologous immune complex nephritis (AICN) and anti-GBM glomerulonephritis demonstrated normal levels of blood flow per unit weight of tissue, despite a 50 percent reduction in glomerular filtration rate [19]. Since histologic damage was severe in those types of renal disease, it is clear that blood flow rose significantly in the relatively undamaged portions of the kidney. There is also evidence in experimental models of renal failure of an alteration in the pattern of blood flow distribution, with disproportionate increases in flow occurring in deep cortical and probably medullary zones [20]. Similar studies have not been performed in patients with parenchymal renal disease or after surgical ablation.

Changes in renal hemodynamics have important functional implications. First, the rise in glomerular blood flow provides a means to maintain or increase the rate of glomerular filtration and the filtered load of water and solutes for subsequent excretion. Second, the increase in blood flow to nephron segments favors the excretion of substances derived from tubular secretion since the rate of solute delivery to sites for cellular extraction is increased.

Whether nephron filtration rate increases or falls after renal mass is reduced depends on the cause of renal insufficiency. Surgical removal of tissue is associated with compensatory increases in nephron glomerular filtration rate, which rose 55 percent in the contralateral kidney after uninephrectomy and 140 percent in the remnant kidney after excision of 70 percent of the initial renal mass [4,10]. Supernormal levels of nephron filtration rate have also been found by micropuncture in superficial nephrons of the partially infarcted kidney [21] and in experimental models of pyelonephritis [22]. In contrast to the homogeneous rise to supernormal levels found after surgical ablation of renal mass, marked heterogeneity in single nephron filtration rate has been demonstrated in acute and chronic forms of glomerulonephritis [19,23]. The actual level of nephron glomerular filtration rate in parenchymal renal disease is probably determined by the extent of the injury reaction, duration of disease process, and adequacy of compensatory mechanisms. For example, mean superficial nephron GFR was reduced 50 percent one week after induction of autologous immune complex nephritis [23] but rose to control levels after 5 to 20 months [19]. Individual rates of nephron glomerular filtration rate in this model of glomerulonephritis ranged from markedly depressed to supernormal levels.

The rate of filtration per nephron (SNGFR) may be represented by the formula:

$$SNGFR = K_f (P_{GC} - P_T) - (\pi_{GC} - \pi_T)$$

where K_f is the ultrafiltration coefficient of the glomerular capillaries (hydraulic conductivity per unit area times glomerular surface area), P_{GC} and P_T are the mean glomerular capillary hydrostatic pressure and hydrostatic pressure in tubular fluid, respectively. The symbols π_{GC} and π_T represent the mean colloid osmotic pressure in glomerular capillary plasma and glomerular filtrate, respectively. In this equation, the net driving force for ultrafiltration (P_{UF}) is equal to the difference between hydrostatic and osmotic forces acting across the capillary wall. Using micropuncture techniques, an attempt has been made to analyze the dynamic factors that govern SNGFR in animals with surgical reduction in renal mass and in animals with immunologically induced glomerulonephritis. Following removal of one kidney, reducing nephron population by one-half, GFR in superficial nephrons increased 84 percent and plasma flow to individual glomeruli rose by 79 percent [24]. The compensatory increase in nephron GFR was found to result, in part, from an adaptive increase in transcapillary hydrostatic pressure difference, which rose from 34 to 40 mm Hg, and, in part, from the rise in glomerular plasma flow. The latter change was estimated to account for approximately three-fourths of the increase in nephron GFR. Mean net driving force for ultrafiltration was also found to be significantly increased in the early phase of nephrotoxic serum nephritis, produced by injection of antiglomerular basement membrane antibodies [25]. In that experimental model, mean nephron GFR was not different from normal, despite a fall in K_f. The actual level of nephron GFR was, therefore, apparently determined by the extent to which the increase in P_{UF} was able to offset the fall in K_f.

FUNCTIONAL ADAPTATION: SODIUM EXCRETION

Maintenance of external balance of solutes requires a rate of excretion equal to the rate at which solutes enter body fluids each day. The excretion per nephron, therefore, must increase as the number of surviving nephrons decreases, if the dietary intake and/or endogenous production rate is unchanged. Studies in man with progressive renal disease and in experimental models of renal insufficiency have demonstrated that the capacity to maintain external balance differs for the multiple solutes which are eliminated by the urinary route. A highly efficient adaptive process regulating the urinary excretion of sodium preserves external sodium balance until filtration rate and filtered load of sodium fall to approximately one-twentieth of normal levels [26]. Since an upper limit of nephron excretion of sodium is reached at about that level, a further decline in filtration rate results in retention of sodium and edema formation unless dietary intake is reduced. With respect to other solutes, such as phosphate, non-volatile hydrogen ion, and potassium, a ceiling on the adaptive increase in nephron excretion occurs when overall filtration rate falls to a level of approximately one-fifth of normal [26]. For some solutes, such as urea, adaptive tubular transport changes do not occur and an increase in nephron excretion is dependent upon a rise in filtered load after plasma concentration levels rise.

Sodium salts comprise 90 percent or more of the solute contained in extracellular fluid and determine its actual volume. Although the intestinal tract and sweat glands participate as sodium excretory pathways, sodium balance is governed primarily by the kidney. The bulk of filtered sodium, 60–70 percent, is reabsorbed isoosmotically in the proximal tubule, 25–30 percent is reabsorbed in the loop of Henle, and the remaining 9–10 percent in the distal tubule and collecting duct. The rate of urinary

excretion is determined by small but precise variations in the fraction of filtered sodium reabsorbed by renal tubular cells. As overall glomerular filtration rate and filtered load of sodium decline the maintenance of sodium balance requires a progressive decrease in fractional reabsorption. In severe renal insufficiency, fractional excretion has been shown to achieve levels of 20–30 percent in man [26].

The affector element in the homeostatic system regulating sodium balance presumably senses extracellular fluid volume in some way. An increase in sodium intake in a subject with intact kidney function, or a reduction in nephron population in an individual with constant sodium intake, causes an increase in excretory load per nephron. A reduction in glomerular filtration rate requires a much larger change in fractional sodium excretion than an increase in sodium intake in a person with a normal filtration rate to maintain constant extracellular volume. The filtered load of sodium exceeds 25,000 mEq each day in the person with intact kidney function. An increase in fractional excretion of 0.5 percent results in an increment in sodium excretion of 125 mEq. In contrast, when the filtered load has declined to a level one-tenth of normal, 2,500 mEq per day, an increase in urinary sodium excretion of 125 mEq represents a five percent rise in fractional excretion.

Micropuncture studies in animals with renal insufficiency, including both experimental models of chronic glomerulonephritis and animals with surgical reduction of the nephron population, have shown that final adjustments in regulating overall sodium reabsorption are made primarily at sites beyond the proximal tubule [19,23,27]. In the model of autologous immune complex nephritis, for example, absolute reabsorption in the proximal tubule varied in direct proportion to single nephron filtration rate at levels from 5 to 90 nl per min, as compared with a normal level of approximately 40 nl per min [19]. Moreover, analysis of more distal sites along the nephron by micropuncture, demonstrated that fractional reabsorption by the loop of Henle and distal convolution was also similar to the pattern found in normal non-diuretic animals. The collecting duct system, therefore, probably plays an important role in modulating fractional sodium reabsorption after reduction in nephron population, since fractional excretion of sodium rises in animals with renal insufficiency despite unaltered rates of reabsorption up to the last portions of the distal tubule accessible to analysis. Since the distal tubule and collecting duct, however, reabsorb approximately 10 percent of filtered sodium, a reduction in sodium reabsorption at more proximal nephron sites probably occurs when fractional excretion exceeds that level. This change may result from expansion of the extracellular fluid volume or from the inhibitory action of parathormone on proximal tubule function [28].

Several theories have been proposed to explain the high rates of fractional sodium excretion in subjects with reduced filtration rate. In patients with advanced renal failure, the high plasma levels of urea and other solutes have been held responsible for creating a large solute load for the few residual nephrons, thus impairing the ability of the tubule to maximally reabsorb sodium [29]. Indeed, observations in experimental animals have demonstrated that when the osmotic excretory load per nephron exceeds five to six times normal, a significant increment in fractional sodium excretion rate occurs [30]. This hypothesis, however, fails to explain the wide variation in the ability of patients with renal insufficiency to maintain sodium balance as the intake of sodium is changed despite constant excretory loads of solute per nephron. Moreover, this mechanism fails to explain the progressive rise in fractional sodium excretion in the early stages of chronic renal failure before the occurrence of large increases in solute load in residual nephrons.

A recent report by Danovitch, Bourgoignie, and Bricker [31] has provided a new insight into the nature of the mechanisms regulating sodium excretion in patients with renal failure. Although abrupt reductions in sodium intake caused sodium wasting in patients with severe renal insufficiency, a gradual reduction in dietary sodium intake resulted in a remarkable adjustment of sodium excretion to equal intake. In the five patients examined in their study with glomerular filtration rates varying from 5.2 to 16.0 ml per minute, sodium balance was maintained while ingesting an average of 5 mEq per day, in the absence of a reduction in either plasma volume, glomerular filtration rate, or absolute urea excretion. Although reversibility of the salt-losing tendency in chronic uremia had been demonstrated in animals with a remnant kidney [32], the clinical study was especially dramatic since the subjects had severe parenchymal damage.

Recent interest, particularly from Bricker's laboratory, has focused on the possibility that a "natriuretic hormone" serves as a modulator for sodium excretion in uremia. A natriuretic hormone has also been postulated to increase fractional sodium excretion during volume expansion of subjects with intact renal function [33]. Evidence for the existence of such a factor in renal insufficiency has been reviewed recently [34]. Sera of chronically uremic patients and dogs with high fractional sodium excretion rates contain a factor which inhibits sodium transport by the frog skin and toad bladder, and is natriuretic under experimentally controlled conditions in the rat. This material has also been shown to inhibit sodium transport in the rabbit collecting duct [35]. A factor with the same characteristics is found in the urine of uremic subjects and appears to correlate with the concurrent patterns of sodium excretion [34]. Chemically, the natriuretic factor has a molecular weight of less than 1,000, is inactivated by peptidase enzymes, and appears to be acidic, nonvolatile, and lipid soluble. Future studies concerned with the determinations of chemical composition of this material and its relative biological importance in regulating sodium excretion in chronic renal failure will be awaited with interest.

In addition, intrarenal physical forces, involving changes in post glomerular oncotic pressure and peritubular capillary hydrostatic pressure, have been considered as potentially important factors in the regulation of sodium excretion in renal failure. Studies in normal animals have shown that alterations in oncotic and hydrostatic pressures in peritubular capillaries influence net sodium transport in the proximal tubule [36,37]. As noted above, however, recent evidence suggests that sodium excretion is regulated primarily by adjustments in fractional excretion made beyond the proximal tubule. Moreover, in a series of studies performed in animals with chronic glomerulonephritis, glomerulotubular balance was maintained in proximal tubules despite considerable diversity in nephron filtration rate and structure [19,23]. These findings reduce the likelihood that Starling forces play an important role in regulating sodium transport. For these factors to be important in the regulation of glomerulotubular balance of single nephrons in the diseased kidney, each nephron should be surrounded only by peritubular capillaries from its own efferent arteriole. Since a free communication between peritubular capillaries has been demonstrated [38], it is unlikely that the oncotic pressure in each efferent arteriole is dependent on that nephron's filtration fraction. Volume expansion, however, probably acts to reduce proximal reabsorption of sodium through changes in oncotic pressure within peritubular capillaries. It is possible, therefore, that intrarenal physical forces do play an important role in volume expanded subjects with renal insufficiency, characterized by high levels of fractional sodium excretion exceeding 8–10 percent.

Lastly, high rates of fractional sodium excretion in some patients with renal failure may result from anatomic damage predominantly to tubules and an impaired intrinsic ability to reabsorb sodium [39]. Sodium excretion in this group of patients does not respond to reduction of dietary sodium and requires large salt supplements to prevent volume contraction. Although the question of obligate salt wasting in patients with tubulointerstitial disease should be reevaluated in light of the recent observation on the response to gradual reductions in salt intake, it seems likely that structural damage predominantly to medullary areas impairs sodium conservation [40]. Clinical studies have shown that patients with tubulointerstitial damage excreted larger amounts of sodium while on a low intake of sodium, compared to patients with glomerulonephritis with comparable levels of glomerular filtrate rate [39].

FUNCTIONAL ADAPTATION: DIVALENT IONS

The marked disorder in calcium metabolism that occurs in patients with renal failure has been reviewed elsewhere [41]. Calcium homeostasis is influenced by a fall in intestinal absorption, due to impaired vitamin D metabolism, and by endogenous release of calcium from bone caused by the effects of parathyroid hormone and metabolic acidosis. The tendency of patients with renal insufficiency to retain phosphate (see below) and to have impaired gut calcium absorption is largely responsible for their predictable elevation of serum parathyroid hormone levels. Modifications in the renal handling of calcium in patients with renal insufficiency results in a fall in the absolute rate of calcium excretion. Fractional calcium excretion, however, remains relatively normal until GFR has decreased to 25 to 30 percent of normal; further declines in GFR are associated with increases in fractional calcium excretion [42]. The renal handling of calcium appears to be influenced by several factors. The low absolute excretory rates are related to (1) the fall in filtered calcium load as a consequence of the reduction in overall GFR and the tendency of plasma levels of ionized calcium to decrease [42], and (2) stimulation of tubular reabsorption of calcium by parathormone. The rise in fractional excretion which occurs in advanced renal failure is accompanied by augmented fractional sodium excretion rates and has been associated with the osmotic diuresis that occurs at the more advanced stages of renal insufficiency [42].

The decrease in absolute calcium excretion in patients with renal insufficiency is an appropriate homeostatic response. In normal man ingesting a diet containing approximtely 1,000 mg of calcium per day an additional 200 mg is added to the intestinal pool by secretion [43]. Fecal calcium excretion averages 800 mg per day while total intestinal calcium absorption is about 400 mg per day. Therefore, to maintain body calcium stores at a constant level, the kidney must excrete approximately 200 mg of calcium each day. As renal failure progresses, net intestinal calcium absorption is markedly reduced [44], due in part to a reduction in the dietary intake of calcium, but predominantly due to the fall in the intestinal absorption of calcium [45]. Metabolic balance studies in patients with renal failure indicate that despite low absolute urinary excretion rates, overall balance is achieved or is negative to a minor degree [46,47].

Renal handling of calcium, like that of other electrolytes, is modified by the type of renal damage. Better et al. [42] examined calcium excretion rates in patients with predominantly tubulointerstitial disease and found higher fractional excretion rates compared to patients with predominantly glomerular disease. The enhanced clear-

ance rates in the former group apparently were related to an intrinsic defect in calcium reabsorption since, at any given sodium excretion rate, patients with tubulointerstitial disease had a higher rate of calcium excretion than the patients with glomerular disease. Similarly, azotemic animals with ablation of the renal papilla have significantly higher rates of calcium excretion than azotemic animals with ablation of cortical tissue, despite comparable levels of GFR and sodium and phosphate excretion rates [48]. As pointed out by Coburn [49], the absolute excretion rates of calcium in patients with interstitial disease, although low, may be inappropriately high and thus contribute to a significant overall negative balance.

Phosphate balance is maintained in patients with progressive renal disase on a normal intake until the glomerular filtration rate falls below 25 ml per minute [50]. A further decline in overall renal function results in positive phosphate balance and hyperphosphatemia unless dietary intake is reduced below the usual intake of about 1.0 gm per day. Since urinary phosphate is derived from the glomerular ultrafiltrate, the compensatory mechanism involved in preserving balance in the early stages of renal insufficiency involves a reduction in reabsorption of filtered phosphate. This mechanism fails after fractional excretion reaches levels of 75 to 90 percent. Phosphate reabsorption occurs mainly in the proximal tubule where the rate of net transport exceeds that of water, resulting in a fall in the tubular fluid to plasma ratio of phosphate to values less than 1.0 [51].

Parathyroid hormone plays a key role in the regulation of phosphate reabsorption by depressing net transport, predominantly in the proximal, but also in distal portions of the nephron [52]. The primary mechanism responsible for maintaining normal rates of absolute phosphate excretion in renal insufficiency, through a rise in fractional excretion, involves an increase in levels of parathyroid hormone. Slatopolsky et al. [53] demonstrated a reversal of the high rates of fractional excretion in subjects with severe renal failure after maneuvers were introduced to reduce parathyroid hormone production. Furthermore, parathyroidectomy in animals with renal insufficiency reduces fractional excretion of phosphate to less than one percent [48].

FUNCTIONAL ADAPTATIONS: POTASSIUM SECRETION

Thus far in this analysis, the adaptive mechanisms for increasing nephron excretion rates of solutes, after reduction of nephron population, have involved modifications in net fractional reabsorption. Since urinary potassium derives predominantly from potassium secreted by tubular cells, adaptive changes in the rate of cell uptake of potassium and corresponding rates of addition of cell potassium to tubular urine are required to maintain potassium homeostasis in renal insufficiency. Clinical observations indicate that this process is successful until overall glomerular filtration rate is reduced to approximately one-fifth of normal.

Micropuncture studies have shown that 90 percent or more of filtered potassium is reabsorbed in the proximal tubule and loop of Henle [54]. Potassium secreted by cells lining the distal tubule and collecting duct system, therefore, account for most of potassium excreted in the final urine. The question of which segment, distal tubule or collecting duct, plays the major role in that process is unresolved at the present time. It seems likely, however, that potassium is transported by a transcellular route and that the rate of transport is influenced by the rate of uptake across the basolateral membrane, the intracellular pool of potassium and the electrochemical gradients across the opposing cell membranes, basolateral and luminal. Systemic and intrarenal factors which are known to influence the process of potassium secretion have been reviewed recently [54].

An increase in the excretory load of potassium per nephron results in a rise in secretion rate and appears to involve two processes—one immediate and the other delayed. An acute increase in potassium load provided, for example, by infusing potassium salts, was associated with an immediate rise in urinary excretion [55]. That response suggests that the mechanism for potassium secretion, unsaturated under ordinary conditions, is stimulated by increases in plasma potassium. A chronic increase in excretory load, due to chronic dietary loading, results in a qualitative change in the secretory mechanism. In addition to high baseline rates of potassium secretion, this condition, termed "renal potassium adaptation," is characterized by accelerated rates of secretion during acute infusion of potassium salts compared to normal non-adapted animals [55]. The stimulus for this type of adaptation is undetermined since plasma potassium is normal. It is possible, however, that transient elevations of plasma potassium occur during feeding.

Potassium adaptation also has been demonstrated in animals with renal insufficiency since the excretory load per nephron rises in subjects with renal insufficiency ingesting a normal dietary intake of potassium, due to a reduction in nephron population. In dogs with a unilateral remnant kidney, potassium excretion increased strikingly within 18 hours of contralateral nephrectomy and by 7 days, excretion rates were 146 percent of the concurrent filtered load of potassium in the remnant kidney [56]. The adaptive response for renal potassium handling has been shown to result from the increase in nephron potassium load since adaptation failed to occur in experiments in which potassium intake was reduced proportionately with the decrease in glomerular filtration rate [57].

Fecal excretion of potassium is also important in maintaining potassium balance in patients with renal failure. Balance studies have shown a rise in fecal excretion from a level of 12 percent of intake in normal individuals to an average of 34 percent in patients with renal insufficiency [58]. Evidence has been provided to suggest that fecal potassium is derived from intestinal secretion rather than reduced intestinal absorption, since the amount of stool potassium was unaltered by reduction in intake. Since potassium is secreted by the mammalian colon, in contrast to small bowel where absorption occurs, it seemed likely that potassium adaptation occurs in both epithelia normally poised towards secretion—distal nephron and colon.

Recent studies have analyzed the process of potassium adaptation in colonic mucosal cells and provide insight into the mechanism leading to accelerated rates of potassium movement. Chronic dietary loading in animals with intact kidney function [59] and reduction in nephron population in animals maintained on a normal diet [60] resulted in colonic potassium adaptation. Secretion was elevated in experimental animals above control levels under baseline conditions and during the acute intravenous administration of potassium salt. The capacity to respond to acute loading with an augmented rate of net secretion was associated with two characteristics, (1) an increase in the specific activity of Na-K-ATPase, and (2) an increase in transmural electrical potential difference.

Similar features also characterize renal potassium adaptation. An increase in Na-K-ATPase activity in outer medullary tissue occurs in both potassium loaded rats [61] and in animals with renal insufficiency [57]. Although the electrical characteristics of the distal nephron have not been studied in animal models of renal failure, a marked increase in luminal negativity along the distal tubule has been found in potassium loaded rats [62].

Unidirectional movement of potassium by transport epithelia involves cellular uptake across the basolateral membrane via a process that requires the Na-K-ATPase

pump. It is not certain whether cell uptake occurs against an electrochemical gradient or not. Once within the cell potassium moves down an electrochemical gradient, across the luminal membrane, by passive forces. Adaptation appears to occur because of a change in two steps in transcellular movement. First, the elevated activity of Na-K-ATPase is thought to result from an increase in the number of pump sites along the basolateral membrane involved in cell uptake of potassium. Second, the increase in luminal negativity increases the downhill electrochemical gradient for the movement of potassium from capillary blood to luminal fluid. The primary factor responsible for these changes has not been defined. It is uncertain, for example, whether the electrical and enzymatic alterations are secondary to an increase in the rate of cell entry of sodium from luminal fluid. This change would be expected to depolarize the luminal membrane, thus increasing transepithelial potential difference, and increase extrusion of cell sodium across the basolateral membrane. The Na-K-ATPase pump is thought to also participate in transepithelial sodium movement and an increase in enzyme activity correlated with elevated rates of net absorption [63]. Alternatively, a rise in cell potassium concentration, due to a primary increase in cell uptake, could result in hyperpolarization of the basolateral membrane. Hopefully, the further elucidation of this process will provide greater understanding of the adaptive cellular mechanism for enhancing potassium secretion in both the distal nephron and colon.

Although it has not been established which distal portion of the nephron is primarily responsible for potassium adaptation, recent studies have indicated that medullary structures are important for maximal excretion rates to occur. The response to acute infusion of potassium salts was blunted in animals with renal insufficiency due to surgical damage to the inner medulla, compared to animals with a similar degree of renal insufficiency, produced by surgical ablation of the cortex [64]. Correlation between different types of renal damage and the capacity to excrete potassium may have important clinical implications with respect to the ability of patients to avoid the lethal effects of hyperkalemia.

FUNCTIONAL ADAPTATIONS: ACID EXCRETION

On a normal diet the rate of metabolic hydrogen ion production in man equals 50 to 100 mEq daily. The term "metabolic hydrogen ion" refers to hydrogen ions produced in association with anions other than HCO_3^- and not eliminated from the body by respiration. External balance of hydrogen ion, therefore, requires the net excretion rate to equal the production rate and, as overall renal function declines, a proportional increase in excretion rate of hydrogen ions in surviving nephrons. Compensatory mechanisms are usually successful in increasing total excretion of hydrogen ions in surviving nephrons, thus avoiding metabolic acidosis, until GFR falls to about 20 percent of normal.

Metabolic hydrogen ions are excreted by the kidney in three chemical forms: (1) as free hydrogen ions, (2) as ammonium ions, NH_4^+, and (3) as titratable acid. The amount of free hydrogen ion excreted in urine is exceedingly small, but since this quantity determines urine pH, its influence on the amount of hydrogen ion excreted in the other two forms is of major importance. On a normal diet, healthy kidneys excrete about 60 percent of metabolically produced hydrogen ion as ammonium ions each day, and the remaining 40 percent as titratable acid. Total hydrogen ion present in the urine can, therefore, be determined as the sum of NH_4^+ and titratable acid excretion. In order to determine net hydrogen ion excretion, the quantity of bicarbonate ion in the urine must also be taken into account since each bicarbonate

ion in the urine results in net loss of one H+ ion. Thus, net hydrogen ion excretion is equal to the sum of the rates of NH_4^+ and titratable acid excretion minus the rate of bicarbonate excretion.

Hydrogen ion is secreted by renal tubular cells and results in the development of a large H+ gradient between tubular urine and blood [65]. Normal subjects and patients with renal failure can produce urine with a pH as low as 4.5, when appropriately stimulated. Compared to blood, therefore, with a pH of 7.4, a concentration difference of 1,000 to 1 can be established in final tubular urine. The ability to maintain a high concentration of H^+ in tubular urine appears to depend on the conductivity of the luminal cell membrane for hydrogen ion [66] which decreases along the course of the nephron. Micropuncture measurements have shown that the tubular fluid pH gradually falls along the proximal tubule to about 7.0 and declines further in the distal tubule to a value of approximately 6.5 [67]. Direct catheterization of the papillary collecting ducts has demonstrated that a further sharp drop in pH occurs in that segment [68]. These data indicate that hydrogen ion secretion occurs along the entire length of the nephron but that the collecting duct system has a special role because of the capacity of that portion of the nephron to develop a minimally low pH.

In order for hydrogen ions secreted into tubular fluid to result in net hydrogen ion excretion, bicarbonate ions must be effectively reabsorbed from the glomerular filtrate. In the human kidney with a normal filtration rate, the magnitude of this process exceeds 4,000 mEq per day. This process requires careful regulation since an impairment of 1 to 2 percent in efficiency could neutralize the entire net hydrogen ion excreted. Micropuncture analysis has shown that most of filtered bicarbonate in normal animals in acid-base balance is reabsorbed along the proximal tubule, leaving approximately 10 percent of the filtered load to enter the early distal tubule [69]. The extent of this process, however, is variable and is regulated by a number of factors including pCO_2, potassium and chloride balance, and the relative volume of extracellular fluid [70]. It has also been shown that parathormone reduces bicarbonate reabsorption in the proximal tubule. Considerable attention has been given to a possible impairment in bicarbonate reabsorption in chronic renal failure, resulting in a bicarbonate leak. Relman, for example, has argued that the mechanism for bicarbonate conservation is impaired in patients with progressive renal disease since bicarbonate excretion persists in some individuals despite a fall in plasma levels to values below 22 to 24 mEq/L [71]. He has regarded this finding as evidence for a defect in renal bicarbonate handling. Recently a supernormal capacity for renal bicarbonate reabsorption has been demonstrated in the dog with a remnant kidney, characterized by an increased threshold and elevated maximal reabsorption capacity when those functions are factored by GFR [72]. The observations, made in man with diffuse parenchymal disease and in the dog with segmental renal infarction, are probably not contradictory since in the first case structural damage is most likely heterogeneous and in the second surviving nephrons were structurally intact and homogeneous and compensatory growth was predominant in the proximal tubule.

Studies in patients with renal insufficiency have shown that titratable acid excretion remains normal or is reduced only slightly as renal failure advances [73,74]. Titratable acid is formed predominantly from phosphate salts. Phosphate is present in large amounts in urine and its pK is midway between the pH of plasma and the minimal urine pH. Thus, the phosphate buffer system is optimal for buffering urine. The persistence of relatively unimpaired rates of total titratable acid excretion as the nephron population declines is associated with the progressive rise in fractional

excretion of phosphate and is linked, therefore, to the mechanism which maintains external phosphate balance. As discussed earlier, these processes maintain normal absolute excretory rates of phosphate until the GFR falls to a level of approximately 25 ml/min [75].

In addition to the availability of adequate amounts of dibasic phosphate to H^+ secretory sites along the nephron, the formation of titratable acid is dependent upon two additional factors. First, since titratable acid formation is inversely dependent on pH, the ability of patients with chronic renal disease to lower urinary pH to levels produced by healthy kidneys is an important determinant [74]. Second, in order to increase titratable acid formation as more phosphate buffer is made available to secretory sites, an increase in the rate of H^+ secretion is required. Studies in normal individuals and patients with renal failure have demonstrated that the rate of H^+ secretion was adjusted to maintain a fairly constant pH despite variations in the rate of excretion of buffer ions [74,76]. During administration of neutral phosphate, a linear increase in titratable acid excretion occurred, predicted solely on the limits imposed by blood and urine pH. These data indicate this titratable acid formation was not limited by H^+ secretory rate.

The urinary excretion of ammonium, NH_4^+, provides the second major pathway for the excretion of H^+. Studies of patients with advanced renal failure have shown that metabolic acidosis primarily results from a marked reduction in ammonium excretion [77]. Although the decline in ammonium excretion was initially thought to result from an impairment in ammonia production by renal tubular cells, subsequent studies in man [73] and in experimental animals [78,79] have shown an adaptive increase in ammonium excretion per nephron. It seems likely, therefore, that despite compensatory adjustments to increase the formation and excretion of ammonium by residual nephrons that process is inadequate to maintain normal levels of excretion when renal mass becomes severely reduced.

The cause of this adaptive change in nephron excretion of ammonium has not been defined, although the presence of systemic acidosis can be expected to stimulate cell production of ammonia, as occurs in normal subjects. In a study of patients with severe renal insufficiency, the failure to increase ammonium excretion further during chronic administration of exogenous NH_4Cl was interpreted as suggesting near maximal levels of ammoniagenesis under baseline conditions [80]. A rise in cellular production independent of acidosis may also be operative in the early stages of renal insufficiency, since an increase in *in vitro* production rates of ammonia has been demonstrated in slices of renal tissue obtained from animals with a remnant kidney and a normal blood pH [81]. Further studies are needed to provide a better understanding of ammonia metabolism in renal failure and of factors that may contribute to compensatory changes in NH_4^+ excretion. For example, ammonia production has not been determined *in vivo* in either animal models of renal failure or in patients with renal disease. Furthermore, although NH_4^+ excretion rates have been examined in severe renal failure, there is a paucity of information on ammonia metabolism in the early stages of renal insufficiency.

Clinical and laboratory studies have shown that the capacity to excrete NH_4^+ in chronic renal disease is influenced by the type of renal injury. For example, the minimal urine pH was significantly elevated above normal in patients with predominantly tubulointerstitial disease [74]. Impairment in urinary acidification would be expected to reduce the ability to excrete both ammonium and titratable acid. In addition, after surgical removal of the renal papilla in rats a marked blunting of NH_4^+ excretion was found, although there was no impairment in ability to achieve

normal urine pH, compared to normal animals or animals with a remnant kidney [64]. The mechanism responsible for reduced ammonia excretion was not determined. Since a renal cortico-medullary gradient for ammonia has been demonstrated in normal animals [82] and probably plays a role in regulating urinary NH_4^+ excretion, it is possible that disruption of that process in diseases characterized by medullary damage reduces the absolute amount of ammonia diffusing into tubular urine.

With respect to compensatory mechanisms involved in maintaining H^+ balance in renal failure, there is evidence that extra-renal factors are also important. Lemann first called attention to the possible role of bone tissue as a buffer source in chronic metabolic acidosis [83]. He found that despite a positive cumulative H^+ balance in normal subjects receiving a heavy load of hydrogen ion, serum bicarbonate levels reached a steady-state and calcium balance was persistently negative. Similar findings have been made in patients with chronic renal failure and suggest that acidosis stimulates the exchange of hydrogen ions for other cations, particularly calcium in bone [84]. Bone tissue, therefore, may provide a large reservoir for buffering H^+. As a result of this function, acidosis may have an important action in the development of bone disease in patients with chronic renal failure.

FUNCTIONAL ADAPTATION: CONCENTRATING AND DILUTING ABILITY

The loss of concentrating ability by the kidney in chronic renal failure is a common occurrence. As renal disease advances, maximal urinary osmolality falls progressively from a normal level of 800 to 1,000 mOsm/Kg H_2O toward a value of approximately 300 mOsm/Kg H_2O—a condition termed isosthenuria. In some patients with renal injury involving medullary structures predominantly, a hypotonic urine may be elaborated [85].

An understanding of the mechanism of the concentrating defect in the diseased kidney must take into account known factors involved in urinary concentration in the intact kidney. This subject has recently been extensively reviewed [86].

It has been suggested that the capacity to transfer Na+ and Cl^- across the tubular epithelium of the ascending limb into the medullary interstitium proceeds normally in chronic renal disease. In micropuncture analysis of late proximal and early distal tubular fluid, fractional reabsorption of ions in the loop has been observed to be normal in rats with a remnant kidney [87], chronic pyelonephritis [88], and immunologically induced renal disease [23]. However, at the higher rate of solute excretion per nephron, due to the osmotic diuresis that occurs in severe renal failure, solute reabsorption in the loop was probably reduced. Moreover, in the experimental studies cited, only nephrons with short loops were examined and it is possible that nephrons with loops extending into the inner medulla may have different functional characteristics.

An osmotic diuresis increases urine flow rate and reduces U/P osmolality ratios. The mechanism for this effect involves the impairment in sodium chloride reabsorption in proximal nephron segments, the delivery of larger amounts of isotonic or hypotonic fluid to the collecting duct system, and impaired outflux of water from tubular urine due to the presence of non-absorbable substances [89,90]. Although increased delivery of water to collecting duct sites results in proportional rises in free water absorption ($T^c_{H_2O}$), the urine to plasma osmolality ratio falls. This latter effect may result from a shift in the point away from the cortex and outer medulla and toward the papilla where hypotonic fluid passes to isotonicity. Since absolute water

absorption is greater in passing from hypotonicity to isotonicity, than during the change from isotonicity to hypertonicity, it is possible that dilution of the interstitium in the inner medulla and papilla may reduce maximum U/Posm.

Other factors than the increased solute load per nephron are important determinants of the impaired concentrating ability of patients with renal failure. Thus, when the solute load per unit of GFR was increased in normal subjects to levels observed in patients with renal failure, maximum U/P osmolality and $T^c_{H_2O}$ remained significantly greater in the subjects with normal renal function [91]. Damage to the medullary vasculature with subsequent derangement of the counter current system and wash out of medullary solutes by increased medullary blood flow may be important factors responsible for the failure to generate a normal cortico-papillary concentration gradient in patients with renal failure. These mechanisms may be relatively important since Gilbert et al. [92] have recently demonstrated a defect in intrarenal recycling of urea in rats with pyelonephritis and a functional "urea sink" in the inner medullary regions which obliterates the normal concentration gradient for Na^+, Cl^-, and urea. In addition, in some patients with predominantly medullary damage, a change in the permeability of the collecting duct epithelium to water may further contribute to the concentrating defect.

Patients with renal insufficiency fail to reduce urine osmolality to normal levels and exhibit reduced free water clearance (C_{H_2O}) [93]. This impairment was felt to be largely due to the effects of the osmotic diuresis that accompanies substantial reductions in glomerular filtration rate. Thus, in patients [93] and various experimental models [90], both the rate of free water clearance per unit GFR (C_{H_2O})/GFR) and the production of urine with low osmolality during water diuresis has been shown to be similar to values obtained in normal subjects whose solute load per unit GFR was increased to values observed in patients with renal failure. It must be recalled, however, that the quantitative excretion of free water falls in proportion to GFR and, therefore, patients with renal failure are more susceptible to water intoxication and hyponatremia than an individual with intact renal function receiving the same absolute water load.

CONCLUSION

It is apparent from observations made in patients with renal disease and in animals with reduced glomerular filtration rate that renal tissue is capable of remarkable adaptive changes in structure and function. These changes attempt to preserve the homeostasis of body fluid composition as renal tissue is progressively damaged or destroyed. Our comprehension, however, of these processes remains, in large part, phenomenologic. Investigative efforts have provided a better understanding of the overall characteristics of the adaptive response and the role of individual nephron segments in compensatory changes. Little insight, however, has been provided into the basic processes which govern alterations in renal growth or cellular transport mechanisms. Further studies designed to examine many unresolved questions concerned with structural and functional adaptation after reduction in nephron population are likely to disclose intriguing aspects of regulation in biological systems.

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