Implications of Low Nephron Number at Birth David Barker was the first to describe the association between low birth weight and later cardiovascular death. This was followed by studies relating low birth weight to risk for diabetes, stroke, hypertension, and CKD. It has been found that there is an inverse relationship between nephron number and blood pressure in adults. This relationship was found in Caucasians but not in African Americans. Approximately one-third of children with a single functioning kidney at the age of 10 years had signs of renal injury as determined by the presence of hypertension, albuminuria, or the use of renoprotective drugs. Another study revealed that 20–40% of patients born with a single functional kidney had renal failure requiring dialysis by 30 years of age.

ADAPTIVE RESPONSES OF THE KIDNEY TO REDUCED KIDNEY MASS THAT CHARACTERIZES CHRONIC KIDNEY DISEASE

In the early stages of CKD, there are many adaptations structurally and functionally that limit the consequences of the loss of nephrons on total-body homeostasis. In later stages of disease, however, these adaptations are insufficient to counteract the consequences of nephron loss and in fact often become maladaptive.

Counterbalance Renal counterbalance was defined by Hinman in 1923 as "an attempt on the part of the less injured or uninjured portion (of the kidney) to take over the work of the more injured portion." Hinman defined "renal reserve" to be of two types: "native reserve, which is the normal physiological response to stimulation . . . and acquired reserve, which involves growth or compensation due to overstimulation." It was known that removal of one kidney results in an increase in size of the contralateral kidney. If, instead of nephrectomy, one kidney is rendered ischemic and the other left intact, there is a resultant atrophy of the postischemic kidney. If the contralateral kidney is removed, however, before the atrophy becomes too severe, then the postischemic kidney increases markedly in size. With the contralateral kidney in place, there is vasoconstriction and reduced renal blood flow to the postischemic kidney. This is rapidly reversed, however, when the contralateral normal kidney is removed. The factors responsible for the persistent initial (prenephrectomy) vasoconstriction and those responsible for the rapid vasodilation and enhanced growth after contralateral nephrectomy are unknown.

Hypertrophy Because nephrons of mammals, in contrast to those of fish, cannot regenerate, the loss of functional units of the kidney, either due to disease or surgery, results in anatomic and functional changes in the remaining nephrons. As described above, there is increased blood flow to remaining glomeruli with potentially adverse effects over time of the resultant increased size of the remaining glomeruli and hyperfiltration (Fig. 333e-1). In addition, there is hypertrophy of the tubules. Some of the mediators of this hypertrophy of the remaining functional tubules are listed in Table 333e-2. In the adult, within a few weeks after unilateral nephrectomy for donation of a kidney, the GFR is approximately 70% of the prenephrectomy value. It then remains relatively stable for most patients over 15–20 years. The hyperfiltration is related to an increase in renal blood flow likely secondary to dilatation of the afferent arterioles potentially due to increases in nitric oxide (NO) production. The rate of increase in GFR is slower in the adult than it is in the young after nephrectomy. There are a number of factors that have been implicated at the cellular and nephron level to account for the compensatory hypertrophy that ensues after removal of functional nephrons (Table 333e-2).

With increased blood flow to the kidney, there is glomerular hypertension (i.e., an increase in glomerular capillary pressure). There is increased wall tension and force on the capillary wall that is counteracted by contractile properties of the endothelium and elastic properties of the glomerular basement membrane. The force is conveyed to podocytes, which adapt by reinforcing cell cycle arrest and increasing cell adhesion in an adaptive attempt to maintain the delicate architecture of the interdigitating foot processes. Over time, however, these increased forces due to glomerular hypertension lead to podocyte damage and glomerulosclerosis.

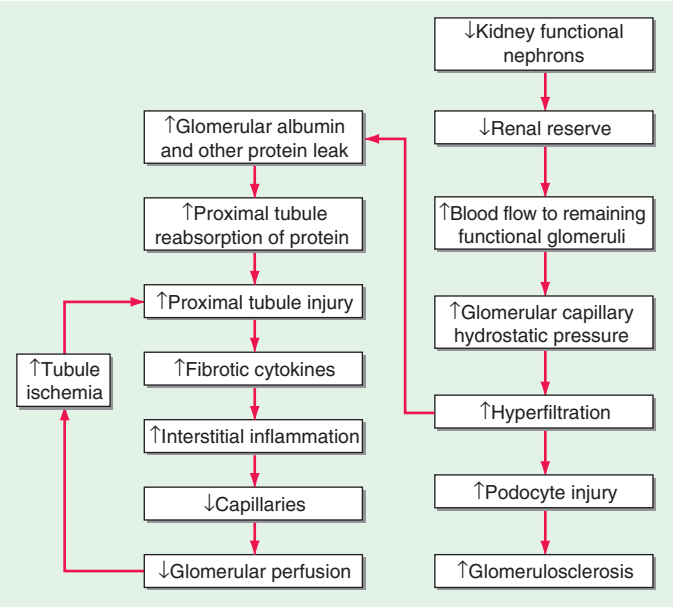

FIGURE 333e-1 Some of the pathophysiologic mechanisms involved with the maladaptive response to a reduction in the number of functional nephrons due to prenatal factors or postnatal disease processes.

Other Systemic and Renal Adaptations to Reduced Nephron Function With reduced functional nephrons, as is seen in CKD, there are many other systemic adaptations that occur to preserve the *milieu intérieur* because the kidney is involved in so many regulatory networks that are then stressed when there is dysfunction. In the 1960s, Neil Bricker introduced the "intact nephron hypothesis." According to his concept, with decreases in the number of functioning nephrons, each remaining nephron has to adapt to carry a larger burden of transport, synthetic function, and regulatory function.

POTASSIUM Under normal and abnormal conditions, most of the filtered potassium is reabsorbed in the proximal tubule so that excretion is determined by secretion by the distal nephron. Potassium handling is altered in CKD protecting the organism somewhat from lethal hyperkalemia. Hyperkalemia is a common feature of individuals with CKD. Hyperkalemia (if not severe and dangerous) is adaptive in that it promotes potassium secretion by the principal cells of the collecting duct. When patients with CKD are given a potassium load, they can excrete it at the same rate as patients with normal renal function except that they do so at a higher serum potassium, consistent with the view that the hyperkalemia facilitates potassium excretion. The direct effect of hyperkalemia on potassium secretion by the distal nephron is independent of changes in aldosterone levels, but "normal" levels of aldosterone are necessary to see the effect of hyperkalemia on potassium excretion. Elevated potassium stimulates the production of aldosterone, and this effect is also seen in patients with CKD. Aldosterone increases the density and activity of the basolateral Na^+-K^+ ATPase and

TABLE 333e-2 FACTORS IMPLICATED IN COMPENSATORY RENAL GROWTH AFTER NEPHRON LOSS

Increased renal blood flow
Increased tubular absorption of Na with decreased distal delivery and decreased afferent arterial resistance due to adaptive tubuloglomerular feedback
Hepatocyte growth factor
Glucose transporters
Increased renal nerve activity
Insulin-like growth factor
Mammalian target of rapamycin (mTOR) signaling pathway activation
$p21^{Waf1}$, $p27^{kip1}$, and $p57^{kip2}$
Transforming growth factor β