333e Adaptation of the Kidney to Injury

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Many years ago Claude Bernard (1878) introduced the concepts of *milieu extérieur* (the environment where an organism lives) and a *milieu intérieur* (the environment in which the tissues of that organism live). He argued that the milieu intérieur varied very little and that there were vital mechanisms that functioned to maintain this internal environment constant. Walter B. Cannon later extended these concepts by recognizing that the constancy of the internal state, which he termed the *homeostatic state*, was evidence of physiologic mechanisms that act to maintain this minimal variability. In higher animals, the plasma is maintained remarkably constant in composition both within an individual and among individuals. The kidney plays a vital role in this constancy. The kidney changes the composition of the urine to maintain electrolyte and acid-base balance and can produce hormones that can maintain constancy of blood hemoglobin and mineral metabolism. When the kidney is injured, the remaining functional mass responds and attempts to continue to maintain the milieu intérieur. It is remarkable how well the residual nephrons can perform in this task so that in many cases homeostasis is maintained until the glomerular filtration rate (GFR) drops to very low levels. At this point, the functional tissue can no longer compensate. In this chapter, we will discuss a number of these compensatory adaptations that the kidney makes in response to injury in an attempt to protect itself and protect the milieu intérieur. A theme that permeates, however, is that these adaptive processes can often be maladaptive and contribute to enhanced renal dysfunction, facilitating a positive feedback process that is inherently unstable.

RESPONSES OF THE KIDNEY TO REDUCED NUMBERS OF NEPHRONS DURING DEVELOPMENT

Renal disease is associated with a reduction in functional nephrons. The rest of the kidney adapts to this reduction by increasing blood flow to and the size of the remaining glomeruli and increasing size and function of the remaining tubules. Robert Platt, in 1936, argued that "…a high glomerular pressure, together with loss of nephrons (destroyed by disease) [is] an explanation of the peculiarities of renal function in this stage of kidney disease." The raised glomerular pressure will increase the amount of filtrate produced by each nephron and thus compensate for a time for the destruction of part of the kidney. But eventually there are too few nephrons remaining to produce an adequate filtrate, even though they may work under the highest possible pressure, associated with a high systemic blood pressure. The responses to kidney injury can be both adaptive and maladaptive, and in many cases, the early adaptive responses can become maladaptive over time, leading to progressive decline in the anatomic and functional integrity of the kidney. As described previously, the early responses are likely in many cases motivated by attempts to maintain the constancy of the milieu intérieur for the survival of the organism (Claude Bernard).

Barry Brenner in the 1960s and 1970s carried out micropuncture experiments to define the pressures in glomerular capillaries as well as afferent and efferent resistances and modeled the behavior of the factors that governed glomerular filtration in health and disease. According to the Brenner Hyperfiltration Hypothesis, a reduction in the number of nephrons results in glomerular hypertension, hyperfiltration, and enlargement of glomeruli and this hyperfiltration results in damage to those glomeruli over time and ultimately decreased kidney function. According to this hypothesis, a positive feedback process is set into motion whereby injury to the glomeruli will result in further hyperfiltration to other glomeruli and hence more accelerated injury to those glomeruli. Since nephrons are not generated after 34–36 weeks of gestation or after birth (if earlier than 34–36 weeks) in humans, this hypothesis implies a deterministic effect of low nephron numbers at birth. There is over a 10-fold variation in the number of nephrons per kidney in the population (200,000 to over 2.5 million). This variation is not explained by kidney size in the adult. Children born with low birth weights would be more prone to kidney disease as adults. There are many reasons why there might be reduced nephron numbers at birth: developmental abnormalities, genetic predisposition, and environmental factors, such as malnutrition. There are thought to be interactions between these various factors. Reduced nephron mass can also occur with chronic kidney disease (CKD) in the adult, and the response of the kidney is similar qualitatively with hyperfiltration of the remaining nephrons.

Developmental Abnormalities There are many congenital abnormalities of the kidney and urinary tract (CAKUT). Dysplastic kidneys have varying degrees of abnormalities that interfere with their function. Anatomically abnormal kidneys can be associated with abnormalities of the lower urinary tract. Urinary tract abnormalities resulting in obstruction or vesicoureteric reflux can dramatically alter the normal development of the kidney nephrons. Dysplastic or hypoplastic kidneys can be cystic in patterns that are distinct from polycystic kidney disease. Of course, autosomal recessive kidney disease can result in widespread cyst formation.

Hypoplastic kidneys are characterized by a reduced number of functional nephrons. One definition of hypoplastic kidneys is as follows: "Kidney mass below two standard deviations of that of age-matched normal [individuals] or a combined kidney mass of less than half normal for the patient's age." Renal agenesis and cystic dysplasia often affects only one kidney. This results in hypertrophy of the other kidney if it is unaffected by any congenital abnormality itself. Although there is hypertrophy in size, it is not clear if this is associated with an increase in the number of nephrons on the contralateral side.

The prevalence of CAKUT has been generally found to be between 0.003 and 0.2%, depending on the population studied. This excludes fetuses with transient upper renal tract dilatation likely related to the high rate of fetal urine flow rate. In the adult U.S. Renal Data System (USRDS) of patients with end-stage kidney disease, approximately 0.6% are listed as having dysplastic or hypoplastic kidneys as a primary cause of the disease. This is likely an underestimate, however, because many patients with "small kidneys" may be misdiagnosed with chronic glomerulonephritis or chronic pyelonephritis.

Environmental Contributions to Reduced Nephron Mass The most important environmental factor responsible for reduced nephron number is growth restriction within the uterus. This has been associated with disease processes such as diabetes mellitus in the mother, but there also is a strong genetic disposition. Low-birth-weight children are more likely to be born to mothers who, themselves, were born with low birth weight. There are clearly other environmental factors. Caloric restriction during pregnancy in humans has been associated with altered glucose as adults and increased risk for hypertension. In one study, it was found that if women were calorie restricted in midgestation, the time of most rapid nephrogenesis, there was a threefold incidence of albuminuria in their children when they were tested as adults. Factors such as deficiency in vitamin A, sodium, zinc, or iron have been implicated as predisposing to abnormal kidney development. Other environmental factors that can influence kidney development are medications taken by the mother, such as dexamethasone, angiotensin-converting enzyme inhibitors, and angiotensin receptor antagonists (Table 333e-1). Protein restriction in mice during pregnancy can reduce lifespan of the offspring by 200 days. Obesity may play an important role in determining kidney outcome long term in patients with reduced kidney mass. It has been shown in mice fed a high-fat diet that the rodents that had reduced nephron number had a greater incidence of hypertension and renal fibrosis.

TABLE 333e-1 DRUGS THAT INHIBIT NEPHROGENESIS

Dexamethasone
Angiotensin-converting enzyme inhibitors
Angiotensin receptor blockers
Gentamicin
Nonsteroidal anti-inflammatory drugs