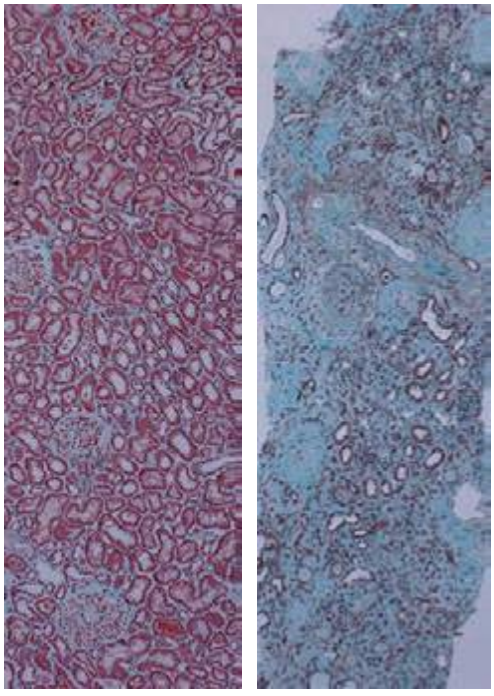

FIGURE 335-3 ***Left:*** Low-power photomicrograph of a normal kidney showing normal glomeruli and healthy tubulointerstitium without fibrosis. ***Right:*** Low-power photomicrograph of chronic kidney disease with sclerosis of many glomeruli and severe tubulointerstitial fibrosis (Masson trichrome, ×40 magnification). *(Slides courtesy of the late Dr. Andrew Herzenberg.)*

The equations for estimating GFR are valid only if the patient is in steady state, that is, the serum creatinine is neither rising nor falling over days.

Measurement of albuminuria is also helpful for monitoring nephron injury and the response to therapy in many forms of CKD, especially chronic glomerular diseases. Although an accurate 24-h urine collection is the standard for measurement of albuminuria, the measurement of protein-to-creatinine ratio in a spot first-morning urine sample is often more practical to obtain and correlates well, but not perfectly, with 24-h urine collections. *Microalbuminuria* (Fig. 335-1, stage A2) refers to the excretion of amounts of albumin too small to detect by urinary dipstick or conventional measures of urine protein. It is a good screening test for early detection of renal disease, and may be a marker for the presence of microvascular disease in general. If a patient has a large amount of excreted albumin, there is no reason to test for microalbuminuria.

Stages 1 and 2 CKD are usually not associated with any symptoms arising from the decrement in GFR. If the decline in GFR progresses to stages 3 and 4, clinical and laboratory complications of CKD become more prominent. Virtually all organ systems are affected, but the most evident complications include anemia and associated easy fatigability; decreased appetite with progressive malnutrition; abnormalities in calcium, phosphorus, and mineral-regulating hormones, such as $1,25(OH)_2D_3$ (calcitriol), parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF-23); and abnormalities in sodium, potassium, water, and acid-base homeostasis. Many patients, especially the elderly, will have eGFR values compatible with stage 2 or 3 CKD. However, the majority of these patients will show no further deterioration of renal function. The primary care physician is advised to recheck kidney function, and if it is stable and not associated with proteinuria, the patient can usually be managed in this setting. However, if there is evidence of decline of GFR, uncontrolled hypertension, or proteinuria, referral to a nephrologist is appropriate. If the patient progresses to stage 5 CKD, toxins accumulate such that patients usually experience a marked disturbance in their activities of daily living, well-being, nutritional status, and water and electrolyte homeostasis, eventuating in the *uremic syndrome.*

TABLE 335-1 RECOMMENDED EQUATIONS FOR ESTIMATION OF GLOMERULAR FILTRATION RATE (GFR) USING SERUM CREATININE CONCENTRATION (S_{CR}), AGE, SEX, RACE, AND BODY WEIGHT

1. Equation from the Modification of Diet in Renal Disease study
Estimated GFR (mL/min per 1.73 m^2) = $1.86 \times (S_{Cr})^{-1.154} \times (age)^{-0.203}$
Multiply by 0.742 for women
Multiply by 1.21 for African ancestry
2. CKD-EPI equation
$GFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age}$
Multiply by 1.018 for women
Multiply by 1.159 for African ancestry
where S_{Cr} is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of S_{Cr}/κ or 1, and max indicates the maximum of S_{Cr}/κ or 1.

Abbreviation: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

ETIOLOGY AND EPIDEMIOLOGY

It has been estimated from population survey data that at least 6% of the adult population in the United States has CKD at stages 1 and 2. An additional 4.5% of the U.S. population is estimated to have stages 3 and 4 CKD. Table 335-2 lists the five most frequent categories of causes of CKD, cumulatively accounting for greater than 90% of the CKD disease burden worldwide. The relative contribution of each category varies among different geographic regions. The most frequent cause of CKD in North America and Europe is diabetic nephropathy, most often secondary to type 2 diabetes mellitus. Patients with newly diagnosed CKD often also present with hypertension. When no overt evidence for a primary glomerular or tubulointerstitial kidney disease process is present, CKD is often attributed to hypertension. However, it is now appreciated that such individuals can be considered in two categories. The first includes patients with a silent primary glomerulopathy, such as focal segmental glomerulosclerosis, without the overt nephrotic or nephritic manifestations of glomerular disease (Chap. 338). The second includes patients in whom progressive nephrosclerosis and hypertension is the renal correlate of a systemic vascular disease, often also involving large- and small-vessel cardiac and cerebral pathology. This latter combination is especially common in the elderly, in whom chronic renal ischemia as a cause of CKD may be underdiagnosed. The increasing incidence of CKD in the elderly has been ascribed, in part, to decreased mortality rate from the cardiac and cerebral complications of atherosclerotic vascular disease, enabling a greater segment of the population to eventually manifest the renal component of generalized vascular disease. Nevertheless, it should be appreciated that the vast majority of such patients with early stages of CKD will succumb to the cardiovascular and cerebrovascular consequences of the vascular disease before they can progress to the most advanced stages of CKD. Indeed, even a minor decrement in GFR or the presence of albuminuria is now recognized as a major risk factor for cardiovascular disease.

PATHOPHYSIOLOGY AND BIOCHEMISTRY OF UREMIA

Although serum urea and creatinine concentrations are used to measure the excretory capacity of the kidneys, accumulation of these two molecules themselves does not account for the many symptoms and signs that characterize the uremic syndrome in advanced renal failure.

TABLE 335-2 LEADING CATEGORIES OF ETIOLOGIES OF CKD[a]

- Diabetic nephropathy
- Glomerulonephritis
- Hypertension-associated CKD (includes vascular and ischemic kidney disease and primary glomerular disease with associated hypertension)
- Autosomal dominant polycystic kidney disease
- Other cystic and tubulointerstitial nephropathy

[a]Relative contribution of each category varies with geographic region and race.