Acute Renal Failure and Toxic Nephropathy

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1. Introduction

Acute renal failure is a common clinical syndrome. This syndrome can be caused by prerenal functional hemodynamic processes, intrarenal structural injury, or postrenal obstructive disorders. Prerenal acute renal failure, or prerenal azotemia, results from a persistent, significant decline in renal blood flow (RBF), which leads to a decline in the rate of glomerular filtration (GFR) and rising levels of blood urea nitrogen (BUN) and plasma creatinine. Usually this decline in renal perfusion is a component of a generalized process of poor tissue perfusion, but selective declines in RBF, and hence GFR, may develop disproportionately to blood flow to other tissues. A variety of drugs, most notably agents that inhibit prostaglandin synthesis, have been demonstrated to produce nephrotoxic side effects by an ability to promote selective declines in RBF and GFR.1 With regard to intrarenal structural processes, several factors make the kidney especially susceptible to toxic injury. The high rates of delivery of compounds to the kidney, concentration of drugs in tubule lumens and interstitium, and transcellular transport of toxins by
the kidney make the renal tubular cells especially vulnerable to toxic injury.² The high metabolic demands for the normal transport activities of renal tubular cells and the virtual absolute requirement for oxidative metabolism as an energy source by proximal tubular cells make the renal tubular cells also keenly susceptible to ischemic injury.³ Both toxic and ischemic insults have the ability to cause substantial renal structural damage to produce acute renal excretory failure.

Toxic and postischemic acute renal failure results from a complex, and still incompletely understood, interplay between cellular, nephronal, and hemodynamic events.⁴ It is now generally accepted that the occurrence of persistent acute renal failure correlates with the presence of renal tubular cell injury.⁵,⁶ The loss of normal renal tubule cell function, loss of continuity of the tubular epithelium, and formation of debris from injured tubules all contribute critically to the derangements in nephron function that occur during acute renal failure. But since nephrons function as units in series, injury localized to limited nephron segments may lead to substantial renal failure if the tubular obstruction from cellular debris, or backleak of glomerular filtrate, or secondary compensatory alterations in glomerular hemodynamics is sufficient to compromise function of the whole nephron. The structural heterogeneity of the kidney and the complex interplay of vascular, nephronal, and cellular events in the pathophysiology of acute renal failure pose substantial difficulty in delineating the direct toxic potential of a variety of compounds associated with nephrotoxic acute renal failure. In this regard, recent work has provided a better understanding of the pathophysiology of two important drugs with well-known nephrotoxicity, radiographic contrast agents and cyclosporine. This chapter will review these newer insights and correlate this new understanding to the clinical features of these two nephrotoxic disorders.

Increased understanding of the events involved in the pathogenesis of ischemic acute renal failure has also emphasized the importance of the associated renal tubular cell injury. Intranephronal obstruction of tubule lumens with debris from damaged cells and backleak across damaged epithelial surfaces have been shown to play significant roles in producing the reductions in GFR seen in ischemic acute renal failure.⁴ The potential contribution to loss of renal function by sublethally injured tubules has also been emphasized by microperfusion and micropuncture studies demonstrating marked functional abnormalities in such tubules.⁴ Very recent studies have highlighted the importance of the balance between energy consumption and energy production in determining the maintenance of renal tubular cell viability.⁷,⁸ Important roles have also been suggested for phospholipase activation and phospholipid degradation, for free-radical production and lipid peroxidation, and for al-