Nephrotoxicity of radiographic contrast agents is an important cause of acute renal failure even when measures are taken to reduce these toxic effects. Such toxic effects prolong hospital stays, add to the cost of medical care, and can be fatal. The incidence of radiographic-contrast-agent–induced acute renal failure, currently estimated to be as high as 50 percent among patients with diabetes mellitus and preexisting renal disease who receive contrast agents, is likely to remain high as the use of invasive radiologic procedures to diagnose and treat complex disease continues to grow.

Prevention or mitigation of renal failure after the administration of a radiographic contrast agent has been notably difficult. Calcium-channel antagonists, adenosine antagonists, and dopamine have all been used without convincing evidence of benefit. In a recent multicenter trial, atrial natriuretic peptide failed to reduce the risk of contrast-agent–induced nephropathy despite promising preliminary experimental and clinical results.1 When given before the contrast agent, mannitol and furosemide each reduced renal function more than saline alone.2 Disappointingly, despite encouraging experimental data, endothelin-receptor antagonists actually exacerbated radiographic-contrast-agent–induced nephrotoxicity in a recent prospective, multicenter, randomized trial.3

Thus, the decidedly low-technology approach described by Tepel et al. in this issue of the Journal,4 an approach that seems to be effective in ameliorating nephropathy caused by radiographic contrast agents, will be greeted with great interest. Just 1200 mg of acetylcysteine per day, given orally in divided doses on the day before and on the day of the administration of the radiocontrast agent, prevented the expected decline in renal function in all patients with moderate renal insufficiency, and therefore high risk, who were undergoing computed tomography. Because of their high-risk status, each patient received saline and a low-osmolality nonionic radiocontrast agent; such agents are associated with a significantly lower likelihood of acute renal failure than are high-osmolality agents. Thus, it could be argued that the
observed effect of acetylcysteine would have been even greater if these preventive measures had not been taken.

Acetylcysteine, a thiol-containing antioxidant that is perhaps more familiar under its proprietary names, Mucomyst and Mucosil, has been used to treat a variety of pulmonary diseases and to treat acute acetaminophen poisoning. Recently, however, it has been used successfully to ameliorate the toxic effects of a variety of experimentally or clinically induced ischemia–reperfusion syndromes of the heart, kidney, lung, and liver.\textsuperscript{5,6,7} In each of these syndromes, it is thought that the activity of acetylcysteine is related to its action as a free-radical scavenger, or as a reactive sulfhydryl compound that increases the reducing capacity of the cell. How it would act to prevent the nephrotoxic effects of contrast agents is not known, but certain characteristics of the syndrome permit reasonable speculation about acetylcysteine's mechanism of action.

Renal failure does not occur in laboratory animals given radiographic contrast agents unless the systemic and renal circulation is compromised in some way. Induction of congestive heart failure, reduction of renal mass, salt depletion, hypercholesterolemia, and inhibition of the synthesis of nitric oxide and prostaglandins, key regulators of the renal circulation, can each promote contrast-agent–induced renal failure. These perturbations resemble clinical conditions that are known to increase the risk of acute renal failure in patients who receive contrast agents. Brezis and Rosen\textsuperscript{8} have speculated that such renal failure occurs because of the vulnerability of the renal medullary circulation to stimuli that disrupt the balance between the high metabolic needs of the tubular segments of the renal medulla and their hypoxic environment. This balance is normally maintained by the interplay between vasodilator and vasoconstrictor influences, mediated by the activity of the nitric oxide, prostaglandin, and endothelin systems within the medulla. Infusion of radiographic contrast agents, with the attendant increases in osmotic load and viscosity, increases the hypoxia of the renal medulla,\textsuperscript{7} and such hypoxia may not be tolerated if renal circulation is compromised. Indeed, in diabetic patients with renal failure, who are at the highest risk for the development of acute renal failure when they must undergo scanning with contrast agents, medullary hypoxia and impaired endothelium-derived vasorelaxation are already present. There is also evidence that renal free-radical production increases after the administration of a contrast agent.\textsuperscript{9} Infusion of superoxide dismutase and allopurinol, each of which should reduce free-radical content, ameliorated contrast-agent–induced declines in perfusion. Under such conditions of medullary hypoxia and free-radical attack, how does acetylcysteine ameliorate renal failure?

First, acetylcysteine may reduce the ability of generated oxygen free radicals to damage cells by scavenging them, as has been observed after myocardial infarction.\textsuperscript{5} It may also increase the biologic effects of nitric oxide by combining with nitric oxide to form $\text{S}$-nitrosothiol, which is a more stable form and a potent vasodilator. This interaction may also limit the production of the damaging peroxinitrite radical, since acetylcysteine would compete with the superoxide radical for nitric oxide. Acetylcysteine also increases the expression of nitric oxide synthase and may thus improve blood flow as well.

Finally, it is important to consider the cellular response to oxidant stress in general and the observed effect of acetylcysteine in inhibiting cell death under these conditions. Oxidants activate a signal-
transduction cascade and molecular response that may engage the cell-death pathway and provoke apoptosis. Such pathways seem to be sensitive to the prevailing redox state of the cell and are inhibited by acetylcysteine. Acetylcysteine inhibits cell death induced by ischemia–reperfusion injury in the kidney,\(^6\) in the liver and lung,\(^7\) and after balloon angioplasty.\(^10\) Thus, acetylcysteine promotes pathways that lead to repair and survival whenever cells are under oxidant stress. It is not surprising, therefore, that acetylcysteine has salutary effects in many instances of cell stress and organ failure.

Considering the disappointing results of other attempts to prevent radiographic-agent–induced nephropathy, the results of Tepel et al. with acetylcysteine are encouraging. Their study should rekindle interest in this deceptively simple compound; it should also encourage others to confirm the results in a larger number of patients and to extend the use of acetylcysteine to patients with even more seriously compromised renal function. Diabetic patients with markedly reduced renal function, in whom coronary angiography is often delayed because of the considerable risks to renal function entailed by angiography, are of special interest in this regard. The low cost of acetylcysteine, its general availability and ease of administration, its limited side effects, and the importance of the problem are all compelling reasons to pursue such studies.

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