EVIDENCE SUGGESTING A ROLE FOR REACTIVE OXYGEN METABOLITES IN ISCHEMIC ACUTE RENAL FAILURE

- Enhanced generation of reactive oxygen metabolites and xanthine oxidase and increased conversion of xanthine dehydrogenase to oxidase occur in in vitro and in vivo models of injury.
- Lipid peroxidation occurs in in vitro and in vivo models of injury, and this can be prevented by scavengers of reactive oxygen metabolites, xanthine oxidase inhibitors, or iron chelators.
- Glutathione redox ratio, a parameter of "oxidant stress" decreases during ischemia and markedly increases on reperfusion.
- Scavengers of reative oxygen metabolites, antioxidants, xanthine oxidase inhibitors, and iron chelators protect against injury.
- A diet deficient in selenium and vitamin E increases susceptibility to injury.
- Inhibition of catalase exacerbates injury, and transgenic mice with increased superoxide dismutase activity are less susceptible to injury.

FIGURE 14-25

Evidence suggesting a role for reactive oxygen metabolites in acute renal failure. The increased ROS production results from two major sources: the conversion of hypoxanthine to xanthine by xanthine dehydrogenase and the oxidation of NADH by NADH oxidase(s). During the period of ischemia, oxygen deprivation results in the massive dephosphorylation of adenine nucleotides to hypoxanthine. Normally, hypoxanthine is metabolized by xanthine dehydrogenase which uses NAD^+ rather than oxygen as the acceptor of electrons and does not generate free radicals. However, during ischemia, xanthine dehydrogenase is converted to xanthine oxidase. When oxygen becomes available during reperfusion, the metabolism of hypoxanthine by xanthine oxidase generates superoxide. Conversion of NAD^+ to its reduced form, NADH, and the accumulation of NADH occurs during ischemia. During the reperfusion period, the conversion of NADH back to NAD^+ by NADH oxidase also results in a burst of superoxide production. (*From* Ueda *et al*. [23]; with permission.)

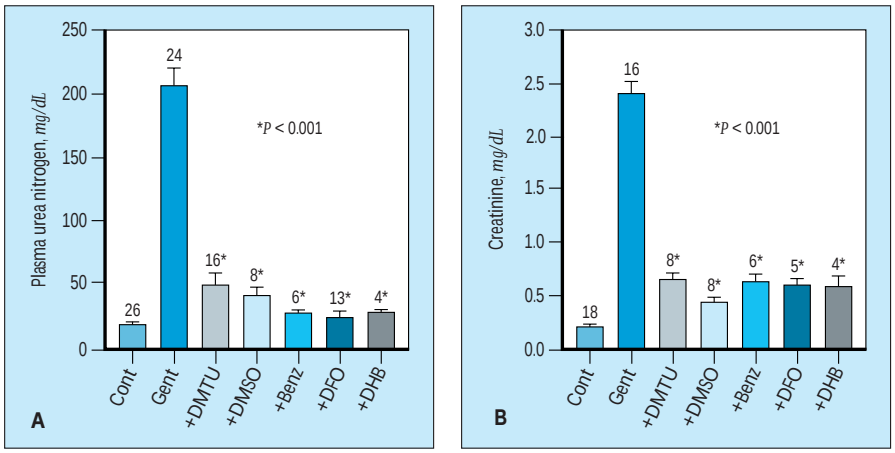


FIGURE 14-26

Effect of different scavengers of reactive oxygen metabolites and iron chelators on, **A**, blood urea nitrogen (BUN) and, **B**, creatinine in gentamicin-induced acute renal failure. The numbers shown above the error bars indicate the number of animals in each group. Benz—sodium benzoate; Cont—control group; DFO—deferoxamine; DHB—2,3 dihydroxybenzoic acid; DMSO—dimethyl sulfoxide; DMTU—dimethylthiourea; Gent—gentamicin group. (*From* Ueda *et al*. [23]; with permission.)

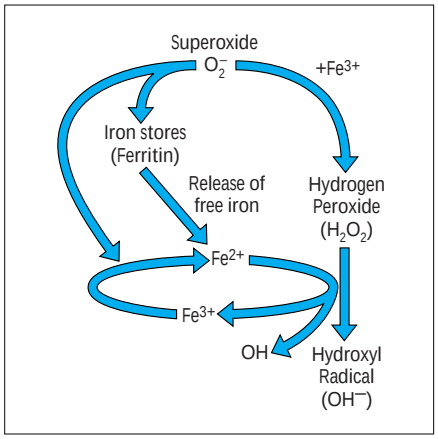


FIGURE 14-27

Production of the hydroxyl radical: the Haber-Weiss reaction. Superoxide is converted to hydrogen peroxide by superoxide dismutase. Superoxide and hydrogen peroxide per se are not highly reactive and cytotoxic. However, hydrogen peroxide can be converted to the highly reactive and injurious hydroxyl radical by an iron-catalyzed reaction that requires the presence of free reduced iron. The availability of free "catalytic iron" is a critical determinant of hydroxyl radical production. In addition to providing a source of hydroxyl radical, superoxide potentiates hydroxyl radical production in two ways: by releasing free iron from iron stores such as ferritin and by reducing ferric iron and recycling the available free iron back to the ferrous form. The heme moiety of hemoglobin, myoglobin, or cytochrome present in normal cells can be oxidized to metheme (Fe^{3+}). The further oxidation of metheme results in the production of an oxyferryl moiety (Fe^{4+}=O), which is a long-lived, strong oxidant which likely plays a role in the cellular injury associated with hemoglobinuria and myoglobinuria.

Activated leukocytes produce superoxide and hydrogen peroxide via the activity of a membrane-bound enzyme NADPH oxidase. This superoxide and hydrogen peroxide can be converted to hydroxyl radical via the Haber-Weiss reaction. Also, the enzyme myeloperoxidase, which is specific to leukocytes, converts hydrogen peroxide to another highly reactive and injurious oxidant, hypochlorous acid.

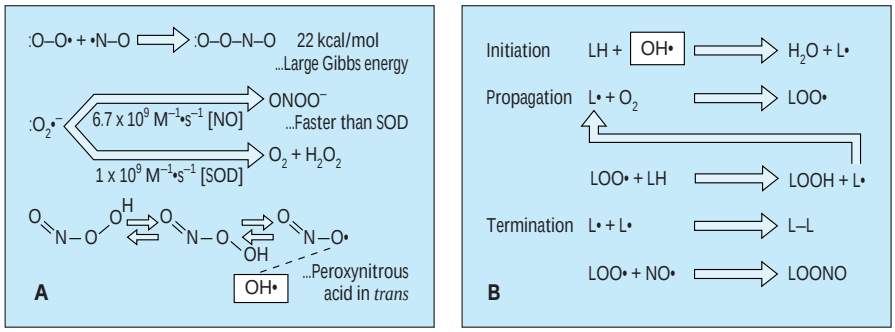
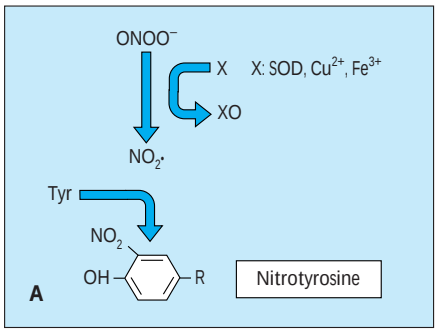
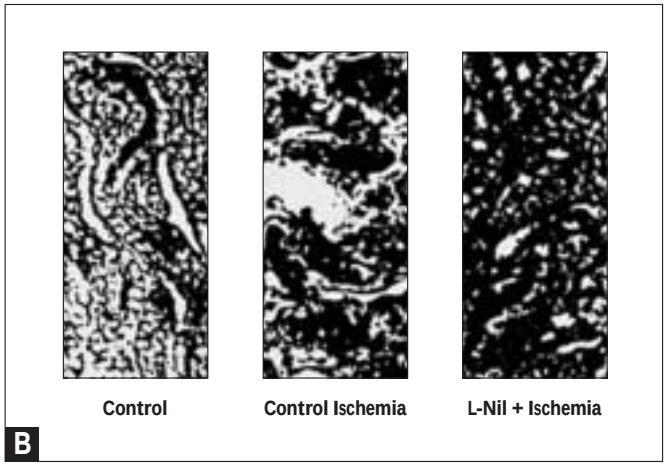
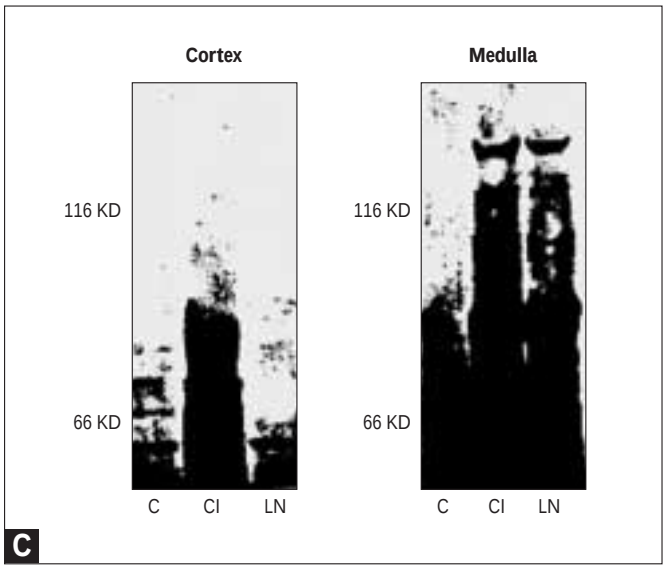


FIGURE 14-28

Cell injury: point of convergence between the reduced oxygen intermediates–generating and reduced nitrogen intermediates–generating pathways, **A**, and mechanisms of lipid peroxidation, **B**.







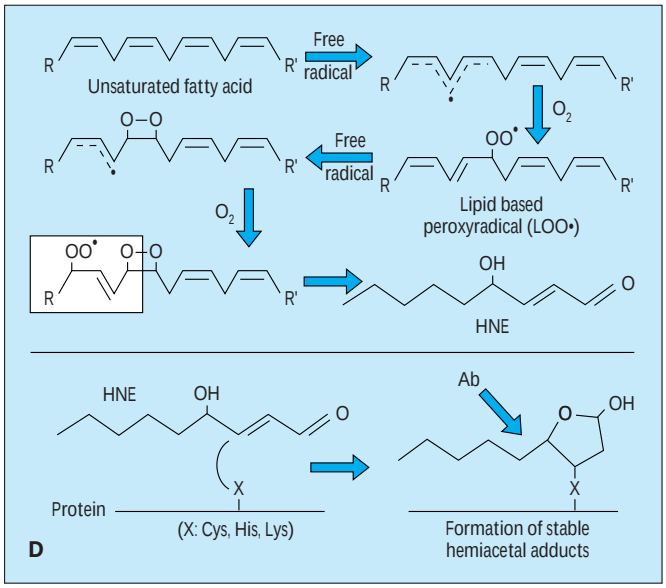
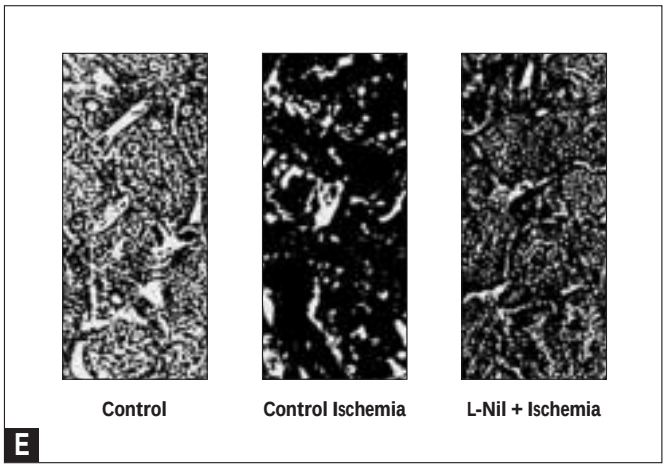


FIGURE 14-29

Detection of peroxynitrite production and lipid peroxidation in ischemic acute renal failure. **A**, Formation of nitrotyrosine as an indicator of ONOO- production. Interactions between reactive oxygen species such as the hydroxyl radical results in injury to the ribose-phosphate backbone of DNA. This results in single- and double-strand breaks. ROS can also cause modification and deletion of individual bases within the DNA molecule. Interaction between reactive oxygen and nitrogen species results in injury to the ribose-phosphate backbone of DNA, nuclear DNA fragmentation (single- and double-strand breaks) and activation of poly-(ADP)-ribose synthase. **B**, Immunohistochemical staining of kidneys with antibodies to nitrotyrosine. **C**, Western blot analysis of nitrotyrosine. **D**, Reactions describing lipid peroxidation and formation of hemiacetal products. The interaction of oxygen radicals with lipid bilayers leads to the removal of hydrogen atoms from the unsaturated fatty acids bound to phospholipid. This process is called lipid peroxidation. In addition to impairing the structural and functional integrity of cell membranes, lipid peroxidation can lead to a self-perpetuating chain reaction in which additional ROS are generated.

(Continued on next page)



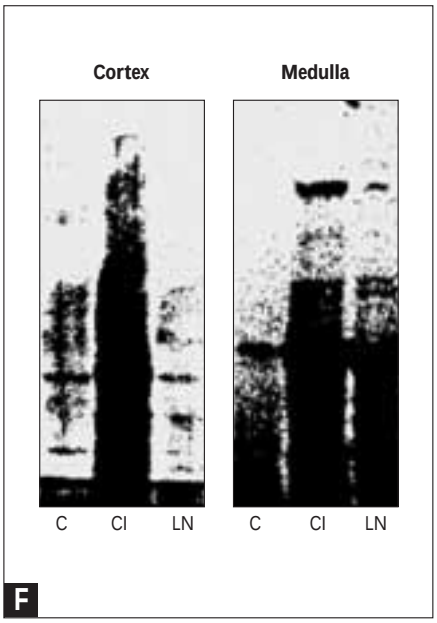


FIGURE 14-29 *(Continued)*

E, Immunohistochemical staining of kidneys with antibodies to HNE–modified proteins. **F**, Western blot analysis of HNE expression. C—control; CI—central ischemia; LN—ischemia with L-Nil pretreatment (*Courtesy of* E. Noiri, MD.)

Leukocytes in Acute Renal Failure

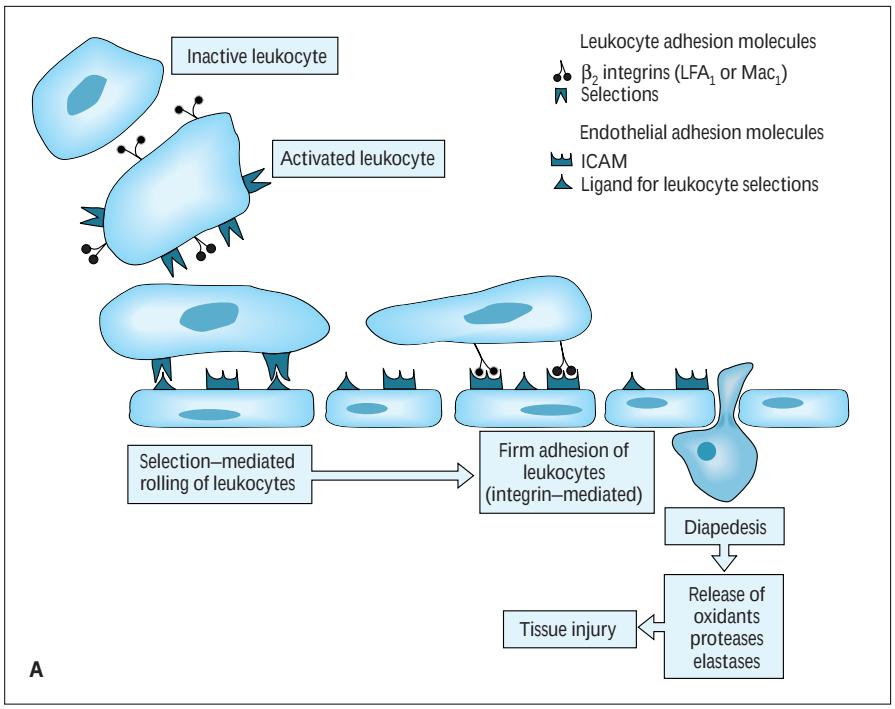


FIGURE 14-30

Role of adhesion molecules in mediating leukocyte attachment to endothelium. **A**, The normal inflammatory response is mediated by the release of cytokines that induce leukocyte chemotaxis and activation. The initial interaction of leukocytes with endothelium is mediated by the selectins and their ligands both of which are present on leukocytes and endothelial cells,

(Continued on next page)