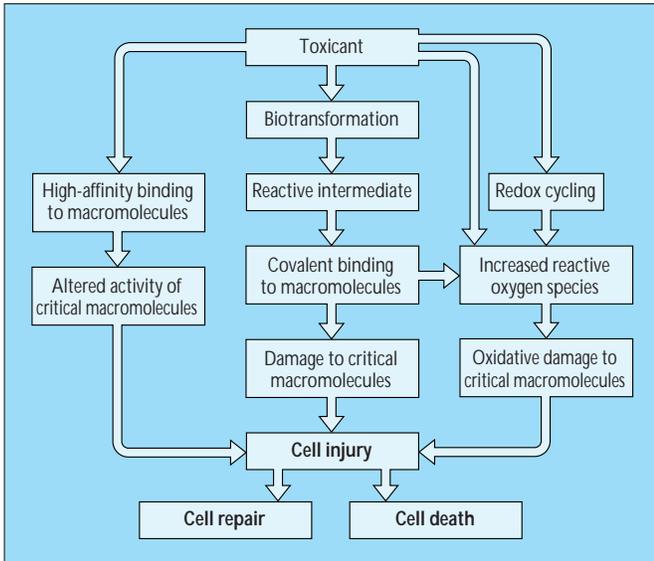


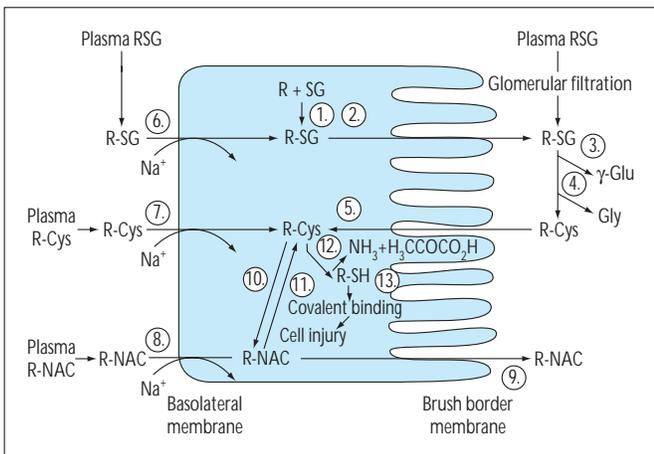
**FIGURE 15-14**

The importance of cellular transport in mediating toxicity. Proximal tubular uptake of inorganic mercury is thought to be the result of the transport of mercuric conjugates (eg, diglutathione mercury conjugate [GSH-Hg-GSH], dicysteine mercuric conjugate [CYS-Hg-CYS]). At the luminal membrane, GSH-Hg-GSH appears to be metabolized by  $\gamma$ -glutamyl transferase ( $\gamma$ -GT) and a dipeptidase to form CYS-Hg-CYS. The CYS-Hg-CYS may be taken up by an amino acid transporter. At the basolateral membrane, mercuric conjugates appear to be transported by the organic anion transporter. ( $\alpha$ -Ketoglutarate and the dicarboxylate transporter seem to play important roles in basolateral membrane uptake of mercuric conjugates. Uptake of mercuric-protein conjugates by endocytosis may play a minor role in the uptake of inorganic mercury transport. PAH—*para*-aminohippurate. (Courtesy of Dr. R. K. Zalups.)



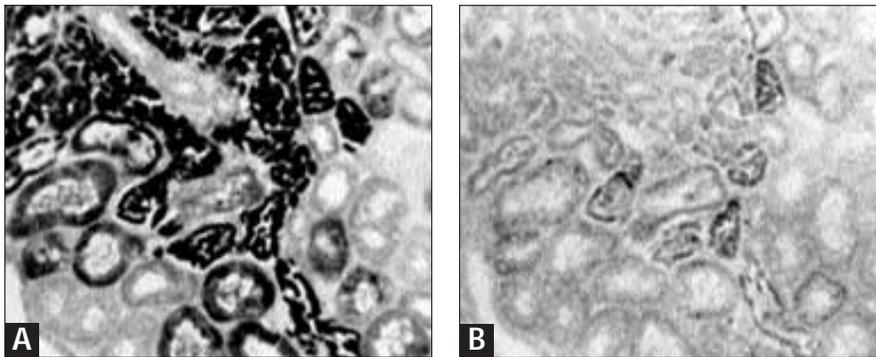
**FIGURE 15-15**

Covalent and noncovalent binding versus oxidative stress mechanisms of cell injury. Nephrotoxicants are generally thought to produce cell injury and death through one of two mechanisms, either alone or in combination. In some cases the toxicant may have a high affinity for a specific macromolecule or class of macromolecules that results in altered activity (increase or decrease) of these molecules, resulting in cell injury. Alternatively, the parent nephrotoxicant may not be toxic until it is biotransformed into a reactive intermediate that binds covalently to macromolecules and in turn alters their activity, resulting in cell injury. Finally, the toxicant may increase reactive oxygen species in the cells directly, after being biotransformed into a reactive intermediate or through redox cycling. The resulting increase in reactive oxygen species results in oxidative damage and cell injury.

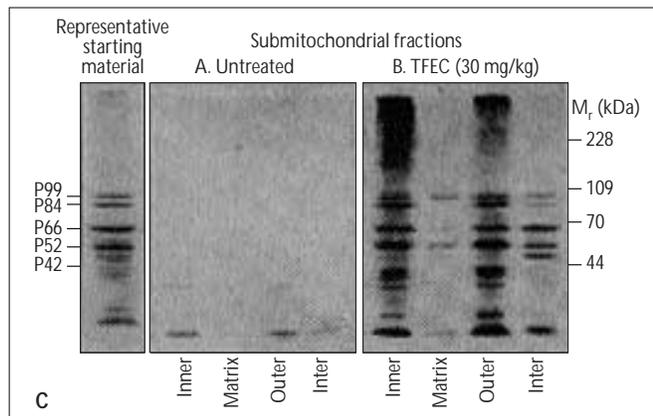


**FIGURE 15-16**

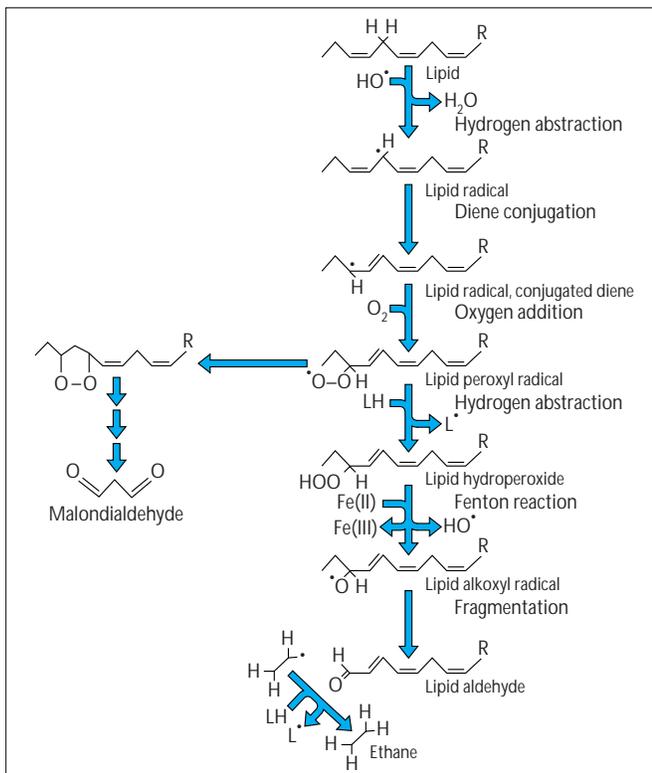
This figure illustrates the renal proximal tubular uptake, biotransformation, and toxicity of glutathione and cysteine conjugates and mercapturic acids of haloalkanes and haloalkenes (R). 1) Formation of a glutathione conjugate within the renal cell (R-SG). 2) Secretion of the R-SG into the lumen. 3) Removal of the  $\gamma$ -glutamyl residue ( $\gamma$ -Glu) by  $\gamma$ -glutamyl transferase. 4) Removal of the glycyl residue (Gly) by a dipeptidase. 5) Luminal uptake of the cysteine conjugate (R-Cys). Basolateral membrane uptake of R-SG (6), R-Cys (7), and a mercapturic acid (N-acetyl cysteine conjugate; R-NAC) (8). 9) Secretion of R-NAC into the lumen. 10) Acetylation of R-Cys to form R-NAC. 11) Deacetylation of R-NAC to form R-Cys. 12) Biotransformation of the penultimate nephrotoxic species (R-Cys) by cysteine conjugate  $\beta$ -lyase to a reactive intermediate (R-SH), ammonia, and pyruvate. 13) Binding of the reactive thiol to cellular macromolecules (eg, lipids, proteins) and initiation of cell injury. (Adapted from Monks and Lau [5]; with permission.)

**FIGURE 15-17**

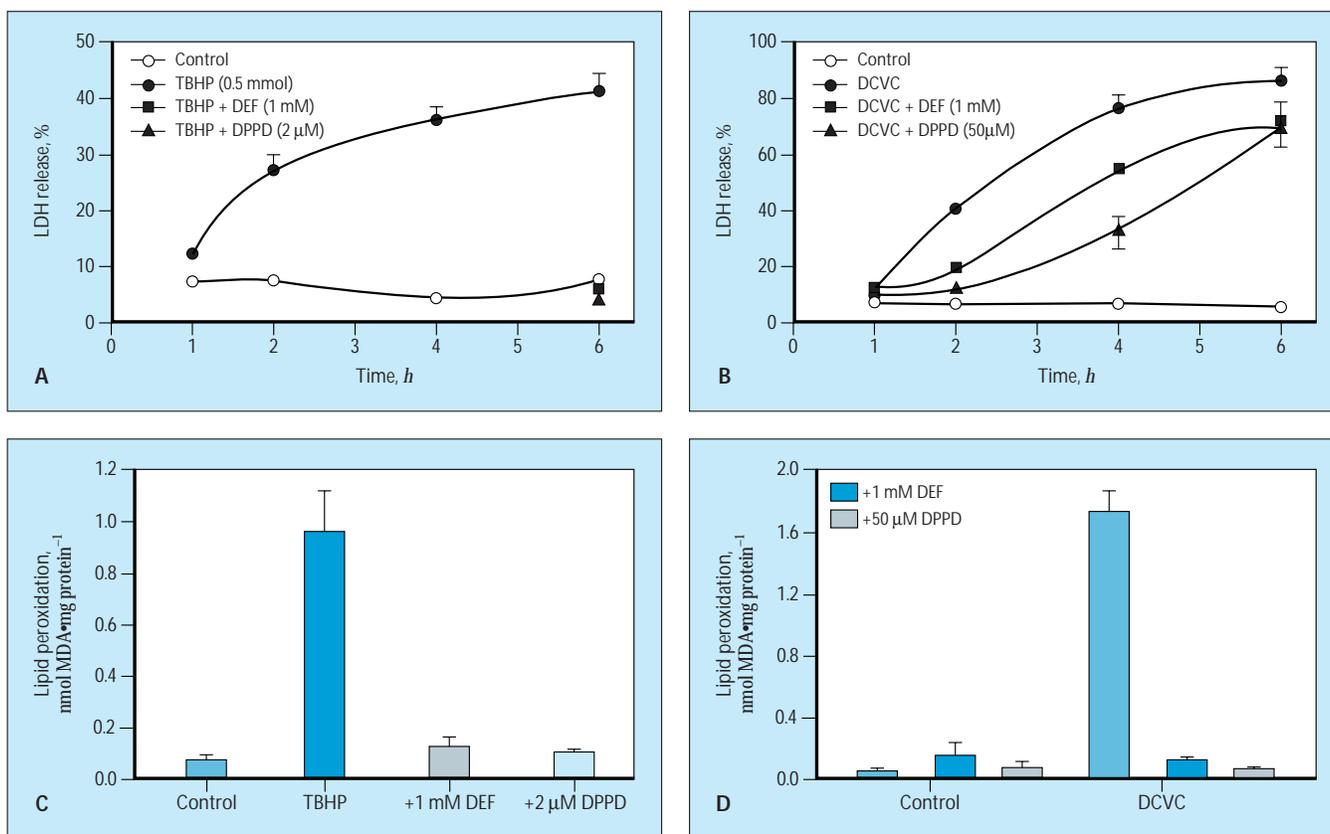
Covalent binding of a nephrotoxicant metabolite in vivo to rat kidney tissue, localization of binding to the mitochondria, and identification of three proteins that bind to the nephrotoxicant. **A**, Binding of tetrafluoroethyl-L-cysteine (TFEC) metabolites in vivo to rat kidney tissue detected immunohistochemically. Staining was localized to the S3 segments of the proximal tubule, the segment that undergoes necrosis. **B**, Immunoreactivity in untreated rat kidneys. **C**, Isolation and fractionation of renal cortical mitochondria from untreated and TFEC treated rats and immunoblot analysis revealed numerous proteins that bind to the nephrotoxicant (inner-inner membrane, matrix-soluble matrix, outer-outer membrane, inter-intermembrane space). The identity of three of the proteins that bound to the nephrotoxicant: P84, mortalin (HSP70-like); P66, HSP 60; and P42, aspartate aminotransferase.  $M_r$ —relative molecular weight. (From Hayden *et al.* [6], and Bruschi *et al.* [7]; with permission.)



## Lipid peroxidation and mitochondrial dysfunction

**FIGURE 15-18**

A simplified scheme of lipid peroxidation. The first step, hydrogen abstraction from the lipid by a radical (eg, hydroxyl), results in the formation of a lipid radical. Rearrangement of the lipid radical results in conjugated diene formation. The addition of oxygen results in a lipid peroxy radical. Additional hydrogen abstraction results in the formation of a lipid hydroperoxide. The Fenton reaction produces a lipid alkoxy radical and lipid fragmentation, resulting in lipid aldehydes and ethane. Alternatively, the lipid peroxy radical can undergo a series of reactions that result in the formation of malondialdehyde.

**FIGURE 15-19**

**A–D.** Similarities and differences between oxidant-induced and halocarbon-cysteine conjugate-induced renal proximal tubular lipid peroxidation and cell death. The model oxidant *t*-butylhydroperoxide (TBHP) and the halocarbon-cysteine conjugate dichlorovinyl-L-cysteine (DCVC) caused extensive lipid peroxidation after 1 hour of exposure and cell death (lactate dehydrogenase (LDH) release) over 6-hours' exposure. The iron chelator deferoxamine (DEF) and the antioxidant *N,N'*-diphenyl-1,4-phenylenediamine (DPPD) completely blocked both the lipid

peroxidation and cell death caused by TBHP. In contrast, while DEF and DPPD completely blocked the lipid peroxidation caused by DCVC, cell death was only delayed. These results suggest that the iron-mediated oxidative stress caused by TBHP is responsible for the observed toxicity, whereas the iron-mediated oxidative stress caused by DCVC accelerates cell death. One reason that cells die in the absence of iron-mediated oxidative stress is that DCVC causes marked mitochondrial dysfunction. (Data from Groves *et al.* [8], and Schellmann [9].)

### ALTERATION OF RENAL TUBULAR CELL ENERGETICS AFTER EXPOSURE TO TOXICANTS

Decreased oxygen delivery secondary to vasoconstriction  
 Inhibition of mitochondrial respiration  
 Increased tubular cell oxygen consumption

**FIGURE 15-20**

Mechanisms by which nephrotoxicants can alter renal tubular cell energetics.