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Lydia M Bilinsky* (lydia.m.bilinsky@gmail.com). *Modeling liver glutathione redox balance metabolism and the action of agents which promote oxidative stress in liver: applications to arsenical poisoning and acetaminophen overdose.*

Reactive oxygen species such as hydrogen peroxide (H_2O_2) are a byproduct of normal cellular metabolism, but when present at high concentrations, a situation referred to as “oxidative stress,” cause cytotoxicity. A major line of defense against oxidative stress is the glutathione redox cycle, in which H_2O_2 combines with two molecules of glutathione (GSH, the reduced form) to form glutathione disulfide (GSSG, the oxidized form); GSH is then regenerated from GSSG. The relative levels of GSSG and GSH (the “glutathione redox balance”) provide a measure of intracellular oxidative stress. I present an ODE model of the biochemical reactions which determine glutathione redox balance in liver. I then show how this model can be used as a starting point in the creation of models of liver injury induced by drugs or toxins thought to act via the induction of extreme oxidative stress. The examples of acetaminophen overdose and exposure to the arsenical dimethylarsinous acid (DMAIII) are presented; a major result is the prediction that extreme GSH depletion is the immediate cause of cytotoxic oxidative stress. I also describe a tipping-point phenomenon in which agents which only modestly increase endogenous H_2O_2 production can cause lethal oxidative stress after a delay period. (Received September 17, 2019)