

### Learning Objective #1

Summarize the six major types of drug-induced liver disease.

- 1. Cytotoxic (Direct Hepatocellular Death):** Drug binds covalently to intracellular proteins to disrupt cellular functions. May involve formation of free radicals, ROS, or electrophilic radicals, leading to oxidative stress and disruption of ionic gradients, cell membranes, actin, and ATP generation. Liver cells become sensitized to cytokines. Cell death may be zonal (centrilobular) or non-zonal (diffuse).
- 2. Immune-mediated:** Toxins undergo biotransformation to form adducts or haptens, which travel to Kupffer cell membranes to evoke an immune response via MHC I and MHC II. Humoral *and* cellular immune responses lead to inflammation and produce liver damage.
- 3. Steatosis:** Toxins inhibit elimination of FA by inhibiting microsomal TG transfer protein (MTP), which is normally responsible for forming TG-rich VLDLs and mitochondrial oxidation. Leads to accumulation of FA in the mitochondria. Microvesicular steatosis indicates acute injury, whereas macrovesicular steatosis indicates chronic injury.
- 4. Cholestatic Injury:** Substances secreted into the bile canaliculus cause direct bile duct injury and disable bile salt transport proteins.
- 5. Vascular Injury:** Veno-occlusion and congestive hepatotoxicity. Dilation of hepatic sinusoids produce blood-filled cavities within the liver.
- 6. Neoplastic:** Benign or malignant neoplasms

### Learning Objective #2

List common medications and herbals that are known to cause liver disease and the most likely mechanism of liver toxicity.

### Learning Objective #3

List appropriate risk factors for drug-induced hepatic and cholestatic diseases.

### Learning Objective #4

Calculate an R-value for evaluating drug-induced liver injury and its implications.

### Learning Objective #5

Outline appropriate steps in both the prevention and management of drug-induced hepatic and cholestatic disease.

### Self-Assessment Questions

1. According to the acute liver failure registry which of the following agents causes the MOST acute liver failure cases?\*

- A. Phenytoin
- B. Acetaminophen
- C. Complementary & Alternative Medicine
- D. Antimicrobials
- E. Valproic Acid

### Self-Assessment Questions (cont)

2. Which of the following is/are considered a type of drug-induced liver injury (DILI)? (Select all that apply)

- A. Direct hepatocellular
- B. Immune-mediated
- C. Steatosis
- D. Cholestatic
- E. Vascular

