Key points:
- Hepatocytes produce procoagulant, anticoagulant and fibrinolytic proteins, and removes both normal and abnormal clotting factors from circulation
  - Therefore in any hepatic disease a wide variety of coagulation disorders are possible
  - Abnormalities are most commonly seen in chronic liver disease
- Bile provides
  - Source of bile acids for fat digestion and absorption
  - Excretory route for metabolites and toxins
  - Additional HCO3- for buffering H+ in duodenum

Hepatocytes:
- 60-80% of cell mass
- Contribute to nutrient metabolism, coagulation factor synthesis, and immune surveillance
- Generate ‘primary bile’ and transport to canaliculi; secretion is poorly controlled, mostly occurs due to osmotic gradient
- Lifespan of 5-6 months
- Organised into plates separated by sinusoids with a fenestrated endothelial cell lining
  - Endothelial cells separated from hepatocytes by space of Disse which drains lymph

Cholangiocytes:
- 3-10% of liver cell mass
- Secrete water, bicarb and cations to modify the canalicular bile as it passes through the bile ducts; secretion is well regulated
- Antigen presenting cells
**Kupffer Cells**
- = stellate macrophages -> phagocytose pathogens and particulate matter
- 2-5% of cellular mass, located in sinusoids
- Express complement receptor immunoglobulins
- In disease states produce inflammatory mediators, activate toll-like receptors and TNF-a
- Also involved in metabolism of haemoglobin

- Zone 1 received greatest oxygen supply but also highest concentrations of toxins from portal system

**Liver function**

**Metabolism:**
- *Carbohydrates*
  - early in fasting glucose is generated from glycogen in liver and under regulation of hepatic glycogen phosphorylase and phosphorylase kinase
  - After prolonged fasting glucose is generated from gluconeogenesis from substrates like amino-acids, lactate and glycerol
  - Both gluconeogenesis and glycogenolysis produce glucose-6-phosphate which needs to be dephosphorlated by glucose-6-phosphatase-alpha
    - there are altered quantities of this in glycogen storage diseases - fasting will result in severe hypoglycaemia due to lack of all endogenous glucose production

- *Proteins*
  - The liver deaminates amino acids converting them to carbohydrates and lipids
  - Also creates amino acids by maintain and transamination
- Synthesises many proteins including albumin, fibrinogen, many globulins, clotting factors, enzymes

- **Lipids**
  - **Exogenous transport**
    - For metabolism of dietary lipids (triglyceride, cholesterol, phospholipids and fat soluble vitamins
    - Hepatocytes endocytose chylomicrons in circulation
  - **Endogenous transport**
    - For metabolism of endogenously produced lipids
    - Liver produces triglycerides and cholesterol, and forms into very-low-density lipoprotein
    - VLDL are transported to capillary beds where triglycerides are hydrolysed
  - **Reverse transport**
    - Transport of cholesterol from the periphery in HDL

- **Nucleic acid synthesis**
- **Porphyrin excretion**
- **Metals**
  - Stores iron as ferritin
  - Incorporates copper into proteins
    - Cholestasis results in copper retention
- **Vitamins**
  - Bile absorbs fat soluble vitamins (ADEK); cannot be absorbed without normal bile secretion
  - Phosphorylation of water soluble vitamins occurs in the liver to produce important coenzymes
  - Liver stores vitamins
    - 95% of vitamin A is stored in liver (stellate cells and hepatocytes); 1-2 year supply
    - Large amounts of all water soluble vitamins except vitamin C are stored

**Bile Secretion**

Provides:
- Source of bile acids for fat digestion and absorption
- Excretory route for metabolites and xenobiotics
- Additional HCO₃⁻ for buffering H⁺ in duodenum
- In the absence of neural/hormonal stimulation (e.g. when fasting) the gallbladder is relaxed and the sphincter of Oddi is contracted so bile is stored
  - Whilst stored there is reabsorption of water and electrolytes so bile becomes more concentrated
- During feeding ACh stimulation and cholecystokinin activate gallbladder contraction and sphincter relaxation
- **Bile acids**
  - Synthesized from cholesterol -> chenodeoxycholic acid and cholic acid
  - Become conjugated and dissociate to salts
  - When in intestinal lumen some of these become dehydroxylated by bacteria -> deoxycholic acid, lithocholic acid
  - Bile salts act as detergent to emulsify fat droplets, and assist absorption by forming micelles
  - Most secrete bile salts are absorbed in ileum and reenter portal flow
Coagulation Factors
- Liver produces procoagulant, anticoagulant and fibrinolytic proteins, and removes both normal and abnormal clotting factors from circulation
- Synthesises I, II, V, VII, VIII?, IX, X, XI and XII
- Activates vitamin K dependent factors and protein C
- Hepatic failure may result in a variety of factor deficiencies and may even result in DIC
- Coagulation abnormalities most commonly seen in dogs with chronic hepatitis/cirrhosis

Detoxification
- Cytochrome P450 catalyses the oxidation of a variety of chemicals - both foreign and endobiotic (steroids, vitamins, prostaglandins, fatty acids)
- Diet and ageing induce significant changes in expression of genes involved in production of P450 enzymes
- Occurs in 2 phases
  - 1 = modification reactions, drugs are hydrolysed or oxidised
  - 2. = conjugation reactions, usually (but not always) occurs after phase 1 reactions
- 75-80% of hepatic blood flow comes from GI tract/spleen via portal vein, bringing drugs, toxins, antigens, nutrients and bacteria
  - Some of the hepatic metabolism detoxifies these compounds, but other compounds will have their toxicity activated
- Ammonia
  - produced by amino acid metabolism
  - converted to urea via the urea cycle to help with excretion
  - In liver failure there is failure of this cycle, so build up of nitrogenous wastes -> hepatic encephalopathy
  - Colon is the most important source of ammonia; it is produced by bacteria then enters portal circulation
- Endogenous hormones
  - Also metabolised by the liver
  - Liver disease has been reported to result in changes in concentration of free and total cortisol -> clinical and biochem characteristics of PDH including polyuria

Immune surveillance
- Liver must be able to tolerate the large number of antigens derived from the GI tract and to effectively eliminate pathologic microorganisms
- Hepatocytes do not directly interact with leukocytes
  - Sinusoidal endothelial cells and Kupffer cells interact with the leukocytes
  - Endothelial cells are primarily responsible for clearance of antigens from the blood
  - These cells can act as antigen presenting cells for T cells

Regeneration
- Carried out by all mature liver cell types
- Two main steps in gene expression for regeneration
  - (1) Priming - transition from quiescent hepatocyte to the cell cycle; must be primed before they can respond to growth factors
    - TND, IL6, IL22 and ROS all very important
- (2) Progression beyond G1 of cell cycle
  - Hepatocyte growth factor, transforming growth factor-alpha
  - Once cell cycle genes are expressed replication becomes autonomous, independent of growth factors
- Hepatocyte proliferation progresses from the periportal areas outwards, with those surrounding central being the last to undergo replication
- Biliary epithelial cell replication occurs after that of hepatocytes
- Liver function can be restored after loss of 65-70% of liver via hepatectomy, and takes place over 7-14 days

QUESTIONS:
1. Describe the pathophysiologic basis of hepatic encephalopathy with particular regard to ammonium concentrations.

2. True or false: Natural killer cells contribute to immune surveillance in the liver by phagocytosis of pathogens and particulate matter.

ANSWERS:
1. Loss of functional liver mass -> inability to clear ammonia via urea cycle. Ammonia is produced primarily by GI flora, enters portal circulation -> increased release of glutamate -> neuronal excitation in brain

2. True or false: Natural killer cells contribute to immune surveillance in the liver by phagocytosis of pathogens and particulate matter.

FALSE. Kupffer cells phagocytose, NK induce apoptosis.