I. Liver Physiology

a. Describe the storage, synthetic, metabolic, and excretory functions of the liver and identify the physiological consequences of hepatic disease.

The liver is composed of lobules, 0.8 to 2 mm in diameter. They comprise a central vein (which drains to the hepatic vein) surrounded by plates of hepatocytes sandwiching bile canaliculi and surrounded by the space of Disse (which drains to lymphatics). Between the plates are sinusoids filled with blood derived from the hepatic artery (350 ml/min) and portal vein (1.1 l/min).

The liver receives a total of 29% of resting cardiac output. It is a low-resistance circulation, the portal vein being at 9 mmHg and hepatic vein at 0 mmHg. In cirrhosis, the vascular resistance is increased. In right heart failure, venous pooling in the liver can amount to 2 l (normal 450 ml). With high intrahepatic capillary pressure, fluid is rapidly transudated into lymph and directly into the abdominal cavity as ascites. This involves loss of plasma protein.

Kupffer cells in the sinusoids are part of the mononuclear phagocytosing system, removing bacteria from portal blood very effectively.

Carbohydrate metabolism (glucose buffering)

glycogen synthesis
polymerized from UDP-glucose
hydrolyzed by phosphorylase to glucose 1-PO₄. Phosphorylase is activated by adrenaline or glucagon via cAMP and enzyme intermediates.
represents up to 8% of hepatocytes' weight
conversion of galactose and fructose to glucose
galactose (+ATP) \rightarrow ~ 1-PO₄ ↔ UDP ~ ↔ UDP glucose \rightarrow glycogen
fructose (+ATP) \rightarrow ~ 6-PO₄ ↔ glucose 6-PO₄ ↔ ~ 1-PO₄ ↔ UDP ~
Only glucose is readily released back into blood by the action of glucose phosphatase on glucose 6-PO₄.

gluconeogenesis
from glycerol released from fats or by deamination and conversion of many amino-acids (e.g. alanine \rightarrow pyruvic acid + NH₃). This is promoted by glucocorticoids via liberation of amino-acids from protein catabolism in peripheral tissues.

Fat metabolism
oxidation of fatty acids
Triglycerides are split into glycerol (\rightarrow gluconeogenesis) and fatty acids. Fatty acids are split by β oxidation into a shorter fatty acid, acetyl-CoA, FADH₂, NADH and H⁺. The net gain from oxidation of a molecule of stearic acid (C₁₇H₃₅COOH) is 146 ATP. Acetyl-CoA can enter the TCAC or is converted to acetoacetic acid which circulates to peripheral tissues as acetoacetic acid, β-hydroxybutyrate and acetone (ketone bodies). These are converted back to acetyl-CoA in cells and enter the TCAC provided that there is adequate oxaloacetic acid (derived from carbohydrate metabolism), otherwise ketosis develops.

synthesis of lipoproteins
The liver synthesizes VLDL, a lipoprotein containing large amount of triglyceride and some cholesterol and bearing the apoprotein B-100 marker. VLDL circulates to the periphery where lipoprotein lipase hydrolyzes the triglycerides, allowing free fatty acids and glycerol to be taken up by peripheral tissue. The VLDL thus becomes IDL and then LDL, containing mainly cholesterol esters. IDL and LDL are taken up by the liver and by peripheral tissue by pinocytosis following binding of apo B-100 to its receptor. HDL is formed in the liver and bears apo A-I or A-II on its surface. It is thought to absorb cholesterol from vessels. The details of its circulation are not
fully known.
synthesis of cholesterol and phospholipids
90% of phospholipids are synthesized in the liver and transported via lipoproteins. They are a heterogeneous group of compounds, all containing fatty acids and at least one phosphoric acid radical; most also contain a quaternary nitrogen. They include lecithins, cephalins and sphingomyelin and are required for the formation of cell membranes, lipoproteins, and in specialized applications such as sphingomyelin in nerve sheaths, thromboplastin in clotting and as phosphate donors.

Cholesterol is synthesized de novo in the liver from acetyl-CoA. The rate-limiting step in synthesis is at hydroxymethylglutaryl-CoA reductase which is directly inhibited by cholesterol and by statin drugs. The plasma level of cholesterol is determined partly by dietary intake and substantially by the availability of acetyl-CoA in the liver (which is determined by dietary saturated fat intake).

Most cholesterol in the body is in cell membranes where it affects fluidity of the membrane and also deposits in the stratum corneum to improve the waterproofing of the skin. The majority of non-membranous cholesterol is converted to cholic acid in the liver and conjugated with glycine or taurine to form bile salts which solublize fats in the gut and are reabsorbed (enterohepatic circulation). A small amount is used in the synthesis of steroid hormones.

synthesis of fatty acids from glucose or amino-acids
Excess acetyl-CoA can be converted to fatty acids.
\[
\text{acetyl-CoA} + \text{CO}_2 + \text{ATP} \leftrightarrow \text{malonyl-CoA} + \text{ADP} + \text{PO}_4^{3-}
\]
\[
\text{malonyl-CoA} + \text{acetyl-CoA} + 2\text{NADPH} + 2\text{H}^+ \rightarrow \text{butyryl-CoA} + \text{CoA} + \text{CO}_2 + 2\text{NADP}^+ + \text{H}_2\text{O}.
\]
This process is repeated until the fatty acid is 14-18 carbons long, when the fatty acids are condensed with glycerol to form triglycerides. This process is about 85% efficient in storing energy from glucose. Triglycerides are stored in the liver or transported to peripheral fat cells via lipoproteins.

Protein metabolism
storage of amino acids
After absorption from the gut, amino acids are rapidly taken up by cells in the liver and throughout the body by active transport and facilitate diffusion. They are rapidly incorporated into proteins. Intracellular protein is in equilibrium with free amino acids and so is readily broken down for release of amino acids back into the circulation or for their metabolism.

Uptake of amino acids and synthesis of protein is promoted by GH and insulin and antagonized by glucocorticoids.

Albumin is also taken up directly by phagocytosing cells and broken down to amino acids which are then released into circulation.

transamination of amino acids
Nonessential amino acids are formed in the liver primarily by the synthesis of the appropriate α-keto acid followed by transfer of an amino radical from glutamine, glutamate, aspartate or asparagine.
glutamine + pyruvic a. → α-ketoglutamic a. + alanine
Several of the aminotransferase enzymes which catalyze these reactions are derivatives of pyridoxine (B₆).

deamination of amino acids
Deamination predominantly occurs by the same pathway as transamination, with the amino radical transferred from an amino acid to α-ketoglutamic acid and subsequent deamination of glutamine:

\[
glutamine + NAD^+ + H_2O \rightarrow \alpha\text{-ketoglutamic a.} + \text{NADH} + H^+ + NH_3
\]

The α-ketoacid derived from the amino acid which was deaminated can be oxidized, usually through the TCAC.

formation of urea
The NH₃ generated by deamination is toxic and so is used to synthesize urea:

\[
\text{ornithine} + \text{CO}_2 + \text{NH}_3 \rightarrow \text{citrulline} + \text{H}_2\text{O}
\]
\[
\text{citrulline} + \text{NH}_3 \rightarrow \text{arginine} + \text{H}_2\text{O} \rightarrow \text{urea} + \text{ornithine}
\]

\[
\text{net: } 2\text{NH}_3 + \text{CO}_2 \rightarrow \text{H}_2\text{N-CO-NH}_2 + \text{H}_2\text{O}
\]

Urea is cleared by the kidneys.

synthesis of plasma proteins
90% of plasma proteins are formed in the liver (the remainder are mainly immunoglobulins). Albumin, fibrinogen and globulins as well as clotting factors and some hormones are formed in the liver. The rate of synthesis is 15-50g/day.

Secretion of bile
The liver secretes 600-1200 ml of bile a day. It forms in the bile canaliculi between plates of hepatocytes and passes into collecting ducts, hepatic ducts and the bile duct. The lining of these ducts add volume, Na⁺ and HCO₃⁻ to the bile in response to secretin. Some empties directly into the duodenum and the remainder is temporarily stored in the gall bladder where it is concentrated.

Bile contains plasma electrolytes, bile salts, bilirubin, cholesterol, fatty acids and lecithin. It is relatively alkaline. The mixture may become supersaturated with cholesterol or bile salts, leading to the formation of stones. Emptying of the gallbladder is initiated by cholecystokinin after a meal.

Other functions
The liver stores vitamins A, D and B₁₂.

It stores excess iron by binding with apoferritin to form ferritin, as well as synthesizing transferrin for the transport and absorption of iron.

Detoxification of many drugs and metabolism of many hormones occurs in the liver. Many compounds are oxidized or demethylated by the cytochrome P450 system of enzymes, others are conjugated with UDP by glucuronyl transferase, competing with bilirubin for this pathway.

Excretion of bilirubin
Bilirubin is derived from the breakdown of haem in tissue macrophages. It circulates bound to albumin and is absorbed into hepatocytes. Here it is conjugated with glucuronic acid (80%), sulfate (10%) or other compounds and excreted by active transport into the bile.

In the gut, some conjugated bilirubin is converted to urobilinogen by bacteria which is reabsorbed and filtered by the kidneys, appearing in the urine where it is oxidized to urobilin. Urobilinogen which is not absorbed in the gut is converted to stercobilinogen and oxidized to stercobilin.

Physiological consequences of hepatic disease

Carbohydrate metabolism
reduced ability to metabolize a glucose load
reduced sensitivity to insulin both in the liver and peripherally
reduced ability to metabolize lactate
reduced glycogen stores

Protein metabolism
disrupted metabolism of non-branched-chain amino acids, leading to elevation
in circulating levels of aromatic amino acids
impairment of the urea cycle and a rise in plasma ammonia
secondary rise in ammonia due to poor excretion of urea and NH₃ by the
kidneys with enterohepatic circulation of urea (converted in the gut to NH₃)
and potentiation of the effect of NH₃ because of alkalosis.

Lipid metabolism
the pathogenesis of fatty liver is uncertain
possibly reduced synthesis of apoproteins, causes accumulation of triglycerides
possibly increased synthesis of lipids
longstanding cholestatic disease causes increased LDL and cholesterol and
reduced HDL

Synthetic functions
reduced albumin synthesis, reducing plasma oncotic pressure and binding
sites
reduced clotting factor synthesis (II, V, VII, IX, X) except for fibrinogen

Metabolism of drugs and hormones
portosystemic shunting
decreased phase I and II reactions
↑ insulin, glucagon, oestrogens

b. Describe the clinical laboratory assessment of liver function and hepatic failure.

Assessment of liver function with laboratory tests requires serial measurements of
parameters related to different hepatic functions, interpreted in a clinical context.
Bilirubin metabolism is assessed by plasma conjugated and unconjugated bilirubin,
assessing the conjugation and excretion functions. Elevated conjugated bilirubin can also be
detected by dipstick testing of urine.
Hepatocellular enzyme levels in plasma are used to assess cellular injury.
Aminotransferases (AST and ALT) reflect cellular injury. ALT is more specific to liver
tissue and is less elevated in alcoholic hepatitis. Alkaline phosphatase is not specific to liver
tissue but is elevated in cholestasis of any cause. γ-Glutamyl transferase is a sensitive
indicator of biliary disease and is elevated by all causes of induction of microsomal
enzymes.
Serum proteins provide an indicator of the synthetic function of the liver. Albumin
has a half-life of about 20 days and is reduced in severe cirrhosis, and also by malnutrition,
nephrotic syndrome and other causes. Clotting factors II, VII, IX, X, V and fibrinogen are
produced in the liver. A prolonged INR may indicate a failure of synthesis of these factors
(especially VII) due to hepatic failure or vitamin K malabsorption.
Other tests include blood ammonia, which is elevated in hepatic failure due to
impairment of the urea cycle and correlates with encephalopathy. Elevated triglycerides
and abnormal lipoproteins may also reflect impaired lipid metabolism.
Specific tests for causes of liver disease include hepatitis serology, antimicrosomal
antibody (PBC), antinuclear antibodies (SLE), α-fetoprotein (hepatoma), Fe studies
(haemochomatosis), ceruloplasmin (Wilson’s disease), and dozens of other specific tests.

c. Describe the handling of bilirubin in the body.

Bilirubin is derived from the breakdown of haem in tissue macrophages. It circulates
bound to albumin and is absorbed into hepatocytes. Here it is conjugated with glucuronic
acid (80%), sulfate (10%) or other compounds and excreted by active transport into the bile.
In the gut, some conjugated bilirubin is converted to urobilinogen by bacteria which
is reabsorbed and filtered by the kidneys, appearing in the urine where it is oxidized to
urobilin. Urobilinogen which is not absorbed in the gut is converted to stercobilinogen and
oxidized to stercobilin.
d. Describe the anatomical and physiological considerations in hepatic blood flow, and the changes that occur with anaesthesia.

e. Outline the reticulo-endothelial functions of the liver.

The venous sinusoids in the liver are lined with Kupffer cells, the mononuclear phagocytosing cells of the liver. Portal blood usually contains significant numbers of enteric organisms, especially gram negative bacteria, and Kupffer cells phagocytose foreign organisms, preventing them from entering the systemic circulation.

f. Explain the protective function of the liver between the gut and body.

The liver provides a barrier between the portal and systemic circulations. In its reticulo-endothelial functions it acts as an effective barrier against infection. It also acts as a metabolic buffer between the highly variable contents of the gut and portal blood and the tightly controlled systemic circulation.

By absorbing, storing and releasing glucose, fat and amino acids, the liver plays a vital role in homeostasis. It also stores and releases vitamins A, D and B₁₂. It metabolizes or deactivates most of the biologically active compounds absorbed from the gut, such as drugs and bacterial toxins. It performs many of the same functions in systemic blood entering from the hepatic artery, processing a total of 29% of cardiac output.

g. Describe the portal circulation and its significance.

The gut receives its blood supply from the coeliac axis, superior and inferior mesenteric arteries. Venous drainage from the gut from the level of the lower oesophagus to the anal canal ultimately drains into the portal vein and into the liver. The total flow from the portal vein is about 1.1 l/min at about 9 mmHg. All substances absorbed from the gut, with the exception of lipids which pass into the lymph, must pass through the liver before entering the systemic circulation.

Cirrhosis or right heart failure cause an increased resistance to flow in the liver, leading to a rise in pressure in the portal venous system. This causes transudation of fluid into the gut and peritoneal cavity, and in the long term, dilatation of veins at the sites of portosystemic anastomosis: the lower oesophagus, bare area of the liver, umbilicus and anal canal.