

LIVER PHYSIOLOGY

- (a) *To describe the storage, synthetic, metabolic and excretory functions of the liver and to identify the physiological consequences of hepatic disease.*
- (b) *To describe the clinical laboratory assessment of liver function and hepatic failure.*
- (c) *To describe the handling of bilirubin in the body.*
- (d) *To describe the anatomical and physiological considerations in hepatic blood flow, and the changes that occur with anaesthesia.*
- (e) *To outline the reticulo-endothelial functions of the liver.*
- (f) *To explain the protective function of the liver between the gut and the body.*
- (g) *To describe the portal circulation and its significance.*

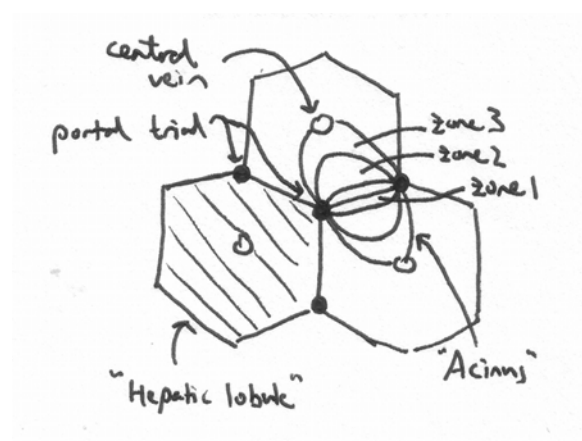
Functional Anatomy of the Liver:

(I) Microanatomy of the liver:

- Liver is the largest visceral organ → 1.2-1.5 kg
- It has two basic units:
 - (1) Hepatic Lobule (basic histological unit)
 - Consists of a central hepatic efferent venule (aka. central vein) with cords of a single layer of hepatocytes and sinusoids converging into it
 - (2) Acinus (basic functional unit)
 - Parenchymal mass formed between the two central veins and portal triads
 - Blood enters acinus from terminal branches of hepatic arteriole and portal venule (from portal triad) → drain into sinusoids → then into central vein
 - Divided into 3 functional zones:
 - Periportal (zone 1) – Receives sinusoidal blood first (so blood has highest O₂ content) → vital as it has highest metabolic rate (due to protein synthesis). Also secretes glucose into blood for use in zone 3
 - Medilobular (zone 2) – Receives blood next (which now has lower O₂ content). This zone has moderate metabolic activity
 - Centrilobular (zone 3) – Receive sinusoidal blood last (has lowest O₂ content now). This zone has ↑ [CYP450] vital for metabolism and drug biotransformation → uses glucose secreted from zone 1

Note → Zone 1 is most affected by toxins/poisons (as it receives sinusoidal blood first), while zone 3 is most affected by ↓ HbF and ↓ hypoxaemia (as it receives poorly oxygenated sinusoidal blood last)

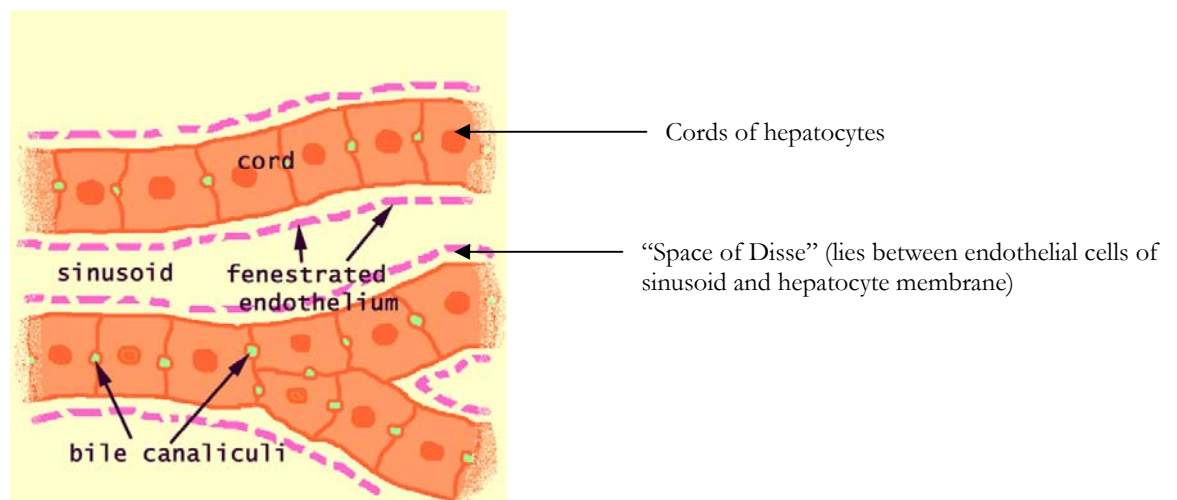
- Portal Triad → consists of Hepatic arteriole and Portal venule (as small branches of hepatic artery and portal vein, respectively), running in parallel with a Bile canaliculi
- Hepatic Sinusoid:
 - Low pressure microcirculatory system of the acinus → formed by anastomosis of a hepatic arteriole with a portal venule → contains sphincters at hepatic arterioles, hepatic venous sinusoid and arteriolar-portal shunts
 - Role → (i) Facilitates exchange of nutrients/waste between blood and hepatocytes, and (ii) Act as a reservoir for blood (depending on sphincter tone)



(II) Cells of the liver:

- (1) Hepatocytes
 - Forms bulk of the liver (60% cell mass; 80% volume) → cords of hepatocytes (in single layer) are arranged in laminae through which sinusoids interconnect

- Polygonal with 3 key surfaces → (i) Space of Disse (sinusoidal), (ii) Bile canaliculi, and (ii) adjacent hepatocyte → Nb. Microvilli exists on the sinusoidal and bile canaliculi sides to allow ↑ secretion/absorption functions
- Contains organelles that carry out most of the liver's function → rER (protein synthesis), sER (drug biotransformation, bilirubin metabolism, urea synthesis), peroxisome (FA β -oxidation), golgi apparatus (glycoprotein synthesis; storage of albumin, bile, lipoproteins), lysosome (deposit bile, ferritin, copper, autolytic enzymes), mitochondria (ATP for metabolism, metabolism of steroids and nucleic acids, deamination of catecholamines), and microtubules (bile secretion)
- (2) Kupffer cells
 - 2nd most common cell in liver (40% cell mass; 20% volume) → macrophages that line the sinusoids within "space of Disse"
 - Role → Reticulo-endothelial functions of the liver (phagocytosis of bacteria, destruction of endotoxins, protein denaturation, accumulate ferritin/haemosiderin, haemopoietic function (in utero only))
- (3) Fenestrated endothelial cells
 - They line the sinusoids → allow molecular exchange of substrates/waste between hepatocyte and sinusoids (via Space of Disse)
- (4) Pitt cells
 - Mobile lymphocytes (Active NK cells) attached to sinusoidal endothelium → defensive role against infection and tumour cells
- (5) Ito cells
 - Fat- and retinoid-storing cells that can transform to contractile cells with cytokine stimulation, and deposit collagen causing fibrosis (cirrhosis)



Functions of the Liver:

(1) Metabolic functions:

Carbohydrate metabolism:

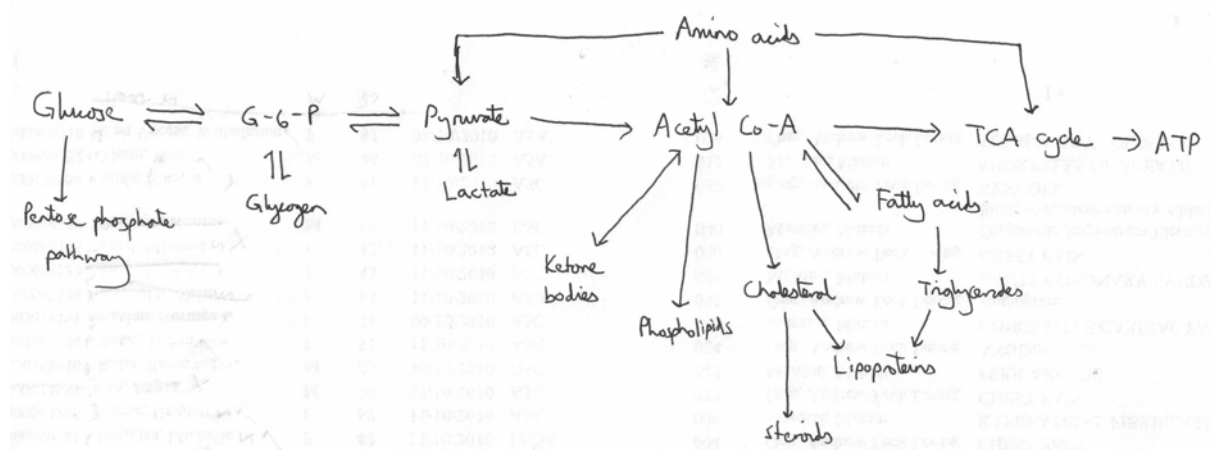
- (a) Glucostat role → maintain BGL within strict limits
 - o ↓ BGL → ↑ glucagon (and counter-regulatory hormones) and ↓ insulin → stimulates hepatic glycogenolysis and gluconeogenesis (inhibits glycogen synthesis and glycolysis)
 - o ↑ BGL → ↑ insulin and ↓ glucagon (and counter-regulatory hormones) → stimulates hepatic glycogen synthesis and glycolysis (inhibits gluconeogenesis and glycogenolysis)
- (b) Uptake of dietary monosaccharides from portal vein → convert complex sugars to glucose:
 - o Dietary monosaccharides are taken up passively via an insulin-independent GLUT 2 transporter → liver converts complex sugars (fructose and galactose) into glucose → liver glucokinase then converts glucose to G6P
 - o This facilitates continuous uptake of glucose (and other monosaccharides) into hepatocyte → via passive diffusion along their [] gradients

Note → 10% of dietary glucose is stored as glycogen, 40% converted to TAGs as fat stores, and 50% used in glycolysis (forms ATP for other liver functions)

- (c) Glycolysis of glucose for:
 - o (i) Energy production → 38 ATP made from aerobic glycolysis and [O] phosphorylation (via TCA and ETC)
 - o (ii) Lipogenesis → pyruvate is used to form acetyl-coA → which is used to form LCFA's (later stored as TAGs)
- (d) Glycogen metabolism:
 - o Glycogenolysis – Hepatic glycogen is degraded to G6P (via Glycogen phosphatase), then to glucose via Glucose 6-Phosphatase (an enzyme specific to the liver only)
 - o Glycogen synthesis – Glucose is converted to G6P (via liver glucokinase) → converted to G1P → then to UDP-glucose → Glycogen synthetase then builds up glycogen using UDP-glucose substrates

Note – Glucose stored in glycogen is produced 1^oly from gluconeogenesis (esp lactate) → only 10% dietary glucose is used for storage in glycogen!

- (e) Gluconeogenesis → glucose is derived 1^oly from lactate, but also from pyruvate, glycerol (from TAGs), and glucogenic a.a's (esp Ala and Glu)
- (f) Metabolism of lactate (derived peripherally from anaerobic metabolism) → converted to pyruvate (via Cori cycle) → which is then used for:
 - o (i) Conversion to glucose via gluconeogenesis (70% of lactate)
 - o (ii) Conversion to acetyl-CoA (30% of lactate)
- (g) Pentose phosphate shunt → glucose is converted to NADPH and ribose-5-phosphate → NADPH is vital for biotransformation of steroid hormones and drugs



Lipid metabolism:

- (a) Fatty acid oxidation for energy production:
 - During starvation, LCFAs are released from adipocytes → transport to liver where it is degraded into Acetyl-CoA (via β -oxidation)
 - Acetyl-CoA → TCA cycle → produce ATP
- (b) Ketone production:
 - During starvation, acetyl-CoA generated by β -oxidation → converted to HMG-CoA in liver → then to ketone bodies (AcAc, β -OH-butyric acid, acetone) that is used as an alternate fuel source in liver, heart and brain
- (c) Metabolism of TAGs (and fat stores):
 - Lipogenesis – Acetyl-CoA (produced from glucose or a.a. metabolism) is used to synthesise LCFAs → combined with glycerol-phosphate to form TAGs → add to liver (or peripheral) fat stores
 - Lipolysis – Hydrolysis of liver (or peripheral) fat stores → TAGs broken down into FAs and glycerol
- (d) Synthesis of cholesterol:
 - Acetyl-CoA is converted to HMG-CoA in the liver → then to mevalonic acid (by rate-limiting HMG CoA reductase) → then finally cholesterol

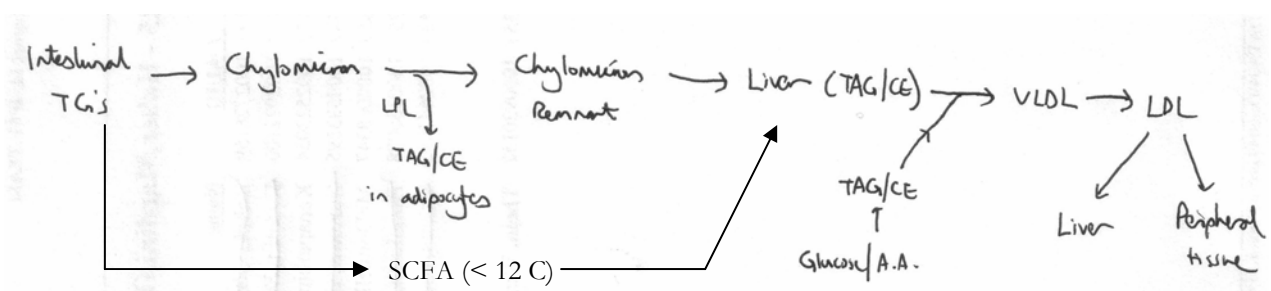
Aside: Hepatic cholesterol is derived from:

- (i) Diet (via Chylomicron remnants)
- (ii) Peripheral sources (via LDL from adipocytes)
- (iii) “De novo” synthesis from Acetyl CoA (as above)

Aside: Fate of hepatic cholesterol:

- (i) Exported as lipoproteins (Eg. VLDL)
- (ii) Secreted directly into bile
- (iii) Converted bile salts (via 7 α -hydroxylase)
- (iv) Incorporated into steroid hormones
- (v) Incorporated into cell membranes

- (e) Synthesis of phospholipids
 - Formed from Acetyl CoA → incorporated in cell membranes and lipoproteins
- (f) Lipoprotein handling for peripheral distribution of lipids:
 - Intestinal TAGs are absorbed as digested components (glycerol, FAs, MAG, DAG) → transported to the liver by two means:
 - (i) Short-chain FAs (< 12 C) → transferred directly to liver via portal vein without re-esterification
 - (ii) Long-chain FAs → re-esterified to form TAGs and packaged with cholesterol esters within Chylomicrons → transported through lymphatics systemically to adipocytes where they release lipids there for storage → Chylomicron remnants with remaining lipids are then taken up by liver
 - In the liver, TAGs are either (i) reconstituted from FAs/glycerol from chylomicron remnants, or (ii) synthesised via lipogenesis (see above) → they are then packaged with cholesterol esters (see hepatic cholesterol sources above), phospholipids, non-esterified FAs and proteins in VLDL → converted to LDL to distribute lipids to peripherally → then return back to liver



Protein metabolism:

- (a) Protein anabolism → liver produces all plasma proteins EXCEPT immunoglobulins
 - o Produces 1^oly albumin (marker of long term liver function), but also globulins and fibrinogen
 - o Includes – (i) Transport proteins (Eg. lipoproteins, transferrin, ceruloplasmin), (ii) Haematological proteins (Eg. CFs, fibrinolytics, haptoglobin, coagulation inhibitors), (iii) Immune proteins (Eg. complement, acute phase proteins), (iv) Enzymes (Eg. ALT, AST, ALP), (v) Hormones (Eg. IGF-1, TPO, EPO, angiotensinogen), (vi) Creatine

Aside → Creatine is synthesised by liver from 3 a.a. (glycine, arginine, methionine) → it is used in muscle as an energy store (ATP + creatine → phosphocreatine + ADP) → later metabolised to creatinine and excreted in urine

- (b) Protein catabolism → protein is broken down into a.a.
- (c) Amino acid metabolism → a.a.'s are metabolised to:
 - o (i) Other a.a. that the body needs (I.e. Δ dietary a.a. into non-essential a.a.)

Aside: Non-essential a.a. → Ala, Asp, Citrulline, Cys, Glu, Ser, Tyr, OH-proline

- o (ii) Glucose via gluconeogenesis (using glucogenic a.a.)
- o (iii) Acetyl-CoA (using ketogenic a.a.) → used in TCA cycle (for ATP production), or for synthesis of TAGs, cholesterol, phospholipids and ketone bodies
- o (iv) Substrates (other than acetyl-CoA) for use in TCA cycle (for ATP production)
- o (v) NH₃ (via a.a. deamination) → then to urea (see urea cycle)

Metabolism of nucleic acids:

- (a) Synthesises purine and pyrimidine bases
- (b) Metabolises purines (via [O] to uric acid, or by recycling them via “salvage pathway”) and pyrimidines (by degrading them to NH₃ → to urea cycle)

Metabolism of endogenous compounds and drugs/xenobiotics:

- Endogenous compounds and drugs/xenobiotics are generally lipophilic (I.e. partly ionised) → difficult to excrete in bile or urine
- Liver metabolises these compounds via the following reactions so they are (i) ↑ hydrophilic to facilitate excretion in urine or bile, and (ii) generally ↓ active/toxic:
 - o (1) Phase I reactions
 - They (i) ↑ reactivity of compound (to permit phase 2 reactions) and (ii) ↑ H₂O solubility of compound
 - Involves – (i) Oxidation (major) → via CYP450, (ii) Reduction → via reductase, (iii) Hydrolysis → via hydrolyase

Note – Metabolites of phase 1 reactions may be pharmacologically active and/or toxic (Eg. paracetamol metabolite)

- o (2) Phase II reactions
 - “Conjugation reactions” add polar groups to phase I metabolites → make them even more hydrophilic
 - Involves – (i) Glucuronidation (major) → via Glucuronosyl transferases, (ii) Sulphation, (iii) Acetylation

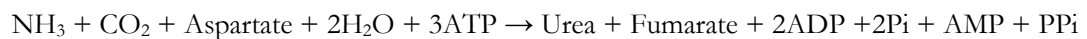
Note – All these reactions occur in the cytoplasm → EXCEPT phase I oxidation (occurs in sER)

(2) Storage functions:

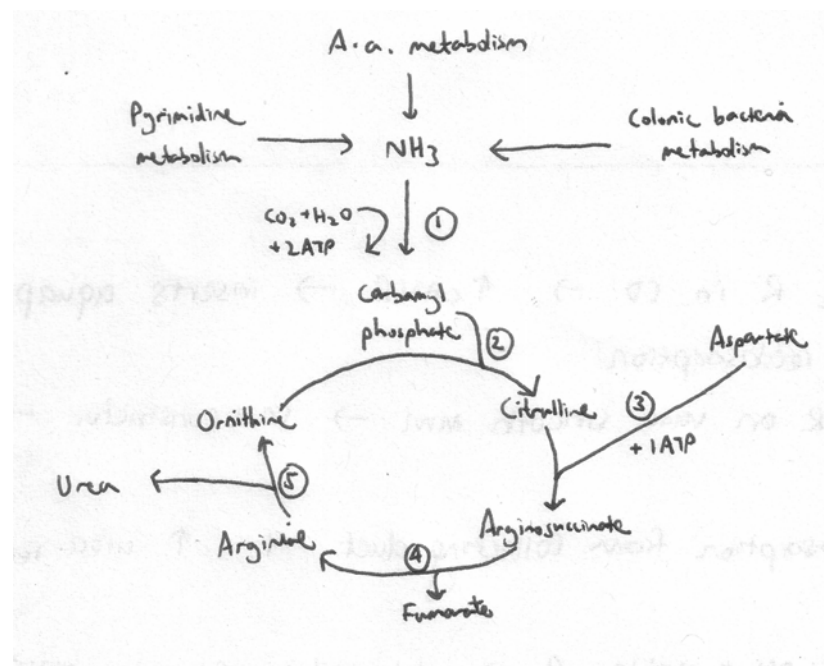
- (a) Glycogen store (adult has ~100 g of glycogen in liver) → permits glucostat function
- (b) Fat store
- (c) Vitamin store – Fat-soluble vitamins (ADEK) and vitamin B12
- (d) Metals store (especially iron and copper)
- (e) Blood reservoir:
 - o Hepatic sinusoids and portal venous system are very compliant → can normally store 500 mL of blood (10% BV)
 - o With hypervolaemia → additional 1000 mL can be stored (total 1500 mL) → due to ↑↑ compliance (or distensibility) of the system at higher venous pressures
 - o With hypovolaemia → 350 mL of stored blood can be returned to circulation → due to (i) relaxation of hepatic venule sphincters (allows portal blood to bypass sinusoids → directly enters hepatic vein), and (ii) mobilisation of sinusoidal blood in response to systemic catecholamines

(3) Production of urea (via Urea Cycle):

- Ammonia (NH₃) is an end-product of – (i) Amino acid metabolism (via deamination), (ii) Pyrimidine metabolism, and (iii) Metabolism by colonic bacteria (to some degree)
- NH₃ is toxic to the body → thus, the liver converts it to Urea (via “Urea Cycle”) → this is less toxic and is excreted from the body via the kidneys
- The “Urea Cycle” is an ATP-dependent process (3 ATP used) whereby Urea and Fumarate are formed from NH₃, Aspartate, CO₂ and H₂O:



- The cycle has five key reactions → the first 2 reactions occur in the mitochondria, while the last 3 occur in the cytoplasm:



(4) Production of bile:

- Liver produces 1 L bile/day → passes into gallbladder for concentration to 20% volume
- Bile contains → (a) Bile salts (see below), (b) Bilirubin (see below), (c) Water and electrolytes (esp NaHCO₃), (d) Lipids and proteins

Aside: Metabolism of bilirubin

- (1) “Unconjugated bilirubin” is formed by the breakdown of haemproteins by macrophages within the reticulo-endothelial system (esp Hb breakdown in spleen and BM):
 - o Haemproteins (1°ly Hb (85%), but also Mb, CYP, catalases) → broken down into (i) haem and (ii) other moieties (Eg. globin)
 - o Haem is then processed by two enzymes:
 - (i) Haem oxygenase – Converts $O_2 + \text{Haem} \rightarrow \text{Biliverdin (green)} + \text{Fe}^{2+} + \text{CO}$ (Nb. CO is excreted via lungs and Fe^{2+} is recycled)
 - (ii) Biliverdin reductase – Reduces biliverdin → “unconjugated” bilirubin (black)
- (2) “Unconjugated bilirubin” (not H_2O -soluble) is bound to albumin in plasma → transported to liver → enters hepatocyte via facilitated diffusion through a membrane-bound transport carrier (OATP transporter)
- (3) It is then converted in sER by UDP-Glucuronyltransferase into a H_2O -soluble “conjugated bilirubin” (bilirubin mono- and diglucuronide):
 - o (i) UDP-Glucuronic acid + Bilirubin → Bilirubin Monoglucuronide + UDP
 - o (ii) 2x Bilirubin Monoglucuronide → Bilirubin Diglucuronide + Bilirubin
- (4) “Conjugated bilirubin” is then actively secreted (via MRP-2) into bile canaliculi → added as one of the components of bile → passed into intestines
- (5) Intestinal flora (esp large intestines) converts it into Urobilinogen where it is then either:
 - o (i) Reabsorbed into the portal circulation (via Enterohepatic circulation) → then excreted by the kidney as Urobilin
 - o (2) Converted to Stercobilinogen → excreted in faeces as Stercobilin (gives faeces its brown colour)

Aside: Overview of bile salts:

- Functions of bile salts:
 - o (1) Facilitate intestinal digestion of lipids → aids pancreatic lipase activity
 - o (2) Enhances intestinal absorption of lipids (fat, cholesterol, phospholipids, and fat-soluble vitamins) → by (i) emulsifying lipids (by ↓ surface tension → breaks down fat), and (ii) forming “micelles” (as it is amphipathic)
 - o (3) Keeps cholesterol solubilised within gallbladder (Ie. prevents gallstones!)
 - o (4) Induces intestinal motility (Ie. endogenous laxative)
 - o (5) Choleric action → bile salts stimulate the hepatocytes to produce MORE bile (via Bile-dependent biliary secretion)
- Formation and handling of bile salts:
 - o (1) 1° bile acids (cholic acid and chenodeoxycholic acid) are produced in hepatocytes from cholesterol → then conjugated with glycine (75%) and taurine (25%) to ↑ their H_2O solubility → then actively excreted in bile
 - o (2) They are metabolised by intestinal bacteria (esp large intestines) to form 2° bile acids (deoxycholic acid and lithocholic acid)
 - o (3) 1° and 2° bile acids become “Bile salts” when they combine with Na^+ or K^+
 - o (4) 95% of bile salts are reabsorbed in terminal ileum → recirculated to liver via the portal circulation (“enterohepatic circulation”) → so both 1° and 2° bile salts can be found in bile!
 - o (4) Only 5% of bile salts are lost in faeces
- Turnover of bile salts:
 - o Rate of hepatic production of bile acid (~0.2-0.5 g/day) EQUALS rate of bile acid loss in the intestines → this low rate of production/loss is due to bile acid recycling via “enterohepatic circulation”
 - o The body has a “total” storage pool of bile acids of 3 g → during a meal, 9 g of bile salts are needed (Ie. this pool is recycled 3X). Thus, with 3x meals/day the “effective” bile acid pool can ↑ up to 27 g (Ie. this 3g pool is recycled up to 9X)

Important to note: Biliary fistula

- Causes → (i) Loss of H_2O (dehydration), (ii) Loss of bile salts (fat malabsorption, steatorrhoea, and fat-soluble vitamin deficiency), (iii) Loss of electrolytes (Na^+ , K^+ , Cl^-), and (iv) Loss of HCO_3^- (non-raised AG metabolic acidosis)

(5) Forms part of the “Reticulo-endothelial system”:

- Liver is the largest reticulo-endothelial organ → contains Kupffer cells (tissue macrophages) that line the hepatic sinusoids → functions include:
 - o (i) Immunological (part of “Innate immunity”) – Filter portal blood from GIT before it enters systemic circulation (phagocytose bacteria, denature endotoxins, activate complement, induce AIR, and lyse tumour cell)
 - o (ii) Iron regulation – Accumulates iron (as ferritin and haemosiderin) → recycles it to BM for Hb production
 - o (iii) Haematopoietic function (mainly in foetus)
 - o (iv) Coagulation (produces vWF for clotting)
 - o (v) Bilirubin metabolism (produces bilirubin from haemprotein breakdown)

Aside: Reticulo-endothelial system

- Form part of the “innate immune” system → comprises of tissue macrophages/monocytes:
 - o (i) Kupffer cells in hepatic sinusoids
 - o (ii) Macrophages in sinusoids of BM and spleen
 - o (iii) Pulmonary alveolar macrophages
 - o (iv) Macrophages in LNs
 - o (v) Microglial cells in CNs
 - o (vi) Osteoclasts in bone
- Their functions include:
 - o (i) Antigen presentation → elicit “adaptive” immune response
 - o (ii) Phagocytosis (of bacteria, tumour cells, endotoxins, debris) in tissues
 - o (iii) Production of chemicals (Eg. cytokines in response to infection and regulate haematopoiesis, complement activation)

(6) Haematological functions:

- (a) Haematopoiesis (via synthesis of EPO – mainly in utero; only 10% of adults)
- (b) Platelet synthesis (via synthesis of thrombopoietin)
- (c) Coagulation (production of clotting factors, coagulation inhibitors, fibrinolytics)

(7) Endocrine functions:

- (a) Activation of hormones (Eg. conversion of dietary or epithelial cholecalciferol → 25-HO-cholecalciferol, conversion of thyroid hormone (T4 to T3))
- (b) Production of hormones and their precursors (Eg. IGF-1, TPO, EPO, angiotensinogen)
- (c) Inactivation and excretion of hormones (Eg. T4, peptide hormones (insulin), steroid hormones (aldosterone, androgens, oestrogens), Etc.)

(8) Acid-base balance:

- (a) CO₂ production from substrate oxidation → produces 20% of body's CO₂ which is excreted by the lungs
- (b) Metabolism of acid anions
 - o Endogenous anions (Eg. lactate, ketoacids) do NOT cause net H⁺ production in the body → this is because the H⁺ produced peripherally is consumed in the liver when these anions are metabolised there
 - o Exogenous anions (Eg. citrate in PRBC, acetate/gluconate in IVF) do NOT cause net H⁺ production in the body (assuming they are not given with H⁺) → when they are metabolised by the liver they consume H⁺ → resulting in net HCO₃⁻ production
- (c) Amino acid metabolism → contributes 70% of “fixed acid” production (50 mmol/day)
- (d) NH₃ metabolism via urea cycle → produces H⁺

Hepatic Blood Flow:

Overview of hepatic blood flow and O₂ demand:

- Total hepatic blood flow is 1.5 L/min (30% of C.O.) → the liver receives blood supply (and oxygenation) from BOTH:
 - (1) Hepatic artery:
 - Derived from abdominal aorta via coeliac artery (hepatic branch)
 - Supplies liver with (i) 30% of total HBF (300-500 mL/min), and (ii) 40-50% total hepatic O₂ supply (well-oxygenated blood; SaO₂ → 98%)
 - Characterised by → High pressure (90-100 mmHg), high flow velocity (16-18 cm/s), and high-resistance arteriolar system (such that arteriolar pressure ↓ to 35 mmHg)
 - Blood flow autoregulated → dependent on metabolic demand post-prandially
 - (2) Hepatic portal vein:
 - Drains blood from GI tract (Eg. intestines, stomach, pancreas, gallbladder) and spleen → contains digestive products (GIT), and waste products of RBC destruction (spleen)
 - Supplies liver with (i) 70% of total HBF (1000-1200 mL/min), and (ii) 50-60% total hepatic O₂ supply (poorly oxygenated blood; SvO₂ 50-85%)
- Aside:

 - Fasting → SvO₂ ~85% (↑↑ than MVB due to ↑ mesenteric arterial shunting through the intestinal capillaries, which drain into portal veins)
 - Post-prandially → SvO₂ ↓ to ~ 50%
- Characterised by → Low pressure (5-10 mmHg), low flow velocity (9 cm/s), low resistance portal venous system (5-10% of that in hepatic artery), and VALVELESS venous system
 - Blood flow NOT autoregulated → dependent on blood flow to GIT/spleen
- Hepatic O₂ consumption and extraction:
 - Hepatic O₂ consumption is 50 mL O₂/min (20% of body's O₂ consumption → same as brain and skeletal muscle!)
 - Hepatic O₂ extraction is very efficient (cf. other organs) → this is important b/c O₂ consumption can be maintained with ↓ total HBF by ↑↑↑ O₂ extraction at sinusoids!

Aside: With acute haemorrhage → ↓ O₂ supply due to (i) ↓ total HBF (↓ PV > HA) and (ii) mobilisation of 50% sinusoidal blood reserve into systemic circulation → BUT O₂ delivery maintained due to ↑↑↑ sinusoidal O₂ extraction

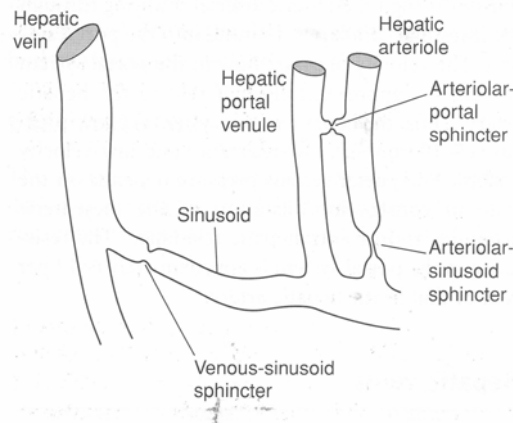
Hepatic microvasculature:

- “Sinusoids” are the low pressure microvascular capillary system of acinus → produced from anastomosis of hepatic arteriole and portal venule
- Role of sinusoids:
 - (i) Facilitates exchange of nutrients/waste between blood and hepatocytes
 - (ii) Act as a reservoir for blood

Aside:

- Hepatic sinusoids and portal venous system are very compliant → can normally store 500 mL of blood (10% BV)
- With hypervolaemia → additional 1000 mL can be stored (total 1500 mL) → due to ↑↑ compliance (or distensibility) of the system at higher venous pressures
- With hypovolaemia → 350 mL of stored blood can be returned to circulation → due to (i) relaxation of hepatic venule sphincters (allows portal blood to bypass sinusoids → directly enters hepatic vein), and (ii) mobilisation of sinusoidal blood in response to systemic catecholamines

- It is a low pressure system (2 mmHg) → due to high resistance pre-sinusoidal sphincters (esp arteriolar-sinusoid and arteriolar-portal sphincters)
- Blood within these sinusoids flow from the periphery of the acinus (where “portal triad” lies) → into central vein → then into hepatic vein
- There are three sets of sphincters implicated in the sinusoidal system:
 - (i) Arteriolar-Portal sphincter (between the hepatic arteriole and portal venule)
 - (ii) Arteriolar-Sinusoid sphincter (between the hepatic arteriole and sinusoid)
 - (iii) Venous-Sinusoid sphincter (between the sinusoid and hepatic vein)



Hepatic vein:

- Hepatic veins receive sinusoidal blood via the central veins → blood leaves liver into IVC

Control of hepatic blood flow:

$$\text{Hepatic arterial blood flow} = \frac{\text{MAP} - \text{Hepatic venous pressure (HVP)}}{\text{Hepatic vascular resistance (HVR)}}$$

$$\text{Portal venous blood flow} = \frac{\text{Portal venous pressure} - \text{HVP}}{\text{HVR}}$$

Thus → factors that influence (i) MAP, (ii) PVP, (iii) HVP, and (iv) HVR control HBF!

Intrinsic regulation of HBF:

- Autoregulation of HBF:
 - (i) Hepatic artery is autoregulated
 - ↓ hepatic arterial pressure → hepatic arterial blood flow is maintained by ↓ hepatic artery resistance (UNTIL $P_{\text{SYSTOLIC}} < 80 \text{ mmHg}$)
 - ↑ hepatic arterial pressure → flow maintained due to ↑ hepatic artery resistance
 - (ii) Portal vein is NOT autoregulated
 - Portal vein flow is LINEARLY related to portal venous pressure (Ie. ↑ portal venous pressure = ↑ portal venous flow)

Note: “Hepatic arterial buffer response” exists → semi-reciprocal interrelationship between HA and PV blood flow based upon the autoregulatory nature of these vessels:

- (i) Δ PV blood flow → causes a compensatory Δ HA blood flow (as HA is autoregulated) → maintains HBF:
 - ↓ PV blood flow → compensatory ↑ HA blood flow 2° ↓ HA resistance (due to vasodilation triggered by build-up of adenosine metabolite)
 - ↑ PV blood flow → compensatory ↓ HA blood flow 2° ↑ HA resistance (due to reflex vasoconstriction triggered by a myogenic mechanism)
- (ii) Δ HA blood flow does NOT cause a compensatory Δ in PV blood flow (as PV is NOT autoregulated) → thus HBF cannot be maintained

Extrinsic control of HBF:

- (1) Neuroendocrine factors:
 - o Catecholamines:
 - NAd/Adr – (i) PV constriction (α), (ii) HA constriction initially (α) $\rightarrow$ dilation later on (β), and (iii) HV constriction (α) $\rightarrow$ generally cause $\uparrow$ HVR $\rightarrow$ $\downarrow$ HBF
 - Dopamine – Minimal effects at physiological conditions
- Hepatic artery has $\rightarrow$ (i) α -receptors, (ii) β -receptors, and (iii) DA receptors
Portal vein has $\rightarrow$ (i) α -receptors, and (ii) DA receptors
Hepatic vein has $\rightarrow$ α -receptors
- o AII – HA, PV and HV constriction $\rightarrow$ $\uparrow$ HVR $\rightarrow$ $\downarrow$ HBF
 - o ADH – Only PV constriction $\rightarrow$ $\uparrow$ HVR $\rightarrow$ $\downarrow$ HBF
 - o Glucagon – Both HA and PV dilation $\rightarrow$ $\downarrow$ HVR $\rightarrow$ $\uparrow$ HBF
 - o VIP/Secretion – Dilate HA only $\rightarrow$ $\downarrow$ HVR $\rightarrow$ $\uparrow$ HBF
 - (2) External factors:
 - o Physiological:
 - Δ MAP/C.O. – $\uparrow$ MAP/C.O. $\rightarrow$ $\uparrow$ HBF; $\downarrow$ MAP/C.O. $\rightarrow$ $\downarrow$ HBF
 - Spontaneous breathing – $\uparrow$ hepatic venous outflow with inspiration ($\uparrow$ HBF), and $\downarrow$ with expiration ($\downarrow$ HBF)
 - Exercise – $\downarrow$ HBF due to splanchnic vasoconstriction ($\uparrow$ HVR)
 - Feeding – $\uparrow$ HBF due to increased intestinal blood flow ($\uparrow$ PVP)
 - PaCO_2 – $\downarrow$ PaCO_2 causes $\downarrow$ HBF due to $\downarrow$ PV blood flow (PV constriction and $\uparrow$ HVR); opposite with $\uparrow$ PaCO_2
 - PaO_2 – $\uparrow$ PaO_2 has little effect on HBF; $\downarrow$ PaO_2 initially $\downarrow$ HA blood flow (but this normalizes in 30 mins) and has minimal effects on PV blood flow
 - o Iatrogenic/pathophysiological:
 - MAP/C.O. – $\uparrow$ MAP/C.O. (Eg. inotropes) $\rightarrow$ $\uparrow$ HBF; $\downarrow$ MAP/C.O. (Eg. shock due to anaphylaxis, hypovolaemia, cardiogenic) $\rightarrow$ $\downarrow$ HBF
 - IPPV/PEEP – $\downarrow$ HBF due to a $\downarrow$ C.O./MAP and $\uparrow$ HVP
 - Surgical factors (Eg. laparoscopy, ligation, Etc.) $\rightarrow$ $\downarrow$ HBF due to external compression on vessels, SNS activation or local reflexes
 - Anaesthetic factors (see below)

Effect of anaesthesia on HBF:

- (1) Spinal and epidural anaesthesia:
 - o $\downarrow$ HBF (and O_2 delivery) due to (i) $\downarrow$ PV blood flow (main factor), and (ii) $\downarrow$ C.O./MAP
- (2) IV induction agents (Eg. propofol, thiopentone, etomidate):
 - o Dose-dependent $\downarrow$ HBF (and O_2 delivery) due to (i) $\downarrow$ C.O. and (ii) Obtundation of “Hepatic arterial buffer” mechanism (Ie. $\downarrow$ PV blood flow will not invoke reflex $\uparrow$ HA blood flow to maintain HBF)
- (3) Inhalational agents
 - o Halothane – $\downarrow\downarrow\downarrow$ HBF and O_2 delivery (greatest $\downarrow$ cf. other agents) due to (i) Obtundation of “hepatic arterial buffer” mechanism and (ii) $\downarrow$ C.O.
 - o Enflurane – Like halothane but less severe
 - o Isoflurane, Desflurane and Sevoflurane – HBF and O_2 delivery maintained (esp with isoflurane) or slightly $\downarrow$ despite $\downarrow$ PV blood flow/ $\downarrow$ C.O. $\rightarrow$ due to preservation of “hepatic arterial buffer” mechanism (Ie. no Δ or reflex $\uparrow$ in HA blood flow)

Measuring hepatic blood flow:

Direct method of measuring HBF:

- “Electromagnetic flowmeters” around each respective vessels at laparotomy $\rightarrow$ used to measure HA and PV blood flows

- Limited use due to → (i) effect of GA and devices on HBF, and (ii) ↑ invasiveness

Indirect method of measuring HBF (using Fick's Principle):

Important to note → “Fick's principle” – Law of conservation of matter → at a given time, the quantity of substance entering a compartment in the inflowing of blood must EQUAL the sum of substance accumulating in the compartment and of that leaving in the outflowing flood

- (1) Clearance techniques
 - o HBF estimated by clearance of indocyanine green (ICG) dye:
 - ICG dye is only removed from circulation by liver (100% biliary excretion) and lacks enterohepatic recycling
 - It is measured in blood by spectrophotometry (805 nm absorption peak)
 - o There are two techniques:
 - (i) Single ICG bolus technique → single IV bolus of ICG is given and venous samples are collected every 2 minutes for 14 minutes. Concentration-time delay curves are analysed to determine its clearance

$$\text{Hepatic blood flow} = \frac{\text{Clearance}}{\text{Extraction ratio}}$$

$$\text{Clearance} = \frac{\text{Dose}}{\text{AUC of conc. vs time}}$$

Extraction ratio of ICG is 0.74

- (ii) Continuous ICG infusion technique → ICG infused for 20 mins to achieve steady-state/equilibrium (I.e. infusion rate = hepatic uptake) → samples taken simultaneously from any peripheral artery ($\approx$ hepatic arterial [ICG]) and a cannulated hepatic vein (= hepatic vein [ICG])

$$\text{Hepatic blood flow} = \frac{\text{Clearance}}{\text{Extraction ratio}}$$

$$\text{Clearance} = \frac{\text{Infusion rate}}{\text{Hepatic arterial [ICG]}}$$

$$\text{Extraction ratio} = \frac{(\text{Hepatic arterial [ICG]} - \text{Hepatic venous [ICG]})}{\text{Hepatic arterial [ICG]}}$$

- (2) Reticuloendothelial cell uptake
 - o Kupffer cells remove radiolabelled colloidal substances (Eg. 131-iodine-albumin, colloid gold-198, Tc-99 sulphur colloid particles)
 - o Thus, HBF is estimated by the clearance rate of these substances from circulation → inject substance then use “gamma camera” to produce “isotope uptake-time” curves (I.e. determine AUC of uptake vs time) to determine its clearance

$$\text{Hepatic blood flow} = \frac{\text{Clearance}}{\text{Extraction ratio}}$$

$$\text{Clearance} = \frac{\text{Dose}}{\text{AUC of conc. vs time}}$$

Liver Function Tests:

Principles of liver function tests (LFTs):

- (1) They indicate presence of liver injury
- (2) They test hypotheses about types of hepatobiliary pathophysiology → BUT do NOT ascertain precise cause of hepatobiliary disease (I.e. need biopsy, serology, Etc.)
- (3) The tests are very sensitive BUT non-specific (Eg. many other causes of derangements)

Table of LFT values and clinical significance:

Test	Reference range	Clinical significance
Synthetic function:		
Coagulation studies (INR and PT)	INR > 1.2 PT 10-15 s	- Hepatocytes synthesise clotting factors (incl vitamin K-dependent CFs) - ↑ PT or INR suggests either (i) impaired CF synthesis (hepatocellular damage → acute liver dysfunction), or (ii) vitamin K malabsorption (cholestasis) - Non-specific → also can suggest warfarin use, DIC, Etc.
Serum proteins (including albumin, globulin, fibrinogen)	Total protein 60-80 g/L Albumin 35-45 g/L Globulin 25-35 g/L Fibrinogen 2-4 g/L	- Liver synthesises nearly all plasma proteins (except Ig's) - ↓ serum total protein, albumin, globulin and fibrinogen levels suggest impaired synthetic function due to hepatocellular damage - Non-specific → also can suggest nephrotic syndrome, malnutrition states, burns, Etc. - Note – Albumin is a long-term marker of liver function (as t ½ 20 days) → ↓ albumin means chronic liver dysfunction (as it can be normal with acute liver disease)
Serum platelet and Hb	Hb 100-130 g/L Plt 150-450 x 10 ⁹ /L	- Liver produces TPO (and 10% of EPO) → ↓ Hb and platelet counts suggest hepatocellular damage - Non-specific → other causes of anaemia (Eg. Fe and vitamin B12 deficiencies, haemolysis, Etc.) and ↓ platelets (Eg. ITP, HTS, Etc.)
Metabolic function:		
Plasma ammonia/urea	NH ₃ < 35 umol/L Urea 3-7 umol/L	- Liver converts toxic NH ₃ (metabolite of a.a. and pyrimidine) into less toxic urea for renal excretion via the “urea cycle” - ↑ NH ₃ and ↓ urea suggests hepatocellular damage
Plasma glucose	BGL 4-8 mmol/L	- Liver has vital role in glucostat function (glycolysis, glycogen metabolism, gluconeogenesis) - BGL derangements suggest hepatocellular dysfunction - Non-specific → also can suggest DM, insulin use, Etc.
Serum bilirubin (total and direct bilirubin)	Total bilirubin < 20 umol/L Direct bilirubin < 5 umol/L	- Unconjugated (indirect) bilirubin is produced in RE system from breakdown of haem from haemoproteins (esp Hb) → conjugated in liver before it is excreted in bile - Total and direct bilirubin levels are measured → indirect levels are calculated from these figures - ↑ total bilirubin can be due to: - (i) ↑ direct bilirubin → suggests cholestasis due to impaired excretion of bile - (ii) ↑ indirect bilirubin → suggests a prehepatic cause (Eg. haemolysis, Gilbert's syndrome) - (iii) ↑ direct and indirect bilirubin (mixed) → suggests hepatic disease a/w impaired hepatic uptake and conjugation of bilirubin
Hepatocellular injury:		
Serum aminotransferases (AST and ALT)	AST < 30 IU/L ALT < 20 IU/L	- AST and ALT are enzymes found in hepatocyte mitochondria → ↑ AST and ALT indicates hepatocellular damage → release enzymes in blood - ALT is specific to hepatocytes only → so ↑ ALT:AST

		ratio strongly suggests hepatocellular damage - AST is less specific to hepatocytes → also found in heart, RBC, skeletal muscle → so ↓ ALT:AST ratio less likely a/w hepatocellular dysfunction
Serum lactate dehydrogenase (LDH)	LDH 140-280 IU/L	- LDH is found in hepatocytes → ↑ LDH with hepatocellular damage → release enzymes in blood - Non-specific → also found in heart, pancreas, RBC, skeletal muscle, lungs, placenta → MI, cancer, haemolysis, pancreatitis, Etc.
Cholestasis:		
Serum alkaline phosphatase (ALP) and γ-glutamyl-transpeptidase (GGT)	ALP < 100 IU/L GGT < 50 IU/L	- ALT and GGT are enzymes found on hepatocytes AND ductal cells along bile duct/canaliculus - ↑ ALP and GGT suggest hepatobiliary disease (intra- and extra hepatic cholestasis) - GGT ↑ alone is non-specific → can be induced by EtOH or drug ingestion - ALP ↑ alone is non-specific → it is produced elsewhere (Ie. bone → Paget's disease; placenta)

Physiological Consequences of Hepatic Disease:

GI effects:

- (1) Portal HTN → due to distorted hepatic anatomy/hepatocellular damage
- (2) Development of portosystemic venous collaterals (Eg. gastro-oesophageal, haemorrhoidal, periumbilical, retroperitoneal) → due to portal HTN
- (3) Ascites → due to portal HTN ($\uparrow$ plasma $P_{\text{HYDROSTATIC}}$), hypoalbuminaemia ($\downarrow$ plasma P_{ONCOTIC}), and net $\text{Na}^+/\text{H}_2\text{O}$ retention ($\uparrow$ ECFV)

CNS effects:

Hepatic encephalopathy → due to build up to toxins (Eg. ammonia) that the liver usually metabolises

CVS effects:

Hyperdynamic circulatory state ($\uparrow$ C.O. by 50%) due to → (i) Portosystemic shunting, (ii) $\downarrow$ SVR, and (iii) $\uparrow$ ECFV

Respiratory effects:

Hypoxaemia → due to (i) V/Q mismatching (intrapulmonary arteriovenous shunting a/w hepatopulmonary syndrome, atelectasis and pleural effusions a/w ascites), and (ii) hypoventilation (due to elevated diaphragm from ascites)

Renal effects:

- (1) Oedematous state due to $\uparrow$ ECFV → caused by (i) hypoalbuminaemia and (ii) $\uparrow$ ECFV
- (2) $\uparrow$ ECFV due to net Na^+ and H_2O retention → “effective” PV is $\downarrow$ (due to ascites/oedema) → relative hypovolaemia triggers $\uparrow$ RAAS/SNS effect
 - (3) Hyponatraemia (despite net Na^+ retention → due to dilution by excess H_2O retention)
 - (4) Hypokalaemia (due to 2° hyperaldosteronism)
 - (5) Renal failure due to “hepatorenal syndrome”

Haematological effects:

- (1) Coagulopathy/impaired haemostasis due to → (i) impaired CF production (impaired synthesis, lack of Vitamin K reabsorption), and (ii) thrombocytopaenia (TPO deficiency and hypersplenism)
- (2) Anaemia → due to loss of EPO, nutritional deficiencies (esp minerals/vitamins), BM suppression
- (3) Infection risk → due to (i) leukopaenia (hypersplenism) and (ii) risk of SBP (ascites)
- (4) Hypersplenism and splenomegaly (due to portal HTN)

Metabolic effects:

- (1) Jaundice → due to impaired bilirubin metabolism
- (2) Hypoglycaemia → due to deranged glucostat function (impaired regulation of glycogen storage and gluconeogenesis)
- (3) Hypoalbuminaemia and hypoproteinaemia → due to impaired synthetic function
- (4) Alkalosis → respiratory alkalosis due to hyperventilation (compensate for hypoxaemia); metabolic alkalosis due to secondary hyperaldosteronism
- (5) Impaired biotransformation of endogenous compounds and xenobiotics
- (6) Mineral (Fe/Cu) and vitamin deficiencies → impaired vitamin/mineral storage
- (7) Fat malabsorption (esp fat-soluble vitamins) and steatorrhea → due to lack of bile salts