CHOLESTEROL
OBJECTIVES:
1. For **cholesterol**:
   a) list its physiological functions
   b) describe its synthesis
   c) list groups of hormones produced from it
2. For **bile acids (salts)**:
   a) list their physiological functions
   b) describe their synthesis
CHOLESTEROL FACTS

- synthesized from acetyl CoA and eliminated as bile acids
- precursor of all other steroids in the body
- in foods of animal origin
- amphipathic lipid (hydrophobic and hydrophilic portions)
- storage form is cholesterol ester found in most tissues.

Cholesterol ester (1st ring only)
R = fatty acid hydrocarbon chain
CHOLESTEROL FACTS

- essential structural component of membranes
- transported in the circulation in lipoproteins
The physiological roles of cholesterol include:

a) an important lipid component of biological membranes,
b) precursor of steroid hormones and
c) source of bile acids.

Bile acids are polar derivatives of cholesterol and aid in:

a) lipid digestion
b) lipid absorption
c) cholesterol excretion
Cholesterol synthesis pathway
Figure 2. The four stages of cholesterol biosynthesis.

Stage 1
- Acetyl CoA (C₂)
- HMG-CoA
- NADPH
- HMG-CoA Reductase
- Mevalonate (C₆)
- NADP⁺
- NADPH
- NADP⁺
- Mevalonate is feedback inhibitor
- Mevalonate is rate-determining step
- Target site for statin drugs

Stage 2
- Mevalonate
- Squalene (C₃₀)
- Several Condensation Steps
- 3ATP
- 3ADP
- Active Isoprenoids (C₅)
- NADPH
- NADP⁺
- Squalene (C₃₀)
- Cholesterol (C₂₇)

Stage 3
- Squalene (C₃₀)
- Cyclization
- Squalene epoxidase/cyclase
- Lanosterol (C₃₀)
- 3 CH₃
- Oxygen (O₂)
- (19 steps)

Stage 4
- Lanosterol (C₃₀)
- Cholesterol (C₂₇)
- Oxygen (O₂)
HMG-CoA reductase is the regulatory enzyme of cholesterol pathway synthesis. It is inhibited by antihyperlipidaemic drug; statin and dietary cholesterol, but stimulated by Insulin through decreasing c AMP.
Bile acids synthesis
The initial reaction, $7\alpha$-hydroxylase, in the conversion of cholesterol to bile acids.

- **Rate-determining step**
- Repressed (decreased synthesis) by bile salts
- Induced (increased synthesis) by cholesterol
Primary bile acids are: cholic acid and chenodeoxycholic acid (synthesized from cholesterol in the liver)

Secondary bile acids are: deoxycholic acid and lithocholic acid (from primary in S.I by intestinal flora).
General pathways for the synthesis of aldosterone and cortisol in the adrenal cortex

Activated to turn on pathways

Cholesterol → Pregnenolone → Progesterone

Progesterone → 11-Deoxy-cortisone → Aldosterone

Progesterone → 11-Deoxy-cortisol → Cortisol

21-hydroxylase
Figure 7. Photobiosynthesis of vitamin D₃ and its metabolism.

Provitamin D₃ (7-dehydrocholesterol: Intermediate in cholesterol synthesis)

Vitamin D₃

25(OH) D₃

1,25(OH)₂ D₃ (active hormone form)

Liver 25-OHase

Kidney 1-OHase

OHase = hydroxylase

Specific receptors in intestine, bone, kidney

Ca: Intestinal absorption Renal reabsorption

PO₄: Intestinal absorption Renal reabsorption

UV from sunlight Skin

Diet

UV from sunlight Skin