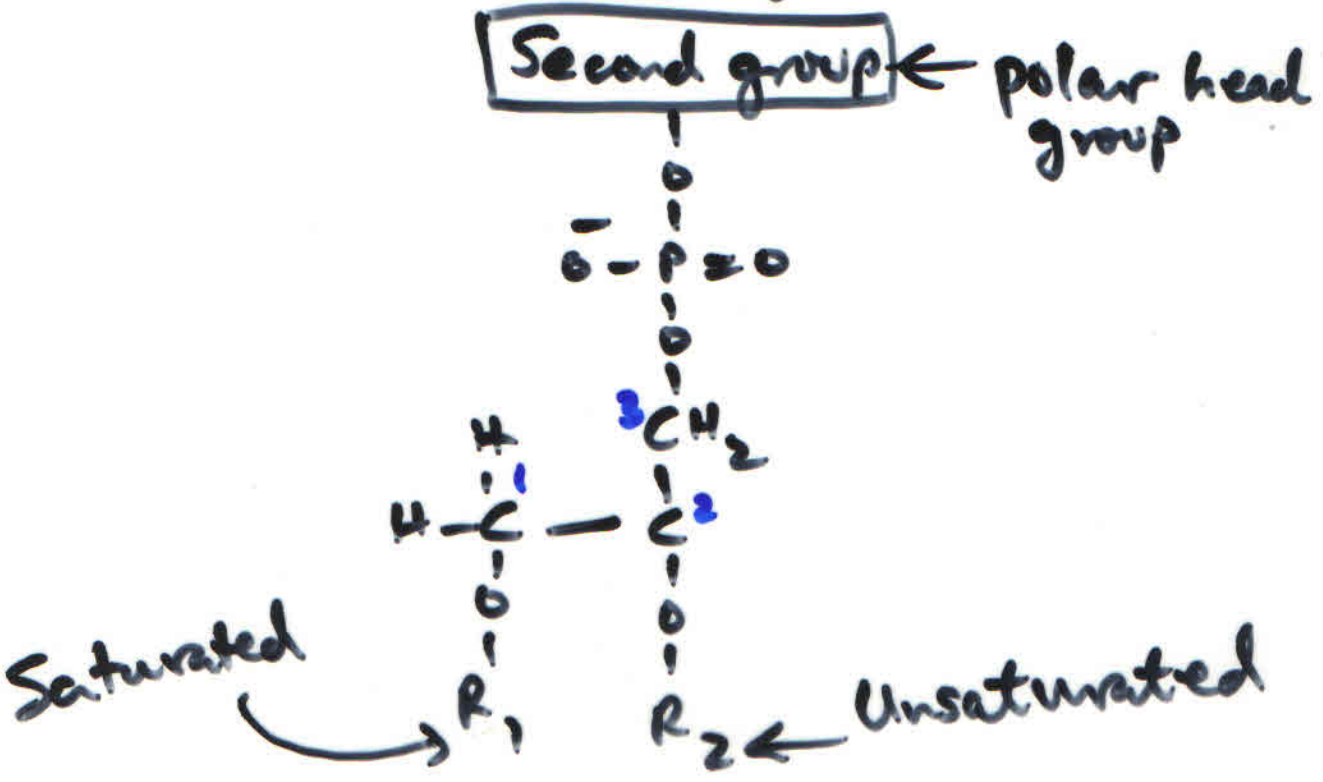
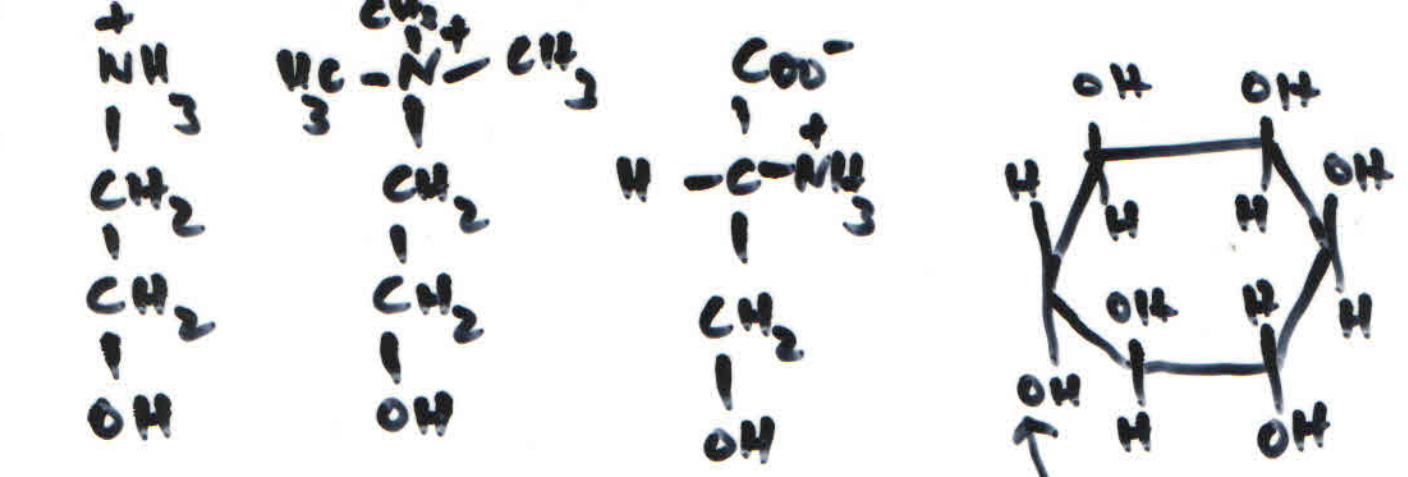
BIOSYNTHESIS OF PHOSPHOGLYCERIDES

- Occurs in the SER (surface).
- They are amphipathic.
- Chemistry: - differ from TGs in having one or more polar head groups in addition to their hydrocarbon tails.
  - Contain 2 FAs esterified to the 1st and 2nd -OH groups of glycerol. The 3rd -OH group forms an ester linkage with phosphoric acid.
  - Linked to phosphoric acid (esterified) is another second group which gives the name of the phosphoglyceride.





Ethanolamine Choline Serine linked to phosphate

Inositol

Phosphatidyl-ethanolamine ①

Phosphatidyl-choline ②

③ Phosphatidyl-serine

④ Phosphatidylinositol

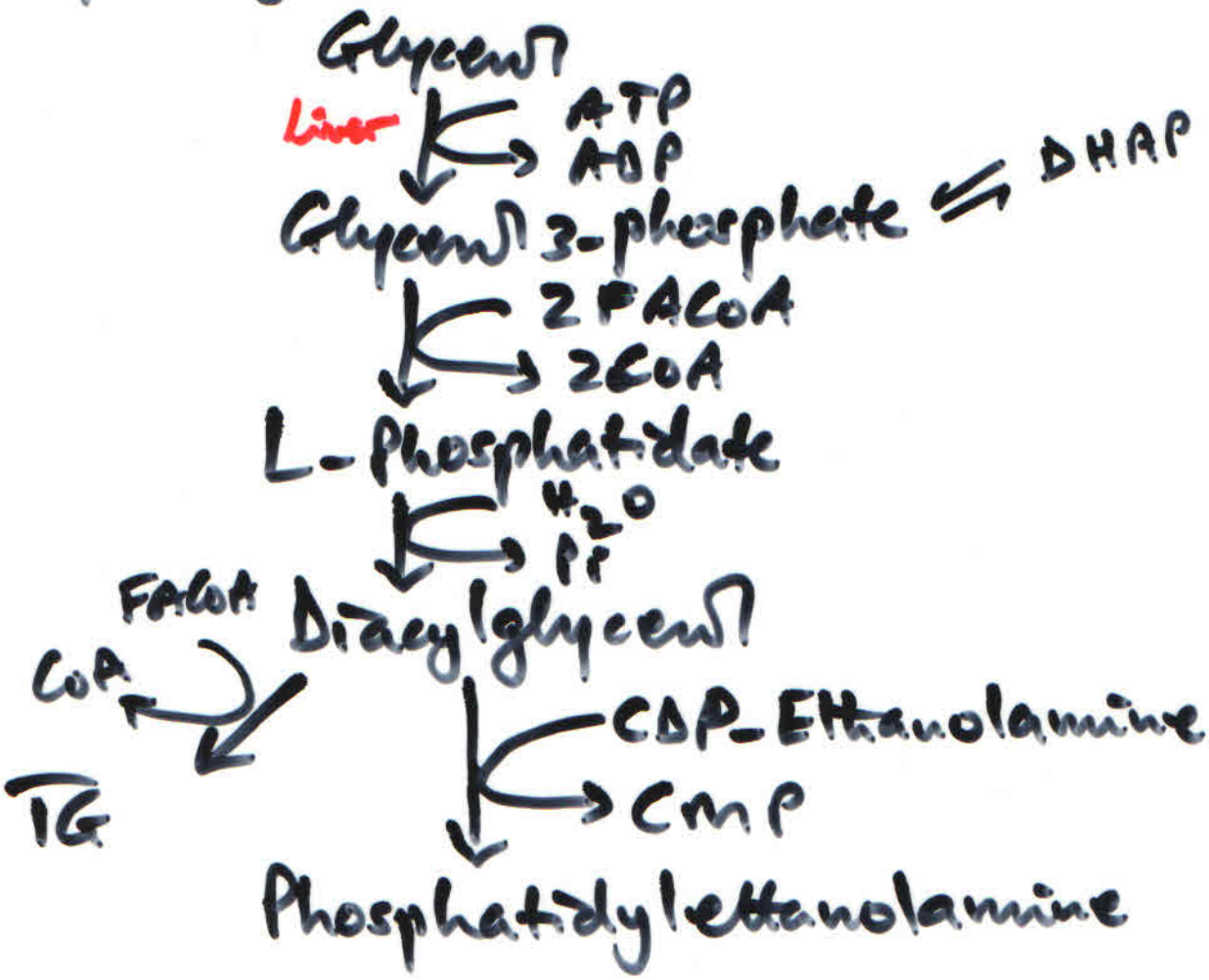
⑤ Cardiolipin

"double" phosphoglyceride

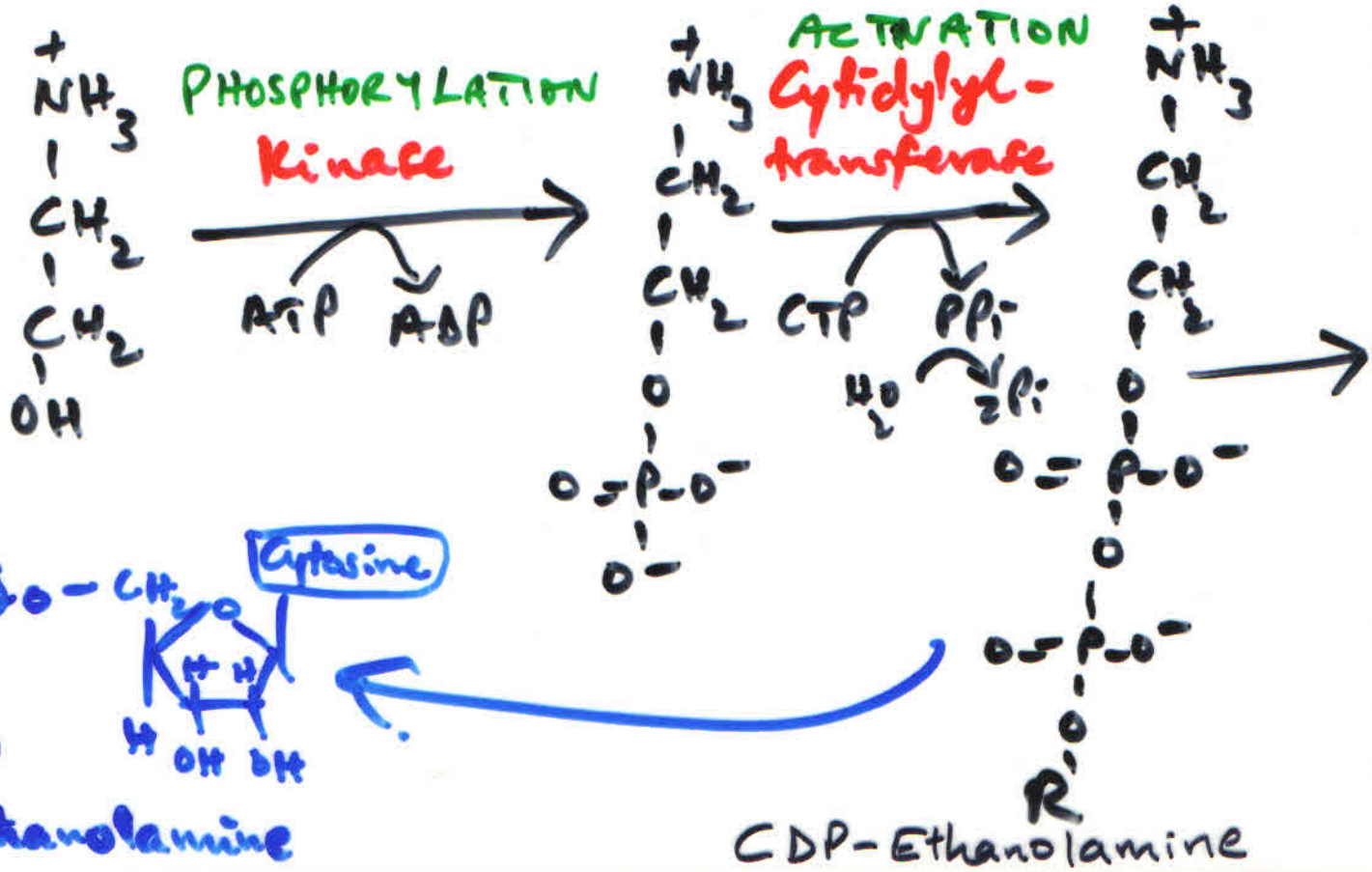
4 FAs + 3 Glycerol + 3 Phosphates

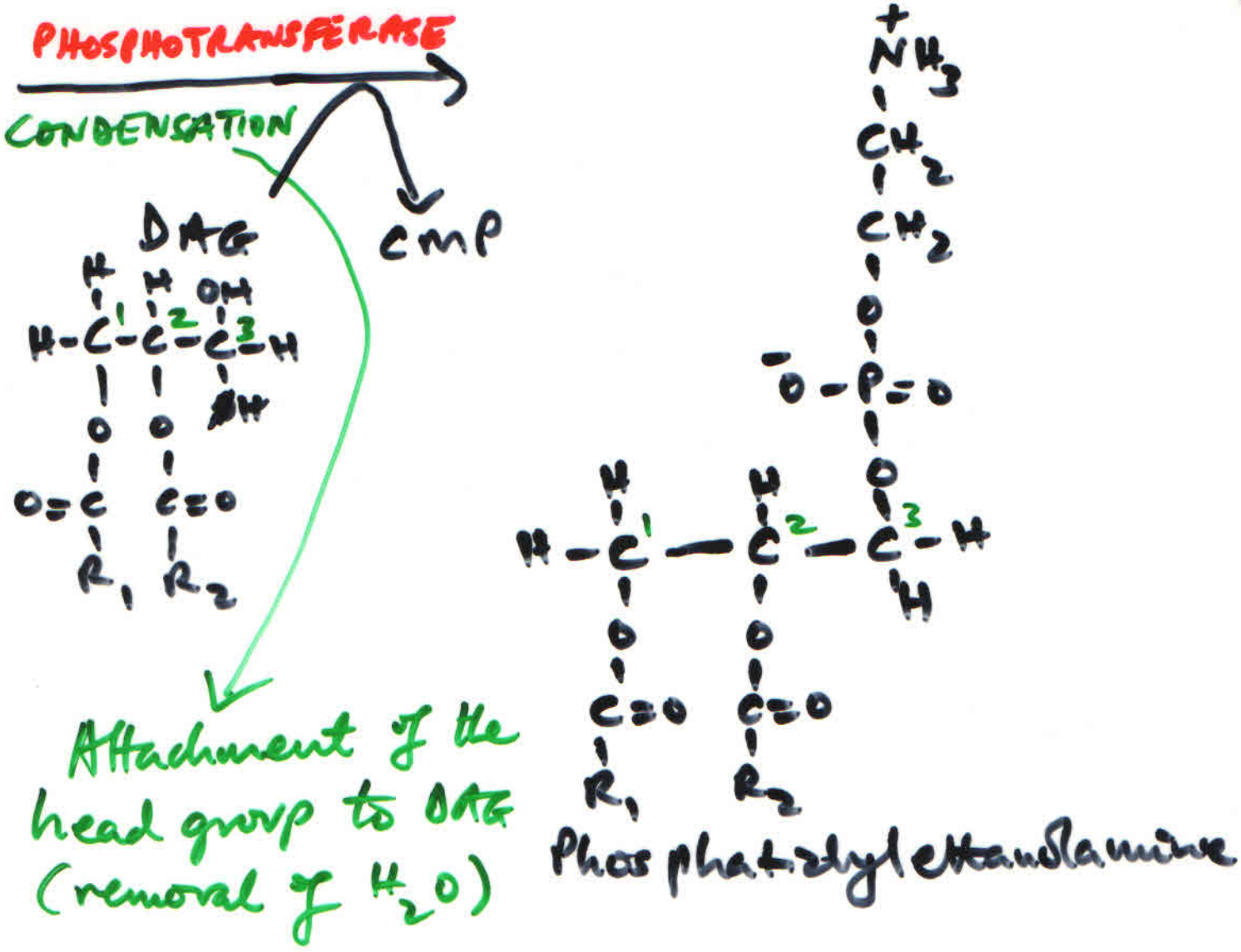
* Synthesis of phosphoglycerides and TGs are related as they contain FAs and glycerol. Their pathways are linked at first but differ in later stages.

e.g. Phosphatidylethanolamine



Precursors = Glycerol + FACoA + ATP + CTP + Ethanolamine





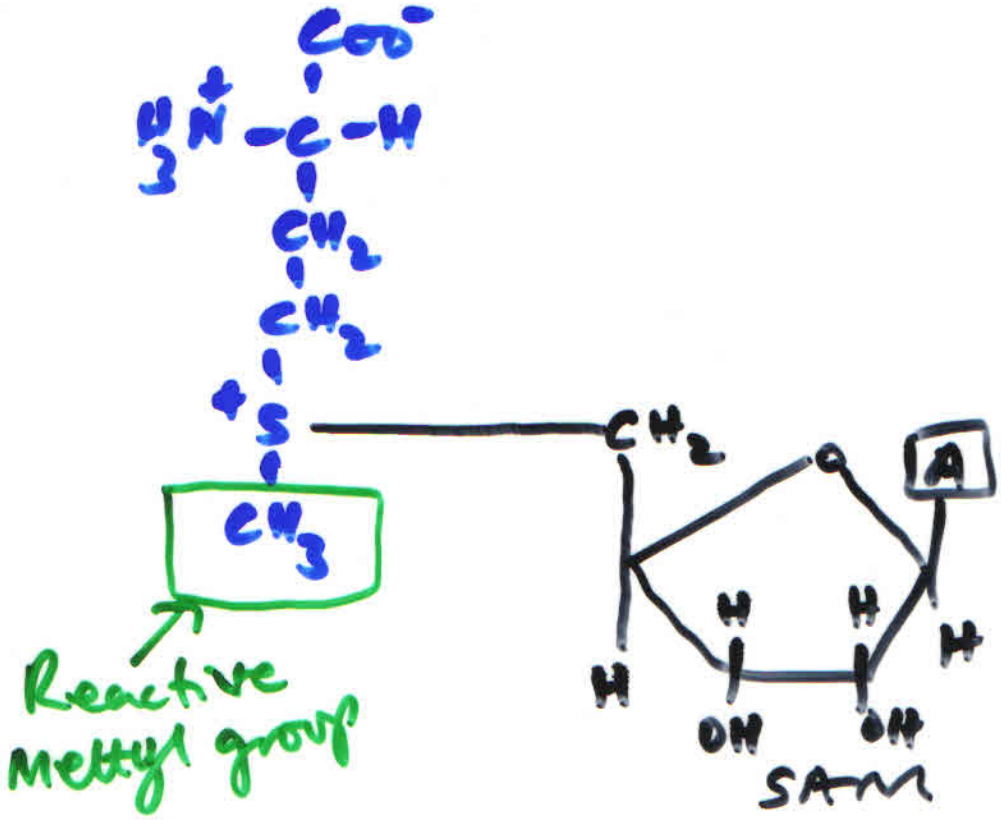
Synthesis of phosphatidylcholine

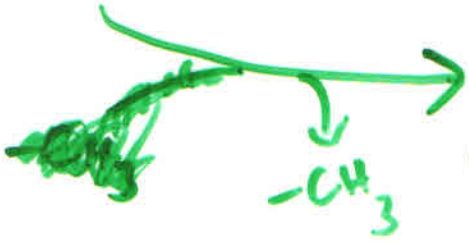
Is made by 2 different pathways

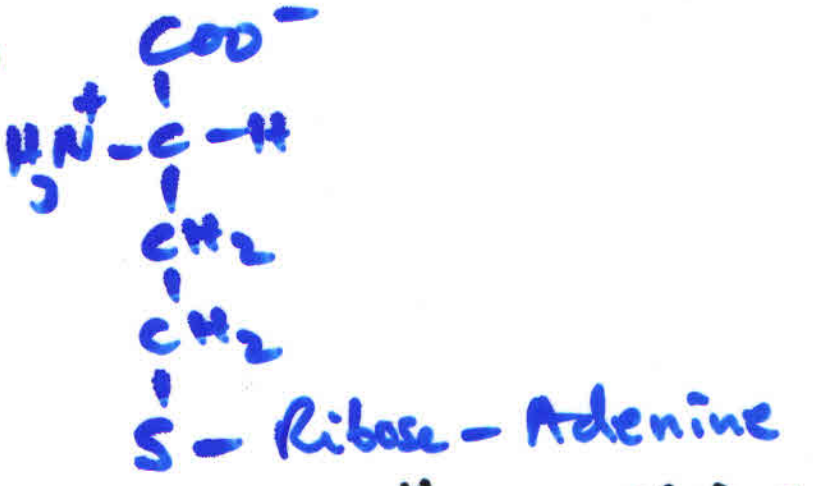
(i) De novo pathway = "from the beginning"

Made from phosphatidylethanolamine by 3 methylation steps. The methyl group donor is S-Adenosylmethionine (SAM) - an activated form of methionine in which the methyl group is reactive.

NB SAM = Adomet







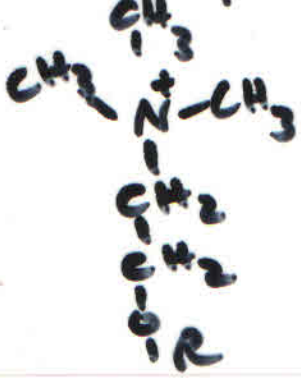
S-Adenosylhomocysteine
(SAH)

Phosphatidylethanolamine

3 STEPS → (Methyltransferase)

3 SAM
3 S-Adenosylhomocysteine

Phosphatidyltrimethylethanolamine
(Phosphatidylcholine)



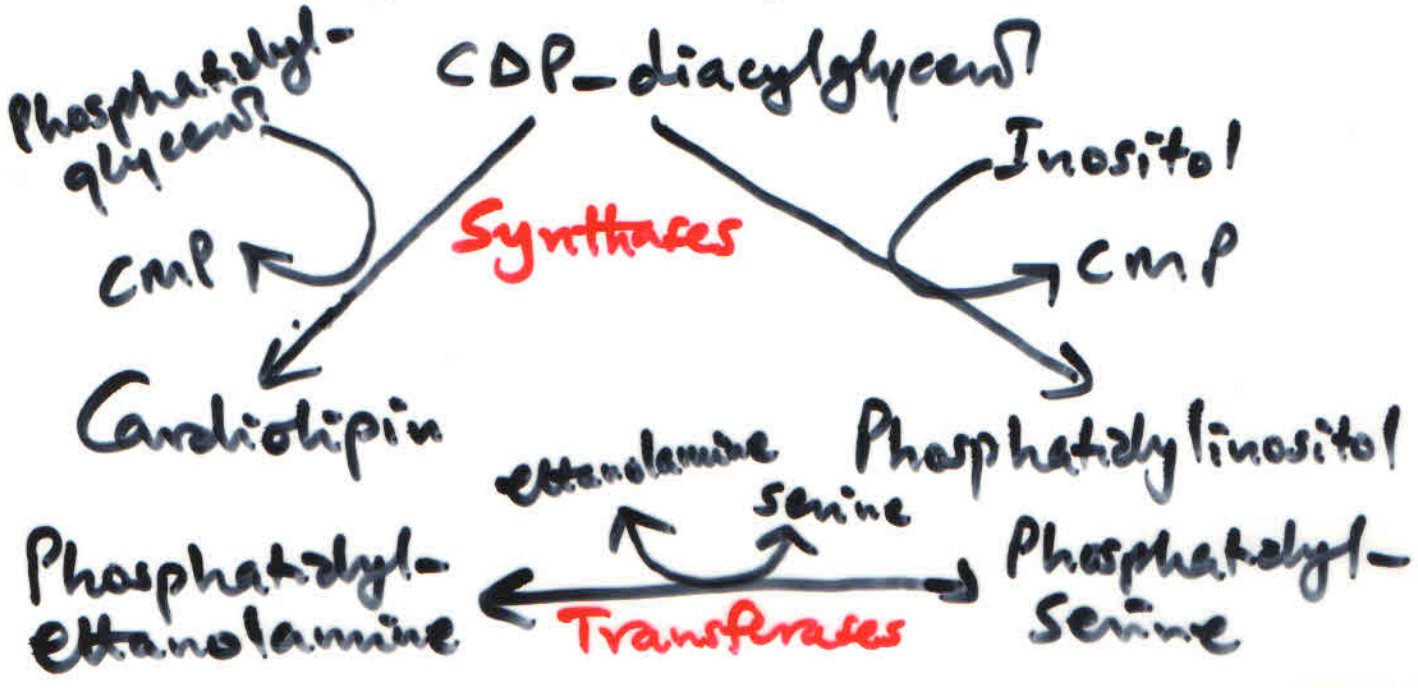
(iii) Salvage pathway

Choline that is obtained from the metabolic degradation of phosphatidylcholine is salvaged and used all over again to rebuild phosphatidylcholine;

Phosphorylation → Activation → Condensation

Choline: - Serves as a supplementary vitamin. Salvage pathway is vital in case of lack of methionine in diet.

NB Phosphatidylserine, phosphatidylinositol and Cardiolipin are made in pathways similar to the de novo pathways of phosphatidylethanolamine and Phosphatidylcholine;



BIOSYNTHESIS OF CHOLESTEROL

- It is a sterol – sterols are structural lipids present in the membranes of most eukaryotic cells.
- It is a component of plasma lipoproteins.
- Precursor of steroids e.g. Bile acids, hormones and Vit. D.
- Most publicized lipid because of the strong correlation between high levels of cholesterol in the blood and the incidence of diseases of the cardiovascular system in humans.
- * It is **not** required in the human diet because the **liver** can synthesize it from simple precursors i.e. AcetylCoA or acetate.

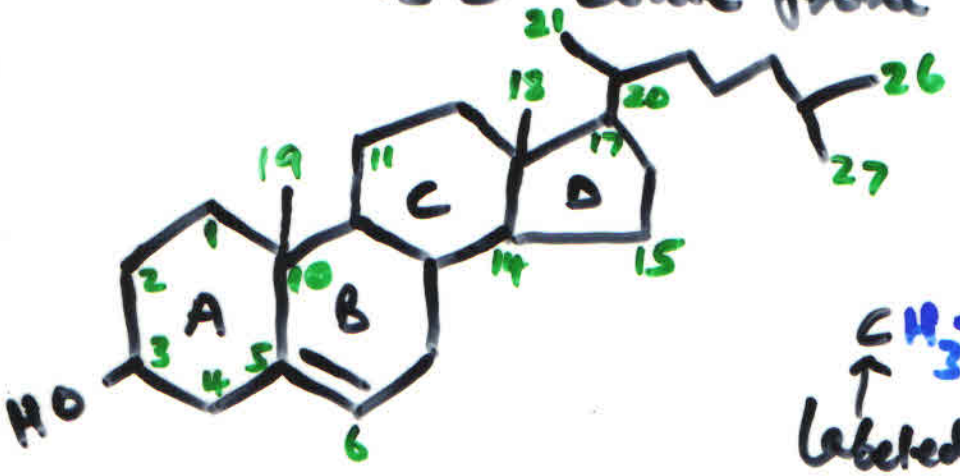
Acetate → → → 27 Carbon Cholesterol

Acetate (CH_3COO^-) → Isoprene units → Cholesterol

Isoprene ($CH_2 = C(CH_3) - CH = CH_2$) → Other natural lipids e.g. Vits. A, E & K. Carotenoids, Co Q, Dolichols

Chemistry

- 4 fused rings that are rigid and offers no rotation at C-C bonds.
- 27C < 12C come from $-COO-$
  15C come from CH_3-



CH_3-COOH

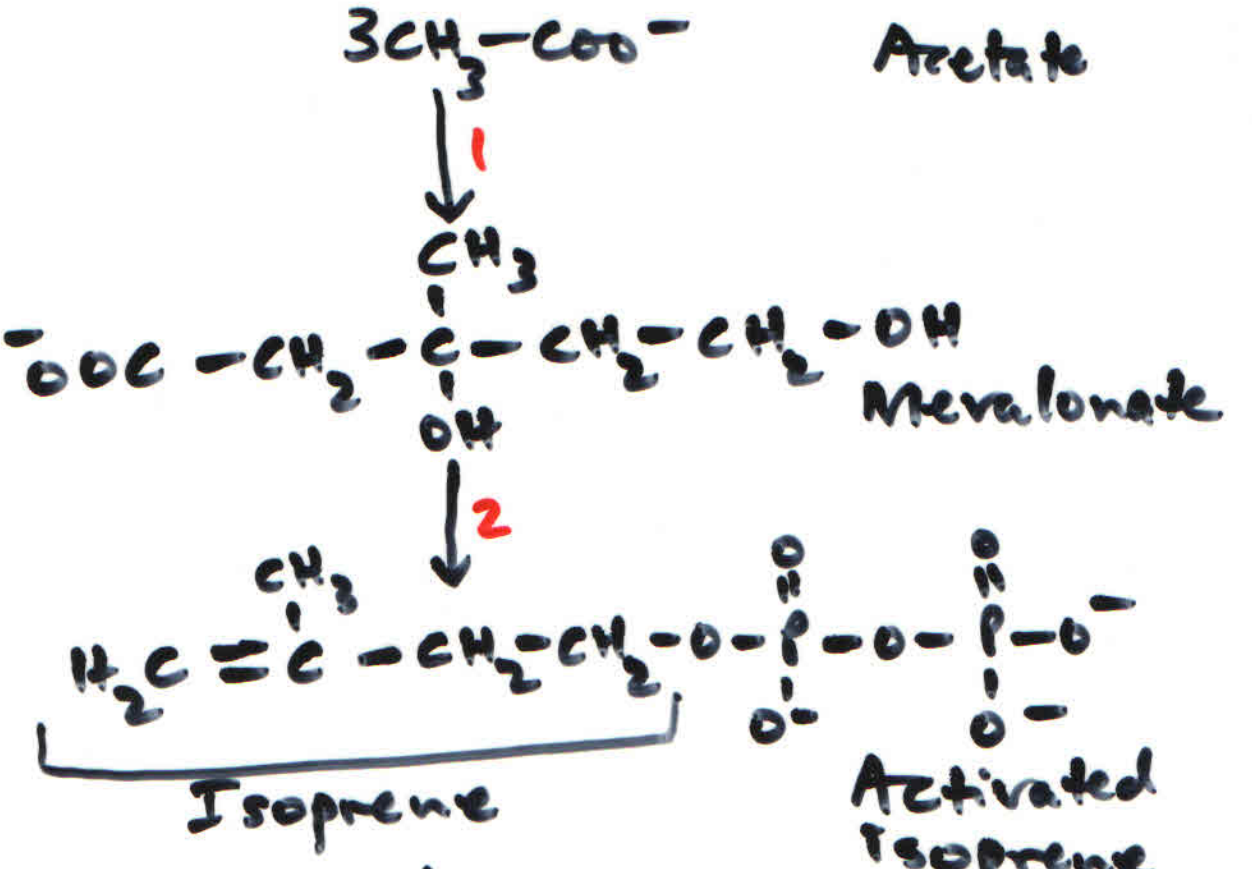
labeled ↑ ↑ labeled

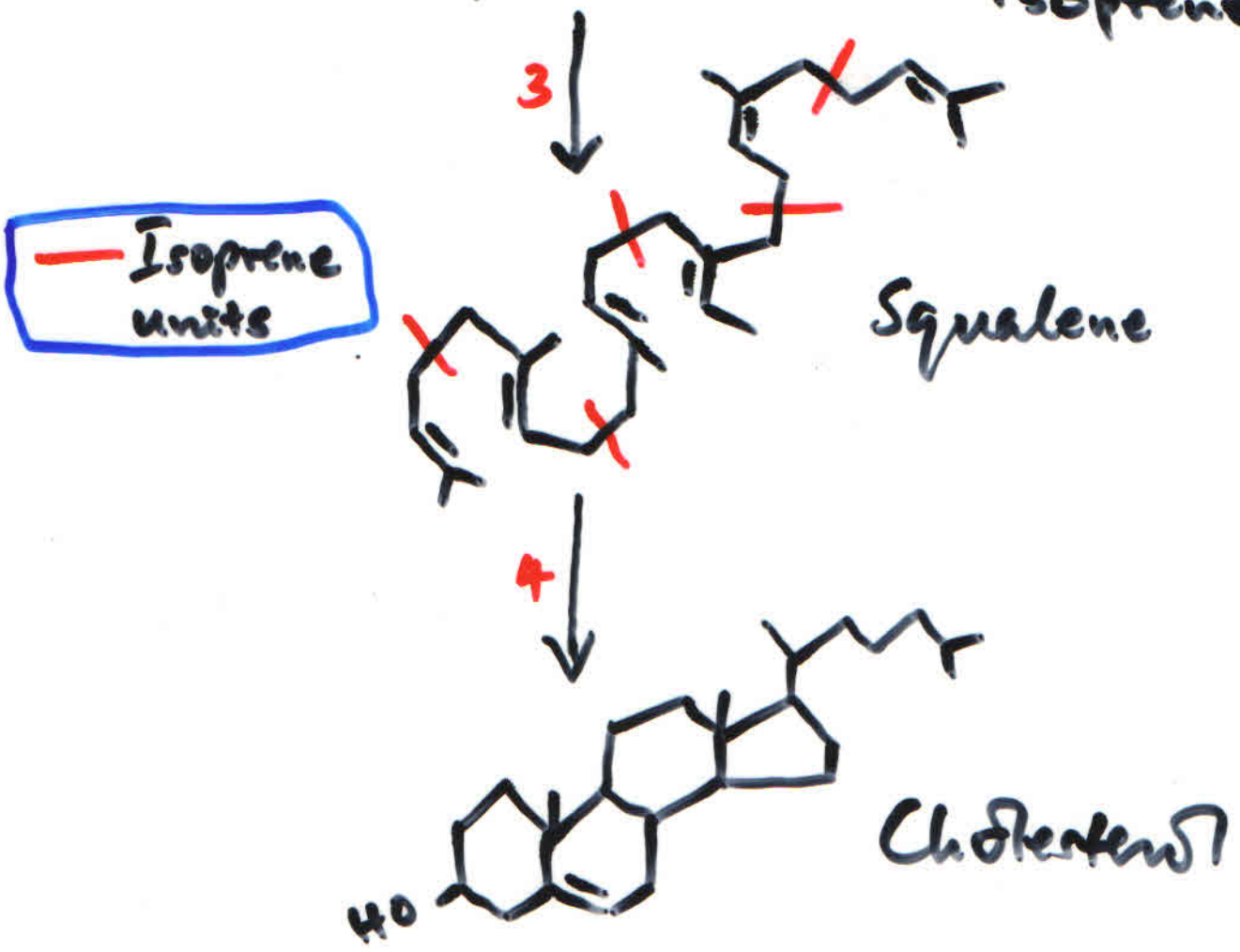
Cholesterol is made from acetylCoA in 4 stages;

1. Synthesis of mevalonate from acetate.
2. Conversion of mevalonate to 2-activated Isoprenes.
3. Condensation of 6-activated isoprene units to form squalene.
4. Conversion of squalene to the 4-ring nucleus.

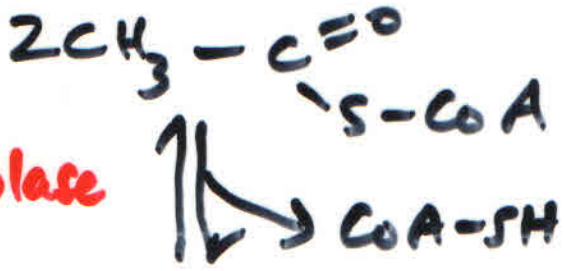
Acetate (2C) $\xrightarrow{1}$ Mevalonate (6C) $\xrightarrow{2}$ [Isoprene (5C)]$_n$ $\xrightarrow{3}$

Squalene (30C) $\xrightarrow{4}$ Cholesterol (27C)



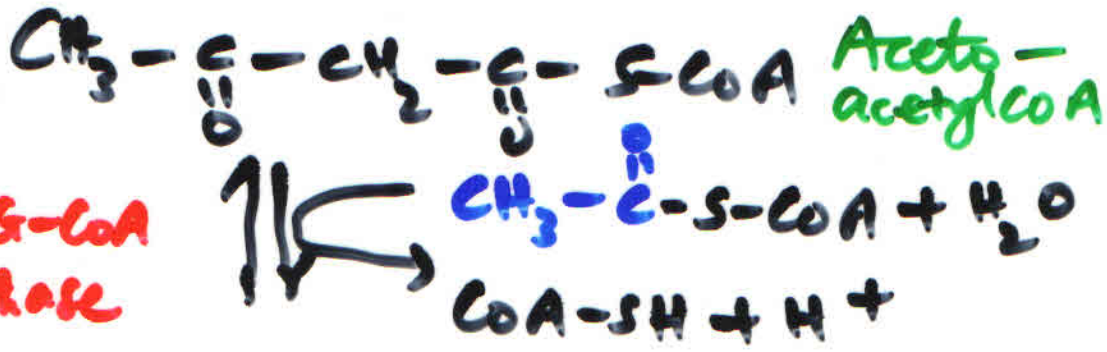


Ist Stage – most important because it contains the regulation point of cholesterol synthesis.



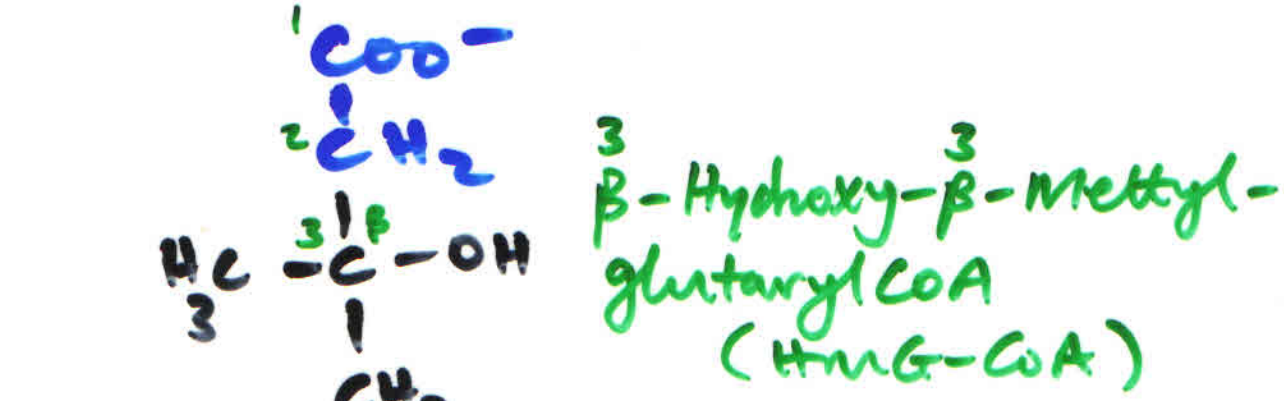
2 Acetyl CoA

Thiolase

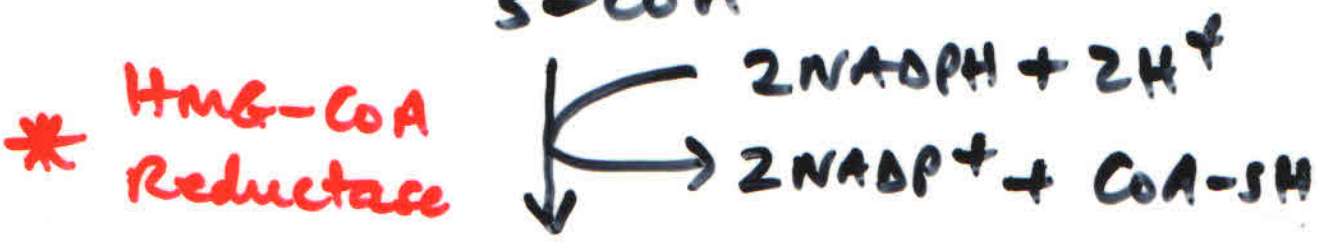


Aceto-acetyl CoA

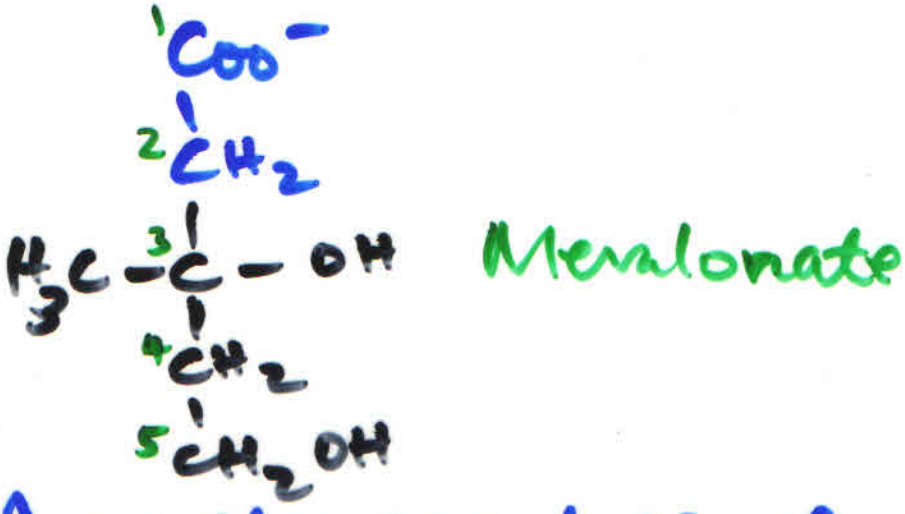
HMG-CoA Synthase



β-Hydroxy-β-Methyl-glutaryl CoA (HMG-CoA)



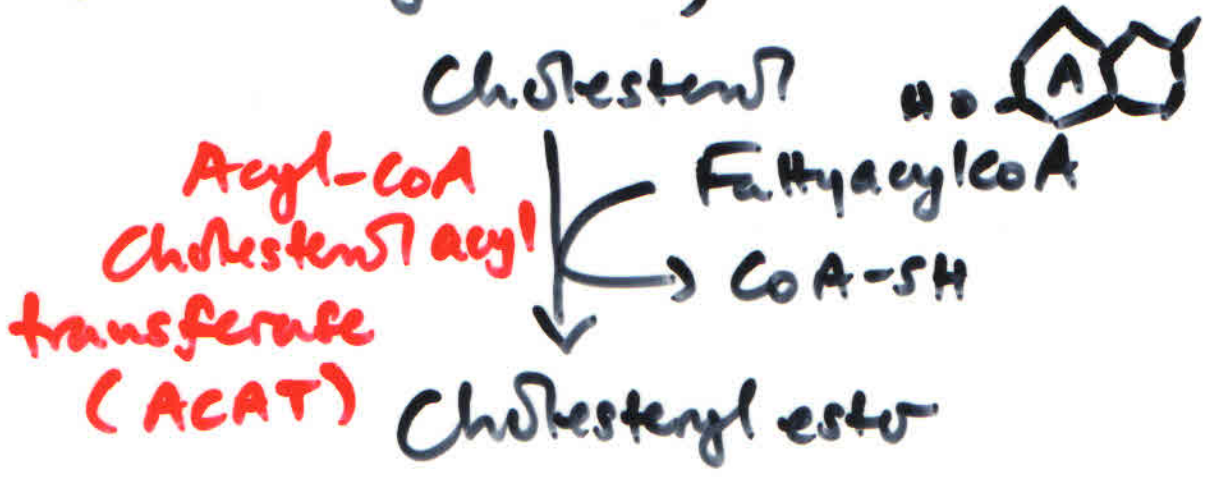
* HMG-CoA Reductase

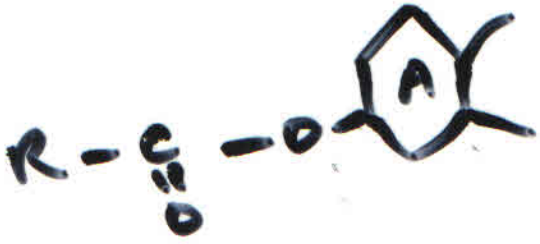


Mevalonate

The 3rd Acetyl CoA provides C1 and C2 of mevalonate.

may
Cholesterol made be converted to bile acids (which aid in digestion) and cholesteryl esters;





Cholesterol, cholesteryl esters, like TGs, phosphoglycerides are essentially insoluble in water.

From the liver, they are transported as plasma lipoproteins mainly in form of VLDL and LDL. Once they get to the storage tissue, they enter the cell via receptor-mediated endocytosis. The LDL receptor is a integral glycoprotein and it is recycled.

Familial hypercholesterolaemia = ↑ Cholesterol in plasma.

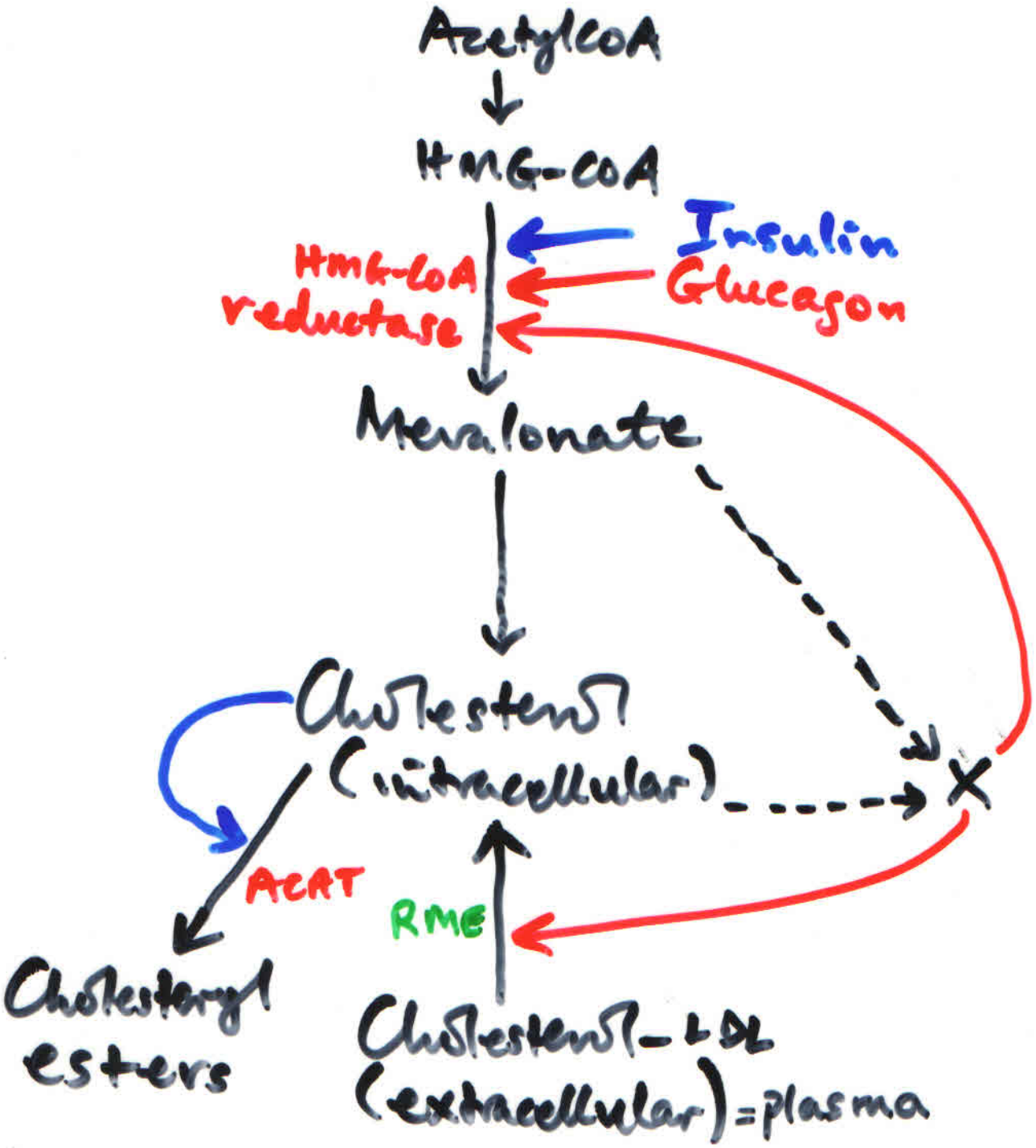
— Defect in LDL uptake by the receptor

Problem:
1) Synthesis of the receptor (LDL)
2) Its transport to the cell surface
3) Its ability to bind LDL.
4) Its association with other components of the membrane.

Regulation of Cholesterol synthesis

1. Intracellular cholesterol inhibits synthesis of cholesterol. It inhibits HmG-CoA reductase as end-product inhibition.
2. Its synthesis is under hormonal regulation.
   Glucagon — inhibits
   Insulin — stimulates
3. Unidentified metabolites of cholesterol and mevalonate also modulate the HmG-CoA reductase.

See scheme — next page



Unregulated cholesterol production ⟶ Atherosclerosis = accumulation of cholesterol in blood vessels ⟶ myocardial infarction.

Drugs: 1) Lovastatin, Compactin – inhibit HMG-CoA reductase ⟶ "Mevalonate"

2) Mevinolin – resembles HMG-CoA competitive inhibitor.

3) β-Sitosterol – oral administration

MAJOR CLASSES OF HUMAN PLASMA LIPOPROTEINS AND THEIR PROPERTIES

Lipoprotein	Particle size (nm)	Density (g/ml)	Composition (wt.%) Protein	Phospholipids	Free Cholesterol	Cholesteryl esters	TGs
Chylomicrons	50-200	<1.006	2	9	1	3	85
VLDL	28-70	0.95-1.006	10	18	7	12	50
LDL	20-25	1.006-1.063	23	20	8	37	10
HDL	8-11	1.063-1.210	55	24	2	15	4

Chylomicrons