The phosphorylation of mevalonate and presence of pyrophosphate in subsequent structures help keep these water-insoluble compounds in solution.

Pyrophosphate is released in each of these four condensation steps, making the reactions irreversible.

Beginning with squalene, the intermediates in cholesterol biosynthesis are nonphosphorylated and are so hydrophobic that they require an intracellular sterol carrier protein to keep them soluble.
Regulation of HMG CoA reductase

1. regulation of gene expression by SREBP
2. phosphorylation state
3. regulation by hormones (insulin, glucagon)
4. inhibition by statin drugs
Regulation of HMG CoA reductase

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Degradation of Cholesterol

- The ring structure of cholesterol cannot be metabolized to \( \text{CO}_2 \) and \( \text{H}_2\text{O} \) in humans.
- The sterol ring nucleus is eliminated from the body by conversion to bile acids and bile salts.
Degradation of Cholesterol

- The theme is for cholesterol to be converted to a relatively soluble amphipathic molecule.

- As a bonus, these molecules are used as emulsifying agents during digestion.
Delivery of fatty acids and cholesterol via plasma lipoproteins
Chylomicrons deliver TAG’s and return to the liver
VLDL (pre-LDL) deliver some TAG’s and bulk cholesterol
LDL delivers cholesterol directly to the interior of cells
HDL are secreted ‘empty’ and scavenge cholesterol
In cells, cholesterol distributes into membranes

• cholesterol has limited flexibility and is a fairly rigid structure.

• stiffens the membrane and makes it less permeable

• it can interact with and affect the structure of integral membrane proteins
lipid rafts form due to spontaneous segregation between DHA and SL containing membrane lipids
Cholesterol is less soluble in (artificial) membranes high in unsaturated acyl chains
Lipid rafts are thought to promote molecular assemblies and to drive conformational changes in membrane proteins.