Oxidation of Fatty Acid

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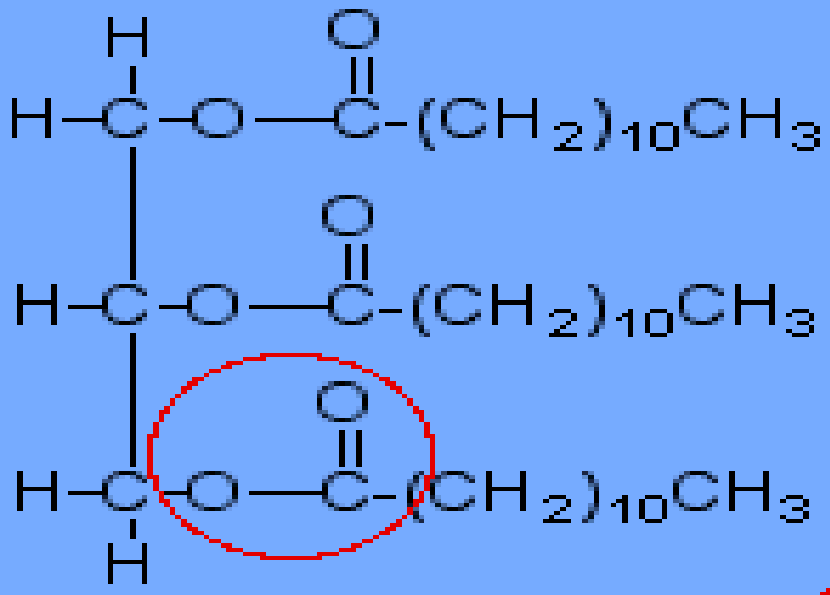
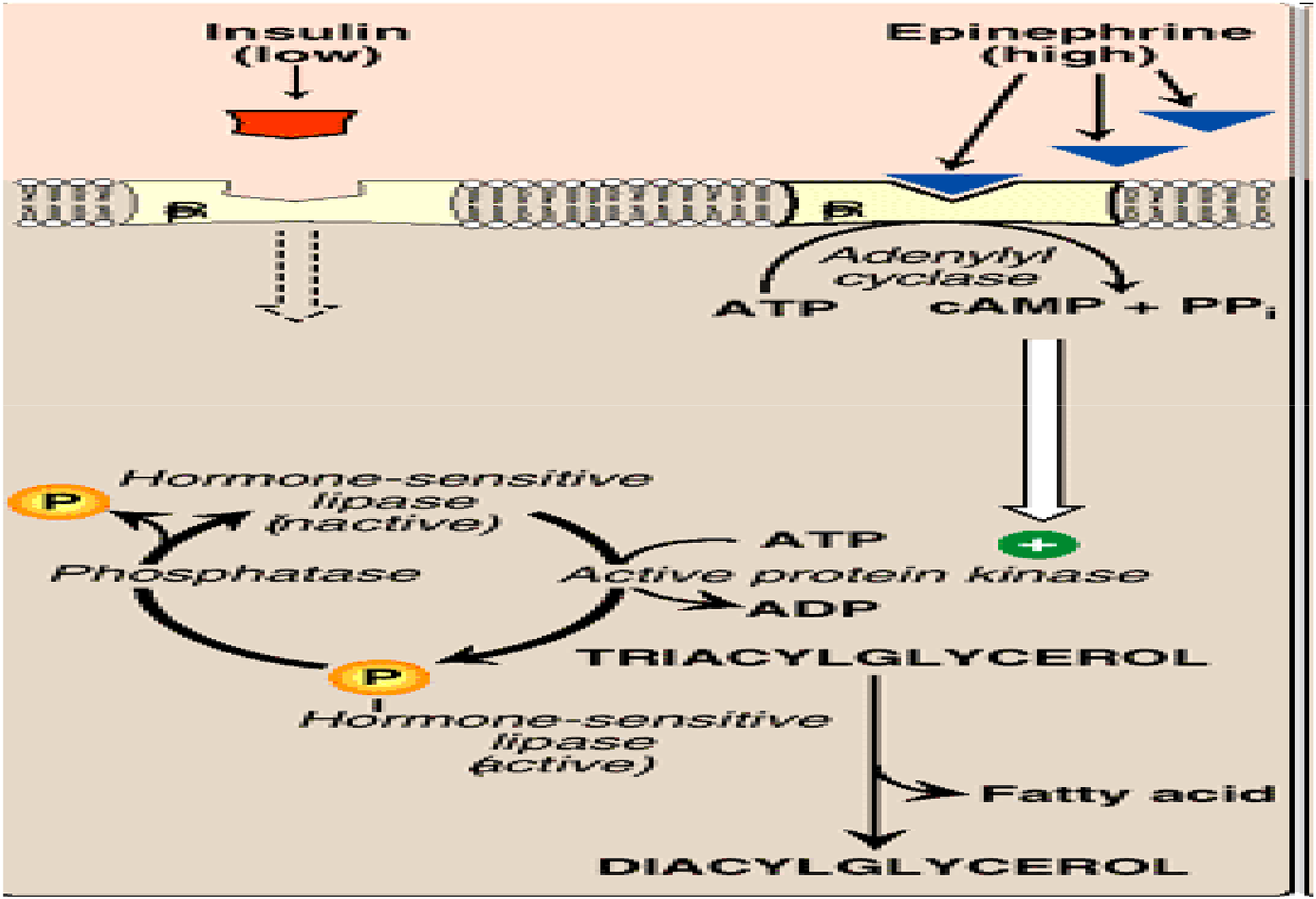
Surat

Trilauroylglycerol



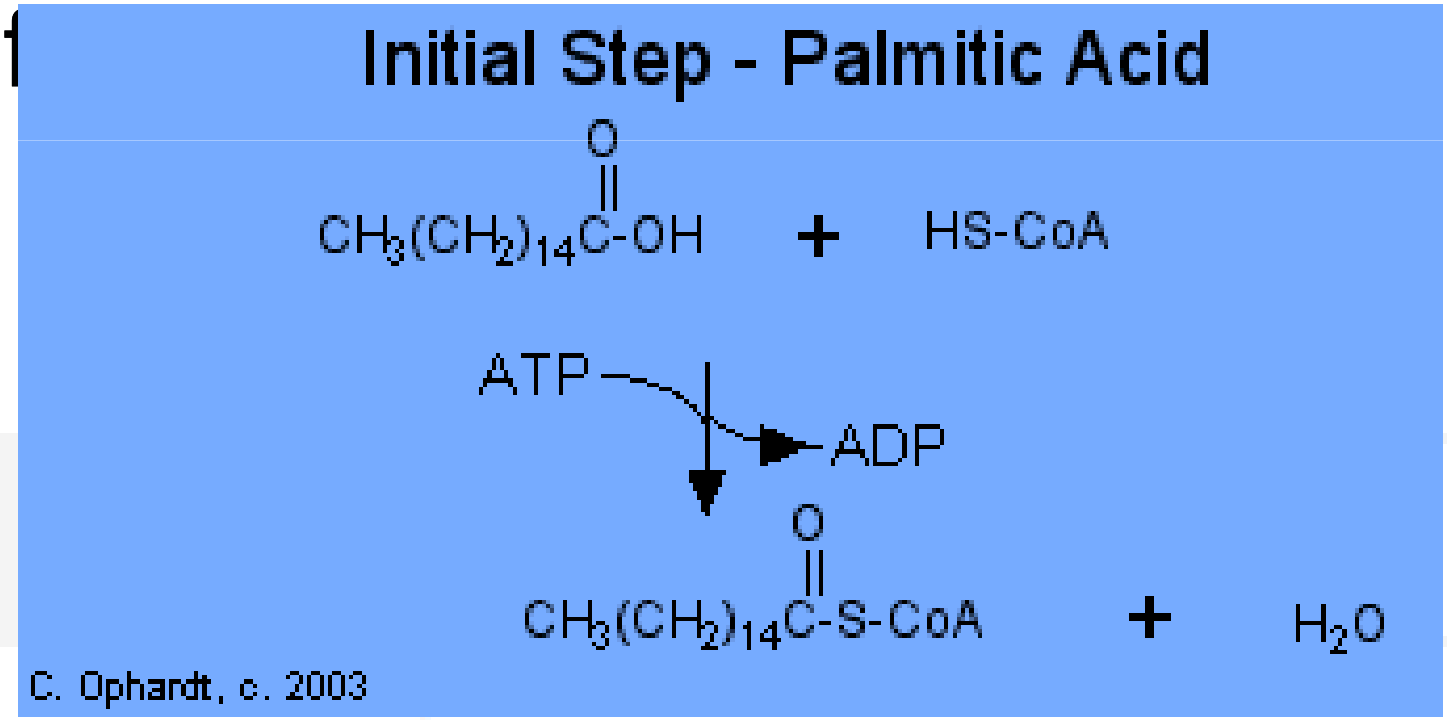
Ester Groups

Mobilization of Stored Fats

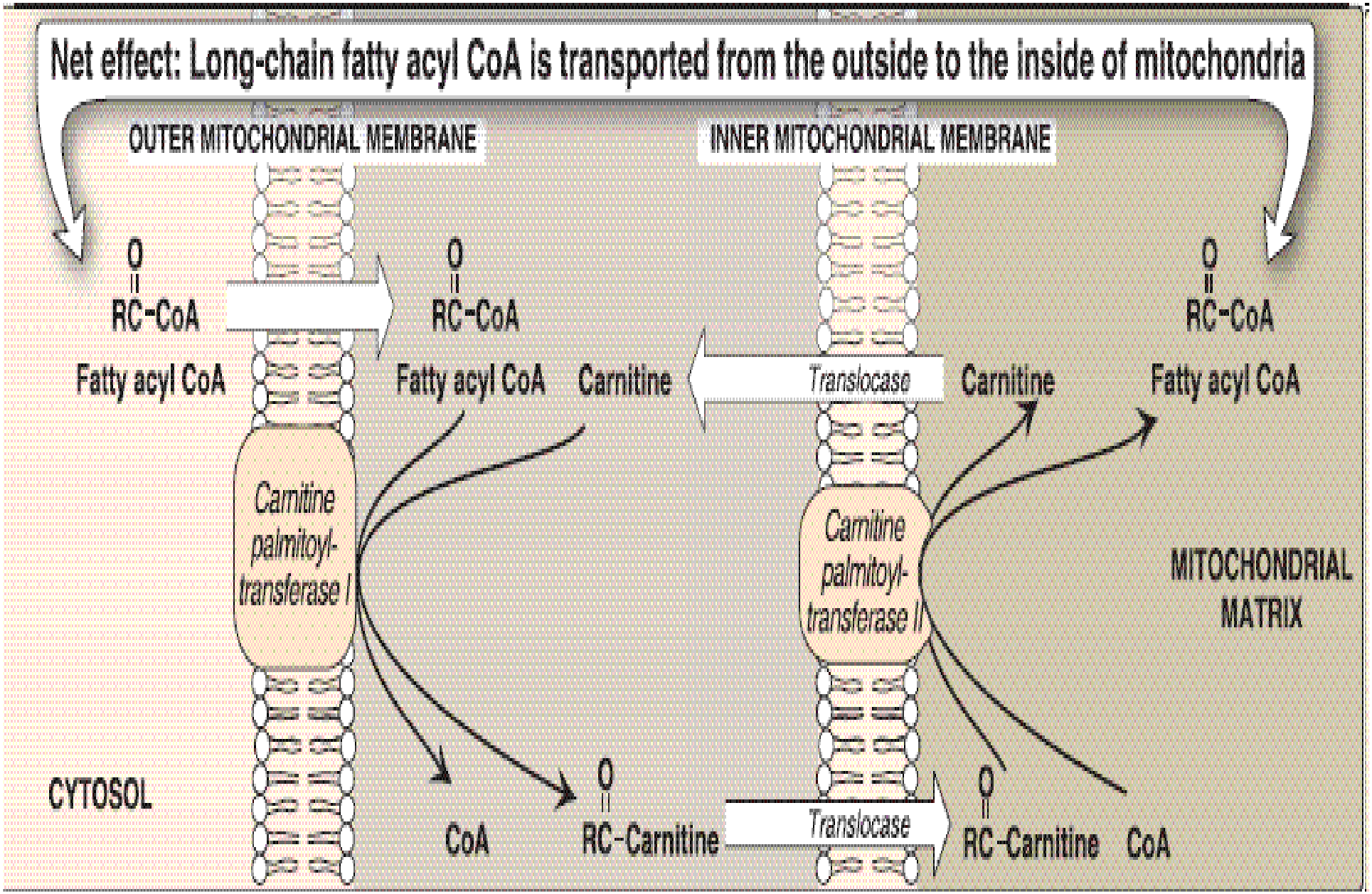


Fatty Acid Oxidation

- Initial Step: Requires an ATP to synthesize acetyl CoA with the



Carnitine Shuttle



***Malonyl CoA inhibits* CPT-I**

- Presence of Malonyl CoA indicate fatty acid synthesis in the cytosol.
- So at that time of fatty acid synthesis ,the newly made palmitatic acid cannot be transferred into the mitochondria for oxidation of fatty acid, for degraded.
- *"Malonyl CoA inhibits Carnitine Palmityl Transferase-1 (CPT-I)"*
- Fatty acid oxidation is also regulated by the acetyl CoA to CoA ratio: As the ratio increases, the thiolase reaction decreases.

Sources of carnitine :

- Diet - mainly from meat.
- Synthesized from lysine and methionine – in Liver & Kidney.

Carnitine deficiencies result

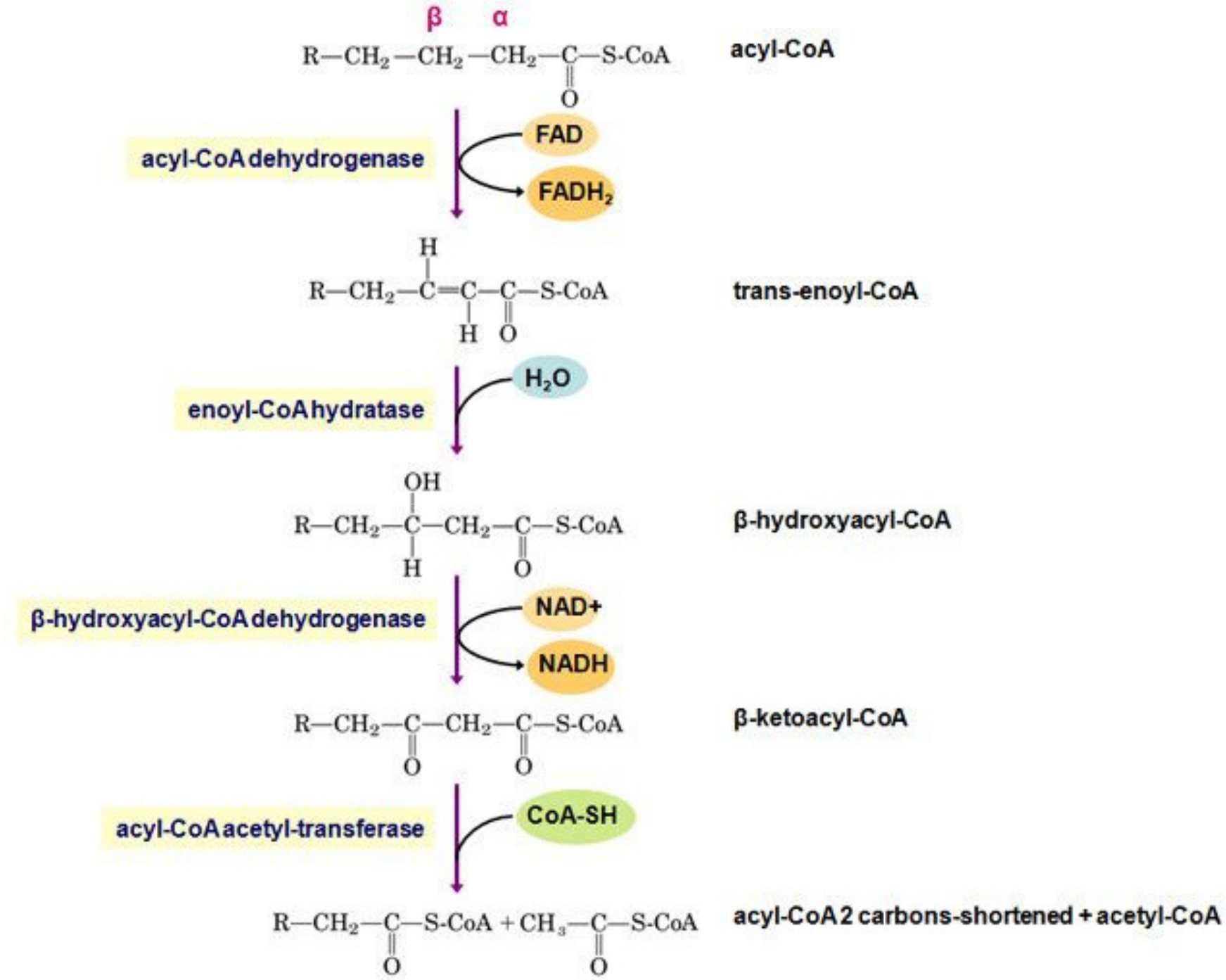
- Decreased use of LCFA as a metabolic fuel.
- Lead to severe hypoglycemia and coma.

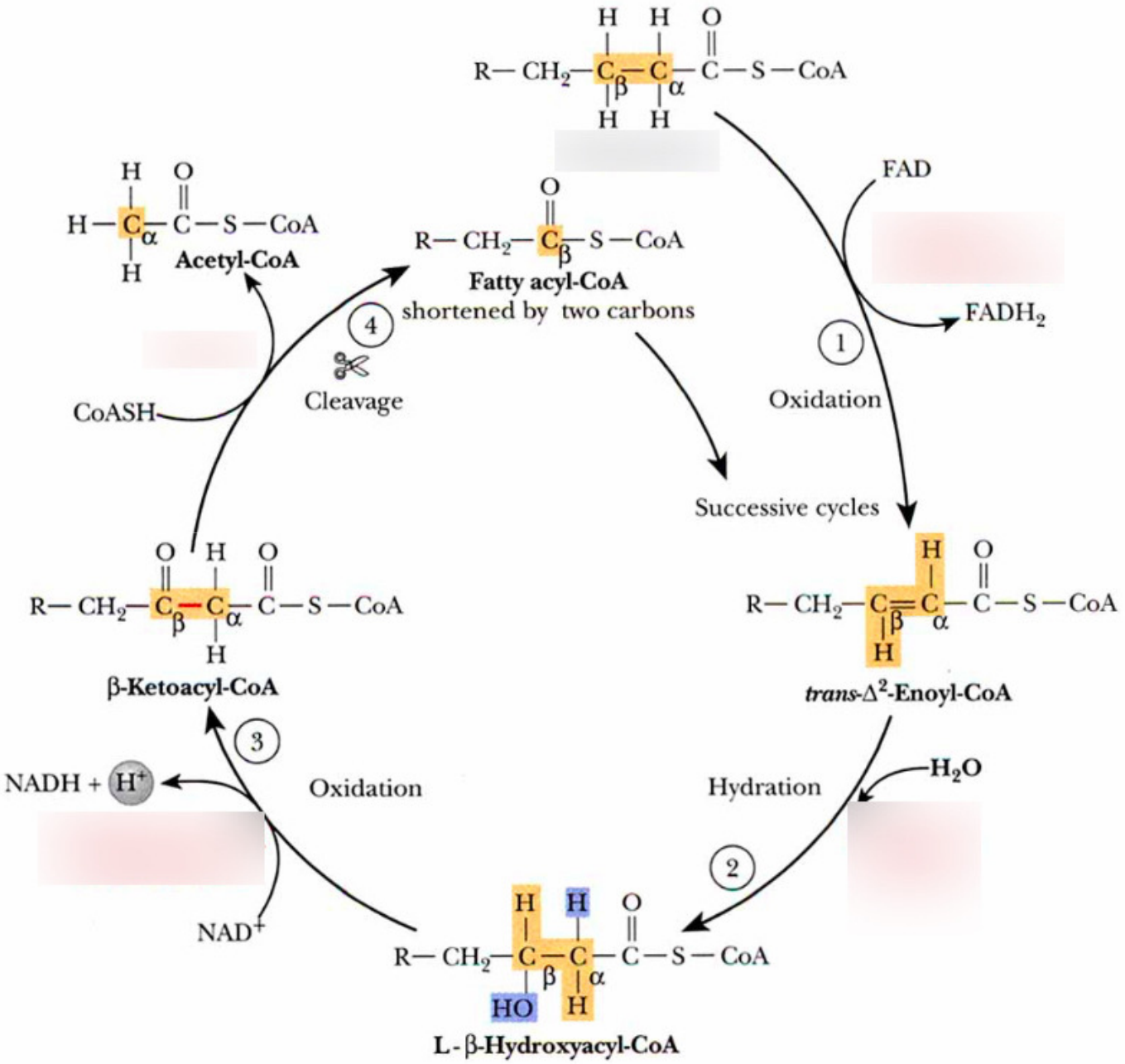
Secondary carnitine deficiency

- Liver disease - decreased synthesis of carnitine
- Pregnancy, severe infections, burns, or trauma - increased requirement
- Hemodialysis - Removes carnitine from the blood.
- Malnutrition
- Strict vegetarian

Treatment includes

- avoidance of prolonged fasting
- Take a diet high in carbohydrate and low in LCFA.
- More diet with medium-chain fatty acid.
- Carnitine suppliment.


β α
R—CH2—CH2—CH2—C—S-CoA
O
acyl-CoA
acyl-CoA dehydrogenase
FAD
FADH2
H
R—CH2—C=C—C—S-CoA
H O
trans-enoyl-CoA
enoyl-CoA hydratase
H2O
OH
R—CH2—C—CH2—C—S-CoA
H O
β-hydroxyacyl-CoA
β-hydroxyacyl-CoA dehydrogenase
NAD+
NADH
R—CH2—C—CH2—C—S-CoA
O O
β-ketoacyl-CoA
acyl-CoA acetyl-transferase
CoA-SH
R—CH2—C—S-CoA + CH3—C—S-CoA
O O
acyl-CoA 2 carbons-shortened + acetyl-CoA


Acetyl-CoA
Fatty acyl-CoA
shortened by two carbons
FAD
FADH2
1
Oxidation
Successive cycles
trans-Δ2-Enoyl-CoA
H2O
Hydration
2
L-β-Hydroxyacyl-CoA
NAD+
NADH + H+
3
Oxidation
β-Ketoacyl-CoA
4
Cleavage
CoASH

Cycles of β-Oxidation

The length of a fatty acid:

- **Determines the number of oxidations and**
- **The total number of acetyl CoA groups.**

Carbons in Fatty Acid	Acetyl CoA (C/2)	β-Oxidation Cycles (C/2 –1)
12	6	5
14	7	6
16	8	7
18	9	8

Palmitic Acid -ATP Synthesis

- Palmitic Acid is C-16
- Initiating Step - requires 1 ATP (text says 2)
- Step 1 - FAD into e.t.c. = 2 ATP
- Step 3 - NAD+ into e.t.c. = 3 ATP
- **Total ATP per turn of spiral = 5 ATP**

Example with Palmitic Acid = 16 carbons = 8 acetyl groups

- Number of turns of fatty acid spiral = 8-1 = 7 turns
- ATP from fatty acid spiral = 7 turns and 5 per turn = 35 ATP.
- **NET ATP from Fatty Acid Spiral = 35 - 1 = 34 ATP**

Palmitic Acid (C-16) -ATP Synthesis

ATP Synthesis form Acetyl Coa Through Citric Acid Cycle

In Citric Acid Cycle

1 GTP = 1 ATP

3 NADH = 3 x 3 = 9 ATP

1 FADH = 2 x 1 = 2 ATP

Total ATP per Acetyl Coa in TCA cycle = 12

- 8 Acetyl CoA = 8 turns C.A.C.
- 8 turns x 12 ATP/C.A.C.= 96 ATP
- **GRAND TOTAL** = 35 – 1 + 96 = **130 ATP**

Defects in beta oxidation

- Defect in transport of fatty acids into mitochondria
- Defect in oxidation
- Deficient energy production by oxidation of long chain fatty acids.
- Common features are :

1. Hypoketotic hypoglycemia
2. Hyperammonemia
3. Skeletal muscle weakness
4. Liver disease

- Acyl carnitine accumulates when the **transferases or translocase** is deficient.
- Dietary supplementation of carnitine has been found to improve the symptoms in some case.

Organic aciduria

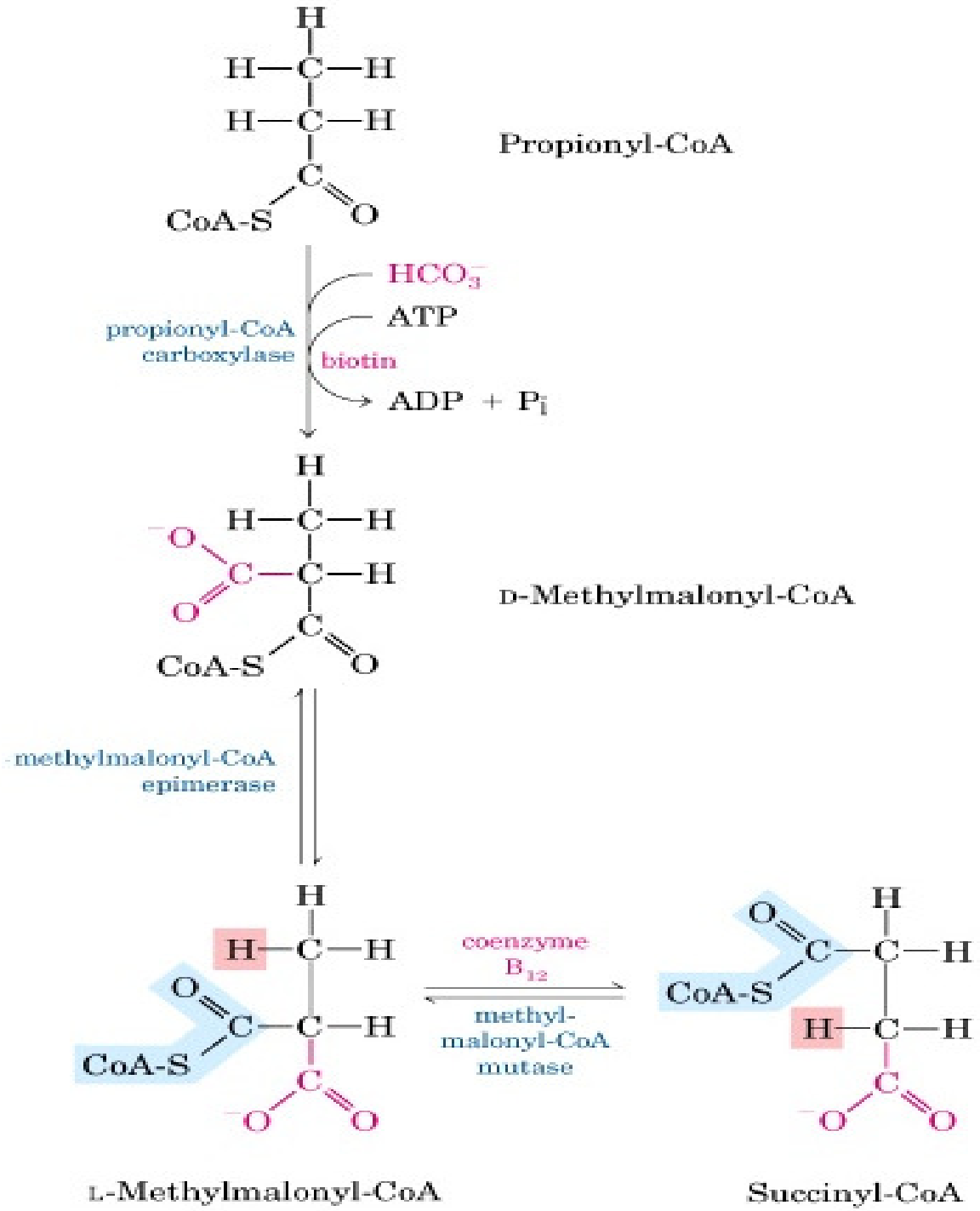
- Disorders of
  - fatty acid metabolism
  - branched chain and aromatic amino acids metabolism
  - citric acid cycle.
- Incidence of medium chain ***acyl coA dehydrogenase*** deficiency is about 1 in 2500 live birth
- Second most common inborn error of metabolism.
- Characterised by
  - Accumulation of organic acids in body tissues
  - Their excretion in urine.
  - **Acidosis , vomiting , convulsions and coma.**
  - The children often die in infancy
  - Mental and physical retardation.

Organic aciduria

- Diagnosis
  - Presence of organic acid in urine by chromatography.
- Dietary restriction , cofactor therapy and substrate removal are the general lines of management .

Odd chain Fatty acid Oxidation

- The odd chain fatty acids are oxidised exactly in the same manner as even chain fatty acids.
- Successive removal of 2 carbon units
- At the and , one 3 carbon unit, propionyl coA is produced.


Propionyl-CoA
HCO3−
ATP
propionyl-CoA carboxylase
biotin
ADP + Pi
D-Methylmalonyl-CoA
methylmalonyl-CoA epimerase
coenzyme B12
methyl-malonyl-CoA mutase
L-Methylmalonyl-CoA
Succinyl-CoA
CoA-S

Propionate is Glucogenic

- However, propionate is entering into the citric acid cycle at a point after CO2 elimination steps, so propionate can be channeled to gluconeogenesis.
- Thus 3-carbon units from odd chain fatty acids are glucogenic.
- Cows milk contain significant amount of odd chain fatty acid.

Inborn errors of propionate metabolism

- Propionyl coA carboxylase deficiency
  - Characterised by propionic acidemia
  - Ketoacidosis
  - Developmental abnormality.
- Methyl malonic aciduria.
  - Some time responds to treatment with vitamin B12.
  - Deficiency of adenosyl B12 with deficient mutase activity.
  - The second type do not respond to cynocobalamin
  - Deficiency of the enzyme racemase and mutase.
  - The methyl malonate affects the metabolism of brain leading to mental retardation in these cases.

Alpha oxidation

- Important in brain.
- Occurs in the endoplasmic reticulum
- Does not need activation
- From the carboxyl end .
- Removing carbon atoms one at a time
- Does not require CoA,
- Does not generate energy.
- Alpha- oxidation is mainly used for Branch chain fatty acids E.g. Phytanic acid.
- It is derived from milk and animal fat.

Refsum's disease

- Due to lack of alpha-hydroxylase (phytanic acid oxidase)
- Alpha oxidation dose not occur
- Phytanic acid accumulates.
- Severe neurological symptoms,
  - polyneuropathy
  - nerve deafness
  - cerebellar ataxia.
- Symptoms is observed with restricted dietary intake of phytanic acid.
- Milk is a good source of phytanic acid , which may be avoided.

Omega oxidation

- Minor pathway
- Occurs in Microsomes.
- Occurs from omega end – methyl end
- Need NADH and Cytochrome P-450.
- Omega oxidation is defective and dicarboxylic acids (6C and 8C acids) are excreted in urine causing dicarboxylic aciduria.