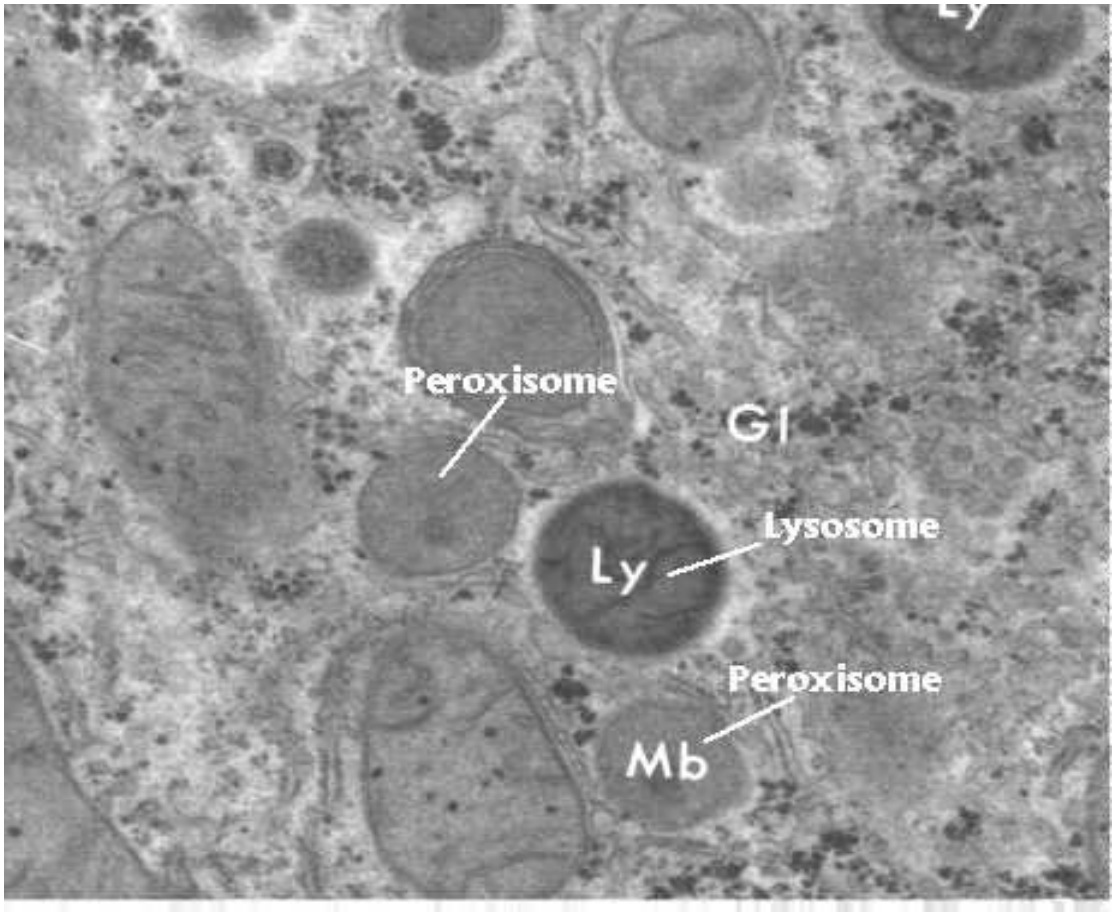
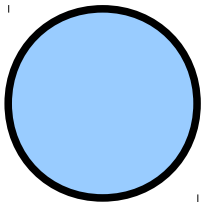
Hereditary disorders of peroxisomal metabolism



http://www.cytochemistry.net/Cell-biology/PEROX.JPG

Peroxisomes



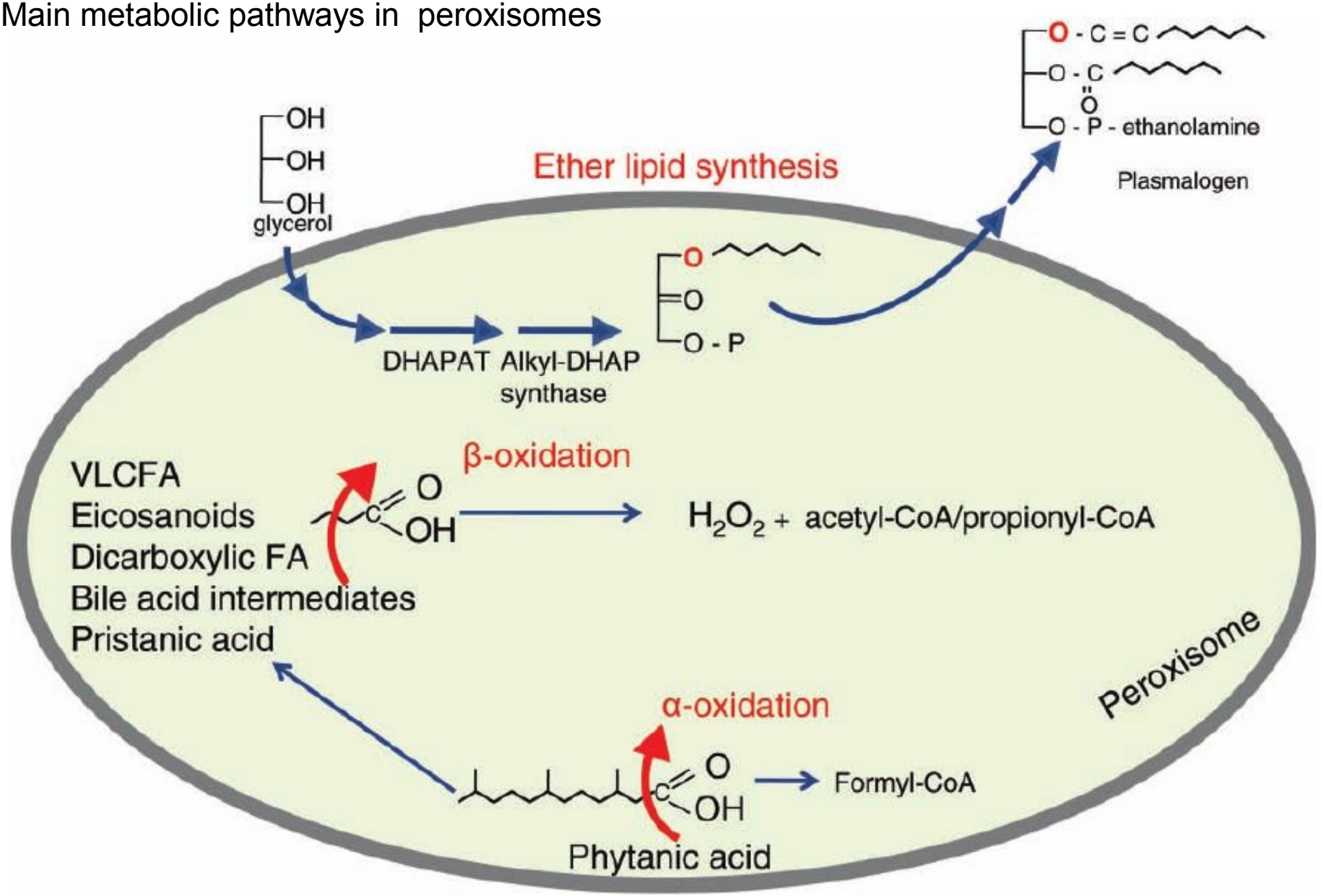
single membrane organelles

from less than 100 to more than 1000 per eukaryotic cell

more than 50 enzymes

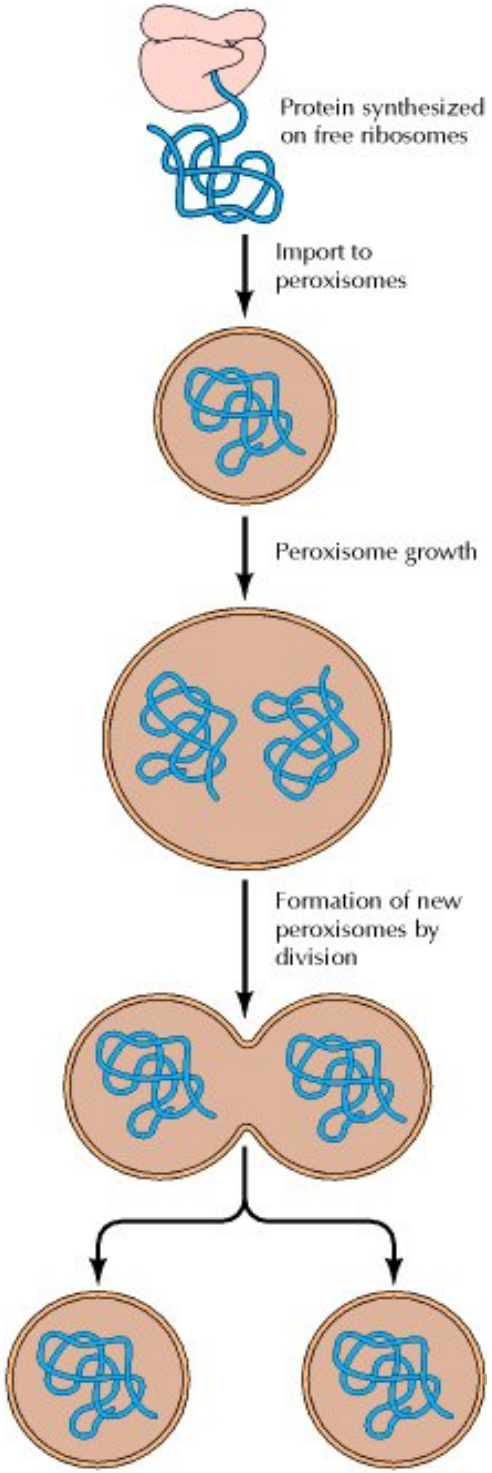
beta-oxidation of very long chain fatty acids
biosynthesis of ether phospholipids (plasmalogens)
biosynthesis of bile acids
biosynthesis of isoprene compounds
production of hydrogen peroxide, catalase

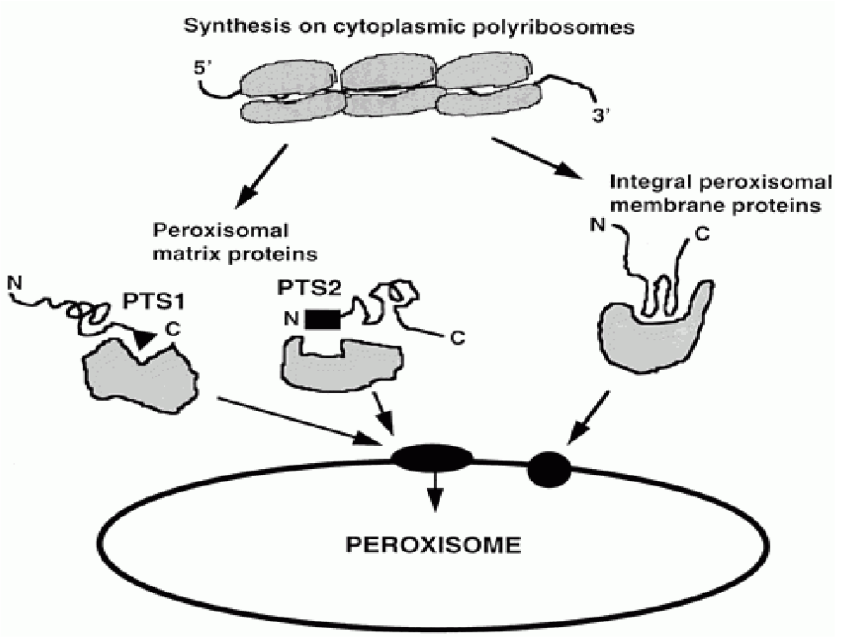
Main metabolic pathways in peroxisomes

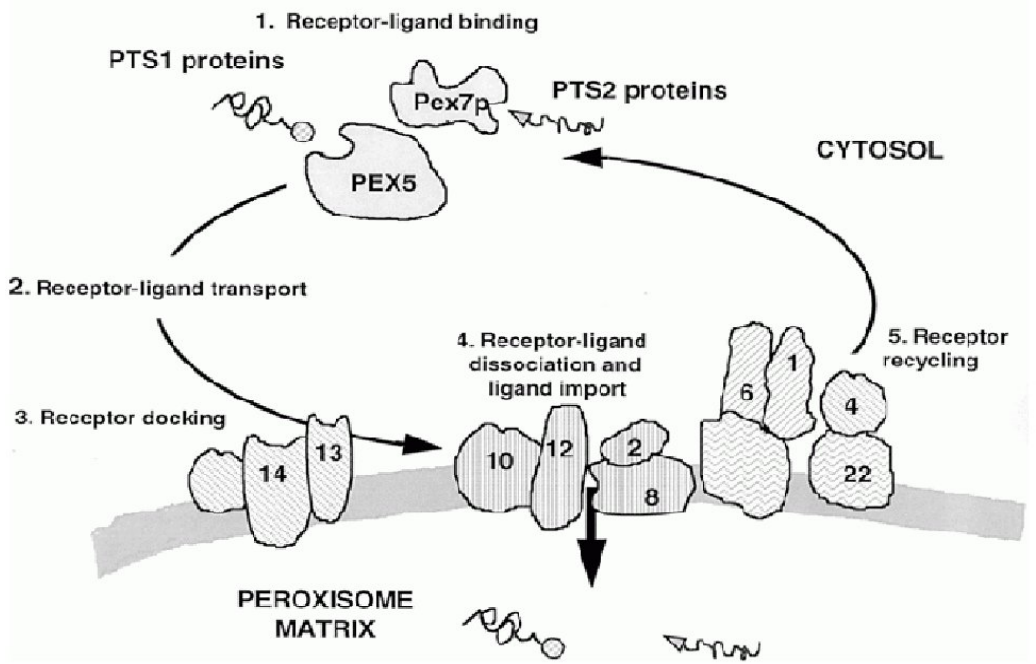


The Neuroscientist / Vol. 15, No. 4, August 2009

Biogenesis of peroxisomes







Biogenesis of peroxisomes

Synthesis of matrix proteins on **free ribosomes in cytoplasm**

Receptor-mediated import of proteins into organelle

C-terminal peroxisome targeting sequence PTS1
((S/A/C)-(K/R/H)-L-COOH)

PTS1 is recognized by a cytosolic receptor PEX5

Few matrix proteins are targeted by N-terminal PTS2 ((R/K)(L/V/I)X_5(Q/H)(L/A)

Membrane proteins – also synthesized on free ribosomes and imported

PEX genes encode peroxins

Peroxins are necessary for peroxisome biogenesis

PTS1, PTS2, other cytosolic and integral membrane proteins
e.g. PEX5 is a receptor for PTS1

Involved in the import of peroxisomal matrix and membrane proteins

15 known genes in humans

Disorders of peroxisome biogenesis

Complex developmental and metabolic phenotypes

Most severe phenotype: Zellweger syndrome
Milder : Infantile Refsume disease

Peroxisomal ghosts – aberrant peroxisomal structures, "empty" peroxisomal membranes

Severe disruption of **peroxisomal functions**

Zellweger syndrome

Described by dr.Hans Zellweger in 1961

Cerebrohepatorenal syndrome

Incidence cca 1:50 000 births

Peroxisomal proteins were not properly compartmentalized ("Peroxisomal ghosts")

Other milder disorders of peroxisomal biogenesis were described

- **Neonatal ALD**
- **Infantile Refsum disease**

Rhizomelic chondrodystrophia punctata

Zellweger syndrome

Facial dysmorphia: full forehead, hypoplastic supraorbital ridges, large anterior fontanelle, epicanthal folds, broad nasal bridge,

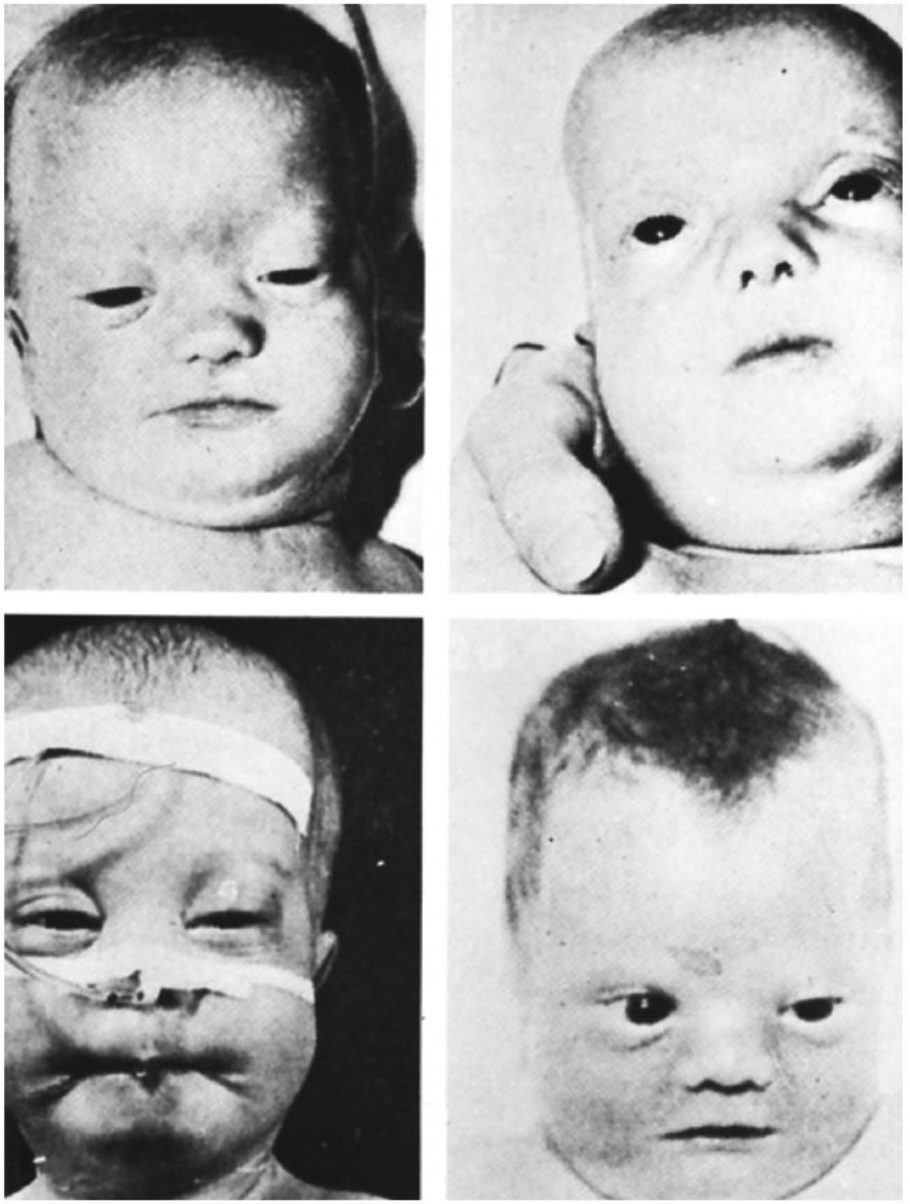
Ocular abnormalities: cataracts, glaucoma, corneal clouding, pigmentary retinopathy, optic nerve dysplasia

Severe hypotonia, weakness, seizures

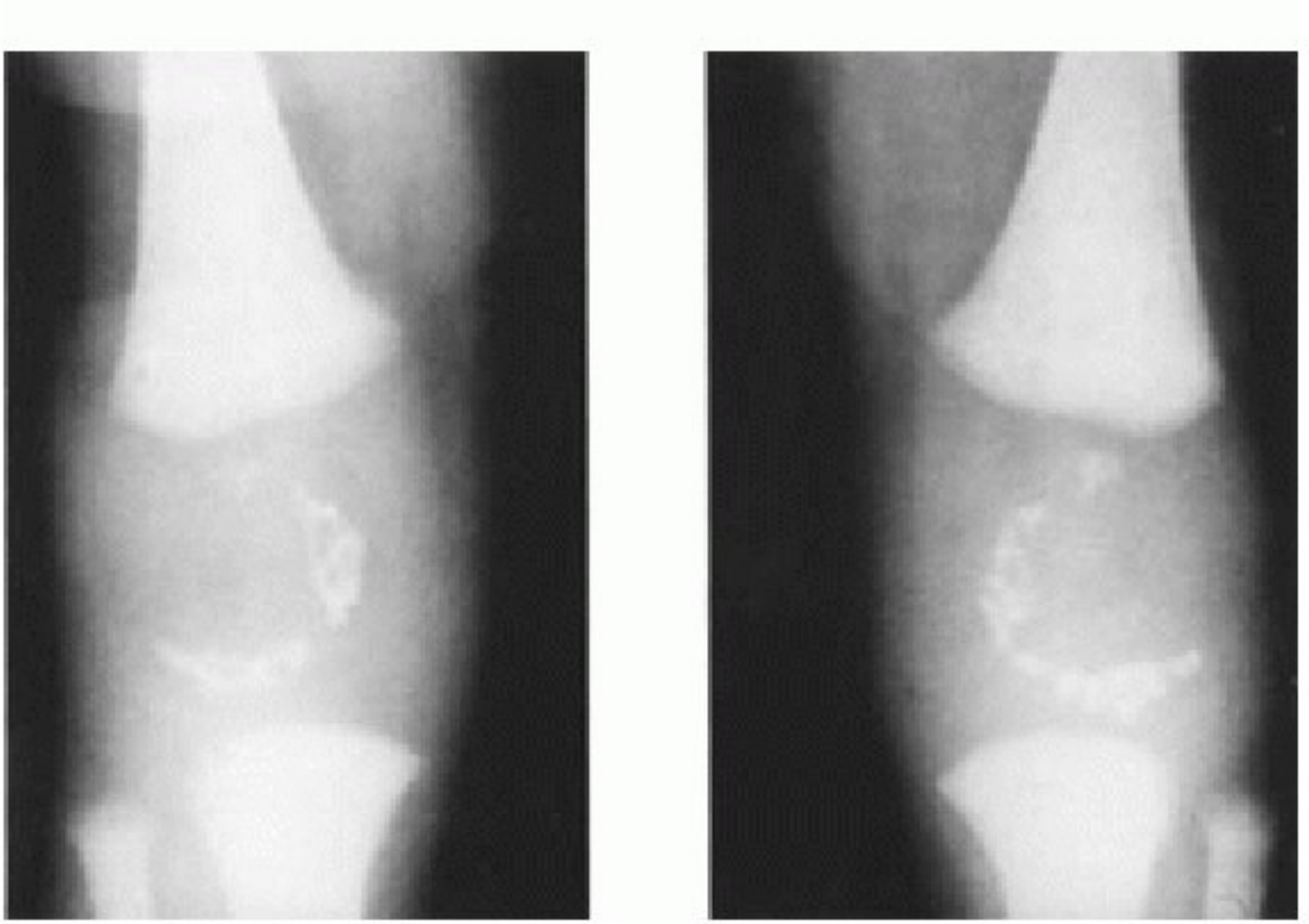
Abnormal punctate calcifications in the patella and epiphyses of the long bones

Renal cysts

Zellweger syndrome



Punctate calcifications („calcific stippling“) in the patella



Neonatal adrenoleukodystrophy, infantile Refsume disease

Peroxisomes may be present

Dysmorphic features are less striking or even absent

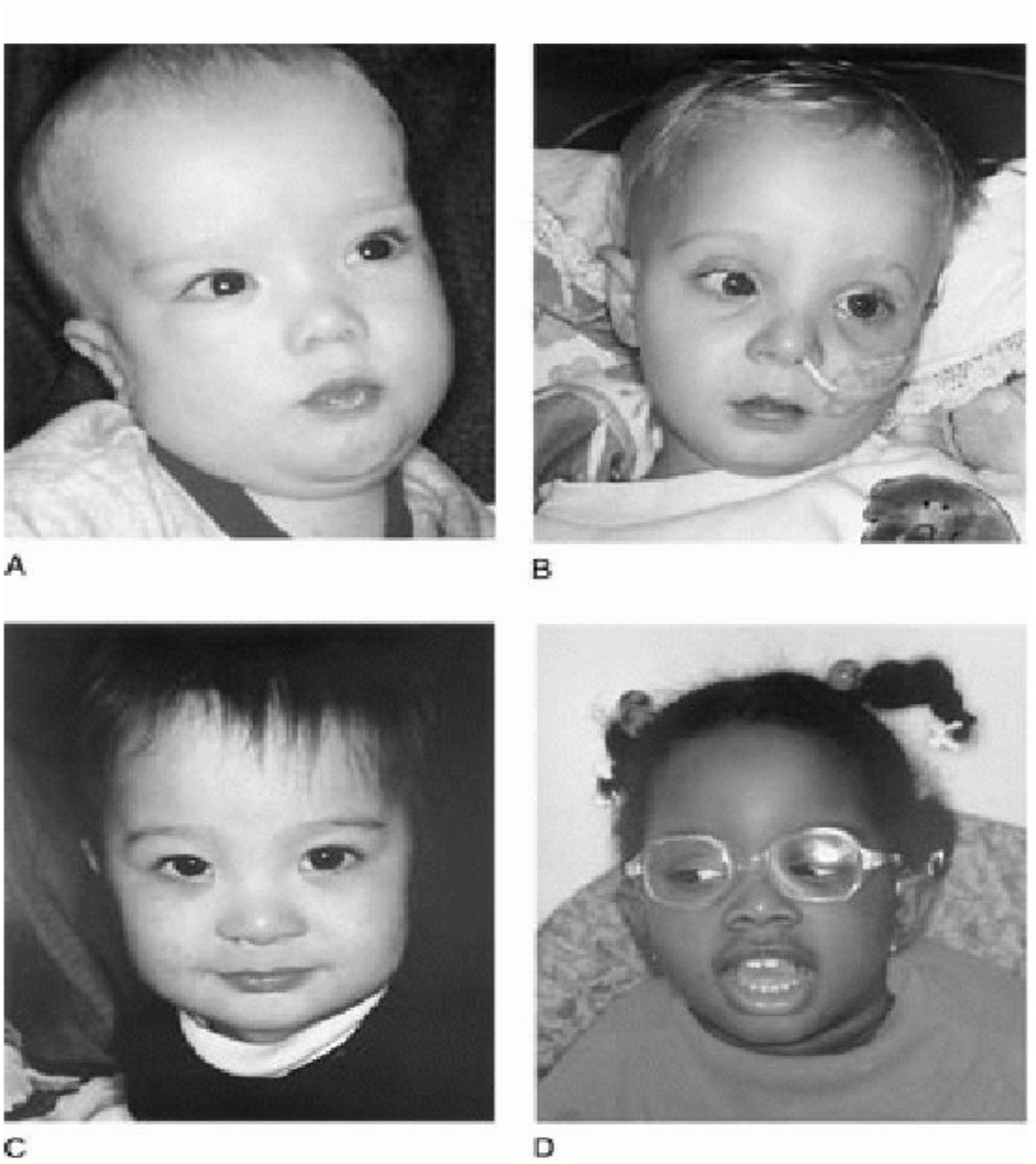
Oftern longer survival, psychomotor retardation

Demyelination, polymicrogyria, atrophic adrenals

Sensorineural hearing loss

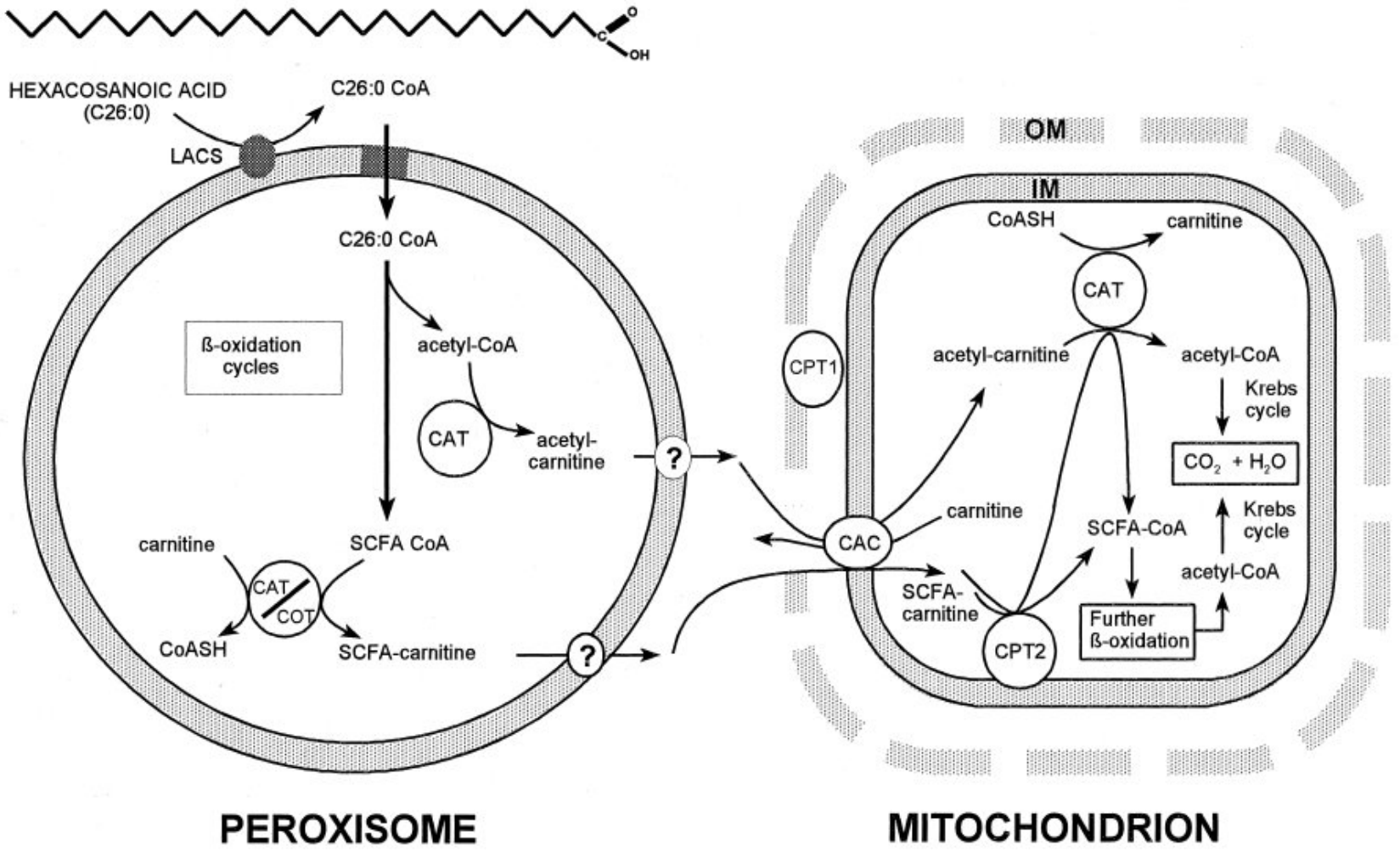
Pigment retinopathy

Neonatal adrenoleukodystrophy, infantile refsume disease



X-linked adrenoleukodystrophy

Intracellular oxidation of C26:0



Peroxisomal oxidation of fatty acids acids

Different proteins – not enzymes involved in mitochondrial BOX, different regulation

4 enzymatic reactions catalyzed by 3 enzymes :

1.acyl-CoA oxidase,
2.multifunctional protein (enoylCoA hydratase, hydroxyacyl-CoA dehydrogenase),
3.3-oxoacyl-CoA-thiolase

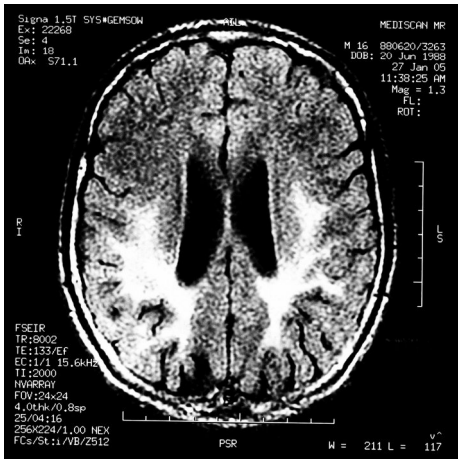
FAD-linked acylCoA oxidases : enzyme bound $FADH_2$ is directly reoxidized by molecular O_2 to produce H_2O_2

„Activation“ of VLCFA by thioesterification to CoA
fatty acid:CoA ligases (Acyl CoA synthetases)

$$\rightarrow \text{R-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-OH} + \text{ATP} + \text{CoA-SH}$$

$$\rightarrow \text{R-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-S-CoA} + \text{AMP} + \text{PP}_\text{i}$$

X-linked adrenoleukodystrophy



X-linked disease, ALDP: Xq28

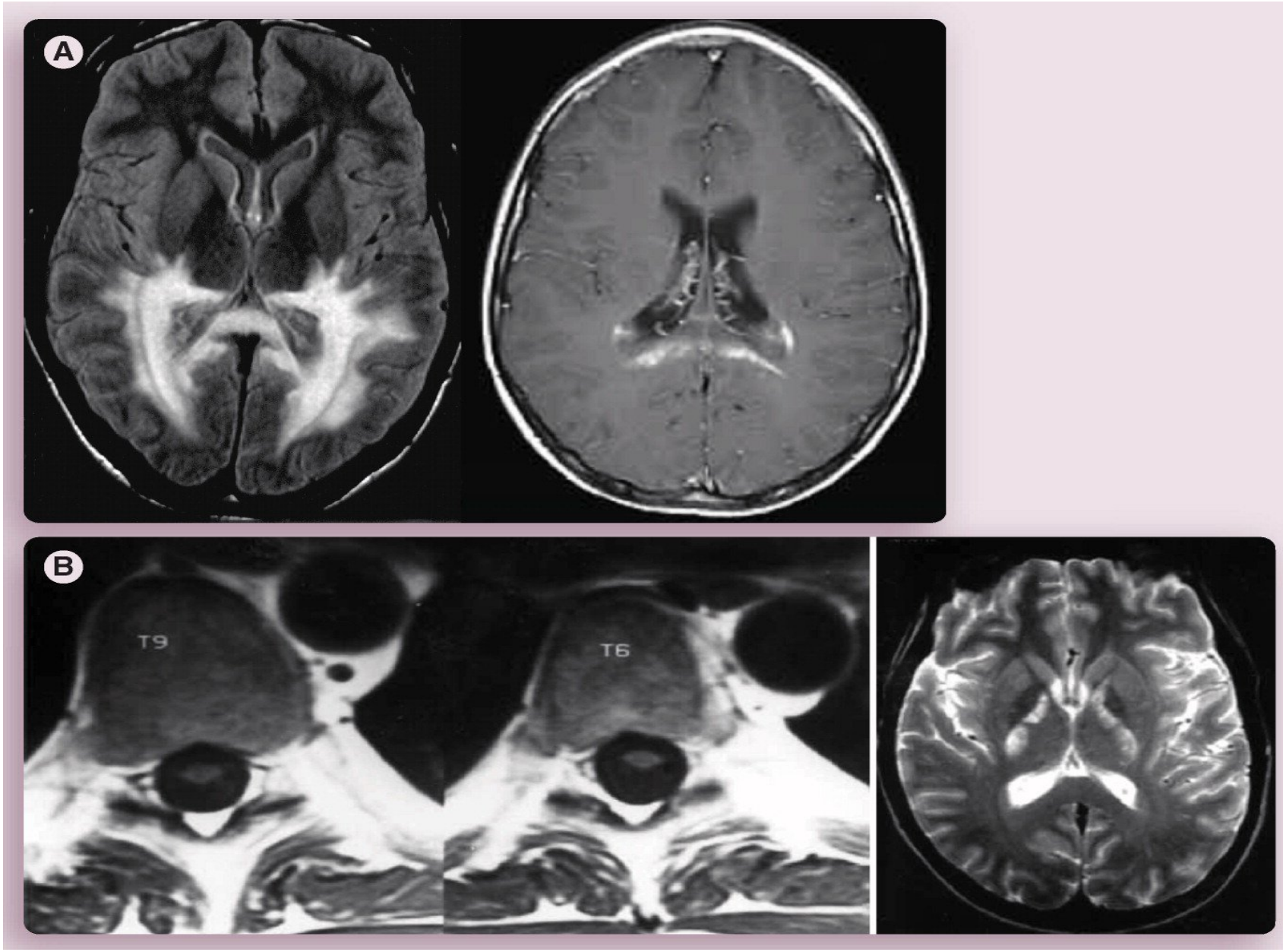
ABC half-transporter ALDP: functions as a homodimer and accepts acyl-CoA esters

Cerebral X-ALD - a rapidly progressive intensely inflammatory myelinopathy that may involve autoimmune mechanisms.

Adrenomyeloneuropathy is a noninflammatory distal axonopathy involving mainly the spinal cord long tracts
and to a lesser extent peripheral nerves. “Atrophy” of spinal cord
Addison disease
Asymptomatic
Heterozygous females

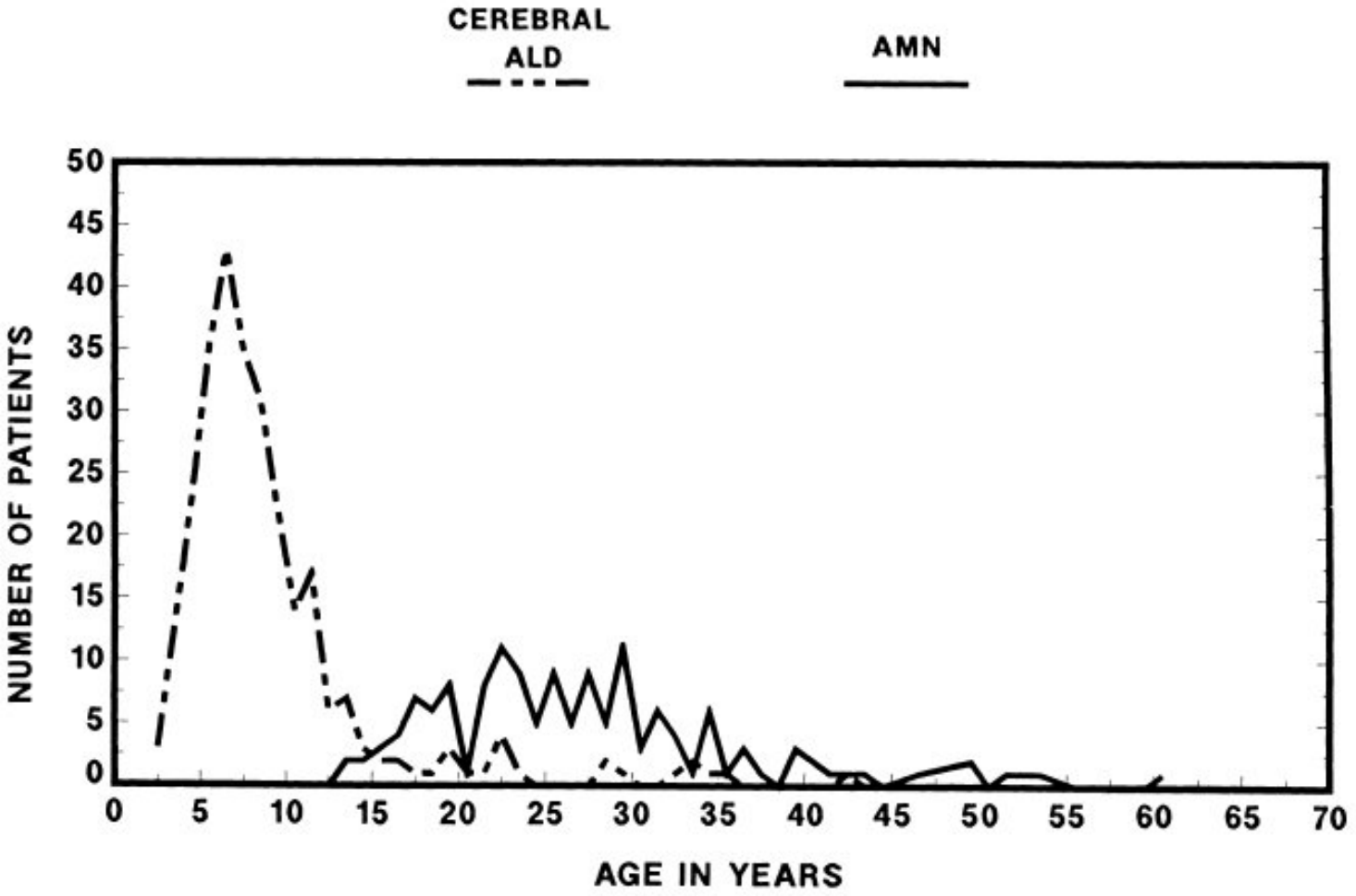
Biochemical defect at the level of long-chain acyl-CoA synthetase - elevated levels of very-long chain fatty acids

MRI-pattern of X-ALD



Expert Review of Neurotherapeutics 2008, Vol. 8, No. 9, Pages 1367-1379

AGE OF ONSET OF NEUROLOGICAL SYMPTOMS OF CEREBRAL FORMS OF ADRENOLEUKODYSTROPHY AND ADRENOMYELONEUROPATHY



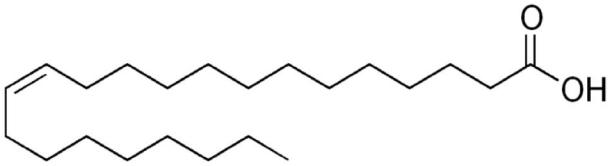
Lorenzo's oil

A 4 : 1 mixture of glyceryl trioleate and glyceryl trierucate

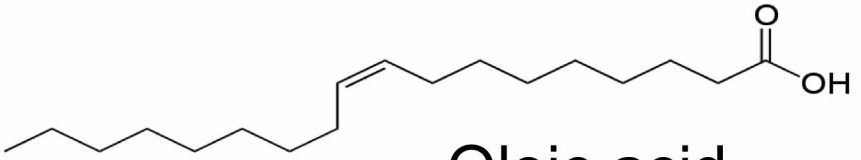
Normalizes the levels of VLCFA in the plasma of X-ALD patients.

Possibly partially effective in prevention of progression in patients without neurological symptoms/adrenomyeloneuropathy

Developed by Augusto Odone



Erucic acid



Oleic acid

Hugo Moser

Alopecia in adrenomyeloneuropathy