Hereditary disorders of sugar metabolism

Disorders of metabolism of monosaccharides („small molecules“)

Fructose

Galactose

Disorders of metabolism of polysaccharides („ large molecules“)

Glycogen storage disorders (also lack of product)

Disorders of glycosylation of proteins

product deficiency

Inherited disorders of fructose metabolism

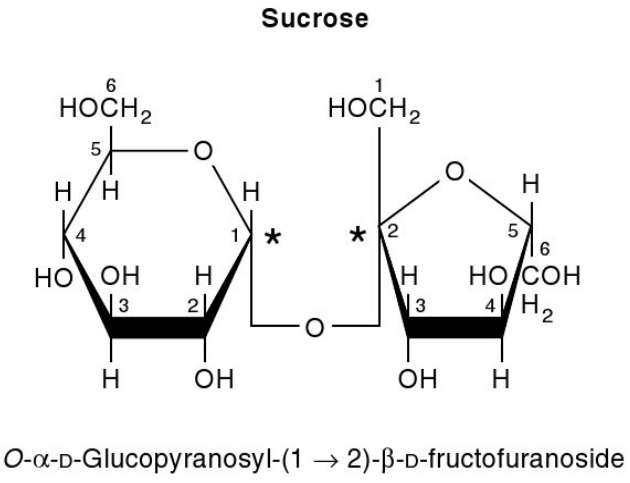
Fructose

Fructose (β-D-fructofuranose)

Honey, vegetables and fruits

Saccharose

Frucose is the main sugar of seminal fluid



O-α-D-Glucopyranosyl-(1 → 2)-β-D-fructofuranoside

raffinose, stachyose, inulin - no role in human nutrition

sorbitol – sugar alcohol, derived from glucose, abundant in fruits. Sorbitol dehydrogenase converts sorbitol to fructose - a source of fructose.

GLUT5 – glucose transporter isoform is probably responsible for fructose transport in the small intestine

Fructose is probably transported into the liver by the same system as glucose and galactose

Inherited disorders of fructose metabolism

Daily intake of fructose in Western diets: 100 g

Metabolised in liver, kidney, intestine

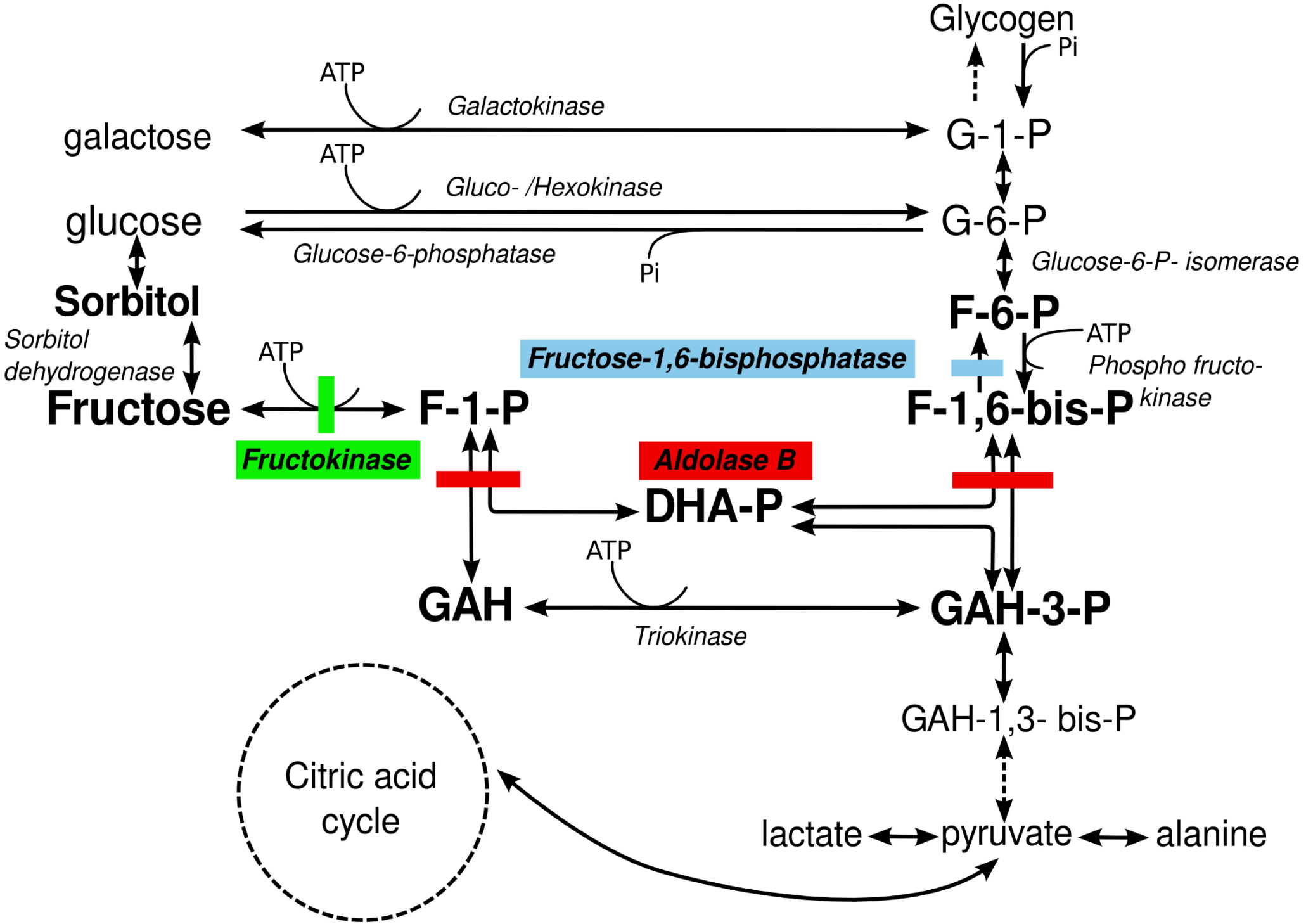
Intravenous fructose in high-doses is toxic: hyperuricemia, hyperlactacidemia, utrastructural changes in the liver.

Essential fructosuria

Hereditary fructose intolerance (aldolase B deficiency)

Hereditary fructose 1,6-bisphosphatase deficiency

Autosomal recessive disorders


Glycogen
Pi
ATP
Galactokinase
galactose
G-1-P
ATP
Gluco- /Hexokinase
glucose
G-6-P
Glucose-6-phosphatase
Pi
Glucose-6-P- isomerase
Sorbitol
F-6-P
Sorbitol dehydrogenase
ATP
Fructose-1,6-bisphosphatase
ATP
Phospho fructo-kinase
Fructose
F-1-P
F-1,6-bis-P
Fructokinase
Aldolase B
DHA-P
ATP
GAH
GAH-3-P
Triokinase
GAH-1,3- bis-P
Citric acid cycle
lactate
pyruvate
alanine

Toxicity of fructose

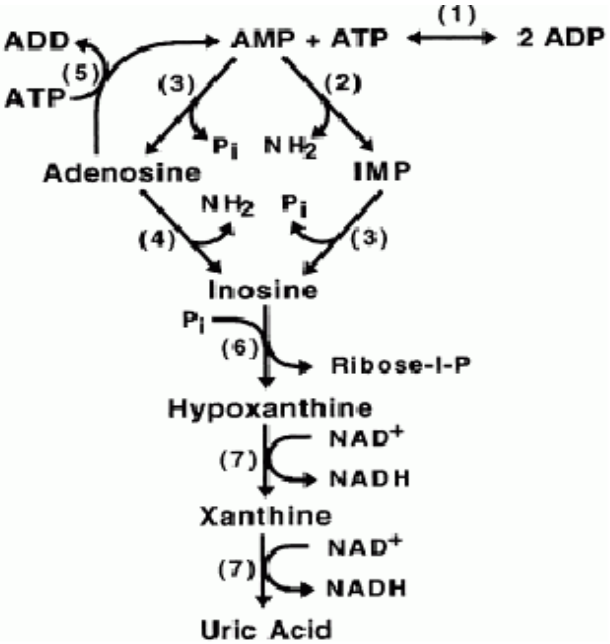
Rapid accumulation of fructose -1-phosphate

The utilization of F-1-P is limited by **triokinase**

Depletion af ATP

Hyperuricemia
Hyperuricemic effect of fructose results from the **degradation of adenine nucleotides (ATP)**.

Adenine dinucleotides → → → uric acid



Increase in lactate

Hereditary fructose intolerance

Deficiency of **fructoaldolase B** of the liver, kidney cortex (isoenzymes A,B,C)

Severe hypoglycemia upon ingestion of fructose

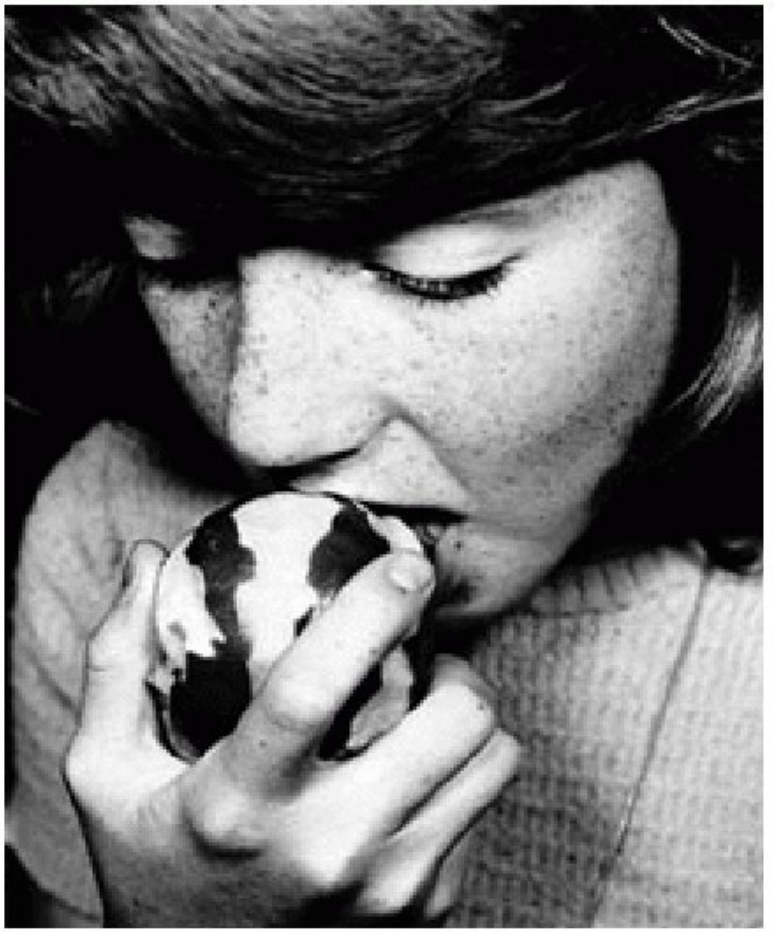
Prolonged fructose intake : poor feeding, vomiting, hepatomegaly jaundice hemorrage, proxima tubular renal syndrome, hepatic failure, death

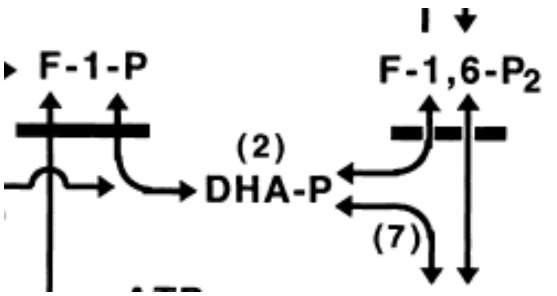
Strong distaste for fructose containig foods

Fructose -1- phosphate inhibits gluconeogenesis : phosphorylase and aldolase

Patients are healthy on fructose-free food

Diagnostics: (i.v. fructose tolerance test), DNA analysis.





Hereditary fructose 1,6-bisphosphatase deficiency

Fructose 1,6-bisphosphatase catalyzes **the irreversible splitting of fructose 1,6-bisphosphate** into fructose 6-phosphate and inorganic phosphate (P)

Autosomal recessive disorder

Severe disorder of gluconeogenesis, gluconeogenetic precursors (amino-acids, lactate, ketones) accumulate after depletion glycogen in the patients

Episodes of hyperventilation, apnea, hypoglycemia, ketosis and lactic acidosis, potentially lethal course

Episodes often triggered by fasting and infection

Aversion to sweets does not develop, tolerance to fasting improves with age

Essential fructosuria

Deficiency of liver fructokinase

Asymptomatic metabolic anomaly - benign

Hyperfructosemia and hyperfructosuria

Hereditary disorders of galactose metabolism

Hereditary disorders of galactose metabolism

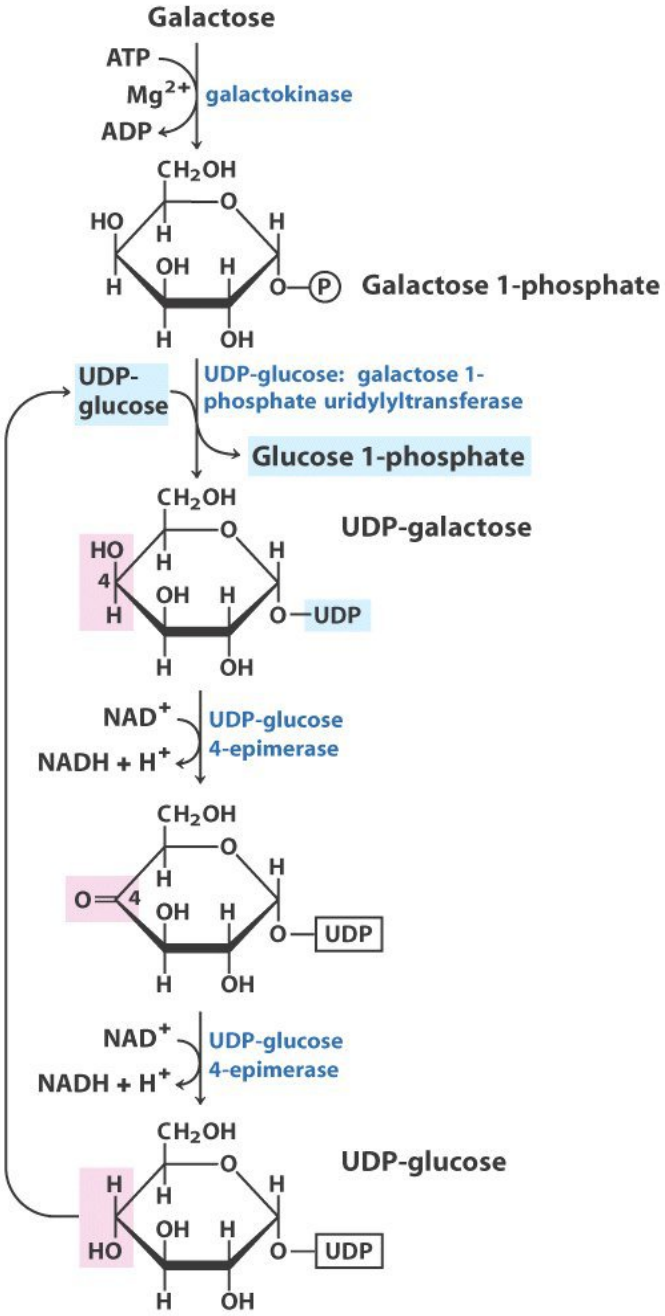
The main sources of galactose are milk and milk products.

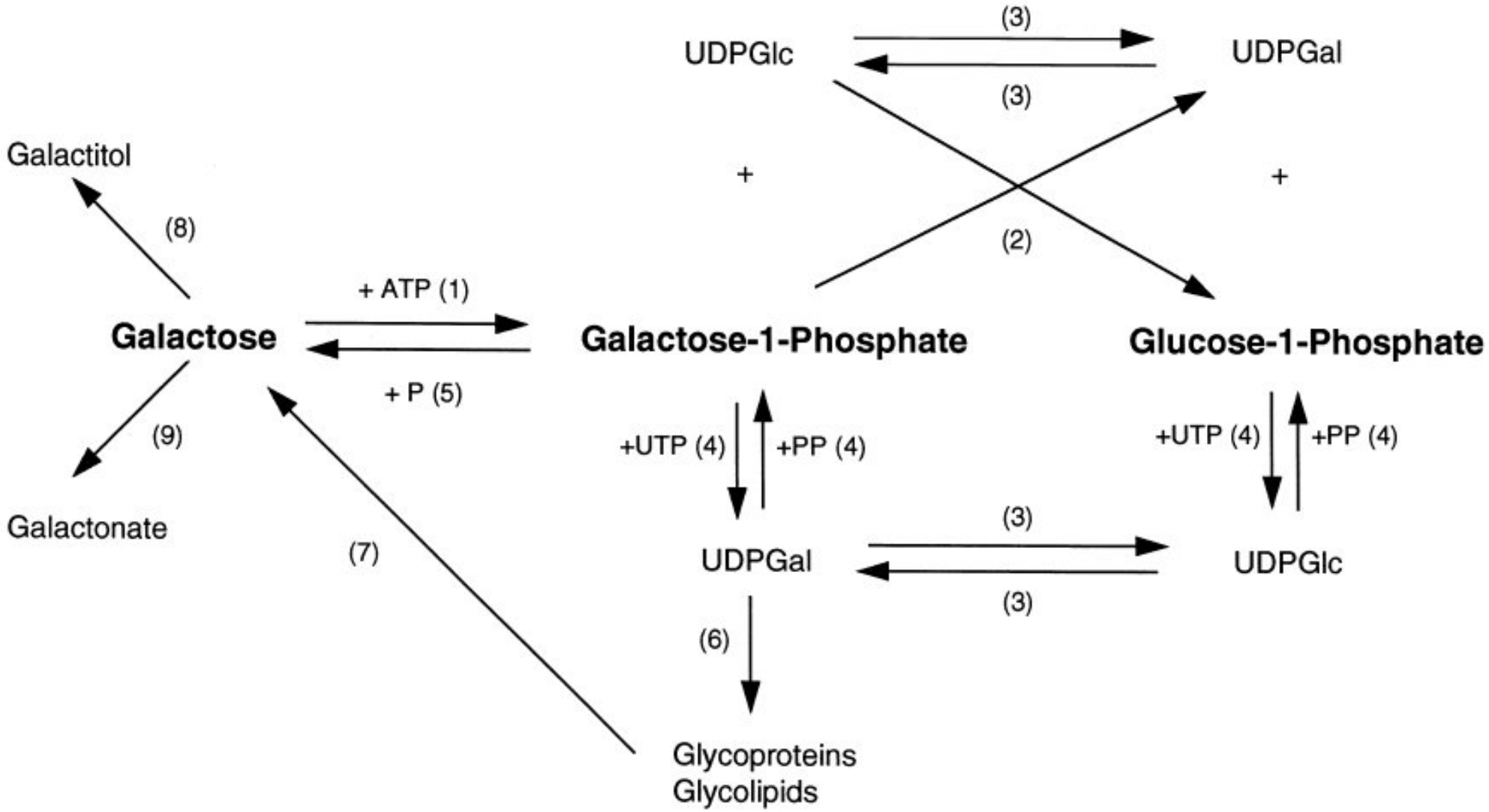
Galactose is present as the disaccharide **lactose** (β-D-galactopyranosyl-(1→4)-D-glucose)

<u>Genetic disorders:</u>
Galactokinase

Galactose-1-phosphate uridyltransferase

Uridine diphosphate galactose 4-epimerase.




UDPGlc
(3)
UDPGal
(3)
Galactitol
+
+
(8)
(2)
+ ATP (1)
Galactose
Galactose-1-Phosphate
Glucose-1-Phosphate
+ P (5)
(9)
+UTP (4)
+PP (4)
+UTP (4)
+PP (4)
Galactonate
(3)
(7)
UDPGal
UDPGlc
(3)
(6)
Glycoproteins
Glycolipids

Classical galactosemia: galactose-1-phosphate uridyltransferase deficiency

In the first weeks of life: poor feeding and weight loss, vomiting, diarrhea, lethargy,and hypotonia.

Severe liver dysfunction, hepatomegaly, icterus, vomiting, lethargy
bleeding tendencies, septicemia, renal tubular syndrome

Cataracts

Elevated galactose, galactitol, galactose-1-phosphate

Long-term complications
effects on cognitive development,
ovarian failure in females
An ataxic neurologic disease.

AR, incidence 1:40 000- 60 000,
Neonatal screening for galactose in some countries

Variants (Duarte)

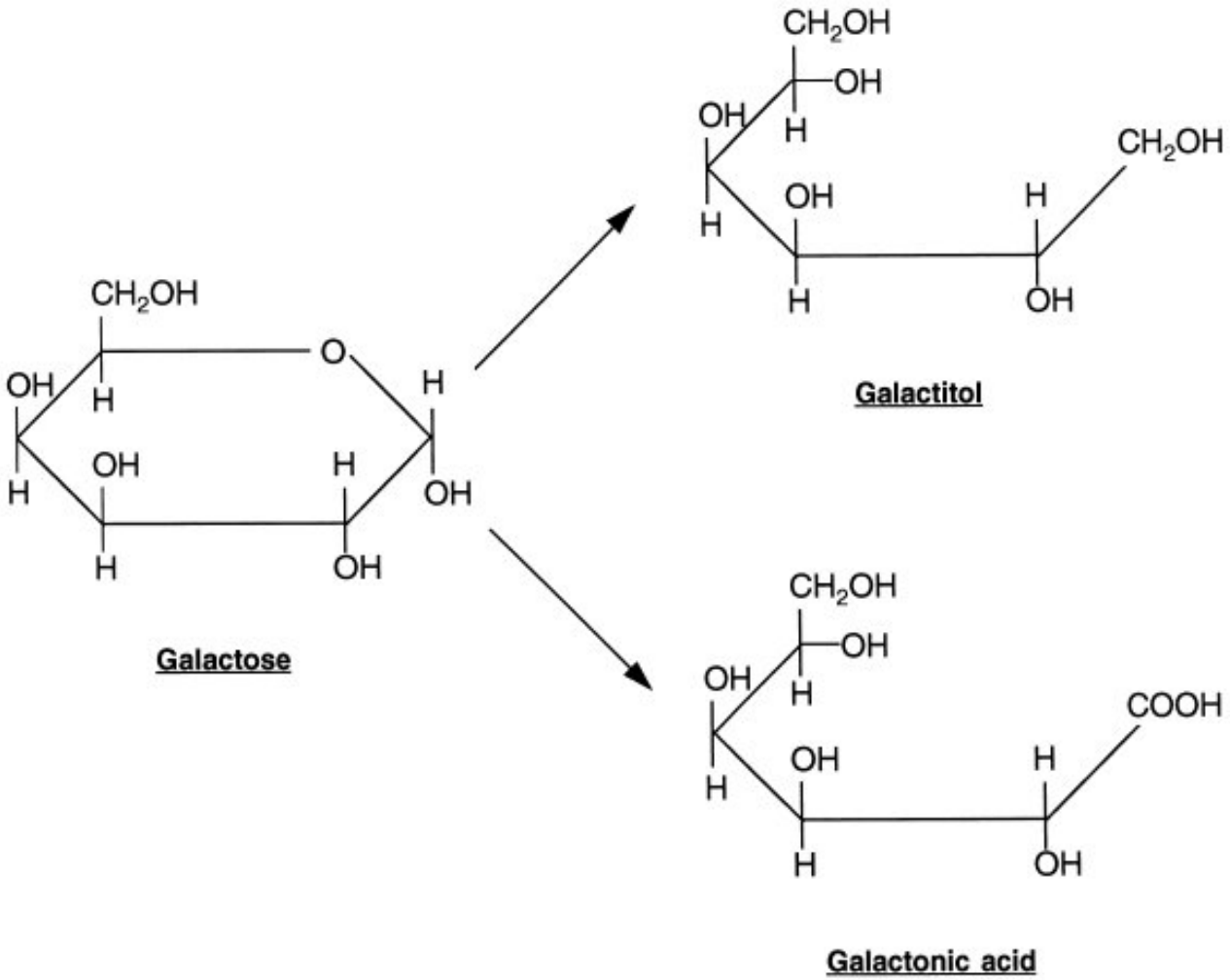


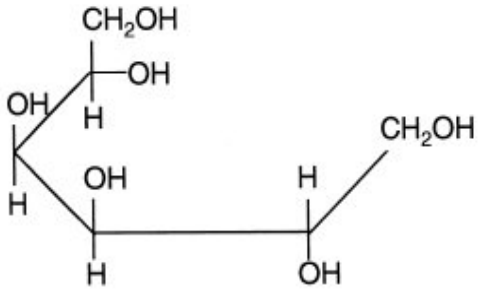
Fig. 72-3 The conversion of galactose to galactitol by a nonspecific aldose reductase and to galactonic acid by aldehyde dehydrogenase.

Brit. J. Ophthal. (1953) 37, 655.

FIGURE.—Ophthalmoscopic appearance of the lenses at 6 weeks.

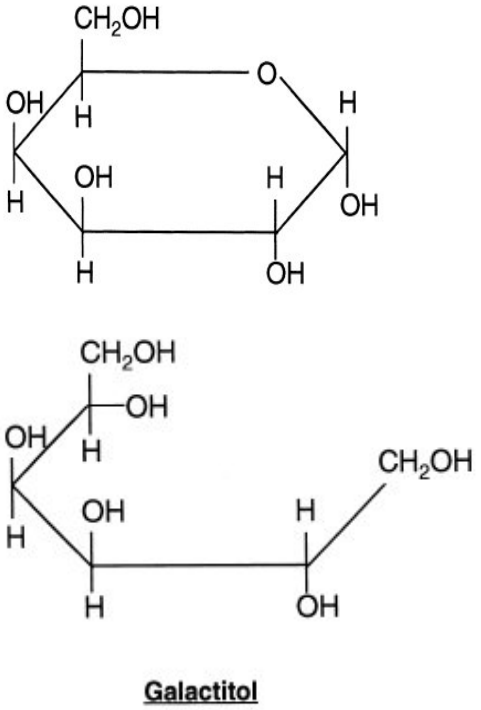
Cataracts in classical galactosemia

Galactitol – osmotic swelling of lens fibres



Galactitol

Galactokinase deficiency



Galactitol

Cataracts - usually bilateral and detectable in the early weeks of life

Pseudotumor cerebri

Galactitol – osmotic oedema of lens

Treatable by galactose-restricted diet, cataract can resolve

Autosomal recesive, rare condition (cca 1:200 000)

Uridine diphosphate galactose 4-epimerase deficiency

Severe form:

Severe deficiency of epimerase activity

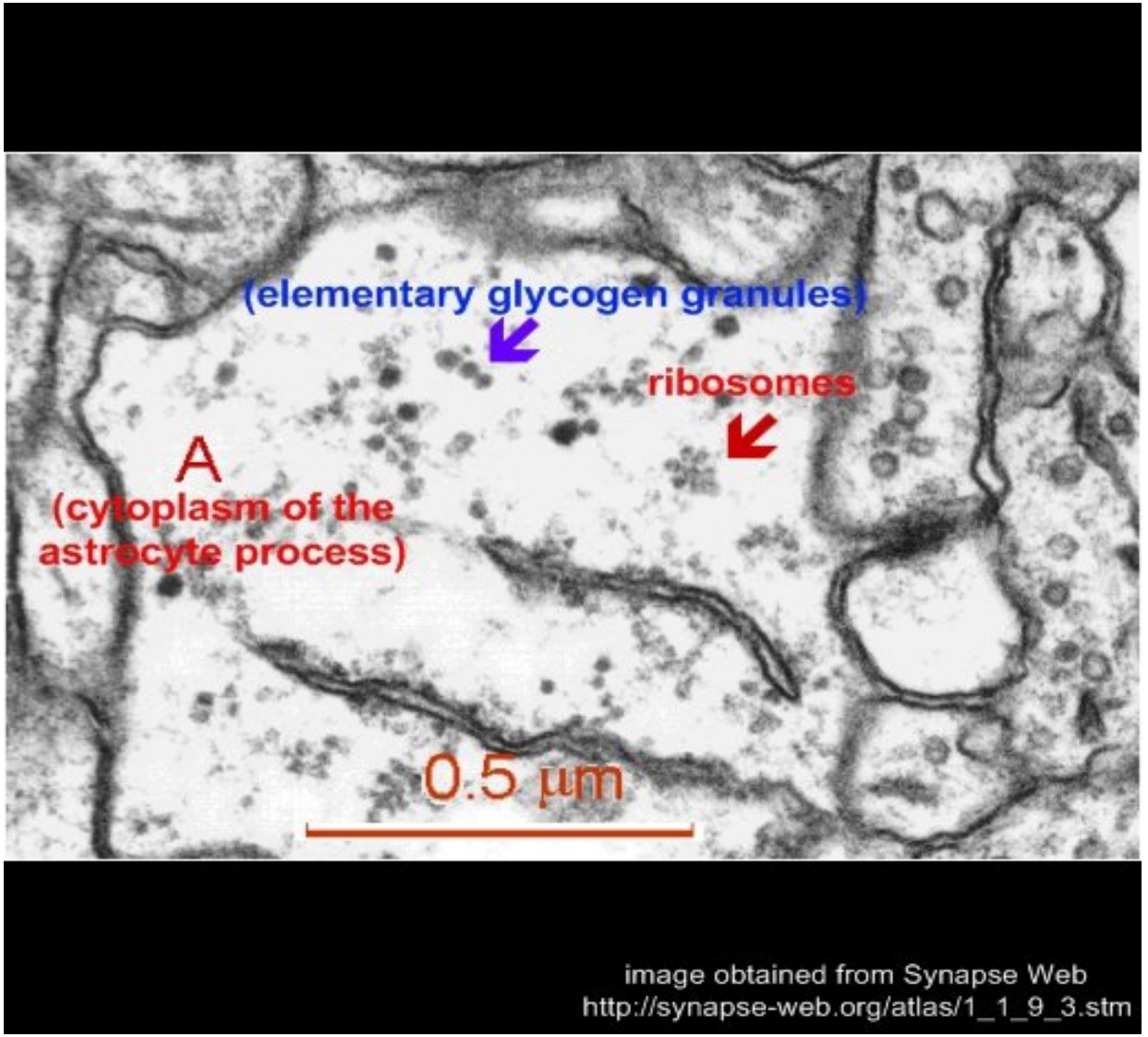
Newborns with vomiting, hepatopthy resembling classical galactosemia.
Mental retardation

Mild form:

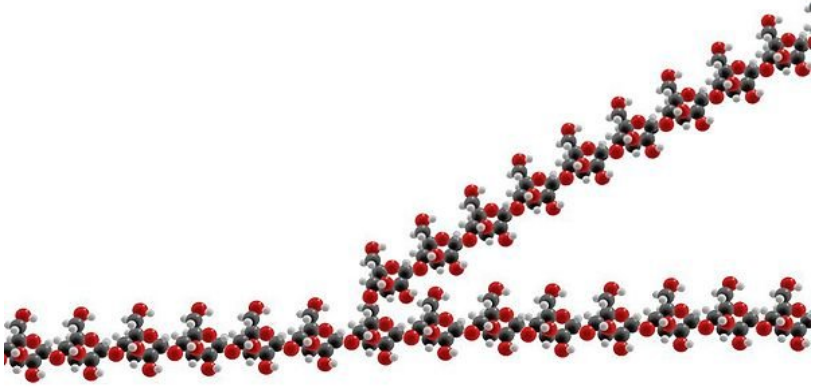
Partial deficiency of epimerase deficiency
In most patients apparently benign condition

Autosomal recessive

Hereditary disorders of glycogen metabolism



Glycogenoses
Glycogen storage disorders



wikipedia

Glucose: primary source of energy for eukaryotic cells

Glycogen: macromolecular storage form of glucose
– branched chain polysacharide composed of glucose units.

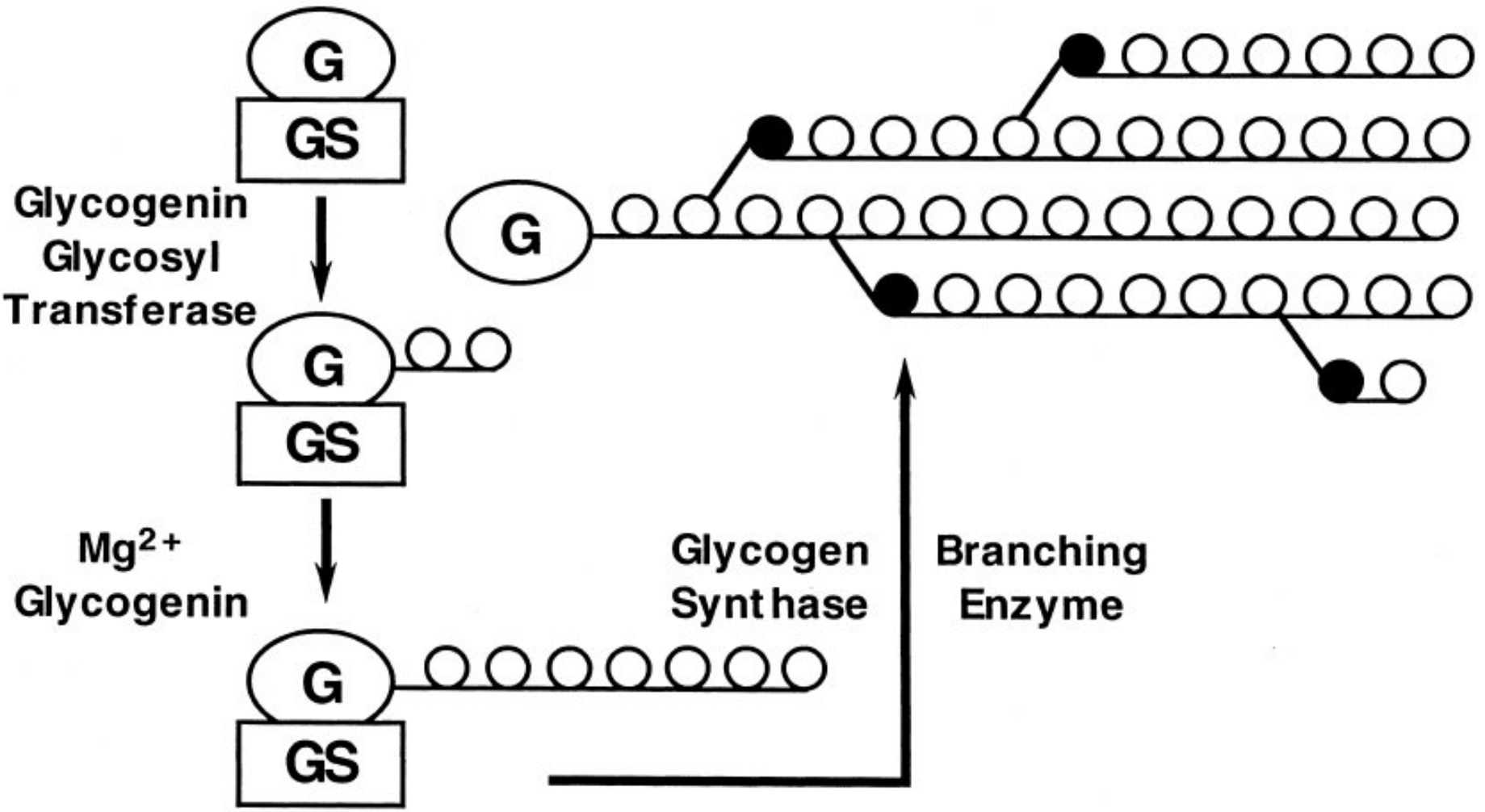
straight chains **α-1,4 linkages**
branching points **α-1,6 linkages** at intervals of 4-10 glucose residues

Serves as an important source of energy between meals. Especially abundant in the **liver** and in the **muscle**

In the muscle: glycogen β particles- up to 60 000 glucose residues
In the liver: α particles „aggregates“ β particles, glycosomes

Synthesis of glycogen: protein „primer“ - **glycogenin**

Glycogenoses: hereditary enzymopathies that result in storage of abnormal amounts and/or forms of glycogen


G
GS
Glycogenin
Glycosyl
Transferase
G
GS
Mg2+
Glycogenin
G
GS
G
Glycogen
Synthase
Branching
Enzyme

Glycogen storage diseases - overview

Hepatic glycogenoses – present principally either with ***hypoglycemia*** (GSD I, GSD III, GSD 0) or isolated ***hepatomegaly*** (GSD VI, GSD IV, GSD IX)

Muscle glycogenoses – present with exercise intolerance (GSD V, GSD VII and some very rare deficiencies)

Generalized glycogenosis and GSDs presenting with myopathy and cardiomyopathy

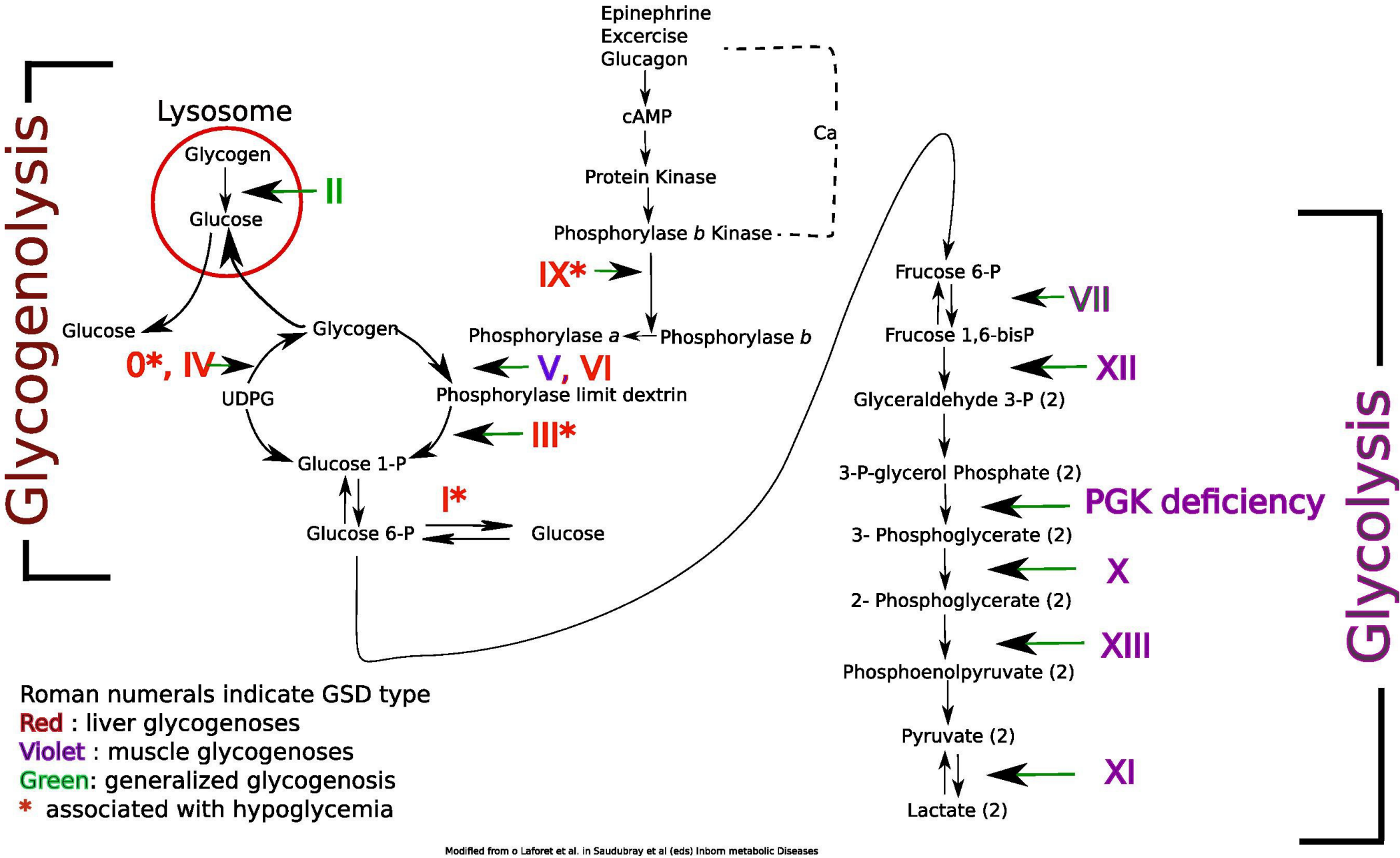
GSD II - deficiency of lysosomal alpha glucosidase , presents with myopathy and cardiomyopathy

(deficiency of LAMP 2 – disorder of autophagy – see lecture on lysosomal diseases)

AMP-activated protein kinase deficiency – presents with adult cardiomyopathy and Wolf-Parkinson-White syndrome

Brain glycogenoses – present with adult neurodegeneration, epilepsy and acumulation of polyglucosan bodies.

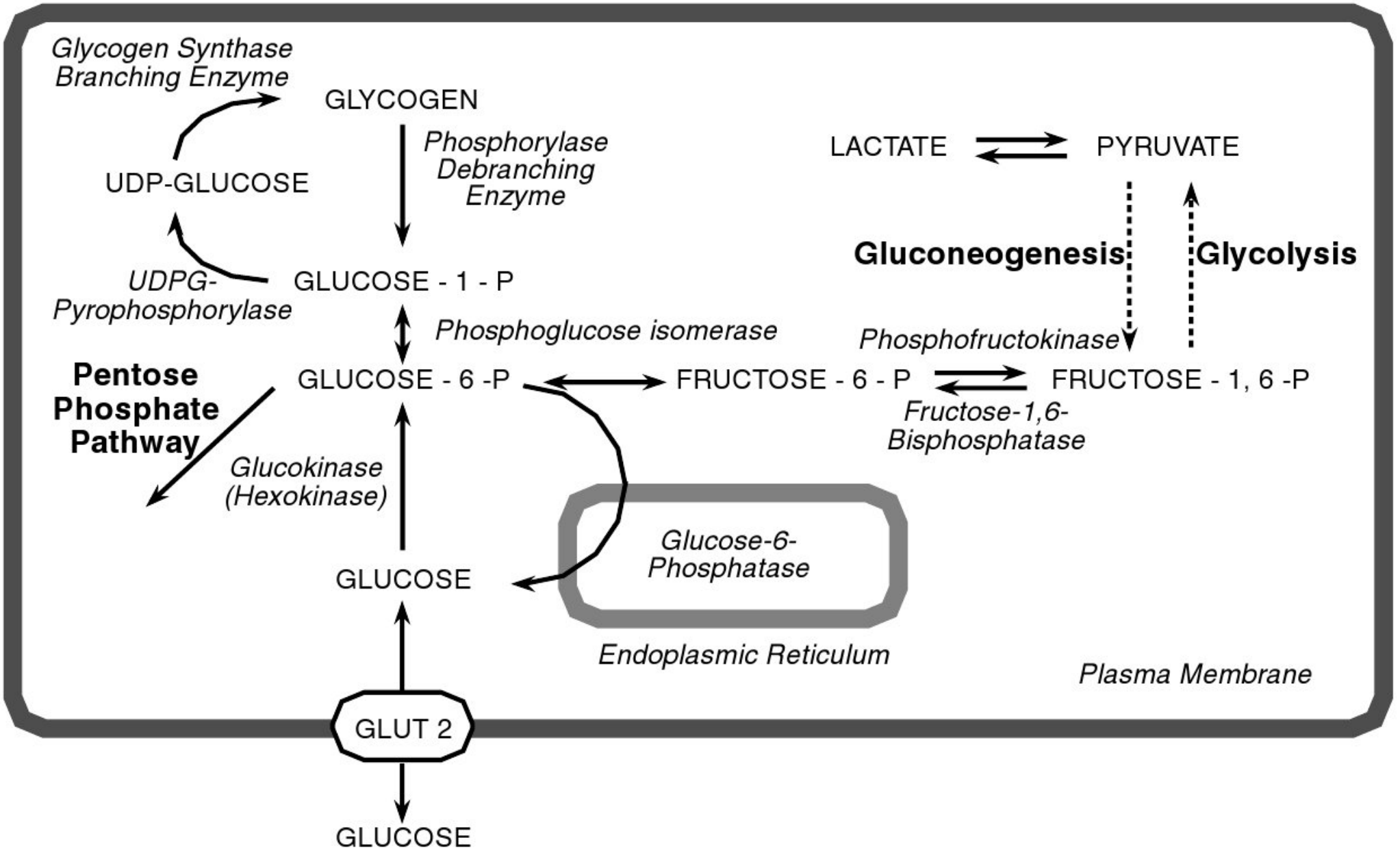
Glycogen metabolism and glycogen storage disorders



Roman numerals indicate GSD type
Red : liver glycogenoses
Violet : muscle glycogenoses
Green: generalized glycogenosis
* associated with hypoglycemia

Modified from o Laforet et al. in Saudubray et al (eds) Inborn metabolic Diseases

Cell compartments and glycogen metabolism



Liver glycogenoses

Fasting hypoglycemia, hepatomegaly, growth retardation

5 types - most common is type I (von Gierke disease- glucose-6-phosphatase deficiency)

or hepatomegaly without tendency to hypoglycemia

Muscle glycogenoses

Intolerance of exercise , cramps induced by exercise, rhabromyolysis, the heart is not affected

6 types

Generalized glycogenosis and GSDs presenting with myopathy and cardiomyopathy

Type II (Pompe disease) – deficiency of lysosomal α-1,4-glucosidase

- lysosomal storage of normal glycogen
- activated AMP protein kinase deficiency: W-P-W syndrome

Brain glycogenoses

Adult polyglucosan body disease, Lafora disease and other disorders associated with accumulation of polyglucosan bodies in the brain

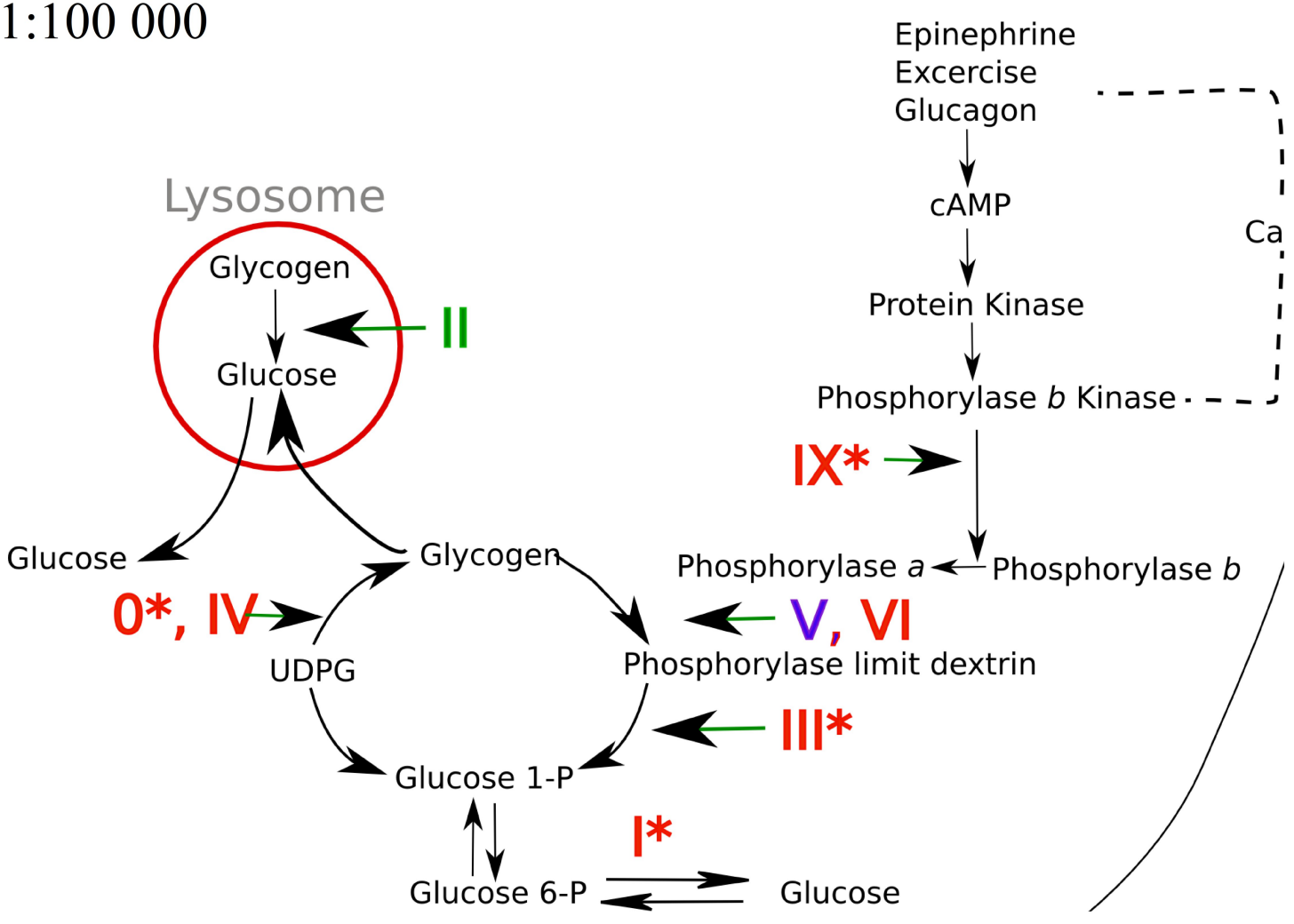
neurodegenerative disease with adult onset, epilepsy,

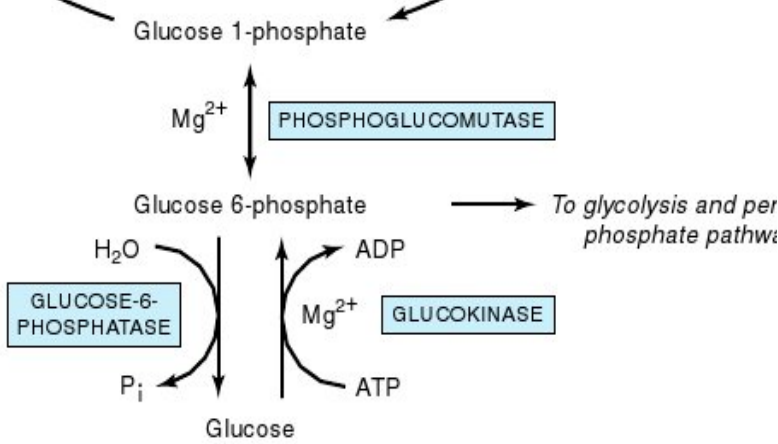
- accumulation of polyglucosan bodies

Liver glycogenoses

Fasting hypoglycemia, hepatomegaly, growth retardation
or *hepatomegaly without tendency to hypoglycemia*

prototypical GSD: GSD I (von Gierke disease- glucose-6-phosphatase deficiency), incidence approx. 1:100 000
common: GSD IX: phosphorylase kinase deficiency :
incidence approx. 1:100 000

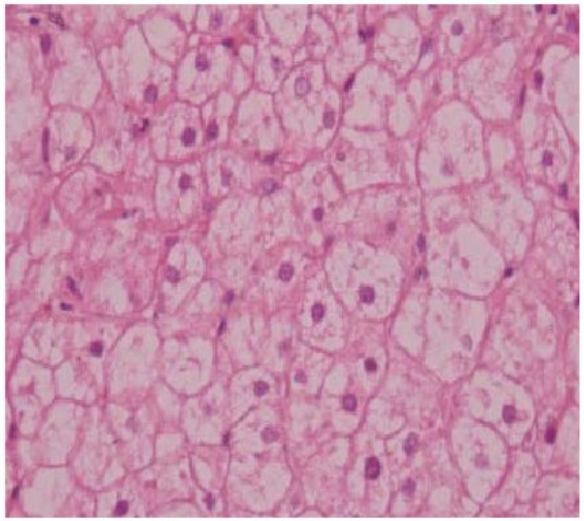




Type I Glycogen Storage Disease (Glucose 6-Phosphatase Deficiency, von Gierke Disease)

Excessive accumulation of glycogen in liver, kidney and intestinal mucosa

Patients usually present in infancy with hepatomegaly and/or hypoglycaemic seizures, hyperlactacidemia after a short fast



Gout, hyperlipidemia (hypertriglyceridemia), skin xanthomas

Doll-like face, thin extremities, short stature, protuberant abdomen (hepatomegaly), inflammatory bowel disease

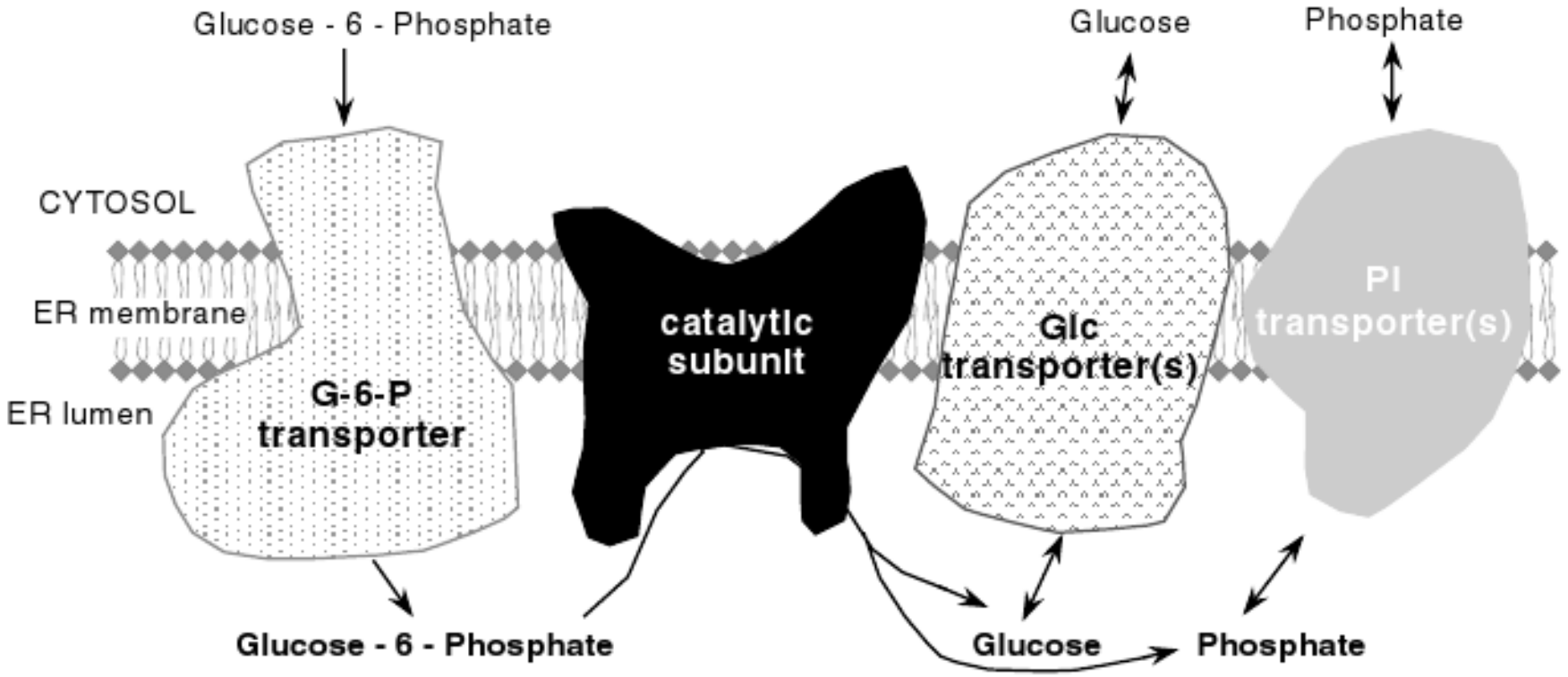
Fibrosis, liver adenomas -cave: malignant transformation, Atherosclerosis

Fasting tolerance improves with age, long-term complications

Treatment : frequent feeding, nocturnal nasogastric drips in infancy, uncooked cornstarch, liver transplantation

Autosomal recessive, overall incidence is 1:10000, frequent in Ashkenazi
The diagnosis is based on clinical presentation, abnormal blood/plasma concentrations of glucose, lactate, uric acid, triglycerides, and lipids, and molecular genetic testing.

Glucose -6-phosphatase system

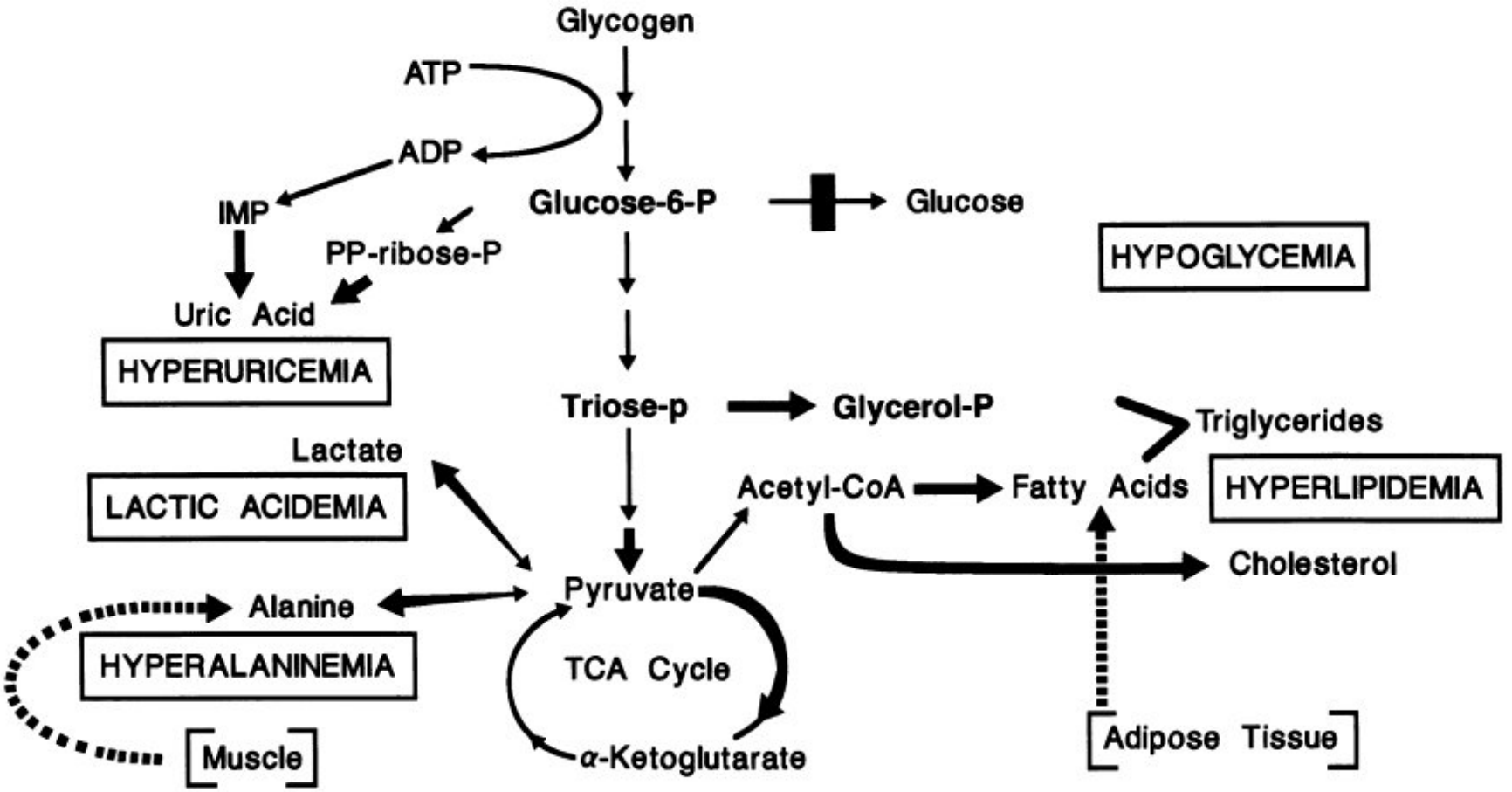


Localized to <u>luminal</u> face of ER

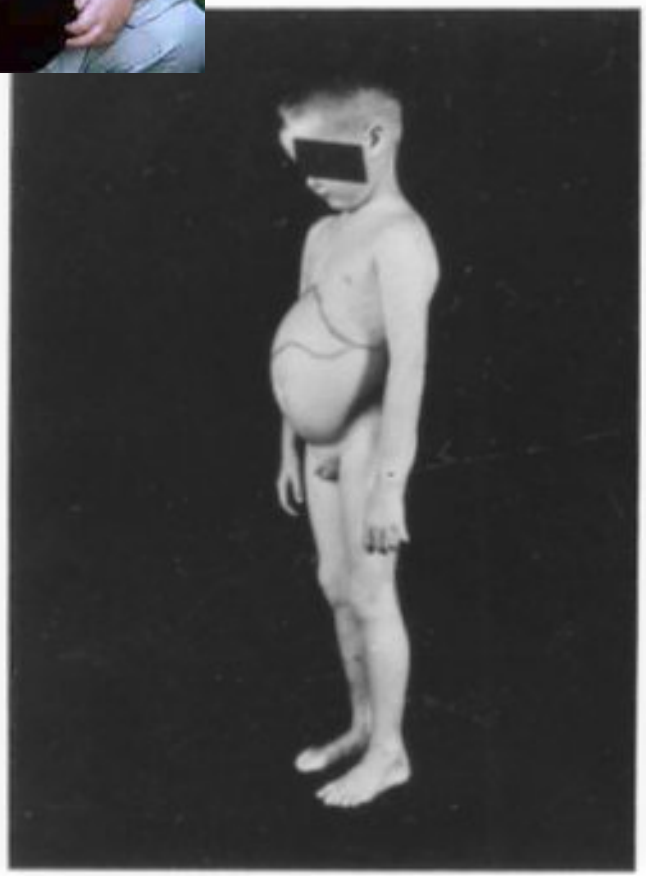
Type Ia GSD: deficient activity of phosphatase
Type Ib GSD: a defect in the microsomal membrane transport system of G-6-P
Type Ic GSD: a defect in microsomal phosphate or pyrophosphate transport,

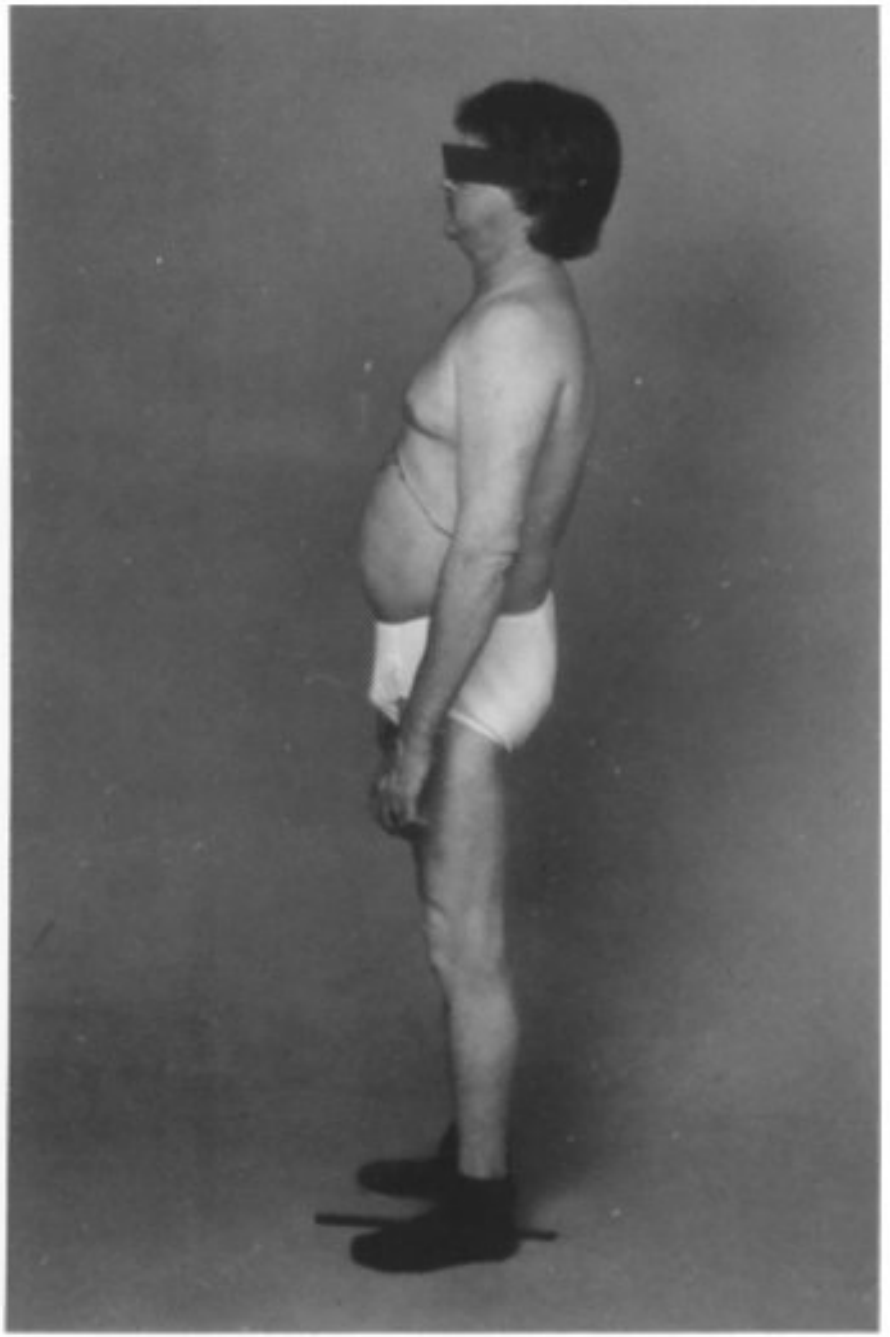
Non-a types associated with neutropenia and inflamarory bowel disease with recurrent bacterial infections and oral ulcers

The metabolic consequences of GSD I



http://www.curegsd.org/faces.htm





A

Type III Glycogen Storage Disease (Debrancher Deficiency; Limit Dextrinosis; Cori or Forbes Disease)

Both liver and muscle are affected: frequent cirrhosis, myopathy, often cardiomyopathy, with fasting ketotic hypoglycemia

about 15% percent of patients have only hepatic presentation

myopathic presentation - also in adulthood

Abnormal glycogen: limit dextrin

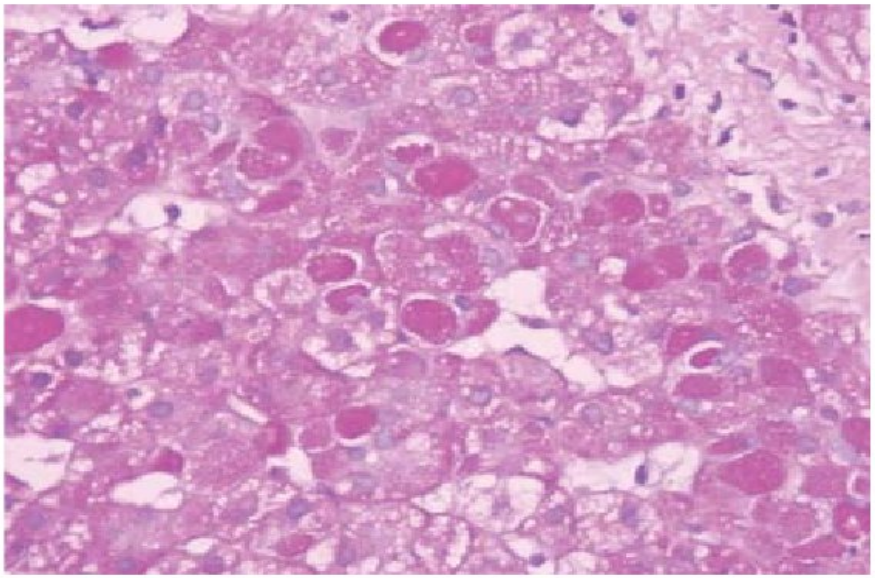
Type IV (Branching Enzyme Deficiency, Amylopectinosis, or Andersen Disease)

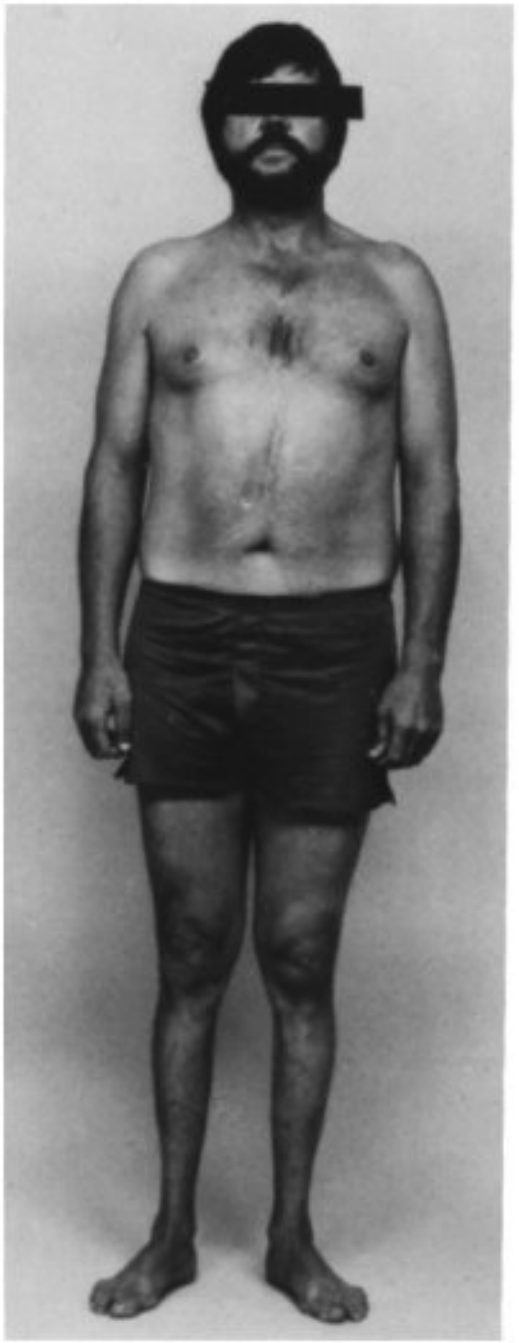
Abnormal glycogen resembling amylopectin – fewer branching points

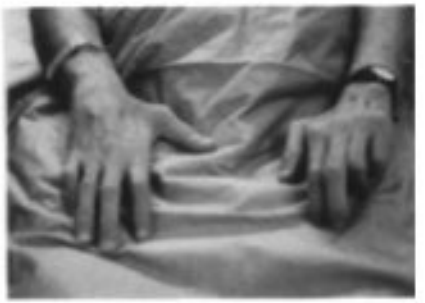
presents in infancy with liver failure leading to cirrhosis, rare hypoglycemias, cardiomyopathy

death at 4-5 years withou liver transplantation

Neuromuscular presentation - accumulation of polyglucosan bodies in tissues - myopathy , adult polyglucosan body disease







GSD III

Type III Glycogen Storage Disease (Debrancher Deficiency; Limit Dextrinosis; Cori or Forbes Disease)

Both liver and muscle are affected: frequent cirrhosis, myopathy, often cardiomyopathy, with fasting ketotic hypoglycemia

about 15% percent of patients have only hepatic presentation

myopathic presentation - also in adulthood

Abnormal glycogen: limit dextrin

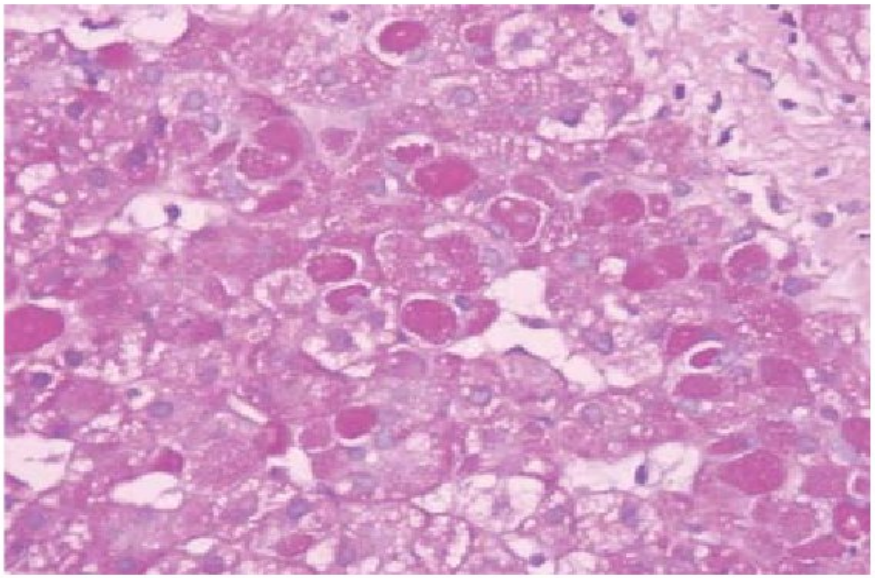
Type IV (Branching Enzyme Deficiency, Amylopectinosis, or Andersen Disease)

Abnormal glycogen resembling amylopectin – fewer branching points

presents in infancy with liver failure leading to cirrhosis, rare hypoglycemias, cardiomyopathy

death at 4-5 years withou liver transplantation

Neuromuscular presentation - accumulation of polyglucosan bodies in tissues - myopathy , adult polyglucosan body disease



Note : the aim of this and the slide is to show complexity of molecular pathology. The the text in small print will not be required at the exam.

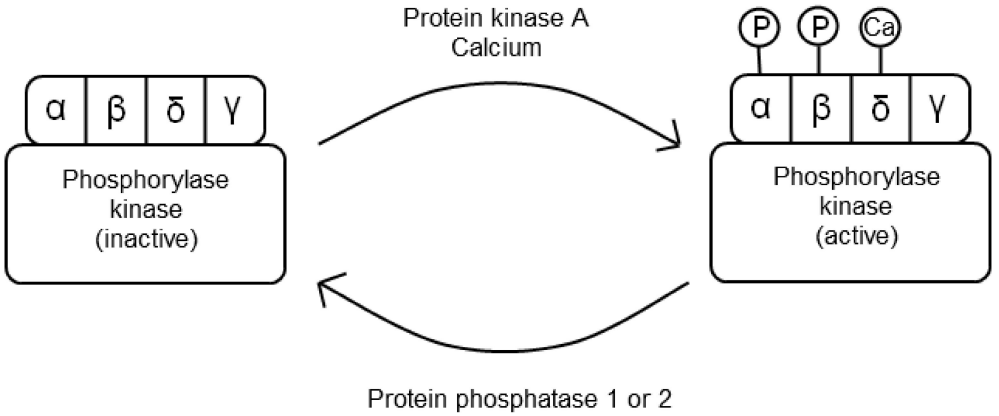
Type IX Glycogen Storage Disease (deficiency of phosphorylase kinase (PhK) and subunits)

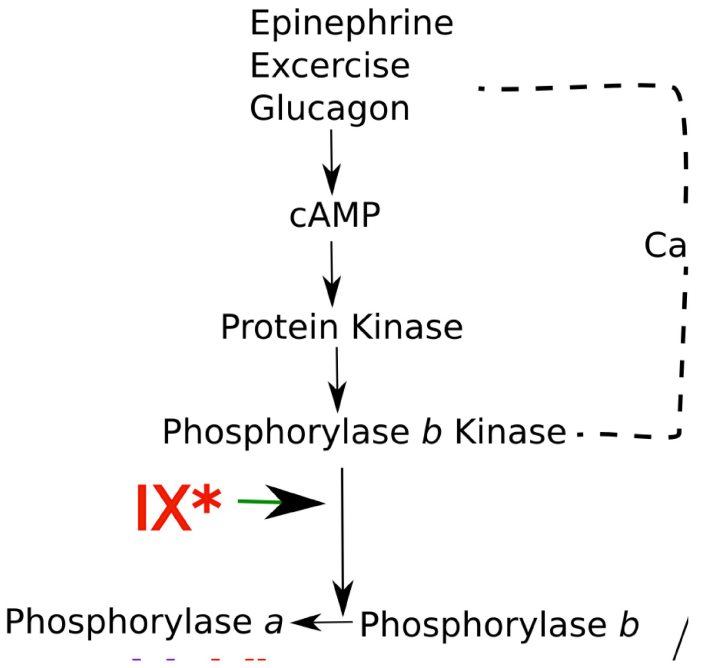
Degradation of glycogen is regulated by a metabolic cascade resulting in activation of glycogen phosphorylase by phosphorylase kinase

Phosphorylase kinase enzyme has four copies of 4 subunits each - α, β, γ, δ. Subunit γ is catalytic, subunits α and β are regulatory, δ is calmodulin.

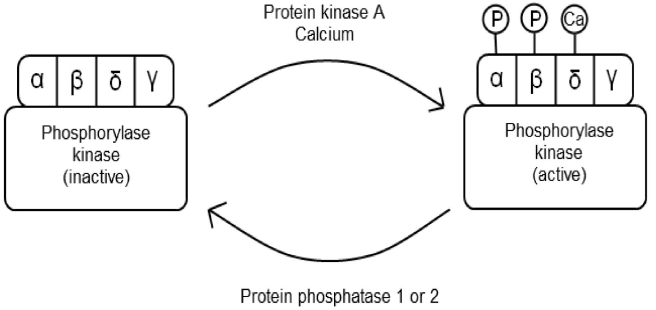
The most common form (90% of cases), liver PhK deficiency (X-linked liver glycogenosis) is due to the deficiency of liver form of α subunit

deficiency of muscle form of α subunit: X - linked muscle glycogenosis
deficiency of subunit β: autosomal recessive PhK deficiency in liver and muscle;
deficiency of subunit γ, autosomal recessive liver PhK deficiency.





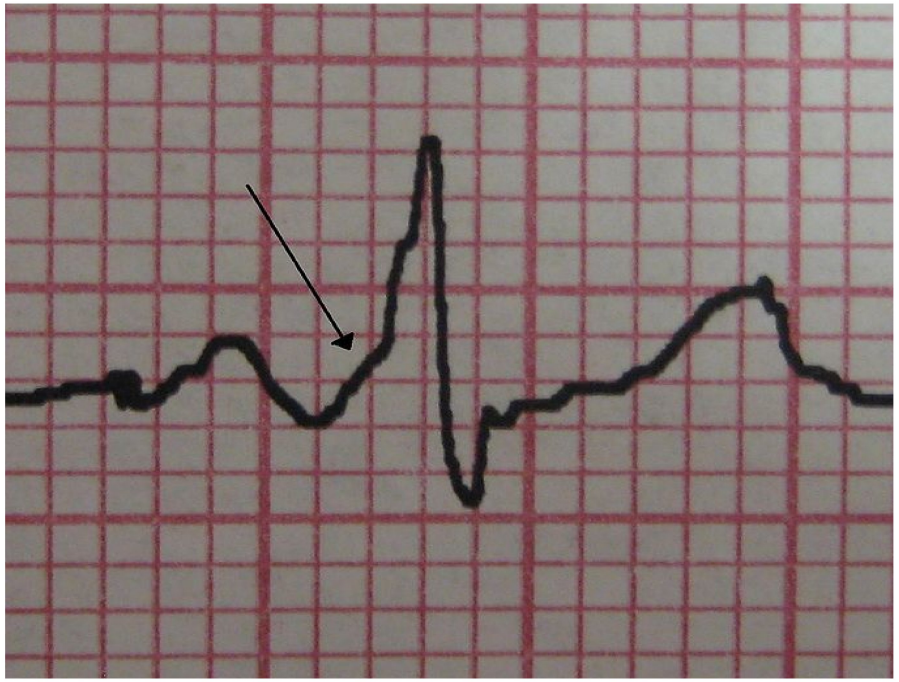
AMP-activated Protein Kinase (AMPK) Deficiency



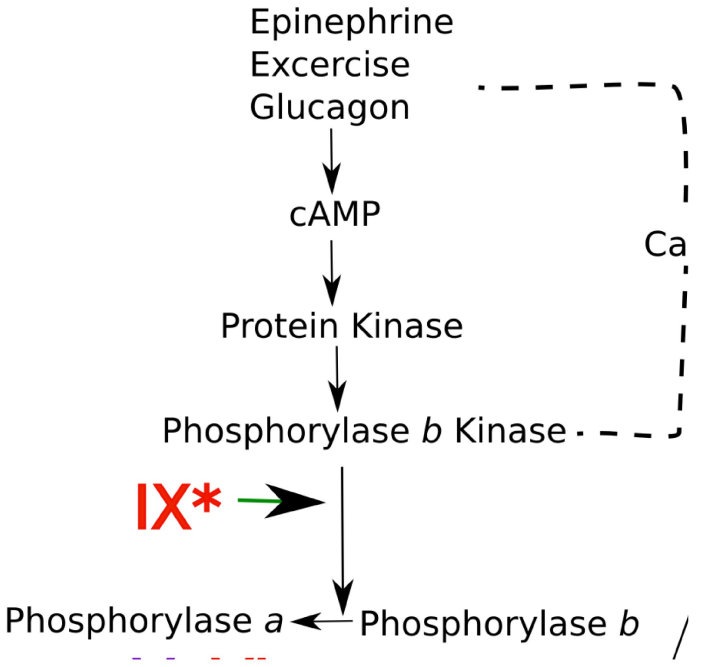
AMPK activates phosphorylase kinase

AMPK is a cellular energy sensor. It is activated by exercise in muscle and an increase in the AMP/ATP ratio. Heterotrimeric complex: a catalytic subunit (α) and two regulatory γ.

Mutations in the gene enconding γ subunit (PRKAG2) cause ventricular pre-excitation (Wolf-Parkinson-White syndrome) predisposing to supraventricular arrythmias. Fully penetrant autosomal dominant trait.



Arrow : typical delta wave of W-P-W syndrome



Note : the aim of this and the slide is to show complexity of molecular pathology. The the text in small print will not be required at the exam.

Brain glycogenoses

Adult polyglucosan body disease

Deficiency of the branching enzyme (GSD IV) in astrocytes leads to accumulation of polyglucosan bodies in the brain and slowly progressive neurode-generative disorder

wikimedia commons

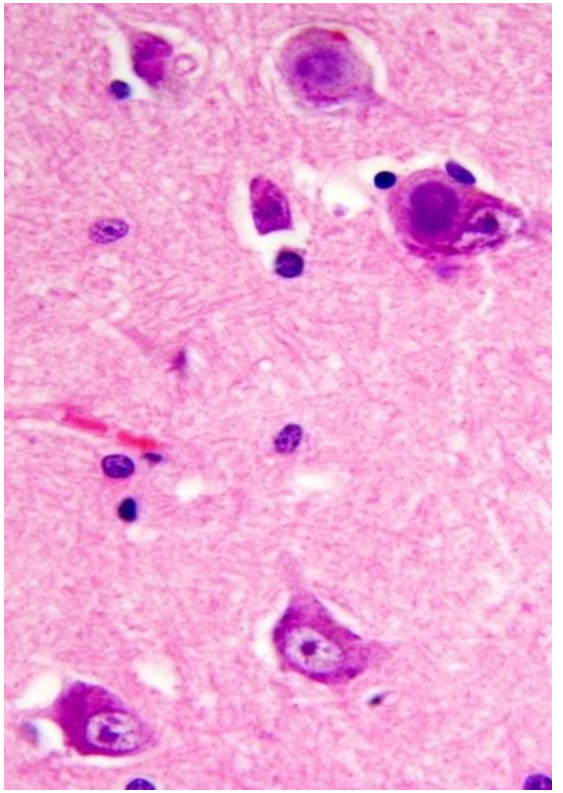
http://frontalcortex.com/gallery/pics/gliageek_Lafora400.jpg

Slowly progressive gait disturbance, urinary incontinence,
loss of sensitivity in lower extremities, later cognitive decline
In peripheral nerves and in the brain storage of amylopectin-like glycogen in polyglucosan bodies
Rare, found almost exclusively in Ashkenazi Jewish patients, AR

Lafora disease
Progressive severe myocloclonic epilepsy with onset usually in adolescence, progressive dementia, aphasia, apraxia
Leads to vegetative state and death in 10 years from onset

Lafora bodies in neurons - abnormal glycogen storage

Mutations in laforin carbohydrate-binding phosphatase and the malin E3 ubiquitin ligase
Enzyme deficiency is not known



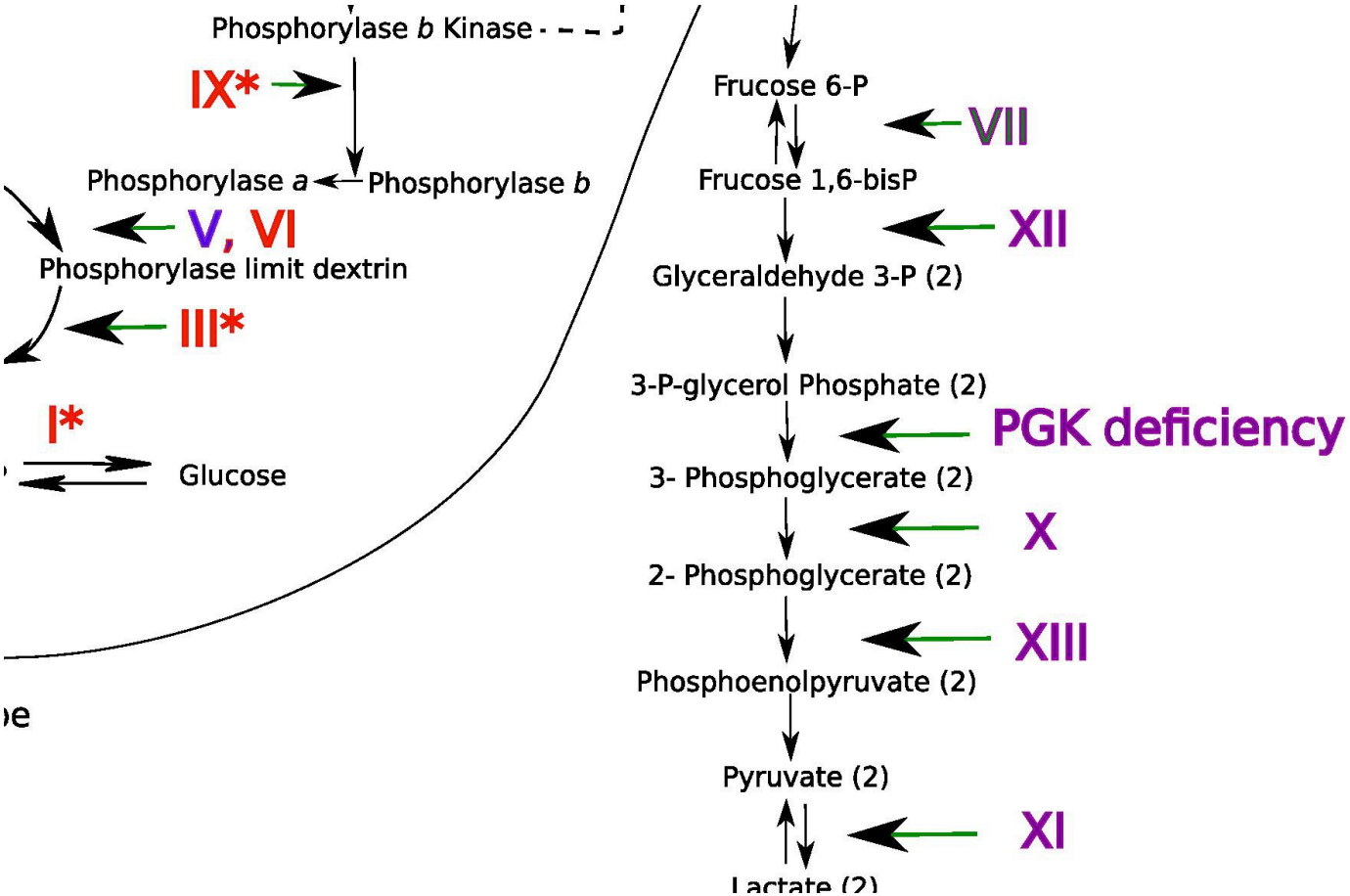
Muscle glycogenoses (without cardiac involvement)

Excercise intolerance, often followed by rhabdomyolysis

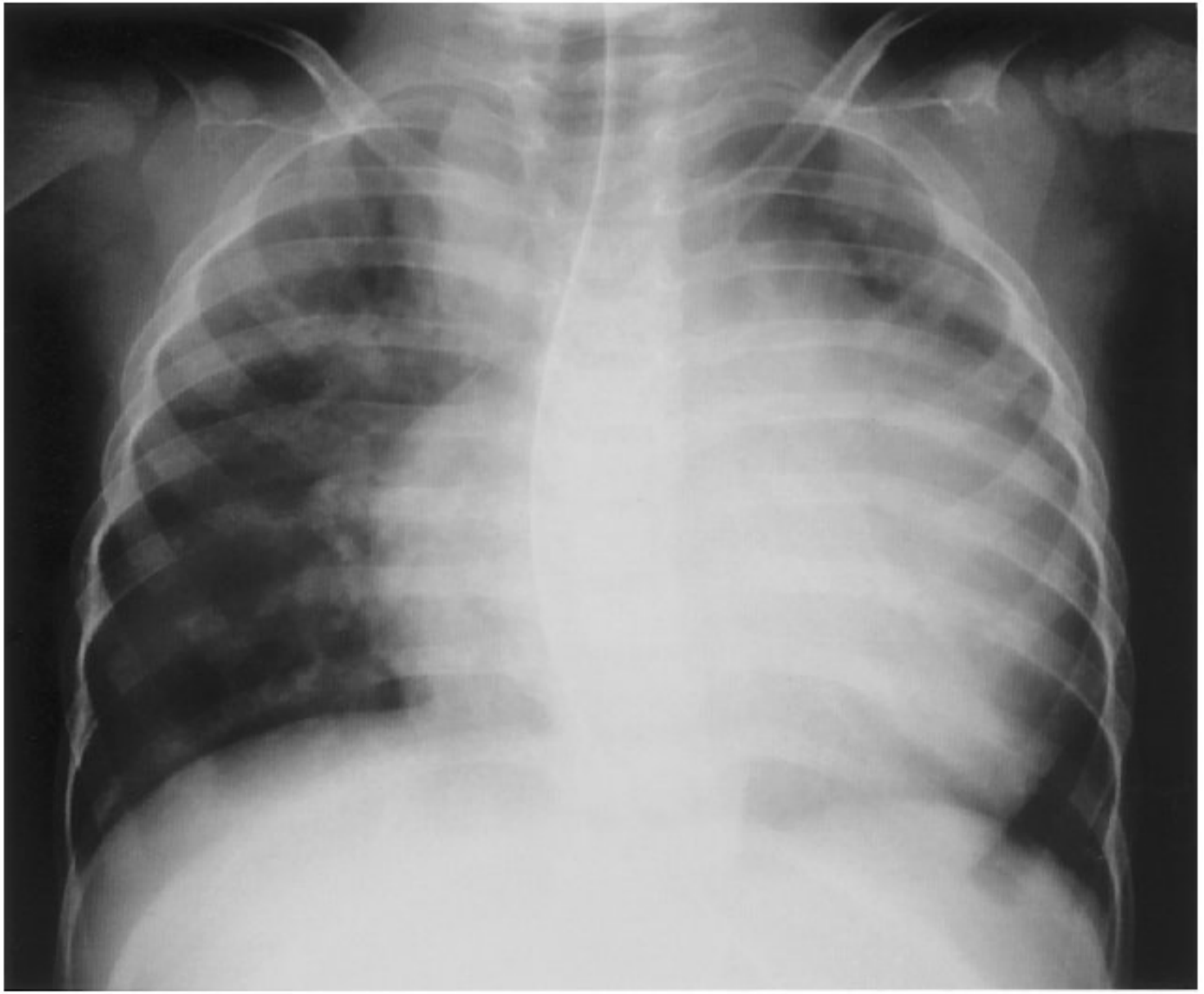
prototypical : GSD V, McArdrle disease, deficiency of myophosphorylase
myalgia and stifness of exercising muscles relieved by rest, often rhabdomyolysis, later in life may be present muscle wasting

AR inheritance

no pharmacological treatment



Generalized glycogenosis: Morbus Pompe



M.Pompe

Deficiency of lysosomal acid alpha-glucosidase (acid maltase)
Lysosomal storage of glycogen with normal structure

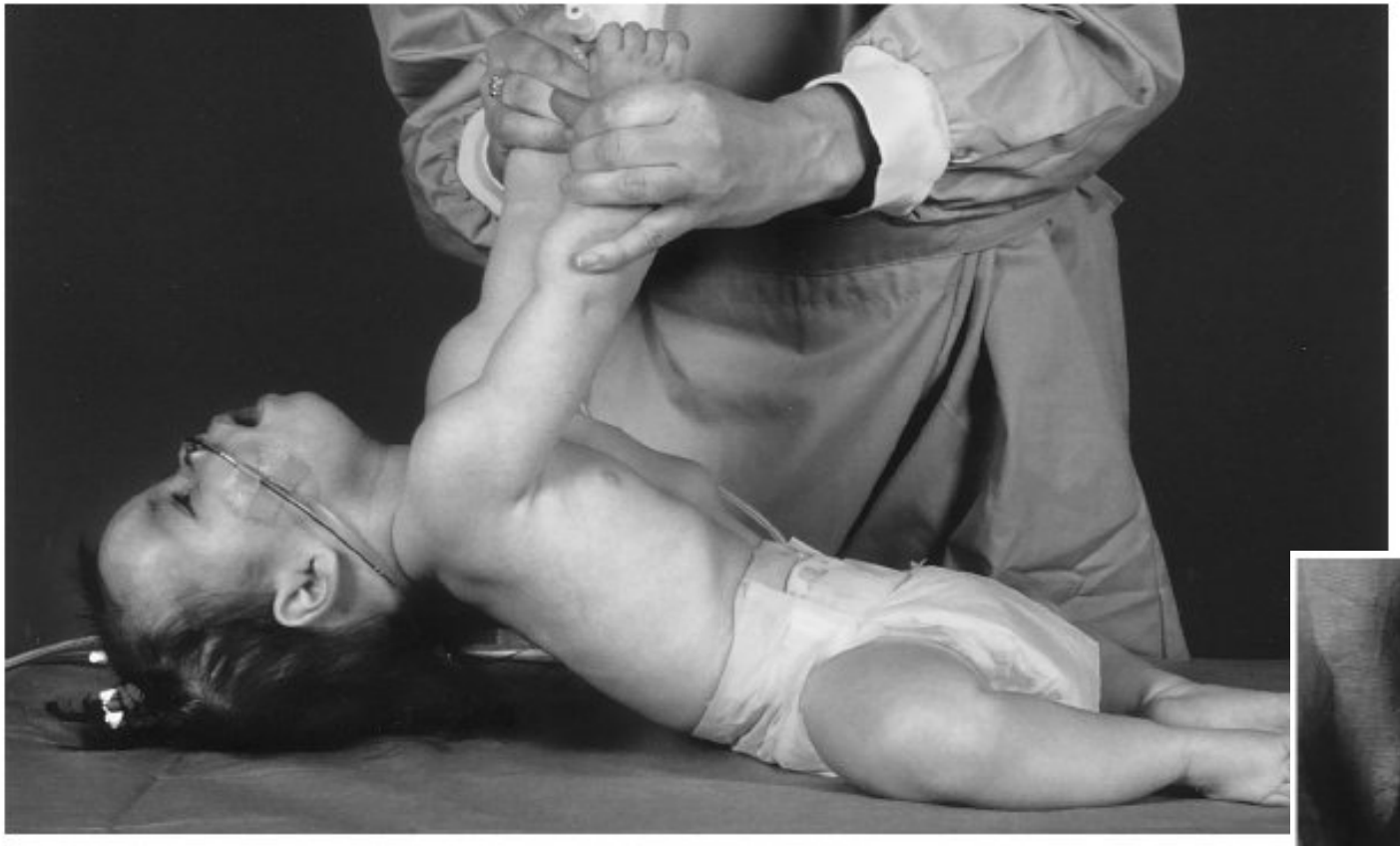
Infantile type:
First symptoms in the first months of life: cardiomegaly, muscle weakness, macroglossia
Progressive course, death due to cardiopulmonary failure in the first two years of life

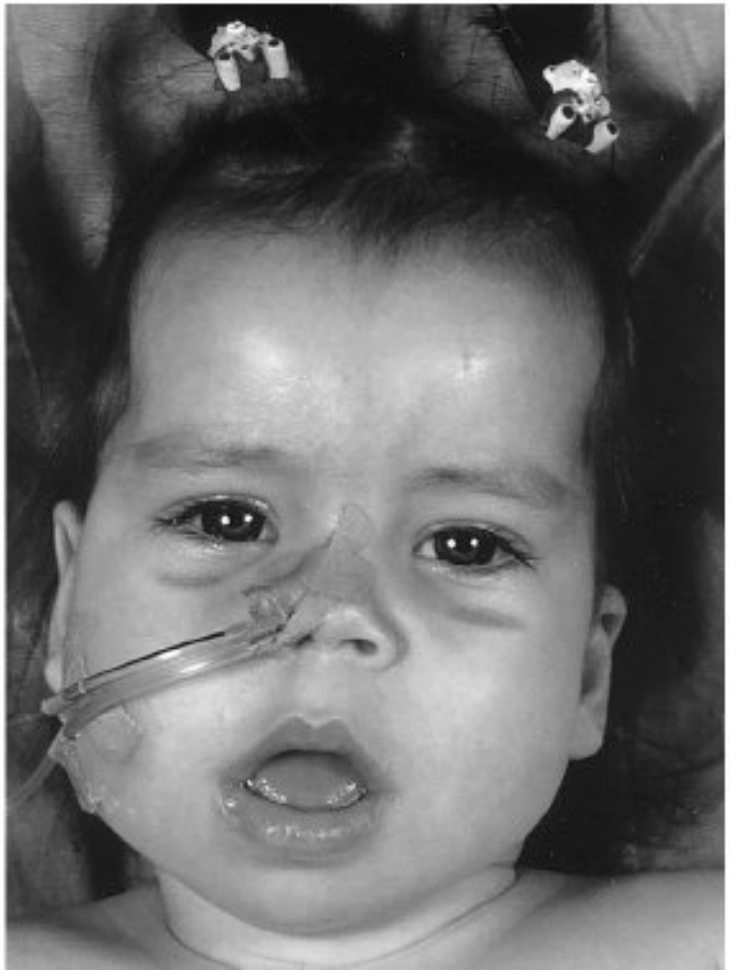
Adult type
Slowly progressive proximal myopathy and/or slowly progressive respiratory failure
Heart is not affected

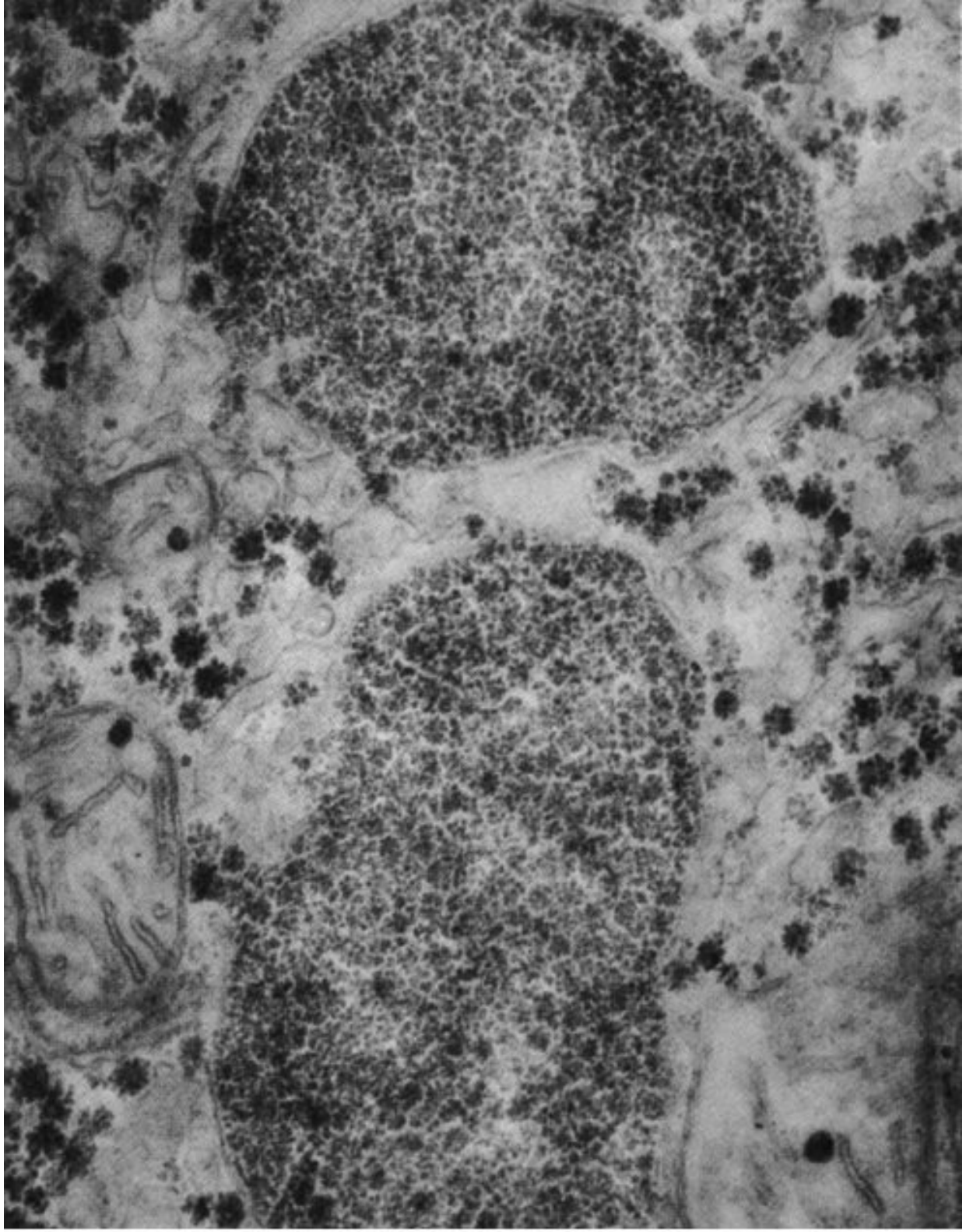
Intermediate types

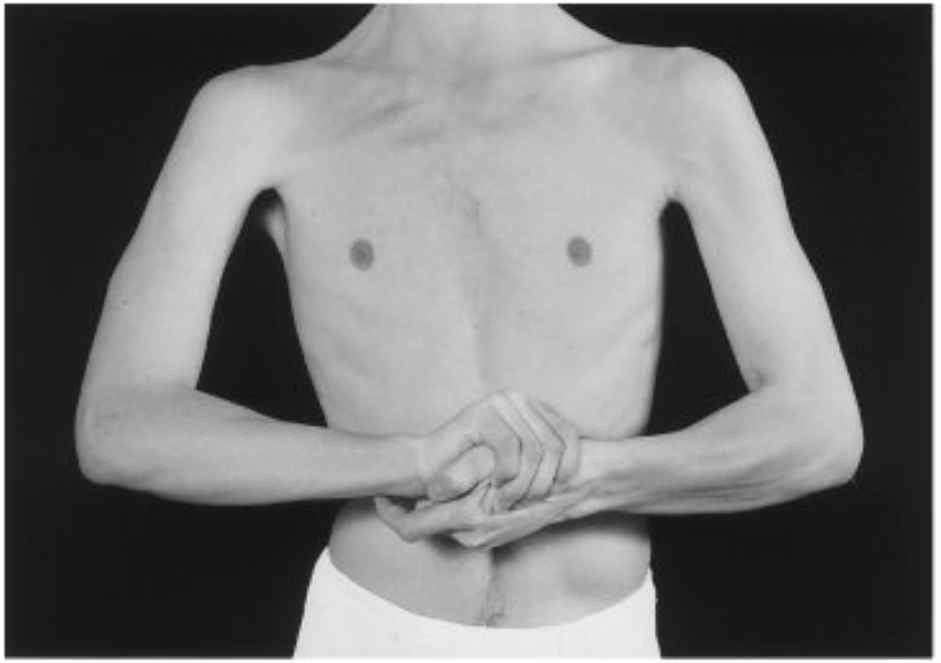
Diagnostics:
proof of glycogen storage in tissues
measurement of enzyme activity

Treatment
Enzyme supplementation therapy (Myozyme)









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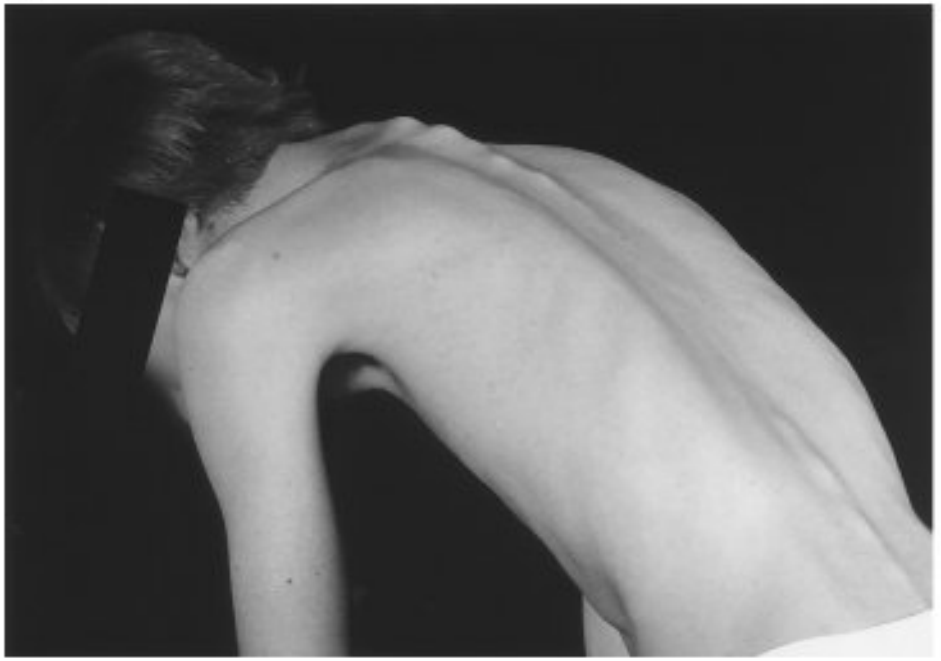
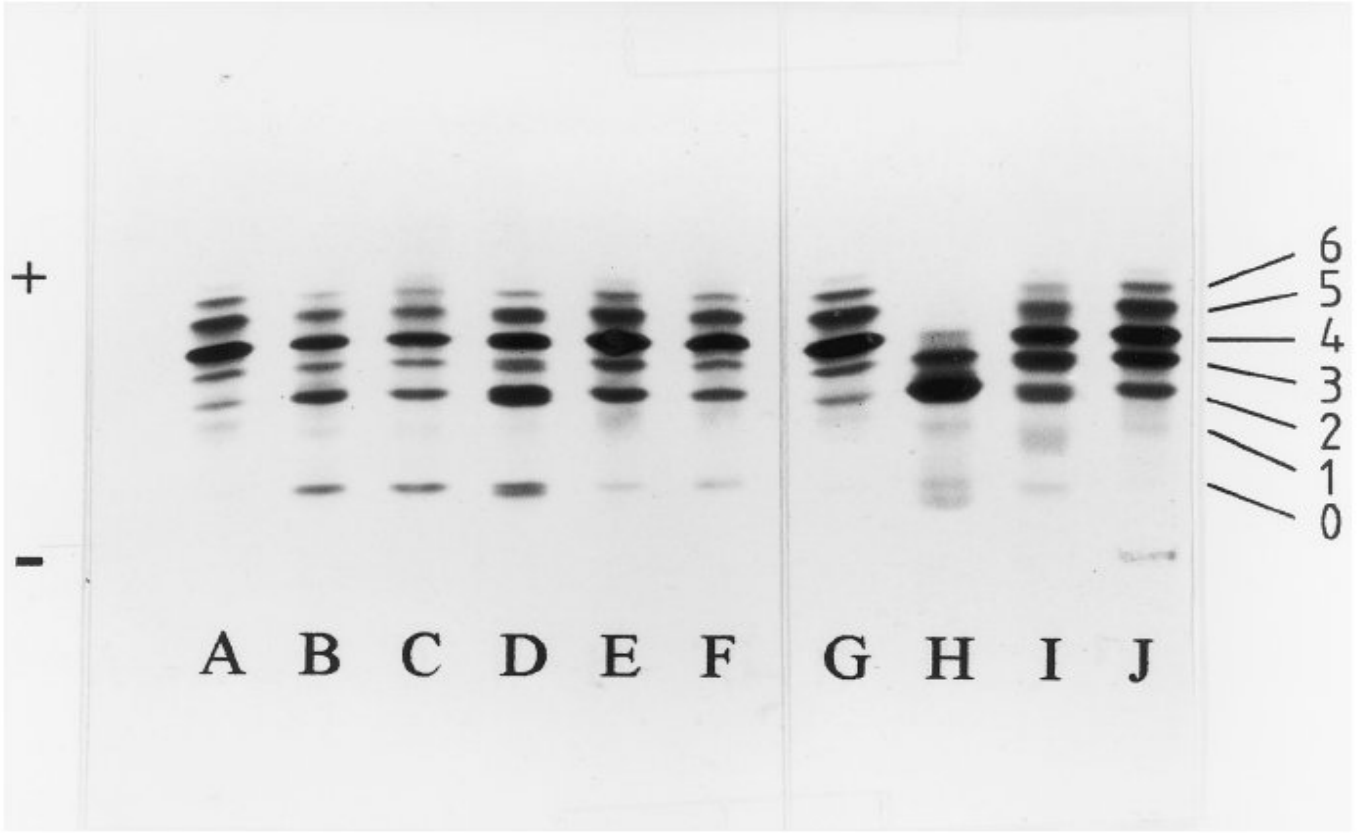


B

Congenital disorders of glycosylation (CDG)

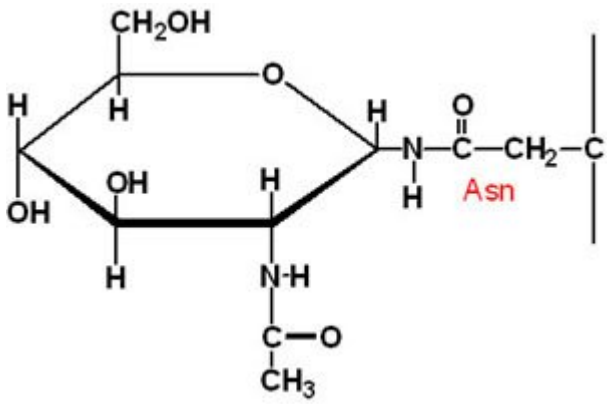


Glycoproteins

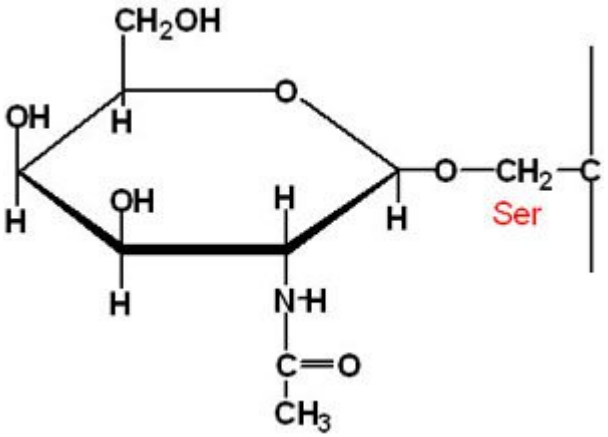
N-glycosylation

O-glycosylation

Disorders of glycosylation:
CDGs (previously known as carbohydrate-deficient glycoprotein syndromes)



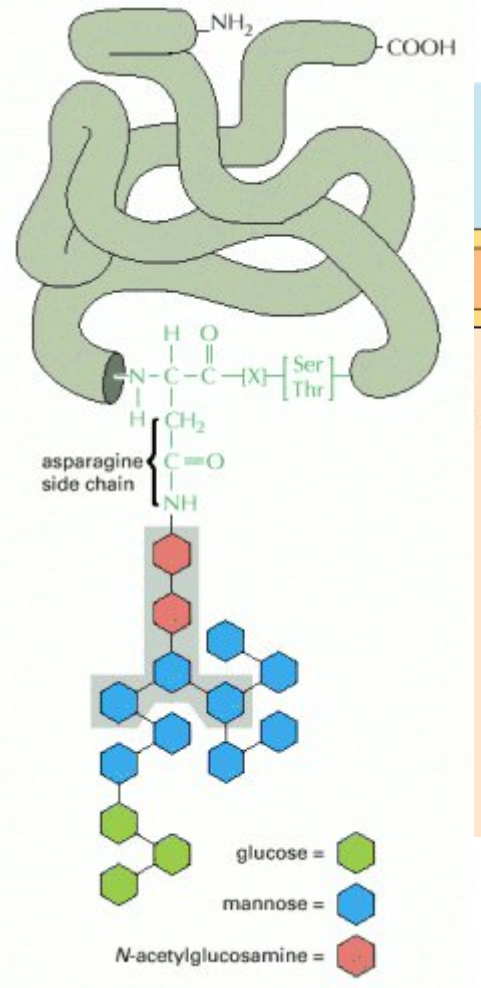
N-glycosylation
Asn-X-Ser/Thr

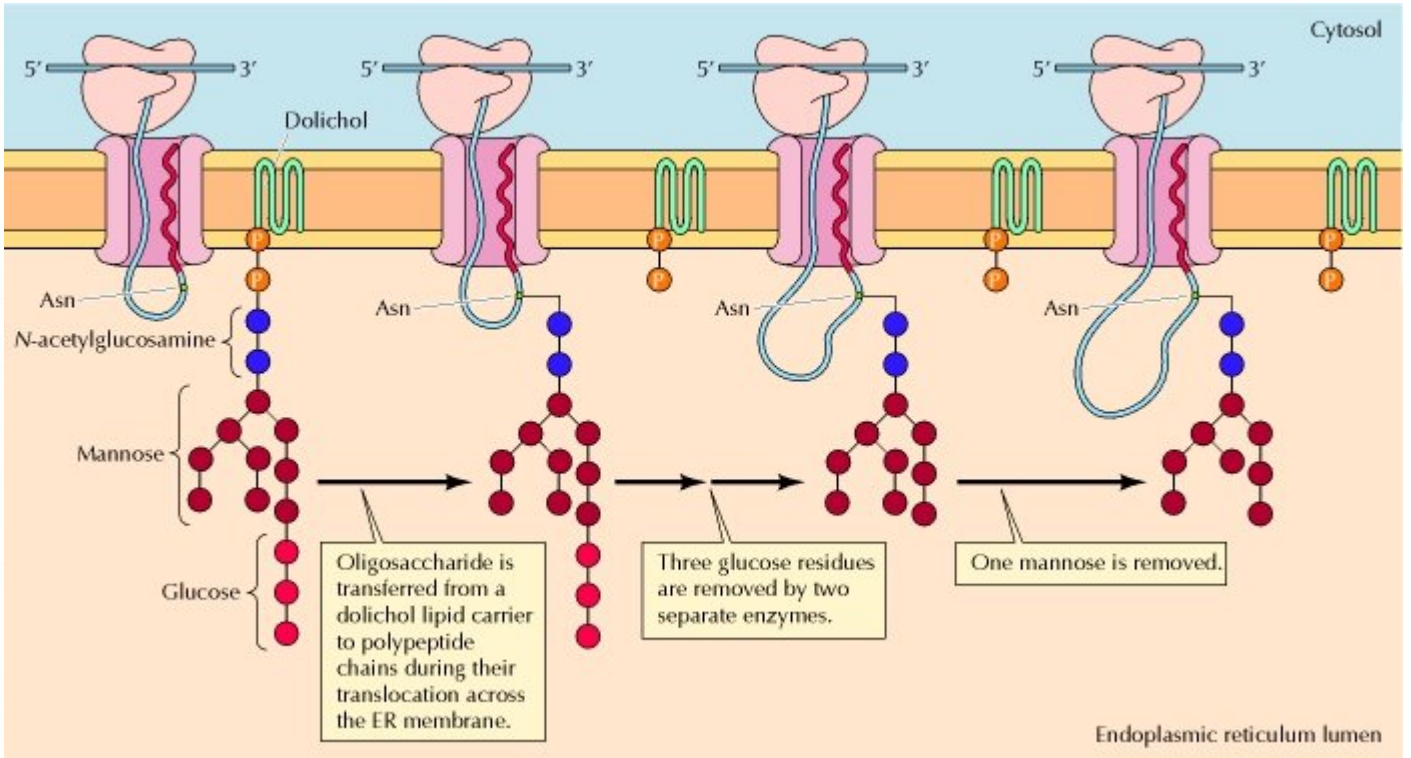


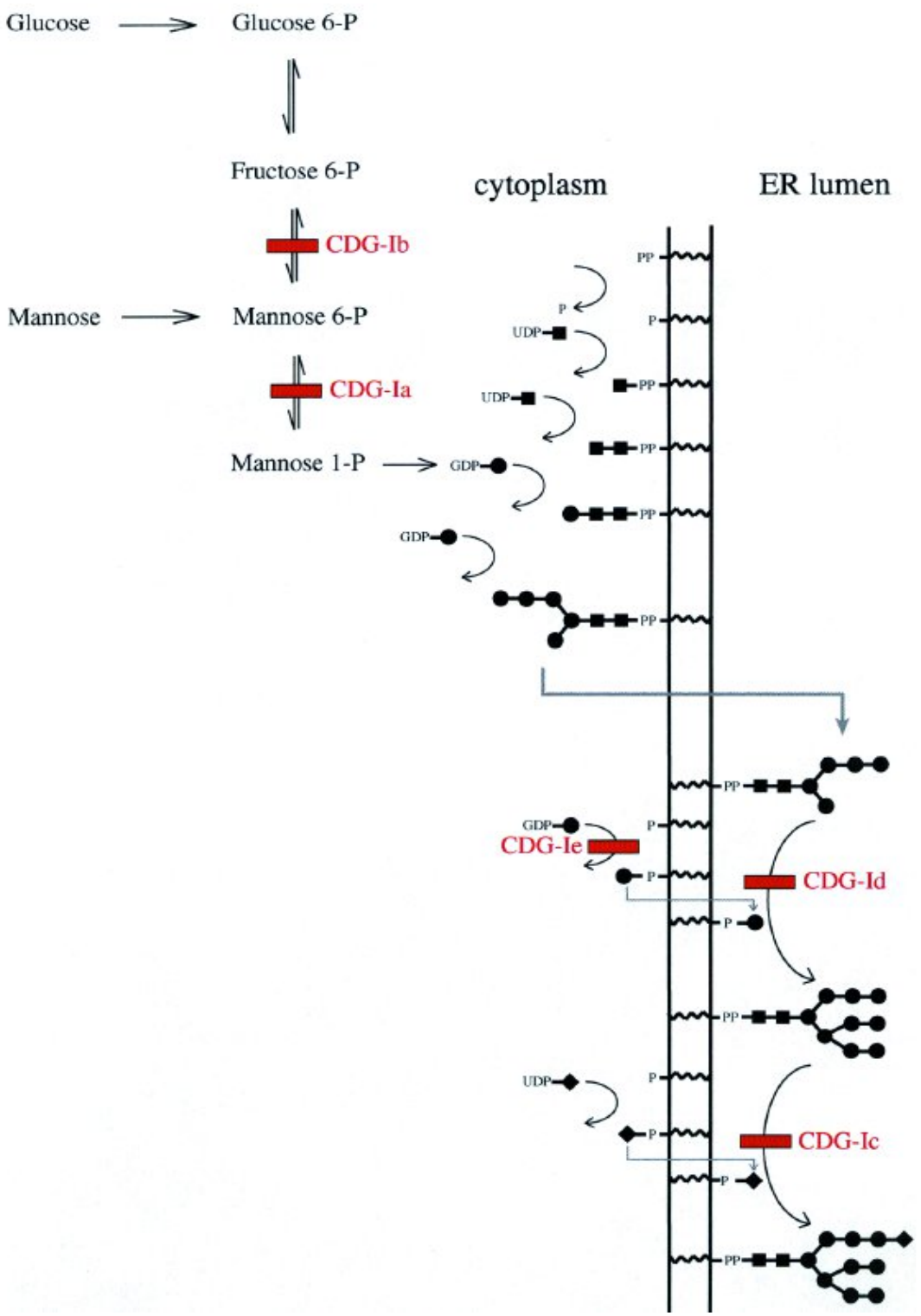
O-glycosylation
Thr, Ser

Most Proteins Synthesized in the Rough ER Are Glycosylated by the Addition of a Common N-linked Oligosaccharide

Precursor oligosaccharide is held in the ER membrane by dolichol,



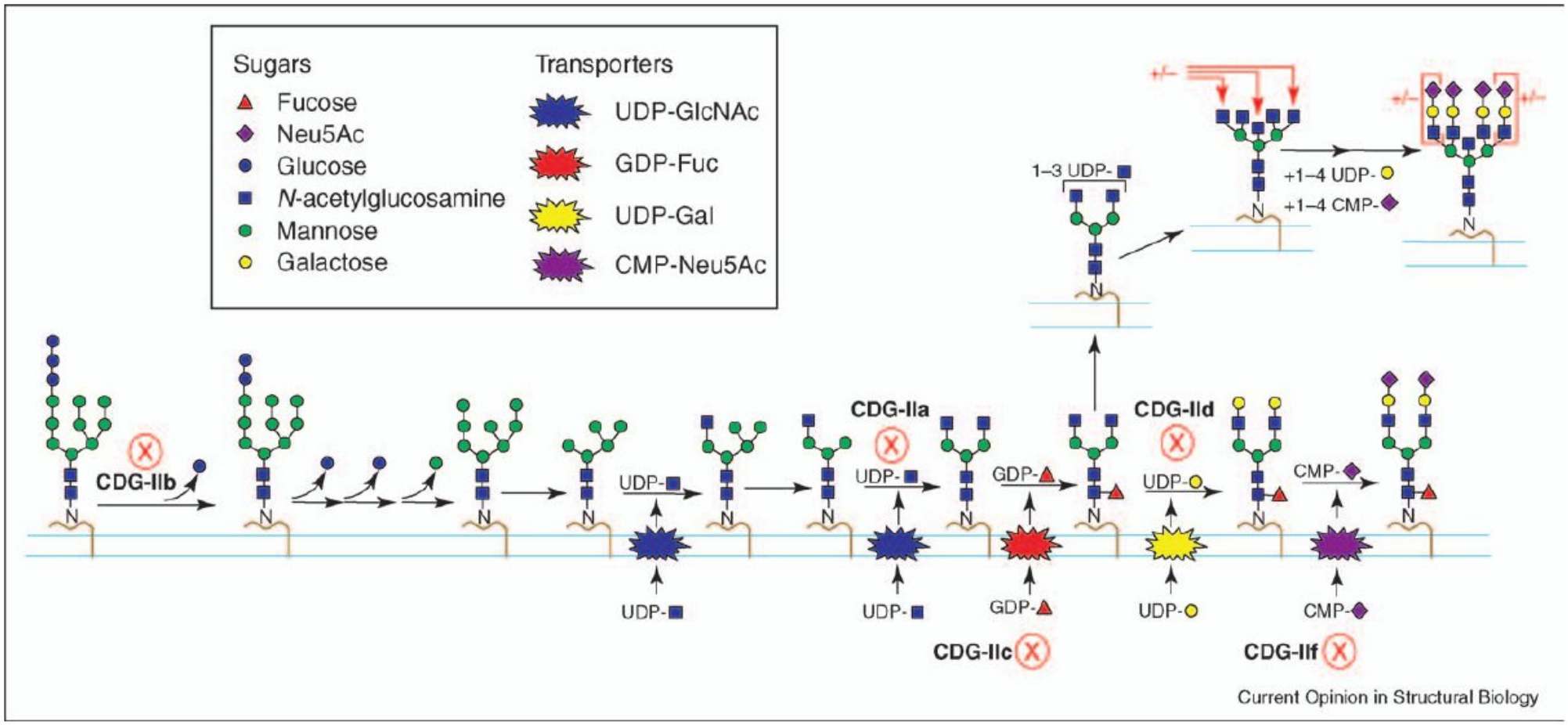




$Man_5GlcNac_2$

$Glc_3Man_9GlcNac_2$

Processing of oligosaccharide chains of glycoproteins in ER and Golgi



Jaak Jaeken

Congenital disorders of N-glycosylation

CGD I: >16 disorders of N-glycan assembly (CDG Ia-m) including dolichol-phosphate synthesis defects

(CDGIa : phosphomannomutase 2 deficiency)

CDGII: >8 disorders of processing of N-glycans

Congenital disorders of O-glycosylation

> 6 disorders

Disorders of glycolipid glycosylation

3 disorders: GM3 synthase deficiency, ...

Highly variable phenotype
Autosomal recessive disorders
Autosomal dominant : 1 disorder (hereditary multiple exostoses sy.)

Congenital disorders of glycosylation

Aberrant protein glycosylation

Diagnostic paradigm:
analysis of glycans → molecular defect

Screening:
Isolectric focusing of **sialyltransferin** in defects of N-linked glycans
Isolectric focusing of **apo CIII** in defects of N-linked glycans

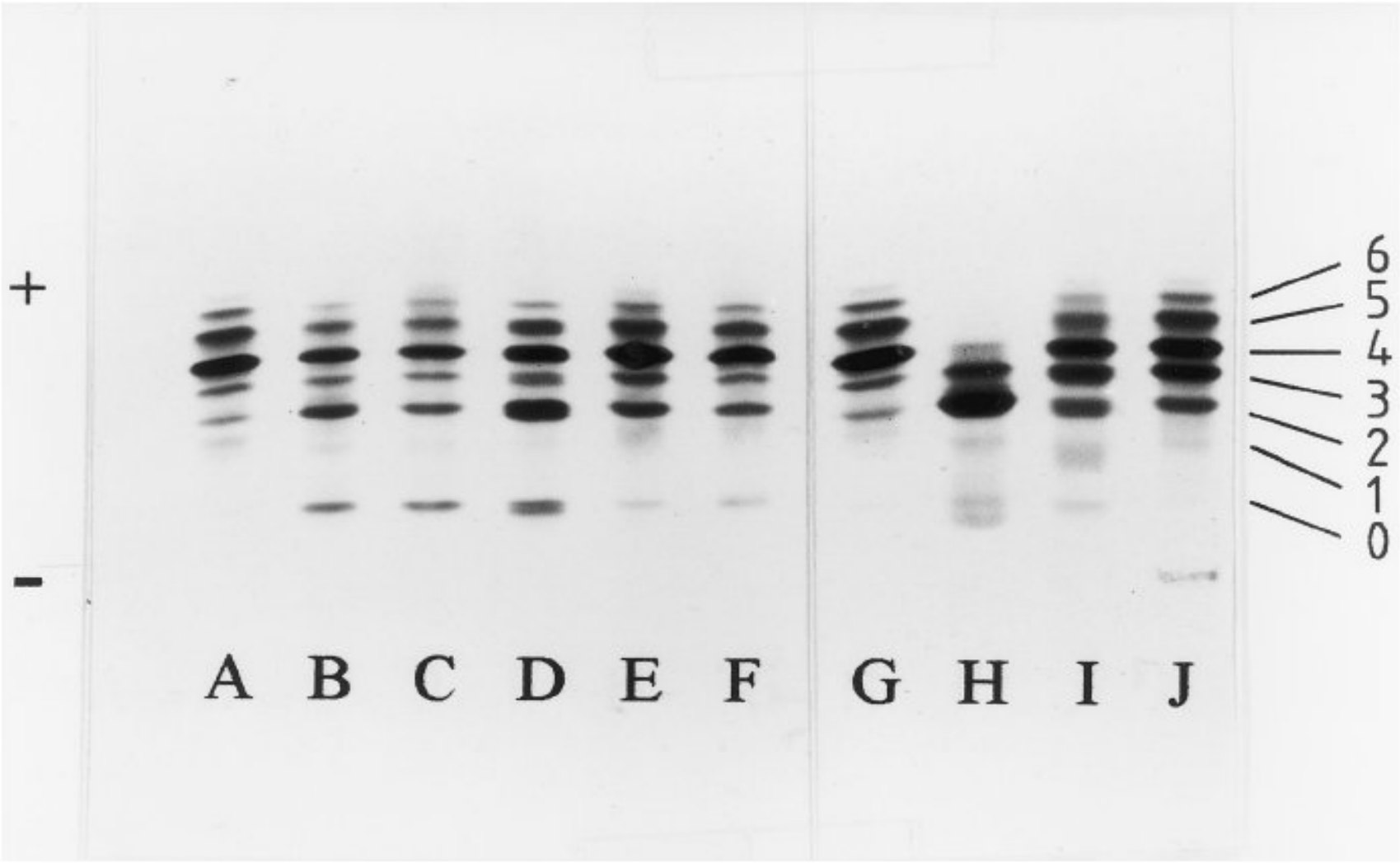
Structural analysis of glycans

Measurement of enzyme activities

Mutation analysis

CDG-x: abnormal glycosylation detected by screening techniques, but with unknown molecular defect

Isoelectrofocusing of serum sialotransferins



A, G controls,
B to F : **type-I pattern**
B phosphomannomutase def., C phosphomannose isomerase (PMI) deficiency D, hypoglucosylation defect; E, F unidentifed
H to J : **type-II pattern**
H, N-acetylglucosaminyltransferase (GnT II) def; I, Junidenti®ed

Glycoproteins Reported to Be Abnormal in Phosphomannomutase Deficiency and Showing an Abnormal Pattern on Isoelectrofocusing, Two-dimensional Electrophoresis, Western Blotting, and/or Decreased or Increased Concentration or Enzymatic Activity

Serum

Transport Proteins

Apoprotein B, apoprotein CII, apoprotein E, ceruloplasminhaptoglobin, α2-macroglobulin, retinol-binding protein, sehormone-binding globulin, thyroxine-binding globulin, transcobalamin II, transcortin, transferrin, vitamin D-binding globulin

Coagulation and Anticoagulation Factors

Antithrombin, α2-antiplasmin, coagulation factors II, V, VI, VIIIIX, X, XI, and XII, heparin cofactor II, plasminogen, protein C, protein S

Hormones

Follicle-stimulating hormone, l

Lysosomal Enzymes

Arylsulphatase A, α-fucosidase

Other Enzymes

N-Acetylglucosaminidase, carb

Other Glycoproteins

Amyloid P α1-acid glycoprotei sterin, complement C3a, complement C4a, complement C1 esterase inhibitor, α2-HSglycoprotein, immunoglobulin G, orosomucoid, peptide PLS:29peptide PLS:34, Zn-a2-glycoprotein

Glycosylation defects lead to abnormal glycoproteins, which normally have diverse functions

Cerebrospinal Fluid

β-Trace protein, transferrin

Leukocytes

Lysosomal Enzymes

α-Fucosidase, β-glucuronidase, α-iduronidase, α-mannosidase, β-mannosidase

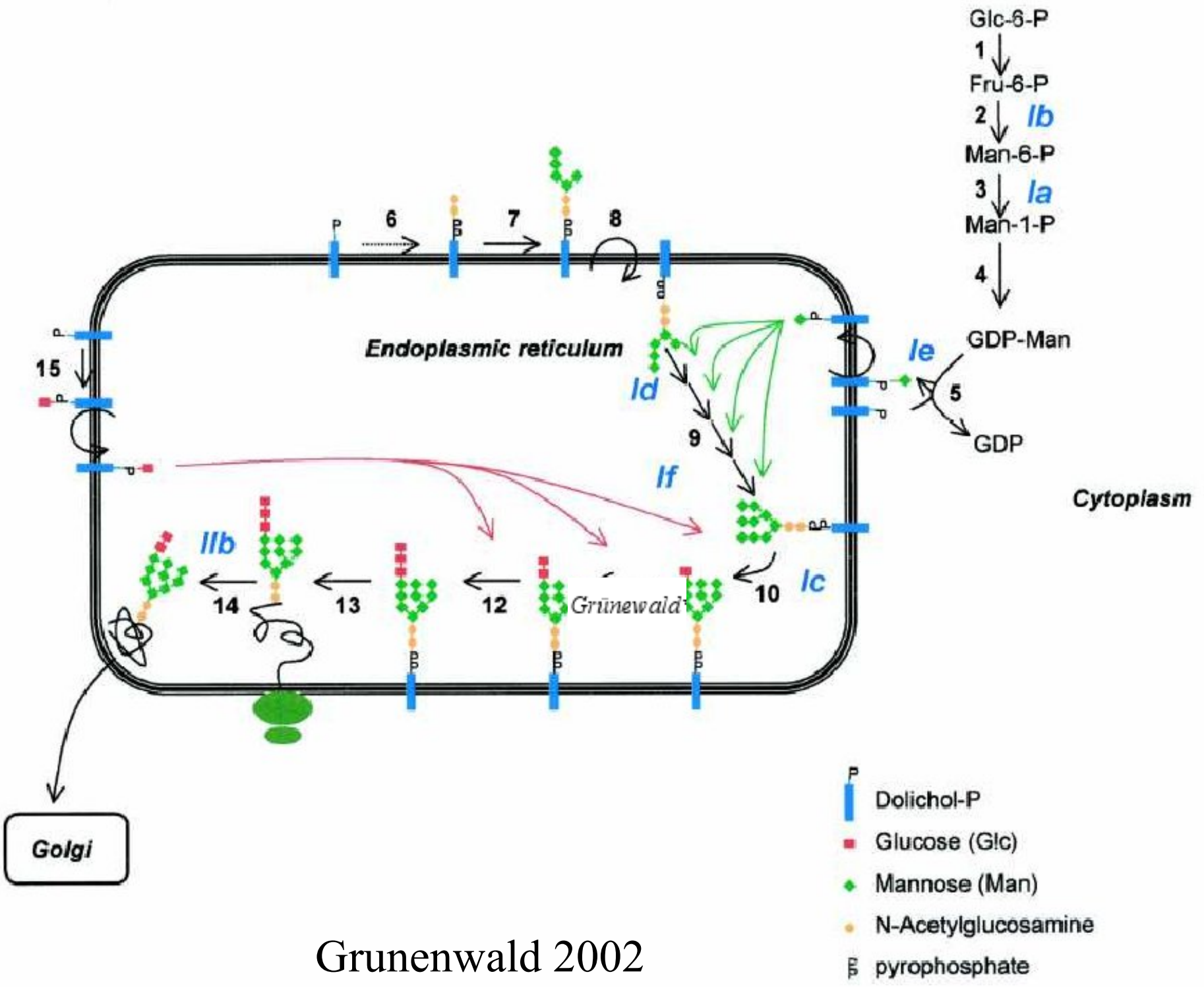
Sialoglycoproteins on B lymphocytes

Fibroblasts

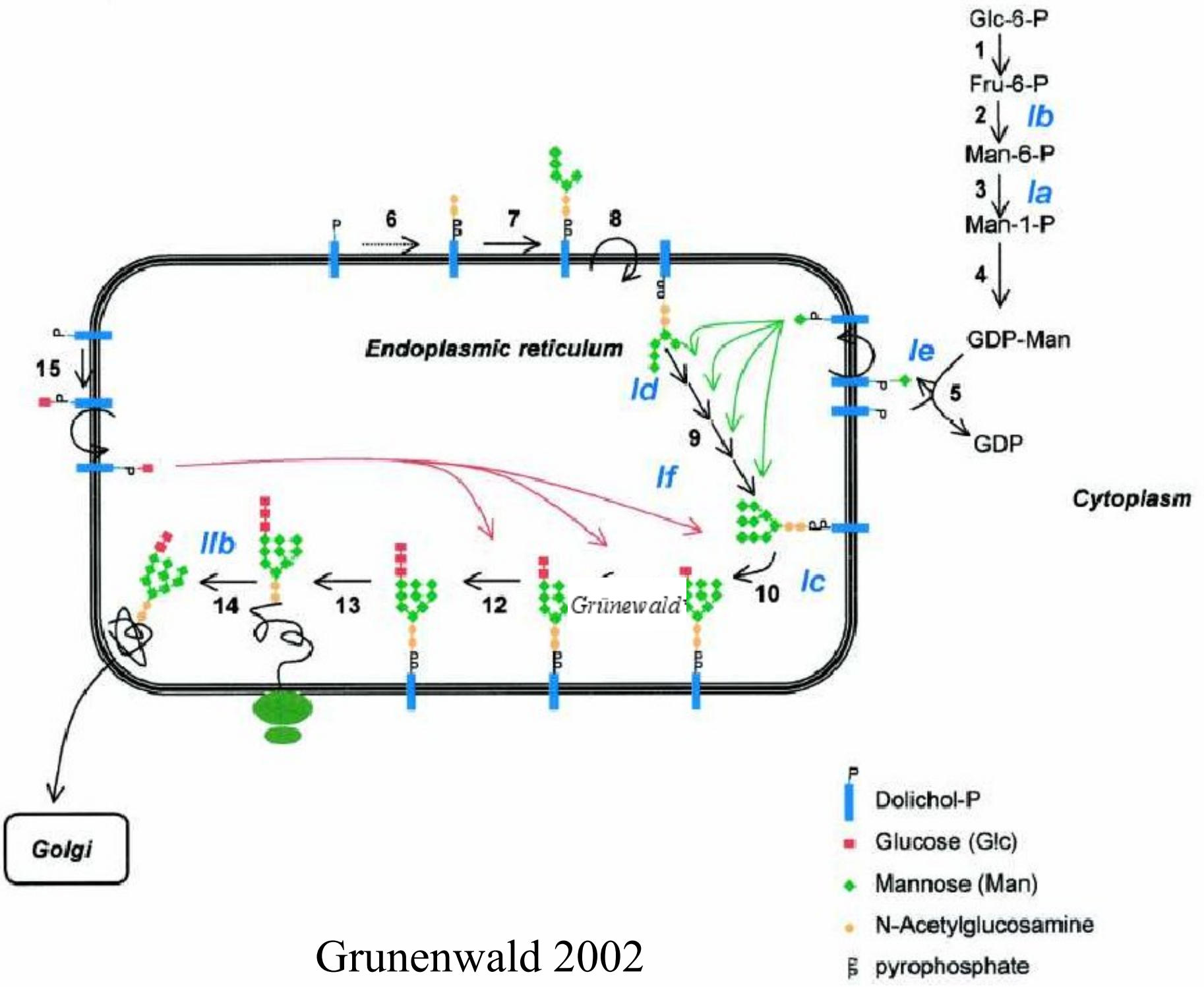
Biglycan, decorin

Liver

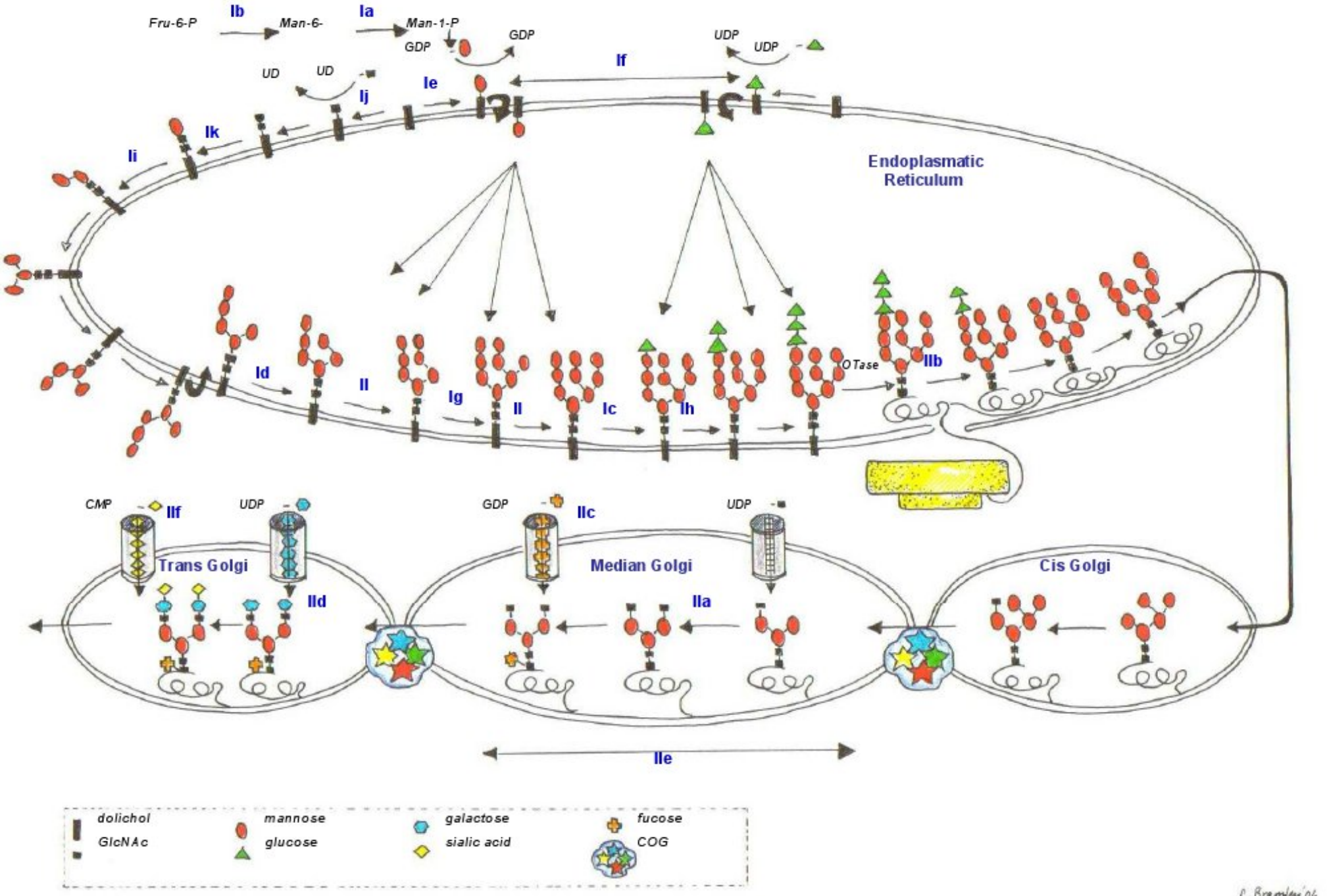
α1-Acid glycoprotein, α1-antitrypsin, haptoglobin, transferrin



Grunenwald 2002



Grunenwald 2002



Grünewald 2007

Today, more than 70 disorders of glycosylation are known

...

and we still do not know all of them

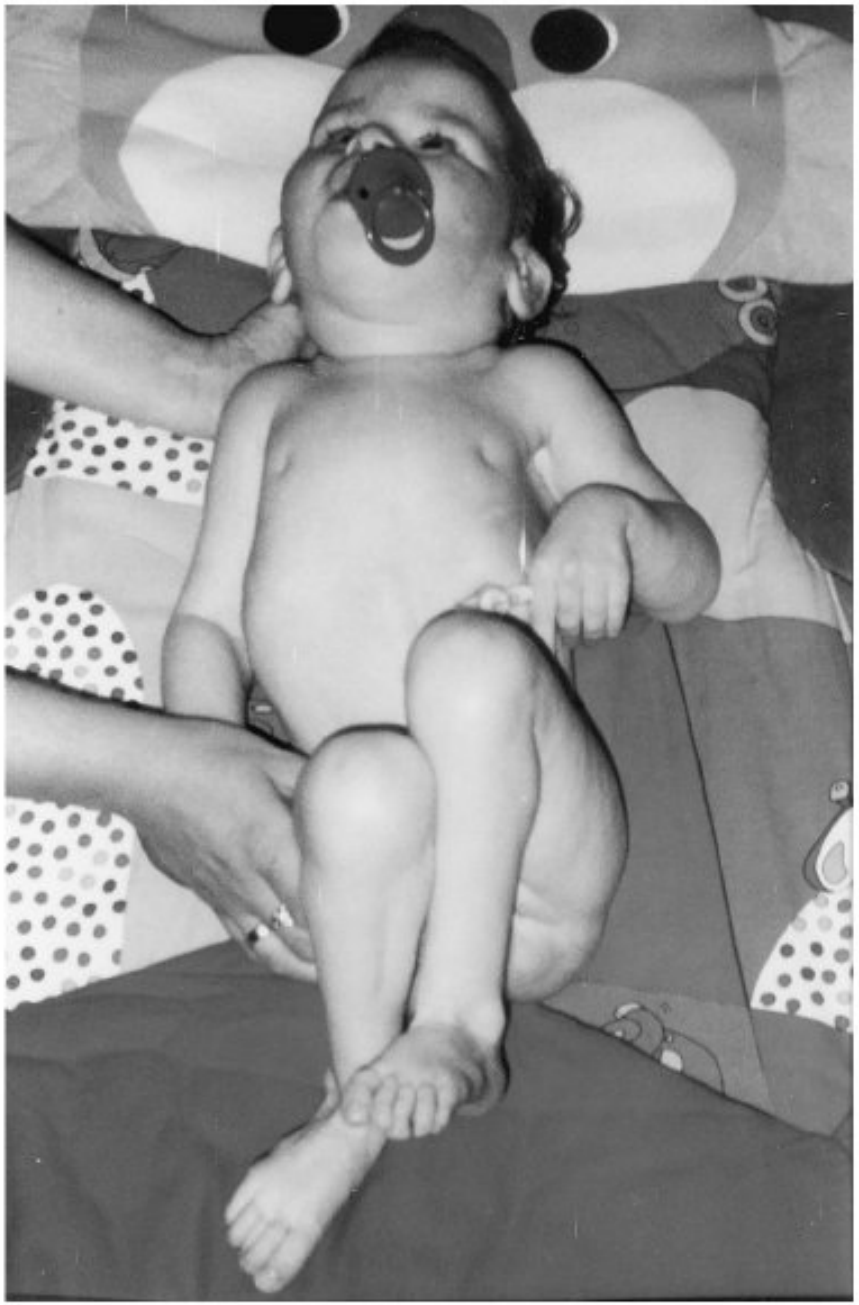
recent review:
Understanding Human Glycosylation Disorders: Biochemistry Leads the Charge. Hudson H. Freeze. THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 288, NO. 10, pp. 6936 –6945, March 8, 2013

http://www.jbc.org/content/288/10/6936.full

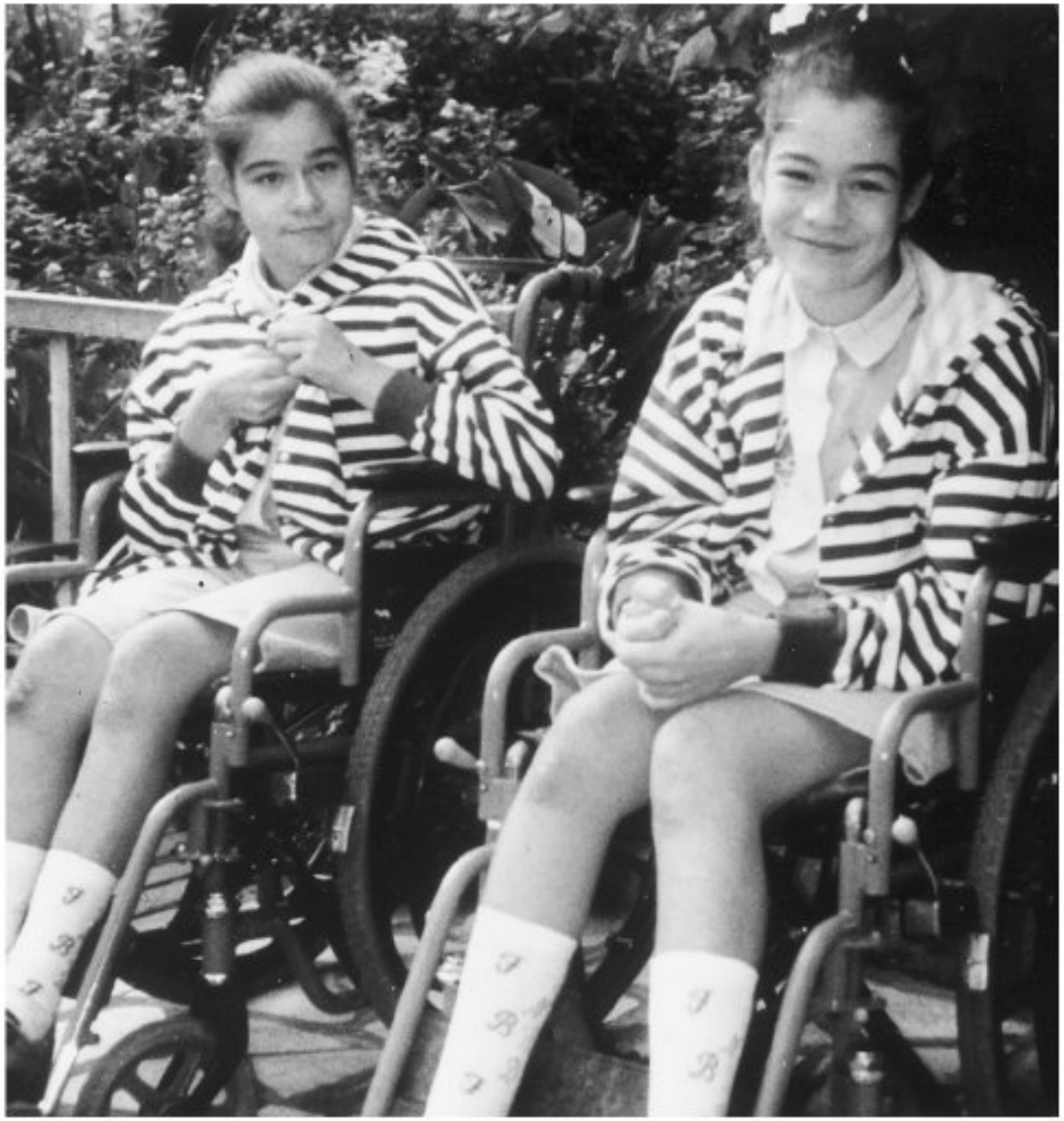
Neurology	axial hypotonia; hyporeflexia; developmental delay; seizures; stroke-like events; micro- and macrocephaly; myopathy
Gastroenterology/ Hepatology	failure to thrive; vomiting; protein-losing enteropathy; liver dysfunction; hepatomegaly; cholangitis; chronic diarrhoea
Neonatology	hydrops; ascites; multiorgan failure; failure to thrive; floppy baby
Haematology	thrombocytosis; thrombocytopenia; coagulopathy; thrombosis; anaemia; leukocytosis, thrombocytopenia
Endocrinology	hyperinsulinemic hypoglycemia; hypothyroidism; hypergonadotropic hypogonadism; growth retardation
Clinical genetics	dysmorphic features
Orthopaedics	osteopenia; joint contractures; kyphosis/scoliosis; short limbs; arthrogryposis
Ophthalmology	abnormal eye movements; squint; cataract; retinitis pigmentosa; nystagmus; iris coloboma; cortical blindness
Radiology	cerebellar hypoplasia; calcification of white matter; delayed myelinisation; micropolygyria; renal hyperechogenecity
Histology	liver fibrosis; liver cirrhosis; lamellar inclusions in hepatocytes; intestinal villus atrophy
Dermatology	ichthyosis; abnormal fat distribution
Nephrology	nephrotic syndrome; tubulopathy; cystic kidneys
Immunology	recurrent infections; hypogammaglobulinaemia
Cardiology	cardiomyopathy; pericardial effusions
Biochemistry	hypoalbuminaemia; elevated transaminases; low cholesterol, triglycerides; decreased antithrombin III; decreased factor VIII and XI; decreased protein C and S; elevated FSH, LH and prolactin; elevated TSH, low free T4

Patients with CDGs can be referred to specialists in different fields of medicine

Phosphomannomutase 2 deficiency

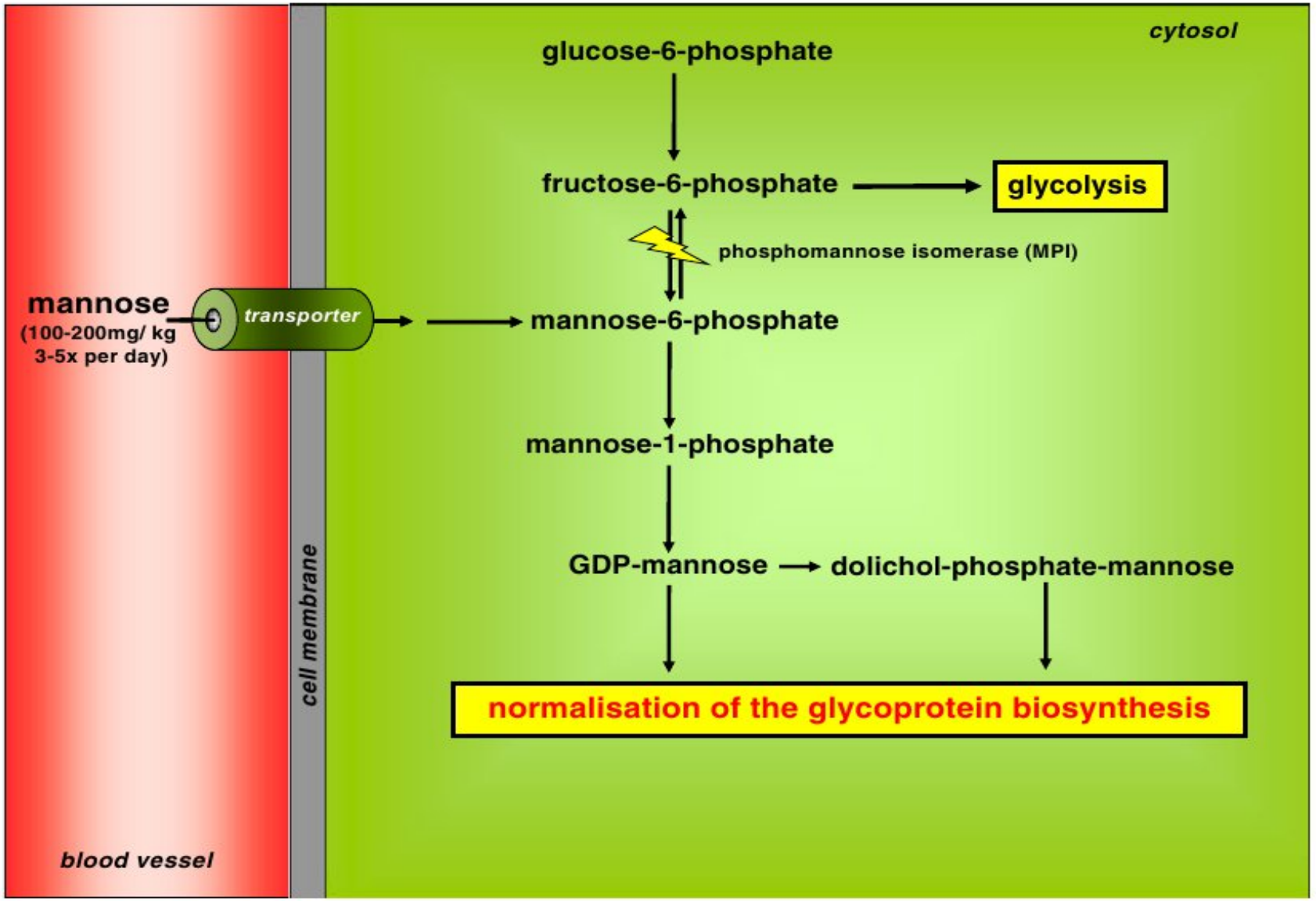


A



B

Treatment of phosphomannose isomerase deficiency by mannose supplementation



Disorders *o*-linked glycosylation

A number of rare disorders with highly variable clinical presentation

Examples:

α-Dystroglycanopathies – a group of disorder that adds O-mannose-linked glycans to α-dystr
Congeninal muscular dystrophies

X -linked paroxysmal nocturnal hemoglobinuria
Defect in synthesis of GPI-anchor (gene PIG-A)

Walker-Warburg syndrome
brain and eye malformations, muscular dystrophy
defect in synthesis of mannosylated *O*-linked oligosaccharides

Hereditary multiple exostoses
Dominant disorder
deficiency of two glucosyltranferases that function in synhesis of heparan sulfate