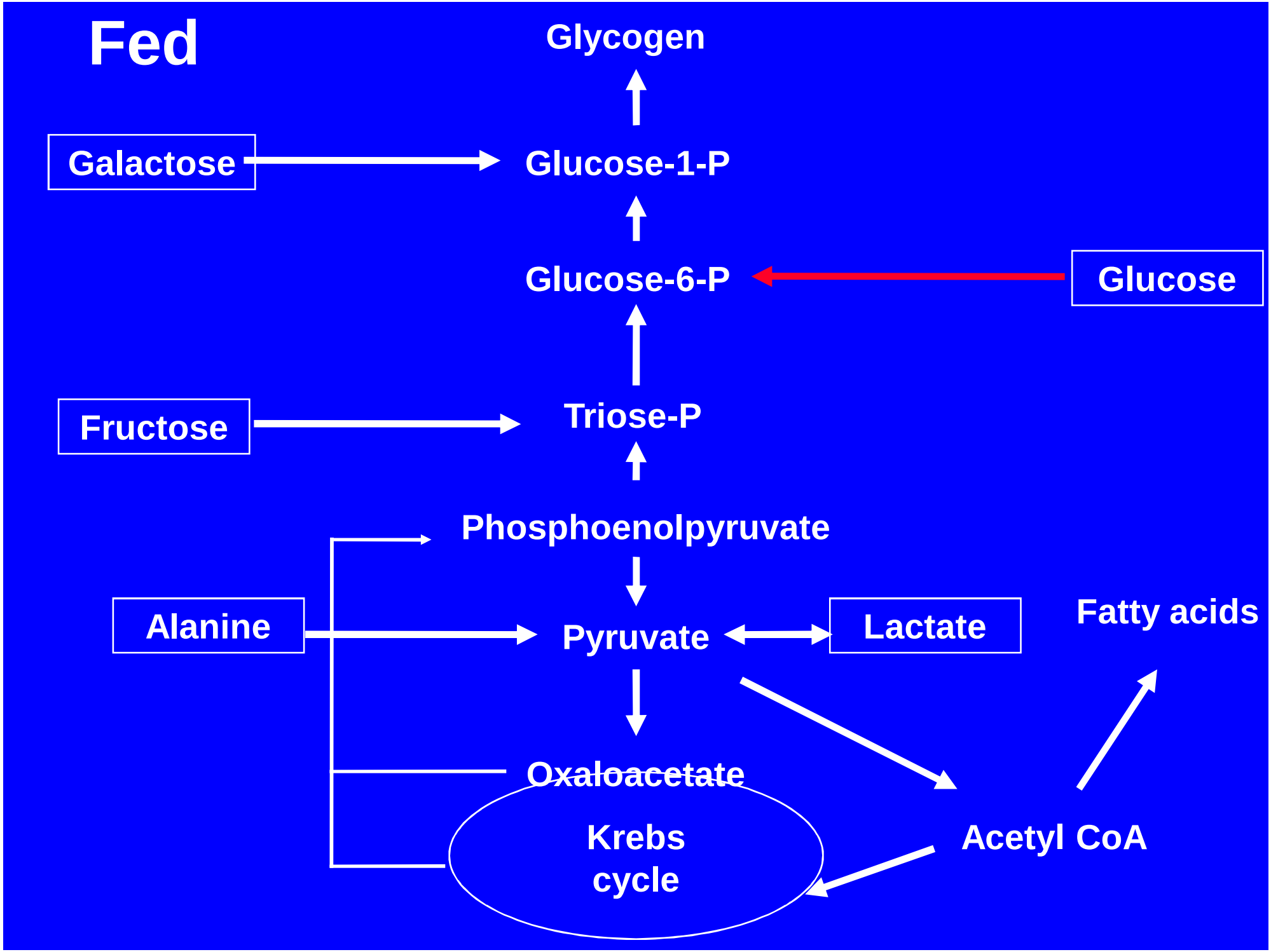
Glycogen function

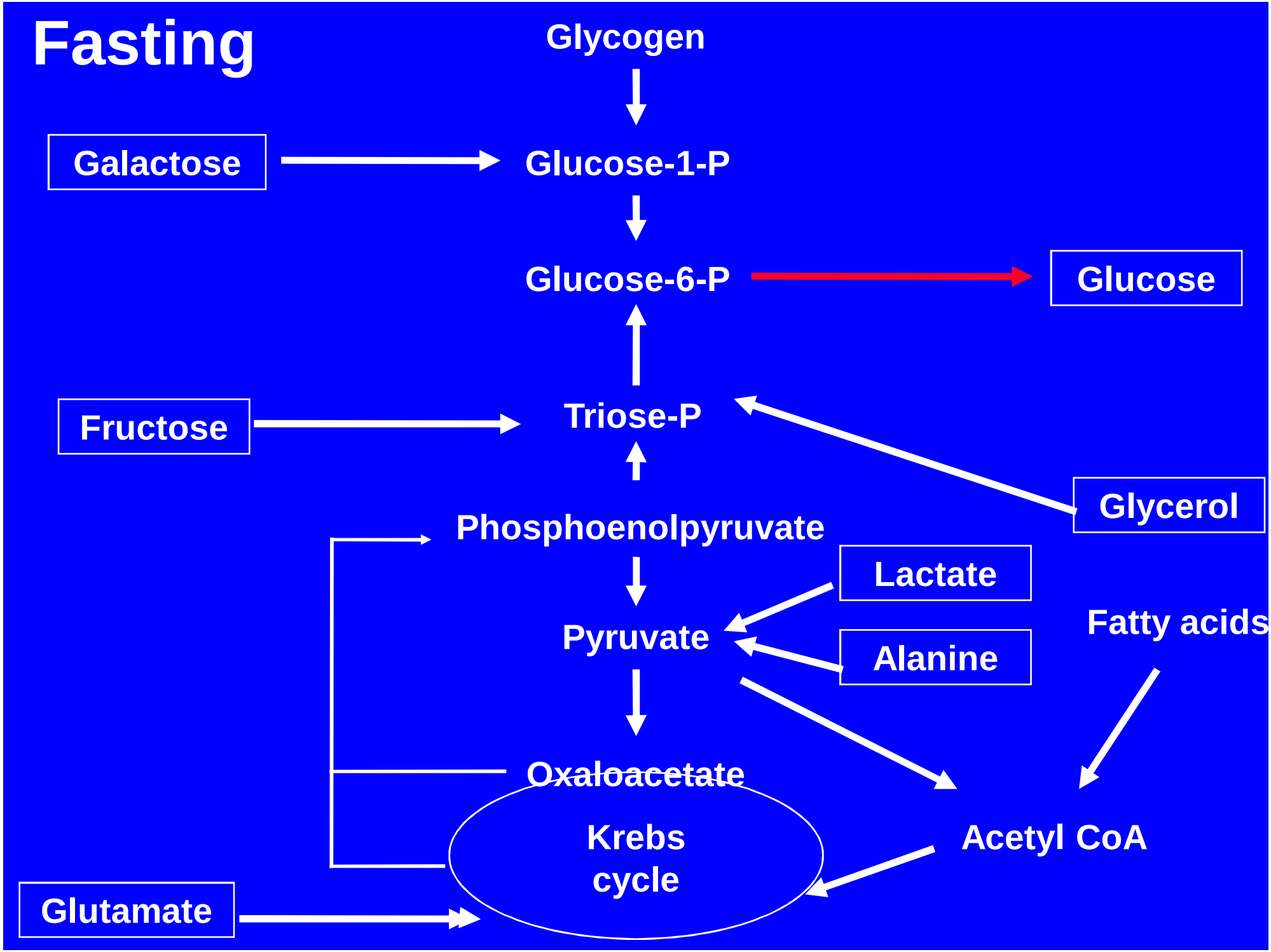
Cellular glucose store

- **Liver** **Body “sump”**
- **Brain** **Local emergency store**
- **Muscle** **Local short term use**

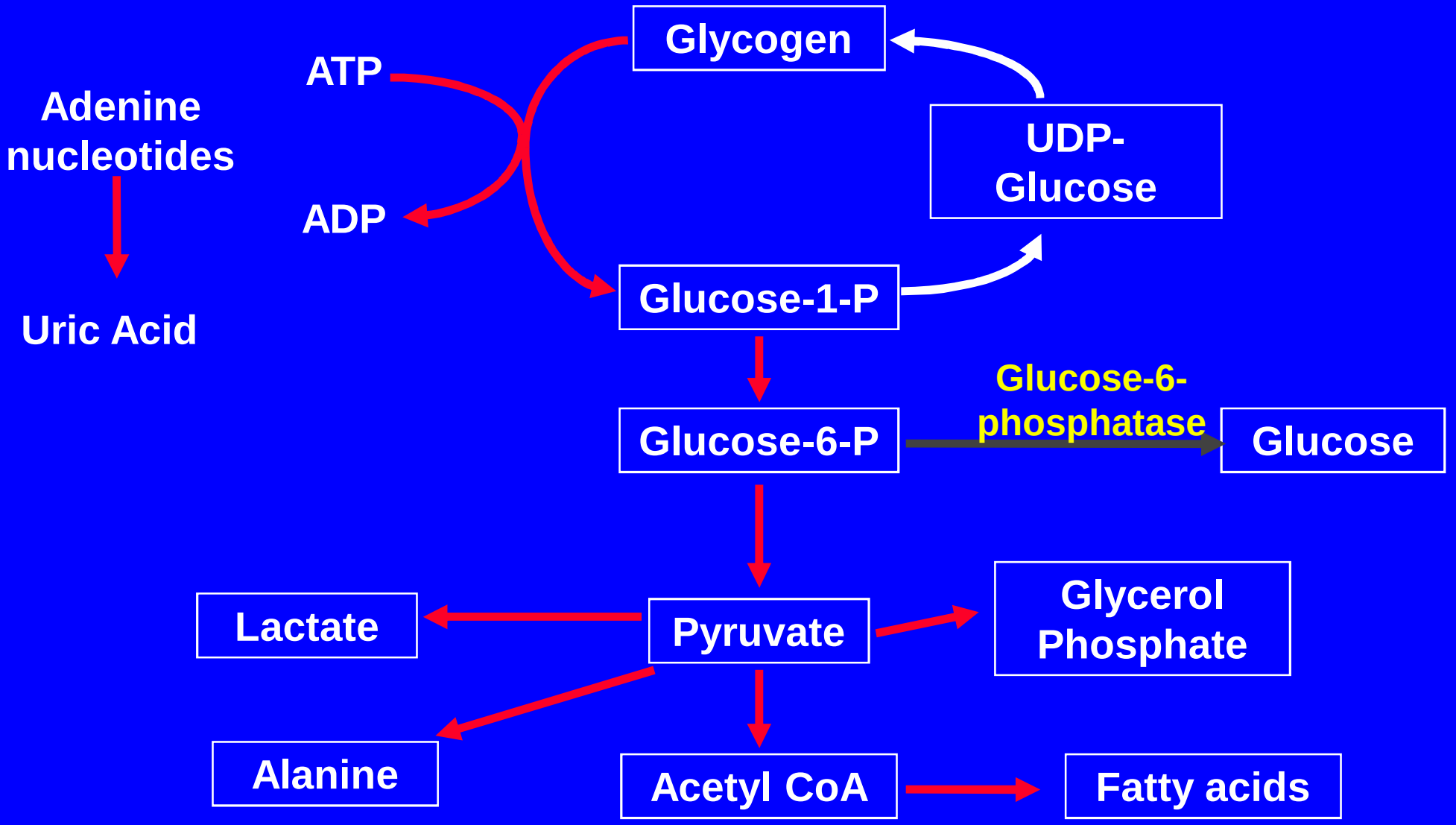
Glycogen storage diseases

- Accumulation abnormal amount/type glycogen
- Hypoglycaemia, lactic acidosis, hepatomegaly
- Hepatic - Types 1, 3, 4, 6 and 9


Fed
Glycogen
Galactose
Glucose-1-P
Glucose-6-P
Glucose
Fructose
Triose-P
Phosphoenolpyruvate
Alanine
Pyruvate
Lactate
Fatty acids
Oxaloacetate
Krebs cycle
Acetyl CoA


Fasting
Glycogen
Galactose
Glucose-1-P
Glucose-6-P
Glucose
Fructose
Triose-P
Glycerol
Phosphoenolpyruvate
Lactate
Pyruvate
Alanine
Fatty acids
Oxaloacetate
Krebs cycle
Acetyl CoA
Glutamate

Glycogen Storage Disease Type 1



Metabolic consequences of Glucose-6-phosphatase deficiency

- Fasting hypoglycaemia
- Lactic acidosis
- Hyperuricaemia
  - Increased production
  - Decreased renal clearance
- Hyperlipidaemia
  - Increased production
  - Decreased clearance

GSD 1a

- 1929 Described by von Gierke
- 1959 Glucose phosphatase deficiency described Cori + Cori
- 1993 cDNA and mutations described lei et al

GSD 1a
Clinical features

- 3-4 months hypoglycaemia, hepatomegaly
- Doll-like facies
- Central obesity pattern
- Abdominal distension
- Short stature
- Bleeding tendency

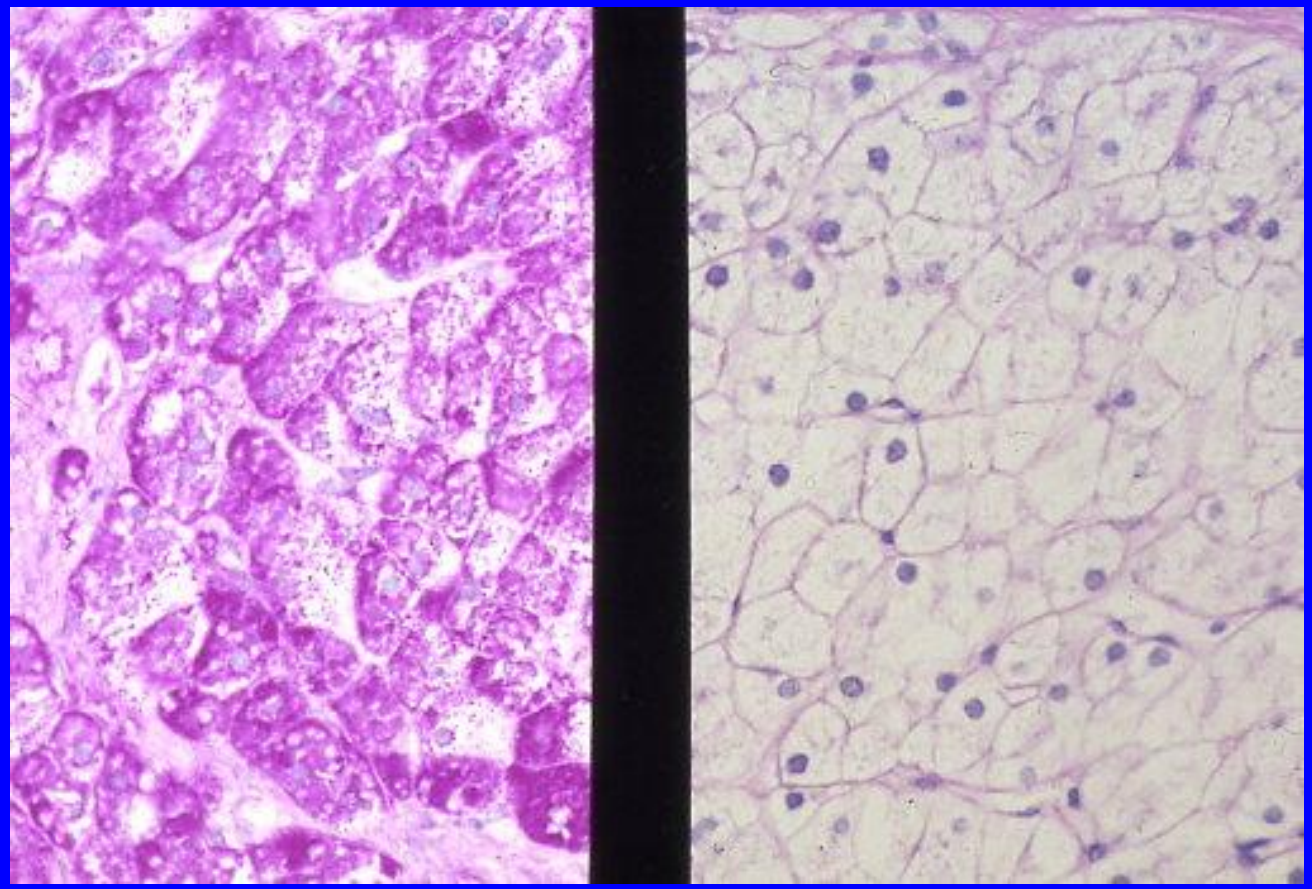
GSD 1a
Laboratory findings

- Hypoglycemia
- Lactic acidosis
- Hyperlipidaemia
- Hyperuricaemia

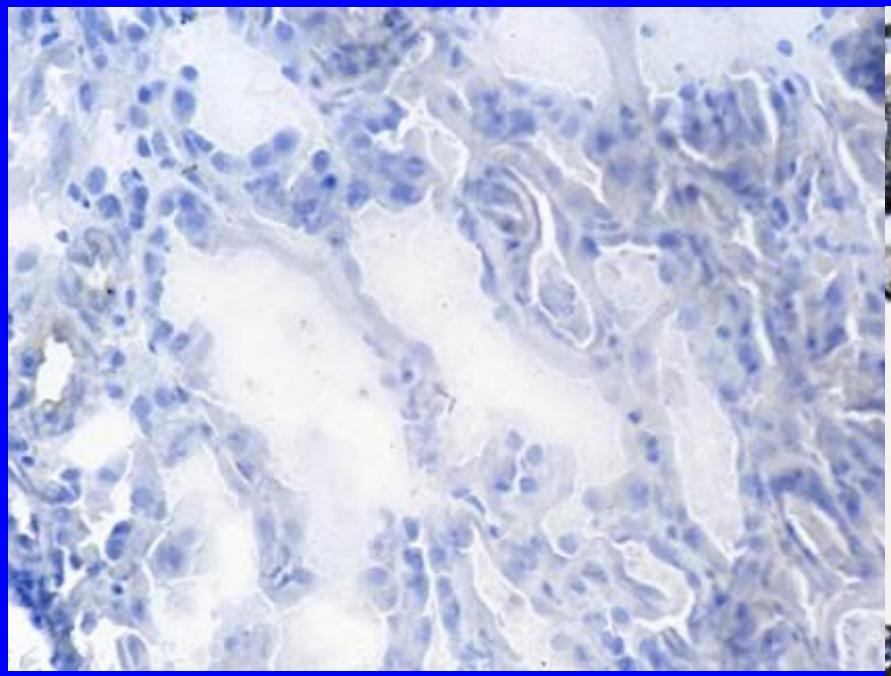
GSD 1a
Diagnosis

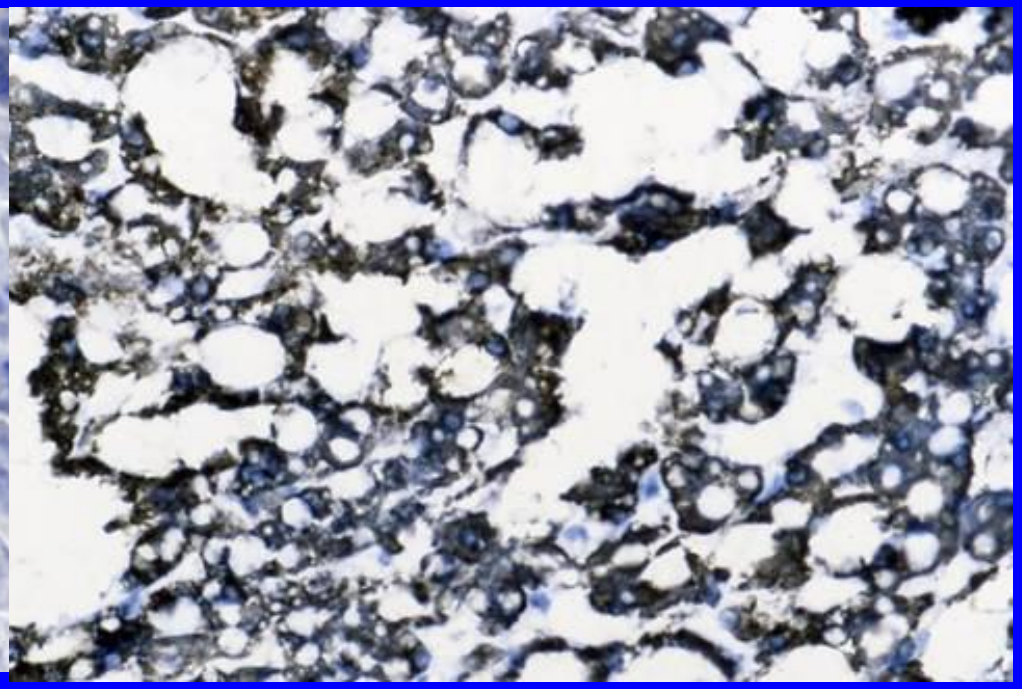
- Baseline bloods
- Stimulation tests
- Histochemistry
- Enzyme assay
- DNA

Liver histology in GSD 1a
pre – post diastase



Immunostain for glucose 6 phosphatase

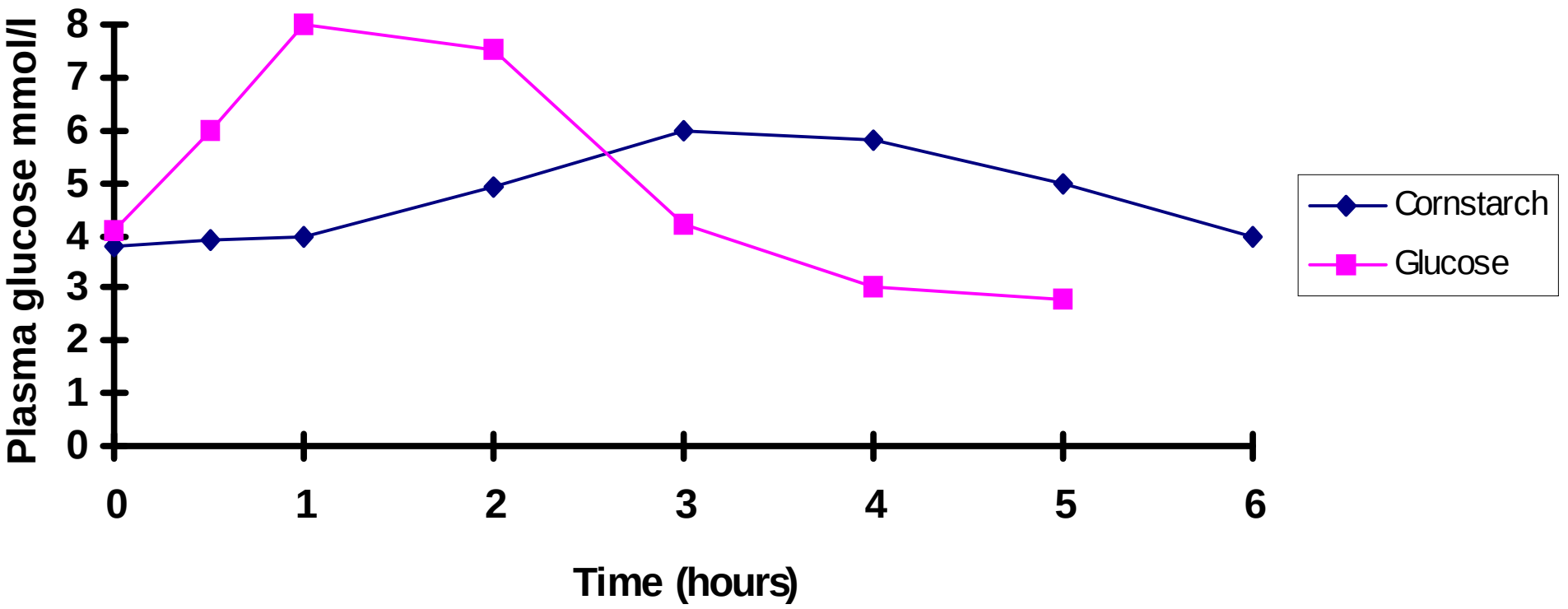




GSD 1a
Management

- Overnight tube feeds or glucose
- Frequent daytime feeds
- Uncooked corn starch
- Allopurinol
- Liver transplantation

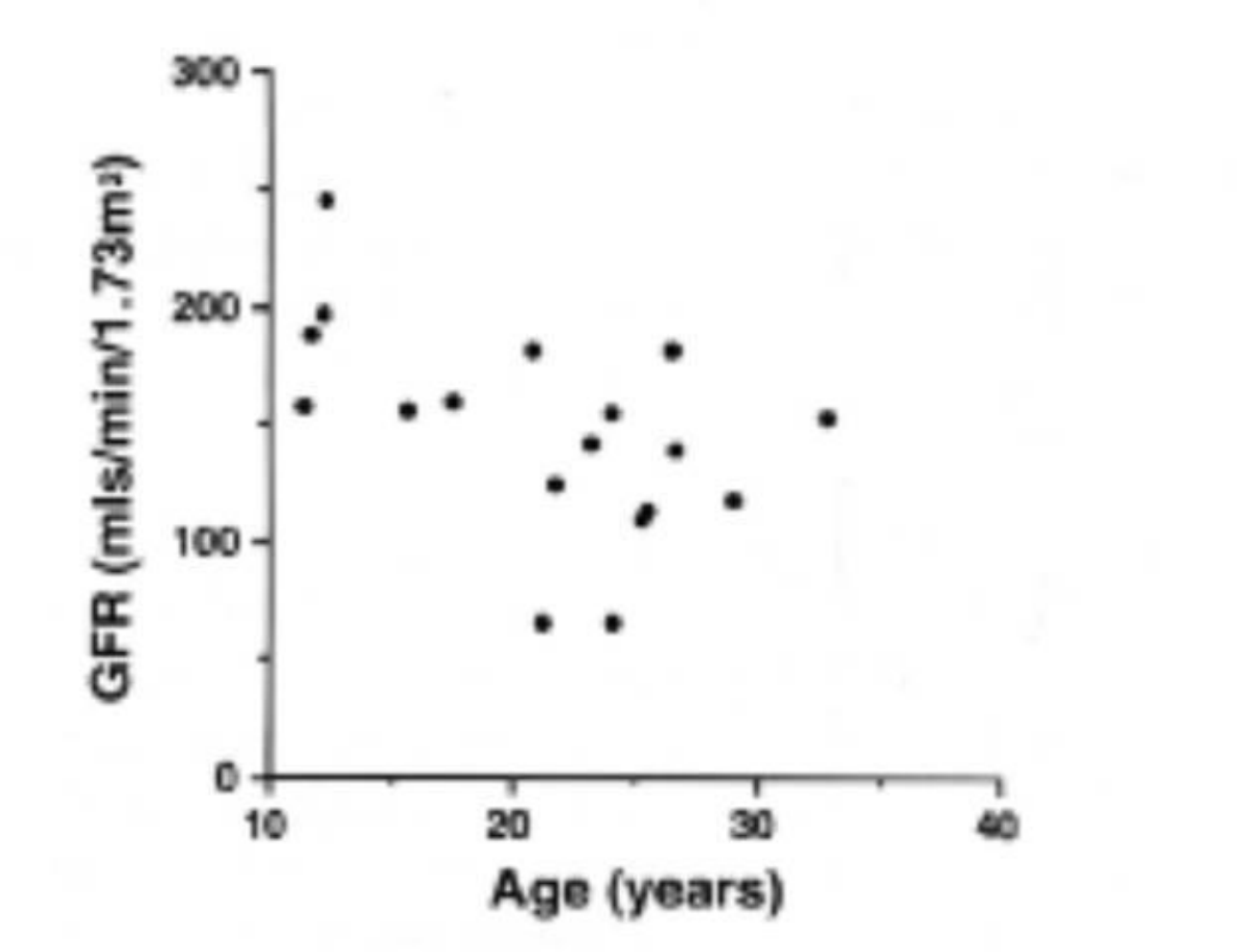
Effect of cornstarch vs glucose in GSD



GSD 1a
Renal involvement

- Silent hyperfiltration
- Proteinuria
- Glomerular sclerosis
- Progressive renal failure
- Renal tubular dysfunction at all ages
- Renal calculi
- Nephrocalcinosis

GFR changes with age in GSD 1a



GSD 1a
Hepatic adenomata

- Generally after puberty
- Incidence 20-75%
- Low grade malignant potential
- Haemorrhage

- “Focal fatty sparing”
- Related to metabolic control

GSD 1a
Hepatocellular carcinoma

- Develop in adenomata
- 10 years after adenoma development
- Mean age at diagnosis 37 (19-49) years
- AFP/CEA usually negative

Hyperlipidaemia in GSD 1

- High VLDL - Hypertiglyceridaemia
- High LDL-Cholesterol,
- Low HDL-cholesterol,
- N or ↓ Apo A-1,2 D
- ↑ Apo C-1,2 B,E ↑↑ Apo C-3

- Increased lipolysis + high FFA
- Decreased peripheral clearance

Hyperlipidaemia in GSD 1

- Is this atherogenic?
  - 3/37 Adults type 1a (median age 28) IHD
  - Most studies suggest no increase CHD
- Is there a protective factor?
  - Low Von Willebrand factor
  - Increased reverse cholesterol transport
  - Increased antioxidants (esp urate?)

Other consequences of Hyperlipidaemia in GSD 1

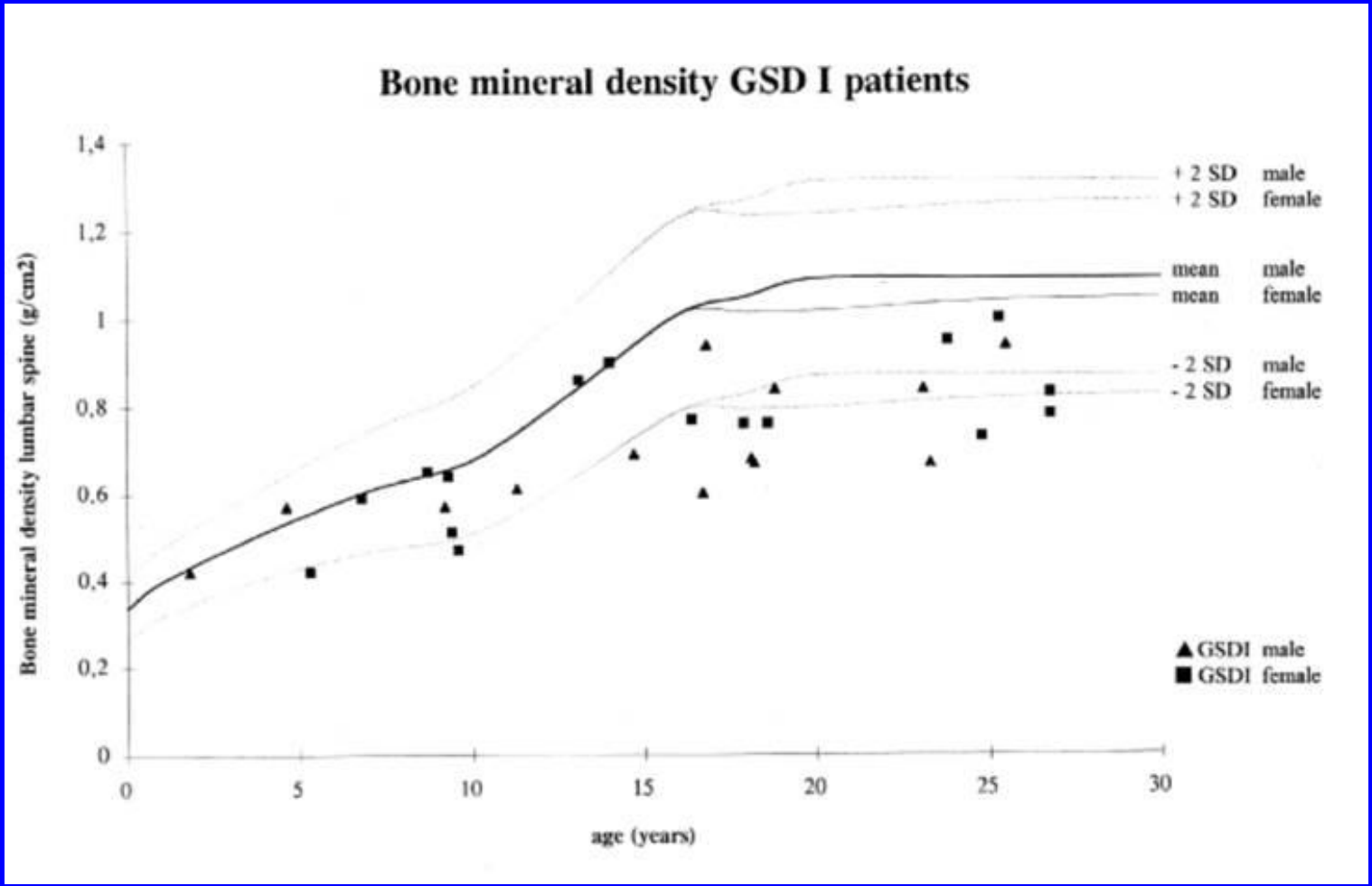
- Nephrotoxic?

  Decreased proteinuria with improved lipid control
- Pancreatitis

Treatment of hyperlipidaemia in GSD 1

- Diet
- Fibrates
- Fish oil
- Statins

Bone density in GSD 1a



GSD 1a
Bone mineralisation

- Significant reduction in bone density
- Decreased calcium intake
- ? Insufficient turnover
- Hypercalcuria
- Lactic acidosis

Growth problems

- Poor linear growth
- Delayed puberty

GSD 1a
Polycystic ovaries

- Invariable structurally after age 5
- ? related to hyperinsulinism
- Menstrual disturbance relatively uncommon
- ? effect on fertility

Hyperuricaemia

- common at presentation
- recurs after puberty
- clinical gout well recognised
- usually responds to Allopurinol

GSD 1a
Management

- Overnight tube feeds or glucose
- Frequent daytime feeds
- Uncooked corn starch
- Allopurinol
- ?Liver transplantation

Liver transplantation

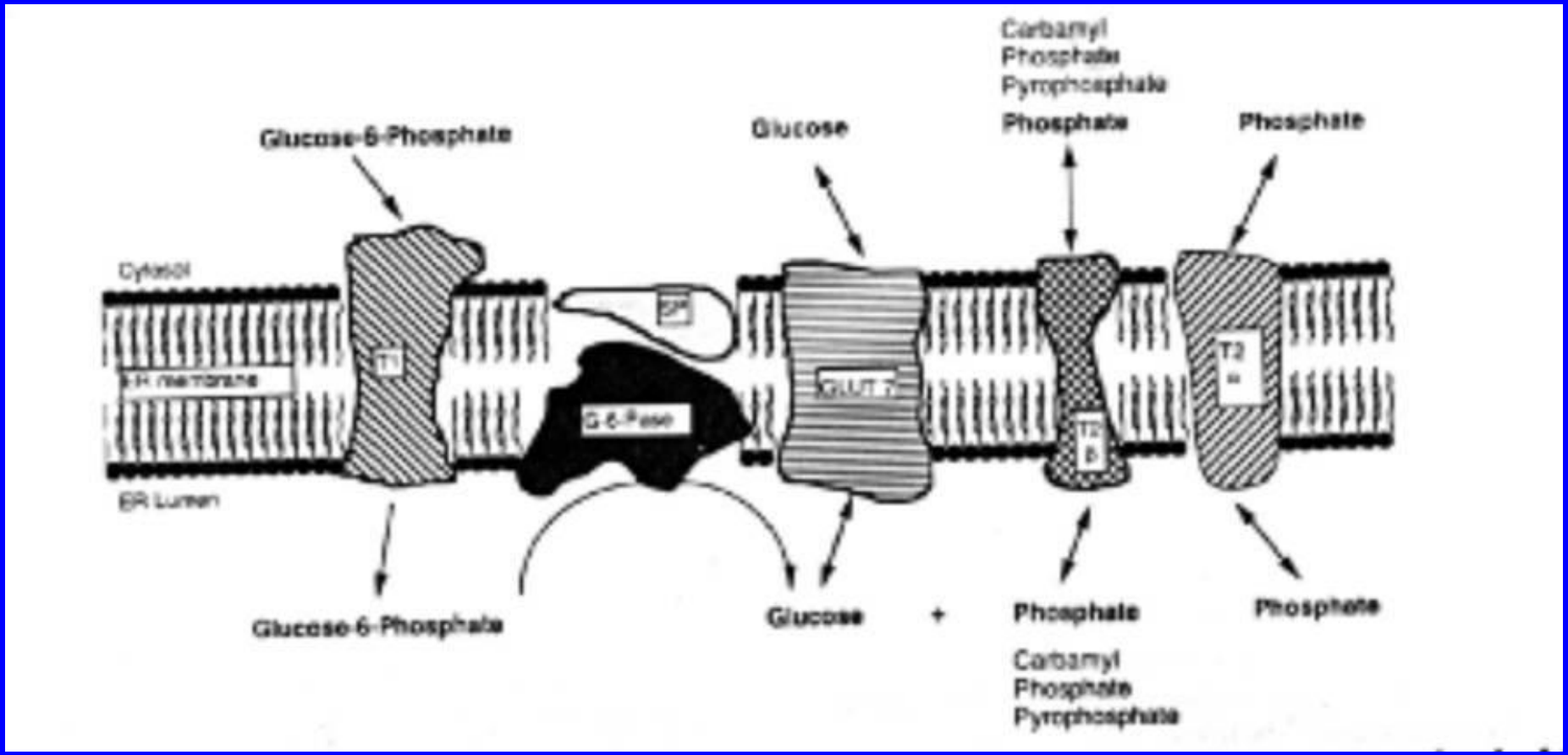
- Correction of metabolic defect
- Improved growth
- Treatment of adenomata/HCC
- Renal vulnerability

Adult outcome
37 adults GSD 1a

- **Short stature 90%**
- **Hepatomegaly 100%**
- **Anaemia 81%**
- **Hyperlipidaemia 100%**
- **Hyperuruicaemia 89%**
- **Osteopenia or fracture 27%**
- **Majority in work or college**

Talente et al 1994

Postulated hepatic microsomal glucose-6-phosphatase system



GSD 1 non a

- Glucose 6 phosphate transporter deficiency
- Neutropenia
- Inflammatory bowel disease
- Gene described 1998
- Expressed in liver, kidney and haematological precursors
- Common mutation in Asian population
- Treatment as GSD 1a
- May need G-CSF

GSD 1 non a

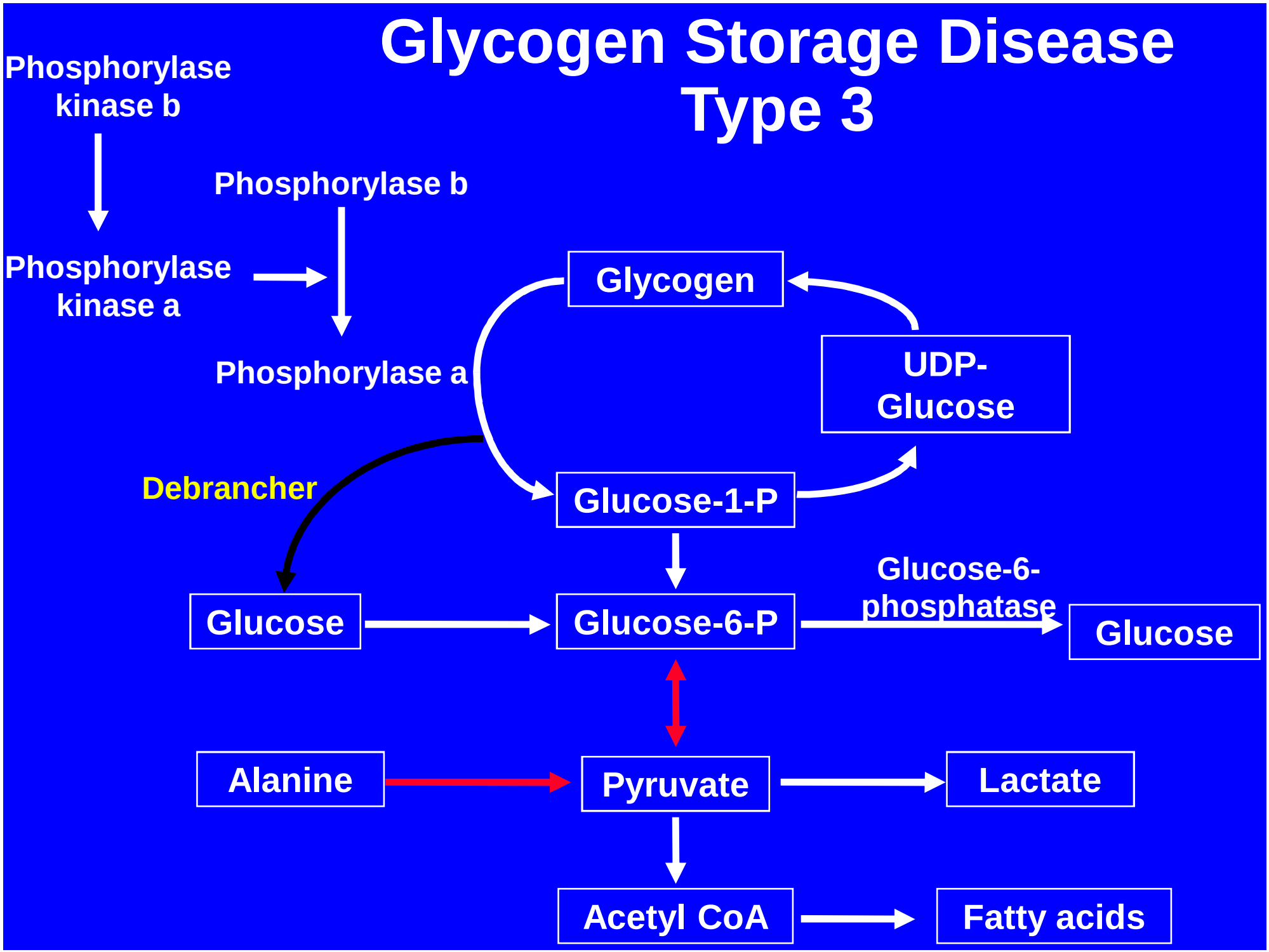
- Nutritional outcome poorer
- Intolerant of UCS
- High risk for osteopenia
- Liver transplantation successful

  Neutropenia persists but improved

GSD 3

- 1952 Cori described “limit dextrinosis”
- 1956 Debrancher deficiency confirmed
- 3a Muscle and liver (85%)
- 3b Liver only (15%)

Glycogen Storage Disease Type 3



GSD 3
Clinical features

- Infancy may like type 1
- Hypoglycaemia less prominent
- Hepatic fibrosis common
- Myopathy increases with age
- Ventricular hypertrophy common
- Cardiac dysfunction less common

GSD 3
Biochemical features

- Lactate and urate normal
- Transaminases increased
- CK increased (type 3a)
- Hypercholesterolaemia
- Postprandial glucagon stimulation normal

GSD 3
Diagnosis

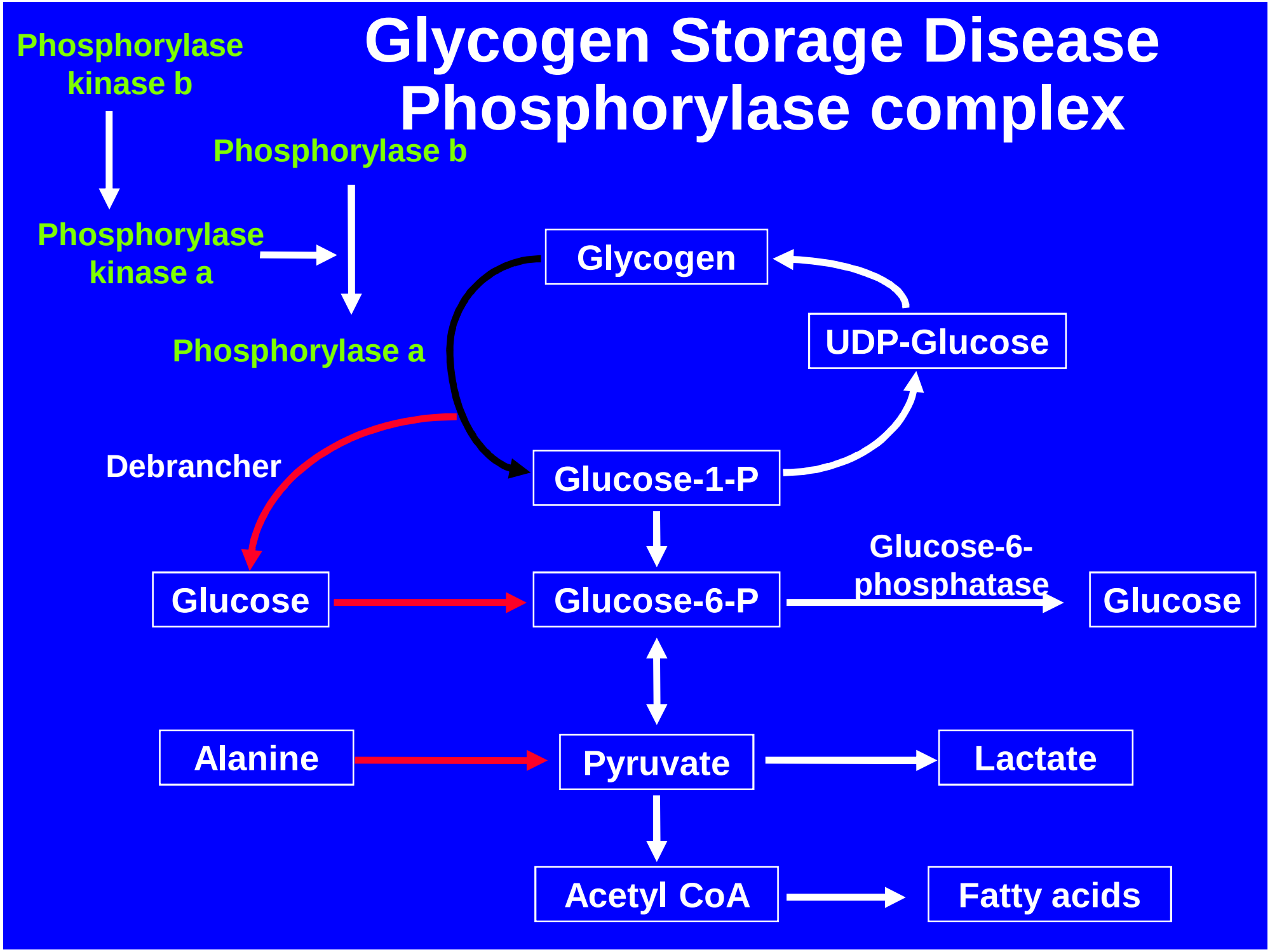
- Increased glycogen — Erythrocytes, Liver, Muscle
- Debrancher deficiency — Erythrocytes, Fibroblasts, Liver, Muscle
- DNA

GSD 3
Management

- Frequent high protein feeds
- Nighttime protein supplement
- Overnight feeds/UCS if necessary
- Lipid lowering agents

- Outcome related to severity of liver disease, myopathy/cardiomyopathy

Glycogen Storage Disease Phosphorylase complex



GSD 6/9

- Phosphorylase and Phosphorylase kinase deficiencies
- Phosphorylase chromosome 14

- Kinase 4 subunits, 3 autosomal 1 X (75%)
- Differential expression in different tissues
-

Phosphorylase kinase

- 4 subunits (α, β, γ, δ)
- In liver isoform
- α encoded PHKA2, X linked (commonest)
- β encoded PHKB, 16q12-q13
- γ encoded PHKG2, 16p12.1-p11.2

GSD 6/9

- Presents early childhood
- Hepatomegaly, abdominal distension
- Mildly abnormal liver function and lipids
- Post prandial ketosis
- Lactate and urate usually normal
- Short stature
- Motor developmental delay

GSD 6/9
Diagnosis

- RBC glycogen, Phosphorylase and kinase
- Liver biopsy rarely necessary
- Increasingly mutation detection

GSD 6/9 Management

- Supportive
- Occasionally nightime UCS
- Outlook excellent
- Spontaneous catch up growth
- Occasional residual liver disease

GSD 9
PHKG2 mutations

- **More severe phenotype**
- **Muscular weakness (normal CK) and fatigue**
- **Rickets**
- **Developmental delay**
- **Progressive liver disease**
- **Occasional cirrhosis**

GSD 6/9
Other types

- Liver phosphorylase deficiency
- Autosomal liver and muscle phosphorylase kinase deficiency
- Muscle-specific phosphorylase kinase deficiency
- Cardiac-specific phosphorylase kinase deficiency

GSD 4

- **Brancher deficiency**
- **Amylopectin like material**

Liver

Heart

Skin

CNS

GSD 4
Clinical features
Liver type

- Hepatosplenomegaly
- Infantile cirrhosis
- Poor growth
- Progressive liver disease
- Cardiomyopathy

GSD 4
Clinical features
Neuromuscular type

- **Infantile**

  Hypotonia, muscular atrophy, early death

- **Childhood**

  Myopathy, cardiomyopathy

- **Adulthood**

  CNS dysfunction, neuropathy

  adult polyglucosan body disease

GSD 4
Diagnosis

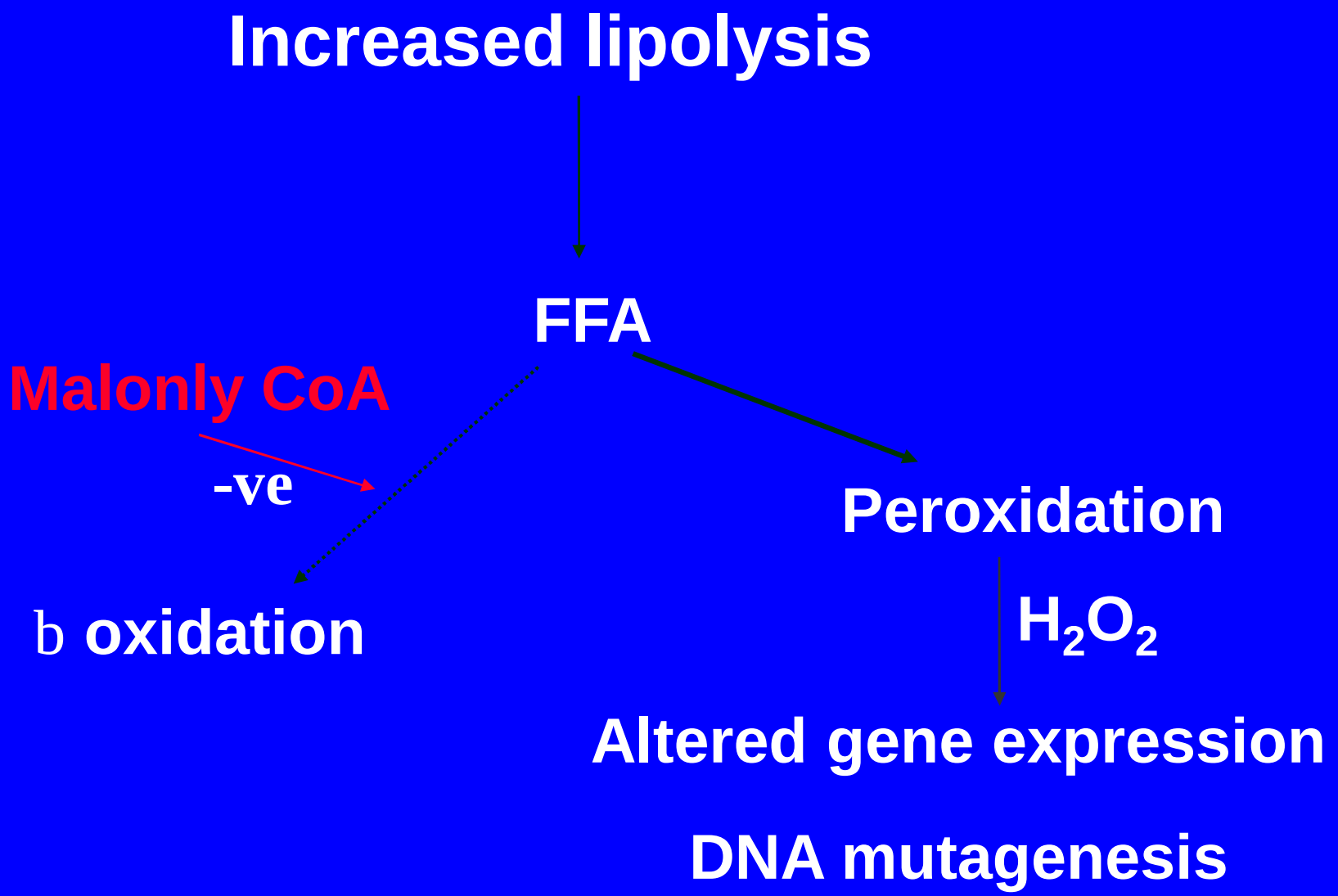
- Hepatic PAS+, diastase resistant granules

- Enzyme deficiency
  - Liver
  - Muscle
  - Fibroblasts
  - Erythrocytes
  - Leucocytes

GSD 4
Management hepatic type

- Dietary treatment unnecessary
- Progressive course
- Liver transplantation
- Progressive cardiomyopathy may develop

GSD 1a
Aetiology of adenoma



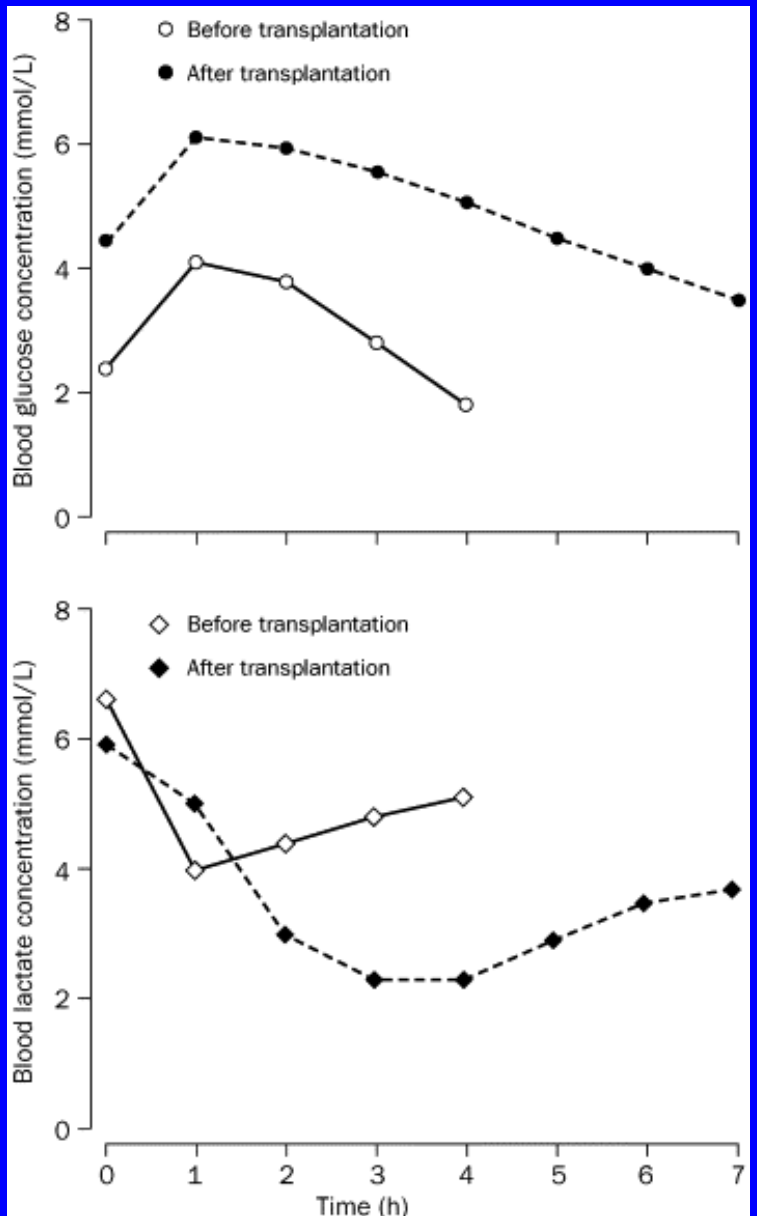
GSD 1d

- Postulated deficiency in Glut ?
- Microsomal glucose transporter
- 1 case (not genetically characterised)
- Clinically similar to GSD 1a

Hepatocyte transplantation

- 47 year old lady
- Aged 3 diagnosed GSD 1a
- Recent poor control
- Lactic acidosis, hepatic adenomata
- Infusion $2x10^9$ hepatocytes via portal vein
- Immunesuppression decreased to tacrolimus monotherapy

Effect of hepatocyte transplant in GSD 1a glucose load



GSD 1a
Monitoring

Date						
Blood pressure [mmHg]						
Fasting bloods for:						
Hb [g/dl]						
WCC [10^9/l]						
Platelets [10^9/l]						
Calcium [mmol/l]						
Phosphate [mmol/l]						
Alk. Phosphatase [u/l]						
ALT [u/l]						
AST [u/l]						
Albumin [g/l]						
Cholesterol [mmol/l]						
Triglycerides [mmol/l]						
Uric acid [µ mol/l]						
Creatinine [µ mol/l]						
reatine Kinase [u/l] (if type III)						
Glucose [mmol/l]						
Urine						
EMU						
Dipstick (fresh sample):						
(If pH>8: renal ultrasound)						

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37 adults GSD 1a

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- **Anaemia 81%**
- **Hyperlipidaemia 100%**
- **Hyperuricaemia 89%**
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Talente et al 1994

Urinary retinol binding protein in type 1a GSD