Biochemical Genetics

Genetics in Medicine - 0504321

2022-2023 Second Semester

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METABOLIC DISORDER DEFINITION

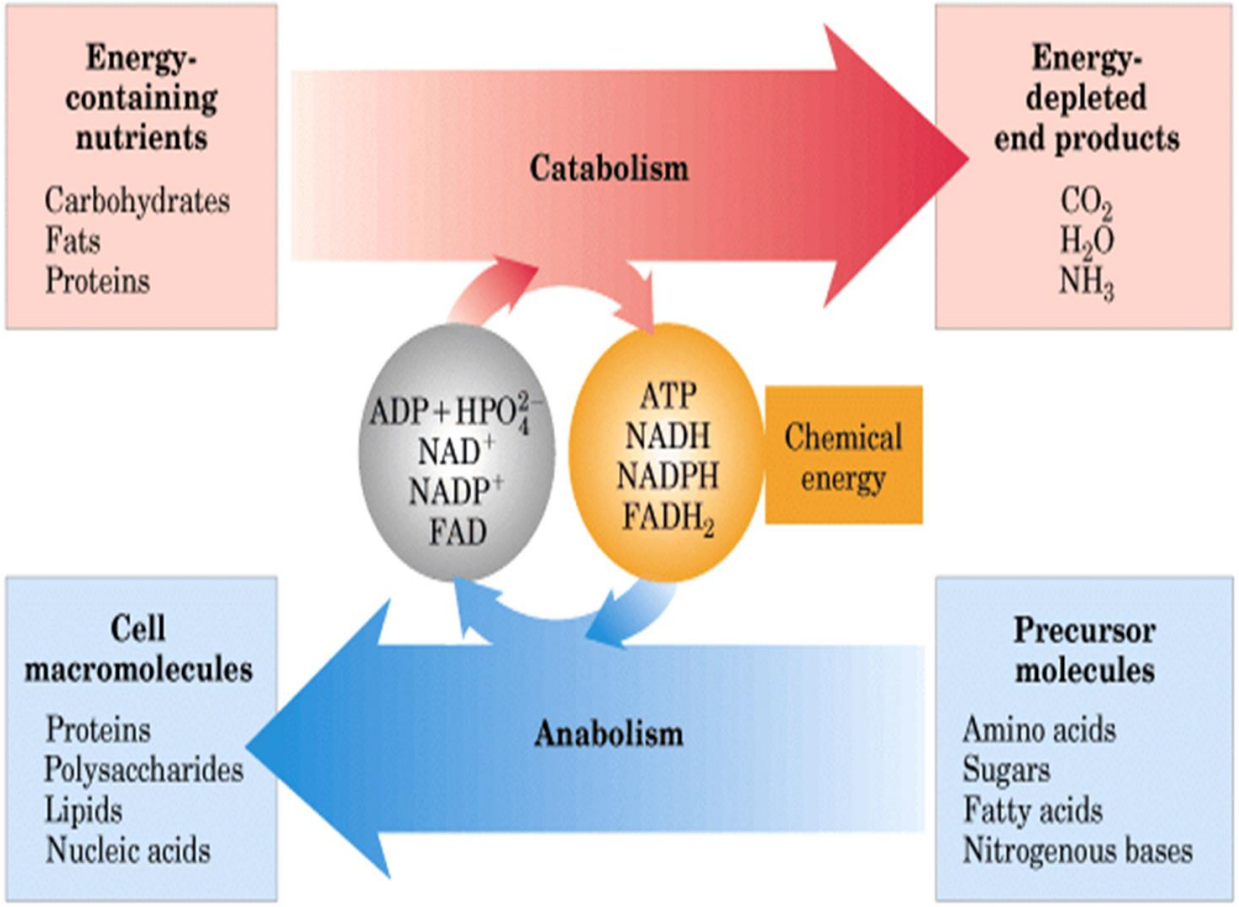
Metabolism refers to the ongoing biochemical processes that maintain the functioning of living organisms. It is the balance of two processes:

- **Catabolism:** Producing energy from breaking down larger molecules into smaller ones. For example, this may involve breaking down carbohydrate molecules into glucose.

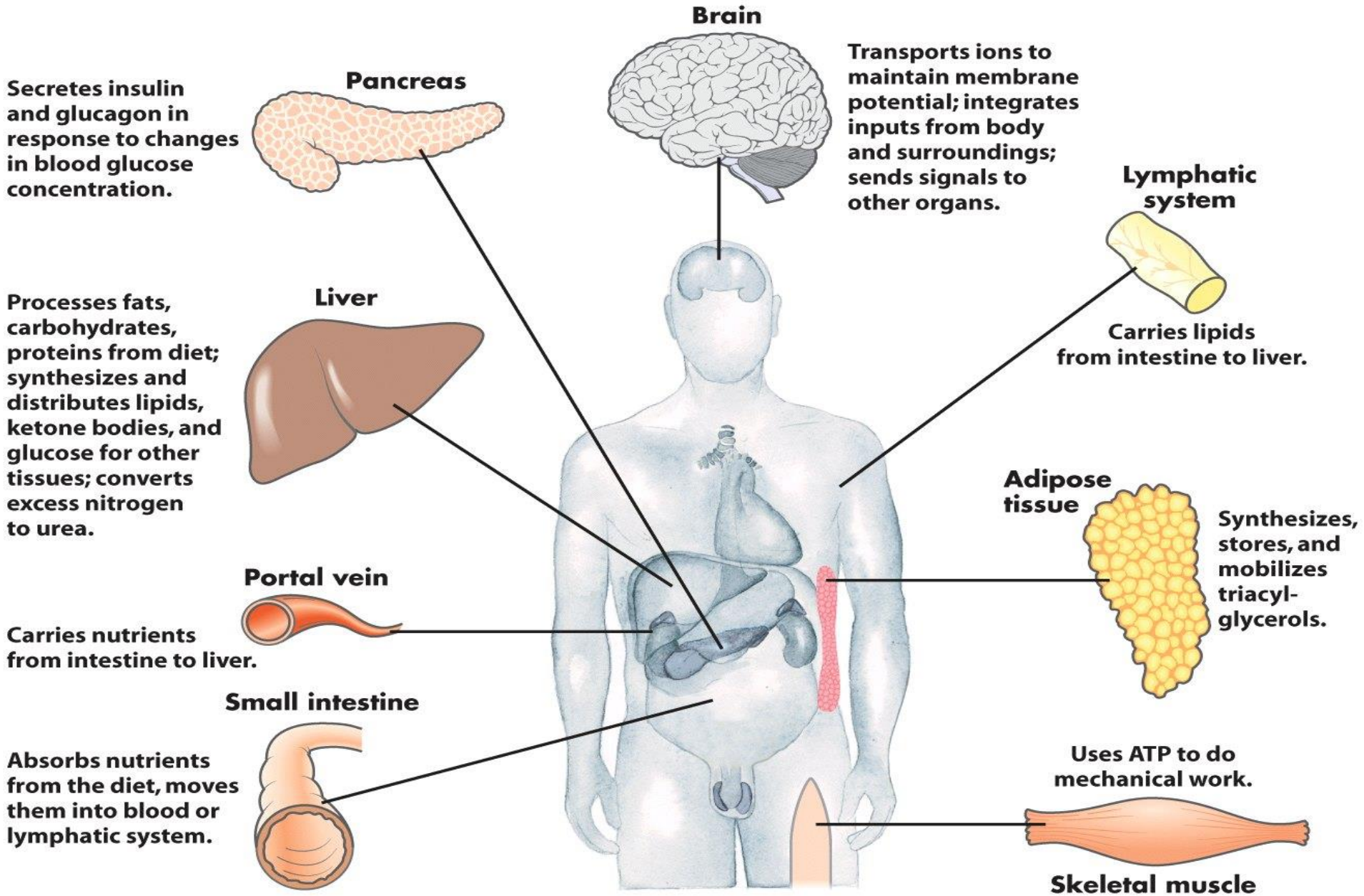
- **Anabolism:** Consuming energy to build new cells, maintaining body tissues, and storing energy.

Examples of causes:

- **Genetics:**
- **Organ dysfunction**
- **Mitochondrial dysfunction:**



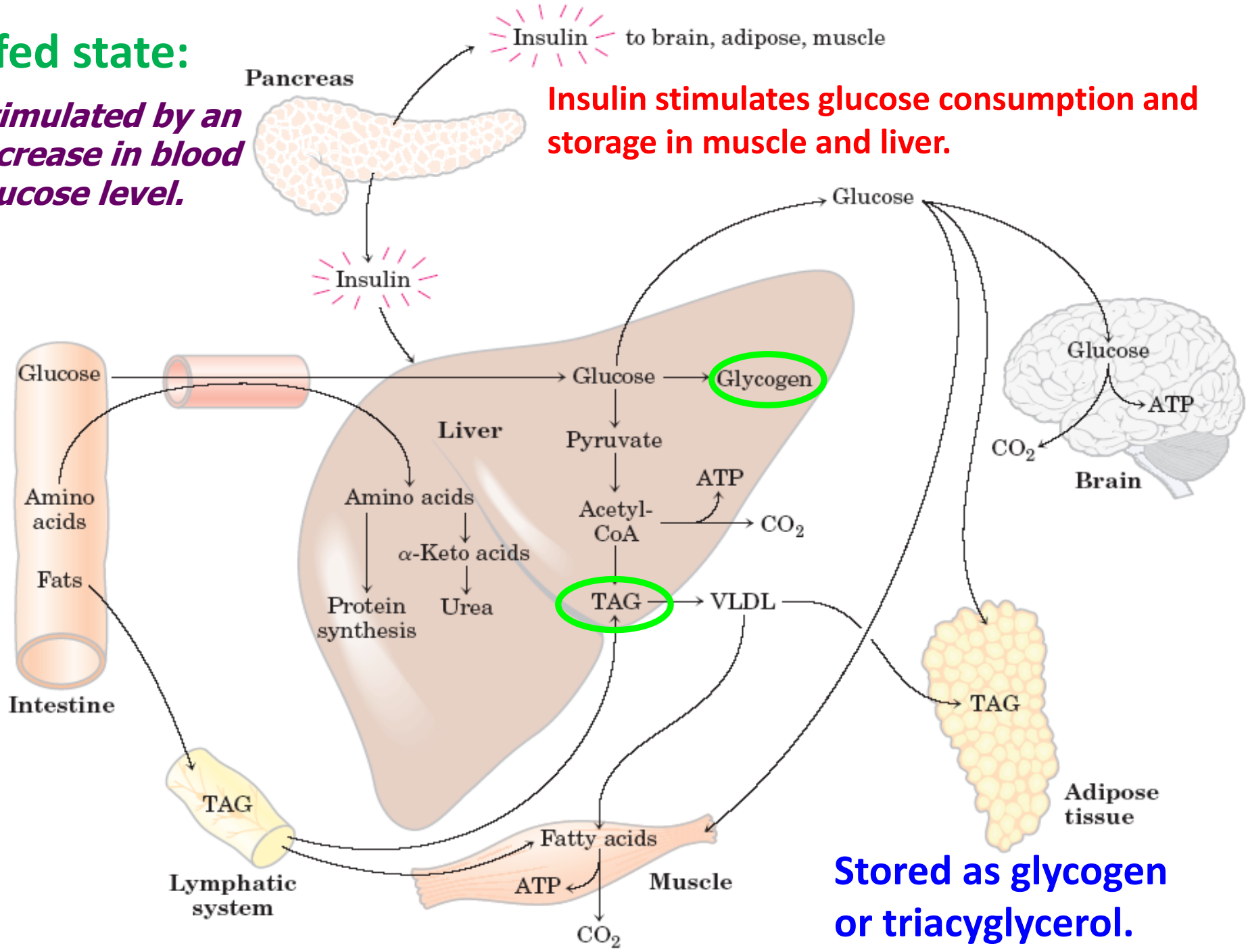
Metabolic Profile of Organs



The well-fed state:

Stimulated by an increase in blood glucose level.

Insulin stimulates glucose consumption and storage in muscle and liver.



Stored as glycogen or triacyglycerol.

BIOCHEMICAL DISEASES (BD), aka IEM

Carbohydrate Metabolism Disorder
Galactosemia
Glycerol Kinase Deficiency
Glycogen Storage Diseases

Organic Acid Disorders
Propionic Acidemia
Isovaleric Acidemia
Methylmalonic Acidemia

Amino Acid Disorders
Phenylketonuria
Tyrisonemia
Maple Syrup Urine Disease
Nonketotic Hyperglycinemia
Homocystinuria
Glutaric Acidemia Type I

Urea Cycle Defects
Carbamoyl phosphate synthetase I deficiency
Ornithine transcarbamylase deficiency
Citrillinemia
Argininosuccinic Aciduria
Argininemia

WHEN TO SUSPECT BD?

- Usually Normal infant at birth (term)
- Illness presentation within first 48 hours of age

- **FAMILY HISTORY**
  - Neonatal death of unclear etiology
  - History of child with neurologic deterioration
  - History of multiple miscarriages
  - Consanguinity

- **CLINICAL PRESENTATION**
  - Poor oral intake &/or vomiting
  - Lethargy coma, seizures,
  - Hepatosplenomegaly, dysmorphic features
  - Cataracts

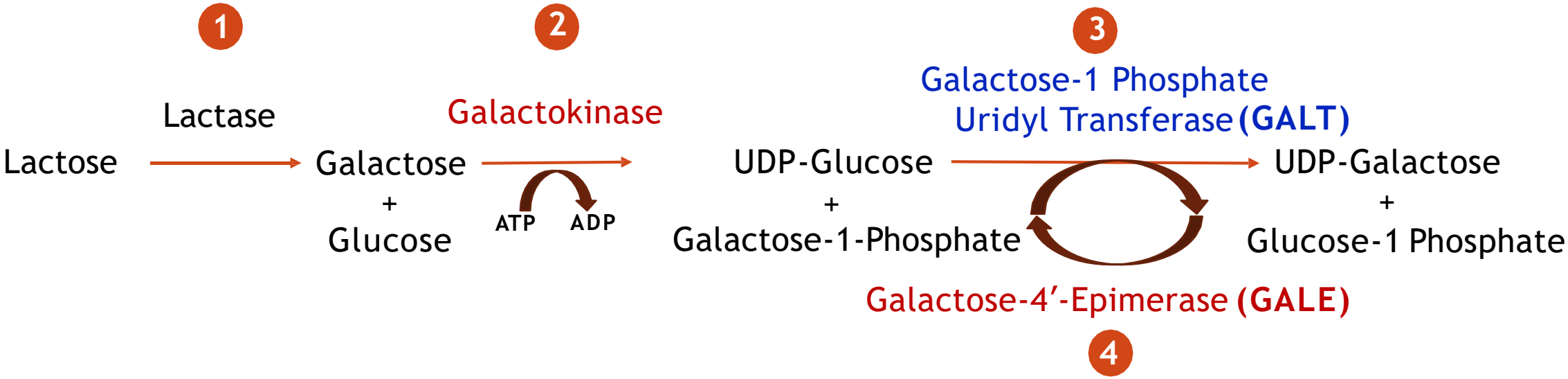
Inborn Errors of Metabolism Categories		Incidence/ Inheritance	Enzyme Deficiency	Symptom Onset
Disorders of Carbohydrate Metabolism	Galactosemia	1:40,000 AR	1. Galactose-1-Phosphate Uridyltransferase (GALT) 2. Galactose epimerase	First few days of life
	Glycogen Storage Disease (Von Gierke)	1:100,000 AR	Glucose-6 -Phosphatase	By 2 years of age
Disorders of Amino Acid Metabolism	Phenylketonuria (PKU)	1:15,000 AR	1. Phenylalinine Hydroxylase 2. Biopterin defect	First few months of life
	Maple Syrup Urine Disease	1:150,000 AR	Branched chain 3-Ketoacid Dehydrogenase Complex	3-5 days of age
	Tyrosinemia type I	Rare AR	Fumarylacetoacetate hydroxylase	Birth to first few months of life
	Glutaric Acidemia	1:30-40,000 AR	Glutaryl-CoA Dehydrogenase	Infancy or early childhood
	Urea Cycle Defects	1:30,000		Varies

CARBOHYDRATE METABOLISM DISORDERS

GALACTOSEMIA

- **Autosomal recessive** disorder of galactose metabolism
- **Three forms:** Classic galactosemia, Galactokinase deficiency, Galactose-4′-epimerase deficiency
- **Screening:** Measures GALT activity &/OR Galactose and Galactose-1-Phosphate
- **Clinical Presentation:** Lethargy, poor feeding, jaundice, **cataracts**, ***E. coli* sepsis**
- **Laboratory findings:** ↓glucose, ↑ total bilirubin, hyperchloremic metabolic acidosis*, normal lactate, normal pyruvate
- **Diagnostic Test**
  - Urinary reducing substances*
  - Whole blood or erythrocyte GALT activity and erythrocyte red cell galactose-1-phosphate
- **Treatment:** Strict dietary lactose /galactose restriction
- **Long term Prognosis:** Mild growth failure, learning disabilities, ataxia, tremor and verbal dyspraxia
  - Ovarian failure, also probable infertility in males

GALACTOSEMIA PATHWAY



Diagnosis in Absence of Enzyme

1. Lactose intolerance
2. Galactokinase — Cataracts (late in childhood)
3. Classic Galactosemia — Cataracts, diarrhea, jaundice, intellectual disability and liver failure (first few months of life)
4. Galactose-4′-Epimerase Deficiency — Cataracts, diarrhea, jaundice, intellectual disability and liver failure (first few months of life)

GLYCEROL KINASE DEFECTIENCY

- **X-linked recessive** defect in glycerol kinase
- **Clinical Presentation: Isolated Symptomatic: Lethargy, vomiting, acidosis, ketotic hypoglycemia**
- **Lab Findings:** Pseudotriglyceridemia (elevated glycerol interferes with assay for triglycerides)
- **Diagnostic studies: FISH analysis to assess for deletion**
- **Treatment:** Manage SYMPTOMS as indicated by using corticosteroids, glucose infusion, or mineralocorticoids
- **PROGNOSIS:** Infantile form is associated with severe developmental delay

GLYCOGEN STORAGE DISEASE

Type	Enzyme defect	Eponym	Hypoglycemia	Hyperlipidemia	Symptoms	Others
GSD type 1	Glucose-6-phosphatase	Von Gierke's	Yes	Yes	Growth failure	Lactic acidosis, hyperuricemia
GSD type 2	Acid maltase	Pompe's	No	No	Death by age ~ 2 years	Heart failure Myopathy
GSD type 3	Glycogen debrancher	Cori's or Forbes'	Yes	Yes		Myopathy
GSD type 4	Glycogen branching enzyme	Andersen	No	No	Failure to thrive, death at age ~ 5 years	Liver cirrhosis
GSD type 5	Muscle glycogen phosphorylase	McArdle	No	No		Renal failure by myoglobinuria
GSD type 6	Liver glycogen phosphorylase	Hers' disease	Yes	No		
GSD type 7	Muscle phosphofructokinase	Tarui's disease	No	No	Growth retardation	Hemolytic anemia
GSD type 9	Phosphorylase kinase PHKA2		No	Yes	Delayed motor development, growth retardation	
GSD type 11	Glucose transporter GLUT2	Fanconi-Bickel Syndrome	Yes	No		
GSD type 12	Aldolase A	Red cell aldolase deficiency	?	?		Exercise intolerance
GSD type 13	B-enolase		?	?		Exercise intolerance

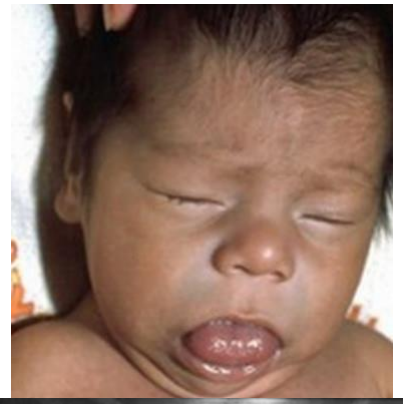
VON GIERKE DISEASE (GSD 1A)

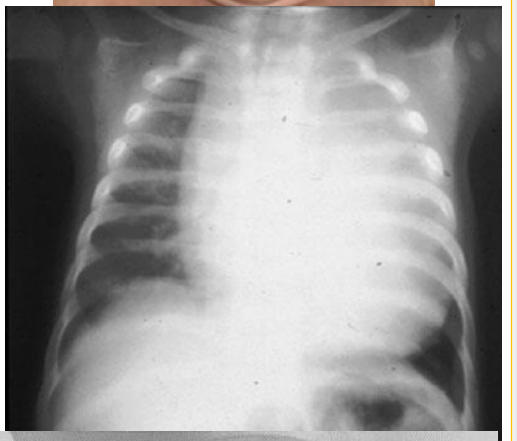
- **Autosomal recessive** defect in **glucose-6-phosphatase** → glycogen accumulates in the liver
- **Clinical Presentation:** Normal at birth. Hypoglycemia presents when infants start to sleep through the night (prolonged fasting). Hepatomegaly
  - May present in neonatal period
- **Lab Findings: Hypoglycemia**, lactic acidosis, ↑urea, ↑ lipids and triglycerides
- **Diagnostic studies**
  - Liver biopsy glycogen and assay for enzyme
  - DNA testing may obviate need for liver biopsy
- **Treatment:** Avoidance of fasting. Continuous nighttime feeds in infancy. Corn starch.

POMPE DISEASE (GSD 2)

- **Autosomal recessive** disorder of

  α 1,4-glucosidase
- **Clinical Presentation:** Normal at birth. Then onset of muscle weakness, feeding and breathing difficulty
  - Infantile: dilated cardiomyopathy, failure to thrive, hypotonia, macroglossia
- **Lab Findings: NO hypoglycemia!!!,** ↑CPK
- **Diagnostic studies:** Assay enzyme in lymphocytes, muscle or fibroblasts
- **Treatment:** Enzyme Replacement Therapy available
  - since 2006





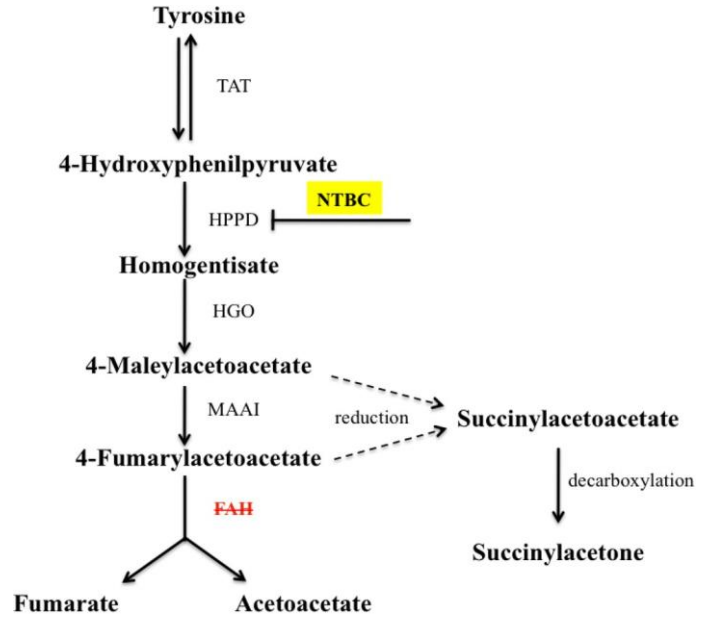
DISORDERS OF AMINO ACIDS METABOLISM

PHENYLKETONEURIA (PKU)

- **Autosomal recessive** disorder in which phenylalanine can not be converted to tyrosine
- **Enzyme Defect:** Phenylalanine Hydroxylase (chromosome 12q24.1)
- **Clinical Presentation:** Normal at birth. > 50% affected infants present with the following signs:
  - Vomiting, irritability, eczematoid rash, peculiar odor 'musty', fair-hair and skin
- **Screening:** Test for elevated levels of phenylalanine
- **Diagnostic studies**
  - If positive screen, quantitative analysis of serum phenylalanine and tyrosine
- **Treatment:** Limit dietary intake of phenylalanine.
  - Followed by dietician and Phe levels are monitored closely
- **Long term Prognosis:** If untreated severe intellectual disability IQ < 30. Acquired microcephaly
  - Damage becomes irreversible by 8 weeks of age

TYROSINEMIA

	Enzyme Defect	Clinical Presentation	Diagnostic Studies	Treatment	Prognosis
Type I	Fumarylacetoacetate hydroxylase	Failure to thrive (FTT) Hepatomegaly Hepatoblastoma RTA Rickets	Succinylacetone in urine ↑ levels of tyrosine in plasma	Diet low in tyrosine and phenylalanine -NTBC	Infants are affected early with high risk of mortality
Type II	Tyrosine Aminotransferase	Corneal ulcers or dendritic keratitis 50% with intellectual disability Red papular lesions on their palms and soles No liver toxicity		Diet low in tyrosine	Diet may not be curative



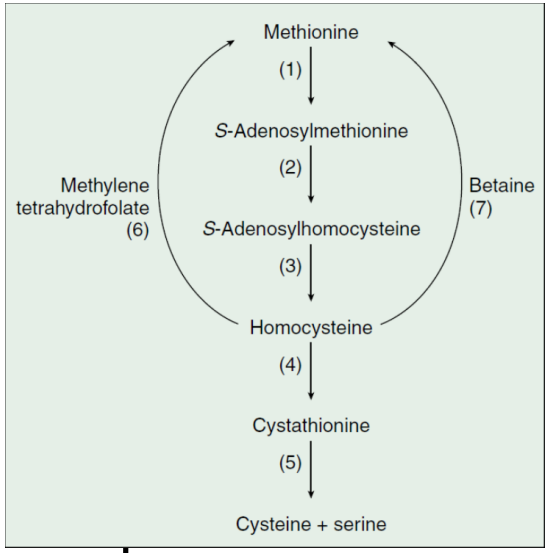
MAPLE SYRUP UTINE DISEASE

- **Autosomal recessive** disorder of branched chain amino acid metabolism (valine, leucine and isoleucine
- **Enzyme Defect:**
  - Defect in **oxidative decarboxylation of ketoacids**
- **Clinical Presentation:** Feeding difficulty, irregular respirations, loss of Moro reflex, bicyclinc motion of legs/swimming with arms, severe seizures, opisthotonos and rigidity
- **Diagnostic Test**
  - Plasma amino acid: ↑ leucine, isoleucine & valine
  - Urine organic acids – branched chain 2-keto and 2-hydroxy acids
  - Presence of **alloisoleucine** is diagnostic
- **Treatment:** Strict dietary control of leucine, isoleucine and valine restriction
- **Long term Prognosis:**
  - Rapid progression to death within 2-4 weeks if no treatment initiated

GLUTARIC ACIDEMIA TYPE 1

- **Autosomal recessive** disorder resulting in defect in the catabolic pathway of lysine, hydroxylysine and tryptophan
- **Enzyme Defect:** Glutaryl-CoA Dehydrogenase (on chromosome 19)
- **Clinical Presentation:** Macrocephaly at birth, normal development until illness or metabolic stressor
  - → hypotonia and dystonia 'mimics acute onset CNS infection*
  - CT/MRI brain findings are present at birth (see images next)
  - Can cause subdural hematomas and retinal hemorrhages
- **Diagnostic Test**
  - Urine organic acids: ↑ glutaric acid and 3-hydroxyglutaric acids
    - Plasma **carnitine** levels are low
  - Prenatal diagnosis: increased concentrations of glutaric acid in amniotic fluid – DNA test preferred
- **Treatment:** L-carnitine, riboflavin & special diet
  - When acutely ill provide IV fluids containing glucose
- **Long term Prognosis:** Mild growth failure, learning disabilities and verbal dyspraxia
  - 5 % of patients will be asymptomatic
  - 35 % of patients will have severe disease despite optimal therapy

HOMOCYSTINURIA



- **Autosomal recessive** disorder of methionine metabolism
- **Enzyme Defect:** Cystathionine β-synthetase (chromosome21q)
- **Screening** YES (Elevated methionine)
- **Clinical Presentation:** Marfanoid habitus, developmental delay, downward /medial lens dislocation, osteoporosis and increased risk of arterial/venous thromboembolism
  - Presents within first 10years
- **Diagnostic Test**
  - Blood and urine test for excess homocysteine and methionine. Low level of cysteine
  - Liver biopsy and enzyme assay for enzymatic activity
- **Treatment:** Large doses of pyridoxine (B6), B12 and folic acid. Diet low in methionine
  - Supplementation with Betaine
- **Long term Prognosis:** Intellectual disability is fairly common

ORGANIC ACID DISORDERS

PROPIONIC ACIDEMIA

- **Autosomal recessive** defect in propionyl CoA carboxylase
- **Clinical Presentation:** Neonatal onset: Lethargy and coma
- **Lab Findings:** ↑↑**ammonia,** anion gap metabolic acidosis, neutropenia, thrombocytopenia,
  - hyperglycinemia
  - **Diagnostic Test**
    - Elevated propionyl carnitine.
    - Plasma amino acid: ↑ Glycine
    - Urine organic acid: ↑ Methylcitrate
    - Enzyme assay on leukocytes
- **Treatment:**
  - **Diet**
  - **Carnitine**
  - **Biotin (Cofactor for enzyme)**

ISOVALETIC ACIDEMIA

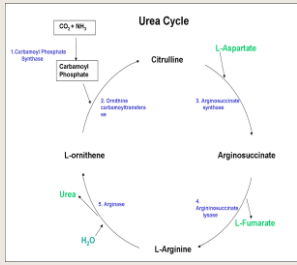
- **Autosomal recessive** defect in leucine metabolism
- **Enzyme Defect:** Isovaleryl-CoA dehydrogenase deficiency
- **Clinical Presentation: "Odor of sweaty feet"**
  - Onset in newborn periods – severe metabolic acidosis, ketosis with vomiting → coma and death
  - Onset in infancy- symptoms are preceded by an infection or increased protein intake
    - Subsequent chronic intermittent pancytopenia and acidosis
- **FL State Newborn Screen** YES
- **Diagnostic Test**
  - Urine organic acids
  - Prenatal diagnosis is possible
- **Treatment:**
  - **Acute:** IV glucose
  - **Chronic:** Restricting leucine intake and prescribing carnitine &/or glycine

METHYLMALOMOIC ADODEMIA

- **Autosomal recessive** disorder that ultimately inhibits methylmalonyl-CoA mutase function.
- 1/55,000 live births in the Finland
- **Enzyme Defect:** Mutase deficiency and Cobalamin A, B, C, D, F and X deficiency
- **Clinical Presentation:** Early: hyperammonemia, ketoacidosis and thrombocytopenia
  - Late onset: complication is renal failure and cardiomyopathy
- **Diagnostic Test**
  - **Urine organic acids (increased methylmalonic acid and abnormal ketone bodies)**
  - **Elevated homocysteine levels**
- **Treatment:** Restriction of dietary protein. Betaine and IM B_{12} vitamin only for cobalamin C, E and some D deficiencies
  - Liver and kidney transplants may be curative

UREA CYCLE DEFECTS

Urea Cycle Defects	Incidence/ Inheritance	Deficiency	Symptom Onset	Presentation	Labs
CPSDeficiency	1:70-100,000 AR	Carbamoyl phosphate synthetase I	By 5 days of age	Lethargy, hypotonia, vomiting and poor feeding Death if undiagnose d	↑Ammonia ↑CSF Glutamine Respiratory alkalosis Low BUN ↑Glutamine, alanine, asparagine ↓Citrulline ↓Argninine ↓Urine orotic acid
Ornithine Transcarbamylase (OTC) Deficiency	1:70,000 X-linked (Most common)	Ornithine Transcarbamylase	24-48 hours	Lethargy, hypotonia, vomiting and poor feeding Death if undiagnose d	↑Ammonia ↑CSF Glutamine Respiratory alkalosis Low BUN ↑Glutamine, Alanine, Asparagine ↓Citrulline ↓Argninine ↑Urine orotic acid
Citrillinemia	AR	Arginoinosuccinate synthetase deficiency	Late onset; preceded by stressor		↑Ammonia ↓Argninine
Argininosuccinic Aciduria	AR	Argininocuccinate lyase deficiency	Late onset; preceded by stressor	Trichorrhexis nodosa Episodic coma	↑Ammonia ↓Argninine
Argininemia	AR	Arginase deficiency	Late onset; preceded by stressor	Progressive splastic diplegia, tremor, ataxia	↑Ammonia Normal Argninine



Hyperlipoproteinemias

Type I Hyperlipoproteinemia	Lipoprotein Lipase Deficiency Increased Chylomicrons and VLDL Hypertriglyceridemia
Type II a Hyperlipoproteinemia	Defect in LDL Receptors Increased LDL levels in blood Hyperbetalipoproteinemia Hypercholesterolemia
Type II b Hyperlipoproteinemia	Increased production of Apo B Increased production of VLDL and impaired LDL catabolism Increased VLDL and LDL

Type III

amilial Dysbeta
ipoproteinemias

Defect in ApoE
Broad Beta Disease
Increased IDL

Type IV

Hyper-pre-β-Lipoproteinemia

Impaired VLDL metabolism.

Increased VLDL

Due to acquired conditions:

- ❑ **Obesity**
- ❑ **Alcoholism**
- ❑ **Diabetes mellitus**

Type V

Combined Hyperlipoproteinemia

Increased VLDL and Chylomicrons

Due to acquired conditions:

- ❑ Obesity
- ❑ Alcoholism
- ❑ Diabetes mellitus