Metabolic Diseases

SCBM 341 General Pathology
What is a metabolic disease?

- “Inborn errors of metabolism”
- inborn error: an inherited (i.e. genetic) disorder
- metabolism: chemical or physical changes undergone by substances in a biological system
- “any disease originating in our chemical individuality”
What is a metabolic disease?

- Garrod’s hypothesis

A → B → C

- product deficiency

D

- substrate excess
- toxic metabolite
What is a metabolic disease?

- Small molecule disease
  - Carbohydrate
  - Protein
  - Lipid
  - Nucleic Acids

- Organelle disease
  - Lysosomes
  - Mitochondria
  - Peroxisomes
  - Cytoplasm
How do metabolic diseases present in the neonate? 

- Acute life threatening illness
  - encephalopathy - lethargy, irritability, coma
  - vomiting
  - respiratory distress

- Seizures, Hypertonia

- Hepatomegaly (enlarged liver)

- Hepatic dysfunction / jaundice

- Odour, Dysmorphism, FTT (failure to thrive), Hiccoughs
How do you recognize a metabolic disorder ??

- Index of suspicion
  - eg “with any full-term infant who has no antecedent maternal fever or PROM (premature rupture of the membranes) and who is sick enough to warrant a blood culture or LP, one should proceed with a few simple lab tests.

- Simple laboratory tests
  - Glucose, Electrolytes, Gas, Ketones, BUN (blood urea nitrogen), Creatinine
  - Lactate, Ammonia, Bilirubin, LFT
  - Amino acids, Organic acids, Reducing subst.
Index of suspicion

Family History

- Most IEM’s are recessive - a negative family history is not reassuring!
- **CONSANGUINITY**, ethnicity, inbreeding
- neonatal deaths, fetal losses
- maternal family history
  - males - X-linked disorders
  - all - mitochondrial DNA is maternally inherited

- A positive family history may be helpful!
Index of suspicion

History

- CAN YOU EXPLAIN THE SYMPTOMS?
- Timing of onset of symptoms
  - after feeds were started?
- Response to therapies
Index of suspicion

Physical examination

- General – dysmorphisms (abnormality in shape or size), ODOR
- H&N - cataracts, retinitis pigmentosa
- CNS - tone, seizures, tense fontanelle
- Resp - Kussmaul’s, tachypnea
- CVS - myocardial dysfunction
- Abdo - HEPATOMEGALY
- Skin - jaundice
Index of suspicion

Laboratory

- ANION GAP METABOLIC ACIDOSIS
- Normal anion gap metabolic acidosis
- Respiratory alkalosis
- Low BUN relative to creatinine
- Hypoglycemia
  - especially with hepatomegaly
  - non-ketotic
A parting thought ...

- Metabolic diseases are individually rare, but as a group are not uncommon.
- Their presentations in the neonate are often non-specific at the outset.
- Many are treatable.
- The most difficult step in diagnosis is considering the possibility!
Inborn errors of metabolism
Inborn Errors of Metabolism

An inherited enzyme deficiency leading to the disruption of normal bodily metabolism

- Accumulation of a toxic substrate (compound acted upon by an enzyme in a chemical reaction)
- Impaired formation of a product normally produced by the deficient enzyme
Three Types

- Type 1: Silent Disorders
- Type 2: Acute Metabolic Crises
- Type 3: Neurological Deterioration
Type 1: Silent Disorders

- Do not manifest life-threatening crises
- Untreated could lead to brain damage and developmental disabilities
- Example: PKU (Phenylketonuria)
PKU

- Error of amino acids metabolism
- No acute clinical symptoms
- Untreated leads to mental retardation
- Associated complications: behavior disorders, cataracts, skin disorders, and movement disorders
- First newborn screening test was developed in 1959
- Treatment: phenylalalaine restricted diet
  (specialized formulas available)
Type 2: Acute Metabolic Crisis

- Life threatening in infancy
- Children are protected in utero by maternal circulation which provide missing product or remove toxic substance
- Example OTC (Urea Cycle Disorders)
OTC

- Appear to be unaffected at birth
- In a few days develop vomiting, respiratory distress, lethargy, and may slip into coma.
- Symptoms mimic other illnesses
- Untreated results in death
- Treated can result in severe developmental disabilities
Type 3: Progressive Neurological Deterioration

- Examples: Tay Sachs disease
  Gaucher disease
  Metachromatic leukodystrophy

- DNA analysis show: mutations
Mutations

- Nonfunctioning enzyme results:
  - Early Childhood - progressive loss of motor and cognitive skills
  - Pre-School - non responsive state
  - Adolescence - death
Other Mutations

- Partial Dysfunctioning Enzymes
  - Life Threatening Metabolic Crisis
  - ADH
  - LD
  - MR

- Mutations are detected by Newborn Screening and Diagnostic Testing
Treatment

- Dietary Restriction
- Supplement deficient product
- Stimulate alternate pathway
- Supply vitamin co-factor
- Organ transplantation
- Enzyme replacement therapy
- Gene Therapy
Children in School

- Life long treatment
- At risk for ADHD
  - LD
  - MR
- Awareness of diet restrictions
- Accommodations
Metabolic disorders testable on **Newborn Screen**

- Congenital **Hypothyroidism**
- Phenylketonuria (PKU)
- **Galactosemia**
- Galactokinase deficiency
- Maple syrup urine disease
- **Homocystinuria**
- Biotinidase deficiency
Categories of IEMs are as follows:

- Disorders of protein metabolism
  (eg, amino acidopathies, organic acidopathies, and urea cycle defects)
- Disorders of carbohydrate metabolism
  (eg, carbohydrate intolerance disorders, glycogen storage disorders, disorders of gluconeogenesis and glycogenolysis)
- Lysosomal storage disorders
- Fatty acid oxidation defects
- Mitochondrial disorders
- Peroxisomal disorders
Pathophysiology:

- Single gene defects result in abnormalities in the synthesis or catabolism of proteins, carbohydrates, or fats.
- Most are due to a defect in an enzyme or transport protein, which results in a block in a metabolic pathway.
- Effects are due to toxic accumulations of substrates before the block, intermediates from alternative metabolic pathways, and/or defects in energy production and utilization caused by a deficiency of products beyond the block.
- Nearly every metabolic disease has several forms that vary in age of onset, clinical severity and, often, mode of inheritance.
Frequency:

**In the US:** The incidence, collectively, is estimated to be 1 in 5000 live births. The frequencies for each individual IEM vary, but most are very rare. Of term infants who develop symptoms of sepsis without known risk factors, as many as 20% may have an IEM.

**Internationally:** The overall incidence is similar to that of US. The frequency for individual diseases varies based on racial and ethnic composition of the population.
Mortality/Morbidity:

IEMs can affect any organ system and usually do affect multiple organ systems.

Manifestations vary from those of acute life-threatening disease to subacute progressive degenerative disorder.

Progression may be unrelenting with rapid life-threatening deterioration over hours, episodic with intermittent decompensations and asymptomatic intervals, or insidious with slow degeneration over decades.
Disorders of nucleic acid metabolism
Purine metabolism
Adenine phosphoribosyltransferase deficiency
The normal function of adenine phosphoribosyltransferase (APRT) is the removal of adenine derived as metabolic waste from the polyamine pathway and the alternative route of adenine metabolism to the extremely insoluble 2,8-dihydroxyadenine, which is operative when APRT is inactive. The alternative pathway is catalysed by xanthine oxidase.
Hypoxanthine-guanine phosphoribosyltransferase (HPRT, EC 2.4.2. 8)

HGPRT catalyses the transfer of the phosphoribosyl moiety of PP-ribose-P to the 9 position of the purine ring of the bases hypoxanthine and guanine to form inosine monophosphate (IMP) and guanosine monophosphate (GMP) respectively.

HGPRT is a cytoplasmic enzyme present in virtually all tissues, with highest activity in brain and testes.
The salvage pathway of the purine bases, hypoxanthine and guanine, to IMP and GMP, respectively, catalysed by HGPRT (1) in the presence of PP-ribose-P. The defect in HPRT is shown.
The importance of HPRT in the normal interplay between synthesis and salvage is demonstrated by the biochemical and clinical consequences associated with HPRT deficiency.

Gross uric acid overproduction results from the inability to recycle either hypoxanthine or guanine, which interrupts the inosinate cycle producing a lack of feedback control of synthesis, accompanied by rapid catabolism of these bases to uric acid. PP-ribose-P not utilized in the salvage reaction of the inosinate cycle is considered to provide an additional stimulus to de novo synthesis and uric acid overproduction.
The defect is readily detectable in erythrocyte hemolysates and in culture fibroblasts.

HGPRT is determined by a gene on the long arm of the x-chromosome at Xq26.

The disease is transmitted as an X-linked recessive trait.

Lesch-Nyhan syndrome

Allopurinal has been effective reducing concentrations of uric acid.
Phosphoribosyl pyrophosphate synthetase superactivity

Phosphoribosyl pyrophosphate synthetase (PRPS, EC 2.7.6.1) catalyses the transfer of the pyrophosphate group of ATP to ribose-5-phosphate to form PP-ribose-P.

The enzyme exists as a complex aggregate of up to 32 subunits, only the 16 and 32 subunits having significant activity. It requires Mg$^{2+}$, is activated by inorganic phosphate, and is subject to complex regulation by different nucleotide end-products of the pathways for which PP-ribose-P is a substrate, particularly ADP and GDP.
PP-ribose-P acts as an allosteric regulator of the first specific reaction of de novo purine biosynthesis, in which the interaction of glutamine and PP-ribose-P is catalysed by amidophosphoribosyl transferase, producing a slow activation of the amidotransferase by changing it from a large, inactive dimer to an active monomer.

Purine nucleotides cause a rapid reversal of this process, producing the inactive form.

Variant forms of PRPS have been described, insensitive to normal regulatory functions, or with a raised specific activity. This results in continuous PP-ribose-P synthesis which stimulates de novo purine production, resulting in accelerated uric acid formation and overexcretion.
The role of PP-ribose-P in the de novo synthesis of IMP and adenosine (AXP) and guanosine (GXP) nucleotides, and the feedback control normally exerted by these nucleotides on de novo purine synthesis.
Purine nucleotides are a class of compounds that are involved in various metabolic processes. One of the enzymes that play a crucial role in this process is Purine nucleoside phosphorylase (PNP). This enzyme catalyzes the degradation of nucleosides, such as inosine and guanosine, and their deoxyanalogues to their corresponding bases.

The mechanism of PNP is essentially a reversible reaction, but base formation is favored because intracellular phosphate levels usually exceed those of either ribose-1-phosphate or deoxyribose-1-phosphate.

Although this is essentially a reversible reaction, base formation is favored because intracellular phosphate levels normally exceed those of either ribose-1-phosphate or deoxyribose-1-phosphate. Thus, PNP plays a vital role in the 'inosinate cycle' of the purine salvage pathway and has a wide tissue distribution.

Purine nucleotide phosphorylase deficiency is a genetic disorder associated with the inability of the body to properly degrade nucleosides, leading to accumulation of toxic purine nucleotides in T and B cells.
The necessity of purine nucleoside phosphorylase (PNP) for the normal catabolism and salvage of both nucleosides and deoxynucleosides, resulting in the accumulation of dGTP, exclusively, in the absence of the enzyme, since kinases do not exist for the other nucleosides in man. The lack of functional HGPRT activity, through absence of substrate, in PNP deficiency is also apparent.
Disorders of pyrimidine metabolism
Hereditary orotic aciduria

The UMP synthase (UMPS) complex, a bifunctional protein comprising the enzymes orotic acid phosphoribosyltransferase (OPRT) and orotidine-5'-monophosphate decarboxylase (ODC), which catalyse the last two steps of the de novo pyrimidine synthesis, resulting in the formation of UMP. Overexcretion formation can occur by the alternative pathway indicated during therapy with ODC inhibitors.
Dihydropyrimidine dehydrogenase (DHPD) is responsible for the catabolism of the end-products of pyrimidine metabolism (uracil and thymine) to dihydrouracil and dihydrothymine. A deficiency of DHPD leads to accumulation of uracil and thymine. Dihydropyrimidine amidohydrolase (DHPA) catalyses the next step in the further catabolism of dihydrouracil and dihydrothymine to amino acids. A deficiency of DHPA results in the accumulation of small amounts of uracil and thymine together with larger amounts of the dihydroderivatives.
CDP-choline phosphotransferase catalyses the last step in the synthesis of phosphatidyl choline. A deficiency of this enzyme is proposed as the metabolic basis for the selective accumulation of CDO-choline in the erythrocytes of rare patients with an unusual form of haemolytic anaemia.
Disorders of protein metabolism
WHAT IS TYROSINEMIA?

Hereditary tyrosinemia is a genetic inborn error of metabolism associated with severe liver disease in infancy. The disease is inherited in an autosomal recessive fashion which means that in order to have the disease, a child must inherit two defective genes, one from each parent. In families where both parents are carriers of the gene for the disease, there is a one in four risk that a child will have tyrosinemia.

About one person in 100,000 is affected with tyrosinemia globally.
HOW IS TYROSINEMIA CAUSED?

Tyrosine is an amino acid which is found in most animal and plant proteins. The metabolism of tyrosine in humans takes place primarily in the liver.

Tyrosinemia is caused by an absence of the enzyme fumarylacetoacetate hydrolase (FAH) which is essential in the metabolism of tyrosine. The absence of FAH leads to an accumulation of toxic metabolic products in various body tissues, which in turn results in progressive damage to the liver and kidneys.
WHAT ARE THE SYMPTOMS OF TYROSINEMIA?

The clinical features of the disease ten to fall into two categories, acute and chronic.

In the so-called acute form of the disease, abnormalities appear in the first month of life. Babies may show poor weight gain, an enlarged liver and spleen, a distended abdomen, swelling of the legs, and an increased tendency to bleeding, particularly nose bleeds. Jaundice may or may not be prominent. Despite vigorous therapy, death from hepatic failure frequently occurs between three and nine months of age unless a liver transplantation is performed.

Some children have a more chronic form of tyrosinemia with a gradual onset and less severe clinical features. In these children, enlargement of the liver and spleen are prominent, the abdomen is distended with fluid, weight gain may be poor, and vomiting and diarrhoea occur frequently. Affected patients usually develop cirrhosis and its complications. These children also require liver transplantation.
Methionine synthesis

\[ \text{N}^5\text{-Methyl-H}_4\text{folate} + \text{Homocysteine} \xrightarrow{\text{Methionine synthase}} \text{Methionine} + \text{H}_4\text{folate} \]

\[ \text{H}_4\text{folate accepts methyl groups in a number of different reactions and is converted back to N}^5\text{-Methyl-H}_4\text{folate} \]
Homocystinuria

Cystathionine Synthase

methionine → S-adenosyl-methionine (SAM)

THF → N\(^5\)-methyl-THF

Cystathionine Synthase

Cystathionine

Homocysteine → S-adenosyl-homocysteine

Cysteine
Homocystinuria

MAJOR PHENOTYPIC EXPRESSION
Ectopia lentis, vascular occlusive disease, malar flush, osteoporosis, accumulation of homocystine and methionine and defective activity of cystathionine synthase.

Methionine $\rightarrow$ S-Adenosylmethionine

$\text{S-Adenosylhomocysteine} \rightarrow \text{S-Adenosylhomocysteine}$

$\text{NH}_2 \text{HOOCCHCH}_2\text{CH}_2\text{SH} + \text{HOCH}_2\text{CHCOOH}$

$\text{NH}_2 \text{HOOCCHCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{CHCOOH}$

Cystathionine Synthase

$\text{H}_2\text{O}$

$\text{NH}_2 \text{HOOCCHCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{CHCOOH}$

Homocystine

氨酸
Fig. 21.2  M.G., a 6-year-old boy with homocystinuria. He had short stature and genu valgum.

Fig. 21.3  Closer view illustrates M.G.'s eyes. Subluxed lenses had previously been removed bilaterally, after which he developed glaucoma in the left eye. He had fair skin and hair and a pronounced malar flush.

Fig. 21.4  The dislocated lens in homocystinuria is usually downward, while in Marfan syndrome it is upward.
Phenylketonuria

Phenylalanine Hydroxylase

Phenylalanine $\rightarrow$ tyrosine

$\text{NH}_3^+\text{CH}_2\text{CH-COO}^-\text{NH}_3^+$

$\text{O}_2 + \text{tetrahydrobiopterin} \rightarrow \text{H}_2\text{O} + \text{dihydrobiopterin}$

$\text{HO-CH}_2\text{CH-COO}^-\text{NH}_3^+$

Phenylalanine Hydroxylase

7,8-dihydrobiopterin

Glu

His

His

PDB 1DMW

Phenylalanine Hydroxylase
Phenylketonuria

(Klug & Cummings 1997)
Fig. 19.1 Metabolism of phenylalanine. The site of the defect in PKU is in phenylalanine hydroxylase. The compounds which accumulate as a consequence of the block are shown below.

Fig. 19.2 A positive ferric chloride test in a patient with untreated PKU.
Fig. 19.5 B.A. and L.A. Severely retarded, institutionalized brothers with untreated PKU. They were quite fair of hair and skin.
**Fig. 19.3** The face of this patient with PKU illustrates the rather subtle eczematoid rash. The brown eyes remind us that not all patients with this disease have blue eyes. In addition, he had epicanthal folds and a left internal strabismus.

**Fig. 19.4** L.S. This patient was diagnosed as having PKU at 10 months of age. The eyes were blue, the skin fair and the hair blond.
Maple syrup urine disease

MAJOR PHENOTYPIC EXPRESSION

Overwhelming illness in the first days of life with lethargy progressive to coma, opisthotonus, and convulsions; recurrent episodes leading to developmental delay; characteristic maple syrup odor, branched-chain aminoacidemia and aminoaciduria; branched-chain oxoaciduria; deficiency of branched-chain ketoacid dehydrogenase.
Alkaptonuria

(Klug & Cummings 1997)
Albinism

1. Phenylalanine $\xrightarrow{\text{Transaminase}}$ Phenylpyruvate (Phenylketone)
2. Phenylalanine $\xrightarrow{\text{Hydroxylase}}$ Deficient in Phenylketonuria
3. Phenylalanine $\xrightarrow{\text{Deficient in Phenylketonuria}}$ Tyrosine $\xrightarrow{\text{Multiple Reactions}}$ Melanins
4. Tyrosine $\xrightarrow{\text{Multiple Reactions}}$ Fumarate + Acetoacetate
Albinism

(Klug & Cummings 1997)
Disorders of carbohydrate metabolism
Pyruvate kinase (PK) deficiency:

This is the next most common red cell enzymopathy after G6PD deficiency, but is rare. It is inherited in an autosomal recessive pattern and is the commonest cause of the so-called "congenital non-spherocytic haemolytic anaemias" (CNSHA).

PK catalyses the conversion of phosphoenolpyruvate to pyruvate with the generation of ATP. Inadequate ATP generation leads to premature red cell death.

There is considerable variation in the severity of haemolysis. Most patients are anaemic or jaundiced in childhood. Gallstones, splenomegaly and skeletal deformities due to marrow expansion may occur. Aplastic crises due to parvovirus have been described.
Phosphoglycerate Kinase and Pyruvate Kinase Function in the Breakdown of Glucose to Pyruvate in Glycolysis and in the Substrate Level Production of ATP

1,3-Bisphosphoglycerate → 3-Phosphoglycerate

Phosphoglycerate Kinase (PGK)

ADP → ATP

Phosphoenolpyruvate → Pyruvate

Pyruvate Kinase (PK)

ADP → ATP

Hereditary hemolytic anemia
Phosphoenolpyruvate + ADP → Pyruvate + ATP

Pyruvate Kinase
Blood film: PK deficiency:

Characteristic "prickle cells" may be seen.
Glycogen storage disease

Glucose (6C) → Glycogen → Pyruvate (3C) → Acetyl-CoA (2C) → Fat → CO₂ and Energy
Case Description

A female baby was delivered normally after an uncomplicated pregnancy. At the time of the infant’s second immunization, she became **fussy** and was seen by a pediatrician, where examination revealed an **enlarged liver**. The baby was referred to a gastroenterologist and later diagnosed to have **Glycogen Storage Disease Type IIIB**.
## Glycogenoses

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Affected Tissue</th>
<th>Enzyme</th>
<th>Inheritance</th>
<th>Gene</th>
<th>Chromosome</th>
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<tr>
<td>Type 0</td>
<td>Liver</td>
<td>Glycogen synthase</td>
<td>AR</td>
<td>GYS2[^{125}]</td>
<td>12p12.2[^{121}]</td>
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<td>Type IA</td>
<td>Liver, kidney, intestine</td>
<td>Glucose-6-phosphatase</td>
<td>AR</td>
<td>G6PC[^{96}]</td>
<td>17q21[^{13}][^{94}]</td>
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<td>Liver</td>
<td>Glucose-6-phosphate transporter (T1)</td>
<td>AR</td>
<td>G6PT1[^{57}][^{104}]</td>
<td>11q23[^{2}][^{81}][^{104}][^{155}]</td>
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<tr>
<td>Type IC</td>
<td>Liver</td>
<td>Phosphate transporter</td>
<td>AR</td>
<td>-</td>
<td>11q23.3-24.2[^{49}][^{135}]</td>
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<td>Type IIIA</td>
<td>Liver, muscle, heart</td>
<td>Glycogen debranching enzyme</td>
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<td>AGL</td>
<td>1p21[^{173}]</td>
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<tr>
<td>Type IIIB</td>
<td>Liver</td>
<td>Glycogen debranching enzyme</td>
<td>AR</td>
<td>AGL</td>
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<td>Type IV</td>
<td>Liver</td>
<td>Glycogen phosphorylase</td>
<td>AR</td>
<td>PYGL[^{26}]</td>
<td>14q21-22[^{118}]</td>
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<td>Type IX</td>
<td>Liver, erythrocytes, leukocytes</td>
<td>Liver isoform of α-subunit of liver and muscle phosphorylase kinase</td>
<td>X-Linked</td>
<td>PHKA2</td>
<td>Xp22.1-p22.2[^{40}][^{68}][^{162}][^{165}]</td>
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<td>Liver, muscle, erythrocytes, leukocytes</td>
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<td>PHKB</td>
<td>16q12-q13[^{54}]</td>
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<td>Testis/liver isoform of γ-subunit of PK</td>
<td>AR</td>
<td>PHKG2</td>
<td>16p11.2-p12.1[^{28}][^{101}]</td>
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Glycogen
Glycogen Storage Diseases

- Type I
- Type II
- Type IV
- Type VII

Diagram showing metabolic pathways related to glycogen storage diseases, with enzymes and substrates labeled.
Glycogen Storage Disease Type IIIb

- Deficiency of debranching enzyme in the liver needed to completely break down glycogen to glucose
- **Hepatomegaly** and hepatic symptoms
  - Usually subside with age
- **Hypoglycemia**, hyperlipidemia, and elevated liver transaminases occur in children
GSD Type III
Debranching Enzyme

- Amylo-1,6-glucosidase
  - Isoenzymes in liver, muscle and heart
  - Transferase function
  - Hydrolytic function
Genetic Hypothesis

- The two forms of GSD Type III are caused by different mutations in the same structural Glycogen Debranching Enzyme gene.
Amylo-1,6-Glucosidase Gene

- The gene consists of 35 exons spanning at least 85 kbp of DNA
- The transcribed mRNA consists of a 4596 bp coding region and a 2371 bp non-coding region
- Type IIIa and IIIb are identical except for sequences in non-translated area
- The tissue isoforms differ at the 5’ end
Inborn errors of metabolism

Autosomal recessive disorder

Incidence estimated to be between 1:50,000 and 1:100,000 births per year in all ethnic groups

Herling and colleagues studied incidence and frequency in British Columbia

— 2.3 children per 100,000 births per year
Inheritance

- Single variant in North African Jews in Israel shows both liver and muscle involvement (GSD IIIa)
  - Incidence of 1:5400 births per year
  - Carrier frequency is 1:35
Inheritance

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</table>

GG = normal
Gg = carrier
Gg = GSD

Both parents are carriers in the case.
Inheritance

- **normal**
- **carrier**
- **GSD**

```
  O  X
    |   |
    |   |
    O  O
    |   |
  O  X
```

“Baby”
Clinical Features

Common presentation

• Hepatomegaly and fibrosis in childhood
• Fasting hypoglycemia (40-50 mg/dl)
• Hyperlipidemia
• Growth retardation
• Elevated serum transaminase levels
  (aspartate aminotransferase and alanine aminotransferase > 500 units/ml)
Clinical Features

Less Common

- Splenomegaly
- Liver cirrhosis
Galactosemia

Galactosemia is an inherited disorder that affects the way the body breaks down certain sugars. Specifically, it affects the way the sugar called galactose is broken down. Galactose can be found in food by itself. A larger sugar called lactose, sometimes called milk sugar, is broken down by the body into galactose and glucose. The body uses glucose for energy. Because of the lack of the enzyme (galactose-1-phosphate uridyl transferase) which helps the body break down the galactose, it then builds up and becomes toxic. In reaction to this build up of galactose the body makes some abnormal chemicals. The build up of galactose and the other chemicals can cause serious health problems like a swollen and inflamed liver, kidney failure, stunted physical and mental growth, and cataracts in the eyes. If the condition is not treated there is a 70% chance that the child could die.
If a galactosemic infant is given milk, unmetabolized milk sugars build up and damage the liver, eyes, kidneys and brain.
Fatty acid oxidation defects
Lysosomal storage diseases

The pathways are shown for the formation and degradation of a variety of sphingolipids, with the hereditary metabolic diseases indicated.

Note that almost all defects in sphingolipid metabolism result in mental retardation and the majority lead to death. Most of the diseases result from an inability to break down sphingolipids (e.g., Tay-Sachs, Fabry's disease).
Report (Lab examination) only 1 page

(mechanisms, clinical correlation, lab investigations, treatments)

**Topic**

1. Tay-Sachs disease
2. Fabry’s disease
3. Gaucher’s disease
4. Farber’s disease
5. Krabbe’s disease
6. Nieman-pick disease
7. Metachromatic leukodystrophy