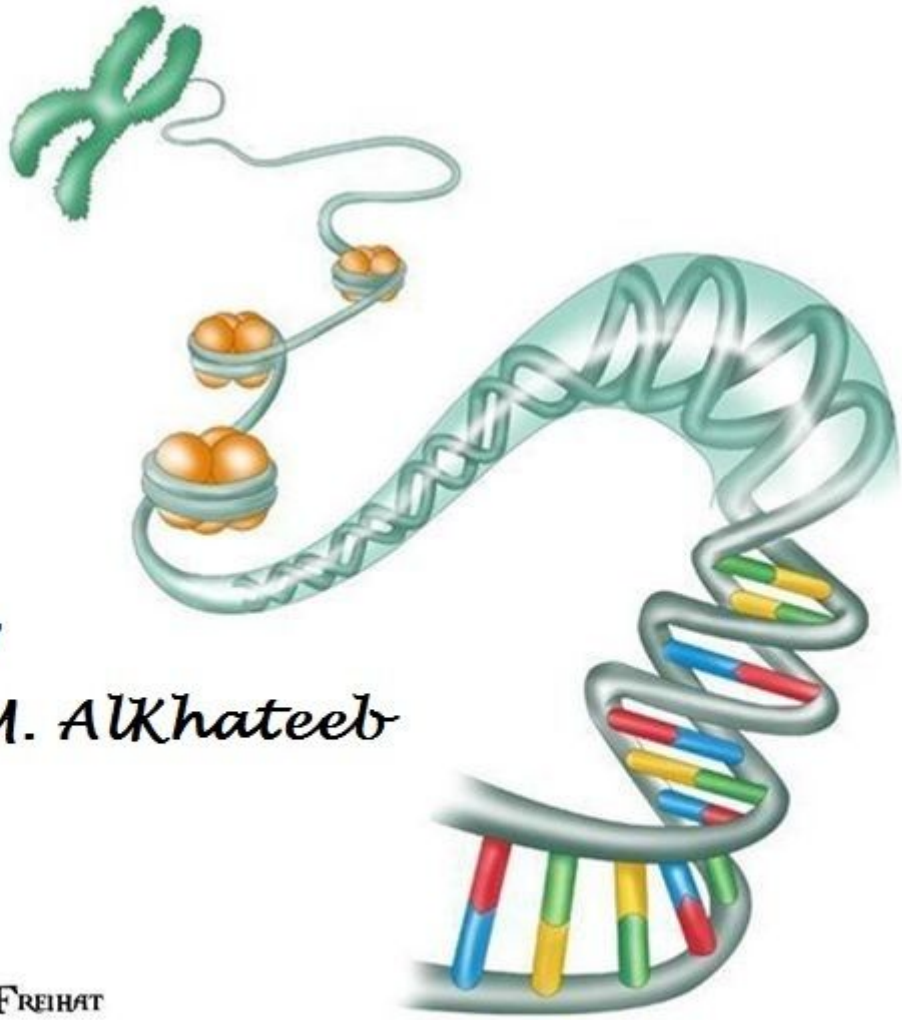
University of Jordan
Faculty of Medicine
Batch 2013-2019

Medical Committee
The University of Jordan

Genetics & Molecular Biology

● Slides ○ Sheet ○ Handout ○ other.....



Lecture: 7

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Inborn Error Of Metabolism

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MGL-8

April 26th 2015

Inborn Error Of Metabolism
Definition of IEM

Group of congenital disorders caused by an inherited defect in a single specific enzyme that results in a disruption or abnormality in a specific metabolic pathway

IEM's in General

- Mostly due to defect in or absence of an enzyme, cofactor or transport protein resulting a block in a specific metabolic pathway
- Generally single gene defects
  - Involve all inheritance patterns, however, most common is autosomal recessive
- Common defects on a biochemical level
  - Transport defects
  - Accumulation of substrate
  - Deficiency of product
  - Secondary inhibition

IEM's in General

- Individually-very rare, Collectively-very common
- Generally present in newborn period or shortly thereafter
  - Typically at end of 1st week of life
  - This will be the focus of this talk
- Key to finding IEM's is not a detailed knowledge of biochemical pathways, but a HIGH INDEX OF SUSPICION in any critically ill neonate

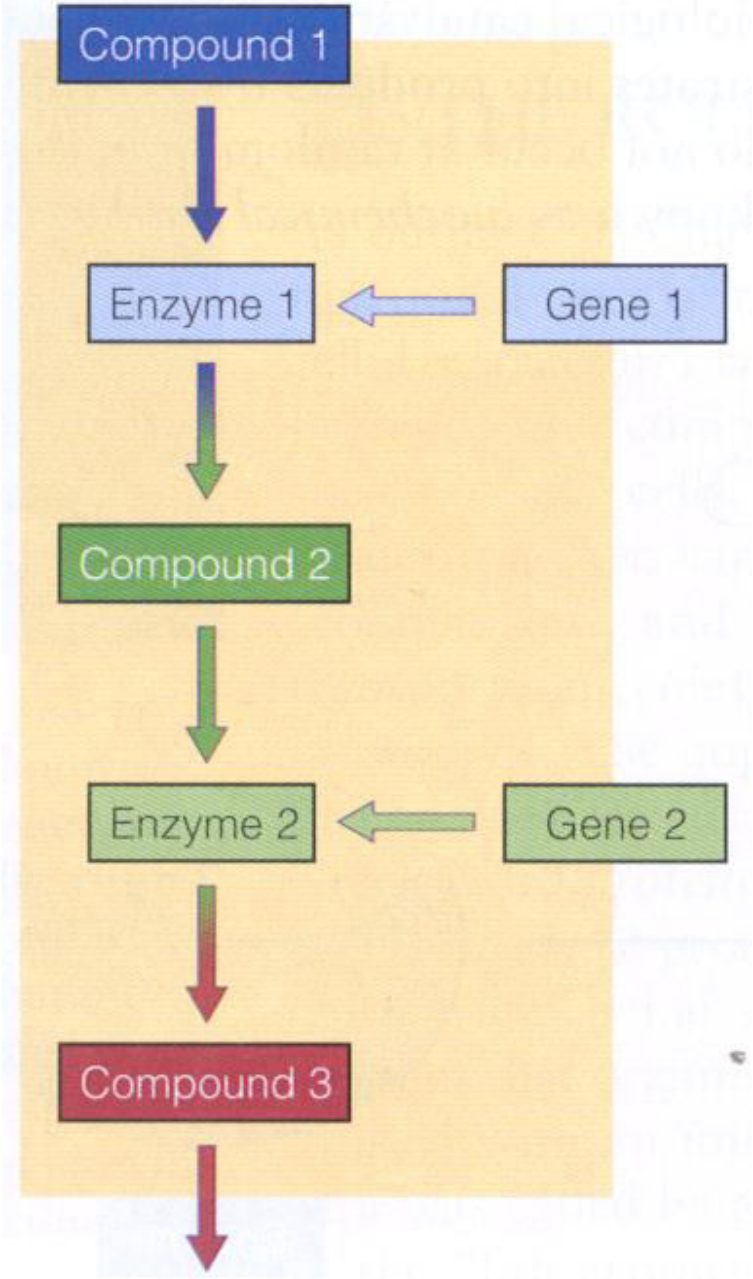
Basic Principles:

- Although individually rare, altogether they are 1:800-5000 incidence.
- Broadly Defined: An inherent deficiency in a key metabolic pathway resulting in
  - Cellular Intoxication
  - Energy deprivation
  - Mixture of the two

METABOLISM

- Metabolism → Catabolism (Breaking down)
  → Anabolism (Building up)

- Enzymes play an important role in facilitating the process by serving as catalysts in the conversion of one chemical (metabolite) to another.



- **Chemical Individuality**

  Garrod 20th Century

  Developed "Inborne Error of Metabolism"

- **Beadle & Tatum**

  Developed one gene one enzyme concept

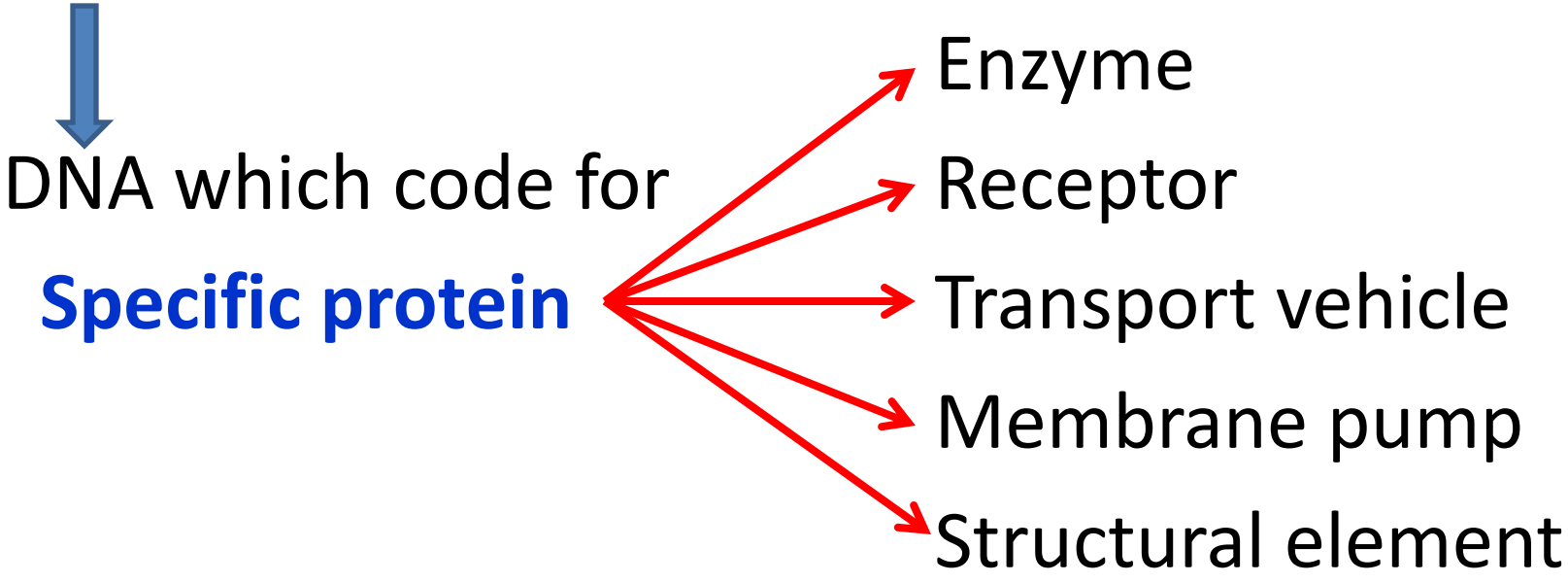
Inborn Errors Overview

General mechanism of problems

- Substrate accumulates to toxic levels
- Toxic byproducts produced from shunting of accumulated substrate
- Deficiency of end product
- Poor regulation results in overproduction of intermediates to toxic level

Inborn Errors Overview

- IEM are disorders in which there is a block at some point in the normal metabolic pathway
- IEMs occur due to mutations in DNA



BASIC IDEA,,,

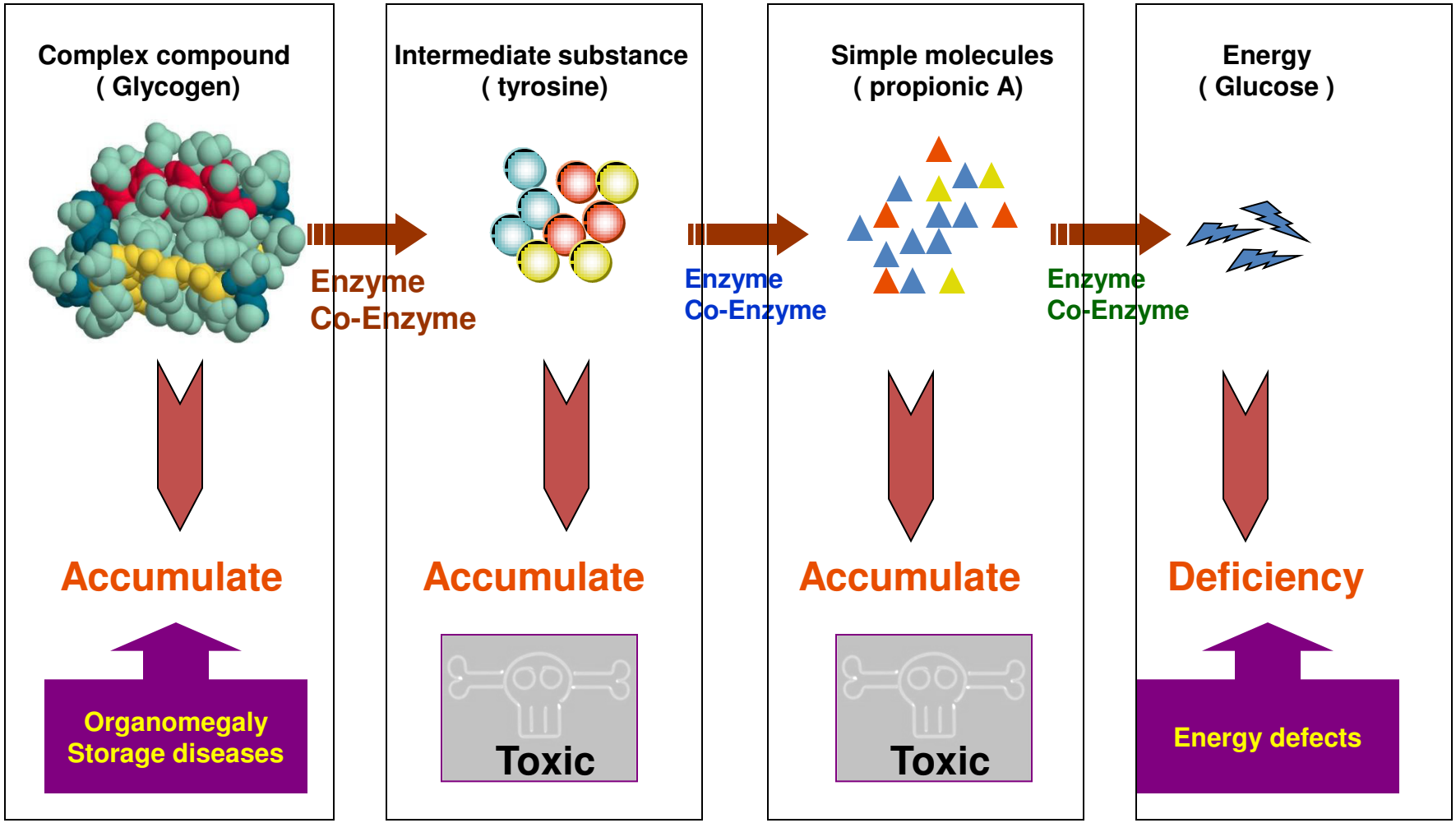
Protein

Sugar

Lipids

- Need factors to break them
- Need close interactions
- Excess is like deficiency

BASIC IDEA,,,


Complex compound
(Glycogen)
Enzyme
Co-Enzyme
Intermediate substance
(tyrosine)
Enzyme
Co-Enzyme
Simple molecules
(propionic A)
Enzyme
Co-Enzyme
Energy
(Glucose)
Accumulate
Accumulate
Accumulate
Deficiency
Organomegaly
Storage diseases
Toxic
Toxic
Energy defects

What is a metabolic disease?

Small molecule disease

- Carbohydrate
- Protein
- Lipid
- Nucleic Acids

Organelle disease

- Lysosomes
- Mitochondria
- Peroxisomes
- Cytoplasm

Types of Inborn Errors

- Protein Disorders
  - Amino Acid
  - Organic
  - Urea Cycle
- Carbohydrate Disorders
  - Galactose, Glucose transport, Glycogen, Fructose
- Fatty Acid Disorders
  - Medium chain acyl-CoA dehydrogenase def.
  - Long chain 3 hydroxycayl-CoA dehydrogenase def.

GENETIC CHARACTERISTIC AND MODE OF INHERITANCE

- IEM are usually Autosomal recessive.
- Consanguinity is always relatively common.
- Some are x-linked recessive condition including:
  - Adrenoleukodystrophy.
  - Agammaglobulinemia.
  - Fabry's disease.
  - Granulomatous disease.
  - Hunter's Syndrome.
  - Lesch – Nyhan Syndrome.
  - Menke's Syndrome.
- A few inherited as Autosomal dominant trait including:

  porphyria, hyperlipedemia, hereditary angioedema.

Inborn Errors of Carbohydrate Metabolism

Carbohydrates are important energy stores, fuels and metabolic intermediates

- Galactosaemia
- Hereditary fructose intolerance
- Glucose-6-phosphate dehydrogenase deficiency
- Glycogen storage diseases
- Pyruvate carboxylase deficiency
- Fructose-1,6-bisphophatase deficiency

Galactosemia

- Results from a disturbance in the conversion of galactose to glucose
- The enzyme deficiency causes an accumulation of galactose in body tissues
- Classic type lacks Galactose-1-phosphate uridyl transferase (GALT)
  - Galactokinase (GALK) deficiency results in infantile cataracts from accumulation of galacticol
  - Galactose epimerase (GALE) deficiency mostly confined to blood cells and most appear normal
- Estimated incidence 1/50,000 births

Galactosemia:

- First 1-2 wks of Life: Presents with hypoglycemia, jaundice, emesis.
- Secondary to intolerance of Galactose. Will be in baby's first meals of breast milk or lactose containing formulas.
- Also index of suspicion for Gram Neg or E.coli sepsis.
- Dx assisted by Non-glucose reducing substances in urine.
- Confirmation by Galactose-1-PO uridyl transferase activity in RBCs.
- Adverse sequelae include Cataracts, MR, persistent liver disease.

Metabolism of Galactose

Lactose

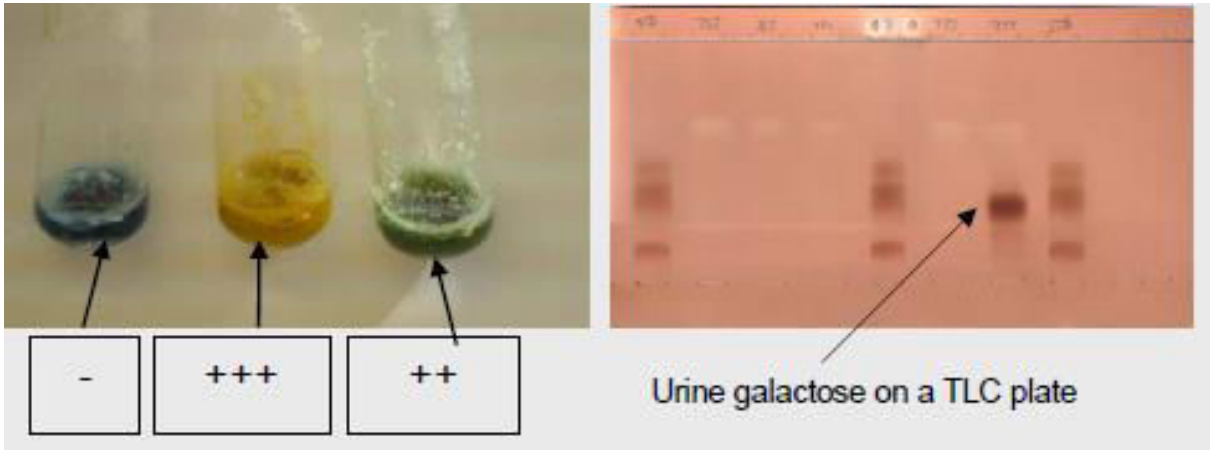
↓ Lactase

Galactose

↓ Galactokinase

Galactose-1phosphate → Glucose

Galactose -1 phosphate Uridyl transferase



Brain
MR

Liver
- Jaundice
- Hepatomegaly
- Cirrhosis

Eyes
Chataract

DISORDERS OF CH METABOLISM

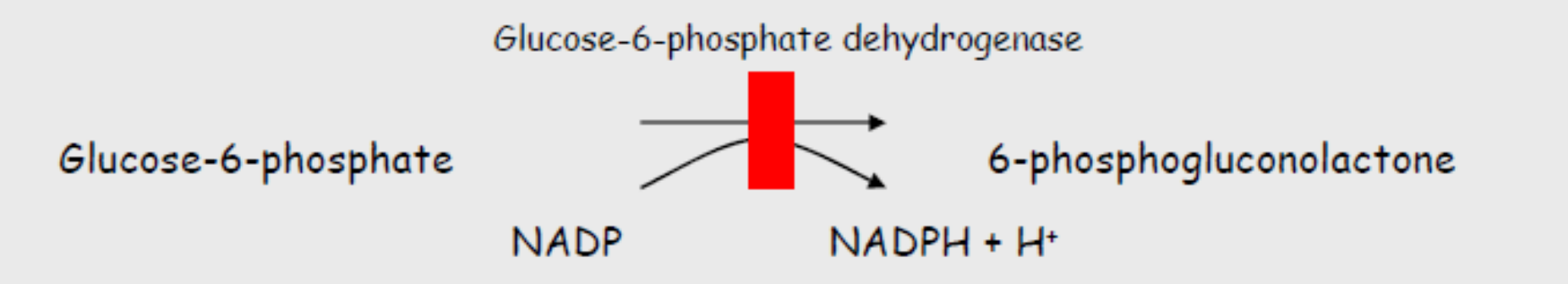
HEREDITARY FRUCTOSE INTOLERANCE:

Fructose 1 phosphate aldolase deficiency

- **Diagnosis**: Fructose in Urine + Enzyme in the intestine mucosa and liver bx
- **Clinical:** Mild to sever
- **Treatment:** Diet restriction

Glucose-6-phosphate dehydrogenase deficiency

- **This is an X-linked defect** , irreversible step of the pentose phosphate pathway.



- Female heterozygotes may have symptoms but the severity varies due to non-random X chromosome inactivation)
- The highest frequency is in Mediterranean, Asian and Africans

Glucose-6-phosphate dehydrogenase deficiency

- The most common manifestations are early neonatal unconjugated jaundice and acute hemolytic anemia. ly clinically asymptomatic in general.
- The hemolytic crises are usually in response to an exogenous trigger such as certain drugs (e.g. antimalarials), food (broad beans) or an infection
- The diagnosis is by measurement of the enzyme activity in erythrocytes

Metabolic Storage Disorders

Types,

- Glycogen storage diseases (GSD)
- Mucopolysaccharidosis (MPS)
- Lysosomal storage diseases or lipidosis (LSD)
- Mucolipidosis
- Peroxisomal diseases

Glycogen Storage Diseases (GSD)

Uridine-Diphosphoglucose

1 **Glycogen synthetase**

Glycogen

Straight chains

2 **Brancher enzyme (GSD-IV)**

Glycogen

Branched structure

Limit dextrin+ Glucose-1-PO4

3 **Debrancher enzyme (GSD-III)**

Glycogen (normal branch) + Glucose

Glucose-1-PO4

4 **Glucose-6-phosphatase (GSD-1)**

Types

- Hepatic/ muscle involvement (GSD-III)
- Isolated Hepatic involvement (GSD-I, IV & VIII)
- Isolated muscle involvement (GSD-V & VII)
- Multiple tissues (GSD-II & IV)

Glycogen Storage Disorders:

- **Type 1= Von Gierke's:**
  - Shortly after birth: Severe lifethreatening Hypoglycemia
  - Lactic acidosis –due to isolated glycolysis of G6Po
  - Hyper-uricemia, hyper lipidemia
  - Increased association with epistaxis
  - *Hepatomegaly
  - **Adverse response to Glucagon with worsening Lactic acidosis
- Management requires IV glucose, and then as output, close NG corn-starch or glucose solution administration to achieve close to nl glucose homeostasis.
- Frequent snacks and meals. Continuous nighttime glucose infusions up to the age of 2.

Glycogen Storage Disorders:

- **Type 2- Pompe's disease:**
- Normal Glucose
- Do to an accumulation of glycogen in lysosomes.
- **Ancient city of Pompeii was destroyed by Mt. Vesuvius- 79 AD**
- Manifested by massive Cardiomegaly, Hepatomegaly, Macroglossia.
- Fatal If results in CHF.
- Limited therapies in Neonatal Variant.
  - Attempts at enzyme replacement ongoing.

Glycogen Storage Diseases

Disorder (approximate % GSD cases)*	Enzyme defect	Most affected tissue(s)	Clinical Features	Diagnostic tests	Sample
GSD II (Pompe's) (15%)	Lysosomal α1,4-glucosidase	Generalised; accumulation of glycogen in lysosomes	Infantile form: cardiomegaly, hypotonia; Juvenile & adult form: skeletal myopathy	Enzyme assay	Leucocytes (with inhibitor)
GSD III (24%)	Debranching enzyme	Liver & muscle (IIIa), liver only (IIIb); storage of large amounts of abnormal glycogen with short outer branches	Hepatomegaly, hypoglycaemia, hyperlipidaemia, growth retardation, muscle weakness	Enzyme assay (& red cell glycogen concentration)	Leucocytes
GSD IV (3.3%)	Branching enzyme	Liver; accumulation of glycogen with fewer branch points and longer chains (poor solubility)	Hepatosplenomegaly, failure to thrive, liver cirrhosis	Enzyme assay	Leucocytes

Glycogen Storage Diseases

Disorder	Enzyme defect	Most affected tissue(s)	Clinical Features	Diagnostic tests	Sample
GSD V McArdle's (2.4%)	Muscle phosphorylase	Muscle; Increased amount of glycogen (normal structure)	Exercise intolerance with muscle cramps	Mutation analysis for common mutations, Ischaemic lactate-ammonia test (and/or enzyme assay)	Blood DNA sample or Muscle biopsy for enzyme assay
GSD VI (see IX)	Liver phosphorylase	Liver; Increased amount of glycogen (normal structure)	Hepatomegaly, growth retardation, mild tendency to hypoglycaemia, mild hyperlipidaemia	Enzyme assay	Leucocytes
GSD VII (0.2%)	Phosphofructo kinase	Muscle, erythrocytes (excess glucose leads to increased formation of glycogen)	Exercise intolerance, haemolytic anaemia	Enzyme assay	Muscle biopsy
GSD IX (30% VI + IX)	Phosphorylase b kinase (defect in one of 4 subunits)	Liver and/or muscle	As for GSD VI (functional deficiency of phosphorylase)	Enzyme assay	Erythrocytes for X-linked liver form (muscle biopsy for muscle form)

Mucopolysaccharidsis

- Hetrogenous caused by reduced degradation of one or more of glycosminoglycans
  - Dermatan sulfate heparin sulfate
  - Keratan sulfate Chondritin sulfate
- MPS are the degradation products of proteoglycans found in the extracellular matrix
- 10 different enzyme deficienies
- **Diagnosis**
  - Clinical, Biochemical and Molecular analysis,
  - Meausrment of the enzyme in fibroblast, leukocytes, serum
  - Prenatal diagnosis on Amniocytes
  - Urine for MPS (heparan , keratan , dermatan)
- **Genetics:** All AR except Hunter syndrome X linked
- **Clinical:** Progressive multisystem deterioration causing:

Mucopolysaccharidsis

Symptoms & signs

- Developmental delay.
- Behavioral dysfunction
- Coarse facial features & other somatic features
- Cloudy cornea
- Abdominal distension (Hepatosplenomegaly)
- Dysostosis multiplex (Scoliosis and gibbous deformity)
- Hearing, Vision, Joint and Cardiovascular dysfunction

Types

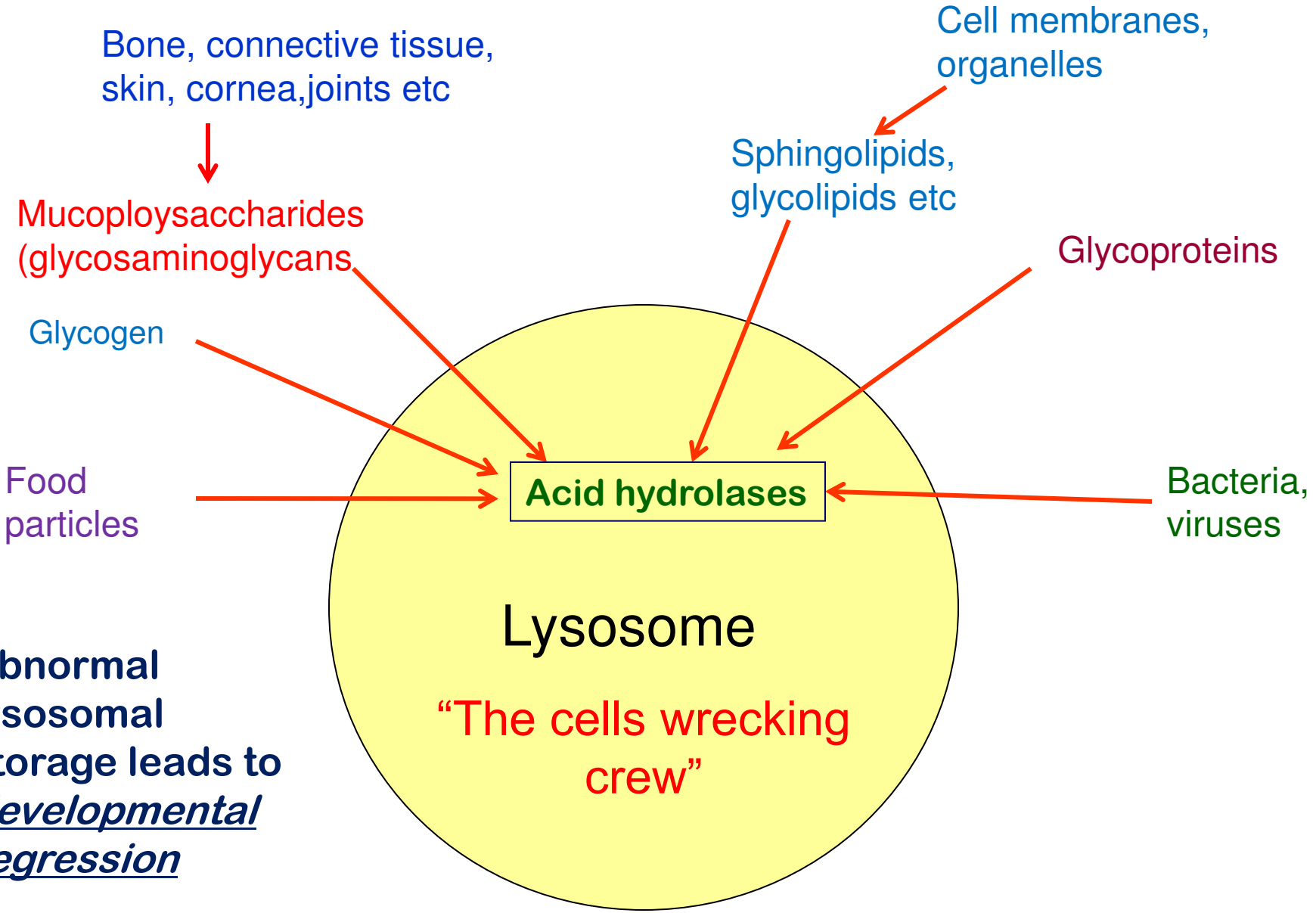
1. Hunter syndrome
2. Hurler syndrome
3. Scheie syndrome
4. Sanfilippo syndrome
5. Morquio disease
6. Maroteaux-Lamy syndrome

Diagnosis: Enzyme detection

1. α-idurondase
2. Iduronate Sulfatase
4. Heparan-N-Sulfatase
5. A:N-Galactosamine-6-sulfate sulfatase
5. B:β-glactosidase

Lysosomal Storage Disorders

- Resulted from accumulation of substrate
- Deficiency or inability to activate or to transport the Enzymes within lysosomes that catalyses stepwise the degradation of:
  - Sphingolipids
  - Glycoproteins
  - Glycolipids
- May be it is a result of genetic drift and natural selection
- Children normal at birth, downhill course of differing duration



Abnormal lysosomal storage leads to *developmental regression*

Lysosomal Disorders
Focus on key differences:

- **Gaucher Disease:**
  - Infantile vs chronic juvenile
  - Organomegaly
  - Bone pain
  - Easy bruisability
  - **low Plts, osteosclerosis, and lytic bone lesions
  - MNEUNOMIC= "Clumsy Gaucho cowboy"

- **Tay-Sachs Disease:**
  - Progressive neurologic degeneration in first YOL and death by age 4-5 yo
  - AR inheritance with classic Jewish Ashkenazi relationship.
  - Increased startle reflex
  - Cherry red macula
  - Macrocephaly

Sphingolipidoses

- **Tay-Sachs disease** **AR** **Hexosaminidase -A**
  - Developmental regression, Blindness,
  - Cherry-red spot, Deafness
- **Gaucher' s disease** **AR** **Glucosylcerarnide Type I**
  - Joint and limb pains, Splenomegaly

    β- Glucosidase Type II
  - Spasticity, fits; death
- **Niemann-Pick disease** **AR** **Sphingomyelinase**
  - Failure to thrive, Hepatomegaly
  - Cherry-red spot, Developmental

LIPIDOSES

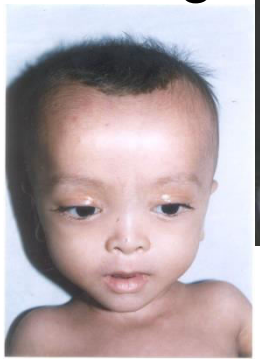
Disease	Enzyme
GM1 Gangliosidosis.	β - galactosidase
GM2 Tay –Sach.	Hexosamindase A
Sandhoff disease.	Hexosamindase A+B
Niemann – Pick disease.	Sphingomylinase
Gaucher's disease.	Acidic – β – Glucosidase
Metachromatic Leukodystrophy.	Arylsulfatase A Neuronal ceroid lipofuscinosis

Peroxisomal Disorders

Zellweger Syndrome Cerebro-hepato-renal syndrome

Clinical signs

- Typical and easily recognized dysmorphic facies.
- Progressive degeneration of Brain/Liver/Kidney, with death ~6 mo after onset.
- Hypotonic, seizures and poor feeding
- Distinctive facies.
- Retinal dystrophy,
- hearing loss, severe DD



Diagnosis

- Biochemical, serum Very Long Chain Fatty Acids- VLCFAs
- Gene test

DISORDERS OF AA METABOLISM

- PHENYLKETONURIA
- ALKAPTONURIA
- OCULOCUTANEOUS ALBINIS
- HOMOCYSTINURIA
- BRANCHED AMINOACIDS

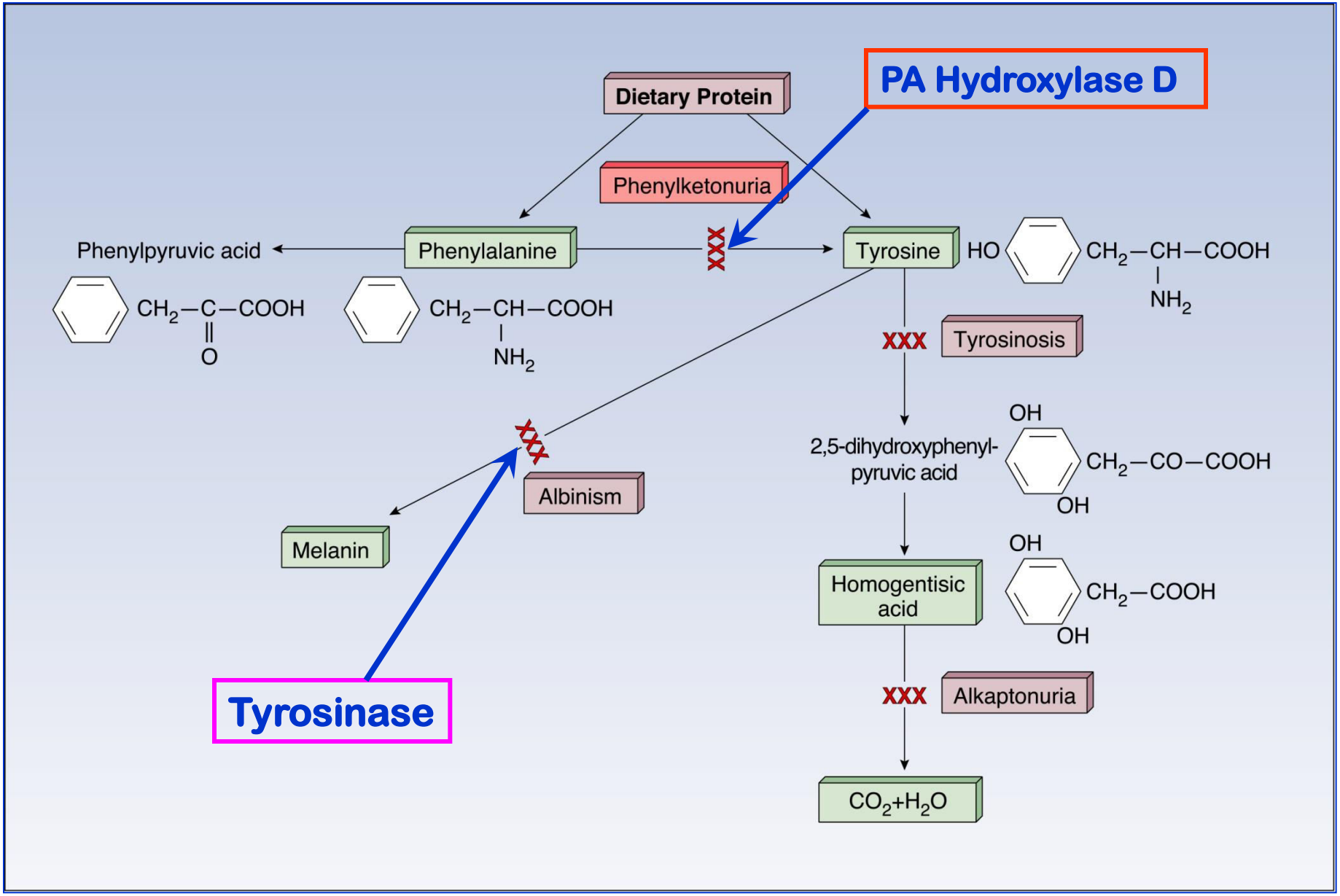
Amino Acidurias:

- Fresh Urine Uric acid and Sulfite Dipstick if neurologic abnormalities are present, low uric acid is suggestive for **molybdenum cofactor deficiency and Sulfite Oxidase Deficiency**.
- Don't forget **PKU**. Basic on newborn scrn, but only does good if results followed up.

Phenylketonuria (PKU):

- **Clinical features:** Development delay in infancy, ? neurological manifestations such as seizures. hyper activity, behavioral disturbances, hyperpigmentation and MR.
- **Incidence:** 1/5000 -1/16000.
- **Genetics:** AR, 12q22-q24, >70 mutations (17 exsons)
- **Basic Defect:** Mutation in the gene of PA hydroxylase.
- **Pathophysiology:** PA or derivatives cause damage in the developing brain
- **Treatment:** Dietary reduction of phenylalanine within 4W
- **Significance:** Inborn Metabolic disorder, The first Dietary restriction treatment. Mass screening of newborns

PHENYLKETONURIA



Types Of PKU

- **PAH Deficient** (97% of cases)
- **Non-PAH Deficient** (3% of cases)

→Defects in tetrahydrobiopterin or other components in related pathways

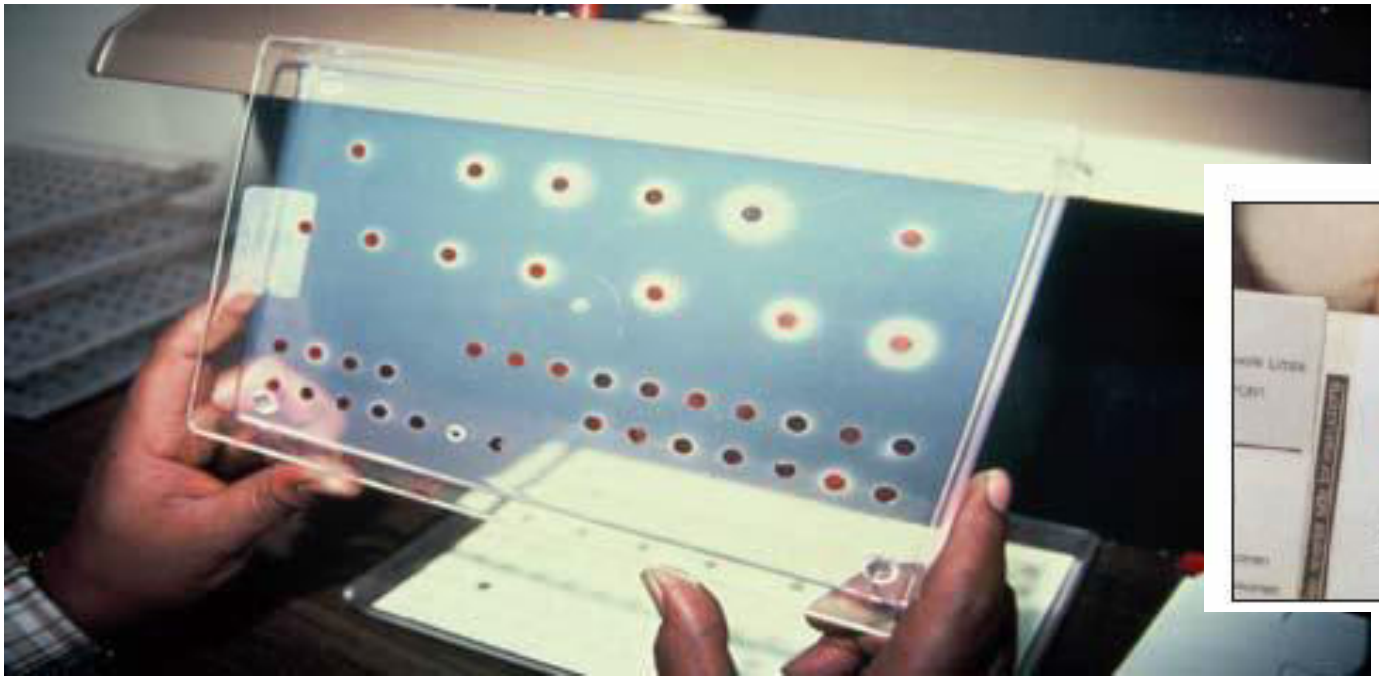
Dihydropteridin reductase or synthetase deficiency

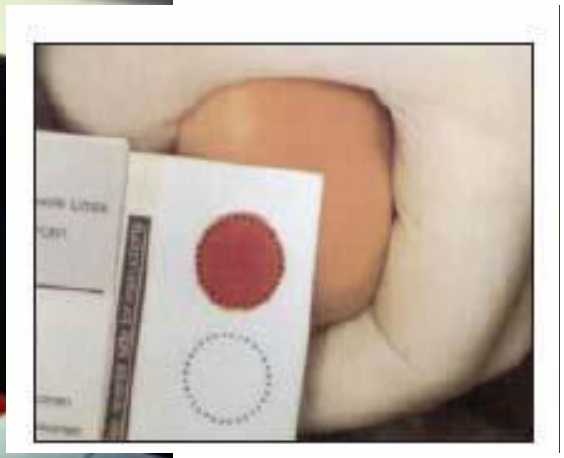
Diagnostic Criteria

- Normal: 120 – 360 umol/L
- PAH Deficient:
  - Mild: 600 – 1200 umol/L
  - Classical: > 1200 umol/L
- Non-PAH Deficient:
  - < 600 umol/L
- Guthrie Bacterial Inhibition Assay
- Confirmation of diagnosis, HPLC of Molecular

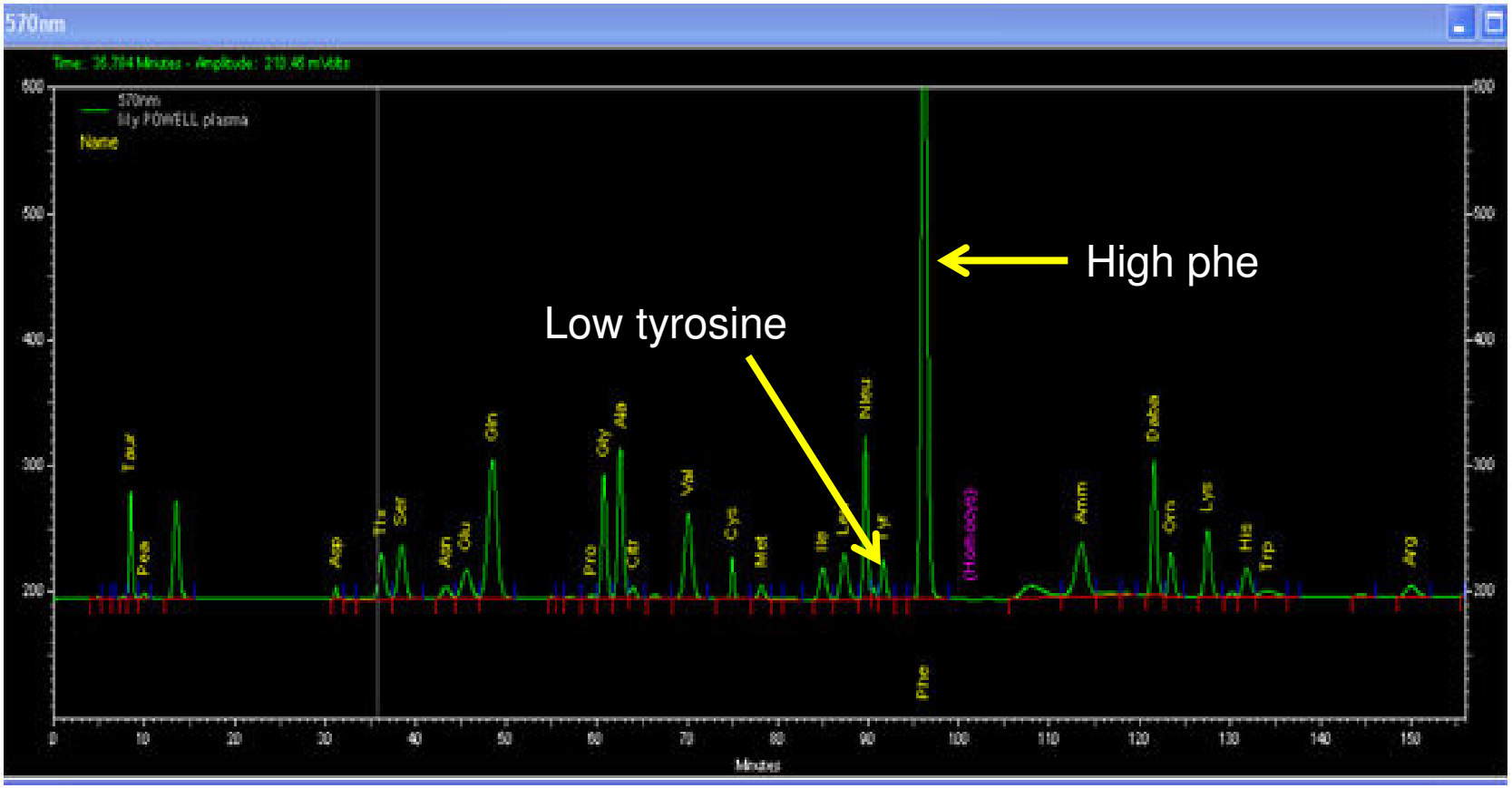
Guthrie Test--1961

1965 - Screening for PKU was mandated legislatively in most of the states in US





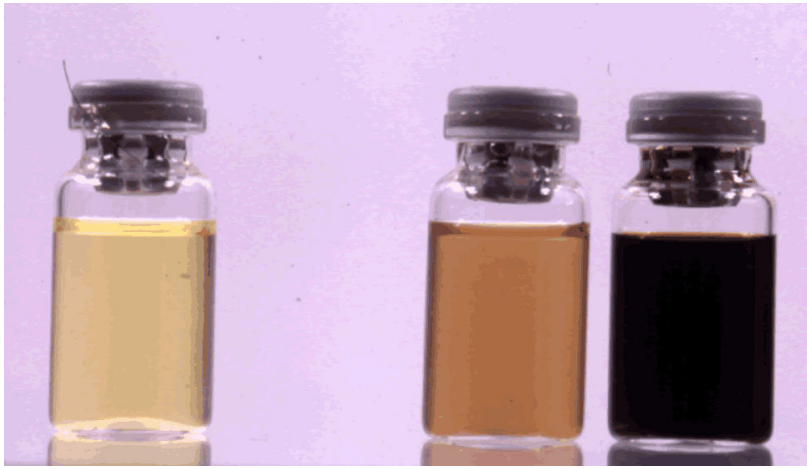
Plasma Amino Acid Profile, PKU



ALKAPTONURIA

- Autosomal Recessive described by Garrod
- Due to Homogenstic acid accumulation
- Excreted in Urine . Dark color in exposure to the air
- Dark pigment deposited in ear wax, cartilage and joints
- Deposition in joints known as Ochronosis in later life can lead to Arthritis

urine



Normal **alkaptonuria**

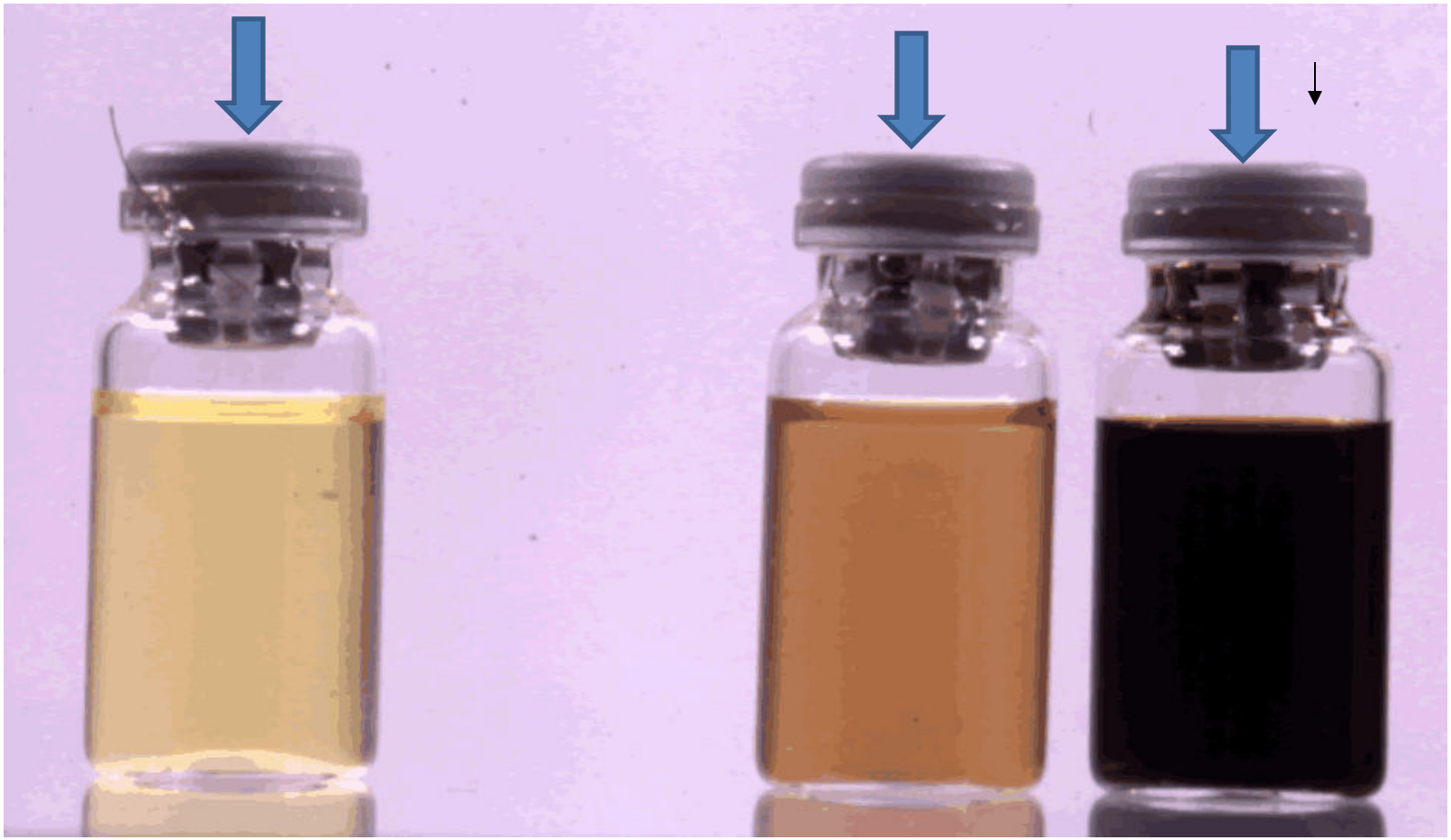
ALKAPTONURIA

- Autosomal Recessive described by Garrod
- Due to Homogenstic acid accumulation
- Excreted in Urine . Dark color in exposure to the air
- Dark pigment deposited in ear wax, cartilage and joints
- Deposition in joints known as Ochronosis in later life can lead to Arthritis

Symptoms of alkaptonuria

Normal urine

Urine from patients with alkaptonuria



Patients may display painless bluish darkening of the outer ears, nose and whites of the eyes. Longer term arthritis often occurs.

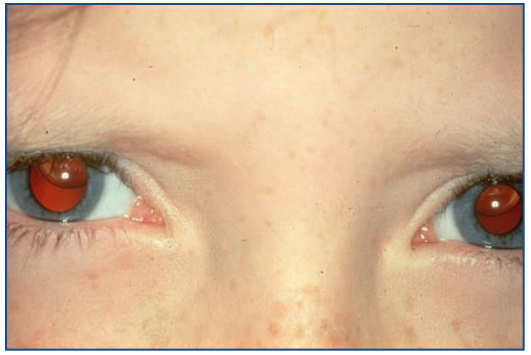
OCULOCUTANEOUS ALBINISM

- OCA is AR due to tyrosinase deficiency no melanine formation
- No pigment in skin, hair, iris and ocular fundus
- Nystagmus
- Genetically and bichemically heterogeneous
  - Classical tyrosinase negative
  - Tyrosinase positive, reduced enzyme level (type 1) OCA 1 located on chromosome11q.
  - OCA 2 on chromosome 15q (pink-eye)
  - Third loci OCA-3 not related to above mentioned

HOMOCYSTINURIA

Sulfur AA metabolism disorders due to Cystathionin β-synthetase

- **Clinically:** MR, fits, Thromboembolic episodes, Osteoporosis, tendency to lens dislocation, scoliosis, long fingers and toes
- **Diagnosis:** positive cyanide nitroprusside in urine confirmed by elevated plasma homocystine
- **Treatment:** diet with low methionine and cystine supplement
- Some are responsive to pyridoxine as
- a cofactor to the deficient enzyme



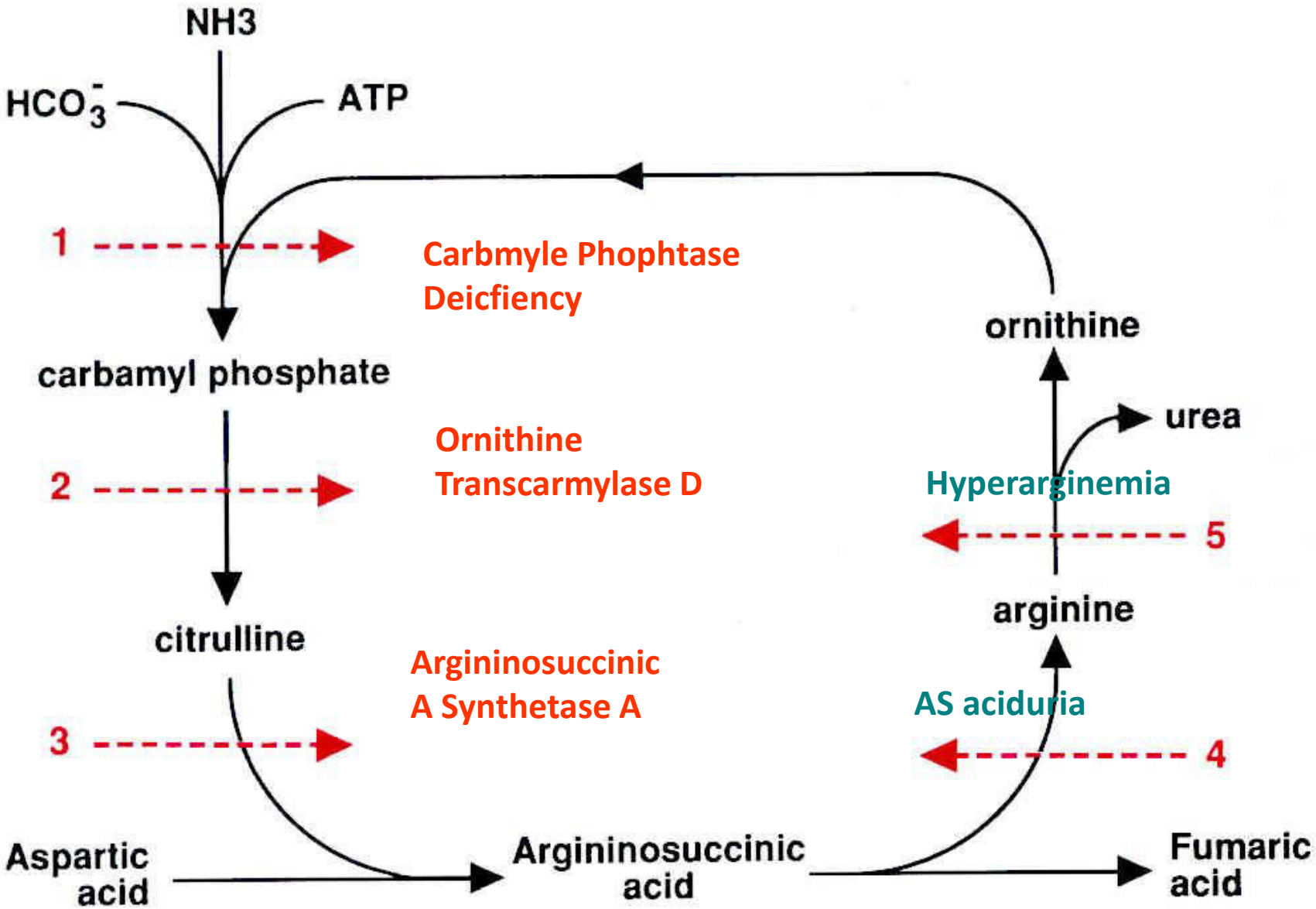
Branched Chain Amino Acids

- 40% of preformed AA used by mammalians are BCAA
  Valine, Leucine, Isoleuchin
- Energy supply through α-ketoacid decarboylase enzyme
- BCAA disease composed of 3 catalytic and 2 regulatory enzyme and encoded by 6 loci
- Deficiency in any one of these enzymes cause MSUD
- Untreated patients, accumulation of BCAAs cause neurodegeneration leads to death in the first few months of life
- Treatment BCAAs restriction diet
- Early detection
- Gene therapy ?????

UREA CYCLE DISORDERS

- **UC main function to prevent accumulation of N_2 waste as urea**
- **UC responsible for de novo arginine synthesis**
- **UC consists of 5 major biochemical reactions, defects in humans:**
  - Carpamyl phosphate synthetase (CPS), AR
  - Ornithin transcarbamylase (OTC), X-linked
  - Argininosuccinic acid synthatase (ASA),AR
  - Argininosuccinase (AS), AR
  - N-acetyl glutamate synthetae (NAGS).AR

UREA CYCLE DISORDERS



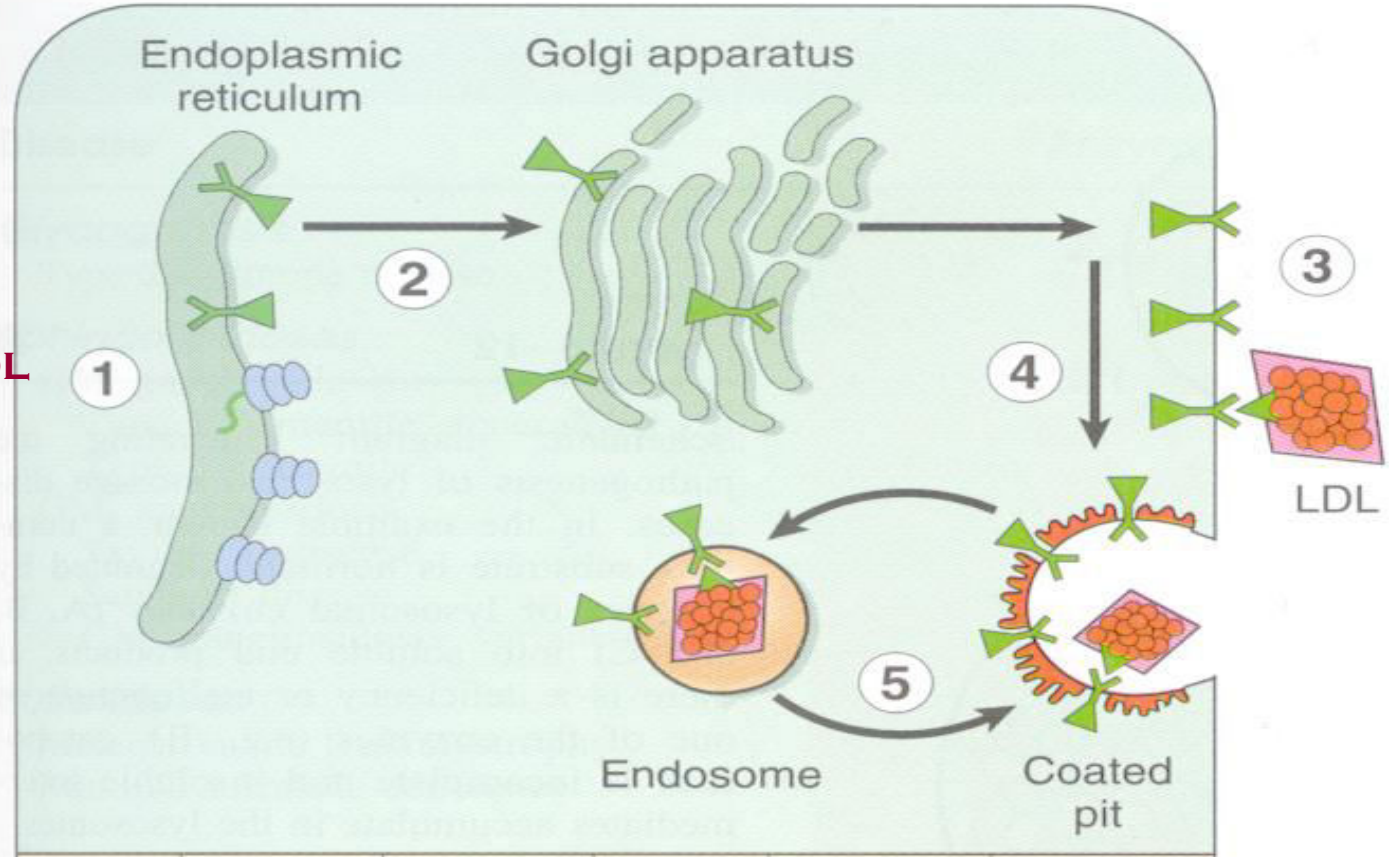
Urea Cycle Defects:

- All but one of the disorders is autosomal recessive.
- Symptom free period and then emesis->lethargy-->>COMA
- Key features:
  - High Ammonia, low BUN
  - Possible Lactic acidosis
  - *Absence of ketonuria*
  - Nl to mild low Glucose
- **Treat high ammonia, infuse glucose, send plasma AAs/OAs, urine orotic acid, and plasma citrulline.
- Infusion of 6ml/kg 10% Arginine HCl over 90 min may help.
- Milder forms may show episodic emesis, confusion, ataxia, and combativeness after high protein meals.

Lipid Metabolism

- Backbone of phosopholipide and sphingolipids **= biological membranes and hormones**
- Intracellular messengers and energy substrate
- Hyperlipidemia, due to defective in lipid transport
- Fatty Acidemias is less common (fatty acid oxidation)
- FA mobilization from adipose tissue to cell = energy substrate in liver, skeletal and cardiac muscles
- FA transport across outer and inner mitochondrial membrane and entry into mitochondrial matrix
- Defects in any of these steps cause disease (Short, Medium & Long chain fatty acidemias)

LDL Receptor Pathway and Regulation of Cholesterol Metabolism



Mutation class	Synthesis	Transport	Binding	Clustering	Recycling
I	X				
II	→	X			
III	→	→	X		
IV	→	→	→	X	
V	→	→	→	→	X

FATTY ACIDS

1. Long Chain
2. Medium Chain
3. Short Chain

Fatty Acid Oxidation Defects (AR)

- Examples are MCAD, LCAD, VLCAD
- Defect in acyl-CoA Dehydrogenase, a mitochondrial duty, and important in fasting state.
- KEY features:
  - Acute attack of life-threatening coma with Hypoglycemia
  - Absence of urine ketones, and reducing substances, nl serum AAs.
  - +/- mild acidosis, or hyperammonemia, elevated LFTs, abnl coags. +/-Hepatomegaly-/+
- Dx with serum Acylcarnitine Profile or fibroblast enzyme assay

Organic Acidemias:

- Acidotic with high anion Gap
- Urine Ketones high
- High to normal Ammonia
- Often present first 2-7 days of life after dietary protein introduced.
- Drunk appearance in infant.
- May have low WBC and Plts.
- Check serum AAs/OAs, Urine AAs/OAs, CSF OAs/AAs.

Organic Acidemia,

Disorders of OA

Disorder	Distinctive features
Propionic acidemia	Ketosis, acidosis, hyperamm neutropenia
Isovaleric acidemia	Sweaty feet odor, acidosis
Methylmalonic acidemia	Ketosis, acidosis, hyperamm neutropenia
3-methylcrotonyl -CoA carboxylase deficiency	Metabolic acidosis, hypoglycemia
HMG-CoA lyase deficiency	Reye syndrome, acidosis, hyperamm, hypoglycemia, no ketosis
Ketothiolase deficiency	Acidosis, ketosis, hypoglycemia
Glutaric acidemia type I	No acidosis; basal ganglia injury with movement disorder

Purine/pyrimidine metabolism

- **Lesch-Nyhan disease** **XR**
  - Hypoxanthine Guanine Phosphoribosyltransferase Deficiency
  - Mental retardation,
  - uncontrolled movements, } Uric Acid Crystals in CNS
  - S58}elf-mutilation

- **Adenosine deaminase deficiency** **AR**
  - Adenosine deaminase Deficiency
  - Severe combined immunodeficiency

- **Purine nucleoside phosphorylase** **AR**
  - Purine nucleoside Phosphorylase deficiency
  - Severe viral infections due to impaired

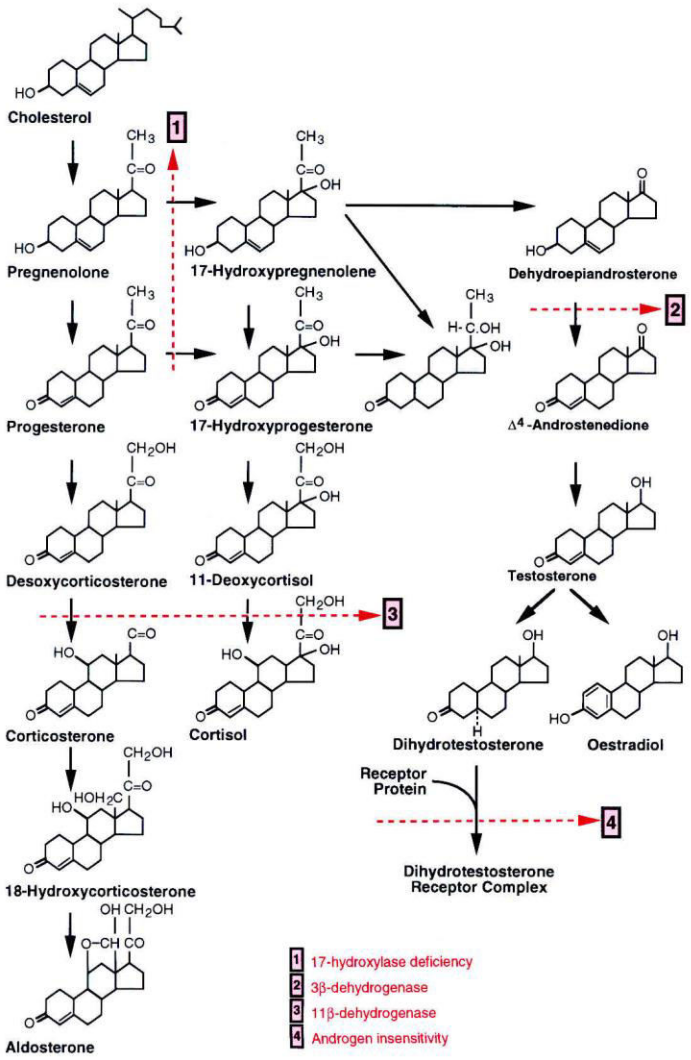
- **Hereditary orotic aciduria** **AR**
  Orotate phosphoribosy ltransferase , Deficiency
  - Orotidine 5'-phosphate Decarboxylase Deficiency
  - Megaloblastic anaemia in the first year of life,
  - Failure to thrive,

Copper Metabolism

- **Wilson** AR ATPase
  - membrane copper
  - Spasticity , Rigidity, Dysphagia, Cirrhosis
  - Transport protein ;
- **Menkes' disease** XR ATPase
  - membrane copper
  - Failure to thrive, Neurological deterioration
  - Transport protein

Steroid Metabolism

- Congenital adrenal hyperplasia AR
- Virilization (any new born female with ambiguous genitalia)
- **Salt-losing**
  - 21-hydroxylase Most common (90%)
  - 11,13-hydroxy!ase,
  - 3 13-dehydrogenase
  - 17a-hydroxylase, very rare
  - 17,20-lyase. Very rare
- **Testicular feminization**
  - Androgen receptor
  - Female external genitalia,
  - Male internal genitalia,
  - Male chromosomes



Every child with unexplained . . .

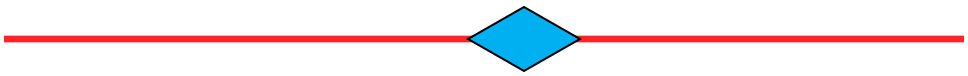
- Neurological deterioration
- Metabolic acidosis
- Hypoglycemia
- Inappropriate ketosis
- Hypotonia
- Cardiomyopathy
- Hepatocellular dysfunction
- Failure to thrive

. . . should be *suspected* of having a metabolic disorder

What to do for the Dying Infant Suspected of Having an IEM

- Autopsy--pref. performed within 4 hours of death
- Tissue and body fluid samples

  Blood, URINE, CSF (ventricular tap), aqueous humour, skin biopsy, muscle and liver--frozen in liquid nitrogen
- Filter paper discs from newborn screen--call lab and ask them not to discard



Laboratory Studies For an Infant Suspected of Having an Inborn Error of Metabolism

- Complete blood count with differential
- Urinalysis
- Blood gases
- Serum electrolytes
- Blood glucose
- Plasma ammonia
- Urine reducing substances
- Urine ketones if acidosis or hypoglycemia present
- Plasma and urine amino acids, quantitative
- Urine organic acids
- Plasma lactate

SUMMARY

Major Inborn Errors of Metabolism Presenting in the Neonate as an Acute Encephalopathy

Disorders	Characteristic Laboratory Findings
Organic acidemias (includes MMA, PA,IVA, MCD and many less common conditions)	Metabolic acidosis with increased anion gap; variably elevated plasma ammonia and lactate; abnormal urine organic acids
Urea cycle defects	Variable respiratory alkalosis; no metabolic acidosis; markedly elevated plasma ammonia; elevated orotic acid in OTCD; abnormal plasma amino acids
Maple syrup urine disease	Metabolic acidosis with increased anion gap; elevated plasma and urine ketones; positive ferric chloride test; abnormal plasma amino acids
Nonketotic hyperglycinemia	No acid-base or electrolyte abnormalities; normal ammonia; abnormal plasma amino acids
Molybdenum co-factor deficiency	No acid-base or electrolyte abnormalities; normal ammonia; normal amino and organic acids; low serum uric acid; elevated sulfites in urine

Abbreviations: MMA, methylmalonic acidemia; PA, propionic acidemia; IVA, isovaleric acidemia; MCD, multiple carboxylase deficiency; OTCD, ornithine transcarbamylase deficiency.

Group I . Disorders involving COMPLEX molecules .	
Lysosomal disorders.	Glycoproteinosis , MPS, Sphingolipidosis .
Peroxisomal disorders .	Zellweger syndrome & Variants , Refsum disease,.
Disorders of intracellular trafficking & processing .	NPD-type C
Disorders of Cholesterol synthesis	Wolman disease
Group II . Disorders that give rise to INTOXICATION .	
Aminoacidopathies .	PKU, MSUD. Homocysteinuria, Tyrosinemia .
Congenital Urea Cycle Defects .	CPT, OTC, Citrullinaemia, ASA. Arginase, NAGS deficiency .
Organic acidemias .	Methylmalonic acidemia .Propionic acidemia . Isovaleric acidemia .Glutaric aciduria type I .
Sugar intolerances .	Galactosemia .Heredietary Fructose intolerance .
Group III . Disorders involving ENERGY METABOLISM	
Glycogenoses (glycogen storage disease) .	
Gluconeogesis defects .	Fructose 1,6-diphosphatase deficiency . Phosphoenolpyruvate carboxykinase .
Congenital Lactic Acidemia .	Pyruvate Carboxylase deficiency . Pyruvate Dehydrogenase deficiency .
Fatty Acid Oxidation defects .	VLCAD, MCAD , etc
Mitochondrial respiratory-chain disorders .	

Inborn Errors of Metabolism Associated With Neonatal Liver Disease and Laboratory Studies Useful in Diagnosis

Disorder	Laboratory Studies
Galactosemia	Urine reducing substances; RBC galactose-1-phosphate uridyl transferase
Hereditary tyrosinemia	Plasma quantitative amino acids; urine succinylacetone a1-Antitrypsin deficiency Quantitative serum a1-antitrypsin; protease inhibitor typing
Neonatal hemochromatosis	Serum ferritin; liver biopsy
Zellweger syndrome	Plasma very long-chain fatty acids
N-Pick disease type C	Skin biopsy for fibroblast culture; studies of cholesterol esterification and accumulation
GSD type IV (brancher deficiency)	Liver biopsy for histology and biochemical analysis or skin biopsy with assay of branching enzyme in cultured fibroblasts