Inborn Error Of Metabolism

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MGL-9

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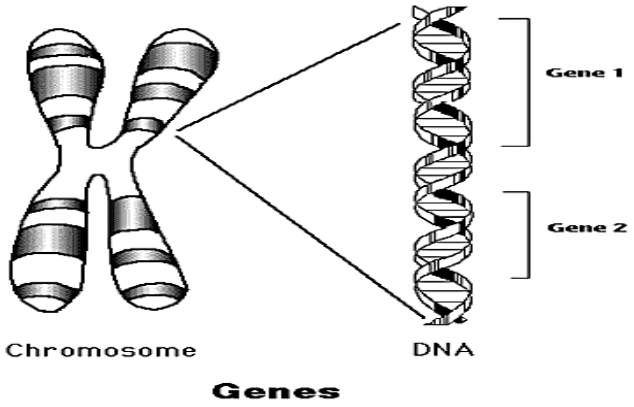
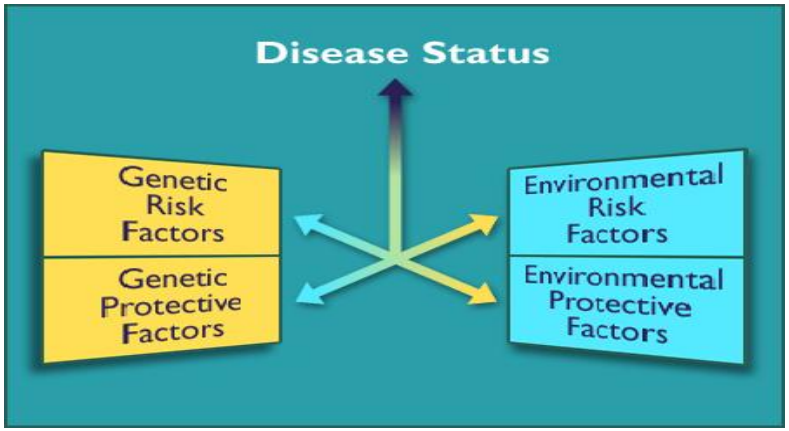
Genetic diseases

- **Single gene disorders**
  - Caused by individual mutant gene
  - ***EXAMPLE : INBORN ERRORS OF METABOLISM***
- **Chromosomal disorders**
  - Numerical disorders
  - Structural disorders
- **Multifactorial disorders**





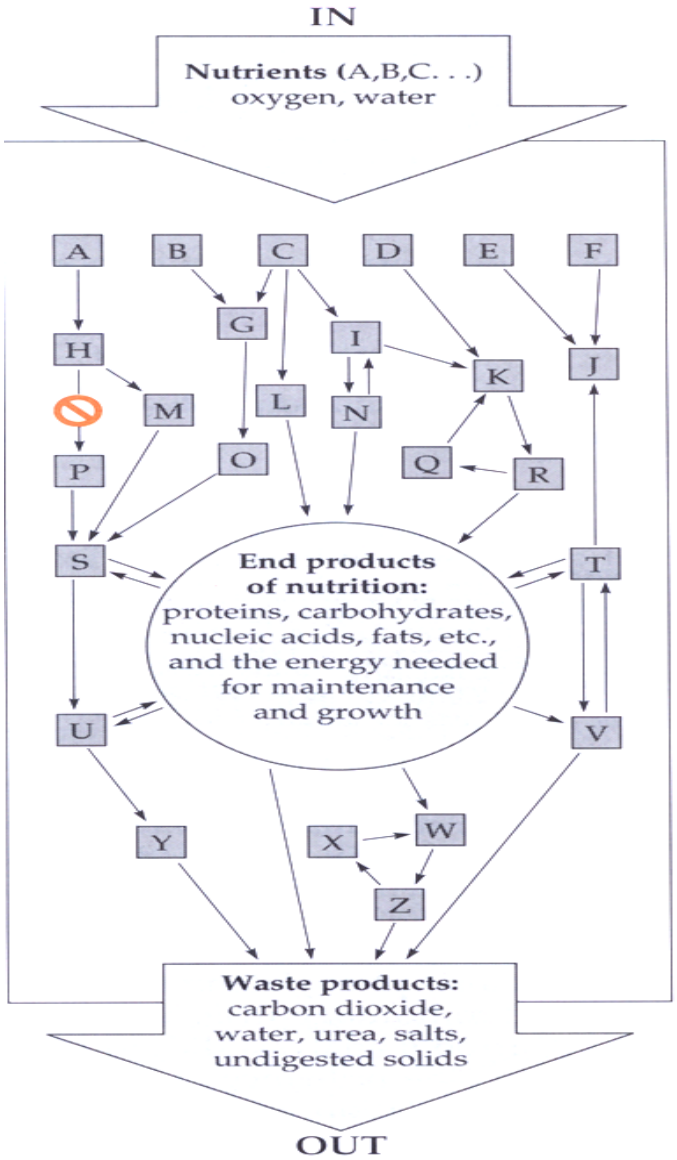
Inborn Error Of Metabolism
Definition of IEM

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

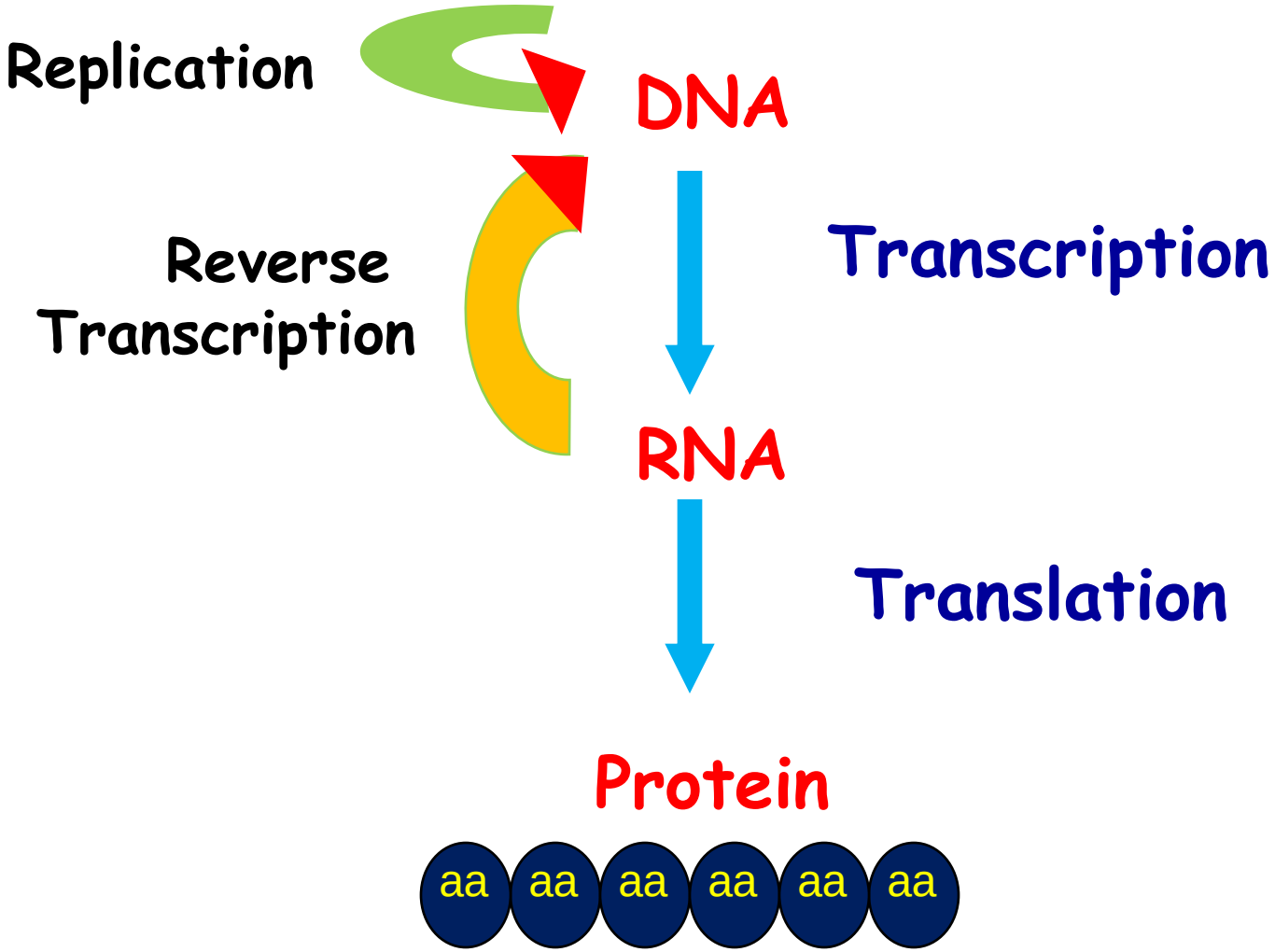
What Are Inborn Errors of Metabolism?

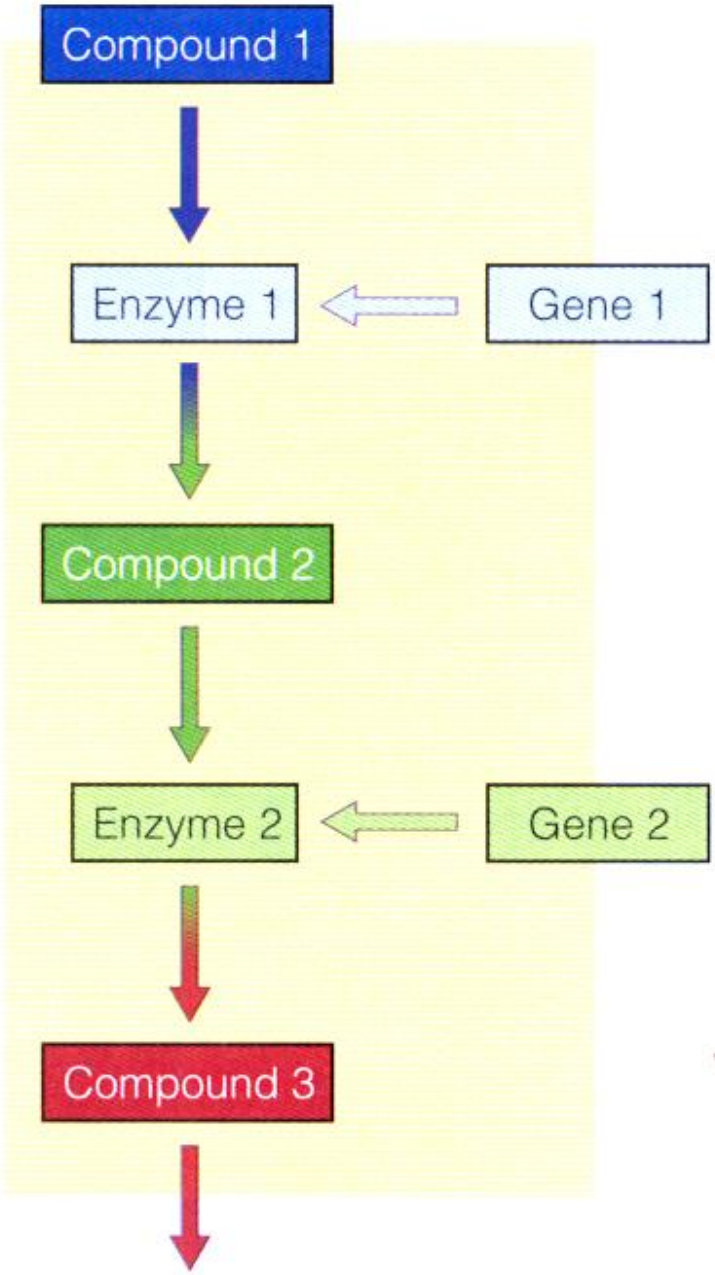
Genetic Disorders that affect the metabolism of food.

- There are missing or defective enzymes necessary to metabolize the food eaten
- Generally they are autosomal recessive traits
- Food not broken down properly may produce chemicals that build up in various parts of the body causing medical problems and learning disorders.



Central Dogma of Genetics





- **Chemical Individuality**

  Garrod 20th Century

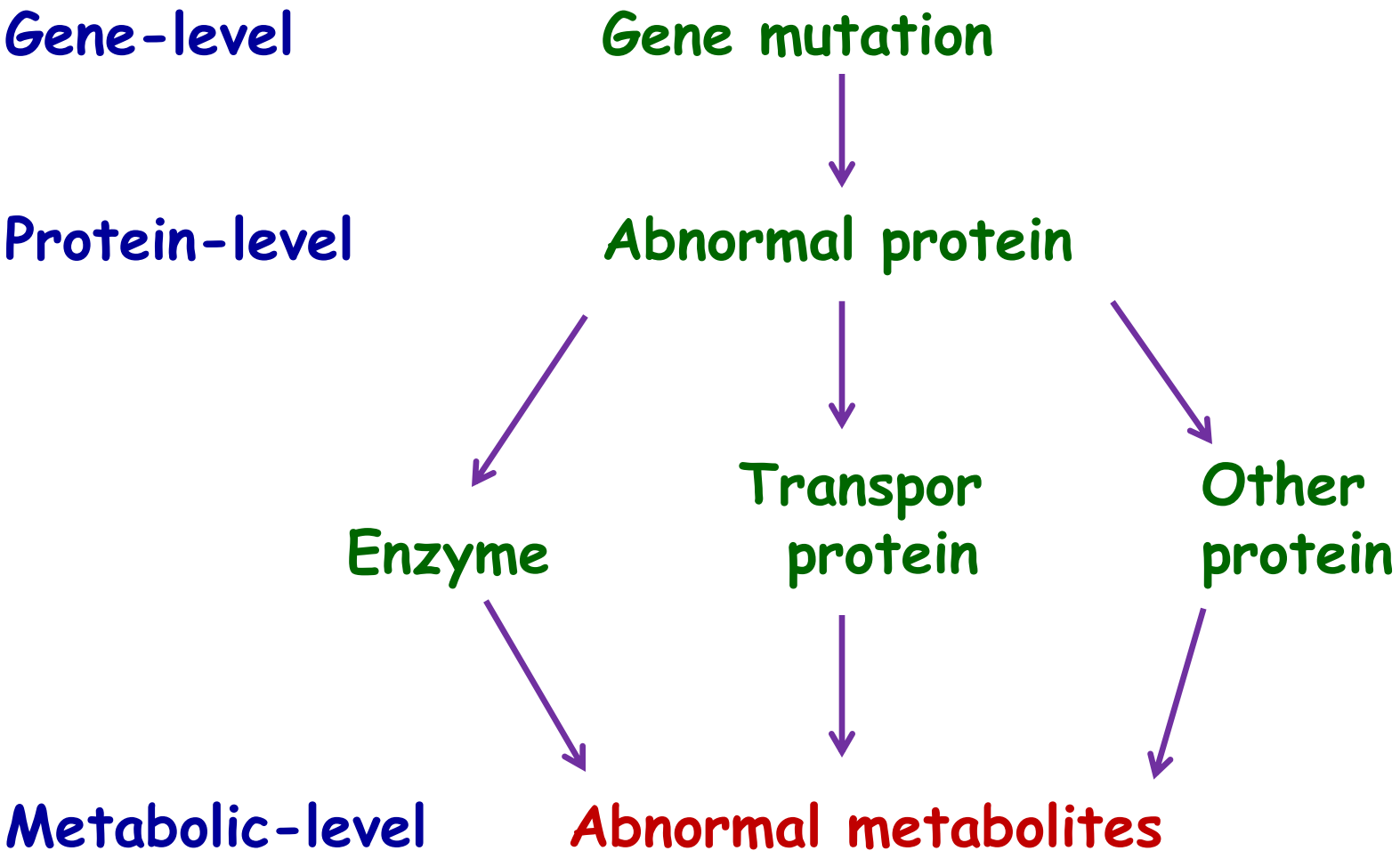
  Developed "Inborne Error of Metabolism"

- **Beadle & Tatum**

  Developed one gene one enzyme concept

Inborn Errors of Metabolism

a genetic disease
also known as biochemical genetics



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

BASIC IDEA,,,

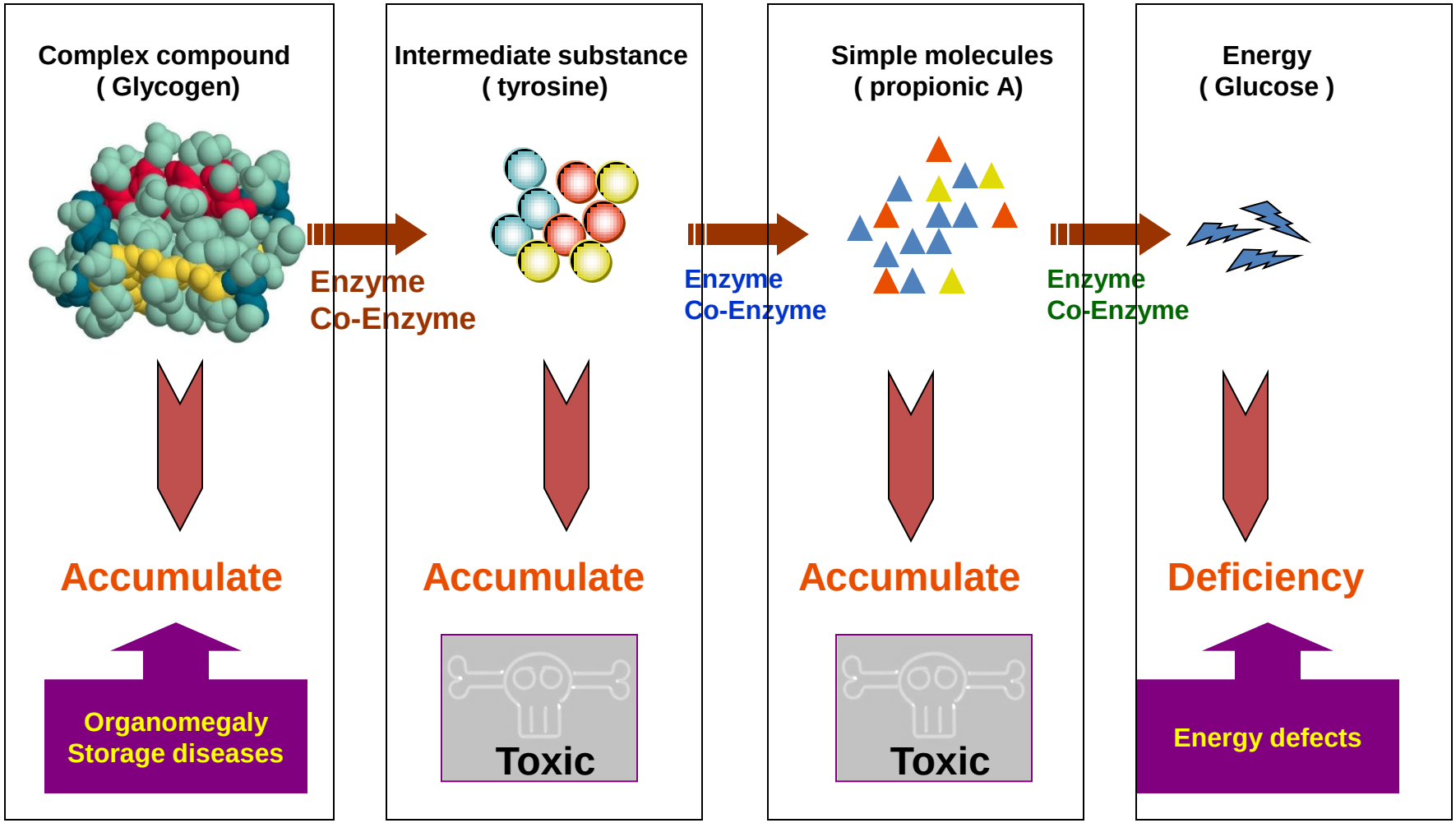
Protein

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
- Routine biochemistry tests e.g. lactate, glucose and second-line metabolic tests e.g. amino acids are essential for the investigation of disorders of carbohydrate metabolism. However, definitive diagnosis is usually achieved by measurement of the activity of the affected enzyme.
- The easiest sample type to obtain is blood (erythrocytes, leucocytes, lymphocytes) but the choice of tissue depends on the pattern of expression of the enzyme in question. For some assays, cultured skin fibroblasts (from a punch biopsy) or liver/muscle biopsies are required.

Inborn Errors of Carbohydrate Metabolism

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

Disorders of Carbohydrate Metabolism

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)
- **Two types:**
  - 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

Metabolism of Galactose

Lactose

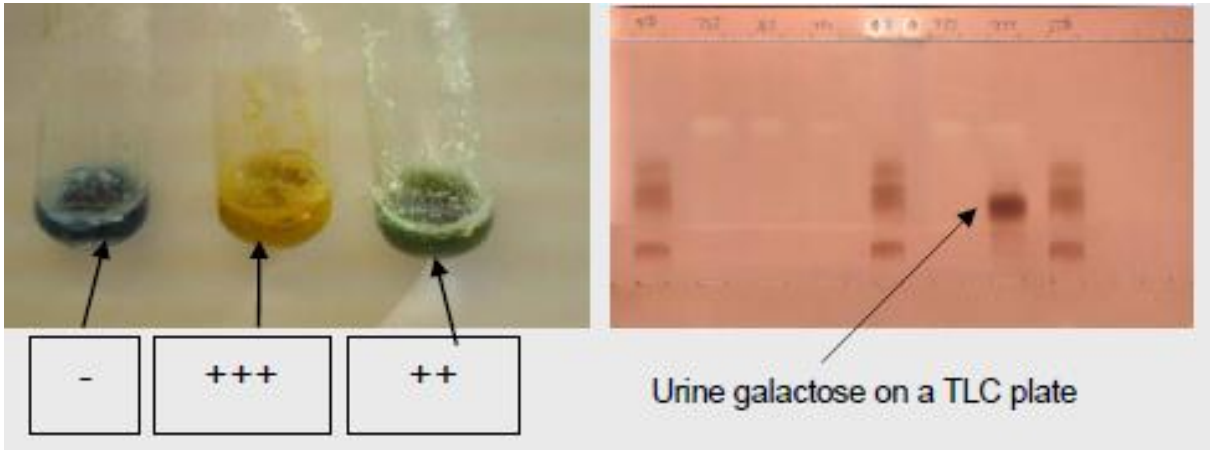
↓ Lactase

Galactose

↓ Galactokinase

Galactose-1phosphate → Glucose

Galactose -1 phosphate
Uridyl transferase



Brain
MR

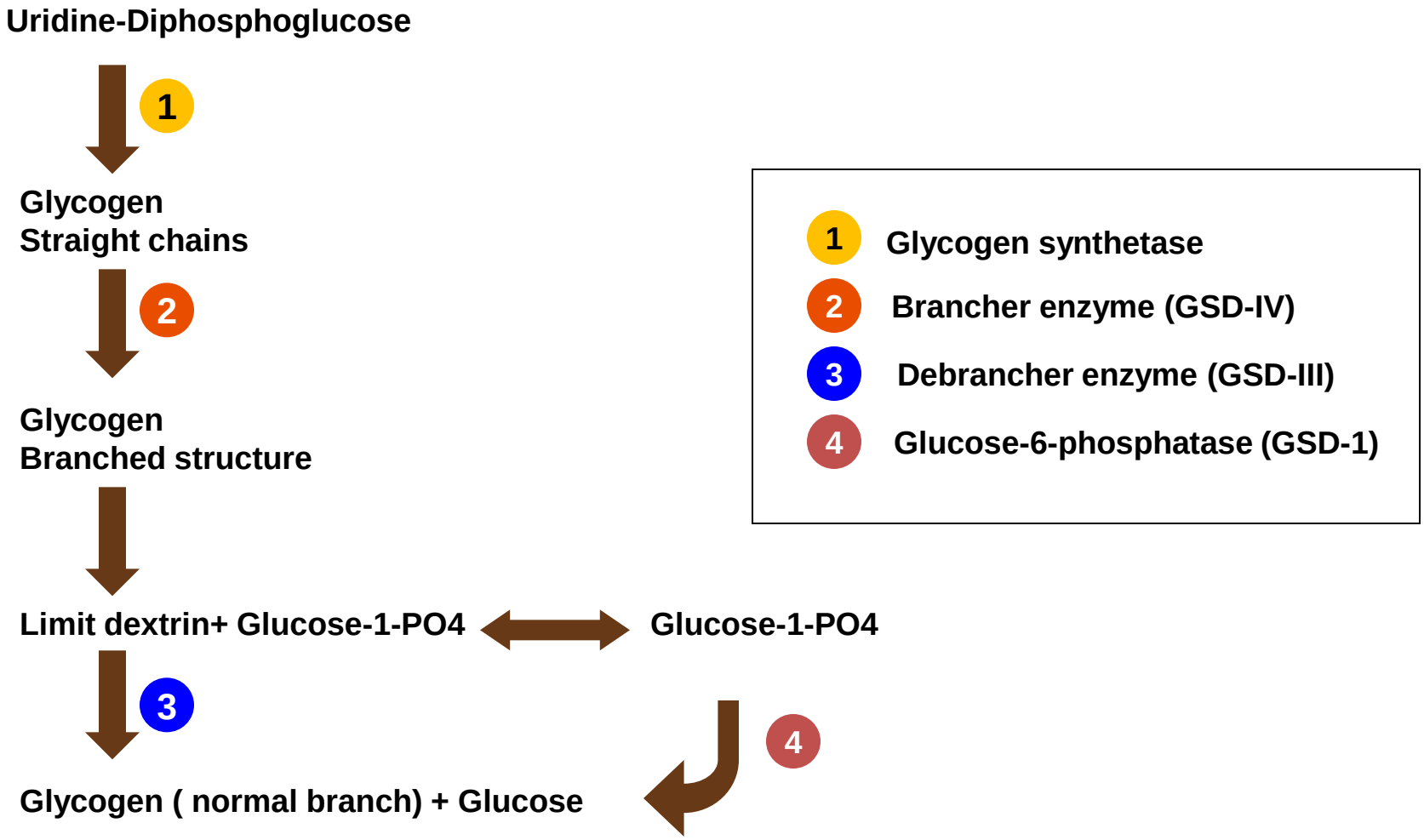
Liver
- Jaundice
- Hepatomegaly
- Cirrhosis

Eyes
Chataract

Glycogen Storage Diseases

- This presents with lactic acidosis, neurological dysfunction (seizures, hypotonia, coma)
- It is a defect in the first step of gluconeogenesis which is the production of oxaloacetate from pyruvate. In addition to the effect on gluconeogenesis, lack of oxaloacetate affects the function of the Krebs cycle and the synthesis of aspartate (required for urea cycle function).
- In the acute neonatal form the lactic acidosis is severe, there is moderately raised plasma ammonia, citrulline (& alanine, lysine, proline) and ketones. Fasting results in hypoglycaemia with a worsening lactic acidosis.
- The diagnosis can be confirmed by assay of pyruvate carboxylase activity in cultured skin fibroblasts
- Patients rarely survive >3 months in the severe form

Glycogen Storage Diseases



Glycogen Storage Diseases

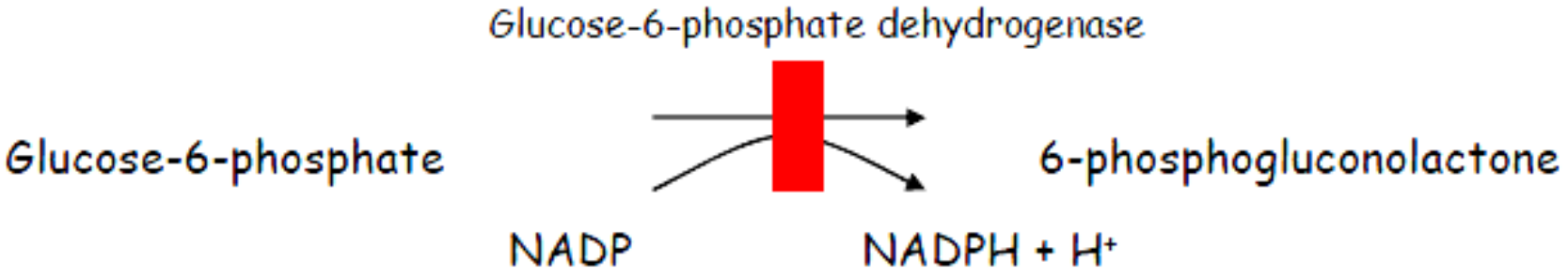
Disorder (approximate % GSD cases)*	Enzyme defect	Most affected tissue(s)	Clinical Features	Diagnostic tests	Sample
GSD II (Pompe's) (15%)	Lysosomal α1,4-glucosidase	Generalised; accumulation of glycogen in lysosomes	Infantile form: cardiomegaly, hypotonia; Juvenile & adult form: skeletal myopathy	Enzyme 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)

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

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

DISORDERS OF AA METABOLISM

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

History and Diagnosis

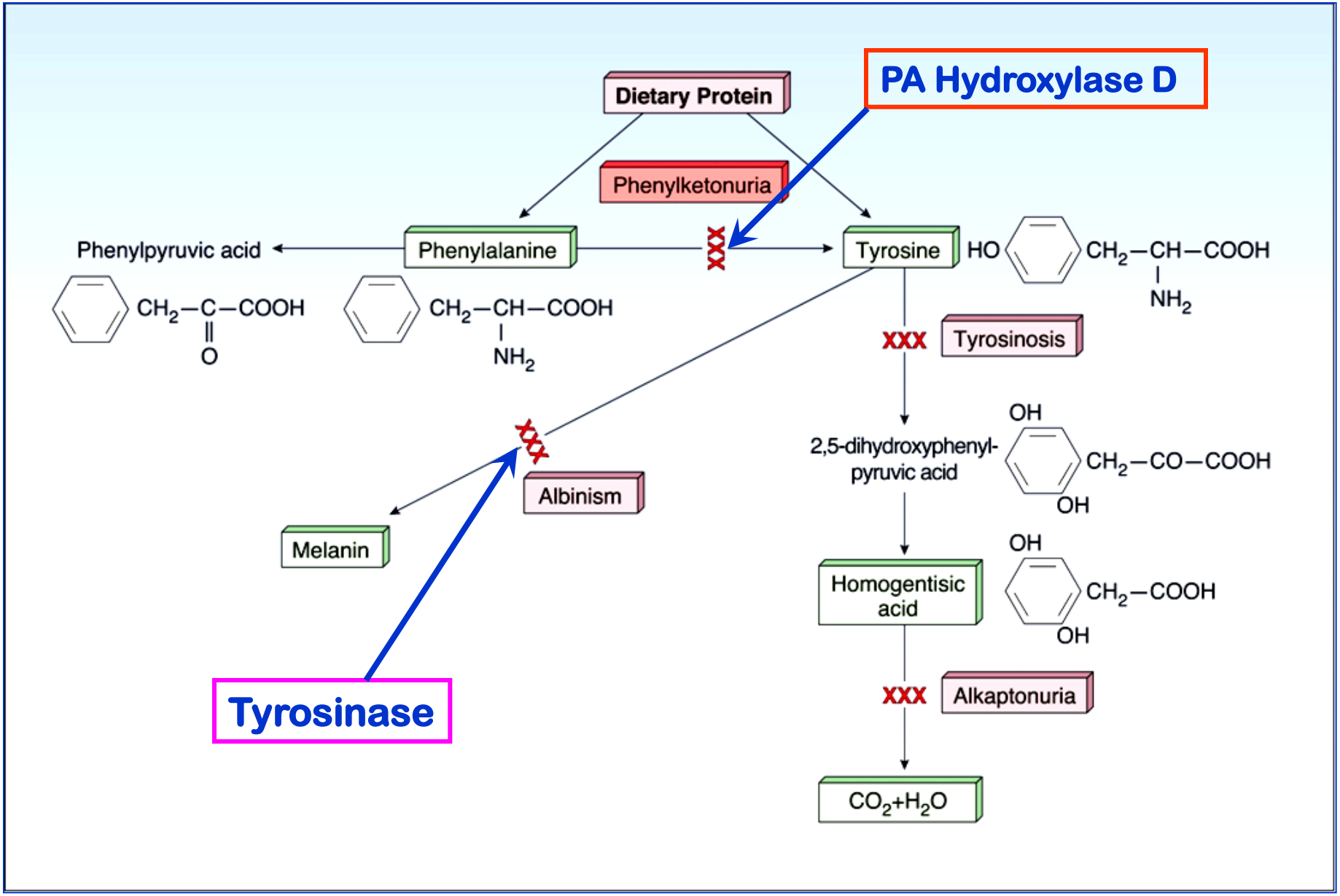
- PKU was discovered in 1934 by Dr. A Folling in Sweden by identifying phenylpyruvic acid in the urine of two siblings who were mentally retarded.
- 1950's Jervis discovered a deficiency of the enzyme phenylalanine dehydrogenase in the liver tissue of an affected patient.
- 1955- Bickel demonstrated that restricting dietary phenylalanine lowers the blood concentration of phenylalanine.

Phenylketonuria (PKU):

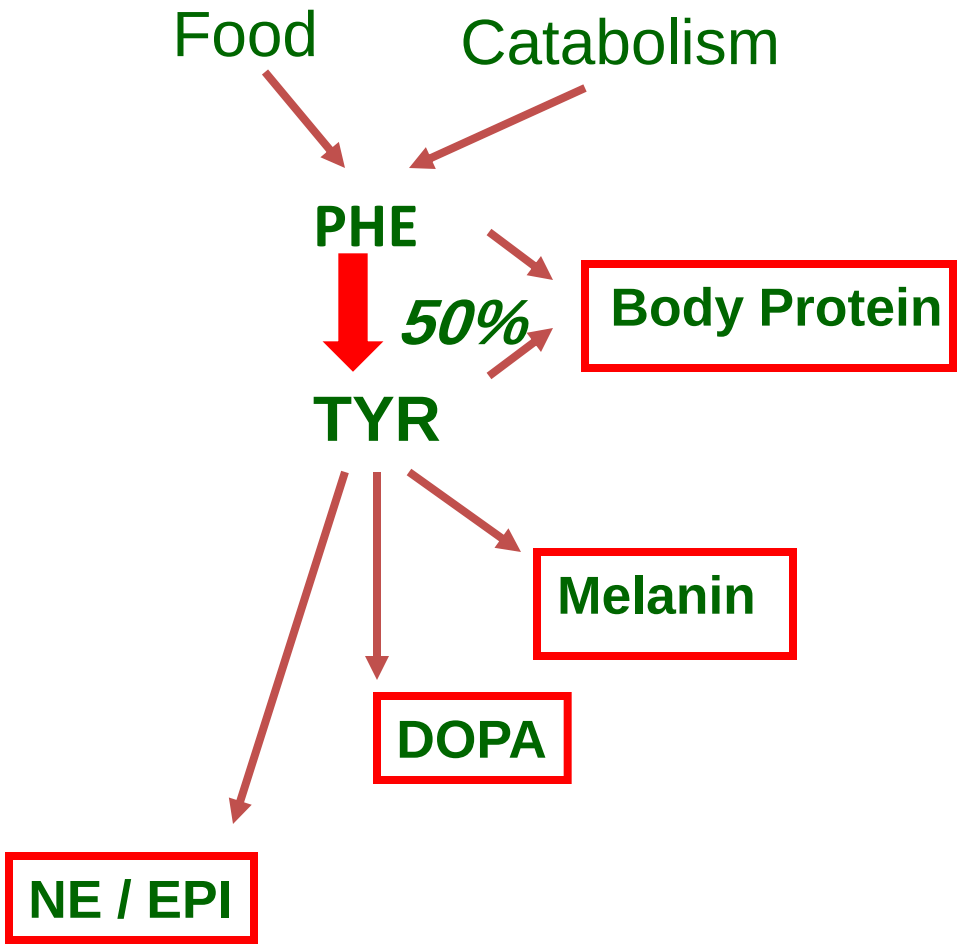
- **Clinical features: Development delay in infancy, ? neurological manifestations such as seizures. hyper activity, behavioral disturbances, hyperpigmentation and MR.**
- **Incidence: 1/5000 -1/16000.**
- **Genetics: AR, 12q22-q24, >70 mutations**
- **Basic Defect: Mutation in the gene of PA hydroxylase.**

- **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



Phenylalanine Metabolism



- Phenylalanine
- Essential AA
- Major interconversions through tyrosine

Two Types

- **PAH Deficient** (97% of cases)
  →Deficiency of PAH

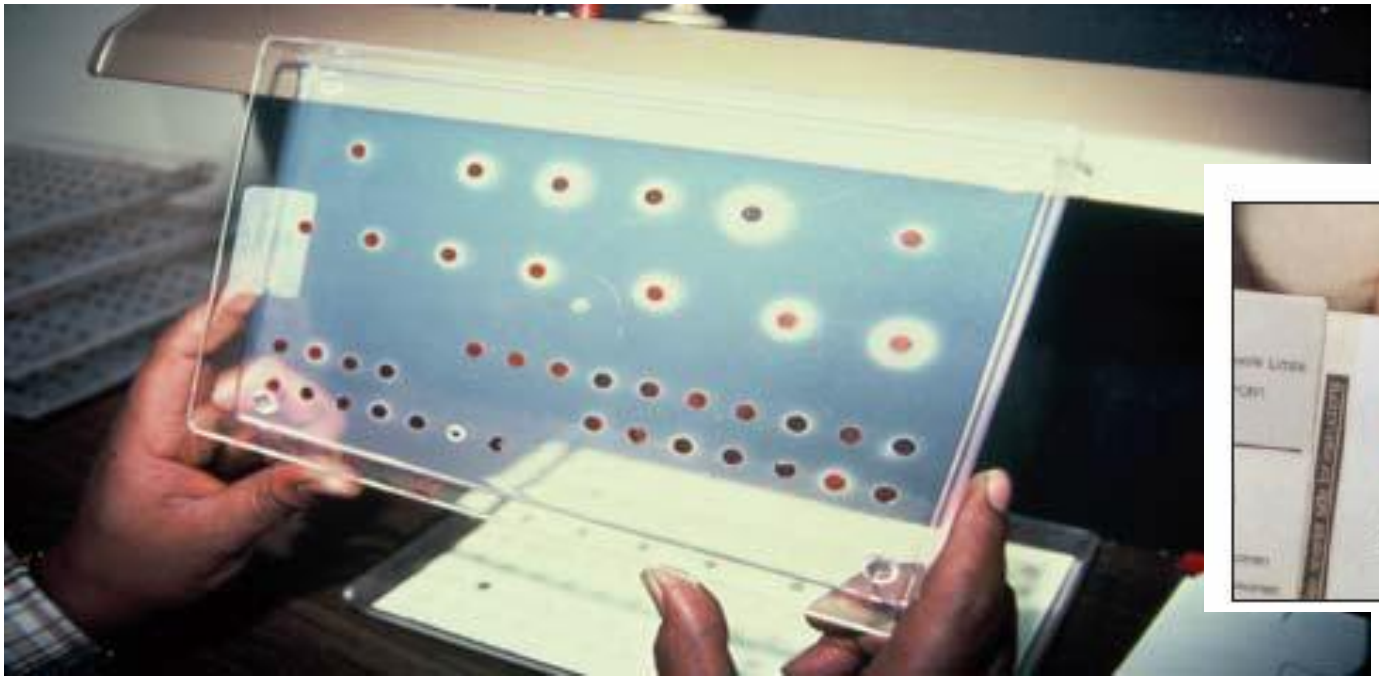
- **Non-PAH Deficient** (3% of cases)
  →Defects in tetrahydrobiopterin or other components in related pathways
  - Dihydropteridin reductase deficiency
  - Dihydrobiopterin synthetase deficiency

Diagnostic Criteria

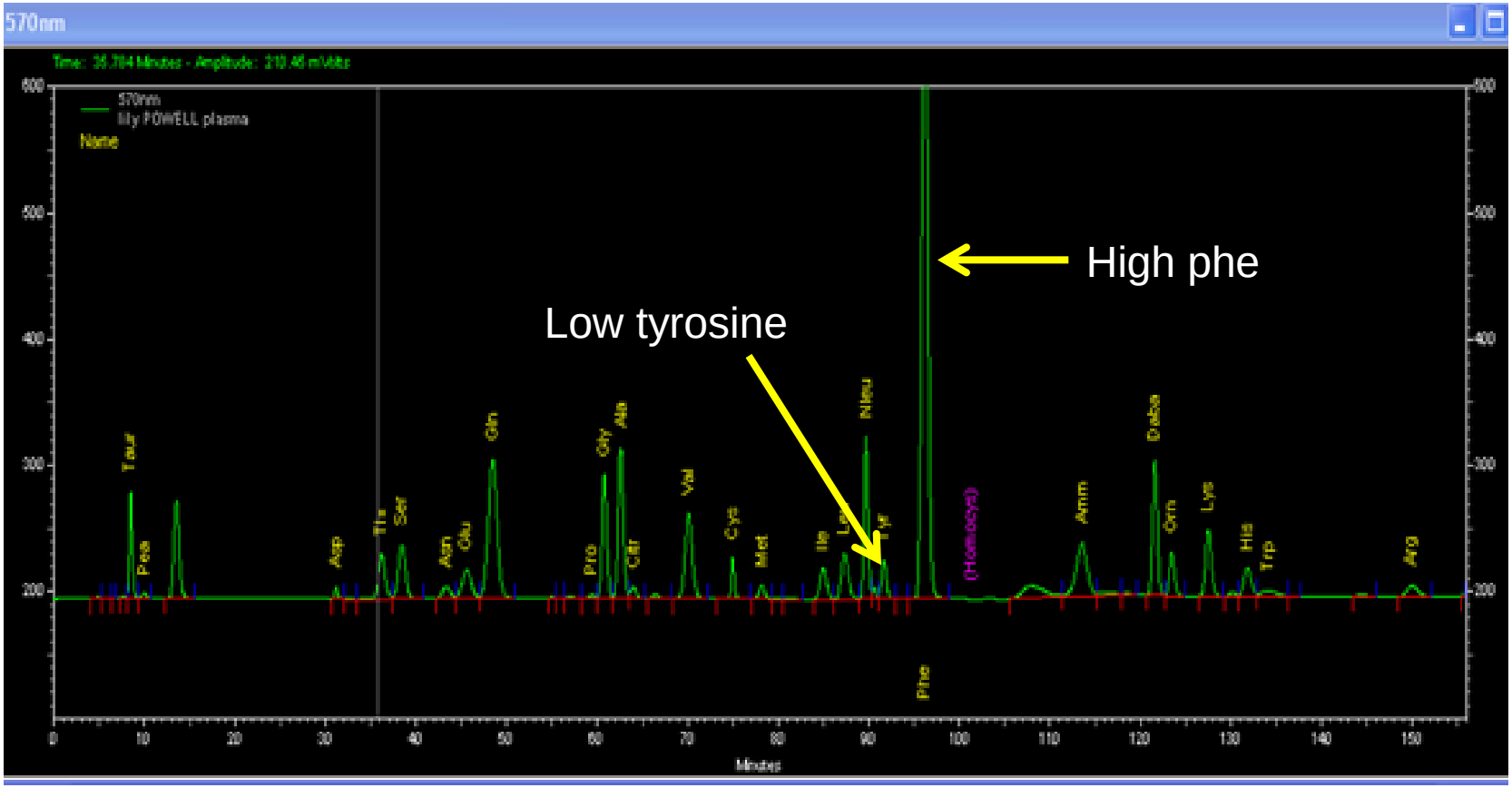
- Normal: 120 – 360 umol/L
- PAH Deficient:
  - Mild: 600 – 1200 umol/L
  - Classical: > 1200 umol/L
- Non-PAH Deficient:
  - < 600 umol/L
- Guthrie Bacterial Inhibition Assay
- Confirmation of diagnosis

Guthrie Test--1961

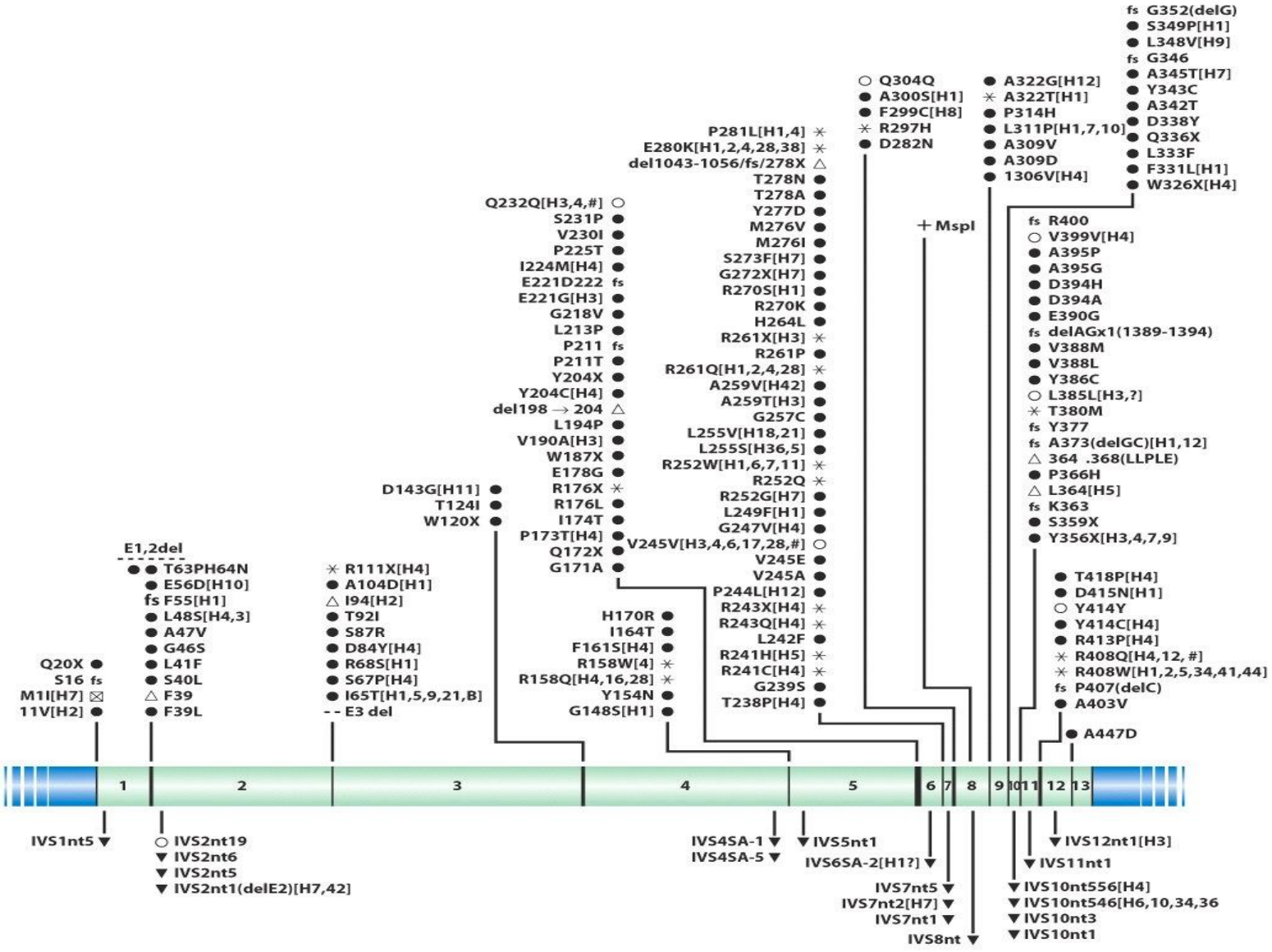
1965 - Screening for PKU was mandated legislatively in most of the states in US



Plasma Amino Acid Profile, PKU



PKU Mutations



Treatment

- Low phenylalanine diet
  - requires careful monitoring
  - risk of tyrosine insufficiency
  - risk vitamin and trace element deficiencies
- ? biopterin supplementation (sapropterin)
- Large Neutral Amino Acids (val, leu, ileu) supplements
- Diet for life
- Management of PKU pregnancies

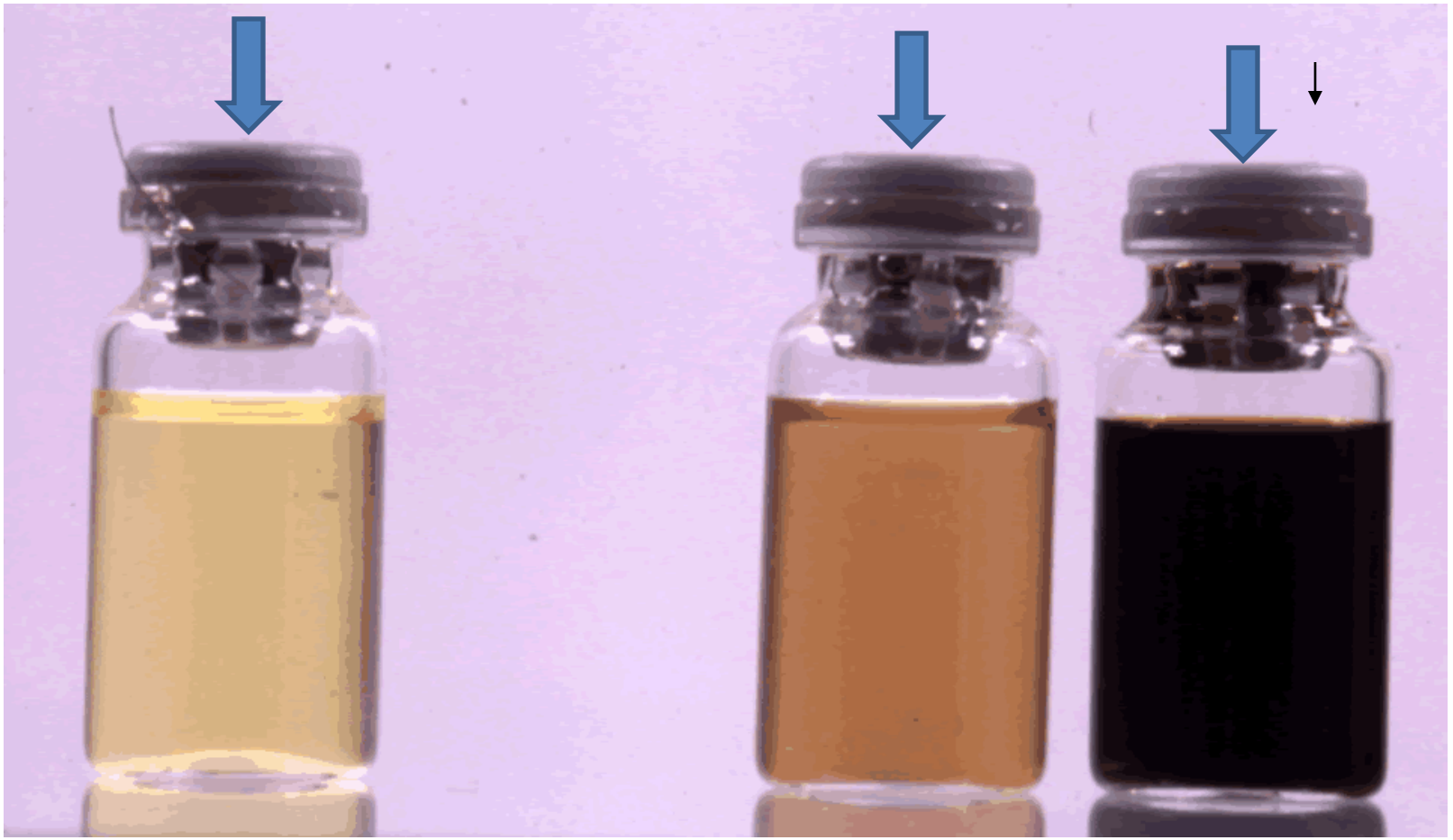
ALKAPTONURIA

- 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

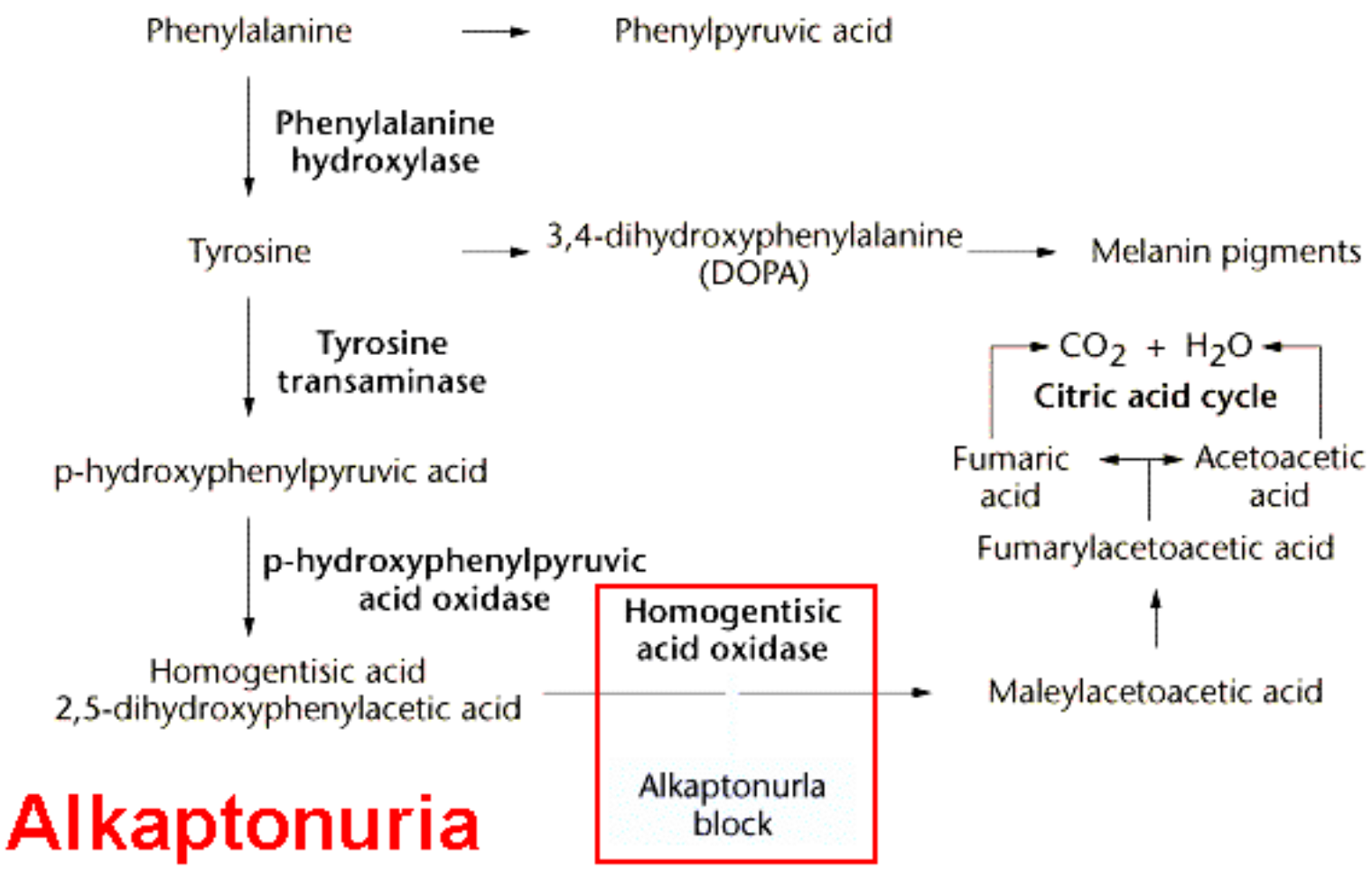
Urine from patients with alkaptonuria



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

Alkaptonuria - Biochemistry

- **Alkaptonuria** reflects the absence of **homogentisic acid oxidase** activity.



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

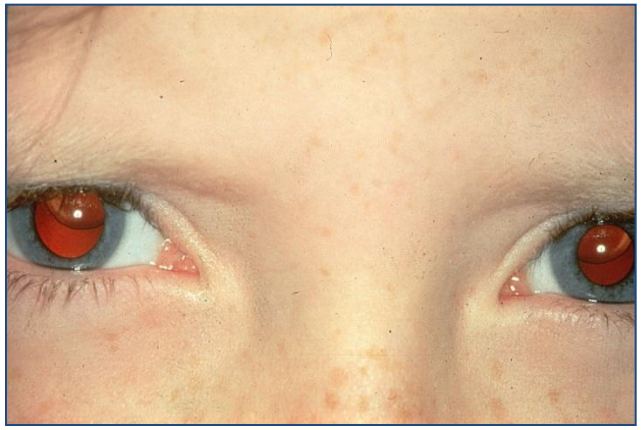
HOMOCYSTINURIA

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

Natural History of Clasical Homocystinuria

- *Lens dislocation:*
  - 82% dislocated by age 10 years
- *Osteoporosis (x-ray):*
  - 64% with osteoporosis by age 15 yrs
- *Vascular events:*
  - 27% had an event by age 15 years
- *Death:*
  - 23% will not survive to age 30 years
- Mental Retardation – approx 50%



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 ?????

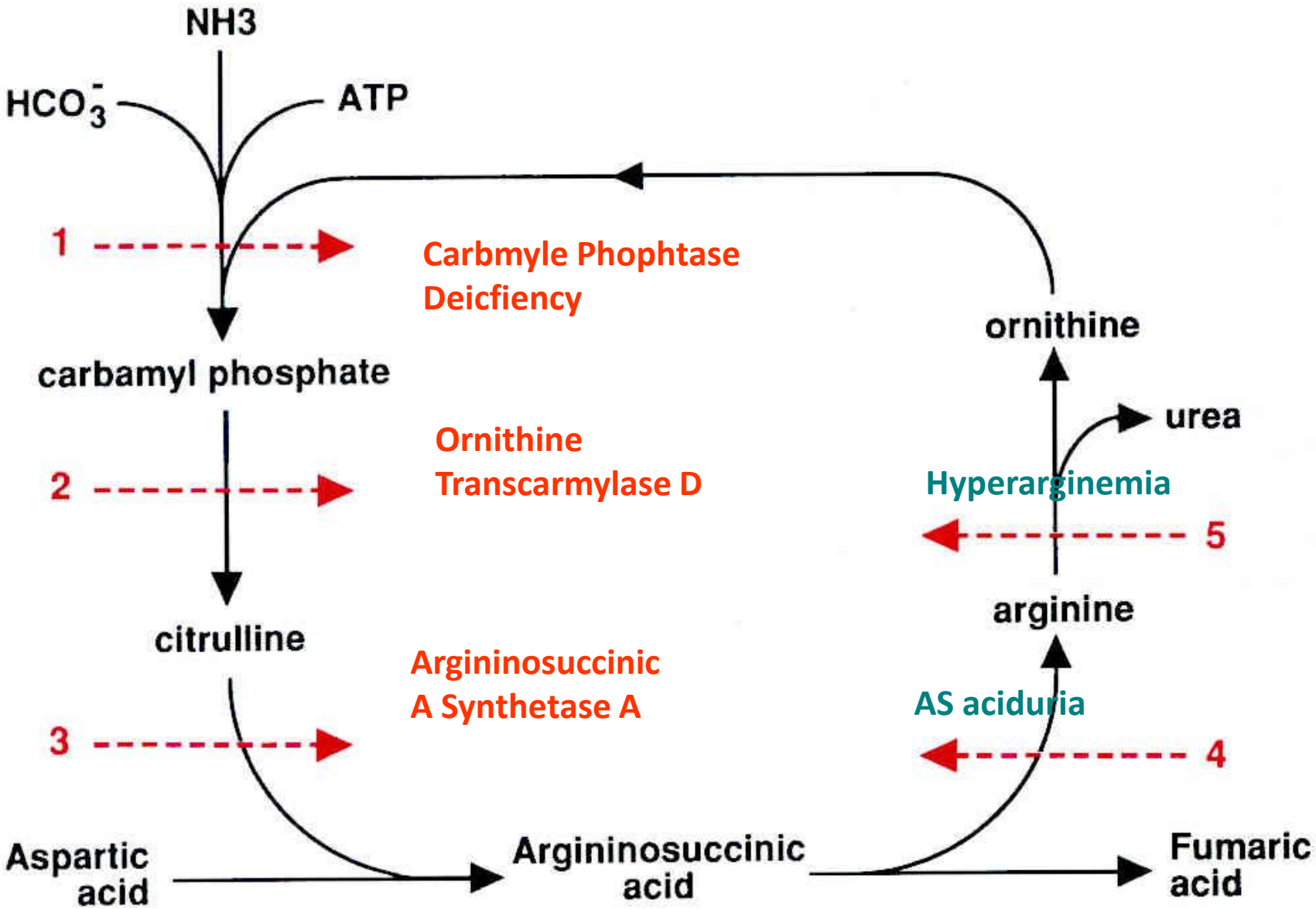
Maple Syrup Urine Disease (MSUD) AR

- Involves the Branch-chain amino acids:
  - Leucine
  - Iso-leucine
  - Valine
- Incidence is 1:200,000
  - Infants appear normal at birth. By four days of age they demonstrate poor feeding, vomiting and lethargy.
  - Urine has a characteristic sweet, malty odor toward the end of the first week of life
- Treatment: Formulas low in the branch chain amino acids

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 DISORDERS

Characteristics

- Neonatal period or anytime
- Wide inter and intra familial variations in the severity of the disease,
- Lethargy, coma. Arginase deficiency cause progressive spastic quadriplegia and Mental retardation
- No acidosis (respiratory alkalosis)
- No ketones (unlike organic acidemia)
- No hypoglycemia
- But there is hyperammonemia

Cystinuria AR

- Characterized by the formation of cystine (cysteine-S-Scysteine) stones in the kidneys, ureter, and bladder.
- Cause of persistent kidney stones, due to defective transepithelial transport of cystine and dibasic amino acids in the kidney and intestine.

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)

FATTY ACIDS

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

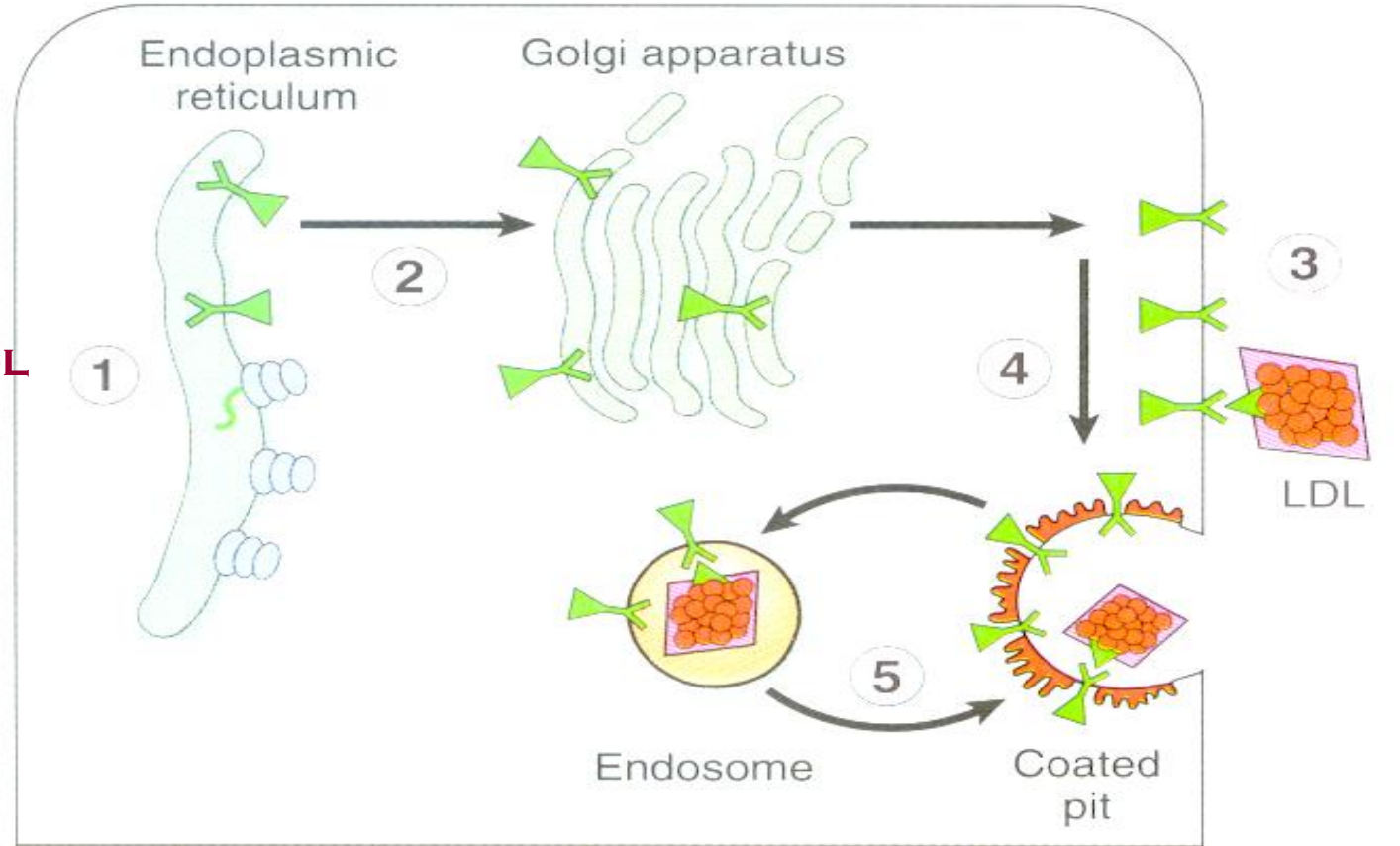
Medium Chain Acyl-CoA Dehydrogenase

- Most common MCAD characterized by Episodic hypoglycemias provoked by fasting .
- Child with MCAD present with Vomiting and lethargy
- No ketonbodies
- Cerebral edema and encephalopathy (Glucose, no fasting)
- **GENETICS:**
  - **Misscence mutation A ⟶ G results in substitution of glucose for lysine**
  - **Insertion**
  - **Deletion**
- **DIAGNOSIS**: DNA analysis in the newborn

Long Chain Acyl-CoA Dehydrogenase

- **LCAD** patients are presented with
  - Fasting induced coma
  - Hepatomegaly
  - Cardiomegaly
  - Muscle weakness
  - Hypotonia
  - Peripheral neuropathy
- Clinical and biochemical characteristics can be differentiated from each others
- **SCAD:** Very few case are reported with variable presentation

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

Organic Acidemia (OA)

- The term "organic acidemia" or "aciduria" applies to a group of disorders characterized by the excretion of non-amino organic acids in urine at birth and for the first few days of life.
- Toxic encephalopathy.
- Difficult to differentiate in acute presentation
- All are autosomal recessive, the commonest **Methylmalonic acidemia** MMA,,,,

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

Organic acidemia

Clinically:

- Healthy NB→ rapidly ill, Ketoacidosis, poor feeding
- Vomiting, dehydration
- Hypotonia, lethargy
- Tachypnea, seizures
- Coma, unusual odors
- Pancreatitis, cardiomyopathy, infection (recurrent).

Lab diagnosis

- Metabolic acidosis
- Hyperammonemia
- Hypoglycemia
- Lactic acidosis
- Anemia, ± thrombocytopenia ± neutropenia
- **Definite diagnosis, Tandem MS & Urine organic acid analysis**

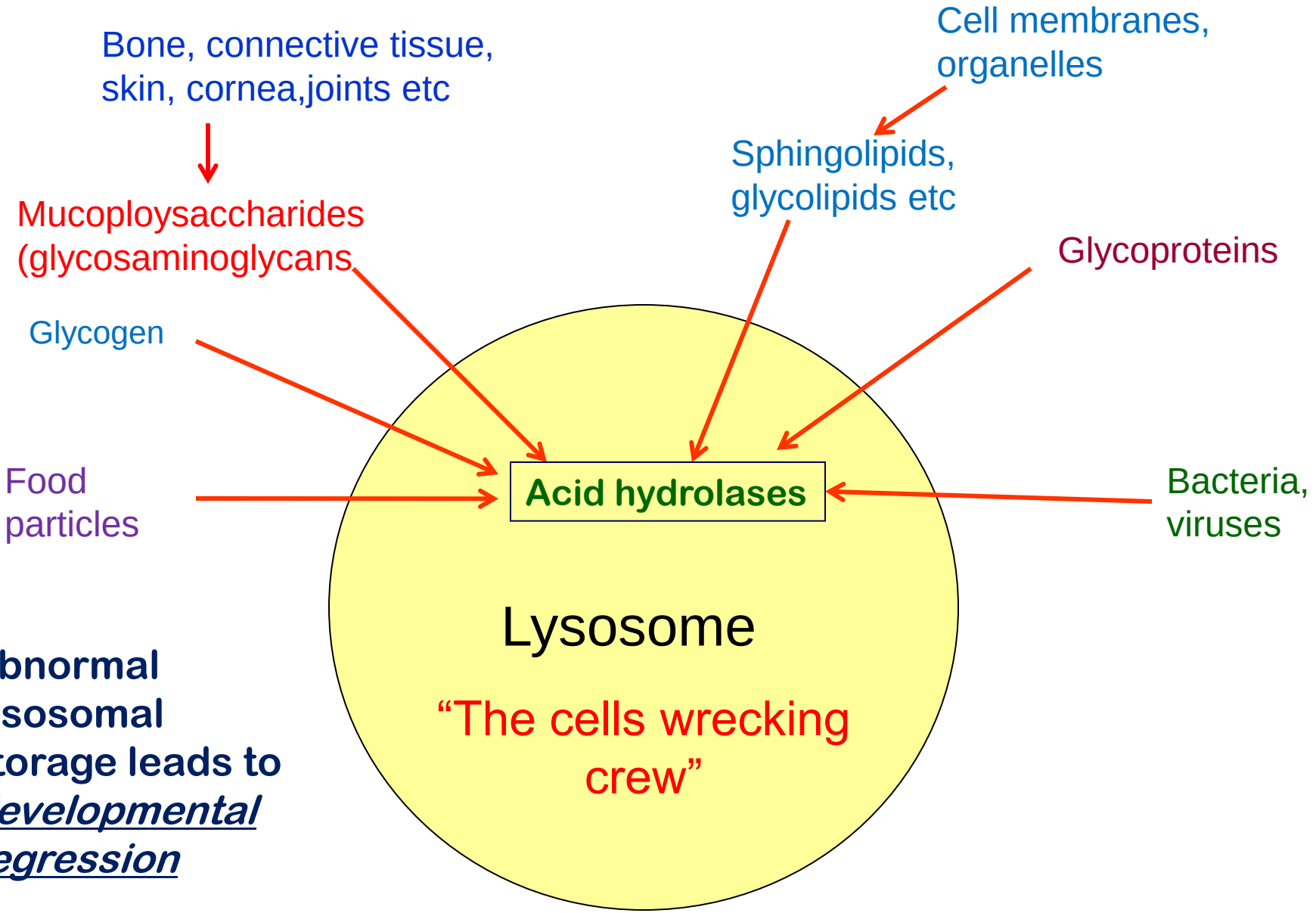
LYSOSOMAL STORAGE DISEASE

- The hydrolytic enzymes within lysosomes are involved in the breakdown of sphingolipids, glycoproteins, and mucopolysaccharides into products.

- These molecular complexes can derive from the turnover of intracellular organelles or enter the cell by phagocytosis,

- A number of genetic diseases lacking lysosomal enzymes result in the progressive accumulation within the cell of partially degraded insoluble products, This condition leads to clinical conditions known as:

lysosomal storage disorders.



Abnormal lysosomal storage leads to *developmental regression*

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:
  - **Glycosaminoglycans (MPS)**
  - **Sphingolipids**
  - **Glycoproteins**
  - **Glycolipids**
- May be it is a result of genetic drift and natural selection
- Children normal at birth, downhill course of differing duration

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

Sphingolipidoses

- **Tay-Sachs disease** **AR** **Hexosaminidase -A**
  - Developmental regression, Blindness,
  - Cherry-red spot, Deafness
- **Gaucher' s disease** **AR** **Glucosylcerarnide Type l**
  - 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

Mucopolysaccharidsis

- Hetrogenous caused by reduced degradation of one or more of glycosminoglycans
  - Dermatan sulfate
  - Keratan sulfate
  - heparin 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 or
- **Genetics:** All AR except Hunter syndrome X linked
- **Clinical:** Progressive multisystem deterioration causing:
  - Hearing, Vision, Joint and Cardiovascular dysfunction

Examples

- Hunter syndrome
- Hurler syndrome
- Scheie syndrome
- Sanfilippo syndrome
- Morquio disease
- Maroteaux-Lamy syndrome

CYSTINOSIS AR

- 1/200,000 births
- Lysosomal storage disease due to impaired transport of cystine out of lysosomes.
- High intracellular cystine content Crystals in many tissues. Clinical Manifestations are age dependent include renal tubular Fanconi syndrome, growth retardation(Infancy syndrome), Renal failure develops by 10 year of year(Late childhood) and cerebral calcification(adolescence period).

Purine/pyrimidine metabolism

- **Lesch-Nyhan disease** **XR**
  - Hypoxanthine Guanine Phosphoribosyltransferase Deficiency
  - Mental retardation,
  - uncontrolled movements, } Uric Acid Crystals in CNS
  - S64}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

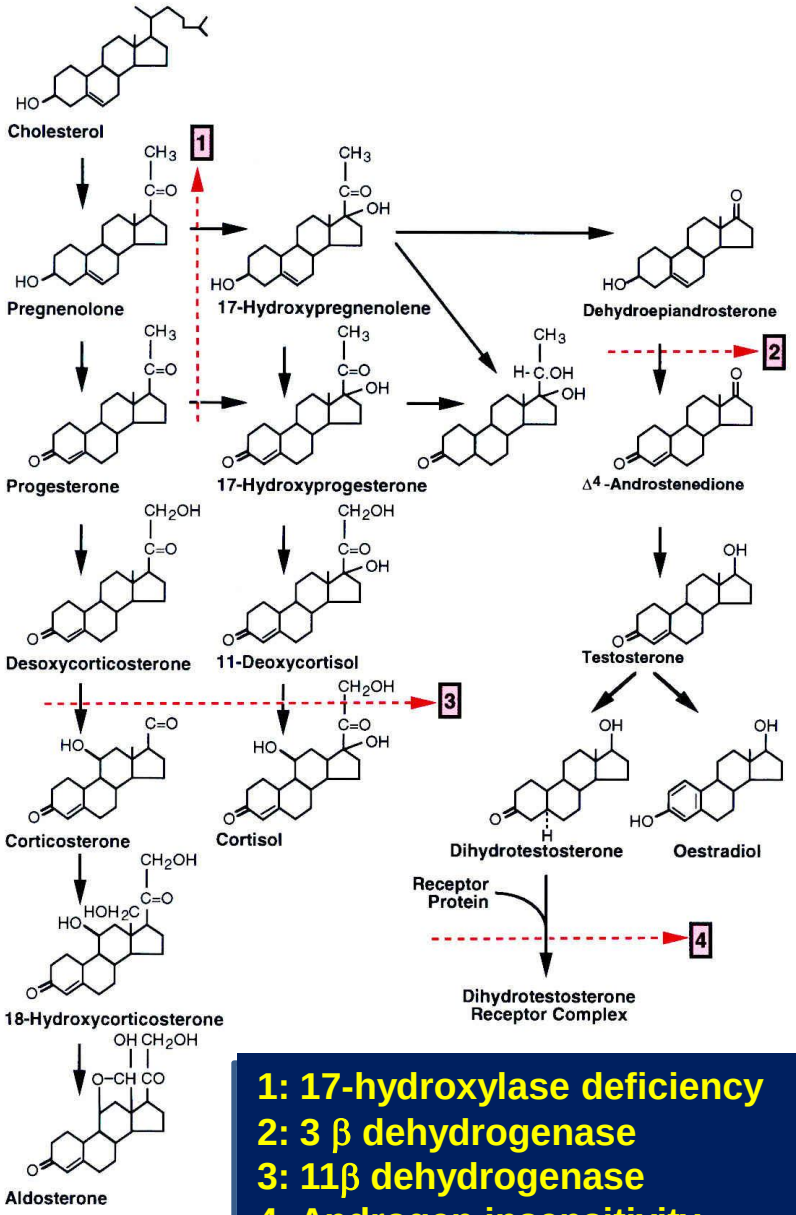
- **Hereditary orotic aciduria** **AR**
  Orotate phosphoribosy ltransferase , Deficiency
  - Orotidine 5'-phosphate Decarboxylase Deficiency
  - Megaloblastic anaemia in the first year of life,
  - Failure to thrive,

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

Steroids Metabolism

There are a number of disorders of steroid metabolism which can lead to **virilization** of a female fetus due to a block in the biosynthetic pathways of cortisol as well as a disorder of **salt loss** due to deficiency of aldosterone



1: 17-hydroxylase deficiency
2: 3 β dehydrogenase
3: 11β dehydrogenase
4: Androgen insensitivity

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 . . .

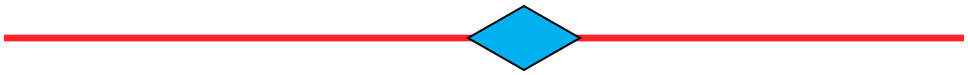
- Neurological deterioration
- Metabolic acidosis
- Hypoglycemia
- Inappropriate ketosis
- Hypotonia
- Cardiomyopathy
- Hepatocellular dysfunction
- Failure to thrive

. . . 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