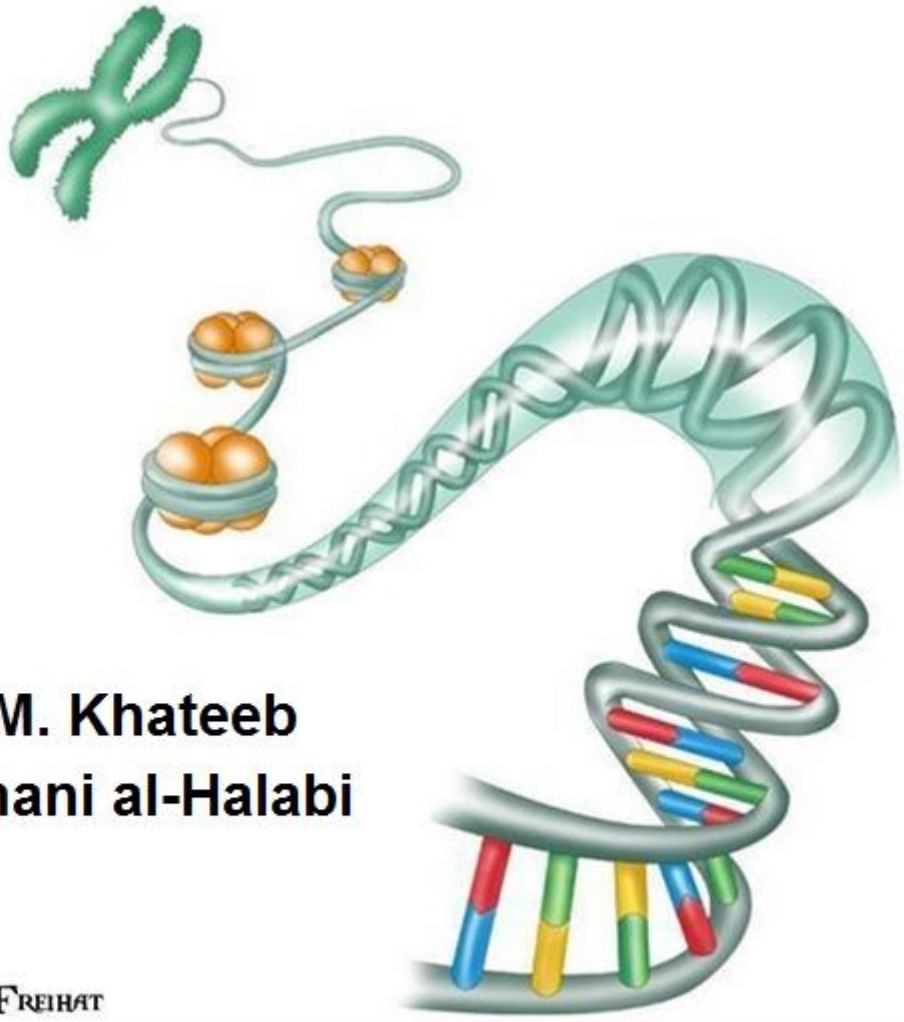
University of Jordan
Faculty of Medicine
Batch 2013-2019

Medical Committee
The University of Jordan

Genetics & Molecular Biology

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



Sheet#: 7

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Mitochondrial Inheritance &

Inborn Errors of Metabolism

In this sheet we'll be discussing two topics.

1- The last "non-traditional" way of inheritance.

2- Inborn Errors of Metabolism.

The first part is a continuation to the previous lectures, but the "Inborn Errors" part is a new topic that you need to study it from the sheets/slides, it's not included in the book.

In this sheet I tried to re-write all the details in the slides and they will be put in boxes.

Pay attention that the doctor didn't discuss all the slides in section1' lecture, he stopped at slide 54.

Introduction:

Before going in a new topic, let's define again the "**Anticipation**". Anticipation -related to trinucleotide expansion- is the appearance of clinical features and mutated phenotypes of a disease with increased severity in new generations.

→ This is because the trinucleotide are repeated more in new generations. For example, in a grandfather you find very mild findings or even no clinical picture, and in the sons you find more sever features, and finally in the grandchildren you'll be seeing the most sever clinical cases.

Pay attention: these trinucleotide expansions may be located in coding regions or non-coding regions. .

One of the most important disorders regarding these expansions is the **Fragile X Syndrome** that's seen among males more than females, and a problem of "**CGG**" over-repeating from 200-2000 times.

The problem here is due to mutation in the **q arm** of the chromosome in a certain "fragile site" at the lower part of the chromosome, and this site can be detected by cytogenic testing and molecular biology techniques to count the trinucleotide expansions (number of repetitions) in a media that lacks Foliate.

The main features and symptoms of this syndrome in **males** are:

- Problems in coagulation
- Mental retardation (intellectual disability)
- Tension , Fever disorders
- Macroorchidism (abnormally large testes; seen in males with fragile X syndrome)
- Long face with large prominent ears
- Emotional problems
- Connective tissue disorders

Among **females**, you clearly can notice mild (less severe) features:

- Mild level of mental retardation

- General behavioral (looks shy) and physical disorders

→ Fragile X syndrome may be expressed in 3 different syndromes:

- **Fragile X syndrome (**200-2000 repeats of CGG){as mentioned above}
- **Fragile X tremor ataxia syndrome** (61-200 repeats) with "Premutation" disorders, including ovaries' involvement in females.
- (44-61 repeats) and this case is considered again an intermediate Premutation or suspicious.

#Using molecular biology ,to count the number of CGG repetitions in the genome of the patient .If its less than 45 → normal person. If its between (55-200 repeats)→ Premutation .If its over 200 → trinucleotide expansion. so the syndrome depends on the CGG repetitions .

* There has been found an association between Fragile X syndrome (FXS) and **Autism**; 1/3 of FXS patients may develop and show Autism throughout their lives.

→ Another disorders related to the expansions and anticipation:

- **Mytonic dystrophy** , "**CTG**" repeats:
  (5-37) times: Normal
  (50-90) times: "Premutation"

Over 1000→the disease will be expressed in children as below:
This disorder is expressed in children, mainly in the form of muscle wasting and mental retardation.

- **Huntington's disease , "CAG**" repeats.

<u>To cap it:</u>
Trinucleotide expansions disorders, in general, are repeats that account for a large proportion of <u>inherited neurogenic diseases</u> characterized mainly by mental retardation.

- Don't forget to use some sensitive tests to look for these expansion to diagnose, treat, or prevent a disease, and to counsel the families regarding the disorders from which they may suffer.

Mitochondrial Inheritance(non-traditional way of inheritance)

Mitochondria: Organelle**s** in the cytoplasm of each cell. They have their own DNA that differs from that of the nucleus and are already independent on it except for few genes.

Mitochondria are essential in energy production, and the enzymes needed for this great function are mainly expressed by the mitochondrial DNA.

[Enzymes like those essential in metabolic activities and oxidative phosphorylation includes: Pyruvate DH, Phosphorylases (remove phosphates), TCA cycle enzymes, Lactate oxidation enzymes]

Mitochondria are found greatly in organs that produce and utilize energy in high rates like: Muscles, Brain, Pancreas, etc. So expect the mitochondrial diseases and their manifestations to be more shown in these organs.

Genetic characteristics of mitochondrial diseases are "Semi-dependent";

- Some proteins (like poly-peptic proteins) are controlled by the mitochondrial DNA , and other some of them are controlled by nuclear DNA.

- Universality of codons is different from the nuclear DNA.

Different codons for different amino acids and functions than those of the nucleus; UGA is a stop codon in nuclear DNA, while it encodes Tryptophan in mitochondrial DNA.

- Maternally Inherited: a patient will get the disease from his mother not father; when a sperm and an ovum meet, the mitochondria in the sperm will degenerate, thus the inheritance of mitochondria , its diseases, and their related phenotypes is maternal in origin.

- Have a Threshold value. (will be discussed later on)

-The mitochondrial DNA is a small circular double stranded DNA,most of the mitochondrial proteins are controlled by nuclear genes or mitochondrial genes and sometimes by both(combination).
-There are 37 mitochondrial genes two of them for ribosomal RNA,22 for tRNA ,and 13 coding polypeptide .

- High rate of mutation; because in the mitochondrial DNA you will find only exons (no introns), and this means that all nucleotides are considered parts of genes and the incidence of getting a mutation is higher.

Mitochondrial diseases vary, and are 40 in number, each of which varies again from mild to very severe form, and that's due to the different features of the inherited mitochondria.

- The incidence is around 1:3000-4000.
- Different diseases have different specific symptoms; but in general, there're some common symptoms include:
  - Poor growth
  - Loss of muscles' coordination, weakness and wasting.
  - Vision and hearing problems
  - Learning problems
  - Developmental delay
  - Mental retardation
  - Heart, kidneys, liver diseases
  - GI disorders
  - Neurological abnormalities; seizures
  - Diabetes due to pancreas involvement
  - Respiratory distress
  - Dementia

- Why do some cases are very severe while others are really mild?
  This is due to the unequal distribution of mutations;
  When a patient inherits the mitochondria, 50% of them may be mutated, but once the cell divides, it won't send the mutated mitochondria equally between the daughter cells, Some new cells will take more mutated mitochondria than the others due to the fact that the cytoplasm isn't usually divided into equal portions.

➔ One cell has 50% mutated mitochondria and the another one has 30% mutated ones only, or sometimes there might not be any mutated ones.
➔ This is related to "Threshold value"; the spectrum of the disease severity (absent-mild-severe-very severe) varies due to different percentages of mutated mitochondria in dividing cell.

- Since the inheritance is only from the mother and she can transfer the mutation to her sons and daughters, and the father won't transfer it ever, it resembles the Autosomal Dominant or X-Linked Dominant inheritance rules.
- You need to differentiate a pedigree related to mitochondrial diseases from other pedigrees.

In a mitochondrial disease' pedigree, you should notice the disease appearance in all generations, however, in some cases there may be a disease-free generation (no member of a certain generation has the disease) and this may be due to incomplete penetrance or various expression

Inborn Errors Of Metabolism

- 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.

- Mostly due to defect in or absence of an enzyme, Absence of a cofactor or transport protein resulting a block in a specific metabolic pathway.

- Generally, due to single gene defects; the enzyme/protein that's affected here is controlled by one gene.

- Involve all inheritance patterns (some are X-linked, some are AD), however, most common is **Autosomal Recessive**

- Common defects on a biochemical level:

* Transport defects

* Accumulation of substrate

* Deficiency of product

* Secondary inhibition

- 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**

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

Metabolism..

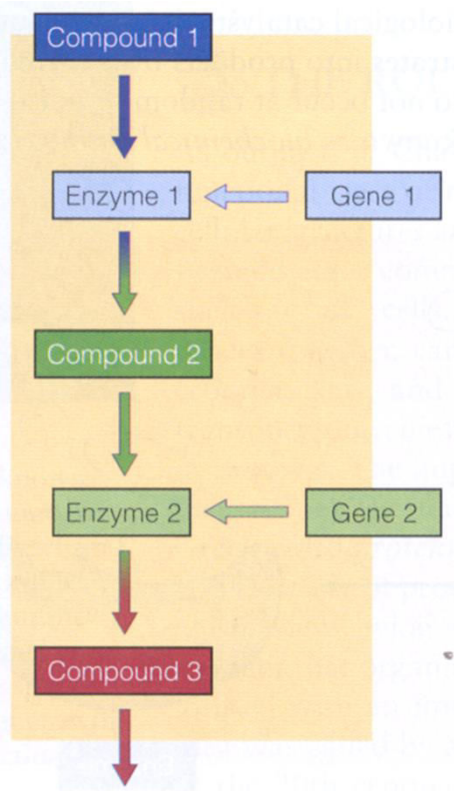
- Anabolism (Building up) vs. Catabolism (Breaking down)
- Needs Enzymes that play an important role in catalyzing the conversion of one chemical to another.

→In any normal metabolic pathway, we start with a compound (protein, lipid, carbs), then through the elementary tract it will be metabolized.

→ Follow the chart; after the effect of enzyme 1 (coded by gene1), the compound will become a new one: compound 2.

Imagine if gene1 is mutated → enzyme 1 isn't functioning → compound 1 will be accumulated.

Then imagine if there's a defect in gene2 → non-functional enzyme 2 → compound 2 will be accumulated.



Inborn error overview ..

General mechanisms 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**

- IEM are disorders in which there is a block at some point in the normal metabolic pathway.
- IEMs occur due to mutations in DNA.
- Mutated DNA will code for Specific abnormal protein:

- Enzyme- Transport vehicle- Receptor - Membrane pump - Structural element

It's all about ingesting proteins, lipids, carbohydrates, they:

-Need factors to break them to their primary components in the body

[If you have deposited glycogen in your body, glycogen will be metabolized by certain enzymes and co-enzymes to produce glucose and different intermediates. But if the needed enzymes/co-enzymes are not functioning, you will be having a glycogen storage disease.]

Remember that you need all the enzymes in the pathway to be functioning properly ;so no intermediates will accumulate and disrupt the production of the final glucose monomers; the accumulation of certain materials is not only wasting energy, these intermediates may be toxic to cells too.

-Need close interactions.

Metabolic diseases can be classified into:

1-Small molecule disease:

-Carbohydrate

-Protein

-Lipid

-Nucleic Acids

2- Large Organelle disease

(Deposition of non-metabolized materials in) :

-Lysosomes

-Mitochondria

-Peroxisomes

-Cytoplasm

Types of inborn errors

1- Protein Disorders:

Amino Acid, Organic acids, Urea Cycle

2- Carbohydrate Disorders:

Galactosemia, Glucose transport, Glycogen, Fructourea.

3- Fatty Acid Disorders:

(Regarding short or very long chains)

Medium chain acyl-CoA dehydrogenase deficiency

Long chain 3 hydroxy acyl-CoA dehydrogenase deficiency

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.
- few are inherited as Autosomal dominant trait including: porphyria, hyperlipedemia, hereditary angioedema.

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Carbohydrate Metabolism

Carbohydrates are important energy stores, fuels and metabolic intermediates.

→ Some disorders related to carbohydrate metabolism:

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

Let's start with Galactosemia

- Results from a disturbance in the conversion

Of galactose to glucose.

- The enzyme deficiency causes an accumulation of galactose in body tissues.

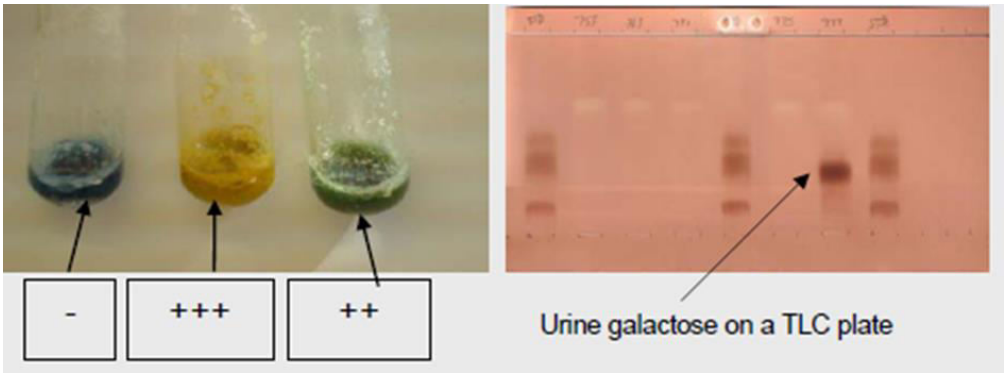
→ Classic type lacks **GAL**actose-1-phosphate uridyl**T**ransferase (**GALT**), this enzyme has 2 sub-types:

  - **Gal**acto**K**inase (GALK) deficiency results in infantile cataracts from accumulation of galacticol.
  - **Gal**actose**E**pimerase (GALE) deficiency mostly confined to blood cells and mostly appear normal .

- Estimated incidence 1/50,000 births
- We can diagnose it by measuring the non-glucose reducing substances in urine.

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.
- Confirmation by Galactose-1-PO uridyl transferase activity in RBCs.
- Adverse sequelae include Cataracts, MR, persistent liver disease.



- The picture to the left shows the test:
- You take different samples of urine then heat them.
- If the sample becomes blue in color : -ve / very mild
- If the sample becomes green in color : ++ve / severe
- If the sample becomes Yellowish/browinsh:+++ve/the most severe .

→ Or we can use thin layer of the sample on chromatography to see the accumulation of galactose.

Recap:

Lactose is metabolized by Lactase to Galactose, then Galactose will be converted to galactose-1phosphate by Galactokinase.

Finally Galactose-1phosphate will be converted to Glucose by Galactose-1phosphate Uridyltransferase enzyme.

→If lactose doesn't complete the pathway to glucose, it with the intermediate (Galactose) will be accumulating in the:

-Eyes: Causing Cataracts

-Liver: Causing Jaundice, Hepatomegly, Cirrhosis.

-Brain: Causing Mental Retardation (MR)

HEREDITARY FRUCTOSE INTOLERANCE:

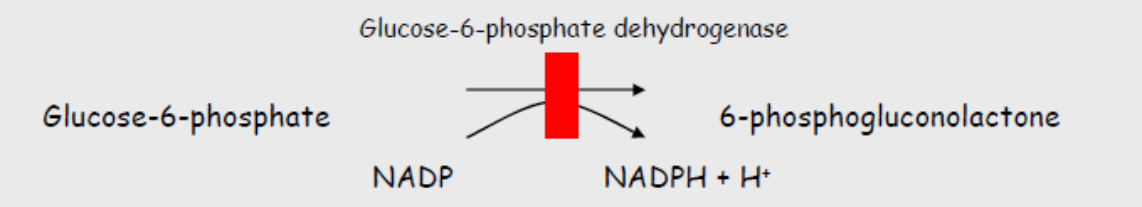
- Fructose 1 phosphate aldolase deficiency
- Diagnosis: Fructose in Urine + Enzyme in the intestine mucosa and liver.
- Clinically: Mild to sever
- Treatment: Diet restriction

Glucose-6-phosphate DH deficiency

- This is an X-linked defect,
- This enzyme controls an 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



- The most common manifestations are early neonatal unconjugated jaundice and acute hemolytic anemia.
- 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 Diseases

-Types:

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

Let's Start with Glycogen Storage Diseases (GSD)

- It may be due to deficiency of Glycogen Synthetase enzyme, then the Uridine-Diphosphoglucose won't be converted to Glycogen straight chains.
- Or (GSD-IV) It may be due to defect in the second enzyme: Branching enzyme, and then the Glycogen straight chains won't be converted to the branched molecule: Limit dextrin + Glucose-1-PO^4.
- Or (GSD-III), the defect may be in the 3rd enzyme: the De-branching enzyme thus the limit dextrin won't be converted to a Normal branched- Glycogyn
- Finally, (GSD-I), the last enzyme: Glucose-6-phosphatase may be deficient , and prevent the conversion of glycogen to glucose.

→ There're 4 types of glycogyn storage diseases:

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

Slides (27-30) are for your own information -as doctor said- , go read them if you're still awake ☺

Mucopolysaccharaidosis..

- These disorders are heterogeneous, mainly due to deficiencies of enzymes involved in Glucosamine and GAGs metabolism.

→reduced degradation of one or more of Glycosminoglycans:

- Dermatan sulfate
- heparin sulfate
- Keratan sulfate
- Chondritin sulfate

→ These molecules are important as substrate to produce GAGs which are the Mucopolysaccharides.

- MPS are the degradation products of proteoglycans found in the extracellular matrix.
- 10 different enzyme deficienies disorders.
- Diagnosis
  - Clinical, Biochemical and Molecular analysis.
  - Meausrment of the enzymes in fibroblast, leukocytes, serum.
  - Prenatal diagnosis on Amniocytes C.
  - Urine for MPS (heparan , keratan , dermatan).

- Genetics: <u>All AR except Hunter syndrome X linked</u>

- Clinical: Progressive multisystem deterioration causing:

  - Developmental delay.
  - Behavioral dysfunction
  - Coarse facial features & other somatic features
  - Cloudy cornea
  - Abdominal distension (Hepatosplenomegaly)
  - Dysostosis multiplex (Scoliosis and gibbous deformity in bones)

- Hearing, Vision, Joint and Cardiovascular dysfunction

Types of Mucopolysaccharaidosis

(SHM)^2

1. **H**unter syndrome (X linked)
2. **H**urler syndrome
3. **S**cheie syndrome
4. **S**anfilippo syndrome
5. **M**orquio disease
6. **M**aroteaux-Lamy syndrome

→To **Diagnose** it, try to detect the following enzymes:

1.α-idurondase

2. Iduronate **Sulfatase**

4. Heparan–N–**Sulfatase**

5. A:N–Galactosamine–6–sulfate **sulfatase**

5. B:β-galactosidase .

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Lysosomal Storage Diseases ..

- Lysosomes are very important organelles that function to eliminate the foreign bodies and waste materials and hydrolyze them by enzymes and acids.
- These materials could be:

- Viruses and Bacteria
- Remnants of connective tissues
- Lipoproteins

- Any deficiency or inability to activate or transport the Enzymes within lysosomes that catalyze stepwise the degradation of:
  - Sphingolipids
  - Glycoproteins

- Glycolipids

Will result in accumulation of the substrates and depositing it in lysosomes →Lysosomal storage disease.

- It may be a result of genetic drift and natural selection

Focus on key differences between the 2 main diseases:

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

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

- Tay-Sachs disease : AR , Hexosaminidase-A Deficiency
  - Developmental regression, Blindness,
  - Cherry-red spot in the eye, Deafness

- Gaucher' s disease : AR,

→ Glucosylceramide Type l Deficiency
  - Joint and limb pains, Splenomegaly

→β- Glucosidase Type II Deficiency
  - Spasticity, fits; death

- Niemann-Pick disease : AR, Sphingomyelinase Deficiency
  - Failure to thrive, Hepatomegaly
  - Cherry-red spot in the eye, Developmental regression

Lipidosis..

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

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Peroxisomal Disorders

Zellweger Syndrome (Cerebro-hepato-renal syndrome)

Clinical signs

- Typical and easily recognized dysmorphic faces.
- Progressive **degeneration of Brain/Liver/Kidney**, with death ~6 mo after onset.
- Hypotonic, **seizures** and **poor feeding**
- Distinctive faces.
- Retinal dystrophy,
- hearing loss, severe DD
- **Very Long Chain Fatty Acids accumulate and cause osmotic diarrhea**

Diagnosis

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

Amino Acids Metabolism & Disorders

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

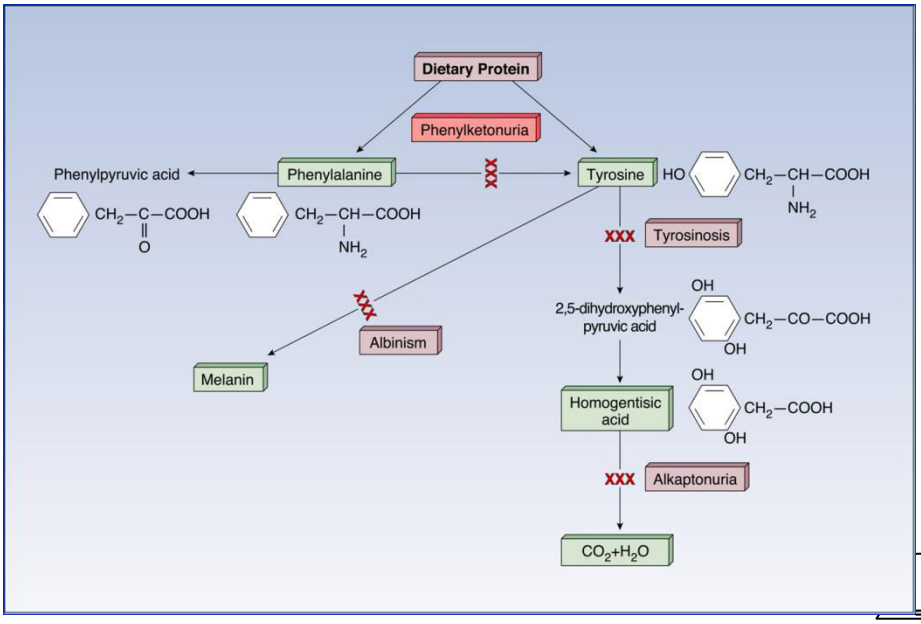
Amino Acidurias

- 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 screen, but only does good if results followed up.

Phenylketonuria

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

- One of the most important errors in metabolism; because if we discover it early there is a treatment for this disease.
- so its one of the diseases that can be used as a screening test for the new borns.
- If not treated , the clinical manifestation is very severe : severe mental retardation , neurological manifestation , seizure hyperactivity , hyperpigmentation (spots on his body) , behavioral disturbances , developmental delay
- Incidence : around 1/5000 -1/16000
  - It is Autosomal Recessive .
  - The mutation is on chromosome # 1
- 71 mutations found
- The Mutation will be in PA Hydroxylase D enzyme
- Developmental delay in brain due to phenylalanine accumulation, damage in brain , severe mental retardation.
- PA is Normally found in food, and it is converted to tyrosine
- If the enzyme is not functioning then PA will accumulate and cause the disease
  - Tyrosine will then be converted to melanin (need Tyrosinase enzyme)
  - If tyrosinase is not functioning then the patient will have **albinism** (no melanin production)
  - The final product is co2 and water
  - If homogentisc acid is not found, the patient will have **alkaptonuria**
- So if we have a problem in PA Metabolism 3 diseases might happen!



Diagnostic critiria:

Normal: 120 – 360 micro mol/L

PAH Deficient:

- Mild: 600 – 1200 micro mol/L
- Classical: > 1200 micro mol/L , severe mental retardation

Non-PAH Deficient:

- < 600 umol/L

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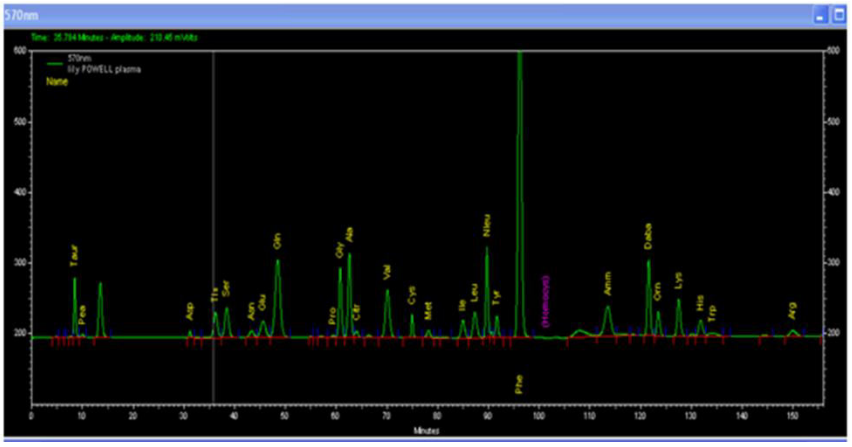
Then you can use some tests:

- Guthrie Bacterial Inhibition Assay
- Confirmation of diagnosis, HPLC(High-performance liquid chromatography) of Molecular

→Plasma amino acid profile PKU:



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

→Defects in tetrahydrobiopterin or other components in related pathways

(Dihydropteridine reductase or synthetase deficiency)

Alkaptonuria

Where the Homogenstic acid enzyme is deficient ,we put urine in a cup then it will have a dark black color because when it is exposed to air the change in color will be used as a diagnosis

- 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**

Oculcutaneous Albinism (the dr didn't explained them in the lecture; this was added by the writer of the sheet from slide 7)

- OCA is AR due to tyrosinase deficiency no melanine formation
- No pigment in skin, hair, iris and ocular fundus
- Nystagmus(condition of involuntary (or voluntary, in rare cases) eye movement)
- Genetically and biochemically 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

Homocystinurua

→Sulfur AA metabolism disorders due to:
Cystathionin β-synthetase deficiency

- Clinically: severe disorder; 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.

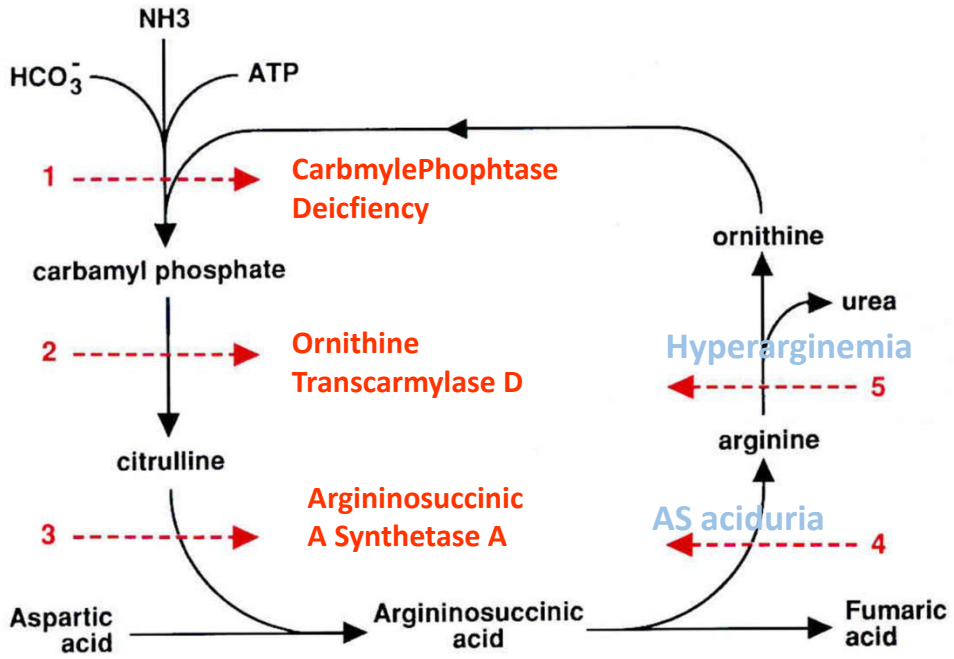
Branched Chain Amino Acids disorders

(the dr didn't explained them in the lecture; this was added by the writer of the sheet from slide 7)

- 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** (Maple syrup urine disease)
- Untreated patients, accumulation of BCAAs cause neuro-degeneration 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 that can be affected** in humans:
  - Carpamyl phosphate synthetase (CPS), **AR**
  - Ornithin trans carbamylase (OTC), X-linked
  - Arginino succinic acid synthatase (ASA),**AR**
  - Argininosuccinase (AS), **AR**
  - N-acetyl glutamate synthetase (NAGS).**AR**
- All are AR except the OTC deficiency: X-linked.

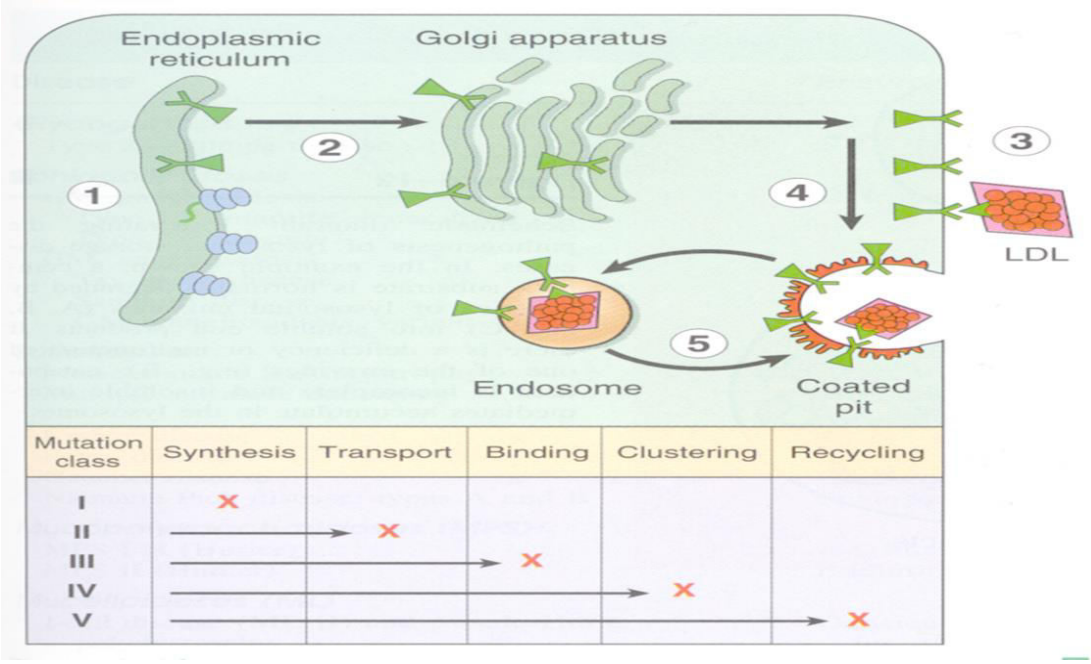


- Symptom free period and then emesis->lethargy-->>COMA
- Key features:
  - High Ammonia, low BUN (**blood urea nitrogen**)
  - Possible Lactic acidosis
  - *Absence of ketonuria*
  - Nl(normal) to mild low Glucose
- **Treat high ammonia, infuse glucose, send plasma AAs/OAs, urine orotic acid, and plasma 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.

Here we are mainly concerned with LDL receptors regulation.

LDL receptors are extremely important in **cardiovascular** diseases

-The defect may be in the center of **synthesis** (ER) then there will be a sever deficiency of receptors (1).
- The defect may be in the **transport** between the ER and the Golgi apparatus (2).
- The defect may be in the ability of the receptor to **bind** to the cell membrane (3).
- The defect may be in the **clustering** mechanism of the receptor after binding to its LDL (4).
- The defect may be in the ability of **lysosomes** to metabolize the Receptor-LDL complex after clustering (5).



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

The final slides, (54-67)

Fatty Acids are:

1- Short chains

2- Medium chains

3- Long chains

→Fatty acids 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

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→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.

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

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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,

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

-steroid are the back bone of all cholesterol hormones, so during the synthesis of these steroids at any stage of synthesis there might be a deficiency if the enzyme is deficient at that stage .

-There are 5 different types, the most common one is 21-hydroxylase (90%) ,where the cortisone isn't synthesized .

Testicular feminization ;is an x-linked disease(translocation between SRY gene from XY chromosome, the end result will effect:

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

Copper Metabolism

-**Wilson disease**; there is a receptor for copper in the membrane and there is deficiency in that receptor.
#symptoms; Spasticity , Rigidity, Dysphagia, Cirrhosis.

Copper Transport protein(is not working);
ceruloplasmin→deficiency in ceruloplasmin.

-In **Menkes' disease** → deficiency in ceruloplasmin and in copper membrane receptor→deposion of copper in neurons→ Failure to thrive, Neurological deterioration.

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

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

Treatment

-treatment depends on the disease that we are concerned about.

-In phenylketonurea →the patient is given a milk without phenylalanine or (lactose free or fructose free meal){this will prevent the disease}

-Glycogen storage disease→supply them with glucose because they are unable to maintain the glucose supply.

-Fluid support.

-Remove some metabolites via dialysis.

-Supply the patient with co factors if they are deficient.

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

-Infants have certain symptoms for ex; vomiting, lethargy, seizers, fits, hyper-ammonemia , comma ,odor, septic appearance infants(septicemia) ,failure to thrive ,neurological deterioration ,metabolic acidosis ,hypoglycemia, inappropriate ketosis ,hypotonia ,hepatocellular dysfunction, arrhythmia and abnormal ear. if you see one of this ,this might give you an indication that the patient might have IEMs.

Summary:

Major IEM present in the neonates as 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

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 .	

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

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THE END

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