Metabolism

فريق طوفان الأقصى

Modified N: 18

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Set correctly , drink enough water , relax ..
Ready, steady , GOOO

بسم الله

Amino Acid Synthesis

- Today we will continue in the metabolism of amino acids , specifically the synthesis of “ non-essential amino acids" (which can be synthesized in our cells)

They are 11

Biosynthesis of Nonessential Amino Acids

Essential: Phe, Val, Thr, Trp, Met, Leu, Ile, Lys & His

Nonessential: Ala, Arg, Asp, Asn, Cys, Glu, Gln, Gly, Pro, Ser &

NOTE: any AA which is directly obtained from diet = essential, any other AA synthesized in our cells even though it's precursor is essential ,we consider it a non-essential AA .

Hint : all amino acids starting with "A,G, C" are non-essential

Nonessential amino acids are synthe

Remember : When phenylalanine is hydroxylated (adding OH) >> Tyr is synthesized.

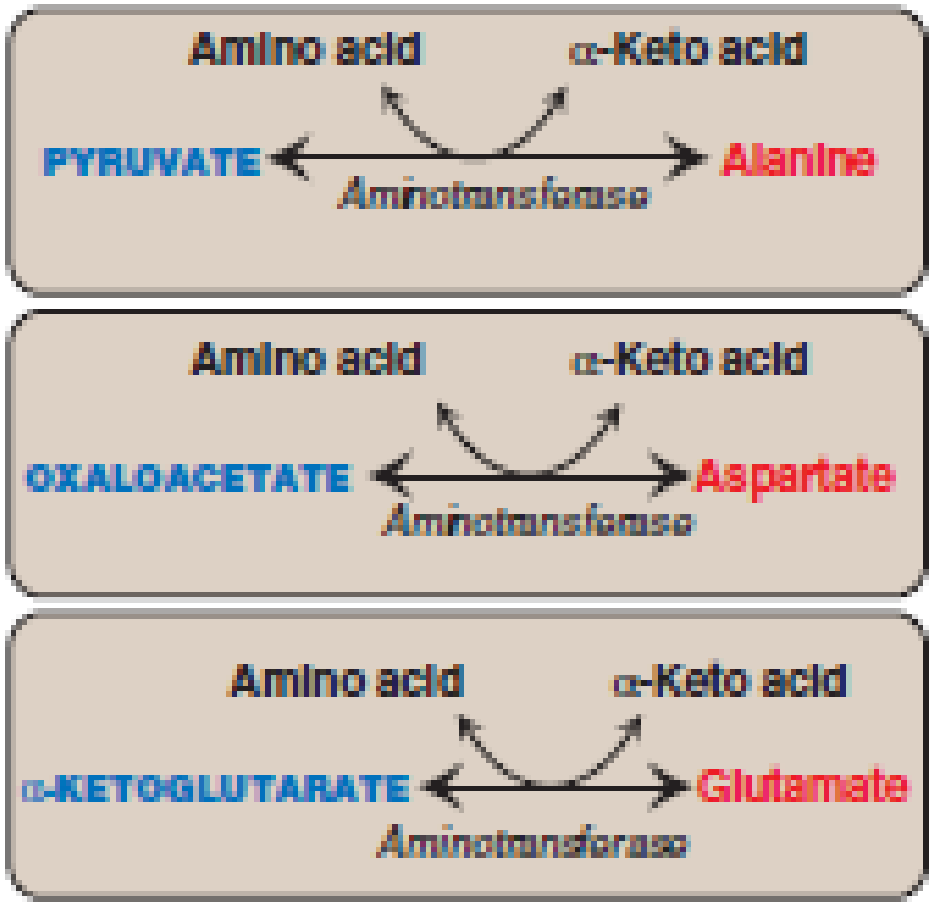
Ser is made from Gly

1. Metabolic intermediates

2. Or from the essential amino acids.

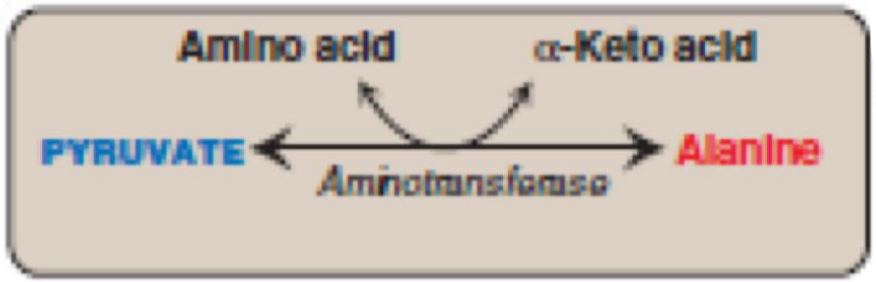
- the first mechanism of synthesizing non-essential AA , is the transamination of a-keto acids

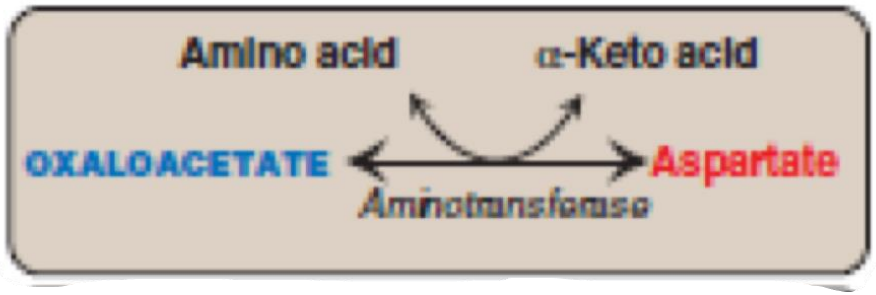
Synthesis from α-keto acids



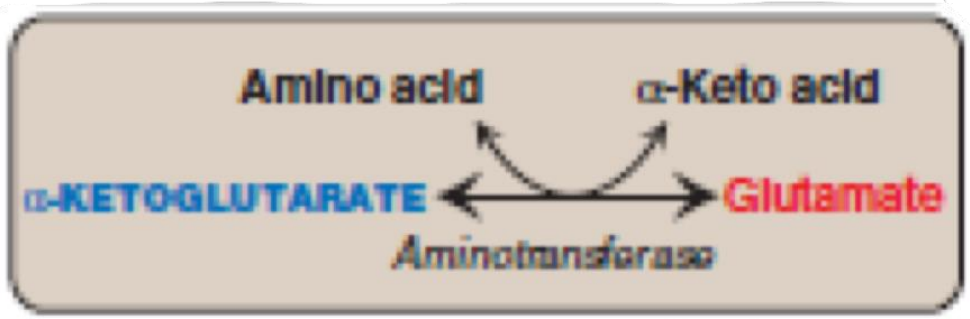
Ala, Asp, and Glu are synthesized by transfer of an amino group to the α-keto acids pyruvate, oxaloacetate, and α-ketoglutarate, respectively.

Glu can also be synthesized by the reverse of oxidative deamination, catalyzed by glutamate dehydrogenase





- **ALT** can transaminate pyruvate by bringing the amino group from glutamate and then : **pyruvate becomes Alanine and Glutamate becomes a-ketoglutarate** .
- **Oxaloacetate** obtains it's amino group from glutamate and **becomes aspartate and again glutamate becomes a-ketoglutarate**

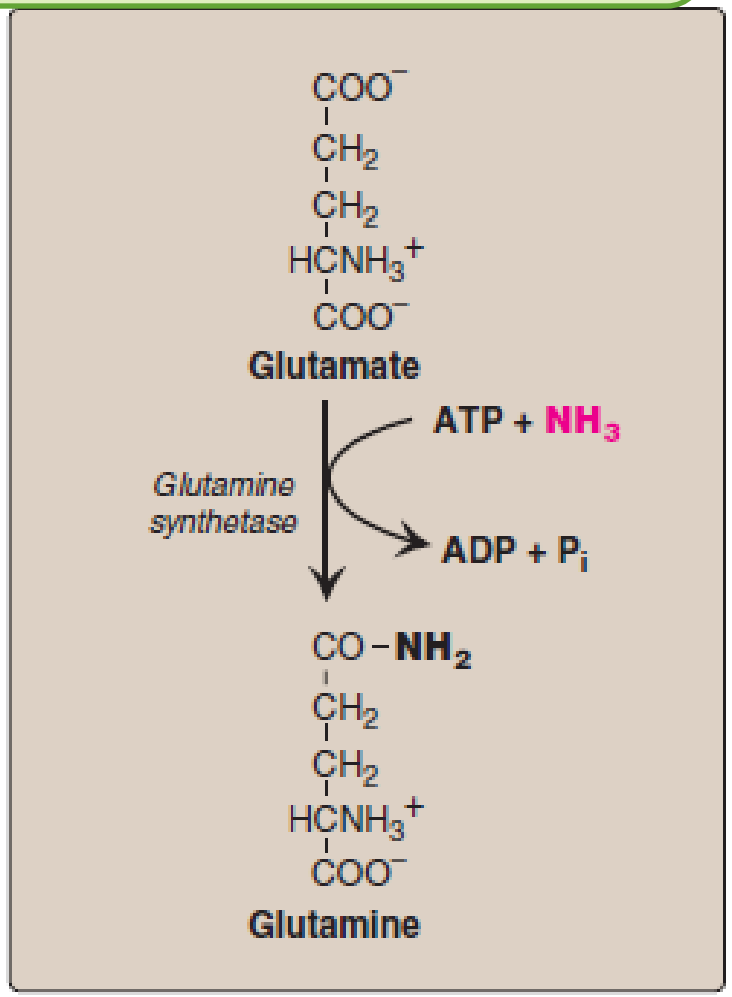


- The third reaction is the reverse of oxidative deamination >> **Reductive Amination .** Oxidative deamination occurs to Glutamate to become a-ketoglutarate but now the **reductive amination will convert a-ketoglutarate to Glutamate** which is catalyzed by glutamate dehydrogenase

Synthesis by amidation

- Formation of amide group , notice that there only in 2 amino acids containing amide group : Gln& Asn

1. Gln is formed from Glu by glutamine synthetase

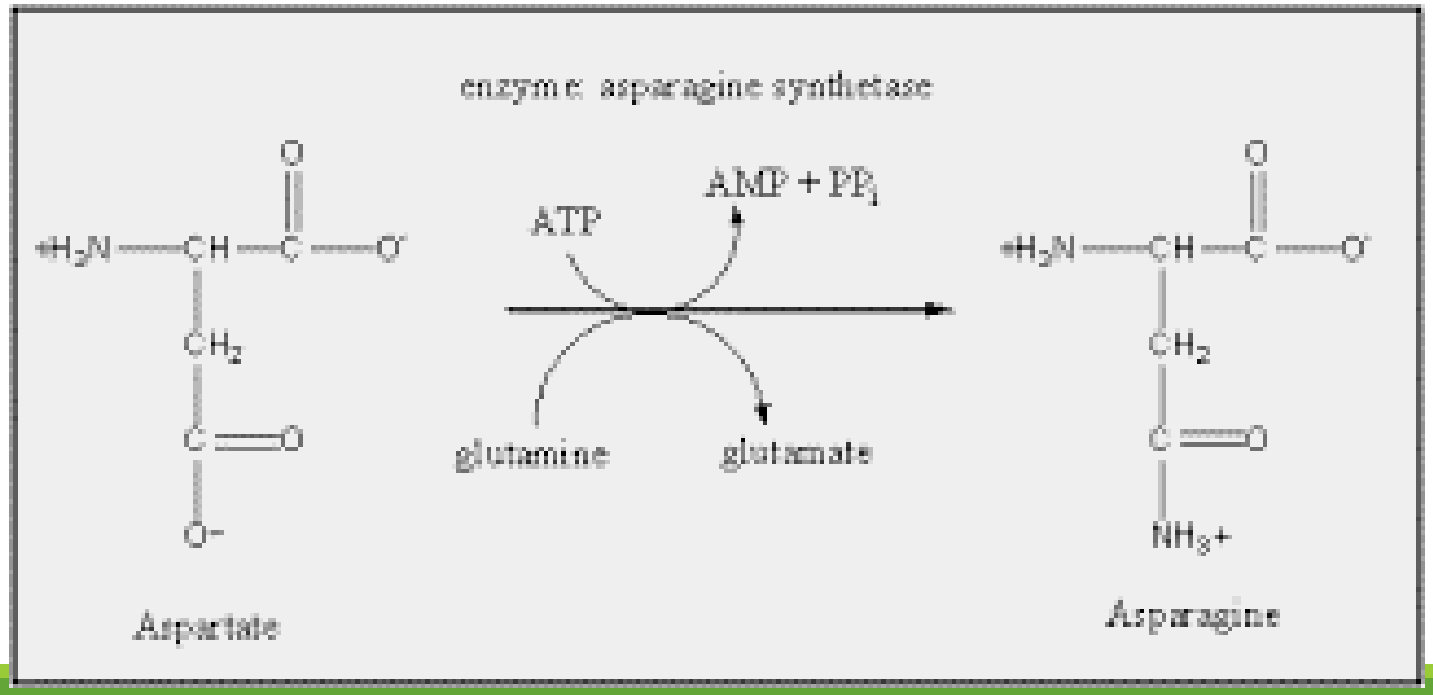


- **NOTE:** Gln is used to transport ammonia , all AA undergo transamination to form Glu , and then it becomes Gln by transporting a **free ammonia** to Glu . This reaction can happen either to transport ammonia to the hepatocytes, for urea cycle to occur , or to use Gln (ex: using it in protein synthesis)
- The enzyme that catalyzes this is Glutamine synthetase , which uses **ATP** that becomes **ADP**

2- Asn is formed from Asp by asparagine synthetase, using glutamine as the amide donor.

- **NOTE:** We add an amine group to the Asp but this time (the amino group doesn't come in the form of free ammonia) , instead it comes **from Glutamine amino acid. Because** the reaction of glutamine has a dual function function, 1. The production of glutamine 2. The transport of ammonia.

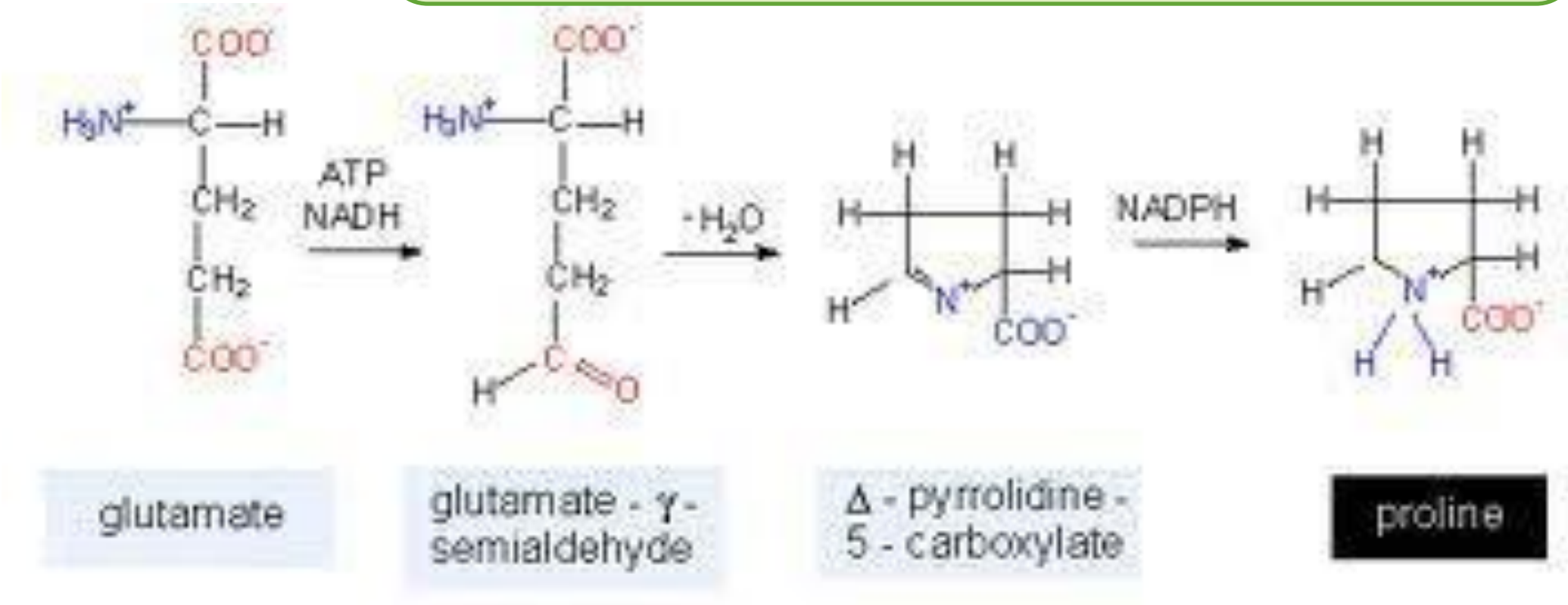
- The enzyme that catalyzes this reaction is **Aspargine synthytase** , which needs an ATP that becomes **AMP** (2phosphate) because there are 2 changes in this reaction vs one in the Gln reaction (just adding the free ammonia to Glu) . Here we have 2 steps, removing the amino group from glutamine and then adding it to Asp , that's why We need more energy for this reaction



هاي التفاصيل مش كتير مهمة لكن الدكتورة ذكرتها عشان الفهم

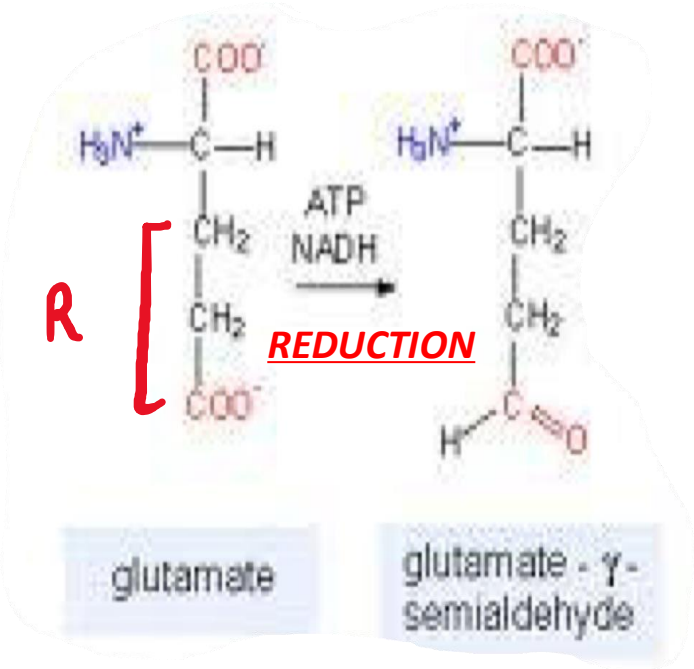
Proline

NOTE: In the degradation of proline the final product is a-ketogluatarate (via glutamate) . Proline > Glu > a-ketogluatarate . So We can use glutamate to make proline

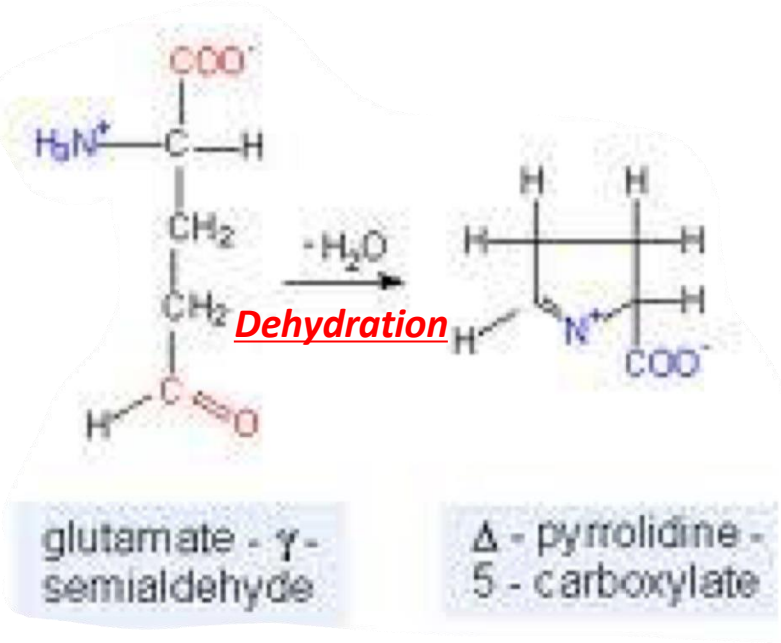


Glutamate is converted to proline by cyclization and reduction

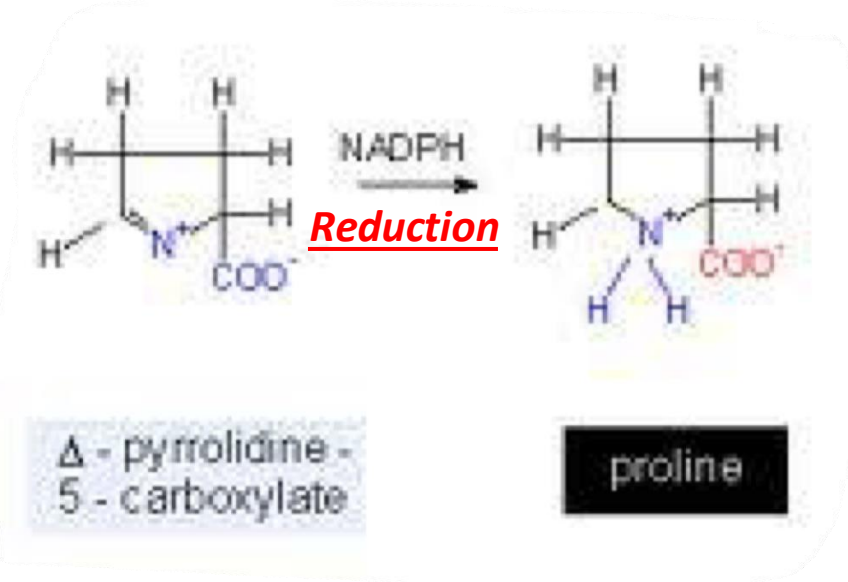
NOTE: In anabolic pathways , reduction happens in general . In degradation oxidation occurs mostly.



I need to connect the R group with the amino group to make proline, but to do this I've to get red of the carboxyl group (specially the oxygen) ,so we start by the reduction of carboxylic group to aldehyde , ATP is needed and NADH is oxidized to NAD+ . The product is glutamate semialdehyde



Now we've to remove the oxygen (in red) , by dehydration reaction (removing water to get red of the oxygen) & cyclization of this compound . The product is pyrrolidine carboxylate



We need to reduce pyrrolidine carboxylate to produce proline , by adding 2 hydrogens, and oxidation of NADPH occur

The details aren't important but what is important to know is that there is series of reactions including : reduction , dehydration , cyclization

Serine, and glycine

1. **Ser** arises from 3-phosphoglycerate that is oxidized to 3-phosphopyruvate, and then transaminated to 3-phospho serine. Serine is formed by hydrolysis of the phosphate ester.

- Ser can also be formed from glycine through transfer of a hydroxymethyl group by serine hydroxymethyl transferase

- Can catalyze both ways of the reaction

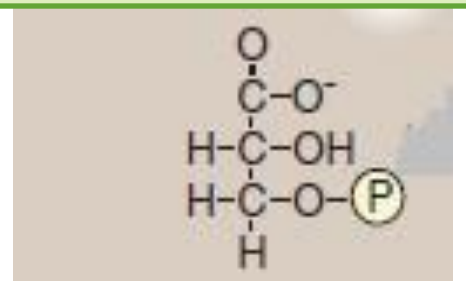
- N^5,N^{10}-methylene- THF is the one carbon donor

2. Gly is synthesized from serine by removal of a hydroxymethyl group, also by serine hydroxymethyl transferase

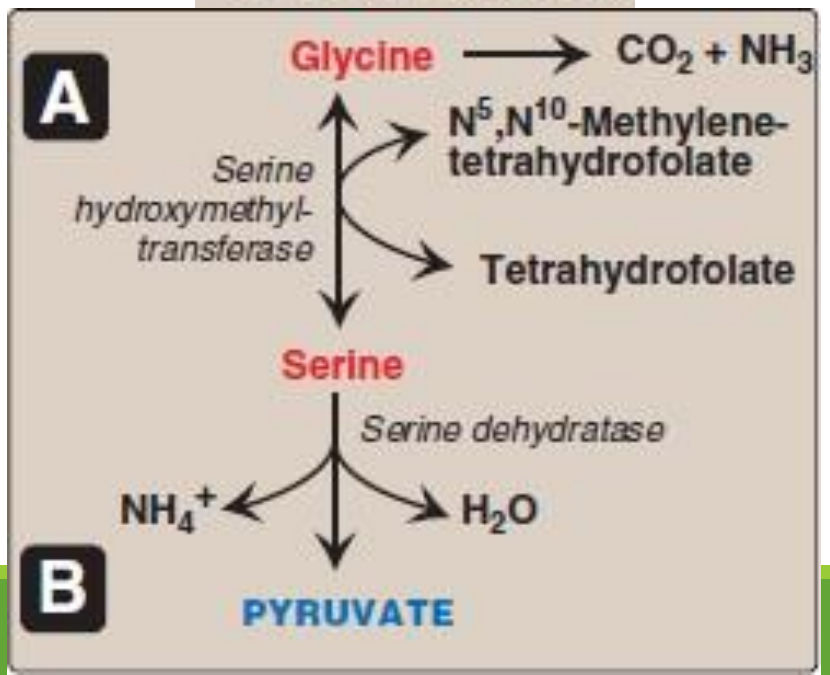
- The hydroxymethyl group will be carried on tetrahydropholate

- THF is the one carbon acceptor.

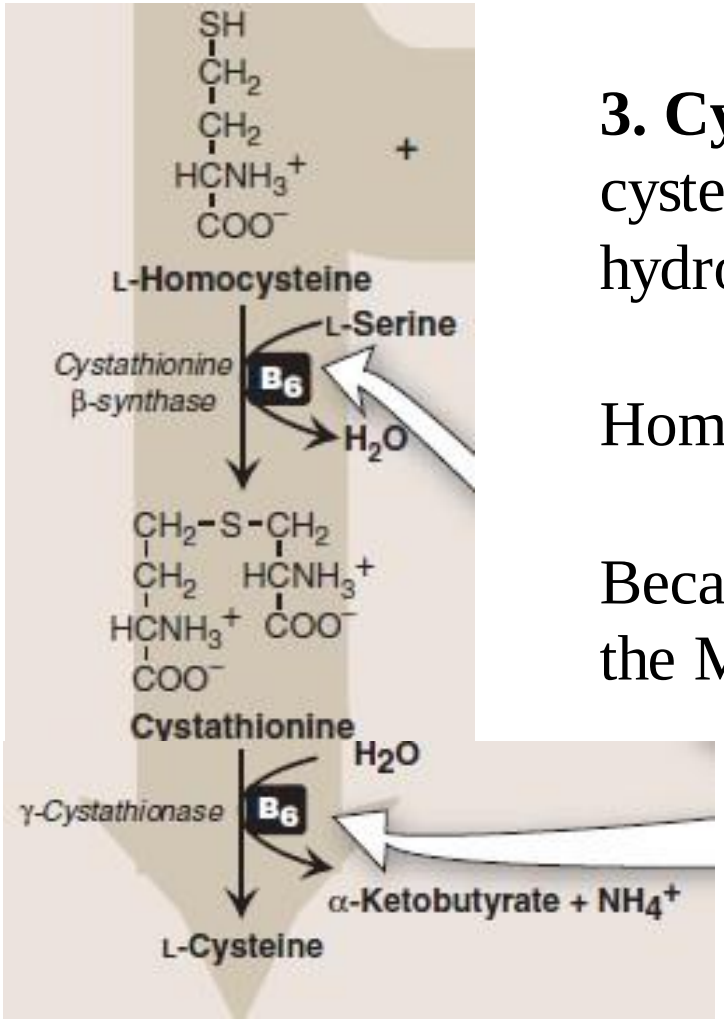
- A glycolytic intermediate, notice it doesn't have nitrogen (it came from glucose) , so we need to remove the phosphate , add nitrogen and some other modifications



3-Phosphoglycerate



Cysteine



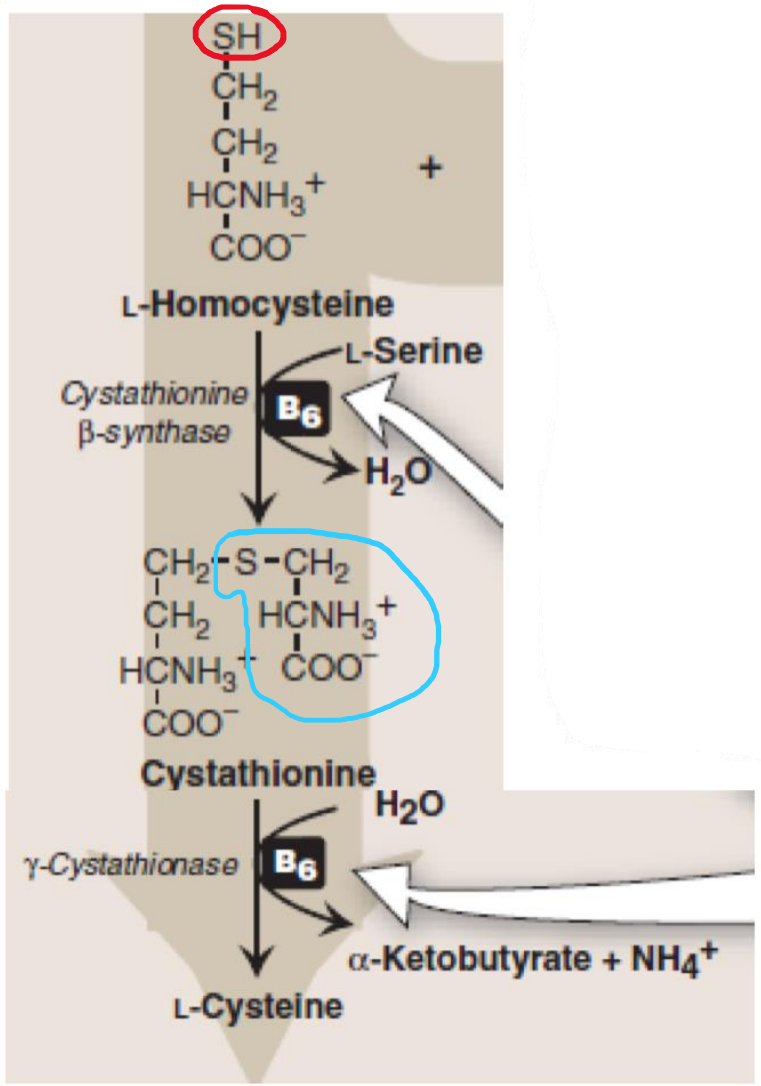
3. Cys is synthesized by two consecutive reactions in which homo cysteine combines with serine, forming cystathionine that is hydrolyzed to α-ketobutyrate and Cys

Homocysteine is derived from Met

Because Met is an essential amino acid, Cys can be synthesized the Met dietary intake is adequate.

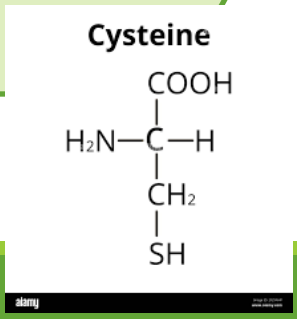
اللهمّ صلّ على سيدنا محمّد صلاة تخرجنا من ظلمات الوهم وتكرمنا بها بنور الفهم
وتوضح لنا ما أُشكِل علينا حتى نفهم ، إنّك أنت تعلم ولا نعلم وأنت علّام الغيوب

It is a piece of cake don't worry :))



- **The complement of this slide :** Cys can be made during the degradation of methionine. Methionine ▶ SAM ▶ SAH ▶ **Homocysteine** (the branching point during the degradation of met) . This homocysteine can be used to make cysteine by adding serine amino acid (v.close in structure to cysteine) but we need to get red of the OH group in serine which is released as H2O molecule together with the hydrogen of the sulfur (in red) . Now I have my serine attached to the sulfur so this is cysteine (in blue) ,the whole compound is called Cystathionine, once Cys is cleaved from that compound the leftover molecule is released as a-ketoglutarate (which then becomes propionyl coA and then succinyl coA) . Free ammonia is also released .The enzyme catalyzing this step is Cystathionase. vitamin B6 is needed in both steps

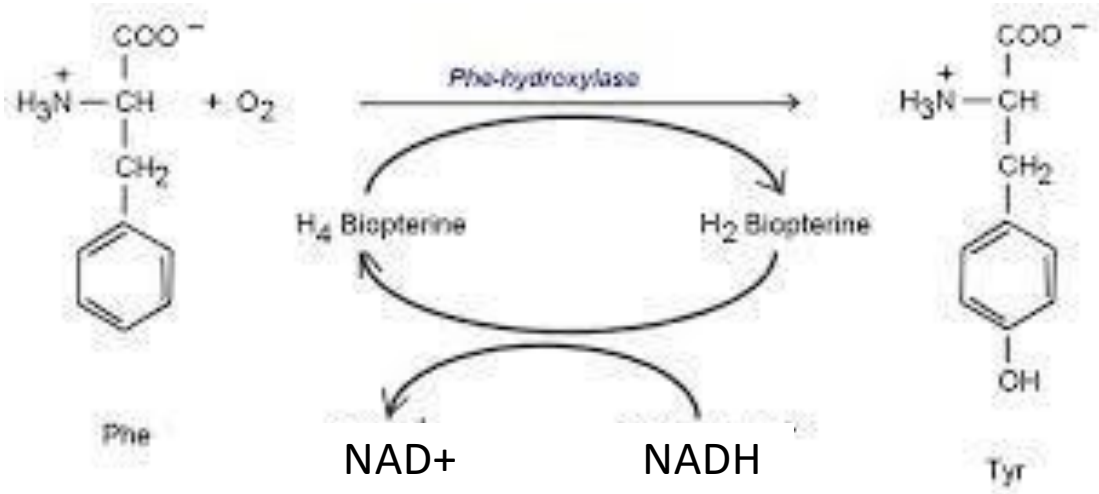
This is the structure of Cys (extra photo)



Tyrosine

Tyr (non essential AA) is formed from Phe (essential AA) by phenylalanine hydroxylase.

The reaction requires molecular oxygen and the coenzyme tetra hydrobiopterin (BH4)



BH4 is oxidized to dihydrobiopterin (BH2).

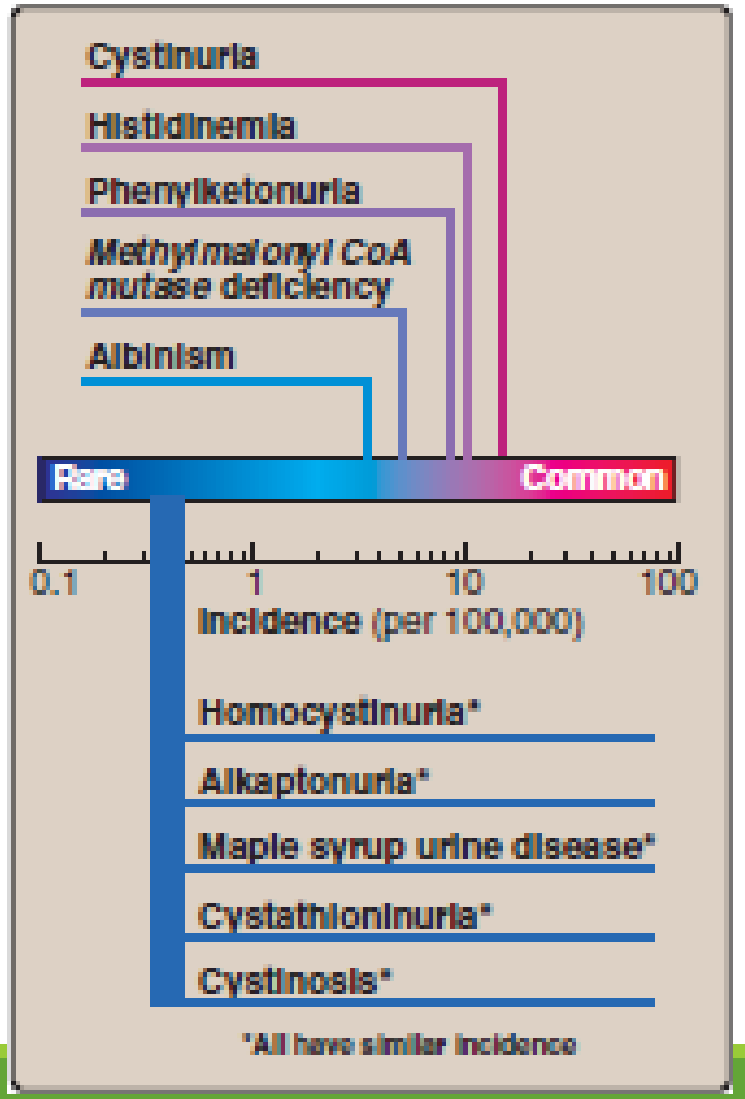
NOTE: It recycles the co enzyme

BH4 is regenerated from BH2 by NADH-requiring dihydropteridine reductase.

2 enzymes are needed here , one for the main reaction and the other to reproduce the coenzyme

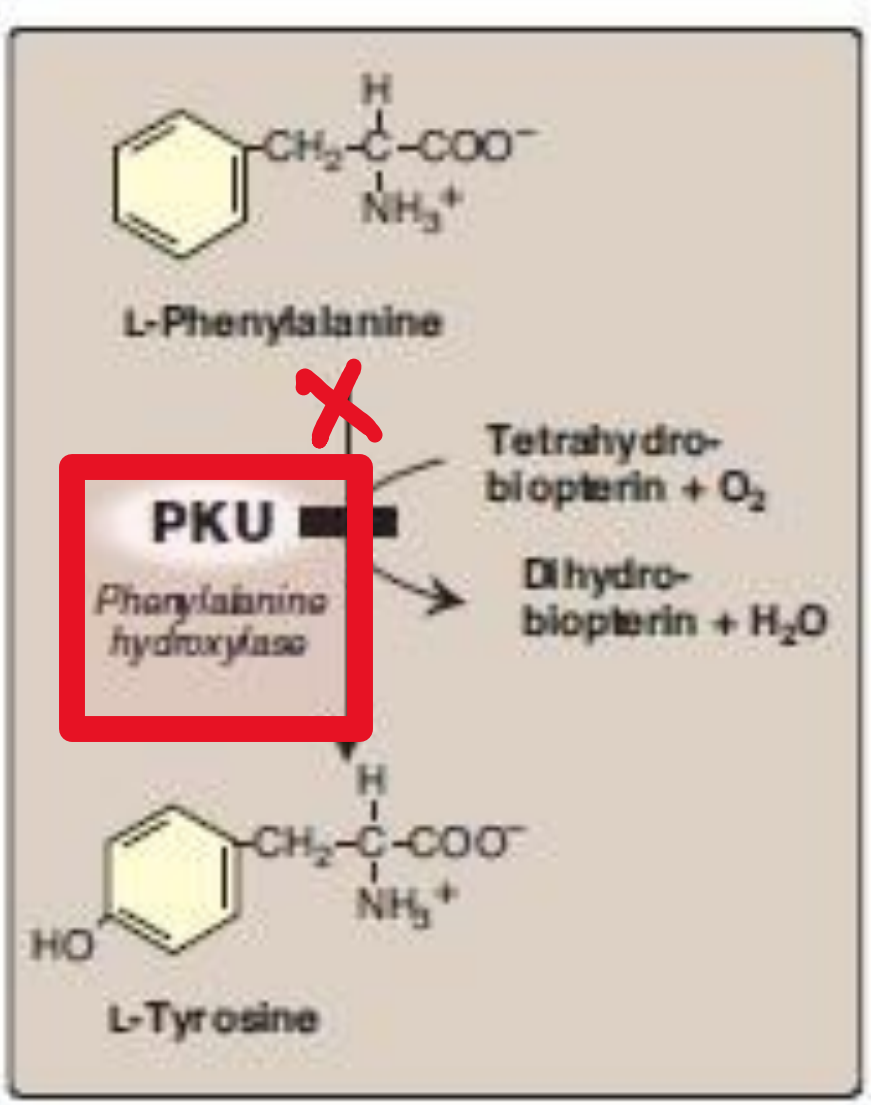
Metabolic defects in amino acid metabolism

The inherited defects of AA metabolism if stay untreated result in mental retardation or other developmental abnormalities because of the harmful accumulation of metabolites.



سبحان الله والحمد لله ولا إله إلّا الله والله أكبر

Metabolic disorders: Phenylketonuria (PKU)



The most common inborn error of amino acid metabolism (prevalence 1:15,000).

(لَقَد خَلَقْنَا الْإِنْسانَ فِي أَحْسَنِ تَقْوِيم)
سبحان الخالق ، كيف خلق فأبدع ،
بتفاصيل لا يمكن للعقل تخيلها ، أي طفرة
طفيفة على إنزيم صغير أدت إلى خلل
جسيم ، ما أضعفنا و ما أقواه سبحانه
وتعالى !

Due to phenylalanine hydroxylase deficiency

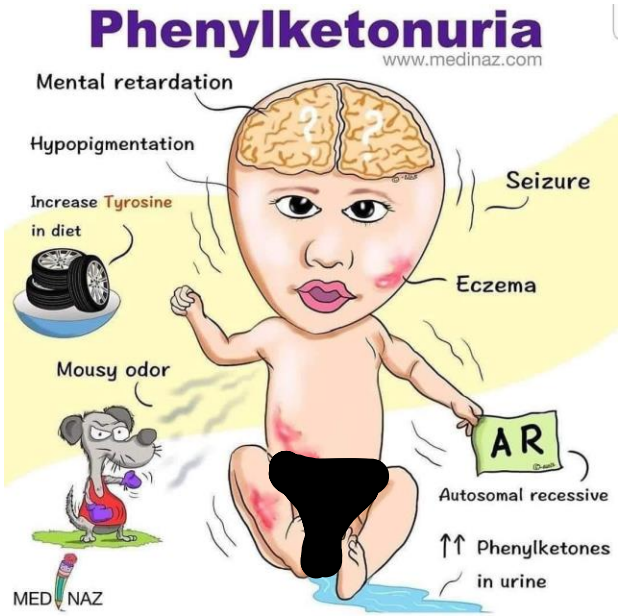
Biochemical changes: accumulation of phenylalanine (and

a deficiency of tyrosine)

Tyr cannot be synthesized from Phe and becomes an essential amino acid.

Caused by any of 100 or more different mutations in the gene that codes for phenylalanine hydroxylase (PAH).

- **NOTE:** the conversion of phenylalanine to tyr is compromised, the Phe will accumulate leading to it's conversion to phenylaceteate ,phenyllactate ,phenylpyruvate



- **The complement of the slide** : people with PKU can't produce their tyr so it becomes essential (they have to obtain it from diet)
- Are babies born with accumulated phe ? **NO** , the maternal enzyme **is covering the fetus during pregnancy so the metabolism of phe is normal** .The test of PKU is one of the most important and essential tests which is done everywhere in the world (almost 10 tests are done after hours from birth and after days)
- It's better to test PKU after a period of time , **to let the baby drink milk (which contains phe) and see if there is a problem** " it is not a genetic test! It is a biochemical test"
- These babies are born **normally** with no mental retardation , **if phe accumulates** and produces phenyl lactate/acetate pyruvate which can cross the blood brain barrier resulting in destruction of neurons causing mental retardation

Characteristics of classic PKU:

- **Elevated phenylalanine** in tissues, plasma, and urine.

- **The characteristic musty "mousey" urine odor** due to phenyllactate, phenylacetate, and phenylpyruvate
- **CNS symptoms:** Mental retardation (IQ < 50), failure to walk or talk, seizures, hyperactivity, tremor, microcephaly, and failure to grow

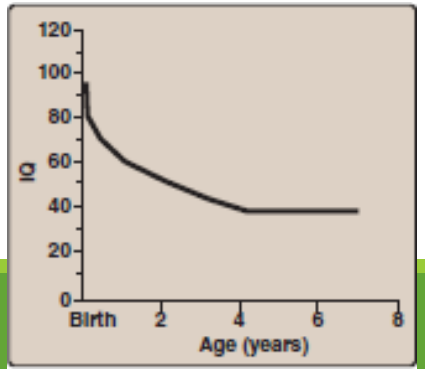
- **Hypopigmentation:** fair hair, light skin color, and blue eyes because the hydroxylation of Tyr by tyrosinase (the first step in melanin formation) is competitively inhibited by the high levels of Phe.

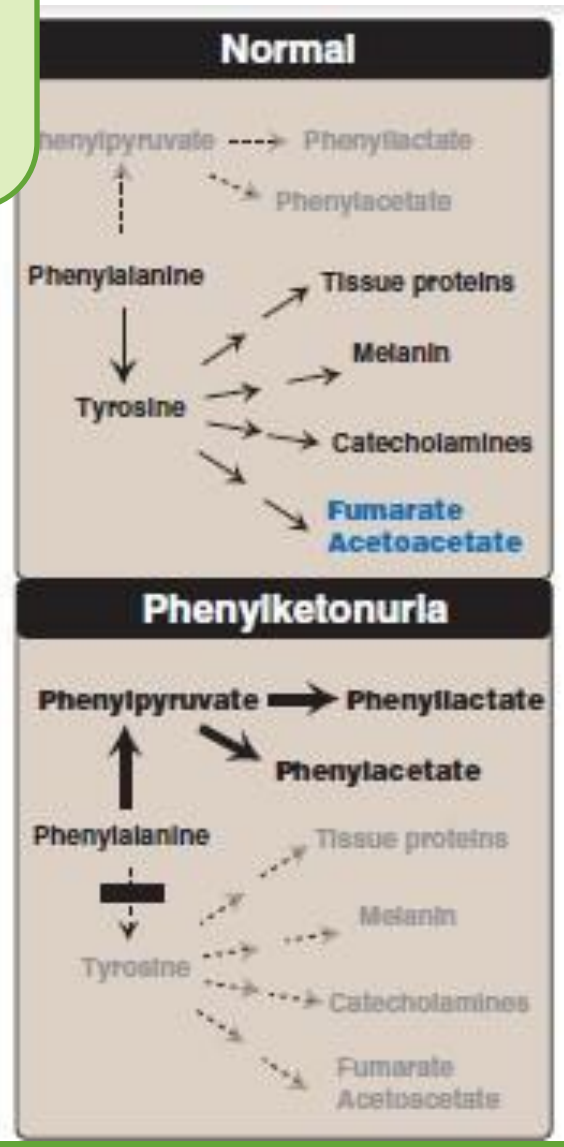
Neonatal screening programs

■ **phenyllactate, phenylacetate, and phenylpyruvate appear in the urine**

■ **Less melanin is formed . Compared to their genetics their skin, hair , eyes should be darker.**

■ **NOTE: compounds containing phenol are smelly , like mousey odor**





Neonatal screening and diagnosis of PKU

PKU is treatable by dietary restriction.

Lack of neonatal symptoms

At birth, infants with PKU have normal blood levels of Phe because the mother clears the extra Phe through placenta

Exposure protein feeding for 24–48 hours elevates Phe, thus, screening should be done after this to avoid false negatives.

Treatment:
Dietary restriction: synthetic amino acid preparations low in Phe, supplemented with natural foods low in Phe content (fruits, vegetables, and certain cereals)

Earlier treatment (prevents neurologic damage days of life) prevents neurologic complications (mental retardation)

Aspartame should be avoided since it contains Phe.

NOTE: it is an artificial sweetener

Maternal PKU

- **Now the question is : What if the Mother has the " PKU " disease ?**

-High blood Phe levels in the mother cause microcephaly, mental retardation, and congenital heart abnormalities in the fetus

-Phenlyalanine is a teratogen (an agent or factor which causes malformation of an embryo).

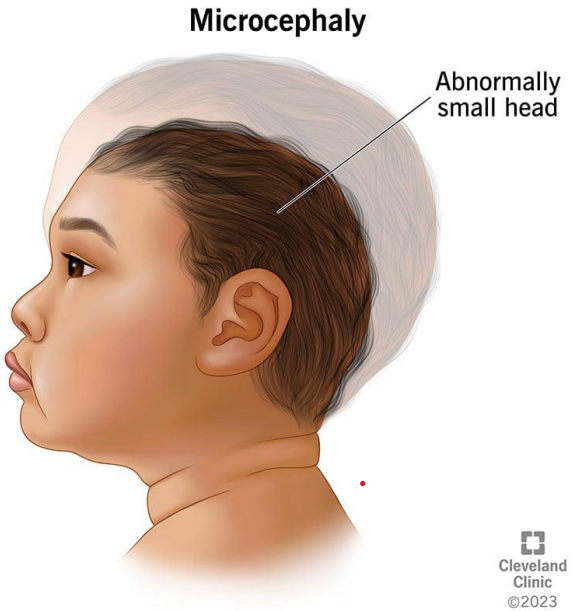
-Dietary control of blood phenylalanine must begin prior to conception, and must be maintained throughout the pregnancy.

- **More severe than the previous case (when the child has a genetic pku , because we can avoid the complications by dietary restrictions) but here , the baby is born with microcephaly (to be discussed)**

- Let’s imagine for example, a girl who had PKU and she was following a planned diet , so as a result , she avoided the mental retardation complication . She grew up and got married, and became pregnant . She has to continue the **dietary restrictions**, to keep the phenylalanine in her blood at normal level , which has to be monitored and **checked continuously** .

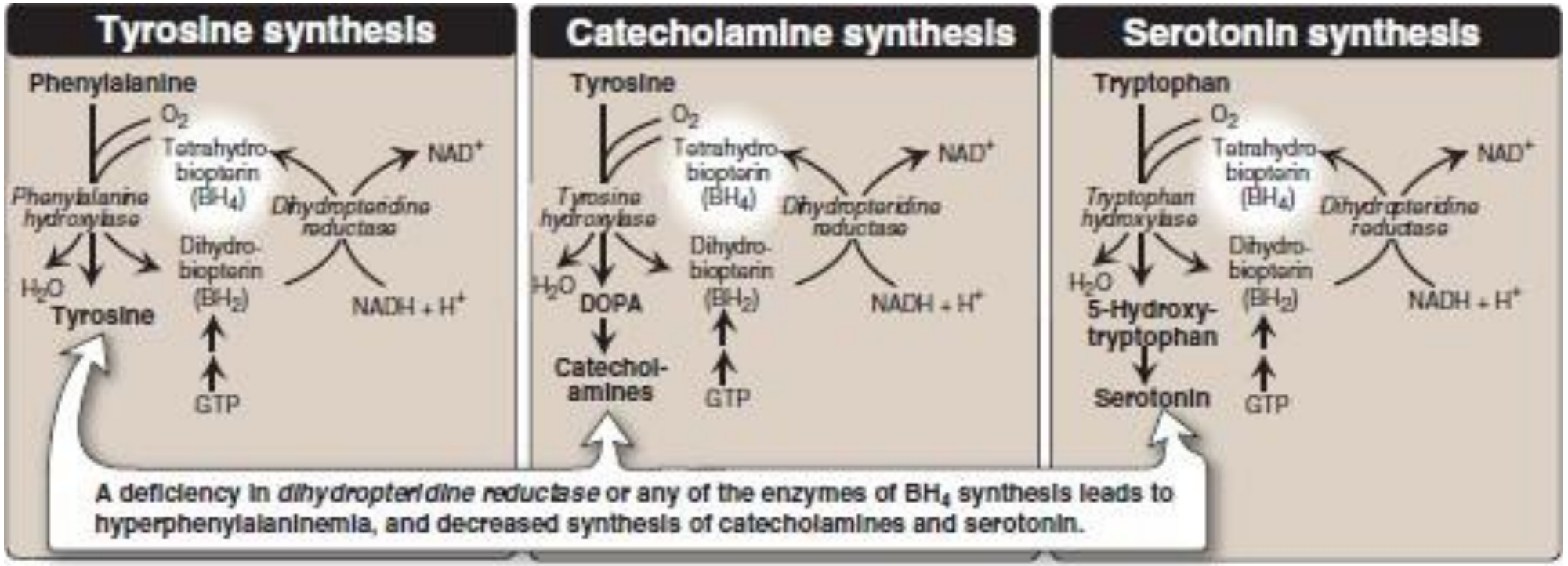
- Phenylalanine can cross the placental barrier, causing a **teratogenic effect** (affecting the development of the fetus) .. So we can conclude that **Phenylalanine is a teratogenic factor** .. The main issue is the high concentration of phenylalanine that accumulates and crosses the placenta, but not every phenylalanine molecule that crosses the placenta is teratogenic (the disease is **concentration dependent**), as a consequence, the baby will have **microcephaly** (explained in the next slide, kindly check it)

- **Microcephaly** is a birth defect where a **baby's head is smaller than expected** when compared to babies of the same sex and age ,so the place which is available for the brain to grow is smaller , and this for sure affects the brain (that's why the size of the head of newborns must be checked continuously) .



Extra pics !!

Metabolic disorders: Hyperphenylalaninemia

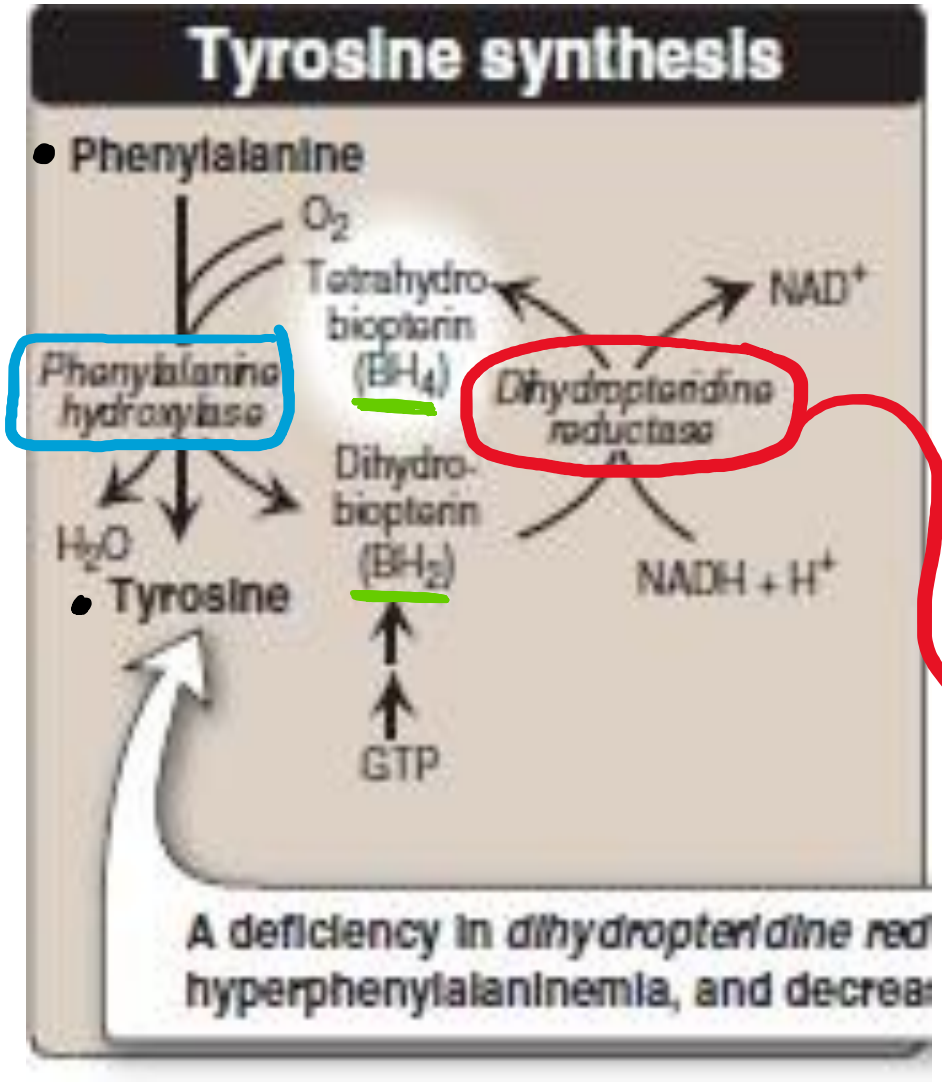


- **Hyperphenylalaninemia : strongly elevated concentrations of the amino acid phenylalanine in the blood.**

Dihydropteridine reductase deficiency:

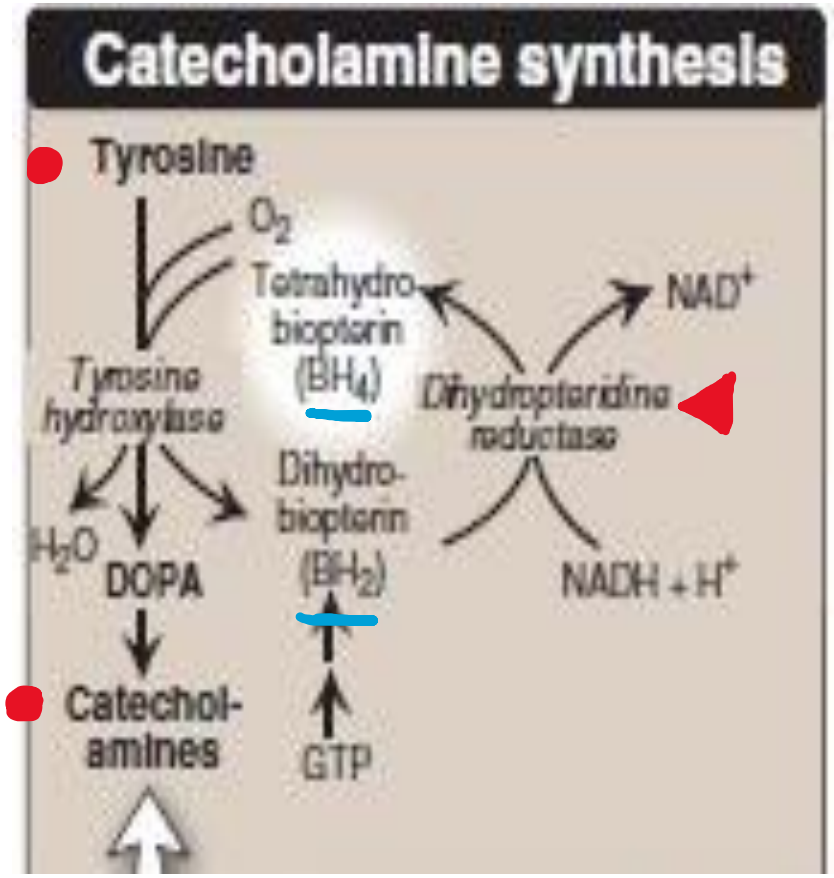
Restricting dietary Phe does not reverse the CNS effects due to deficiencies in neurotransmitters.

Replacement therapy with BH4 or L-DOPA and 5-hydroxytryptophan (products of the affected tyrosine hydroxylase–and tryptophan hydroxylase–catalyzed reactions) improves the clinical outcome



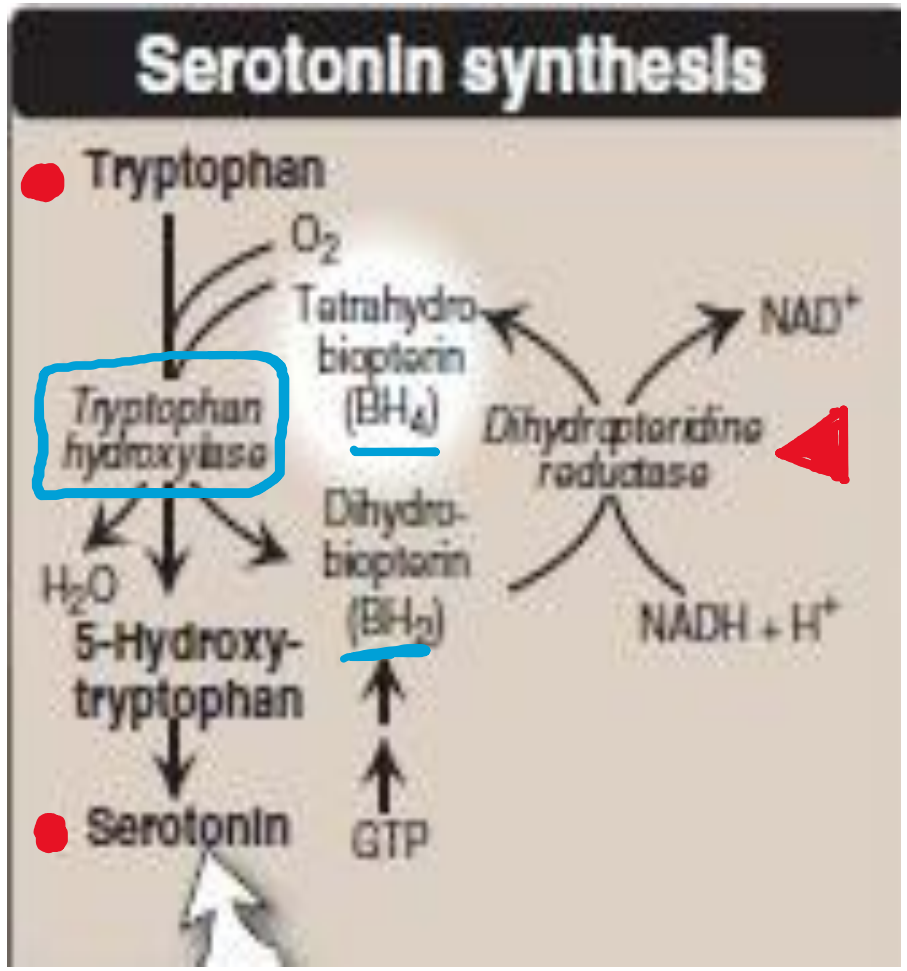
- Here we have a deficiency in the enzyme (Dihydropteridine reductase) that is responsible for the recycling of the coenzyme (BH4) that is needed for this rxn to occur (phenylalanine >> tyrosine) . The deficiency is due to a genetic mutation, this will lead to **accumulation of phenylalanine** so the rxn will be compromised.

- A quick reminder: Phenylalanine to tyrosine needs (**phenylalanine hydroxylase**) this enzyme needs a coenzyme which is (**BH4**) , this coenzyme is converted to **BH2** during the rxn . We need to reproduce BH4 again and this requires the enzyme (Dihydropteridine reductase), which catalyzes the reduction of BH2 to BH4.



- Not only the (phenylalanine >> tyrosine) pathway will be affected, but also any other pathway that needs the the BH4 coenzyme. (hydroxylases usually need this coenzyme).
- We have to know that Tyrosine can be used to synthesize catecholamines (dopamine, epinephrine, norepinephrine) using the Tyrosine hydroxylase . And this enzyme needs the coenzyme BH4 .
- So if we have a deficiency in the dihydropteridine reductase (the enzyme needed to recycle BH4) catecholamines synthesis will be affected.

هرمون السعادة :)



- We can synthesize serotonin from **Tryptophan** amino acid , using **Tryptophan hydroxylase** which requires the BH4 coenzyme. A deficiency in the dihydropteridine reductase (the enzyme needed to recycle BH4) serotonin synthesis will be compromised .
- Serotonin (influencing happiness) is produced and used in the CNS , it doesn't cross the blood brain barrier . It can also be produced in other sites but with different functions.

Albinism

A group of conditions in which a defect in Tyr metabolism results in a deficiency in the production of melanin.

Partial or full absence of pigment from the skin, hair, and eyes.

Inheritance modes:
AR (primary mode), AD, or X-linked.

Complete albinism (tyrosinase-negative oculocutaneous albinism) results from a deficiency of copper-requiring tyrosinase

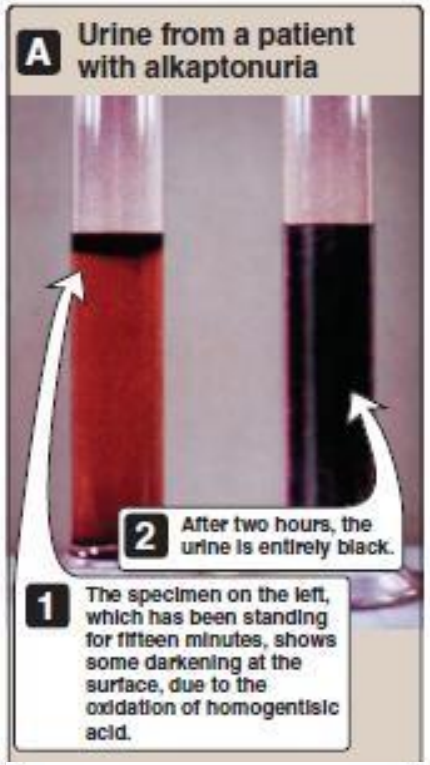
Complete albinism:
The most severe form.
Total absence of pigment from the hair, eyes, and skin, vision defects and photophobia (sunlight hurts their eyes).
Higher risk for skin cancer.

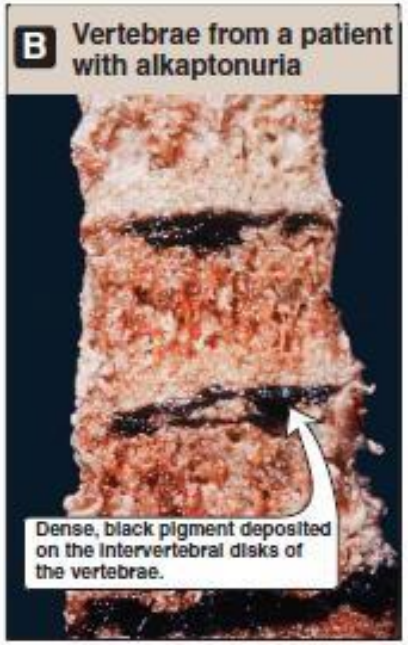
- Albinism is a genetic disease , it might affect different genes in different patients (not a single gene) .
- So there are different modes of inheritance depending on the affected gene .
- Inheritance modes : 1- Autosomal recessive (the most common one) 2- Autosomal dominant 3- the gene is present on X chromosome (associated wit Tyrosine metabolism) >> deficiency in the production of Melanin pigment (Tyrosine is a precursor of melanin)
- People with albinism have very light skin, hair, and eyes, because they have less melanin than usual

Complete albinism:
The most severe form.
Total absence of pigment from the hair, eyes, and skin, vision defects and photophobia (sunlight hurts their eyes).
Higher risk for skin cancer.

- The malanin has a **protective** role in the skin
- Sun light or UV light can cause damages in the DNA , in normal individuals this damage is fixed by repair mechanisms. This correction doesn't occur properly in Albinos , so they are more susceptible for skin cancer.
- Our skin gets darker when exposed to the sun light, and that's simply because the melanin moves from deeper layer to the superficial layer >> protection
- People lacking melanin get burned instead .

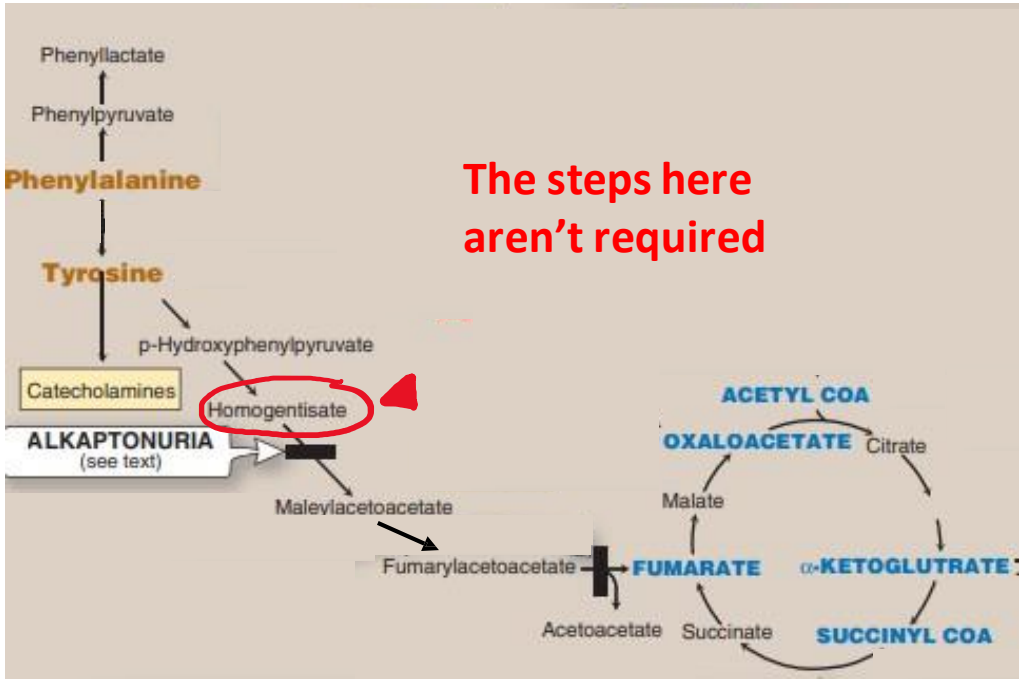
Alkaptonuria (Alcaptonuria) مرض البول الأسود





A rare metabolic condition, however, cases were found in Jordan It's not rare in Jordan

A deficiency in homogentisic acid oxidase, resulting in the accumulation of homogentisic acid (a reaction that occurs in the degradative pathway of Tyr)



Characteristic symptoms: Not life threatening

Patients are usually asymptomatic until age 40.

-Homogentisic aciduria

-Large joint arthritis

-Black ochronotic pigmentation of cartilage and collagenous tissue

-Dark staining of the diapers can indicate the disease in infants

Treatment: diets low in protein—especially in Phe and Tyr reduce homogentisic acid levels, and the pigment deposited in body tissues.

- You should know from the previous lecture that one of the final products of the Tyrosine metabolism is the **FUMARATE** ,HOWEVER, one of the intermediates that are produced during this pathway is the " **homogentistic acid** " that is then oxidized to form the next intermediate using (**homogentistic acid oxidase**)
- Now when there is a deficiency in this enzyme (which means a problem in the Tyrosine metabolism) , the homogentistic acid will accumulate .. (This compound may turn to a black color when accumulation)

- Alkaptonuria is a benign (mild) condition , It **isn't diagnosed early** as well , Unless we leave a diaper of an Alkaptonuria child for some time , we will notice that the **urine turns black** .. This Is the only way to detect this disease early .. Another way that leads the patient to go and check , is the joint **Arthritis** (which is a complication of the Alkaptonuria disease) , The direct cause of the arthritis in Alkaptonuria is indeed the accumulation of homogentisic acid (HGA) in the joints. You'll notice the **black colored cartilage** during the surgery.

Some sources that might help :

https://youtu.be/9Fiu0Pb83BY?si=NOXF170S6r9Xpx5S

https://youtu.be/HYg0Id-C0uQ?si=dZmwSAauc9dFqfG5

https://youtu.be/pjz9gosFkls?si=fdGjl76FpQGvUy4d

https://youtu.be/cDrOAw4mOj4?si=lTqn5nP2e3Wa_Cg2

(لَقَد خَلَقْنَا الْإِنْسانَ فِي أَحْسَنِ تَقْوِيم)

أتقنوا دراستكم يا فتية ، حتى نستغني عن المجرمينَ في غذائنا و دوائنا ولباسنا و كلّ معاشنا ، افعل ذلك كلّه و أنت تستحضر أنّك تحافظ على انتصارات إخوانك ، فالأمّة اليوم أحوج ما تكون إلى أبنائها البَررة ، فإن لم تكُن جراح الأمة في قلبك ، فأنت جرحٌ في قلب الأمة "

لو كُنتَ وحدَك لهانت ، لكنّها أمّةٌ يا فتى ...

V2: Slide 6

Glutamine Instead of Glutamate