A Genetic Defect in Amino Acid Metabolism: Phenylketonuria (PKU)

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History

In 1934, **Dr. Folling**, who worked in Norway, was the first person who describe **Phenylketonuria (PKU)**.

He was contacted by a mother who had two children with mental handicap.

He found a chemical in their urine and he worked out that it was a “phenylketone”.

Because this chemical was present in the urine, the condition was called **Phenylketonuria**.

Definition

Phenyketonuria (PKU) is a genetic disorder that is characterized by an inability of the body to metabolize phenylalanine, caused by a deficiency in **Phenylalanine Hydroxylase (PAH)** enzyme.

The symptoms of PKU

Infants with PKU appear normal at birth.
Many have blue eyes and fairer hair and skin

About 50 % of untreated infants have early symptoms,
such as vomitting, irritability and mousy odor to the urine

Later, some problems can occur,
such as mental retardation, brain damage, seizures,
microcephaly (small head),
prominent cheek and upperjaw bones with widely spaced teeth,
poor development of tooth enamel and decreased body growth

The Factor that Causes PKU

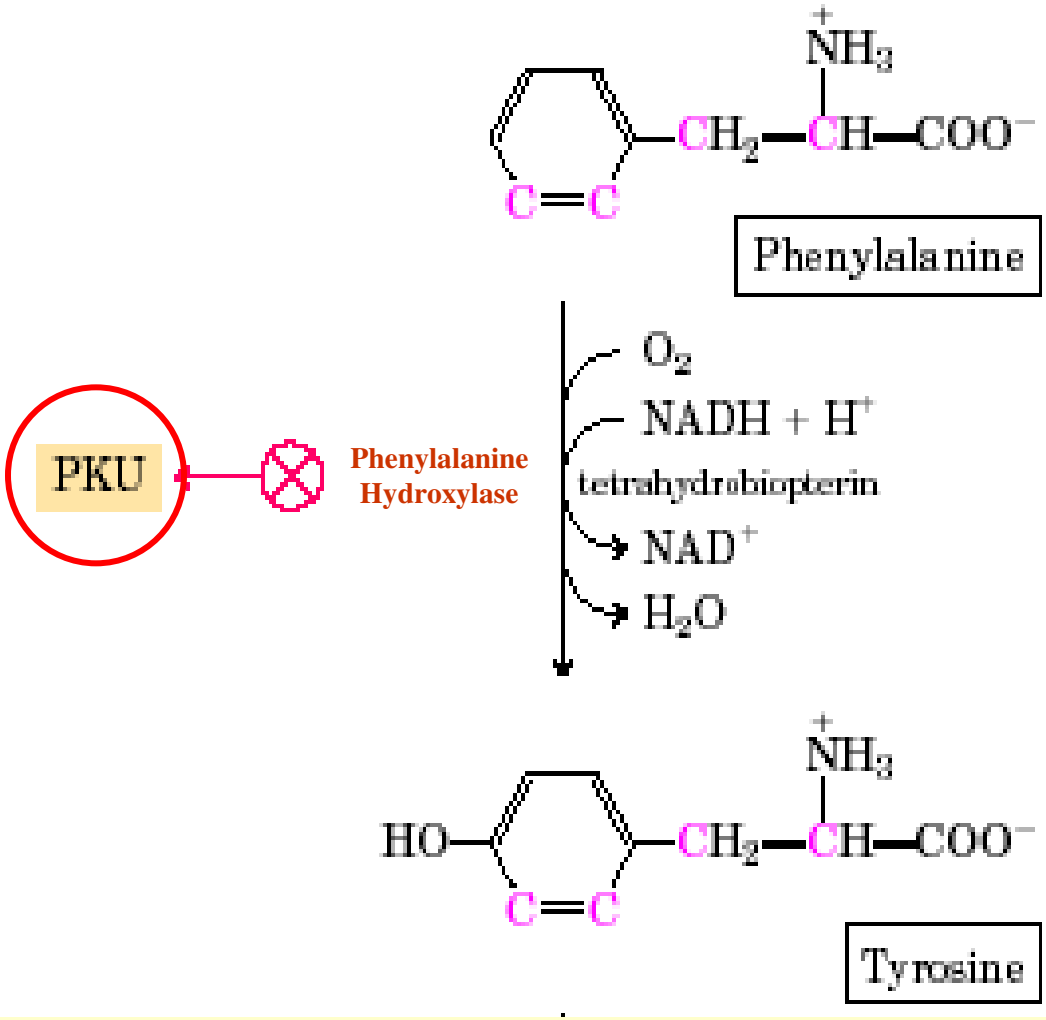
The lack of Phenylalanine Hydroxylase (PAH)

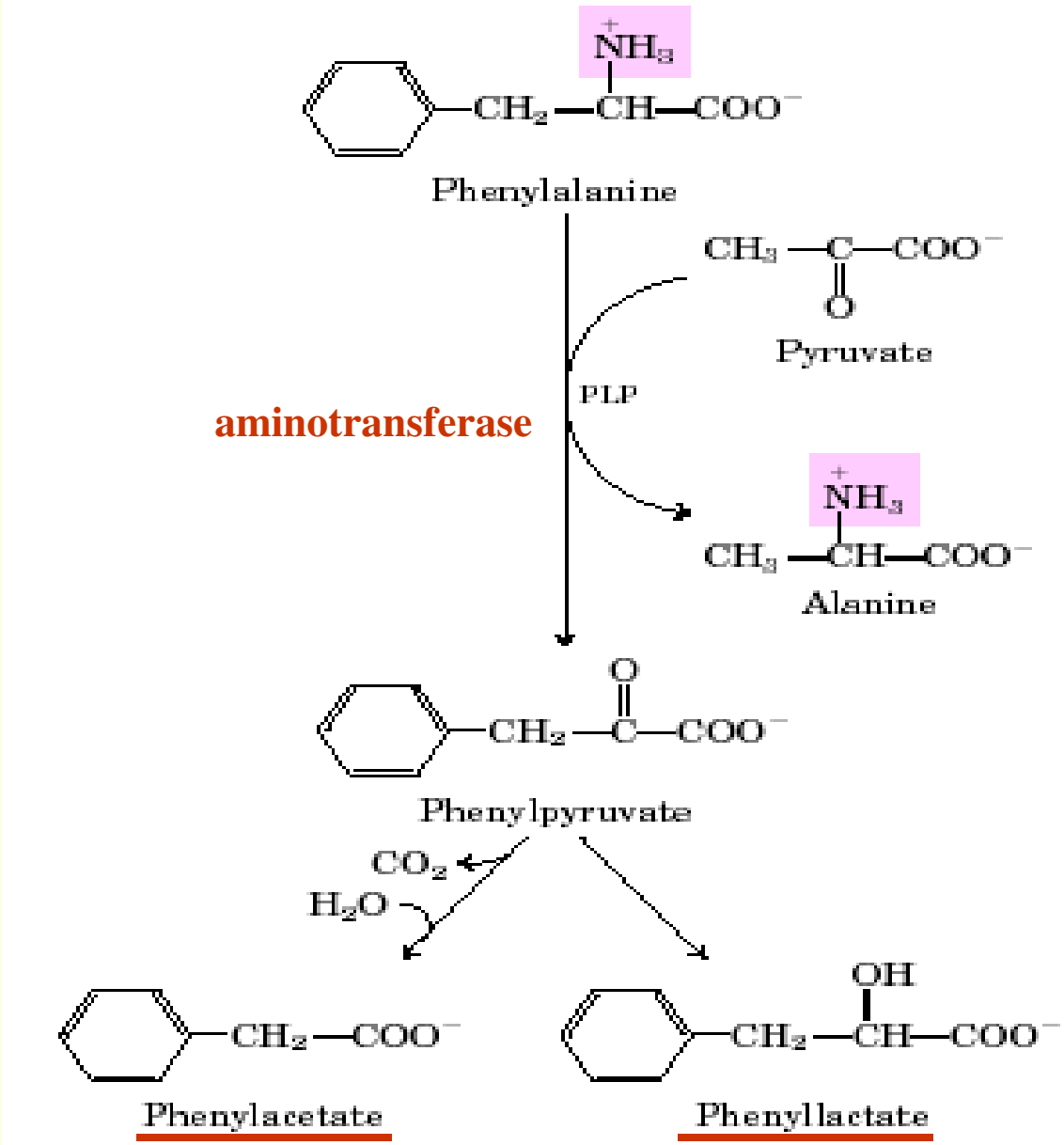
A genetic defect in the gene of PAH

The defect in enzyme that catalyzes the regeneration of tetrahydrobiopterin (cofactor of PAH)

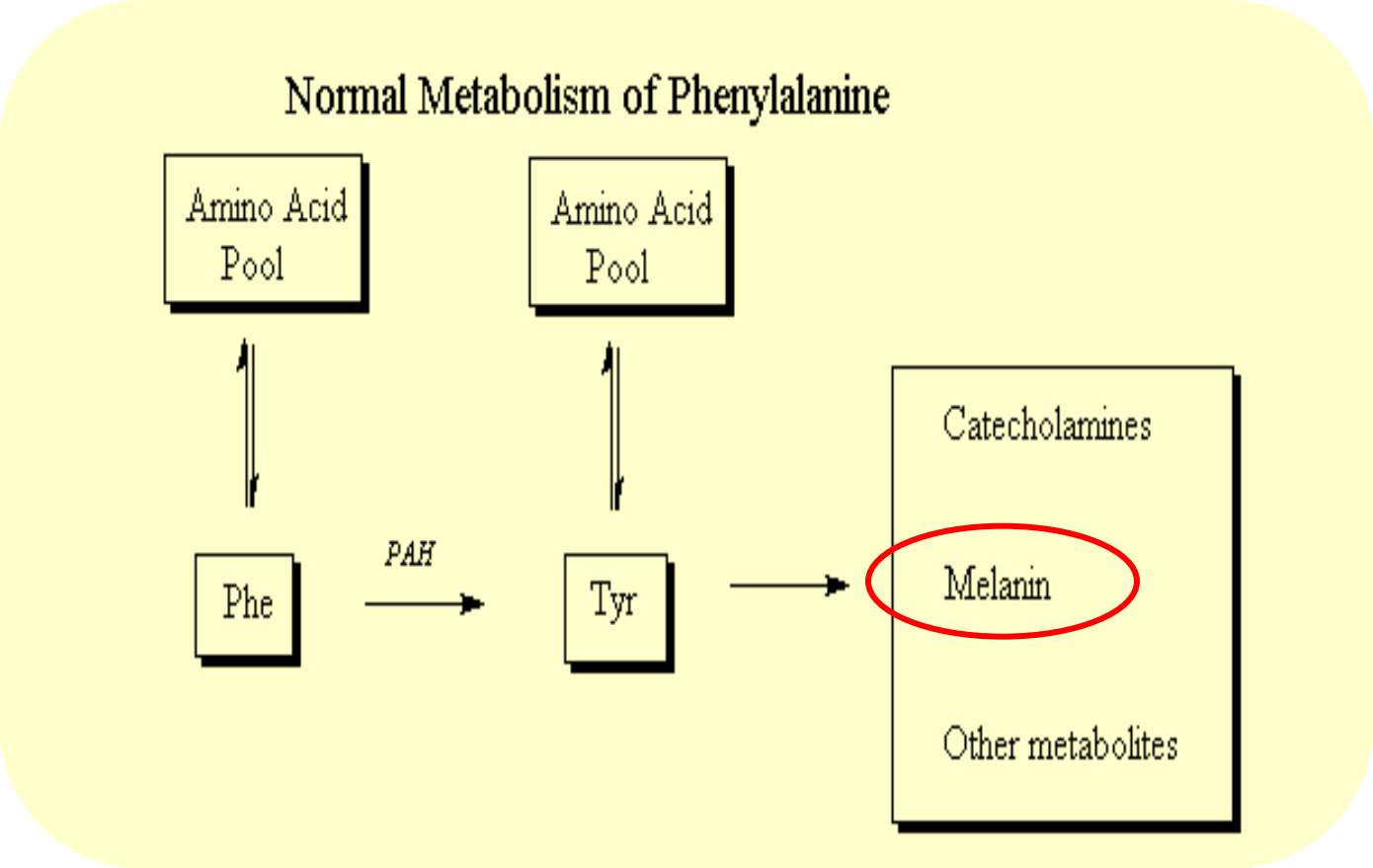
The lack of PAH activity

- PAH normally converts Phenylananine to Tyrosine. Without this enzyme, the catabolism of Phenylalanine is blocked and serum levels of Phenylalanine rise. This condition called **hyperalaninemia**.


NH3
CH2
CH
COO−
C=C
Phenylalanine
O2
NADH + H+
tetrahydrobiopterin
NAD+
H2O
PKU
Phenylalanine
Hydroxylase
HO
NH3
CH2
CH
COO−
C=C
Tyrosine

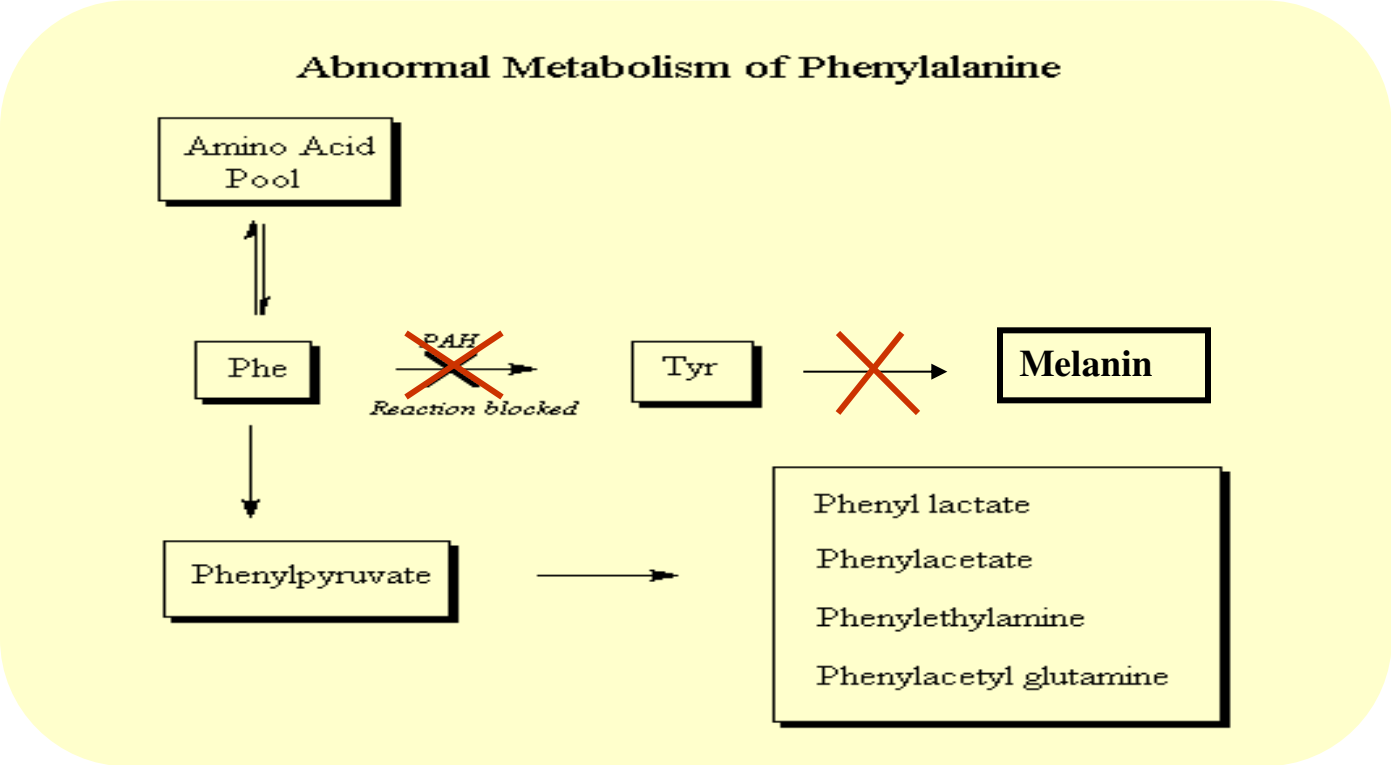

Phenylalanine
Pyruvate
PLP
aminotransferase
Alanine
Phenylpyruvate
CO2
H2O
Phenylacetate
Phenyllactate

Normally, Phenylalanine is oxidized by PAH enzyme to form Tyrosine. From Tyrosine, there are further connections to biosynthesis of catecholamines, melanin and other metabolites.



Melanin is a brown pigment that affect the colour of our skin, hair and eyes.

A child with PKU, PAH is not working properly. This means that phenylalanine cannot be broken-down and its level in blood gets very high. On the other hand, Tyrosine levels tend to be low. It consequences melanin cannot be formed. So, a child with PKU will have blonde hair and blue eyes.



The defect in enzyme that catalyzes the regeneration of tetrahydrobiopterin

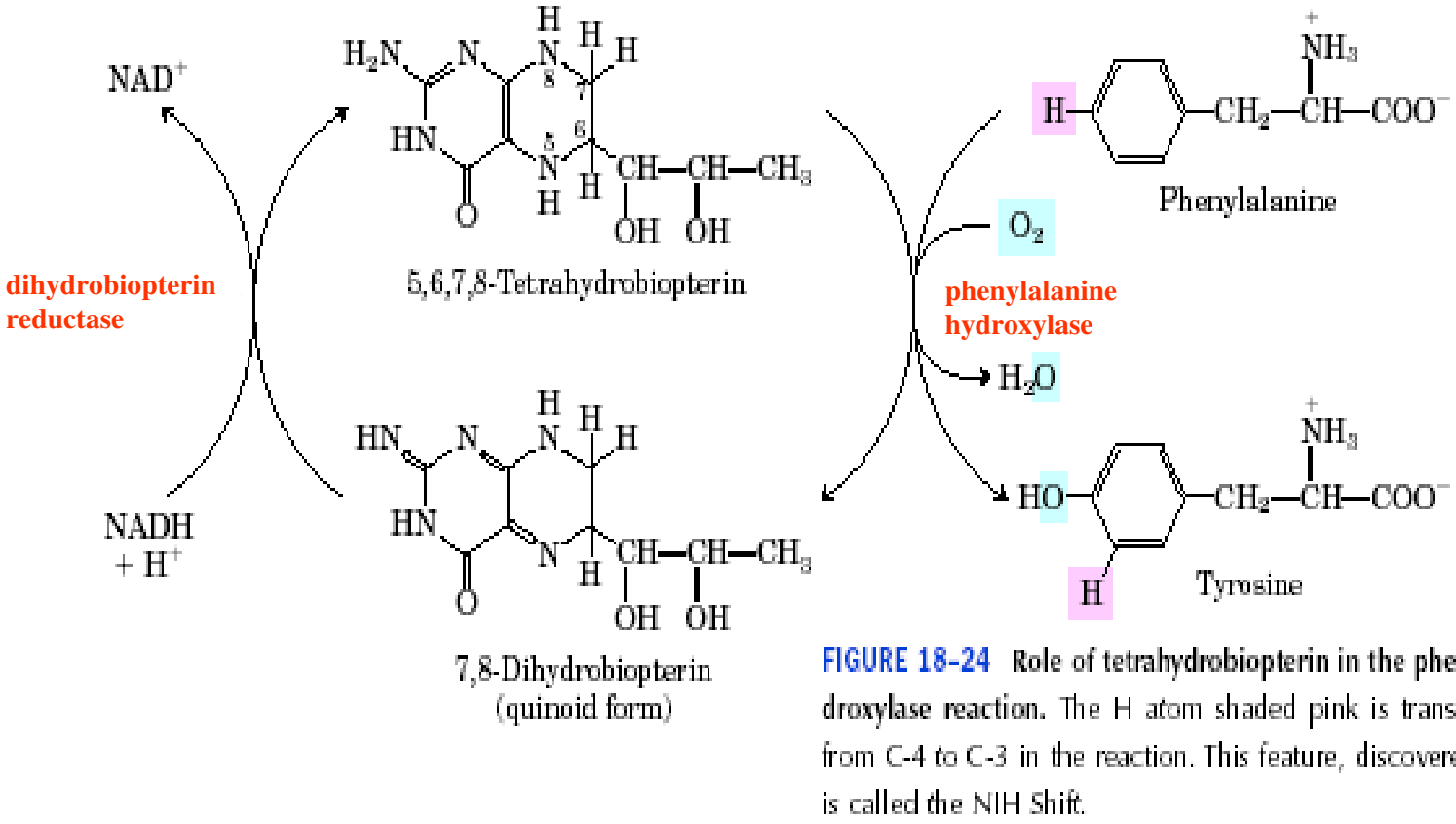
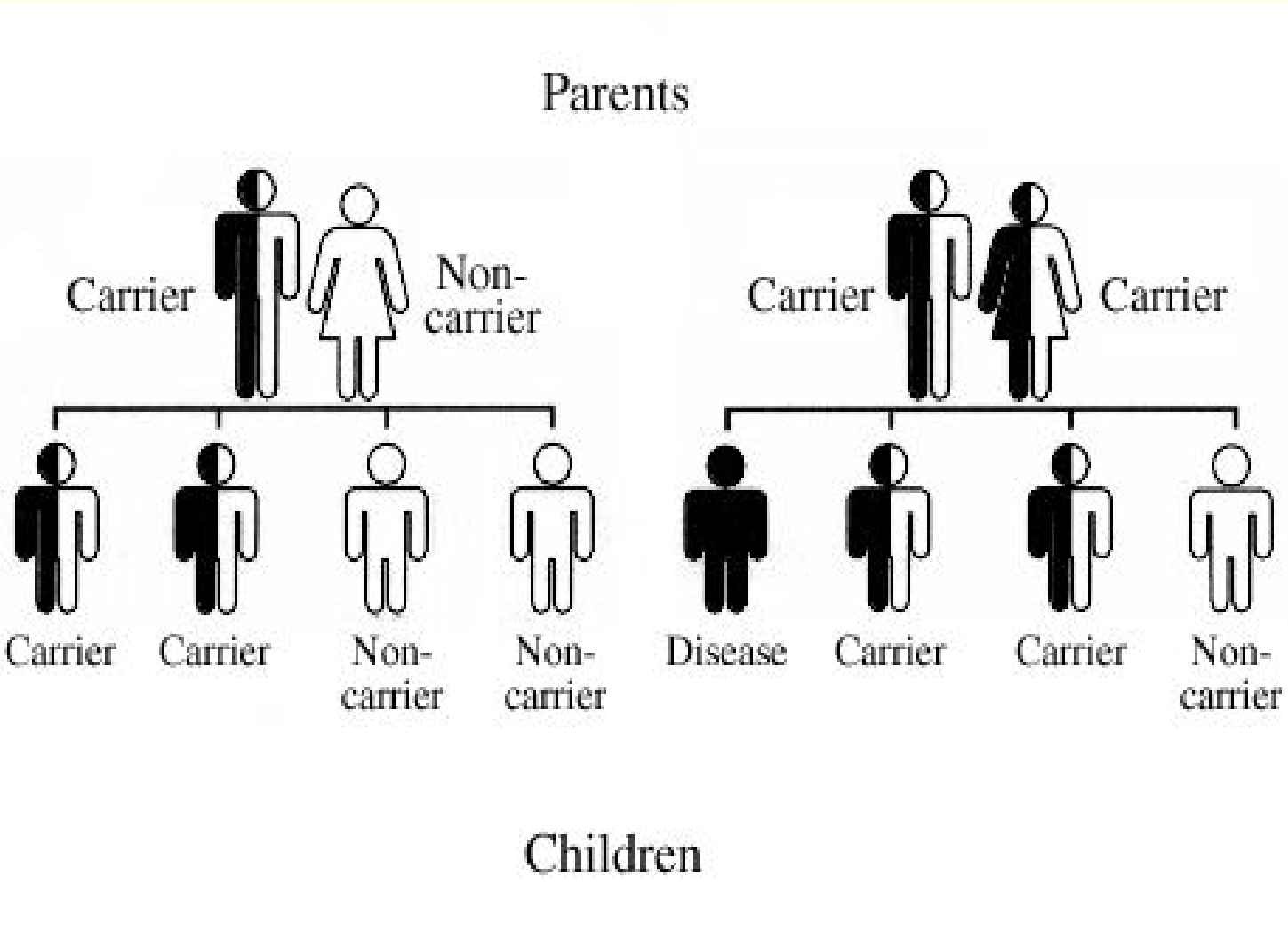


FIGURE 18-24 Role of tetrahydrobiopterin in the phenylalanine hydroxylase reaction. The H atom shaded pink is transferred directly from C-4 to C-3 in the reaction. This feature, discovered at the NIH, is called the NIH Shift.

How does a child have PKU?

To inherit PKU, a child must receive two abnormal PAH genes, one from each parent who has a mutation in PAH gene.

A parent who has one abnormal PAH gene is called a “carrier”.


Parents
Carrier
Non-carrier
Carrier
Carrier
Non-carrier
Non-carrier
Carrier
Carrier
Disease
Carrier
Carrier
Non-carrier
Children

Treatment of PKU

Early identification by newborn Screening Test

With a special diet that is low Phenylalanine

Consume a 'protein substitute' that contains tyrosine and all other amino acids except phenylalanine

Taking BH4 Supplements

Conclusion

- **Phenyketonuria (PKU)** is a genetic disorder that is characterized by an inability of the body to metabolize phenylalanine, caused by a deficiency in **Phenylalanine Hydroxylase (PAH)** enzyme.

- The lack of PAH activity causes Phenylalanine can't be converted into Tyrosine. So the concentration of Phenylalanine in the blood rise to toxic levels.

- Treatments of child with PKU are by **Screening Test** for early identification, with **special diet** that is low Phenylalanine and **consume a 'protein substitute'** that contains tyrosine and all other amino acids except phenylalanine

References

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..Thanks for your attention..