METABOLISM OF PROTEINS AND AMINO ACIDS

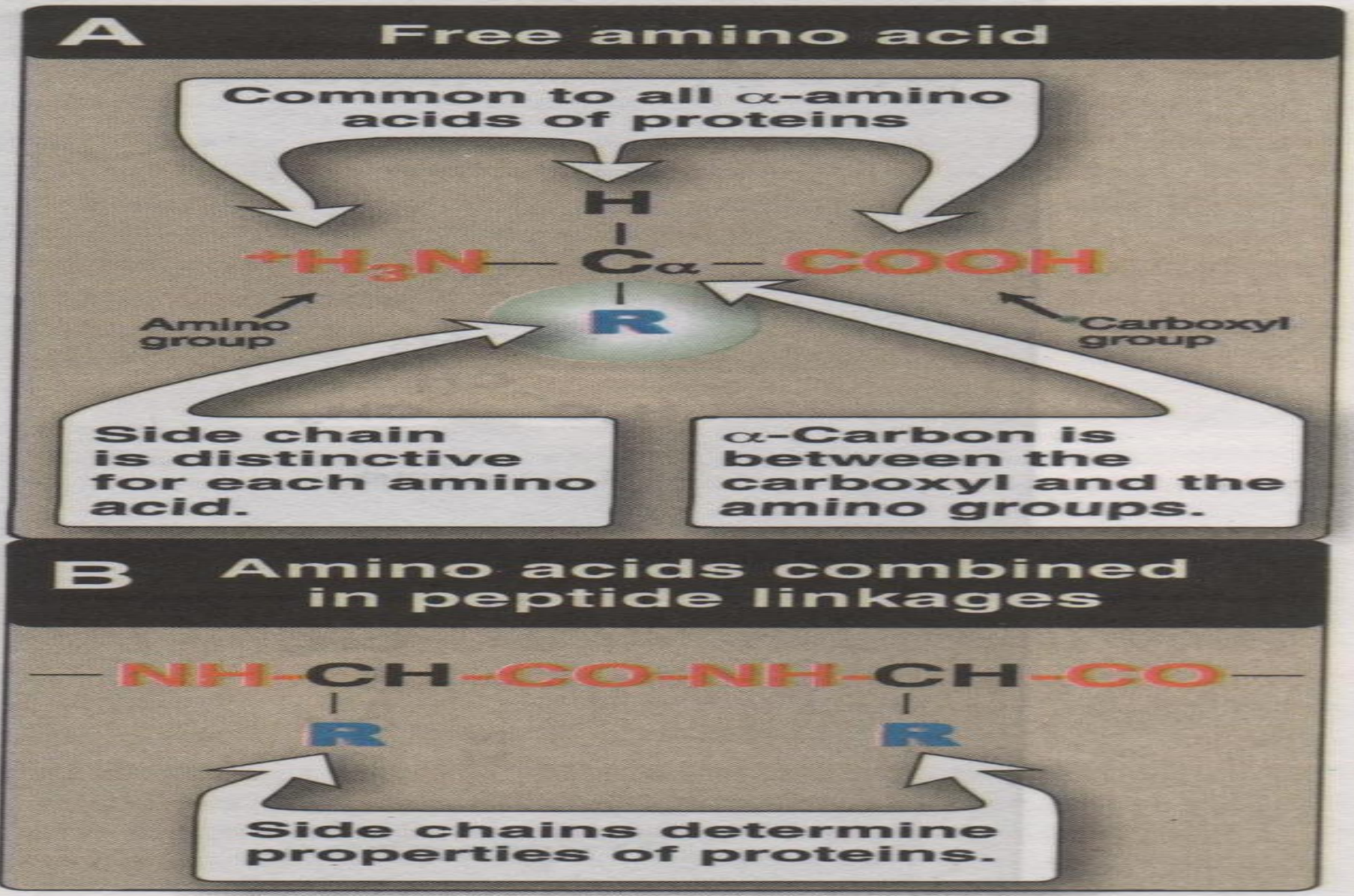
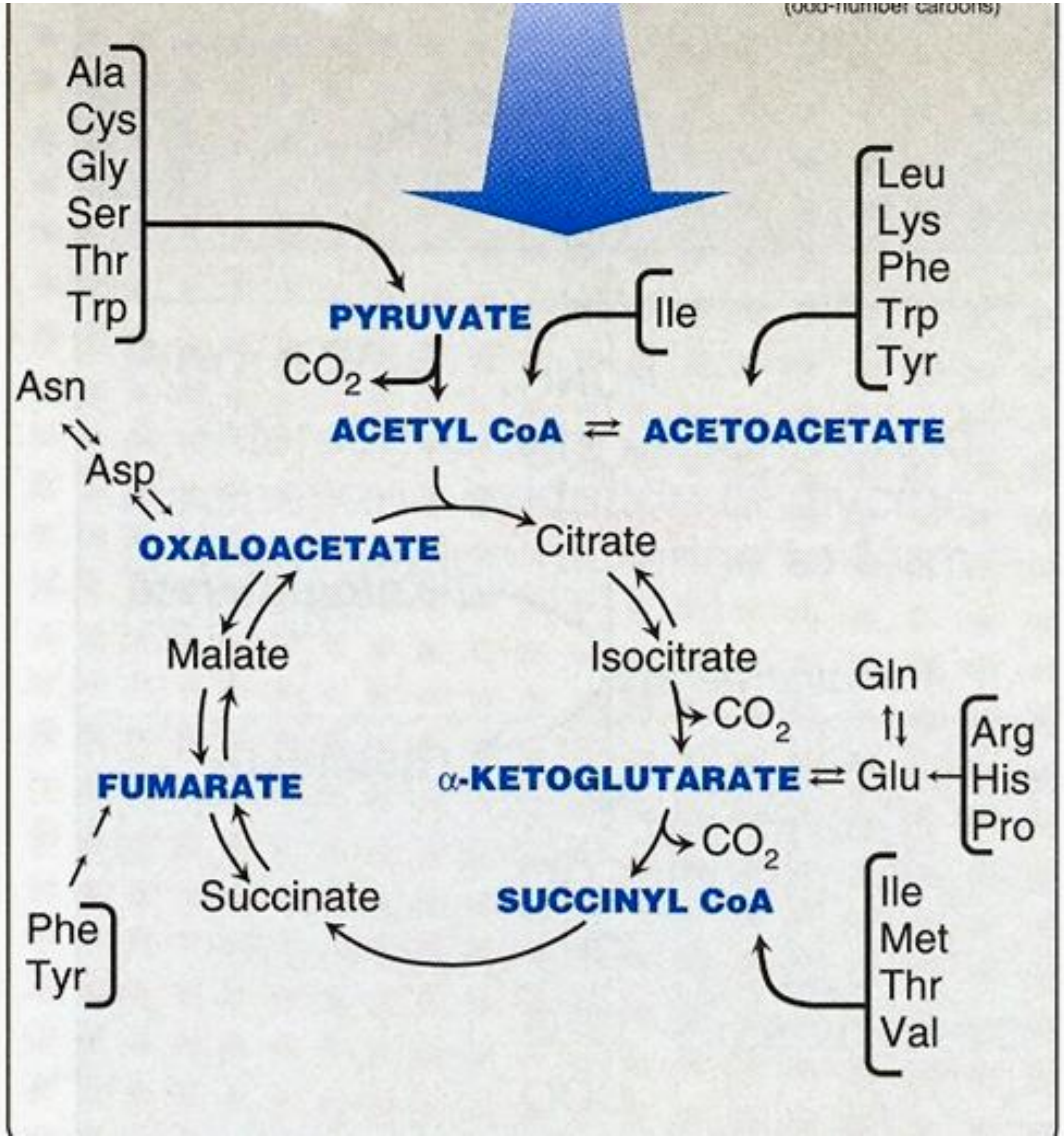


Figure 1.1
Structural features of amino acids (shown in their fully protonated form).


(odd-number carbons)
Ala
Cys
Gly
Ser
Thr
Trp
PYRUVATE
Ile
Leu
Lys
Phe
Trp
Tyr
CO_2
Asn
Asp
ACETYL CoA ⇌ ACETOACETATE
OXALOACETATE
Citrate
Malate
Isocitrate
Gln
CO_2
Arg
His
Pro
FUMARATE
α-KETOGLUTARATE ⇌ Glu
CO_2
Succinate
SUCCINYL CoA
Phe
Tyr
Ile
Met
Thr
Val

	Glucogenic	Glucogenic and Ketogenic	Ketogenic
Nonessential	Alanine Arginine Asparegine Aspartate Cysteine Glutamate Glutamine Glycine Proline Serine	Tyrosine	
Essential	Histidine Methionine Threonine Valine	Isoleucine Phenyl-alanine Tryptophan	Leucine Lysine

Figure 20.2
Classification of amino acids.

Sources of utilisation of Amino Acids

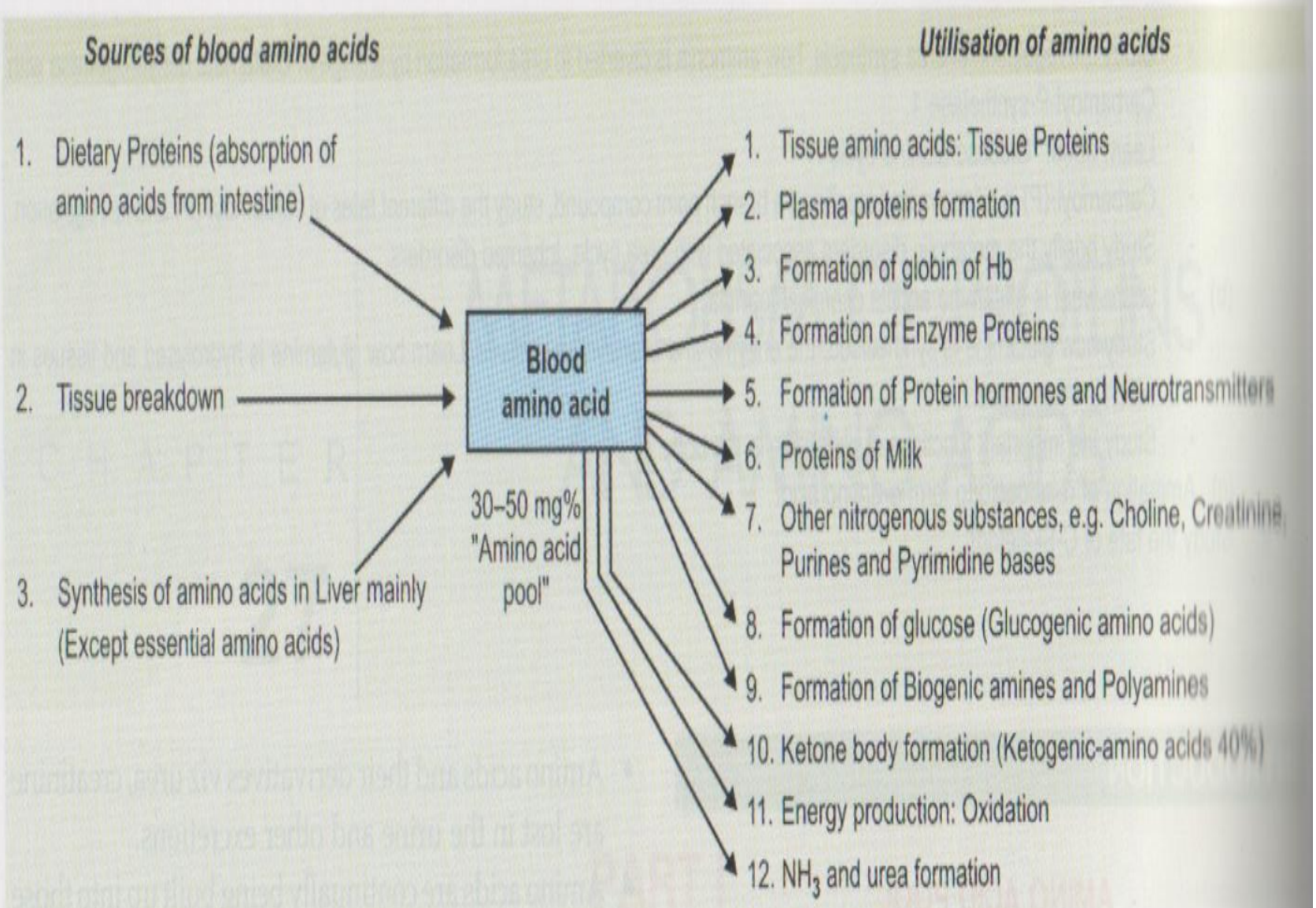


Fig. 27.1: Sources and utilisation of amino acids

CONSEQUENCES OF DIET LOW IN PROTIEN

Deficiency of essential a.acid

Break down of Tissue Protein.

Protein deficiency –KWASHIORKER

CONSEQUENCES OF DIET HIGH IN PROTIEN

Amino group is converted to Ammonia carbon skeleton converted to glucose and Fats.

Protein Degradation

Two major Enzyme systems

1. ATP dependent UbiQuitin – Proteasome system of Cytosole.
2. ATP independent degradative Enzyme system of Lysosome.

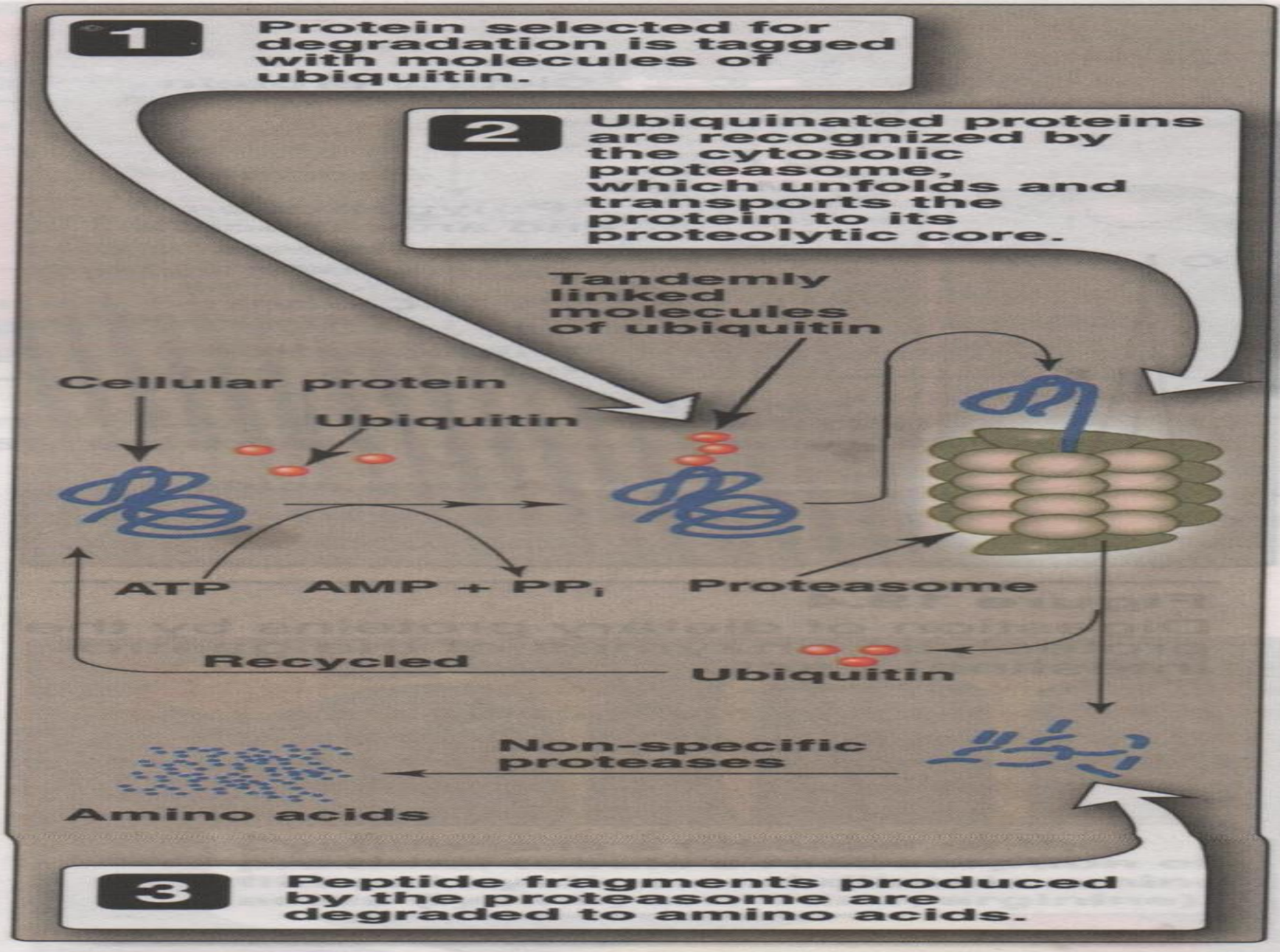


Figure 19.3
The ubiquitin-proteasome degradation pathway of proteins.

Ubiquitin-Proteosome Mechanism

- -Ubiquitin –

Small globular non enzymatic Protein

- -Proteosome
- Large barrel-shaped macromolecule, proteolytic complex
- -UbiQuitination: Occure by peptide linkage of carboxyle group of C-Terminal Glycine of UB to amino group of lysine in the protein substrate.
- It is ATP dependant Process.

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- Large barrel-shaped macromolecule, proteolytic complex
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- It is ATP dependant Process.

Half Life of Proteins

- -Extra cellular protein e.g digestive enzymes and plasma protein = hours or a few days
- -Intra cellular proteins e.g collagen = Months or Years
- -Also influence by amino terminal residue e.g serine = More than 20 hours.
- Aspartate = Only 3 Minutes

Biochemical Reactions Of Amino Acids In The Body

Following are various types of reactions involved in the metabolism of amino acids :

1. Trans-amination
2. Deamination
3. Trans-methylation
4. Deamidation
5. Trans-peptidation
6. Decarboxylation &
7. Interconversion of amino acids.

1. Trans-amination

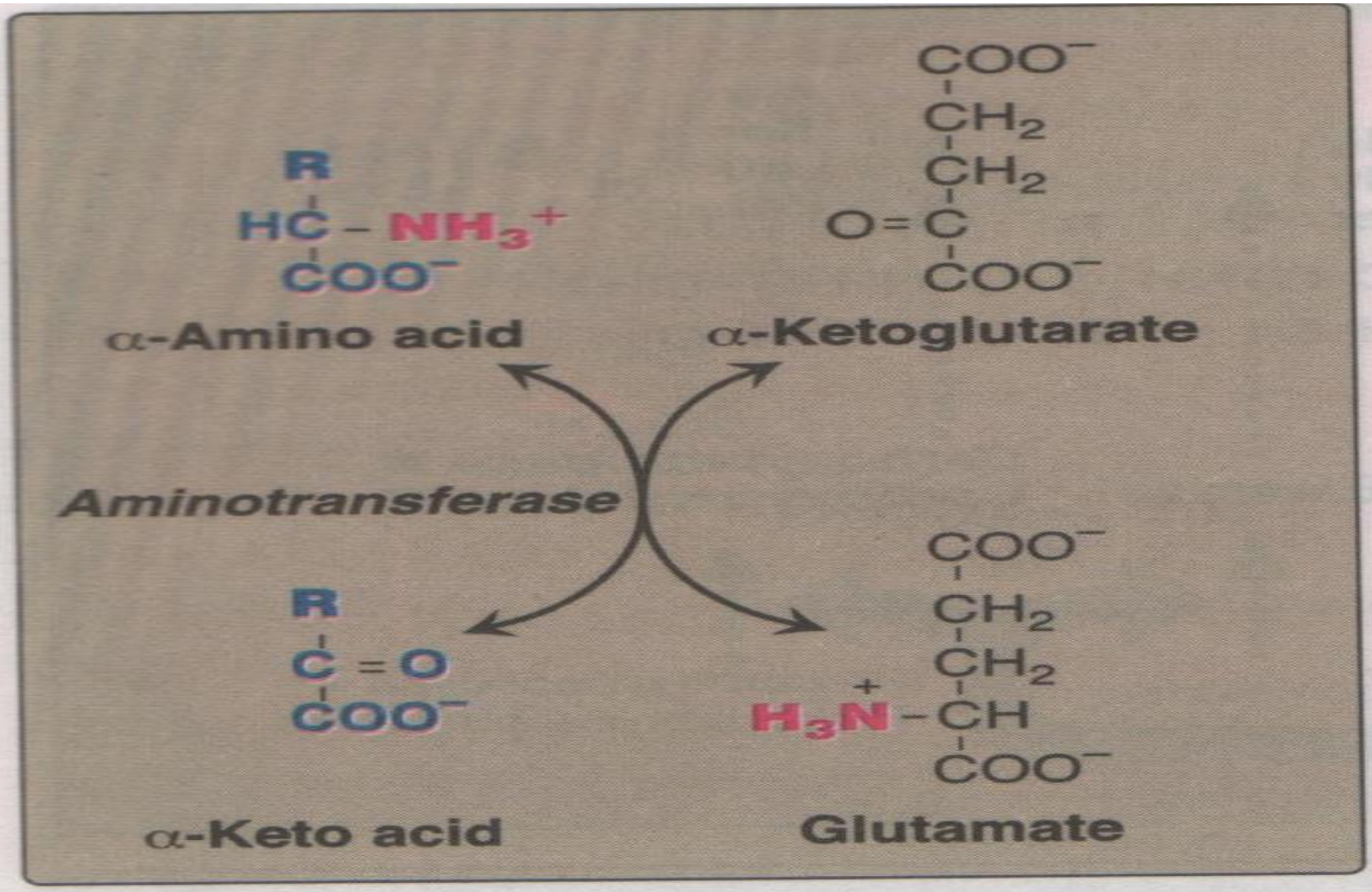


Figure 19.7
Aminotransferase reaction using α-ketoglutarate as the amino-group acceptor.

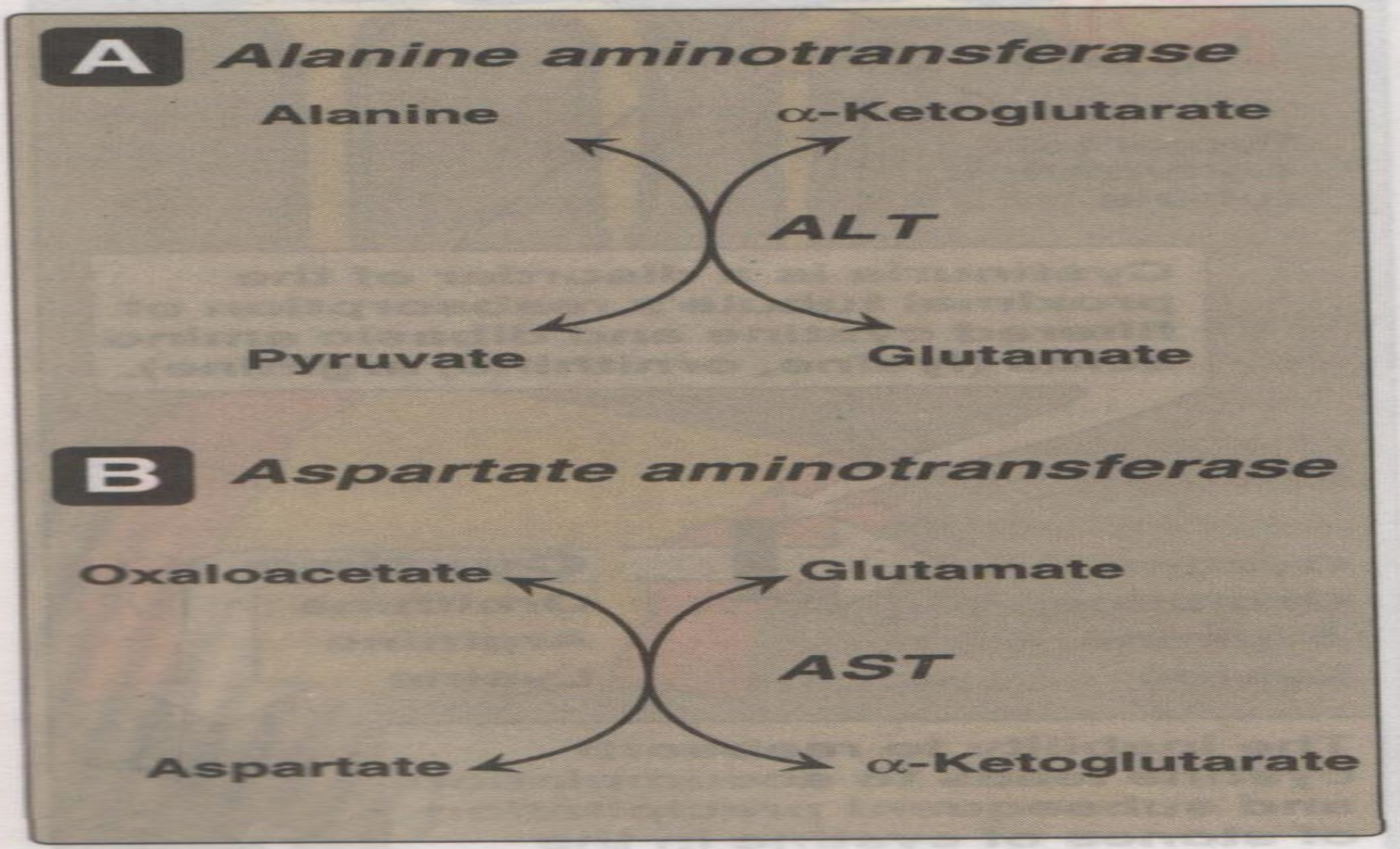


Figure 19.8
Reactions catalyzed during amino acid catabolism. A. *Alanine aminotransferase* (*ALT*). B. *Aspartate aminotransferase* (*AST*).

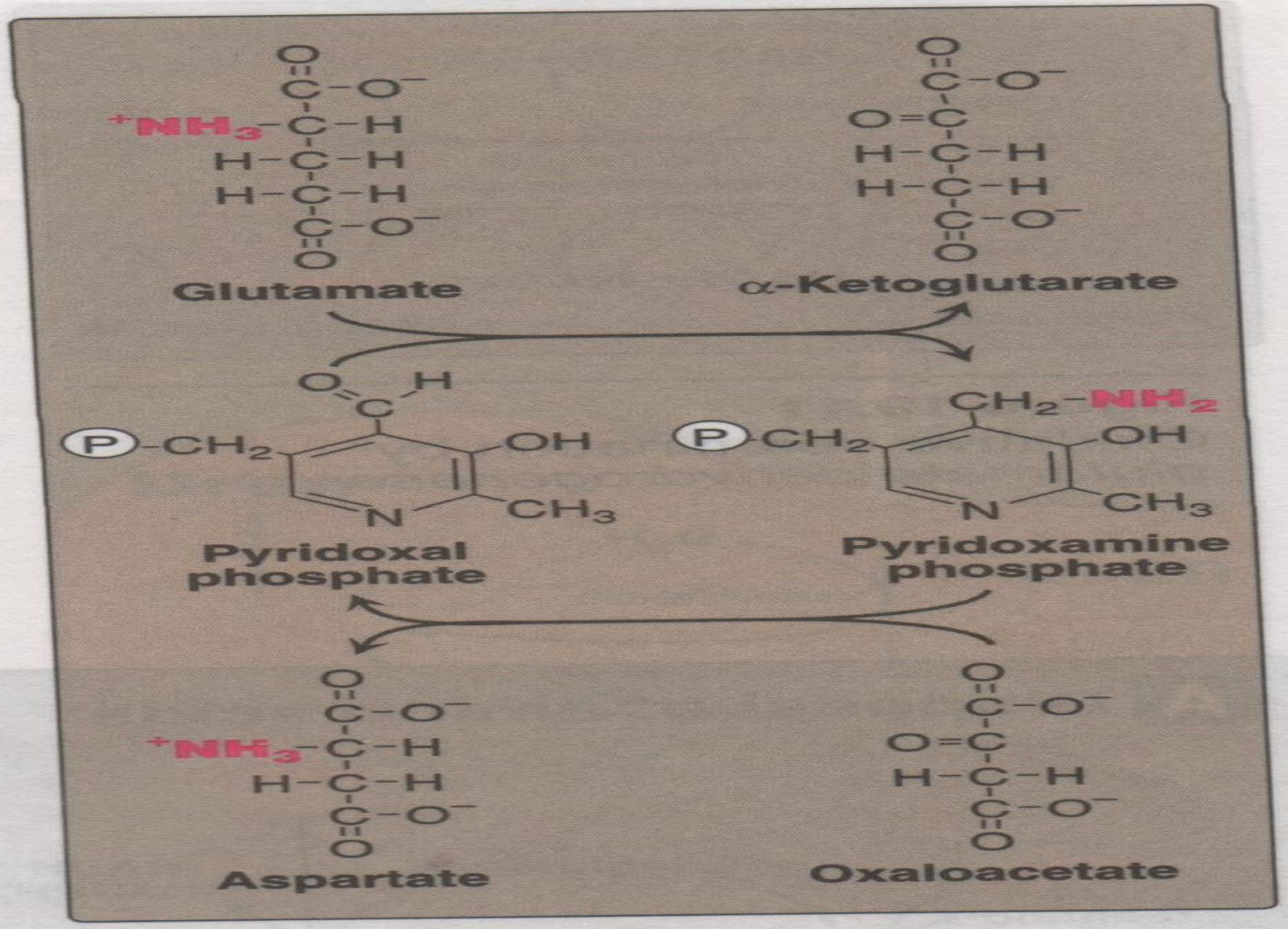


Figure 19.9
Cyclic interconversion of pyridoxal phosphate and pyridoxamine phosphate during the *aspartate aminotransferase* reaction. [Note: Ⓟ = phosphate group.]

- Diagnostic value of Plasma amino Transferases :-
- Normally Intracellular enzymes
- Elevated level indicates damage to the cell rich in these enzymes.
- AST OR SGOT
- ALT OR SGPT

- (a) Liver diseases. Both elevated
- Also have prognostic value
- (b) Nonhepatic diseases e.g M.I , Muscle disorders.

2.Oxidative Deamination

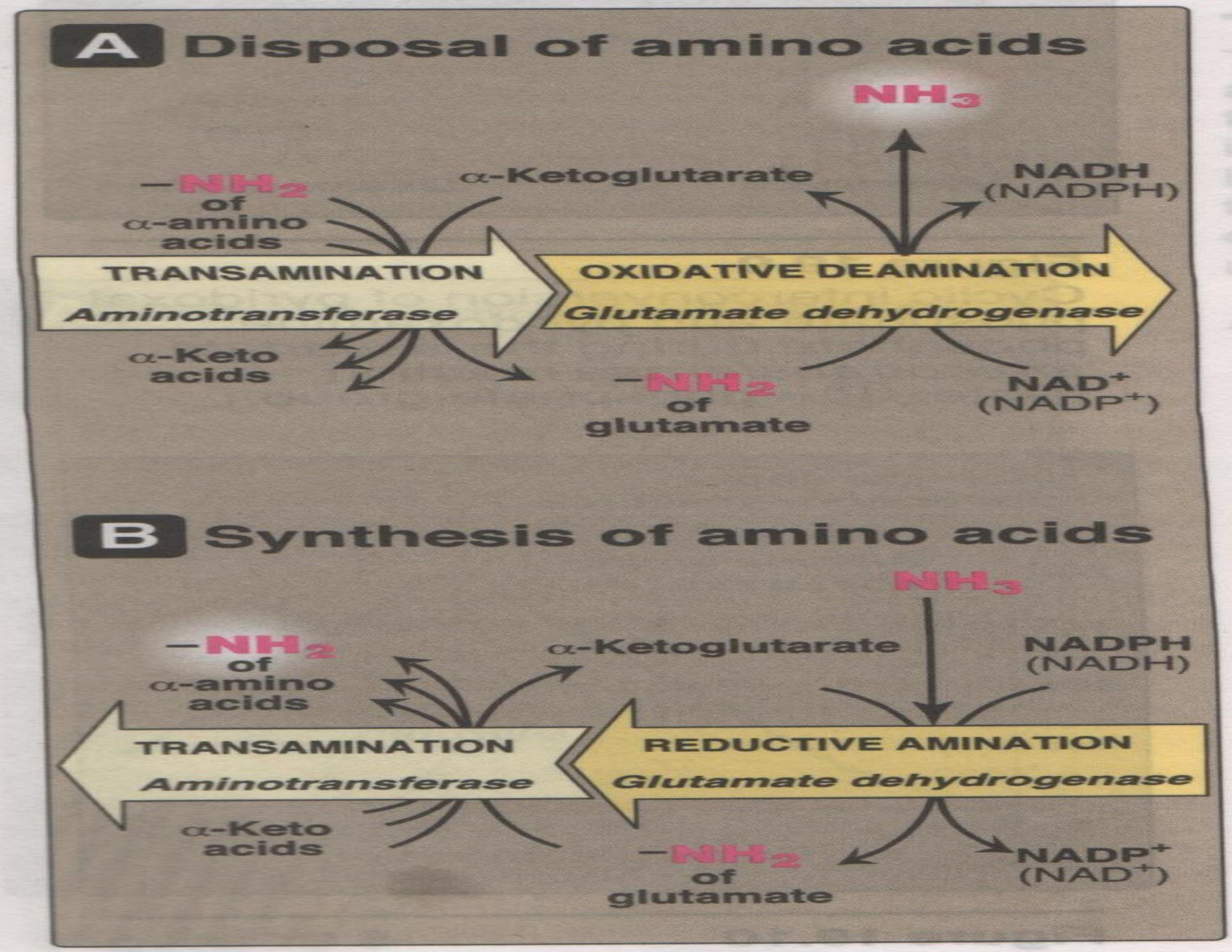


Figure 19.12
Combined actions of *aminotransferase* and *glutamate dehydrogenase* reactions.

Transport of ammonia to the liver

-Two mechanisms

1. Combination of ammonia with glutamate to form non-toxic glutamine
2. Formation of alanine by transamination of pyruvate.

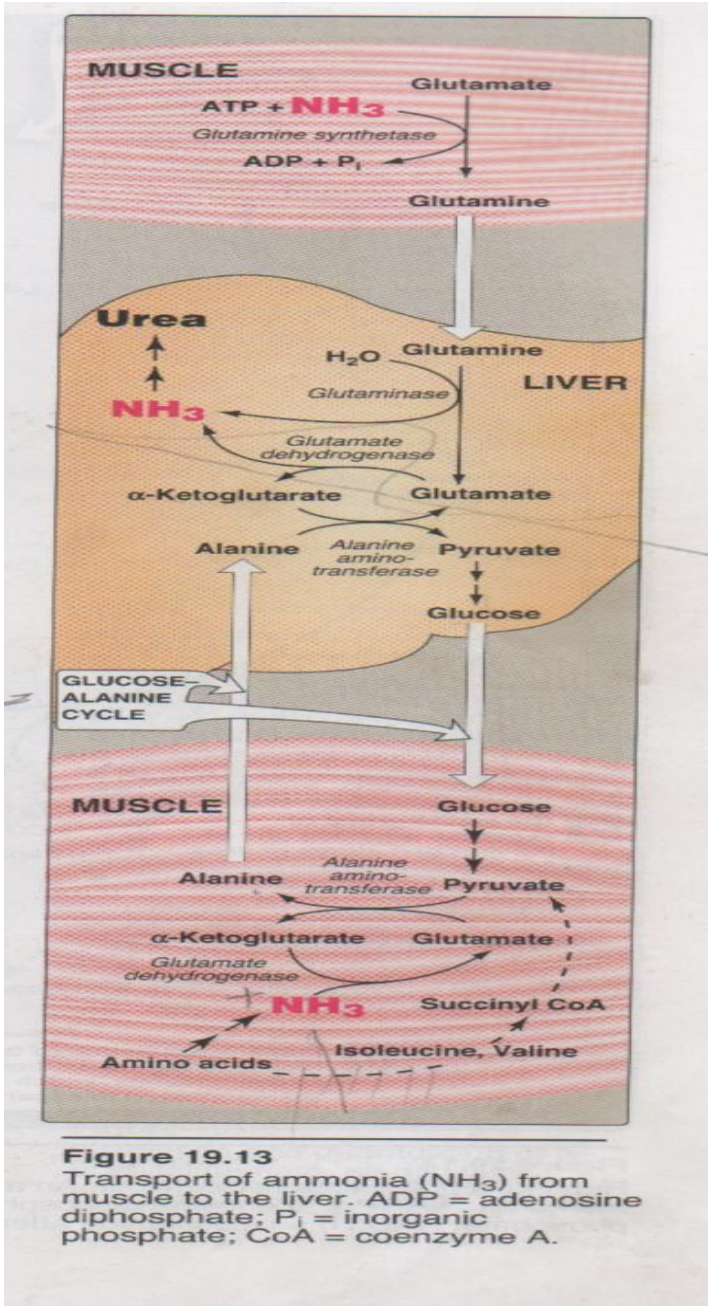
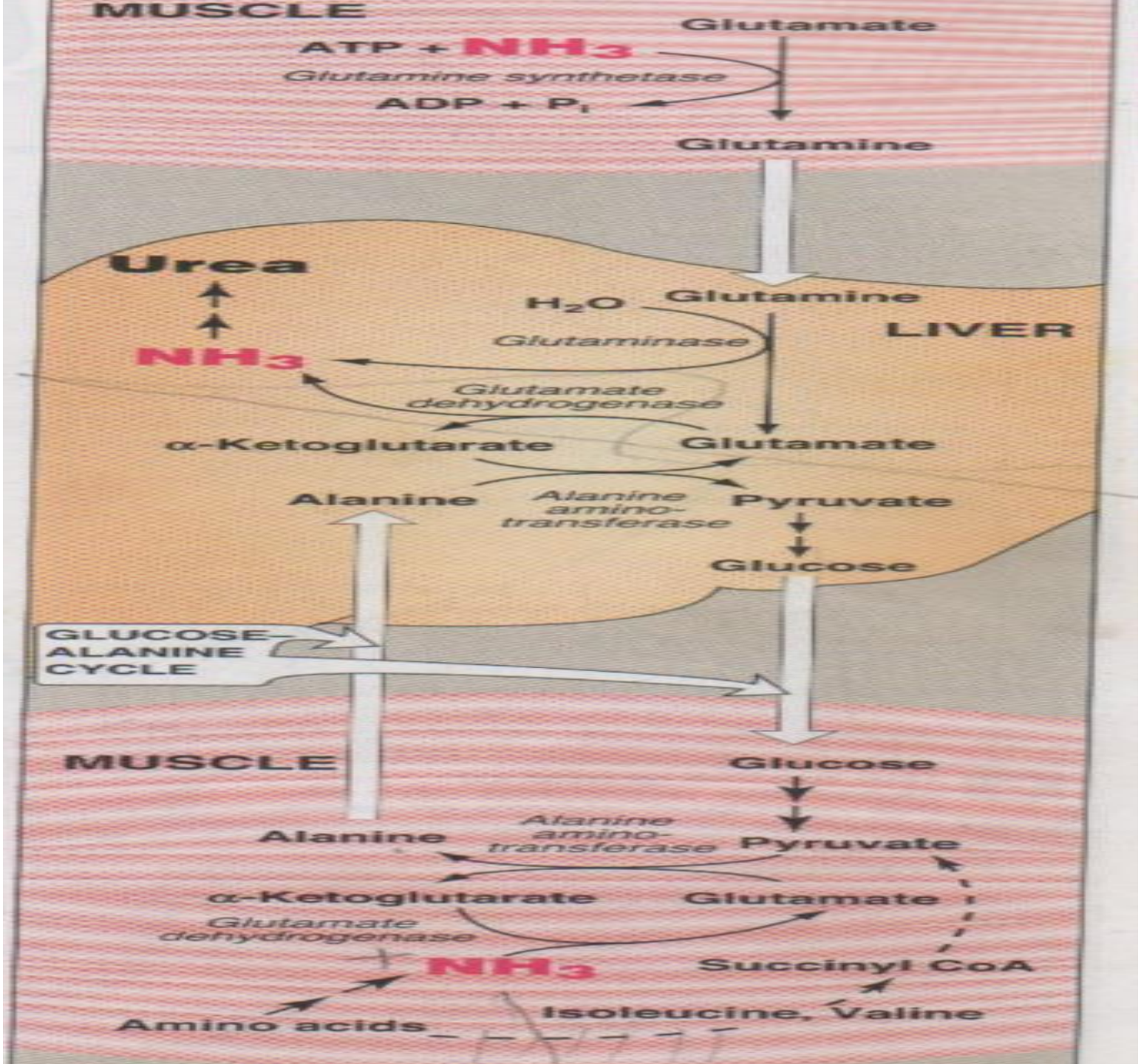


Figure 19.13
Transport of ammonia (NH_3) from muscle to the liver. ADP = adenosine diphosphate; P_i = inorganic phosphate; CoA = coenzyme A.

The transport of alanine from muscle to liver results in a reciprocal transport of glucose to muscles (Glucose –Alanine Cycle)


MUSCLE
Glutamate
ATP + NH3
Glutamine synthetase
ADP + Pi
Glutamine
Urea
H2O
Glutamine
LIVER
Glutaminase
NH3
Glutamate dehydrogenase
α-Ketoglutarate
Glutamate
Alanine
Alanine amino-transferase
Pyruvate
Glucose
GLUCOSE-ALANINE CYCLE
MUSCLE
Glucose
Alanine
Alanine amino-transferase
Pyruvate
α-Ketoglutarate
Glutamate
Glutamate dehydrogenase
NH3
Succinyl CoA
Amino acids
Isoleucine, Valine

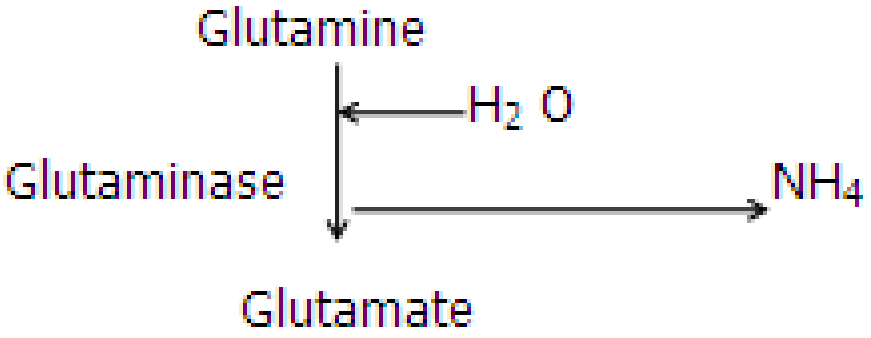
SOURCES OF Ammonia

1. From Amino acid .

- By Transamination and oxidative Deamination

- Quantitatively the most important source

2. From Glutamine



- Imp in acid-base balance

3. By Bacterial degradation of urea in intestine.

4. From Amines by the action of Amine oxidase

- Amines obtained from the diet and Mono amines that serve as Neurotransmitters or hormones

5. From Amino groups attached to the purine and purimidine rings.

Metabolic Fate of NH_3 :-

(A) Urea Formation :.

(B) Formation of Glutamine :-

Some NH_3 is used to aminate Glutamic acid to form Glutamine

(C) Formation of Non Essential a. acids :-

α Ketoacids are aminated to form α amino acids.

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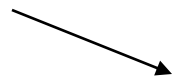
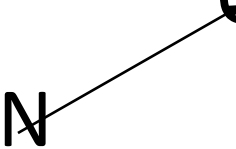
(B) Formation of Glutamine :-

Some NH_3 is used to aminate Glutamic acid to form Glutamine

(C) Formation of Non Essential a. acids :-

α Ketoacids are aminated to form α amino acids.

- Urea Cycle:

- H2N 
  C=O
- H2N 

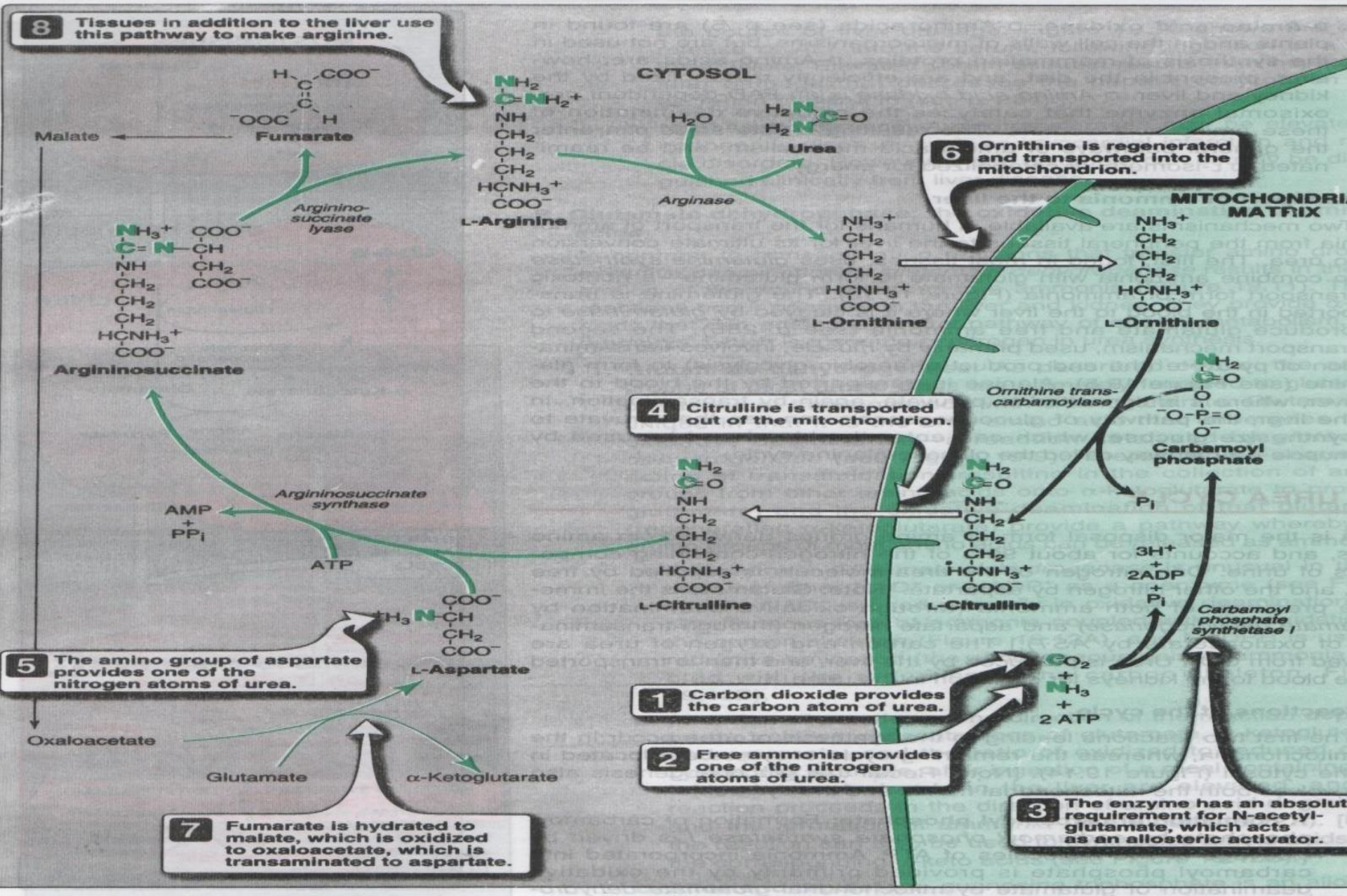


Figure 19.14
Reactions of the urea cycle.

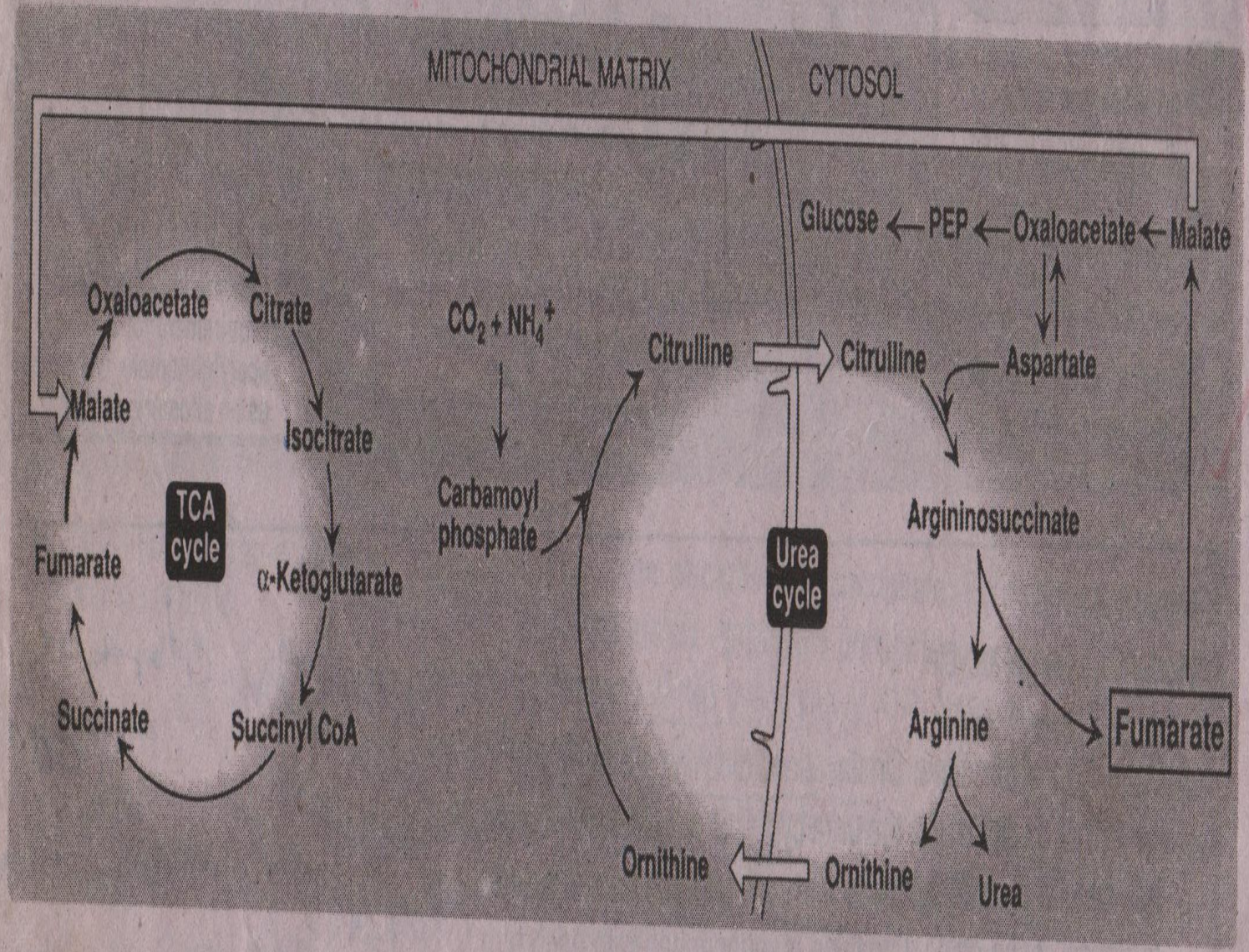


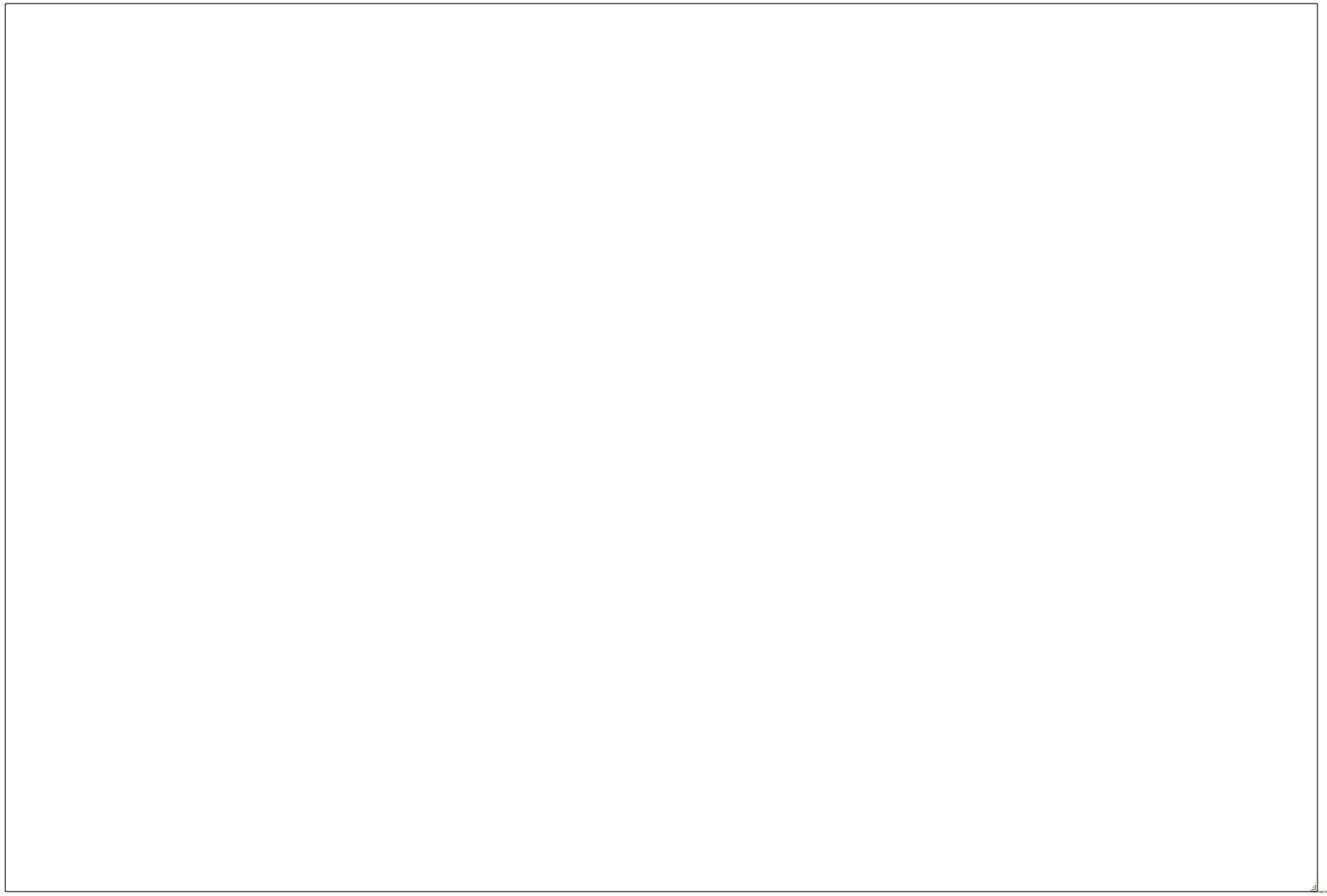
Figure 21.12

Fate of fumarate produced by the urea cycle.

C. Regulation of the urea cycle

N-Acetylglutamate (NAG) is an essential activator for *CPS I*, the rate-limiting step in the urea cycle. It increases the affinity of *CPS*

For ATP



- N-acetylglutamate brings some conformational change in the enzyme which effects the affinity of enzyme for ATP.

- NAG is synthesized from acetyl CoA and glutamate by N-acetylglutamate synthase In a reaction for which arginine is an activator.

The cycle is also regulated by substrate availability (short-term regulation) and enzyme induction (long term)

Fate of urea

1. Mostly filtered and excreted by kidneys
2. A small portion , diffuses from blood in to intestine and is cleaved to co_2 and NH_3 by bacterial urease

- ThisNH$_3$ is partly lost in faces and is partly reabsorbed in to the blood.
- In renal failure, plasma urea level is elevated, so more urea in gut, so more formation of NH_3 causing hyperammonia in these patients.

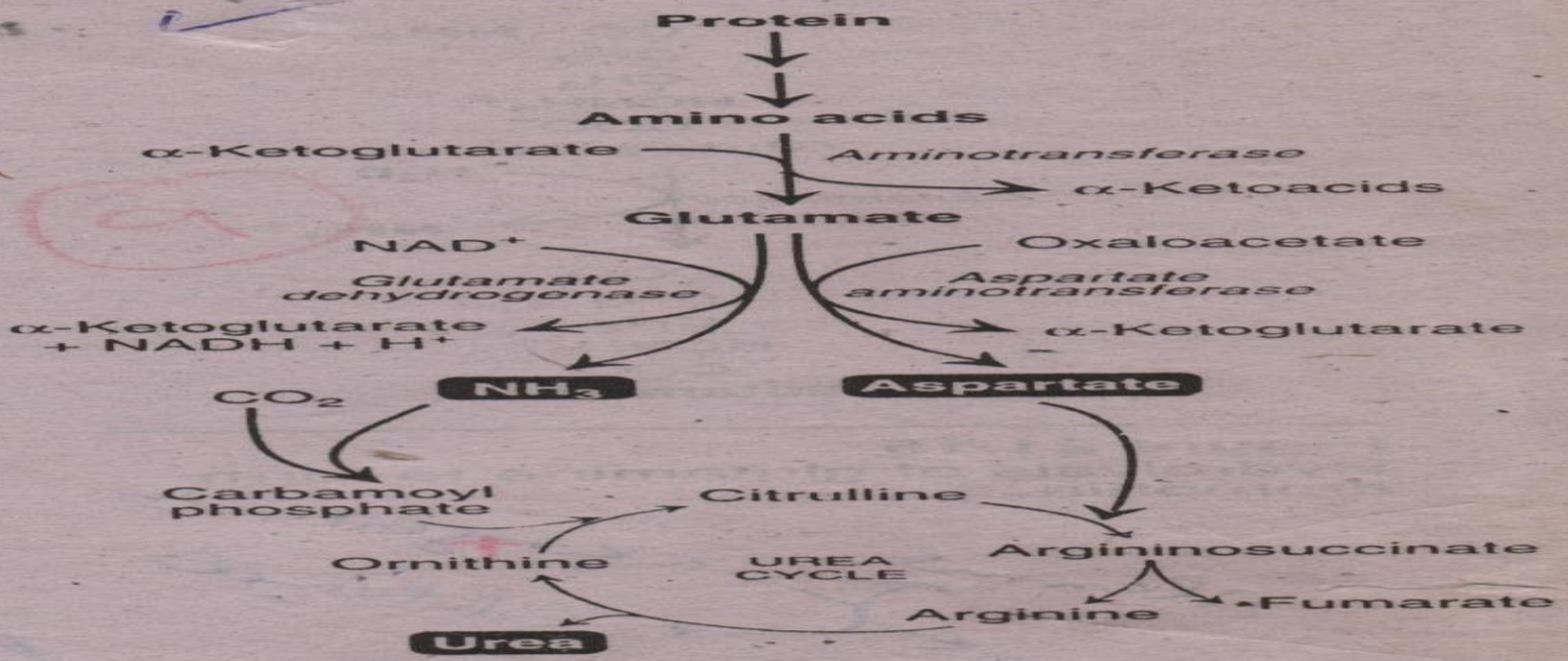


Figure 21.13
Flow of nitrogen from amino acids to urea. Amino groups for urea synthesis are collected in the form of ammonia and aspartate.

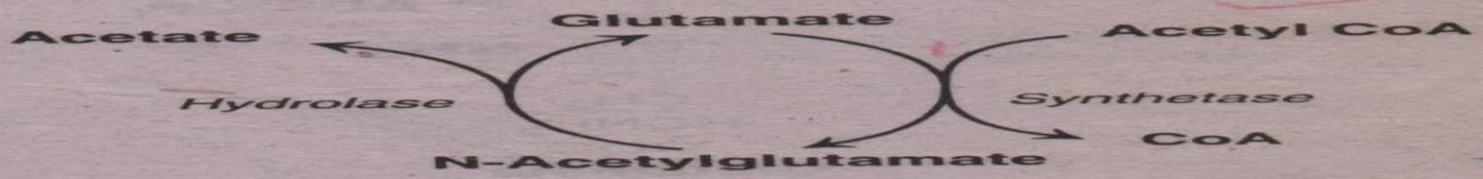


Figure 21.14
Formation and degradation of N-acetylglutamate, an allosteric activator of *carbamoyl phosphate*

Significances of urea cycle

1. Conversion of Toxic Ammonia in to Non –Toxic urea
2. Source of Arginine and Fumarate

a. Arginine : i. Take part in protein synthesis

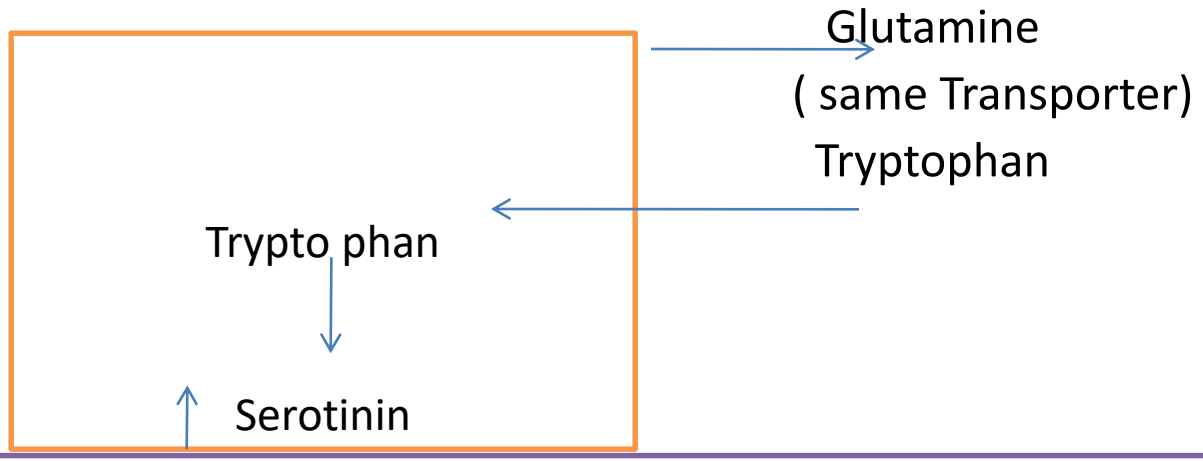
ii. Coverted to NO, which is a powerful vasodilator

iii. It combines with Glycine and thus take part in the synthesis of creatine.

b. Fumarate: i. It is hydrated to malate which is oxidized to oxaloacetate,which in the cytosole is transaminated to asparate and reenter the urea cycle or malate may enter in mitochondria, oxidized to oxaloacetate in TCA cycle, which can be used for gluconeogenesis.

Why NH_3 is Toxic

1. ↑ NH_3 enhances amination of Ketoglutarate of TCA cycle to form Glutamate in brain, so depresses TCA cycle, affecting the cellular respirationespecially the brain, which depends on TCA cycle for its energy.
2. Increased NH_3 enhances " Glutamine" formation from Glutamate so decreased Glutamate , so decreased formation of inhibitory Neurotransmitter GABA.
3. Increased Glutamine enhances out flow of Glutamine from Brain cell



2. Urea

- Normal value -20-40mg/100ml

- Uraemia –Causes

a) Pre-Renal

b) Renal

c) Post Renal

Hyperammonaemia

1. Acquired Hyperammonaemia:-

- Cirrhosis of liver
- Renal failure

2. Inherited hyperammonaemia :-

- Due to genetic defects in the urea cycle enzymes.
- The symptoms of NH_3 INTOXICATION INCLUDE

- A peculiar flapping Tremor
- Slurring of speech
- Bluring of vision
- Coma and death in severe case

Inherited Disorders Associated with urea cycle

1. Hyperammoneamia Type I

- Enzyme deficient : C.P Synthetase I
- Symptoms of Hyperammoneamia

2. Hyperammoneamia Type II

INHERITANCE: X-chromosme linked

- Enzyme deficient : Ornithine Transcarbamyolase
- Symptoms of NH_3 Toxicily
- Increased Level of Glutamine ,NH_3 and ornithine in blood,urine and CSF.

3. Citrulinemia:-

Inheritance : Autosomal recessive

- Enzyme deficient : Arginin succinate synthetase
- Hyperammonemia
- Increased level of NH_3 and citruline in Blood and CSF

4. Arginino Succinic Aciduria:

Inheritance : Autosomal recessive

- Enzyme deficient: Arginino succinase
- Hyperammonemia
- Blood and CSF have increased level of arginino succinate

5. Hyperarginimemia:Enzyme deficient: Arginase

- Hyperammonemia
- Increased level of Ariginine in Blood and CSF

6. Hyperammonemia may occure due to the deficiency of N-acetyl –glutamate deficiency

7. Hyperammonemia may occure due to the deficiency of Ornithine transporter

Disorder	Deficient Enzyme/ protein	Raised Level
1. Deficiency of N-Acetylglutamate	N-Acetylglutamate Synthase	Ammonia
2. Hyperammonemia Type – I	Carbamoyl Phosphate Synthetase – I	Ammonia
3. Hyperammonemia Type – II	Ornithine transcarbamoylase	Ammonia + Orn + Uracil + Orotic acid
4. Citrullinemia	Argininosuccinate Synthetase	NH_3+ Orn + Uracil + Orotic acid + Citrulline
5. Argininosuccinic Aciduria	Argininosuccinase Or Argininosuccinate lyase	NH_3+ Orn + U + OA + Cit + Argininosuccinate
6. Argininemia	Arginase	NH_3+ Orn + U + OA + Cit + Argininosuccinate +Arg
7. HHH Syndrome	Ornithine transporter (Responsible for transport of ornithine from cytosol to mitochondria)	**Ammonia, Ornithine Homocitrulline (Homocirtullinuria)** (When ornithine is not available in mitochondrion ,the Carbamoyl Phosphate condenses with lysine to form homocitrulline)

- Genetically transmitted (as autosomal recessive genes) (Except type- 2 i.e OT.Carbm deficeincy which is X-linked.)
- Clinical features & treatment of all disorders are similar
- Symptoms and consequences can be minimized when low protein diet is administered as frequent small meals to avoid sudden increase in ammonia level.

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Amino Acid Metabolism

3. Transmethylation

- Methyl group of a methyl donor (e.g. methionine) is transferred to other substances (methyl acceptors) ------ catalyzed by methyl transferases or trans-methylases (such methyl group is known as "labile methyl" group).

- Methionine cannot directly supply its -CH_3 group but it has first to be converted to "active methionine" (SAM).

- Methionine condenses with ATP, forming SAM –--- an unusual high energy compound as it contains no phosphate.

METHIONINE METABOLISM

(Sulphur containing ,essential, glucogenic)

METABOLIC ROLE OF METHIONINE

- *Methionine is "glucogenic"*: Propionyl-CoA the endproduct is glucogenic.
- *Cysteine formation:* (see stage 2)
- *Lipotropic function:* "Active" methionine can donate "methyl group" and can form choline from ethanolamine. Choline is lipotropic and prevents accumulation of fat in Liver.
- *Polyamine synthesis:* 'Active' methionine after decarboxylation combines with putrescine to form first polyamine **Spermidine** (Refer, biogenic amines).

- Synthesis and degradation of S-adenosylmethionine (SAM). (From methionine)

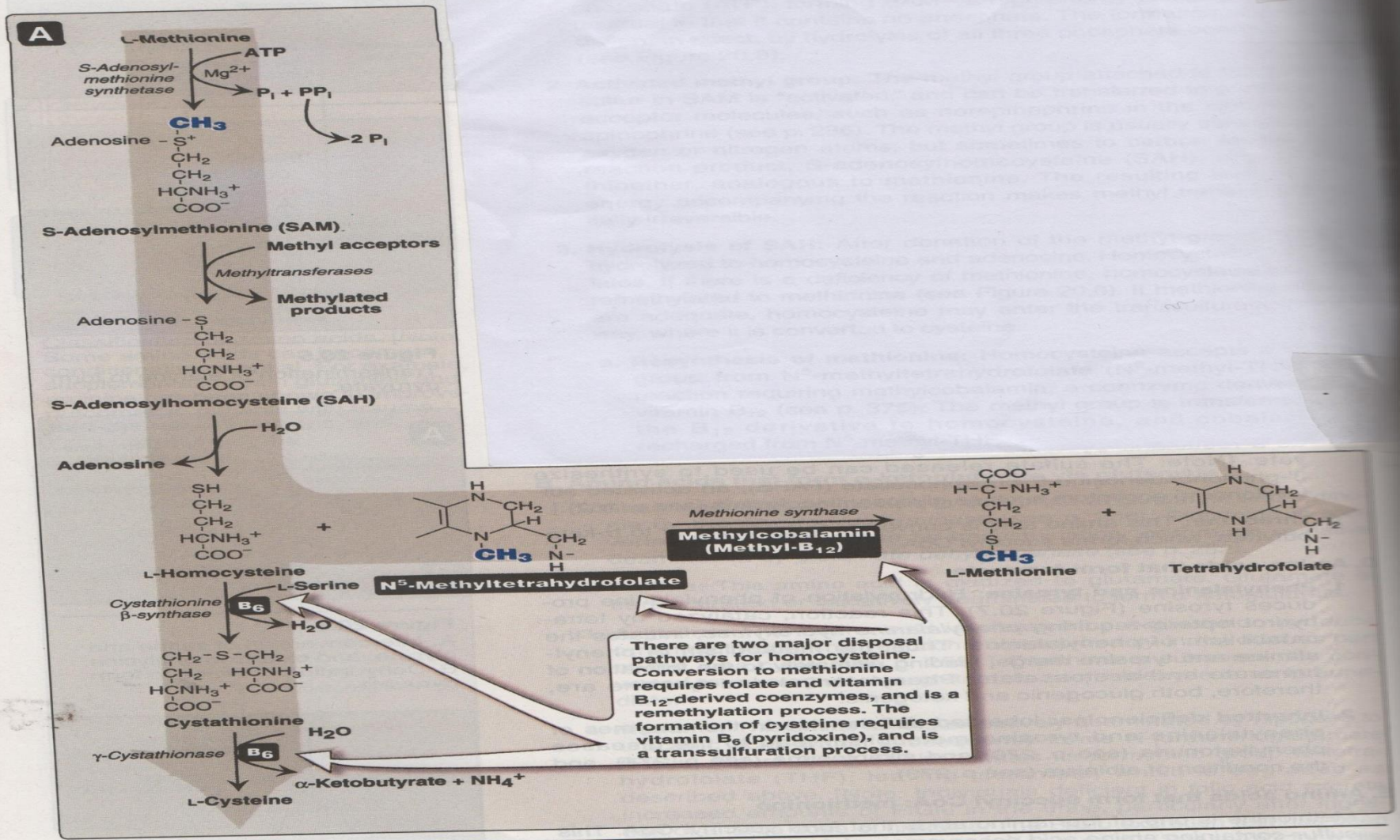
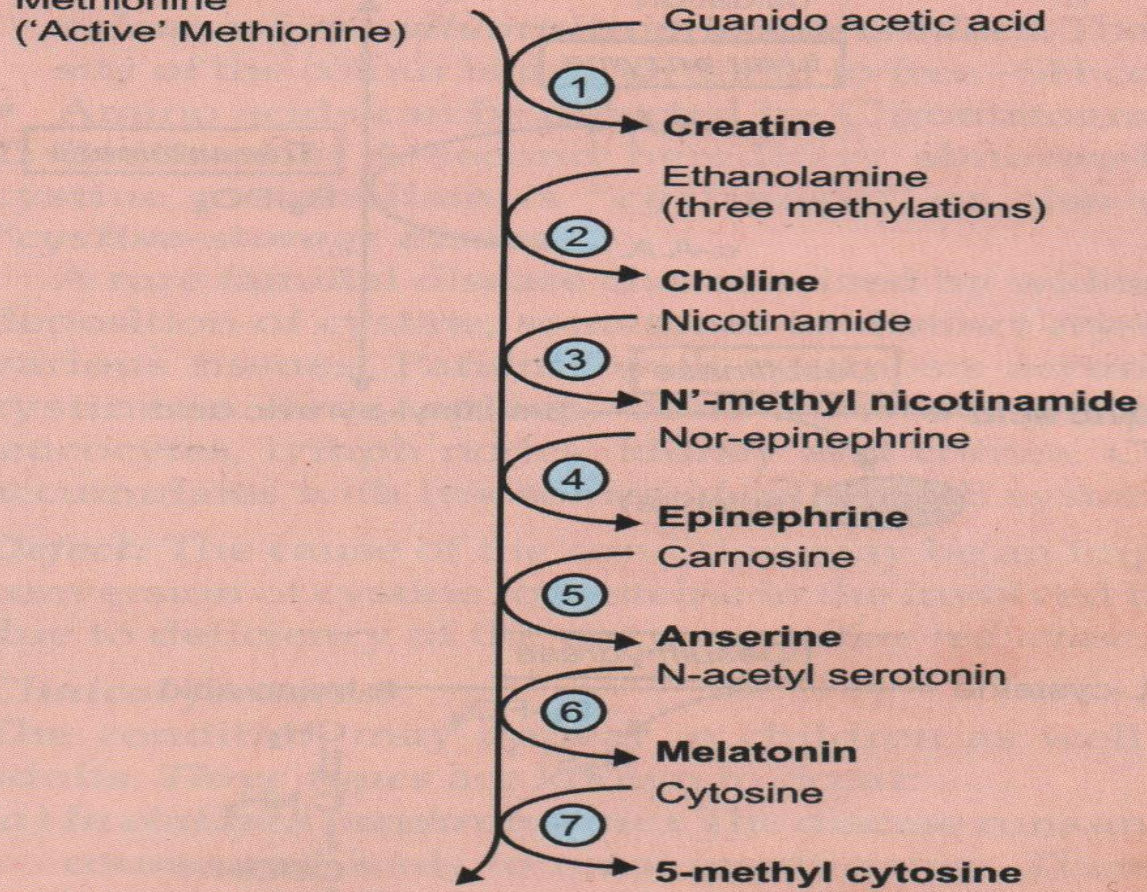


Figure 20.8
Degradation and resynthesis of methionine. [Note: The resynthesis of methionine from homocysteine is the only reaction in which THF both carries and donates a methyl group. In all other reactions, SAM is the methyl group carrier and donor.]

Transmethylation reactions



Other examples are:

8. Homocysteine ⟶ L-Methionine
9. Uracil ⟶ Thymine
10. Orthomethylation of oestrogens.

Elevated homocysteine and decreased folic acid levels in pregnant women are associated with increased incidence of neural tube defects (improper closure, as in spina bifida) in the fetus. Periconceptual supplementation with folate reduces the risk of such defects.

HOMOCYSTINURIA

3. Homocystinuria Type-1 (classical type)

An inborn error of metabolism, which involves the catabolism of methionine or more specifically its metabolic intermediates, homocysteine/and homocystine.

Enzyme deficiency: Genetic deficiency of the enzyme ***cystathionine synthetase.*** The enzyme defect leads to accumulation of homocystine. Plasma level of homocystine increases and excreted in urine ("overflow" aminoaciduria), 50 to 100 mg or more excreted in urine per day. In some cases, S-adenosyl methionine is also excreted.

Incidence: 1 in 60,000 live births.

Clinical features

- **Mental retardation:** In children and surviving adults.
- Some affected individuals, are extraordinarily tall, with long extremities, frequently with flat feet with toes out ***(Charlie-Chaplin gait).***
- Liver is enlarged ***(hepatomegaly).***
- ***Skeletal deformities:*** Involving spine, (vertebrae), and thorax, resulting to kyphosis, scoliosis, arachnodactyly. May

be premature osteoporosis which also accounts to above deformities. X-ray spine shows ***cod fish*** Vertebrae.

- ***Ectopia lentis:*** Curious dislocation of lens of the eye. Not seen at birth, may show at the age of 2 to 3 years.
- ***Life-threatening arterial/venous thrombosis.***
- Most of the patients show abnormal EEG.

Urine: Sodium cyanide-nitroprusside test is positive and helps in diagnosis.

The classical type of homocystinuria is described above. In addition to above classical type, two more types of homocystinurias have been described.

a. Homocystinuria Type-2

- ***Inheritance:*** Autosomal recessive
- ***Enzyme deficiency:*** N^5-methyl-Tetrahydrofolate-homocysteine methyl transferase.
- ***Clinical feature***
  - Mental retardation +
  - No ectopia lentis or thrombotic episodes seen.

Blood: Shows increased level of homocysteine.

Urine: Homocysteine is excreted in urine. Nitroprusside test +ve.

b. Homocystinuria Type-3

- ***Inheritance:*** Autosomal recessive.
- ***Enzyme deficiency:*** N^5, N^{10}-methylene tetrahydrofolate reductase deficiency.
- ***Clinical features***
  - Mental retardation +
  - No ectopia lentis or thrombotic episodes

Blood: Shows increase homocysteine.

Urine: Excretion of homocystine, nitroprusside test +ve.

Note: Both type 2 and type 3 show response to folic acid administration.

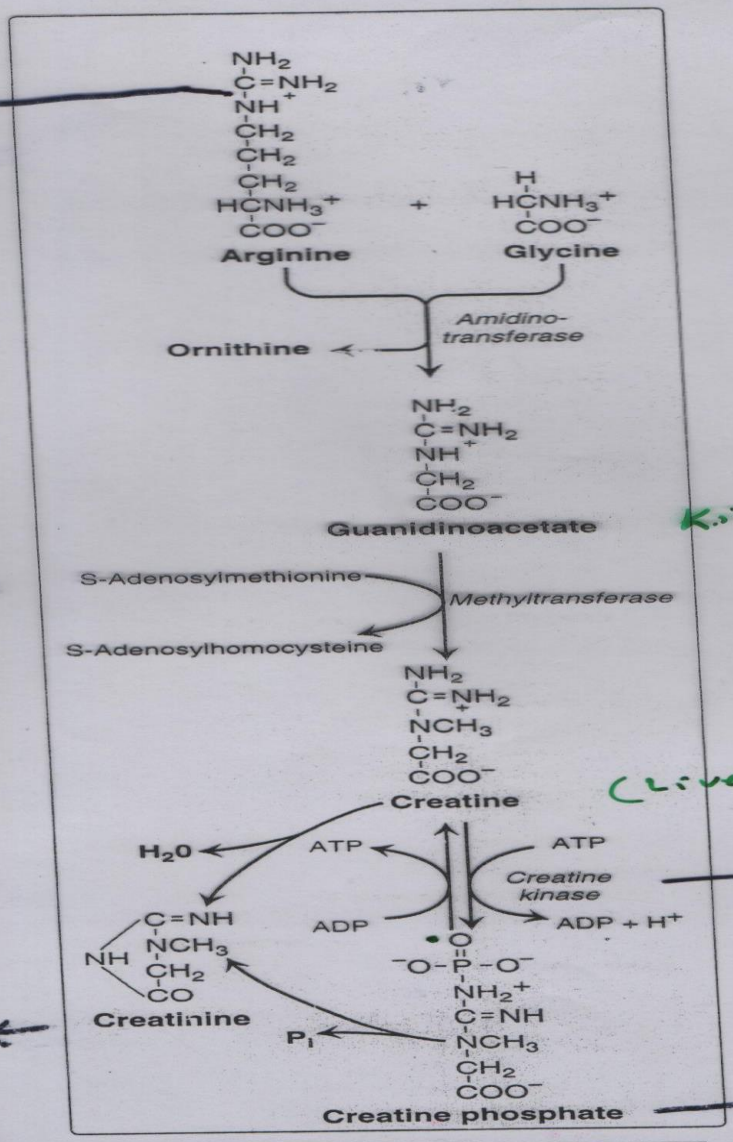
Creatine and Creatinine:—

(3)

ΔG = −10.3 Kcal/mole of creatine-P

ATP ΔG = −7.3 Kcal/mole

Guanidino group or: amidine group



Methyl group

Reversible Phosphorylation

Anhydride of Creatine

- waste Product - excreted in urine

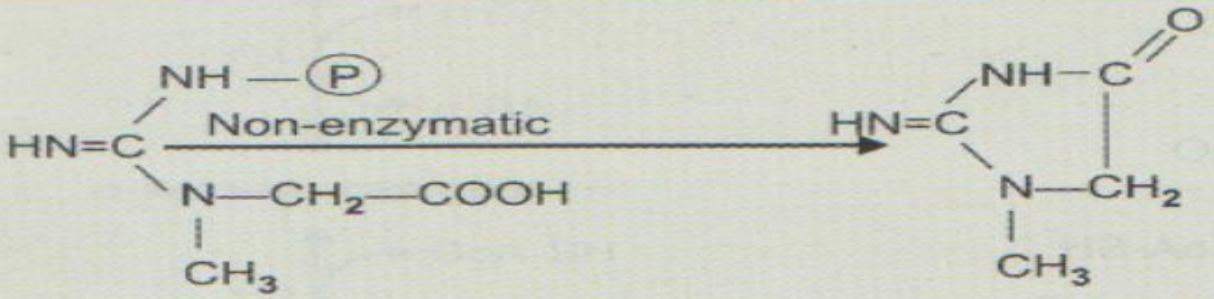
- used to assess Renal functions

High Energy Compound (Muscles)

- Normal Plasma level - 1–1.2 mg/dl
  ↑ in kidney Diseases

Figure 21.16
Synthesis of creatine.

Formation of creatinine



Creatine-(P)
Methyl guanido-acetic acid

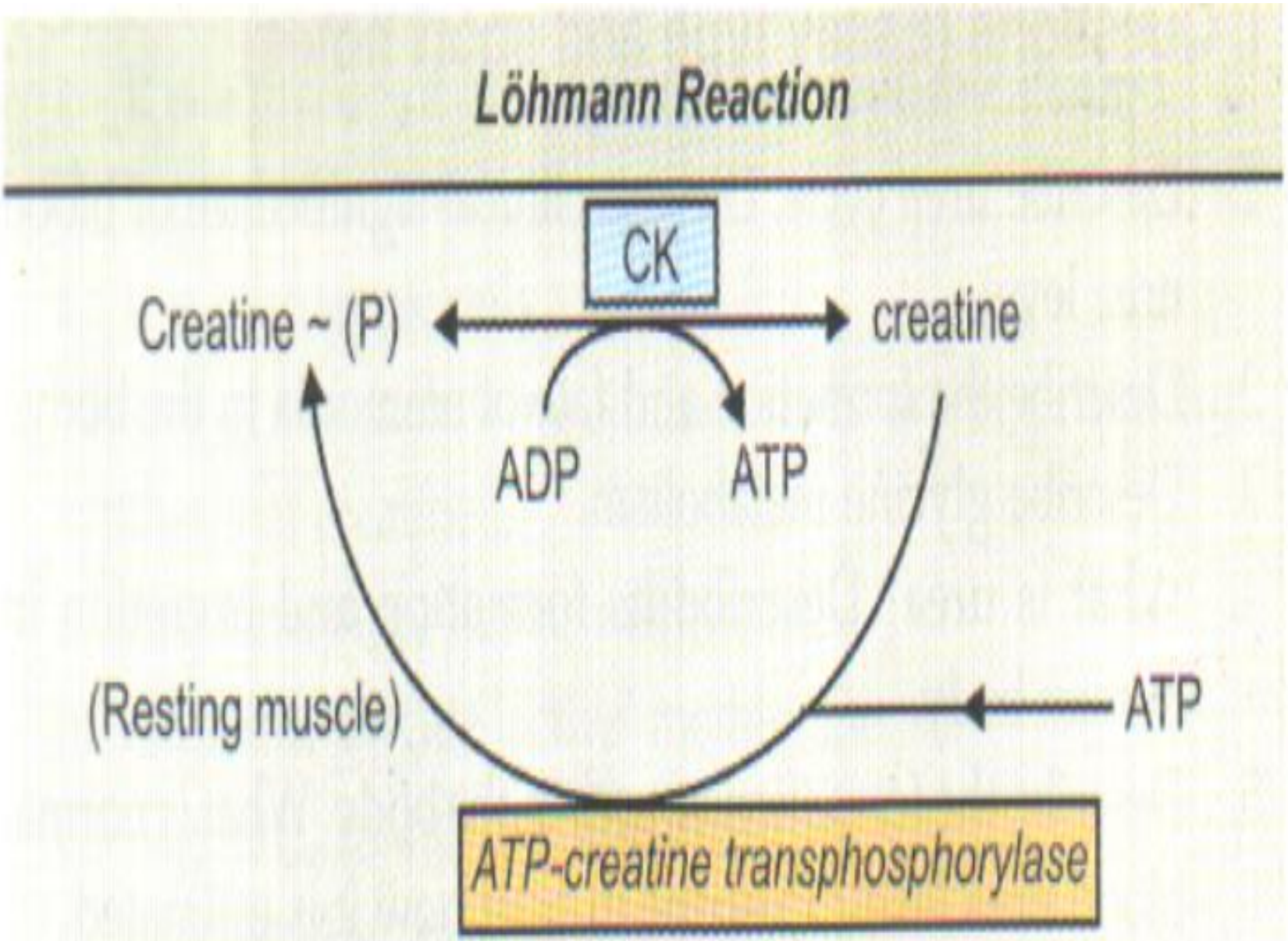
Creatinine
(Anhydride of creatine)

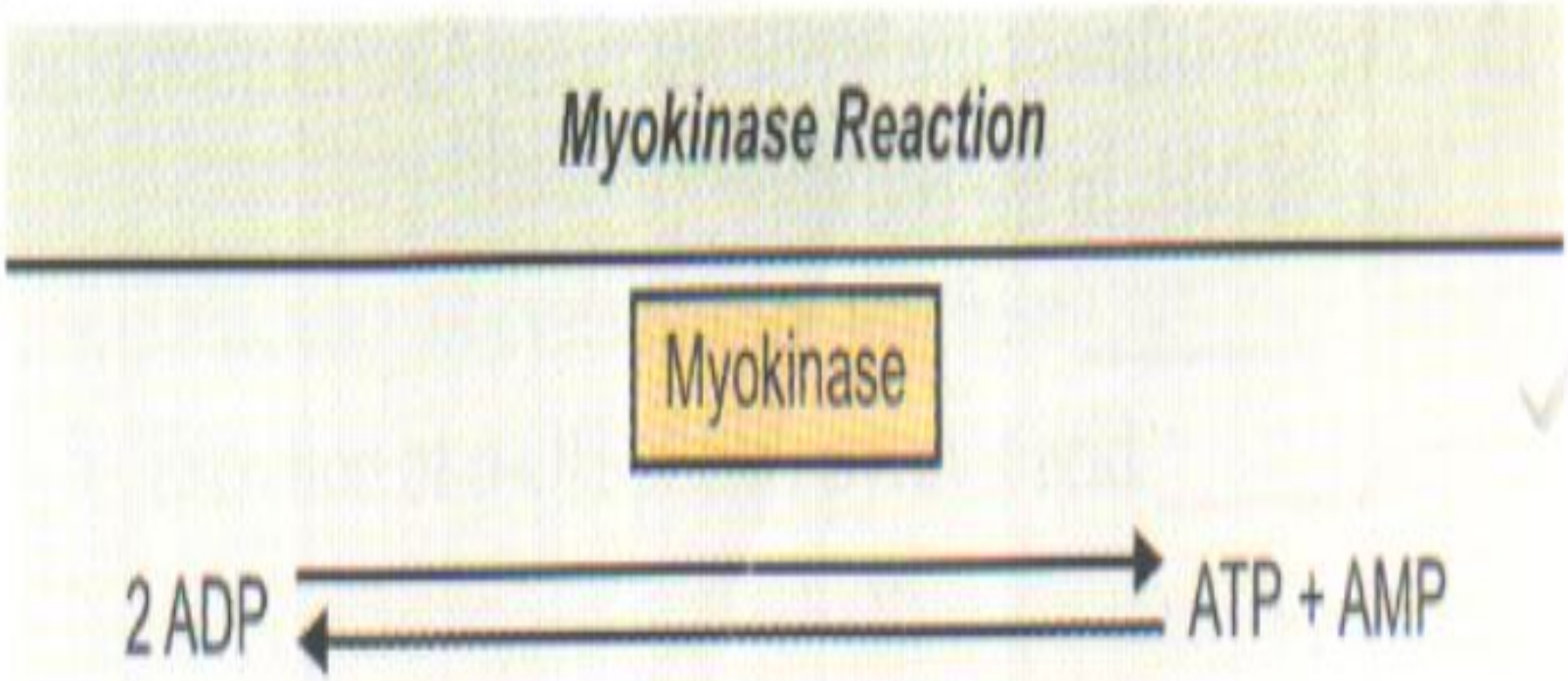
Characteristics of the above reaction

- Reaction is ***irreversible***
- It is ***non-enzymatic***
- Creatinine has ***ring structure.***

Occurrence and Distribution:

A. ***Creatine: It is a normal constituent of the body***. It is present in muscle, brain, liver, testes and in blood. Can occur in ***free*** form and also as ***phosphorylated*** form. The phosphorylated form is called as ***creatine-PO_4*** or ***phosphocreatine*** or ***Phosphagen***. Total amount in adult human body is approximately 120 gm. 98 per cent of total amount is present in muscles, of which 80 per cent occurs in phosphorylated form, 1.3 per cent in nervous system (brain) and 0.5 to 0.7 per cent in tissues.


Löhmann Reaction
CK
Creatine ~ (P)
creatine
ADP
ATP
(Resting muscle)
ATP
ATP-creatine transphosphorylase


Myokinase Reaction
Myokinase
2 ADP
ATP + AMP

6 Decarboxylation Reactions

- Reactions by which Co_2 is removed from CooH group of an a. acid by enzyme , Decarboxylase, present in liver , kidneys, brain and also in micro organism of intestinal tract.
- The enzyme require pyridoxal phosphate as coenzyme.
- The enzymes removes Co_2 from CooH and convert the a.acid is corresponding amines.
- R-CH-CooH $\xrightarrow[B_6\text{-P}]{\text{Decarboxylase}}$ CO_2 + $R.CH_2\text{-}NH_2$
- NH2
- (Amino acid)
- (Amine)

Examples are :-

(i) Histidine → Histamine + CO_2

(ii) 5-Hydroxytryptophan → 5-Hydroxytryptamine + CO_2

(iii) Lysine → Cadaverine + CO_2

(iv) Ornithine → Putrescine + CO_2

(v) Tyrosine → Tyramine + CO_2

(VI) Dihydroxy-phenylalanine (DOPA) → Dopamine + CO_2

(VII) Glutamic Acid → GABA + CO_2

Table 27.1: Biogenic amines and their functions

Nos	Amino acids	Amine	Biologic importance
1.	Tyrosine	• Tyramine	• Increases blood pressure (Vasoconstriction) • Contracts uterus
2.	Tryptophan	• Tryptamine	• Tissue hormone: A derivative 5-OH Tryptamine (Serotonin)
			• Vasoconstriction • BP ↑
		• 5-methoxy Tryptamine (Melatonin)	• Hormone of pineal gland
3.	Histidine	• Histamine	• Vasodilator, Bl. pr ↓ • HCl ↑ • Pepsin ↑
4.	Serine	• Ethanolamine	• Forms choline by three methylations • Constituent of Phospholipid like cephalin
5.	Threonine	• Propanol amine	• Constituent of Vit B_{12}
6.	Cysteine	• β-mercaptoethanolamine	• Constituent of coenzyme A
7.	Aspartic acid	• β-alanine	• Constituent of pantothenic acid (coenz. A) • As a constituent of dipeptide carnosine and Anserine
8.	Glutamic acid	• γ-amino butyric acid (GABA)	• Presynaptic inhibitor in brain. • Forms a bypass in TCA cycle (GABA-shunt)
9.	3,4,-di-OH-phenylalanine (DOPA)	• Dopamine	• Precursor of Epinephrine and Nor-epinephrine
10.	Cysteic acid	• Taurine	• Constituent of Bile acid taurocholic acid
11.	Lysine	• Cadaverine	• Product of Putrefaction in the gut
12.	Ornithine	• Putrescine	• Product of Putrefaction in the gut
13.	Arginine	• Agmatine	• Product of Putrefaction in the gut

Formation of Amines By Decarboxylation :-

Histadine ⟶ Histamine

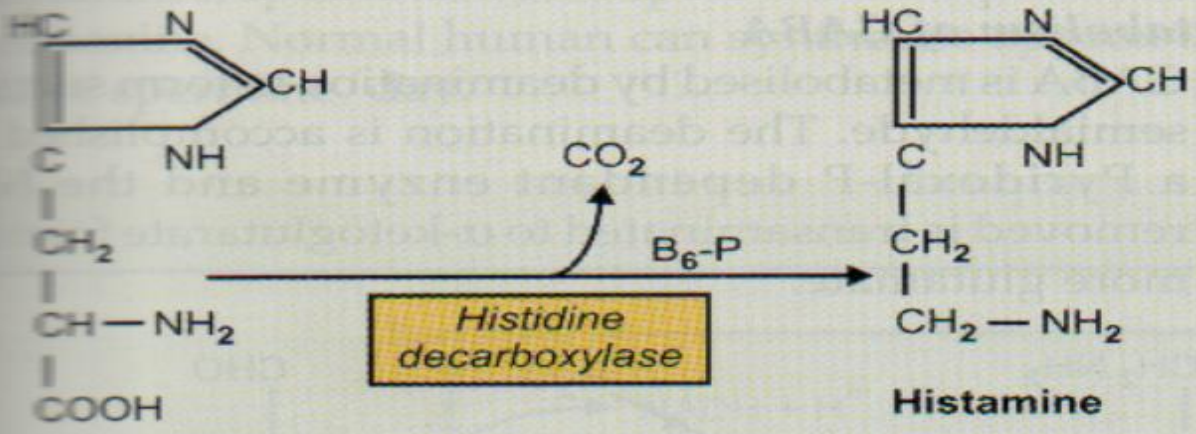
- ↑ Formation as a result of stings of bees and Allergic conditions.
- It Causes vasodilitation, redness, and swelling.
- ↑ Histamine is also formed in allergic Reactions.

Histamine

Histamine is formed by decarboxylation of amino acid "Histidine" by the enzyme ***Histidine decarboxylase*** or aromatic L-amino acid decarboxylase in presence of B_6-PO_4.

Site of Formation

- Mast cells are the chief source of histamine in the tissues and histamine constitutes about 10 per cent of the weight of mast cell granules.



- Also produced by gastric mucosa cells and histaminergic neurones of the central nervous system.
- ***Basophils are the chief source of histamine in the circulating cells.***

Local Action of Histamine

Upon SC injection of hsistamine, it causes (i) pruritus, • erythema, (ii) circumferential flare and a central raised (iii) wheal *(wheal and flare).*

Blockers of Histamine (Antihistaminics)

- ***Blockers of H_1 receptors:*** The anaphylactic reaction can be minimised by pharmacological agents, e.g. Promethazine and Mepyramine which block H_1 receptors.
- ***Blockers of H_2 receptors:*** 'Cimetidine' is used to reduce the gastric acidity in peptic ulcer patients, it is blocker of H_2 receptor.

Actions through H_1 receptors	Actions through H_2 receptors
• Contracts smooth muscle including airways and the GI tract	• Produces bronchodilation
• Increases venular permeability	• Increases vasopermeability and dilation
• Induces nasal mucus production	• Induces airway mucus production
• Causes pruritus, with cutaneous vasodilation	• Also causes pruritus with H_2 receptor, stimulates gastric acid secretion. HCl ↑ and pepsin ↑

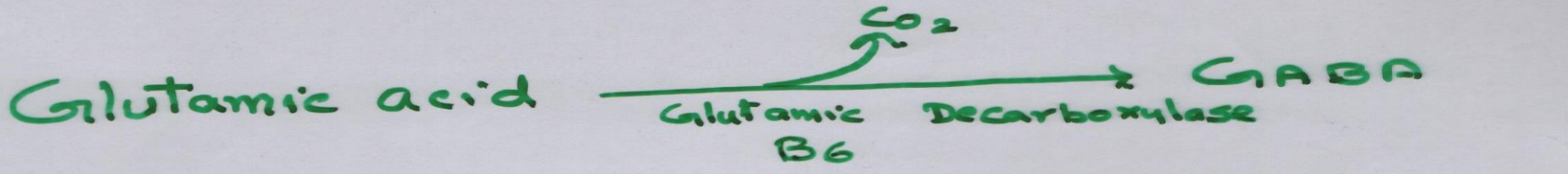
APPLIED CLINICAL ASPECT

Elevated plasma levels of histamine have been demonstrated in:

- Patients with anaphylaxis, provoked by exercise or antigen. Such reactions are related to the explosive liberation of histamine caused by entrance of the sensitizing substances in the tissues.
- During spontaneous episodes of increased symptoms in patients with "mastocytosis", mast cells tumor.
- During experimentally induced angio-oedema in patients with cold urticaria.
- In patients with antigen-induced bronchial asthma.
- Also formed in injured tissues. Excessive liberation of histamine may be related to traumatic shock.
- Histamine markedly depresses blood pressure ↓ and large doses may cause extreme vascular collapse.
- After challenge by specific antigens in patients with 'atopy', histamine demonstrated in nasal lavage fluid and skin blister fluid.

Local Action of Histamine: Upon SC injection of histamine, it causes • pruritus, • erythema, • circumferential flare and a central raised • wheal (***"wheal and flare"***).

(10 Gamma amino butaric acid. GABA



- Decarboxylated Product of Glutamic acid
- Richly Present in Brain, where it acts as an Inhibitory Neurotransmitter.
- Epileptic Fits are attributed to its deficiency.
- Also used for synthesis of Carnitine.

CLINICAL ASPECT

Vit B_6 deficiency in children may be responsible for some of the cases of infantile convulsions. B_6-deficiency causes less formation of GABA leading to neuronal hyperexcitability and convulsions.

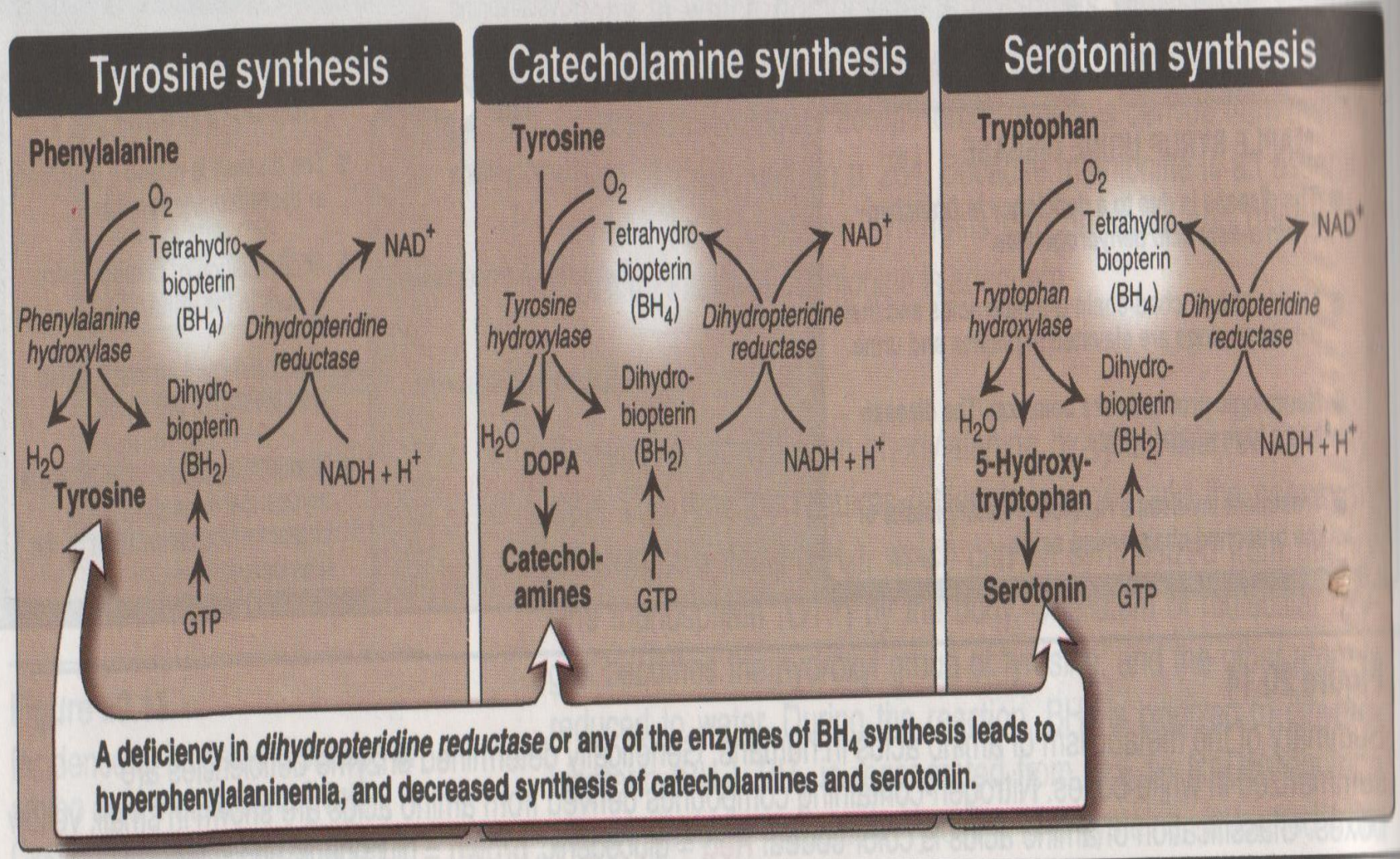
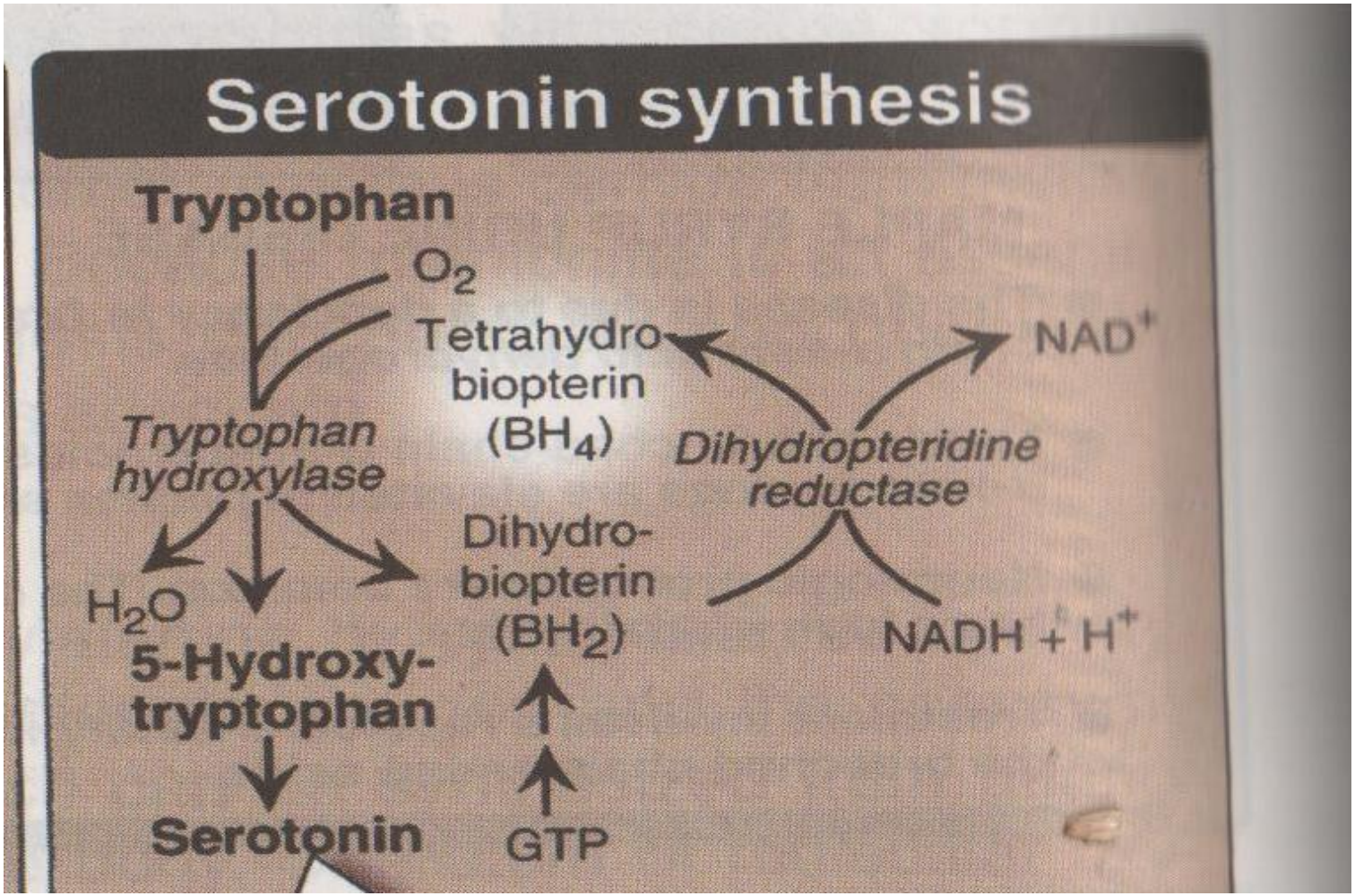
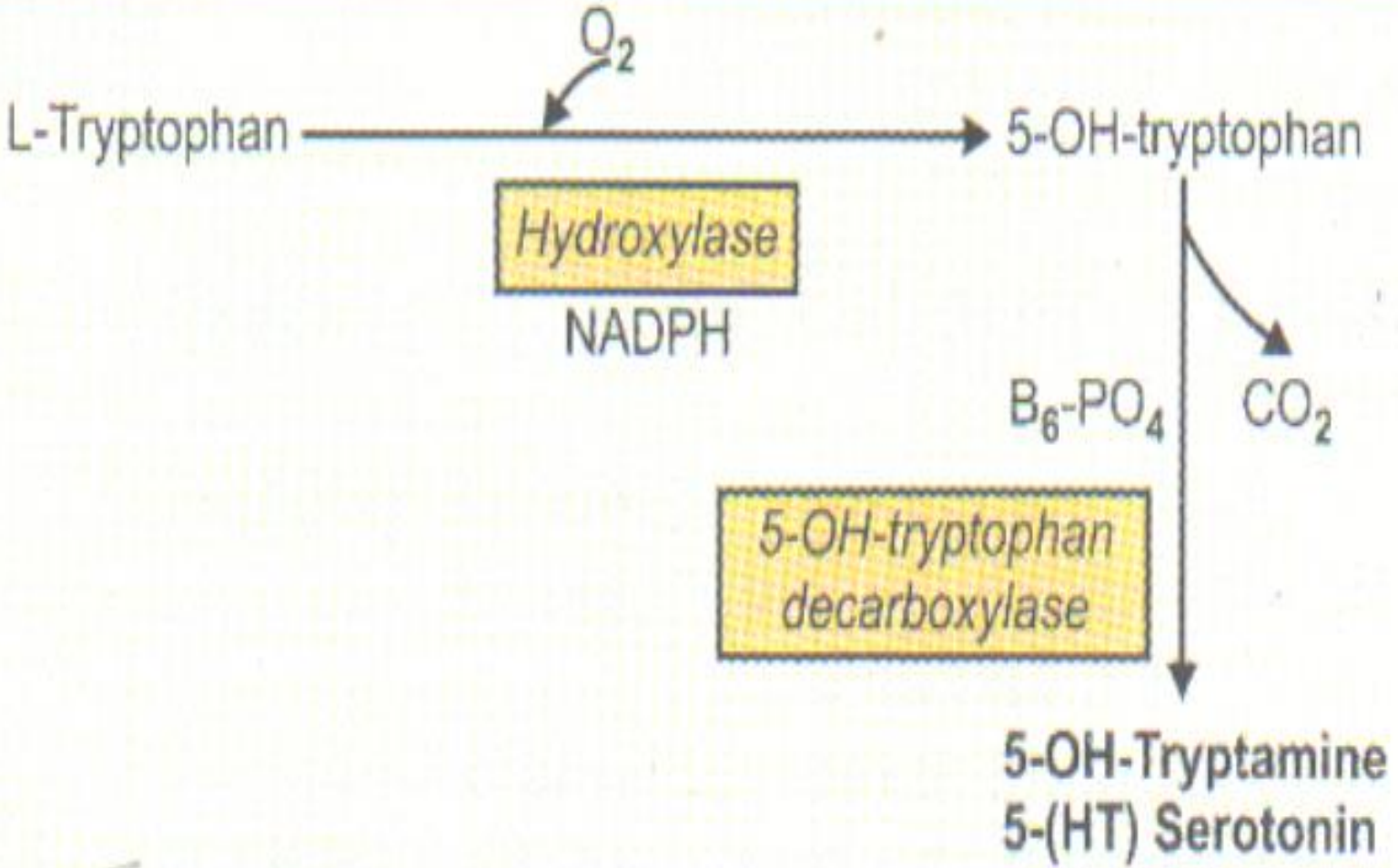


Figure 20.16
Biosynthetic reactions involving amino acids and tetrahydrobiopterin.

SEROTININE


Serotonin synthesis
Tryptophan
O_2
Tetrahydro biopterin (BH_4)
NAD^+
Tryptophan hydroxylase
Dihydropteridine reductase
Dihydro-biopterin (BH_2)
H_2O
$NADH + H^+$
5-Hydroxy-tryptophan
Serotonin
GTP

Formation of Serotonin



Functions

- It is a potent vasoconstrictor
- Produces contraction of smooth muscles
- Stimulator of cerebral activity.

Effects of Serotonin on Brain

Serotonin does not pass *blood-brain barrier* to any significant amount. For action it has to be produced locally from the amino acid.

- Excess of serotonin in brain tissues produces stimulation of cerebral activity (excitation).
- Deficiency of serotonin produces depressant effect.

Catabolism of Serotonin: The enzyme which catalyses the conversion of serotonin to 5-HIAA (5-OH-Indole acetic acid) is called ***Monoamine oxidase (MAO)***. 5-HIAA is excreted in urine. Normal adults excrete about 7 mg HIAA

Effects of drugs on enzyme MAO

- Drugs which inhibit the enzyme, e.g. iproniazide, will prolong serotonin action on the brain and produce a psychic stimulation due to increased cerebral activity.
- Serotonin of the brain is in a bound form. Drugs like reserpine, a common anti-hypertensive drug, acts by releasing the serotonin from its bound form and thus making it readily available to MAO action. Hence reserpine produces a depression of cerebral activity.

CLINICAL ASPECT: CARCINOIDS

A malignant tumor of serotonin producing cells is called **carcinoids (or argentaffinoma)** and the clinical features associated with is called as **carcinoid syndrome**.

Clinical Features: Symptoms are mainly due to presence of excessive amount of serotonin produced by malignant cells. ***Normal persons utilise 1 per cent of tryptophan in serotonin production; in this condition 60 per cent of tryptophan is metabolised by serotonin pathway.*** Consequently symptoms of Pellagra as well as negative N_2 balance can occur.

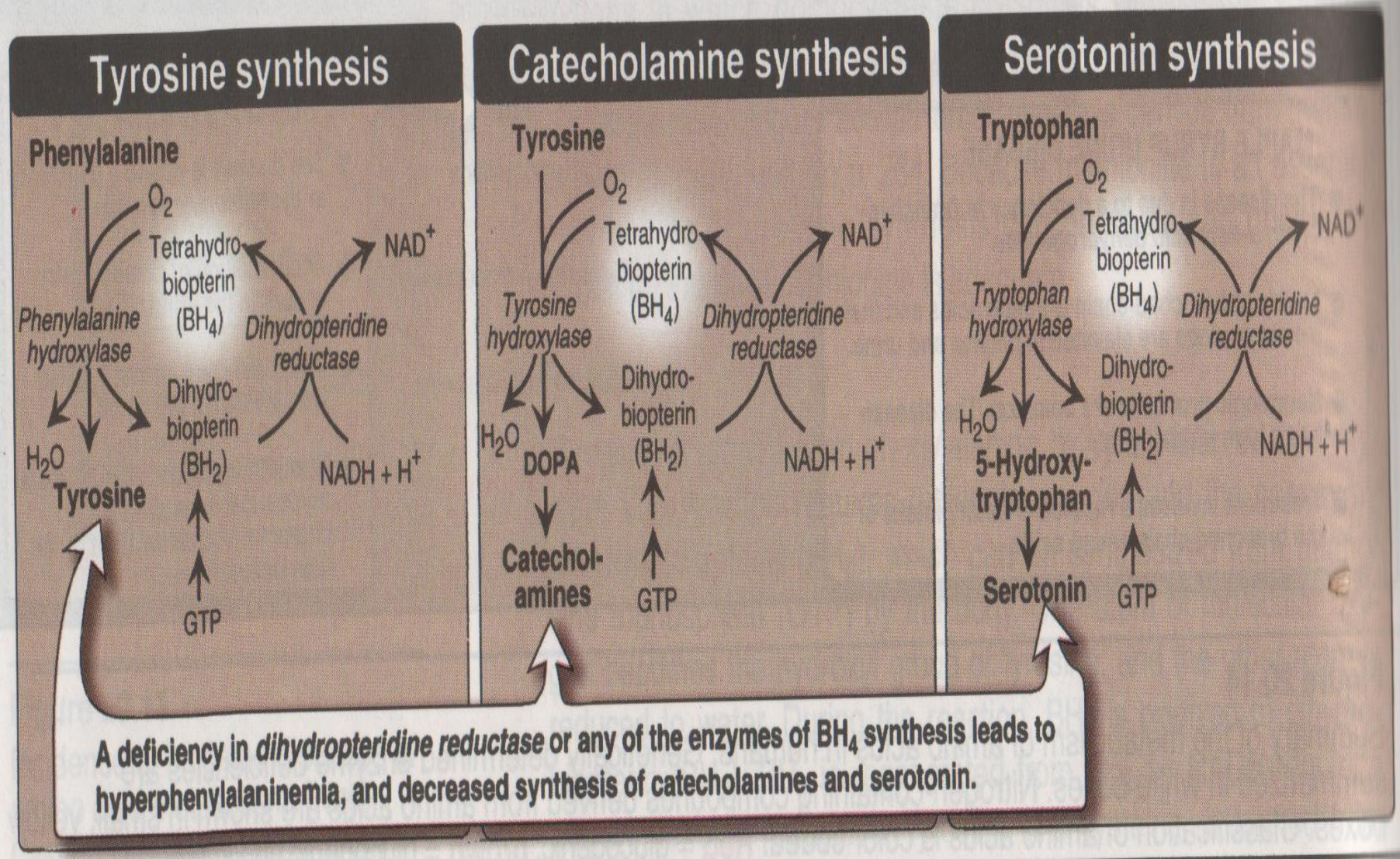


Figure 20.16
Biosynthetic reactions involving amino acids and tetrahydrobiopterin.

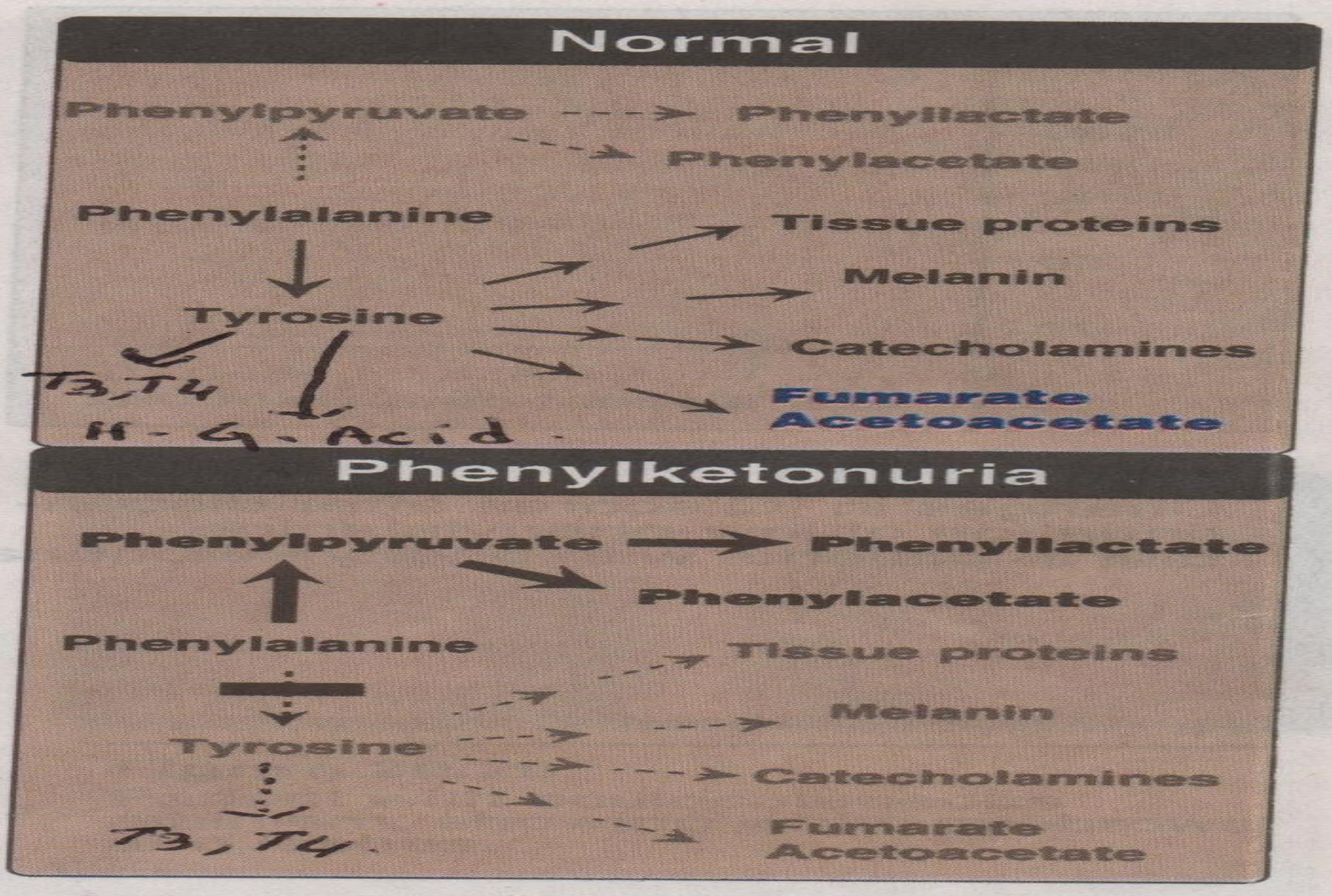
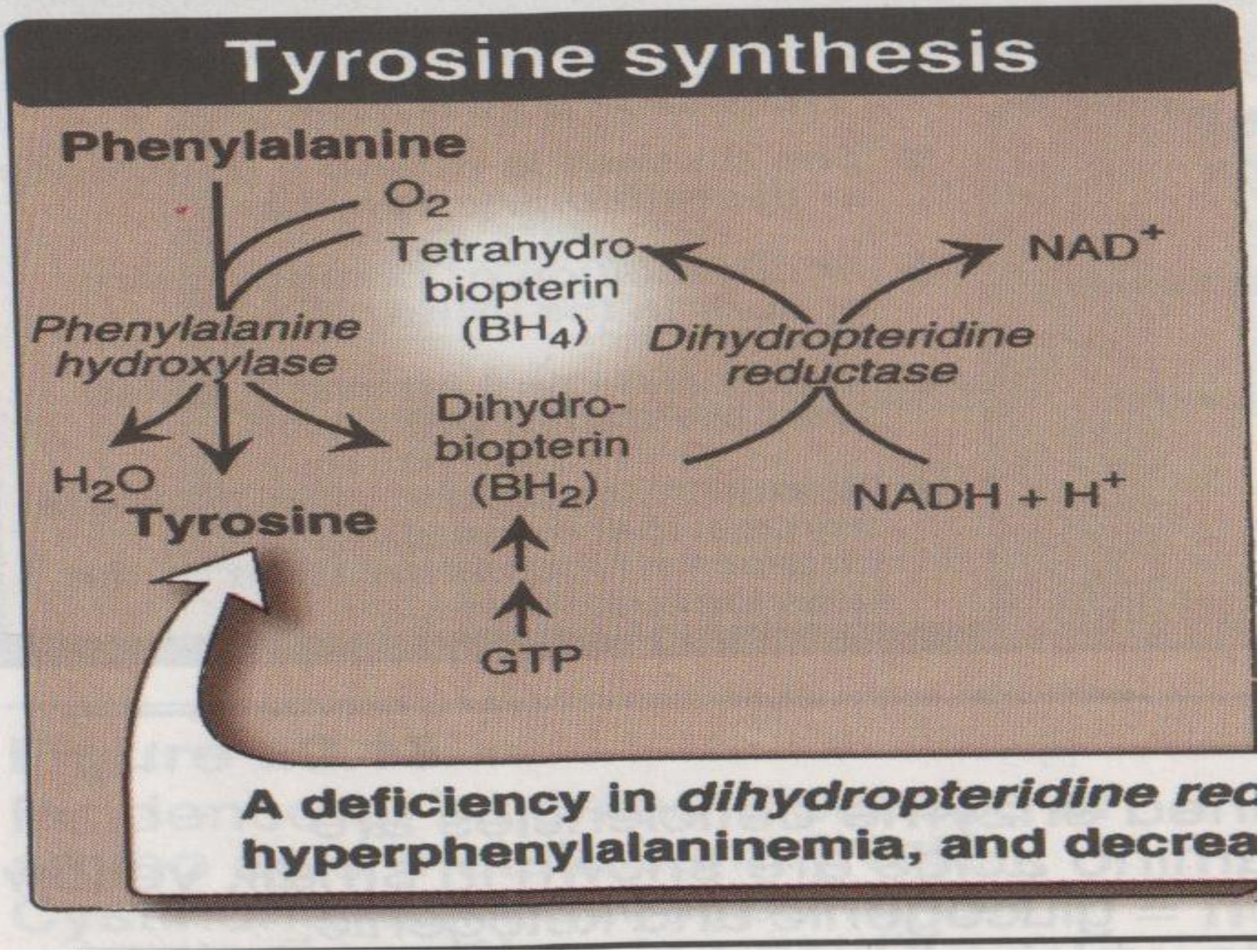
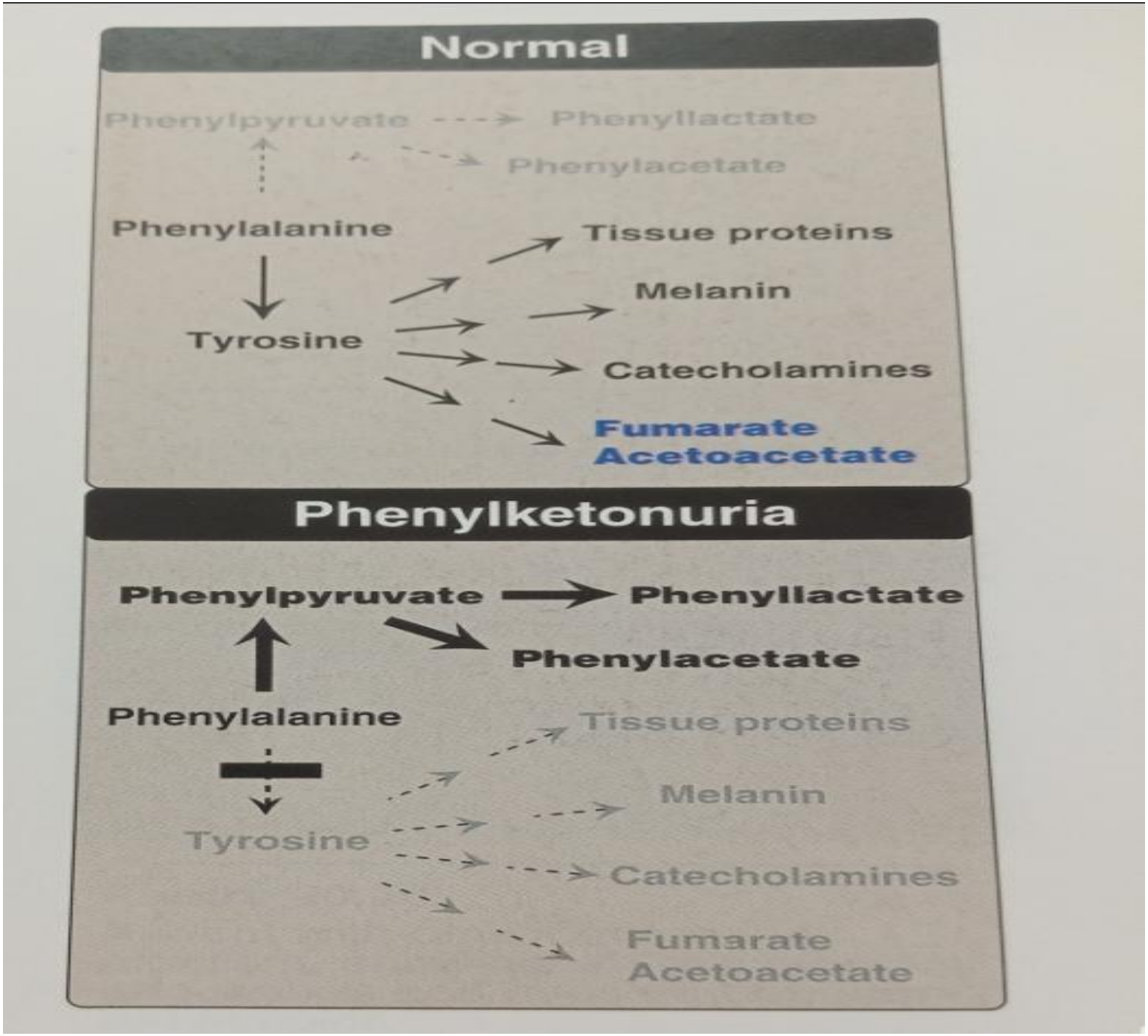


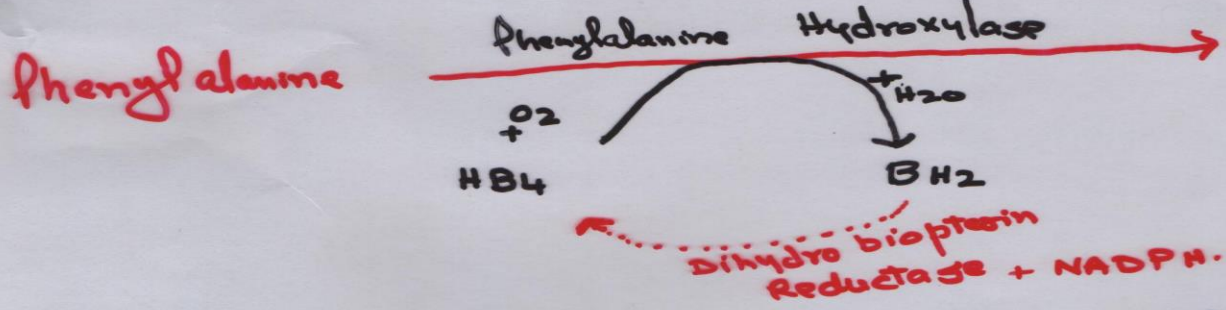
Figure 20.17
Pathways of phenylalanine metabolism in normal individuals and in patients with phenylketonuria.

Phenyl ketonuria


Tyrosine synthesis
Phenylalanine
O_2
Tetrahydro biopterin (BH_4)
NAD^+
Phenylalanine hydroxylase
Dihydropteridine reductase
Dihydro-biopterin (BH_2)
H_2O
Tyrosine
$NADH + H^+$
GTP
A deficiency in dihydropteridine rec
hyperphenylalaninemia, and decrea


Normal
Phenylpyruvate
Phenyllactate
Phenylacetate
Phenylalanine
Tissue proteins
Melanin
Tyrosine
Catecholamines
Fumarate
Acetoacetate
Phenylketonuria
Phenylpyruvate
Phenyllactate
Phenylacetate
Phenylalanine
Tissue proteins
Melanin
Tyrosine
Catecholamines
Fumarate
Acetoacetate

Phenyl Ketonuria (P.K.U) or Hyperphenylalaninemias.



Causes:- - Deficiency of P. A. Hydroxylase (Type I)
The Enzyme is to Converts P. alanine to Tyrosine which is Precursor of dopamine, Epinep and nor Epineph, and thyroid hormones and Melanin
- Low Conversion of Phenylal → Tyrosine also occurs if BH_4 is not regenerated due to defective BH_2 Reductase.
BH_4 is also required in biosynth of Neuro Transmitters dopamine, Norep, Epin, Serotonin

Phenylalanine is diverted to its normal Minor metabolic pathway forming Phenyl Pyruvate (P. Ketone), Phenylacetate and Phenyl lactate
These Metabolites have characteristic Musty (Mousy) odor.

TABLE 27.2: HYPERPHENYLALANINAEMIAS

Type	Condition	Probable enzyme defect	Treatment
I.	Classical type of phenyl ketonuria (PKU)	Phenyl alanine hydroxylase enzyme absent	Low phenyl alanine diet
II.	Persistent hyperphenylalaninaemia	Decreased Phenyl alanine hydroxylase enzyme	None but temporary dietary therapy
III.	Transient mild hyperphenylalaninaemia	Maturational delay of phenyl alanine hydroxylase enzyme	Same as Type II
IV.	Dihydropteridine reductase deficiency	Deficient or absent *dihydropteridine reductase*	Dopa, 5-OH tryptophan, carbi Dopa
V.	Abnormal dihydrobiopterin function	Dihydrobiopterin synthesis defect	Same as Type IV

- ↑ Level of Phenylalanine in blood (over 20mg/100ml) 9
  and urine

- C.N.S Symptoms:- ↑ P.Al impairs brain development
  BH4 is also req for Synth of Neurotransmitters

  Causing Mental retardation, Seizure, Tremors etc.

- Hypopigmentation:-
  Phonylalanine is a competitive inhibitor of Tyrosinase in Melanocytes, causing reduced melanin formation, Causing Fair skin, Light skin color, Blue eyes etc.

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Tyrosine Catabolism :-

Tyrosine —in gut→ **Tyramine and Phenol**

T- Transaminase

Tyrosinemia Type II.
- There is ↑ Tyrosine plasma level
- Eye and Skin changes
- Moderate Mental retardation
- ↑ urinary Tyrosine level

Para Hydroxy Phenyl Pyruvic acid

vit C + vit B12

(Phenyl Pyruvate Hydroxylase (causes addition of new OH group))

Neonatal tyrosinaemia.

Homogentisic acid

Homogentisic oxidase (or cleaves aromatic ring)

Alkaptonuria :-

- urine has H.G. acid, which when is oxid, is converted to brownish black pigment - so the darkening of urine
- there is pigmentation of connective tissues, due to oxidation of homogentisic acid to benzoquinone acetate. → Ochronosis
- Pigment deposition causes arthritis.
- Autosomal recessive disorder.

Maleyl aceto acetic acid

Isomerization

Fumaryl aceto acetic acid

Fumaryl aceto acetate Hydrolase (Hydrolysis)

Tyrosinemia Type I (Tyrosinosis). Plas Tyr ↑.
Infant exhibit ↓ diarrhoea, vomit
Cabbage like odour - fail to grow
death in 6 - 8 months (Hepatic fail)

Fumaric acid + Aceto acetic acid
(Glucogenic Product) (Ketone body)

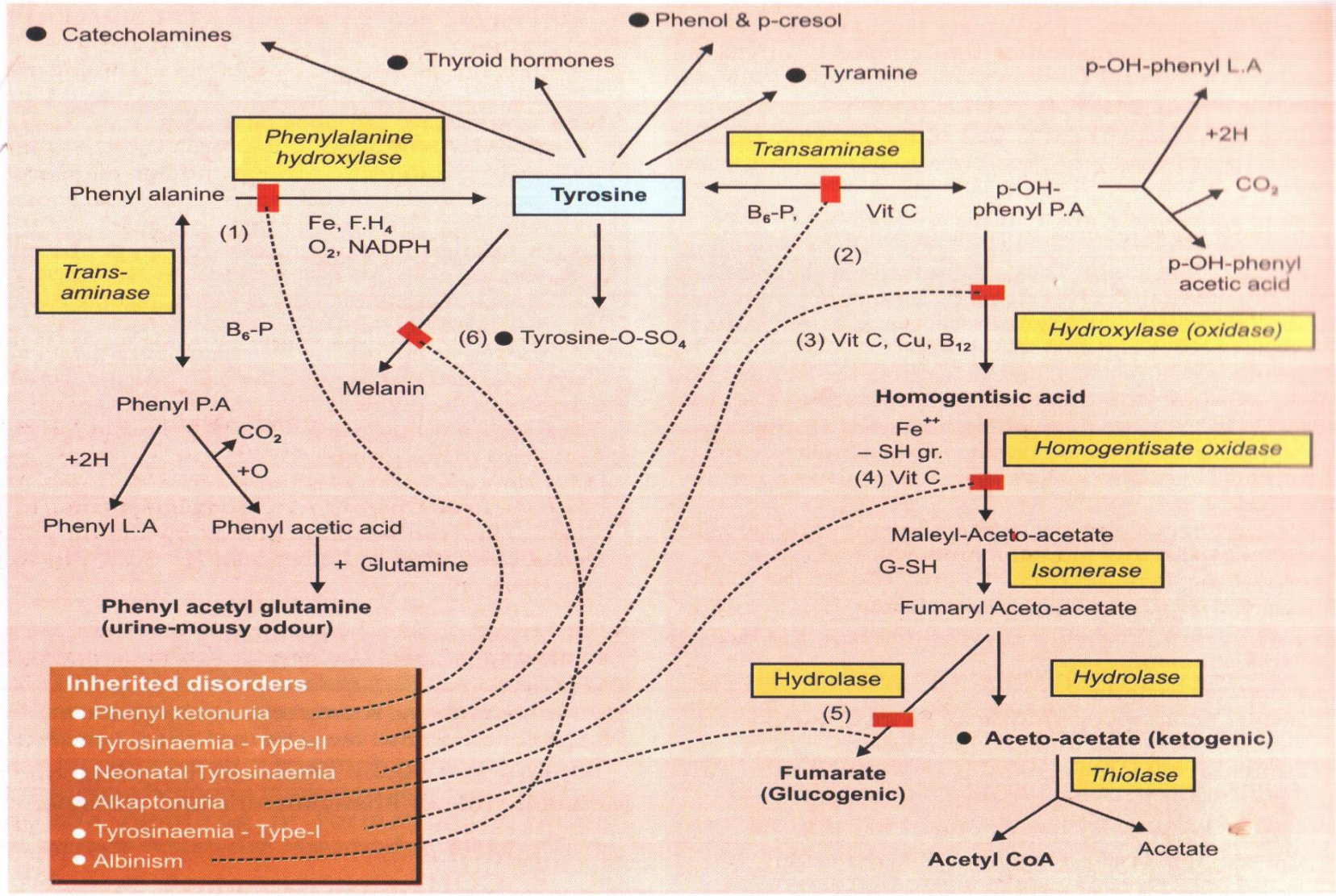


FIG. 27.9: FLOW CHART OF METABOLIC FATE AND METABOLIC ROLE OF PHENYLALANINE AND TYROSINE

Disorders Associated with Phenyl alanine and Tyrosine Metabolism

- 1- Phenyl ketonuria
- 2- Alkaptonuria
- 3- Tyrosinaemia Type-I
- 4- Tyrosinaemia Type-II
- 5-Neonetal Tyrosinaemia
- 6-Albinism

Tyrosine Supplementation Improves

- - Mood, Mental ability and sex Drive
- -Also helps in suppressing appetite and reducing body fats
- - Good sources are –Any meat or dairy products, eggs, almonds and Bananas.

Thyroid Hormones

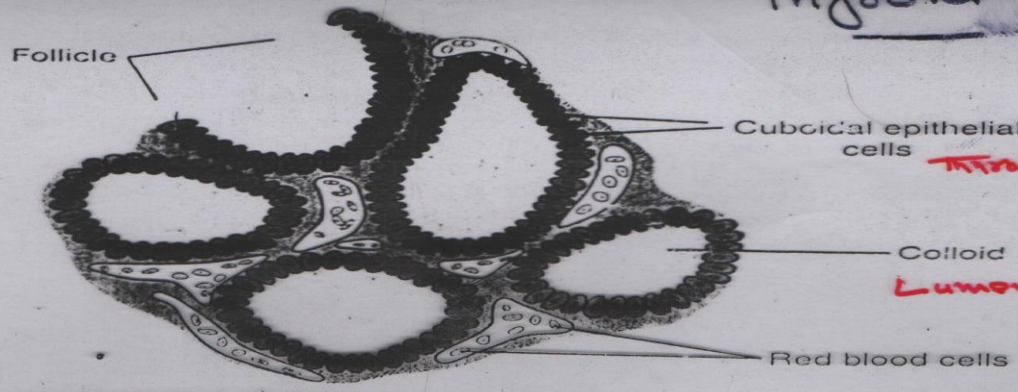


FIGURE 76–1
Microscopic appearance of the thyroid gland, showing secretion of thyroglobulin into the follicles.

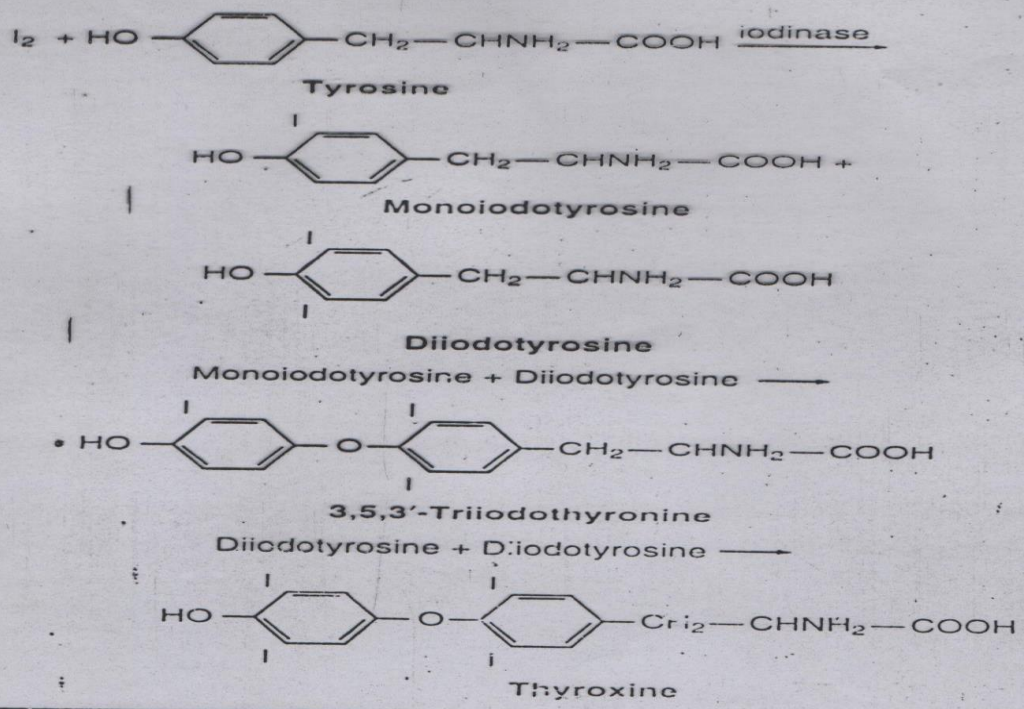


FIGURE 76–3
Chemistry of thyroxine and triiodothyronine formation.

Gluta Thione

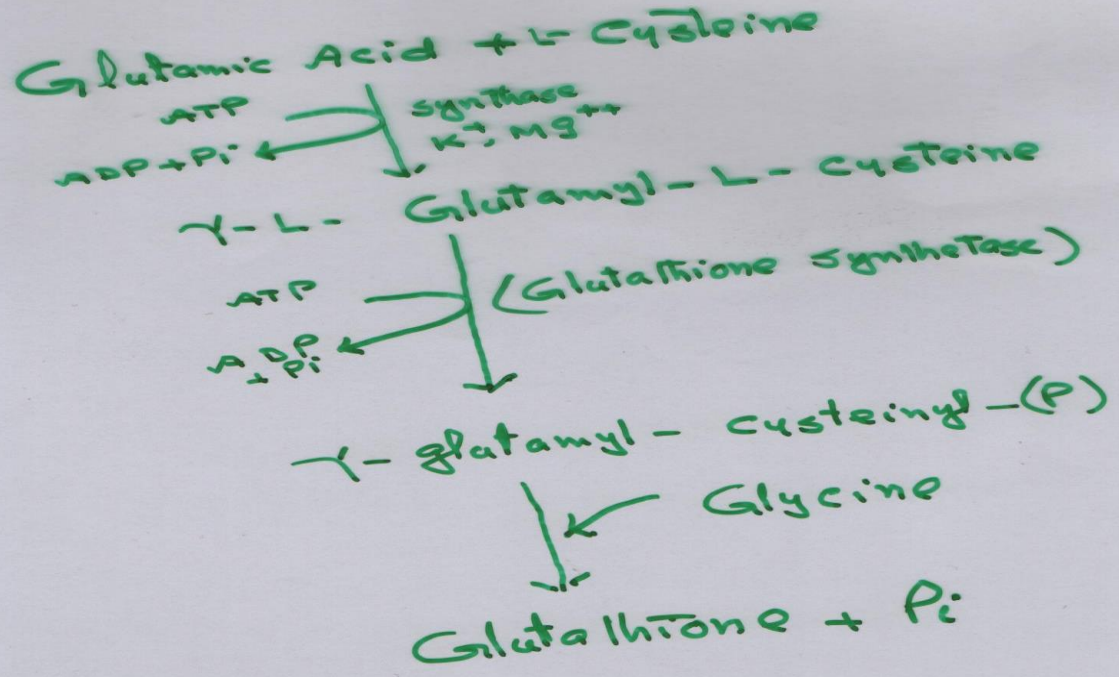
- Tri-peptide OF 3 amino acids.

= Glutamic acid

= Cysteine

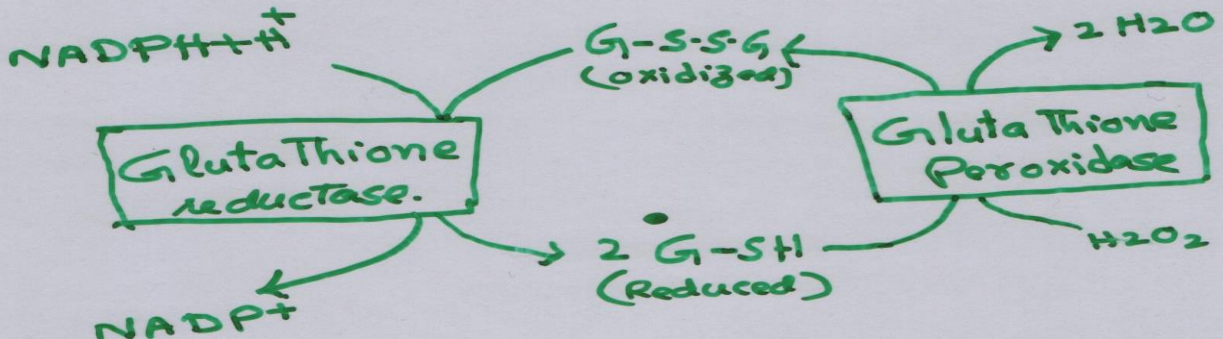
= Glycine.

Synthesis :-



Functions of Glutathione :

- Important reducing agent in the Tissues.



- Oxidized Glutathione is harmful to the Tissues espacially R.B.C and lens protein, and is converted to reduced Glutathione, which is required for integrity of R.B.C membr lens protein

= Catabolism of insulin a degradation

Glutathione (coenzyme)

Glutathione - Insulin Transhydrogenase

= Many -SH group containg Enzymes e.g. glyceraldehyde-3-P-d.H are protected by Glutathione against oxidation.

- G-SH is required as Co-enzyme in reaction Methionine → S-adenosyl Methionine

- G-SH is required as Coenzyme in Cyclo-oxygenase system required for P.G. synthesis.

= Toxic Radicals or Reactive intermediates formed from Molecular oxygen are

O_2 (oxygen) → O_2^- (super oxide) → H_2O_2 (Hydrogen Peroxide) → OH^- (Hydroxyl Radical) → H_2O

S. oxide dismutase

Glut-Perox

= Various Intracellular reducing agents (Antioxidants) are.

=

= Vitamin - E

= Ascorbate = β-carotene.

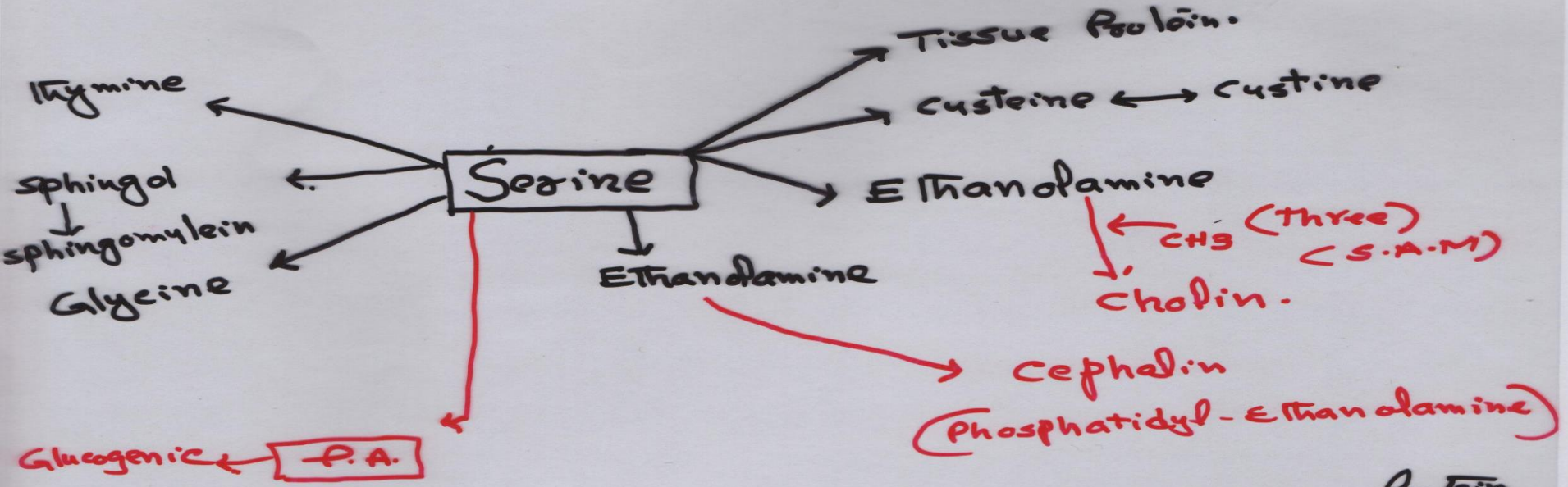
= NADPH = Glutathione

= Catalase = Superoxide dismutase

= Glutathione peroxidase.

Serine

= Non essential, hydroxy a. acid.



- Hydroxy group of serine in an enzyme protein is phosphorylated/dephosphorylated to form active/inactive forms of the enzyme.

Catecholamine Synthesis

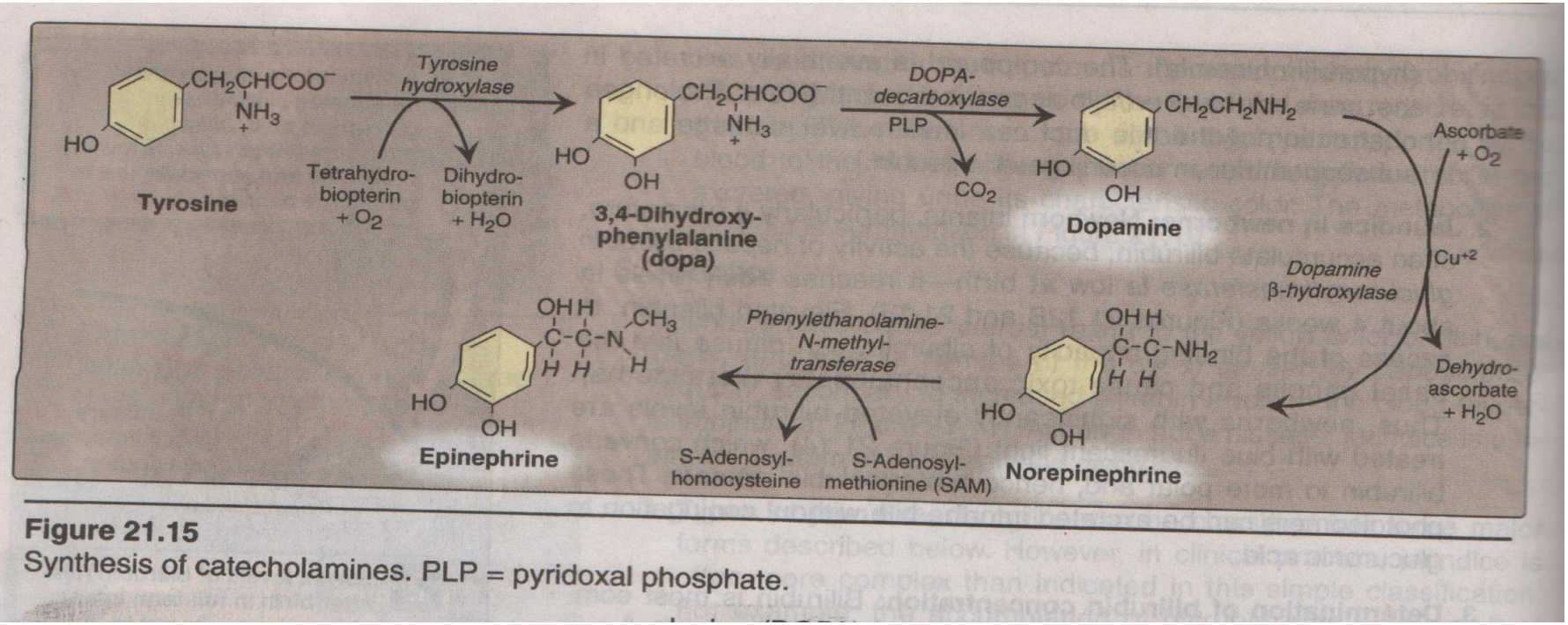
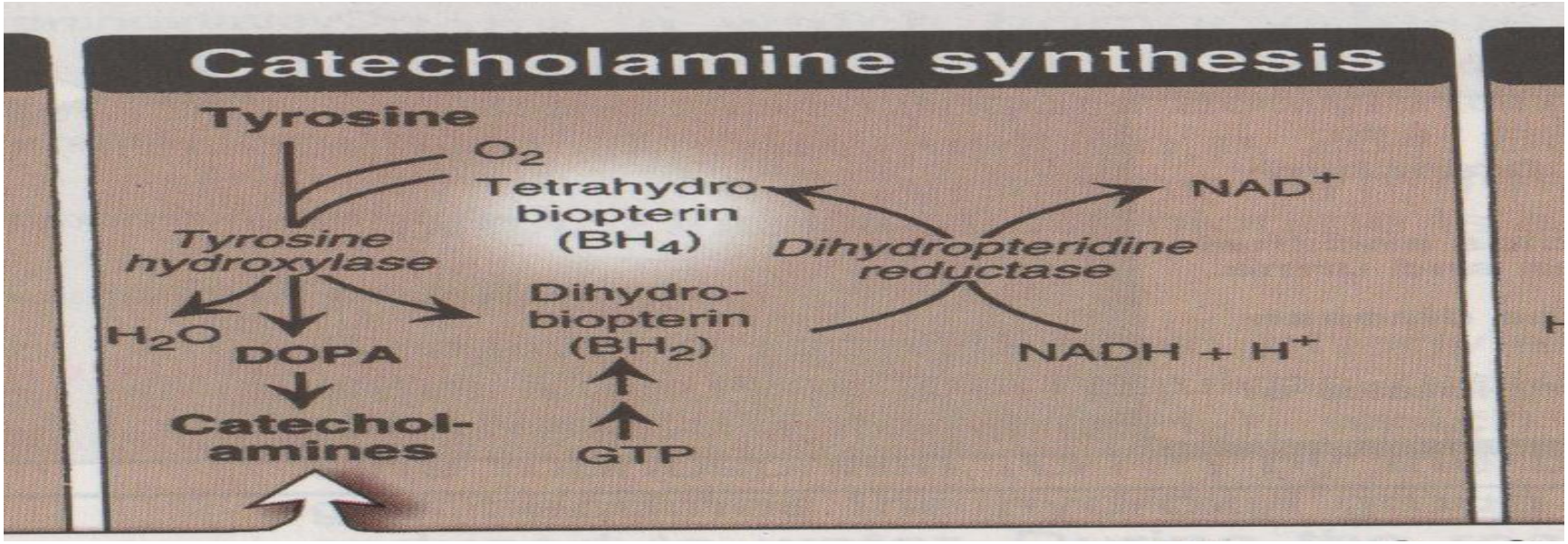


Figure 21.15
Synthesis of catecholamines. PLP = pyridoxal phosphate.



NITRIC OXIDE

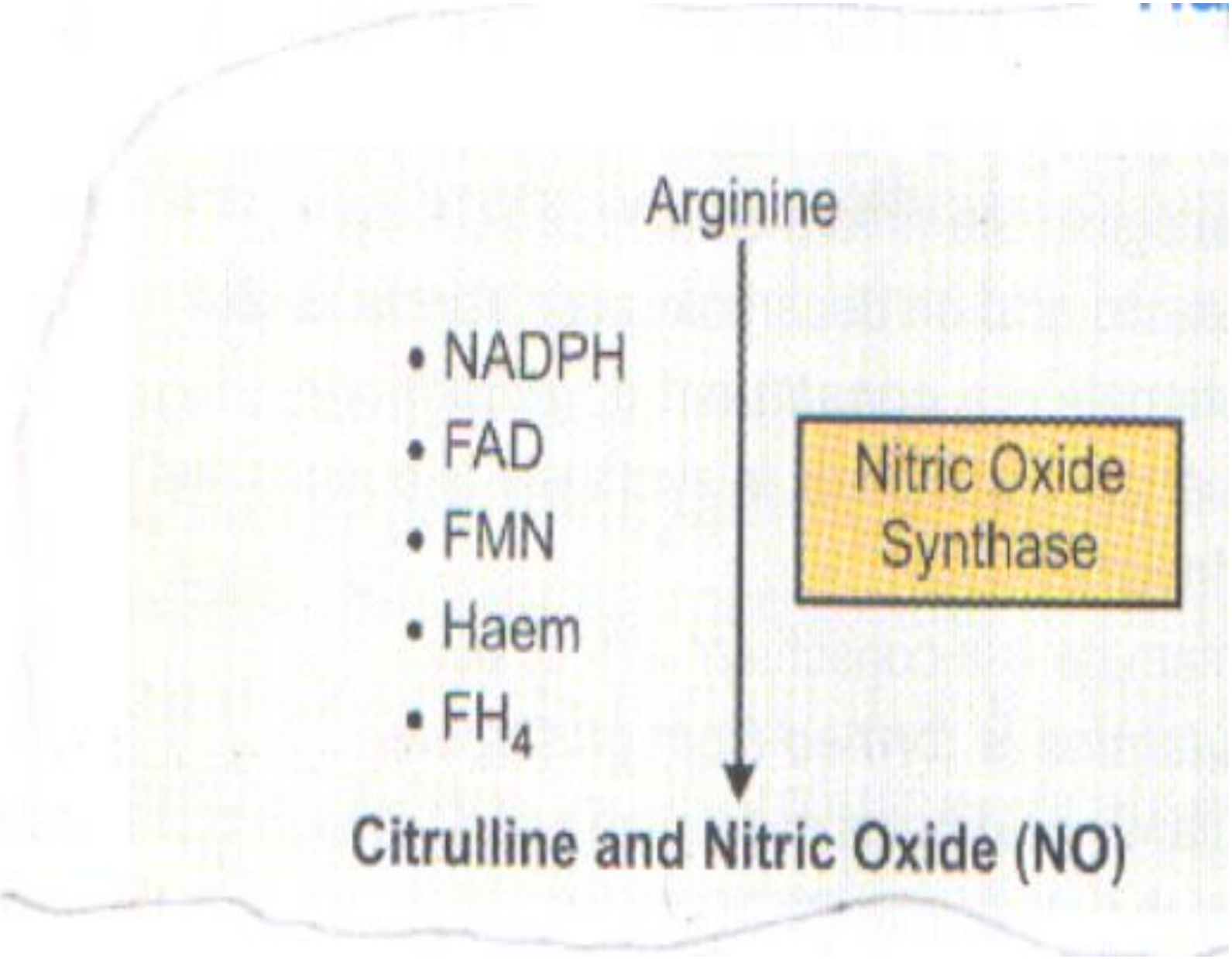
ROLE OF NITRIC OXIDE

Nitric oxide (NO) is formed in the body from amino acid arginine

It is a wonder molecule having diverse biological functions like PGs. Endothelium derived relaxing factor (EDRF) which produces vasodilatation is now proved to be nitric oxide.

Formation of NO

Arginine is acted upon by an enzyme called ***nitrogen oxide synthase***, a cytosolic enzyme and converts arginine to citrulline and nitric oxide (NO).


Arginine
• NADPH
• FAD
• FMN
• Haem
• FH_4
Nitric Oxide Synthase
Citrulline and Nitric Oxide (NO)

Duration of action of NO: Nitric oxide formed in the tissues has a very short half-life, approximately 3 to 4 seconds because it reacts with oxygen and superoxide. The product of the reaction with superoxide is Peroxynitrite ($ONOO^-$), which decomposes to form the highly reactive $OH^{\cdot}$ radical.

Functions of Nitric Oxide

- It acts as a **vasodilator** and causes relaxation of smooth muscles.
- It has important role in the regulation of blood flow and maintaining blood pressure.
- It is involved in penile erection.
- Acts as a **neurotransmitter** in the brain and peripheral autonomic nervous system.
- May have also role in relaxation of skeletal muscles.
- Inhibits adhesion, activation and aggregation of platelets.
- May constitute part of a primitive immune system and may mediate bactericidal actions of macrophages.
- Low level of nitric oxide may be involved in causation of pylorospasm of infantile hypertrophic pyloric stenosis.

CLINICAL ASPECT

- ***Nitroglycerine:*** The important coronary artery vasodilator used in Angina Pectoris acts to increase intracellular release of EDRF (now proved to be NO) and cGMP↑.
- ***In septic shock:*** Bacterial lipopolysaccharide present in blood causes uncontrolled production of NO leading to dilatation of blood vessels and lowering of BP.
- ***In eclampsia and pre-eclampsia:*** The hypertension is due to decreased production of nitric oxide (NO) due to probably formation of ADMA (asymmetric dimethyl arginine).
- ***Iron supplements:*** Iron supplements can dramatically reduce dry cough symptoms in heart patients. Cardiac patients using ACE inhibitors, widely prescribed for hypertension, heart failure and other cardiac conditions often suffer from a dry cough. It is the biggest reason for people stopping taking their medication. Iron supplements act by decreasing the production of Nitric oxide, which is linked to inflammation of the bronchial cells in the lungs.

Metabolism of Cystine

B. Metabolic Role of Cysteine

- *Glucogenic:* Cysteine is catabolised to Pyruvic acid which is glucogenic.
- *Formation of glutathione:* Cysteine is required for synthesis of glutathione. G-SH is the reduced form, active group is SH group. G-S-S-G is the oxidised form.
- *Formation of taurine:* Cysteine is utilised in the formation of 'taurine', which combines with cholic acid (obtained from degradation of cholesterol in Liver,) to form Bile acid 'taurocholic acid'.

INHERITED DISORDERS OF S-CONTAINING AMINO ACIDS

1. Cystinuria

An inherited disorder of cystine metabolism. Excretion of cystine in urine increases 20 to 30 times of normal. Also there occurs increased excretion of diabasic amino acids · **lysine,** · **arginine and** · **ornithine** ***(specific diabasic aminoaciduria).***

Defect: It is considered to be due to a renal transport defect in that reabsorption of the above four amino acids do not occur, ***a single reabsorptive site is involved.***

Complications: Cystine is relatively insoluble amino acid, which may precipitate in renal tubules, ureters and bladder to form ***cystine calculi***. Cystine stones account for 1 to 2 per cent of all urinary tract calculi. It forms a major complication of the disease. A **mixed disulphide** consisting of L-cysteine and L-homocysteine has been found in urine. This is more soluble and thus reduces the tendency to formation of cystine crystals/ and calculi.

Diagnosis

- ***Urine examination:*** Detection of hexagonal, flat crystals in urinary deposit in a patient who is not taking sulpha drugs is pathognomonic.
- ***Cyanide-nitroprusside test (Lewis):*** It is a simple and valuable test. Urine sample is made alkaline with ammonium hydroxide and then sodium cyanide is added and mixed. Sodium cyanide reduces cystine, if any present, to cysteine. ***Cysteine forms magenta-red colour, when sodium***

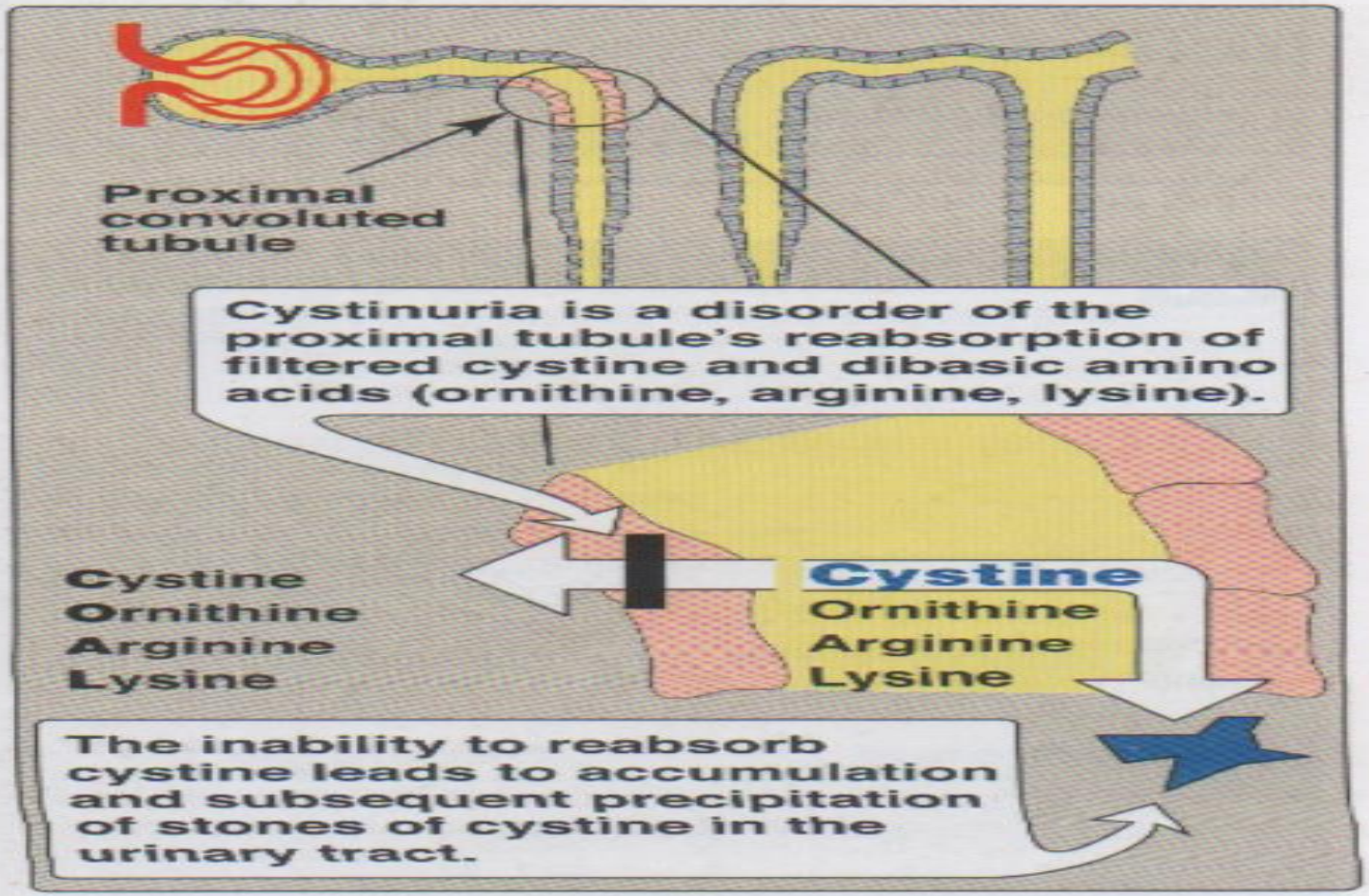


Figure 19.6
Genetic defect seen in cystinuria. [Note: Cystinuria is distinct from cystinosis, a rare defect in the transport of cystine out of lysosomes that results in the formation of cystine crystals within the lysosome and tissue damage.]

GLYCINE METABOLISM

(Non-Essential, glucogenic)

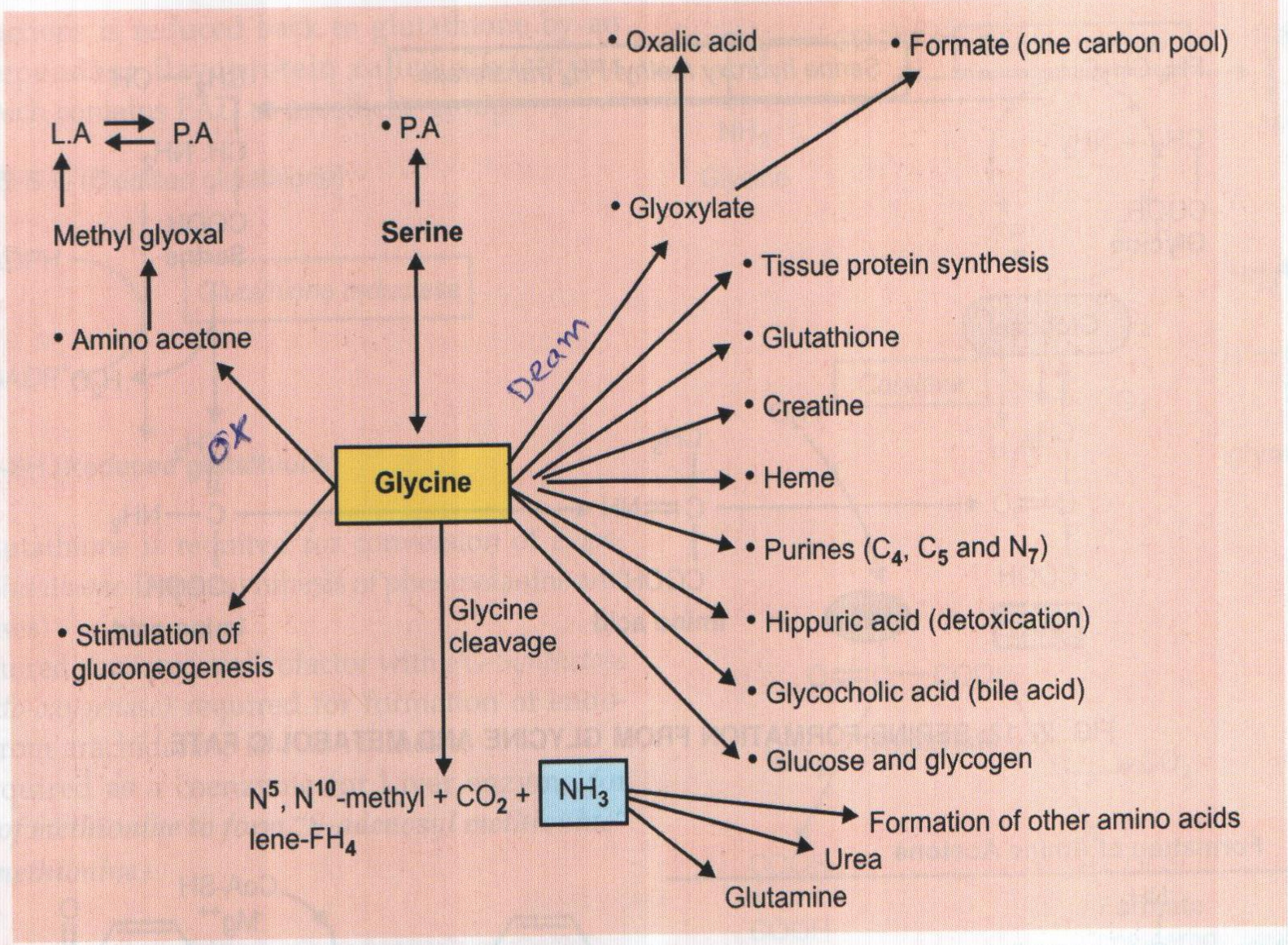


FIG. 27.13: FLOW CHART OF GLYCINE, SHOWING METABOLIC FATE AND METABOLIC ROLE

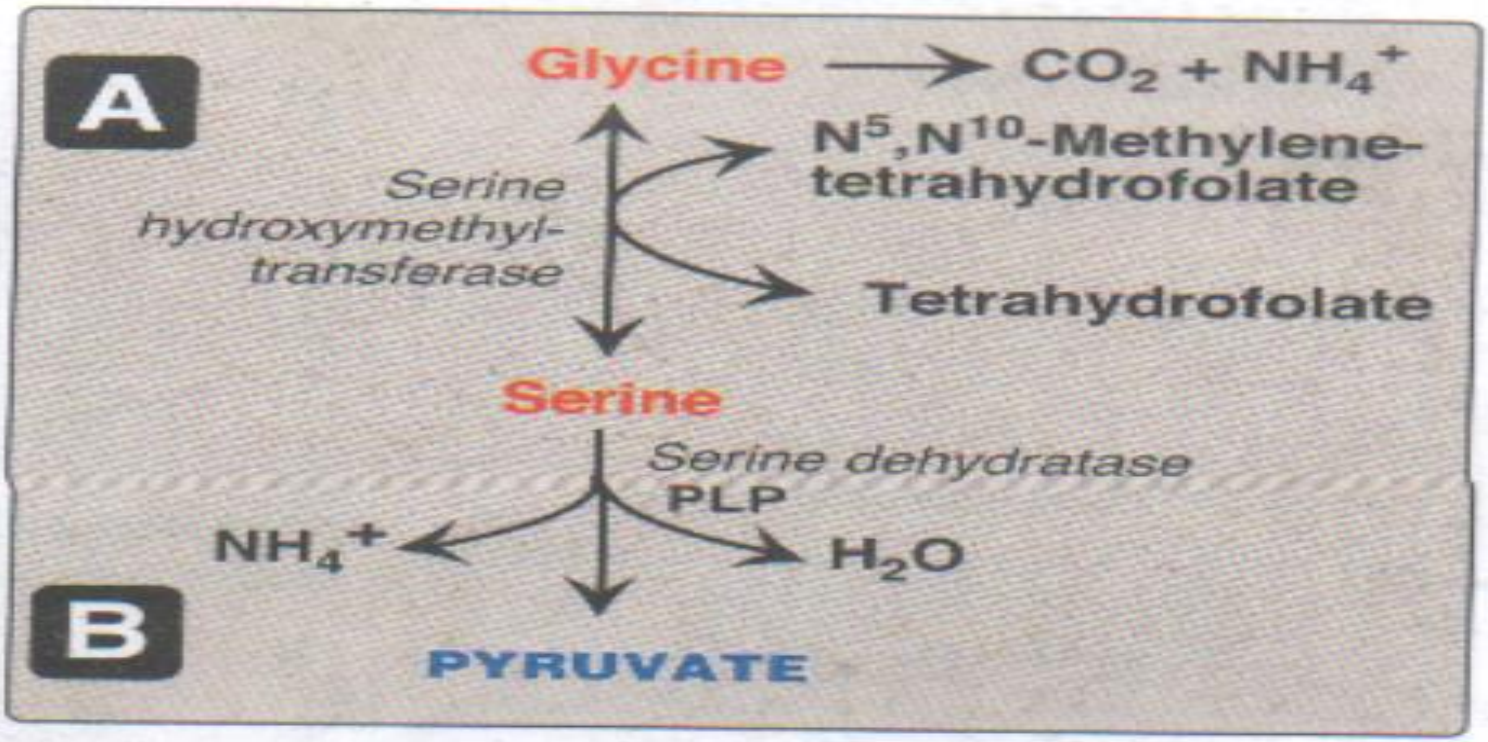
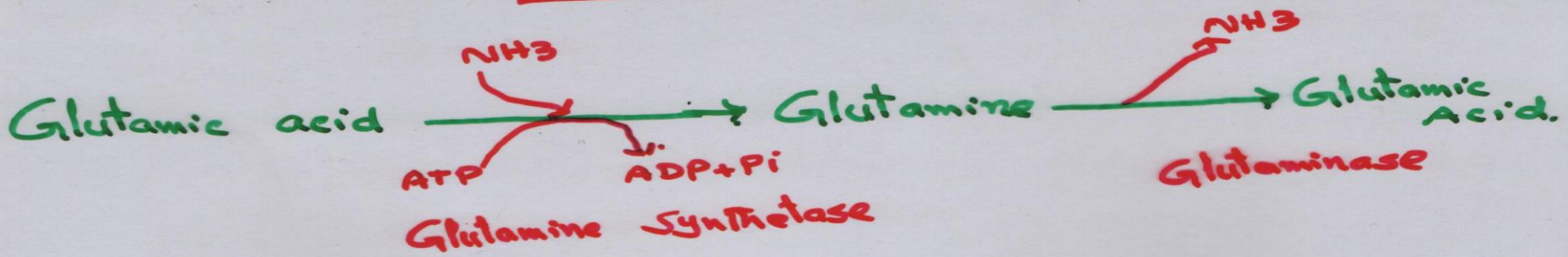


Figure 20.6
A. Interconversion of serine and glycine and oxidation of glycine. B. Dehydration of serine to form pyruvate. PLP = pyridoxal phosphate.

Glutamine



- Detoxification Process.
- Normal value — 6–12 mg/dl.

Biochem Functions:.

1. Fouctose-6-P + Glutamine ⟶ Glucosamine-6-Pg + Glutamate.
2. Formation of GMP
3. Formation of N-Formyl glycinamide (Purine Nucleotide)
4. Formation of cytosolic Carbamyl-P (Pyrimidine Nucleot.)
5. Glutamine saves brain from Toxic effects of NH_3.

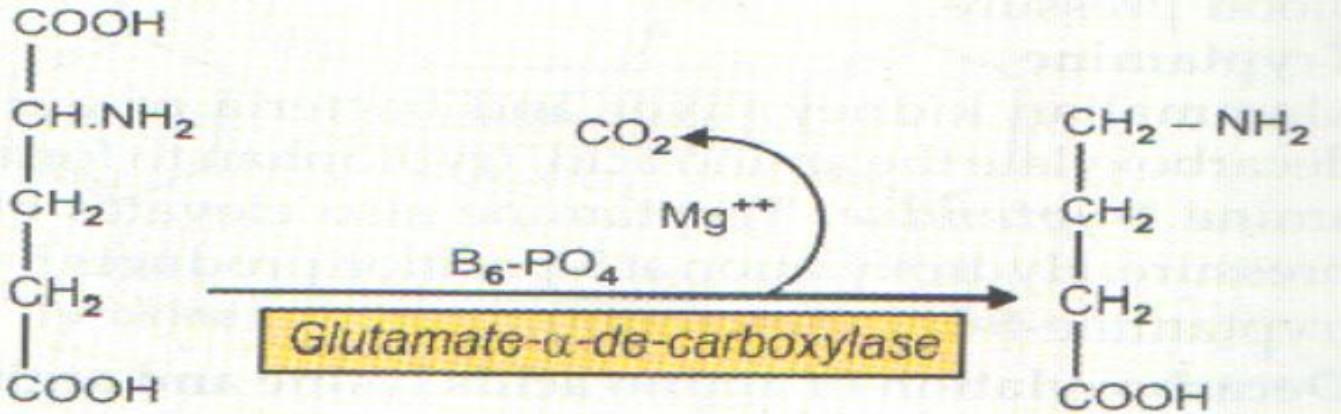
Functions of Glutamate

- - Participates in Transamiantion reactions in nitrogen disposal
- Component of Glutathione and FH_4
- Most abundant excitatory neurotransmitter in the brain
- Decarboxylated to GABA in neurons

5. γ-aminobutyric Acid (GABA) formation:

Decarboxylation of glutamic acid produces γ-amino-butyric acid (GABA).

- Reaction is ***irreversible***
- glutamate *α-decarboxylase* is the enzyme which catalyses the reaction.
- It requires B_6-PO_4 as coenzyme and Mg^{++} as cofactor.



Glutamic acid **γ-aminobutyric acid**

Site of formation

Site of formation

- Principally formed in CN system in the gray matter
- Kidneys

Function of GABA

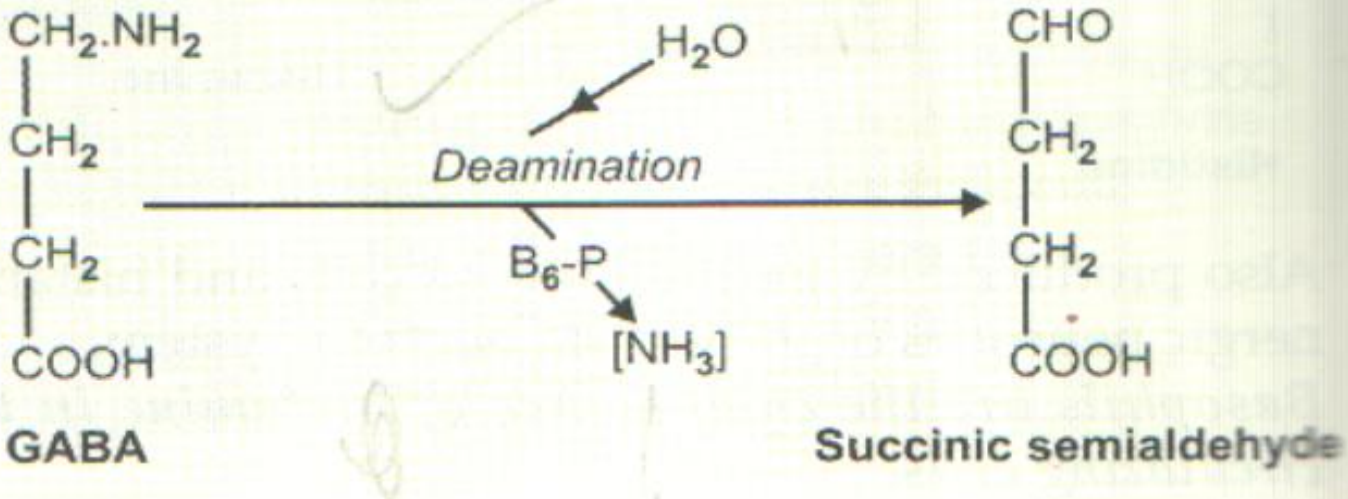
- GABA is known to serve as a normal regulator of neuronal activity being active as an inhibitor (pre-synaptic inhibition0.
- It is released at the axonterminals of neurons in grey matter and acts as inhibitory neurotransmitter by enhancing K^+ permeability of postsynaptic membranes.

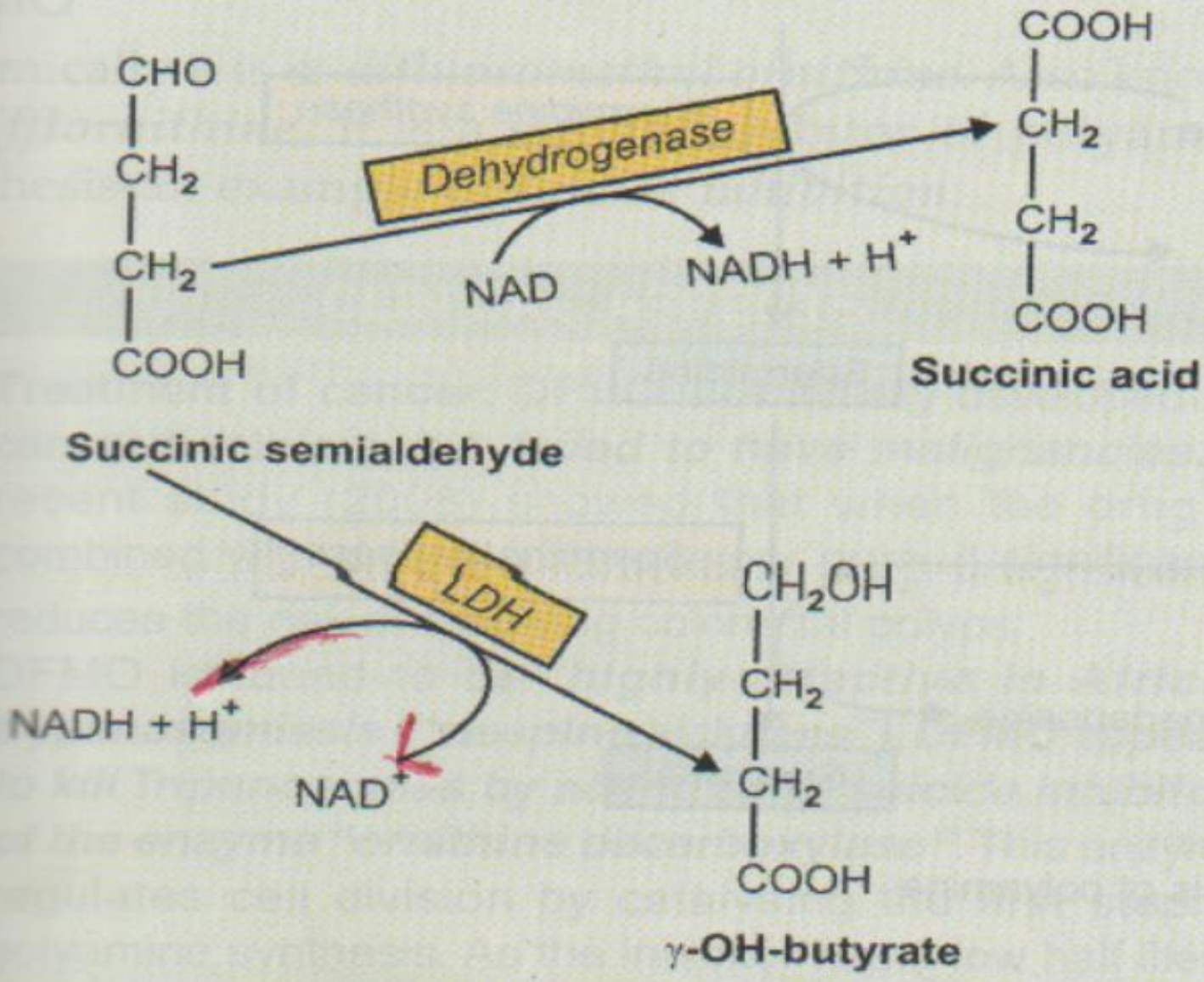
CLINICAL ASPECT

Vit B_6 deficiency in children may be responsible for some of the cases of infantile convulsions. B_6-deficiency causes less formation of GABA leading to neuronal hyperexcitability and convulsions.

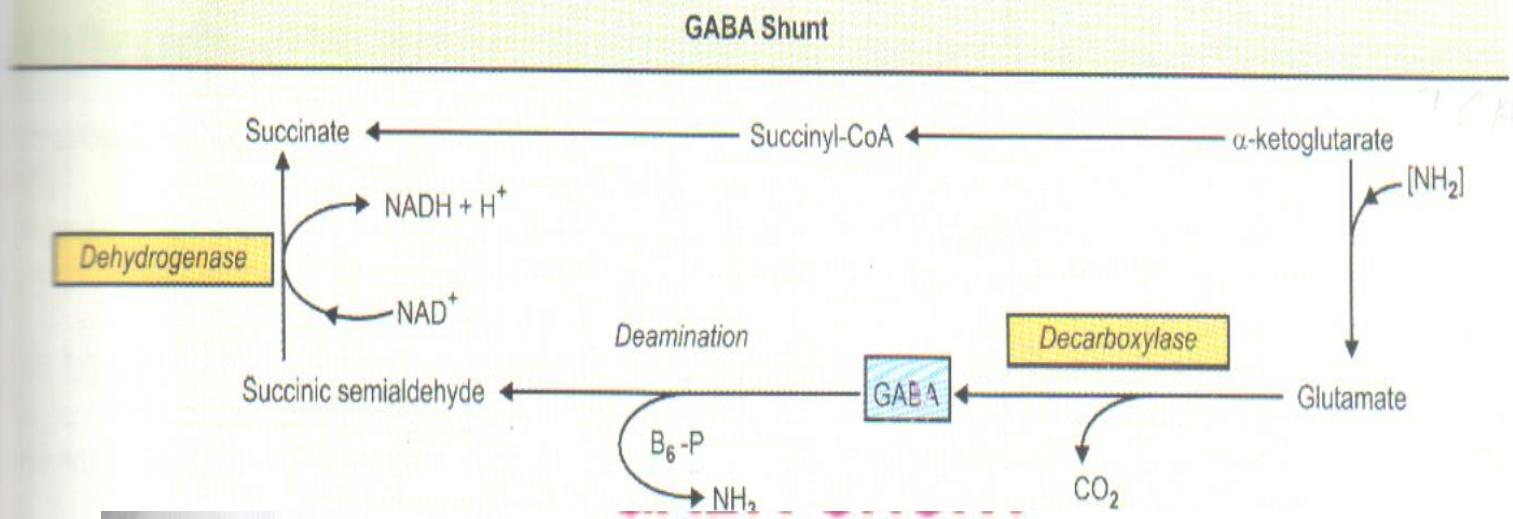
Metabolism of GABA

1. GABA is metabolised by deamination to form succinic semialdehyde. The deamination is accomplished by a Pyridoxal-P dependant enzyme and the NH_3 removed is transaminated to α-ketoglutarate forming more glutamate.




CHO
CH2
CH2
COOH
Dehydrogenase
NAD
NADH + H+
COOH
CH2
CH2
COOH
Succinic acid
Succinic semialdehyde
LDH
NADH + H+
NAD+
CH2OH
CH2
CH2
COOH
γ-OH-butyrate

GABA SHUNT

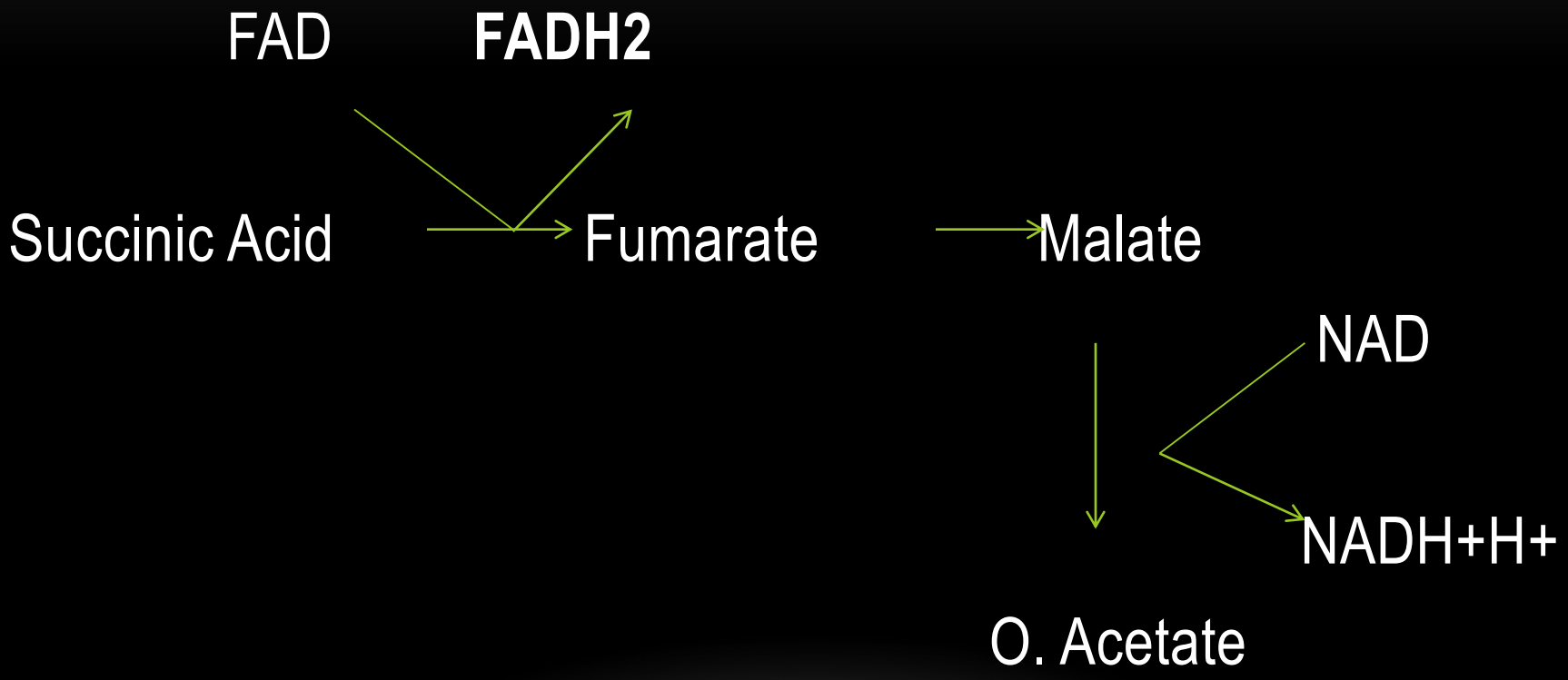


GABA by its conversion to succinic acid **can form a "by-pass" in TCA cycle** and this is called as GABA-shunt

- GABA shunt is a closed loop process, with the dual purpose of producing and conserving the supply of GABA.
- GABA is present in high concentration in brain.

GABA SHUNT

GABA on breakdown is converted in to succinic acid, so it is turned in to energy as it enters in T.C.A cycle.



FADH2 and NADH+H+ will give energy in E.T.C. so by shunting GABA in T.C.A, there is not totally loss of GABA but it gives energy.

Synthesis of Polyamines

Synthesis of Polyamine

6. Polyamines

Types of Polyamines are:

- **Spermidine**
- **Spermine**

Ornithine in addition to its role in urea cycle, serves as the precursor of ubiquitous mammalian and bacterial polyamines, spermidine and spermine. It requires 'active' methionine. Normal human can synthesise approx 0.5 n mol of spermine/day.

Synthesis of Polyamine

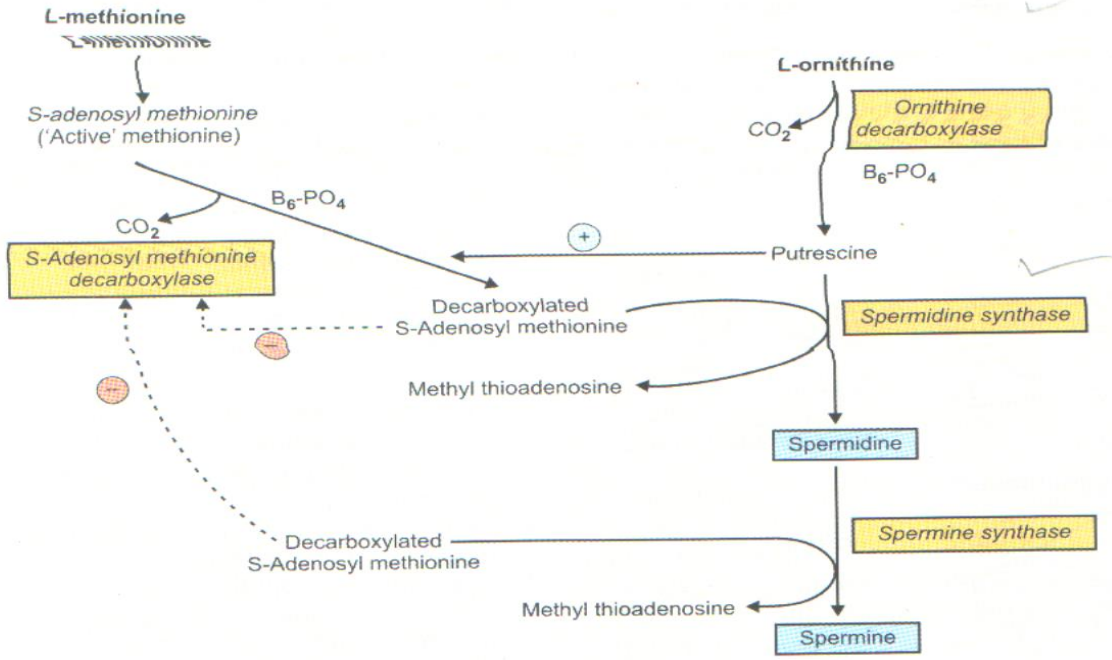


Fig. 27.6: Showing synthesis of polyamine

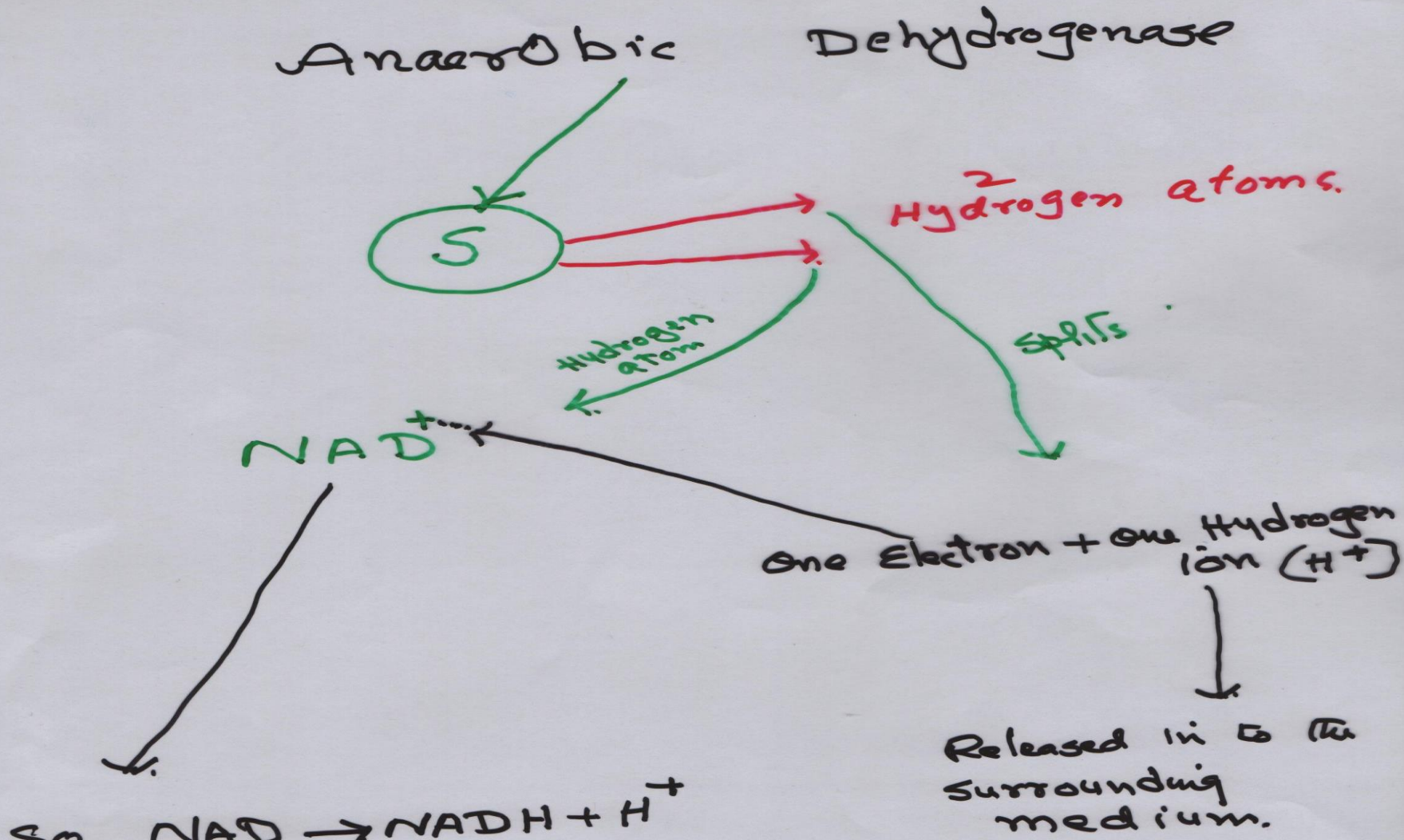
Functions of polyamines

1. They are growth factors required for the growth and proliferation of cells
2. Spermidine has been claimed to be the best marker at tumour cell destruction.

Polyamine Inhibitors

Are used for :

1. Treatment of cancer cells
2. Treatment of Trypanosomiasis (Sleeping Sickness)
3. As hair growth inhibiting agent (Topical applications)


Anaerobic Dehydrogenase
S
2 Hydrogen atoms.
Hydrogen atom
Splits
NAD+
One Electron + one Hydrogen ion (H+)
Released in to the surrounding medium.
So NAD → NADH + H+

Brach Chain Amino Acids

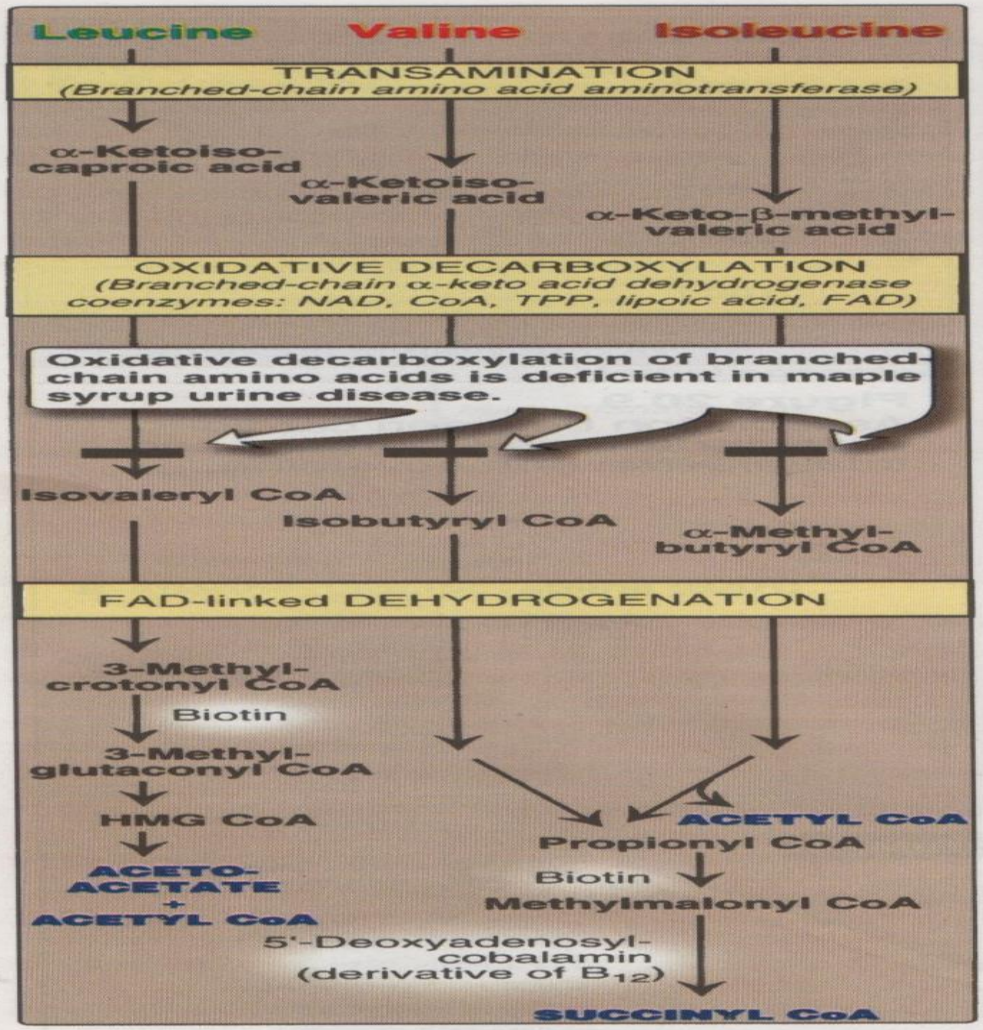


Figure 20.10
Degradation of leucine, valine, and isoleucine. TPP = thiamine pyrophosphate. [Note: *3-Methyl-crotonyl CoA carboxylase* is one of four biotin-requiring carboxylases we have encountered. The other three are *pyruvate carboxylase*, *acetyl CoA carboxylase*, and *propionyl CoA carboxylase*.]

Maple Syrup Urine Disease (Burnt Sugar Smell)

1. Maple Syrup Urine Disease

An inherited disorder of branched chain amino acids.

Enzyme defect: Absence of ***α-ketoacid decarboxylase*** c greatly reduced activity of the enzyme. As a result th conversion of all three branched chain α-ketoacids to CO_2 an acyl CoA-thioesters is interferred with.

Clinical features: The disease is evident by the end of firs week of extrauterine life. Infant does not take feed and ma vomit, poor muscle tone. The patient may exhibit lethargy an

convulsive seizures. Extensive brain damage can occur in surviving children and mental retardation. Without treatment, death usually occurs by the end of the first year of life.

Blood: Plasma levels of the branched chain amino acids leucine, isoleucine, valine and their corresponding α-ketoacids are greatly elevated.

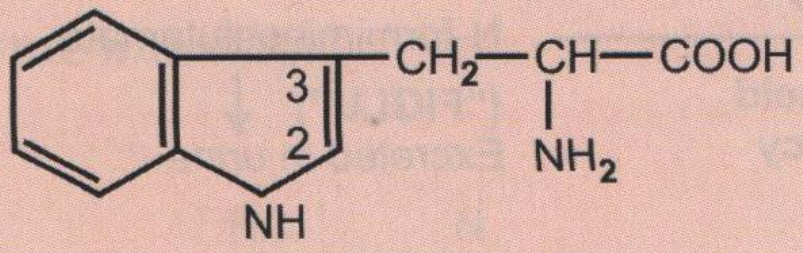
Urine: Branched chain amino acids leucine, isoleucine, valine and their corresponding α-ketoacids are excreted. Hence it is also called as ***Branched-chain ketonuria.*** Small amounts of branched-chain α-OH-acids, formed by reduction of α-keto-acids are also excreted in urine. The urine has characteristic odour, which resembles that of ***maple syrup or burnt sugar,*** hence the name.

TRYPTOPHAN

Points to remember

- It is an ***essential amino acid.*** Omission of tryptophan in diet of man and animals is followed by tissue wasting and negative nitrogen balance.
- It is both ***glucogenic*** and ***ketogenic.***
- ***Tryptophan can synthesize niacin*** (nicotinic acid), a vitamin of B-complex group.
- It is a hetero cyclic amino acid and chemically it is ***"α-amino-β-3-indole propionic acid". It is the only amino acid with an indole ring.***

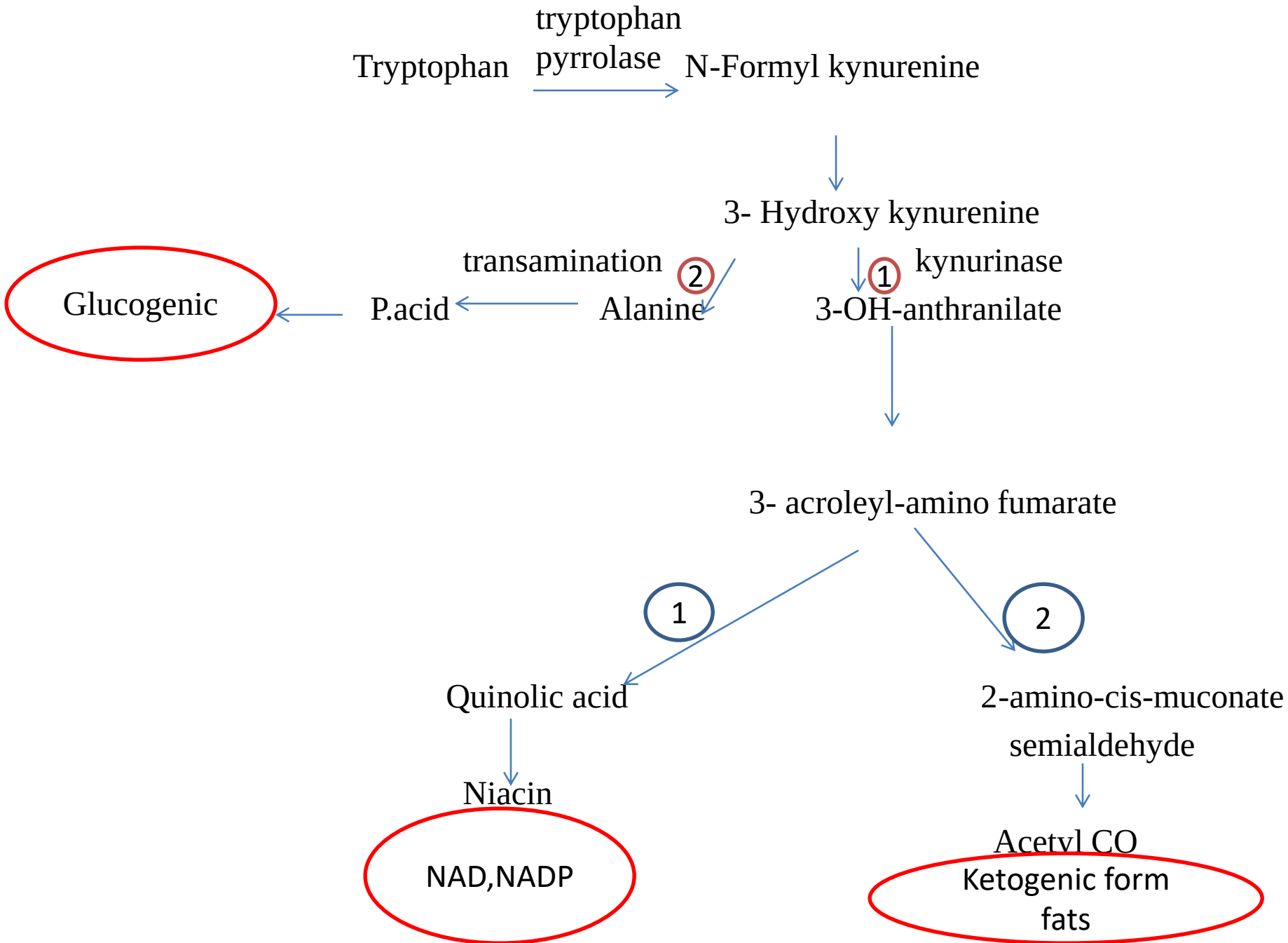
Structure is shown below:



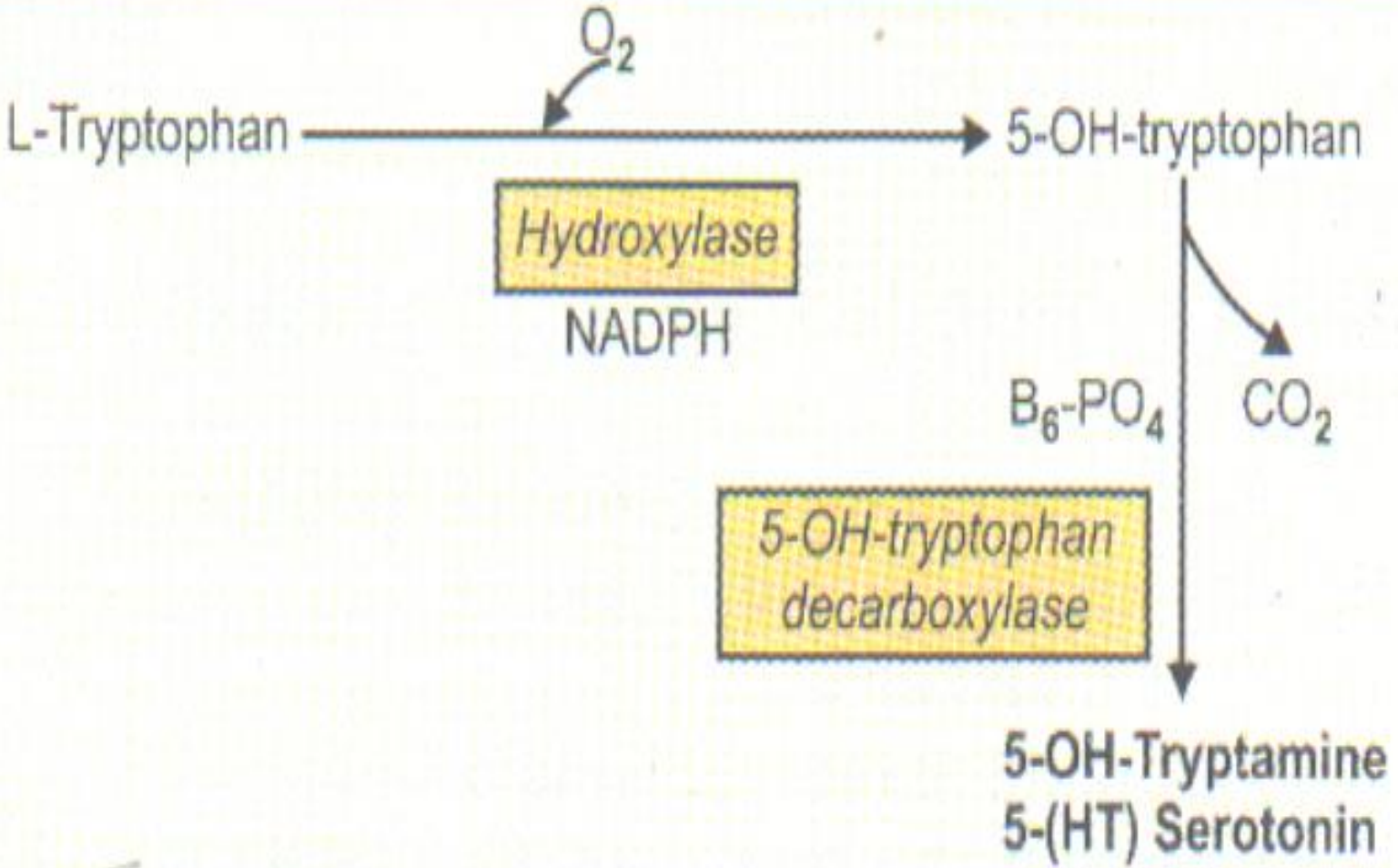
Tryptophan metabolisim

Tryptophan by kynurenine pathway forms

- Glucose
- Fats
- NAD
- NADP


tryptophan
pyrrolase
Tryptophan
N-Formyl kynurenine
3- Hydroxy kynurenine
transamination
2
1
kynurinase
Glucogenic
P.acid
Alanine
3-OH-anthranilate
3- acroleyl-amino fumarate
1
2
Quinolic acid
2-amino-cis-muconate
semialdehyde
Niacin
Acetyl CO
NAD,NADP
Ketogenic form
fats

Formation of Serotonin



Serotenin :

Functions:

1. Vaso contrictor
2. Smooth Muscle Contraction
3. In Brain acts as a Neurotransmitter

Its excess in the Brain stimulates cerebral activities

Its deficiency produces Depression.

After release, serotonin is destroyed by an enzyme MAO

(Mono Amine Oxidase)

MAO Inhibitors are used to treat the patients of depression

These drugs prevent the destruction of serotonin by MAO , So serotonin is accumulated in the brain.

CLINICAL ASPECT

INHERITED DISORDER

Hartnup Disease

A hereditary disorder associated with defective tryptophan metabolism. Named after the family in which it was discovered.

Biochemical defect: It is not known exactly. Probably impaired formation of "transport proteins" for tryptophan and neutral amino acids in intestinal mucosal, renal tubular epithelial cells and the brain. There is defective intestinal and renal transport of tryptophan and other neutral amino acids.

Clinical features: These are characterised by:

- ***Mental retardation.***
- Intermittent cerebellar ataxia and other neurological symptoms.
- ***Pellagra-like skin*** rash—cutaneous hypersensitivity to sunlight.

Blood: Plasma level of tryptophan and other neutral amino acids are reduced.

Faeces and Urine: The neutral amino acids, including tryptophan are excreted in urine and faeces, at least 5 to 10 times of normal average. *Faecal* excretion of tryptophan is specially marked after a "loading" dose of tryptophan given orally.

Urine: Also shows greatly increased amounts of Indoleacetic acid.

Note

There is decreased synthesis of serotonin and nicotinic acid, which accounts for neurological symptoms and pellagra like rash respectively.