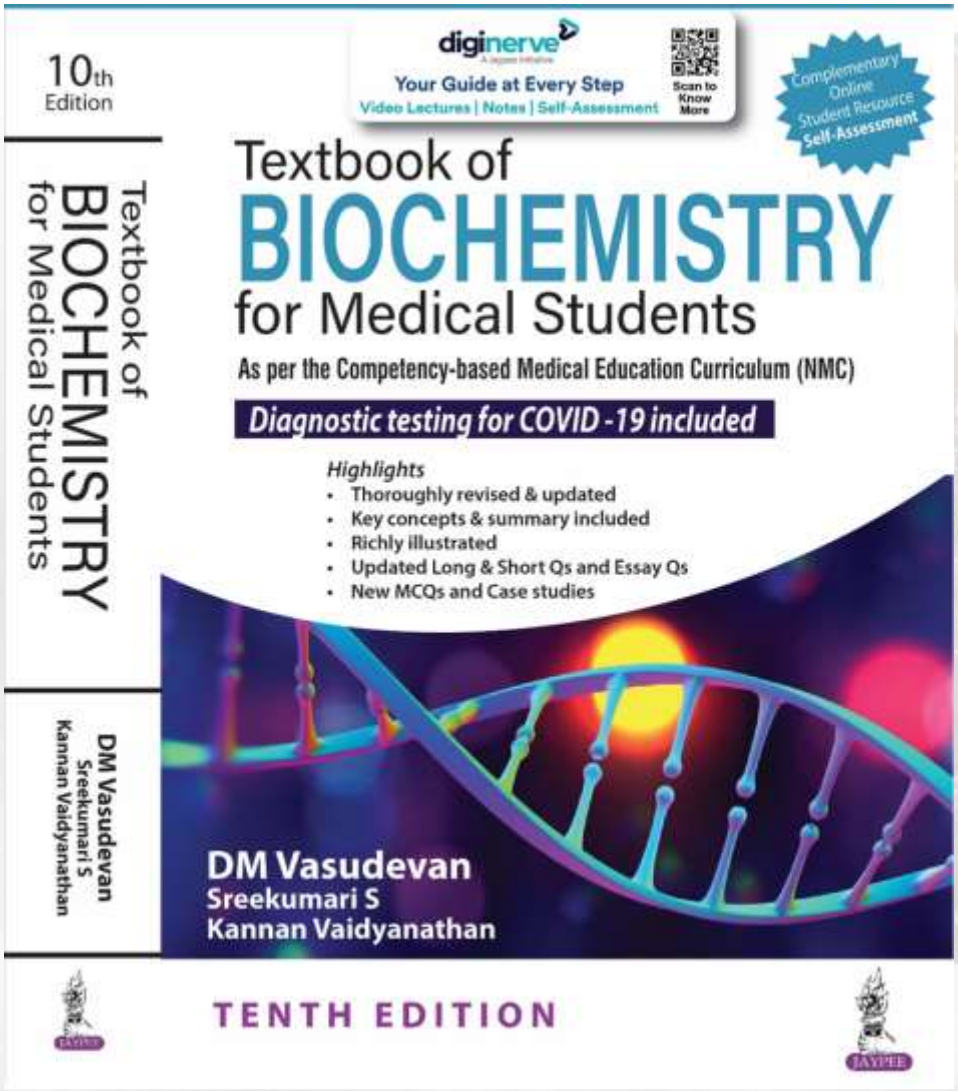
Chapter 16A:

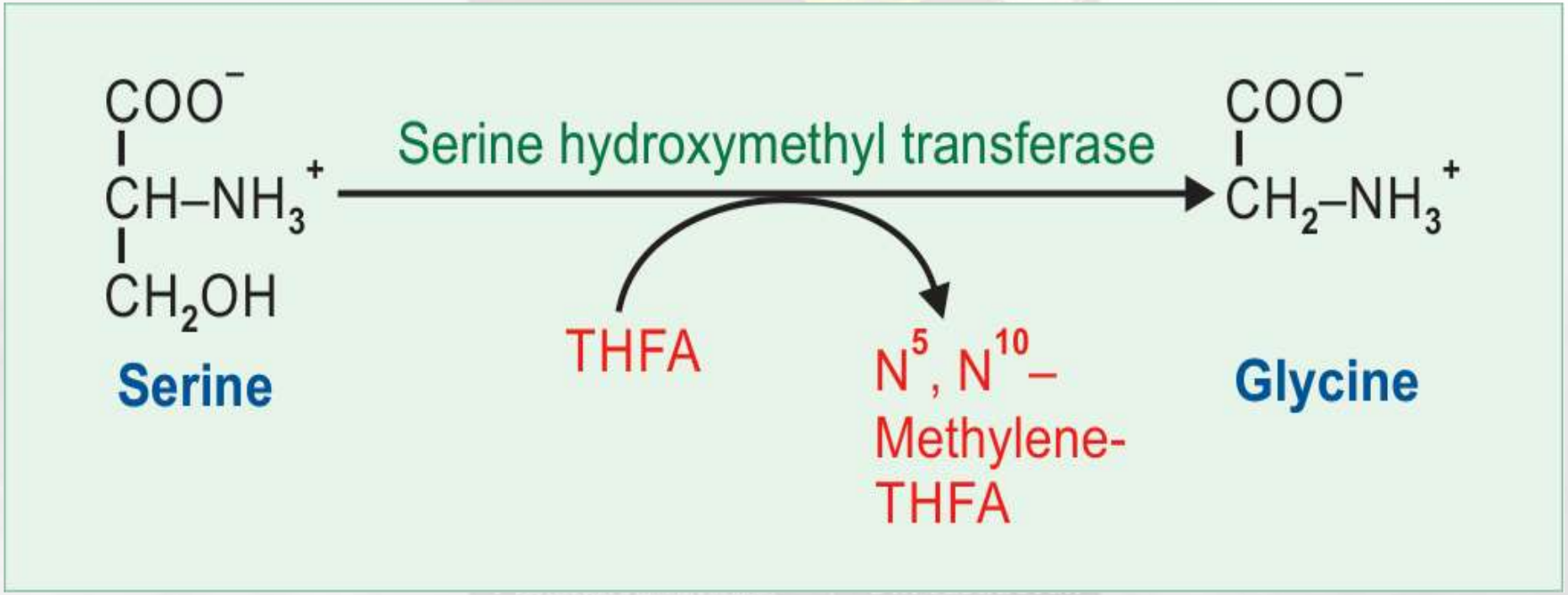
Metabolism of Aliphatic Amino Acids (Gly, Ser, Met, Cys)



Textbook of
BIOCHEMISTRY
for Medical Students

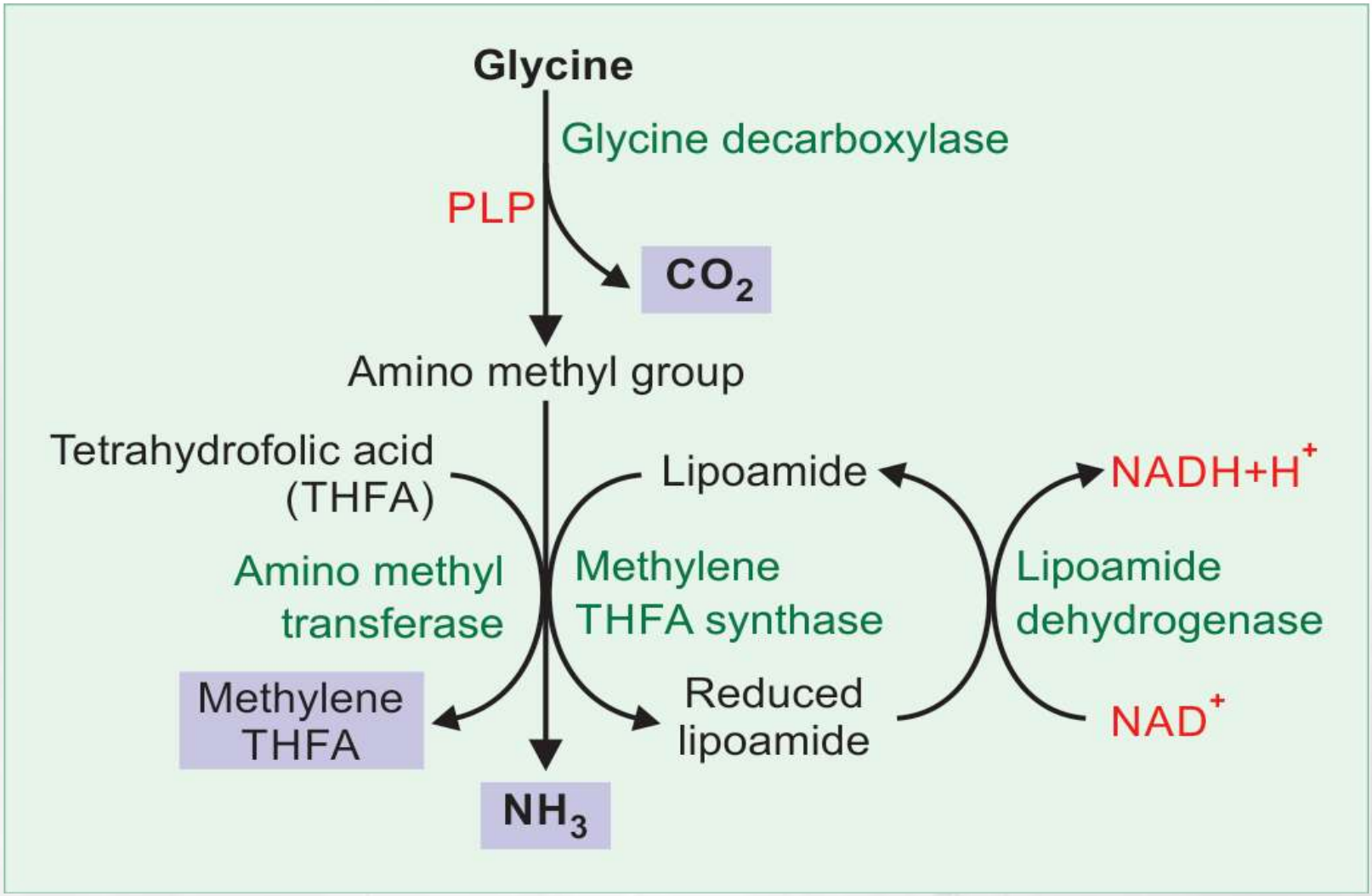
By DM Vasudevan, *et al.*

TENTH EDITION



Formation of glycine from serine.

Formation of glycine from threonine

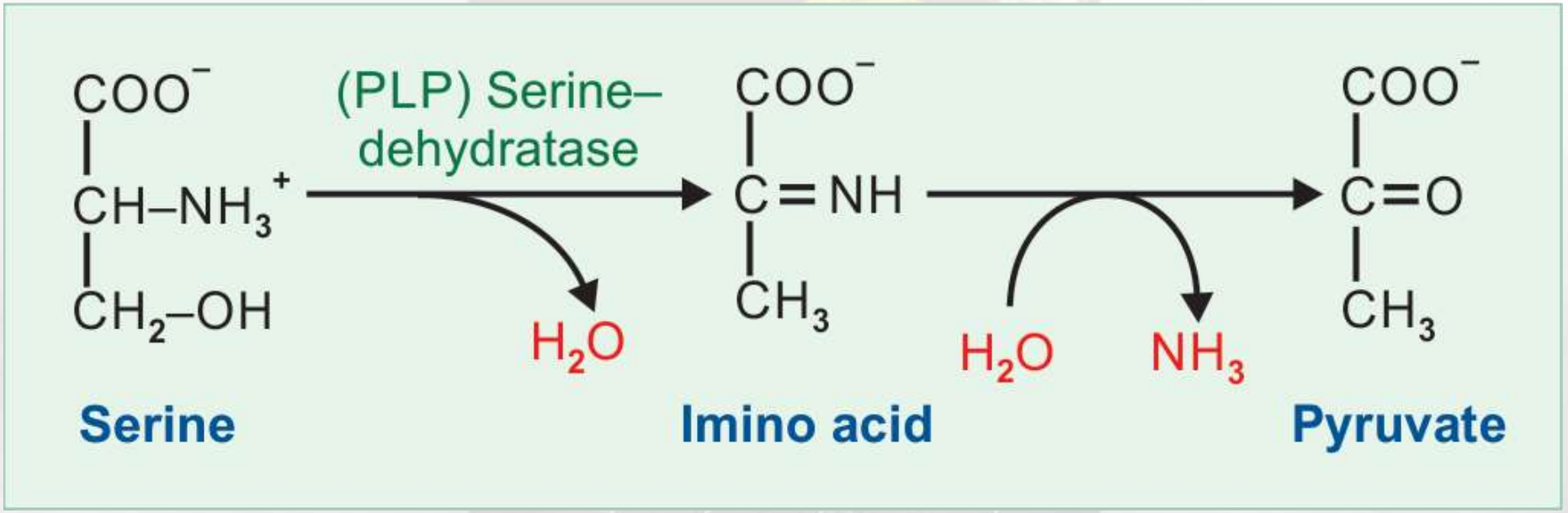


Glycine cleavage system

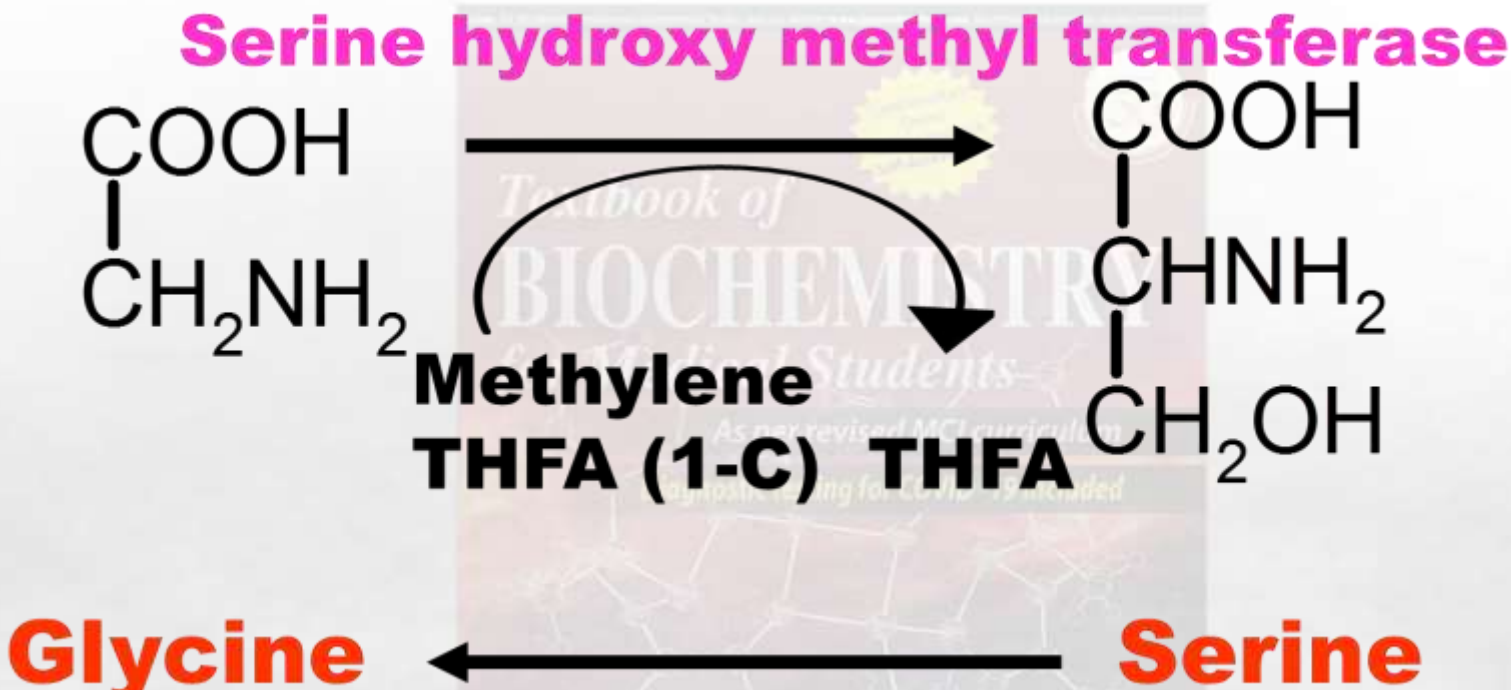
Glycine Cleavage System

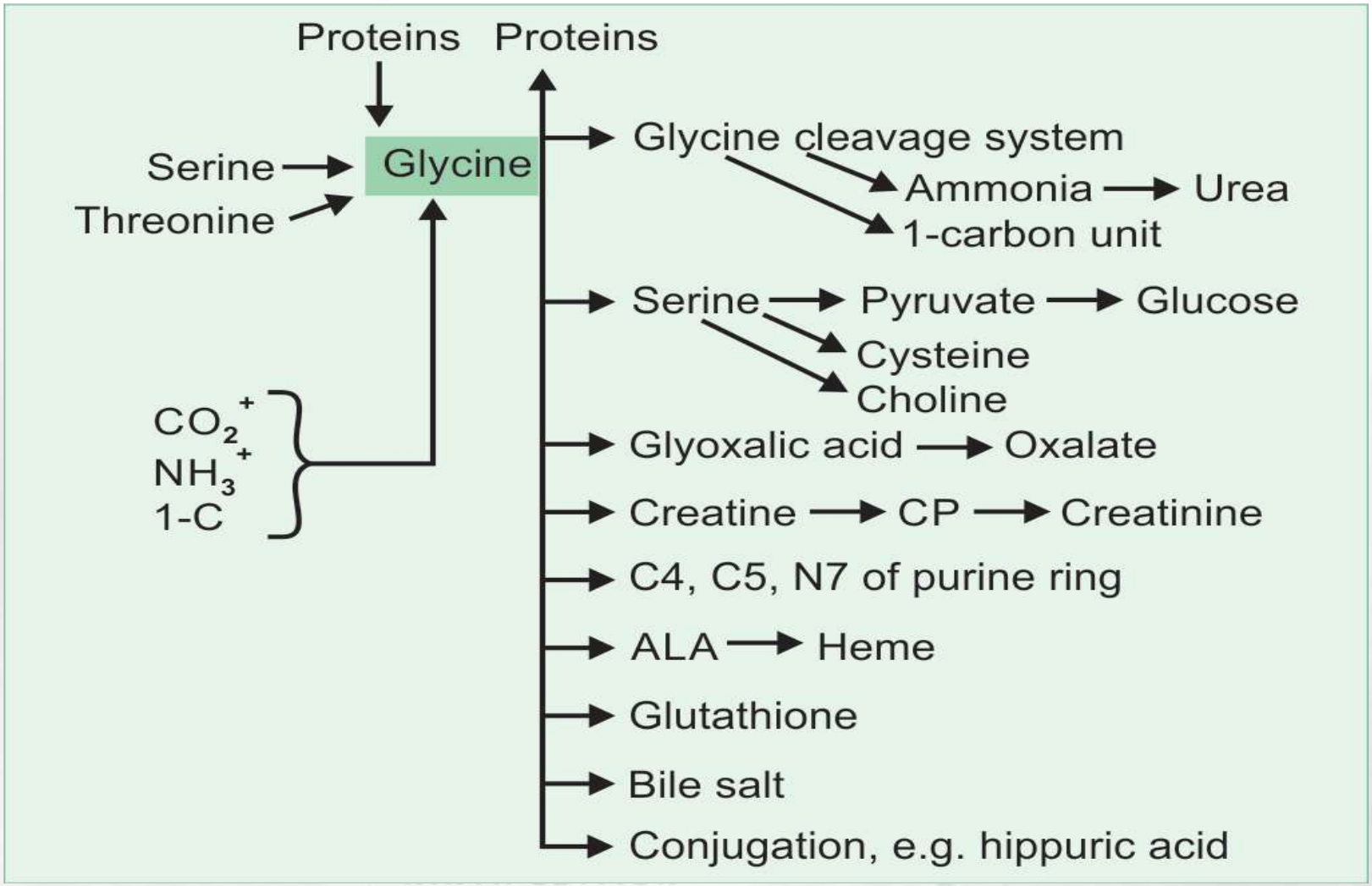
Glycine undergoes oxidative deamination to form NH_3, CO_2 and the one-carbon unit methylene THFA. This pathway is the major catabolic route for glycine. The glycine cleavage system is a **multienzyme complex** consisting of:

- Glycine decarboxylase with pyridoxal phosphate which removes CO_2 from glycine
- Aminomethyltransferase containing lipoamide which releases ammonia
- Methylene THFA synthase which transfers methylene group to THFA
- NAD+ dependent lipoamide dehydrogenase which regenerates lipoamide.



Deamination of serine to pyruvate.


Serine hydroxy methyl transferase
COOH
CH2NH2
COOH
CHNH2
CH2OH
Methylene
THFA (1-C)
THFA
Glycine
Serine

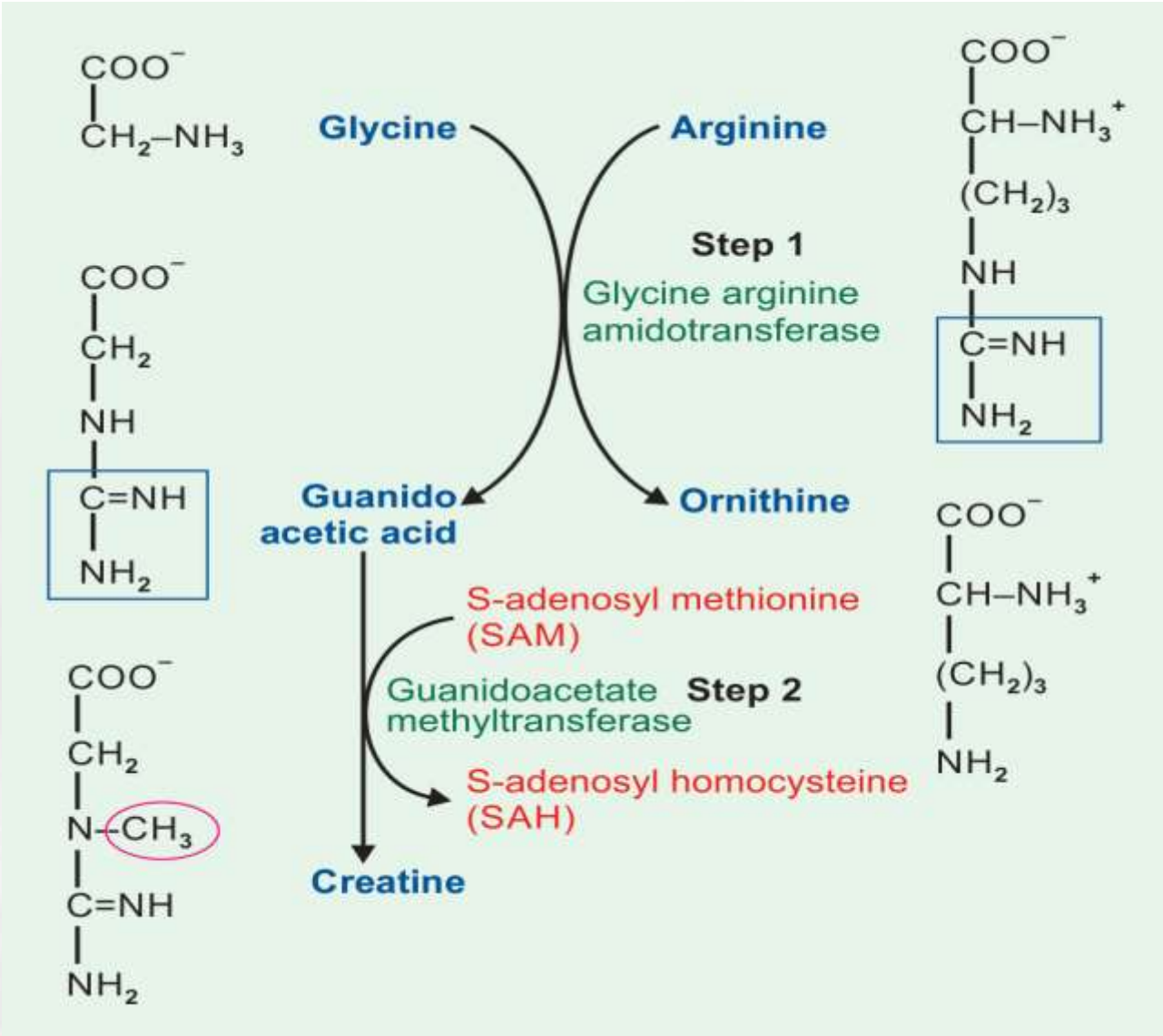


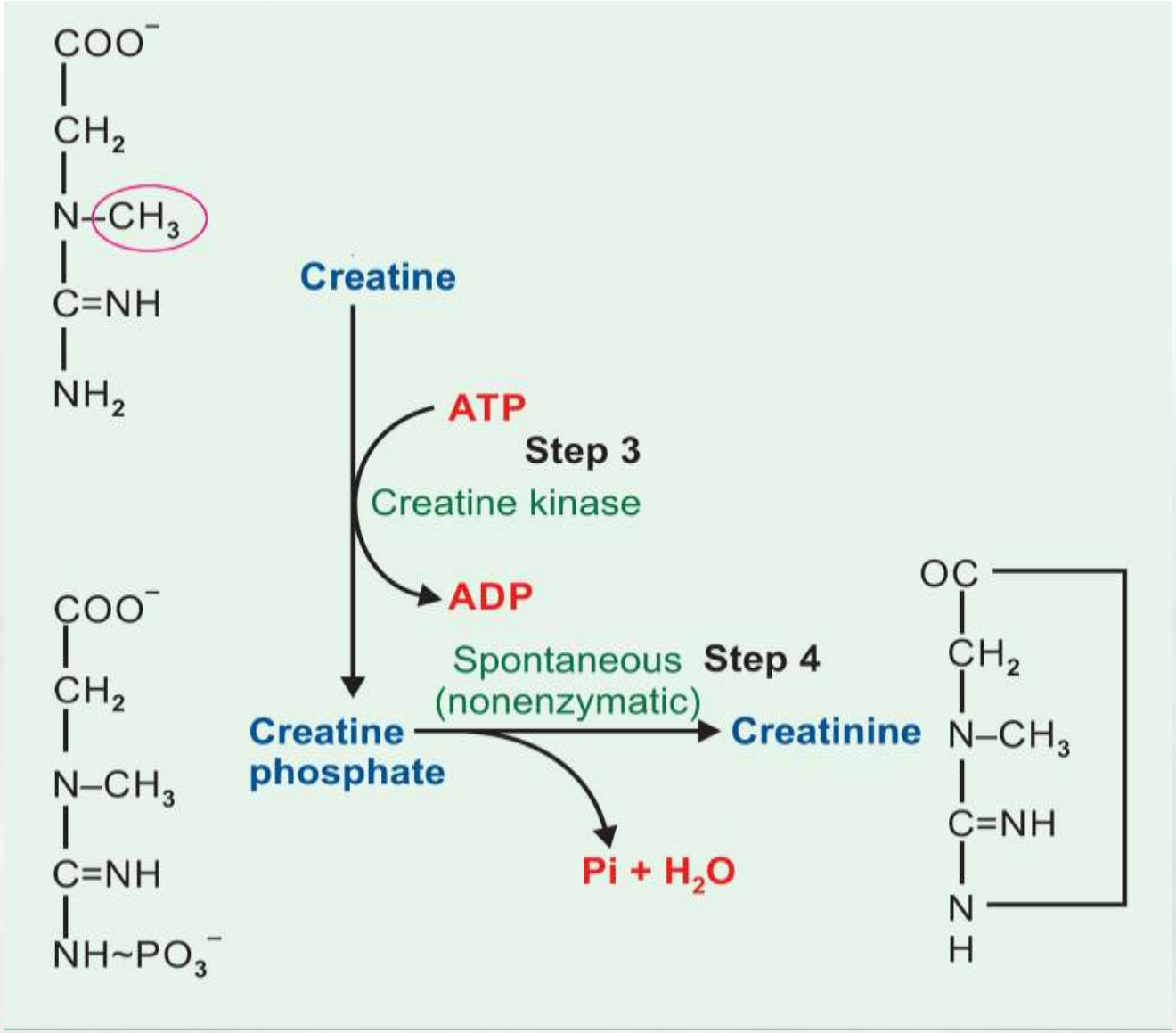
Overview of glycine metabolism

Metabolic Functions of Glycine

Glycine may be used for the biosynthesis of the following compounds and activities

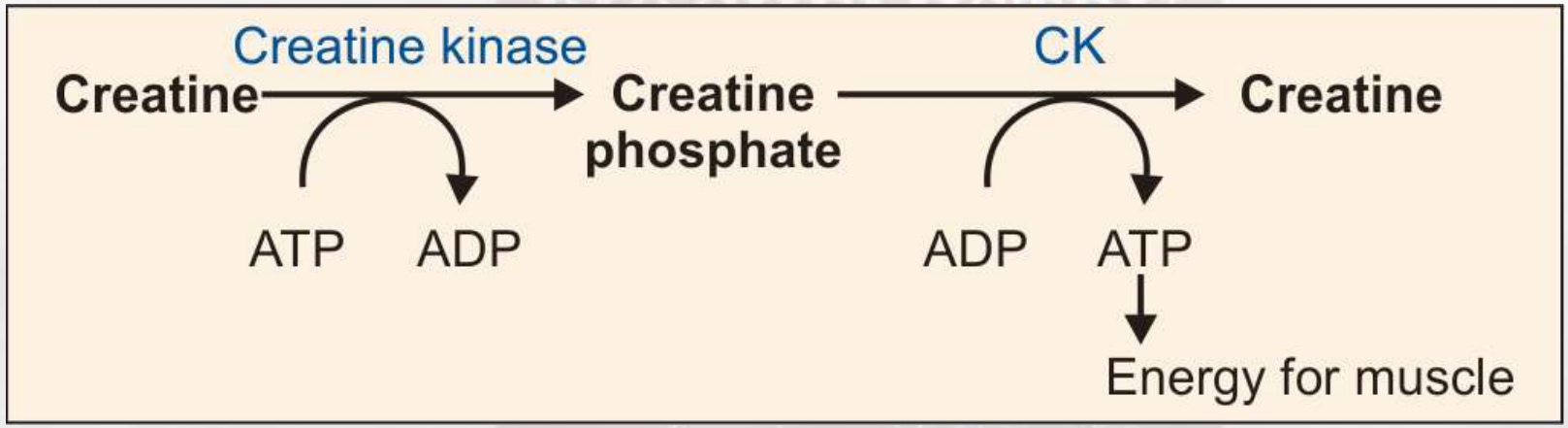
- Creatine, creatine phosphate and creatinine
- Heme
- Purine nucleotides
- Glutathione
- Inhibitory neurotransmitter
- Conversion to serine
- Conjugation of bile acids
- Detoxification of benzoate to form hippurate
- Contributor to one-carbon pool, glycine cleavage system
- Glucogenic.


Glycine
Arginine
Step 1
Glycine arginine amidotransferase
Guanido acetic acid
Ornithine
S-adenosyl methionine (SAM)
Guanidoacetate methyltransferase
Step 2
S-adenosyl homocysteine (SAH)
Creatine


Creatine
ATP
Step 3
Creatine kinase
ADP
Spontaneous (nonenzymatic)
Step 4
Creatine phosphate
Creatinine
Pi + H2O

Creatine Kinase

Muscle -- MM -- Muscular dystrophy
Brain -- BB
Heart -- MB -- Myocardial infarction

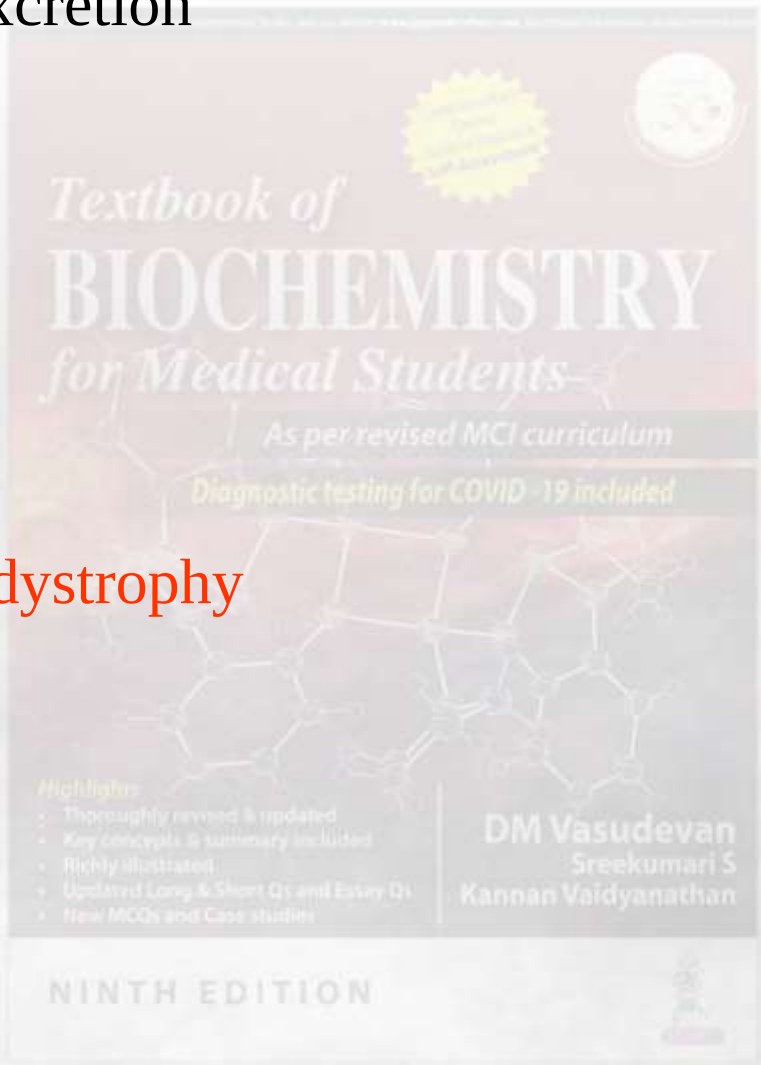


Creatine phosphate is the stored energy in muscle

Creatine

Urinary Creatine excretion
Normal : Negligible
Increased in
Muscle dystrophy
Muscle injuries

Normal Serum level
0.2 - 04 mg /dl
Increased in muscle dystrophy



Serum Creatinine

0.7 to 1.4 mg / dl for Male

0.6 to 1.3 mg / dl for Female

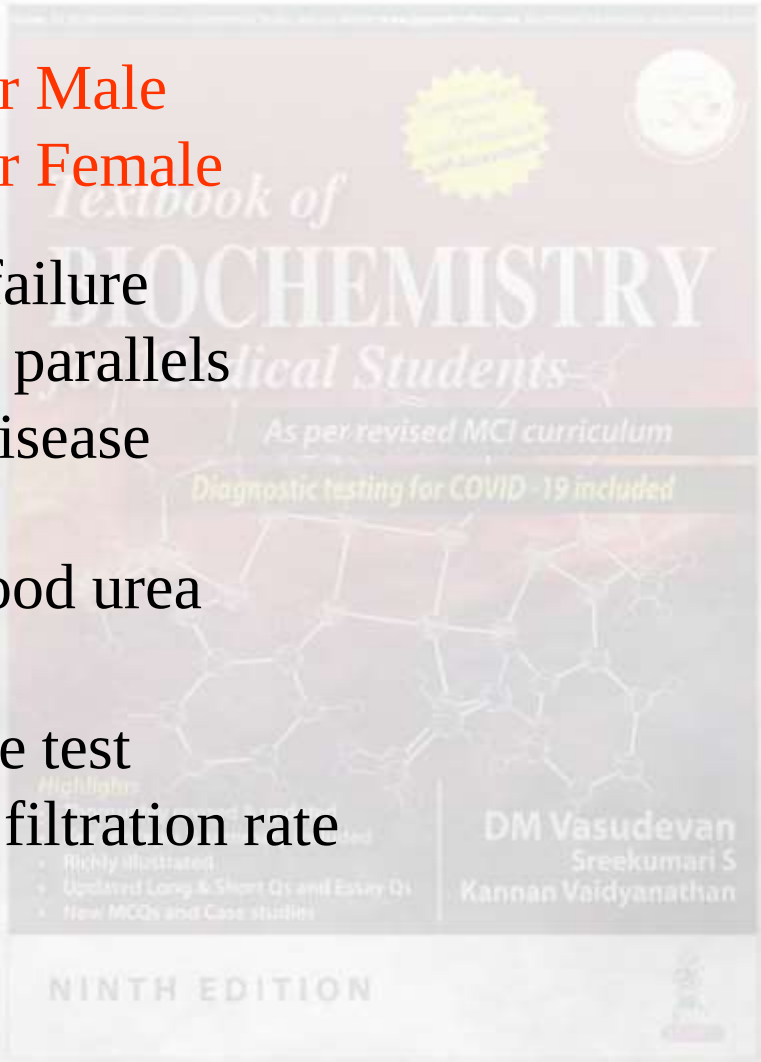
Increased in Renal failure

Serum level usually parallels the severity of the disease

Better index than blood urea

Creatinine clrearance test

Test for Glomerular filtration rate

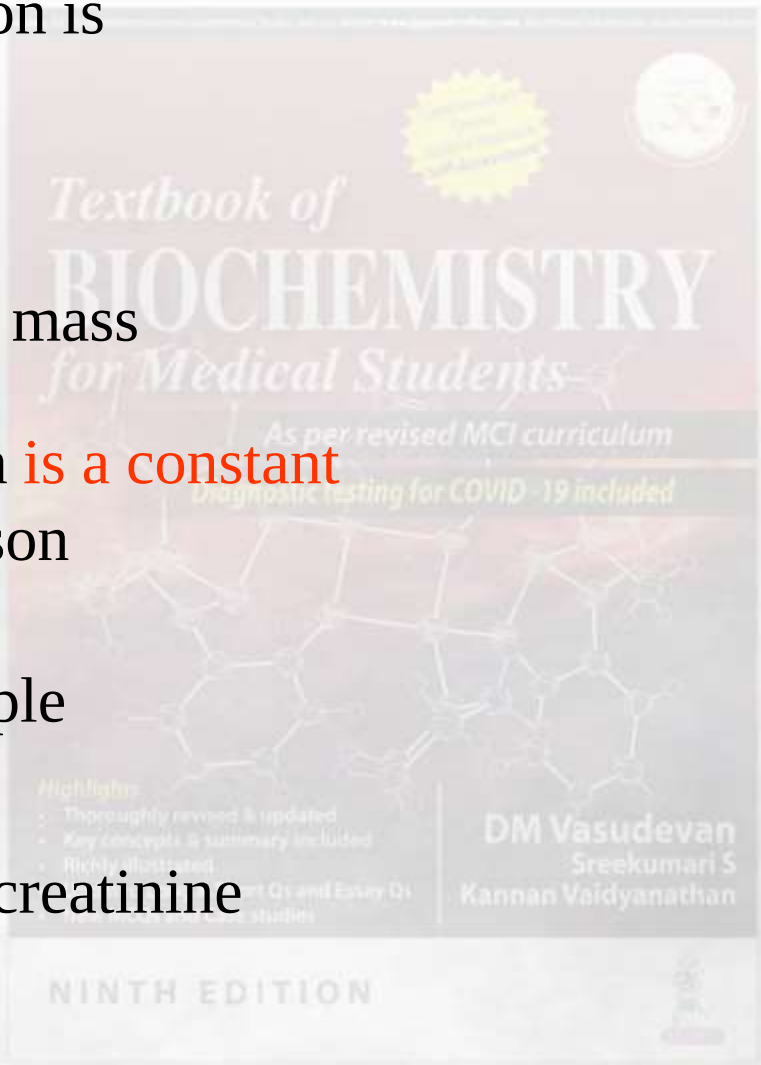


Creatinine production is
spontaneous
continuous
No fluctuation
Depends on Muscle mass

Creatinine excretion is a constant
for a particular person

24 - hour urine sample

Urinary conc / g of creatinine



Glycine + Arginine

↓ Amido transferase, kidney

Guanido acetic acid

↓ Methyl transferase, Liver

CREATINE

↓ Creatine kinase, Muscle

CREATINE PHOSPHATE

↓ Spontaneous, muscle

CREATININE

Clinical Applications of Creatinine and Creatine

Normal serum creatinine level is 0.7 to 1.4 mg/dL and serum creatine level is 0.2–0.4 mg/dL. Creatinine level in blood is a sensitive indicator of **renal function**. As the kidney function is decreased, correspondingly blood creatinine level is increased. Urine contains negligible amount of creatine in normal males. But in the early phase of **muscular dystrophies**, the blood creatine and urinary creatinine are increased. In the end stages of muscular dystrophy, as the muscle mass is considerably reduced, the creatinine level is lowered. Apart from the muscular dystrophies, reduced muscle mass is also the cause for low creatinine in (a) women, (b) old age, (c) bedridden states and d) low protein diet.

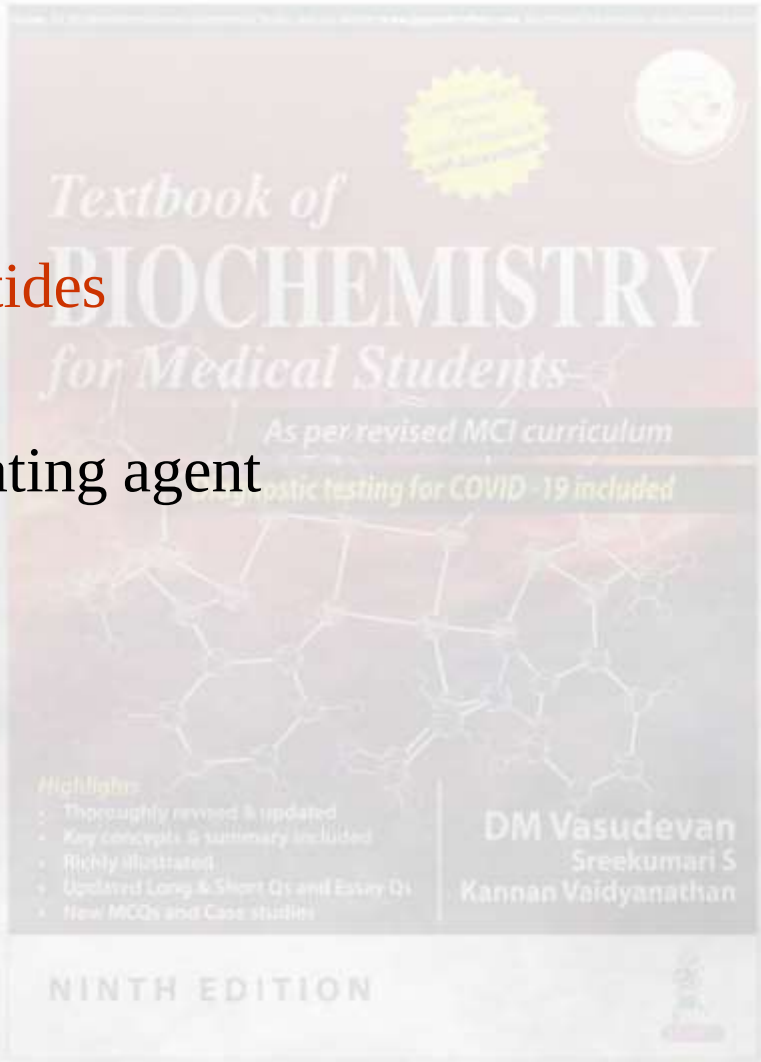
The enzyme creatine kinase (CK), especially the cardiac isoenzyme (CK-MB) is elevated in **myocardial infarction**.

The spontaneous loss of creatine and of phosphocreatine to creatinine requires that creatine be continuously replaced.

Creatine synthesis makes major demands on the metabolism of glycine, arginine and methionine. Children with inborn errors of creatine synthesis or transport present with severe neurological symptoms and a profound depletion of brain creatine. It is evident that creatine plays a critical, though less appreciated role in brain function.

Special Metabolic Functions

- Biosynthesis of
  - Heme
  - Creatine
  - Purine nucleotides
  - Glutathione
- Used as a conjugating agent

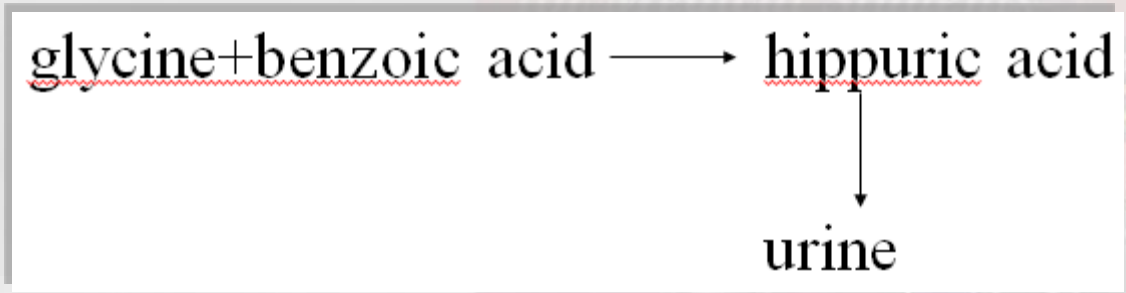


- Conjugates with bile acids

  glyco cholic acid

  glycochenodeoxy cholic acid

- Conjugates with benzoic acid



- Acts as a neurotransmitter

  In brain stem and spinal cord

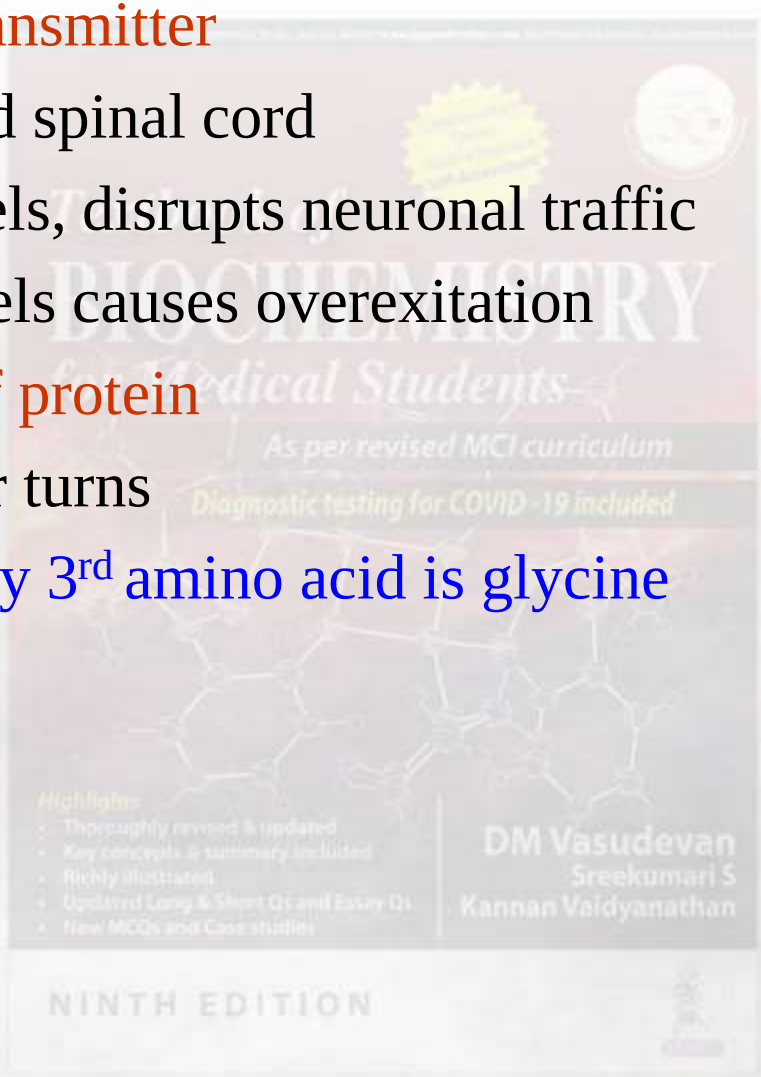
  At moderate levels, disrupts neuronal traffic

  At very high levels causes overexitation

- Is a constituent of protein

  Seen at bends or turns

  In collagen, every 3rd amino acid is glycine



Synthesis of heme

ALA synthase

Glycine → Delta amino levulinic acid

\+

Succinyl CoA

↓

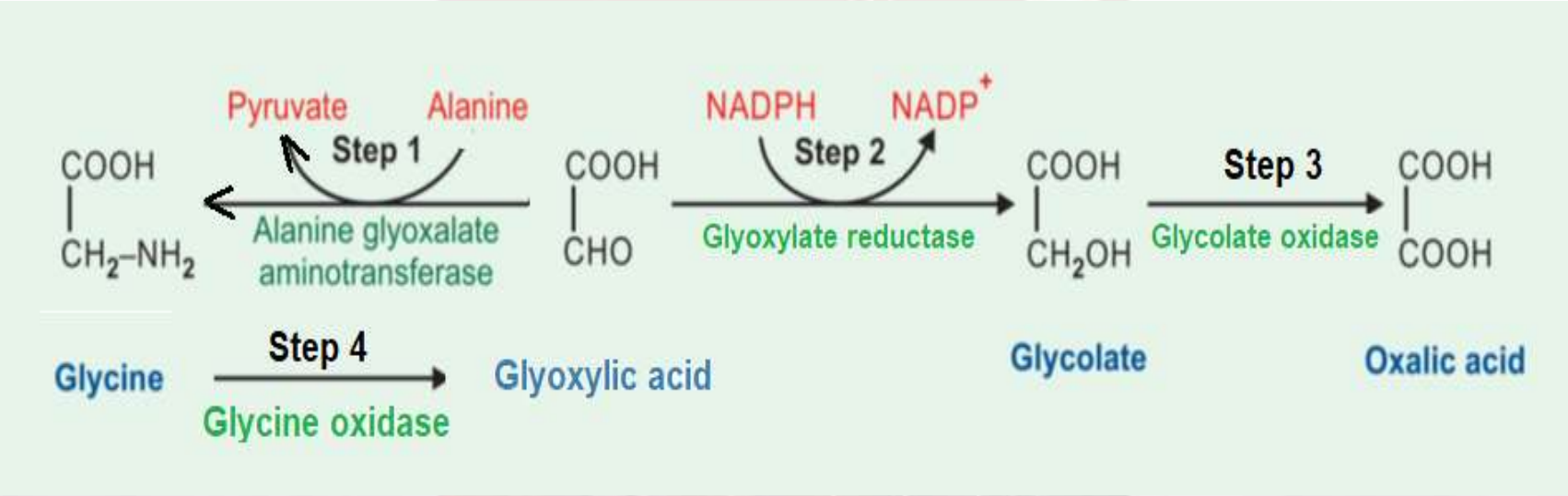
↓

HEME

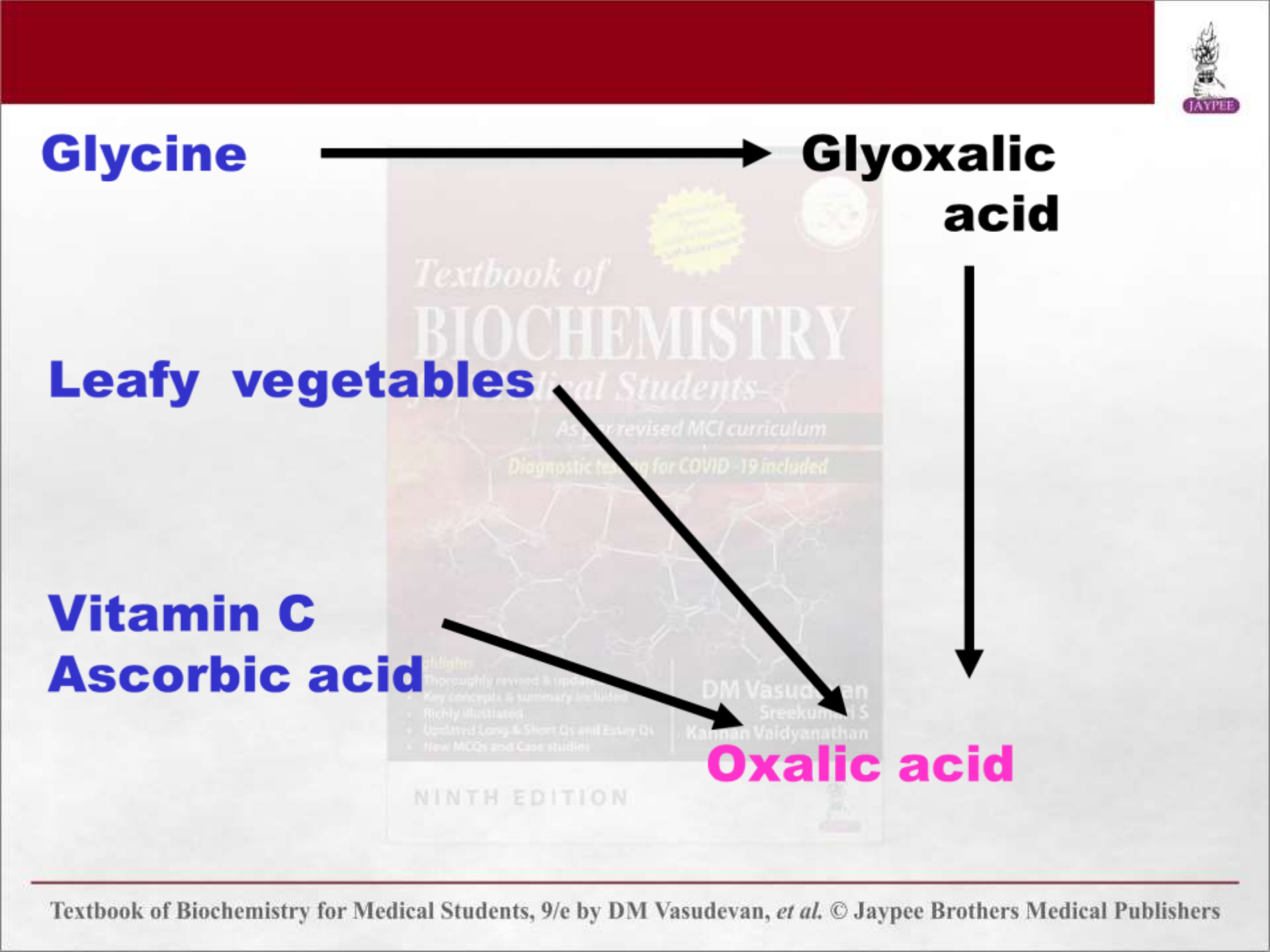
Disorders due to Defective Glycine Metabolism

Non ketotic hyperglycinemia

- Defect in glycine cleavage system
- Glycine level increased in blood, urine & CSF
- Severe mental retardation & seizures
- No effectve management



Explanation for primary hyperoxaluria. Alanine glyoxalate aminotransferase is located in peroxisomes, but in patients, it is located in the cytoplasm and hence inactive.


Glycine
Glyoxalic acid
Leafy vegetables
Vitamin C
Ascorbic acid
Oxalic acid

Primary Hyperoxaluria

due to protein targeting defect

Glyoxylate amino transferase is seen in mitochondria instead of in peroxisomes

Degradation of glyoxylate does not occur

Increased accumulation of glyoxylate & oxalic acid

Oxalates deposit in kidney

Nephrolithiasis, renal colic & hematuria

Extrarenal oxalosis can occur in heart, blood vessels & bone

Type 2 hyperoxaluria

- Milder condition
- Deficient activity of cytoplasmic glyoxylate reductase
- Urolithiasis

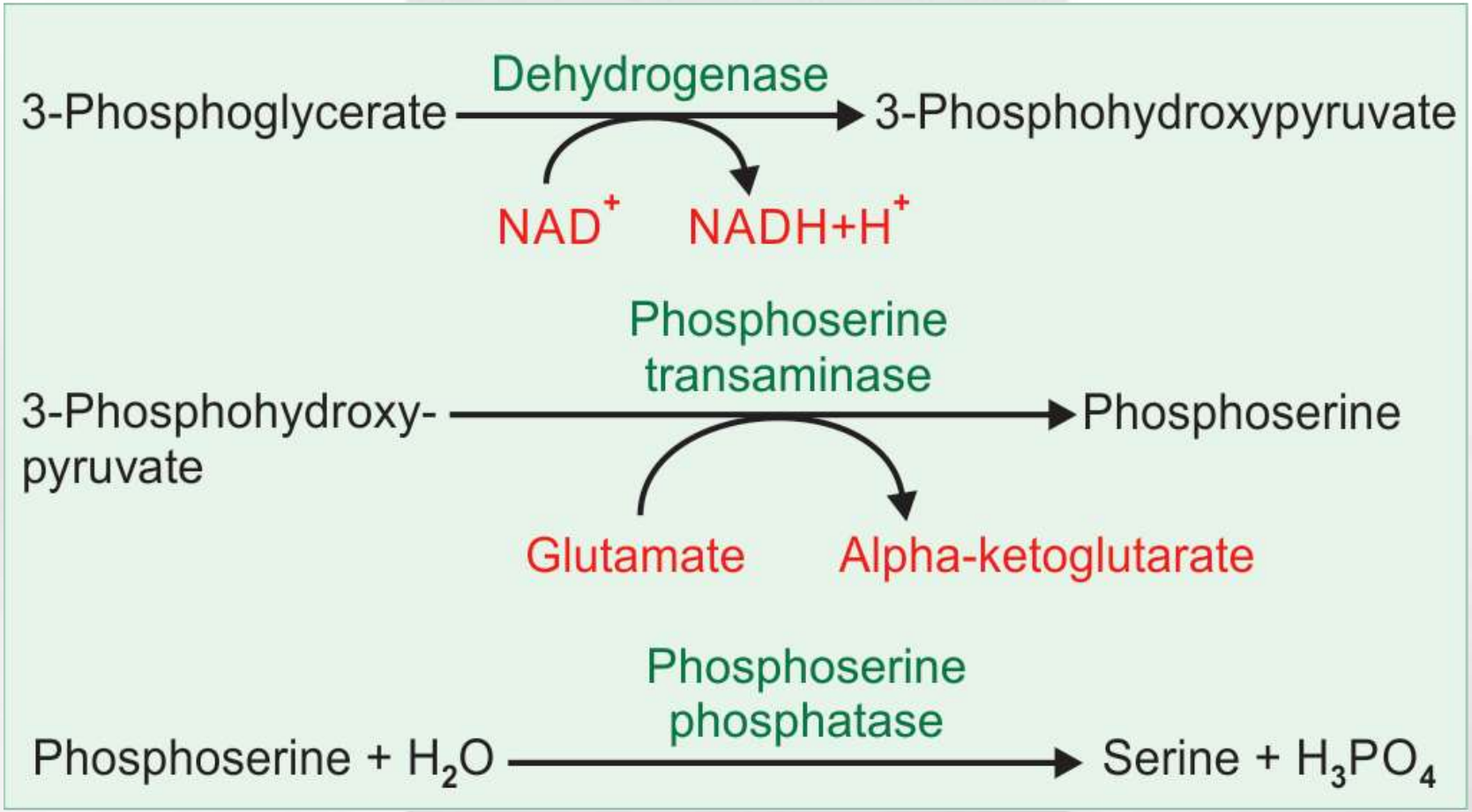
Management

- Increase water intake → Increase oxalate excretion
- Minimize dietary intake of oxalates
- Restrict intake of leafy vegetables, tea, coco, beetroot, spinach etc.

- Sources of serine are:

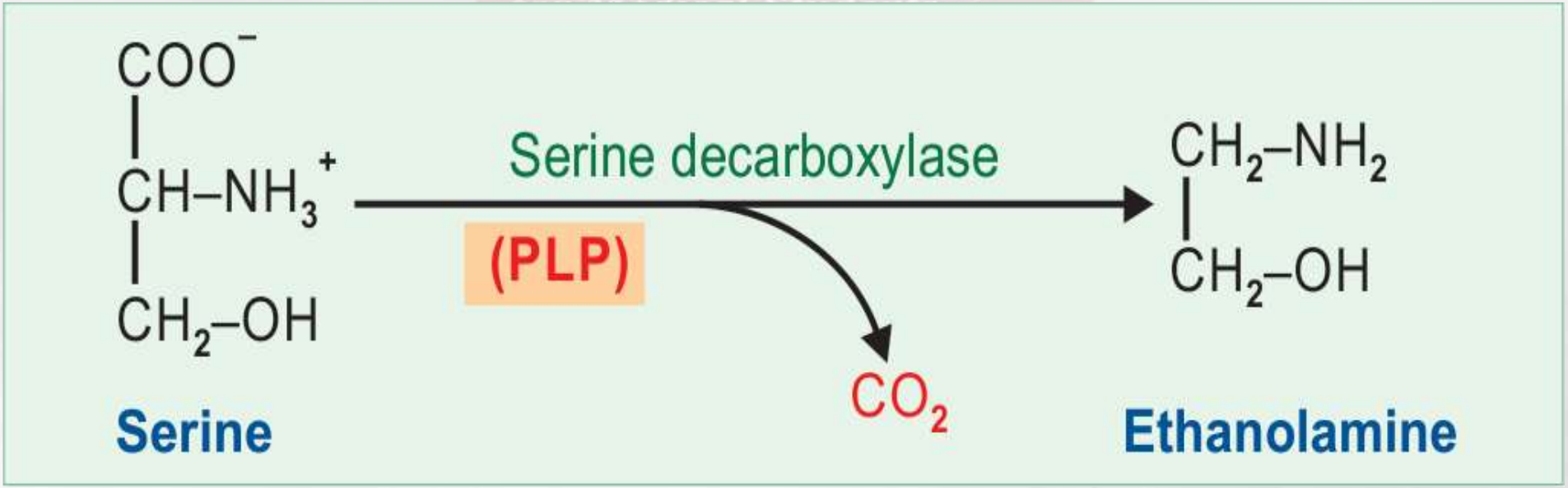
1. **Phosphoglycerate:** This is the major source of serine in the body. The steps involve dehydrogenation, transamination and removal of phosphate group.
2. From **glycine** by reversal of serine hydroxymethyl transferase reaction.
3. Serine may also be formed by transamination of hydroxypyruvate with alanine.

Alanine + Hydroxypyruvate → Pyruvate + Serine



Formation of serine

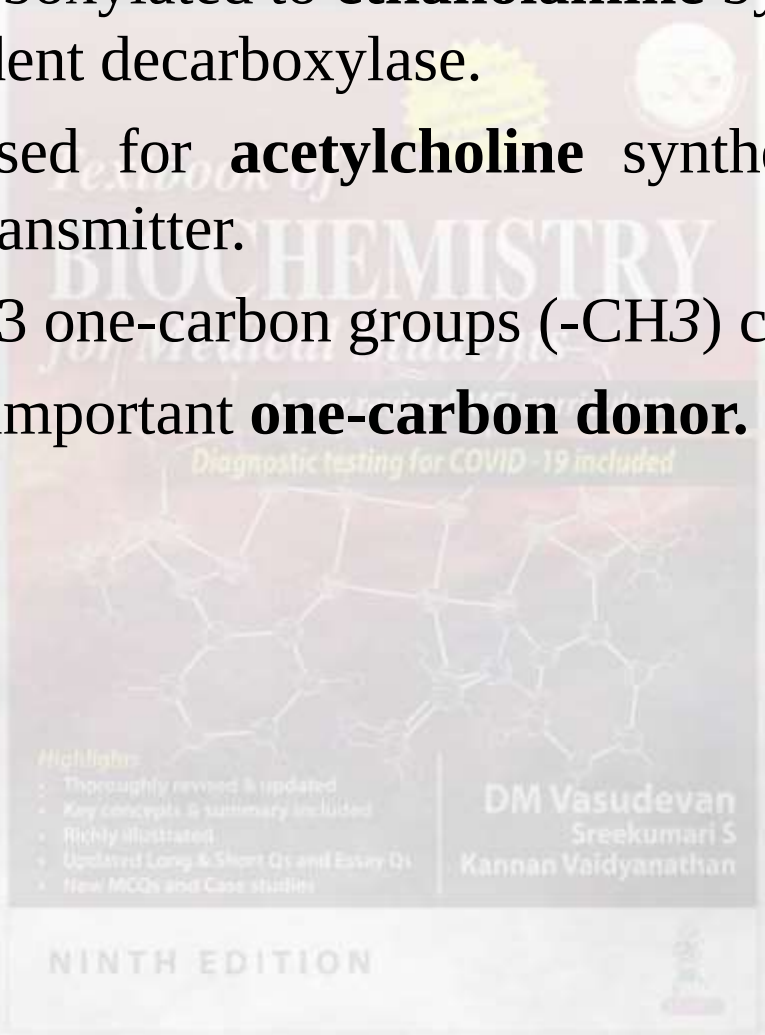
- **Catabolism of Serine**
  1. Deamination to **pyruvate**
  2. Transamination to **hydroxypyruvate**
  3. Serine is **glucogenic.**



Decarboxylation of serine

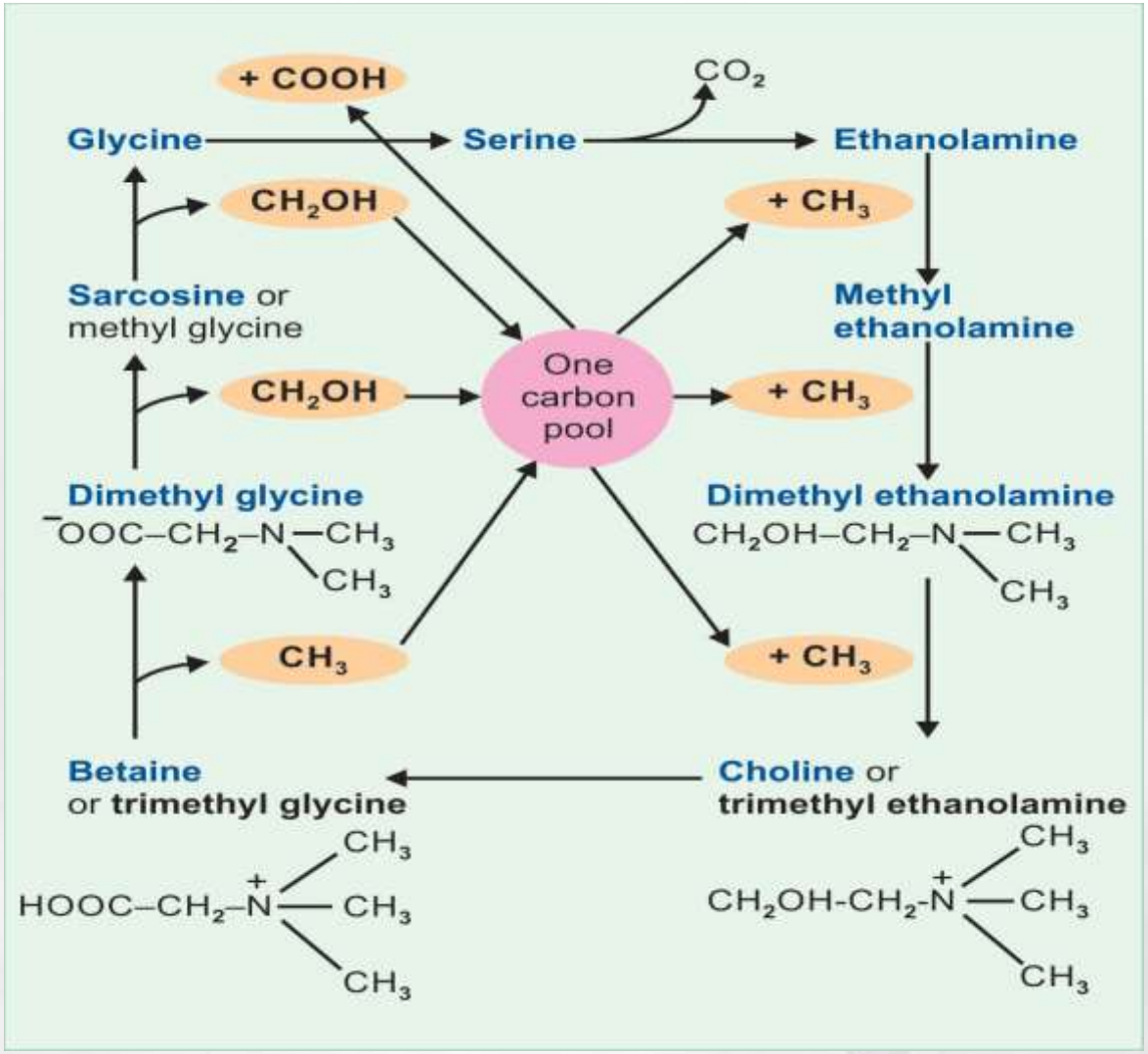
Choline Synthesis

- A. Serine is decarboxylated to **ethanolamine** by a pyridoxal phosphate dependent decarboxylase.
- B. Choline is used for **acetylcholine** synthesis, which is an important neurotransmitter.
- C. From choline, 3 one-carbon groups (-CH3) can be removed.
- So, choline is an important **one-carbon donor.**



Serine as a Component of Protein

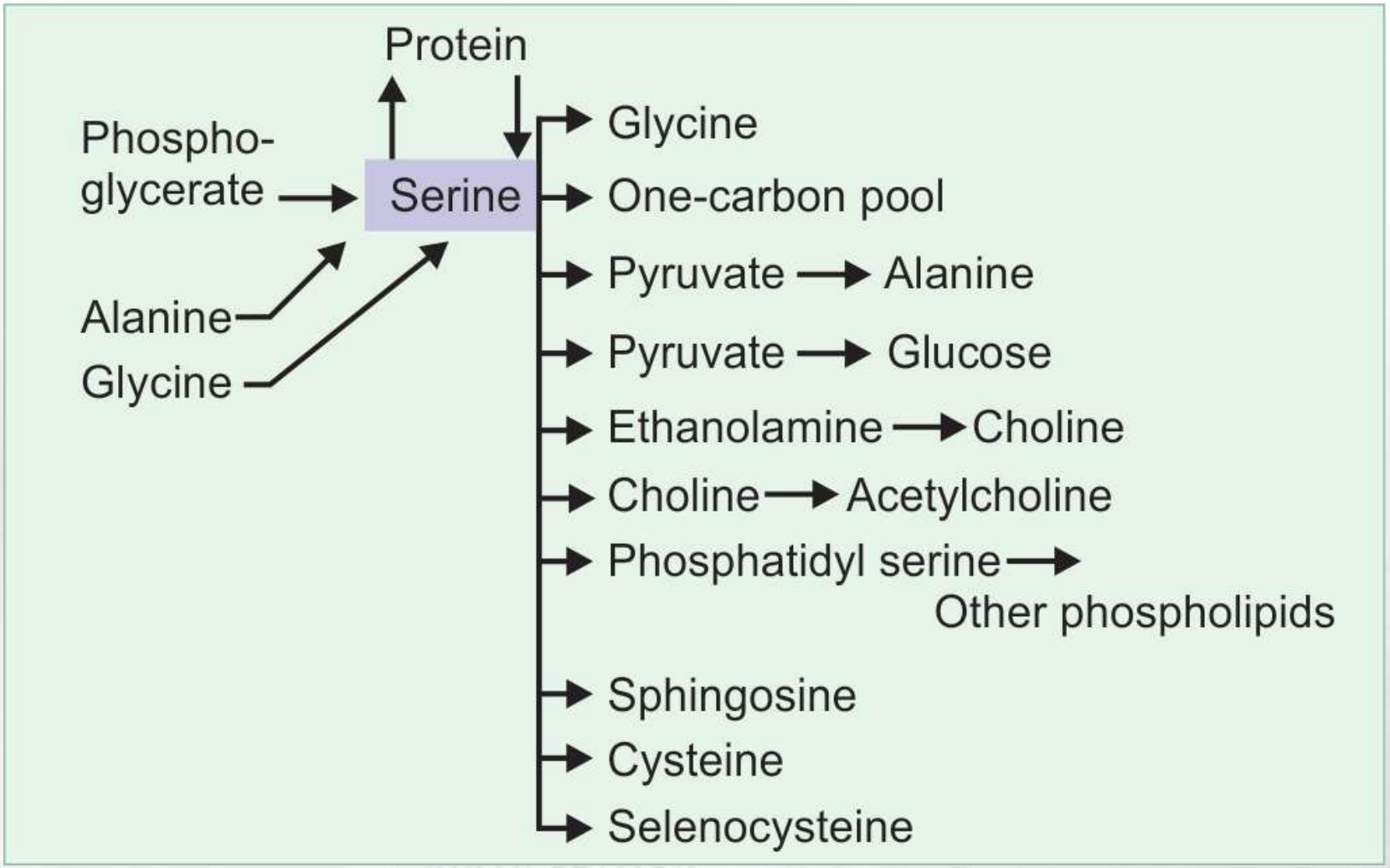
- In **phosphoproteins**, serine serves to esterify phosphate groups, e.g. casein.
- Glycogen phosphorylase is activated by phosphorylation, while pyruvate kinase and phosphofructokinase-2 are activated by dephosphorylation.
- This **covalent modification** serves as a mechanism of regulation of enzyme activity.
- The phosphate group is added by protein kinases which are serine/threonine kinases.
- In **glycoproteins**, the carbohydrate groups are usually attached to the hydroxyl groups of serine or threonine residues of the protein.
- Serine forms the active catalytic residue of many enzymes (serine proteases), e.g. trypsin and coagulation factors.



Glycine serine choline cycle

Selenocysteine (SeCys) (21st Amino Acid)

- Selenocysteine is abbreviated as SeCys.
- It is seen at the active site of the following enzymes:
  a) **Thioredoxin reductase;**
  b) **Glutathione peroxidase**, which scavenges peroxides;
  c) **De-iodinase** that removes iodine from thyroxine to make triiodothyronine and
  d) **Selenoprotein P**, a glycoprotein seen in mammalian blood.
- Their concentration falls in selenium deficiency.
- Its structure is COOH–CHNH2–CH2–SeH.



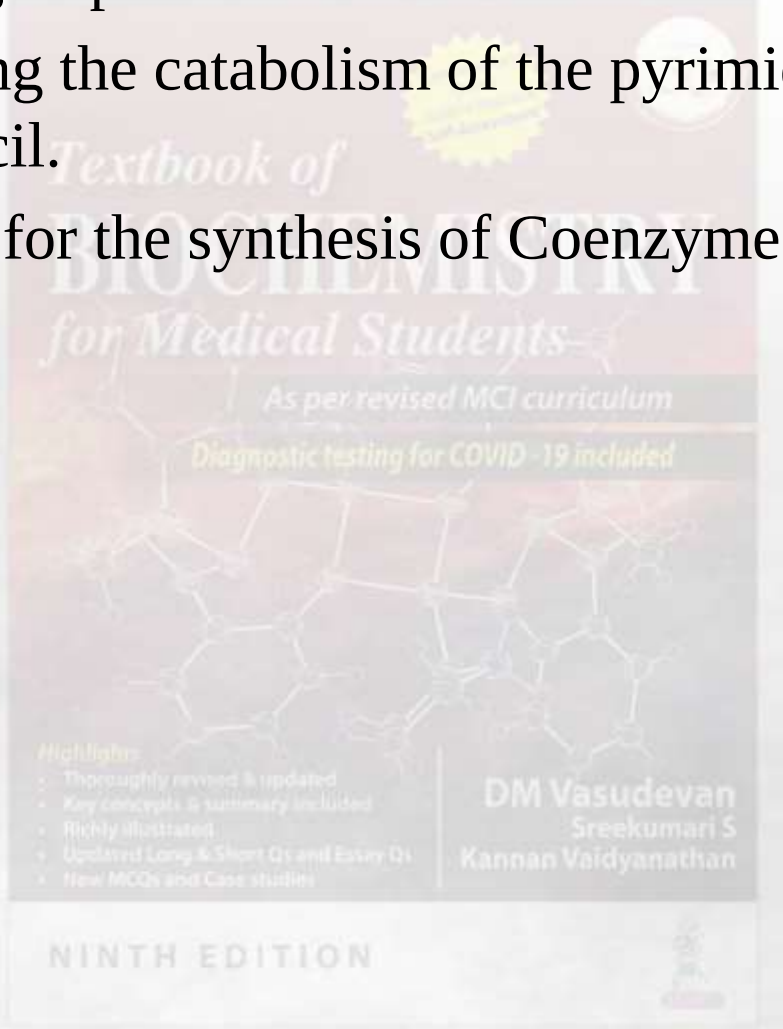
An overview of serine metabolism

Alanine (ALA) (A)

- Alanine is a non-essential **glucogenic** amino acid.
- Alanine can be formed by transamination of pyruvate.
- The enzyme is alanine amino transferase (ALT).
- Pyruvate + Glutamate → Alanine + alpha ketoglutarate
- This reaction requires **pyridoxal phosphate** (PLP).
- ALT level in blood is increased in liver diseases.
- Under conditions of starvation, the glucose alanine cycle is of special metabolic significance.
- Alanine is quantitatively the most important amino acid taken up by the liver from peripheral tissues, particularly from skeletal muscle.
- It forms a major participant in interorgan transport of nitrogen.

Beta Alanine

- Here the amino group is attached to the beta carbon atom.
- It is formed during the catabolism of the pyrimidine bases, cytosine and uracil.
- It is mainly used for the synthesis of Coenzyme A.

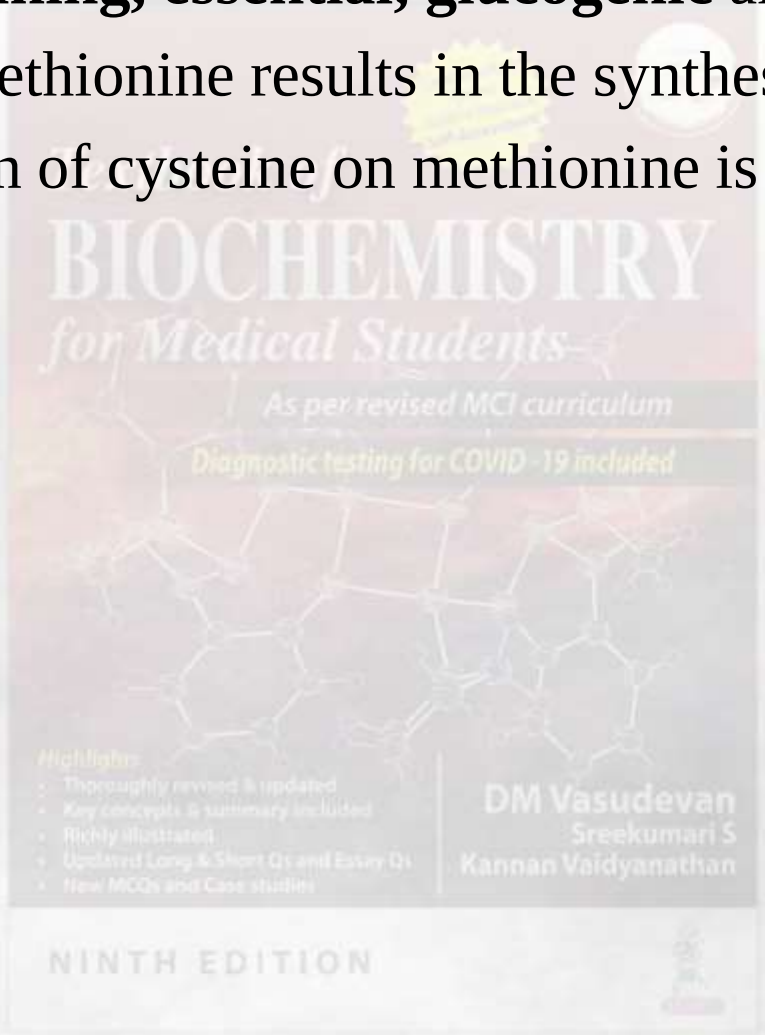


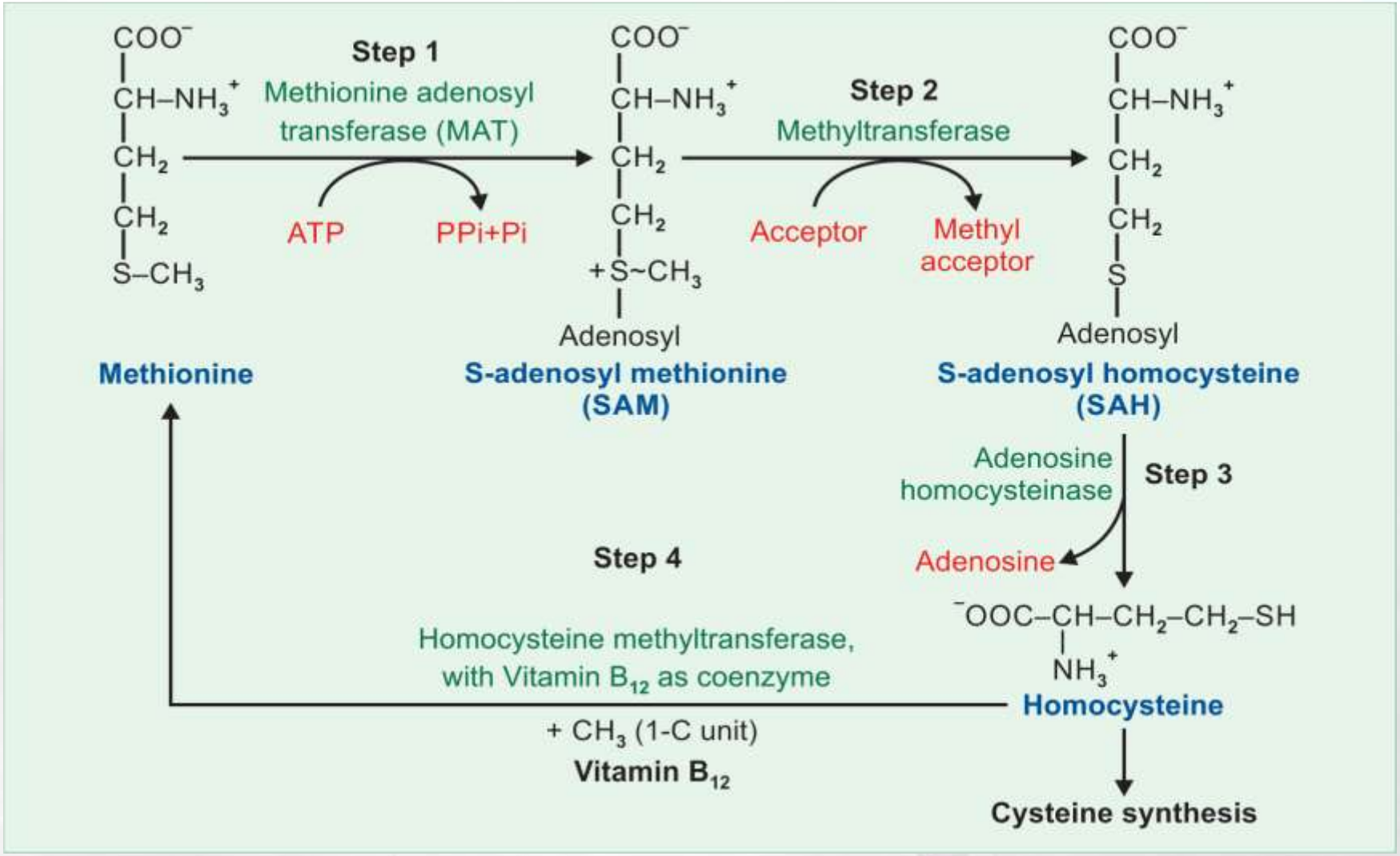
Threonine (THR) (T)

- It is an essential amino acid. It is glucogenic.
- Threonine has 2 asymmetric carbon atoms, hence it has 4 diastereoisomers, namely, D-threonine, L-threonine, Lallothreonine and D-allothreonine.
- Threonine does not directly undergo transamination, but undergoes deamination forming alpha ketobutyric acid.
- The enzyme is threonine dehydratase.
- The OH group of threonine residue in protein serves to provide a site for phosphorylation (as in the case of serine).
- This OH group also serves for combining carbohydrate residues to proteins, so as to make glycoproteins.

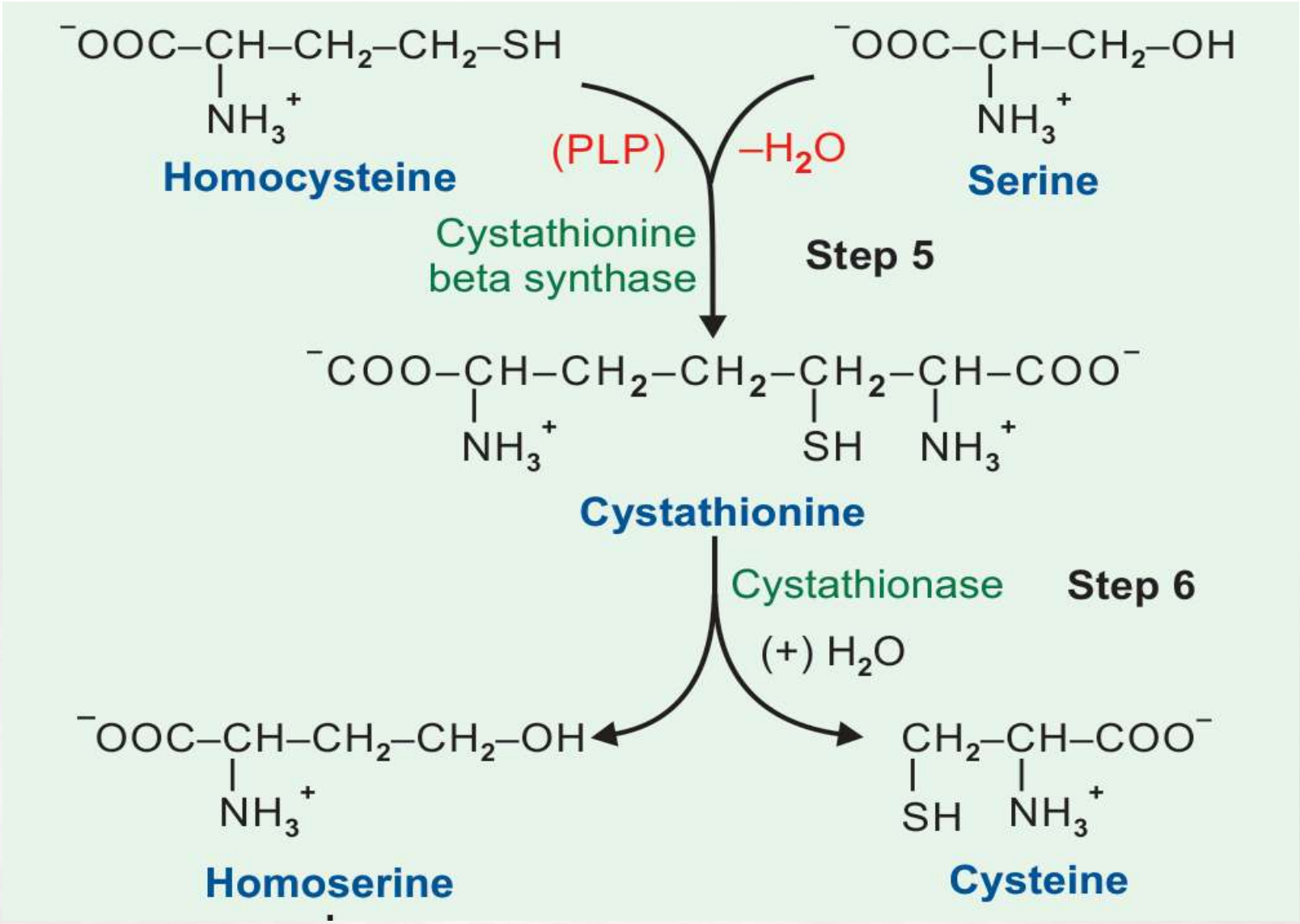
Methionine (MET) (M)

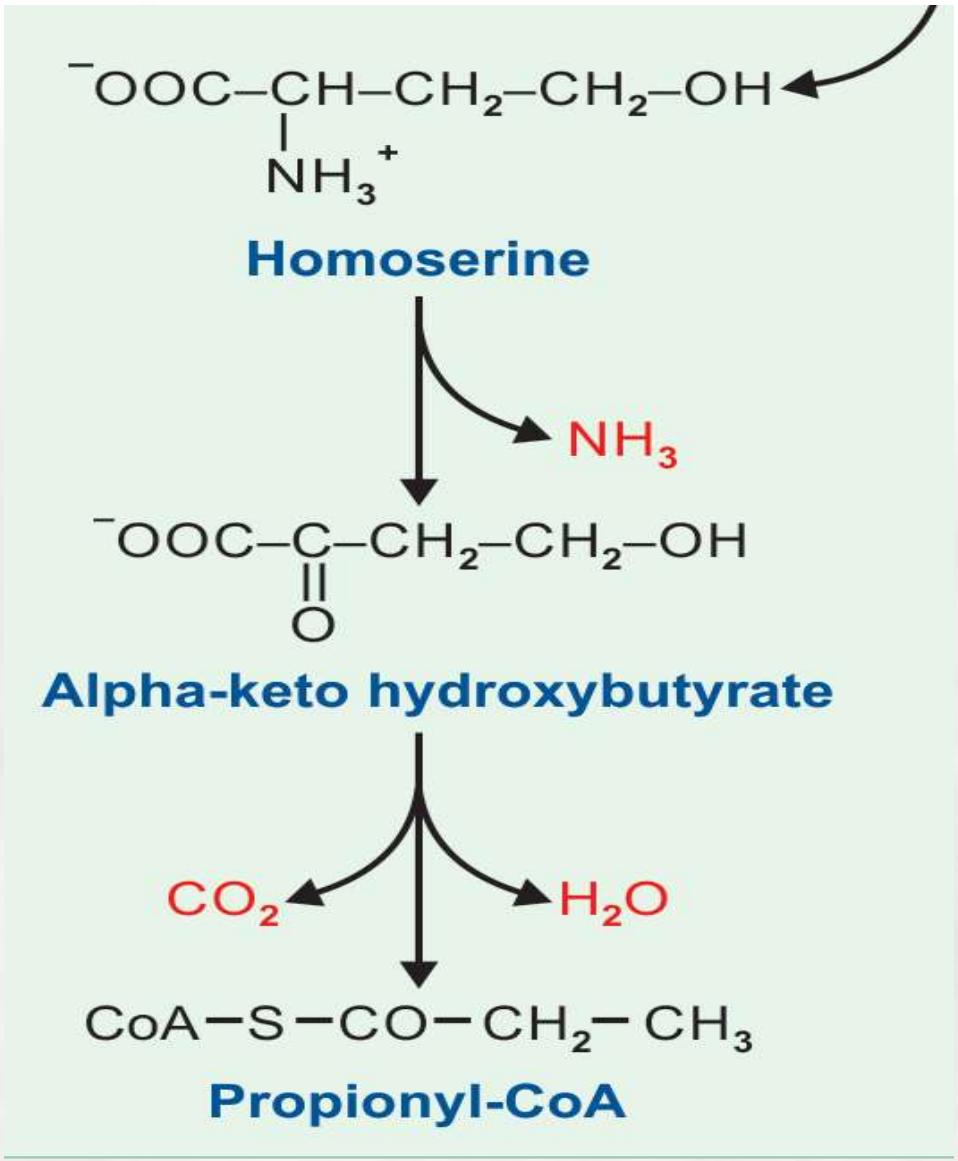
- It is **sulfur-containing, essential, glucogenic** amino acid.
- Degradation of methionine results in the synthesis of cysteine.
- The sparing action of cysteine on methionine is thus explained.

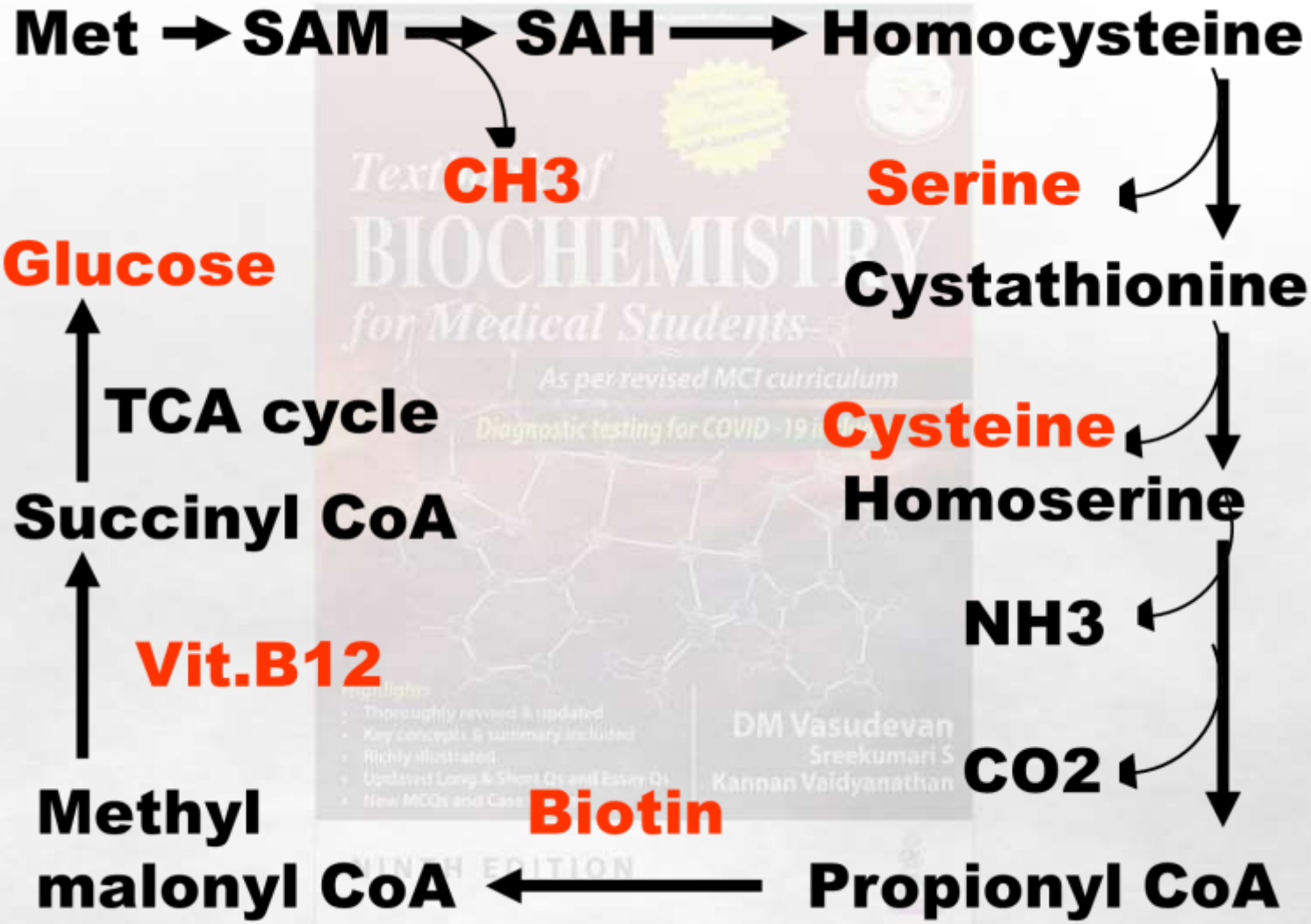


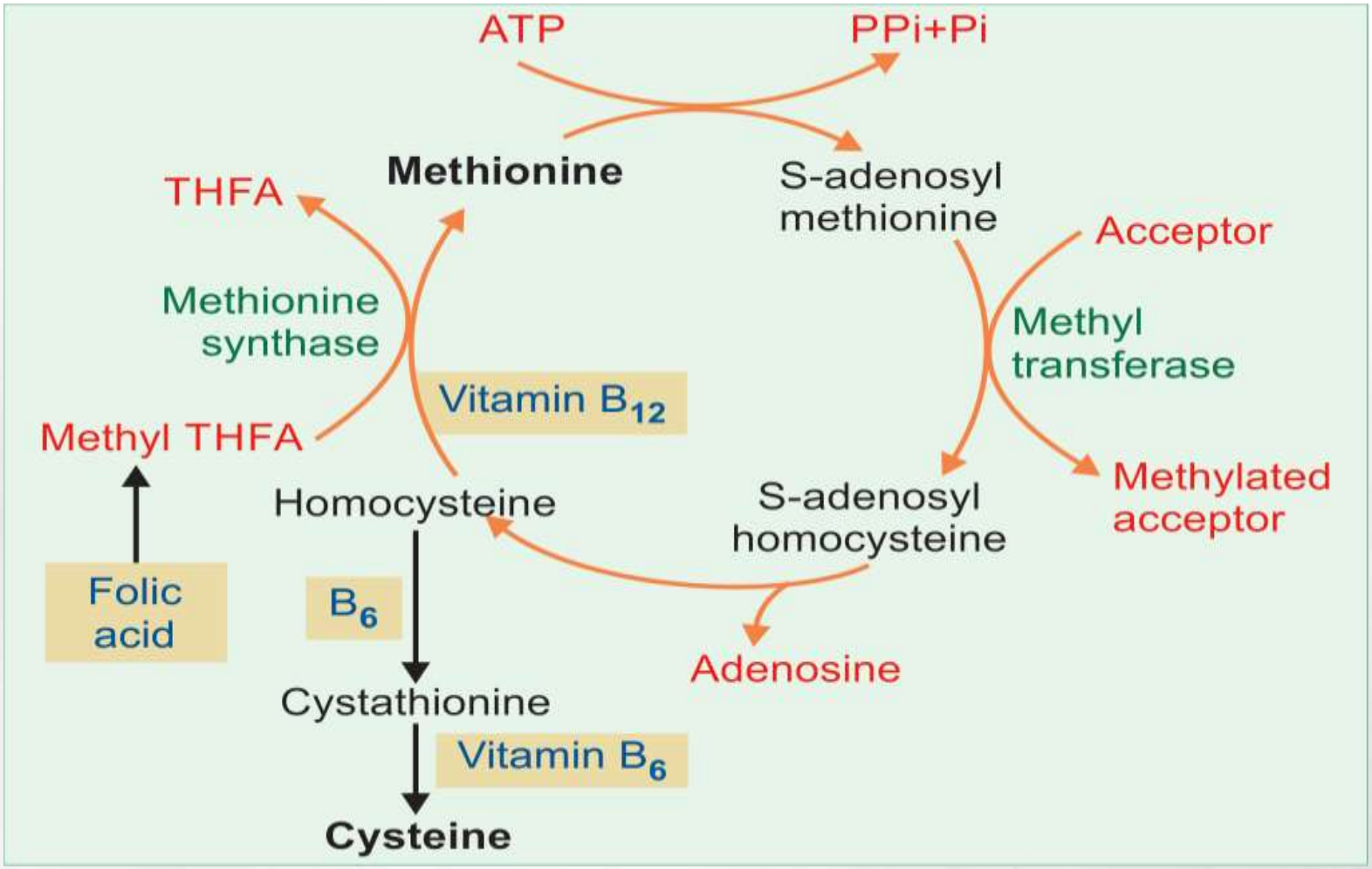


Formation of active methionine

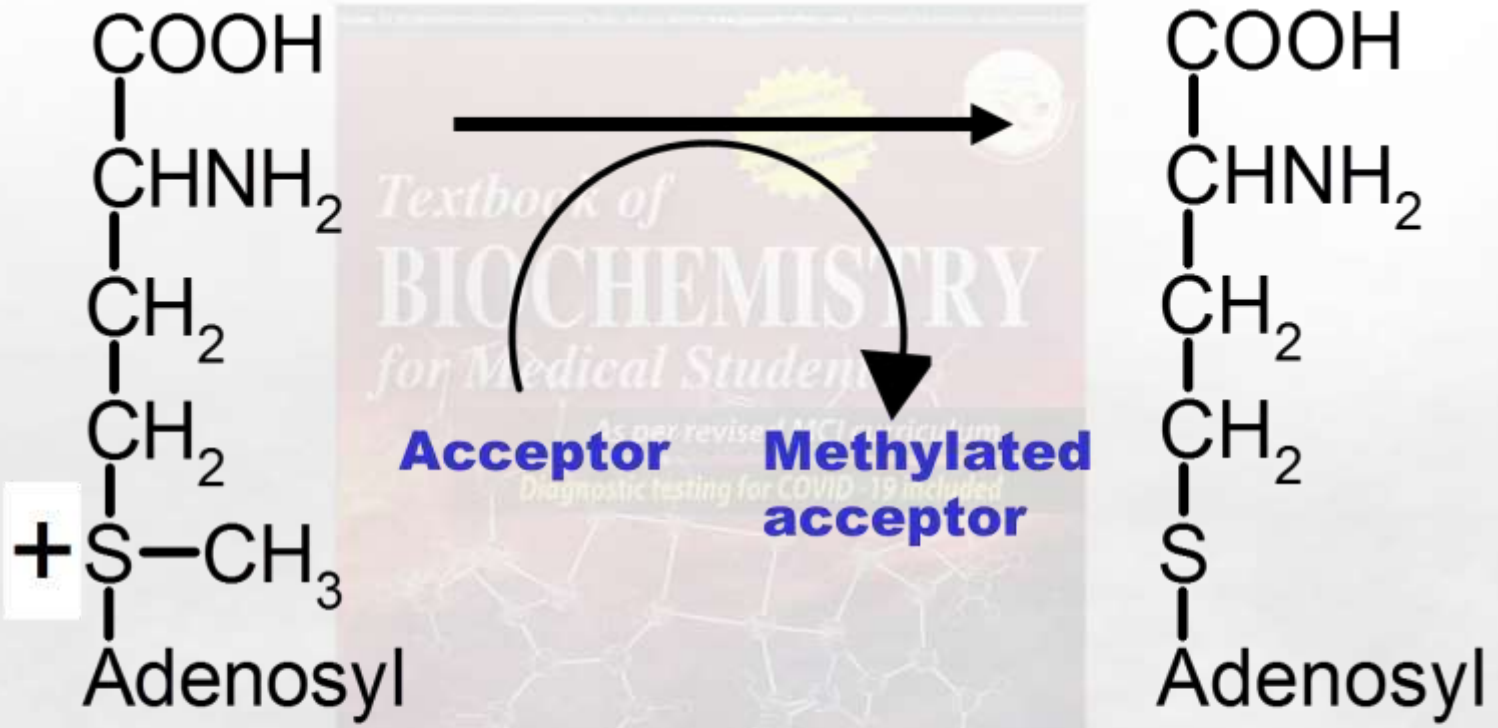

Homocysteine
Serine
(PLP)
–H2O
Cystathionine beta synthase
Step 5
Cystathionine
Cystathionase
Step 6
(+) H2O
Homoserine
Cysteine


$^{-}OOC-CH-CH_2-CH_2-OH$
NH_3^+
Homoserine
NH_3
$^{-}OOC-C-CH_2-CH_2-OH$
O
Alpha-keto hydroxybutyrate
CO_2
H_2O
$CoA-S-CO-CH_2-CH_3$
Propionyl-CoA


Met
SAM
SAH
Homocysteine
CH3
Serine
Glucose
Cystathionine
TCA cycle
Cysteine
Homoserine
Succinyl CoA
NH3
Vit.B12
CO2
Methyl malonyl CoA
Biotin
Propionyl CoA



Conversion of methionine to cysteine.
Note the role played by the vitamins



S-adenosyl methionine (SAM)

S-adenosyl homocysteine (SAH)

Transmethylation Reactions

Methyl acceptor	Methylated product
Guanido acetic acid	Creatine
Nicotinamide	N-methyl nicotinamide
Norepinephrine	Epinephrine
Epinephrine	Metanephrine
Norepinephrine	Normetanephrine
Ethanolamine	Choline
Carnosine	Anserine
Acetyl serotonin	Melatonin
Serine	Choline
Histidine	Methyl histidine
Lysine	Methyl lysine
tRNA	Methylated tRNA


Homocysteine
Serine
Cystathionine synthase (PLP)
Homocystinuria
Cystathionine

Homocystinurias

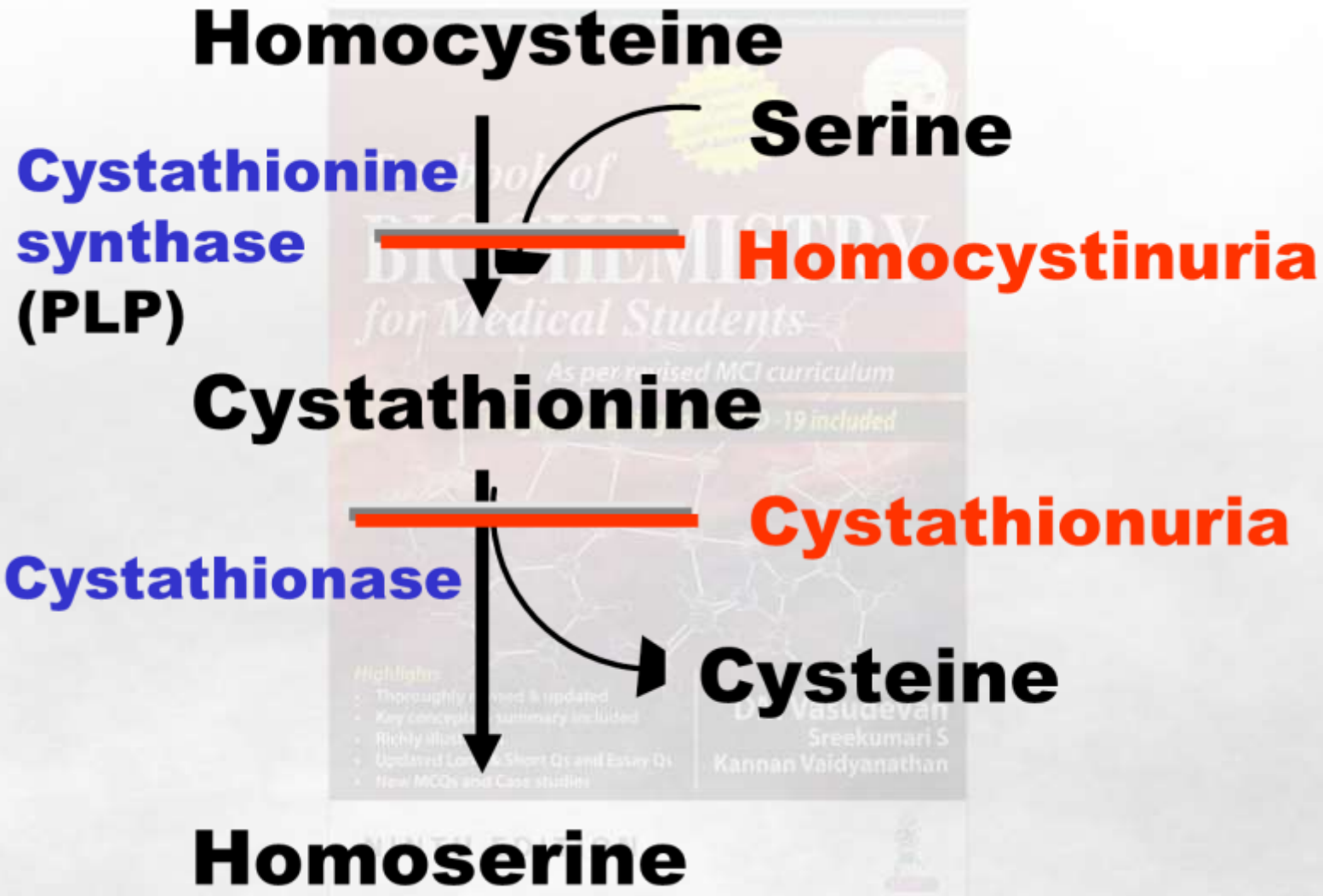
- All of them are autosomal recessive conditions.
- Incidence is 1 in 200,000 births.
- Normal homocysteine level in blood is 5–15 micromol/L.
- In diseases, it may be increased to 50 to 100 times.
- Moderate increase is seen in aged persons, vitamin B12 or B6 deficiency, tobacco smokers, alcoholics and in hypothyroidism.
- Substantial increase is noticed in congenital diseases.
- Large amounts of homocystine are excreted in urine.
- In plasma, homocysteine (with -SH group) and homocystine (disulfide, -S-S- group) exist.
- Both of them are absent in normal urine; but if present, it will be the homocystine (disulfide) form.

- If homocysteine level in blood is increased, there is increased risk for coronary artery diseases.
- An increase of 5 micromol/L of homocysteine in serum elevates the risk of coronary artery disease by as much as cholesterol increase of 20 mg/dl.
- Homocysteine interacts with lysyl residues of collagen and bind to fibrillin producing endothelial dysfunction.
- Providing adequate quantity of pyridoxine, vitamin B12 and folic acid will keep homocysteine in blood at normal levels.

Cystathionine Beta Synthase Deficiency

- It causes elevated plasma levels of methionine and homocysteine.
- There is increased excretion of methionine and homocystine in urine.
- Plasma cysteine is markedly reduced.
- General symptoms are **mental retardation** and **Charley Chaplin gait**.
- Skeletal deformities are also seen.
- In eyes, **ectopia lentis** (subluxation of lens), myopia and glaucoma may be observed.
- Homocysteine causes activation of Hageman's factor.
- This may lead to increased platelet adhesiveness and life-threatening intravascular **thrombosis**.

- **Cyanide-nitroprusside** test will be positive in urine.
- Urinary excretion of homocystine is more than 300 mg/24 h.
- Plasma homocysteine and methionine levels are increased.
- **Treatment** is a diet **low in methionine** and rich in cysteine.
- Sometimes the affinity of apoenzyme to the co-enzyme is reduced. In such cases, pyridoxal phosphate, the co-enzyme given in large quantities (500 mg) will correct the defect.


Homocysteine
Serine
Cystathionine synthase (PLP)
Homocystinuria
Cystathionine
Cystathionuria
Cystathionase
Cysteine
Homoserine

Cystathioninuria

Cystathionase deficiency

Recessive inheritance

Severe mental retardation

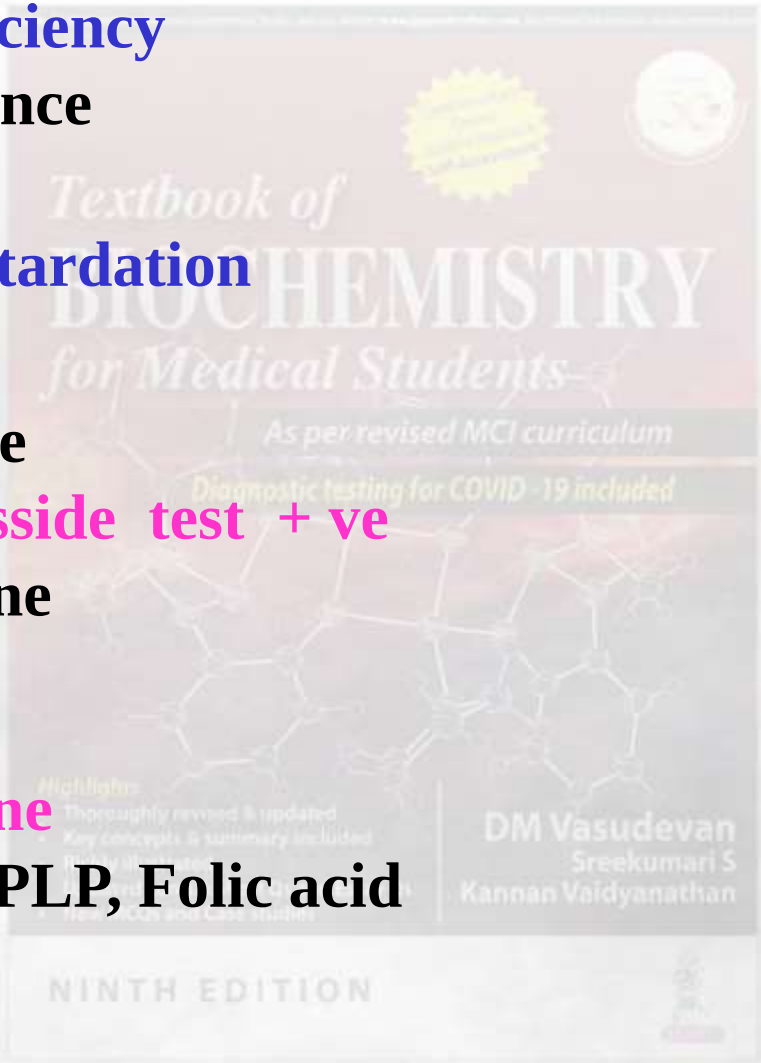
Urine cystathionine

Cyanide-Nitroprusside test + ve

Blood: cystathionine

Restrict Methionine

Supplement: Cys, PLP, Folic acid

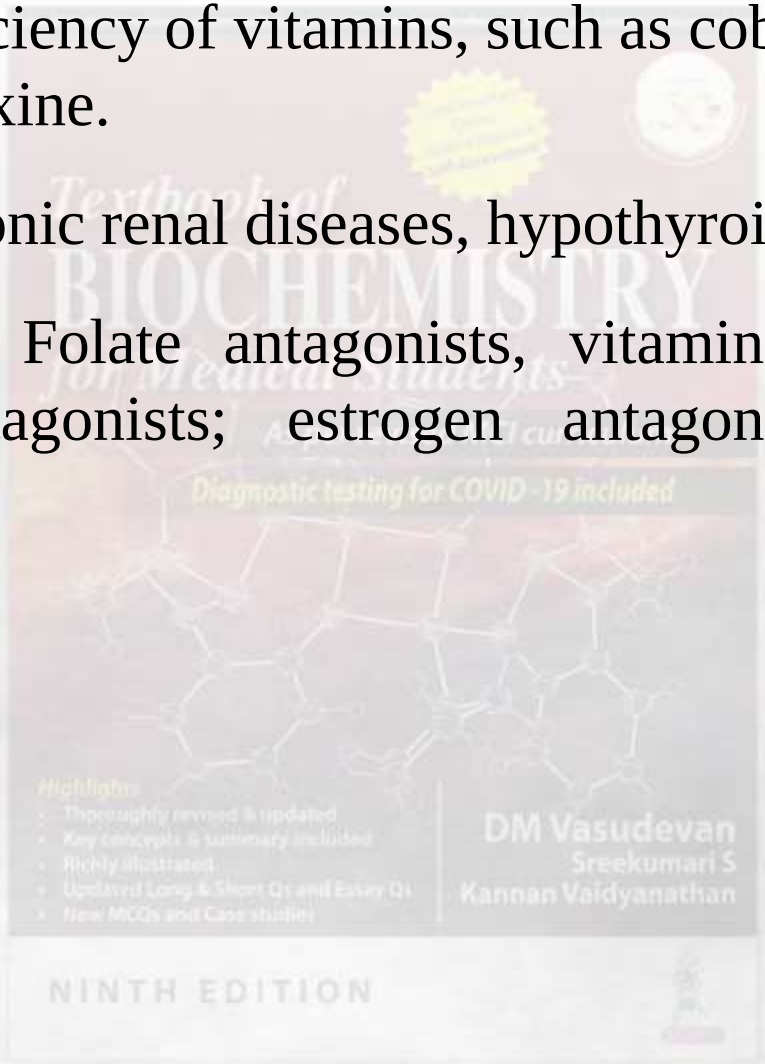


Acquired Hyperhomocysteinemias

a. Nutritional deficiency of vitamins, such as cobalamin, folic acid and pyridoxine.

b. Metabolic: Chronic renal diseases, hypothyroidism.

c. Drug induced: Folate antagonists, vitamin B12 antagonists; pyridoxine antagonists; estrogen antagonists, nitric oxide antagonists.



Amino Acidurias Related to Sulphur Containing Amino Acids

	Cystinuria	Homo-cystinuria	Cystathioni-nuria
Deficiency in	Transport system	Cystathionine synthase	Cystathio-nase
Mental retardation	–	+++	+++
Tissue deposition	–	–	–
Ectopia lentis	–	+	–
Thrombosis	–	+	–
Renal insufficiency	Late	–	–
Renal calculi and crystalluria	+	–	–

	Cystinuria	Homo-cystinuria	Cystathioni-nuria
Amino aciduria	Cystine	Homocystine	Cystathio-nine
Amino acid increased in blood	–	Methionine, Homo-cysteine	Cystathio-nine
Nitroprusside test	++	+++	–
Supplement	Fluid and alkali	Cysteine, Pyridoxine	Cysteine
Restrict	–	Methionine	Met

Clinical Importance of Homocysteine Level in Blood

There is some evidence to associate the increase in homocysteine level in blood and myocardial infarction.

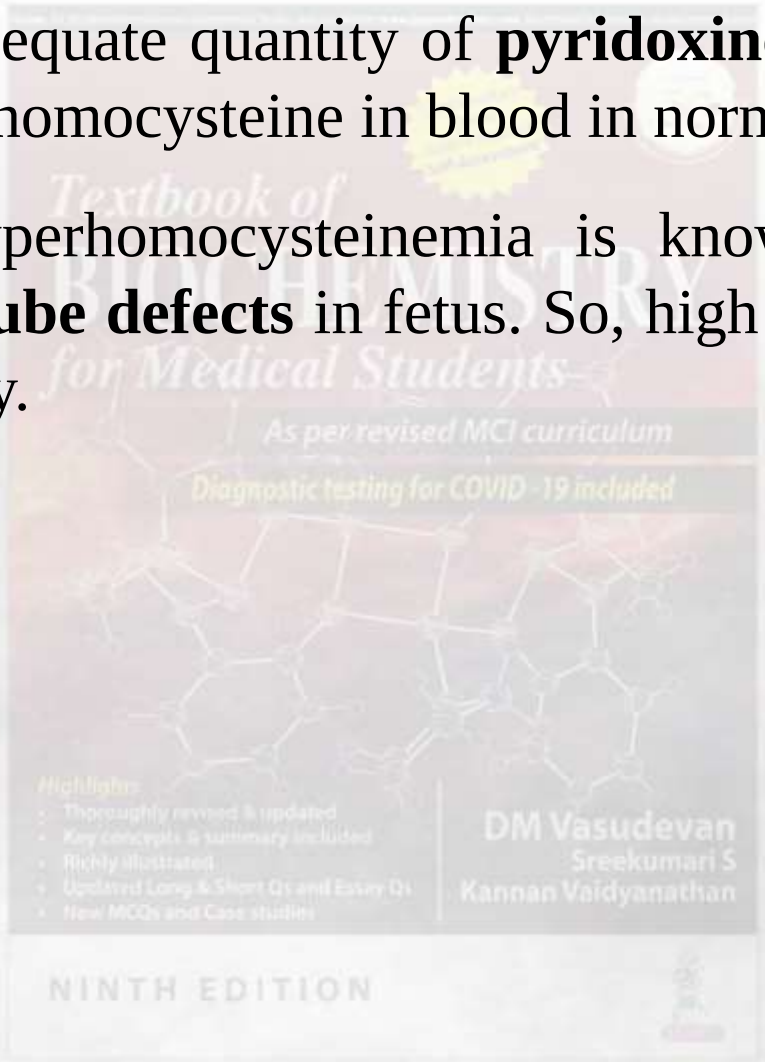
However, this association is weak, and this is only a minor cause for heart attack. An increase of 5 mmol/L of homocysteine in serum elevates the risk of coronary artery disease equivalent to an increase of cholesterol of 20 mg/dl.

Homocysteine interacts with lysyl residues of collagen interfering with **collagen** cross linking.

It forms homocysteine thiolactone, a free radical which thiolates LDL particles. They tend to aggregate and increase the tendency for atherogenesis.

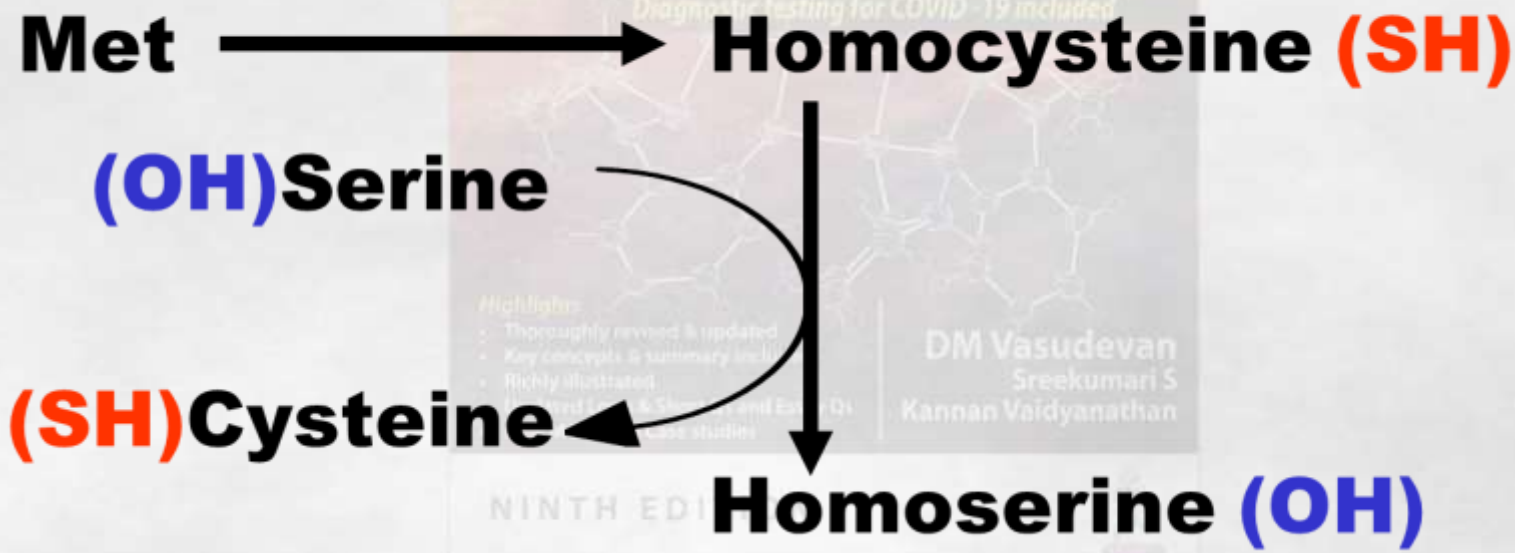
Providing adequate quantity of **pyridoxine, vitamin B12 and folic acid** will keep homocysteine in blood in normal levels.

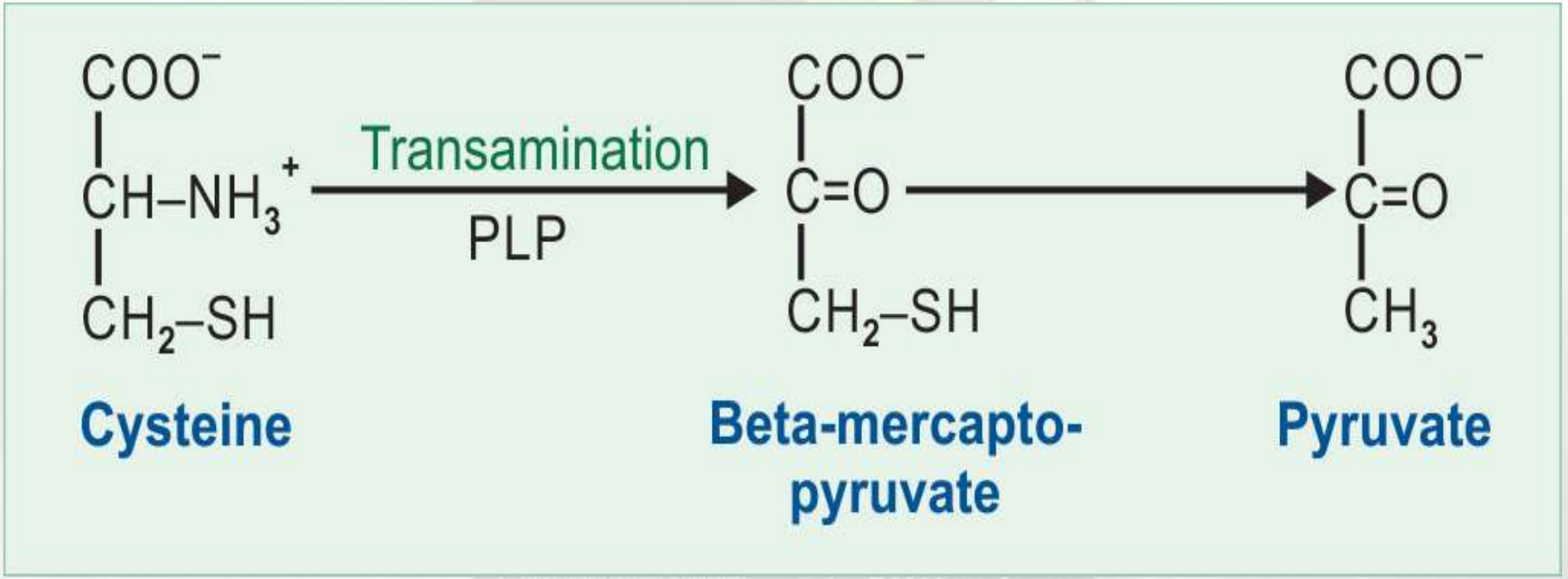
Maternal hyperhomocysteinemia is known to increase the chances of **neural tube defects** in fetus. So, high dose of folic acid is advised in pregnancy.



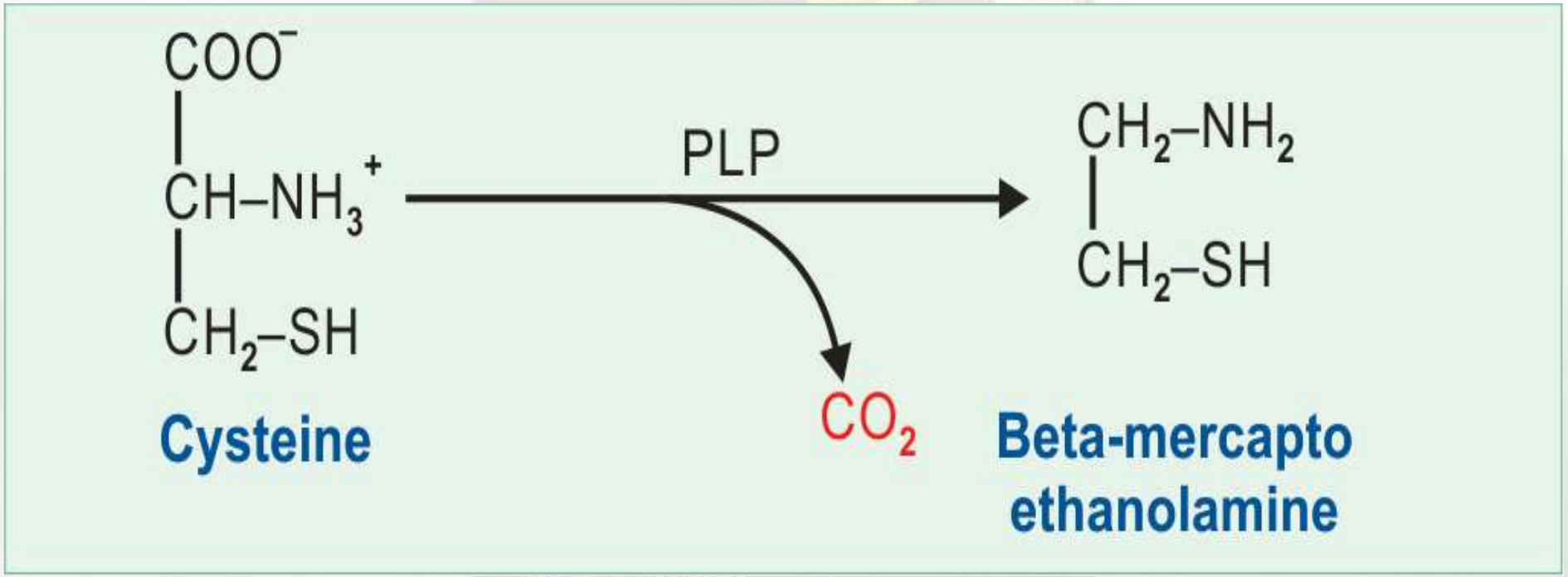
Cysteine Cys C

Suphur containing
Non-essential
Glucogenic

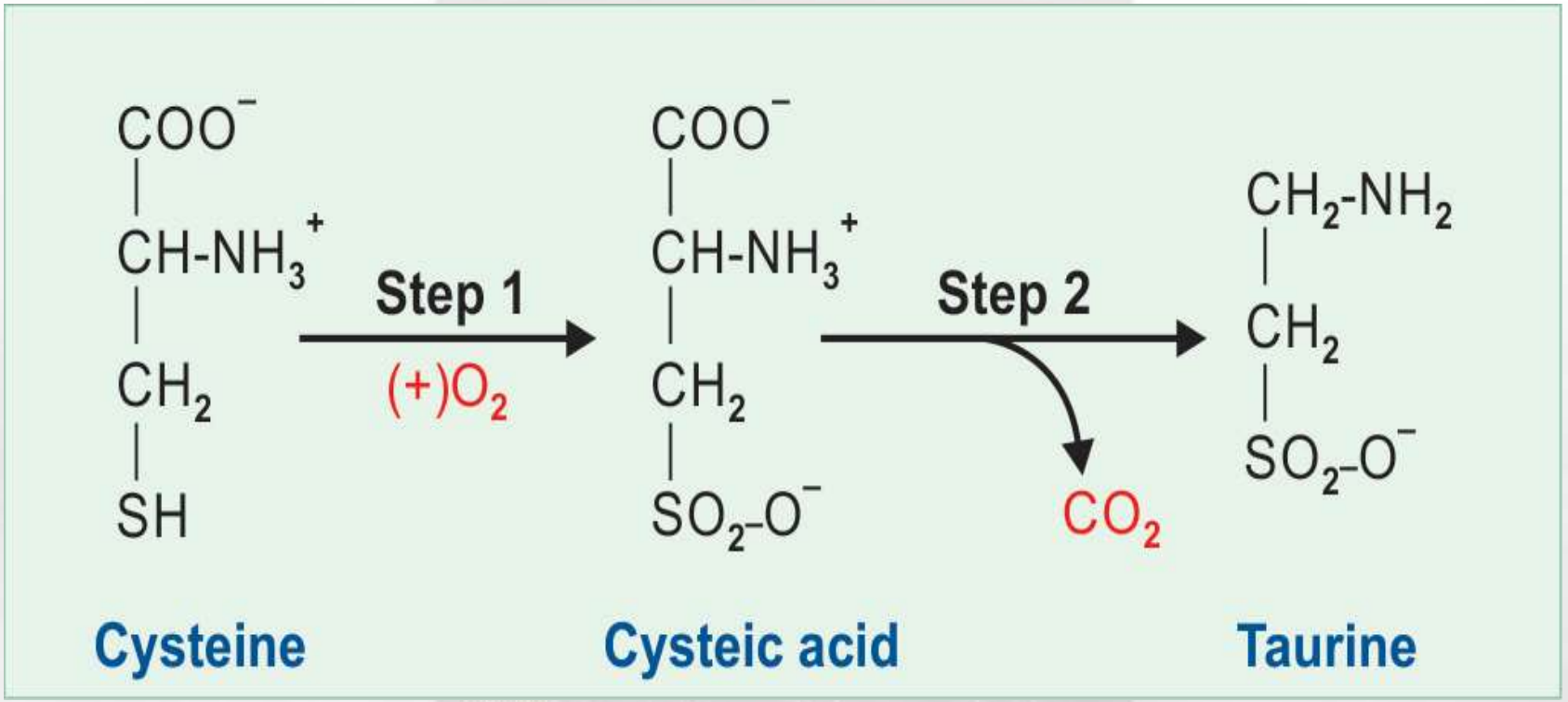




Pyruvate formation from cysteine

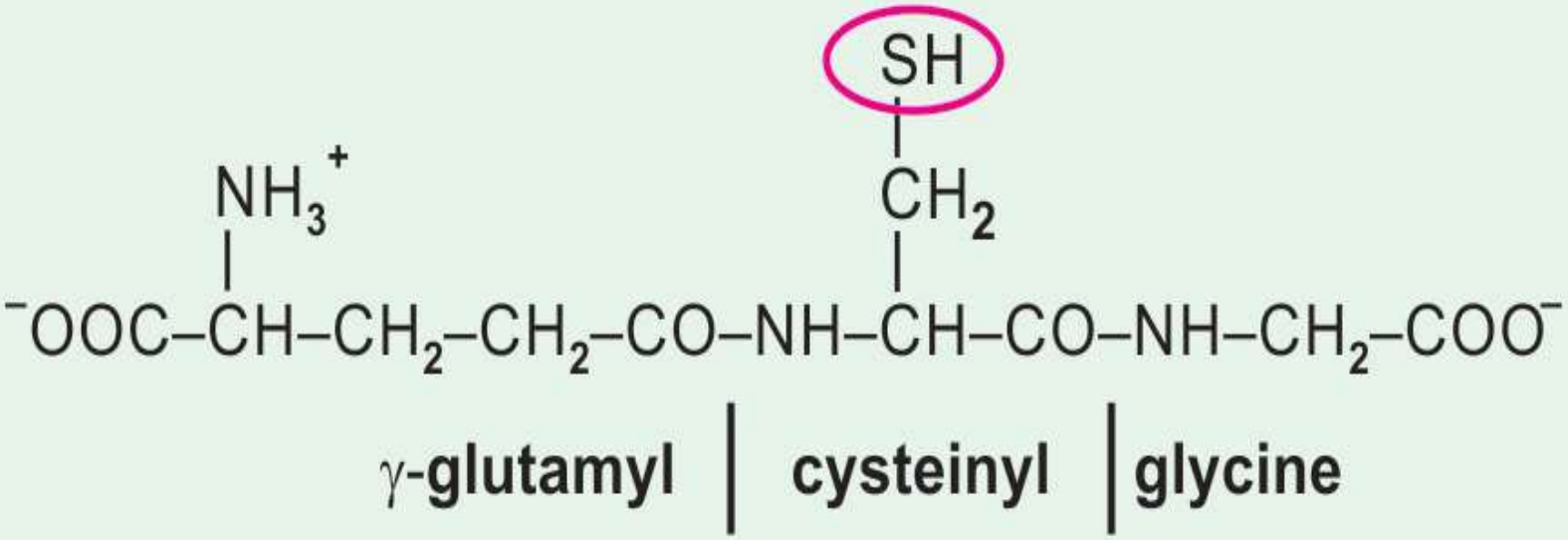


Decarboxylation of cysteine



Formation of taurine from cysteine.

Taurine + Cholyl-CoA → Taurocholate + CoA-SH



Glutathione.

Glutathione GSH

Gamma glutamyl cysteinyl glycine

1. Amino acid absorption

2. Reduction reactions
   a) Maleayl acetoacetate to fumaryl acetoacetate
   b) Fe 3+ to Fe 2+

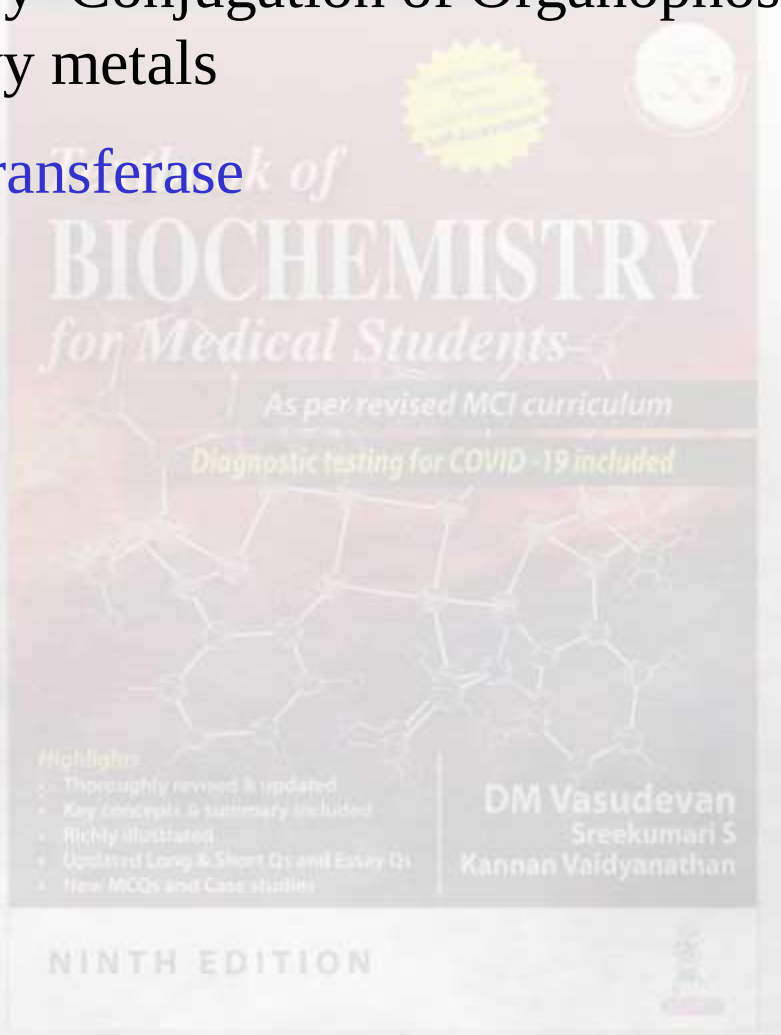
3. Keep enzymes in active state

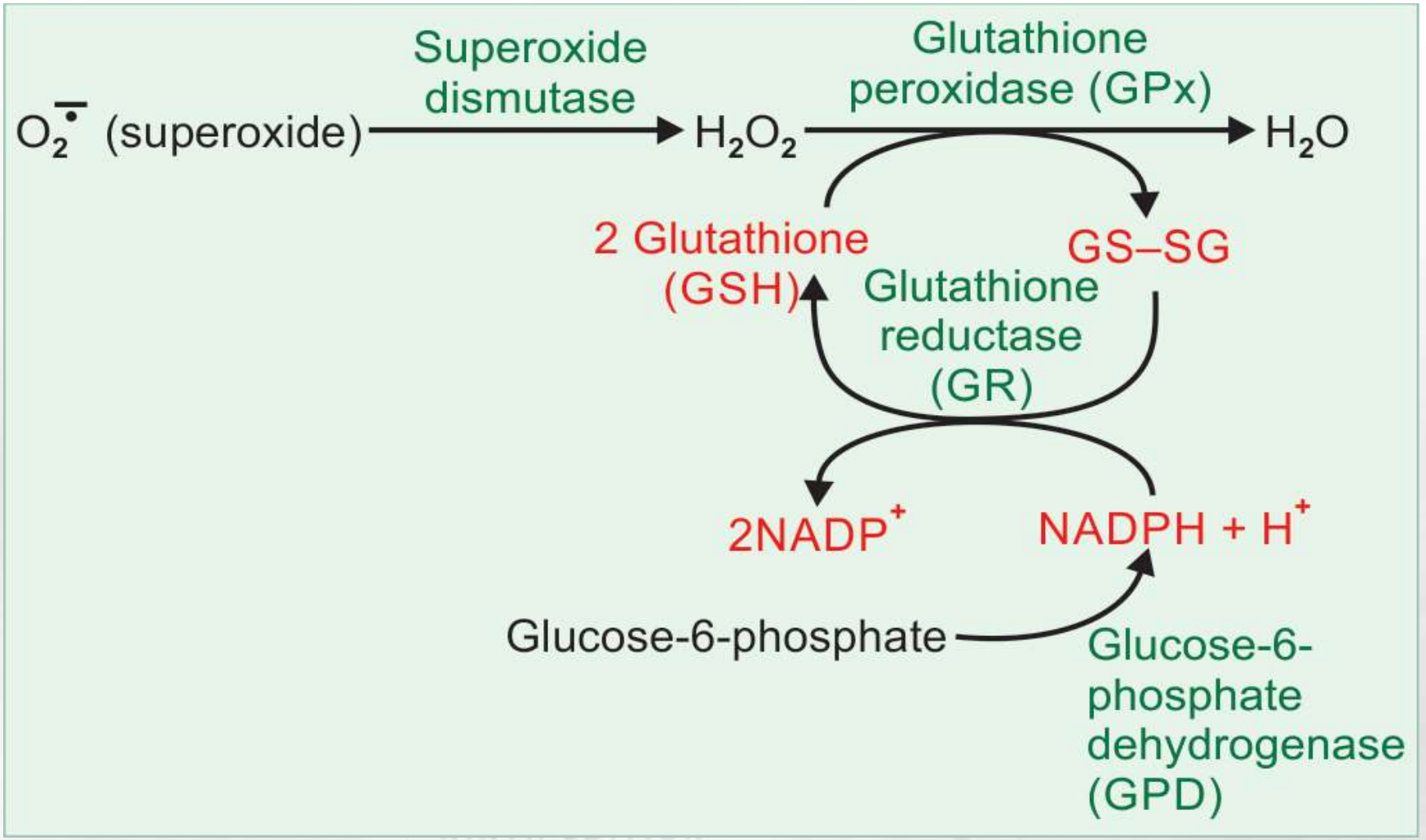
4. RBC membrane integrity
   GSH is maximally seen inside RBC

5. Met hemoglobin to Hemoglobin
   Fe3+ to Fe 2+

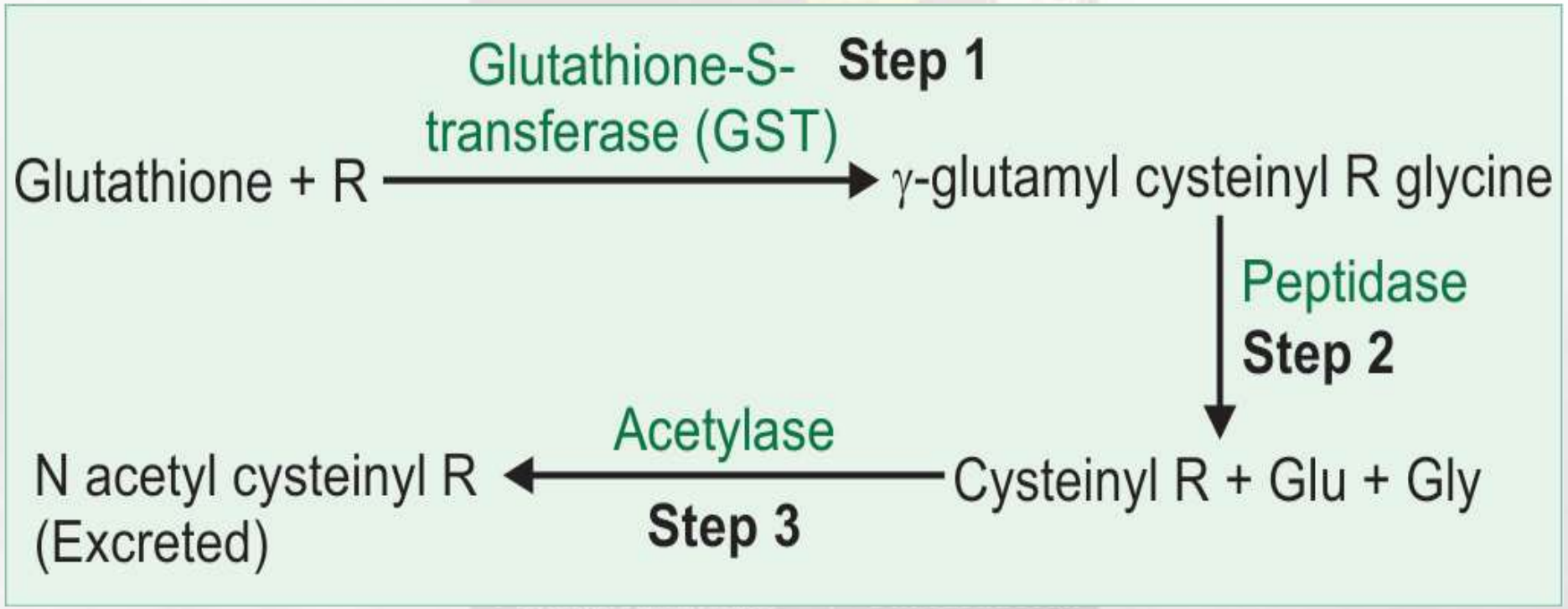
6. Detoxification by Conjugation of Organophosphorus compounds heavy metals

Glutathione-S-transferase





Free radical scavenging by glutathione



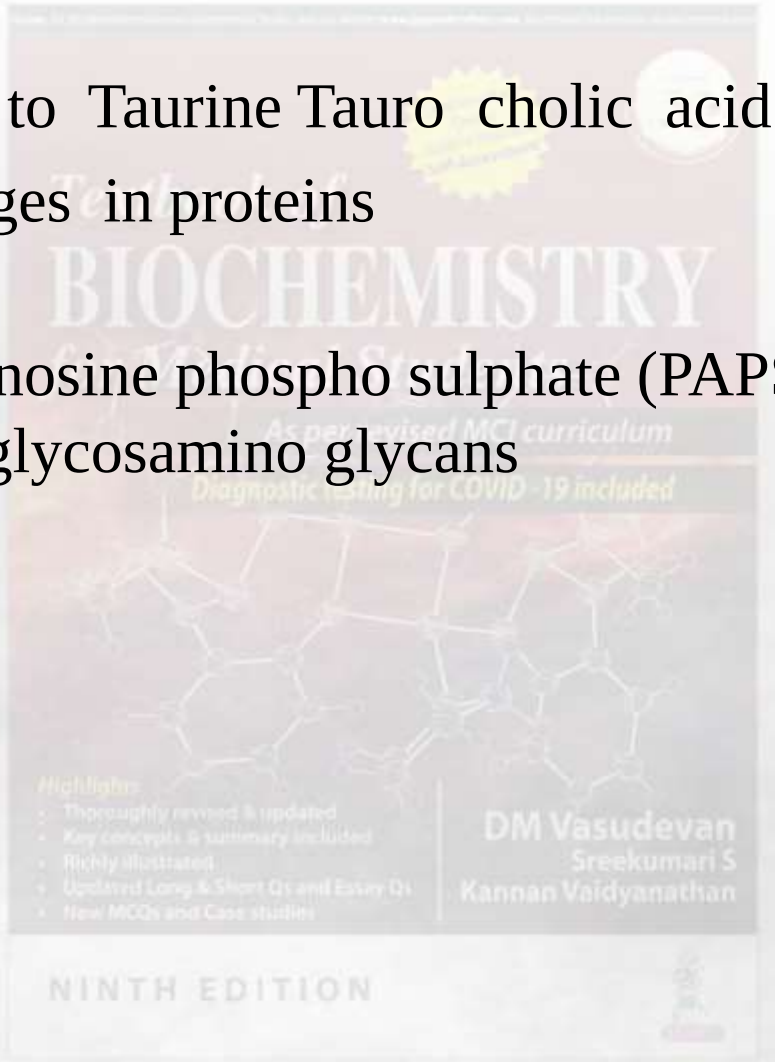
Detoxification by glutathione.

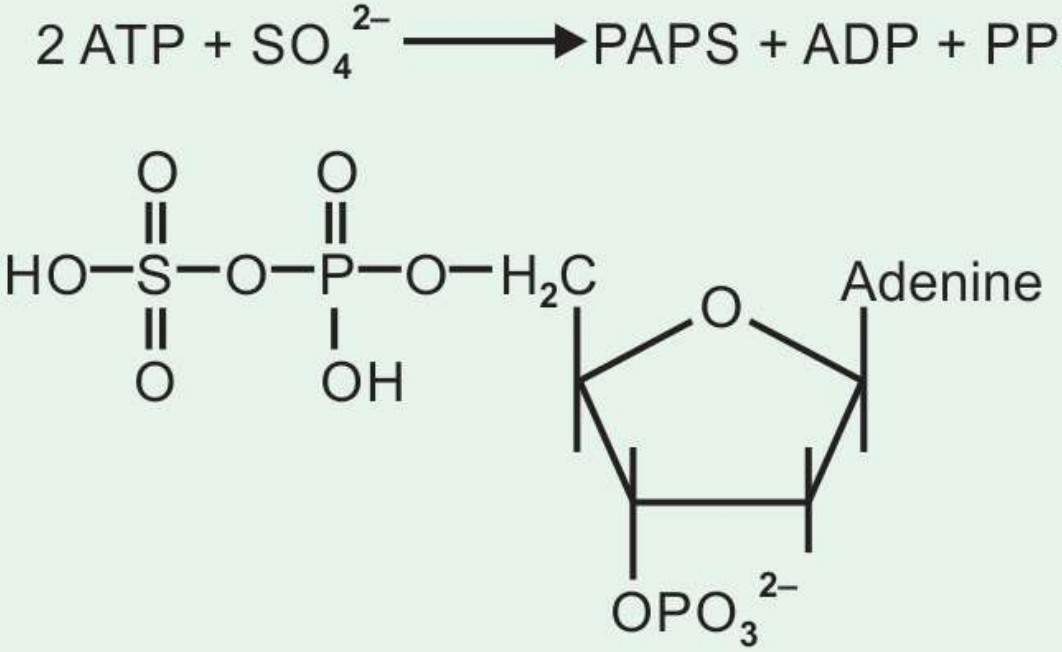
Cysteine

1. Glutathione
2. Decarboxylated to Taurine Tauro cholic acid
3. Disulphide bridges in proteins
4. Active sulphate

   Phospho adenosine phospho sulphate (PAPS)

   Sulphatides glycosamino glycans

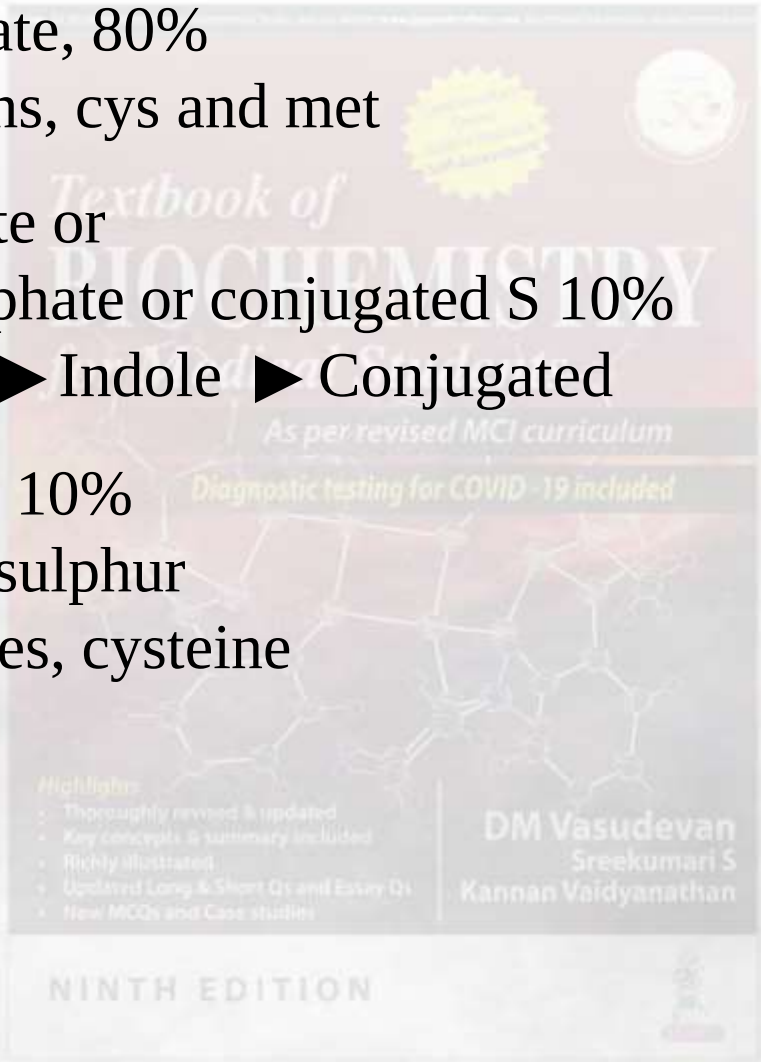


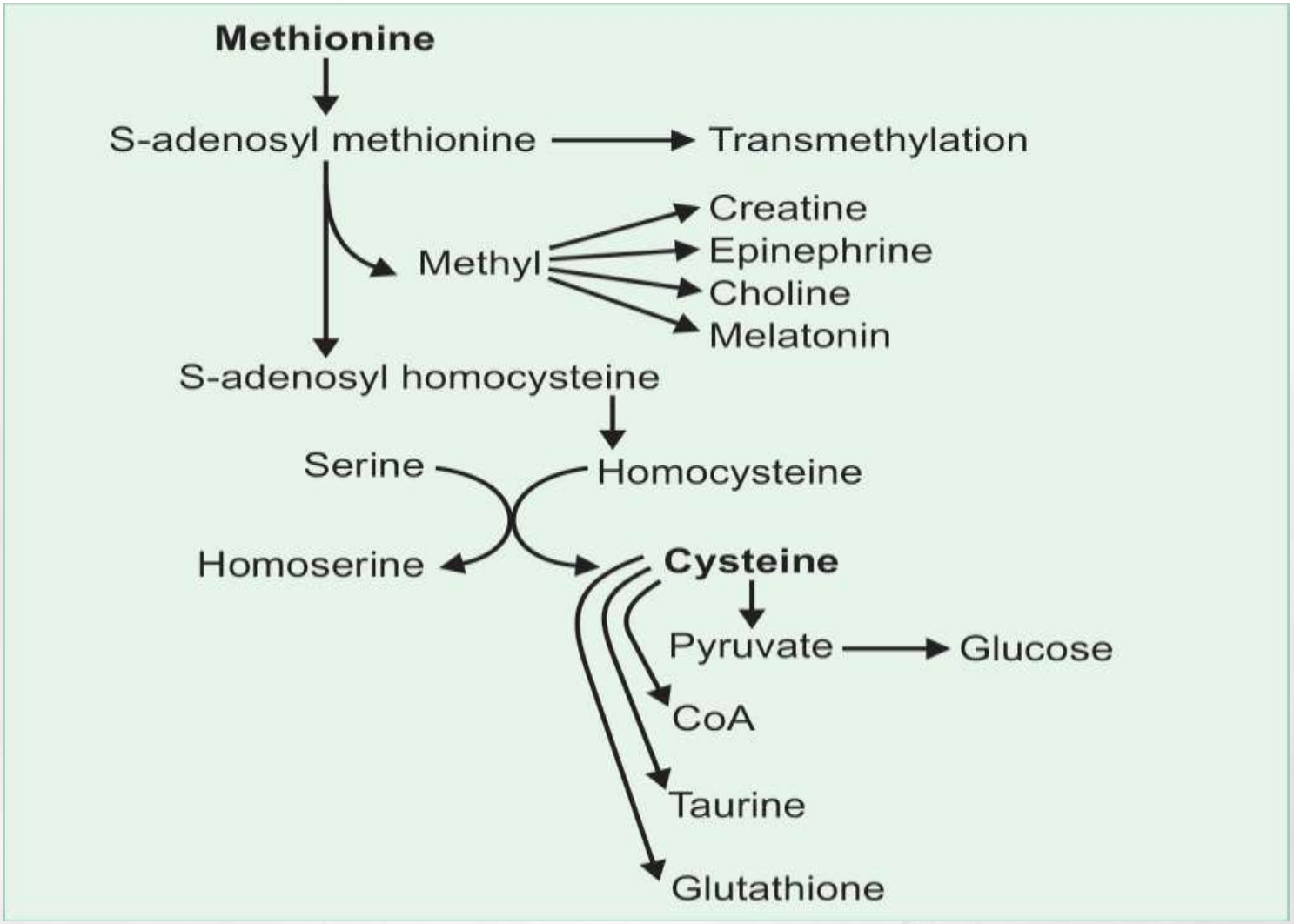


Phosphoadenosine phosphosulfate (PAPS) or active sulfur. Used for sulfuration reactions like synthesis of sulfatides, GAGs & Detoxification of alcoholic and phenolic compounds.

Sulphur in Urine

1. Inorganic sulphate, 80%
   From proteins, cys and met
2. Organic sulphate or
   Ethereal sulphate or conjugated S 10%
   Tryptophan ▶ Indole ▶ Conjugated
3. Neutral sulphur, 10%
   Unoxidised sulphur
   small peptides, cysteine





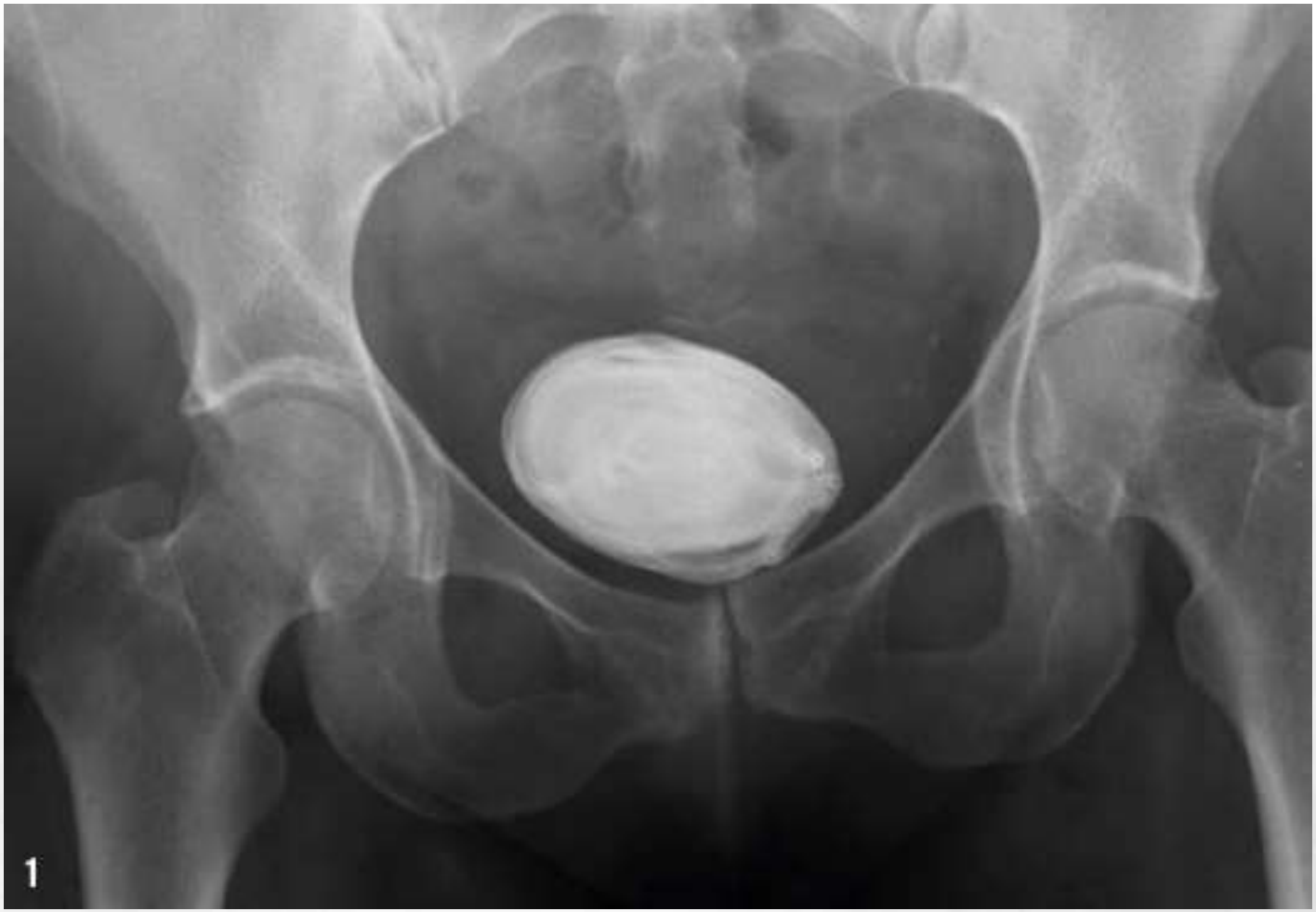
Summary of methionine and cysteine metabolisms

Cystinuria

- Cystinuria is one of the inborn errors of metabolism included in the Garrod's tetrad.
- It is an autosomal **recessive** condition.
- The disorder is attributed to the **deficiency in transport of amino acids**.
- Signs and symptoms include:
  i. Abnormal excretion of cystine and to a lesser extent lysine, ornithine and arginine. Hence the condition is also called **Cystine-lysinuria**.
  ii. Crystalluria and calculi formation. In acidic pH, cysteine crystals are formed in urine.
  iii. Obstructive uropathy, which may lead to renal insufficiency.

iv. Treatment is to increase urinary volume by increasing fluid intake. Solubility of cystine is increased by alkalanization of urine by giving sodium bicarbonate.

- **Cyanide-Nitroprusside Test**
- It is a screening test.
- Urine is made alkaline with ammonium hydroxide and sodium cyanide is added.
- Cystine, if present, is reduced to cysteine.
- Then add sodium nitroprusside to get a magenta-red colored complex.
- Specific aminoaciduria may be confirmed by chromatography.



Cystine stone in the bladder.

Cystinosis

- It is a familial disorder characterized by the widespread deposition of cystine crystals in the lysosomes.
- Cystine accumulates in liver, spleen, and bone marrow.
- There is an abnormality in transport of cysteine which is responsible for the accumulation.
- It is an autosomal recessive condition.
- Microscopy of blood shows cystine crystals in WBCs.
- Treatment policies are to give adequate fluid so as to increase urine output, alkalinization of urine by sodium bicarbonate, as well as administration of D-penicillamine.