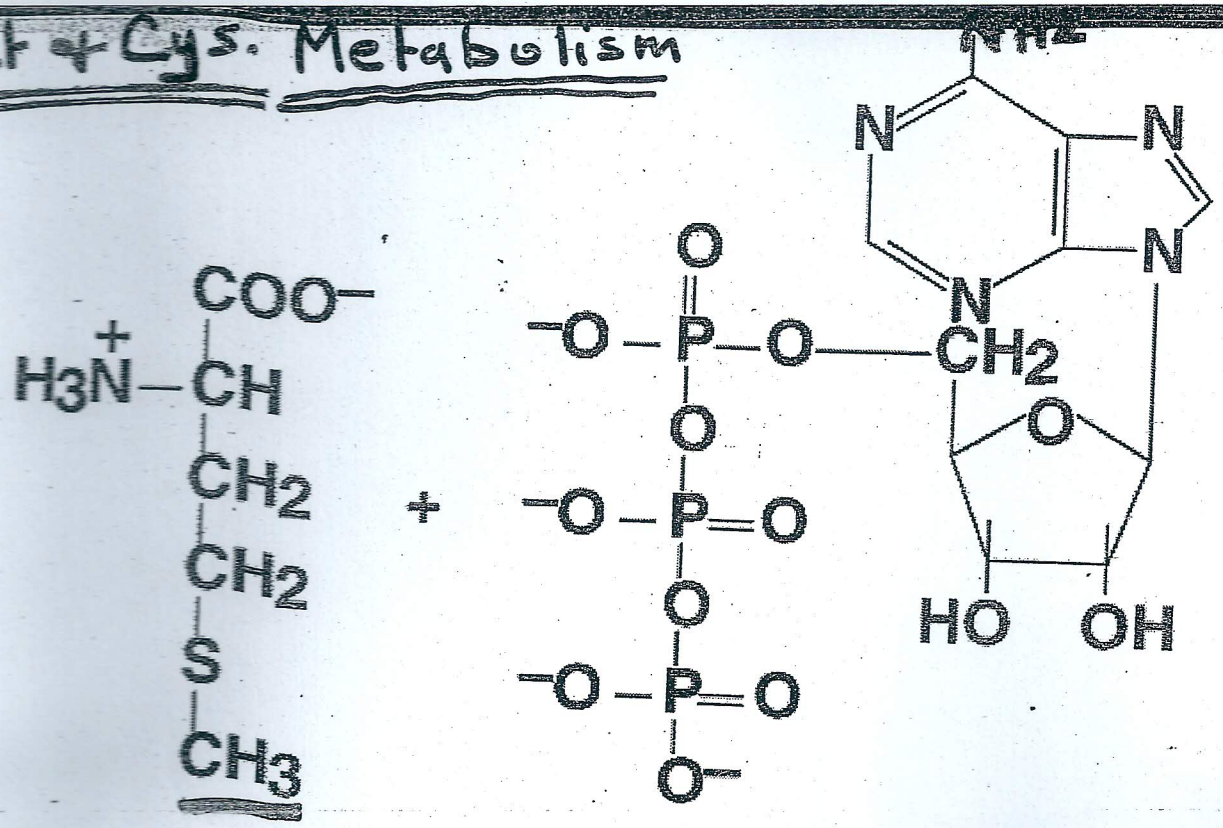
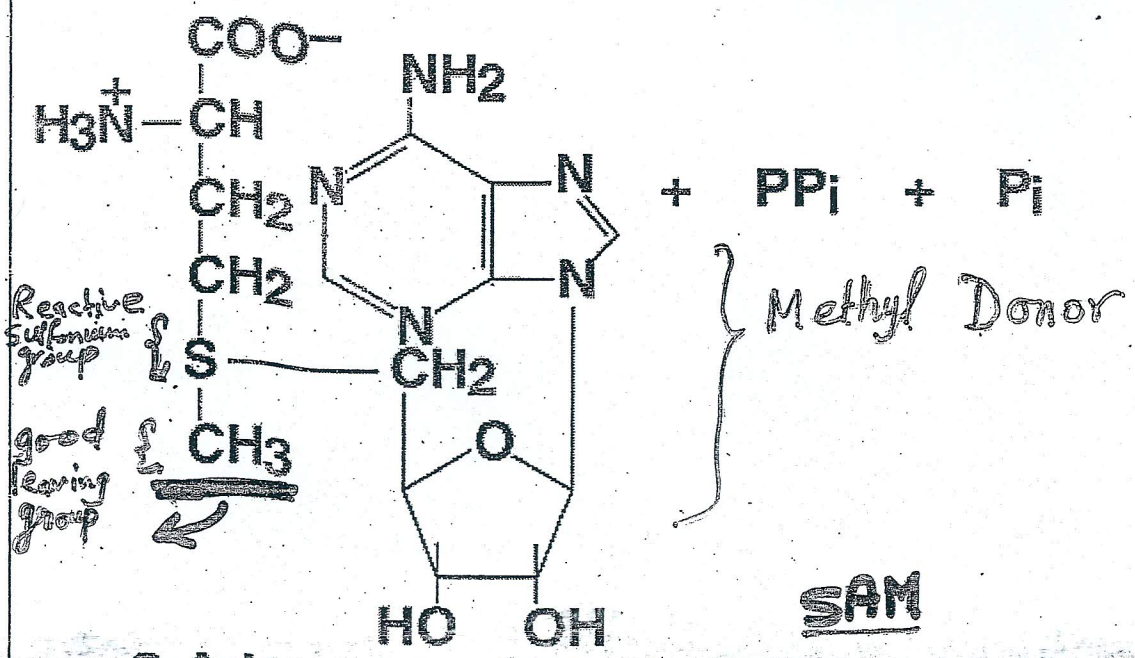
(13)

Met + Cys. Metabolism



Methionine + **ATP**

methionine adenosyltransferase



SAM

S-Adenosylmethionine (AdoMet)

(12)

2

Metabolism of Methionine

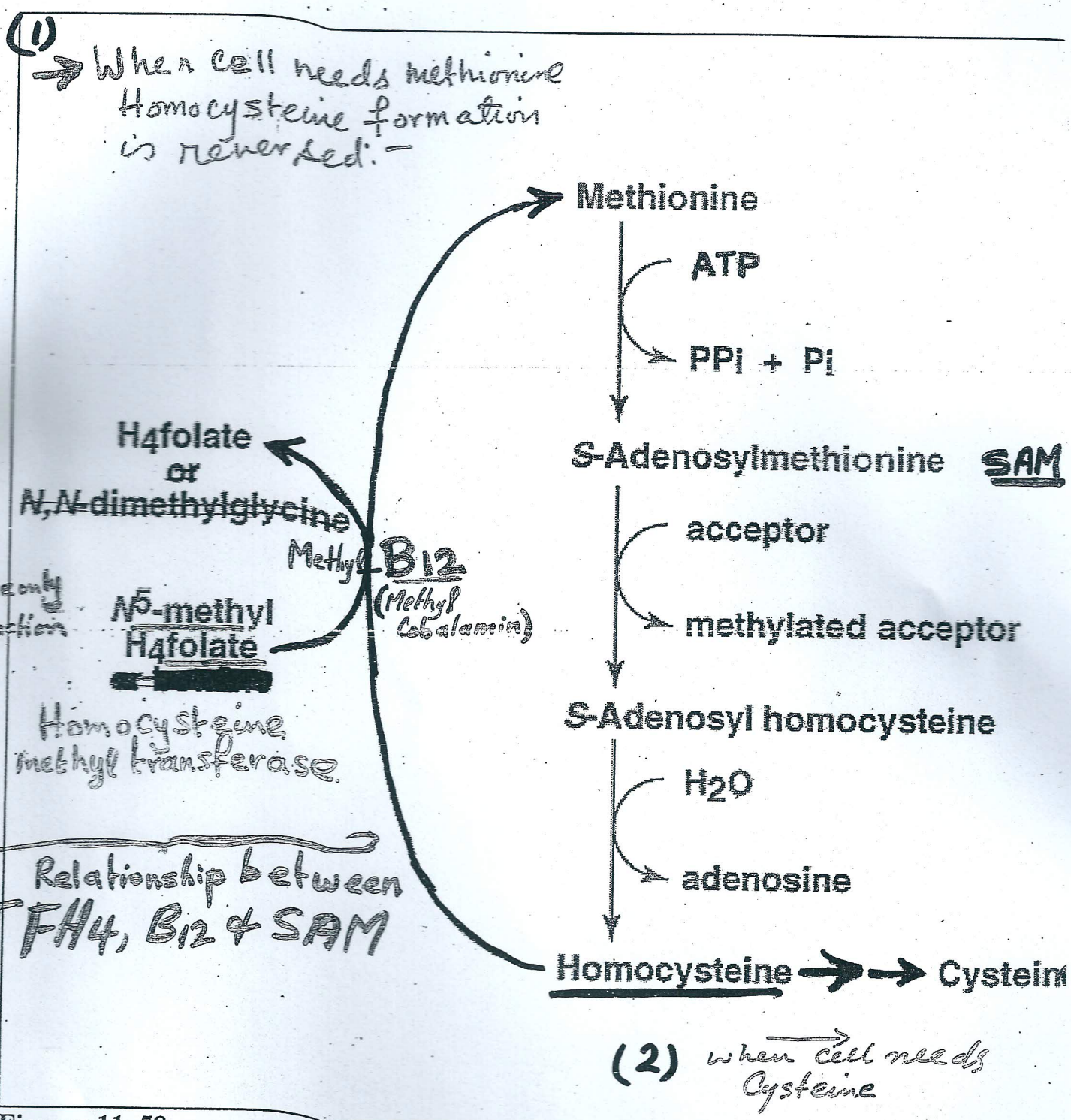


Figure: 11_58
Resynthesis of methionine, a methylcobalamin-dependent reaction.

(11)

When cell needs Cysteine :-

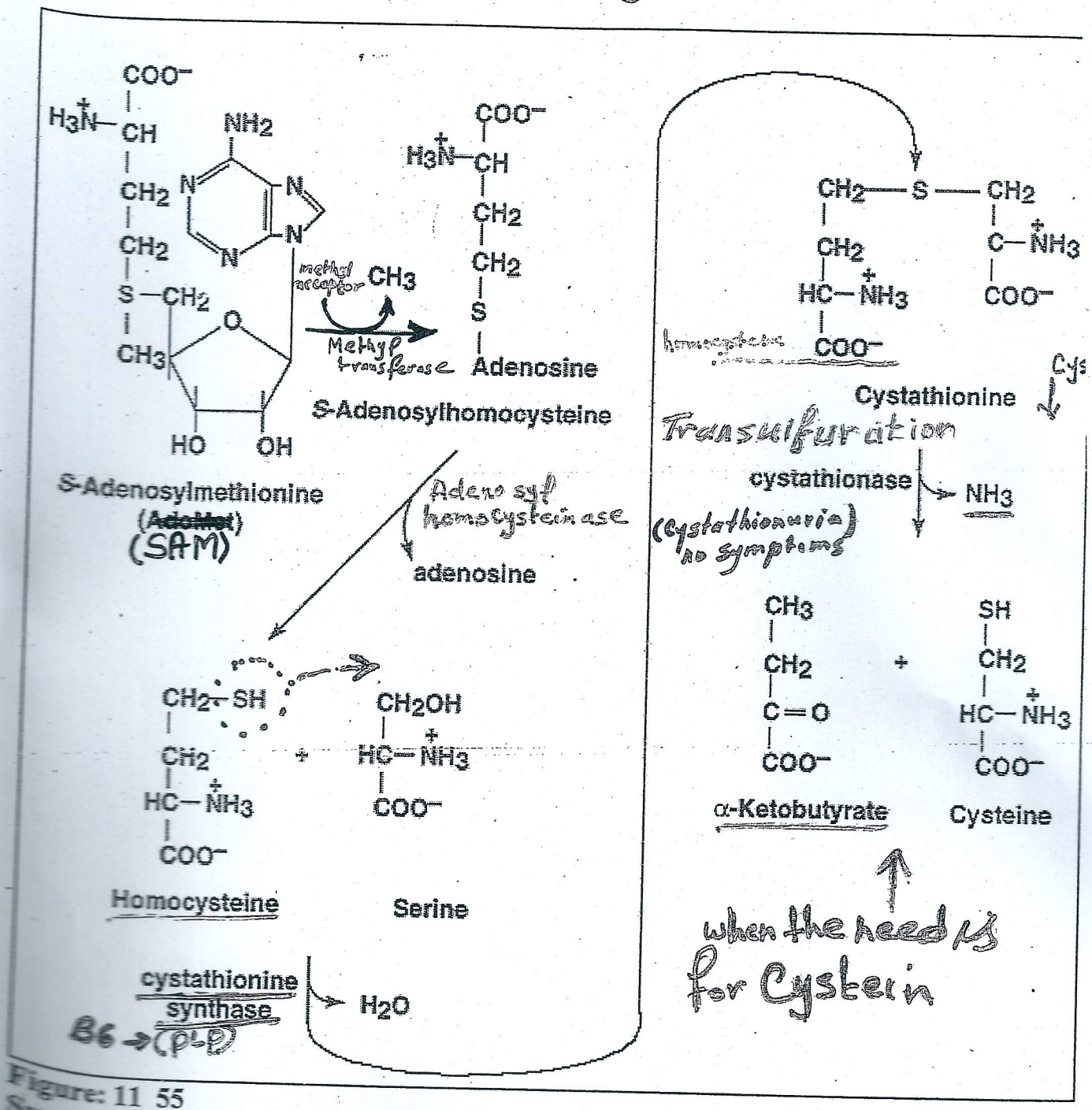


Figure: 11_55
Synthesis of cysteine from S-adenosylmethionine.

- Homocystinuria :-
  - B6-responsive
  - ½-non
  - skeletal abnormalities
  - mental retardation, myocardial infarction

} due to deficiency of Cystathionine synthase
- early myocardial infarction
- Pulmonary embolus

- ↑ Homocystein and vascular disease (↑ homocystein

Specific Reactions Requiring SAM:- 4

- phosphatidylethanol amine $\xrightarrow{SAM}$ phosphatidyl choline
- Norepinephrine $\xrightarrow{SAM}$ Epinephrine

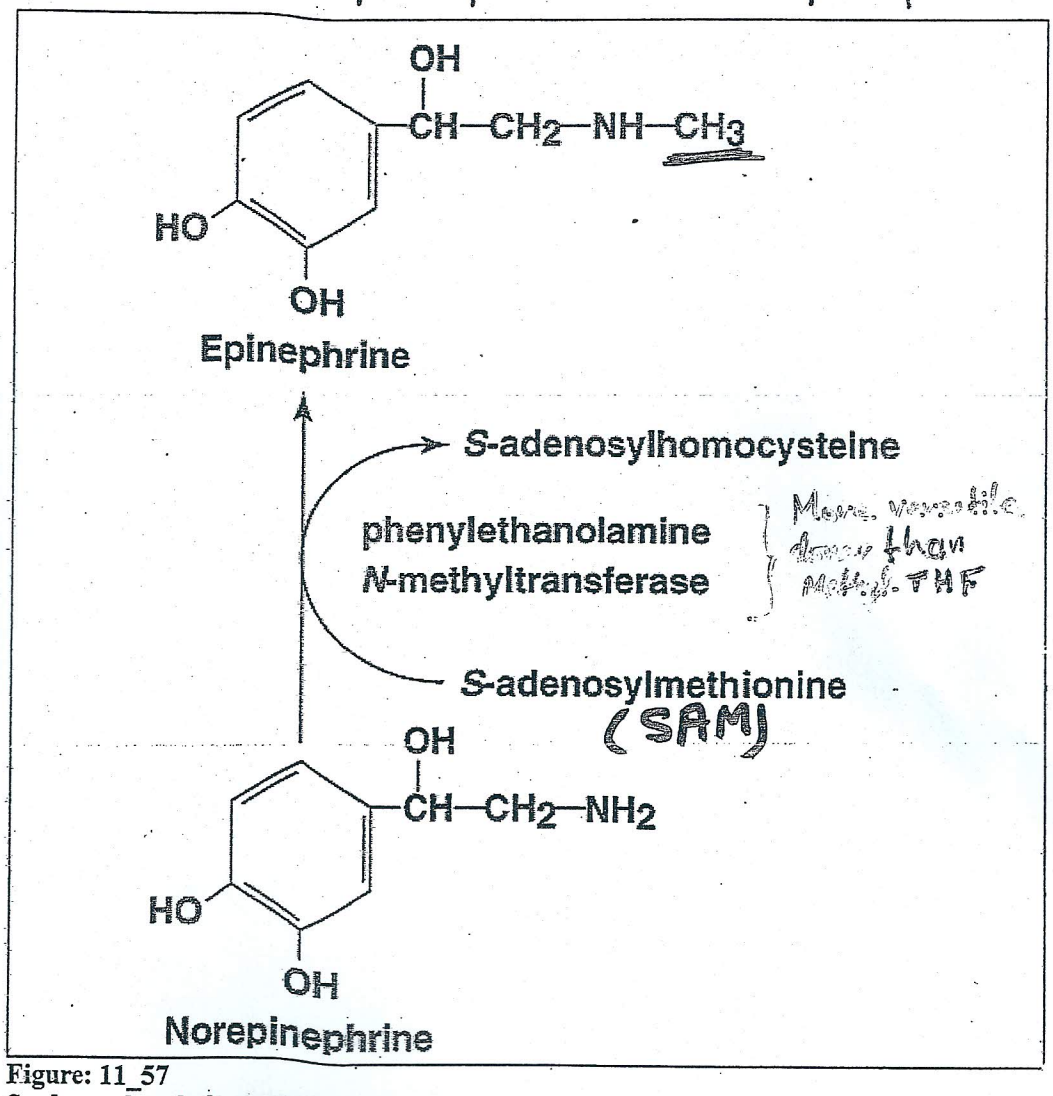


Figure: 11_57
S-adenosylmethyltransferase reaction.

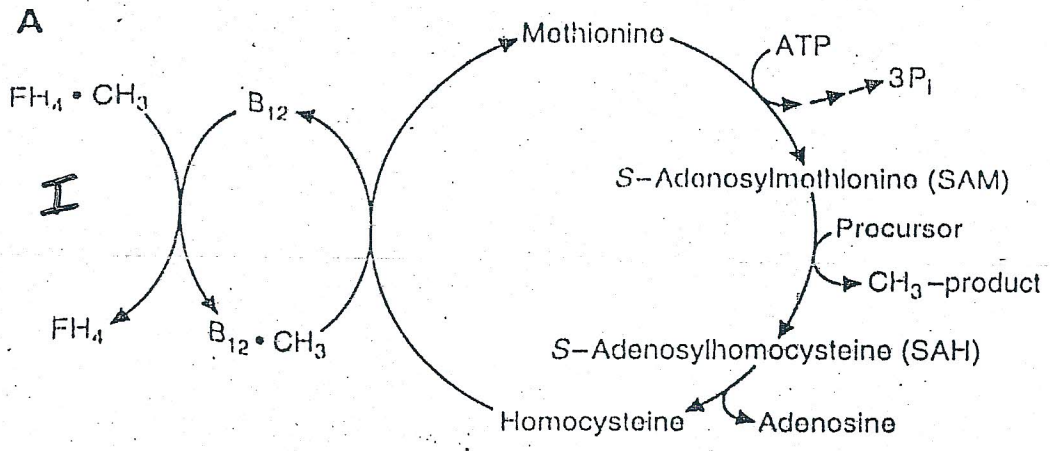
Nucleotides $\xrightarrow{SAM}$ methylated nucleotides

Guanidino acetate $\xrightarrow{SAM}$ Creatine

Acetylserotonin $\xrightarrow{SAM}$ Melatonin

(9)

Relationship of FH_4, B_{12} and SAM

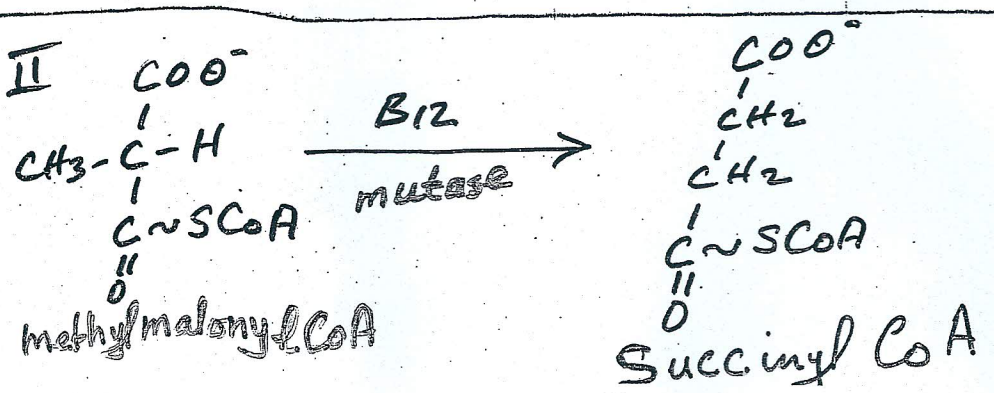


B

Precursor		Methylated product
Noroplnophrine	SAM →	Epinephrine
Guanidinoacetate	SAM →	Creatine
Nucleotides	SAM →	Methylated nucleotides
Phosphatidylethanolamine	SAM →	Phosphatidylcholine
Acetylserotonin	SAM →	Melatonin

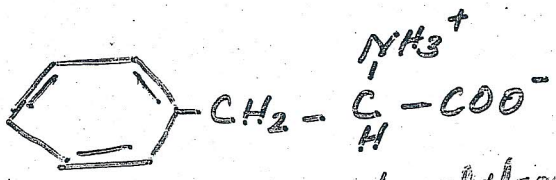
Fig. 40.10. Relationship between FH_4, B_{12}, and SAM. A. Overall scheme. B. Some specific reactions requiring SAM.

II



Degradation of phenylalanine & Tyrosine

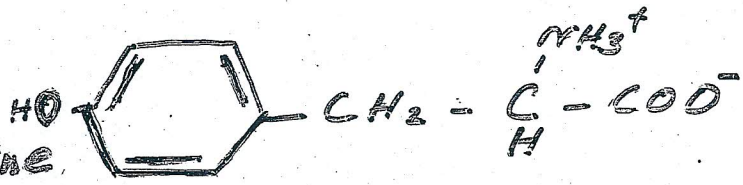
phenyl-alanine



phenylalanine hydroxylase
monooxygenase (mixed-function oxygenase)

↓

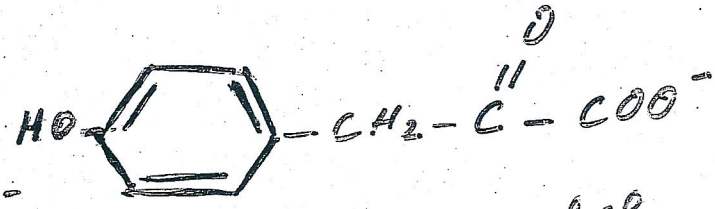
Tyrosine



Transaminase

↓

p-hydroxy-phenylpyruvate



Hydroxylase
dioxygenase (intramolecular dioxygenase)

↓

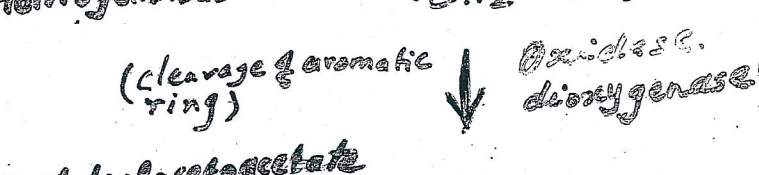
Homogentisate

⇐ Alkaptonuria*

(cleavage of aromatic ring)

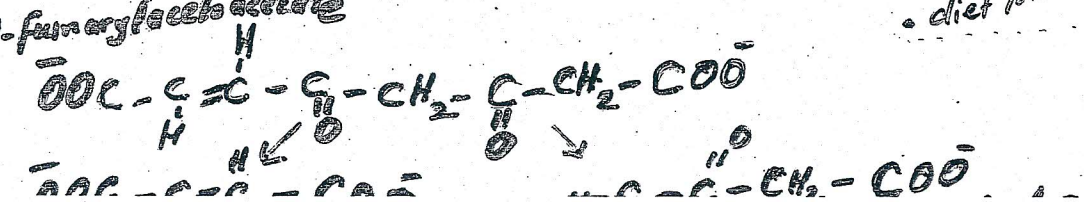
↓ Oxidase
dioxygenase (intramolecular dioxygenase)

4-Maleylacetoacetate



↓

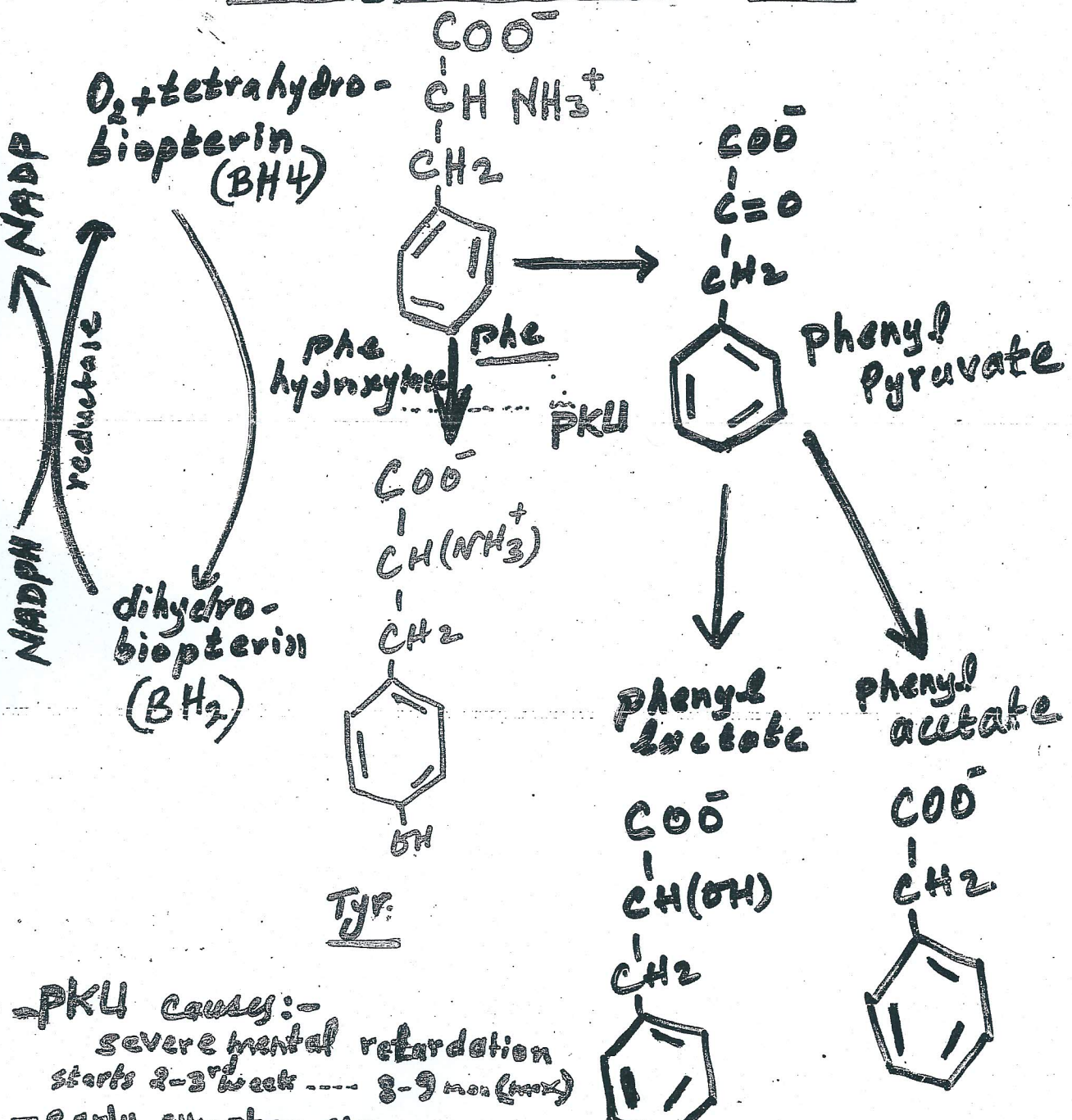
4-fumarylacetoacetate



* large joint arthritis
* black pigmentation of cartilage and collagenous tissue
. Asymptomatic till ~ age of 40.
. diet low in phe & tyr

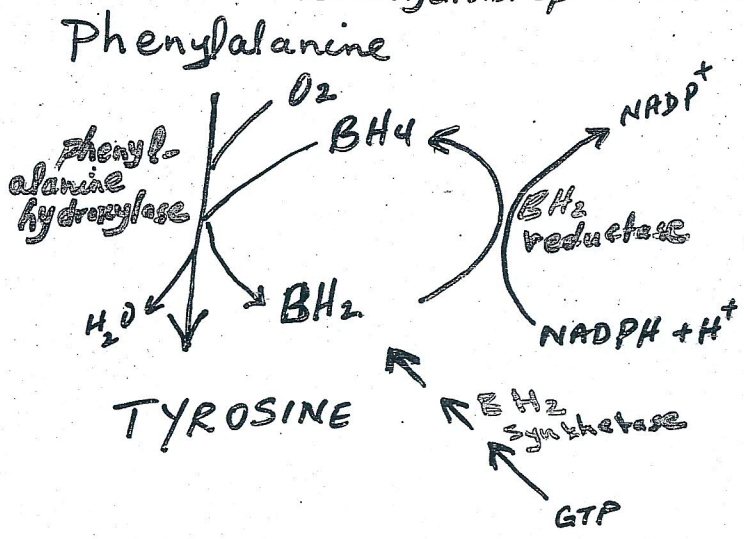
Inborn Errors of Tyrosine & phe metabolism:

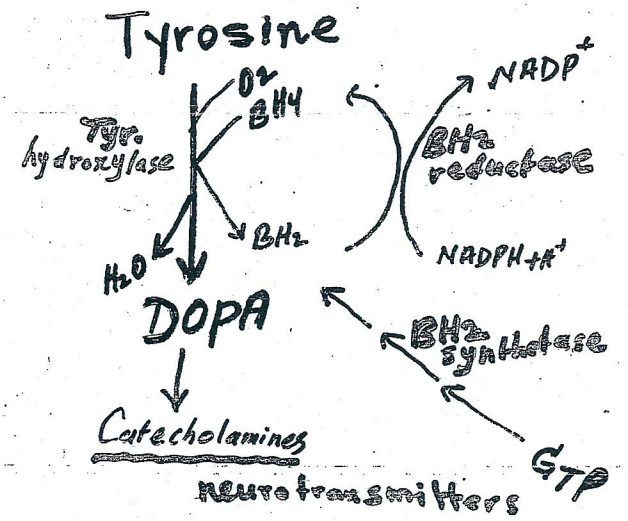
Phenylketonuria (PKU)



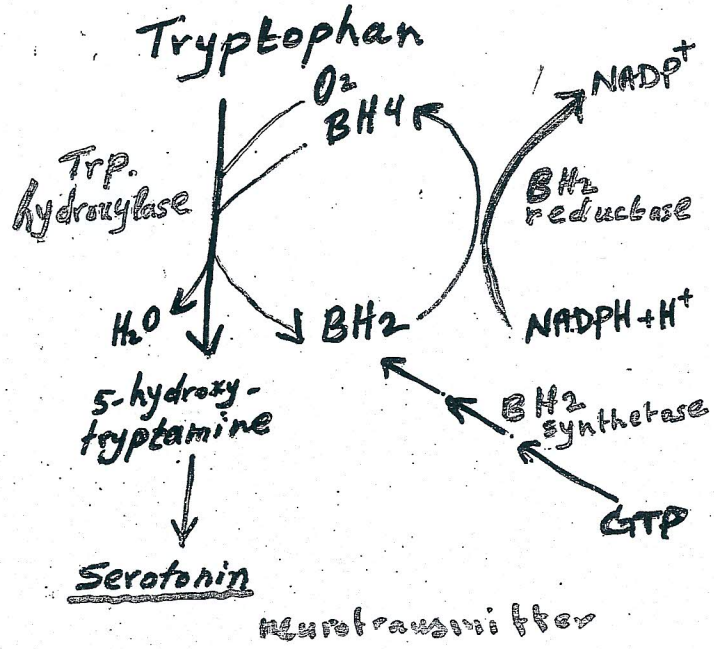
- PKU causes:-
  severe mental retardation
  starts 2-3rd week ---- 8-9 mon (max)
- early symptoms:-
  delayed developement, poor feeding
  vomiting
- Incidence: 1:10,000

Biosynthetic Reactions Involving Amino acids and Tetrahydrobiopterin (BH4)



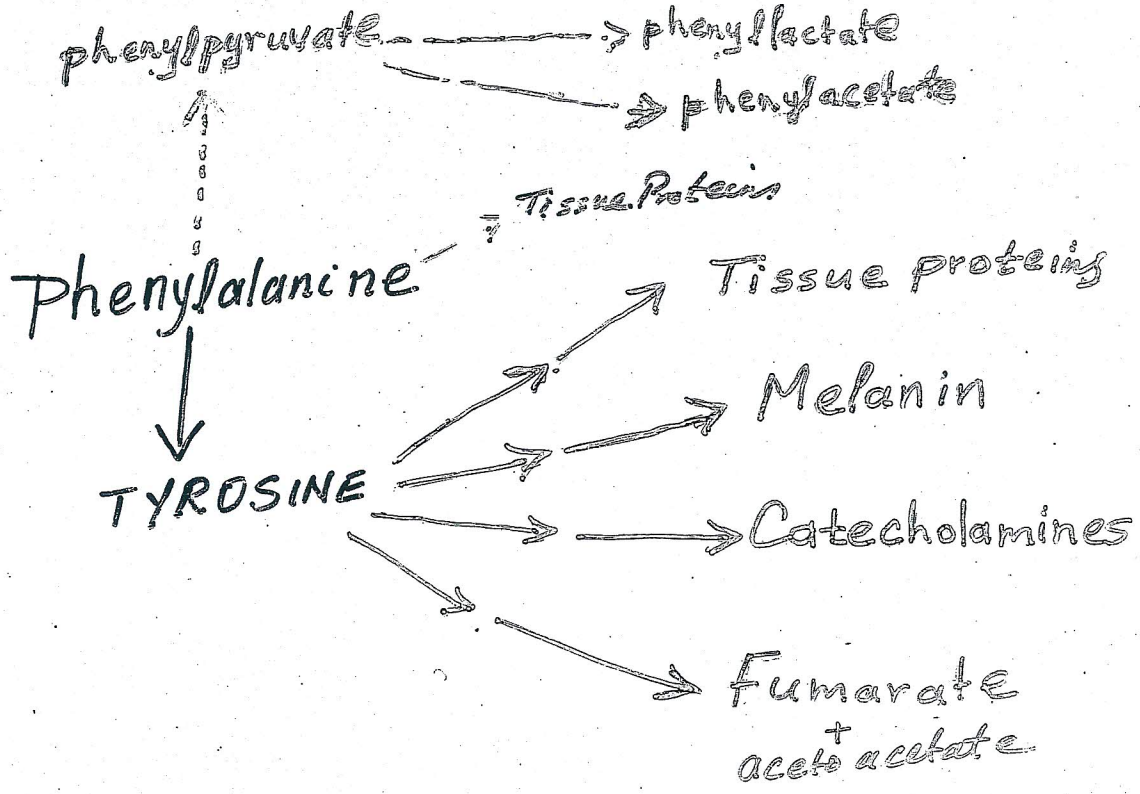


Deficiency in BH_2 reductase or synthetase →
- hyperphenylalaninemia
- decreased synthesis of
  - catecholamines
  - serotonine
- require therapy with BH4 or DOPA and 5-hydroxy trp – not always effective

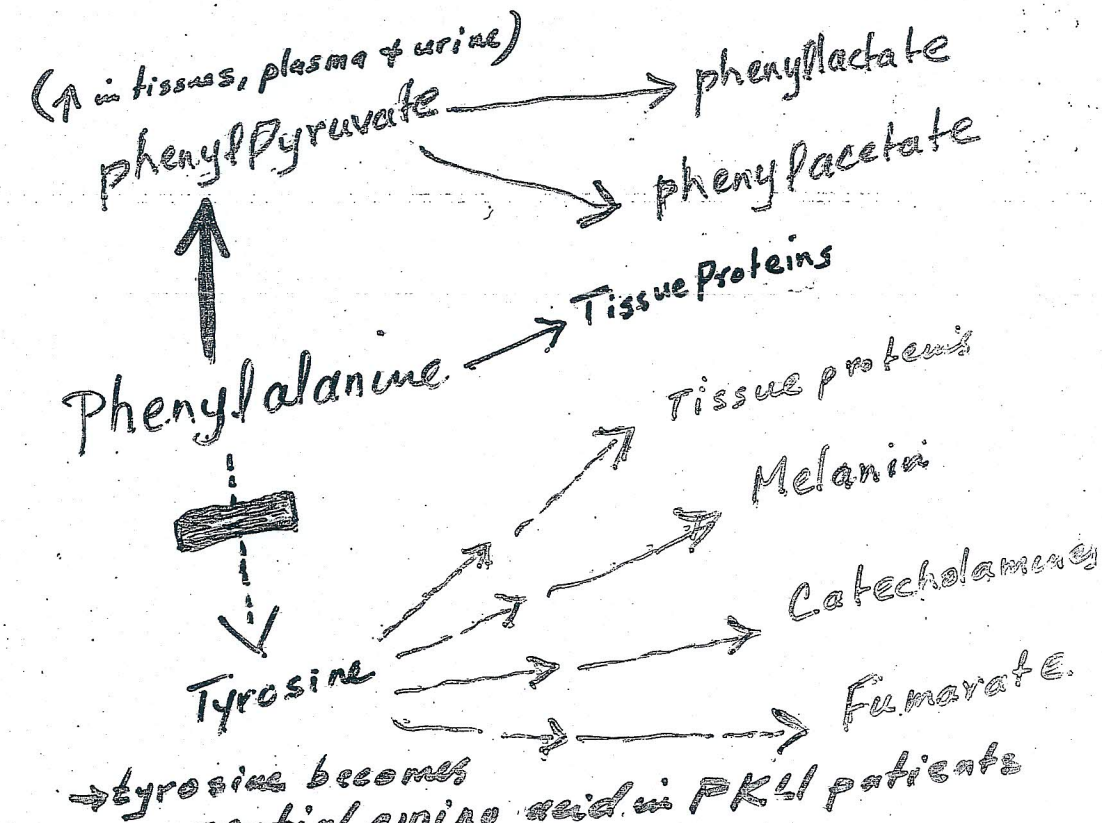


3

NORMAL



Phenylketonuria PKU



→ tyrosine becomes an essential amino acid in PKU patients

Hyperphenylalaninemias

- PKU may be caused by :-

1- Phenylalanine hydroxylase (PAH) deficiency [Prevelance 1 : 11,000]
   - most cases of PKU.

2- Low level of tetrahydrobiopterine due to :-
   1- reductase deficiency
      - most serious of PKU cases
      - require precursors of serotonin & catecholamines.
   2- synthetase deficiency [treated by dietary supplement].

   * both account for 3% of cases of hyperphenylalaninemia

Characteristics of PKU :-

- Elevated level of phenylalanine ↑ ⟶ phenylacetate ↑, ↑ phenylacetate and phenylpyruvate ↑.
- CNS symptoms : mental retardation, failure to walk, talk & grow, seizure, tremor. IQ > 50
- Hypopigmentation:
  Tyrosinase is inhibited by ↑ phenylalanine.

  Tyrosine $\xrightarrow[\text{(Hydroxylation)}]{\text{Tyrosinase}}$ ⟶ ⟶ ⟶ Melanine

- Neonatal Diagnosis of PKU.
  - Early diagnosis is important.
  - Disease is treatable by dietary means.

- Prenatal Diagnosis of PKU :-
  - > 40 different mutation of PAH gene.
  - double heterozygotes are common.
  - 6-10 types of mutations are common.
- Treatment of PKU :-
  - Tyr. becomes essential.
  - Restriction of diet ⟶ low in phe. at least till age 8 ⟶ still mild depression IQ, behavior, mood .....etc.
  - Life-long restriction is recommended.
- Maternal PKU :-

  Maternal PKU syndrom
  - ⟶ mental retardation
    - Congenital heart abnormalities in fetus.
  - Dietary control starts before conceptions.

Albinism :-

Groups of disorders in Tyrosine → → → Melanin.

→ Partial to full absence of pigment.

Several modes of inherittance :

- autosomal recessive.
- autosomal dominant.
- X- linked.

- Most severe form results from TYRUSINASE DEFIEIENCY
  - causing total absence of melanine :
    - white hair, skin and iris color plus vision defects.

    and photophobia → · sun light painful to eyes.
    · sun burns easily.
    · do not tan.

Biosynthesis of Non-essential Amino Acids:

Essential amino acids

Non-essential amino acids

Tyr + Cys. are synthesized from the essential amino acids, Phe + Met.

A. Synthesis from α-Keto acids

1. Ala, Asp, Glu

Pyruvate → TRANSAMINATION → Alanine

Oxaloacetate → TRANSAMINATION → Aspartate

α-Ketoglutarate → TRANSAMINATION → Glutamate

2. Reversal of oxidative deamination:

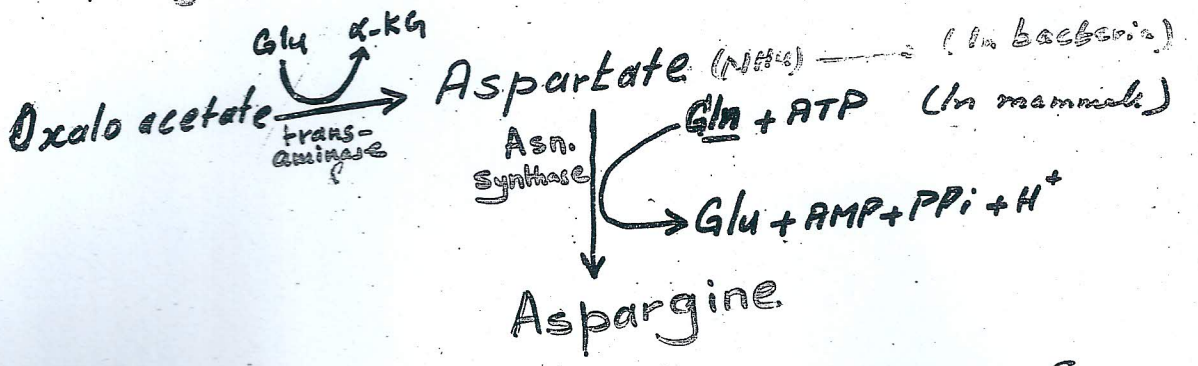
$$\alpha\text{-KG} + NH_4^+ + NADPH \rightleftharpoons NADP^+ + Glu$$

High protein diet Glu → α-KG

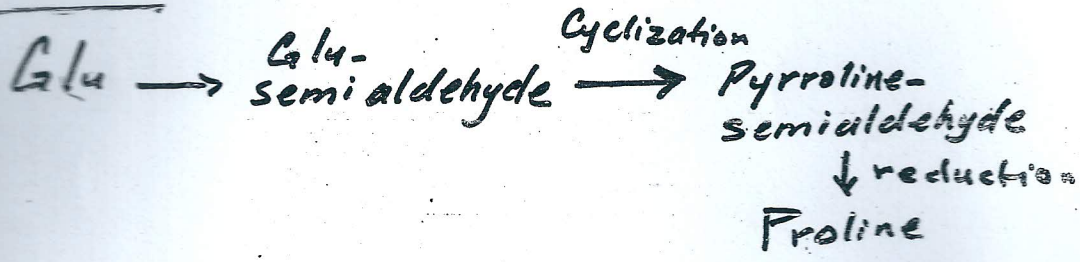
B synthesis by Amidation

1. Glu $\xrightarrow[\text{Gln synthetase}]{ATP + NH_3 \rightarrow ADP + P_i}$ **Gln**

2. Aspargine

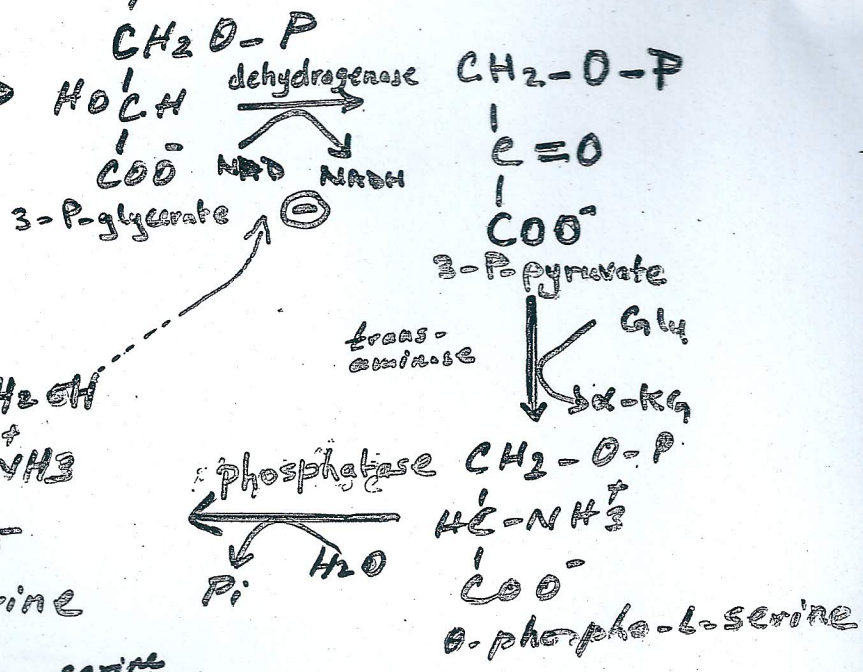


C. Proline

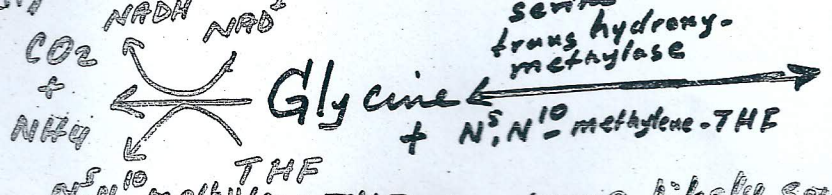


D. Ser., Gly., Cys.

(i) Glycolysis →



(ii)



N^5,N^{10}-methylene-THF ← more likely source of 1-carbon moiety