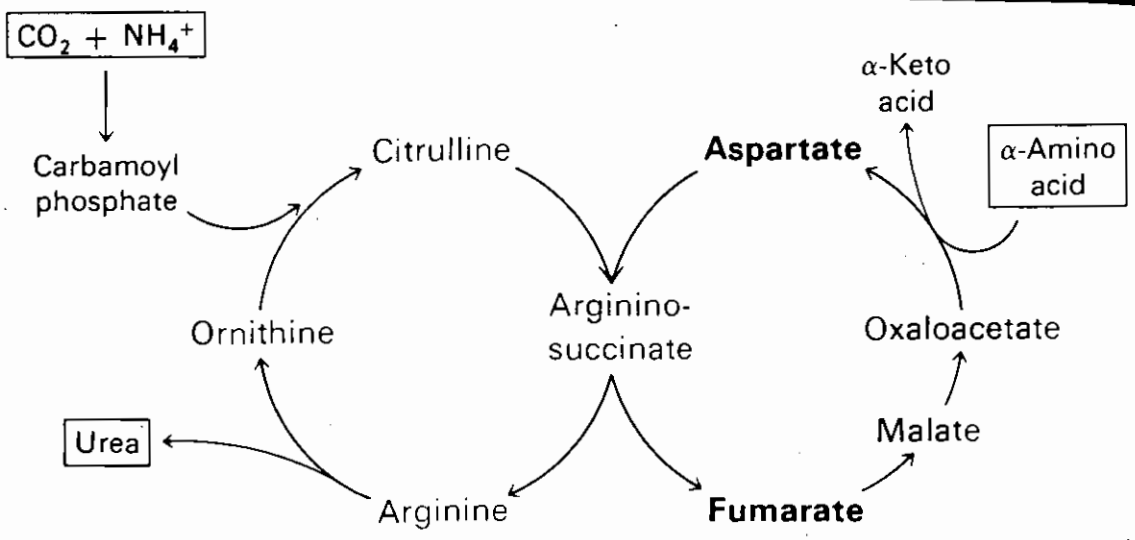
Classification of Amino Acids

	Glucogenic	Glucogenic and Ketogenic	Ketogenic
Non-Essential	Ala	Tyr	
	Arg*		
	Asn		
	Asp		
	Cys		
	Glu		
	Gln		
	Gly		
	His*		
	Pro		
	Ser		
Essential	Met	Isoleucine	leu
	Thr	phe	lys
	Va	Trp	
	His		

Degradation of Amino Acids 1b



Final Products

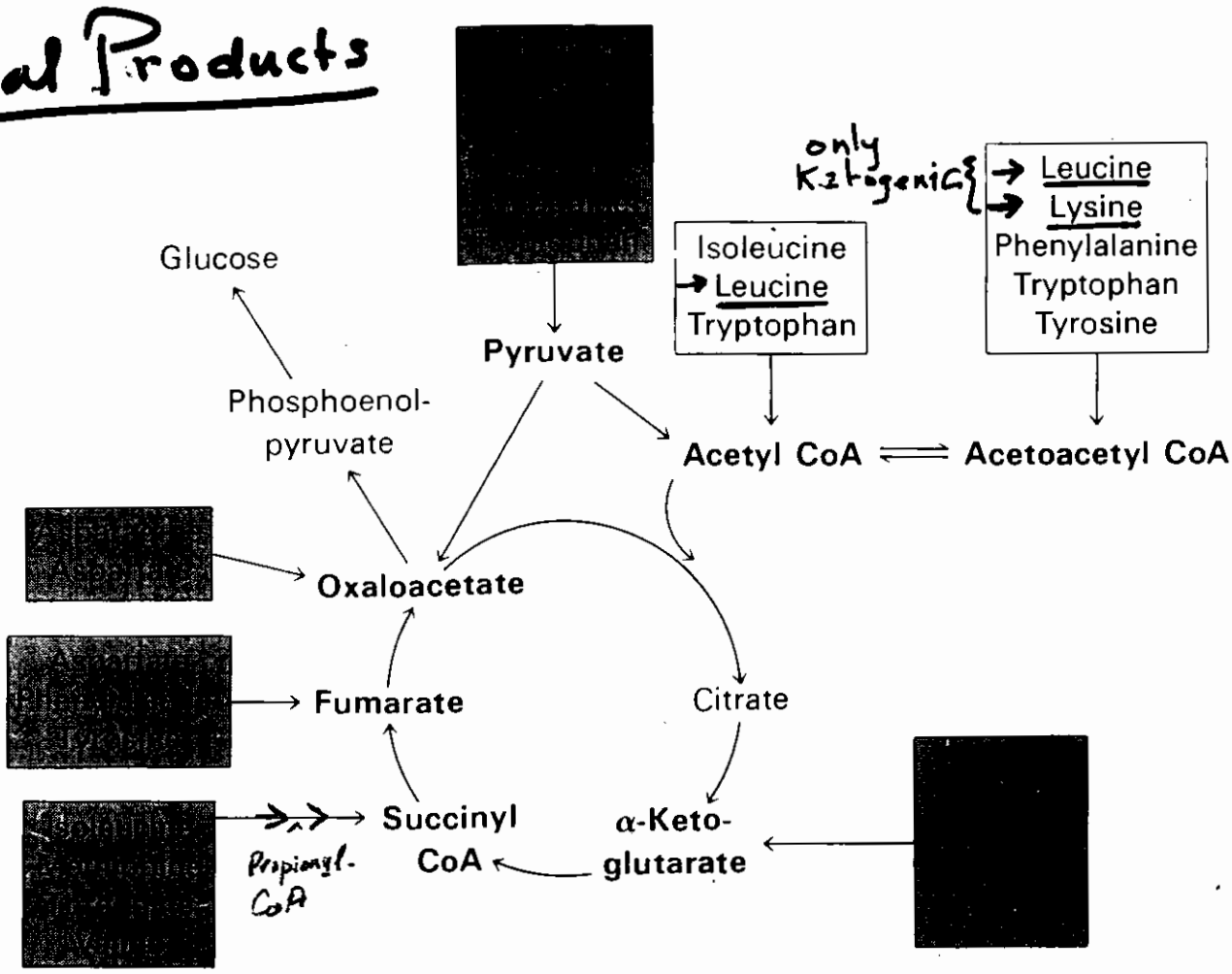


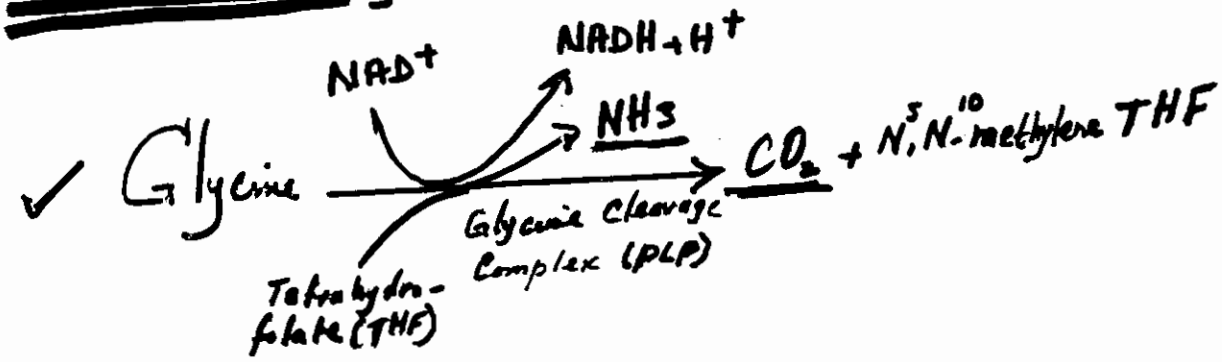
Figure 25-7, page 636; Figure 25-10, page 638

T-85

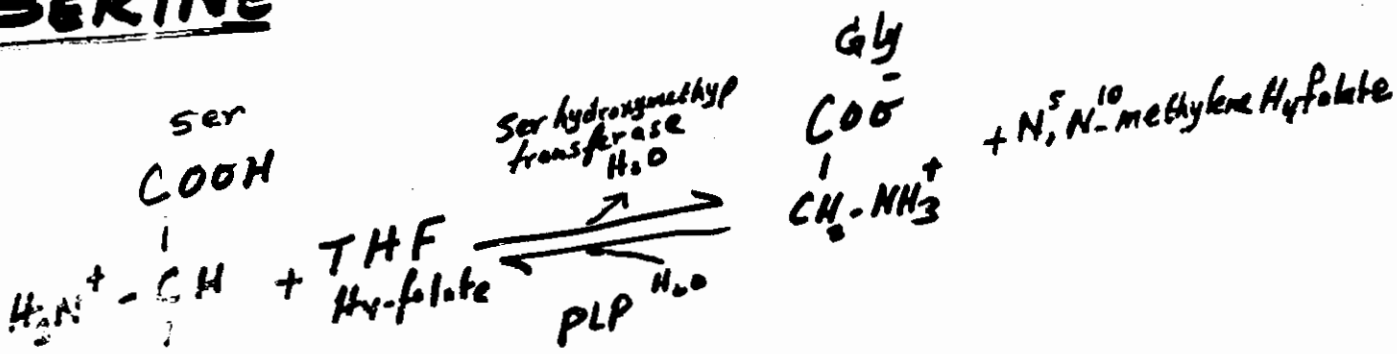
Set I

Degradation of Individual Amino Acids 1C

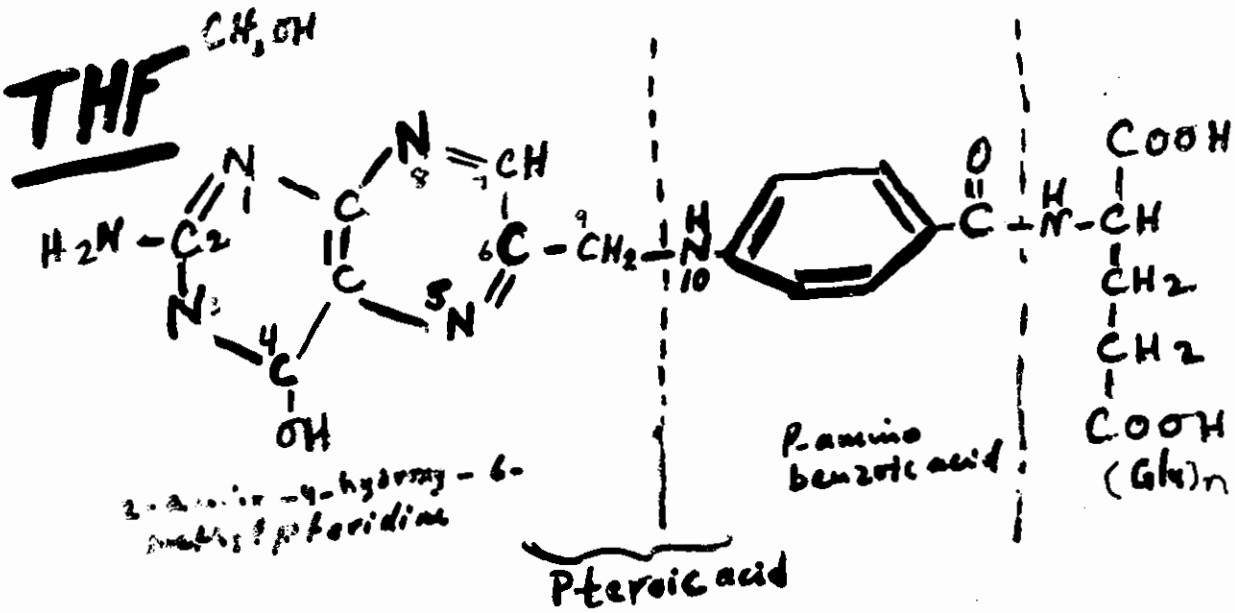
GLYCINE } → CO_2 + NH_3



SERINE

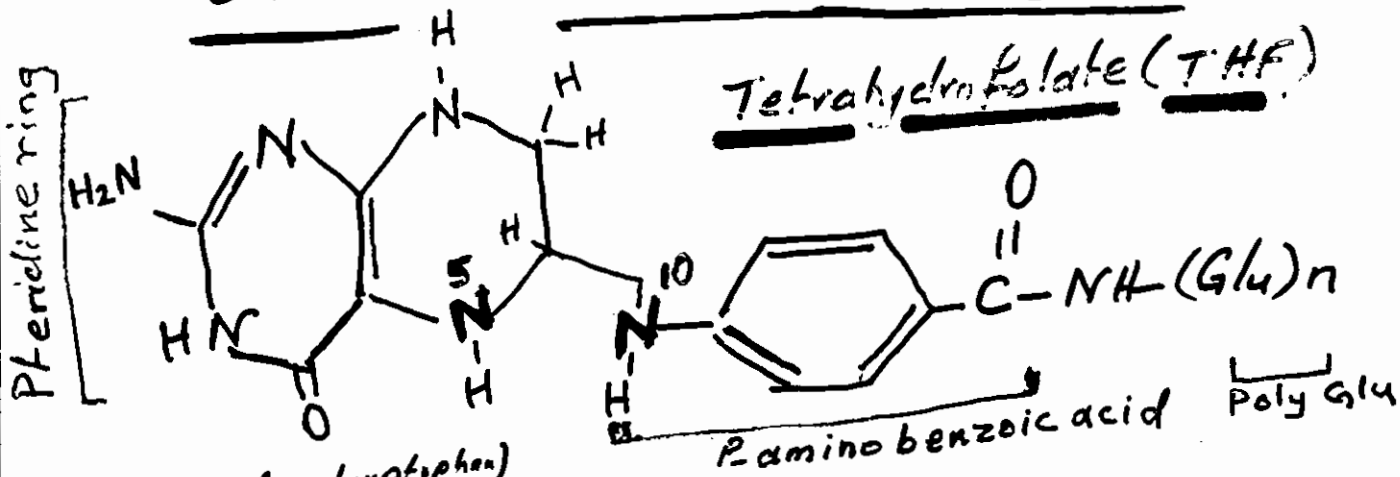


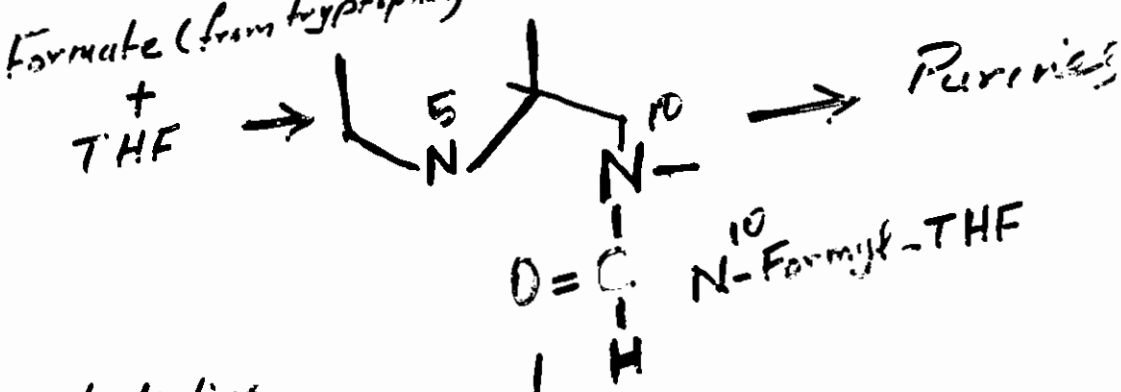
THF

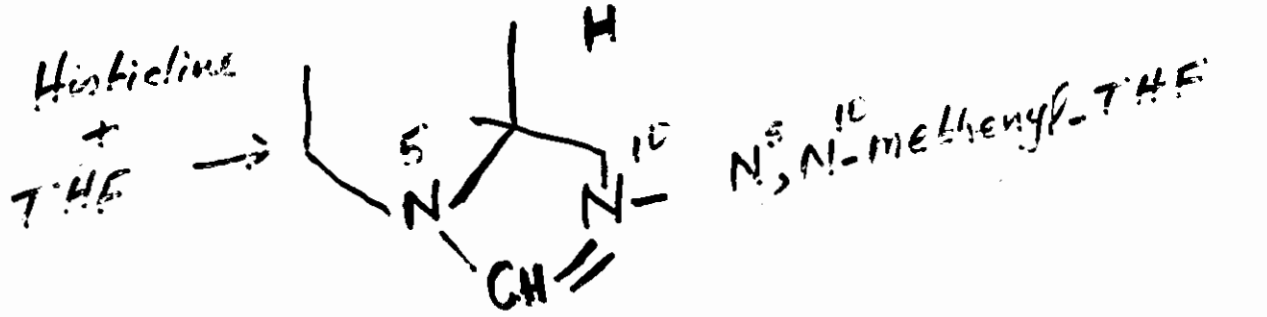


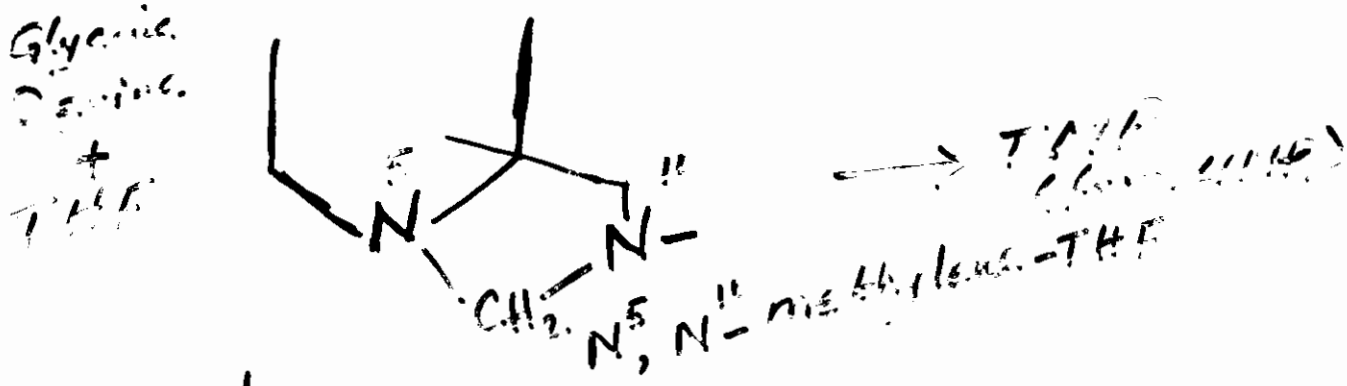
Folic acid (Pteroylglutamic acid)

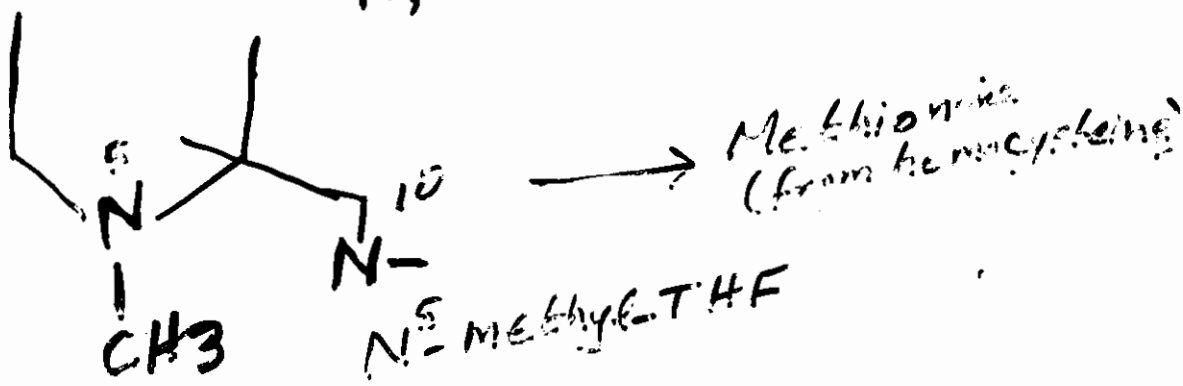
One-carbon unit carried by THF





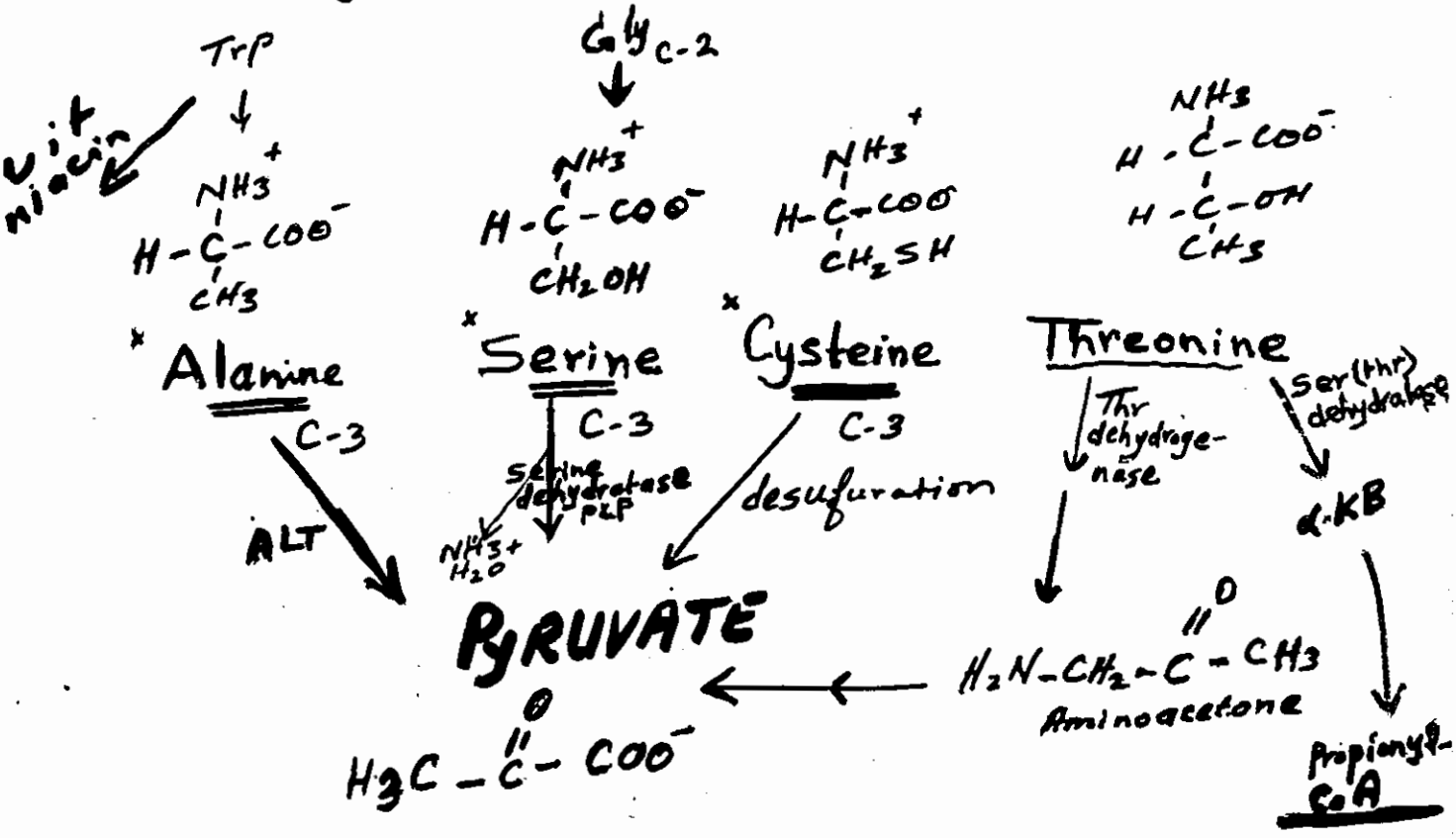






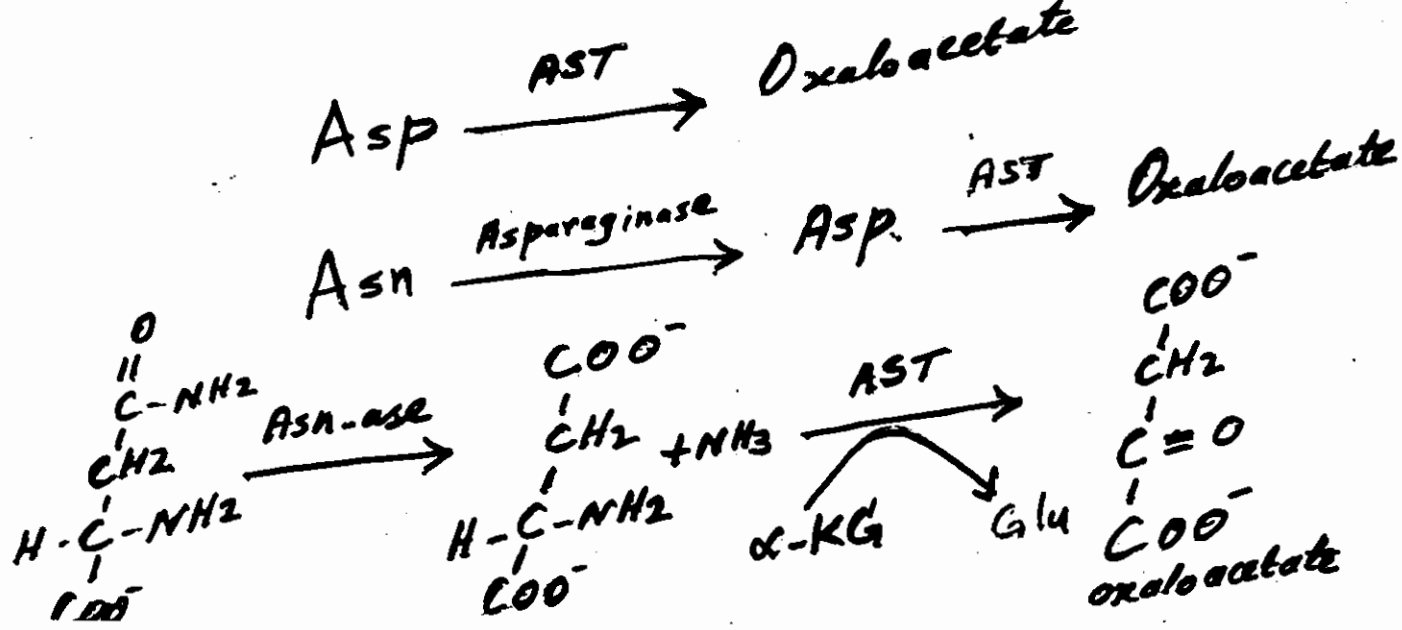
The C_3 Family :-

Ala, Ser, Cys ⟹ Pyruvate



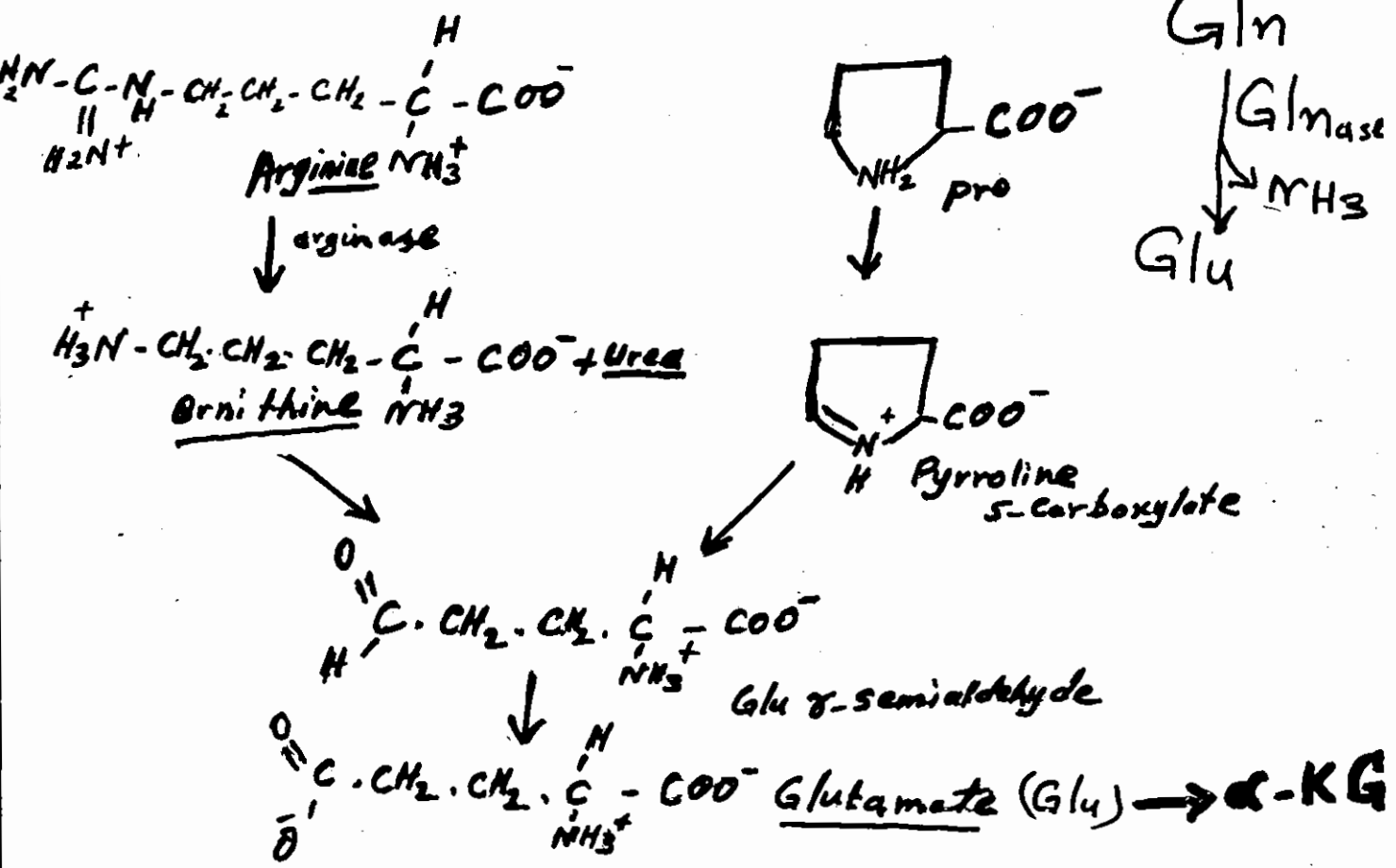
The C_4 Family :-

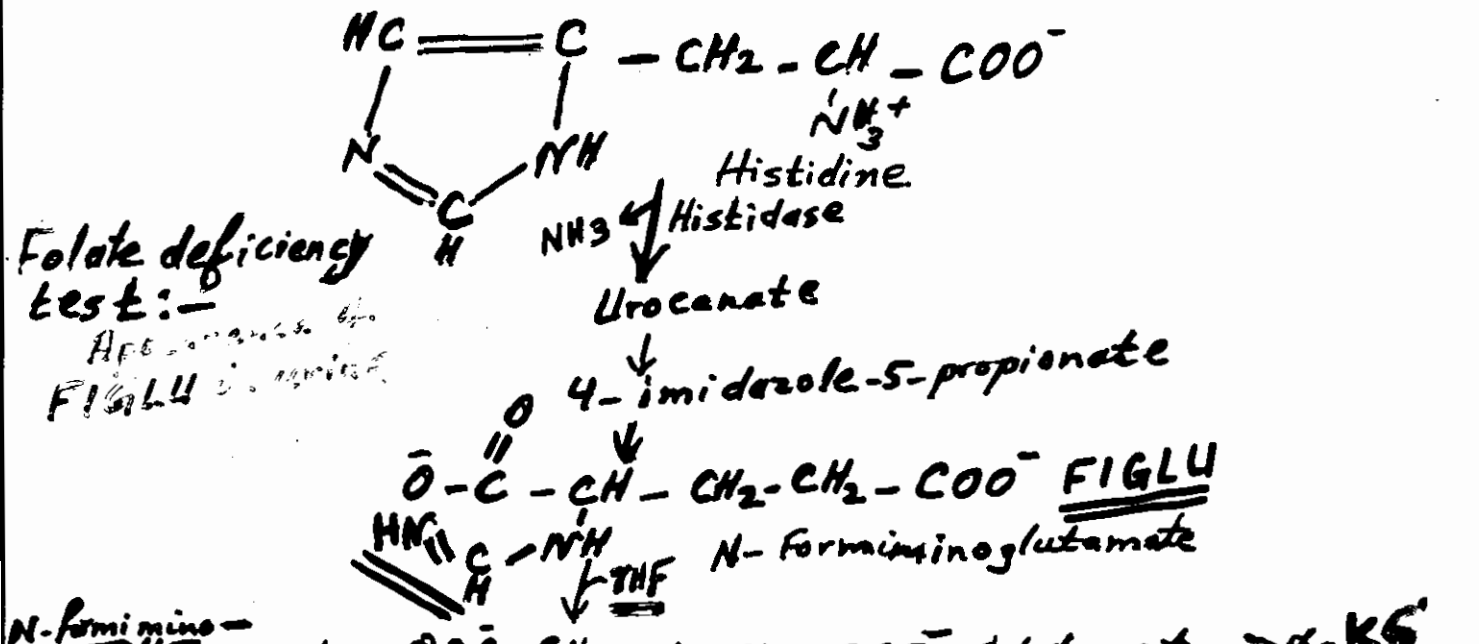
Asp, Asn → Oxaloacetate



Amino acids that form α-ketoglutarate

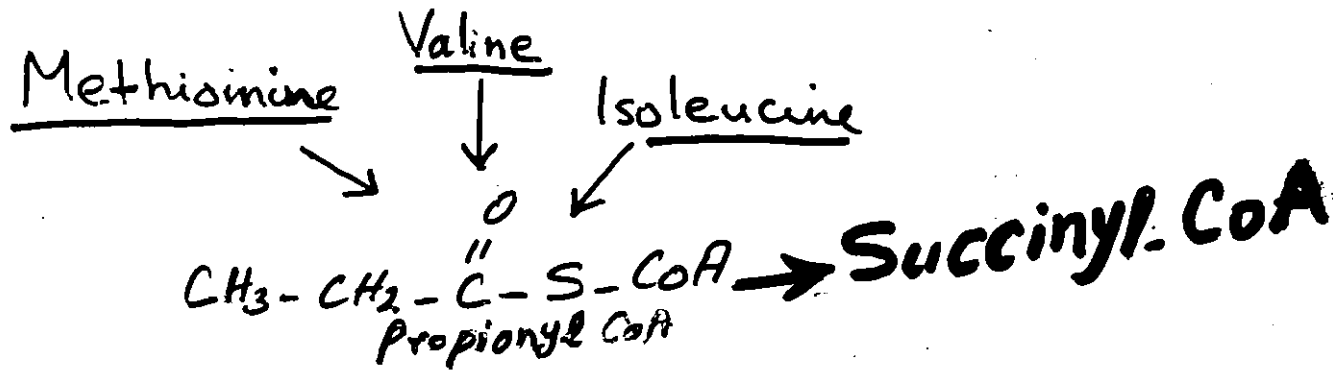
Gln, Pro, Arg, His → Glu → α-KG

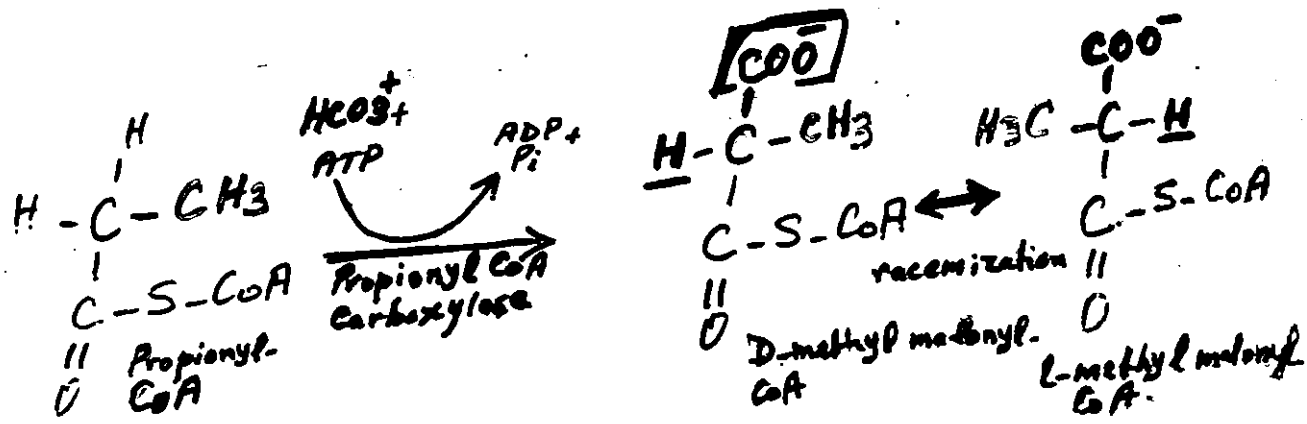


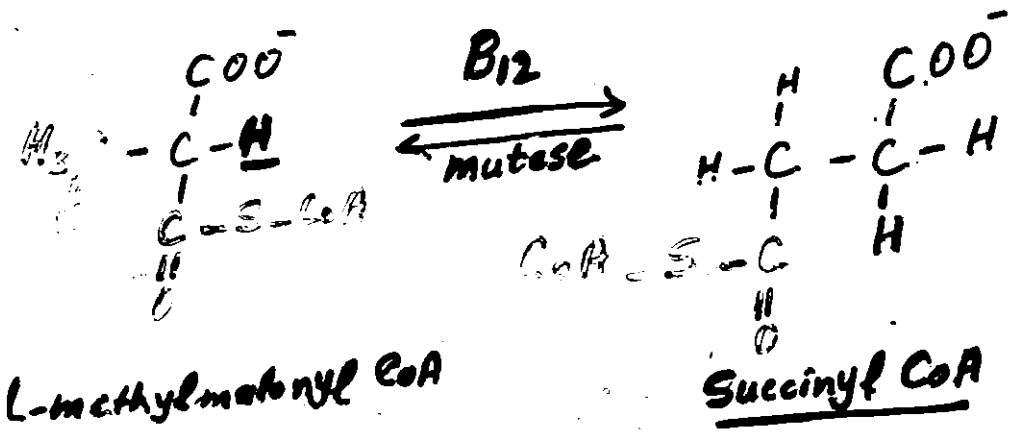


Folate deficiency test:-
Afterwards the FIGLU is excreted

Succinyl Coenzyme is a point of entry for several Non-polar Amino Acids:-







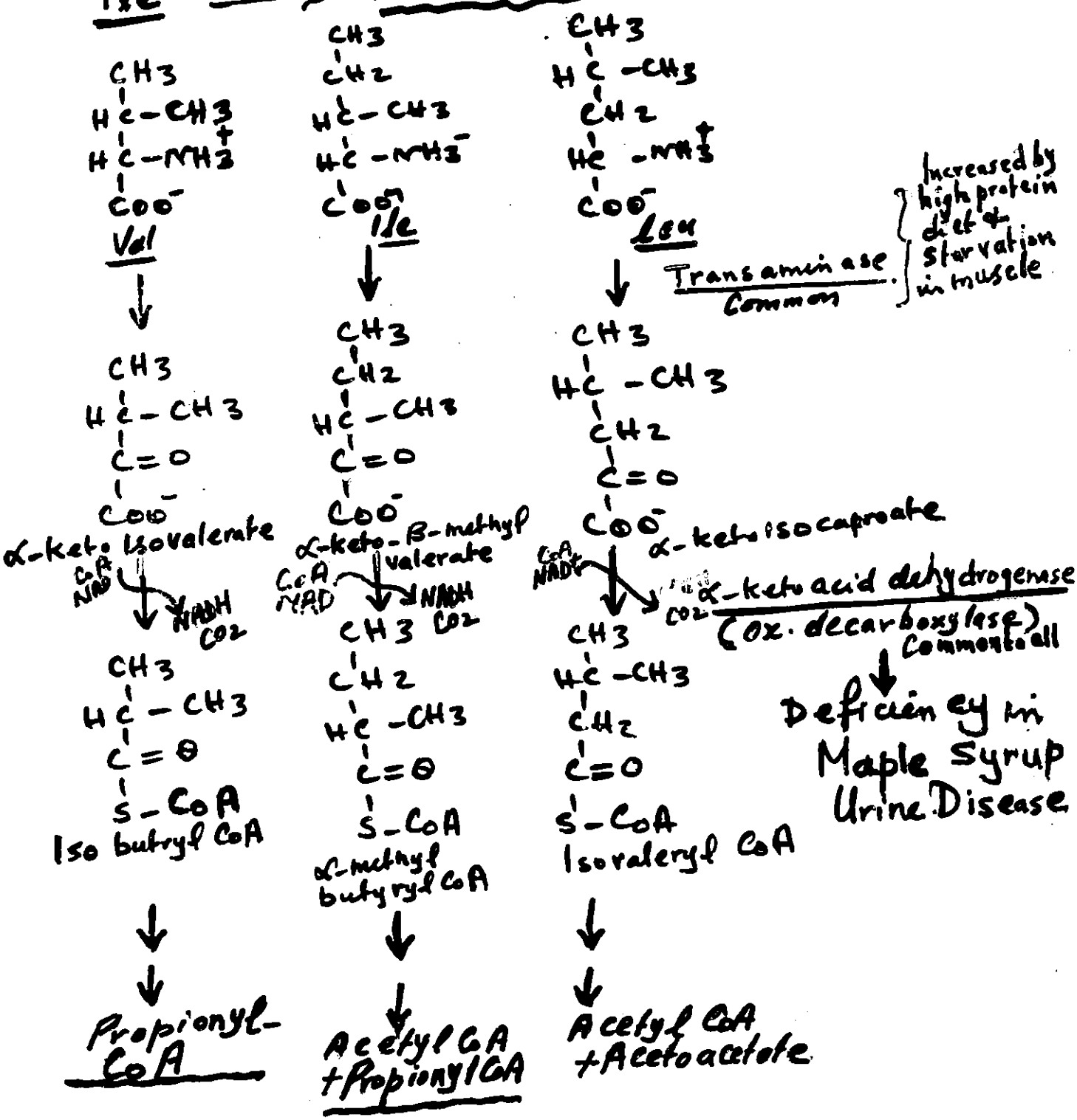
→ Odd-numbered acyl CoA → n acetyl CoA + propionyl CoA
→ cholesterol sidechains → propionyl CoA

Metabolism of Branched chain Amino Acid – (Active in muscle)

Leu → Acetoacetate + acetyl CoA

Val → Succinyl CoA

Ile → Succinyl CoA + acetyl CoA



Branched-chain Amino Acids

Maple Syrup Urine disease

- poor feeding
- vomiting
- acidosis
- mental retardation
- symptoms within first few days
- Restriction of a.a.

- severe
- Intermittant forms

- Thiamine-responsive form

- Neurologic disorders mainly due → ↑ leu

- Maple syrup-like urine → Ileu

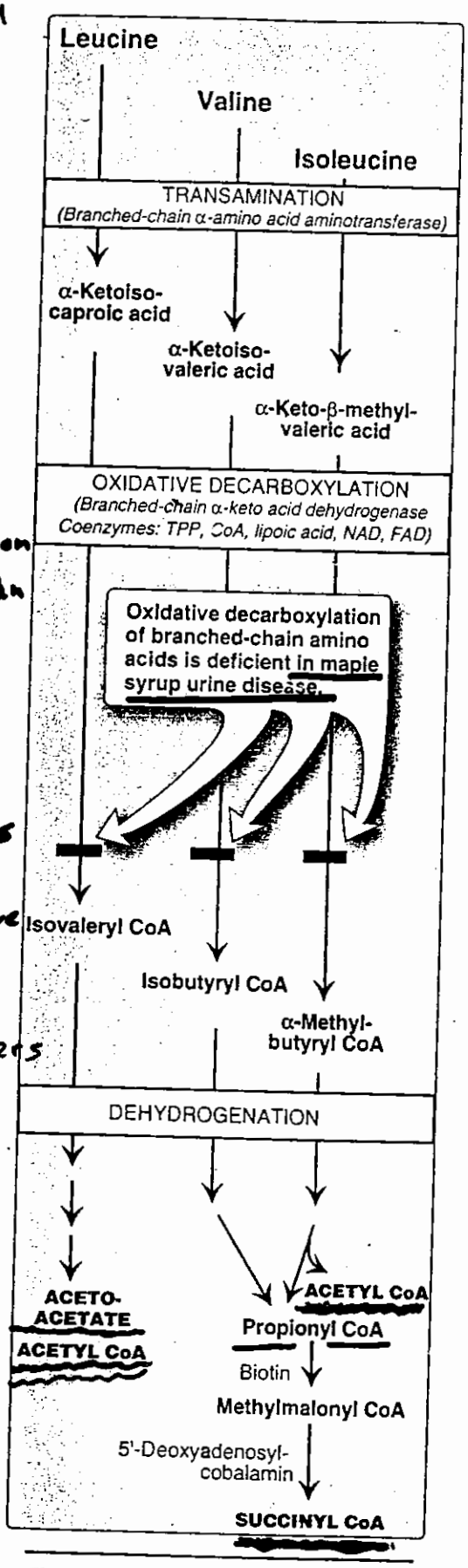


Figure 20.10
Degradation of leucine, valine, and isoleucine. TPP = thiamine pyrophosphate.

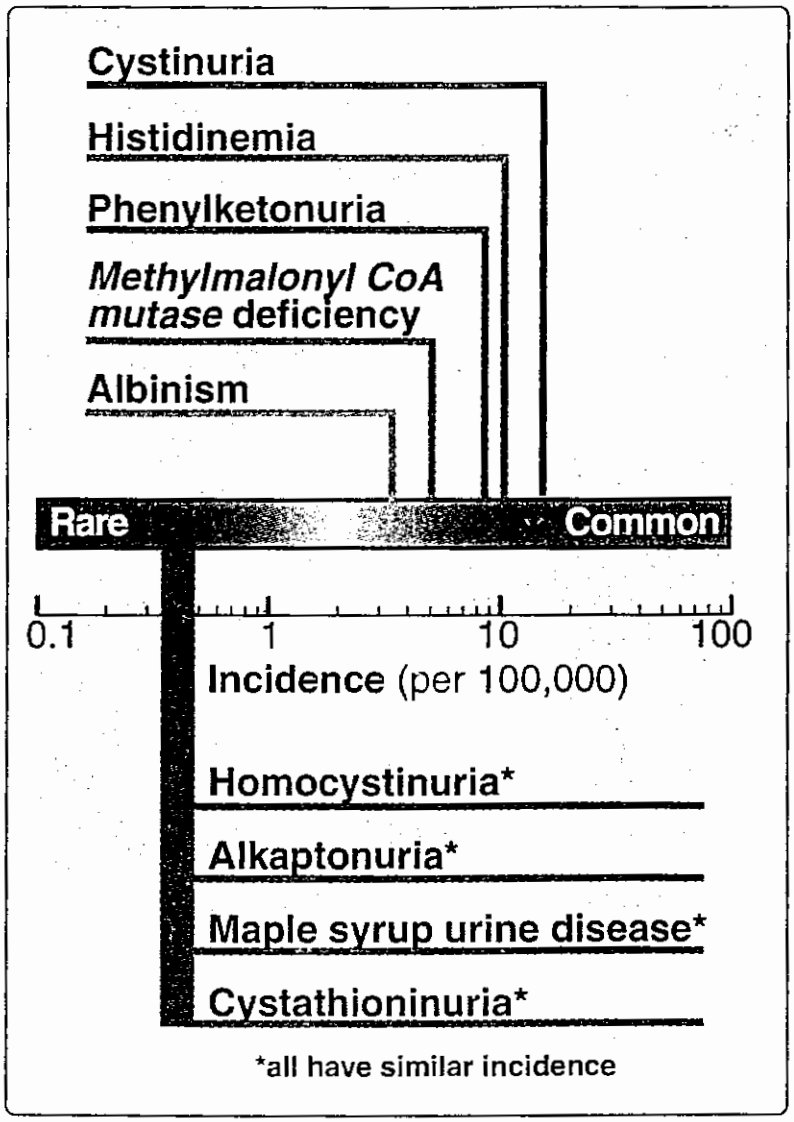
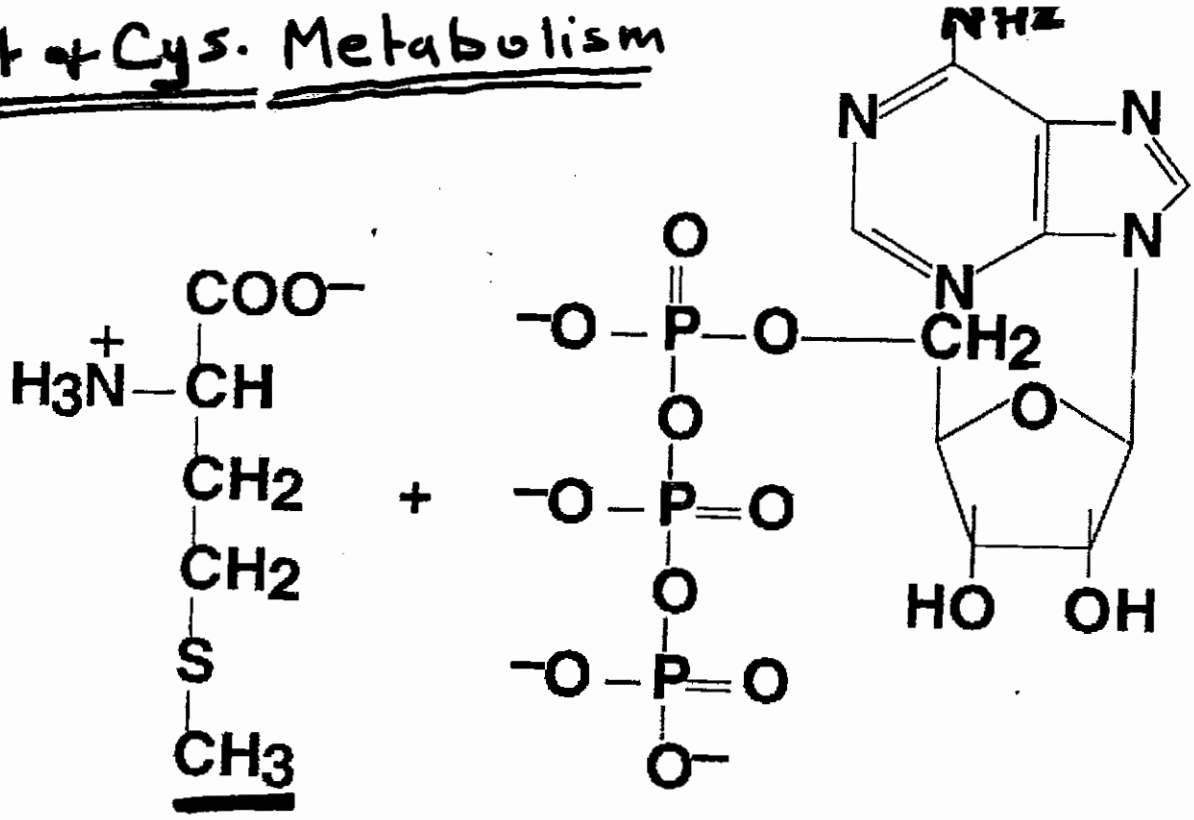


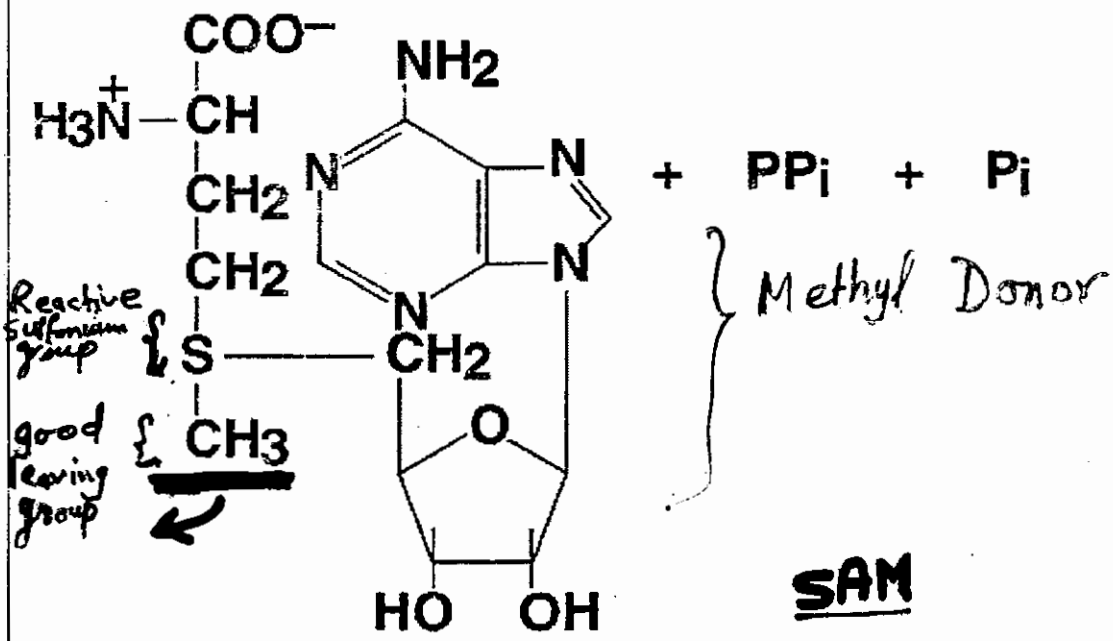
Figure 20.13
Incidence of inherited diseases of amino acid metabolism. [Note: Cystinuria is the most common genetic error of amino acid transport.]

Met + Cys. Metabolism



Methionine + **ATP**

methionine adenosyltransferase



SAM

S-Adenosylmethionine (AdoMet)

Metabolism of Methionine

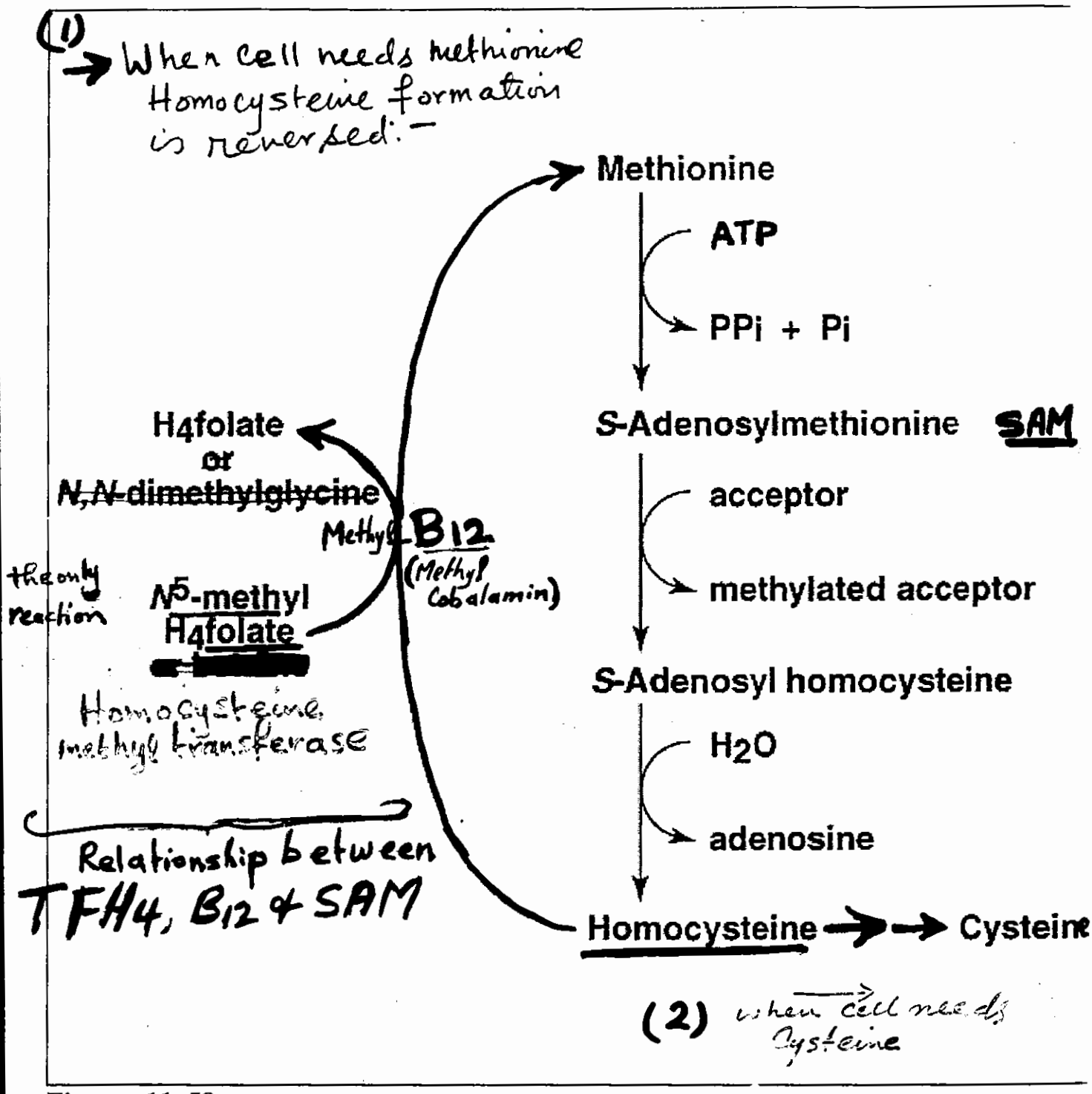


Figure: 11_58
Resynthesis of methionine, a methylcobalamin-dependent reaction.

When cell needs Cysteine:-

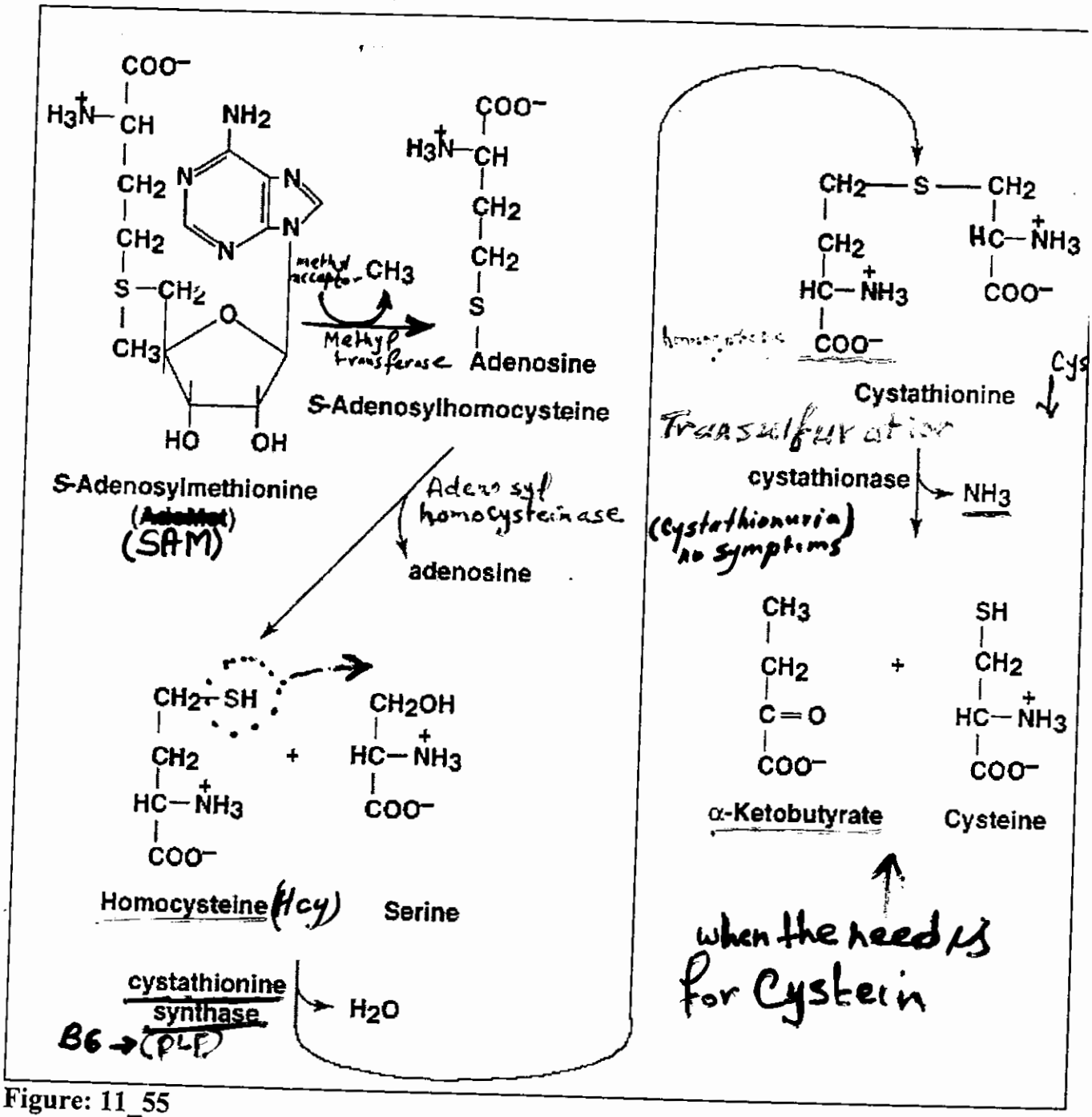


Figure: 11_55
Synthesis of cysteine from S-adenosylmethionine.

- Homocystinuria :-
  - B6-responsive
  - 4-non "
  - skeletal abnormalities
  - mental retardation, myocardial infarction, dislocation of the lens

Most of cases of Homocystinuria is due to deficiency of Cystathionine Synthase
- early myocardial infarction
- Pulmonary embolus

- ↑ Homocystein and vascular disease (Hyperhomocysteinemia)
  - treatment = B12 + B6 + folate + restriction of ...
  - Intake of 3 vit → 1 Hcy

Specific Reactions Requiring SAM:-

- phosphatidylethanol amine $\xrightarrow{SAM}$ phosphatidylcholine
- Norepinephrine $\xrightarrow{SAM}$ Epinephrine

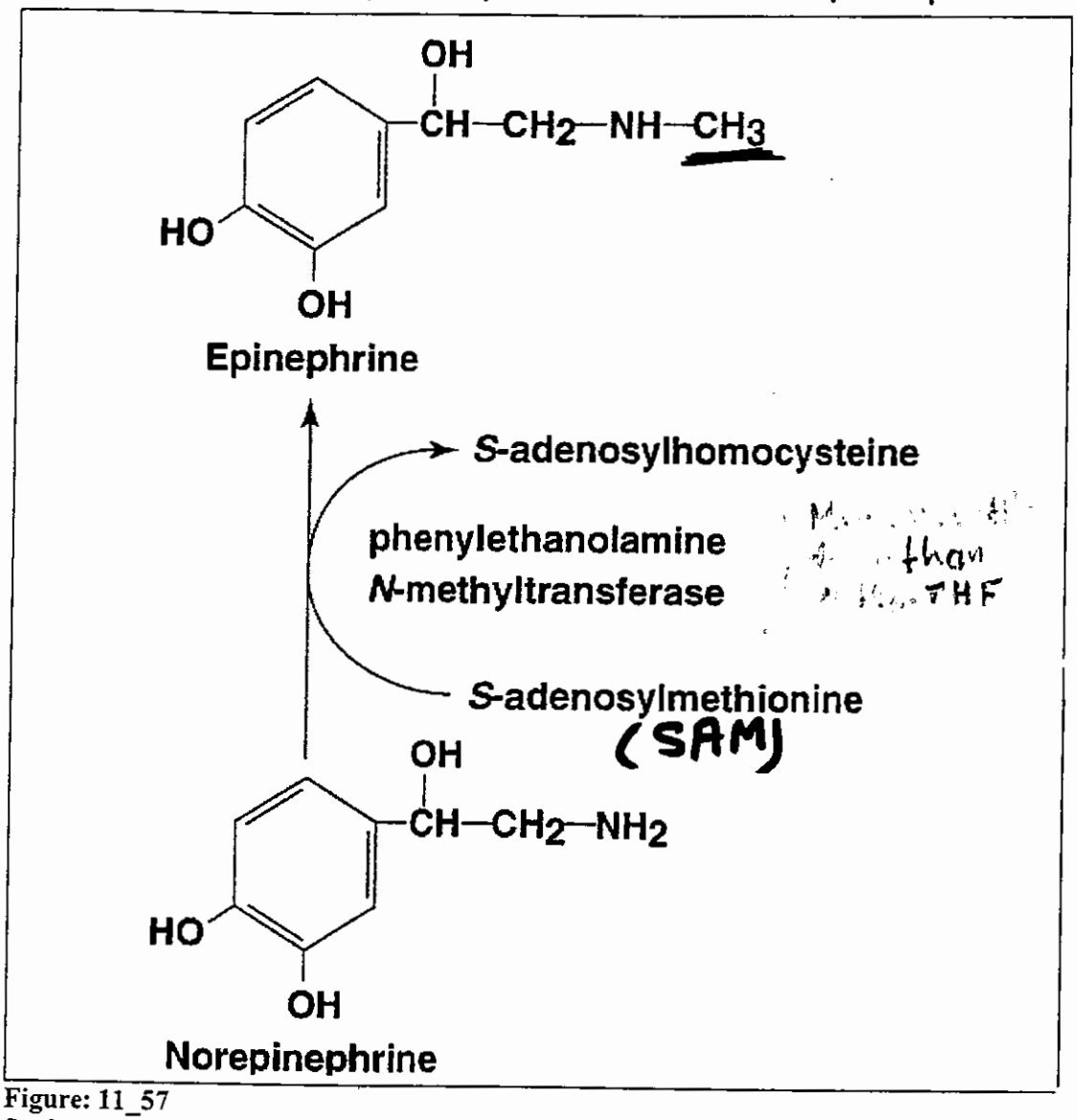
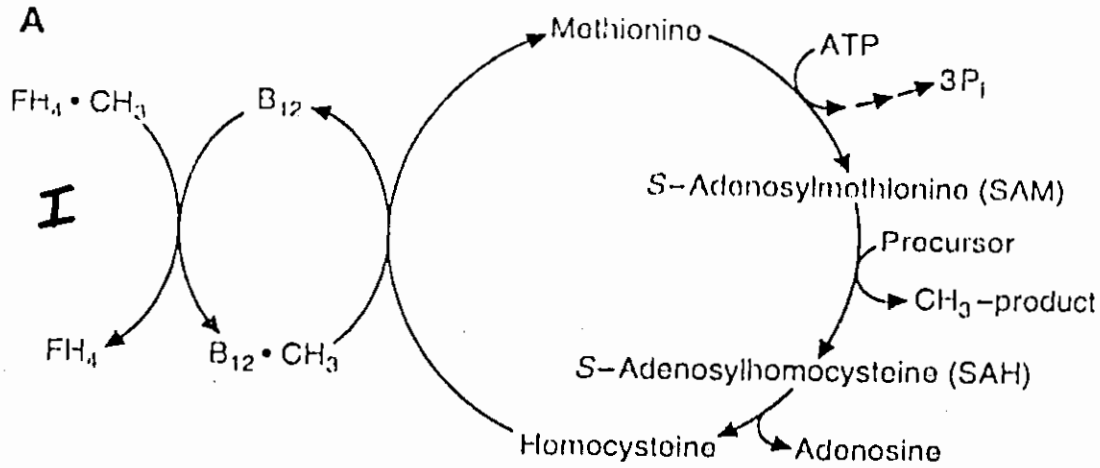


Figure: 11_57
S-adenosylmethyltransferase reaction.

- Nucleotides $\xrightarrow{SAM}$ methylated nucleotides
- Guanidino acetate $\xrightarrow{SAM}$ Creatine
- Acetylserotonin $\xrightarrow{SAM}$ Melatonin

Relationship of FH_4, B_{12} and SAM

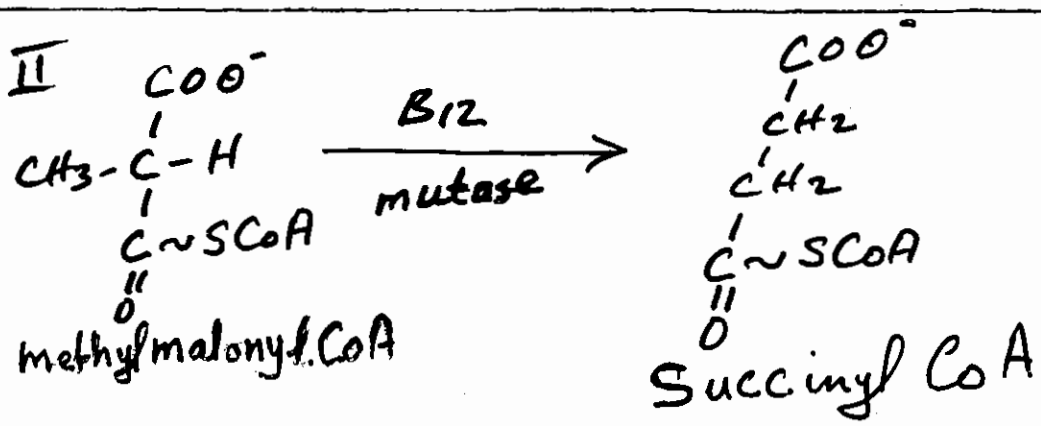


B

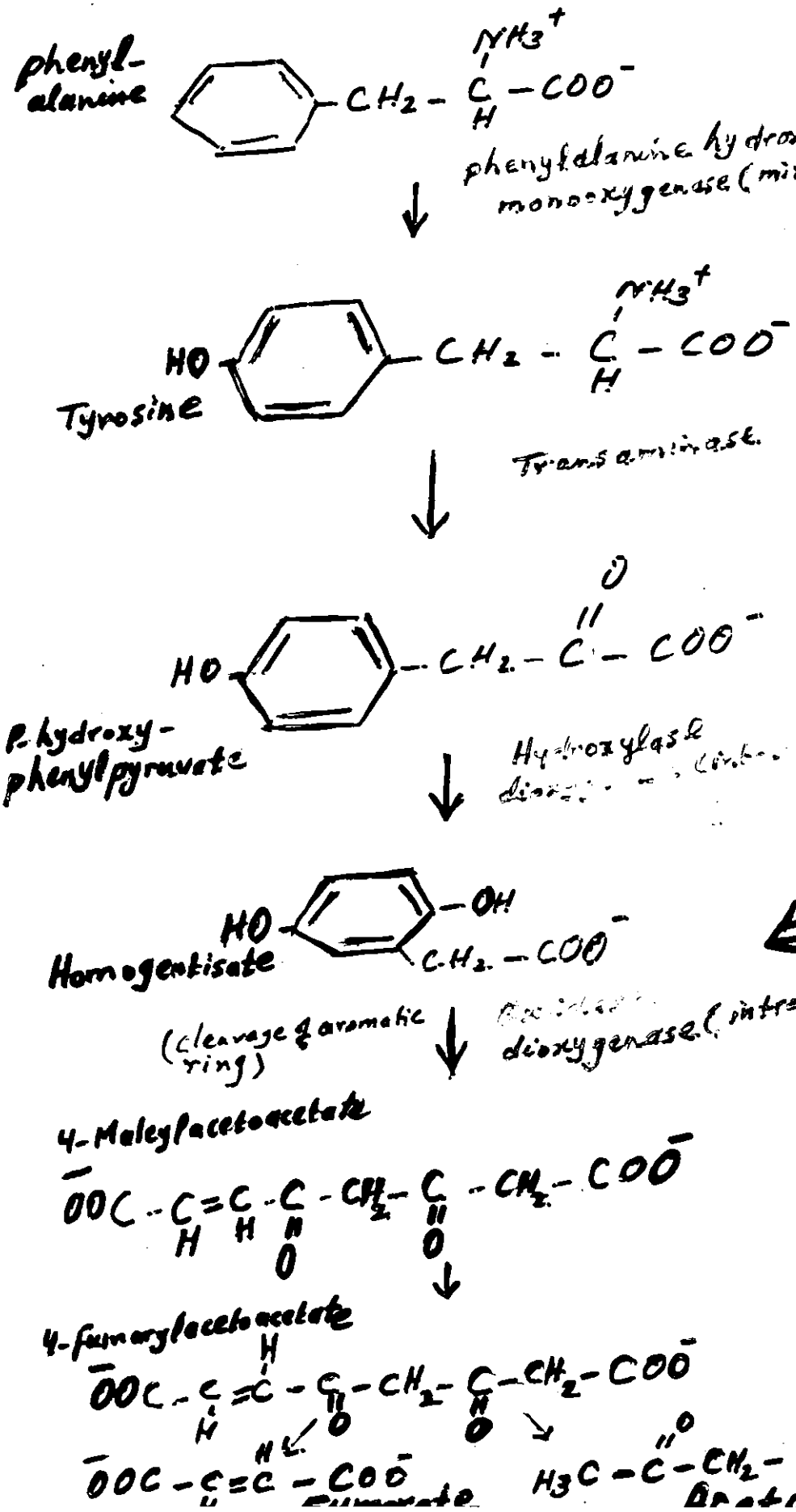
Precursor		Methylated product
Norepinephrine	SAM →	Epinephrine
Guanidinoacetate	SAM →	Creatine
Nucleotides	SAM →	Methylated nucleotides
Phosphatidylethanolamine	SAM →	Phosphatidylcholine
Acetylserotonin	SAM →	Melatonin

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

II



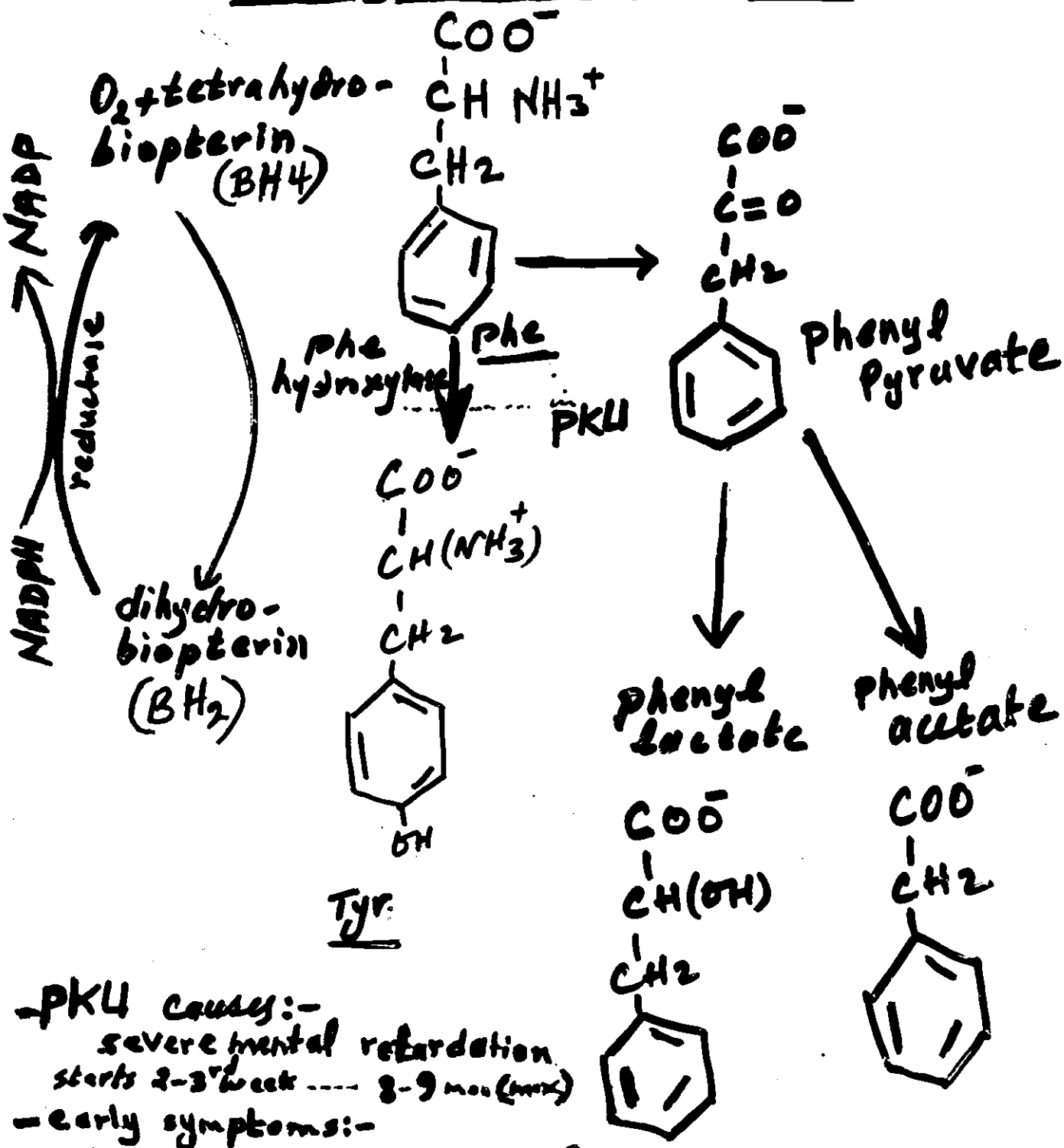
Degradation of phenylalanine & Tyrosine



* 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)

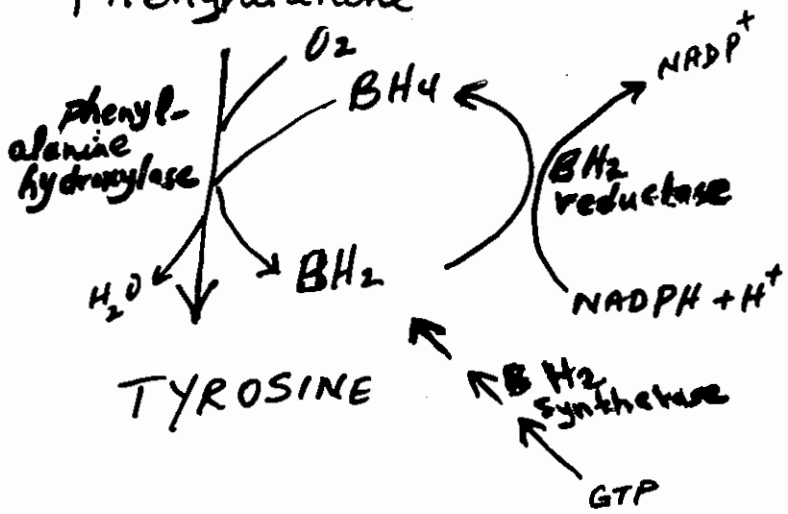


- PKU causes:-
  severe mental retardation
  starts 2-3rd week ---- 8-9 mo. (max)
- early symptoms:-
  delayed developements, poor feeding
  vomiting

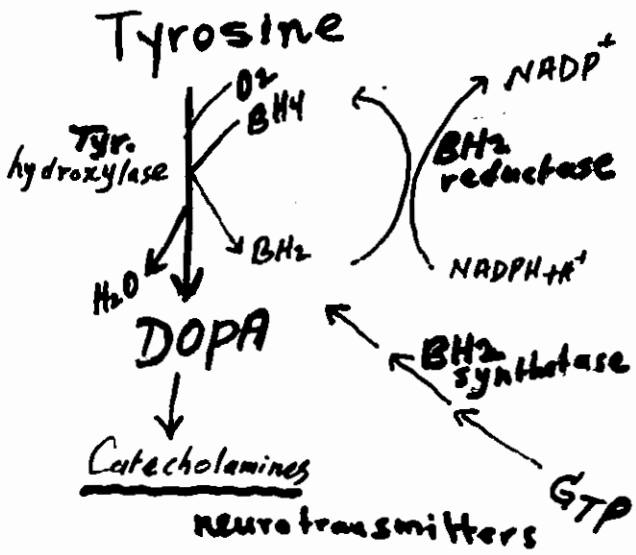
- Incidence: 1:10,000

Biosynthetic Reactions Involving Amino acids and Tetrahydrobiopterin (BH4)

Phenylalanine

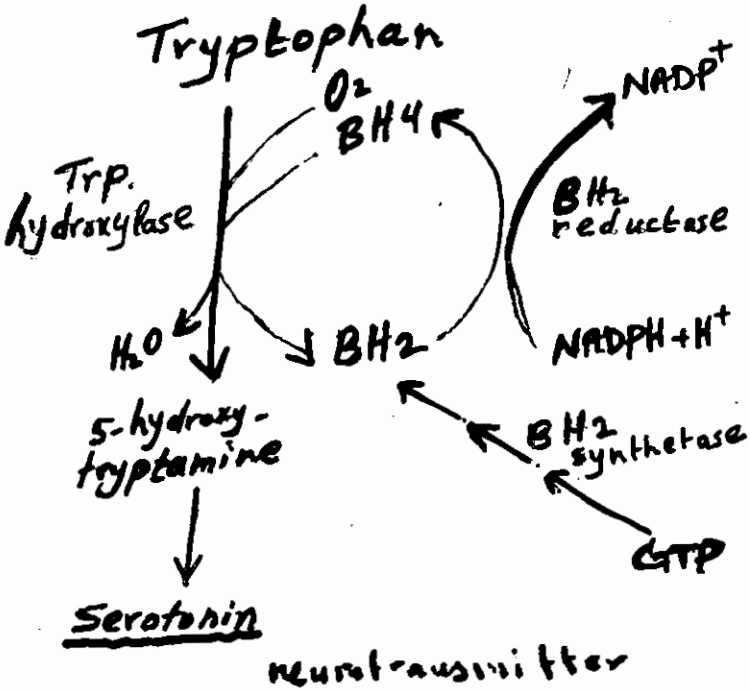


Tyrosine

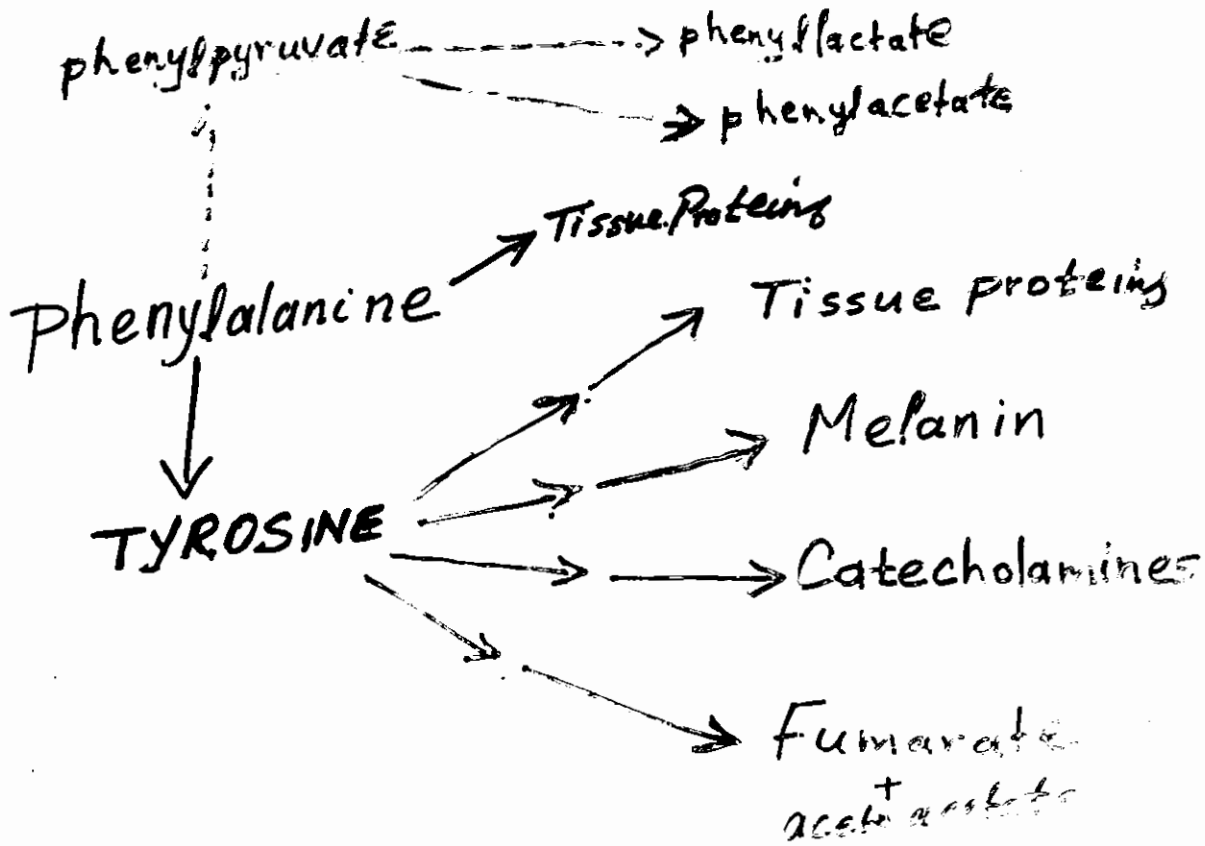


Deficiency in BH_2 reductase or synthetase →
- hyperphenylalaninemia
- decreased synthesis of
  - catecholamines
  - serotonine
- require therapy with BH4 + DOPA and 5-hydroxy trp – not always effective

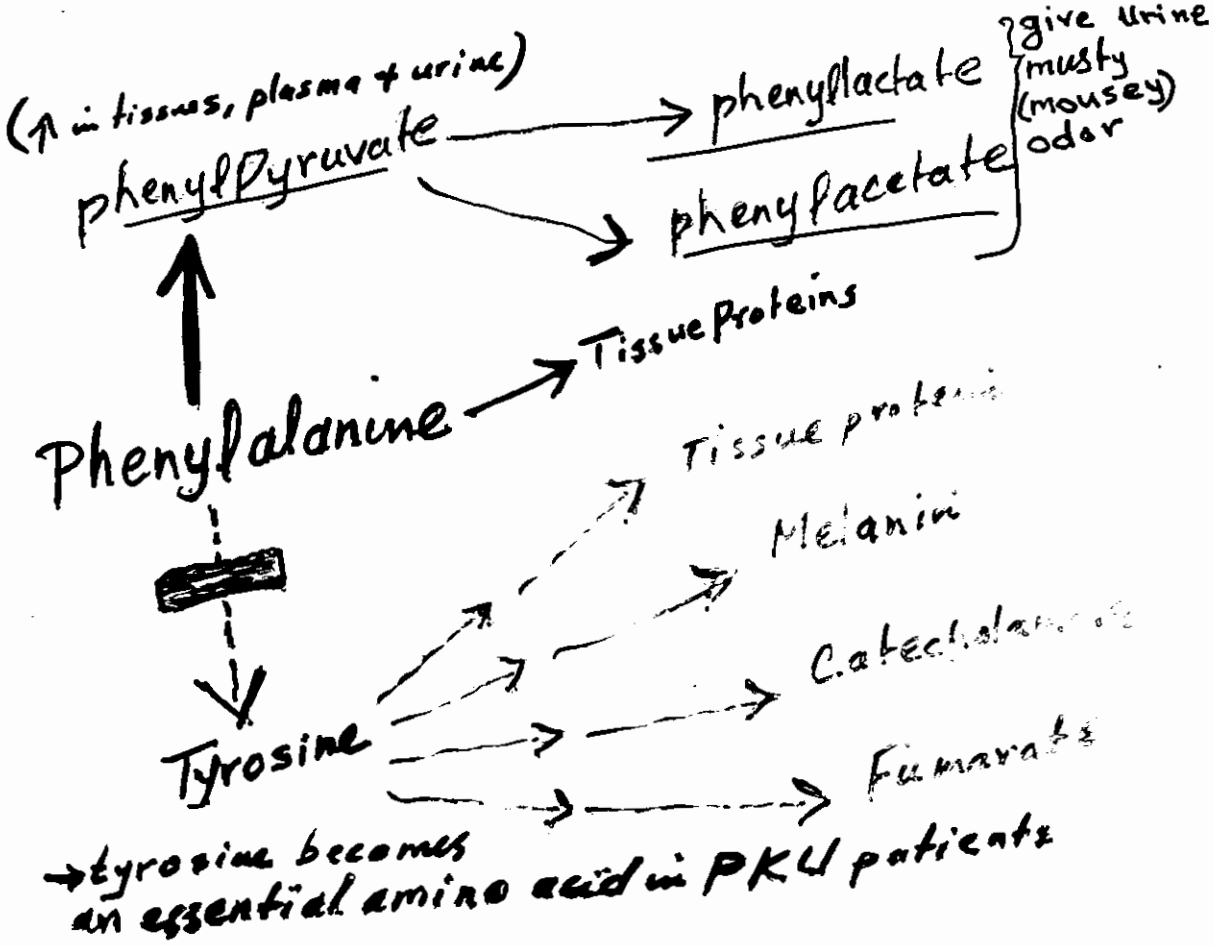
Tryptophan



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 hyperphenylalaniemia

Characteristics of PKU :-

- Elevated level of phenylalanine ↑ ⟶ phenylacetate ↑, ↑ phenylacetate and phenyl pyruvate ↑.
- CNS symptoms : mental retardation, failure to walk, talk & [illegible] seizure, tremor. IQ > 50
- Hypopegmentation:
  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.
  - Lack of neonatal symptoms, Lab. test for elevated phenylalanine is mandatory for detection
  - normal level at birth. Test to be done 1–2 days after protein feeding

- Prenatal Diagnosis of PKU :-

- >100 different mutations 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.
- Avoid ASPARTAN (artificial sweetner)

- Maternal PKU :-

Maternal PKU syndrom

- ⟶ mental retardation
  - Congenital heart abnormalities in fetus.

- Dietary control starts before conceptions.

Albinism:-

Groups of disorders in Tyrosine → → → Melanin.

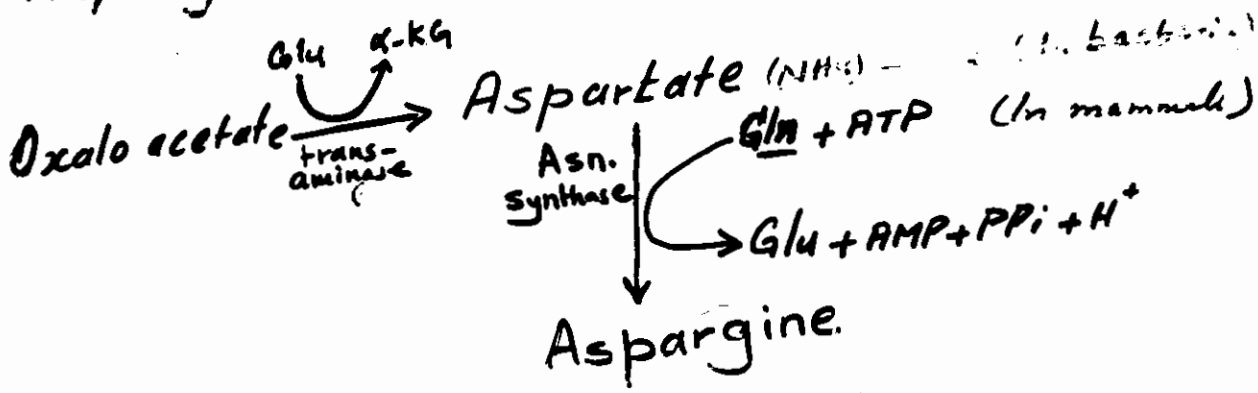
→ Partial to full absence of pigment.

Several modes of inherittance:

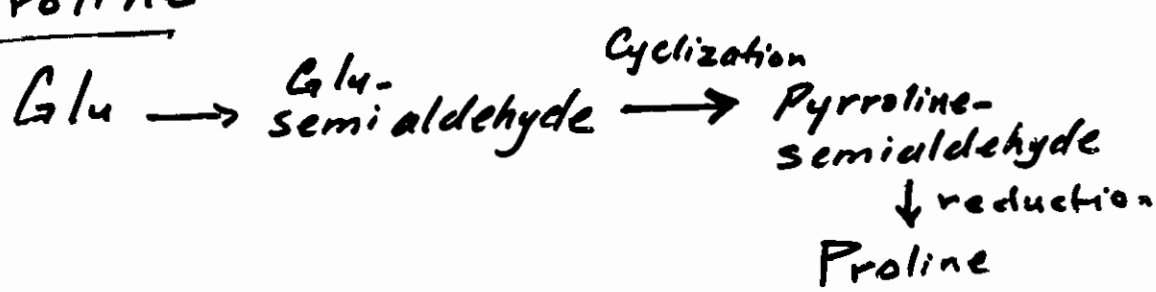
- autosomal recessive.
- autosomal dominant.
- X- linked.

- Most severe form results from TYRUSINASE DEFIEIENCY
  - causing total absence of melanine:
    - white hair, skin and iris color plus vision defects.
      abscence of pigment
      and photophobia → · sun light painful to eyes.
      · sun burns easily.
      · do not tan.

2. Aspargine

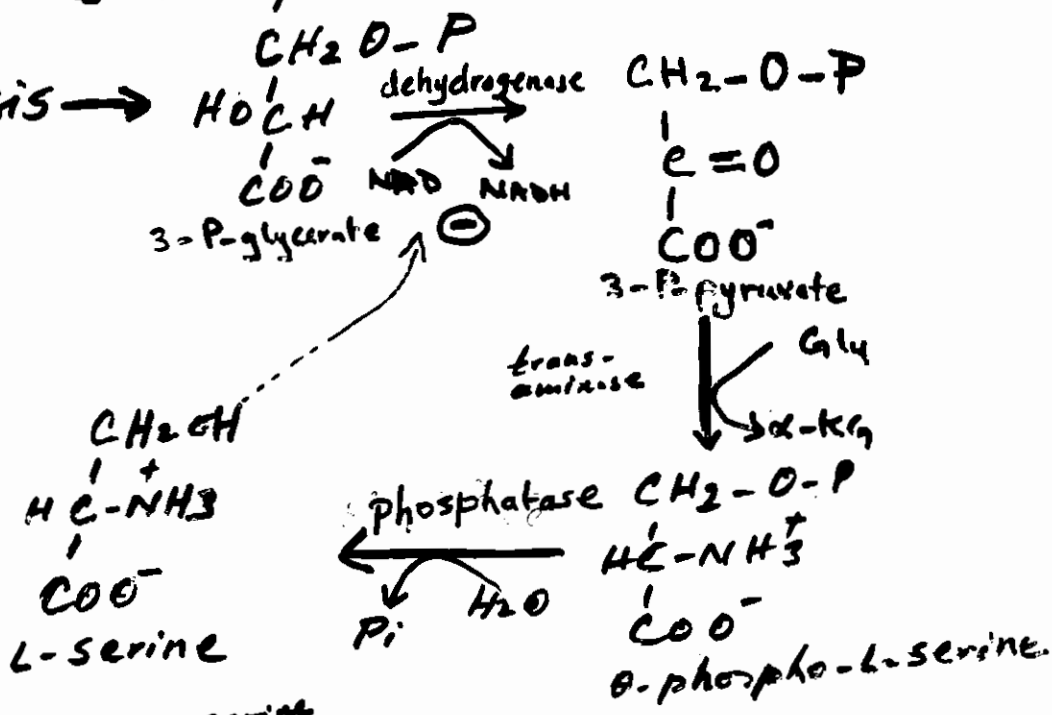


C. Proline



D. Ser., Gly., Cys.

(i) Glycolysis →



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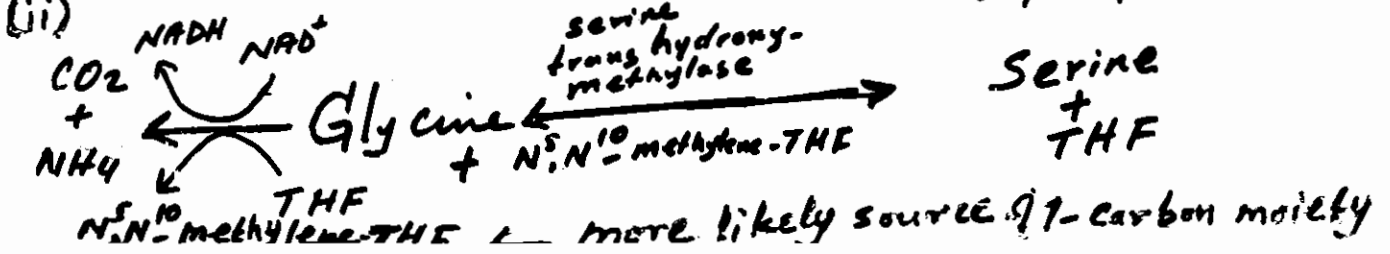


N5,N10-methylene-THF ← more likely source of 1-carbon moiety

Biosynthesis of Non-essential Amino Acids: I

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 deaminat...

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

High protein diet Glu → α-KG

B synthesis by Amidation

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

Biosynthesis of Special Products (I)

✓ - Tyrosine
- Skin → melanin pigment
- Adrenal medulla → Epinephrine
- Brain → Norepinephrine, Dopamine
- Thyroid → Thyroxine

→ a.a. → Bases & DNA + RNA

- Tryptophan
- Liver → Nicotinamide
- Nervous System, Intestinal mucosa, Platelets → Serotinine
- GI bacteria → Indoles

- Histidine → Histamine { chem. messenger, vasodilator

- Glutamate → GABA (γ-aminbutyrate) inhibitory neurotransmitter

✓ - Serine → ethanolamine → (+ choline, + Acetyl CoA) → Acetylcholine

✓ - Gly + Arg → Creatine

→ - Glycine + succinyl CoA → → → Heme

✓ - Glu - Cysteine - Glycine → Glutathione

- Lys $\xrightarrow{\text{methylation}}$ → → CARNITINE

- Ornithine $\xrightarrow[\downarrow CO_2]{}$ Putrescine $\xrightarrow[\downarrow CO_2]{SAM}$ Spermidine $\xrightarrow[\downarrow CO_2]{SAM}$ Spermine

Products formed from tyr & phe

CATECHOLAMINES

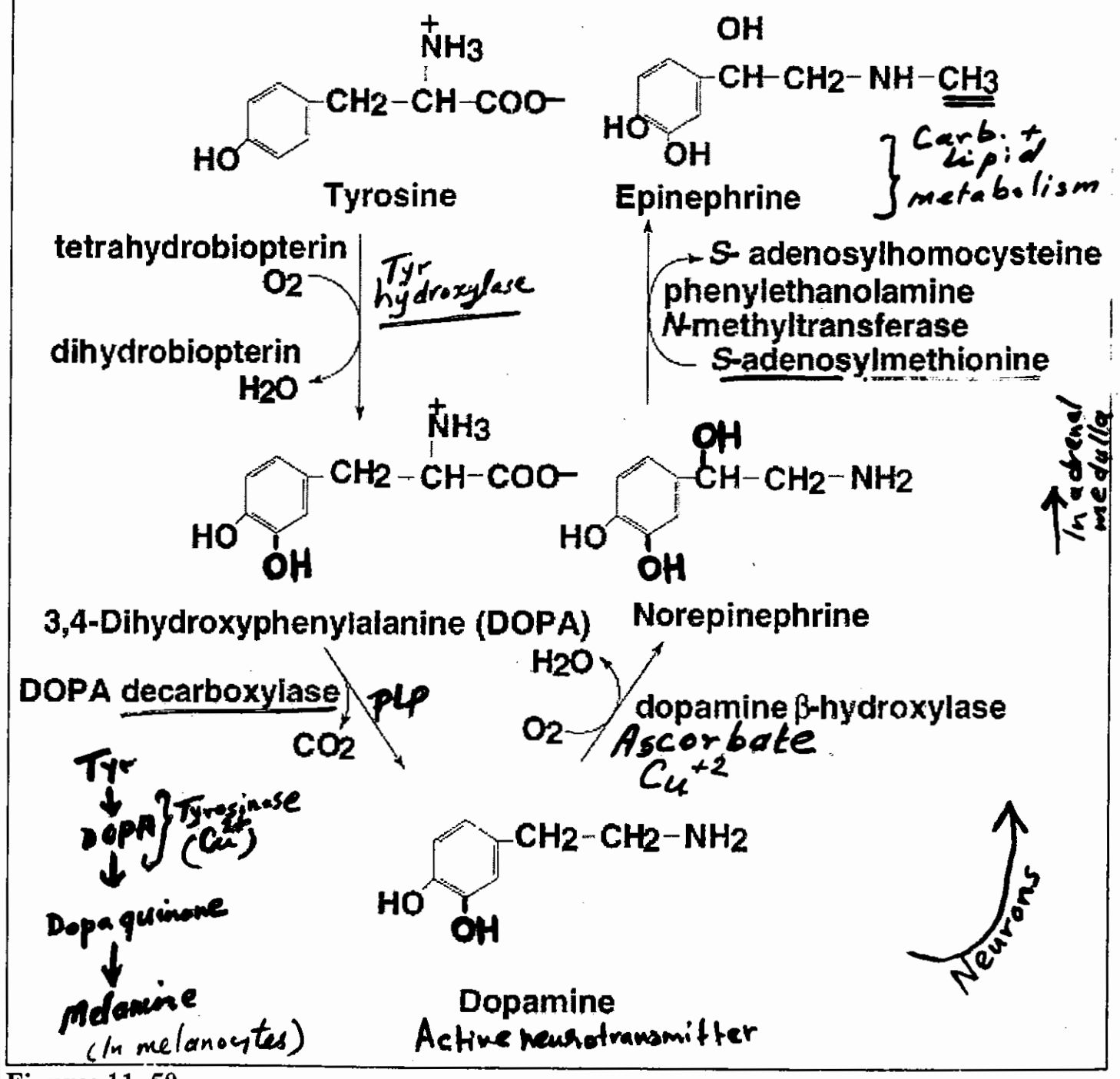
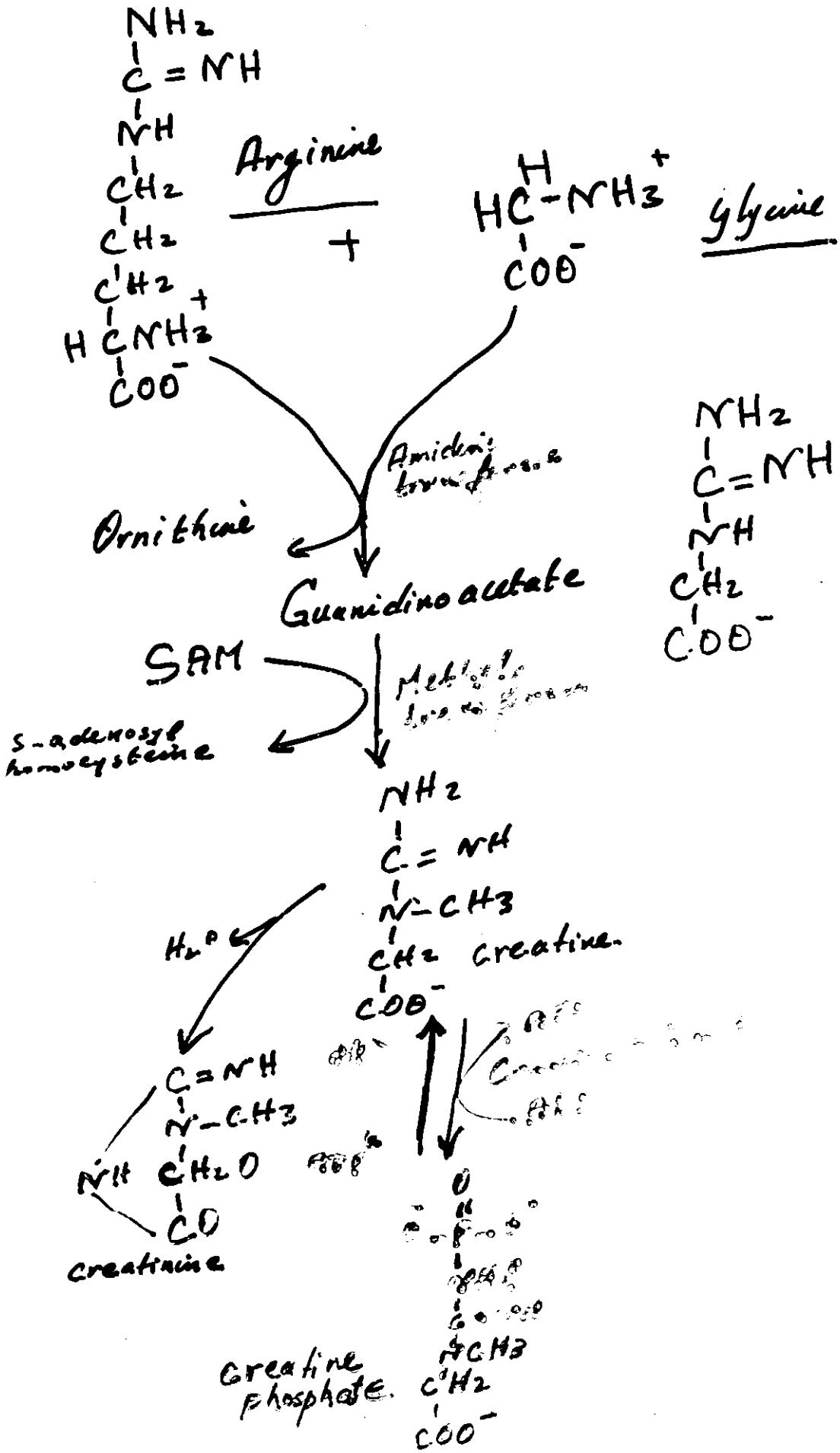


Figure: 11_50
Synthesis of catecholamines.

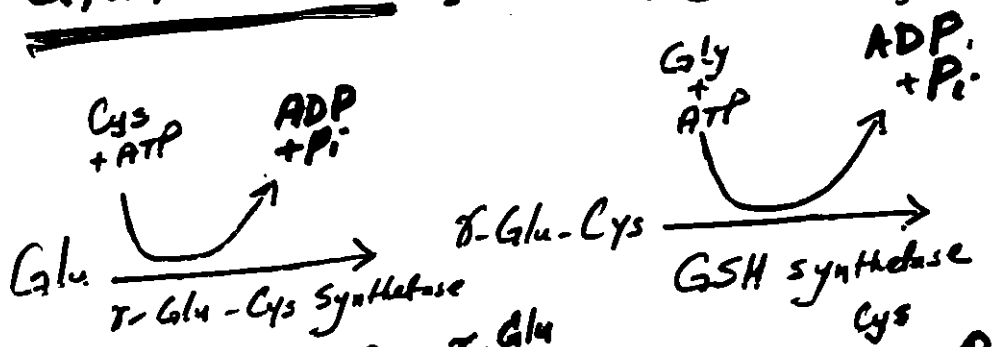
Degradation $\xrightarrow{\text{MAO} + \text{Catechol O-methyl transferase (COMT)}}$ I - Vanillylmandelate (VMA) II - Homovanillic acid } in urine

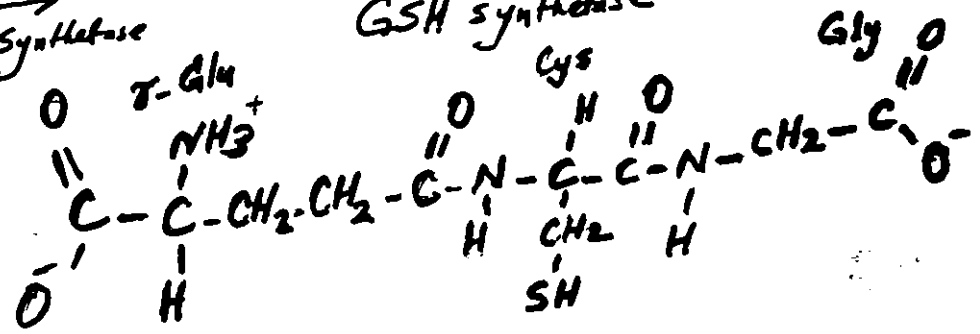
I [Epinephrine, Norepinephrine]
II DOPAMINE

Creatine Metabolism



Glutathion :- Sulfhydryl buffer + An Antioxidant





γ-Glu – Cys – Gly
|
S
|
S
|
γ-Glu – Cys – Gly

GSSG
Oxidized glutathione

$$2\,GSH + R\text{-}O\text{-}OH \xrightarrow{\text{GSH peroxidase}} GSSG + H_2O + ROH$$

$$GSSG \xrightarrow[\text{GSH reductase}]{H^+ + NADPH \;\rightarrow\; NADP^+} 2\,GSH$$

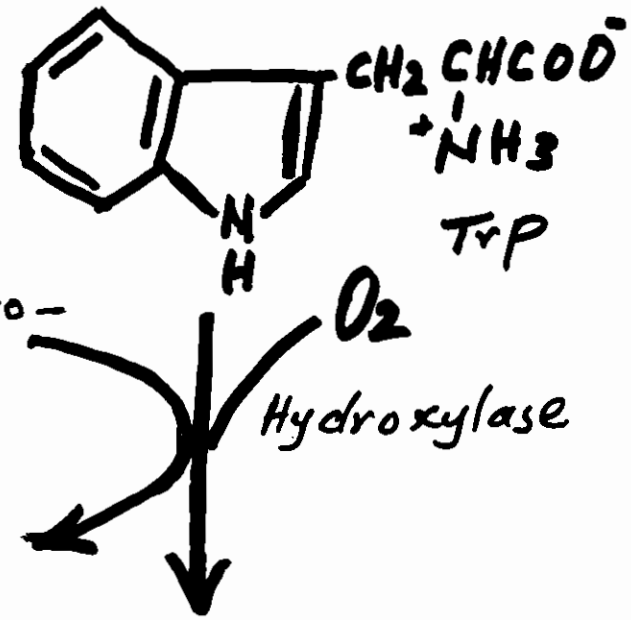
Functions:

- Reductant
- Conjugation of drugs → more polar
- transport of amino acids across cell membrane
- Cofactor for some enzymatic reactions
- Facilitate rearrangement of protein disulfide bonds

Serotonin

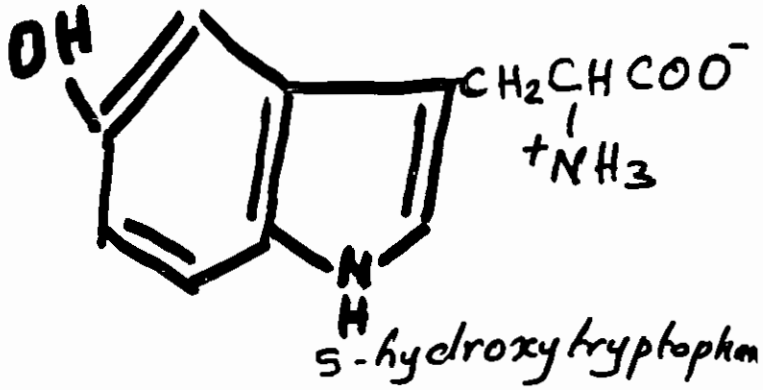
(5-hydroxytryptamin)

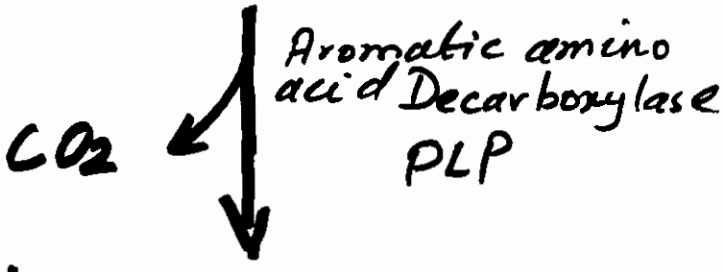
- Synthesized & stored at several sites - (largest in intestinal mucosa)
- Degraded by MAO
- Smaller amounts in CNS (neurotransmitter) & platelet

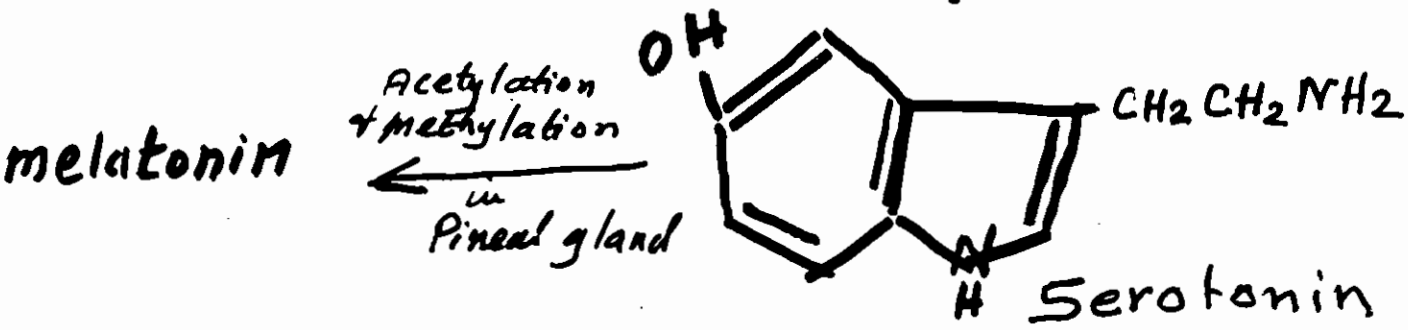


Functions:

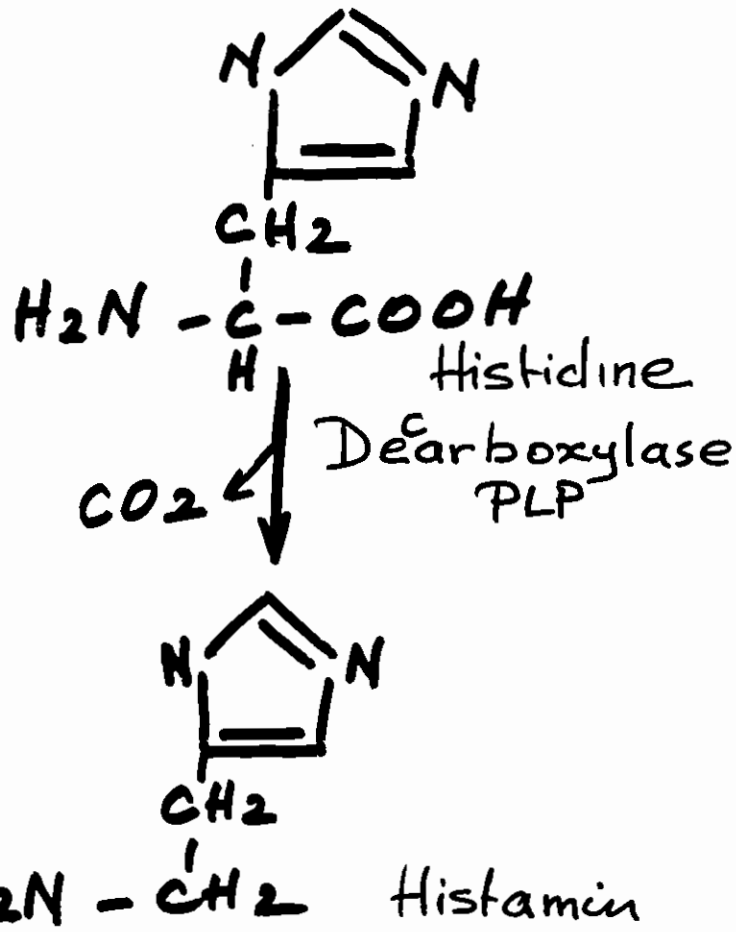
- Pain perception
- Regulation of
  - sleep
  - appetite
  - temp
  - Blood pressure
  - Cognitive functions
  - mood







Histamin



Secreted by mast cells
Chemical messenger:-
- Allergic reactions
- inflammatory "
- Gastric acid secretion
- vasodilator