

Amino Acid Metabolism

.1

Introduction:

Essential Amino Acids

Lys, (Iys or His) Ile, Leu, Val, Met,
Thr, Trp, Phe

Non-essential amino acids

Ketogenic " "

Glucogenic " "

Nitrogen Balance

- Ve

Starvation, prolonged a.a. administration

+ Ve

Growing children, pregnancy
recovery after starvation, wasting
disease

No storage form of amino acids

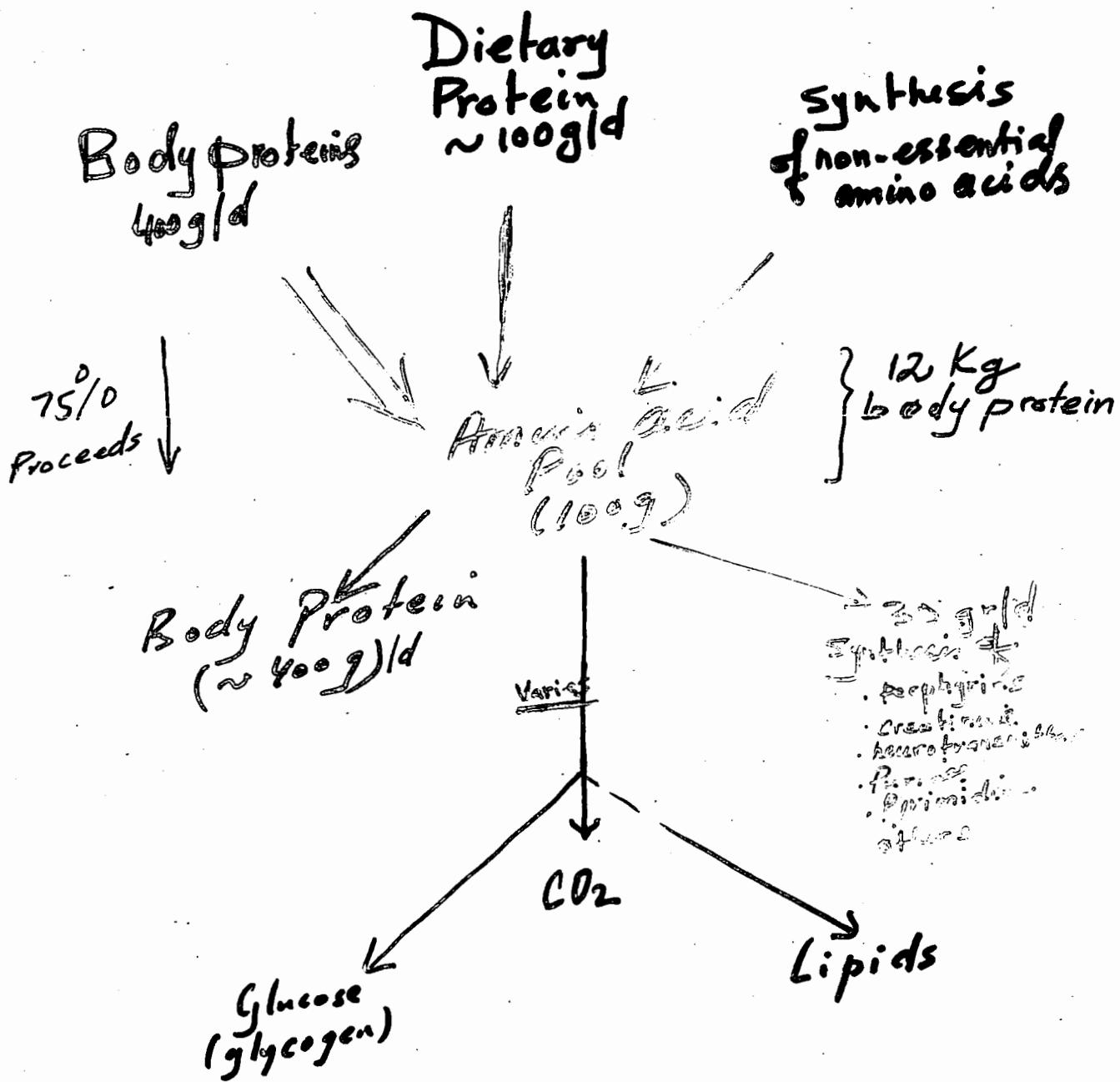
Diet
de novo synthesis
Protein degradation

} → a.a.

Catabolism

Biosynthetic
need

Overall Nitrogen Balance



PROTEIN DEGRADATION

A. Lysosomal Protein turnover:- Acid Hydrolases

ATP-independent system
degrades primarily extra-cellular proteins - taken by endocytosis-Heterophagy and intracellular Protein-Autophagy

B. Ubiquitine-Proteasome Pathway

- degrades endogenous proteins
- Ubiquitination
- tagged proteins recognized by Proteasome
- requires ATP

Chemical Signals for Protein degradation

- oxidized proteins
- tagged with ubiquitin
- Proteins rich in PEST sequence
Pro, Glu, Ser, Thr
- N-terminal ASP-short t½
- N-terminal Ser long t½

Proteins with short t½
reg. proteins, damaged,
misfolded - min or hrs

Long t½ in weeks
majority of cellular proteins

t½ in months or yrs.
Structural proteins e.g. Collagen

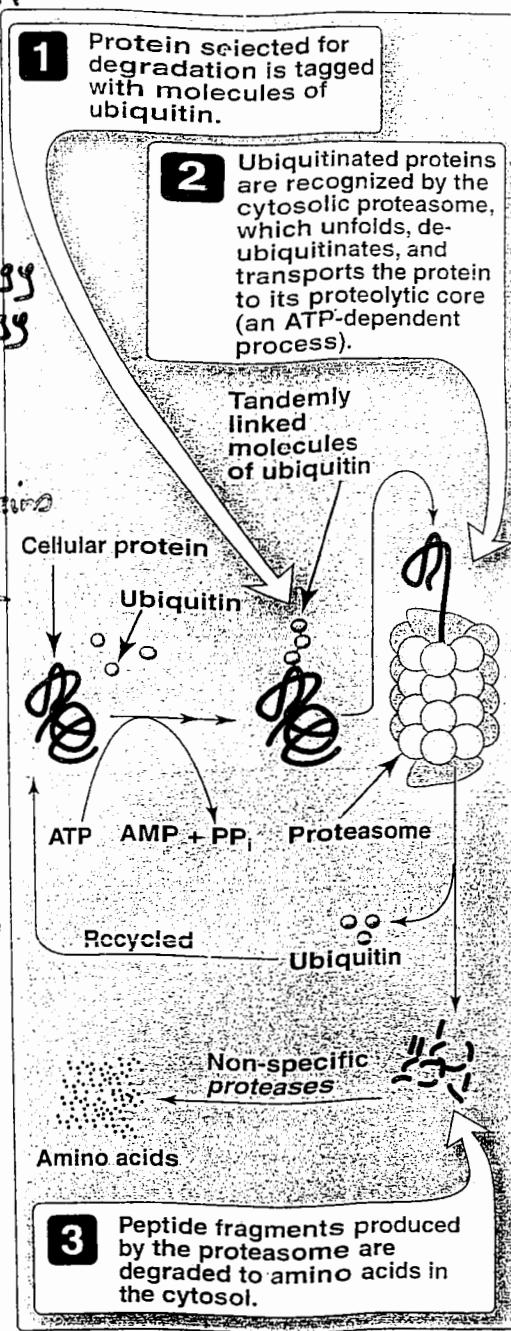
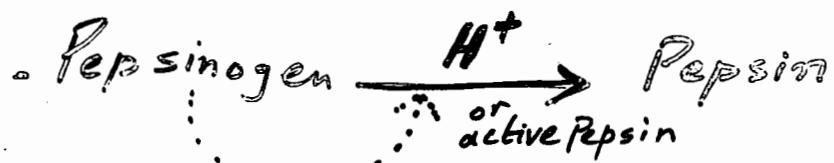


Figure 19.3
The ubiquitin-proteasome degradation pathway of proteins.

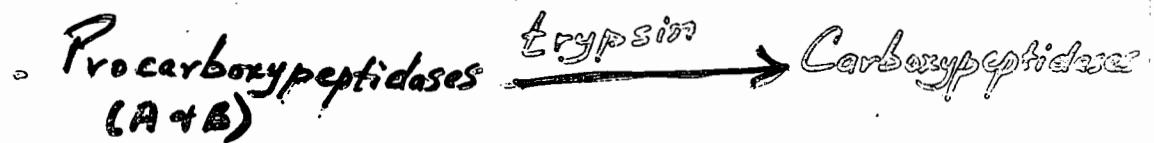
Activation of Gastric & Pancreatic Zymogens

5b

Proenzymes (zymogens) → Active Enzymes



acid-induced conformational change → can cleave itself



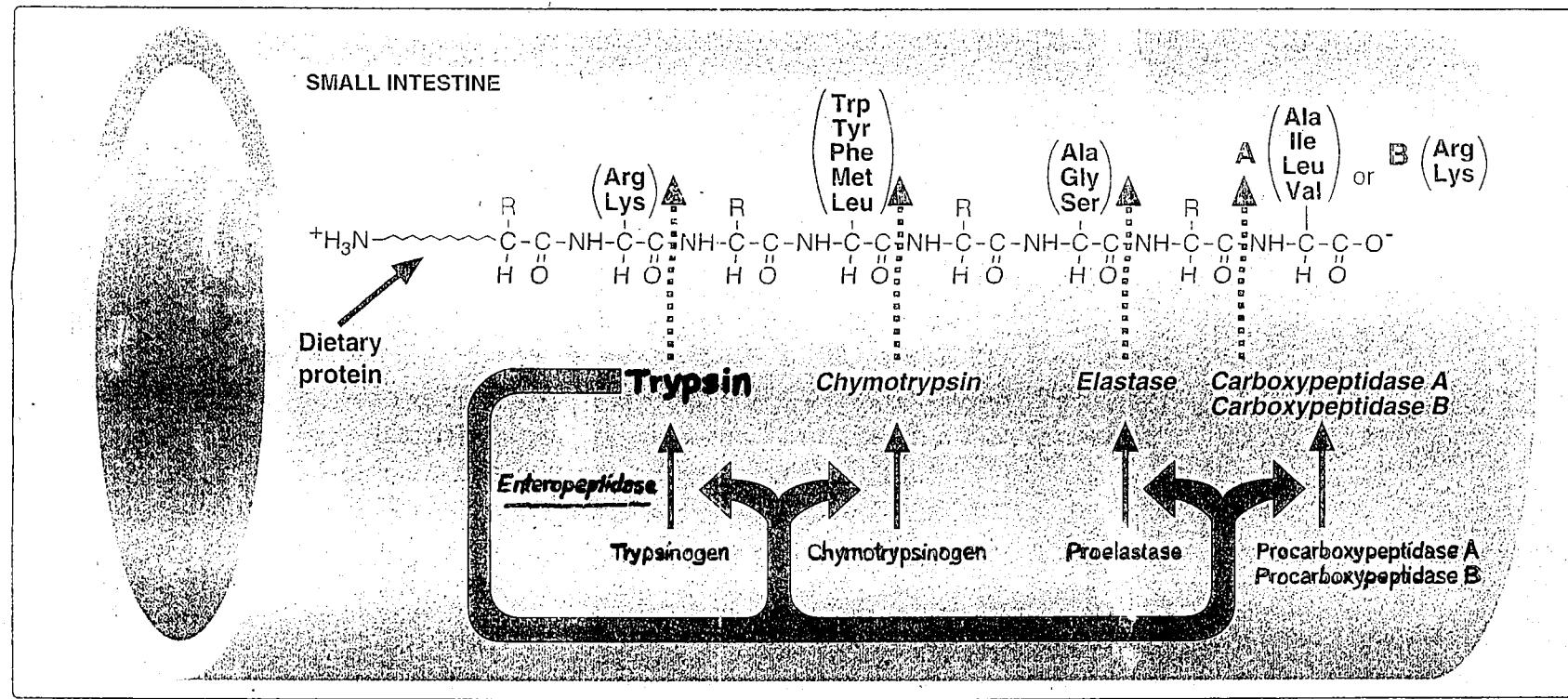


Figure 19.5

Cleavage of dietary protein by proteases from the pancreas. The peptide bonds susceptible to hydrolysis are shown for each of the five major pancreatic proteases. [Note: *Enteropeptidase* is synthesized in the intestine.]

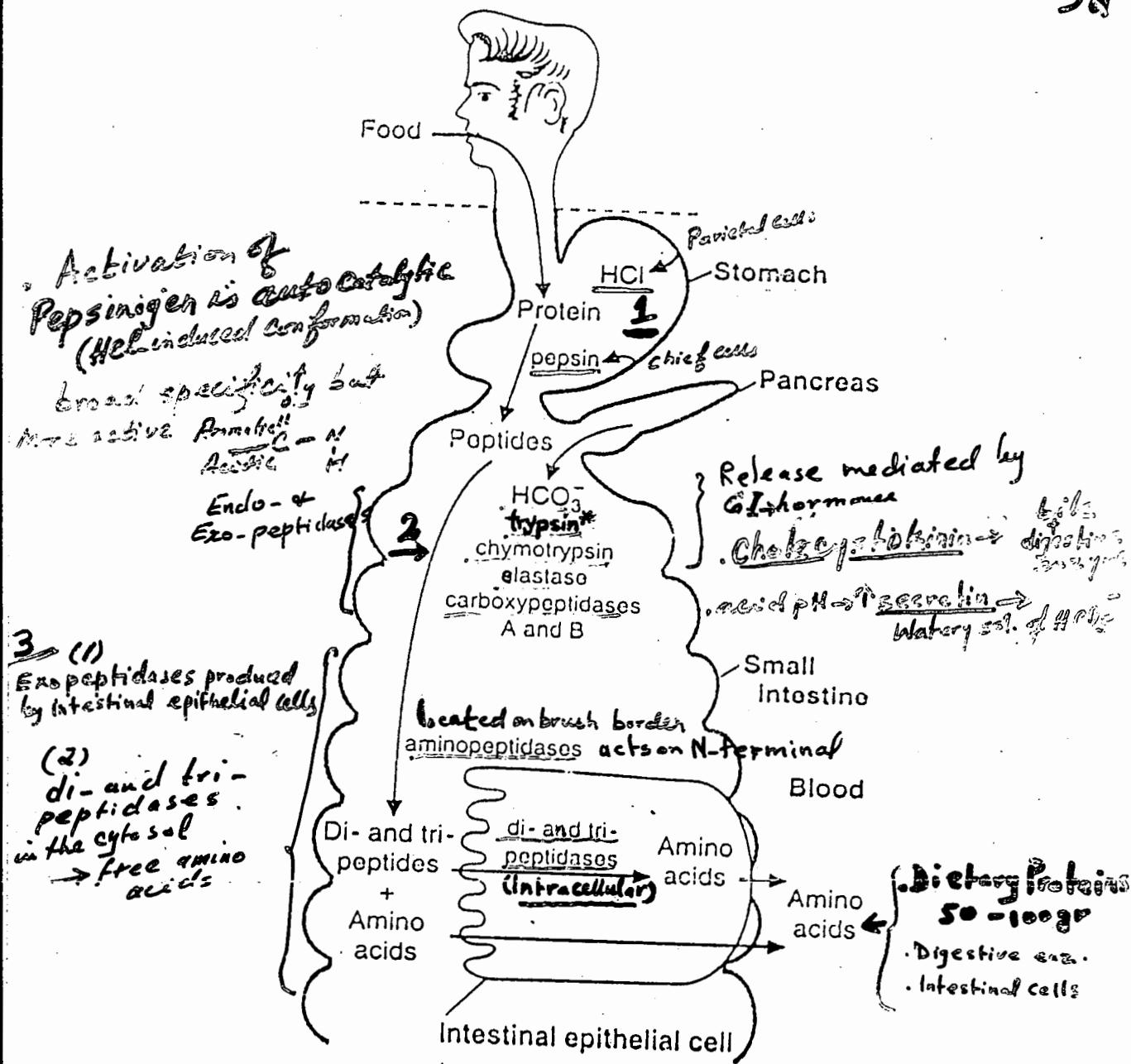


Fig. 37.3. Digestion of proteins. The proteolytic enzymes:- pepsin, trypsin, chymotrypsin, elastase, and the carboxypeptidases, (A+B) are produced as zymogens that are activated by cleavage after they enter the gastrintestinal lumen (see Fig. 37.4).

* At luminal surface of intestinal mucosal cells

Trypsinogen → Trypsin (enterokinase) → Enteropeptidase

- Transport of amino acids into Cells:-

- Major Na^+ -dependent cotransport (in all tissues)
- Less Extent Facilitated

[Glu transport is Na^+ -dependent cotransport in only intestinal and renal epithelia - but facilitated in all others]

- Different Isoforms in different tissues.
- at least 7 different transport systems with overlapping specificities
- Differences between tissues
e.g. Glu present in Liver but not other tissues or as an isoform
- Over-lap in specificities :-
most amino acids have more than one carrier
- Branched-chain amino acids, metabolized primarily by muscle

- Defective transport across intestinal and renal epithelium :-

Cystinuria : - 1 in 7000 individuals

Cystine, Lys, Arg & orn dibasic a.a

• disorder of proximal tubule's reabsorption of filtered orn & dibasic a.a.

• one of the most common inherited diseases

• Kidney stones (calculi) block urinary tract

ABSORPTION OF AMINO ACIDS

I. Secondary Active Na^+ -dependent transport:

(cotransport of Na^+ and amino acids)

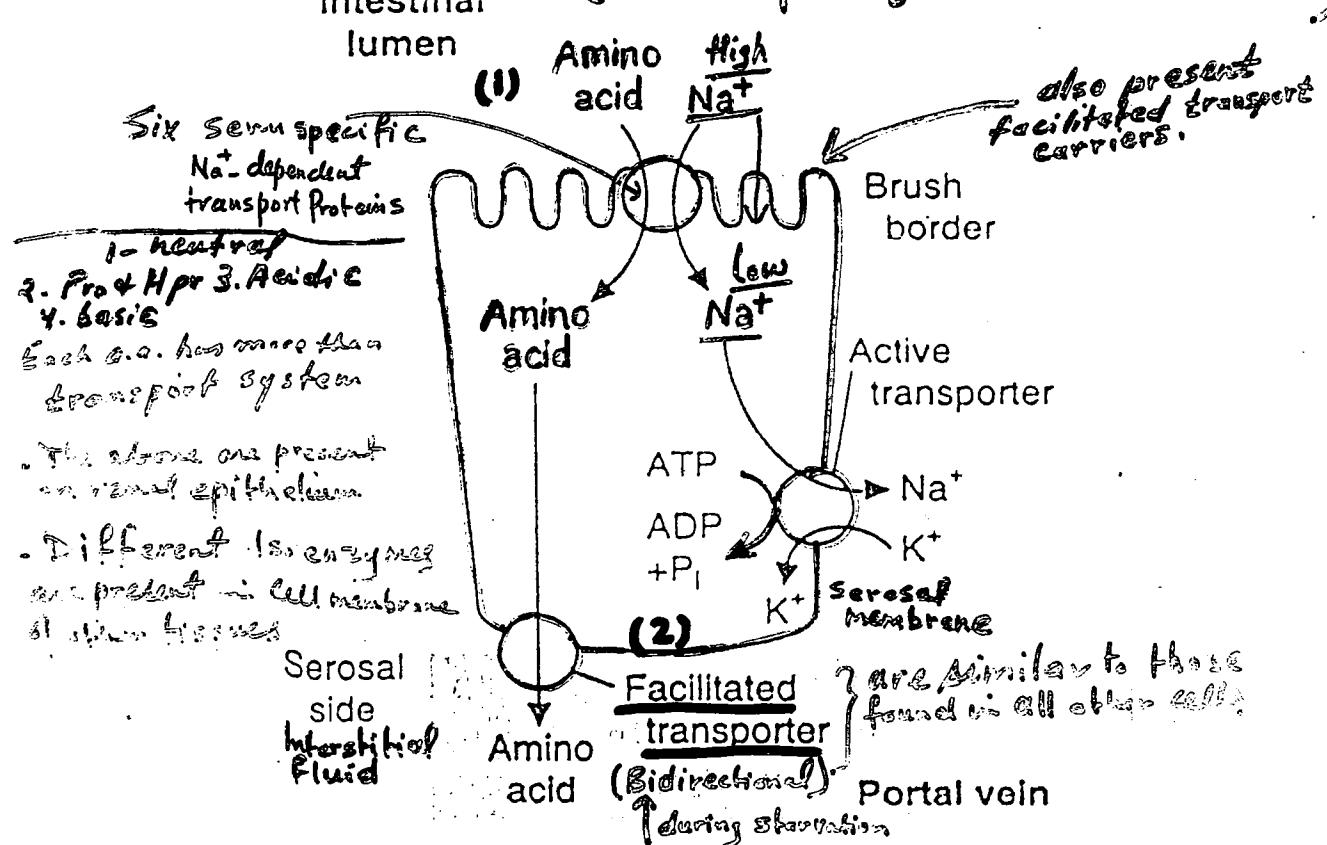
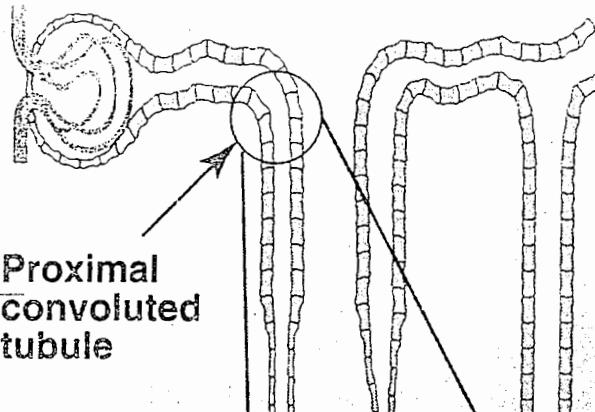


Fig. 37.6. Transepithelial amino acid transport. Na^+ -dependent carriers transport both Na^+ and an amino acid into the intestinal epithelial cell from the intestinal lumen. Na^+ is pumped out on the serosal side (across the basolateral membrane) in exchange for K^+ by the Na^+, K^+ -ATPase. On the serosal side, the amino acid is carried by a facilitated transporter down its concentration gradient into the blood. This process is an example of secondary active transport.

CYSTINURIA



Proximal
convoluted
tubule

Cystinuria is a disorder of the proximal tubule's reabsorption of filtered cystine and dibasic amino acids (lysine, ornithine, arginine).

Cys
Stones ←

Arginine
Cystine
Ornithine
Lysine

Arginine
Cystine
Ornithine
Lysine

The inability to reabsorb cystine leads to accumulation and subsequent precipitation of stones of cystine in the urinary tract.

Nitrogen Metabolism ¹²

Catabolism of amino acids

- Removal of amino groups - a must
 • transamination

 • oxidative deamination

 • Amino groups \longrightarrow Urea

- Carbon skeleton

\longrightarrow Energy + CO_2 + H_2O

\longrightarrow Glucose

\longrightarrow Fatty acids
and Ketone bodies

AMINO ACID METABOLISM

Degradation of Amino Acids:-

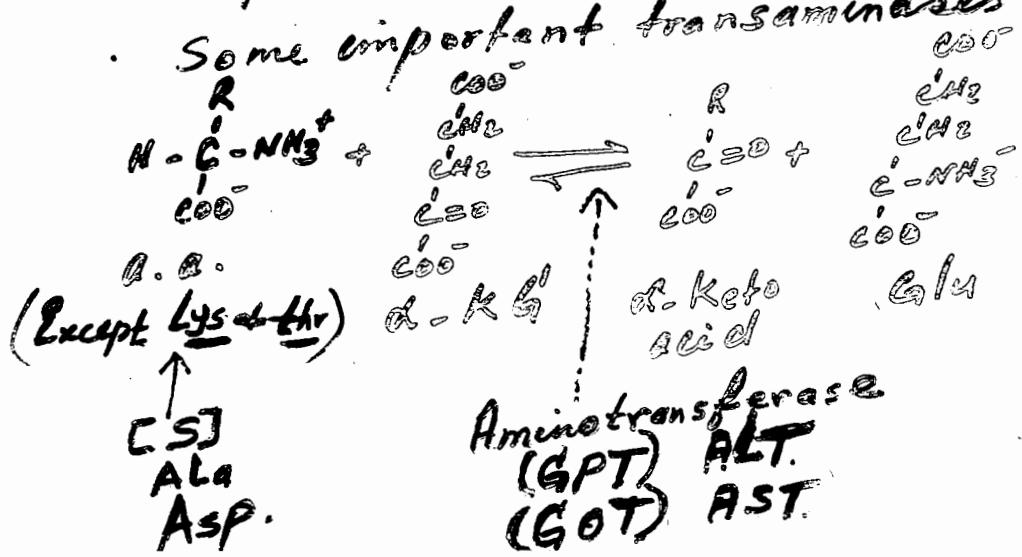
I - Removal of amino group
and its utilization
[Amino acid metabolism]

II - Conversion of the Carbon
chain into $\begin{cases} \text{Carbohydrate} \\ \text{lipid} \\ \text{Energy} + \text{CO}_2 + \text{H}_2\text{O} \end{cases}$

Removal of the amino group

1. Transamination

- Enz.: Transaminases (amino transferases)
- Cofactor: Pyridoxal phosphate (B6)
- Widely distributed
- Equilibrium constant 1 to 10
- Some important transaminases



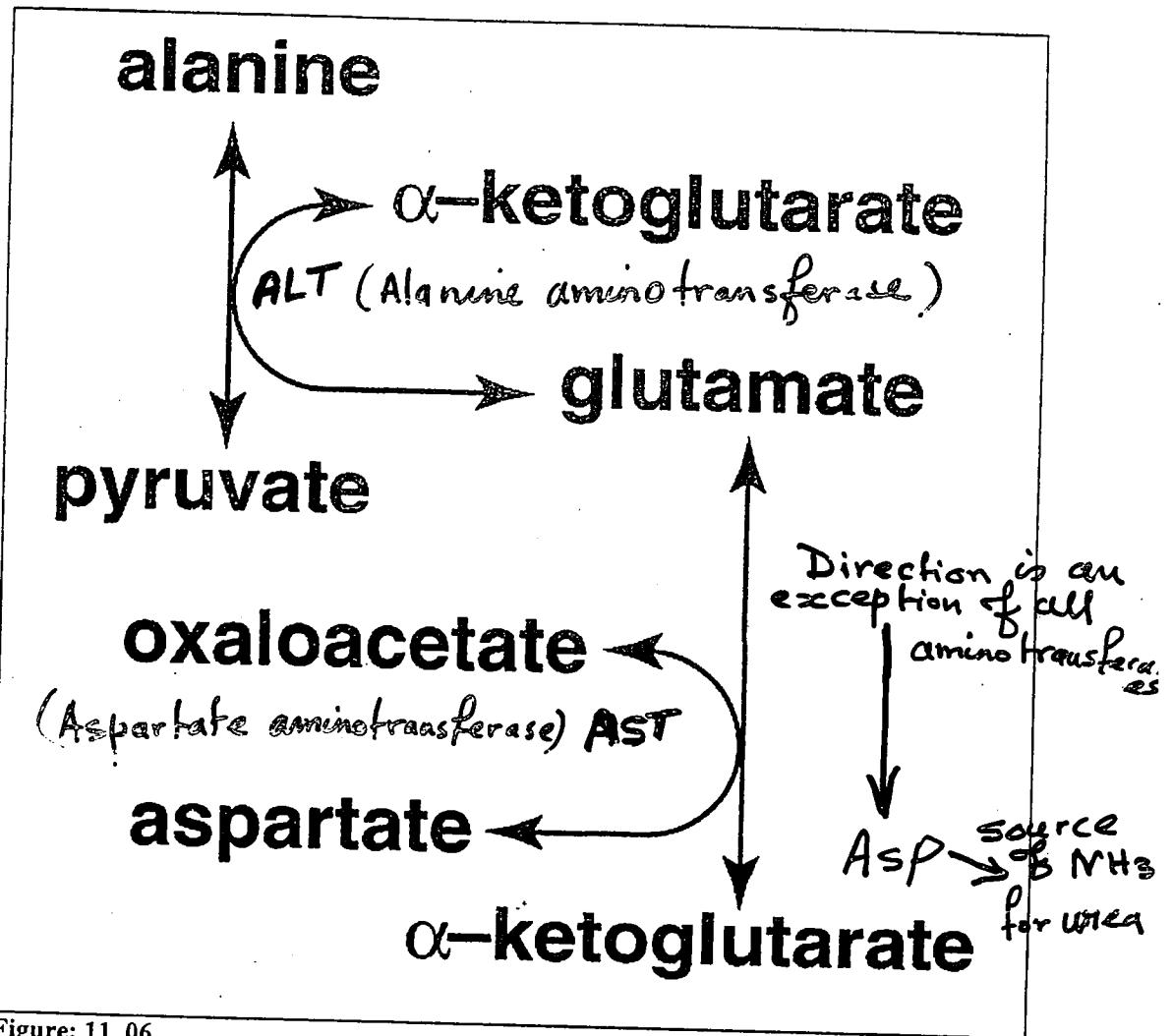
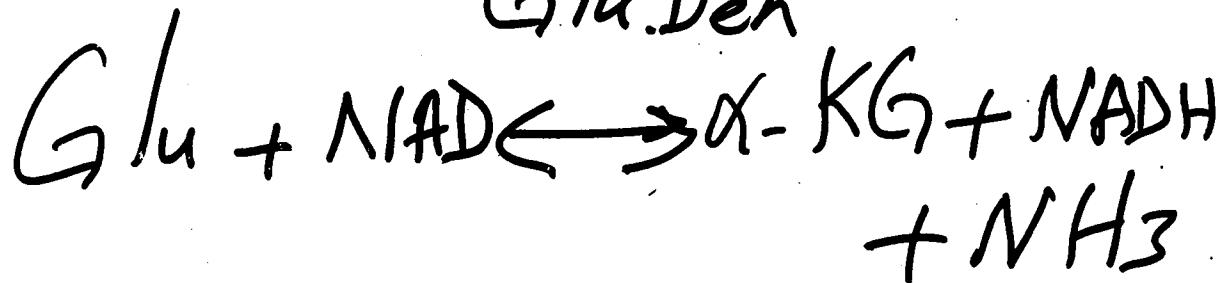


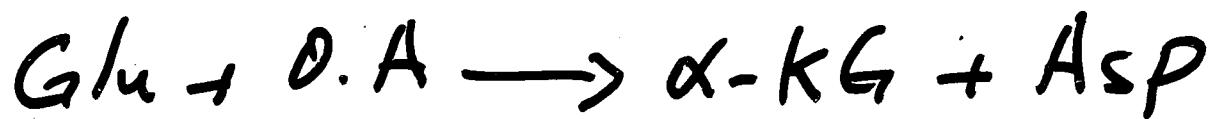
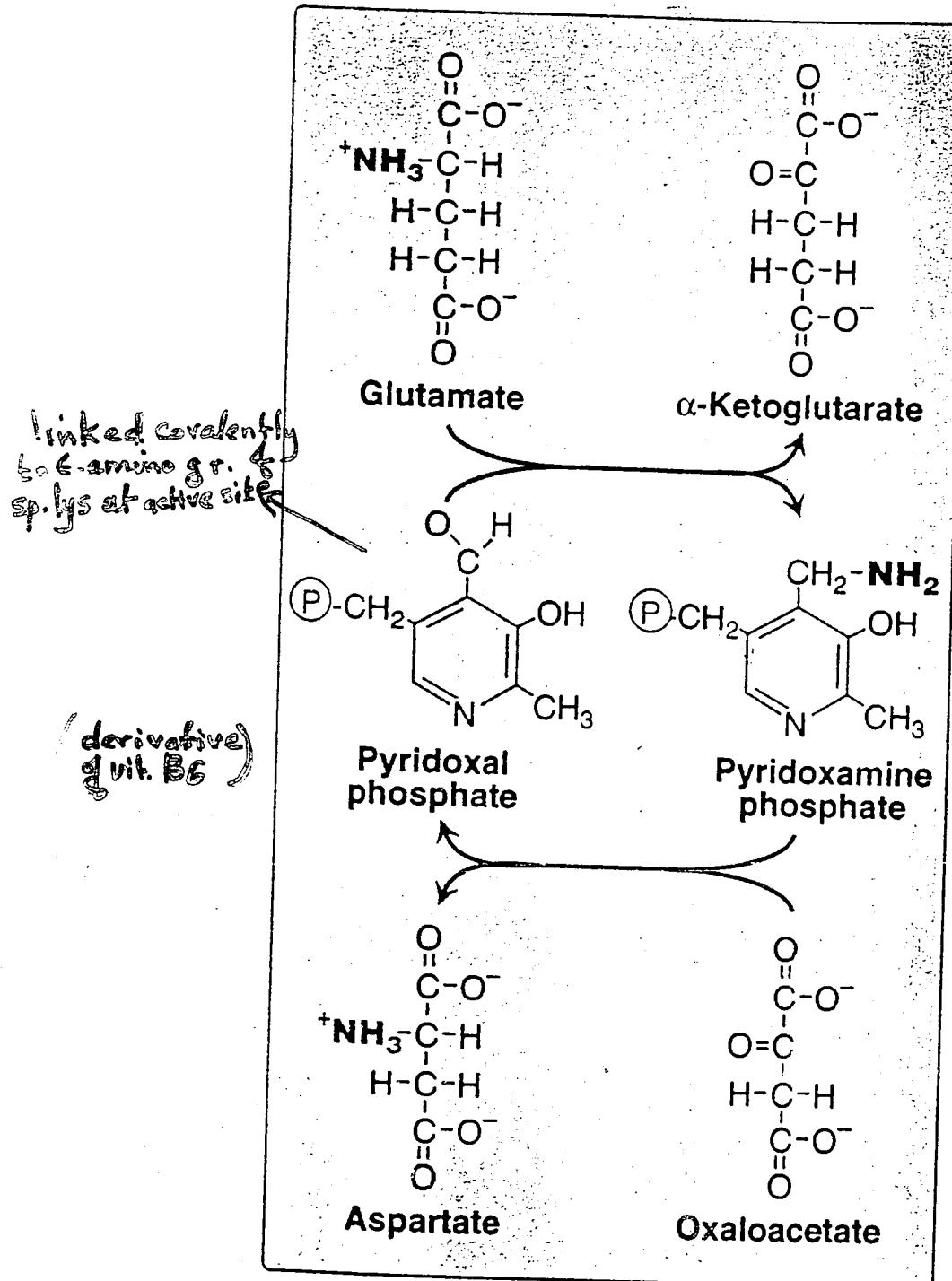
Figure: 11_06
A coupled transamination reaction.
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DX-Deamination

Glu.Deh

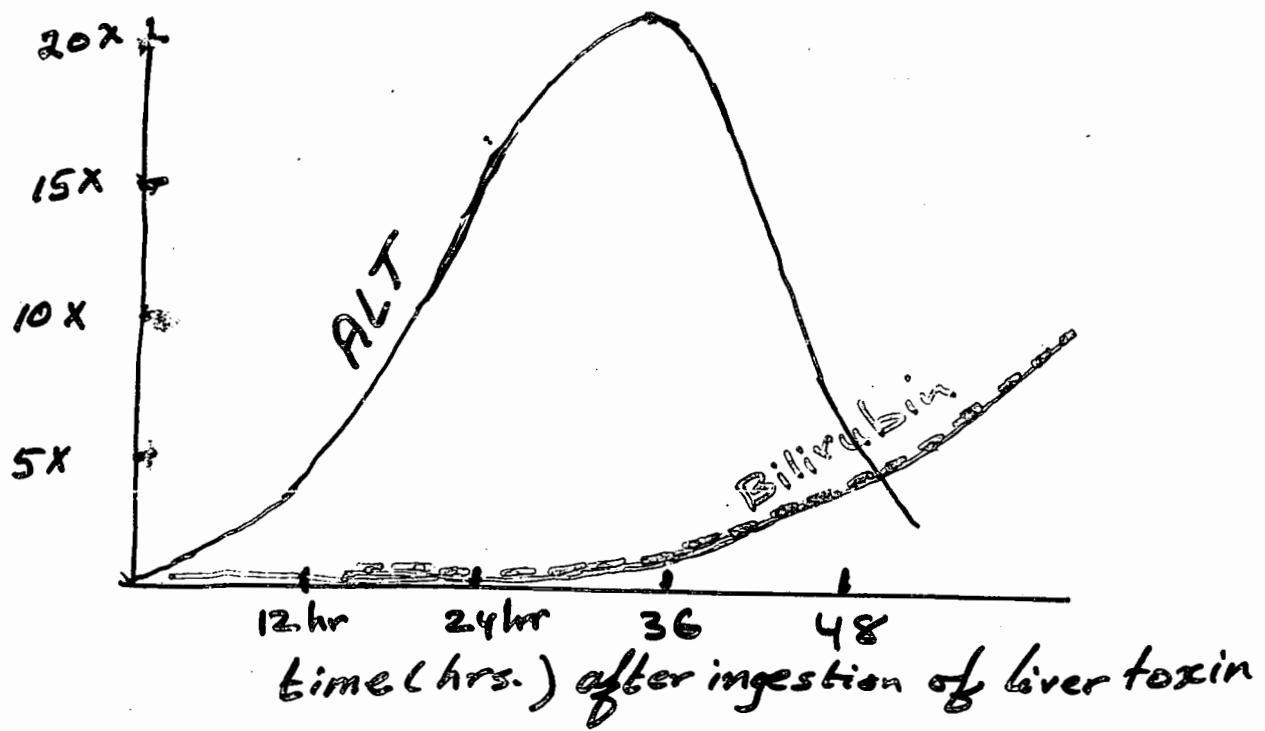


Cyclic Interconversion of the Co-factor 36
in transaminase (amino transferase) reactions



Diagnostic Value of Plasma Aminotransferases

- intracellular enzymes
- low levels in plasma
- ALT and AST have diagnostic value



Liver disease:

- ALT is more specific for liver
- AST is more sensitive (richer in AST)
- AST is elevated in other conditions e.g. damage to cardiac or skeletal muscle

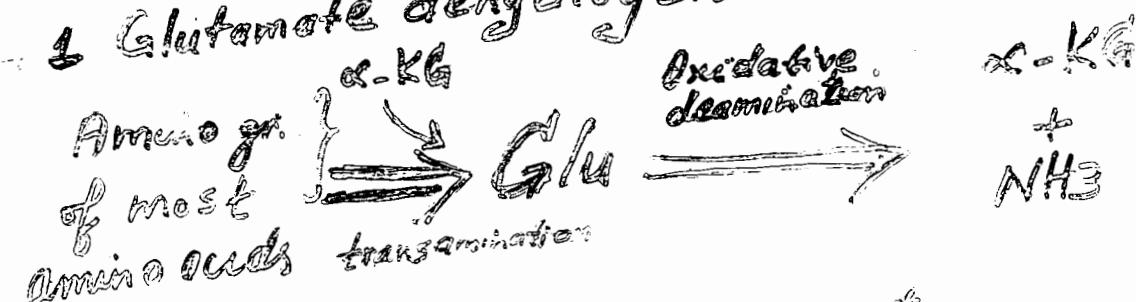
2. Oxidative Deamination



- Functions to liberate ammonia as ammonia

- Occurs primarily in liver & kidney

1 Glutamate dehydrogenase



Cofactors NAD^+ & NRDPH

located in mitochondria (readily reversible)

Direction of reaction depends on the relative concs. of

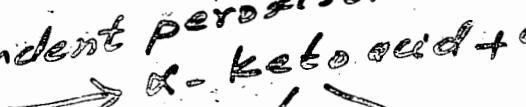
Glu, $\alpha\text{-KG}$, NH_3 , NAD/NADH

After protein-rich meal $\longrightarrow \alpha\text{-KG}$

The reaction in vivo is more likely toward ammonia formation.

2. D-Amino acid Oxidase (DAO)

FAD-dependent peroxisomal enzyme

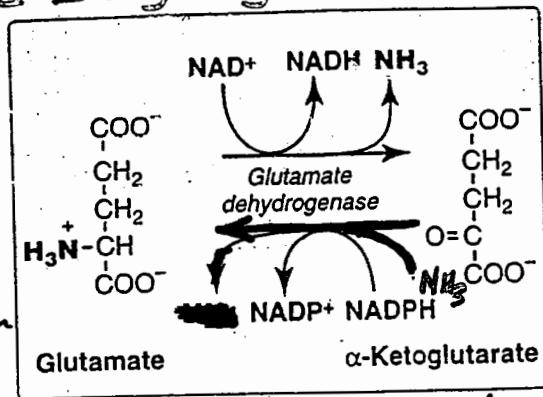


or
oxidized Energy

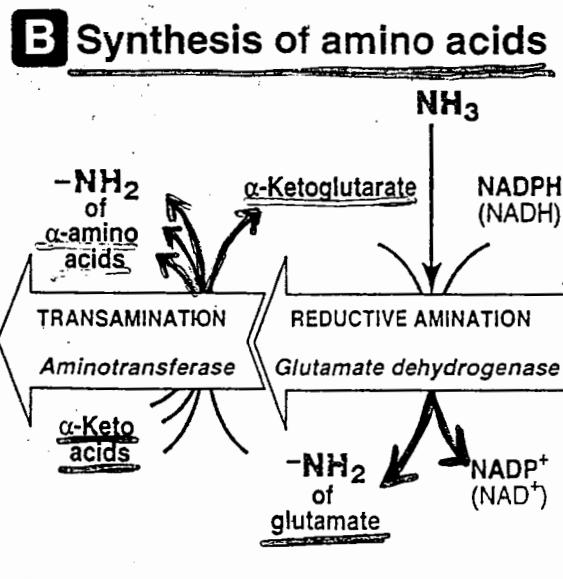
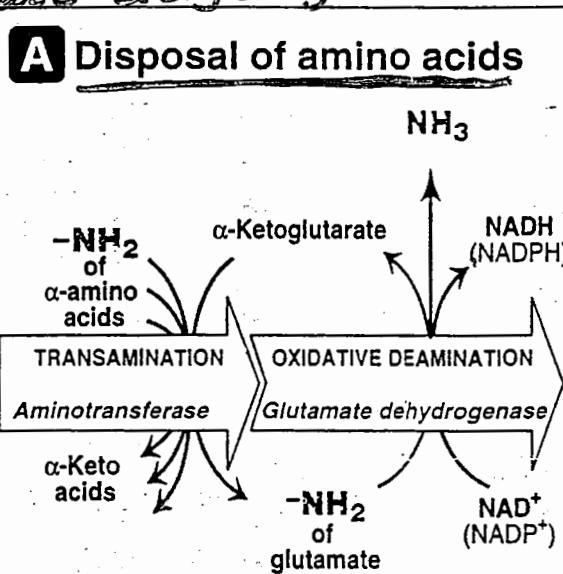
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Oxidative deamination by Glutamate Dehydrogenase :-

- occurs primarily in liver & kidney
- Co-factors
- location
- Direction of reaction

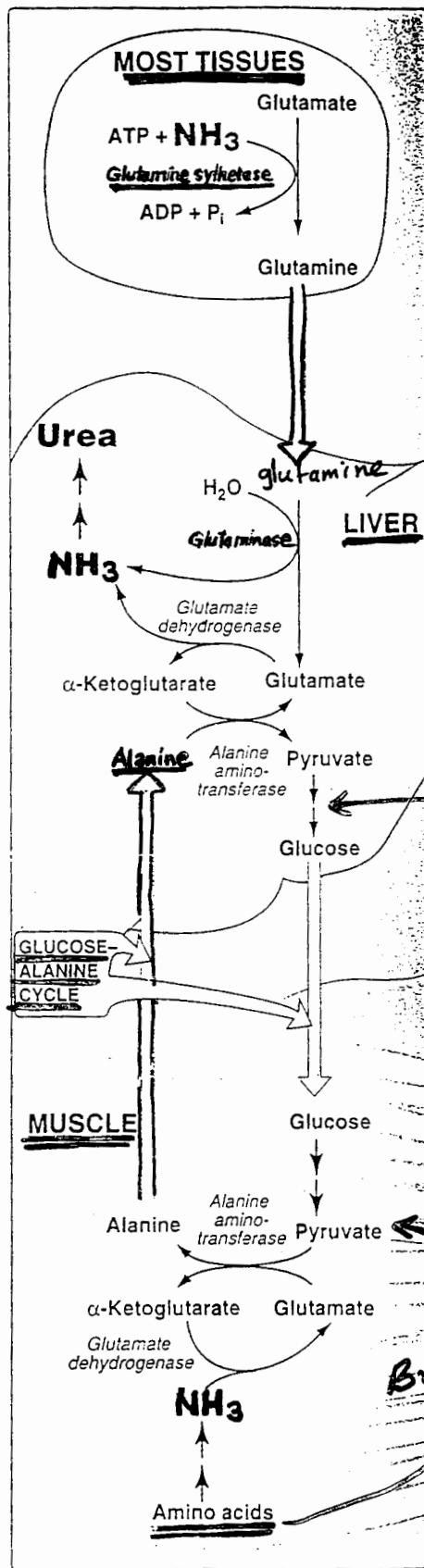


Combined Actions of amino transferase and Glutamate dehydrogenase reactions :-



5

Transport of
Ammonia from
peripheral tissues
to liver.



Gln ↑ highest
a-a. in blood

gluconeogenesis

Alanine - Gly
cycle

succinyl CoA

Branched- amino acids
Isoleucine, Valine

The Urea Cycle

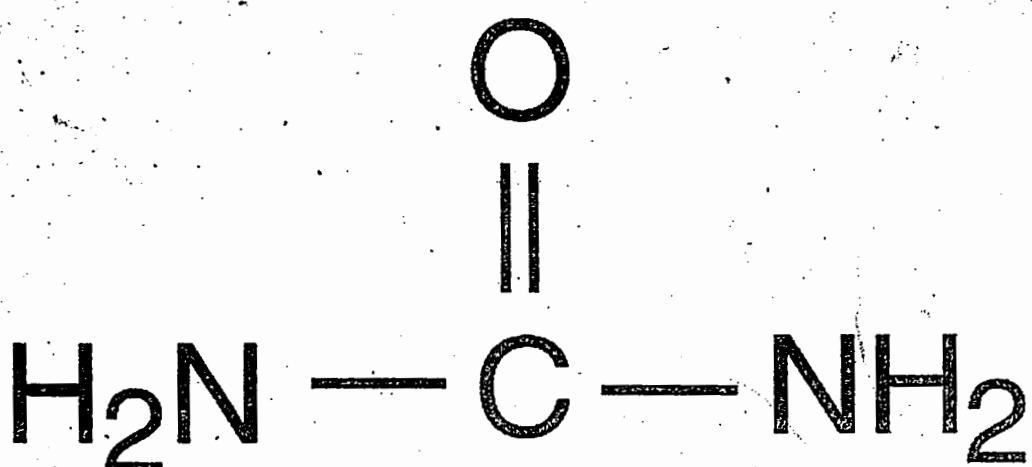


Figure: 11_21

Urea.

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Atoms of Urea

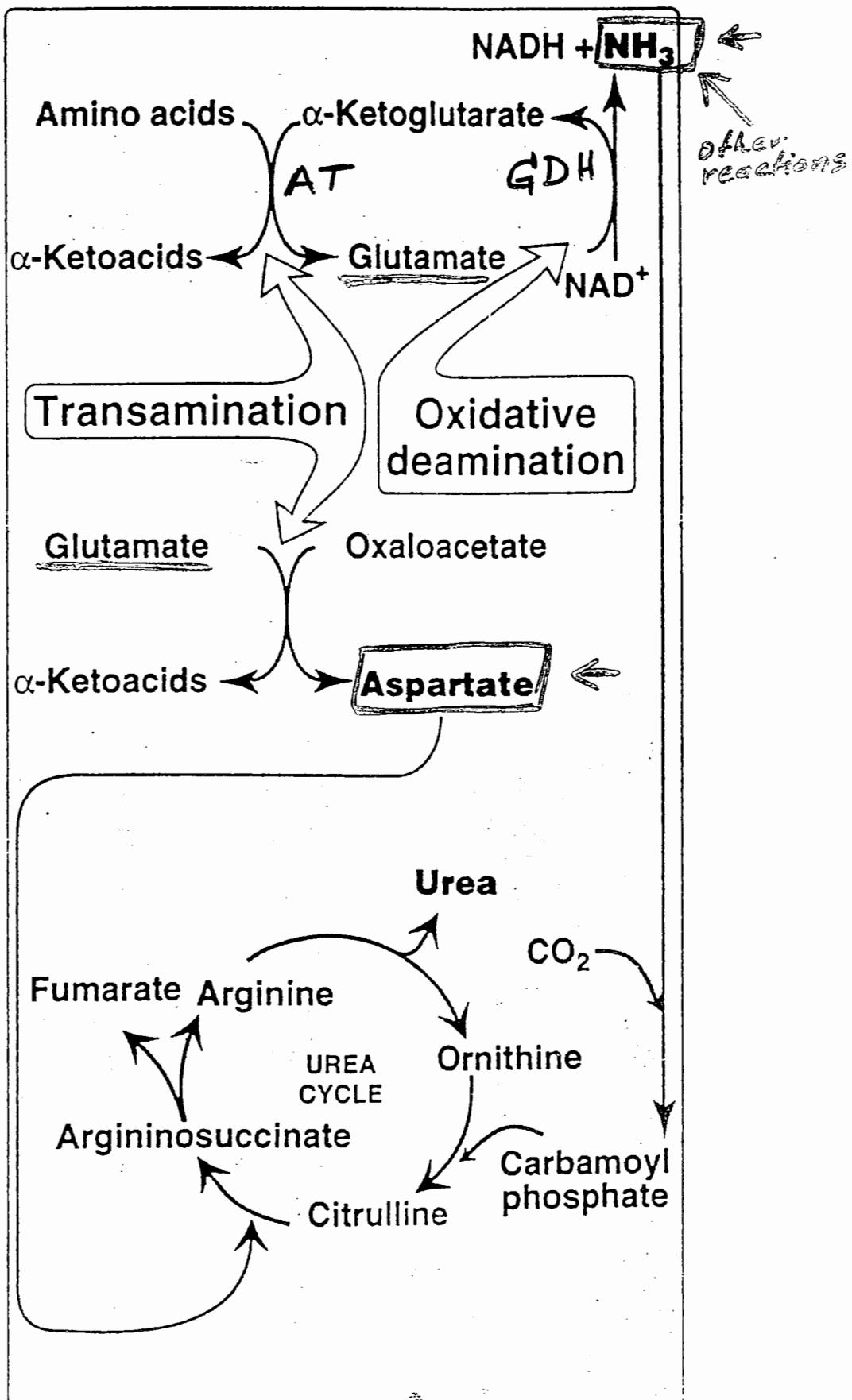
Free NH_3

Aspartate $\rightarrow^{\text{NH}_3}$

Bicarbonate

Flow of nitrogen to urea
 Amino groups of urea are collected in the form of:-

1. Ammonia
2. Aspartate



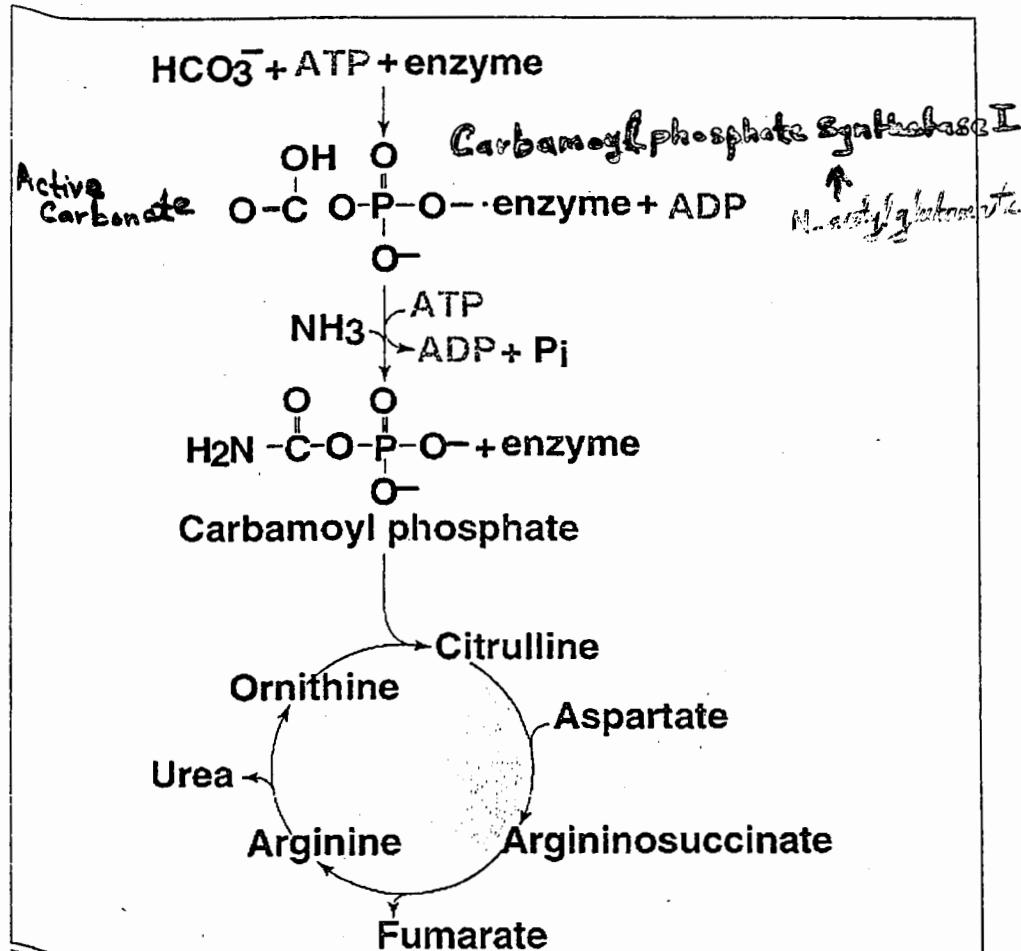
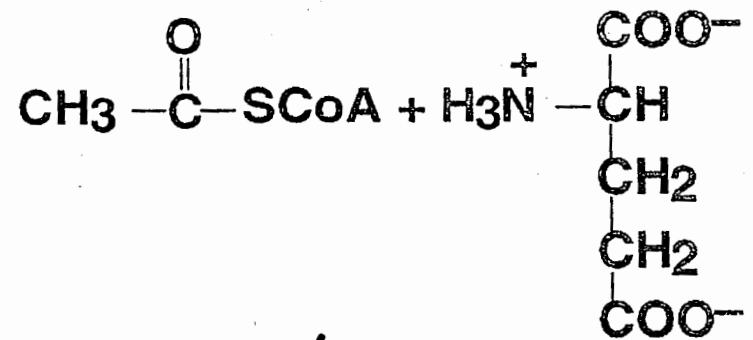


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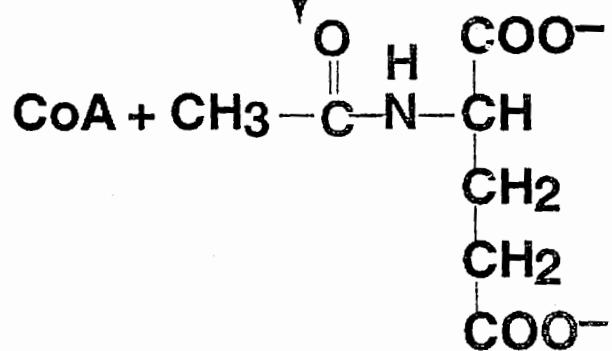
Synthesis of carbamoyl phosphate and entry into urea cycle.

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Acetyl CoA⁺Glutamate

N-acetylglutamate Synthetase
↑arginine



N-Acetylglutamate

Figure: 11_23

Reaction catalyzed by N-acetylglutamate synthetase.

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UREA CYCLE

10

252

19. Amino acids: Disposal of Nitrogen

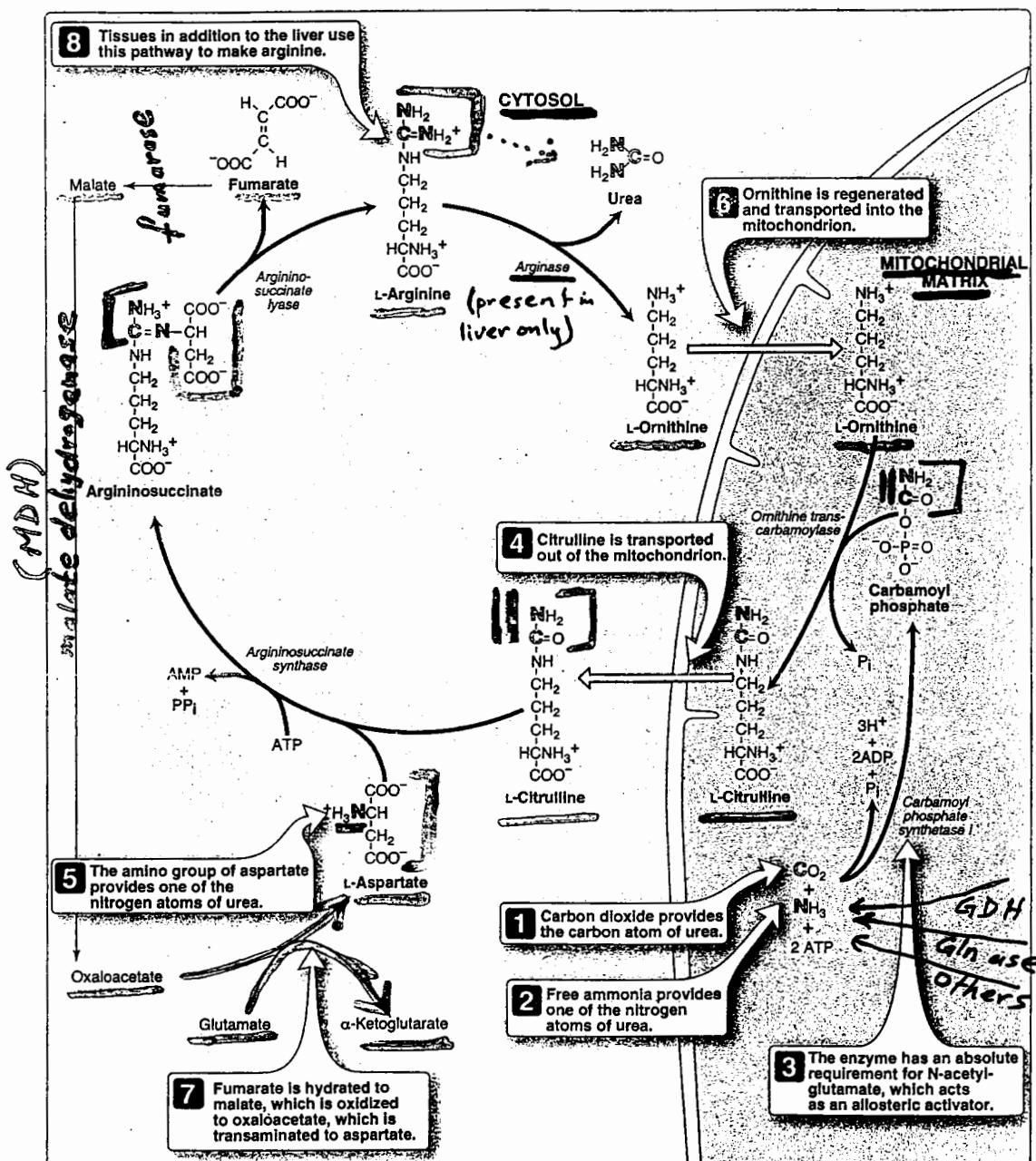


Figure 19.14
Reactions of the urea cycle.

Citrulline/ornithine exchange transport
Regulation of Urea Cycle:-

- Allosteric regulation
- High Protein diet ↑
- Starvation ↑

Metabolic Disorders of Urea Synthesis

Hyperammonemia

13

5-35 μmol/100 ml normal conc.

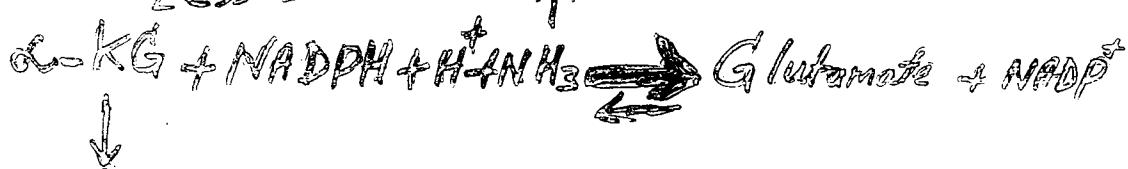
↑ level → intoxication
 ↳ tremors
 → slurring of speech
 → blurring of vision
 ↳ v. high conc. → Coma + death

1. Acquired hyperammonemia

2. Hereditary hyperammonemia

- Enz. deficiency (rare) 1 : 30,000

- Ornithine transcarbamoylase, X-linked, most common
- Urea cycle defects had high morbidity (neurologic) and mortality
- Hyperammonemia due to Arginase deficiency is less severe ↑



Treatments :-

• restricting protein intake

• drugs that bind covalently to amino acids e.g. 3-n.

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Metabolism of AMMONIA

- produced in all tissues
- disposed primarily as urea in the liver
- v. toxic to CNS
- safe transport from peripheral tissues to liver

A. Sources of Ammonia

1. From amino acids :- the most imp.

source, by ~~enzymes~~^{transaminases} & GDH

(Liver, Kidney, Intestine)

2. From Glutamine :- NH_4^+ to urine

Kidney NH_4^+

Gln. Glutaminase

Gln. glutaminase NH_3

Intestinal

NH_3

NH_2

$\text{CD}-\text{CH}_2-\text{CH}_2-\overset{\text{H}}{\underset{\text{NH}_3}{\text{C}}} \text{COO}$

Gln

NH_3

H_2O

Glutaminase

NH_3

$\text{H}-\overset{\text{COO}}{\underset{\text{Glu}}{\text{C}}}-\text{NH}_3$

$\text{H}-\overset{\text{COO}}{\underset{\text{Glu}}{\text{C}}}-\text{NH}_3$

3. From bacterial脲酶, in the intestine

Urea $\xrightarrow{\text{urease}}$ NH_4^+

4. from Amines :- amines in diet, neurotransmitters & hormones

5. from Purines and Pyrimidines metabolism

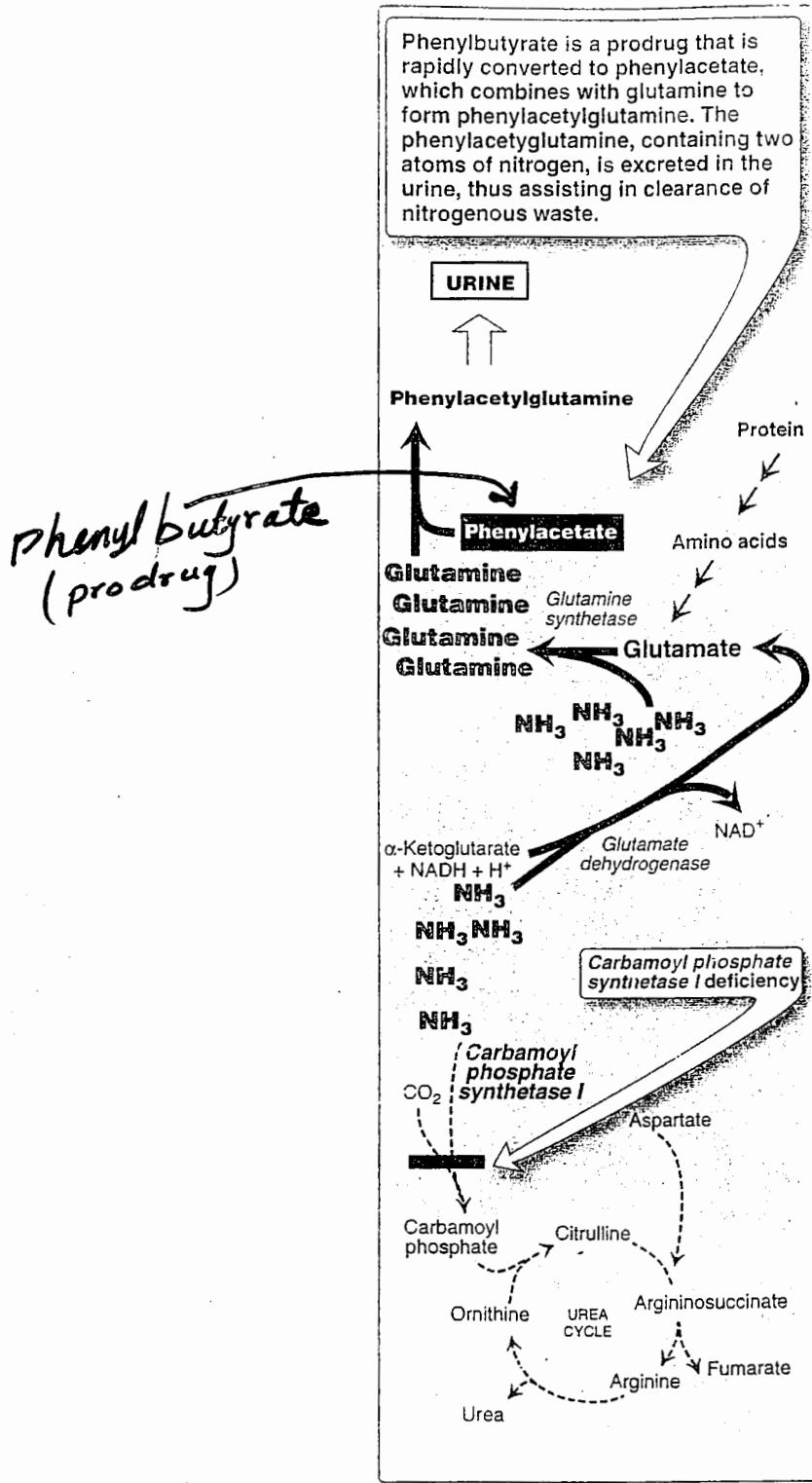
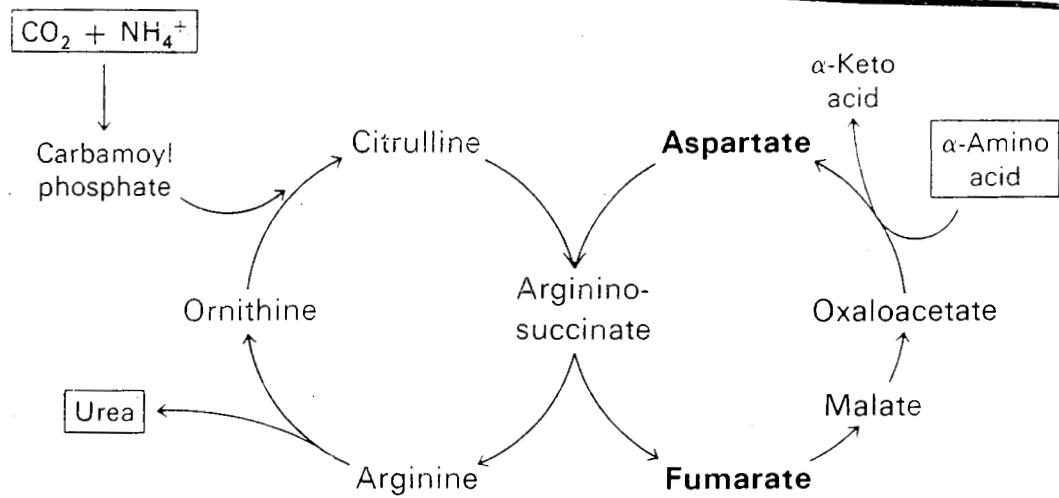


Figure 19.20
Metabolism of nitrogen in a patient with a deficiency in the urea cycle enzyme *carbamoyl phosphate synthetase I*. Treatment with phenylbutyrate converts nitrogenous waste to a form that can be excreted.

Classification of Amino Acids 16

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

Degradation of Amino Acids II



Final Products

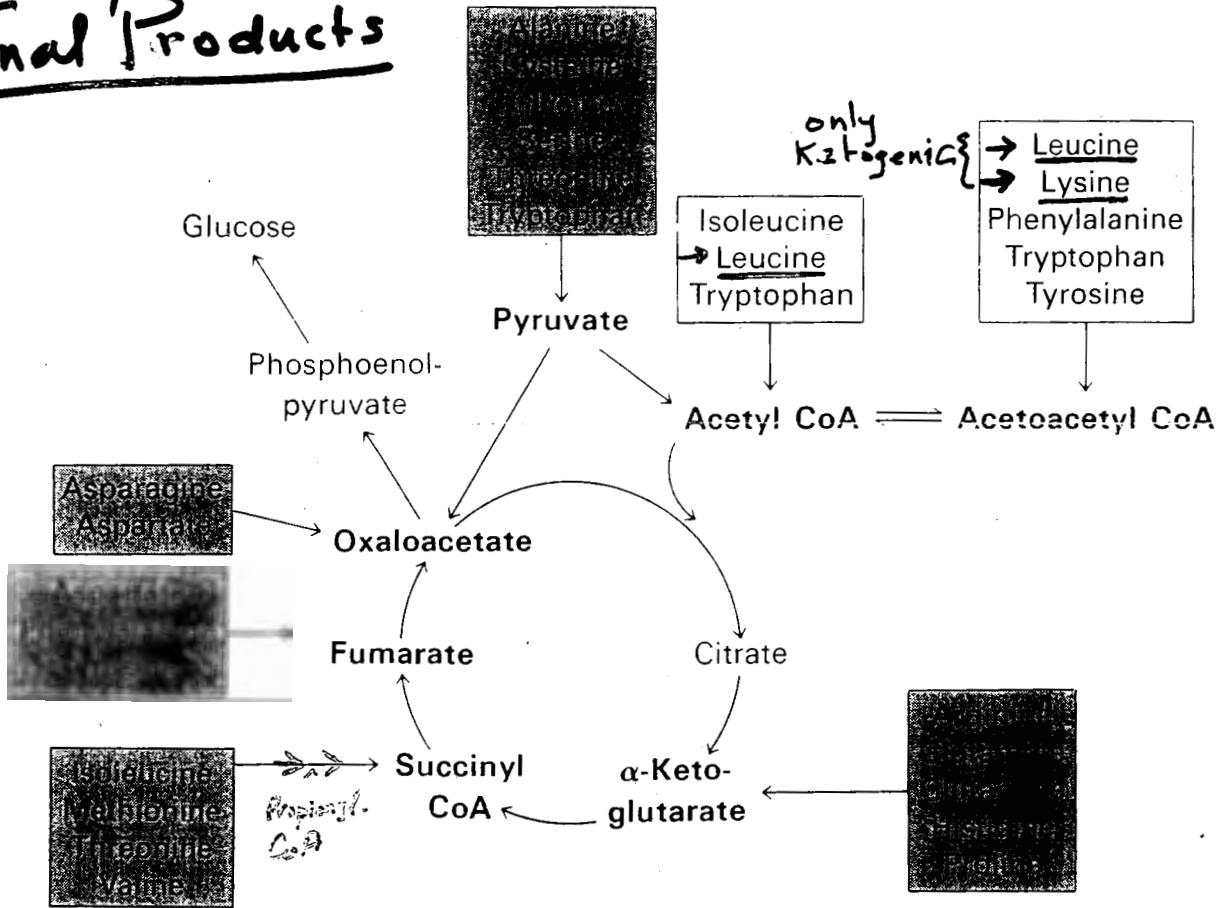


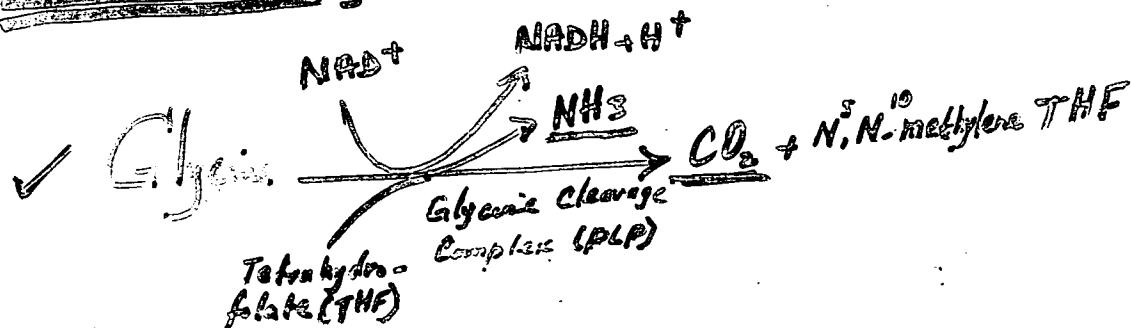
Figure 25-7, page 636; Figure 25-10, page 638

T-85

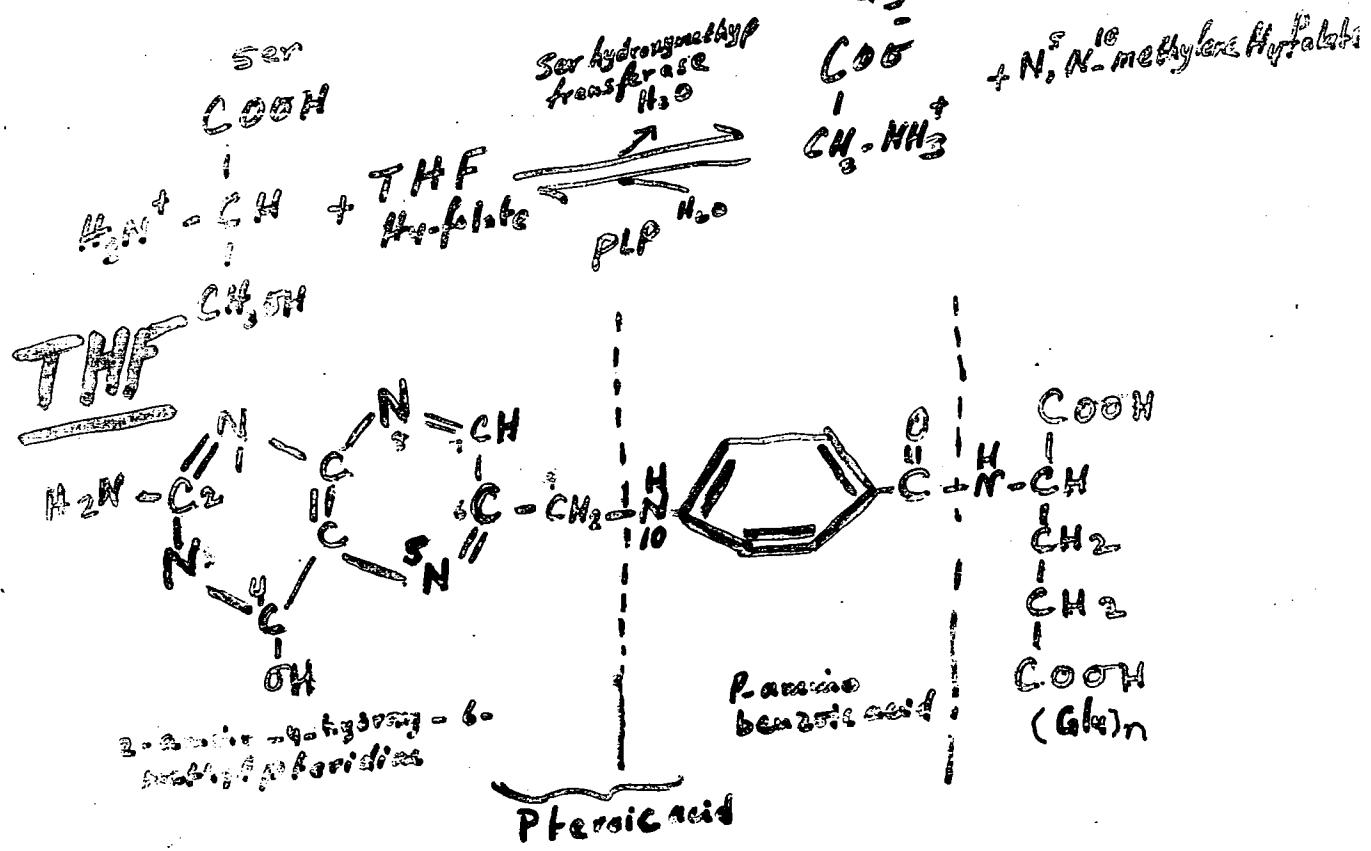
Stryer: Biochemistry, Fourth Edition
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Set I

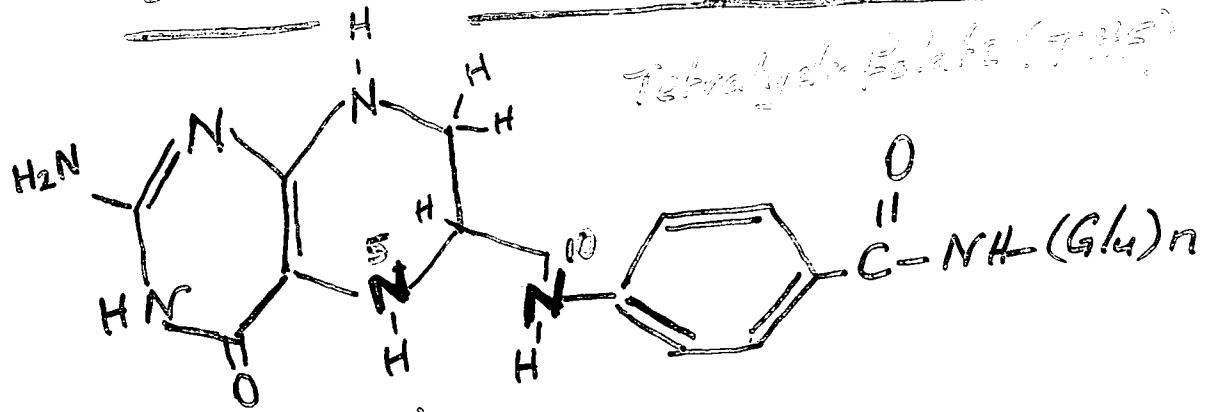
Degradation of Individual Amino Acids



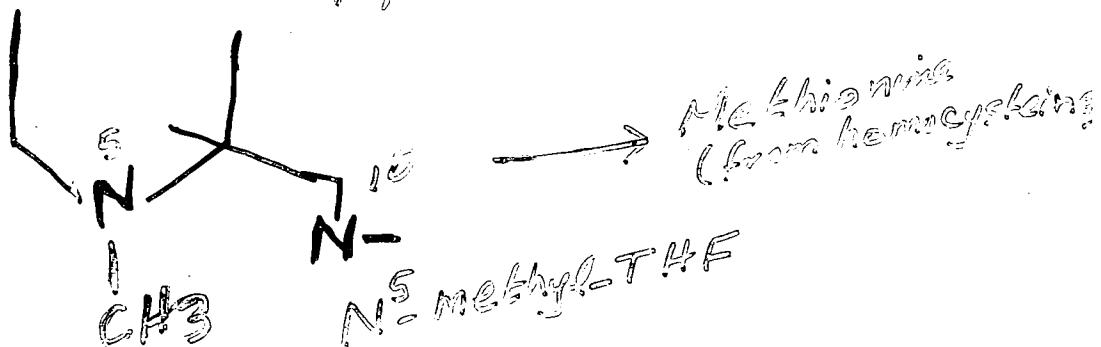
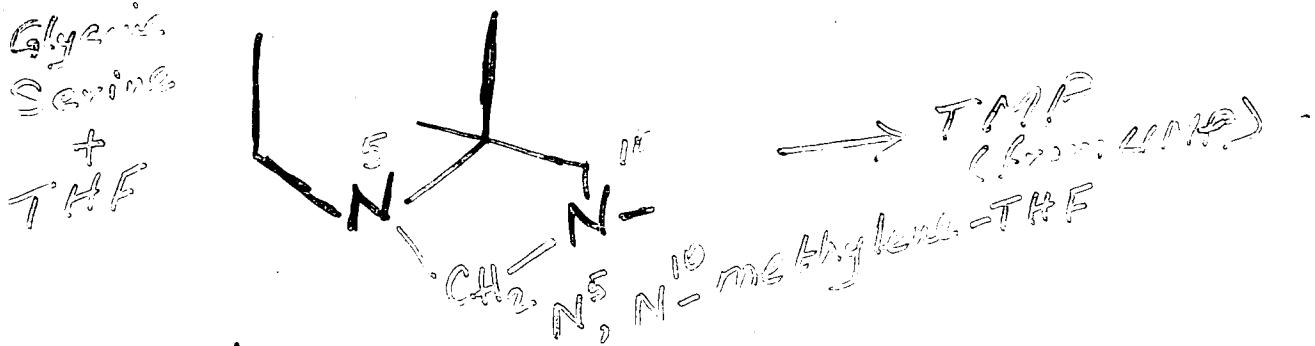
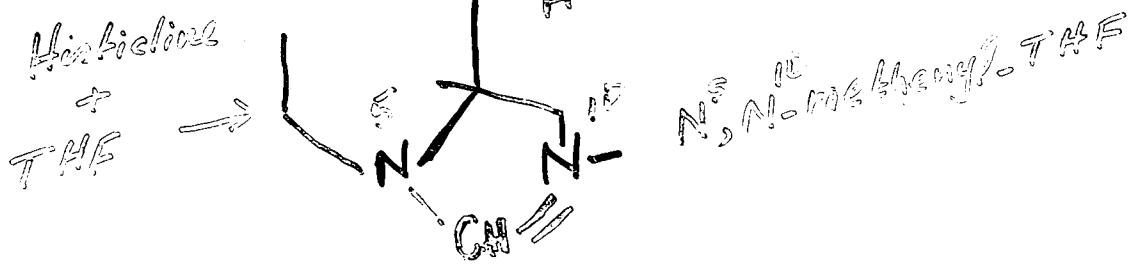
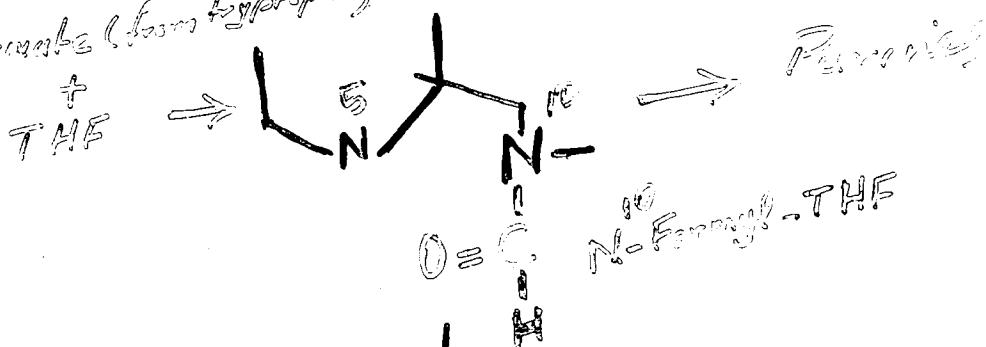
SERINE



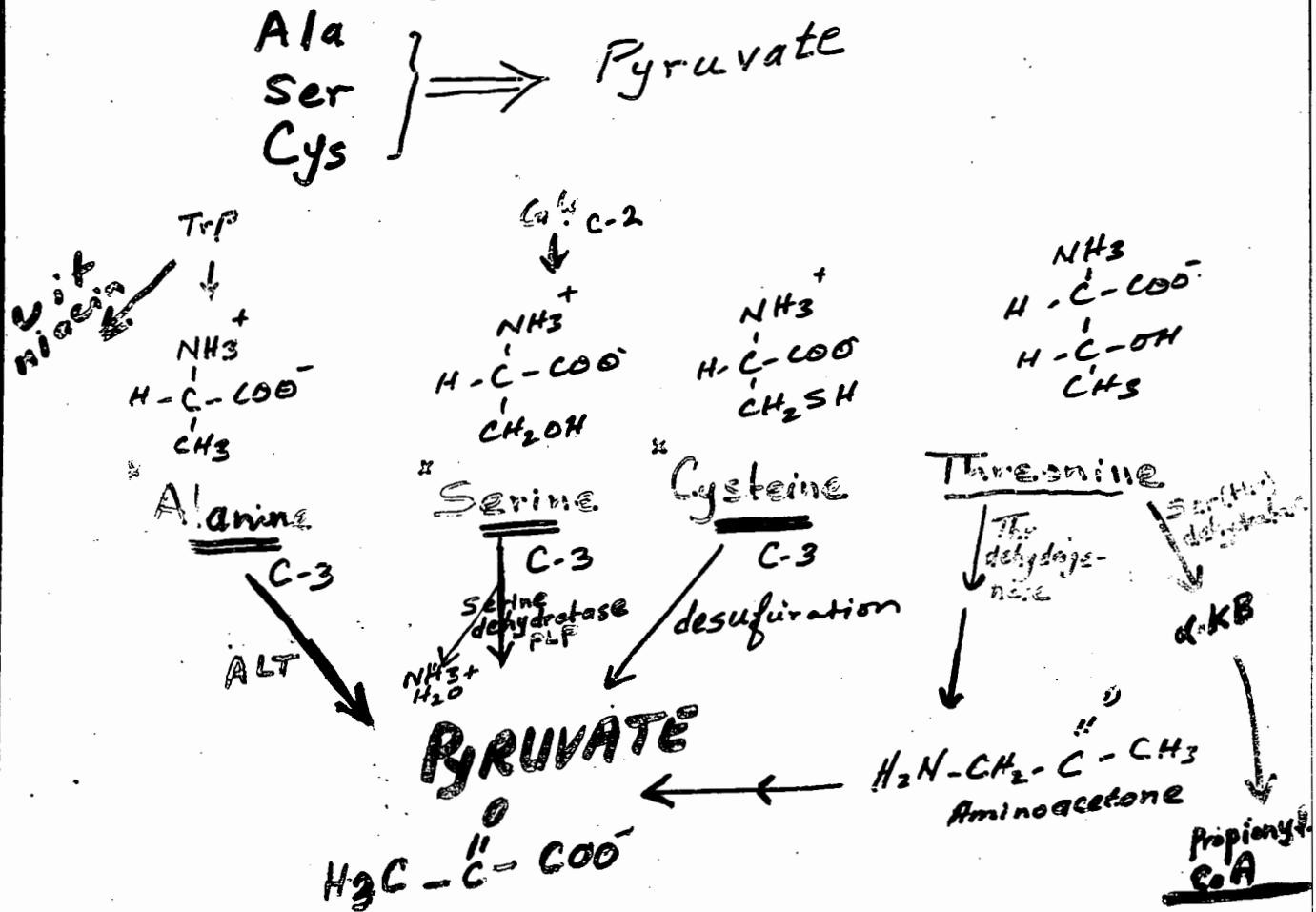
— 1 — and 1 DL - Dihydroxyacid)



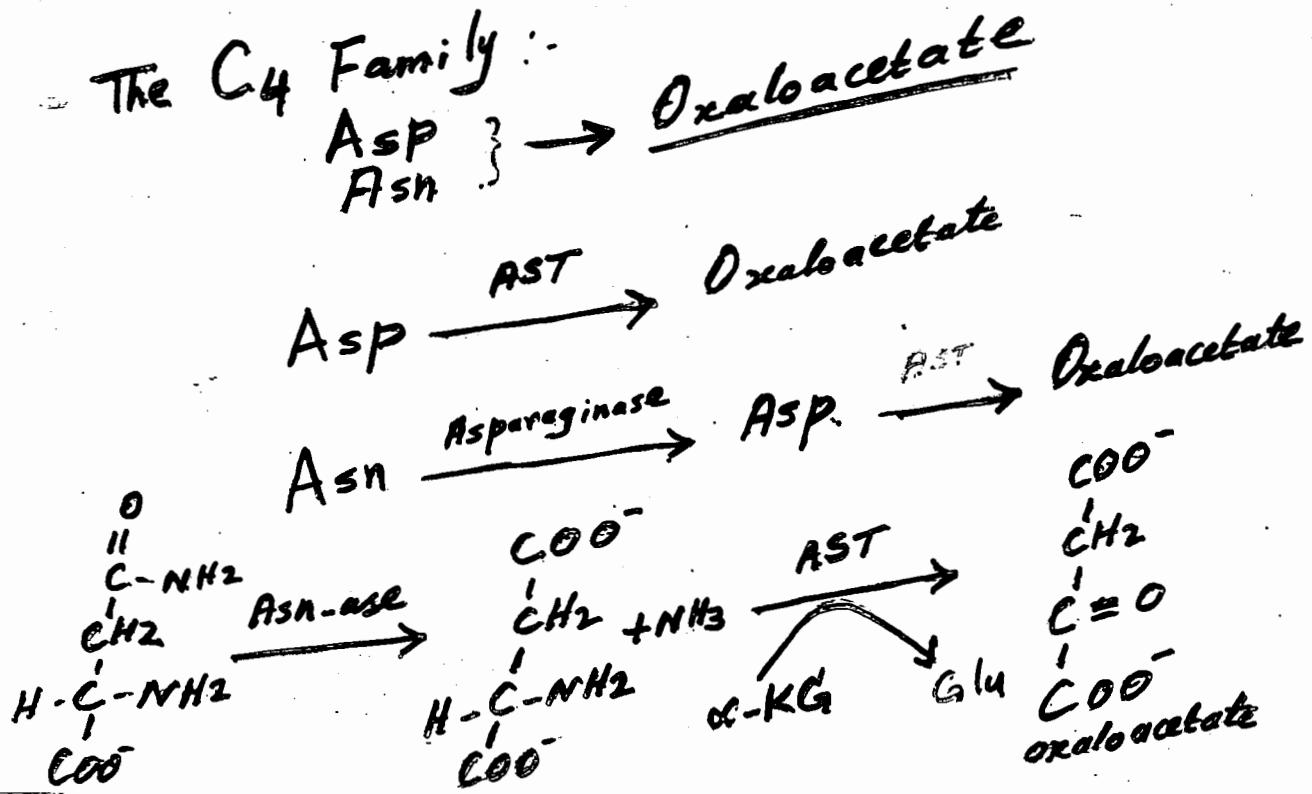
Formate (from hypophosphite)



The C₃ Family :-

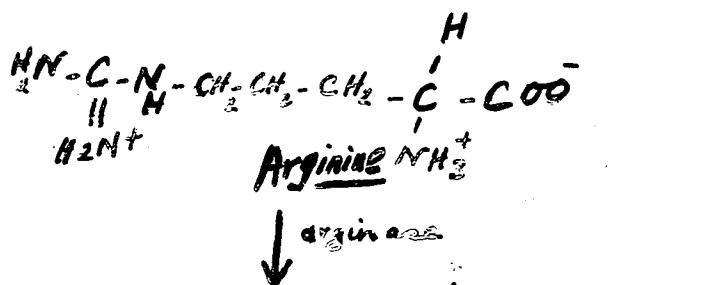
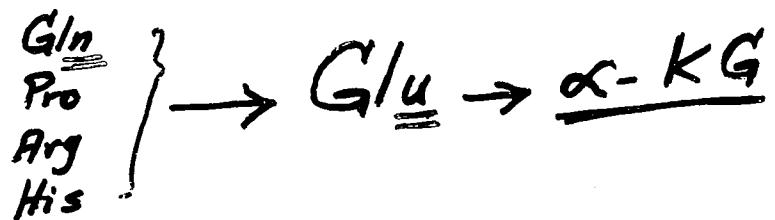


The C₄ Family :-

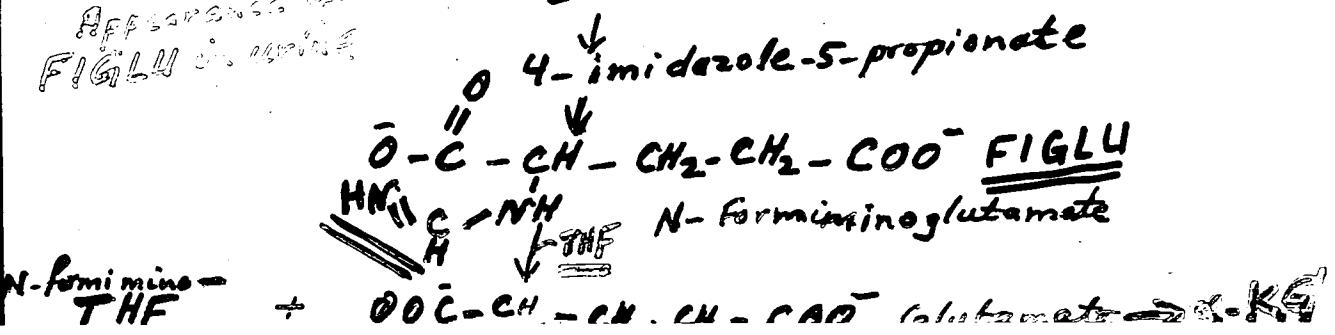
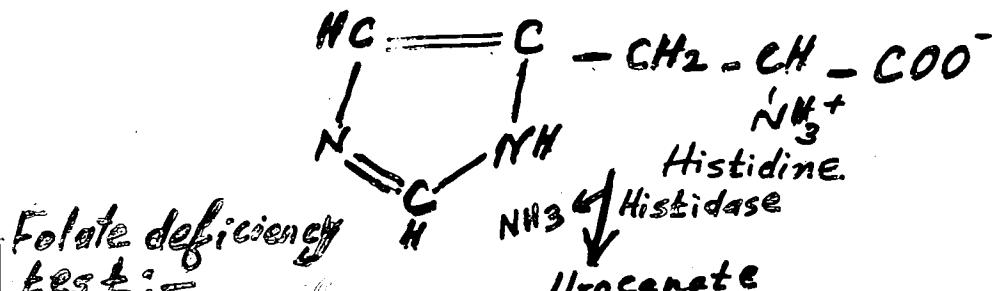
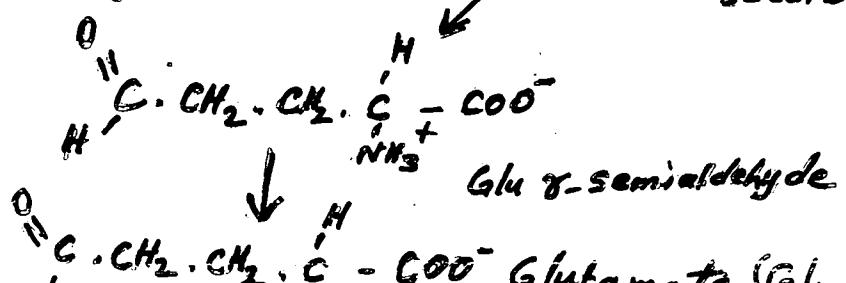
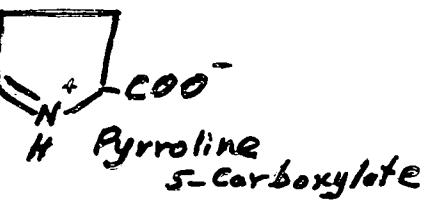
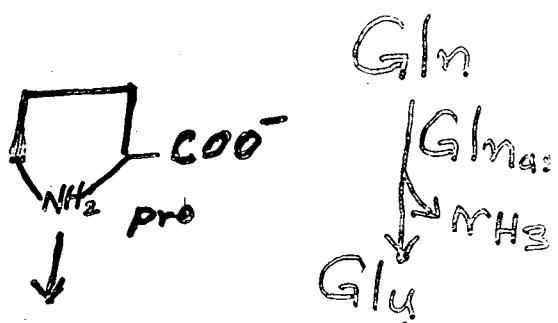
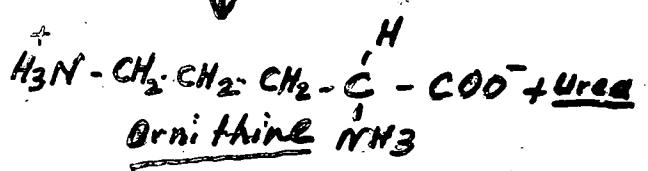


Amino acids that form α -Ketoglutarate

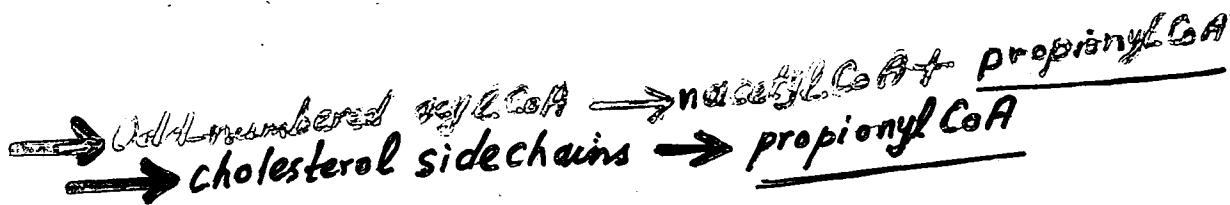
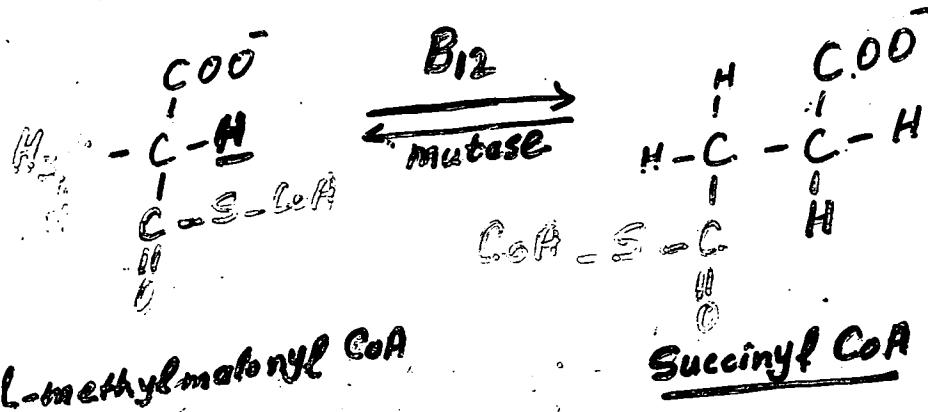
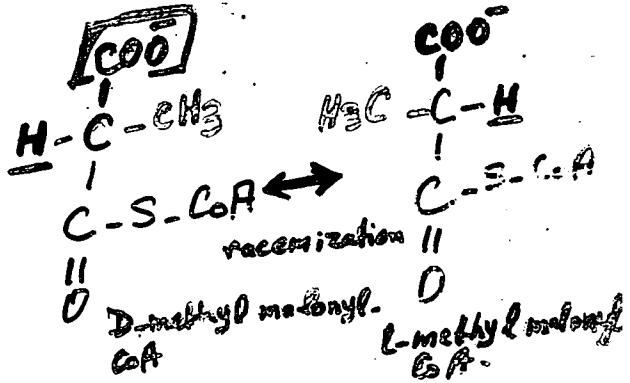
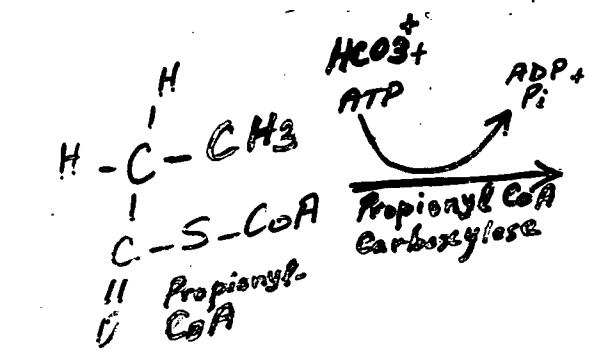
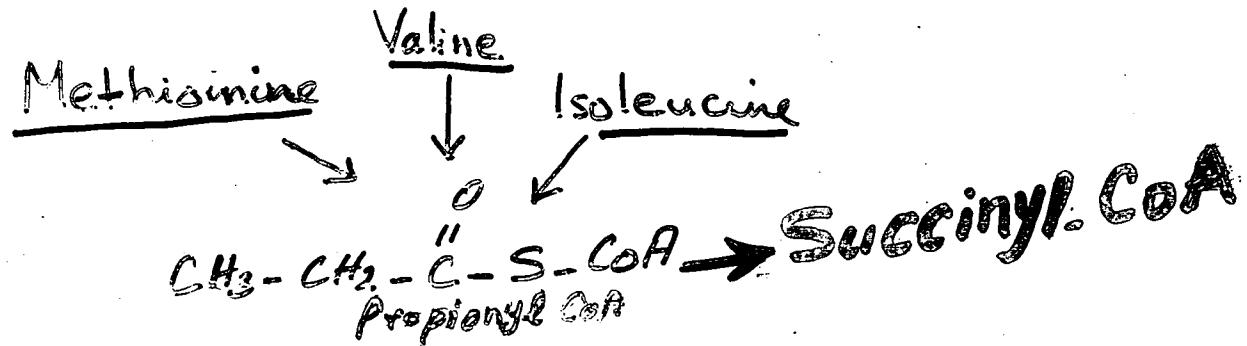
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\downarrow arginase



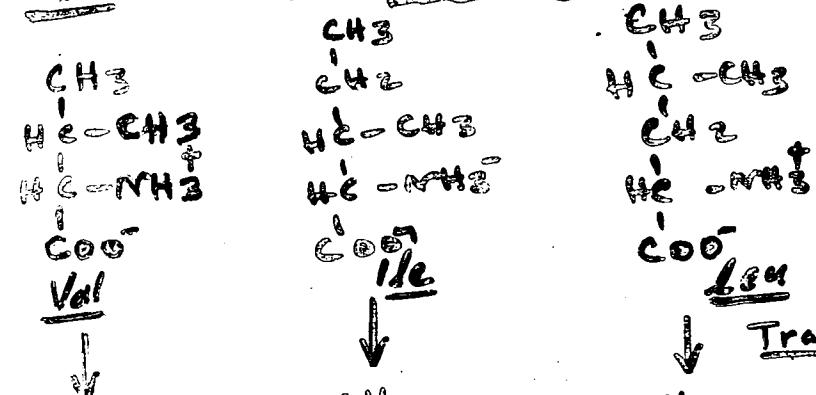
Succinyl Coenzyme is a point of entry
for several Non-polar Amino Acids:-



Metabolism of Branched Chain Amino Acid

(4)

Leu → Acetoacetate + acetyl CoA
Val → Succinyl CoA
Ile → Succinyl CoA + acetyl CoA



α -Keto isovalerate
 $\begin{array}{c} \text{CH}_3 \\ | \\ \text{H}_3\text{C}-\text{CH}_3 \\ | \\ \text{C}=\text{O} \\ | \\ \text{C}_6\text{H}_5 \end{array}$

$\begin{array}{c} \text{CH}_3 \\ | \\ \text{H}_3\text{C}-\text{CH}_3 \\ | \\ \text{C}=\text{O} \\ | \\ \text{S}-\text{CoA} \end{array}$
 Iso butyryl CoA

\downarrow
 \downarrow

Propionyl-CoA

$\begin{array}{c} \text{CH}_3 \\ | \\ \text{H}_3\text{C}-\text{CH}_3 \\ | \\ \text{C}=\text{O} \\ | \\ \text{S}-\text{CoA} \end{array}$
 α -methyl butyryl CoA

\downarrow
Acetyl CoA + Propionyl CoA

$\begin{array}{c} \text{CH}_3 \\ | \\ \text{H}_3\text{C}-\text{CH}_3 \\ | \\ \text{C}=\text{O} \\ | \\ \text{C}_6\text{H}_5 \end{array}$
 α -butyryl CoA

$\begin{array}{c} \text{CH}_3 \\ | \\ \text{H}_3\text{C}-\text{CH}_3 \\ | \\ \text{C}=\text{O} \\ | \\ \text{S}-\text{CoA} \end{array}$
 Isovaleryl CoA

\downarrow
Acetyl CoA + Acetoacetate

\downarrow
Transaminase
 Common

Increased by
 high protein
 diet &
 starvation
 in muscle

$\begin{array}{c} \text{CH}_3 \\ | \\ \text{H}_3\text{C}-\text{CH}_3 \\ | \\ \text{C}=\text{O} \\ | \\ \text{C}_6\text{H}_5 \end{array}$
 α -butyryl CoA

\downarrow
 α -ketoadid dehydrogenase
 (ox. decarboxylase)
 Common to all

$\begin{array}{c} \text{CH}_3 \\ | \\ \text{H}_3\text{C}-\text{CH}_3 \\ | \\ \text{C}=\text{O} \\ | \\ \text{S}-\text{CoA} \end{array}$
 Isovaleryl CoA

\downarrow
Deficiency in

Maple Syrup Urine Disease

Branched-chain Amino Acids

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Maple Syrup Urine disease

- poor feeding
- vomiting
- acidosis
- mental retardation
- symptoms within first few days
- restriction of BCAAs
- severe
- intermittent forms
- Thiamine-responsive form

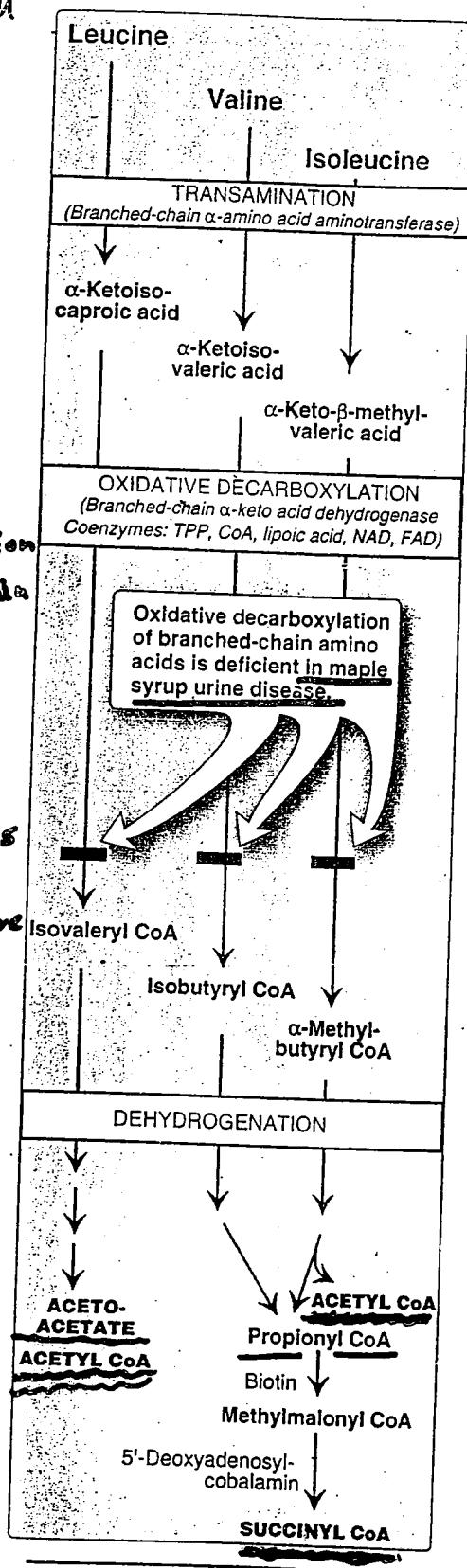


Figure 20.10
Degradation of leucine, valine, and isoleucine. TPP = thiamine pyrophosphate.

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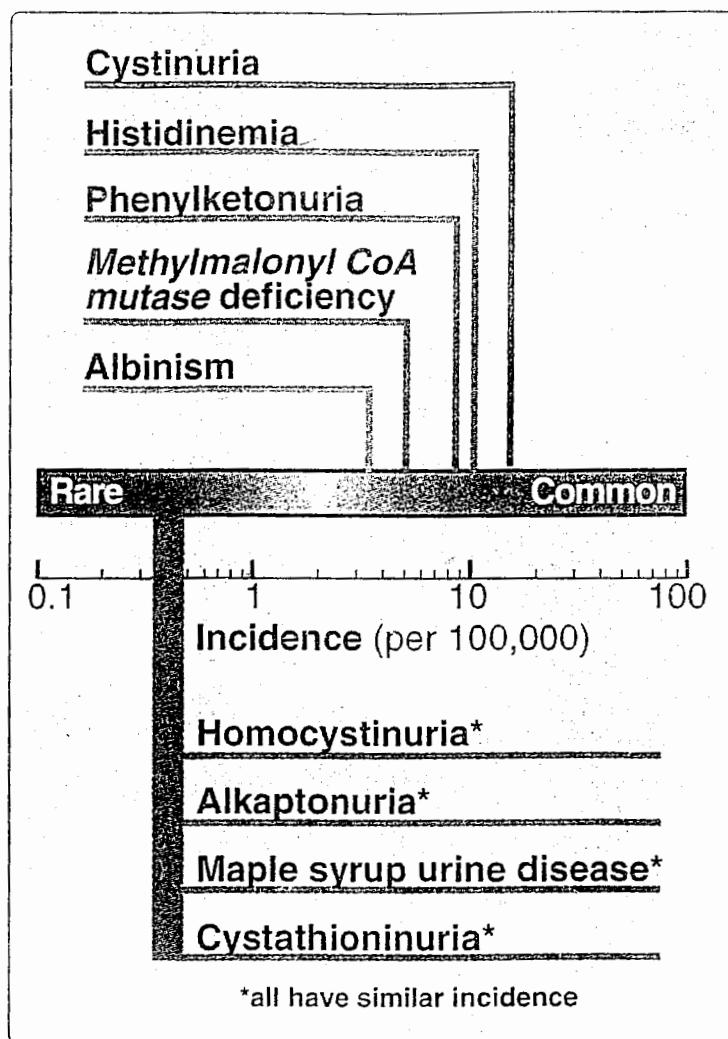


Figure 20.13

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

