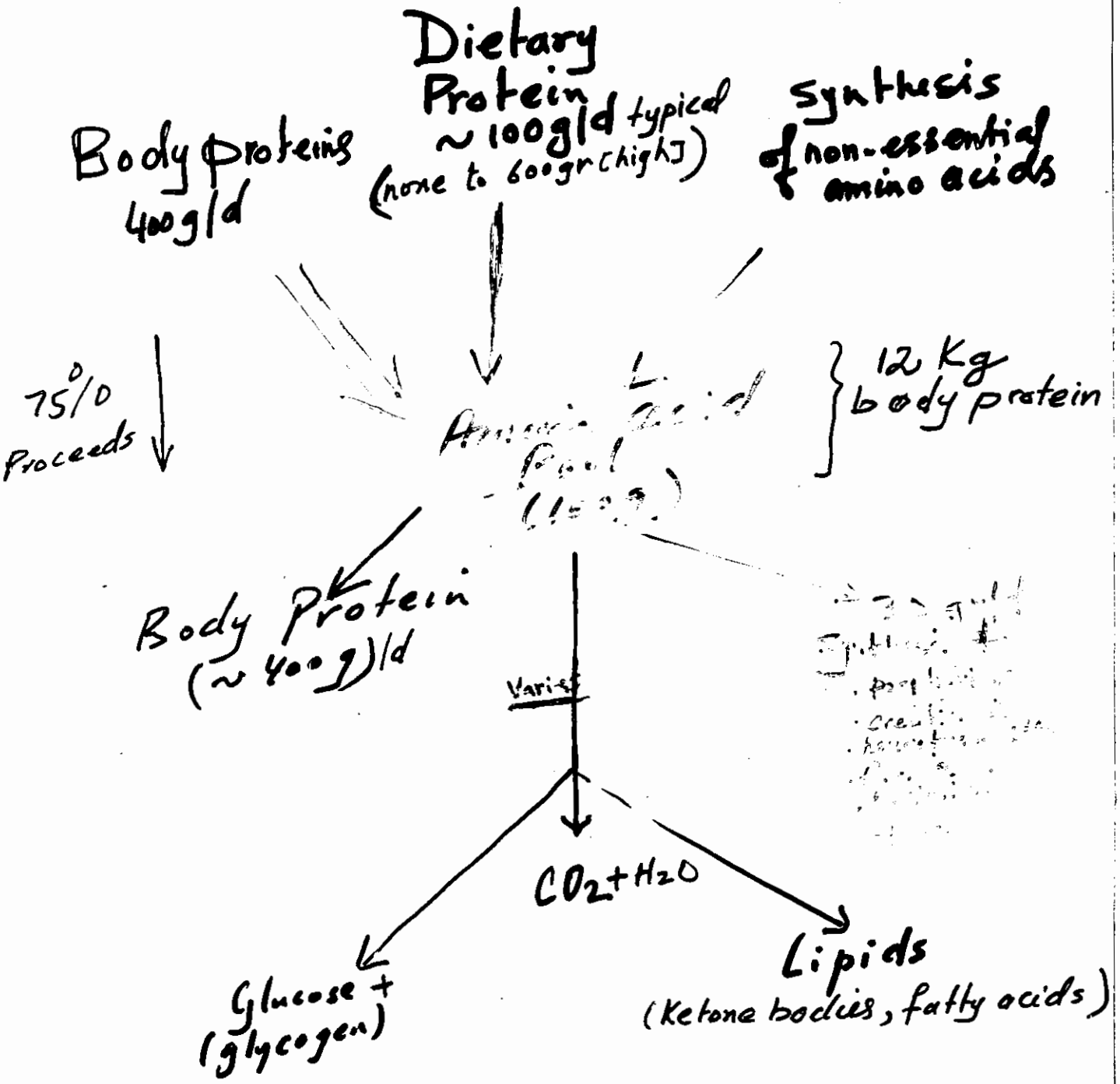
Amino Acid Metabolism

Introduction:

- Essential Amino Acids
  Lys, (< 10 yr His) Ile, Leu, Val, Met, Thr, Trp, Phe
- Non-essential amino acids
- Ketogenic " "
- Glucogenic " "
- Glucogenic + ketogenic " "
- Nitrogen Balance
  - −ve starvation, wasted a.a. [illegible]
  - +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-cellural proteins - taken by endocytosis - Heterophagy and intracellular Proteins - Autophagy

3. Ubiquitine-Proteasome Pathway
- degrades endogenous proteins
- Ubiquitation
- 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 → short t ½
- N-terminal Asp - short t ½
- N-terminal Ser Long t ½

Proteins with short t ½ reg. proteins, damaged, misfolded - min or hrs

Long t ½ in weeks majority of cellular proteins

t ½ in months or yrs. structural proteins e.g. Collagen

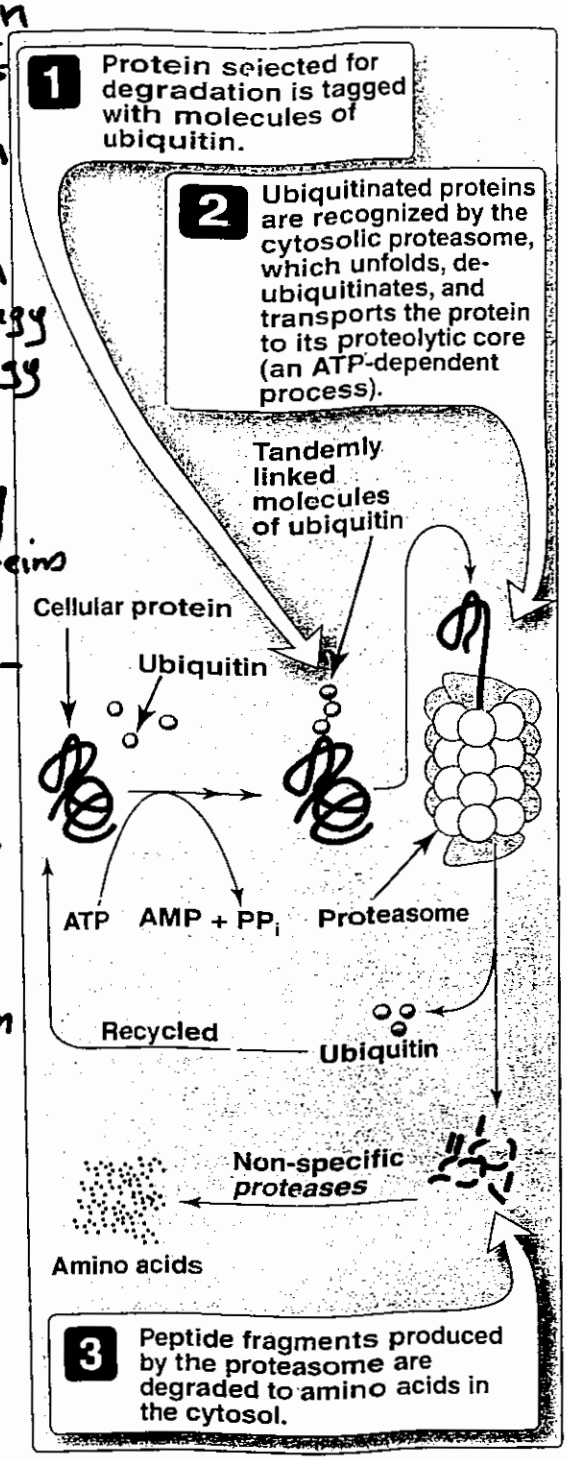


Figure 19.3
The ubiquitin-proteasome degradation pathway of proteins.

- Transport of amino acids into Cells :-

- Major $\xrightarrow[\text{cotransport}]{Na^+\text{-dependent}}$ (in all tissues)

  Less Extent $\xrightarrow{\text{Facilitated}}$

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

- Different Isoforms in different tissues.
  - at least 7 different transport systems with overlapping specifities

  Differences between tissues
  e.g. Gln present in liver but not other tissues or as an isoform present

- 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 cys & dibasic a.a.
- one of the most common inherited diseases
- Kidney stones (calculi) block urinary tract

Activation of Gastric + Pancreatic Zymogens

Proenzymes (zymogens) → Active Enzymes

- Pepsinogen $\xrightarrow{H^+}$ Pepsin
  (or active Pepsin)
  acid-induced conformational change → can cleave itself

- Trypsinogen $\xrightarrow[\text{Trypsin}]{\text{enteropeptidase (enterokinase)}}$ Trypsin

- Chymotrypsinogen $\xrightarrow{\text{trypsin}}$ Chymotrypsin

- Proelastase $\xrightarrow{\text{trypsin}}$ Elastase

- Procarboxypeptidases (A + B) $\xrightarrow{\text{trypsin}}$ Carboxypeptidase

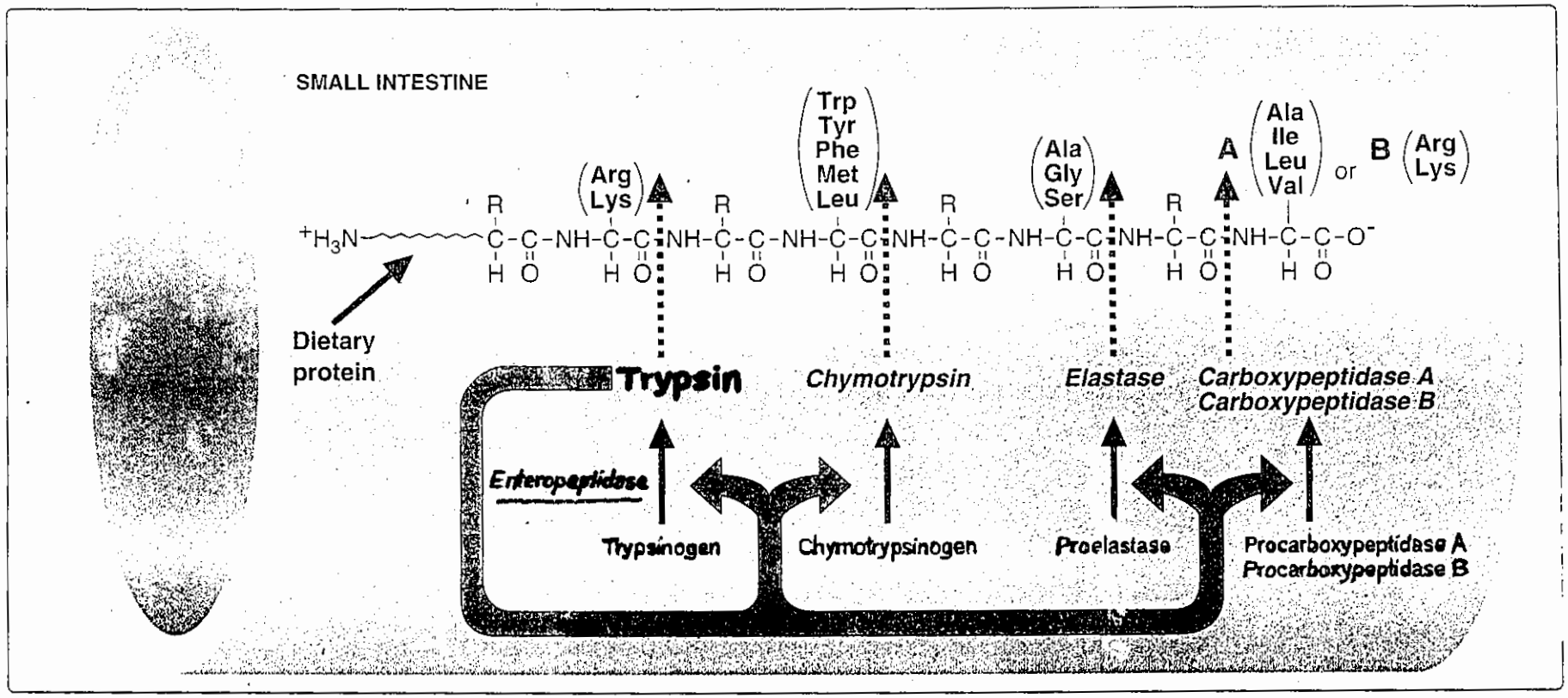


Figure 19.5
Cleavage of dietary protein by proteases from the pancreas. The peptide bonds susceptible to hydrolysis are shown for each of the five major pancreatic proteases. [Note: *Enteropeptidase* is synthesized in the intestine.]

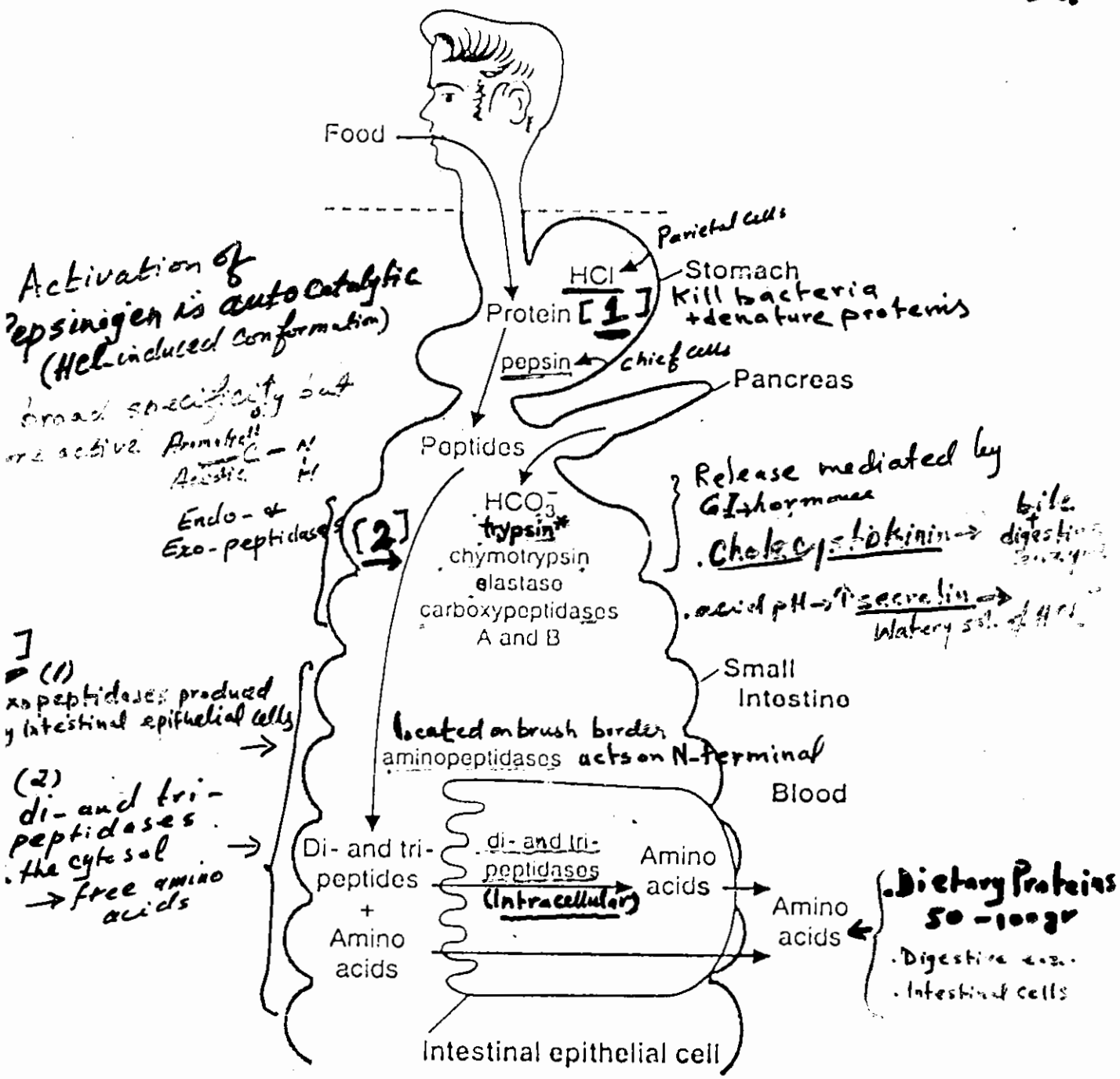


Fig. 37.3. Digestion of proteins. The proteolytic enzymes:- pepsin, trypsin, chymotrypsin, elastase, and the carboxypeptidases, (A + B) are produced as zymogens that are activated by cleavage after they enter the gastreintestinal lumen (see Fig. 37.4).

At luminal surface of intestinal mucosal cells

Trypsinogen $\xrightarrow[\text{(enterokinase)}]{\text{Enteropeptidase}}$ trypsin

ABOSRPTION OF AMINO ACIDS

1- Secondary Active Na^+-dependent transport:
(Cotransport of Na^+ and amino acids)

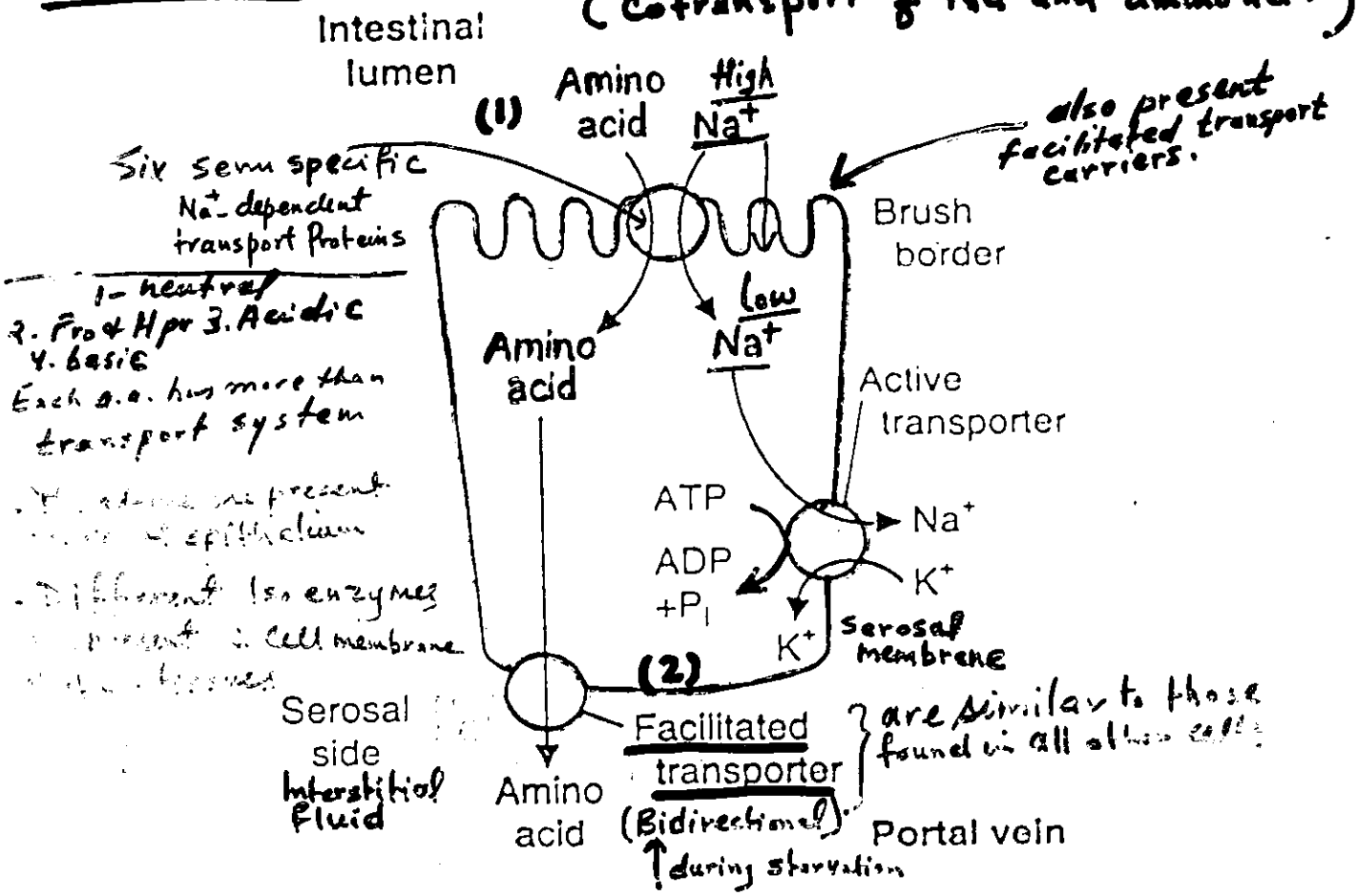
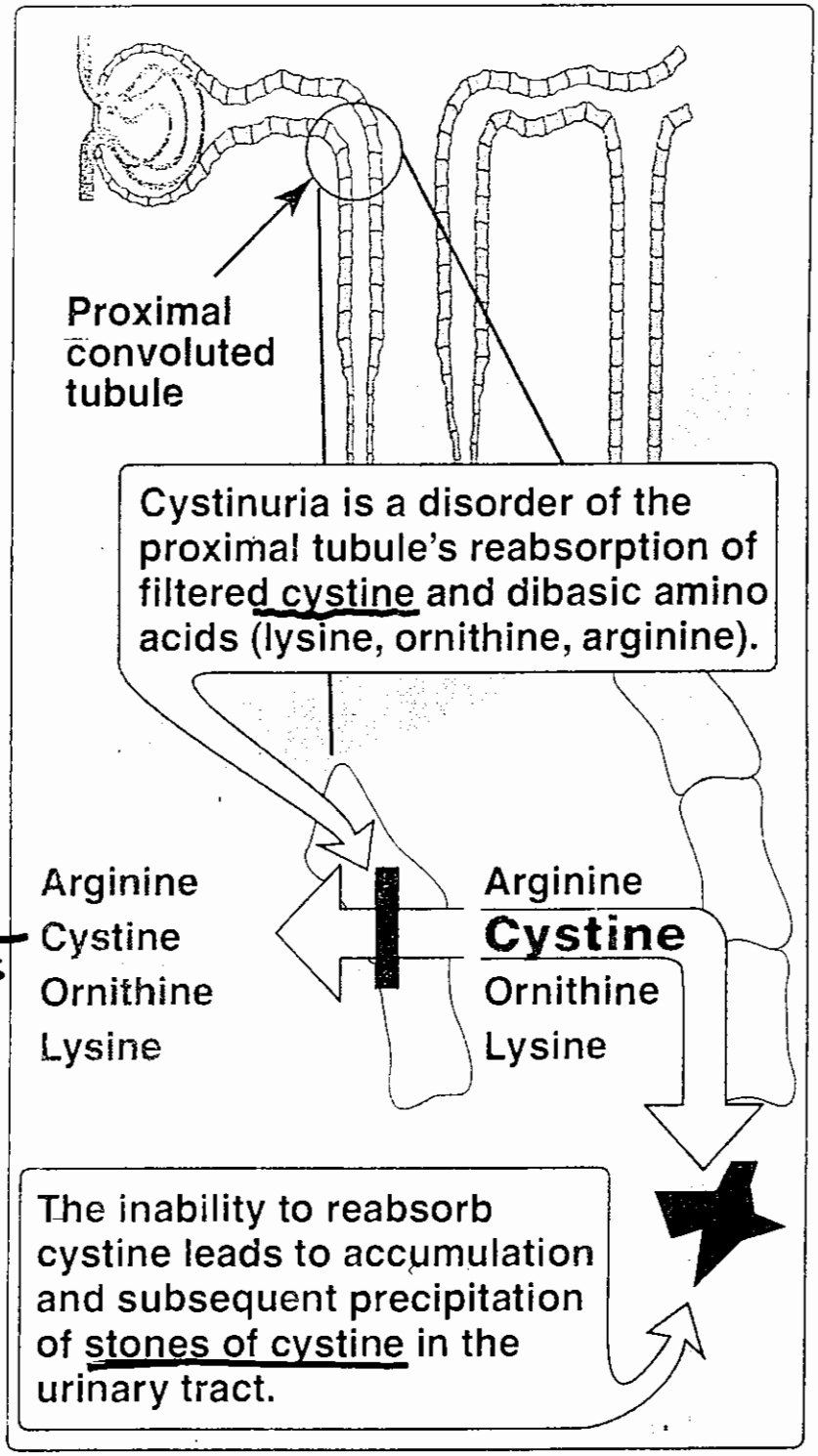


Fig. 37.6. Transepithelial amino acid transport. Na^+-dependent carriers transport both Na^+ and an amino acid into the intestinal epithelial cell from the intestinal lumen. Na^+ is pumped out on the serosal side (across the basolateral membrane) in exchange for K^+ by the Na^+,K^+-ATPase. On the serosal 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



Cys stones

Nitrogen Metabolism

Catabolism of amino acids

- Removal of amino groups - a must for oxidation
  - transamination
  - oxidative deamination
  - Amino groups ⟹ Urea
- Carbon skeleton
  - → Energy + CO_2 + H_2O
  - → Glucose
  - → Fatty acids and ketone bodies

AMINO ACID METABOLISM

Degradation of Amino Acids:-

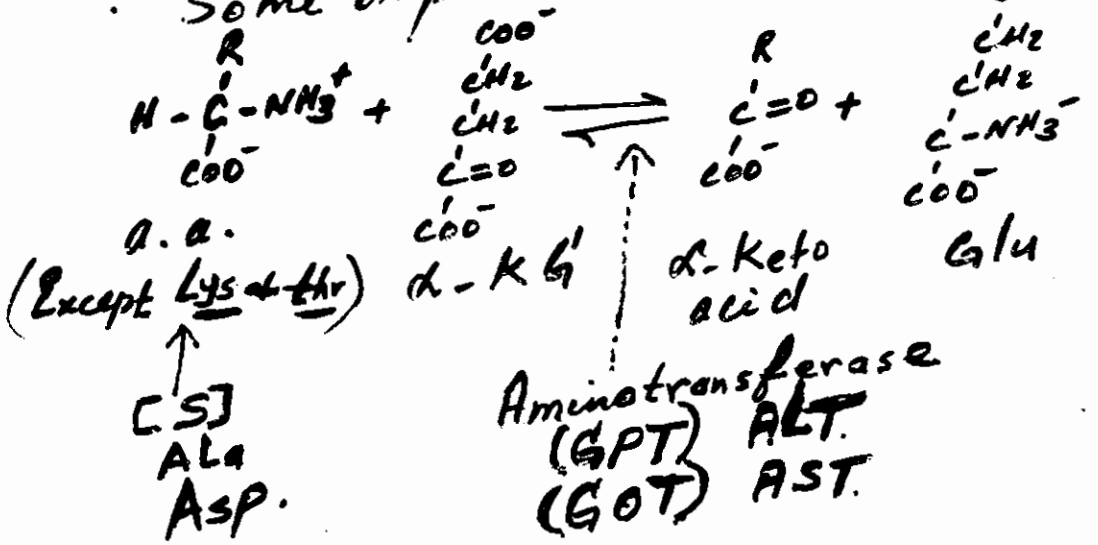
I - Removal of amino group and its utilization [Ammonia Metabolism]

II - Conversion of the carbon chain into
- → Carbohydrate
- → lipid
- → Energy + CO_2 + H_2O

~ REMOVAL OF THE AMINO GROUP

1. Transamination

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



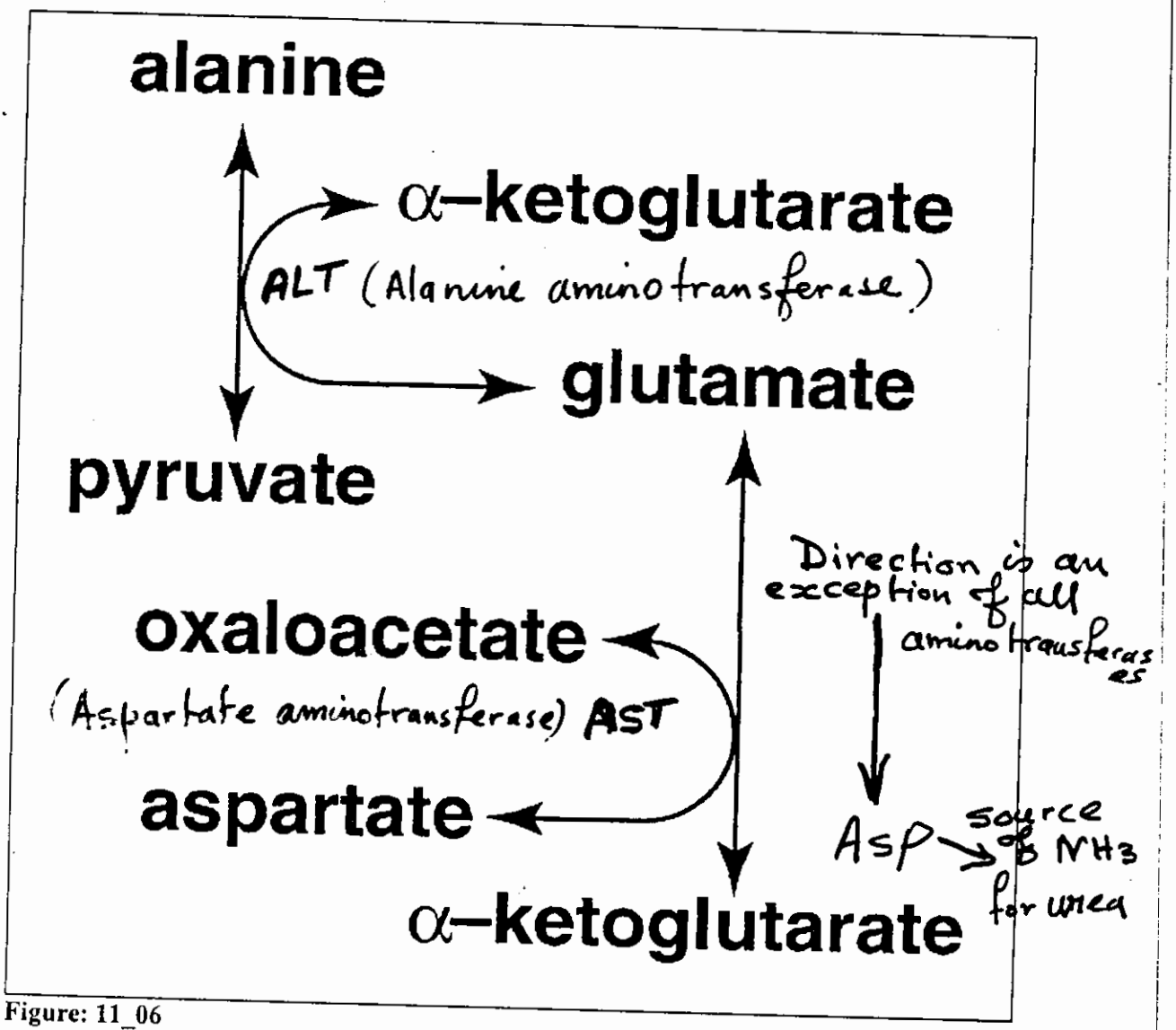


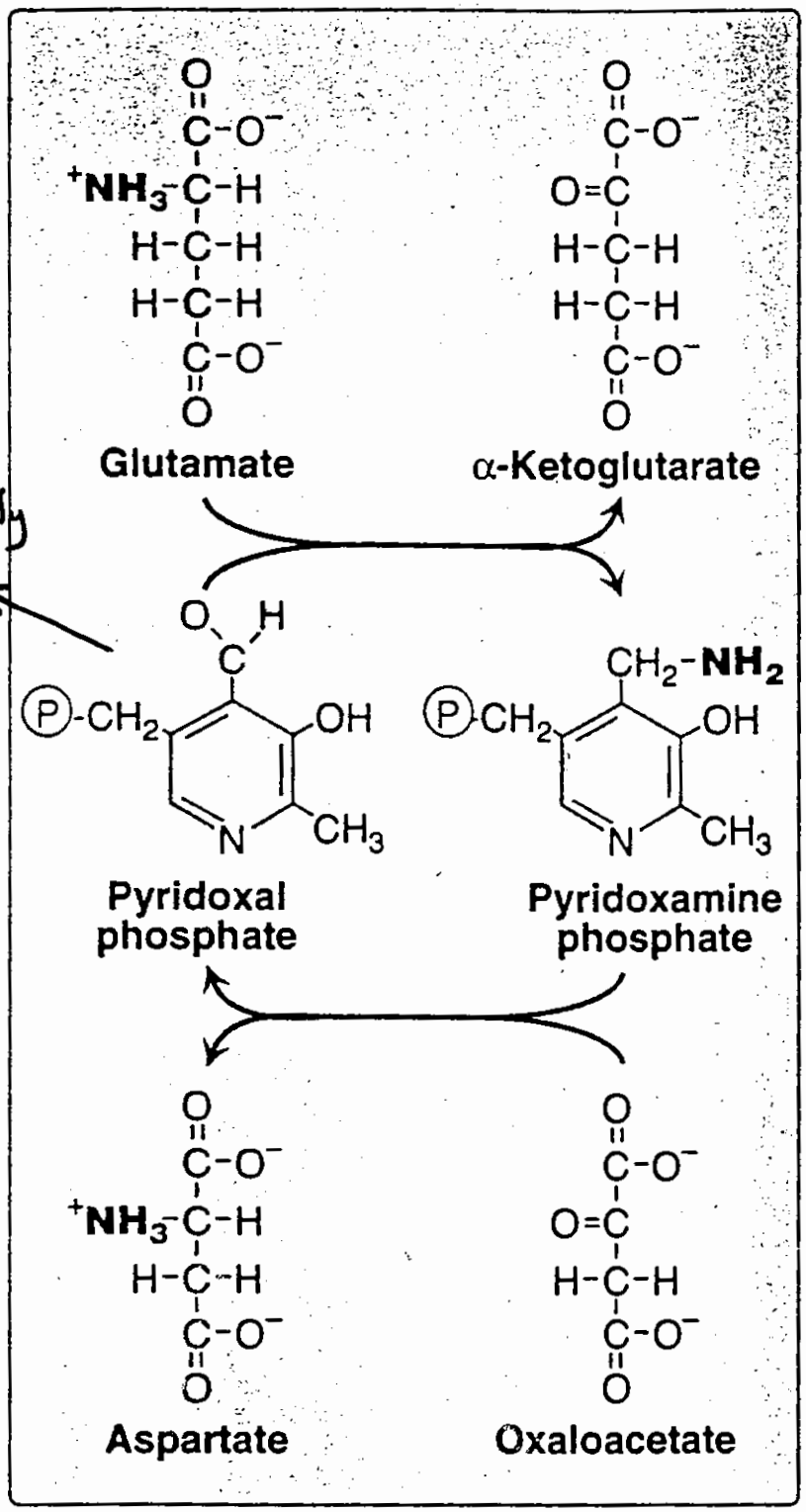
Figure: 11_06
A coupled transamination reaction.

OX.-Deamination

Glu.Deh

$$Glu + NAD \longleftrightarrow \alpha\text{-}KG + NADH + NH_3$$

Cyclic Interconversion of the co-factor in transaminase (aminotransferase) reactions



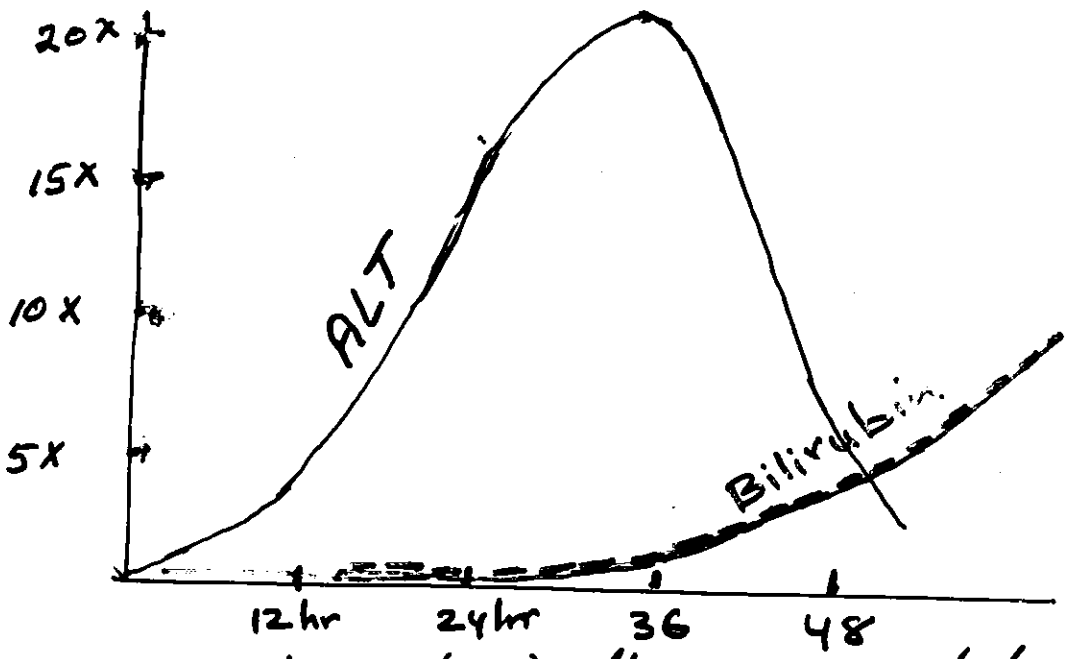
linked covalently to ε-amino gr. of sp. lys at active site

(derivative of vit. B6)

$$Glu + O.A \longrightarrow \alpha\text{-}KG + Asp$$

Diagnostic Value of Plasma Aminotransferases

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



time (hrs.) after ingestion of liver toxin

Liver diease:

- 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

$$Glu + NAD^+ (NADP^+) \underset{NAD^+}{\overset{Glu\ dehydrogenase}{\underset{NADPH}{\rightleftarrows}}} \alpha\text{-}KG + NH_4^+ + NADH\ (NADPH)$$

- Functions to liberate amino gr as ammonia
- Occur primarily in liver & kidney

1 Glutamate dehydrogenase

$$\text{Amino gr. of most amino acids} \xrightarrow[\text{transamination}]{\alpha\text{-}KG} Glu \xrightarrow{\text{Oxidative deamination}} \alpha\text{-}KG + NH_3$$

- Cofactor NAD^+ & $NADP^+$
- Located in the mitochondria
- Direction of reactions (readily reversible) depends on the relative concs. of Glu, α-KG, NH_3, NAD/NADH
- After protein-rich meal → α-KG
- The reaction in vivo is more likely toward ammonia formation.

2. D-Amino acid oxidase (DAO)

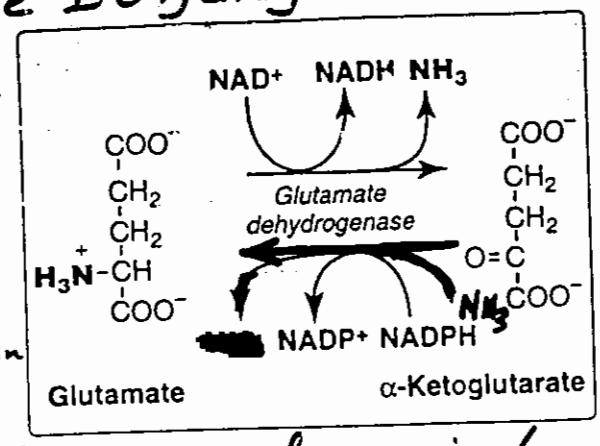
FAD-dependent peroxisomal enzyme

→ α-keto acid + ammonia + H_2O_2

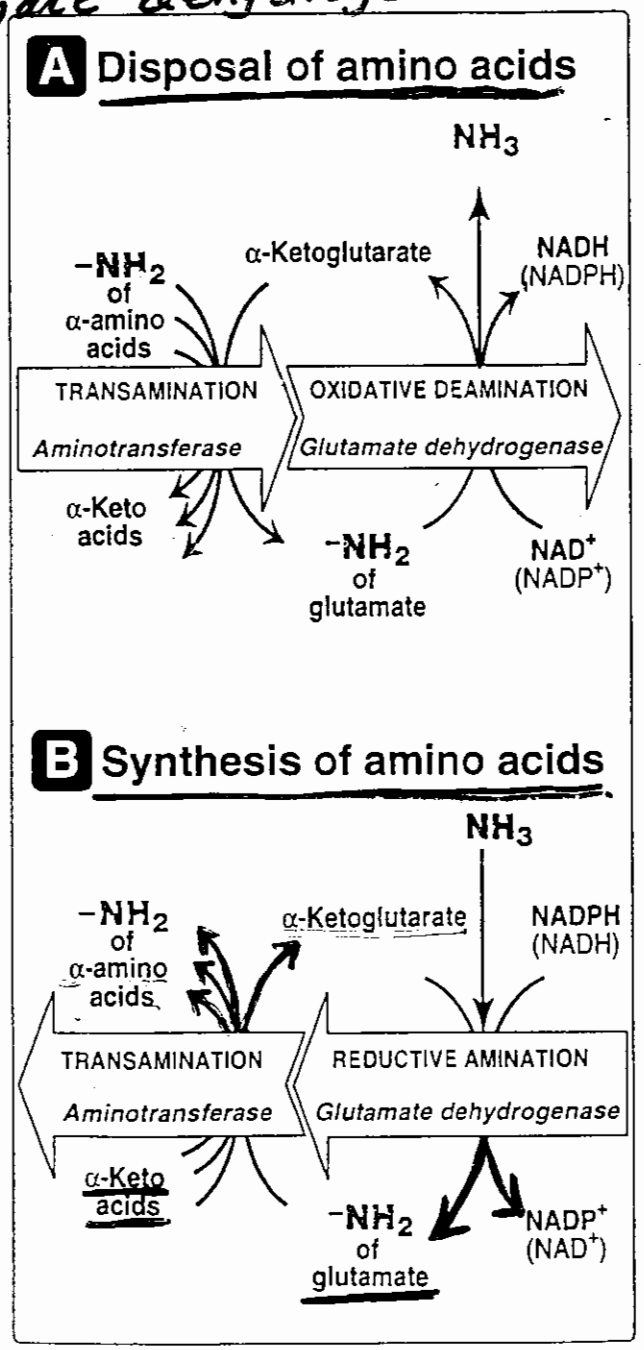
→ reaminated to L-Isomer or → Energy

Oxidative deamination by Glutamate Dehydrogenase :-

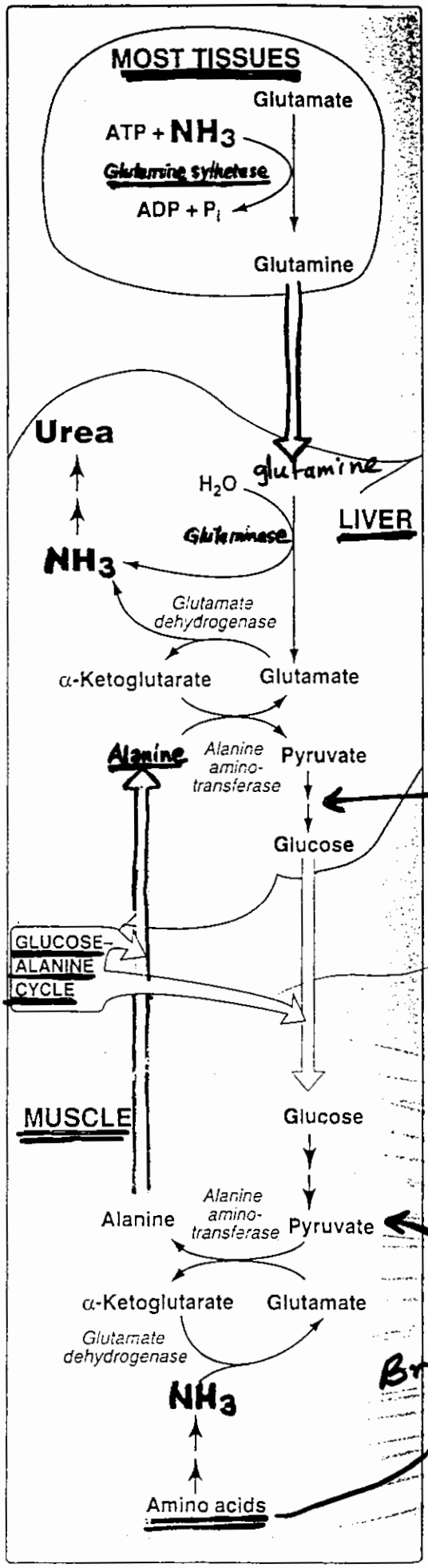
- occurs Primarily in liver + kidney
- Cofactors
- location
- Direction of reaction



Combined Actions of aminotransferase and Glutamate dehydrogenase reactions :-



Transport of Ammonia from peripheral tissues to liver.



Gln ↑ highest a.a. in blood

gluconeogenesis

Alanine - Gln cycle

succinyl CoA

Branched-amino acids
Isoleucine, Valine

The Urea Cycle

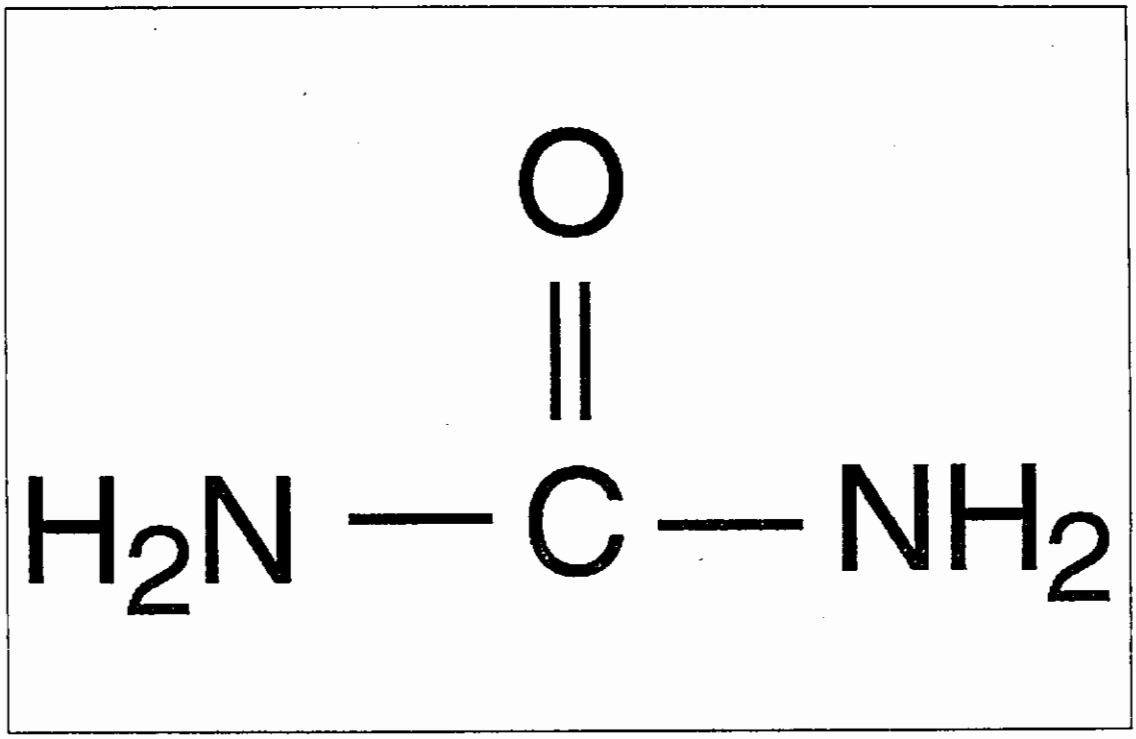


Figure: 11_21
Urea.

Atoms of Urea

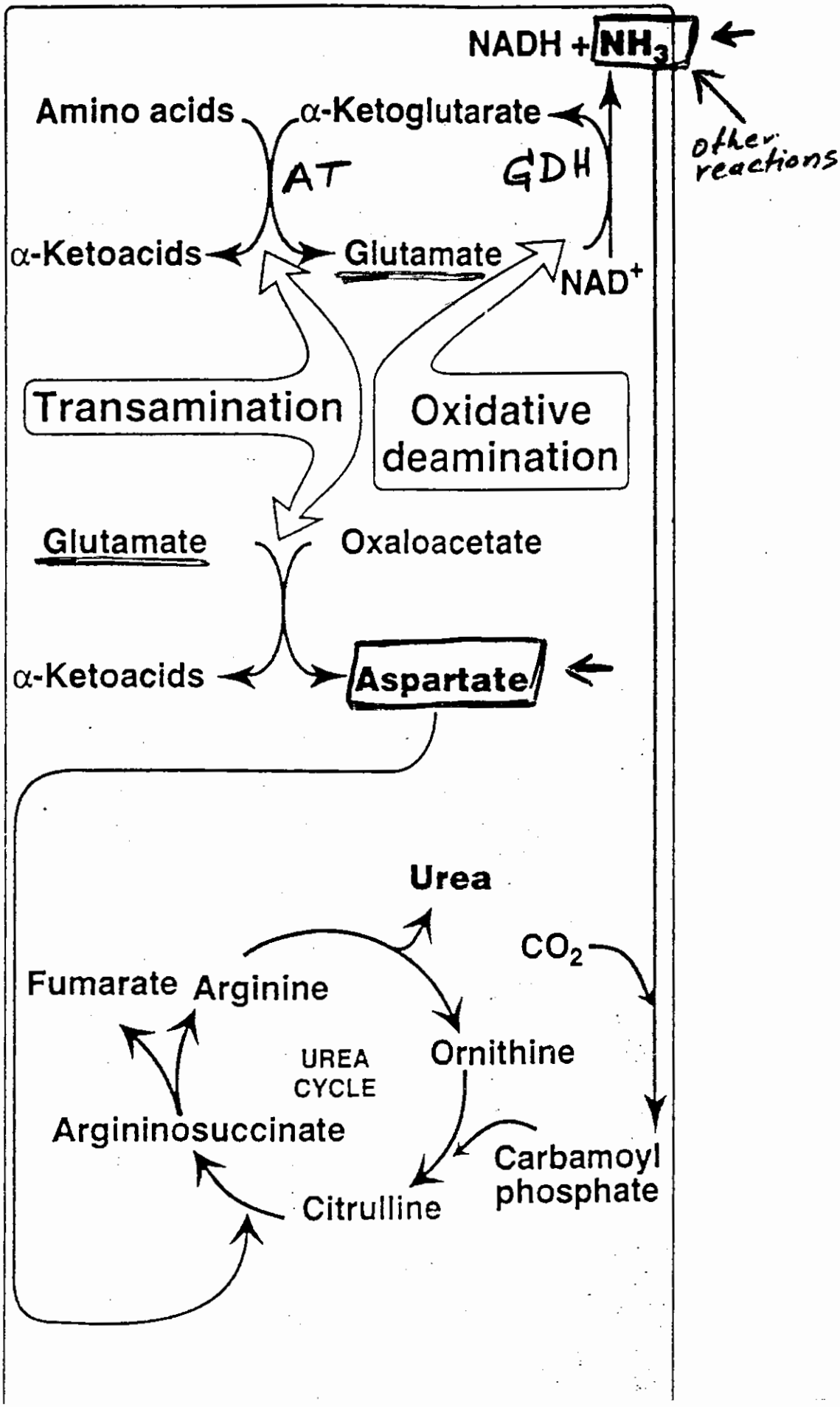
- Free NH_3
- Aspartate → NH_3
- Bicarbonate

Flow of nitrogen to Urea

Amino groups of Urea are collected in the form of:-

1- Ammonia

2- Aspartate



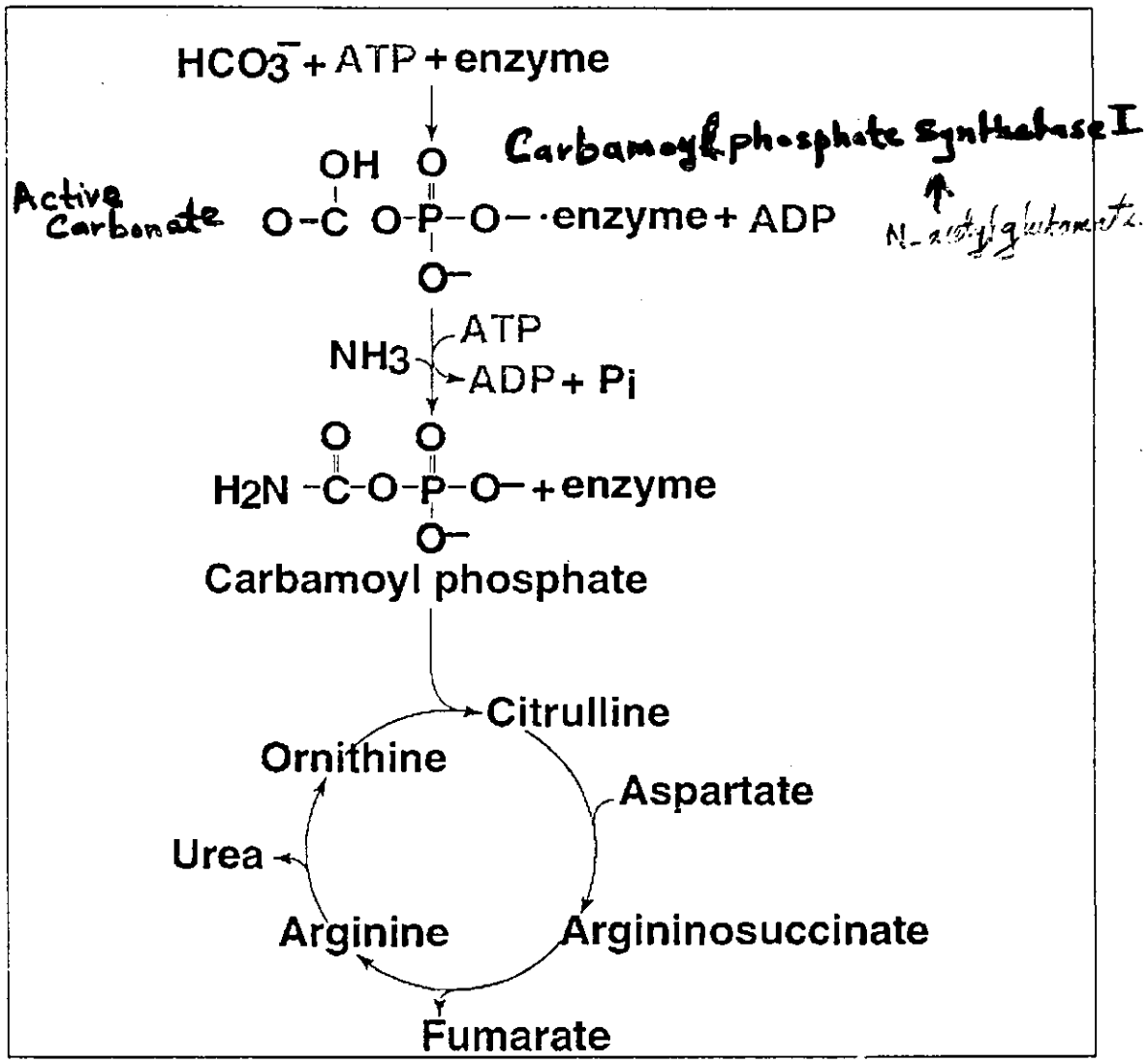


Figure: 11_22
Synthesis of carbamoyl phosphate and entry into urea cycle.

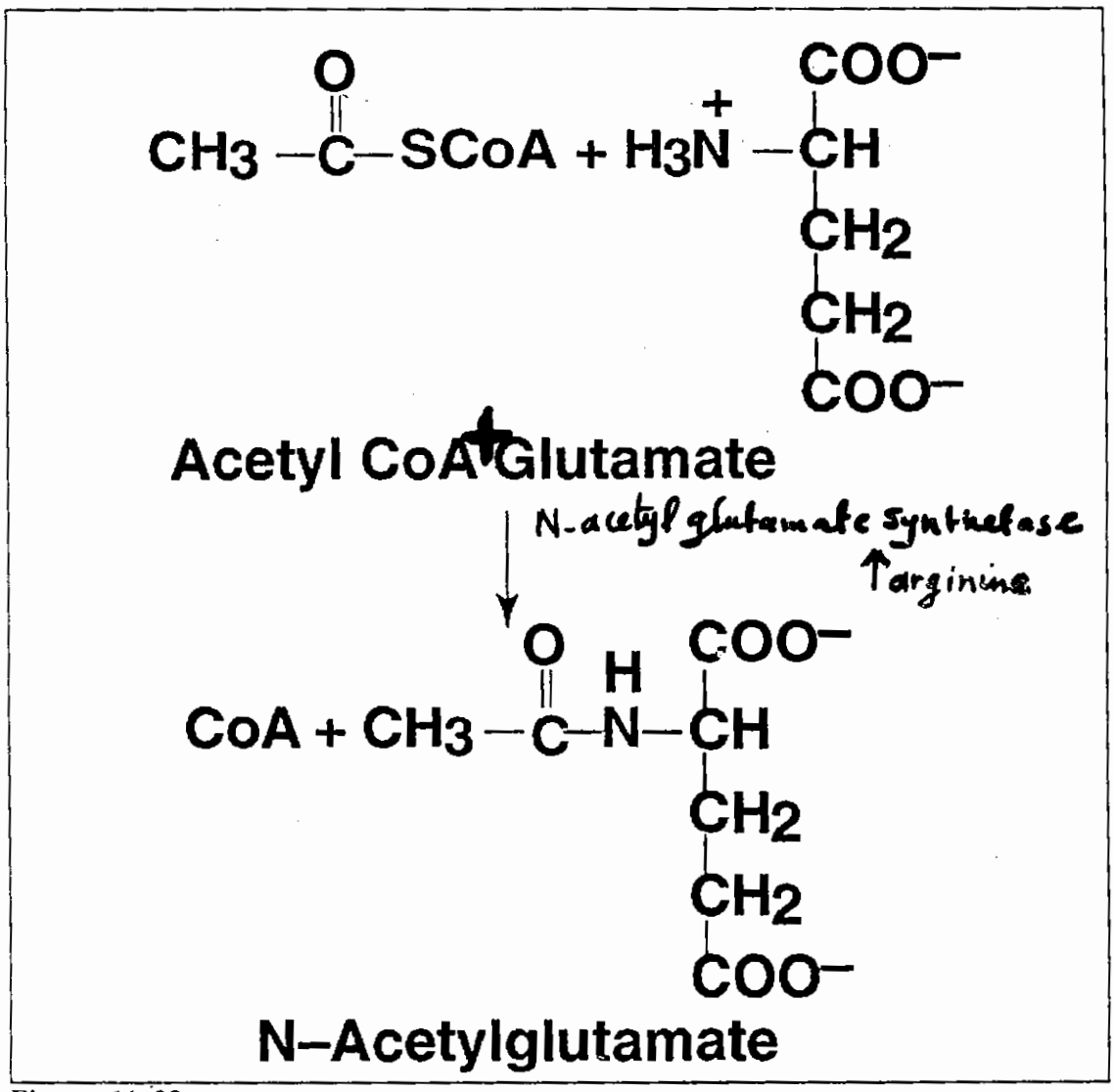


Figure: 11_23
Reaction catalyzed by N-acetylglutamate synthetase.

UREA CYCLE

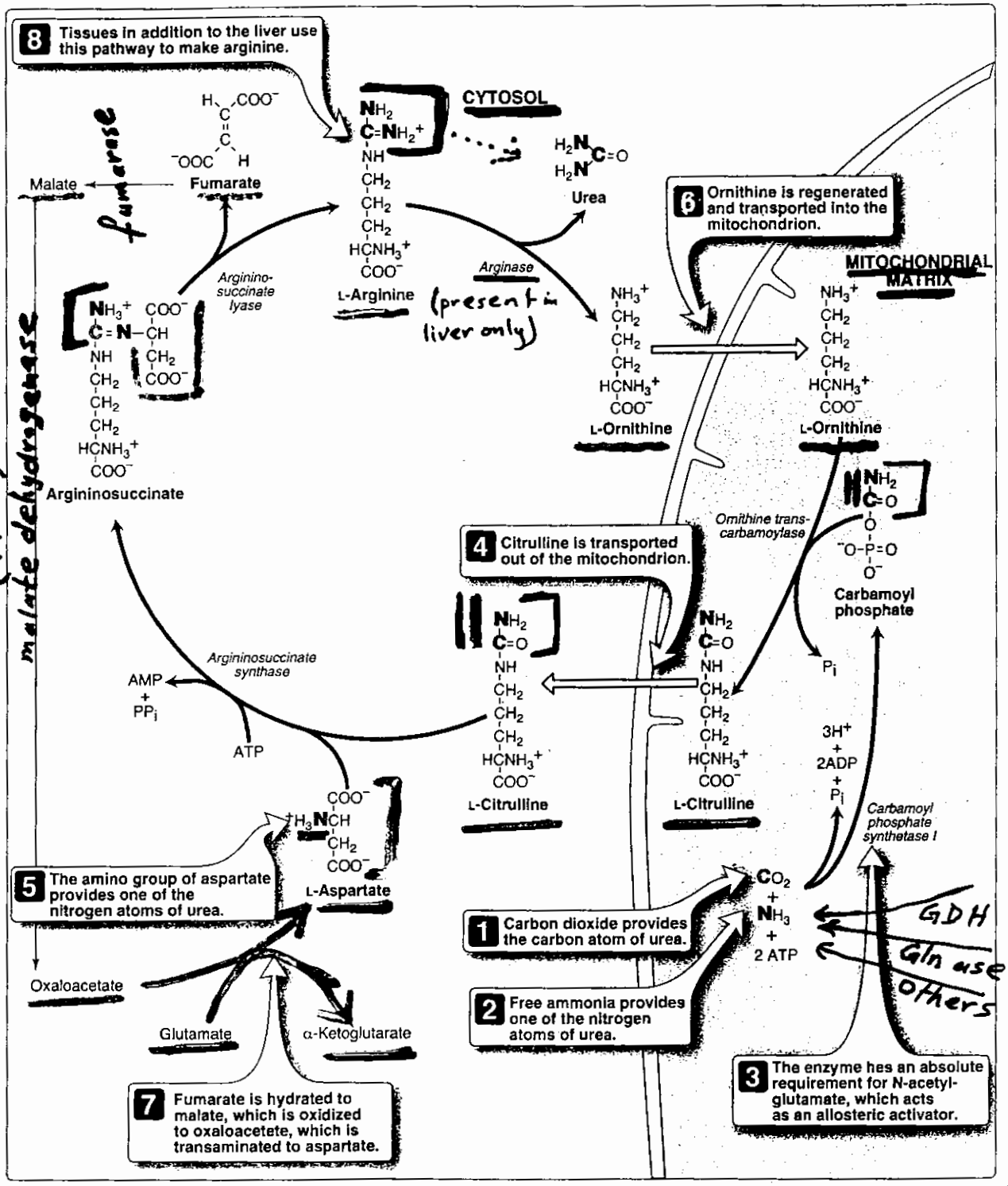


Figure 19.14
Reactions of the urea cycle.

Citrulin/ornithine exchange transport

Regulation of Urea Cycle:-
- Allosteric regulation
- High Protein diet ↑
- Starvation ↑

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

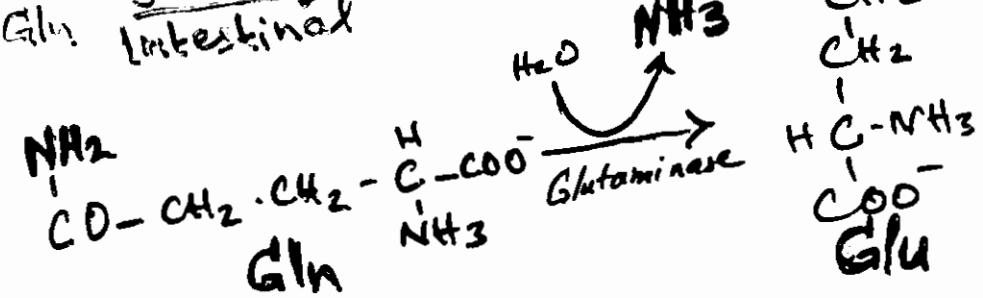
1- From amino acids :- the most impt. source, by [illegible] transferases & GDH

2- From Glutamine :- (Liver), Kidney, Intestine

Kidney [illegible] → [illegible] to urine.

G Glutaminase

Gln $\xrightarrow[\text{Intestinal}]{\text{glutaminase}}$ NH_3



3- From [illegible] rial [illegible] the Intestine

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

4- from Amines [illegible] amines in diet, neurotransmitters & hormones

5- from Purines and Pyrimidines metabolism

Metabolic Disorders of Urea Synthesis

Hyperammonemia

5-35 μmole/100 ml normal conc.

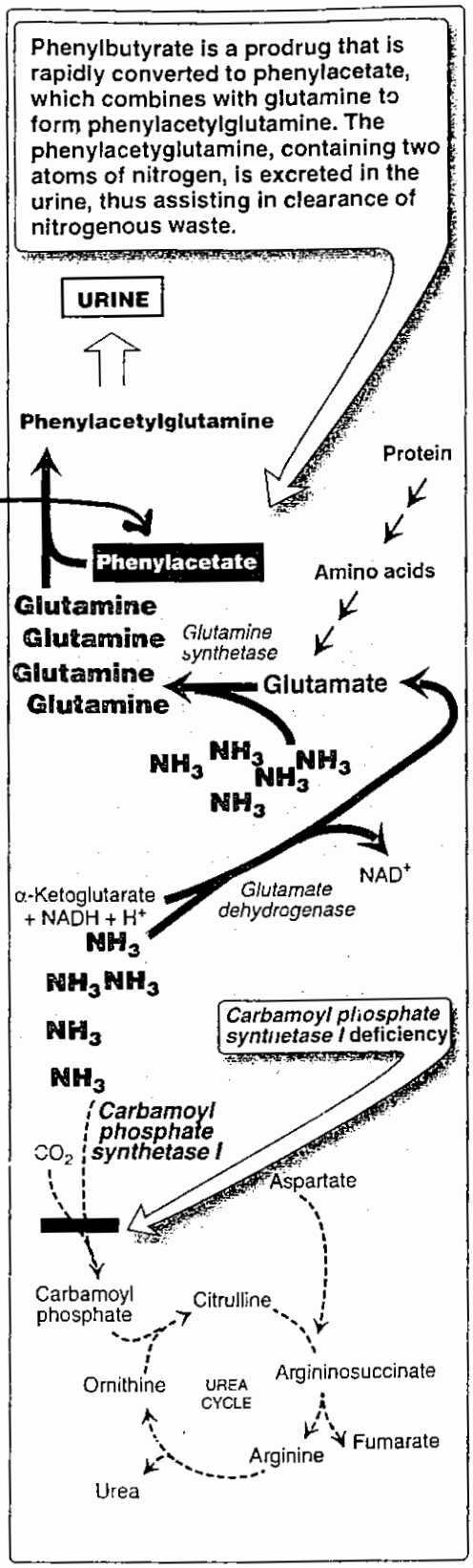
↑level → intoxication → tremors
→ slurring of speach
→ blurring of vision
→ v. high conc. → Coma + death

1. Acquired hyperammonemia

2. Hereditary hyperammonemia
   - Enz. deficiency (rare) 1 : 30,000
   - Ornithine transcarbamoylase, x-linked, most commm
   - Urea cycle defects had high morbidity (neurologic) and mortality
   - Hyperammonemia due to Arginase deficiency is less severe

? α-KG + NADPH + H^+ + NH_3 ⇌ Glutamate + $NADP^+$

- Treatments :-
  - restricting protein intake.
  - drugs that bind covalently to amino acids e.g gln.



phenyl butyrate (prodrug)

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.