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Textbook of BIOCHEMISTRY for BSc NURSING

As per Revised INC Syllabus



Pankaja Naik

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Contents

1. The Metabolism of Carbohydrates and its Alterations **1**

- Definition, Classification, and Functions of Carbohydrates 1
- Digestion and Absorption of Carbohydrates 2
- Metabolism and Related Disorders of Carbohydrates 4
- Glycolysis 5
- Citric Acid Cycle 8
- Gluconeogenesis 10
- Cori Cycle or Lactic Acid Cycle 12
- Glycogen Metabolism 12
- Pentose Phosphate Pathway 15
- Regulation of Blood Glucose 17
- Glycosuria 19
- Diabetes Mellitus 20
- Investigations of Diabetes Mellitus 22
- Hypoglycemia 27

2. The Metabolism of Lipids and its Alterations **31**

- Definition, Classification, and Functions of Lipids 31
- Definition, Classification, and Functions of Fatty Acids 33
- Clinical Significance of Monounsaturated Fatty Acid and Polyunsaturated Fatty Acid 35
- Clinical Significance of Essential Fatty Acids and Trans Fatty Acids 36
- Digestion and Absorption of Lipids 37
- Metabolism of Lipids and Related Disorders 39
- Compounds Formed from Cholesterol 47
- Ketone Bodies: Name, Types and Significance 48
- Lipoproteins, Types and Functions 50
- Atherosclerosis 52
- Lipid Profile 53

3. The Metabolism of Amino Acids and Proteins and its Alterations **59**

- Classification of Amino Acids Based on Nutrition and Metabolic Fate with Examples 59
- Digestion, and Absorption of Proteins 60
- Metabolism of Proteins and Related Disorders 62
- Biologically Important Compounds Synthesized from Various Amino Acids 68
- Inborn Errors of Aromatic Amino Acid Metabolism 70
- Plasma Proteins: Types, Function and Normal Values 74
- Proteinuria: Hypoproteinemia, Hyperglobulinemia 77
- Principle of Electrophoresis: Normal and Abnormal Electrophoretic Patterns 79

4. Clinical Enzymology in Various Disease Conditions **84**

- Classification of Enzymes 84
- Isoenzyme: Definition, Properties and Significance 86
- Enzymes of Diagnostic Importance 87

5. Acid-Base Balance, Imbalance and its Clinical Significance **94**

- Acids, Bases, pH, and Buffers 94
- Regulation of Blood pH 95
- Acid-Base Disorders: Types, Definition and Causes 99
- Arterial Blood Gas: Normal Values 101

6. The Metabolism of Hemoglobin and its Clinical Significance **104**

- Metabolism of Hemoglobin 104
- Heme Catabolism: Heme Degradation Pathway 104
- Jaundice: Type and Causes 106
- Blood and Urine Investigations for the Diagnosis of Jaundice 108

7. Organ Function Tests and Interpretation **111**

- Liver Function Tests 111
- Renal Function Tests 115
- Thyroid Function Tests 118

8. Immunochemistry **123**

- Structure and Functions of Immunoglobulins 123
- Enzyme-linked Immunosorbent Assay: Investigations and Interpretation 127

Index ***133***

The Metabolism of Amino Acids and Proteins and its Alterations

3

Unit	Learning outcomes	Content
3	Explain the metabolism of amino acids and proteins Identify alterations in disease conditions	❖ Classification of amino acids based on nutrition and metabolic fate with examples ❖ Digestion and absorption of proteins ❖ Metabolism of proteins and related disorders ❖ Biologically important compounds synthesized from various amino acids ❖ Inborn errors of aromatic amino acid metabolism ❖ Plasma proteins: Types, functions and normal values ❖ Proteinuria: Hypoproteinemia, hyperglobulinemia ❖ Principle of electrophoresis: Normal and abnormal electrophoretic patterns

INTRODUCTION

Protein is the most important of cell constituents. Proteins are made-up of **amino acids**. They are responsible for almost every function that occurs in the body. A regular and adequate supply of protein in diet is essential for cell integrity and function. Dietary proteins are the primary sources of the **nitrogen** that is metabolized by the body. Adult man requires **70 to 100 g protein per day.**

CLASSIFICATION OF AMINO ACIDS BASED ON NUTRITION AND METABOLIC FATE WITH EXAMPLES

Amino acids are a structural unit of proteins which have a carboxyl group (-COOH) and an amino acid group (-NH2) bound to the same carbon atom called the **α-carbon (Figure 3.1).** Amino acids differ from each other in their **side chains** or **R-groups,** attached to the α-carbon. Amino acids are joined to each other by peptide bonds to form proteins. There are **20 amino acids** are involved in the formation of **proteins**. The 20 amino acids of proteins are often referred to as the **standard amino acids**. The 20 amino acids occur in protein are classified on the basis of:

1. Nutritional requirement of amino acids
2. Metabolic fate of amino acids

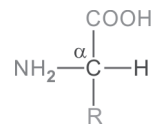


Figure 3.1: General structure of α-amino acid found in protein.

Classification of Amino Acids based on Nutrition

On the basis of nutritional requirement, amino acids are classified into two groups:

1. Essential amino acids
2. Nonessential amino acids.

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Essential Amino Acids

Most microorganisms can synthesize all 20 amino acid, whereas human beings cannot synthesize 10 of them because some of the enzymes required for the synthesis of these amino acids are not present in human body. Therefore, these 10 amino acids must be essentially supplied through the diet. Amino acids that must be supplied in the diet are called **essential amino acids**, whereas the others, which can be synthesized in the body, are termed nonessential amino acids **(Table 3.1)**. Ten amino acids, essential for humans include:

1. Phenylalanine
2. Valine
3. Threonine
4. Tryptophan
5. Isoleucine
6. Methionine
7. Histidine
8. Arginine
9. Lysine
10. Leucine

The mnemonics often used by students are **PVT TIM HALL** Among the ten essential amino acids; **arginine** and **histidine** are known as **semi-essential** amino acids since these amino acids are synthesized partially in human body. Arginine and histidine become essential in diet during periods of rapid growth as in childhood and pregnancy.

A deficiency of even one essential amino acid impairs protein synthesis and leads to a negative nitrogen balance (nitrogen excretion exceeds nitrogen intake). In negative nitrogen balance, more protein is degraded than is synthesized, and so more nitrogen is excreted than is ingested.

Table 3.1: Essential and non-essential amino acids.

Sl. No.	*Essential (PVT TIM HALL)*	*Non-essential*
1.	Phenylalanine	Glycine
2.	Valine	Proline
3.	Threonine	Serine
4.	Tryptophan	Glutamic acid
5.	Isoleucine	Glutamine
6.	Methionine	Alanine
7.	Histidine	Tyrosine
8.	Arginine	Cysteine
9.	Lysine	Aspartic acid
10.	Leucine	Aspargine

Nonessential Amino Acids

Nonessential amino acids can be synthesized in human body and are not required in diet. Ten non-essential amino acids, for humans include:

1. Glycine
2. Proline
3. Serine
4. Glutamic acid
5. Glutamine
6. Alanine
7. Tyrosine
8. Cysteine
9. Aspartic acid
10. Aspargine

Classification of Amino Acids based on Metabolic Fate

On the basis of catabolic end products of amino acids, the twenty standard amino acids are divided in three groups**.**

1. **Glucogenic amino acids:** Those which can be converted into glucose. Fourteen out of the twenty standard amino acids are glucogenic amino acids some of them are glycine, alanine, serine, valine, cysteine, methionine, threonine, etc.
2. **Ketogenic amino acids:** Those which can be converted to ketone bodies. Two amino acids **leucine** and **lysine** are exclusively ketogenic.
3. **Both glucogenic and ketogenic:** Those which can be converted to both glucose and ketone bodies. Four amino acids **isoleucine, phenylalanine, tryptophan** and **tyrosine** are glucogenic and ketogenic.

DIGESTION AND ABSORPTION OF PROTEINS

Proteins are large size molecules (macromolecules). They are polymers of amino acids. A total of 20 different amino acids exist in proteins and hundreds to thousands of these amino acids are attached to each other in long chains to form a protein.

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Dietary **proteins** are very large complex molecules that cannot be **absorbed** from the intestine. To be **absorbed**, dietary **proteins** must be **digested** to small simple molecules (amino acids), which are easily **absorbed** from the intestine. There is no digestion of protein in mouth. It starts in stomach.

Digestion in Stomach

When protein enters the stomach, it stimulates the secretion of the hormone **gastrin,** from gastric mucosal cells, which in turn, stimulates the release of gastric juice containing **hydrochloric acid, pepsinogen** (inactive form of pepsin) and **rennin** in infants.

- **Hydrochloric acid:** It provides an acid environment for the action of pepsin.
- **Pepsin:** It is secreted in an inactive form, **pepsinogen**. It is converted into active pepsin in the gastric juice by the enzymatic action of pepsin itself or by high hydrogen ion concentration **(Figure 3.2)**. Pepsin cleaves long polypeptide chains into a mixture of smaller peptides and some free amino acids.
- **Rennin** is important in the digestive processes of infants. It is absent in adults. Rennin is also called **chymosin** or **rennet**. Action of rennin is to clot milk. The purpose of this reaction is to convert milk into a more solid form to prevent the rapid passage of milk from the stomach of infants.

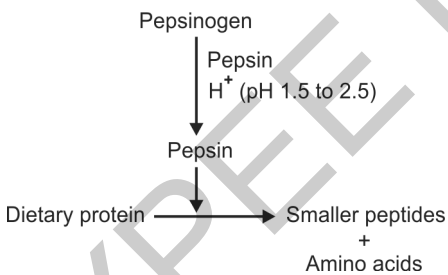


Figure 3.2: Activation of pepsinogen and action of pepsin.

Digestion in Intestine

- Enzymes secreted by pancreas, are **trypsin, chymotrypsin, elastase and carboxypeptidase.** These are secreted in proenzyme (inactive) forms, **trypsinogen, chymotrypsinogen, proelastase** and **procarboxypeptidase**.
- Enteropeptidase activates trypsinogen to trypsin and the activated trypsin in turn activates the chymotrypsinogen, proelastase and procarboxypeptidase **(Figure 3.3)**.
- Trypsin, chymotrypsin elastase and carboxypeptidase hydrolyze polypeptides, resulting from the action of pepsin in the stomach into smaller peptides.
- The digestion products of hydrolysis of protein by pepsin, trypsin, elastase, chymotrypsin and carboxypeptidase are completed by enzymes, **aminopeptidases** and **dipeptidases,** secreted by the mucosa of the small intestine

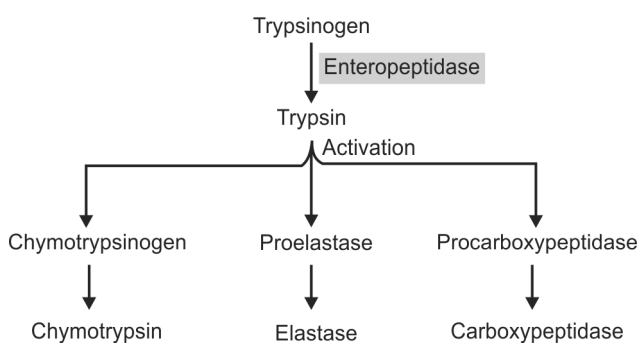


Figure 3.3: Activation of pancreatic proenzymes.

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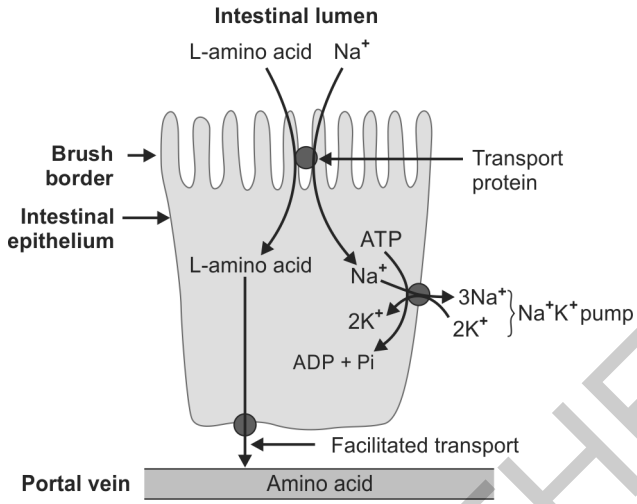


Figure 3.4: Transport of L-amino acid across the intestinal epithelium.

- The hydrolysis of most proteins is thus completed to their constituent **amino acids** which are then ready for absorption into the blood.

Absorption of Amino Acids

- The absorption of most amino acids involves an **active transport mechanism,** requiring ATP and specific transport proteins in the intestinal mucosal cells. Many transporters have Na^+ dependent mechanisms, coupled with Na^+ K^+ pump, similar to those described for glucose absorption **(Figure 3.4)**.
- Amino acids, released by digestion, pass from the gut through hepatic portal vein to the liver.

METABOLISM OF PROTEINS AND RELATED DISORDERS

Proteins are linear chains of amino acids that are linked together by covalent, **peptide bonds.** Each protein has specific and unique sequence of amino acids that defines both its structure and its biologic function.

Functions of Proteins

Some functions that proteins serve are as follows:

1. Proteins act as enzymes, e.g., glucokinase, pepsin, trypsin, etc.
2. Proteins are involved in the process of transport of some biomolecules, e.g.,
   - Hemoglobin transports oxygen
   - Transferrin transports iron
   - Albumin transports fatty acids and bilirubin.
3. Many proteins serve as storage form, e.g.,
   - Apoferritin stores iron in the form of ferritin
   - Myoglobin stores oxygen in muscles.
4. Some proteins have the ability to contract and function in the contractile system of skeletal muscle, e.g.,
   - Actin
   - Myosin
5. Many proteins serve as supporting framework of cells to give biological structure, strength or protection, e.g.,
   - Collagen in bone
   - Cartilage, elastin of ligaments
   - Keratin of hair, nail
6. Many proteins involved in defense mechanism against invasion of foreign substances, such as viruses, bacteria and cells. Examples of defense proteins are:
   - Immunoglobulins or antibodies
   - Fibrinogen and thrombin are blood clotting proteins that prevent loss of

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blood when the vascular system is injured.

7. Some proteins regulate cellular or physiological activity, e.g.,
   - Many hormones, e.g., **insulin,** regulate sugar metabolism; **growth hormone** of pituitary gland regulates growth of the cells.

Metabolism of Proteins

Protein is digested and broken down to **amino acids** which are absorbed into the circulation and taken to the **liver**. Protein metabolism means the various biochemical processes responsible for the **synthesis** and the **breakdown of amino acids**.

The primary role of amino acids is to serve as **building blocks** of synthesis of **tissue protein** and other **biologically important compounds** (discussed later)**.** Amino acids, in excess of those needed for the synthesis of proteins and other important compounds cannot be stored in contrast with fatty acids and glucose, nor are they excreted. Surplus amino acids are oxidized for energy. The liver is the primary site of all amino acid catabolism. The synthesis of the plasma proteins **albumin**, **fibrinogen**, and **globulin** also occur in the liver.

Metabolism of Amino Acids

In the catabolism amino acids, the amino acid first loses their **amino groups** in the form of **ammonia** which is excreted in the form of **urea** in the liver by reactions of the **urea cycle**. **The remaining** carbon skeleton of amino acids, the **α-keto acids** undergo oxidation to carbon dioxide and water by reactions of **citric acid cycle**. The complete catabolism of amino acids includes following stages:

- The removal of **α-amino group** in the form of **ammonia** by:
  - **Transamination** by the enzyme **amino-transferase** also called **transaminase**.
  - **Deamination** by glutamate dehydrogenase
- Disposal of **ammonia** in the form of **urea** in the liver by reactions of the **urea cycle**.
- Disposal (catabolism) of carbon skeleton of amino acids after the removal of α-amino group. The carbon skeletons of 20 amino acids converted into compounds which are intermediates of TCA cycle **(Figure 3.5)**. These carbon skeletons are used for gluconeogenesis or ketogenesis or are completely oxidized to CO_2 and H_2O.
  - Amino acids that are degraded to acetyl-CoA or acetoacetyl-CoA are termed **ketogenic**, because they give rise to ketone bodies. Among 20 amino acids, only **leucine** and **lysine** are purely ketogenic **(Table 3.2).**
  - Amino acids that are degraded to pyruvate, α-ketoglutarate, succinyl-CoA, fumarate or oxaloacetate, are termed **glucogenic** because synthesis of glucose from these amino acids is possible.
  - Isoleucine, phenylalanine, tryptophan and tyrosine are both glucogenic and ketogenic.
  - The other fourteen amino acids are classed as purely glucogenic.

The Removal of α-amino Group in the form of Ammonia

The first stage in amino acid metabolism is removal of **α-amino group.** α-Amino group is removed in the form of **ammonia** by following reactions:

- **Transamination**
- **Deamination**

Transamination

Transamination involves the transfer of α-amino group of α-amino acid to α-keto acid to form new amino acid and a new keto acid. The enzymes that catalyze these reactions are called **aminotransferases** or **transaminases (Figure 3.6)**.

Most transaminases use α-ketoglutarate (α-keto acid) as a common acceptor of

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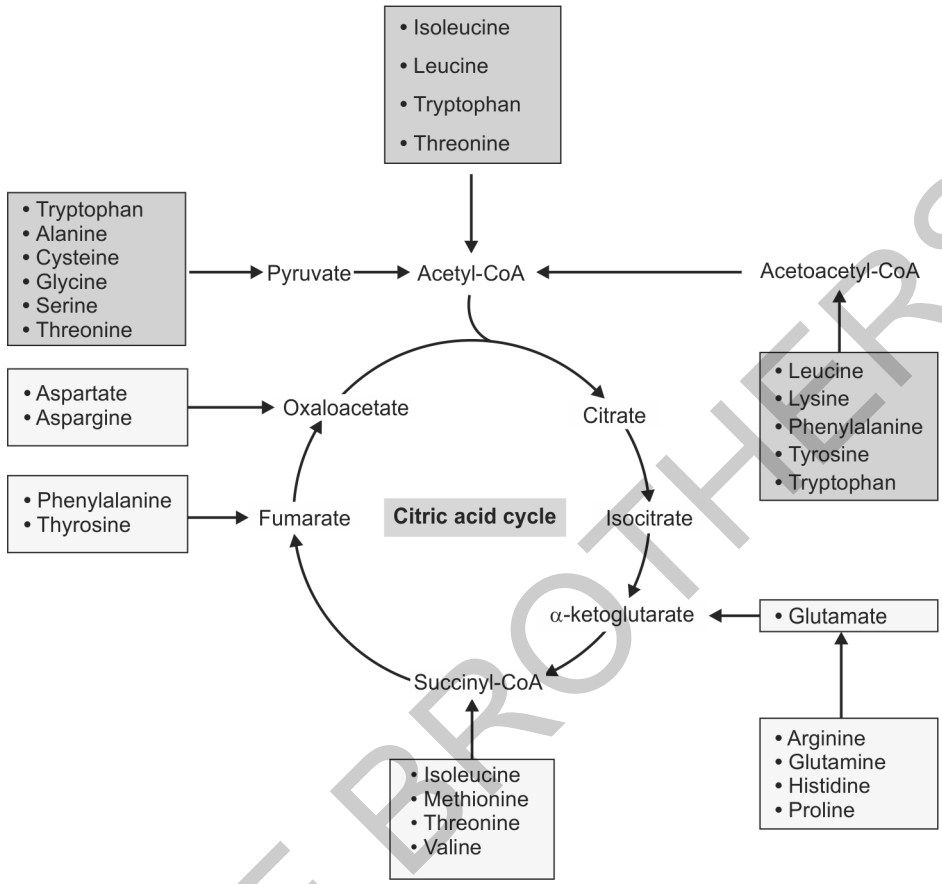


Figure 3.5: Metabolic fate of carbon skeleton of amino acids.

Table 3.2: Classification of amino acids based on metabolic fate.

Exclusive glucogenic	*Exclusive ketogenic*	*Both ketogenic and glucogenic*
• Glycine, alanine, serine	• Leucine	• Tryptophan
• Cysteine, aspartic acid	• Lysine	• Phenylalanine
• Asparagine, glutamic acid		• Tyrosine
• Glutamine, proline, histidine, arginine, methionine, valine		• Threonine • Isoleucine

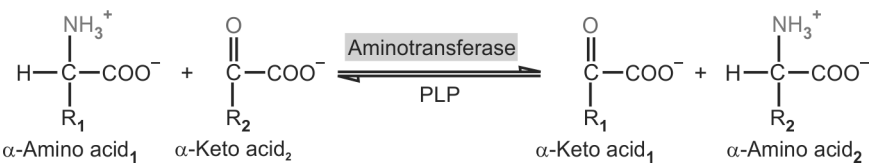


Figure 3.6: Transamination reaction.

amino groups. All transaminases require **pyridoxal phosphate (PLP)** as a coenzyme. Some of the most important transaminases are: **(Figure 3.7)**.

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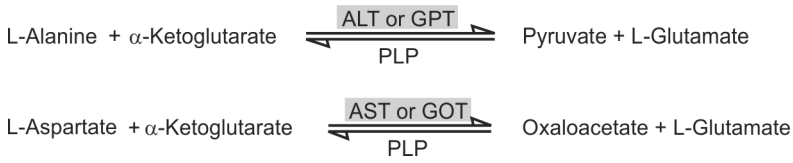


Figure 3.7: Reactions catalyzed by alanine transaminase and aspartate transaminase.

- **Alanine transaminase (ALT)** also called **glutamate pyruvate transaminase (GPT),** catalyzes the transfer of amino group of alanine to α-ketoglutarate resulting in the formation of **pyruvate** and **L-glutamate**.
- **Aspartate transaminase (AST)**, also called **glutamate oxaloacetate transaminase (GOT),** catalyzes the transfer of the amino group of aspartate to α-ketoglutarate, resulting in the formation of **oxaloacetate** and **L-glutamate**.

Amino acids except **lysine, threonine,** and **proline** undergo transamination reaction. It will be noted that there is no net loss of amino groups in transamination reactions.

Significance of transamination reactions

- By transamination reaction the amino groups from various amino acids are collected into one common product **L-glutamate**. This is important because glutamate is the only amino acid whose α-amino group can be directly removed by deamination.
- Serum levels of ALT (GPT) and AST (GOT) are important clinically in the diagnosis of **liver** and **heart disorders**.

Deamination

In deamination reaction, there is removal of **amino group** in the form of **ammonia**. As we have seen, the amino groups from many of the α-amino acids are collected in the liver in the form of the amino group of **L-glutamate**. These amino groups are removed from glutamate in the form of **ammonia** by the action of **L-glutamate dehydrogenase (Figure 3.8)**.

Thus, the net removal of α-amino groups to ammonia requires the combined action of **glutamate transaminase** and **glutamate dehydrogenase**.

Disposal of Ammonia

Ammonia is produced in most tissues. Since ammonia is extremely toxic, it is immediately converted to non-toxic metabolites, such as **glutamate** or **glutamine** and ultimately to **urea.** For the ultimate conversion of ammonia to urea, ammonia is transported to the liver.

Transport of ammonia to the liver

Since free ammonia is highly toxic, it is never transported in free form in blood. In humans, ammonia from the peripheral tissues is transported in the form of **glutamine** to the liver for its ultimate conversion to urea.

In many tissues (liver, kidney and brain), **ammonia** is enzymatically combined with **glutamate** to yield glutamine. The glutamine, so formed is a neutral nontoxic major **transport form of ammonia**. The glutamine is transported by blood to the liver, where it is cleaved to yield **glutamate** and **free ammonia**. The ammonia so formed is converted into **urea** in the **liver.**

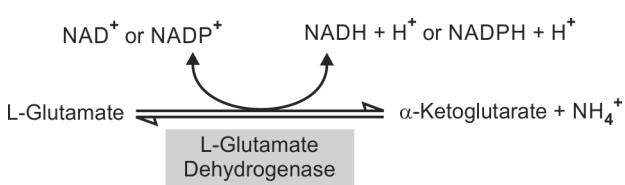


Figure 3.8: Deamination by L-glutamate dehydrogenase.

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Urea Cycle

Ammonia is converted to urea by **"Kreb's Henseleit urea cycle** "which is **exclusively** occur in **liver.** The first two reactions of urea cycle occur in the mitochondria, whereas the remaining reactions occur in the cytosol **(Figure 3.9)**.The sequence of reactions involved in the biosynthesis of urea, summarized in five steps as follows:

1. **Formation of carbamoyl phosphate:** The biosynthesis of urea begins with the condensation of carbon dioxide, ammonia and ATP to form **carbamoyl phosphate**, a reaction catalyzed by mitochondrial **carbamoyl phosphate synthase-I (CPS-I)**. Formation of carbamoyl phosphate requires 2 molecules of ATP.
2. **Formation of citrulline:** Carbamoyl phosphate donates its carbamoyl group to ornithine to form **citrulline** in a reaction catalyzed by **ornithine transcarbamoylase**, a mitochondrial enzyme. The citrulline so formed now leaves the mitochondria and passes into the cytosol of the liver cell.
3. **Formation of argininosuccinate:** Citrulline is transported to cytoplasm, where it condenses with aspartate, a donor of the second amino group of urea. This reaction is catalysed by **argininosuccinate synthetase** which requires ATP. ATP is cleaved into AMP and pyrophosphate.
4. **Formation of arginine and fumarate:** Argininosuccinate is cleaved by **argininosuccinase (also called argininosuccinate lyase)** to form free arginine and fumarate. The fumarate so formed returns to the pool of citric acid cycle intermediates.
5. **Formation of urea and ornithine:** In the last reaction of urea cycle the liver hydrolytic

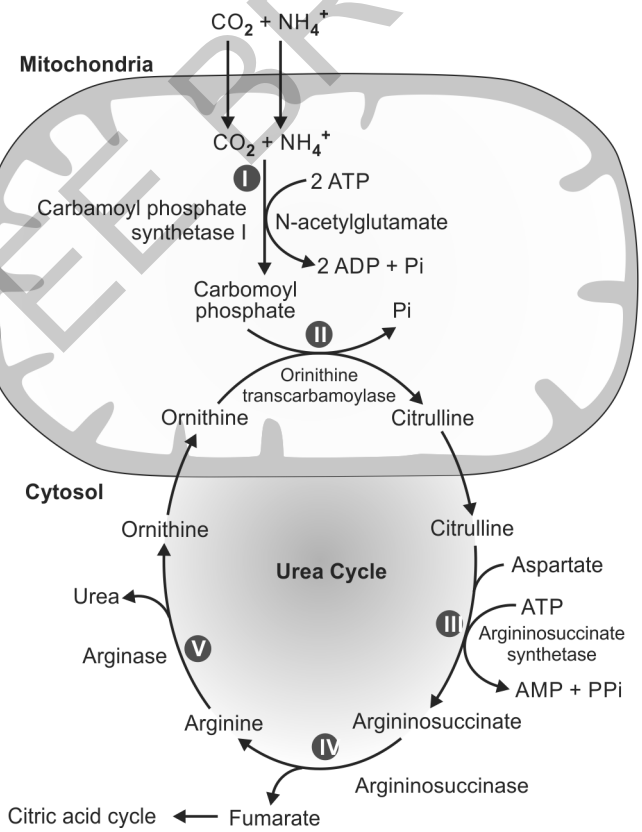


Figure 3.9: Reactions of urea cycle where, CPS-I: Carbamoyl phosphate synthase-I.

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enzyme **arginase**, cleaves arginine to yield urea and ornithine. Ornithine is thus regenerated and can enter mitochondria again to initiate another round of the urea cycle.

Significance of urea cycle

- Urea is the end product of **protein metabolism**
- The toxic **ammonia** is converted into the harmless nontoxic **urea.**
- It disposes off two waste products, **ammonia** and **CO_2**.
- It forms **semi essential** amino acid, **arginine.** Arginine serves as the precursor of the potent muscle relaxants nitric oxide (NO)**.**
- It participates in the regulation of blood pH by removing CO_2.

Metabolic Disorders of Urea Cycle

Genetic defects have been known for each of the urea enzymes. The metabolic disorders of urea biosynthesis are extremely rare. Since urea synthesis converts toxic ammonia to non-toxic urea, all defects in urea synthesis result in **ammonia intoxication**. This intoxication is more severe when the metabolic block occurs at reaction I or II, since it accumulates ammonia itself. Deficiency of later enzymes result in the accumulation of other intermediates of the urea cycle, which are less toxic and therefore severity of symptoms is less.

Disorders caused by genetic defects of urea cycle enzymes are given in **Table 3.3**. The clinical features and treatment of all five disorders are similar.

Symptoms of disorders of urea cycle

Since urea synthesis converts toxic ammonia to non-toxic urea, all defects in urea synthesis result in **increased level of ammonia (hyperammonemia)** that leads to **ammonia intoxication** Symptoms of ammonia intoxication are due to the impaired function of the brain. They include:

- Vomiting
- Nausea
- Ataxia
- Lethargy
- Convulsions
- Slurred speech
- Blurred vision
- Mental retardation.
- Coma and even death

Blood Urea Nitrogen (BUN)

Blood urea nitrogen (BUN) is the measure of **urea level** in the blood. Urea is the metabolic waste product formed by the liver from **ammonia** and excreted through the kidneys. Normal range of blood urea for a healthy adult is **20 to 40 mg/dL**. In clinical practice, blood urea level is taken as an indicator of renal function.

- If kidneys are not able to remove urea from the blood normally, BUN level rises.
- Heart failure, dehydration, or a diet high in protein can also make BUN level higher.
- Liver disease or damage can lower BUN level.
- A low BUN level can occur normally in the second or third trimester of pregnancy.
- The term **uremia** is used to indicate increased blood urea levels. BUN is the less reliable indicator for uremia when compared to blood creatinine.
- For convenience, the causes of high blood urea are subdivided into three classes which are given in **Table 3.4.**

Table 3.3: Disorders caused by genetic defects of urea cycle enzymes.

Disorders	*Defective enzyme*	*Products accumulated*
Hyperammonemia type-I	Carbamoyl phosphate synthetase-I	Ammonia
Hyperammonemia type-II	Ornithine transcarbamoylase	Ammonia
Citrullinemia	Argininosuccinate synthetase	Citrulline
Argininosuccinic aciduria	Argininosuccinase	Argininosuccinate
Argininemia	Arginase	Arginine

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Table 3.4: Causes of high blood urea (Uremia)

Types	*Causes*
Prerenal uremia	• High protein diet • Any cause of increased protein catabolism, e.g., trauma, surgery, extreme starvation, diabetes mellitus, hemorrhage into gastrointestinal tract. • Any cause of impaired renal perfusion, e.g., cardiac failure, ECF loses
Renal uremia	• Any cause that leads to reduced GFR and leads to urea retention
Postrenal uremia	• Any cause of obstruction to urine outflow, e.g., benign prostatic hypertrophy, malignant stricture or obstruction, stone
Reduced plasma urea concentration	• Low protein diet, severe liver disease (decrease synthesis), water retention

Blood Urea Nitrogen-nursing Implications

- A common reason for an increase in BUN is dehydration. The nurse should consider the BUN level, along with the patient's vital signs, intake and output, weight, and skin turgor (as indicators of dehydration).
- An increased BUN may also be caused by anything that causes poor renal perfusion (renal blood flow) or renal dysfunction. Therefore, it is important for the nurse to look at BUN levels in the pathological context of each patient.
- If increase in BUN is because of improper renal perfusion, the renal blood flow must be increased. If there is actual renal damage, then fluids must be restricted or increased, depending on the phase of acute renal failure.
- If kidney dysfunction is the confirmed cause of increased BUN levels, the nurse must restrict the patient from certain foods, especially those with sodium, potassium, and high protein.
- A patient with high level of BUN and creatinine has skin itching and nurses should give proper skin care.
- Patients might experience muscle weakness, fatigue, nausea, and vomiting as the BUN level increases. The person may have decreased mental awareness, including drowsiness and confusion. The nurse should assess the cognitive and physical capabilities of any patient with an increased creatinine and BUN to ensure safe care.
- The nurse may order a creatinine clearance test to evaluate extent of renal damage so that doses of maintenance drugs can be adjusted accordingly.

BIOLOGICALLY IMPORTANT COMPOUNDS SYNTHESIZED FROM VARIOUS AMINO ACIDS

Amino acids, released by hydrolysis of dietary protein, and tissue proteins together constitute the **amino acid.** In contrast to carbohydrates and fat whose major function is to provide energy, the primary role of amino acids released by hydrolysis of dietary protein is used to synthesis of **tissue protein** and other **biologically important compounds** that have various biological roles **(Figure 3.10)**.

Some of the compounds that are derived from amino acids are given below **(Table 3.5)**:

- **Formation of proteins:** Amino acids are joined to each other by peptide bonds to form proteins and peptides.
- **Formation of glucose:** Glucogenic amino acids are converted to glucose in the body.
- Hormone **thyroxine** is synthesized from amino acid **tyrosine**.
- Skin-pigment **melanin** is synthesized from amino acid **tyrosine**.
- Hormone **epinephrine**, **norepinephrine**, and **dihydroxy-phenylalanine (DOPA)** is

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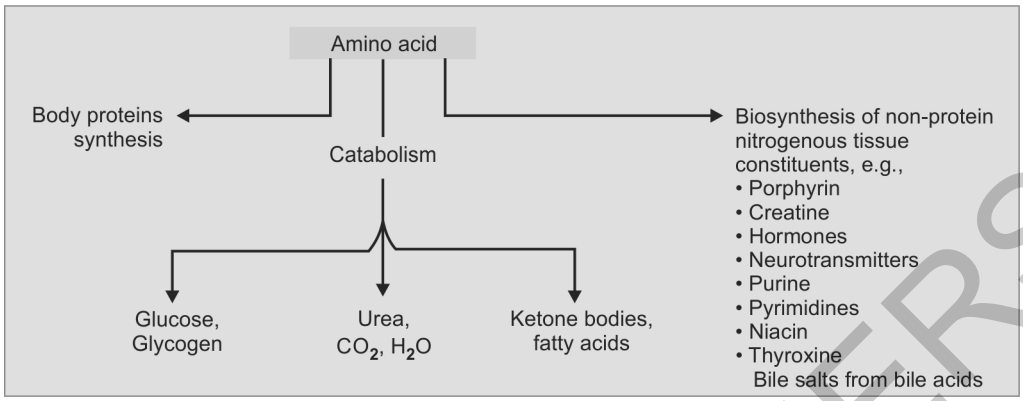


Figure 3.10: Biologically important compounds synthesized from amino acids.

Table 3.5: Biologically important compounds synthesized by various amino acids.

Biologically important compound	*Formed by amino acid*
Hormone, e.g., thyroxine, skin-pigment, e.g., melanin	Tyrosine
Skin-pigment, e.g., melanin	Tyrosine
Hormone, e.g., epinephrine, norepinephrine, and dihydroxyphenylalanine (DOPA)	Tyrosine and Phenylalanine
γ-Aminobutyric acid (GABA) (neurotransmitter)	Glutamic acid
Vitamin niacin	Tryptophan
Creatine	Glycine, arginine and methionine
Bile salts	Glycine
Heme	Glycine
Pyrimidine bases	Aspartic acid and Glutamic acid
Purine bases	Glycine, aspartic acid and glutamine
Histamine	Histidine
Serotonin	Tryptophan
Glutathione	Cysteine, glycine and glutamic acid
Nitric oxide (NO)	Arginine

synthesized from amino acid **tyrosine** and **phenylalanine**.

- **Neurotransmitter, γ-aminobutyric acid (GABA)** is formed from **glutamic acid.**
- **Vitamin niacin** is synthesized from **tryptophan**.
- **Creatine** is synthesised from three amino acids, **Glycine**, **arginine** and **methionine**. Creatin phosphate is present in **muscle** and **brain tissue** and functions as the store form of high energy compound.
- **Pyrimidine bases (thymine, cytosine and uracil)** are derived from amino acids **aspartic acid** and **glutamic acid**. Pyrimidine bases are required for the synthesis of **RNA** and **DNA**.
- **Purine bases (adenine and guanine)** are derived from amino acids **glycine**, **aspartic acid** and **glutamine**. Purine bases are required for the synthesis of **RNA** and **DNA**.
- **Histamine** is synthesized from **histidine**. Histamine is involved in local immune responses. Histamine is involved in the inflammatory response and has a central role as a mediator of itching.
- **Serotonin** a **neurotransmitter is** synthesized from **tryptophan.** Serotonin is a stimulates cerebral activity

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- **Glutathione** (GSH) is an **antioxidant** synthesized from three amino acids; **cysteine**, **glycine** and **glutamic acid. Glutathione** is capable of preventing damage to cellular components caused by reactive oxygen species, such as free radicals, peroxides, lipid peroxides, and heavy metals.
- **Nitric oxide (NO)** is free radical gas produced endogenously from **arginine**. **Nitric oxide** dilates blood vessels, raising blood supply and lowering blood pressure. Conversely, it helps protect tissues from damage due to low blood supply. It also acts a neurotransmitter.
- **Heme** of hemoglobin is synthesized from **glycine** along with **succinyl CoA**.
- **Bile salts**: Bile acids are steroid acids synthesized in the liver. Bile acids are conjugated with **taurine** or **glycine** residues to bile salts.

INBORN ERRORS OF AROMATIC AMINO ACID METABOLISM

Phenylalanine, tyrosine and **tryptophan** are the aromatic amino acids. Phenylalanine and tryptophan are nutritionally essential amino acids but tyrosine is not as it can be synthesized from phenylalanine.

Metabolism and Inborn Errors of Phenylalanine and Tyrosine

Metabolism

Phenylalanine metabolism is initiated by its conversion to **tyrosine** which then undergoes oxidative degradation. Thus, catabolic pathway for phenylalanine and tyrosine is same as follows **(Figure 3.11)**:

- The first step is the hydroxylation of phenylalanine to tyrosine, a reaction catalyzed by **phenylalanine hydroxylase**. This enzyme requires tetrahydrobiopterin (H_4-biopterin) as a cofactor. The cofactor is oxidized to dihydrobiopterin (H_2-biopterin) during this reaction. The dihydrobiopterin is reduced back to tetrahydrobiopterin by **dihydrobiopterin reductase.**
- The next step is transamination of tyrosine with ketoglutarate to P-hydroxyphenyl pyruvate, catalyzed by **tyrosine transaminase**.
- P-hydroxyphenyl pyruvate then forms **homogentisate**. This reaction is catalyzed by **P-hydroxyphenylpyruvate hydroxylase.**
- Homogentisate is then cleaved to yield 4-maleylacetoacetate. This reaction is catalyzed by **homogentisate oxidase**.
- 4-Maleylacetoacetate is then isomerized to 4-fumarylacetoacetate, by an enzyme maleylacetoacetate isomerase.
- Finally, 4-fumarylacetoacetate is hydrolyzed by fumaryl acetoacetate hydrolase to fumarate, a glucogenic intermediate and **acetoacetate**, a ketogenic intermediate. Phenylalanine and tyrosine are therefore, both **glucogenic** and **ketogenic**.

Inborn Errors

Phenylketonuria (PKU)

Phenylketonuria (PKU) is an inborn error of phenylalanine metabolism, associated with the inability to convert **phenylalanine** to **tyrosine**.

Cause

It is caused by a genetic defect in **phenylalanine hydroxylase**, the first enzyme in the catabolic pathway for phenylalanine. Phenylketonuria can also be caused a defect in the enzyme, **dihydrobiopterin reductase** that catalyses the regeneration of tetrahydrobiopterin. PKU caused by deficiency of phenylalanine hydroxylase, is the most commonly seen error.

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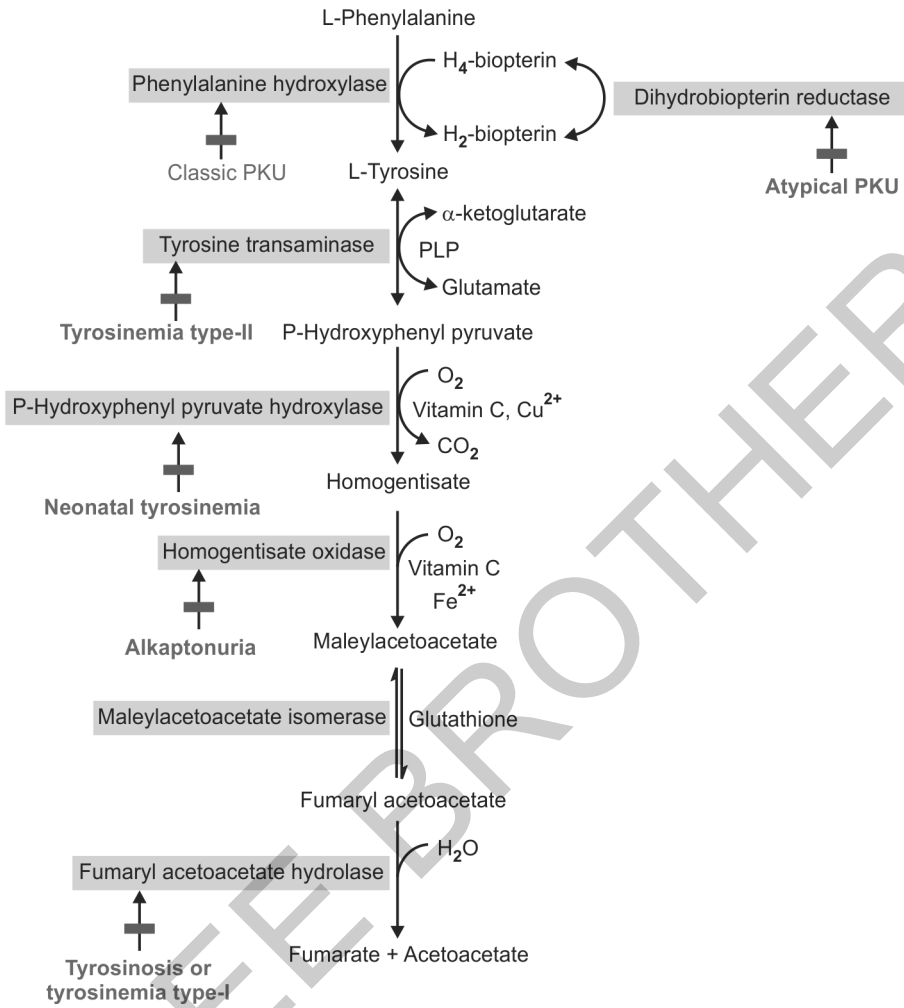


Figure 3.11: Metabolism of phenylalanine and tyrosine showing inborn errors.

Classification of PKU

PKU may be classified into three broad groups, given below. PKU caused by deficiency of phenylalanine hydroxylase, is the most commonly seen error.

- **Classic phenylketonuria** or **hyperphenylalaninemia type-I**, due to defect in phenylalanine hydroxylase
- **Atypical phenylketonuria** or **hyperphenylalaninemia type-II** and III is due to defect in dihydrobiopterin reductase
- **Hyperphenylalaninemia type-IV** and **V** is due to defect in dihydrobiopterin synthesis

Characteristics of PKU

- In PKU, there is an **accumulation of phenylalanine** in tissues and blood and results in its increased excretion in urine, because it cannot be converted into tyrosine. Since PKU patients cannot convert phenylalanine to tyrosine, by normal pathway, phenylalanine converted to **phenylpyruvate.** Phenylalanine and phenylpyruvate (the keto acid) accumulate in blood and tissues and are excreted in the urine, hence the name **"phenylketonuria"**.
- Much of the **phenylpyruvate,** rather being excreted as such, is either decarboxylated

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to **phenyl-acetate**, or reduced to phenyl-lactate. Phenyllactate imparts a characteristic **mousy odor** to the urine, which have traditionally used to detect PKU in infants.

- Accumulation of phenylalanine or its metabolites in early life impairs normal development of the brain causing **mental retardation.** Untreated PKU is life threatening, half die by age 20 years and three quarters by age 30 years.
- Hypopigmentation: Phenylketonurics have a lighter skin color, fair hair and blue eyes due to deficiency of pigment **melanin**.

Tyrosinemia

There are three types of tyrosinemia:

1. Tyrosinemia type-I (Tyrosinosis)
2. Tyrosinemia type-II (Richner-Hanhart syndrome)
3. Tyrosinemia type-III (Neonatal tyrosinemia)

Tyrosinemia type-I

Tyrosinemia type-I, is also called **tyrosinosis**. It is caused by a genetic deficiency of **fumarylacetoacetate hydroxylase**. This defect results in accumulation and excretion of tyrosine and its metabolites, such as P-hydroxyphenylpyruvate, P-hydroxyphenyllactate, P-hydroxyphenylacetate, and tyramine.

The deficiency of enzyme fumarylacetoacetate hydroxylase causes liver failure, kidney dysfunction.

Clinical features

Diarrhea, vomiting and cabbage like odor to skin and urine due to **succinyl acetone** an abnormal metabolite, derived from fumaryl acetoacetate. Death may occur in infancy due to acute liver failure or liver cirrhosis.

Tyrosinemia type-II (richner-hanhart syndrome)

Tyrosinemia type-II is caused by genetic deficiency of hepatic enzyme **tyrosine transaminase.**

Clinical features

- Due to deficiency of hepatic enzyme tyrosine transaminase, the tyrosine cannot be metabolized by its routine pathway and is converted to p-hydroxyphenylacetate, N-acetyltyrosin and tyramine. As a result, the tyrosine and its toxic metabolites accumulate in blood and tissues and excreted in urine.
- The accumulation of tyrosine produces lesions in eye and skin and causes mild mental retardation.

Tyrosinemia type-III (neonatal tyrosinemia)

It is caused by absence of the enzyme **P-hydroxyphenyl-pyruvate hydroxylase**. In neonatal tyrosinemia, serum tyrosine levels are high in premature infants resulting from an immature liver and its limited ability to synthesize the enzyme, P-hydroxyphenyl-pyruvate hydroxylase. As the liver matures, the accumulated tyrosine is metabolized and serum levels decrease to adult levels within 4 to 8 weeks of age. It is benign condition and responds well to ascorbic acid.

Alkaptonuria

This inherited metabolic disorder is due to defect in the enzyme **homogentisate oxidase**, which catalyzes oxidation of homogentisate to maleylacetoacetate **(Figure 3.11)**. As a result, the homogentisate accumulates in blood and body tissues and is excreted in large amounts in urine.

Clinical features

- The urine of alkaptonuric patients becomes dark after being exposed to air. In presence of oxygen, the colorless homogentisate present in urine undergoes spontaneous oxidation to form black brown pigment **alkapton**. The alkapton imparts a characteristic black-brown color to urine.
- Alkaptonuria is a harmless condition. Later in life patients may suffer from deposition of dark colored alkapton pigments in

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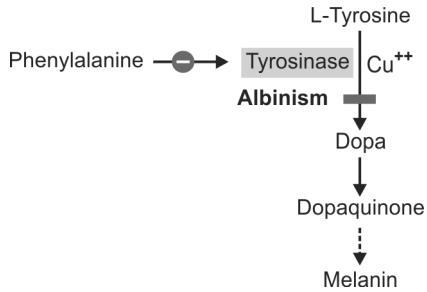


Figure 3.12: Biosynthesis of melanin.

connective tissues and bones. This results in black pigmentation of the sclera, ear, nose and cheeks and the clinical condition is known as ochronosis (because ochre color of the deposit). Ochronosis leads to tissue damage and may develop joint pain, arthritis and backache.

Albinism

It is an inborn error of tyrosine catabolism. It is due to inherited deficiency of enzyme **tyrosinase**. The inherited deficiency of **tyrosinase** impairs the synthesis of melanin from tyrosine **(Figure 3.12).** Melanin is dark pigment of skin, hair, iris, and retinal epithelial cells. Melanin protects the body from harmful radiation of sunlight.

Clinical features

- Impaired synthesis of melanin results in either **hypopigmentation** or no pigmentation of hair, skin and eyes and leads to white hair and skin.
- Albinos are highly **sensitive to sunlight** and can lead to **skin cancer**.
- The lack of melanin pigment in eyes is responsible for **photophobia** (intolerance to light) and **nystagmus.**

Metabolism and Inborn Errors of Tryptophan

Metabolism

Tryptophan is an **essential amino acid**. Tryptophan is oxidized to produce **alanine**, which is **glucogenic** and **acetyl-CoA**, which is **ketogenic**. Thus, tryptophan is both glucogenic and ketogenic. Tryptophan is metabolized as follows:

Tryptophan is oxidized to kynurenine and alanine. Kynurenine is then converted to either **vitamin niacin** or **acetyl-CoA (Figure 3.13)**. For every 60 mg of tryptophan, 1 mg equivalent of niacin can be generated.

Inborn Error

Hartnup disease

- Hartnup disease is an inherited disorder of tryptophan metabolism. This disorder was first of all reported in the family of **Hartnup,** therefore, named Hartnup's disease.
- It is due to defect in the intestinal and renal **transport of tryptophan** and other neutral amino acids and leads to tryptophan deficiency. Tryptophan deficiency

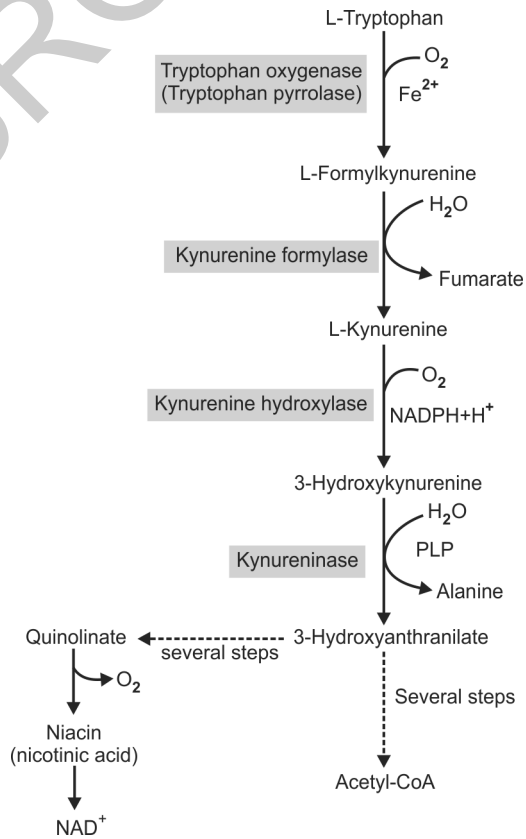


Figure 3.13: Metabolism of tryptophan and biosynthesis of vitamin niacin.

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ultimately leads to decreased synthesis of **vitamin niacin** and **serotonin**.

- Decreased synthesis of niacin leads to **pellagra** like symptoms and decreased serotonin synthesis is responsible for **neurological symptoms** observed in Hartnup's disease.

PLASMA PROTEINS: TYPES, FUNCTION AND NORMAL VALUES

Plasma proteins (also termed blood proteins), are proteins present in blood plasma. Plasma is the clear yellowish fluid portion of blood (55%–60%) in which cell are suspended. **Plasma** is obtained by centrifuging blood that has been treated with an anticoagulant to prevent clotting. Plasma contains a variety of proteins with different functions. Changes in the concentration of plasma proteins can give important clinical information. At present time, over 100 different plasma proteins have been described. We shall see those plasma proteins which are present in significantly high concentrations.

Types of Plasma Proteins

There are major three different types of plasma proteins, each serving different specific functions. The major forms of plasma proteins are:

- Albumin
- Globulins with subtypes
  - α-globulins
  - β-globulins
  - γ-globulins
- **Fibrinogens**

Subtypes of globulins classified on the basis of their position after separation of **serum protein by electrophoresis**. All the **albumin** and **fibrinogen** are synthesized by the **liver** only. Similarly, 50 to 80% of the globulin is formed in the liver. The remainder of the **globulins** is formed almost entirely in the **lymphoid tissues**.

What is plasma and serum?

- **Plasma** is obtained by centrifuging blood that has been treated with an anticoagulant to prevent clotting.
- The **serum** is different from plasma in its protein content. The serum contains only the **albumin** and **globulin**.
- The plasma contains the **albumin** and **globulin** and **fibrinogen**.
- The fibrinogen is absent in serum because, it is converted into fibrin during the coagulation of the blood.

Thus **serum = plasma – fibrinogen**.

Functions of Plasma Proteins

- **Maintenance of colloidal osmotic pressure (oncotic pressure):** The principal function of albumin is to maintain colloidal osmotic pressure in the plasma, which, in turn, prevents loss of plasma from the capillaries and controls the distribution of water in the body.
- **Maintenance of blood pressure:** The plasma proteins provide viscosity to the blood, which is important to maintain the blood pressure. Albumin provides more viscosity than other plasma proteins.
- **Maintenance of acid-base balance:** Proteins play a part in maintaining the blood pH. This is because of the buffering action of protein. Proteins are negatively charged at body pH and therefore, act as bases accepting H^+ ions.
- **Role in transport of metabolites:** Albumin transport many metabolites which are poorly soluble in water, such as:
  - Fatty acids
  - Bilirubin
  - Inorganic constituent of plasma like calcium
  - Certain steroid hormones and drugs
- **Role of protein in defence mechanism of body:** The **gamma globulin** plays an important role in the defence mechanism of the body. These molecules act as **antibodies** and are called **immunoglobulins.**

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- **Involvement in inflammatory responses:** Some proteins are involved in inflammatory (immediate defensive reaction) responses, e.g. **C-reactive protein (CRP)** is involved in body's response to foreign compounds.
- **Enzymatic function of proteins:** The globulins perform a number of enzymatic functions in the plasma, e.g. blood coagulation factors.
- **Role in blood coagulation:** Fibrinogen is essential for the coagulation of blood. During coagulation of blood, the fibrinogen polymerizes into long fibrin thread, thereby forming blood clots that help to repair leaks in the circulating system.

Biological functions of various proteins are summarized in **Table 3.6**.

Table 3.6: Major classes of plasma proteins, and their functions.

Classes	*Principal functions*
Albumin	• Regulation of: ▪ Osmotic pressure of the blood ▪ Distribution of water in the body ▪ Maintenance of blood pressure • Transport many metabolites which are poorly soluble in water, such as: ▪ Fatty acids ▪ Bilirubin ▪ Inorganic constituent of plasma like calcium ▪ Certain steroid hormones and drugs
Globulin	• Transport of: ▪ Copper ▪ Iron ▪ Lipids ▪ Fat-soluble vitamins A, D, E, and K ▪ Thyroxine hormone • Body's defense mechanism • Participation in the immune system (i. e., immunoglobulins)
Fibrinogen	Blood coagulation

The Normal Value of Plasma Proteins

The normal value of plasma proteins are:

- Total protein: 6 to 8 g%
- Albumin (A): 3.5 to 6 g%
- Globulin (G): 2 to 3.5 g%
- Fibrinogen: 200 to 400 mg%
- A/G ratio: 1.2:1 to 2.5:1

The Specialized Role of Different Types of Plasma Proteins

Albumin

Albumin is a major protein in plasma. Albumin is exclusively synthesized by the **liver**. Albumin normally accounts for approximately 54% of the total plasma protein content, or **3.5–6.0 g/dL** of blood.

Functions of albumins

- Albumin's primary function is the maintenance of **colloidal osmotic pressure.** The colloid osmotic pressure of the blood is important in maintaining a balance between the water inside the blood and that in the tissue fluid, around the cells. Thus, albumin plays a predominant role in maintaining blood volume and body fluid distribution.
- When the plasma proteins are deficient, the water in the plasma leaks out into the space around the blood vessels and may result in **edema (Figure 3.14)** symptom of **liver disorders**, **kidney disease** and **malnutrition**.
- Albumin also helps **transport many metabolites** which are poorly soluble in water, such as:
  - Fatty acids
  - Bilirubin
  - Inorganic constituent of plasma like calcium
  - Certain steroid hormones and drugs.
- **Buffering function:** Among the plasma proteins, albumin has maximum buffering

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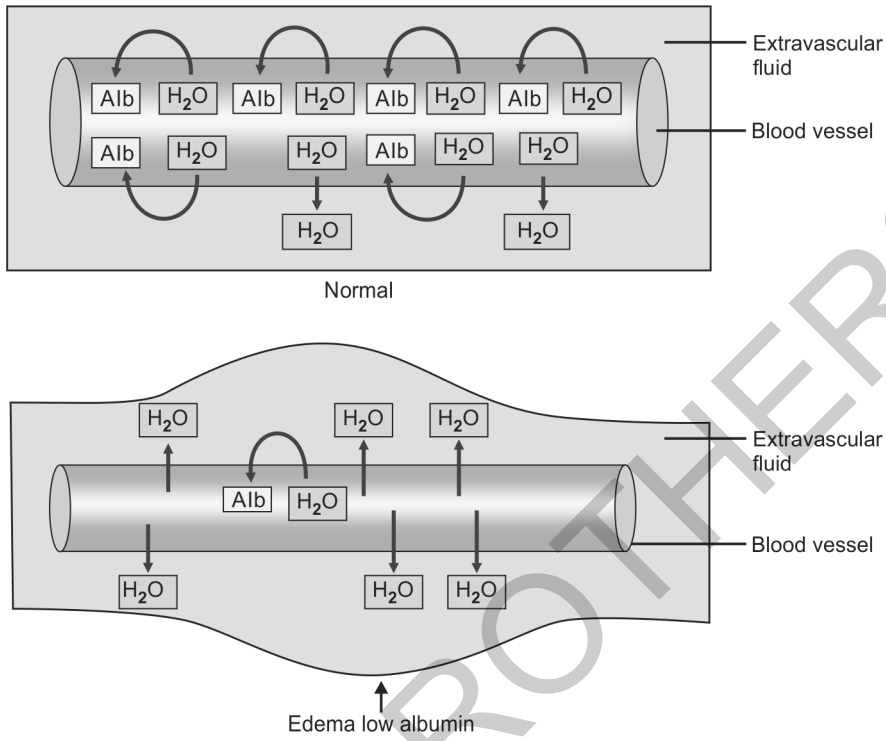


Figure 3.14: Development of edema in hypoalbuminemia where, Alb = albumin.

capacity due to its high concentration in blood.

- **Nutritive function:** Degradation of albumin provides essential amino acids during malnutrition.

Globulins

The second most common plasma proteins are the **globulins**. There are three main subgroups known as **alpha**, **beta,** and **gamma globulins**. Unlike alpha and beta globulins, which are produced in the liver, immunoglobulins (γ- globulins) are produced by specialized leukocytes known as **plasma cells**. Globulins make up approximately 38 percent of the total plasma protein volume, or **2.0–3.5 g/dL** of blood. Globulins are bigger in size than albumin. Globulins constitute several fractions. These are:

- α-globulin: For example, high-density lipoproteins (HDL)
- β-globulin: For example, low-density lipoproteins (LDL)
- γ-globulin: The most **gamma globulins** are immunoglobulins, called **antibodies**. All antibodies are immunoglobulins but all immunoglobulins may not be antibodies. They constitute about 20% of all the plasma proteins. The primary function of antibodies is to protect against infectious agents or their products. Structure, function and characteristics of different types of immunoglobulin are discussed in **Chapter: 8; Immunochemistry**.

Functions of globulins

- The alpha and beta globulins transport iron, copper, lipids, hormone thyroxine and the fat-soluble vitamins A, D, E, and K to the cells.
- Like albumin, they also contribute to osmotic pressure.
- The gamma globulins are proteins involved in immunity and are known as **antibodies**

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or **immunoglobulins**. They are produced by the B lymphocytes. The antibodies are responsible for the body's immune function.

Fibrinogen

The least abundant plasma protein is fibrinogen. Fibrinogen accounts for about 4% of the total plasma protein, or **200 to 400 mg/dL**. Like albumin and the alpha and beta globulins, fibrinogen is synthesized by the liver.

Functions of fibrinogen

It is essential for **blood clotting** process. During blood coagulation, fibrinogen is converted to fibrin which polymerizes to form **fibrin clot**. Plasma level of fibrinogen decreases in severe hepatic diseases.

PROTEINURIA: HYPOPROTEINEMIA, HYPERGLOBULINEMIA

Proteinuria

Normally, the total amount of protein excreted in urine over 24 hours is **less than 150 mg** and is not detectable by routine tests. The presence of protein in urine in excess of this is referred to as **proteinuria**. An excess protein in urine is suggestive of **illness.** The protein excreted is mostly **albumin** and some smaller proteins.

With severe proteinuria, general **hypoproteinemia** can develop which results in diminished **oncotic pressure**. Diminished oncotic pressure leads to **edema**.

Causes of Proteinuria

Proteinuria can be caused by:

- Increased permeability of glomerular membrane (Glomerular proteinuria)
- Reduced tubular reabsorption (Tubular proteinuria)
- Increased concentration of low molecular weight proteins in the plasma (Overload proteinuria).
- Abnormal secretion of protein from the renal tract (Postrenal proteinuria).

Types of Proteinuria

1. **Glomerular proteinuria:** This is the most common and serious type of proteinuria and because most of the excreted protein is albumin glomerular proteinuria is often referred to as **albuminuria.** Protein in urine is the first sign of **glomerular injury.** The glomeruli of kidney are not permeable to plasma proteins and therefore plasma proteins are absent in normal urine. When glomeruli are damaged in diseased conditions, they become more permeable and plasma proteins may appear in urine. Loss of large amounts of plasma albumin in urine results in edema (swelling) of the hands, feet, and face.
   - Glomerular proteinuria is seen in **nephrotic syndrome** and **diabetic nephropathy** due to increased permeability of glomerular membrane. The major protein found in glomerular proteinuria is **albumin**. Excretion of albumin in the range **30 to 300 mg/day** is termed **microalbuminuria.** Microalbuminuria is the earliest sign of renal damage due to **diabetes mellitus** and **hypertension.** Excretion of albumin more than 300 mg/day is indicative of significant damage to the glomerular membrane.
   - In **normal pregnancy,** urine protein excretion may increase slightly (about 300 mg/day). However more severe proteinuria occurs in pre-eclamptic toxemia (a condition in pregnancy characterized by abrupt rise in blood pressure).
   - Functional or **benign proteinuria** is a form of glomerular proteinuria that is probably due to changes of blood flow through the glomeruli. It is seen with; exercise, fever, heart failure, hypertension, etc.

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2. **Tubular proteinuria:** Tubular proteinuria is characterized by the appearance of low molecular weight proteins in the urine due to **reduced tubular reabsorption**. The low molecular weight proteins typically excreted in tubular proteinuria include; β-microglobulin, retinol binding protein, lysozyme, etc. Tubular proteinuria is more commonly associated with glomerular proteinuria. When tubular proteinuria occurs alone, albumin excretion is only slightly increased. Acute tubular proteinuria may occur with **burns** and chronic tubular proteinuria occurs in **cirrhosis**.
3. **Overload proteinuria:** Overload proteinuria is due to increased concentration of abnormal low molecular weight proteins in the plasma, such as immunoglobulin light-chain (Bence–Jones proteinuria). For example, high plasma concentration of immunoglobulin light-chain is seen in **multiple myeloma.**
4. **Postrenal proteinuria:** Postrenal proteinuria is due to abnormal secretion of protein into the urinary tract. Postrenal proteinuria refers to protein arising from the urinary tract below the kidneys and is usually due to inflammation or cancer. Lesions of the urethra, renal pelvis, bladder, and prostate can cause such proteinuria.

Hypoproteinemia

Hypoproteinemia is a condition where there is an abnormally low level of protein in the blood. Decreased levels of plasma albumin are seen in various disorders. Decreased serum protein reduces the **osmotic pressure** of the blood, leading to **loss of fluid** from the intravascular compartment, or the blood vessels, to the interstitial tissues, resulting in **edema (Figure 3. 14)**

Causes

- Nutritional hypoproteinemia is due to severe deficiency of protein in the diet. An example of nutritional hypoproteinemia is **Kwashiorkor**, a type of protein energy malnutrition affecting young children.
- Malabsorption of proteins
- Liver disease can also cause hypoproteinemia by **decreasing synthesis** of plasma proteins like albumin.
- Renal disease like nephrotic syndrome can also result in hypoproteinemia because plasma proteins are lost in the urine.
- Sepsis (whole body infection) resulting in hypoproteinemia.

Hyperglobulinemia

Hyperglobulinemia is an abnormal condition characterized by the increased levels of a certain **immunoglobulin** in the blood. Immunoglobulins are antibodies in blood and tissues that work to remove bacteria, viruses, fungi, and foreign substances from the blood.

Abnormally large amounts of certain immunoglobulins may be found in the plasma in several diseases of human. Hypergammaglobulinemia occur in **infection**, **autoimmune disorder**, or **malignancy**, such as **multiple myeloma**.

There are different types of antibodies in the blood, **IgG, IgA, IgM, IgD**, and **IgE**. The most common antibody is Immunoglobulin G (IgG). People with hyperglobulinemia most often have increased levels of IgG.

In multiple myeloma, a plasma cell cancer results due to abnormally high concentration of serum **immunoglobulins**, usually **IgG** or **IgA**. In multiple myeloma, light chains are produced in excess than heavy chains and enter the blood stream, because they are of relatively low molecular weight, they pass through glomerular membrane and appear in the urine. These protein chains of low

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molecular weight are known as **Bence–Jones Proteins**.

Bence–Jones proteins have the remarkable characteristic of precipitating on heating urine from 45° to 60°C and redissolve when the heating is continued above 80°C. Multiple myeloma with Bence–Jones protein in the urine is called **"light chain disease."**

PRINCIPLE OF ELECTROPHORESIS: NORMAL AND ABNORMAL ELECTROPHORETIC PATTERNS

Definition

Electrophoresis is defined as the **migration** of **charged ions** in an **electric field**. Electrophoresis is a general term that describes the **migration** and **separation** of charged particles (ions) under the influence of an electric field. Application of electric field to solution of ions makes ions to move. Electrophoresis is the most commonly employed analytical technique for the separation of **plasma/serum proteins.**

Principle of Electrophoresis

When charged molecules are placed in an electric field, they migrate toward either the positive or negative pole according to their charge **(Figure 3.15)**. Proteins, which can have either a net positive or net negative charge, can migrate toward the **cathode** or **anode**.

- An electrophoretic system consists of two electrodes of opposite charge (anode, cathode). The system consists of two compartments separated from each other by a partition; one side contains the **anode** and the other the **cathode.**
- Each compartment is filled with a buffer. Barbital buffer of pH 8.6 is often used for separation of serum protein.
- The two compartments are connected by the support medium, holding the sample (serum) to be separated **(Figure 3.16).**
- When a current is applied to the system, the current is carried across the support medium (porous membrane) by the buffer ions. At pH 8.6, all the serum proteins carry a net negative charge and tend to migrate toward the anode.
  - **Albumin** carries the largest charge and therefore, moves the **fastest**.
  - **γ-globulins** have the smallest net charge and move the least distance

Depending upon the mode of operation and separation, electrophoresis is classified into various types.

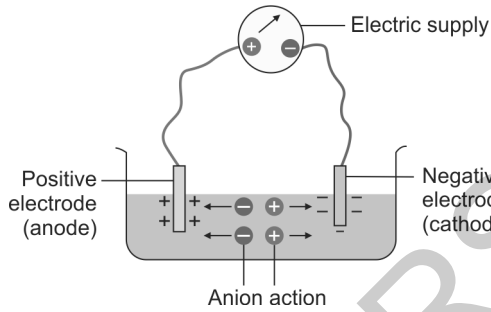


Figure 3.15: Application of electric field to solution of ions makes ions to move.

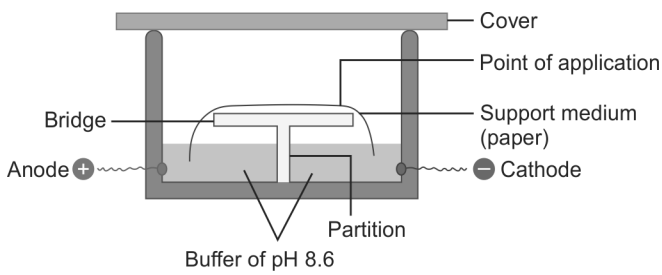


Figure 3.16: Electrophoresis apparatus.

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Clinical Uses of Electrophoresis

- The electrophoresis procedure is used in clinical laboratory for separation of serum proteins, lipoproteins, isoenzymes, hemoglobin and other classes of macromolecules.
- Immunoelectrophoresis is used to determine specific classes of immunoglobulins.
- Identification of antibodies to human immunodeficiency virus (HIV) is based on electrophoretic principle.
- Identification of specific sequences of DNA, used for prenatal diagnosis of inborn errors, diagnosis of viral infections and identification of risk factors for cancer is also based on electrophoretic principle.

Normal Electrophoretic Pattern

Normal serum proteins, separated by electrophoresis generally have **five bands.** These are:

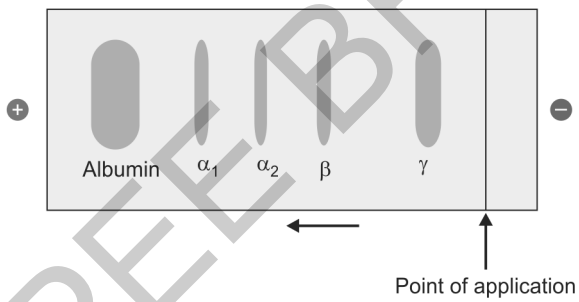
1. Albumin
2. α_1-globulin
3. α_2-globulin
4. β-globulin
5. γ-globulin

At pH 8.6, all the serum proteins carry a net negative charge and migrate towards the anode. Albumin carries the largest charge and therefore, moves the fastest. γ-Globulins have the smallest net charge and move the least distance.

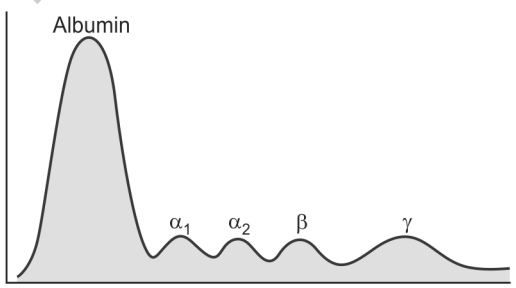
These five bands appear as five peaks on the densitometer graph **(Figures 3.17A and B).** A densitometry is a specialized colorimeter designed to scan and quantities electrophoresis patterns.

Abnormal Electrophoretic Pattern

The serum protein electrophoresis test measures specific proteins in the blood to identify some diseases. Serum protein electrophoretic



A Electrophoretogram of normal serum on cellulose acetate strip



B Densitometric scanning from cellulose acetate strip converts bands to characteristic peaks of albumin, α_1-globulin, α_2-globulin, β-globulin and γ-globulin

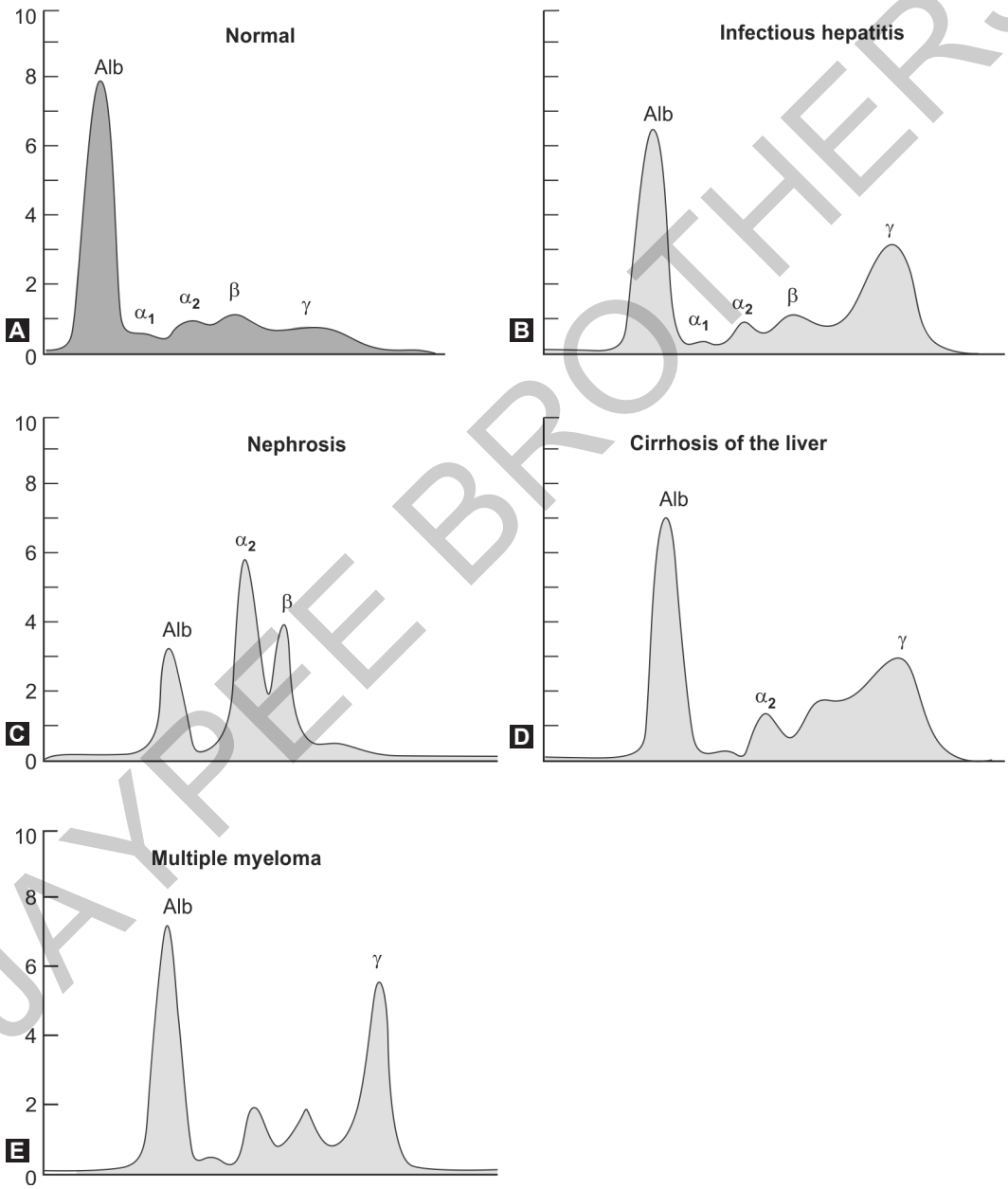
Figures 3.17A and B: Electrophoretic separation of serum proteins: (A) Electrophoretic pattern of normal serum; (B) Densitometric scanning converts five protein bands as five peaks of albumin, α1-globulin, α2-globulin, β-globulin, and γ-globulin.

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patterns provide useful diagnostic information. Certain proteins in the blood may be elevated in infection or some other diseases.

Different electrophoretic patterns of serum associated with various disorders, compared with normal serum are shown in **Figures 3.18A to E**. Changes in serum protein fractions associated with various conditions are given below:

- Infective hepatitis shows slight decrease in albumin and significant increased γ-globulins.
- Liver cirrhosis shows elevations in β and γ-globulins with a decrease in albumin.



Figures 3.18A to E: Different electrophoretic patterns of serum: (A) Normal; (B) Infections hepatitis; (C) Nephrosis; (D) Cirrhosis of the liver; (E) Multiple myeloma.

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- Nephrosis shows low level of albumin, significantly elevated α_2-globulin and elevated β-globulin.
- Multiple myeloma shows marked increase in γ-globulin.

ASSESSMENT QUESTIONS

Long Answer Questions (LAQs)

1. Define amino acids. Classify amino acids based on nutrition and metabolic fate with examples.
2. Describe the digestion and absorption of proteins.
3. Describe urea cycle with its significance.
4. Explain the role of transamination and deamination reactions in the formation of ammonia.
5. Describe the inborn disorders associated with metabolism of phenylalanine and tyrosine.
6. Define electrophoresis. Give its principle and normal and abnormal electrophoretic patterns.
7. Which are the different types of plasma proteins? Write their normal values and functions.
8. What is proteinuria? Write its causes and add a note on hypoproteinemia.

Short Notes

1. Essential amino acids.
2. Biologically important compounds synthesized from various amino acids.
3. Nutritional classification of amino acids.
4. Causes of proteinuria.
5. Hypoproteinemia.
6. Hyperglobulinemia.

Very Short Answers

1. Types of immunoglobulins.
2. Clinical significance of transamination.
3. Name enzymes, which are deficient in phenylketonuria.
4. Name enzyme which is deficient in alkaptonuria.
5. Name enzyme which is deficient in albinism.
6. Name different types of plasma proteins.
7. Give four functions of albumin.
8. What is proteinuria? Give any two causes of it.
9. Give four functions of globulin.
10. What is hyperglobulinemia? Give any two conditions of hyperglobulinemia.
11. What is a Bence–Jones protein?
12. Give two significances of urea cycle.
13. Give two biologically important compound derived from tyrosine.
14. Give two biologically important compound derived from tryptophan.
15. Name essential amino acids.
16. Name exclusive ketogenic amino acids.
17. Name glucogenic amino acids.
18. Write enzymes required for the digestion of proteins.
19. Give normal values of different plasma proteins.
20. Give number and name of fractions of normal serum proteins separated by electrophoresis.

MULTIPLE CHOICE QUESTIONS (MCQs)

1. Which of the following amino acid is exclusively ketogenic?
a. Leucine b. Phenylalanine
c. Threonine d. Isoleucine

2. In humans all of the following amino acids are essential, *except:*
a. Valine b. Isoleucine
c. Glycine d. Phenylalanine

3. Glycine is used for synthesis of the following, *except:*
a. Haem b. Thyroxine
c. Bile salt d. Creatin

4. An aromatic amino acid is:
a. Lysine b. Tyrosine
c. Glycine d. Arginine

5. Which one of the following is semi-essential amino acid for humans?
a. Valine b. Arginine
c. Lysine d. Tyrosine

6. Which of the following amino acid cannot undergo transamination?
a. Lysine b. Alanine
c. Aspartic acid d. Glutamic acid

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7. All of the following are synthesized from tyrosine, *except*:
a. Melanin b. Serotonin
c. Dopamine d. Epinephrine

8. The reactions of urea cycle occur in:
a. The cytosol
b. The mitochondria
c. The mitochondrial matrix and the cytosol
d. Lysosomes

9. All of the following statements are true in the transamination of amino acids, *except*:
a. Ammonia is neither consumed nor produced
b. Requires pyridoxal phosphate
c. The amino group acceptor is α-keto acid
d. All amino acids can undergo transamination

10. Which of the following pathways occurs in part in the mitochondria and in part in the cytoplasm?
a. Urea cycle b. TCA cycle
c. Glycolysis d. None of the above

11. The following enzymes are involved in digestion and absorption of protein, *except*:
a. Trypsinogen b. Amylase
c. Pepsin d. Chymotrypsin

12. The main site of urea synthesis in mammals is:
a. Liver b. Skin
c. Intestine d. Kidney

13. The enzymes of urea synthesis are found in:
a. Mitochondria only
b. Cytosol only
c. Both mitochondria and cytosol
d. Nucleus

14. Tryptophan is a precursor of:
a. Melatonin b. Thyroid hormones
c. Melanin d. Epinephrine

15. Serotonin is synthesized from:
a. Serine b. Alanine
c. Tyrosine d. Tryptophan

16. Out of 200 different amino acids form in nature the number of amino acids present in protein?
a. 20 b. 25
c. 40 d. 35

17. The major end product of protein metabolism in man is:
a. Glycine b. Uric acid
c. Urea d. NH_3

18. In humans, NH3 is detoxified in liver as:
a. Creatinine b. Uric acid
c. Urea d. Uronic acid

19. In multiple myeloma which of the following plasma protein level is increased?
a. Albumin b. Hemopexin
c. α1-fetoprotein d. γ-globulin

20. Normal serum proteins, separated by electrophoresis generally have:
a. Five bands b. Four bands
c. six bands d. Three bands

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Answers

1. a	2. c	3. b	4. b	5. b	6. a	7. b	8. c	9. d	10. a
11. b	12. a	13. c	14. a	15. d	16. a	17. c	18. c	19. d	20. a

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