IV- Metabolism of phenylalanine and tyrosine:

1- Formation of tyrosine from phenylalanine:
Tyrosine is formed from phenylalanine by the reaction catalyzed by phenylalanine hydroxylase (monooxygenase). This reaction is irreversible thus phenylalanine is nutritionally essential while tyrosine is not, provided that diet contains adequate quantities of phenylalanine:

1- Conversion of tyrosine to fumarate (glycogenic) and acetoacetate (ketogenic):
4- **Formation of melanin pigment:**

Melanin is a dark brown pigment formed in melanocytes in skin, hair, retina under the effect of the pituitary melanocyte-stimulating hormone (MSH) resulting in darkening of skin:

5- **Biosynthesis of norepinephrine and epinephrine:**

Cells of neural origin convert tyrosine to epinephrine and norepinephrine. While dopa is an intermediate in the formation of both melanin and norepinephrine, different enzymes hydroxylate tyrosine in melanocytes and other cell types:
6- **Formation of thyroid hormones:**

The thyroid gland is a small gland situated in the neck, wrapped around the trachea just below the larynx. It secretes hormones that increase the metabolic rate and oxygen consumption and are necessary for proper growth and development. The thyroid, also, secretes calcitonin, a hormone that participates in the regulation of plasma Ca\(^{2+}\) concentration by inhibiting bone resorption. Thyroid disease is common in women, with prevalence in the community of 3-5%.

*Thyroxine (T\(_4\)) and tri-iodothyronine (T\(_3\)) are together known as the 'thyroid hormones'. They are synthesized in the thyroid gland by iodination and coupling of two tyrosine molecules whilst attached to a complex protein called thyroglobulin. T\(_4\) has four iodine atoms while T\(_3\) has three:*
**Biosynthesis of thyroid hormones**

1- **Concentration of iodide in thyroid gland (iodide trapping):** the thyroid is able to concentrate I\(^-\) against a strong electrochemical gradient. This is an energy-dependent process and is linked to the ATPase-dependent Na\(^+\)-K\(^+\) pump.

2- **Oxidation of I\(^-\) to active iodine [I]:**

\[
\text{I}^- + \text{H}_2\text{O}_2 + 2\text{H}^+ \xrightarrow{\text{Iodine peroxidase}} 2\text{active I} + \text{H}_2\text{O}
\]

3- **Organification (Iodination of tyrosine):**

Oxidized iodine reacts with the tyrosyl residue in the **thyroglobulin (Tgb)** (a glycoprotein) as follows:

\[\text{Active I} + \text{Tyrosine (Tgb)} \rightarrow \text{MIT} \rightarrow \text{DIT}\]

*MIT and DIT are conjugated to the Tgb*

2- **Coupling reaction:**

\[
\text{MIT} + \text{DIT} \rightarrow \text{1,5,3'-Triiodothyronine (T3)} + \text{alanine}
\]

\[
2\text{DIT} \rightarrow \text{3,5,3',5'-Tetraiodothyronine (thyroxine T4)} + \text{alanine}
\]

The coupling reaction occurs within the thyroglobulin molecule. The formed thyroid hormones remain as integral parts of Tgb until the latter is degraded. Tgb hydrolysis is stimulated by TSH but inhibited by I\(^-\); this latter effect is occasionally exploited by using KI to treat hyperthyroidism.
The thyroid gland secretes mostly T\(_4\) whose concentration in plasma is around 100nmol/l. The peripheral tissues, especially the liver and kidney, deiodinate T\(_4\) to produce approximately two-thirds of the circulating T\(_3\) present at a lower concentration of around 2 nmol/l. Most cells are capable of taking up T\(_4\) and deiodinating it to the more biologically active T\(_3\). It is T\(_3\) which binds to receptors and triggers the end-organ effects of the thyroid hormones. Alternatively, T\(_4\) can be metabolized to reverse T\(_3\) (rT\(_3\)) which is biologically inactive. By modulating the relative production of T\(_3\) and rT\(_3\), tissues can 'fine tune' their local thyroid status. *Exactly how this is accomplished is not yet fully understood.*

**THYROID HORMONE ACTION**

Thyroid hormones are essential for the normal maturation and metabolism of all the tissues in the body. Thyroid hormone effects on metabolism are diverse. The rates of protein and carbohydrate synthesis and catabolism are influenced.

1. They induce hyperglycemia by increasing glucose absorption and stimulating glycogenolysis.
2. Stimulating lipolysis via stimulating adenylate cyclase.
3. At physiological concentrations, they enhance protein synthesis, but in hyperthyroidism, they increase protein catabolism.

**Binding in plasma**

In plasma, over 99.95% of T\(_4\) is transported bound to proteins. Thyroxine binding globulin (TBG) carries 70% of T\(_4\), albumin approximately 25% and transthyretin (formerly called pre-albumin) around 5%. Over 99.5% of T\(_3\) is transported by the same proteins. *It is the unbound, or 'free', T\(_4\) and T\(_3\) concentrations which are important for the biological effects of the hormones,* including the feedback to the pituitary and hypothalamus. Changes in binding protein concentration complicate the interpretation of thyroid hormone results, e.g. in pregnancy.
V- Metabolism of tryptophan:
Tryptophan is an essential amino acid. It is both **glucogenic** and **ketogenic** amino acid. Tryptophan has 2 main pathways:

1- Nicotinic acid pathway:
2- **Serotonin and melatonin pathway:**

![Chemical Diagram]

1- **Serotonin** is synthesized and stored at several sites in the body. By far the largest amount of serotonin is found in cells of the intestinal mucosa. Smaller amounts of serotonin occur in platelets and in CNS. Serotonin has multiple physiological roles, including pain perception, normal and abnormal behaviors, including affective disorders, and regulation of sleep, temperature, and blood pressure.

2- **Melatonin** is formed in the pineal body in the brain from serotonin by N-acetylation followed by O-methylation. Melatonin was shown to have many physiological roles e.g.
   a- It is a potent natural antioxidant.
   b- It induces sleep.
   c- It may be considered as **life clock**, since its level was shown to decrease with aging.
VI- Metabolism of branched-chain amino acids:
The branched chain amino acids, isoleucine, leucine and valine, are essential amino acids. In contrast to other amino acids, they are metabolized primarily by the peripheral tissues (particularly muscle) rather than liver. Because these three amino acids have similar route of catabolism, it is convenient to describe them as a group.

It is clears from above that:
1- **Valine** is a glycogenic amino acid.
2- **Leucine** is a ketogenic amino acid.
3- **Isoleucine** is both glycogenic and ketogenic amino acid.

**Metabolism of creatine and creatinine:**

*Creatine phosphate*, the phosphorylated derivative of creatine found in muscle, is a high-energy compound that can reversibly donate a phosphate group to ADP to form ATP. The reaction, catalyzed by *creatine kinase*, provides a small but rapidly mobilized reserve of high-energy phosphates that can be used to maintain the intracellular level of ATP during the first few minutes of intense muscular contraction.

[Note: Presence of creatine kinase in the plasma is indicative of tissue damage and is used in the diagnosis of myocardial infarction.]

**A. Synthesis of creatine**

Creatine is synthesized from glycine and the guanidino group of arginine, plus a methyl group from S-adenosylmethionine. Creatine is reversibly phosphorylated to *creatine phosphate* (phosphocreatine) by creatine kinase using ATP as phosphate donor. Phosphocreatine functions as a store of high-energy phosphate in muscle. [Note: The amount of phosphocreatine is proportional to the muscle mass.

**B. Degradation of creatine**

Creatine and phosphocreatine spontaneously cyclize at a slow but constant rate to form creatinine, which is excreted in the urine. The amount of creatinine excreted from the body is proportional to the total creatine phosphate content of the body, and thus can be used to estimate muscle mass. When muscle mass decreases for any reason (for example, from paralysis or muscular dystrophy), the creatinine content of the urine falls. In addition, any rise in blood creatinine is a sensitive indicator of kidney malfunction, because creatinine is normally rapidly removed from the blood and excreted. A typical adult male excretes about 15 mmol of creatinine per day. The constancy of this excretion is sometimes used to test the reliability of collected 24-hour urine samples, as too little creatinine in the total urine may indicate an incomplete sample.
**Metabolism of Histidine** (essential and Glucogenic amino acid):

1- Histidine ---------- decarboxylation --------→ Histamine.
2- Biotransformation to glutamate and one carbon atom (formoimino-):

```
\[
\begin{align*}
\text{Histidine} & \xrightarrow{\text{Histidinase}} \text{Histamine} \\
\text{N} & \xrightarrow{\text{Urocanase}} \text{N-Formo imino glutamate (FIGlu)} \\
\alpha\text{-Keto-glutarate} & \xrightarrow{\text{H}_4\text{Folate}} \text{Glucose} \\
\text{Proline} & \xrightarrow{\text{Proline Dehydrogenase}} \text{Arginine} \\
\text{Glutamate-semialdehyde} & \xrightarrow{\text{Dehydrogenase}} \alpha\text{-ketoglutarate}
\end{align*}
\]
```

**Catabolism of Proline (imino acid) and Arginine to glutamate and \(\alpha\)-ketoglutarate:**
Metabolism of Glutamate (Non-essential and Glucogenic amino acid):

Metabolism of Aspartate (Non-essential and Glucogenic amino acid):