Thyroid Gland

The thyroid is made of multiple acini (follicles). Each spherical follicle is surrounded by a single layer of cells and filled with pink-staining proteinaceous material called colloid. When the gland is inactive, the colloid is abundant, the follicles are large, and the cells lining them are flat. When the gland is active, the follicles are small; the cells are cuboidal or columnar.

The chemistry of thyroid hormone:
The principle hormones secreted by the thyroid gland are:

- 3, 5, 3’, 5’- tetra-iodo-thyronine (T4) or thyroxin.
- 3, 5, 3’- tri-iodo-thyronine (T3).
- 3, 3’, 5’- tri-iodo-thyronine (T3) or RT3 (reverse tri-iodo-thyronine).
- 3, 5- Di-iodo-thyronine
- 3- Mono-iodo-thyronine
Formation of Thyroxin:
Thyroid stimulating Hormone
Thyroid stimulating Hormone (TSH) is made up of two subunits, designated α and β. TSH-α is identical to the α subunit of LH, FSH, and hCG-α.
Thyroid stimulating Hormone (TSH) action on thyroid gland
Thyroid stimulating Hormone (TSH), also known as thyrotropin, Thyroid stimulating Hormone (TSH) is an anterior pituitary hormone;
Thyroid stimulating Hormone (TSH) is a glycoprotein with a molecular weight of about 28,000.
Thyroid stimulating Hormone (TSH) increases secretion of thyroxine and triiodothyronine by the thyroid gland.
Thyroid stimulating Hormone (TSH) has the following specific effects on the thyroid gland:
1. Increased proteolysis of the thyroglobulin that has already been stored in the follicles, releasing the thyroid hormones into the circulating blood and diminishing the follicular substance
2. Increased activity of the iodide pump, which increases the rate of “iodide trapping” in the glandular cells, sometimes increasing the ratio of intracellular to extracellular iodide concentration in the glandular substance to as much as eight times normal
3. Increased iodination of tyrosine to form the thyroid hormones
4. Increased size and increased secretory activity of the thyroid cells
5. Increased number of thyroid cells plus a change from cuboidal to columnar cells and much in folding of the thyroid epithelium into the follicles

Fate of Ingested Iodides.
To form normal quantities of thyroxine, about 50 milligrams of ingested iodine in the form of iodides are required each year, or about 1 mg/week. To prevent iodine deficiency, common table salt is iodized with about 1 part sodium iodide to every 100,000 parts sodium chloride.
Iodides ingested orally are absorbed from the gastrointestinal tract into the blood in about the same manner as chlorides. Normally, most of the iodides are rapidly excreted by the kidneys, but only after about one fifth are selectively removed from the circulating blood by the cells of the thyroid gland and used for synthesis of the thyroid hormones.

Formation of thyroid hormone:
The first event in this is binding of TSH with specific TSH receptors on the basal membrane surfaces of the thyroid cell.
This will stimulate G-protein:
A. $\text{Gs} \rightarrow \text{AC} \rightarrow \text{cAMP} \rightarrow \text{activate protein kinase} \rightarrow \text{iodine pump (takes 30 minutes to show effect)}$
B. $\text{Gq} \rightarrow \text{Phospholipase C} \rightarrow \text{DAC} \rightarrow \text{Phospho-Kinase C} \rightarrow \text{synthesis of thyroglobin (require hours or even days and weeks to develop fully)}$

Iodide pump (the sodium-iodide symport) and iodide trapping

Note:
An iodide ion is the ion $\text{I}^-$, occurring when iodine bonds with another element, such as potassium
Iodine symbol $\text{I}_2$; consists of two atoms of iodine stuck together, is not found in nature
The first stage in the formation of thyroid hormones is transport of iodides from the blood into the thyroid glandular cells and follicles.
The basal membrane of the thyroid cell has the specific ability to pump the iodide actively to the interior of the cell. This pumping is called iodide (I) pump and achieved by the action of a sodium-iodide symporter, which co-transport (1 iodide ion + 2 sodium ions across the baso-lateral (plasma) membrane into the cell. Iodide (I) pump is inhibited by thiocyanate (Thiocyanate which is also known as rhodanide is the anion [SCN]− and perchlorate (Perchlorates are the salts derived from perchloric acid (HClO4) anions.

Thyroid cellular mechanisms for iodine transport, thyroxine and triiodothyronine formation, and thyroxine and triiodothyronine release into the blood. DIT, diiodotyrosine; ER, endoplasmic reticulum; L−, iodide ion; I2, iodine; MIT, monoiiodotyrosine; NIS, sodium-iodide symporter; RT3, reverse triiodothyronine; T3, triiodothyronine; T4, thyroxine; TG, thyroglobulin.
The energy for transporting iodide against a concentration gradient comes from the sodium-potassium adenosine triphosphatase (ATPase) pump, which pumps sodium out of the cell, thereby establishing a low intracellular sodium concentration and a gradient for facilitated diffusion of sodium into the cell. This process of concentrating the iodide in the cell is called iodide trapping. In a normal gland, the iodide pump concentrates the iodide to about 30 times its concentration in the blood. When the thyroid gland becomes maximally active, this concentration ratio can rise to as high as 250 times. The rate of iodide trapping by the thyroid is influenced by several factors, the most important being the concentration of TSH; TSH stimulates and hypophysectomy greatly diminishes the activity of the iodide pump in thyroid cells.

Iodide is transported out of the thyroid cells across the apical membrane into the follicle by a chloride-iodide ion counter-transporter molecule called pendrin.

**Formation and Secretion of Thyroglobulin by the Thyroid Cells.**

The thyroid cells are typical protein-secreting glandular cells. The endoplasmic reticulum and Golgi apparatus synthesize and secrete into the follicles a large glycoprotein molecule called thyroglobulin, with a molecular weight of about 335,000. Each molecule of thyroglobulin contains about 70 tyrosine amino acids, and they are the major substrates that combine with iodine to form the thyroid hormones.

**Oxidation of the Iodide Ion.**

The first essential step in the formation of thyroid hormones is conversion of iodide ions to an oxidized form of iodine, either nascent iodine (I⁰: Nascent Iodine is a complete atom, no extra electrons, none missing) or tri-iodide; I₃⁻, which is then capable of combining directly with the amino acid tyrosine. This oxidation of iodine is promoted by the enzyme peroxidase and its accompanying hydrogen peroxide, which provide a potent system capable of oxidizing iodides.

\[
2I^- \rightleftharpoons I₂ + 2e^- \\
I₂ (aq) + I^- \rightleftharpoons I₃^-
\]

The peroxidase is either located in the apical membrane of thyroid follicular epithelial cells or attached to it, thus providing the oxidized iodine at exactly the point in the cell where the thyroglobulin molecule issues forth from the Golgi apparatus and through the cell membrane into the stored thyroid gland colloid.

The peroxidase enzyme is inhibited by propyl-thiouracil. Propyl-thiouracil is used therapeutically to reduce thyroid hormone synthesis for the treatment of hyperthyroidism.
In normal individuals, large doses of iodide act directly on the thyroid to produce a mild and transient inhibition of organic binding of iodide and hence of hormone synthesis. This inhibition is known as the Wolff–Chaikoff effect.

**Iodination of tyrosine and formation of the thyroid hormones (“Organification” of Thyroglobulin):**

The binding of iodine with the thyroglobulin molecule is called organification of the thyroglobulin. Oxidized iodine even in the molecular form will bind directly but slowly with the amino acid tyrosine. In thyroid cells, however, the oxidized iodine is associated with thyroid peroxidase enzyme that causes the process to occur within seconds or minutes. Therefore, almost as rapidly as thyroglobulin is released from the Golgi apparatus or as it is secreted through the apical cell membrane into the follicle, iodine binds with about one sixth of the tyrosine amino acids within the thyroglobulin molecule. Tyrosine is first iodized to monoiodotyrosine and then to diiodotyrosine. Then, during the next few minutes, hours, and even days, more and more of the iodotyrosine residues become coupled with one another.

The major hormonal product of the coupling reaction is the molecule thyroxine (T4), which is formed when two molecules of diiodotyrosine are joined together; the thyroxine then remains part of the thyroglobulin molecule. Or one molecule of monoiodotyrosine couples with one molecule of diiodotyrosine to form triiodothyronine (T3), which represents about one fifteenth of the final hormones. Small amounts of reverse T3 (RT3) are formed by coupling of diiodotyrosine with monoiodotyrosine, but RT3 does not appear to be of functional significance in humans.

**Storage of Thyroglobulin.**

The thyroid gland is unusual among the endocrine glands in its ability to store large amounts of hormone. After synthesis of the thyroid hormones has run its course, each thyroglobulin molecule contains up to 30 thyroxine molecules and a few triiodothyronine molecules. In this form, the thyroid hormones are stored in the follicles in an amount sufficient to supply the body with its normal requirements of thyroid hormones for 2 to 3 months. Therefore, when synthesis of thyroid hormone ceases, the physiological effects of deficiency are not observed for several months.

**Release of thyroxine and tri-iodo-thyronine from the thyroid gland:**
Most of the thyroglobulin is not released into the circulating blood; instead, thyroxine and triiodothyronine are cleaved from the thyroglobulin molecule, and then these free hormones are released.

This process occurs as follows:
A. The apical surface of thyroid cells sends out pseudopod extensions that close around small portions of the colloid to form pinocytic vesicles that enter the apex of the thyroid cell.
B. Then lysosomes in the cell cytoplasm immediately fuse with these vesicles to form digestive vesicles containing digestive enzymes from the lysosomes mixed with the colloid.
C. Multiple proteases among the enzymes digest the thyroglobulin molecules and release thyroxine and triiodothyronine in free form, which then diffuse through the base of the thyroid cell into the surrounding capillaries. Thus, the thyroid hormones are released into the blood.

About three quarters of the iodinated tyrosine in the thyroglobulin never become thyroid hormones but remain monoiodotyrosine and diiodotyrosine. During the digestion of the thyroglobulin molecule to cause release of thyroxine and triiodothyronine (T3 & RT3), these iodinated tyrosines (MIT &DIT) also are freed from the thyroglobulin molecules. However, MIT &DIT are not secreted into the blood. Instead, their iodine is cleaved from them by a deiodinase enzyme that makes virtually all this iodine available again for recycling within the gland for forming additional thyroid hormones. In the congenital absence of this deiodinase enzyme, many persons become iodine deficient because of failure of this recycling process.

In the normal human thyroid, the average distribution of iodination compounds is 23% MIT, 33% DIT, 35% T4 and 7% T3.

**Transport of thyroid hormones:**
Capacity and affinity of plasma proteins for thyroid hormones:
The affinity of the proteins for T4 (i.e., the avidity with which they bind T4 under physiological condition)

<table>
<thead>
<tr>
<th>Protein</th>
<th>Half-life</th>
<th>Affinity</th>
<th>T4 Capacity (mcg/dl)</th>
<th>T4 Distribution</th>
<th>T3 Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>13 days</td>
<td>Lost</td>
<td>22</td>
<td>13%</td>
<td>46%</td>
</tr>
<tr>
<td>trans-thyretin</td>
<td>2 days</td>
<td>modest</td>
<td>120</td>
<td>20%</td>
<td>1%</td>
</tr>
</tbody>
</table>
A pre-albumin formerly called (thyroxin-binding pre-albumin: TBPA) and now called (transthyretin) Rapid thyroid hormone dissociation rate from albumin make albumin a major source of free hormone to tissue
Albumin has the largest capacity to bind T₄ (i.e. it can bind most T₄ before becoming saturated)
Albumin binds T₄ and T₃ with lesser affinity than thyroxin-binding globulin or transthyretin, but it has a high plasma concentration
T₃ binds almost exclusively to TBG and albumin; TBPA binds only negligible amounts of T₃
Normally, 99.98% of the T₄ in plasma is bound (i.e. only 0.02% is found free).
Only 0.2% of plasma T₃ is free. The remaining 99.8% is protein-bound
T₄ bound strongly to plasma protein
T₃ is not bound strongly to plasma protein.
The lesser binding of T₃ correlates with the facts that T₃ has a shorter half-life than T₄ and that its action on the tissues is much more rapid. RT₃ also bind TBG.

Fluctuation in binding:
When there is a sudden, sustain increase in the concentration of thyroid-binding protein in the plasma, the concentration of free thyroid hormones falls. This change is temporary, however, because the decrease in the concentration of free thyroid hormones in the circulation stimulates TSH secretion, which in turn causes an increase in the production of free thyroid hormones. A new equilibrium is eventually reached at which the total quantity of the thyroid hormones in the blood is elevated but the concentration of free hormones, the rate of their metabolism, and the rate of TSH secretion are normal. Corresponding changes in the opposite direction occur when the concentration of thyroid-binding protein is reduced. Consequently, patients with elevated or decreased concentrations of binding proteins, particularly TBG, are neither hyper- nor hypothyroid; i.e. they are eu-thyroid.
TBG levels are elevated in estrogen- treated patients and during pregnancy, as well as after treatment with various drugs. They are depressed by gluco-corticoids, androgen. Changes in total plasma T₄ and T₃ can also be produced by changes in plasma concentration of albumin and pre-albumin.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Concentrations of Binding Proteins</th>
<th>Total Plasma T₄, T₃, RT₃</th>
<th>Free Plasma T₄, T₃, RT₃</th>
<th>Plasma TSH</th>
<th>Clinical State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthyroidism</td>
<td>Normal</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Hyperthyroid</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Normal</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Hypothyroid</td>
</tr>
<tr>
<td>Estrogens &amp; pregnancy</td>
<td>High</td>
<td>High</td>
<td>Normal</td>
<td>Normal</td>
<td>Euthyroid</td>
</tr>
<tr>
<td>Glucocorticoids &amp; androgens</td>
<td>Low</td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
<td>Euthyroid</td>
</tr>
</tbody>
</table>

Metabolism of thyroid hormones:
T₄ and T₃ are de-iodinated in the liver, the kidney, and many other tissues.
One-third of the circulating T₄ is normally converted to T₃ in adult humans, and 45% is converted to RT₃.
Only 13% of the circulating T₃ is secreted by the by the thyroid and 87% is formed by de-iodination of T₄; similarly, only 5% of the circulating RT₃ is secreted by the thyroid and 95% is formed by de-iodination of T₄.
It should be noted as well as there are marked differences in the ratio of T₃ to T₄ in various tissue.
Two tissues that have very high ratios are the pituitary and the cerebral cortex. The deiodinase enzyme is an enzyme that scavenges iodide by removing it from iodinated tyrosine residues in the thyroid gland (it is called Iodo-tyrosine de-iodinase, also known as Iodo-tyrosine dehalogenase 1). Iodothyronine deiodinases is subfamily of deiodinase enzyme and is of three different de-iodinase kinds: D1, D2, and D3. All are unique in that they contain the rare amino acid \textit{sleno-cysteine}, with selenium in place of sulfur, and selenium is essential for their enzymatic activity. D1 appears to be primarily responsible for monitoring the formation of T3 from T4 in the periphery. D1 and D2 bio-activate T4 by removal iodine at position 5’ and contributes to formation of T3. D3 bio-inactivate T4 by removal iodine at position 5 and contributes to formation of RT3 in the blood and tissue. Overall, the de-iodinase appears to be responsible for maintaining the differences in T3/T4 ratios in various tissues in the body. Half the thyroxine in the blood is released to the tissue cells about every 6 days, whereas half the triiodothyronine—because of its lower affinity—is released to the cells in about 1 day. Upon entering the tissue cells, both thyroxine and triiodothyronine again bind with intracellular proteins, with the thyroxine binding more strongly than the triiodothyronine. Therefore, they are again stored, but this time in the target cells themselves, and they are used slowly over a period of days or weeks.

\textbf{Fluctuations in de-iodination:}

1. \textit{Age:}
   Much more RT3 and much less T3 are formed during fetal life. At birth TSH surges during the first 30 minutes. Hyperthyroid state. T4, T3, RT3 drop and return to that of adult over 4 to 6 weeks after birth.

2. \textit{De-iodinase Enzyme changes:}
   1. Various drugs inhibit de-iodinase (like amiodarone), producing a fall in the plasma T3 and a rise in the plasma RT3 level.
   2. Selenium deficiency has the same effect.
   3. A wide variety of non-thyroidal illness also depresses de-iodinase. These include burns, trauma, advanced cancer, cirrhosis, renal failure, myocardial infarction, and febrile states. The low-T3 state produced by these conditions disappears with recovery. It is difficult to decide whether individual with the low-T3 state produced by illness have mild hypothyroidism.
3. Diet: It has a clear-cut effect on conversion of T₄ to T₃. In fasted individuals, plasma T₃ is reduced 10 to 20% in 24 hours and about 50% in 3 to 7 days, with a corresponding rise in RT₃. Free and bound T₄ levels remain normal. During more prolonged starvation, RT₃ returns to normal but T₃ remains depressed. At the same time, the BMR (Basal Metabolic Rate) falls and urinary nitrogen excretion, an index of protein breakdown, is decreased. Thus, the decline in T₃ conserves calories and protein. Conversely, overfeeding increase T₃ and reduces RT₃.

### Thyroid Hormones Have Slow Onset and Long Duration of Action.

<table>
<thead>
<tr>
<th></th>
<th>latent period</th>
<th>Maximum activity</th>
<th>half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>triiodothyronine</td>
<td>6 to 12 hour</td>
<td>2 to 3 days</td>
<td>1 day</td>
</tr>
<tr>
<td>thyroxine</td>
<td>2 to 3 days</td>
<td>10 to 12 days</td>
<td>5 to 7 days</td>
</tr>
</tbody>
</table>

The actions of triiodothyronine occur about four times as rapidly as those of thyroxine. Some of the thyroxine activity persists for as long as 6 weeks to 2 months. Most of the latency and the prolonged period of action of these hormones are probably caused by their binding with proteins both in the plasma and in the tissue cells, followed by their slow release.

### Thyroid Hormones Activate Nuclear Receptors

1) T₃ and T₄ are lipid soluble proteins and can cross the cell membrane of the target cells easily.
2) Before acting on the genes to increase genetic transcription, one iodide is removed from almost all the thyroxine, thus forming triiodothyronine by (D₂ deiodinase).
3) Intracellular thyroid hormone receptors have tenfold affinity for T₃ than they have to T₄, for that T₃ is much more potent than T₄.
Consequently, more than 90 percent of the thyroid hormone molecules that bind with the receptors is triiodothyronine.
3) Thyroid hormones have intra-cellular effects
   A. genomic cellular effects (Slow effect: hours to days)
The thyroid hormone receptor (TR) usually forms a heterodimer with retinoid X receptor (RXR) at specific thyroid hormone response elements (TRE) on the DNA. Retinoid X receptor become activated and initiate the transcription process. Large numbers of different types of messenger RNA are then formed, followed within another few minutes or hours by RNA translation on the cytoplasmic ribosomes to form hundreds of new intracellular proteins.

B. Non-genomic cellular effects (Fast effect: minutes)
Non-genomic thyroid hormone action have been described in several tissues, including the heart and pituitary, as well as adipose tissue. Non-genomic thyroid hormone action appears to be the plasma membrane, cytoplasm, and perhaps some cell organelles such as mitochondria. Non-genomic thyroid hormone action include the regulation of ion channels and oxidative phosphorylation and appear to involve the activation of intracellular secondary messengers such as cyclic adenosine monophosphate (cAMP) or protein kinase signaling cascades.

Effects of thyroid hormones:
A. Increase Basal metabolic effects:
Basal metabolic rate (BMR): is the minimum amount of energy required by body to maintain life at complete physical and mental rest in post absorptive rest.
Maintain life (like work of heart, renal tubule, GI motility, ion transport across membrane etc.)
Basal metabolic rate (BMR) by the following steps:
a. is the amount of O2 (in milliliters) consumed per unit of time
b. corrected to standard temperature and pressure
c. converted to energy production by multiplying by 4.82 kcal/L of O2 consumed
d. corrected to surface area with factor time
Normal BMR
a. Adult male 35-38 cal/ sq.m/hr; b. adult women: 32-35 cal/ sq.m/hr
BMR value between -15% and +20% is considered normal
Factors affecting BMR:
1. Surface area: directly proportional to surface area
2. Sex: men have marginally higher BMR (5%) than female
3. Age: on infant and growing children is higher. In adult BMR decreases at rate of 2% per decade
4. Hormones: thyroid hormones, (mainly) and epinephrine, sex hormones, cortisol, growth hormones all increase BMR
5. Physical activity: BMR increase with exercise
6. Environment: BMR is higher in cold climates, compared to warm climates
7. Starvation: during starvation a decrease in BMR up to 50% has been reported
8. Fever: BMR increase by 10% for every 1ºC rise in body temperature
9. Diseases: BMR is elevated in infection, leukemia, cardiac failure, hypertension etc.
Because thyroid hormone increases metabolism in almost all cells of the body, excessive quantities of the hormone can occasionally increase the basal metabolic rate 60 to 100 percent above normal.

Secondary effects of increase basal metabolic effects of thyroid hormone:
1) Calorigenic action
Calorigenic action means increase body temperature
Calorigenic action is because thyroid hormones ↑ ATP production ↑ BMR ↑ body temperature
Some of the calorigenic effect of thyroid hormone is due to:
A. Thyroid hormones
   ▼
   Increase the number and activity of mitochondria 
   ▼
   Increases the rate of formation of ATP to energize cellular function

B. Thyroid hormones
   ▼
   Increase the activity of the membrane-bound Na-K ATPase
   ▼
   Increases the rate of transport of both sodium and potassium ions through the cell membranes
   ▼
   Increases the amount of heat produced in the body,

C. Thyroid hormones
   ▼
   Cell membrane of most cells to become leaky to Na ions
   ▼
   Increase the activity of the membrane-bound Na-K ATPase
   ▼
   Increases the rate of transport of both sodium and potassium ions through the cell membranes
   ▼
   Increases the amount of heat produced in the body

2) Stimulation of oxygen consumption.
   T₃ and T₄ increase the oxygen consumption of almost all metabolically active tissue.
   The exceptions are the adult brain, testes, uterus, lymph nodes, spleen, and anterior pituitary.
   T₄ actually depresses the oxygen consumption of the anterior pituitary, presumably because it inhibits
   TSH secretion.

3) Decreased Body Weight.
   A greatly increased amount of thyroid hormone almost always decreases body weight and a greatly
   decreased amount of thyroid hormone almost always increases body weight; however, these effects do
   not always occur because thyroid hormone also increases the appetite, which may counterbalance the
   change in the metabolic rate.

   Effects secondary to calorigenesis:

1. Effects on protein metabolism:
   ① When the BMR is increased by thyroid hormones in adult's nitrogen urine excretion is increased;
   if food intake is not increased, endogenous protein and fat stores are catabolized and weight is lost. In
   hypothyroid children, small dose of thyroid hormones causes a positive nitrogen balance because they
   stimulate growth, but large dose cause protein catabolism similar to that produced in the adult. The K
   liberated during protein catabolism appears in the urine, and there is an increase in urinary hexosamine
   (Hexosamines are amino sugars created by adding an amine group to a hexose. Examples include:
   Fructosamine (based upon fructose) Galactosamine & Glucosamine) and uric acid excretion.

2. Effects on carbohydrate metabolism:
Thyroid hormone stimulates almost all aspects of carbohydrate metabolism including:

i. Rapid uptake of glucose by the cells.

ii. Enhance gluconeogenesis and glycolysis.

iii. Increase rate of glucose absorption from GIT.

iv. Increase insulin secretion.

v. Accelerate the degradation of insulin.

All these actions have a hyperglycemic effect and, if the pancreatic reserve is low, may lead to B cell exhaustion.

3. Effects on fat metabolism:

All aspects of fat metabolism are enhanced, in particular:

i. Lipid is mobilized rapidly from the fat tissue, which decrease the fat stores of the body to a greater extent than almost any other tissue element.

ii. Increase the free fatty acid concentration in the plasma.

iii. Greatly accelerates the oxidation of free fatty acids by the cells.

Increase thyroid hormones decrease the concentration of cholesterol, phospholipids, and triglycerides in the plasma, even though it increases the free fatty acids.

The possible mechanisms by which the thyroid hormone lowers the cholesterol level are:

One of the mechanisms by which thyroid hormone decreases plasma cholesterol concentration is to increase significantly cholesterol secretion in the bile and consequent loss in the feces. A possible mechanism for the increased cholesterol secretion is that thyroid hormone induces increased numbers of low-density lipoprotein receptors on the liver cells, leading to rapid removal of low-density lipoproteins from the plasma by the liver and subsequent secretion of cholesterol in these lipoproteins by the liver cells.

4. Increased requirement for vitamins:

Because thyroid hormones increase the quantity of many bodily enzymes and because vitamins are essential parts of some of the enzymes or co-enzymes, thyroid hormones cause increase need for vitamins. Therefore, a relative vitamin deficiency can occur when excess thyroid hormone is secreted. Thyroid hormones are necessary for hepatic concentration of carotene to vitamin A, and the accumulation of carotene in the blood stream (carotenemia) in hypothyroidism is responsible for the yellowish tint of the skin. Carotenemia can be distinguished from jaundice because in the former condition the sclera is not yellow.

B. Effects of thyroid hormones on cardiovascular system:

1. Increase blood flow and cardiac output:

Thyroid hormones

▼

More rapid utilization of oxygen than normal

▼

Increase metabolism in the tissue

▼

Release of greater than normal quantities of metabolic end products from the tissues.
Vasodilatation in most body tissue ▼
Increasing tissue blood flow ▼
Increase cardiac output
Sometimes rising to 60% more above normal when excessive thyroid hormone is present and falling to only 50% of normal in very severe hypothyroidism

NOTE:
The rates of blood flow in the skin especially increase because of the increased need for heat elimination from the body.

2. Increase heart rate:
The rate increases considerably more under the influence of thyroid hormone than would be expected from the increase in cardiac output. Therefore, thyroid hormone seems to have a direct effect on the excitability of the heart as T3 may influence the sensitivity of the sympathetic system, which in turn increases the heart rate. This effect is of particular physical signs that the clinical use in determining whether a patient has excessive or diminished thyroid hormone production.

3. Increased heart strength:
a. Mild increase thyroid hormone
The increased enzymatic activity caused by increased thyroid hormone production apparently increases the strength of the heart. This is analogous to the increase in heart strength that occurs in mild fevers and during exercise.
b. Marked increase of thyroid hormone
The heart muscle strength becomes depressed because of long-term excessive protein catabolism. Indeed, some severely thyrotoxic patients die of cardiac de-compensation secondary to myocardial failure and to increased cardiac load imposed by the increase in cardiac output (high cardiac failure).

4. Normal arterial pressure:
The mean arterial pressure usually remains about normal after administration of thyroid hormone. However, because of increased blood flow through the tissues between heartbeats, the pulse pressure is often increased, with the systolic pressure elevated in hyperthyroidism 10 to 15 mmHg (due to increase strength of the heart) and the diastolic pressure reduced a corresponding amount (due to vasodilation caused by Calorigenic effect).

T₃ is not formed from T₄ in myocytes and vascular smooth muscles to any degree (due to absence of D2 de-iodonase), but circulatory T₃ enters the myocytes, combines with its receptors, and enters the nucleus, where it promotes the expression of some genes and inhibits the expression of others. Those that are enhanced include the genes for

1. α-myosin heavy chain,
2. sarcoplasmic reticulum Ca-ATPase,
3. β-adrenergic receptors,
4. G proteins,
5. Na-K ATPase, and
6. certain K channels.

Those that are inhibited include the genes for
β- myosin heavy chain, phospholamban, two types of adenylyl cyclase, T₃ nuclear receptors, and the Na-Ca exchanger.

The net result is increased heart rate and force of contraction.

The heart contains two types of myosin heavy chain (MHC) isoforms, α-MHC and β-MHC. Increase α-MHC level by treatment with thyroid hormone, will increases the speed of cardiac contraction.

<table>
<thead>
<tr>
<th>Location</th>
<th>α-MHC</th>
<th>β-MHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATPase</td>
<td>atria</td>
<td>ventricle</td>
</tr>
<tr>
<td>hypothyroidism</td>
<td>increase</td>
<td>Not affected</td>
</tr>
<tr>
<td>Gene expression in hypothyroidism</td>
<td>depress</td>
<td>enhanced</td>
</tr>
</tbody>
</table>

C. Effects of thyroid hormones on the nervous system:

- Thyroid hormones enter the brain in adult
- Thyroid hormones are found in gray matter in numerous different locations.
- In addition, astrocytes in the brain convert T₄ to T₃ and there is a sharp increase in brain D₂ (de-iodinase) activity after thyroidectomy that is reversed within 4 hours by a single intravenous does of T₃.
- Some of the effects of thyroid hormones on the brain are probably secondary to increased responsiveness to catecholamine, with consequent increased activation of the reticular activation system.

- Thyroid hormones have marked effects on brain development. The parts of the CNS most affected are the cerebral cortex and the basal ganglia. In addition, the cochlea is also affected.
- Consequently, thyroid hormone deficiency during development causes retardation, motor rigidity.

During hyperthyroidism clinically the following could be seen:

i. Reaction time of stretch reflex is shortened.
ii. Increased cerebration.
iii. Extreme nervousness and many psychoneurotic tendencies. Such as anxiety complexes, extreme worry, and paranoia.
iv. Feeling of constant tiredness, because of
   a. the excitable effects of thyroid hormone on the synapses,
   b. it is difficult to sleep.
v. Fine muscle tremor. This tremor is believed to be caused by reactivity of the neuronal synapses in the areas of the spinal cord that control muscle tone.

D. Effects of thyroid hormones on skeletal muscle:

- Muscle weakness occurs in most patient in most patients with hyperthyroidism (thyro-toxic myopathy), and when the hyperthyroidism is sever and prolonged, the myopathy may be sever. The muscle weakness may be due in part to increased protein catabolism.
Thyroid hormones affect the expression of the MHC (myosin heavy chain) genes in skeletal as well as cardiac muscle. However, the effects produced are complex and their relation to the myopathy is not established.

Hypothyroidism is also associated with muscle weakness, cramps, and stiffness.

E. Effects of thyroid hormone on growth:

Thyroid hormones are essential for normal growth and skeletal maturation.

A. In children with hypothyroidism,
   a. the rate of growth is greatly retarded.
   b. growth hormones secretion is also depressed as thyroid hormones potentate the effect of growth hormone on the tissue.
   c. bone age is less than chronologie age (the actual measure of time elapsed since a person's birth).

Hypothyroid dwarfs (also known as cretins)

B. In children with hyperthyroidism, excessive skeletal growth often occurs, causing the child to become considerably taller at an earlier age. However, the bones also mature more rapidly and the epiphyses close at an early age, so the duration of growth and the eventual height of the adult actually may be shortened.

F. Effects of thyroid hormone on sexual function:

In male:
   i. Hypothyroidism: loss of libido.
   ii. Hyperthyroidism: impotence.

In female:
   i. Hypothyroidism: menorrhagia, polymenorrhea.
   ii. Hyperthyroidism: amenorrhea, oligomenorrhea.

G. Effects of thyroid hormone on gastrointestinal tract:

Hyperthyroidism associated with
   a. Increase appetite and food intake.
   b. Increase both the rate of secretion of digestive juices and the motility of GIT.
   c. Diarrhea often results in hyperthyroidism.

Lack of thyroid hormone can cause constipation.

H. Effects of thyroid hormone on respiration:
The increased rate of metabolism increases the utilization of oxygen and formation of carbon dioxide; these effects activate all the mechanisms that increase the rate and depth of respiration.

I. Other effects of thyroid hormone:
Skin: the normally contains a verity of proteins combined with polysaccharides, hyaluronic acid, and chondroitin sulfuric acid. In hypothyroidism, these complexes accumulate, promoting water retention and the characteristic puffiness of the skin (myxedema). When thyroid hormones are administered, the proteins are metabolized, and diuresis continues until the myxedema is cleared.

Milk secretion: milk secretion is decreased in hypothyroidism and stimulated by thyroid hormones.

J. Effect on Other Endocrine Glands.
Increased thyroid hormone increases the rates of secretion of several other endocrine glands, but it also increases the need of the tissues for the hormones.

For instance, increased thyroxine secretion

A. Increase insulin secretion:
Increases the rate of glucose metabolism almost everywhere in the body and therefore causes a corresponding need for increased insulin secretion by the pancreas.

B. Increase parathyroid hormone:
Increase thyroid hormone increases many metabolic activities related to bone formation and, as a consequence, increases the need for parathyroid hormone.

C. Increase in adrenocorticotropic hormone
Thyroid hormone increases the rate at which adrenal glucocorticoids are inactivated by the liver. This increased rate of inactivation leads to feedback increase in adrenocorticotropic hormone production by the anterior pituitary and, therefore, an increased rate of glucocorticoid secretion by the adrenal glands.

The factors affecting TSH and TRH (thyroid releasing hormone) are:
1. Exposure to cold stimulate the release of TSH and TRH in experimental animals and human infants, the rise produced by cold in adult human is negligible. Consequently, in adult, increased heat production due to increased thyroid hormone secretion (thyroid hormone thermo-genesis) play little if any role in the response to cold.
2. Excitement and anxiety (condition that greatly stimulate the sympathetic nervous system) cause an acute decrease in secretion TSH and TRH.

Feedback control of thyroid secretion:
The negative feedback effect of thyroid hormones on TSH secretion is excreted in part at the hypothalamic level, but it is also due in large part to an action on the pituitary, science T4 and T3 block the increase in TSH secretion by TRH.

**Hypothyroidism:**
The syndrome of adult hypothyroidism is generally called (Myxedema) . Hypothyroidism may be the end result of number of diseases of the thyroid gland, or it may be secondary to pituitary failure (pituitary hypothyroidism) or hypothalamic failure (hypothalamic hypothyroidism).

**Hyperthyroidism:**
The most common cause of hyperthyroidism is Graves' disease, which account for 60 to 80% of the cases. The condition (which for unknown reasons is much common in women) is an auto-immune disease in which

Thyroid stimulating hormone receptor antibodies (TSHRAb):
TSHR-SAbs in at least 80% of patients with Graves' disease.
These antibodies have TSH agonist activity, thereby stimulating hormone synthesis and release.
This produces marked T4 and T3 secretion and enlargement of the thyroid gland (Goiter).
However, due to the feedback effects of T4 and T3. Plasma TSH is low, not high.
TSHR-SAbs includes two types of autoantibodies that attach to proteins in the thyroid to which TSH normally binds (TSH receptors):
a. Thyroid stimulating immunoglobulin (TSI) binds to receptors and promotes the production of thyroid hormones that has a similar effect to TSH but much longer time leading to hyperthyroidism.
b. Thyroid binding inhibitory immunoglobulin (TBII) blocks TSH from binding to receptors, blocking production of thyroid hormones and resulting in hypothyroidism.
TBII is not routinely tested, but TSI is often used to help diagnose Graves disease.
| **TABLE 7-5** Pathophysiology of the Thyroid Gland |

<table>
<thead>
<tr>
<th><strong>Symptoms</strong></th>
<th><strong>Hyperthyroidism</strong></th>
<th><strong>Hypothyroidism</strong></th>
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<tbody>
<tr>
<td></td>
<td>↑ metabolic rate</td>
<td>↓ metabolic rate</td>
</tr>
<tr>
<td></td>
<td>Weight loss</td>
<td>Weight gain</td>
</tr>
<tr>
<td></td>
<td>Negative nitrogen balance</td>
<td>Positive nitrogen balance</td>
</tr>
<tr>
<td></td>
<td>↑ heat production (sweating)</td>
<td>↓ heat production (cold sensitivity)</td>
</tr>
<tr>
<td></td>
<td>↑ cardiac output</td>
<td>↓ cardiac output</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>Hypoventilation</td>
</tr>
<tr>
<td></td>
<td>Tremor, weakness</td>
<td>Lethargy, mental slowness</td>
</tr>
<tr>
<td></td>
<td>Exophthalmos</td>
<td>Drooping eyelids</td>
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<tr>
<td></td>
<td>Goiter</td>
<td>Myxedema</td>
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</tbody>
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<table>
<thead>
<tr>
<th><strong>Causes</strong></th>
<th><strong>Hyperthyroidism</strong></th>
<th><strong>Hypothyroidism</strong></th>
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<tbody>
<tr>
<td></td>
<td>Graves' disease (antibodies to TSH receptor)</td>
<td>Thyroiditis (autoimmune thyroiditis; Hashimoto's thyroiditis)</td>
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<tr>
<td></td>
<td>Thyroid neoplasm</td>
<td>Surgical removal of thyroid</td>
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<td></td>
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<td>I- deficiency</td>
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<td></td>
<td></td>
<td>Cretinism (congenital)</td>
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<table>
<thead>
<tr>
<th><strong>TSH levels</strong></th>
<th><strong>Hyperthyroidism</strong></th>
<th><strong>Hypothyroidism</strong></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>↓ (because of feedback inhibition on anterior pituitary by high thyroid hormone levels)</td>
<td>↑ (because of decreased feedback inhibition on anterior pituitary by low thyroid hormone levels)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ (if primary defect is in hypothalamus or anterior pituitary)</td>
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</tbody>
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<table>
<thead>
<tr>
<th><strong>Treatment</strong></th>
<th><strong>Hyperthyroidism</strong></th>
<th><strong>Hypothyroidism</strong></th>
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<tbody>
<tr>
<td></td>
<td>Propylthiouracil (inhibits thyroid hormone synthesis by blocking peroxidase)</td>
<td>Thyroid hormone replacement</td>
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<tr>
<td></td>
<td>Thyroidectomy</td>
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<td></td>
<td>¹³¹I (destroys thyroid)</td>
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<td></td>
<td>β-blockers (adjunct therapy)</td>
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