Thyroid gland (Part 2)
Thyroid Hormones Have Slow Onset and Long Duration of Action. The actions of T3 occur about four times as rapidly as those of T4. Some of the T4 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.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Latent Period</th>
<th>Maximum Activity</th>
<th>Half-Life</th>
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</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>
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</tbody>
</table>

Approximate prolonged effect on the basal metabolic rate caused by administering a single large dose of thyroxine.
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. T₃ is 10 fold has more affinity to Intracellular thyroid hormone receptors than they have to T₄.
4. T₃ is much more potent than T₄. Consequently, more than 90 percent of the thyroid hormone molecules that bind with the receptors is triiodothyronine.

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

1. regulation of ion channels
2. oxidative phosphorylation
3. 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: ① thyroid hormones, (mainly)
and ② epinephrine, ③ sex hormones, ④ cortisol, ⑤ 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 1°C 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

Thyroid hormones increase the energy metabolism of the body in a process called 'thyroid thermogenesis'.

Calorigenic action means increase 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
   - ↑ BMR
   - ↑ Body temperature

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.

$T_3$ and $T_4$ increase the oxygen consumption of almost all metabolically active tissue. The exceptions are the adult brain, testes, uterus, lymph nodes, spleen, and anterior pituitary.

$T_4$ 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:
   - If food intake is not increased, endogenous protein and fat stores are catabolized and weight is lost.
   - When the BMR is increased by thyroid hormones in adult's, nitrogen excretion is increased (negative nitrogen balance).
   - In hypothyroid children,
     a) small dose of thyroid hormones causes a positive nitrogen balance because they stimulate growth,
     b) large dose cause protein catabolism similar to that produced in the adult.

   During protein catabolism:
   1. K liberated appears in the urine.
   2. Increase in urinary hexosamine.
   3. Increase 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. Increase gluconeogenesis and glycolysis.
   iii. Increase rate of 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 decreases 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:

- thyroid hormone induces increased numbers of LDL receptors on the liver cells
- rapid removal of low-density lipoproteins from the plasma by the liver
- increase significantly cholesterol secretion in the bile and consequent loss in the feces

4. Increased requirement for vitamins:

- Because thyroid hormones increase the quantity of many bodily enzymes
- Because vitamins are essential parts of some of the enzymes or co-enzymes, thyroid hormones cause an increased 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
   
   ↓

   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).

$T_3$ is not formed from $T_4$ in myocytes to any degree, but circulatory $T_3$ 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. $\alpha$-myosin heavy chain,
2. sarcoplasmic reticulum Ca-ATPase,
3. $\beta$-adrenergic receptors,
4. G proteins,
5. Na-K ATPase
6. certain K channels.
Those that are inhibited include the genes for
1. β- myosin heavy chain,
2. phospholamban,
3. two types of adenylyl cyclase,
4. T₃ nuclear receptors, and
5. the Na-Ca exchanger.

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

Each myosin molecule consists of two heavy chain and two pairs of light chains

The heart contains two 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>
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<tbody>
<tr>
<td>ATPase</td>
<td>more</td>
<td>less</td>
</tr>
<tr>
<td>hyperthyroidism</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.
- Astrocytes in the brain convert $T_4$ to $T_3$
- There is a sharp increase in brain $D_2$ (de-iodinase) activity after thyroidectomy that is reversed within 4 hours by a single intravenous does of $T_3$.
- Some of the effects of thyroid hormones on the brain are probably secondary to increased responsiveness to catecholamine ▶ increased activation of the reticular activation system.
- In addition, 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 ① anxiety complexes, ② extreme worry, and ③ 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 patients with hyperthyroidism (thyro-toxic myopathy),
- when the hyperthyroidism is severe and prolonged, the myopathy may be severe.
- 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.
- The muscle weakness may be due in part to increased protein catabolism.

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 chronologic 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:
in hypothyroidism milk secretion is decreased
in hyperthyroidism milk secretion is increased
J. Effect on Other Endocrine Glands.
Increased thyroid hormone increases the rates of secretion of several other endocrine glands.
Increased thyroid hormone increases the need of the tissues for the hormones.
For instance, increased thyroxine secretion
A. Increase insulin secretion:
↑thyroid hormone ▶↑rate of glucose metabolism ▶↑insulin secretion by the pancreas.
B. increase parathyroid hormone:
↑thyroid hormone ▶↑many metabolic activities related to bone formation ▶↑the need for parathyroid hormone.
C. increase in adrenocorticotropic hormone
↑thyroid hormone ▶↑the rate at which adrenal glucocorticoids are inactivated by the liver ▶↑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

Thyroid stimulating hormone receptor antibodies (TSHRAb):
TSHR-SAbs is elevated 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.
Cretinism:

Children who suffer from cretinism lack the necessary thyroid hormone in utero or shortly after birth.

- Retarded physical and mental development
- Ossification of bone is delayed
- Tooth development is poor
- Tooth eruption is delayed
- Permanent neurologic damage is evident
- Clinically, the infant is dull and apathetic
- Body temperature usually below normal
- Physically, the tongue is enlarged
- Skin and lips are thick
- Face is broad and puffy
- Nose is flat

**FIGURE 18-2** A clinical picture of an individual with cretinism demonstrates the characteristic flat nose and broad, puffy face. (From Little and Falace’s, Dental Management of the Medically Compromised Patient, ed. 6, Mosby, 2013.)
<table>
<thead>
<tr>
<th>Pathophysiology of the Thyroid Gland</th>
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<tbody>
<tr>
<td><strong>Hyperthyroidism</strong></td>
</tr>
<tr>
<td>Symptoms</td>
</tr>
<tr>
<td>▲ metabolic rate</td>
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<tr>
<td>Weight loss</td>
</tr>
<tr>
<td>Negative nitrogen balance</td>
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<tr>
<td>▲ heat production (sweating)</td>
</tr>
<tr>
<td>▲ cardiac output</td>
</tr>
<tr>
<td>Dyspnea</td>
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<tr>
<td>Tremor, weakness</td>
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<tr>
<td>Exophthalmos</td>
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<tr>
<td>Goiter</td>
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<tr>
<td>Causes</td>
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<tr>
<td>Graves' disease (antibodies to TSH receptor)</td>
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<tr>
<td>Thyroid neoplasm</td>
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<tr>
<td>TSH levels</td>
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<tr>
<td>▼ (because of feedback inhibition on anterior pituitary by high thyroid hormone levels)</td>
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<tr>
<td>Treatment</td>
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<tr>
<td>Propylthiouracil (inhibits thyroid hormone synthesis by blocking peroxidase)</td>
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<tr>
<td>Thyroidectomy</td>
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<tr>
<td>¹³¹I (destroys thyroid)</td>
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<tr>
<td>△-blockers (adjunct therapy)</td>
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<tr>
<td>Positive nitrogen balance</td>
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<tr>
<td>▼ heat production (cold sensitivity)</td>
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<td>▼ cardiac output</td>
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<tr>
<td>Hypoventilation</td>
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<tr>
<td>Lethargy, mental slowness</td>
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<tr>
<td>Drooping eyelids</td>
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<tr>
<td>Myxedema</td>
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<td>Growth and mental retardation</td>
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<tr>
<td>Goiter</td>
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<tr>
<td>Causes</td>
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<tr>
<td>Thyroiditis (autoimmune thyroiditis; Hashimoto's thyroiditis)</td>
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<tr>
<td>Surgical removal of thyroid</td>
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<td>I- deficiency</td>
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<tr>
<td>Cretinism (congenital)</td>
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<tr>
<td>▼ TRH or TSH</td>
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<tr>
<td>Treatment</td>
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<tr>
<td>Thyroid hormone replacement</td>
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