Thyroid gland and thyroid hormones

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BCH 560-Endocrinology
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Endocrine Terms

- **Half-life**: time needed to reduce concentration of hormone in blood to 1/2 its original level.
  - short 1/2 life = rapid removal
  - long 1/2 life = slower clearance

- **Upregulation**: effect of hormone to increase # of receptors and make cells more sensitive to hormone

- **Downregulation**: constant high levels of hormone cause cells to be less sensitive to hormone
Thyroid Gland

- Unique endocrine gland:
  - It maintains a large store of hormones
  - It requires iodide for hormone synthesis
Location

- The thyroid gland is located in the front of the neck attached to the lower part of the voicebox (or larynx) and to the upper part of the windpipe (or trachea). It has two sides or lobes. These lobes are connected by a narrow neck (or isthmus). Each lobe is about 4 cm long and 1 to 2 cm wide.
- The name "thyroid" comes from the Greek word which means "shield".
The follicular cells

- Thyroid epithelial cells - the cells responsible for synthesis of thyroid hormones - are arranged in spheres called thyroid follicles. Follicles are filled with colloid, a proteinaceous depot of thyroid hormone precursor. In the low (left) and high-magnification (right) images of a cat thyroid below, follicles are cut in cross section at different levels, appearing as roughly circular forms of varying size. In standard histologic preparations such as these, colloid stains pink.
Parafollicular cells

- In addition to thyroid epithelial cells, the thyroid gland houses one other important endocrine cell. Nestled in spaces between thyroid follicles are *parafollicular or C cells*, which secrete the hormone calcitonin.
Thyroid Hormones

• Amine Hormones:
  – Triiodothyronine (T3)- Follicular cells
  – Thyroxine (T4)- Follicular cells

• Calcitonin- Parafollicular cells
**Structure**

- Thyroid hormones are derivatives of the amino acid tyrosine bound covalently to iodine. The two principal thyroid hormones are:
  - **thyroxine** (known affectionately as T4 or L-3,5,3',5'-tetraiodothyronine)
  - **triiodothyronine** (T3 or L-3,5,3'-triiodothyronine).

- The **thyroid hormones are basically two tyrosines linked together with the critical addition of iodine at three or four positions on the aromatic rings.** The number and position of the iodines is important. Several other iodinated molecules are generated that have little or no biological activity; e.g. so called "reverse T3" (3,3',5'-T3).
Structure of T3, T4 and rT3

T4 (thyroxine)

T3 (3,5,3'-triiodothyronine)

rT3 (3,3,5'-triiodothyronine)
Iodide Metabolism

• Adequate iodide **prerequisite** for normal synthesis of thyroid hormones.

• Dietary **sources** of iodine:
  - Water, **iodinated salt**, iodated bread, medications, disinfectants.

• Typical **daily intake**: 500µg/d.

• Almost completely absorbed in GIT, and enters the inorganic iodide pool in the ECF.

• Inorganic I⁻ is rapidly cleared by the kidney in presence of normal kidney functions. t1/2= 2Hrs.

• **Sourses of I⁻**
  - Diet
  - I⁻ released from deiodination of thyroid hormones in the peripheral tissues (60µg/d)
  - release (leak) of inorganic iodide by the thyroid. (about 10-50µg/d).
• Iodide is *actively transported* ("trapped") from the extracellular fluid into the thyroid follicular cell.

• Once within the cell, inorganic iodide may either be incorporated into protein ("organified") or diffuse back into the extracellular fluid.

• At equilibrium, the inorganic iodide concentration ratio between the thyroid cell and the serum (T:S iodide gradient) represents the balance between iodide influx and efflux.

• Organic iodine, such as iodinated thyroglobulin, does not contribute to this iodide gradient.

• In the normal thyroid gland, inorganic iodide is organified almost immediately upon entering the cell, so that a high T:S inorganic iodide gradient is not detectable.
Active transport of I^-

Colloid

I^-

K_1 (influx)

K_2 (influx)

S
Serum

T
Thyroid cell

Microvilli

Colloid

The iodide transport mechanism in the thyroid cell.

CIO_4^-, SCN^- block

Propylthiouracil blocks iodination of thyroglobulin
Iodide Organification

- Once within the thyroid cell, inorganic iodide is rapidly oxidized by thyroid peroxidase in the presence of H₂O₂ into a reactive intermediate that is then incorporated into the tyrosine residues of acceptor proteins, mainly thyroglobulin.
- **Thyroid peroxidase** is a membrane-bound hemoprotein that is relatively unstable and therefore difficult to purity.
Fabrication of thyroid hormones is conducted by the enzyme thyroid peroxidase, an integral membrane protein present in the apical (colloid-facing) plasma membrane of thyroid epithelial cells. Thyroid peroxidase catalyzes two sequential reactions:

- Iodination of tyrosines on thyroglobulin (also known as "organification of iodide").
- Synthesis of thyroxine or triiodothyronine from two iodotyrosines.
• Other structurally related anions such as SCN-, \( \text{NO}_3^- \), and \( \text{ClO}_4^- \) competitively inhibit iodide transport.

• If the thyroid iodide organification mechanism is inefficient, inorganic iodide transported into the cell will accumulate.

• Tissues other than the thyroid also have an active transport mechanism for iodide.

• These include gastric mucosa, salivary glands, and the choriod plexus.

• However, unlike the thyroid, these tissues have a minimal capacity for iodide organification and storage of organic iodine.
Iodide clearance

Iodide Clearance:
- From the **kidney**
- From the **thyroid gland**

(The largest iodine pool in the body is the slowly turning over thyroid pool- approx. 1% per day; faster in hyperthyroidism)

- This is almost entirely organic iodine in the form of iodinated thyroglobulin stored as a colloid within the thyroid follicular lumen.

- The thyroid secretes about 75µg/d of organic iodine in the form of thyroid hormones (mainly T4, some T3).

- Secreted hormones binds to a thyroid hormone binding protein.
- The iodine content of the hormonal pool is about 600 $\mu$g.

- Cellular uptake of thyroid hormone from the pool is about 75 $\mu$g of iodine /d.

- Of this 75 $\mu$g of thyroid hormone iodine, about 60 $\mu$g reenters the ECF iodide pool following intracellular enzymatic deiodination of the thyroid hormones.

- The remainder (15 $\mu$g) is conjugated in the liver and excreted in the bile.
RAIU
(Radioactive iodide uptake)

- Useful index of thyroid function
- Normal: 20-50% of the ingested dose.
- Increase iodide in diet has led to a decrease of RAIU to 5-25% (in USA).
- In iodide deficiency it is increased.
- Higher in hyperthyroidism and lower in hypothyroidism. —some exceptions may exist.
Thyroglobulin
T3 and T4 Synthesis on thyroglobulin
Synthesis of T3 and T4
Iodotyrosine Coupling

- Iodinated tyrosine residues in thyroglobulin combine to form iodothyronines.
- Thus, DIT couples with DIT to form thyroxine and MIT with DIT to form triiodothyronine.
- Two theories of iodothyronine formation: intramolecular coupling and intermolecular coupling.
- In the former, 2 peptide-linked DIT molecules couple while still part of the thyroglobulin polypeptide chain – a process that may involve generation of free radicals of DIT.
- In intermolecular coupling, there is evidence that DIT is liberated from thyroglobulin and in turn converted into its pyruvic acid analogue diiodohydroxyphenylpyruvic acid (DiHPPA) by tyrosine transaminase.
**Iodotyrosine Coupling**

- After conversion to its enol form and subsequent oxidation by H$_2$O$_2$ and thyroid peroxidase to the DIHPPA hydroperoxide, this intermediate then couples with DIT present within the thyroglobulin molecule to form thyroxine.
- Thyroid peroxidase plays an important role.
- Thyroid peroxidase catalyzes all steps in the synthesis of iodothyronines.
- A defect in the coupling mechanism results in diminished T$_4$ and T$_3$ formation from DIT and MIT.
- This may be related to inadequate concentration of precursor iodotyrosines or to a defect in the enzymes, responsible for coupling.
- As an example of the first possibility, in iodine deficiency, poorly iodinated thyroglobulin contains fewer iodotyrosine molecules overall and more MIT relative to DIT.
Present concepts of thyroglobulin iodination

**Enzyme**
(?) NADPH+-Cytochrome C reductase

**Reaction**
H$_2$O$_2$ generation

**II**
Iodide oxidation

**III**
Iodination reaction contd..

**Diagram:**
- HMP
- NADPH → NADP
- FAD → FADH$_2$
- Reduced Cytochrome C ↔ Cytochrome C
- O$_2$
- H$_2$O$_2$
- I$^-$ → ?I$^0$
- Tg - Tyrosine
Transaminase

Tautomerase
(Peroxidase)

IV
Coupling
reaction

DIT

DIHPPA  Keto

DIHPPA  Enol

DIHPPA  Hydroperoxide

Thyroglobulin-DIT

Thyroglobulin-DIT

Peroxidase

Intramolecular coupling

Thyroglobin-T₄

OR

Thyroglobin-T₃

DIHPPA=diiodohydrophenylpyruvic acid
iodinated thyroglobulin

Colloid

endocytosis

lysosome

Extracellular fluid (into blood)
Thyroid Hormone Secretion

- Thyroglobulin is stored extracellularly in the follicular-lumen.
- Therefore, as a prerequisite for thyroid hormone secretion into the blood, thyroglobulin must first re-enter the thyroid cell and undergo proteolysis.
- A small quantity of intact thyroglobulin enters the circulation, some by way of the lymphatics.
- This leakage can be increased when the thyroid cells are damaged, such as occurs in thyroiditis, hyperthyroidism, or papillary or follicular thyroid carcinoma.
- Iodinated thyroglobulin is stored adjacent to the epithelial border.
- The most recently iodinated thyroglobulin may be the first to be secreted.
• This has been called the “last come, first served” principle.
• Not all follicles in the thyroid are of the same size, and their thyroglobulin turnover rates vary considerably.
• The smaller follicles turn over their contents at a faster rate.

1) **Pseudopods** from the apical cell surface extend into the colloid in the follicular lumen, and large colloid droplets is enclosed in membrane derived from the apical cell border.

2) **Electron-dense lysosomes** migrate apically, meet the incoming colloid droplets, and fuse with them to produce phagolysosomes. The phagolysosomes continue their migration toward the basal aspect of the cell, during which time they become smaller and more dense as the lysosomal proteases hydrolyze the thyroglobulin.
3) T4 and, to a much lesser degree, T3, liberated from thyroglobulin by the proteolytic process, pass from the phagolysosome into the blood by a mechanism that is presently unknown.

- Most of the liberated iodotyrosines (MIT and DIT) are deiodinated by iodotyrosine deiodinase, releasing free iodide.
(3) Proteolysis of thyroglobulin

(2) Phagolysosomes being formed by fusion of lysosome and colloid droplet

(1) Endocytosis of colloid droplet.

Lysosome Containing protease

Colloid droplet

Follicular colloid

Thyroglobulin

Pseudopods of apical membrane

Capillary

Schematic representation of thyroid hormone secretion.
Production Of Thyroid Hormones

Dietary iodide (I\(^-\); atomic wt. 127)

A. Rapid absorption

FOLLICULAR CELLS

I\(^-\)

ATP

- 50 mV

Na\(^+\)

K\(^+\)

B. Iodide trap

Electrochemical gradient

Thyroglobulin to Golgi complex

C. Endoplasmic reticulum

MIT

DIT

I\(^-\)/I\(^-\)

Peroxidase

MIT

DIT

I\(^-\)

TG

T\(_3\)

T\(_4\)

D. Vesicles

E. Colloid droplets by pinocytosis

F. Lysosomal peptidases

G. MIT and DIT

Deiodinase

H. TSH stimulates thyroid hormone synthesis and secretion

Fig. 28-1

KM c
Control of Thyroid Hormone Synthesis and Secretion

• Each of the processes in thyroid hormone synthesis are stimulated by thyroid-stimulating hormone from the anterior pituitary gland.
• Binding of TSH to its receptors on thyroid epithelial cells stimulates synthesis of the iodine transporter, thyroid peroxidase and thyroglobulin.
• The magnitude of the TSH signal also sets the rate of endocytosis of colloid - high concentrations of TSH lead to faster rates of endocytosis, and hence, thyroid hormone release into the circulation.
• Conversely, when TSH levels are low, rates of thyroid hormone synthesis and release diminish.
Control of Thyroid hormone synthesis

Cold exposure

Hypothalamus

Thyrotropin-releasing hormone

Anterior pituitary

Thyrotropin

Thyroid

Thyroxine

Negative feedback
Regulation of Thyroid Function

- Thyroid hormone synthesis and secretion are regulated by extrathyroidal (thyrotropin) and intrathyroidal autoregulatory mechanisms.

- Although thyrotropin (TSH) is the major modulator of thyroid activity, the importance of autoregulation is receiving increasing recognition.
TSH (Revision)

- TSH is a **glycoprotein** (MW 28,000); 15% carbohydrate) secreted by specialized cells (**thyrotrophs**) in the **anterior pituitary**.
- TSH consists of **2 polypeptide chains**.
- The alpha chain is nearly identical to the alpha chains of LH, FSH, and chorionic gonadotropin (hCG).
- TSH specificity is determined by the **uniquely different beta chain**, which is critical for recognition of the TSH receptor.
- TSH biological activity is present only when the **2 chains** are combined.
- The **half-life** of TSH in plasma is very short (about an hour).
- TSH secretion by the pituitary is modulated by thyroid hormone in a **negative feedback** regulatory mechanism.
Actions of TSH on the Thyroid

TSH has many effects on the thyroid, the net result of which is increased thyroid hormone secretion.

1) Most TSH actions are produced by binding to specific thyroid plasma membrane receptors with the subsequent stimulation of adenylate cyclase activity and cAMP generation.

2) TSH affects the iodide transport mechanism in a biphasic manner. There is an initial acute (4-hour) decrease in the iodide thyroidisemum (T:S).

3) TSH (and cAMP) stimulate iodide organification (incorporation of iodide into thyroglobulin) primarily by increasing $\text{H}_2\text{O}_2$ generation.
4) Acute TSH stimulation (1-2 minutes) increases pseudopod formation at the apical cell border, followed by endocytosis of colloid, phagolysosome formation, and the subsequent secretion of thyroid hormones.

5) **Chronic TSH** stimulation increases thyroid transcriptional and translational activity and ultimately produces **hyperplasia and goiter**.

6) Many other effects of TSH on thyroid metabolism have been described. These include: increased glucose oxidation via the pentose phosphate pathway, phospholipid turnover, and increased precursor uptake into thyroid cells.
Other Thyroid Stimulators

- Other stimulators of cAMP generation, particularly epinephrine and prostaglandins, can increase thyroid hormone secretion under experimental conditions.
Thyroid Autoregulation

- The thyroid is able to regulate its uptake of iodide and thyroid hormone synthesis by intrathyroidal mechanisms independent of TSH. e.g:
  A. Wolff-Chalkoff Block:
  B. Sensitivity to TSH:
  C. Thyroid Hormone Secretion:
  D. Other Examples of Autoregulation:
A. Wolff-Chalkoff Block:

- When increasing amounts of I\(^-\) are given to experimental animals, inhibition of iodide organification occurs at a critical level of intrathyroidal inorganic I\(^-\).
- Thyroglobulin iodination and thyroid hormone synthesis subsequently decrease.
- This is known as the Wolff Chaikoff block.
- The normal thyroid gland escapes from the Wolff-Chaikoff block – and hypothyroidism does not ensue – because of intrathyroidal feedback inhibition of the iodide transport mechanism by an as yet unidentified organic iodine intermediate; i.e. the ability of the thyroid to trap iodide and to maintain a high T:S ratio is reduced.
B. Sensitivity to TSH:

• The thyroid is able to "sense" its organic iodide content and alter its sensitivity to TSH stimulation.

• For example, when animals receiving a high-iodide diet are injected with TSH, they develop less of a goiter than do iodide-deficient animals injected with the same amount of TSH.
C. Thyroid Hormone Secretion:

- The Wolff-Chaikoff block must be distinguished from the rapid and transient decrease in thyroid hormone secretion induced by iodide, especially in hyperthyroidism.

- This involves inhibition of lysosomal activity and thyroglobulin endocytosis by iodide, resulting in decreased $T_3$ and $T_4$ release.
D. Other Examples of Autoregulation:

- During periods of iodide insufficiency, the ratio of T3 to T4 secreted by the thyroid is increased.

- Since T₃ is more potent than T₄, the thyroid is therefore, able to utilize available iodide more efficiently when the supply is limited.
Thyroid Hormones in Plasma

- Thyroid hormones (T₄ and T₃) in plasma are largely bound to protein.
- Only about 0.04% of the T₄ and 0.4% of the T₃ circulate "free" in the unbound state.
- The present concept is that only the free hormones enter cells, produce their biologic effects, and are in turn metabolized.
- Only the free hormone regulates the pituitary feedback mechanism.
- A dynamic equilibrium exists between the plasma and intracellular free hormone pools.
• **Protein-bound thyroid**, hormones are therefore a very large reservoir that is slowly drawn upon as the free hormone dissociates from the binding proteins and enters the cells.

• Thyroid secretion is precisely regulated to replenish the metabolized thyroid hormones.

• Very little thyroid hormone is lost in the urine.

• There are 3 major thyroid hormone-binding proteins in plasma.
  - Thyroid Hormone-Binding Globulin (TBG)
  - Thyroxine-Binding Prealbumin (TBPA)
  - Albumin
A. Thyroid Hormone-Binding Globulin (TBG):

- TBG is a monomeric glycoprotein.
- It is the thyroid hormone-binding protein at lowest concentration in plasma.
- Each molecular has a single binding site for $T_4$ or $T_3$.
- Despite its very low concentration, it is the protein with the highest affinity for thyroid hormones ($T_4 > T_3$).
B. Thyroxine-Binding Prealbumin (TBPA):

- TBPA is present at intermediate concentration.
- TBPA binds essentially no $T_3$.
- Even though its concentration in plasma is 20 times that of TBG, TBPA binds much less $T_4$ and TBG.
C. Albumin:

- Albumin has the lowest affinity for $T_4$ and $T_3$.
- However, it binds significant amounts of thyroid hormone (approximately 10% of $T_4$ and 30% of $T_3$), because it is present in plasma at very high concentration.
Representative iodothyronine kinetic values in a euthyroid human

<table>
<thead>
<tr>
<th></th>
<th>T4</th>
<th>T3</th>
<th>rT3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum levels:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total, µg/dL (nmol/L)</td>
<td>8 (103)</td>
<td>0.12 (1.84)</td>
<td>0.04 (0.51)</td>
</tr>
<tr>
<td>Free, ng/dL (pmol/L)</td>
<td>2.1 (27)</td>
<td>0.28 (4.3)</td>
<td>0.24 (3.69)</td>
</tr>
<tr>
<td>Body pool, µg (nmol)</td>
<td>800 (1023)</td>
<td>46 (70.7)</td>
<td>40 (61.5)</td>
</tr>
<tr>
<td>Distribution volume (L)</td>
<td>10</td>
<td>38</td>
<td>98</td>
</tr>
<tr>
<td>Metabolic clearance rate (MCR) (L/d)</td>
<td>1</td>
<td>22</td>
<td>90</td>
</tr>
<tr>
<td>Production (disposal) rate. MCRX serum concentration, µg/d (nmol/d)</td>
<td>80 (103)</td>
<td>26 (34)</td>
<td>36 (46)</td>
</tr>
<tr>
<td>Half-life in plasma (t_{1/2}) (days)</td>
<td>7</td>
<td>1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

(Note: T₄ µg/dL x 12.87 = nmol/L; T₃ µg/dL x 15.38 = nmol/L)
Conditions or factors associated with decreased conversion of $T_4$ to $T_3$

1. Fetal life.
2. Caloric restriction.
3. Hepatic disease.
4. Major systemic illness.
5. Drugs:
   • Propylthiouracil.
   • Glucocorticoids.
   • Propranolol (mild effect).
   • Iodinated x-ray contrast agent (iopanoic acid, ipodate sodium).
Kinetics of Thyroid Hormone Interaction with Plasma Binding Proteins:

• T4 and T3 bind reversibly with each binding protein according to the law of mass action.
• Because of the high affinity of the binding proteins for thyroid hormones, the concentrations of free $T_4$ and $T_3$ in plasma are negligible compared to the concentrations of protein-bound hormones.
• The binding of thyroid hormones to plasma binding proteins may vary considerably.
• Low or high TBG levels are uncommon genetic traits that can produce abnormal levels in total hormone concentrations, with the free (metabolically active) hormone levels.
Factors influencing the concentration of protein-bound thyroid hormones in serum

A. Increased TBG Concentration:
   3. Diseases (acute infectious hepatitis, hypothyroidism).

B. Decreased TBG Concentration:
   2. Drugs (androgenic steroids, glucocorticoids).
   3. Major systemic illness (protein malnutrition, nephrotic syndrome, cirrhosis, hyperthyroidism).

C. Drugs Affecting Thyroid Hormone Binding to Normal Concentrations of Binding Protein:
   1. Phenytoin (Dilantin).
   2. Salicylates.
   3. Phenylbutazone.
   4. Mitotane (Lysodren, o,p′-DDD).
   5. Heparin.
Thyroid Hormone Metabolism

- T₄ is the major secretary product of the normal thyroid.
- The major pathway of T₄ metabolism is via the progressive deiodination of the molecule.
- The initial deiodination of T₄ may occur in the outer ring, producing T₃ (3,3', 5-T3); or in the inner ring, producing reverse T₃ (rT3; 3,3', 5'T₃).
- Less than 20% of total T₃ is produced in the thyroid.
- The remaining 80-90% is derived from outer (phenolic) ring monodeiodination of T₄ in the peripheral tissues.
- T₄ and T₃ in the plasma are metabolized by the peripheral tissues and subsequently excreted.
- Although the catabolic products of T₄ are generally less biologically active than the parent compound, some metabolites do have biologic activity and, as in the case of T₃, even exceed the biologic potency of T₄.
**Differences between iodothyronine 5'- deiodinase type I and type II.**

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue (primary localization)</td>
<td>Liver, kidney, muscle</td>
<td>Brain, pituitary, brown adipose tissue, and skin.</td>
</tr>
<tr>
<td>Inhibition by propylthiouracil</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Substrate affinity</td>
<td>rT₃ &gt; T₄</td>
<td>T₄ = rT₃</td>
</tr>
<tr>
<td>Enzyme kinetics</td>
<td>Ping-pong</td>
<td>Sequential</td>
</tr>
<tr>
<td>Influence of hypothyroidism</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
</tbody>
</table>
 Thyroid Hormone Metabolism

• In addition to the deiodinative pathways of T4 metabolism, minor metabolic pathways of uncertain importance include the following:
  1) Oxidative deamination of the iodothyronines into their acetic acid derivatives.
  2) Phenolic conjugation into glucuronide or sulfate derivatives.
  3) Decarboxylation of thyroxine to thyroxamine.
  4) Cleavage of the ether link between the 2 phenol rings of the iodothyronine.
Thyroid Hormone – Mode of Action
Structure of Intracellular Receptors

• Steroid and thyroid hormone receptors are members of a large group ("superfamily") of transcription factors, adding to the complexity of the response. All of these receptors are composed of a single polypeptide chain that has three distinct domains:
  – The amino-terminus: In most cases, this region is involved in activating or stimulating transcription by interacting with other components of the transcriptional machinery. The sequence is highly variable among different receptors.
  – DNA binding domain: Amino acids in this region are responsible for binding of the receptor to specific sequences of DNA.
  – The carboxy-terminus or ligand-binding domain: This is the region that binds hormone.
Thyroid hormone Receptor
Physiologic Effects of Thyroid Hormones
• **Growth:** Thyroid hormones are **necessary for normal growth in children and young animals**, as evidenced by the growth-retardation observed in thyroid deficiency. Not surprisingly, the growth-promoting effect of thyroid hormones is intimately intertwined with that of growth hormone, a clear indication that complex physiologic processes like growth, depend upon multiple endocrine controls.

• **Development:** A classical experiment in endocrinology was the demonstration that tadpoles deprived of thyroid hormone failed to undergo metamorphosis into frogs. Of critical importance in mammals is the fact that **normal levels of thyroid hormone are essential to the development of the fetal and neonatal brain.**
Summary of Thyroid Hormone Actions

1. **Effects on Fetal Development:**
   - Critically important in fetal development, particularly of the neural and skeletal systems.
   - Thus, intrauterine hypothyroidism leads to cretinism (mental retardation and dwarfism).
   - Fetus is dependent upon hormones synthesized by its own thyroid gland from about 11 weeks gestation.

2. **Effects on Oxygen Consumption & Heat Production:**
   - The basal metabolic rate (O\(_2\) consumption, at rest, by the whole animal) increases in hyperthyroidism and decreases in hypothyroidism.
   - Postnatally, thyroid hormones increase O\(_2\) consumption in all tissues except the brain, spleen, and testis.
3. **Cardiovascular Effects:**
   - Thyroid hormones have marked chronotropic and inotropic effects on the heart.
   - Low cardiac output with bradycardia and slow myocardial contraction and relaxation are characteristic of hypothyroidism.
   - The reverse occurs in hyperthyroidism.

4. **Sympathetic Effects:**
   - Many thyroid hormone effects are similar to those induced by catecholamines.
   - Hyperthyroid patients are more sensitive to catecholamines.
5. **Pulmonary Effects:**
   - Thyroid hormones are necessary for normal hypoxic and hypercapnic drive to the respiratory centers.
   - Hypoventilation with hypoxia and hypercapnia is a consequence of severe hypothyroidism.

6. **Hematopoietic Effects:**
   - Thyroid hormones increase erythropoiesis, possibly because of increased O2 utilization by tissues leading to increased erythropoietin production.
7. **Endocrine Effects:**

- Thyroid hormones generally increase the metabolism and clearance of various hormones and pharmacologic agents.
- For example, steroid hormone clearances are increased, leading to compensatory increases in production rates.
- Serum prolactin levels are increased in about 40% of patients with primary hypothyroidism.
- The growth hormone response to stimuli such as hypoglycemia is reduced in primary hypothyroidism.
- Thyroid hormones are necessary for normal LH and FSH secretion.

8. **Musculoskeletal Effects:**

- Thyroid hormones have a potent stimulatory effect on bone turnover, increasing both bone formation and resorption
Abnormalities of the Thyroid Hormones
Abnormalities of the thyroid hormones

• Hyperthyroidism
• Hypothyroidism
Hyperthyroidism

- “Hyperthyroidism” refers to overactivity of the thyroid gland leading to excessive synthesis of thyroid hormones and accelerated metabolism in the peripheral tissues. The secretion of thyroid hormone is no longer under the regulatory control of the hypothalamic-pituitary center.

- The terms hyperthyroidism and thyrotoxicosis are used interchangeably, irrespective of whether the disorder is caused by endogenous overproduction or excessive ingestion of thyroid hormones.
Contd…

- Hyperthyroidism results from condition in which the thyroid releases too much hormones over a short (acute) or long (chronic) period of time. Many diseases and conditions can cause this problem, including:
  - Graves' disease
  - Non-cancerous growths of the thyroid gland or pituitary gland
  - Tumors of the testes or ovaries
  - Inflammation (irritation and swelling) of the thyroid due to viral infections or other causes
  - Ingestion of excessive amounts of thyroid hormone
  - Ingestion of excessive iodine
- **Graves' disease** accounts for 85% of all cases of hyperthyroidism.
Major Causes

- **Graves' disease**: An autoimmune disease.
- **Hyperfunctioning thyroid nodules** (toxic adenoma, toxic multinodular goiter, Plummer's disease): A hyperthyroidism due to one or more adenomas of the thyroid gland that produce too much thyroxine.
- **Thyroiditis**: Due to inflammation of the thyroid gland for unknown reasons. The inflammation can cause excess thyroid hormone stored in the gland to leak into the bloodstream. One rare type of thyroiditis, known as subacute thyroiditis, causes pain in the thyroid gland. Other types are painless and may sometimes occur after pregnancy (postpartum thyroiditis).
<table>
<thead>
<tr>
<th>Cause</th>
<th>Pathophysiology</th>
<th>Gland size*</th>
<th>Nodularity</th>
<th>Tenderness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxic adenoma</td>
<td>Autonomous hormone production</td>
<td>Decreased</td>
<td>Single node</td>
<td>Nontender</td>
</tr>
<tr>
<td>Toxic multinodular goiter</td>
<td>Autonomous hormone production</td>
<td>Increased</td>
<td>Multiple nodules</td>
<td>Tender</td>
</tr>
<tr>
<td>Subacute thyroiditis</td>
<td>Leakage of hormone from gland</td>
<td>Increased</td>
<td>None</td>
<td>Tender</td>
</tr>
<tr>
<td>Lymphocytic thyroiditis, postpartum thyroiditis, medication-induced thyroiditis</td>
<td>Leakage of hormone from gland</td>
<td>Moderately increased</td>
<td>None</td>
<td>Nontender</td>
</tr>
<tr>
<td>Graves' disease (thyroid-stimulating antibody)</td>
<td>Increased glandular stimulation (substance causing stimulation)</td>
<td>Increased</td>
<td>None</td>
<td>Nontender</td>
</tr>
<tr>
<td>Condition</td>
<td>Increased glandular stimulation (substance causing stimulation)</td>
<td>Increased</td>
<td>Appearance</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td>------------</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td>Iodine-induced hyperfunctioning of thyroid gland (iodide ingestion, radiographic contrast, amiodarone [Cordarone])</td>
<td>Increased glandular stimulation (substance causing stimulation)</td>
<td>Increased</td>
<td>Multiple nodules or no nodules</td>
<td>Nontender</td>
</tr>
<tr>
<td>Functioning pituitary adenoma (thyroid-stimulating hormone); trophoplastic tumors (human chorionic gonadotropin)</td>
<td>Increased glandular stimulation (substance causing stimulation)</td>
<td>Increased</td>
<td>None</td>
<td>Nontender</td>
</tr>
<tr>
<td>Factitial hyperthyroidism</td>
<td>Exogenous hormone intake</td>
<td>Decreased</td>
<td>None</td>
<td>Nontender</td>
</tr>
<tr>
<td>Struma ovarii; metastatic thyroid cancer</td>
<td>Extraglandular production</td>
<td>Decreased</td>
<td>None</td>
<td>Nontender</td>
</tr>
</tbody>
</table>

*In most cases.

Information from references 6 and 7.
Symptoms

• **Weight loss**: Sudden weight loss, even when appetite and food intake remain normal or increase
• **Increased appetite**
• **Nervousness**, anxiety or anxiety attacks, irritability
• **Restlessness**
• **Tremor** — usually a fine trembling in hands and fingers
• **Rapid heartbeat** (tachycardia) — up to 200 beats per minute, irregular heartbeat (arrhythmia) or pounding of the heart (palpitations)
• **Heat intolerance**
• **Increased sweating**
• **Fatigue**
• **Frequent bowel movements**
• **Menstrual irregularities** in women
• **Goiter** (visibly enlarged thyroid) may be present
Additional associated symptoms:

- Weakness
- Sleeping difficulty
- Clammy skin
- Skin blushing or flushing
- Bounding pulse
- Nausea and vomiting
- Lack of menstruation
- Itching - overall
- Heartbeat sensations
- Hand tremor
- Hair loss
- Diarrhea
- Breast development in men
- High blood pressure
- Protruding eyes (exophthalmos)
Diagnosis

Depends on signs and symptoms and laboratory analysis:

• **Vital signs** (temperature, pulse, rate of breathing, blood pressure) show increased heart rate. Systolic blood pressure may be elevated. Physical examination may reveal thyroid enlargement or goiter.

• **Laboratory tests** that evaluate thyroid function:
  - Serum TSH is usually decreased
  - TRH Test.
  - T3 and free T4 are usually elevated
  - Thyroid Binding Globulin.
  - Iodine thyroid scan
  - Thyroid Scan
  - Thyroid Ultrasound
  - Thyroid Antibodies.
  - Thyroid Needle Biopsy.
Thyroid scans

Thyroid Scans are used for the following reasons:

- Identifying nodules and determining if they are "hot" or "cold".

- Measuring the size of the goiter prior to treatment.

- Follow-up of thyroid cancer patients after surgery.

- Locating thyroid tissue outside the neck, i.e. base of the tongue or in the chest.
Other tests

Hyperthyroidism may also alter the results of the following tests:
• Vitamin B-12
• Triglycerides
• Radioactive iodine uptake
• Glucose level
• Cholesterol level
• Antithyroglobulin antibody
Signs and symptoms of hyperthyroidism

Measure TSH level.

Suppressed TSH level

Measure free T₄ level.

Normal

Measure free T₃ level.

Normal

Subclinical hyperthyroidism
Resolving hyperthyroidism
Medication
Pregnancy
Nonthyroid illness

Elevated

T₃ toxicosis

High

Primary hyperthyroidism

Thyroid uptake

Low

Measure thyroglobulin.

Decreased

Exogenous hormone

Increased

Thyroiditis
Iodide exposure
Extraglandular production

Graves' disease

Multiple areas

Toxic multinodular goiter

Nodular

One "hot" area

Diffuse

Toxic adenoma

High

Secondary hyperthyroidism

Image pituitary gland
Treatment

• Treatment varies depending on the cause of the condition and the severity of symptoms.

• Hyperthyroidism is usually treated with antithyroid medications, radioactive iodine (which destroys the thyroid and thus stops the excess production of hormones), or surgery to remove the thyroid.

• If the thyroid must be removed with radiation or surgery, replacement thyroid hormones must be taken for the rest of the person's life.

• Beta-blockers like propranolol are used to treat some of the symptoms including rapid heart rate, sweating, and anxiety until the hyperthyroidism can be controlled.
Prognosis

• Generally hyperthyroidism is generally treatable and rarely fatal.

• However, hyperthyroidism caused by Graves' disease is usually **progressive** and has many associated **complications**, some of which are severe and affect quality of life.

• These include complications caused by use of radioactive iodine, surgery, and medications to replace thyroid hormones.
Complications

- **Cardiac complications** include rapid heart rate, congestive heart failure, and atrial fibrillation.
- **Thyroid crisis or "storm"** is an acute worsening of the symptoms of hyperthyroidism that may occur with infection or stress. Fever, decreased mental alertness, and abdominal pain may occur, and immediate hospitalization is indicated.
- Hyperthyroidism increases the risk for **osteoporosis**.
- There may be complications related to surgery, including visible scarring of the neck, hoarseness due to nerve damage to the voicebox, and a low calcium level because of damage to the parathyroid glands.
- **Complications** may be related to replacement of thyroid hormones. If too little hormone is given, symptoms of underactive thyroid can occur including fatigue, increased cholesterol levels, mild weight gain, depression, and slowing of mental and physical activity.
Graves Disease
Graves' disease is a common cause of hyperthyroidism, an over-production of thyroid hormone, which causes enlargement of the thyroid and other symptoms such as exophthalmos, heat intolerance and anxiety.

In hypothyroidism the thyroid gland can be small or large (goiter), depending on the cause of low levels of thyroid hormone.

Atrophied thyroid

Normal thyroid

Enlarged thyroid

Diffuse goiter

Exophthalmos (bulging eyes)
Proposed mechanism of Graves' disease pathogenesis.
Graves Disease

- Graves' disease is an autoimmune disease -- the immune system attacks the thyroid gland and produces antibodies against TSH receptors. These antibodies mimic TSH and cause overactivity of the thyroid gland (hyperthyroidism).
Causes, incidence, and risk factors

• Graves' disease is the most common cause of hyperthyroidism. The production of thyroid hormone is increased, causing a wide range of symptoms from anxiety and restlessness to insomnia and weight loss. In addition, the eyeballs may begin to protrude (exophthalmos) causing irritation and tearing.

• Graves' disease is caused by inappropriate immune system activation that targets the thyroid gland and causes overproduction of thyroid hormones. Risk factors are being a woman over 20 years old, although the disorder may occur at any age and may affect men.
Symptoms

- Protruding eyes (less common in children)
- Weight loss
- Increased appetite
- Nervousness
- Restlessness
- Heat intolerance
- Increased sweating
- Fatigue
- Muscle weakness
- Double vision
- Eye irritation
- Breast enlargement in men (possible)
- Tremor
- Frequent bowel movements
- Menstrual irregularities in women
- Goiter (possible)
Sometimes an uncommon problem called Graves' ophthalmopathy may affect your eyes. In this disorder, your eyeballs protrude beyond their normal protective orbit when tissues and muscles behind your eyes swell, pushing the eyeballs forward. This can cause the front surface of your eyeballs to become very dry. Other signs and symptoms of Graves' ophthalmopathy include:

- Red or swollen eyes
- Widening of the space between your eyelids
- Excessive tearing or discomfort in one or both eyes
- Light sensitivity, blurry or double vision, inflammation, or reduced eye movement
Signs and tests

• Physical examination shows an increased heart rate. Examination of the neck may show thyroid enlargement or goiter.
• **Serum TSH** is decreased
• Serum T3, free T4 are elevated
• **Radioactive iodine uptake** is usually high
• This disease may also alter the following test results:
• **TSI**
• **Orbit CT scan**
Treatment

- The purpose of treatment is to control the overactivity of the thyroid gland. Beta-blockers such as propranolol are often used to treat symptoms of rapid heart rate, sweating, and anxiety until the hyperthyroidism is controlled. Hyperthyroidism is treated with antithyroid medications, radioactive iodine or surgery.
- Both radiation and surgery result in the need for lifelong use of replacement thyroid hormones, because these treatments destroy or remove the gland.
- The eye problems related to Graves' disease usually resolve when the hyperthyroidism is effectively treated with medications, radiation or surgery. Sometimes use of prednisone (a steroid medication which suppresses the immune system) is required to reduce eye irritation and swelling.
- Taping the eyes closed at night to prevent drying may sometimes be required. Sunglasses and eyedrops may lessen irritation of the eyes. Rarely, surgery may be needed to return the eyes to their normal position.
For most people, Graves' disease responds well to treatment. However, thyroid surgery or radioactive iodine will sometimes cause hypothyroidism, which can lead to weight gain, depression and mental and physical sluggishness. Antithyroid medications can also have serious side effects.
Complications

• Eye problems associated with the disease (called Graves' ophthalmopathy or exophthalmos)
• Cardiac complications including rapid heart rate, congestive heart failure (especially in the elderly) and atrial fibrillation
• Thyroid crisis or storm, a severe worsening of the symptoms of overactivity of the thyroid gland
• Increased risk for osteoporosis
• Inadequate levels of thyroid hormone medications following surgery or radiation, leading to fatigue, elevated cholesterol levels, mild weight gain, depression and mental and physical sluggishness
• Complications related to surgery, including visible scarring of the neck and hoarseness due to damage of the nerve to the voicebox, and low calcium levels due to damage to the parathyroid glands.
• This image shows enlargement of the thyroid gland and extension down behind the breastbone (retrosternal space). The image, called a scintiscan, was generated using a radioactive isotope.
Painless (silent) thyroiditis

- Painless (silent) thyroiditis is an inflammation of the thyroid gland characterized by passing hyperthyroidism, followed by hypothyroidism and recovery.
Causes, incidence, and risk factors

• The cause of this type of thyroiditis is unknown. The disease affects women more often than men and usually develops in people between age 13 and 80. The symptoms are those of hyperthyroidism (overactivity of the thyroid gland), and may last for 3 months or less.
Symptoms

- Symptoms in painless thyroiditis are usually mild. Most symptoms are due to hyperthyroidism and may include:
  - weight loss
  - increased appetite
  - nervousness, restlessness
  - heat intolerance
  - increased sweating
  - fatigue
  - muscle cramps
  - frequent bowel movements
  - menstrual irregularities
  - weakness
  - irritability
  - palpitations
Signs and tests

- A **physical examination** reveals an enlarged thyroid gland. The **pulse** (heart rate) may be rapid and the hands may shake.
- **Radioactive iodine uptake** is decreased.
- Serum **T3** and **T4** are elevated.
- A **thyroid biopsy** shows invasion of lymphocytes (a type of white blood cells) into the gland.
Treatment

• Treatment is based on symptoms. Beta-blockers (Propranolol and others) relieve rapid heart rate and excessive sweating. Generally, painless thyroiditis will resolve on its own in time.
prognosis

• The disease is usually resolved within 1 year, with the acute phase ending in 3 months. Some people may develop hypothyroidism over time, so regular follow-up is recommended.
Complications

• hypothyroidism
Factitious hyperthyroidism

- Factitious hyperthyroidism is when your body has too much thyroid hormone, caused by taking too much thyroid hormone medication.
Causes, incidence, and risk factors

- The thyroid gland produces the hormones thyroxine (T4) and triiodothyronine (T3). In most cases of hyperthyroidism, the thyroid gland itself is producing too much these hormones.
- However, you can also get hyperthyroidism by taking too much thyroid hormone medication. This is called factitious hyperthyroidism. Thyroid hormone medication has been available since 1891 and is used to treat hypothyroidism. Factitious hyperthyroidism may occur when thyroid hormone is prescribed to treat hypothyroidism and the prescribed dose is too high.
- It can also occur when a person intentionally takes too much thyroid hormone. People with psychiatric disorders such as Munchausen syndrome deliberately (and usually secretively) take these hormones.
- Patients attempting to lose weight and seeking to receive fraudulent insurance compensation also sometimes misuse thyroid hormone. Children may occasionally require treatment for accidental ingestion of thyroid hormone pills.
- In rare cases, factitious hyperthyroidism has been found to be caused by eating meat contaminated with thyroid gland tissue.
Symptoms

• The symptoms of factitious hyperthyroidism are identical to the symptoms of hyperthyroidism caused by the thyroid gland, with the following exceptions:
  • There is no goiter. The thyroid gland is usually small.
  • The eyes do not protrude, as they do in Graves' disease (the most common type of hyperthyroidism).
  • The skin over the shins does not thicken, as it occasionally does with Graves' disease.
Signs and tests

• The following test results may indicate hyperthyroidism:
  • **TSH** -- low
  • Total **T4** -- high
  • Free T4 -- high
  • Total **T3** -- high
  • Thyroglobulin -- low
  • **Radioactive iodine uptake** -- low
Treatment

• The patient would have to stop taking thyroid hormone, or if it is medically necessary, the dose must be reduced.

• The patient would be re-evaluated in 2 to 4 weeks to be sure that signs and symptoms of hyperthyroidism are gone. This also helps to confirm the diagnosis.
(prognosis

- Factitious hyperthyroidism will clear up on its own when thyroid hormone is stopped or the prescribed dose is lowered.)
Complications

• If factitious hyperthyroidism is long-standing, patients are at risk for the same complications as those of untreated or improperly treated hyperthyroidism caused by the thyroid gland.

• These complications include the following:
  • Irregular heart rhythm
  • Atrial fibrillation
  • Chest pain (angina)
  • Heart attack
  • Loss of bone mass (if severe, osteoporosis)
  • Weight loss
Hypothyroidism (Myxedema; Adult hypothyroidism)

- Hypothyroidism is a condition in which the thyroid gland fails to produce enough thyroid hormone
Causes, incidence, and risk factors

- The most common cause of hypothyroidism is Hashimoto's thyroiditis, a disease of the thyroid gland where the body's immune system attacks the gland. Failure of the pituitary gland to secrete a hormone to stimulate the thyroid gland (secondary hypothyroidism) is a less common cause of hypothyroidism. Other causes include congenital defects, surgical removal of the thyroid gland, irradiation of the gland, or inflammatory conditions.

- Risk factors include age over 50 years, female gender, obesity, thyroid surgery, and exposure of the neck to X-ray or radiation treatments.
Symptoms

- Early symptoms:
  - weakness
  - fatigue
  - cold intolerance
  - constipation
  - weight gain (unintentional)
  - depression
  - joint or muscle pain
  - thin, brittle fingernails
  - thin and brittle hair
  - paleness
• Late symptoms:
  • slow speech
  • dry flaky skin
  • thickening of the skin
  • puffy face, hands and feet
  • decreased taste and smell
  • thinning of eyebrows
  • hoarseness
  • abnormal menstrual periods
• Additional symptoms that may be associated with this disease:
  • overall swelling
  • muscle spasms (cramps)
  • muscle pain
  • muscle atrophy
  • uncoordinated movement
  • absent menstruation
  • joint stiffness
  • dry hair
  • hair loss
  • facial swelling
  • drowsiness
  • appetite loss
  • ankle, feet, and leg swelling
  • short stature
  • separated sutures
  • delayed formation or absence of teeth
Signs and tests

- A **physical examination** reveals delayed relaxation of muscles during tests of reflexes. Pale, yellow skin; loss of the outer edge of the eyebrows; thin and brittle hair; coarse facial features; brittle nails; firm swelling of the arms and legs; and mental slowing may be noted. **Vital signs** may reveal slow **heart rate**, **low blood pressure**, and low temperature.
- A **chest X-ray** may reveal an enlarged heart.
- Laboratory tests to determine thyroid function include:
  - **T4 test** (low)
  - **serum TSH** (high in primary hypothyroidism, low or low-normal in secondary hypothyroidism)
- Additional laboratory abnormalities may include:
  - increased cholesterol levels
  - increased liver enzymes
  - increased serum **prolactin**
  - low **serum sodium**
  - a complete blood count (**CBC**) that shows **anemia**
Treatment

• The purpose of treatment is to replace the deficient thyroid hormone. Levothyroxine is the most commonly used medication. The lowest dose effective in relieving symptoms and normalizing the TSH is used. Life-long therapy is needed. Medication must be continued even when symptoms subside. Thyroid hormone levels should be monitored yearly after a stable dose of medication is determined.

• After replacement therapy has begun, report any symptoms of increased thyroid activity (hyperthyroidism) such as restlessness, rapid weight loss, and sweating.

• Myxedema coma is a medical emergency that occurs when the body's level of thyroid hormones becomes extremely low. It is treated with intravenous thyroid replacement and steroid therapy. Supportive therapy of oxygen, assisted ventilation, fluid replacement, and intensive-care nursing may be indicated.
prognosis

• With treatment, return to the normal state is usual. Life-long medication is needed. Myxedema coma can result in death.
Complications

• Myxedema coma, the most severe form of hypothyroidism, is rare. It may be caused by an infection, illness, exposure to cold, or certain medications in an individual with untreated hypothyroidism. Symptoms and signs of myxedema coma include unresponsiveness, decreased breathing, low blood pressure, low blood sugar, and below normal temperature.

• Other complications are heart disease, increased risk of infection, infertility, and miscarriage.
Prevention

• There is no prevention for hypothyroidism; however, screening tests in newborns can detect congenital hypothyroidism.
– Signs and symptoms
– Clinical Statistics
– Diagnosis
– Treatment
– Clinical outcomes of undertreatment and overtreatment
– Follow-up care
Graves disease

- Graves disease is caused by stimulation of the thyroid by antibodies which bind to TSH receptors and mimic the effect of prolonged TSH stimulation.
- These TSH-receptor antibodies result from abnormal immunoregulation permitting generation and expansion of clone(s) of antibody-producing cells in genetically predisposed individuals with specific HLA-D subtypes.
- Spontaneous exacerbations and remissions of Graves disease can occur.
- The environmental triggers are still not well characterised, but postpartum exacerbation is common, and such a history should be sought routinely when Graves disease is diagnosed.
Excess iodine can precipitate active Graves disease by providing more substrate for hormone synthesis and possibly also by disturbing immune function. Persistence or recurrence of Graves disease is more likely when there is a previous history of recurrent disease, in the presence of a large goitre, when T3 excess persists despite control of T4 with thionamide therapy, and when TSH-receptor antibody persists during thionamide therapy. In addition to hyperthyroidism, other autoimmune manifestations of Graves disease are Graves ophthalmopathy (Box 3) and Graves dermopathy (pretibial myxoedema). Autoimmune thyroid disease is associated with some other, less common, autoimmune diseases, including pernicious anaemia and Addison’s disease.
Management of Graves disease

• The three modalities of therapy for Graves disease are:
  – blocking synthesis of thyroid hormone with antithyroid drugs;
  – subtotal or “near-total” thyroidectomy; and
  – destruction of the thyroid by radioactive iodine (radio-iodine ablation).
While each modality is satisfactory in rendering the patient euthyroid, none is ideal, as all have a risk of adverse effects and none but total thyroidectomy eliminates the risk of recurrence. Although total thyroidectomy virtually eliminates this risk, it is at the expense of a certain requirement for thyroid hormone replacement. Selecting treatment for an individual depends on many factors, not least being patient choice and physician bias. In the United States, radioiodine is the preferred primary modality, but, in Europe and Australia, antithyroid drug therapy is preferred for patients with a first episode of Graves hyperthyroidism, ahead of radioiodine and, lastly, surgery.
• **Antithyroid drugs:** Most patients with Graves disease require short-term (several months) treatment with an antithyroid drug (thionamide) before consideration of longer-term or definitive therapy. Prolonged thionamide therapy (12–18 months in a first episode\(^8\)) has the advantage of avoiding surgery with its inherent risks and destruction of the thyroid by radioiodine, and seems to give the best chance of sustained remission. Nonetheless, the risk of relapse is greater than 50%.

• Thionamide dose must be individualised, depending on the initial severity of disease and response, but an initial divided dose of 10–30 mg daily of carbimazole is usually satisfactory. Response should be assessed after 2–4 weeks and periodically thereafter, with a minimum eventual frequency of every third month. Initial high doses should be progressively reduced to once-daily maintenance doses of 2.5–10 mg/day (Box 4).
• Combined thionamide and thyroxine therapy (block–replace regimen) is useful for patients with unstable hyperthyroidism, in whom small variations in thionamide dose cause major fluctuations in thyroid function, but does not increase the likelihood of long-term remission.9

• Beta-blocker drugs are useful adjuncts for rapid symptomatic relief in hyperthyroidism. Standard doses reduce heart rate, sweating and tremor, but do not influence hypermetabolism or hormone levels. Non-selective β-blockers have generally been preferred for their better effect on tremor.
• **Radioiodine ablation**: Ablative therapy with radioiodine is recommended for patients with recurrent hyperthyroidism or hyperthyroidism that persists after a prolonged course of antithyroid drugs. Reassuringly, several large, long-term studies have shown no increased risk of thyroid cancer, leukaemia, other malignancies, reproductive abnormalities or congenital abnormalities in the offspring of treated patients. It is thus the default option for definitive therapy in adolescents and adults. More caution is recommended in children because of the known greater risk of inducing thyroid nodules and carcinoma from external irradiation and other radionuclide exposure in childhood.

• Radioiodine therapy does not achieve euthyroidism immediately, necessitating low-dose thionamide therapy for several months in many patients. Occasionally, early (usually transient) hypothyroidism occurs, with low serum free T4 levels without TSH elevation, as TSH is often suppressed for weeks to months after hyperthyroidism.
While each modality is satisfactory in rendering the patient euthyroid,\textsuperscript{6} none is ideal, as all have a risk of adverse effects and none but total thyroidectomy eliminates the risk of recurrence. Although total thyroidectomy virtually eliminates this risk, it is at the expense of a certain requirement for thyroid hormone replacement. Selecting treatment for an individual depends on many factors, not least being patient choice and physician bias. In the United States, radioiodine is the preferred primary modality, but, in Europe and Australia, antithyroid drug therapy is preferred for patients with a first episode of Graves hyperthyroidism, ahead of radioiodine and, lastly, surgery.\textsuperscript{7}
Toxic multinodular goitre
Causes of hyperthyroidism

- Graves disease
- Multinodular goitre
  - Autonomously functioning single thyroid nodule (adenoma)
- Thyroiditis (subacute, postpartum, lymphocytic)
- Factitious hyperthyroidism (thyroid hormone ingestion)
- Functioning thyroid carcinoma (follicular carcinoma)
- hCG-mediated (hyperemesis gravidarum, trophoblastic disease)
- Fetal and neonatal hyperthyroidism (TSH-receptor-antibody-mediated)
- Struma ovarii
- TSH-secreting pituitary tumour
- Partial (pituitary-selective) thyroid hormone resistance
<table>
<thead>
<tr>
<th><strong>High TSH</strong></th>
<th><strong>Normal TSH</strong></th>
<th><strong>Low T4</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High T4</strong></td>
<td><em>In vivo or in vitro</em> artefact Pituitary hyperthyroidism [TSHoma] Thyroid hormone resistance</td>
<td>Mild thyroid failure (primary) (also termed subclinical hypothyroidism and diminished thyroid reserve)</td>
</tr>
<tr>
<td><strong>Normal TSH</strong></td>
<td>As above Sampling within 6 h of thyroxine dose</td>
<td>Normal (in patients taking thyroxine, TSH &gt; 3 mU/L may indicate subtle underreplacement)</td>
</tr>
<tr>
<td><strong>Low TSH</strong></td>
<td>Hyperthyroidism (for this diagnosis, TSH must be suppressed rather than just low)</td>
<td>Subclinical hyperthyroidism Subtle thyroxine overreplacement Thyroid autonomy (multinodular goitre or autonomous functioning thyroid nodule) Non-thyroidal illness</td>
</tr>
</tbody>
</table>
Graves Disease is the most common cause of hyperthyroidism (60-80%) of all cases.
Females are affected more frequently than men 10:1.5
Monozygotic twins show 50% concordance rates
Incidence peaks from ages 20-40
Incidence is similar in whites and Asians, but is somewhat decreased for African Americans
Signs and Symptoms

- Tremulousness or jitteriness
- Exophthalmos
- Weight loss despite excellent appetite – hypermetabolic state
- Insomnia
- Fatigue
- Palpitations
- Heat intolerance
- Sweating
- Diarrhea
- Deterioration in handwriting
- Menstrual irregularities
- Muscle weakness/wasting manifested as exercise intolerance or difficulty climbing stairs
- Eye symptoms, which may include pain or diplopia
- Nervousness
- Tachycardia
- Goiter
- Elevated plasma levels of thyroxin and/or triiodothyronine
Exophthalmos in Graves Disease

Lid Lag in Graves Disease
Diagnosis of Hyperthyroidism

- TSH – expect this to be low
- Free T4 – expect to be high
- Nuclear thyroid scintigraphy iodine 123 uptake and scan – expect iodine uptake to increased
- Anti-thyroperoxidase antibody levels
- TSH-receptor stimulating autoantibody levels (TSI levels)
Treatments for Hyperthyroidism

- Medical therapy with antithyroid drugs such as propylthiouracil or methimazole
- Ablation of the thyroid gland with radioactive iodine
- Subtotal thyroidectomy
- Self-limited causes of hyperthyroidism, such as subacute thyroiditis, iodine-induced hyperthyroidism, and exogenous administration of T4, can be treated symptomatically. For more significant cardiovascular symptoms, beta-adrenergic blockade with propranolol can be helpful.
Clinical Outcomes of Inadequately treated Hyperthyroidism

- **Thyrotoxicosis.** A life-threatening thyrotoxic crisis (ie, thyroid storm) can occur: fever, tachycardia, neurologic abnormalities, and hypertension, followed by hypotension and shock. It can be *Fatal.*

- **Thyroid storm** occurs in patients who have unrecognized or inadequately treated thyrotoxicosis and a superimposed precipitating event such as thyroid surgery, nonthyroidal surgery, infection, or trauma.

- Initially the acute mortality rate was nearly 100%. In current practice, with aggressive therapy and early recognition of the syndrome, the mortality rate is approximately *20%.*

- **Severe Weight loss** with catabolism of bone and muscle.
- **Cardiac complications** and psychocognitive complications

- **Osteoporosis** in men and women. The effect can be particularly devastating in women, in whom the disease may compound the bone loss secondary to chronic anovulation or menopause. *Bone loss is accelerated* in patients with hyperthyroidism.
Clinical Outcomes of Inadequately treated Hyperthyroidism

- Sarcopenia and Myopathy

- Neonatal hyperthyroidism

- Apathetic hyperthyroidism - the only presenting features may be unexplained weight loss or cardiac symptoms such as **atrial fibrillation** and **congestive heart failure**.

- Cardiac hypertrophy has been reported in thyrotoxicosis of different etiologies.

- Severe acropachy can be disabling and can lead to **total loss of hand function** - clubbing of fingers with osteoarthropathy, including periosteal new bone formation, may occur.

- Ophthalmopathy - compromised **vision and blindness**. Visual loss due to **corneal lesions or optic nerve compression** can be seen.
Follow-up Care

• Patients who have been treated for hyperthyroidism need to be followed closely because they may develop HYPOthyroidism or recurrent hyperthyroidism. Follow-up care includes the following:
  – Reducing medications after 4-6 weeks; the patient should be totally off anti-thyroid medication in 12-18 months
  – Check thyroid function tests every 4-6 weeks
  – Monitor closely for remission.
References

• Hyperthyroidism:
  www.emedicine.com/med/topic1109.htm
• Hyperthyroidism:
  www.emedicine.com/ped/topic1099.htm
• Pictures from: www.thachers.org/images/Graves.jpg
Congenital Hypothyroidism