THYROID GLAND ANATOMY:
- Butterfly-shaped gland located in neck region sitting on either side of the trachea
- Thyroid follicles (spheres of a layer of thyroid epithelial cells) surrounding colloid (gelatinous material)

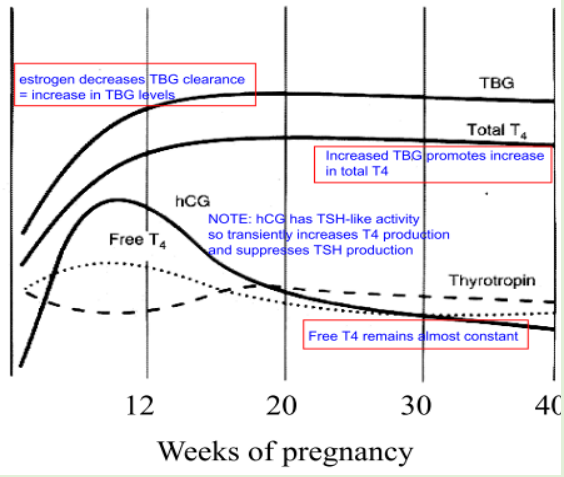
THYROID HORMONES:
- Thyroxine T4: major circulating form of TH
- Triiodothyronine T3: responsible for biological activity

REGULATION OF THYROID HORMONE PRODUCTION:
1. Hypothalamus releases TRH to the pituitary gland → increase production of TSH
2. TSH acts at specific receptors (TSH-R) on thyroid to increase expression of NIS, thyroid peroxidase, and thyroglobulin → increases hormone synthesis and release
   > Also increases growth & differentiation of thyroid follicles
3. Negative feedback: as levels of TH increase (in particular T3), it feeds back on the pituitary and hypothalamus to decrease the release of their hormones

REGULATION OF TH PRODUCTION BY IODIDE:
- Synthesis of TH depends on adequate intake of dietary iodine
  - Highest amounts of naturally occurring iodine found in seafood and seaweed (concentrated from seawater)
- Iodine deficiency major cause of thyroid dysfunction globally
  - BUT not seen in Canada because Health Canada requires the iodization of table salt
- Iodide exerts an "autoregulatory" effect at level of thyroid:
  - Plasma iodide levels inversely regulate activity of NIS
    > As iodine intake falls, uptake of iodide by the gland increases to maintain TH synthesis
  - HOWEVER, very large doses of iodide inhibit iodination of thyroglobulin & release of TH
    > Inhibition is only transient (downregulation of NIS → reduced uptake of iodide → hormone production & release resume)

THYROID HORMONE TRANSPORT:
- Circulating T4 and T3 almost entirely bound to plasma proteins:
  - **Thyroxine binding globulin** (TBG) most important
- Bound and free TH is in reversible equilibrium
  - Only free is metabolically active
- In normal thyroid function, an increase (or decrease) in TBG levels will result in an increase (or decrease) in TOTAL (bound + free) hormone, but minimal changes in free hormone

EXAMPLE: ESTROGEN-INDUCED INCREASE IN TBG IN PREGNANCY



SYNTHESIS & SECRETION OF THYROID HORMONES:
1. Uptake of iodide and transport to extracellular component of follicular cells
   a. Iodide is concentrated in thyroid follicle cells by active transport via Na+/I- symporter (NIS)
      > NIS is highly expressed in thyroid gland (low levels in other tissues) → allows use of radioactive iodine for dx & txt of hyperthyroidism & thyroid cancer with limited effects on other organs
   b. Iodide is effluxed into extracellular colloid by iodide channel in apical membrane
2. Formation of thyroid hormone in extracellular colloid
   a. **Thyroid peroxidase (TPO)*** incorporates iodine into tyrosine residues in thyroglobulin at:
      - Carbon 3 → monoiodotyrosine (MIT)
      - Carbon 3 and 5 → diiodotyrosine (DIT)
   b. TPO also couples:
      - MIT + DIT → T3
      - DIT + DIT → T4

   * TPO located on apical surface of thyroid follicular cell
3. Release into the circulation
   a. Endocytosis of colloid that contains thyroglobulin (back into thyroid follicle cell)
   b. Lysosomal degradation of thyroglobulin with release of T4 and T3
      > Some T4 is deiodinated in thyroid to T3 (which is also released into blood)
   c. Released MIT and DIT can be deiodinated within the thyroid and iodide is recycled for new hormone synthesis

DEIODINASES: REGULATION IN THYROID HORMONE LEVELS
- Catalyze:
  a. 5'-deiodination of T4 to T3 – type 1 or 2
  b. T4 to reverse T3 (rT3) – type 1 or 3 *(inactivating)*
  c. T3 to T2 – type 3 *(inactivating)*
- Three types:
  - Type 1: major source of circulating T3
    - Blocked by propylthiouracil (PTU) – thoamide anti-thyroid drug
  - Type 2: major source of intracellular T3 (found in brain, pituitary, muscle, fat, etc)
  - Type 3: major inactivating deiodinase

PHYSIOLOGICAL FUNCTION OF THYROID HORMONES:
1) Growth and development
   a. Fetal and neonatal CNS development
   b. Skeletal growth (with GH)
2) Metabolism
   a. Increase basal metabolic rate, oxygen consumption
   b. Stimulate adipose tissue lipolysis
   c. Increase muscle protein breakdown
3) Actions on the heart
   a. Increase rate and force of cardiac contraction
   b. Sensitize heart to catecholamines

MECHANISM OF THYROID HORMONE ACTION:
- Nuclear thyroid hormone receptors (TR) are bound to thyroid hormone response elements (TRE) mainly has heterodimers with retinoid X receptors (RXR)
  > In absence of T3, binding of co-repressor (CoR) proteins repress its action
  > When T3 enters nucleus, it's binding to TR promotes dissociation of CoR, recruitment of coactivators (CoA), and altered gene expression

COMPARISON OF PROPERTIES OF T4 AND T3:

	T4	T3
Serum concentration		
Total	8 ug/Dl	0.14 ug/dL
% free	0.02 %	0.3 %
Serum half-life	7 days	0.75 days
Fraction from thyroid	100%	20%
Intracellular hormone fraction	20%	70%
Relative receptor binding affinity	1	10

EVALUATION OF THYROID FUNCTION:

TSH	• Most sensitive and useful index of primary thyroid disease and effectiveness of txt • Usually used as initial test for investigation of thyroid disease • Normal levels usually 0.5 – 5.0 mU/L > If abnormal, followed by measurement of TH levels
Free serum T4 (FT4)	• Preferable to measuring total T4 levels (which can vary due to changes in TBG = unrelated to thyroid disease) • Correlated with TSH better than FT3 levels because is principle hormone released in response to TSH • In most cases, FT4 is sufficient to confirm diagnosis
Free serum T3 (FT3)	• Not indicated in hypothyroidism • Used when hyperthyroidism is suspected (due to suppression of TSH) but FT4 is not elevated > 2-5% of hyperthyroid pts experience elevation of ONLY T3 levels

THYROID FUNCTION TESTING:

Recommended when non-specific S/S are present in pts at risk:

- Hx of thyroid disease
- Strong family hx of thyroid disease
- Diagnosis of autoimmune disease
- Past hx of neck irradiation
- Drug therapies such as lithium and amiodarone
- Women over age 50
- Elderly patients
- Women 6 wk – 6 mo post-partum

THYROID DISORDERS: GOITER

- Any enlargement of the thyroid gland
- May be associated with no change, increase or decrease in hormone secretion, depending on cause

SIMPLE OR NON-TOXIC GOITER: thyroid enlargement without functional, inflammatory, or neoplastic changes

- Occurs when the thyroid gland does not secrete sufficient hormone to meet tissue demands
  - > Results in increased release of TSH or increased sensitivity of thyroid to TSH
  - > Resulting increase in functioning mass of thyroid overcomes mild impairment of hormone production, and pt becomes metabolically normal
- Can result from iodine deficiency, defect in hormone synthesis

HYPERTHYROIDISM: results from an increase in secretion of thyroid hormones

- Primary or secondary
- Vary in severity

CAUSES OF HYPERTHYROIDISM:

- **Graves Disease:** most common
  - 10x more common in women; 20-50 years of age
  - Autoimmune disease, with IgG antibodies (TRAb or TSI) that bind to and stimulate the TSH receptor on thyroid
    - 80% also have TPO antibodies
- Toxic multinodular goiter: multiple autonomous thyroid nodules
- Toxic adenoma: solitary, benign thyroid tumor
- TSH-secreting pituitary adenoma

TYPICAL LAB FINDINGS:

	TSH	Ft4	Ft3
Subclinical hyperthyroidism	Low	Normal	
Clinical hyperthyroidism	Elevated	Usually elevated	Elevated

S/S:

- Heat intolerance, weight loss, tremor, difficulty sleeping, anxiety, irritability, flushed skin, tachycardia
- Atrial fibrillation can occur in elderly
- Increased bone loss and risk of osteoporotic fracture

SPECIFIC TO GRAVE'S DISEASE:

- Graves opthalmopathy (exophthalmos or proptosis) – 30%
  - Lid retraction, periorbital edema, protrusion of eye
  - Can lead to discomfort, impaired vision
  - Due to cytokine production by infiltrating T cells (inflammation)
- Graves dermopathy - < 5%
  - Most frequent on lower legs
  - Typically skin is deep pink, with "orange-skin" appearance

THYROID STORM OR THYROTOXIC CRISIS:

- Life-threatening increase in severity of hyperthyroidism (uncommon)
- Usually precipitated in uncontrolled or poorly controlled pts by another medical problem (e.g. infection, surgery)
- Characterized by fever, tachycardia, confusion, N&V
- Fatality rate approx. 20%

HYPOTHYROIDISM: results from insufficient production of thyroid hormone

- Types:
  - Primary: level of thyroid gland
  - Secondary: suprathyroid (at hypothalamus or pituitary gland)
  - Congenital or acquired
- Can vary in severity from very mild to overt

CAUSES OF HYPOTHYROIDISM:

- **Hashimoto's** (chronic lymphocytic) thyroiditis (= inflammation of thyroid)
  - Most common cause of hypothyroidism
  - Older women at particular risk
  - Autoimmune disorder (raised circulating levels of thyroid peroxidase (TPO) antibody)
  - Thyroid cell destruction mediated primarily by cytotoxic T cells
  - Goiter may be present **early in disease**
- **Congenital hypothyroidism:** hypothyroidism in newborn infants (1:3000)
  - Results in severe mental + physical growth retardation if untreated
  - Early treatment is crucial for normal intellectual development
  - Clinical dx is difficult, in Canada we measure TSH levels in neonates
- **Juvenile myxedema:** hypothyroidism in children > 2 years
  - Results in linear growth retardation + delayed puberty if untreated
- **Myxedema coma:** end stage of poorly or un-controlled hypothyroidism
  - Almost always occurs in elderly and precipitated by factors that impair respiration

TYPICAL LAB FINDINGS:

	TSH	Ft4	Ft3
Subclinical hypothyroidism	Borderline elevated	Normal	
Overt hypothyroidism	Elevated	Low	

S/S: everything slows down

- Poor memory & concentration, slow pulse rate, myxedema
- Fatigue, feeling cold, weight gain + poor appetite, hair loss, constipation

THYROID DISORDERS IN PREGNANCY:

Hypothyroidism	Hyperthyroidism
• Increased risk of obstetrical complications (fetal death, gestational HTN) • Can result in cognitive defects (lower IQ defects, impaired psychomotor development) in offspring • Very important to detect and adequately treat hypothyroidism both before and during pregnancy	• If uncontrolled, risk to both mother and fetus: o Miscarriage, pre-term labor, HTN o Still birth, low birth weight, fetal goiter • In Graves Disease: maternal TRAb can cross placenta and cause fetal hyperthyroidism after 20 weeks gestation

POST-PARTUM THYROIDITIS (PPT): 5-10% of women past-partum

- Autoimmune disorder, usually mild and transient
- Significant risk of recurrent PPT in subsequent pregnancies
- Increased risk of developing primary hypothyroidism within 5-10 years