Academic lectures for general medicine
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SPECIAL PATHOPHYSIOLOGY

ENDOCRINE SYSTEM 2

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Figures and tables in this presentation were adapted from various printed and electronic resources and serve strictly for educational purposes.
Thyroid gland

- Physiological review
- Hyperthyroidism
- Congenital hypothyreoidism
- Hypothyreoidism in adulthood
- Goiter
- Thyroid tumors
Thyroid gland – anatomy and physiology

- **Largest endocrine organ in the body** synthetizing, storing, secreting thyroxine (T4) and triiodothyronine (T3) in response to TRH and TSH.
- **Butterfly-shaped organ** (weight 15–25 g) located at the base of the neck on the anterior surface of the trachea.
- **Lobules of spherical follicles** lined by cuboidal-to-flat follicular epithelial cells 50–500 um filled with colloid.
- **C cells** (produce calcitonin at the junction of the upper and middle third of both thyroid lobes)
Thyroid gland (TG) – anatomy and physiology

- **Axis:** hypothalamus (TRH) -> pituitary function (TSH) -> thyroid; iodine access important
- **Iodination of tyrosine (MIT = monoiodotyrosine, DIT = diiodotyrosine)**
- **Coupling MIT + DIT together to form lipophilic T4 (90%) & T3 (10%); storing them bound to TG**
- **Blood transport of T3 & T4 bound to transthyrenin (TBG), albumin & pre-albumin.**

- Increase of basal metabolic rate
- Improves cardiac contractility
- Increases the gain of catecholamines
- Increases bowel motility
- Increases speed of muscle contraction
- Decreases cholesterol (LDL)
- Required for proper fetal neural growth
Cellular action of T3 and T4

- Thyroid hormone transporter
  - D3
  - D2/D1
  - T3
  - T4

- Cytoplasm
  - Corepressor
  - Coactivator

- Nucleus
  - RXR
  - TR
  - TRE

- Activation by D3

- Mitochondrial Action
  - mtDNA
  - T3
  - T4

- Nuclear Action
  - T3
  - T4

- Hypothalamus
  - TRH

- Pituitary gland
  - TSH

- Thyroid gland
  - T4 & T3

- Peripheral tissues
  - T4 & T3
# Physiologic Effects of Thyroid Hormones

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<tr>
<th>Target Tissue</th>
<th>Effect</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Heart</td>
<td>Chronotropic</td>
<td>• Increase number and affinity of adrenergic receptors.</td>
</tr>
<tr>
<td></td>
<td>Inotropic</td>
<td>• Enhance responses to circulating catecholamines.</td>
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<tr>
<td></td>
<td></td>
<td>• Increase proportion of alpha-myosin heavy chain (with higher ATPase activity).</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>Catabolic</td>
<td>• Stimulate lipolysis</td>
</tr>
<tr>
<td>Muscle</td>
<td>Catabolic</td>
<td>• Increase protein breakdown.</td>
</tr>
<tr>
<td>Bone</td>
<td>Developmental and metabolic</td>
<td>• Promote normal growth and skeletal development; accelerate bone turnover.</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Developmental</td>
<td>• Promote normal brain development.</td>
</tr>
<tr>
<td>Gut</td>
<td>Metabolic</td>
<td>• Increase rate of carbohydrate absorption.</td>
</tr>
<tr>
<td>Lipoprotein</td>
<td>Metabolic</td>
<td>• Stimulate formation of LDL receptors.</td>
</tr>
<tr>
<td>Other</td>
<td>Metabolic Calorogenic</td>
<td>• Stimulate oxygen consumption by metabolically active tissues (exceptions: adult brain, testes, uterus, lymph nodes, spleen, anterior pituitary).</td>
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<tr>
<td></td>
<td></td>
<td>• Increase of metabolic rate.</td>
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Hyperthyroidism
# Hyperthyroidism: Causes

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<th>Etiologic Classification</th>
<th>Pathogenetic Mechanism</th>
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<td>Graves' disease</td>
<td>Thyroid-stimulating hormone receptor-stimulating antibody (TSH-R [stim] Ab)</td>
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<tr>
<td>Toxic multinodular goiter</td>
<td>Autonomous hyperfunction</td>
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<tr>
<td>Follicular adenoma</td>
<td>Autonomous hyperfunction</td>
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<tr>
<td>Pituitary adenoma</td>
<td>TSH hypersecretion (rare)</td>
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<tr>
<td>Pituitary insensitivity</td>
<td>Resistance to thyroid hormone (rare)</td>
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<td>Hypothalamic disease</td>
<td>Excess TRH production</td>
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<td>Germ cell tumors: choriocarcinoma, hydatidiform mole</td>
<td>Human chorionic gonadotropin stimulation</td>
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<td>Struma ovarii (ovarian teratoma)</td>
<td>Functioning thyroid elements</td>
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<tr>
<td>Metastatic follicular thyroid carcinoma</td>
<td>Functioning metastases</td>
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<td><strong>Thyroid gland destruction</strong></td>
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<tr>
<td>Lymphocytic thyroiditis</td>
<td>Release of stored hormone</td>
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<tr>
<td>Granulomatous (subacute) thyroiditis</td>
<td>Release of stored hormone</td>
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<tr>
<td>Hashimoto's thyroiditis</td>
<td>Transient release of stored hormone</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
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<tr>
<td>Thyrotoxicosis medicamentosa, factitia</td>
<td>Ingestion of excessive exogenous thyroid hormone</td>
</tr>
</tbody>
</table>
Hypertyroidism - symptoms

- Alertness, emotional lability, nervousness, irritability, poor concentration
- Proximal **muscle weakness** (quadriceps, biceps), fatigability
- **Hyperkinesia**; rapid speech; fine tremor,
- **Tachycardia, palpitations**, widened pulse pressure, accentuated first heart sound;
- **Dyspnea**
- Voracious appetite, **weight loss**
- Hyperdefecation (increased frequency of bowel movements)
- **Sweating**, skin is fine, moist, warm;; onycholysis; Fine & abundant hair;
- **Exophthalmos**; periorbital edema, lid lag, proptosis, staring
- **Heat intolerance**
Clinical findings in hyperthyroidism

- **Symptoms**
  - Alertness, emotional lability, nervousness, irritability, poor concentration
  - Proximal muscle weakness (quadriceps), fatigability
  - Hyperkinesia, fine tremor, rapid speech,
  - Palpitations, tachycardia, atrial fibrillation (resistant to digitalis), widened pulse pressure, accentuated first heart sound; Dyspnea
  - Voracious appetite, weight loss,
  - Hyperdefecation (increased frequency of bowel movements)
  - Sweating, skin is fine, moist, warm; heat intolerance; fine & abundant hair; onycholysis
  - Periorbital edema, lid lag, proptosis, stare, chemosis

- **Laboratory findings**
  - Suppressed serum TSH level
  - Elevated serum free thyroxine, elevated serum total T4, elevated resin T3 or T4 uptake, elevated free thyroxine index
  - Increased radioiodine uptake by thyroid gland (some causes)
  - Increased basal metabolic rate (BMR)
  - Decreased serum cholesterol level
Graves disease

- Most common cause of hyperthyroidism
- anti-TSH receptor antibodies with uncontrolled stimulatory effect on thyroid

**Dg:**
- Symptoms of hyperthyroidism
- Extreme **exophthalmos** and **goiter**
- ↓↓ TSH, n↑ T₄, anti-TSH Ab
- I¹²³ increased uptake.

**Treatments**
- Pharm – Propothyouracil, Methimazole, Propranolol
- Surgical – Subtotal Thyroidectomy
- Radiation – RAI ablation [I¹³¹(µCi/g) x weight / %RAIU]

Graves' dermopathy - lumpy, reddish thickening of the skin (accumulation of proteins).

Exophthalmos, goiter

Graves' acropachy (watch glass nail shape)

Graves' Disease and Hashimoto's Thyroiditis - Autoimmune Disorders Associated with them

- Autoimmune response against different epitopes in thymocytes may lead hyperthyroidism and hypothyroidism

**Endocrine disorders**
- Diabetes mellitus
- Hypoadrenalism,
- autoimmune (Addison's disease)
- Orchitis or oophoritis, autoimmune
- Hypoparathyroidism, idiopathic

**Nonendocrine disorders**
- Pernicious anemia
- Vitiligo
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Immune thrombocytopenic purpura
- Myasthenia gravis
- Sjögren's syndrome
- Primary biliary cirrhosis
- Chronic active hepatitis
Graves' Disease and Hashimoto's Thyroiditis

Histological comparisons

**Normal**
- Inactive
- Active
  - Colloid
  - Reabsorption lacunae
  - Parafollicular cells

**Graves' disease**
- Scanty colloid
- Packed follicles with tall columnar epithelium
- Scattered lymphocytes

**Adenoma**
- Histologically very similar to normal thyroid
- Fibrous capsule
- Compressed rim of residual normal thyroid

**Hashimoto's disease**
- Numerous lymphocytes and plasma cells
- Scattered follicles, often markedly eosinophilic cytoplasm (Hürthle cells)
- Marked fibrosis in late stages
Graves disease

- Perspiration
- Facial flushing
- Loss of weight
- Palpable lymph nodes
- Shortness of breath
- Breast enlargement (Gynecomastia in male)
- Warm, velvety skin
- Muscle wasting
- Rapid pulse
- Warm and moist palms
- Oligomenorrhea or amenorrhea
- Localized myxedema
- Exophthalmos
- Goiter (may have thrill and bruit)
- Palpitation, tachycardia
- Increased appetite
- Diarrhea (occasional)
- Tremor
- Clubbing of fingers (in some patients with severe exophthalmos)
- Muscular weakness, fatigability
Less perspiration than in Graves disease
Patient usually 40 years or older
Less muscle wasting than in Graves disease
Marked shortness of breath
Less breast enlargement or gynecostasia than in Graves disease
Weight loss less than in Graves disease
Very rapid pulse
Palms less moist than in Graves disease
Patient usually postmenopausal
Ankle edema (heart failure)

Nervousness, excitability, restlessness, emotional lability, insomnia
Less than in Graves disease
No ophthalmopathy
Nodular goiter
Less skin warmth than in Graves disease
Marked tachycardia, atrial fibrillation common, heart failure common
Less tremor than in Graves disease
No finger clubbing or nail changes
Less muscular weakness than in Graves disease
No pretibial myxedema

Blood tests:
- Decreased TSH
- Increased free T₃
- Increased total T₄
- Undetectable TSH-i-receptor antibodies
- Decreased total and HDL cholesterol
- Increased sex hormone-binding globulin
- Increased estradiol (in men and women)
- Increased osteocalcin and bone-specific alkaline phosphatase

Laboratory findings:
- Basal metabolic rate: Moderately elevated (25%-30%)
- ¹³¹I uptake: Elevated less than in Graves disease (40%-55%) localized in functioning adenoma

Moderately severe ophthalmopathy
Testing for resiliency
Severe progressive ophthalmopathy
Hypothyroidism
Hypothyroidism

Forms of hypothyroidism
• Primary – malfunction in thyroid gland
• Secondary – pituitary failure
• Tertiary – Hypothalamic failure
• Peripheral resistance – inresponsiveness of tissues to T3 & T4

- Laboratory findings
  - Increased serum TSH level
  - Decreased serum free thyroxine, decreased serum total T4 and T3, decreased T3 or T4 uptake; decreased free thyroxine index
- Cause is determined by geography
- Diagnosis
  - Low FT4, High TSH (Primary, check for antibodies)
  - Low FT4, Low TSH (Secondary or Tertiary, TRH stimulation test, MRI)
- Treatment
  - Levothyroxine (T4) due to longer half life

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<th>SECONDARY CENTRAL (HYPOPITUITARY) HYPOTHYROIDISM</th>
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<td>PIT-1 mutations: Deficiency of TSH, growth hormone, and prolactin</td>
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<tr>
<td>PROP-1 mutations: Deficiency of TSH, GH, prolactin, LH, FSH, ACTH</td>
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<tr>
<th>Thyrotropin-releasing hormone (TRH) deficiency; Isolated?</th>
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<td>Multiple hypothalamic deficiencies (e.g., septo-optic dysplasia)</td>
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<tr>
<td>TRH unresponsiveness Mutations in TRH receptor</td>
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<tr>
<td>TSH deficiency - Mutations in β-chain</td>
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<tr>
<td>Multiple pituitary deficiencies (e.g., craniopharyngioma)</td>
</tr>
<tr>
<td>TSH unresponsiveness Gsα mutation (e.g., type IA)</td>
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<tr>
<td>Mutation in TSH receptor</td>
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<th>PRIMARY HYPOTHYROIDISM (THYROID)</th>
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<td>Defect of fetal thyroid development: Aplasia, hypoplasia, ectopia (dysgenesis)</td>
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<tr>
<th>Defect in thyroid hormone synthesis (e.g., goitrous hypothyroidism):</th>
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<tr>
<td>Iodide transport defect, Thyroid peroxidase defect, Thyroid oxidase mutations: homozygotic permanent; heterozygotic - transient Thyroglobulin synthesis defect, Deiodination defect</td>
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<tr>
<th>Defect in thyroid hormone transport</th>
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<tr>
<td>Iodine deficiency (endemic goiter): Neurologic type, Myxedematous type</td>
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<tr>
<th>Maternal antibodies: Thyrotropin receptor–blocking antibody (TRBAb, thyrotropin-binding inhibitor immunoglobulin)</th>
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<tr>
<td>Maternal medications: Radioiodine, iodides; Propylthiouracil, methimazole; Amiodarone</td>
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1. Congenital hypothyroidism (CH)

- **Df:** thyroid hormone deficiency present at birth; if untreated for months lead to growth delay and permanent mental retardation (cretins).
- **Oc:** 1 from 4000 newborns has severe deficiency; 1 from 2300 have mild to partial!!! Nongoitrous CH "most prevalent inborn endocrine disorder"
- **Et:** in past endemic, now gen., dev. tox. (sporadic)
  - Environmental iodine deficiency (endemic in past);
  - Hypoplasia; Athyreosis
  - Toxic damage: ? organochlorine insecticides, dioxin-like chemicals in the milk of mothers
  - Immuno-damage - maternal antibodies

**Genetic:**
- Defect of T4 and T3 synthesis in normal gland
- Deficiency of TSH, Resistance to TSH,
- Iodine trapping defect, thyroglobulin, and iodotyrosine deiodinase deficiency

**Sy:** CH goitrous (CHG)   CH nonhoitrous (CHNG)
- **Mild to severe thyroid deficiency**
- No or only negligible effects after birth: excessive sleeping, reduced interest in nursing, poor muscle tone, low or hoarse cry, infrequent bowel movements, exaggerated jaundice, low body temperature.

- > ½ of cases of severe hypothyroidism were recognized in the first month of life. Poor delayed grow,
- After years untreated: recognizable facial and body features of cretinism. severe mental impairment, with an IQ < 80

**Very severe fetal deficiency (athyreosis):**
- Larger anterior fontanel, persistence of a posterior fontanel, umbilical hernia, large tongue (macroglossia).
- Growth retardation, short stature, short neck, swelling of face/hands, legs, cool skin, dry skin,
- Neurological retardation: slow reflexes, possible deafness

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<tr>
<th>Type</th>
<th>Locus</th>
<th>Gene</th>
<th>Result</th>
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<tbody>
<tr>
<td>CHNG1</td>
<td>2q13</td>
<td>TSH-R; TSH receptor</td>
<td>TSH resistance</td>
</tr>
<tr>
<td>CHNG2</td>
<td>14q31.1</td>
<td>PAX8; Paired box gene; transcription factor; expression of thyroid-specific genes.</td>
<td>Thyroid dysgenesis</td>
</tr>
<tr>
<td>CHNG3</td>
<td>15q25.3</td>
<td>?</td>
<td>TSH resistance</td>
</tr>
<tr>
<td>CHNG4</td>
<td>1p13.2</td>
<td>TSHB (beta chain of heterodimeric TSH)</td>
<td>TSH resistance</td>
</tr>
<tr>
<td>CHNG5</td>
<td>5q35.1</td>
<td>NKX2-5; NK2 homeobox 5; Tissue specific gene expression</td>
<td>Thyroid dysgenesis</td>
</tr>
</tbody>
</table>
Cretinism

- mental and physical retardation resulting from untreated congenital hypothyroidism, usually due to iodine deficiency from birth because of low iodine levels in the soil and food sources.

Endemic goitre and cretinism in Bolivia. The mother is goitrous but otherwise normal. The daughter is goitrous, mentally retarded, deaf mute, but of normal stature and clinically euthyroid.
2. Postpubertal hypothyroidism - myxedema

- **Decreased vigor**, lethargy, slow thinking, mental clouding, depression
- Fatigability, coldness, weight gain, constipation, low voice
- **Round puffy face**: periorbital edema, swelling of face/hands/legs, slow reflexes, myxedema
- Enlarged tongue, slow speech; hoarseness,
- Cold, dry, thick, scaling skin; Feeling cold, cold intolerance
- Dry, coarse, brittle thickened hair; hair loss; longitudinally ridged nails;
- **Loss of appetite**: weight gain, constipation
- Ascites; pericardial effusion; ankle edema
- Menorrhagia; diminished libido
- **Hypokinesia**: generalized muscle weakness; delayed relaxation of deep tendon reflexes
- Cardiac enlargement; bradycardia, indistinct heart sounds
Postpubertal hypothyroidism - myxedema

**Symptoms**
- Decreased vigor, *lethargy*, slow thinking, mental clouding, depression
- **Round puffy face; periorbital edema,**
- Enlarged tongue, slow speech; hoarseness,
- **Cold, dry, thick, scaling skin:** dry, coarse, brittle thickened hair; hair loss; longitudinally ridged nails; feeling cold, cold intolerance
- Loss of appetite; **weight gain,** constipation
- **Ascites;** pericardial effusion; **ankle edema**
- Menorrhagia; diminished libido
- **Hypokinesia:** generalized muscle weakness; delayed relaxation of deep tendon reflexes
- Cardiac enlargement; bradycardia, indistinct heart sounds

Myxedema: periorbital puffiness closing eyes, after thyroxine therapy (pericardial effusion).

Myxedema, coarse hair, dry skin, pasty colored face: elderly woman stopped medication

Post-operative myxedema. Basal metabolic rate 40%
**Thyroid**

- Dry, brittle hair
- Lethargy, memory impairment, slow cerebration (psychoses may occur)
- Edema of face and eyelids
- Thick tongue, slow speech
- Cold intolerance
- Enlarged heart, poor heart sounds
- Diminished perspiration
- Diastolic hypertension (frequently)
- Coarse (follicular keratoses), cool, dry yellowish (carotenemia) skin
- Slow pulse
- Menorrhagia (amenorrhea may occur late in disease)
- Ascites
- Weakness
- Reflexes, prolonged recovery

- Macroglossia, showing dental impressions

- Characteristic facies in hypothyroidism: coarse features; thick lips; dry skin; puffy eyelids; dull, lethargic expression; coarse hair

- Pudgy hands; chipped nails; dry, wrinkled skin; hyperkeratosis of elbow
Goiter
Goiter

- **Endemic goiter**
  - Caused by dietary deficiency of Iodide
  - Increased TSH stimulates gland growth
  - Also results in cretinism

- **Goiter in developed countries**
  - Hashimoto’s thyroiditis
  - Subacute thyroiditis

- **Other causes**
  - Excess Iodide (Amiodarone, Kelp, Lithium)
  - Adenoma, Malignancy
  - Genetic / Familial hormone synthesis defects
Etiology of goiter

I. Goiter associated with hypo & euthyroidism
   ▪ Iodine turnover
     ▪ Iodine deficiency; defective transport
     ▪ Iodine excess (secretion of hormone)
   ▪ Hormone biosynthesis
     ▪ Defective organification of iodide: absence/reduction of peroxidase; abnormal peroxidase
     ▪ Thyroglobulin (TG): synthesis of an abnormal TG; impaired proteolysis of TG
     ▪ Iodotyrosine: defective deiodination
     ▪ Congenital disorders
   ▪ Exogenous substances and drugs (hormone biosynthesis)
     ▪ Goitrogen in diet, drinking water or medication
     ▪ Thioamides (propylthiouracil, methimazole, carbimazole), Thiocyanates (nitroprusside), Anilide derivatives (sulfonylureas, sulfonamides, aminosalicylic acid, phenylbutazone, aminogluthethimide)
     ▪ Lithium (secretion of hormone)
   ▪ Resistance
     ▪ Pituitary and peripheral resistance to thyroid hormone (receptor defects)
Goiter

II. Goiter associated with hyperthyroidism
- Graves' disease (TSH-R [stim] Ab stimulation of gland)
- Toxic multinodular goiter (Autonomous hyperfunction)
- Germ cell tumor (hCG stimulation of gland)
- Pituitary adenoma (TSH overproduction)
- Thyroiditis ("injury" due to infiltration, and edema)

Thyroid storm

- **Causes**
  - Surgery, Radioactive Iodine, Therapy, Severe Illness

- **Diagnosis**
  - Clinical – tachycardia, hyperpyrexia, thyrotoxicosis symptoms
  - Labs (Low TSH, High T4, FT4)

- **Treatment**
  - Propranolol IV vs. Verapamil IV, Propylthiouracil, Methimazole
  - Sodium Iodide, Acetamenophen, cooling blankets
  - Plasmapheresis (rare), Surgical (rare)
**Euthyroid goiter**

- **Cause** is an inactivation of 5’-deiodinase, resulting in conversion of FT$_4$ to rT$_3$.
- **Occurs** in critically ill patients; may occur with DM, malnutrition, iodine loads, or medications (Amiodarone, PTU, glucocorticoids).
- **Treatment**
  - Avoid above medications
  - Treat primary illness
  - T$_3$, T$_4$ not helpful
**SUBACUTE THYROIDITIS**

- Malaise
- Dysphagia
- Pain radiating to ear
- Thyroid gland visibly enlarged (more on one side)

**CHRONIC LYMPHOCYTIC THYROIDITIS AND FIBROUS THYROIDITIS**

- Hashimoto thyroiditis
- Riedel thyroiditis

**Microscopy of Hashimoto Thyroiditis**
- Mixture of hyperplastic and atrophic follicles with diffuse lymphocytic infiltration
- Thyroid peroxidase and thyroglobulin antibody concentrations can be measured in serum

**Microscopy of Riedel Thyroiditis**
- Macrophage and eosinophilic infiltration with atrophy of follicles (arrows) and marked diffuse fibrosis

**131I (radioactive iodine) uptake**
- Very low

**131I**
- ↑

**Thyroglobulin**
- ↑

**Block by inflammation**
- Enlarged thyroid gland
- Displacement and/or compression of trachea and esophagus
Thyroid gland neoplasms
PAPILLARY THYROID CARCINOMA

May have multiple foci

Two different parts of tumor with prominent papillary projections

May metastasizes chiefly to regional lymph nodes (cervical and mediastinal)

Rarely to skeleton

Very rarely to brain

PRIMARY TUMOR

FOLLICULAR THYROID CARCINOMA

Usually presents as a solitary nonfunctioning nodule

PRIMARY TUMOR

Metastasis

Hematogenous spread to lung and bone

Rare neck lymph node involvement
MEDULLARY THYROID CARCINOMA

Hürthle cell thyroid carcinoma

- Most common site of metastasis: Skeleton
- Less common sites of metastasis: Liver, Kidney
- Metastasis: Skull, to lung (discrete nodule), and to lung (discrete nodule)
- Secondary to regional lymph nodes

Cervical lymph nodes are usually involved
ANAPLASTIC THYROID CARCINOMA

Giant cells

Spindle cells

Compression and invasion of trachea

Rapidly growing tender tumor of neck

TUMORS METASTATIC TO THE THYROID

1. Kidney
2. Lung
3. Breast
4. Head and neck malignancy
5. Gastrointestinal tract (colon, esophagus, stomach)
6. Melanoma
Model of thyroid carcinogenesis

Risk factors (exposure to radiation) genomic instability through direct and indirect mechanisms, early genetic alterations involve MAPK signalling pathway increases genomic instability, activation of RET or BRAF later genetic alterations involve signalling pathways, cell-cycle regulators and various adhesion molecules.

Accelerating the interactions between genomic instability and genetic alterations promotes progression from well-differentiated to undifferentiated thyroid carcinoma.

Three distinct pathways are proposed for neoplastic proliferation of thyroid follicular cells, including hyperfunctioning follicular thyroid adenoma (tumours that are almost always benign), follicular thyroid carcinoma and papillary thyroid carcinoma.

Underexpression of the cyclin-dependent-kinase inhibitor p27KIP1 and overexpression of cyclin D1 are strong predictors of lymph-node metastases in papillary thyroid carcinomas.

Most poorly differentiated and undifferentiated thyroid carcinomas are derived from pre-existing well-differentiated thyroid carcinoma through additional genetic events including catenin (CTNNB1 gene) nuclear accumulation and p53 inactivation, but de novo occurrence might also occur. GNAS1, guanine nucleotide-binding -subunit 1; PPARG, peroxisome proliferation-activated receptor-; TSHR, thyroid stimulating - hormone receptor.
Thyroid follicular cells express cell-surface receptors for thyroid-stimulating hormone (TSH) — these receptors are seven-transmembrane-domain G-protein-coupled receptors. TSH activates this receptor and G proteins such as GS at the cell surface of follicular cells, and induces intracellular production of cyclic AMP (cAMP) by adenylyl cyclase. cAMP stimulates the cAMP-dependent protein kinase A (PKA), which in turn phosphorylates cytoplasmic and nuclear target proteins. One PKA substrate is the nuclear transcription factor CREB, which activates the transcription of cAMP-responsive genes after being phosphorylated by PKA.

Growth factors (GF) induce receptor-tyrosine kinase (RTK) dimerization, resulting in phosphorylation of specific tyrosine residues. Phosphorylation activates intracellular signal transduction pathways, recruiting various transcription factors that are involved in cell proliferation and differentiation, such as MYC and ELK1.


Autocrine and paracrine growth-factor signalling has been implicated in thyroid carcinogenesis. Growth factors and their receptors that signal between stromal and endothelial/carcinoma cells include: fibroblast growth factor (FGF)—FGF receptor (FGFR), epidermal growth factor (EGF)—EGF receptor (EGFR), hepatocyte growth factor (HGF)—MET, and vascular endothelial growth factor (VEGF)—VEGFR. In normal endothelial cells, β-catenin binds the cytoplasmic domain of E-cadherin as an adhesive component, mediating the Wnt signalling pathway. Defects in Wnt signalling occur in carcinoma cells, resulting in β-catenin stabilization and translocation to the nucleus, and expression of cyclin D1 and MYC. Additionally, loss of E-cadherin is associated with increased invasion and cell motility. Fibronectin is upregulated at the protein and mRNA levels in papillary thyroid carcinoma, but its effect on tumour cell proliferation, adhesion and migration remains to be determined.
Cyclin D1 and cyclin E1 cooperate to control the G1 to S phase transition through interactions with retinoblastoma protein (RB). Cyclin D1 and cyclin E1 heterodimerize with cyclin-dependent kinases (CDKs) 4 and 2, respectively, to inactivate the tumour suppressor RB by phosphorylation. Active RB functions as a repressor of E2F transcription factors, whereas inactivation (phosphorylation) of RB allows E2F transcriptional activity. E2F activates the transcription of genes that are involved in the G1 to S phase transition, such as DNA polymerase and thymidine kinase. The CDK inhibitors p16INK4A, p21CIP1 and p27KIP1 impair the activity of cyclin–CDK complexes, thereby preventing phosphorylation of RB. The CDK inhibitors therefore function as tumour suppressors. The tumour suppressor p53 induces cell-cycle arrest by upregulating p21CIP1, which initiates apoptosis. The function of p53 is controlled by negative regulators, including MDM2. The MDM2 protein targets p53 for ubiquitin-mediated degradation, constituting a feedback loop to maintain a low concentration of p53 in the cells.