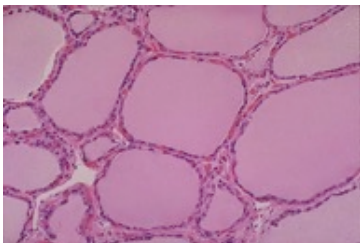
# THYROID GLAND



**NORMAL THYROID GLAND –** Consists of follicles lined by an epithelium that produces colloid on stimulation from TSH & are filled w/ colloid. Colloid contains ***thyroglobulin***, a protein that plays a central role in the synthesis & storage of Thyroid Hormone.

## IODINE

- *Iodine is necessary for the synthesis of thyroid hormone*
- Recommended minimum intake: 150 micrograms/day
- Intake of less than 50 micrograms/day is associated with **goiter**
- High iodine levels inhibit iodine oxidation & organification
- Iodine excess inhibits thyroglobulin proteolysis: **Wolff-Chaikoff Effect** – *reduction of TH levels due to ingestion of large amounts of iodine*

## THYROID HORMONE: Synthesis

- An ***iodide pump*** transports $I^-$ from blood into thyrocytes
- Iodide is oxidized into iodine ($I_2$) by a **peroxidase enzyme** in the follicular cell membrane
- ***Organification*** of iodine: Tyrosine residues of TG react w/ Iodine to form monoiodotyrosine (MIT) & diiodotyrosine (DIT) – Coupling of MIT & DIT forms thyroid hormones $T_3$ & $T_4$
- ***Iodinated TG*** is stored in the follicular lumen until secretion
- When stimulated, thyrocytes take back iodinated TG by endocytosis
- TG is hydrolyzed in lysosomes, releasing MIT, DIT, $T_3$ & $T_4$
  - $T_3$ & $T_4$ are secreted into circulation
  - Residual MIT & DIT are deiodinated by thyroid deiodinase, releasing iodine which is reused
- Most $T_3$ & $T_4$ is bound to **thyroxin-binding globulin (TBG)**
- In peripheral tissues, $T_4$ is converted to $T_3$ (more active form)

## THYROID HORMONE: Hypothalamus-Pituitary-Thyroid Axis

- ↓ $T_3$ & $T_4$ stimulate the release of TRH from the hypothalamus & TSH from the anterior pituitary causing $T_3$ & $T_4$ levels to rise
- ↑ $T_3$ & $T_4$ levels then feedback to suppress the secretion of both TRH & TSH
- TSH binds to the TSH-R on the thyroid follicular epithelium, which causes activation of G proteins, & cAMP-mediated synthesis & release of $T_3$ & $T_4$
- In the periphery, $T_3$ & $T_4$ interact w/ the thyroid hormone receptor (TR) to form a hormone-receptor complex that translocates to the nucleus & binds to thyroid response elements (TREs) on target genes to initiate transcription

## THYROID HORMONE FUNCTION

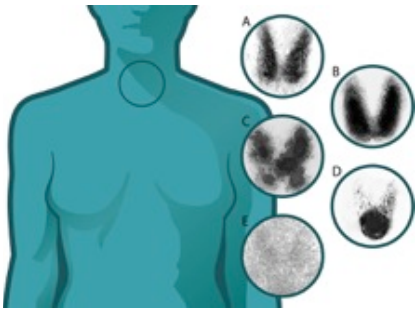
↑ SNS via ↑expression of β-adrenergic-R
↑ BMR via ↑synthesis of $Na^+K^+$ATPase

- **↑ 4 B's:** Brain maturation, Bone growth, $\beta_1$-adrenergic effects, Basal metabolic rate
- **Maturation of CNS** in perinatal period & Regulation of CNS activity
- **Bone growth** & maturation
  - Acts in synergy w/ GH & somatomedin (IGF)
  - Actions are on the growth plate
- Up-regulation of **$\beta_1$-adrenergic receptors** in the heart
- **↑Cardiac output & Ventilation**
- **↑Oxygen consumption, ↑Basal Metabolic Rate** *(except in brain, spleen, gonads)* **& ↑Heat production**
- Stimulation of all **Metabolic Activities**
  - ↑ Glucose absorption in GI, glycogenolysis, gluconeogenesis, glucose oxidation, lipolysis, protein synthesis/degradation
  - Overall effect on protein metabolism: Catabolic

| HYPERTHYROIDISM | HYPOTHYROIDISM |
|---|---|
| ↑ Metabolic rate | ↓ Metabolic rate |
| Weight loss | Weight gain |
| Negative Nitrogen balance | Positive Nitrogen balance |
| ↑ Heat production | ↓ Heat production |
| Heat intolerance, sweating | ↓ Cardiac Output |
| ↑ Cardiac Output *(↓ Diastolic BP)* | Hypoventilation (↓Ventilation) |
| Hyperventilation | *Constipation* |
| *Diarrhea + malabsorption* | Lethargy, mental slowness |
| Tremor, anxiety, hyperactivity | Drooping eyelids |
| Wide, staring gaze + lid lag | Growth & mental retardation *(perinatal)* |
| *Hyperglycemia* | *Hypercholesterolemia* |
| *Hypocholesteremia* | |

# THYROTOXICOSIS & HYPERTHYROIDISM

- **Thyrotoxicosis**: hyper-metabolic state caused by elevated levels of CIRCULATING/FREE $T_3$ & $T_4$
- **Thyrotoxicosis + HYPERTHYROIDISM** due to ***hyper-functioning/overactive*** thyroid gland (majority of cases)
  - Radioactive iodine uptake (RAIU) is increased
  - Tx: **THIONAMIDE** (*methimazole*) interferes w/ hormone synthesis by inhibiting oxidation of $I^-$ to $I_2$
- **Thyrotoxicosis NOT associated w/ Hyperthyroidism** due to the release of ***preformed hormone*** from damaged thyroid gland, ***exogenous source***, etc.
- **HEPATIC FAILURE** → ↓TBG levels → ↓ total TH (but **normal levels** of **free** $T_3$ & $T_4$)
- **PREGNANCY**: ↑TBG → ↑ total TH (but **normal levels** of **free** $T_3$ & $T_4$)




**RADIOACTIVE IODINE UPTAKE (RAIU) TEST**
**A: Normal** – diffuse, even uptake
**B: Graves Disease** – diffuse, increased uptake
**C: Toxic Multinodular Goiter** – multifocal areas, some increased & some decreased
**D: Toxic Adenoma** – single focal area with increased uptake; "hot" nodule
**E: Thyroiditis (Hashimoto)** – diffuse, decreased uptake

## HYPERTHYROIDISM: Thyrotoxicosis Due to Increased Thyroid Function

- **PRIMARY HYPERTHYROIDISM (↓TSH)**
  - **Graves Disease (60-85% of cases)**
  - **Toxic Adenoma** *(benign tumor)*
  - **Toxic Multinodular Goiter**

  **The 3 Most Common Causes of Hyperthyroidism**
  - Iodine-Induced Hyperthyroidism
  - Neonatal Thyrotoxicosis due to Maternal Graves Disease
- **SECONDARY HYPERTHYROIDISM (↑TSH)**
  - Rare
  - Most caused by TSH-producing Pituitary Adenoma
  - **Secondary Hyperthyroidism is associated with ↑ TSH levels, while all other causes of hyperthyroidism are associated with ↓ TSH levels**

## THYROTOXICOSIS NOT ASSOCIATED W/ HYPERTHYROIDISM

- Thyroid gland activity is **depressed**
  - ↑ $T_3/T_4$ will cause negative feedback → ↓TSH
- Usually caused by **injury to thyroid** w/ release of preformed hormone or **extra-thyroidal source** of TH:
  - Hashimoto's Thyroiditis – destruction of thyroid
  - Radiation
  - Exogenous TH intake
  - ***Struma ovarii***: Teratoma of the ovaries predominantly composed of mature thyroid tissue; ectopic thyroid function producing large amounts of $T_3/T_4$ *(can lead to hyperthyroidism)*
  - Metastatic follicular carcinoma
- **Radioactive Iodine Uptake: Near absent**

## THYROTOXICOSIS: Clinical Manifestations

- SKIN: Red, warm, sweaty (heat intolerance), thinning of hair, hyperpigmentation
  - **DERMOPATHY (PRETIBIAL MYXEDEMA)** – *localized lesions of the skin resulting from deposition of hyaluronic acid, usually confined to the pretibial area*; almost exclusively in **GRAVES DISEASE**
- EYES: Staring eyes & lid lag
  - **OPTHALMOPATHY (EXOPHTHALMOS)** occurs almost exclusively in **GRAVES DISEASE**
- CARDIOVASCULAR: ↑ Cardiac output w/ ↑HR, widened pulse pressure, **a-fib**, High Output Cardiac Failure
  - FYI **– 3 Most Common Causes of A-Fib:** Thyrotoxicosis, Ischemic Heart Disease, Mitral Valve Disease
- METABOLIC: Weight loss due to hyper-metabolism, *hypocholesterolemia*, *hyperglycemia*
- RESPIRATORY: ↑$O_2$ consumption & $CO_2$ production → *hyperventilation*; respiratory muscle weakness → dyspnea, tracheal compression from large goiter, exacerbation of asthma, ↑ pulmonary pressure
- GASTROINTESTINAL: gut hyper-motility → *frequent BM*, malabsorption, hyperphagia
- HEMATOLOGIC: normocytic normochromic anemia
- GENITOURINARY: Female – menstrual irregularities & anovulatory cycles; Male – gynecomastia, ↓libido & abnormal spermatogenesis
- BONE: ↑resorption & fracture risk
  - **THYROID ACROPACHY** – *unusual clubbing of the fingers;* associated with **GRAVES DISEASE**
- NEUROPSYCHIATRIC: tremor, behavioral & personality changes, psychosis, agitation, depression, anxiety, restlessness, irritability, emotional lability, insomnia, cognitive impairment

## HYPERTHYROIDISM IN OLD PATIENTS

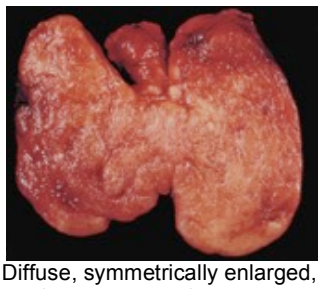
- Older patients may have fewer & blunted manifestations: ***Apathetic Hyperthyroidism***
- ***3 Most Common Signs in Elderly:** weight loss, SOB, a-fib*
  - ***Depression** is often a common symptom in elderly patients*
- *Toxic Multinodular Goiter & Solitary Toxic Adenomas (Plummer Disease) are less frequently seen than Graves, but they represent a higher proportion of hyperthyroidism in the elderly*

## THYROID STORM: Hyperthyroidism

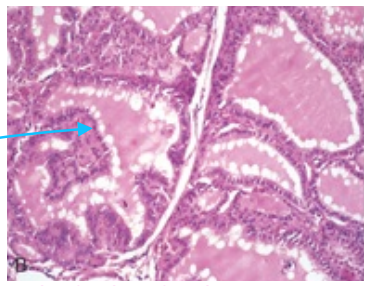
- **MEDICAL EMERGENCY**
- **Most common in patients w/ GRAVES DISEASE**
- **ABRUPT** onset of severe hyperthyroidism, associated with ***fever/hyperthermia & extreme tachycardia***
- Patients may die of cardiac *arrhythmias*
- Precipitated by any form of stress – *surgery, infection, cessation of anti-thyroid medication*

## **GRAVES DISEASE:** Autoimmune **(IgG)**-Mediated Hyperthyroidism (↑TH, ↓TSH)

- **Most Common cause of HYPERTHYROIDISM**
- More common in **FEMALES of childbearing age** (10:1 female to male ratio) – *Affecting 2% of women in the US*
- **CLINICAL MANIFESTATIONS:** *Those of hyperthyroidism + diffuse goiter, **ophthalmopathy (exophthalmos)**, dermopathy (**pretibial myxedema**), thyroid acropachy (clubbing of the fingers)*
- **PATHOGENESIS**
  - *Type II Hypersensitivity Reaction – Non-Cytotoxic*
  - **Cell-mediated Autoimmunity** directed at 4 thyroid antigens: Thyroglobulin, Thyroid Peroxidase, $Na^+$-$I^-$ symporter, TSH receptor
  - **THYROID-STIMULATING IMMUNOGLOBULIN (TSI)** is the most important AutoAb
    - Binds to & activates **TSH receptors → ↑$T_3$ & $T_4$ → ↓ TSH**
    - TSI is specific of Graves Disease, whereas other AutoAb are found in other autoimmune thyroid conditions, such as Hashimoto Thyroiditis
- Graves has a **genetic predisposition** – *40% concordance rate in monozygotic twins*
  - Susceptibility to disease linked to polymorphisms in immune-related genes, CTLA4 & PTPN22
  - Susceptibility also linked to HLA-DR3 allele
- ASSOCIATED AUTOIMMUNE DISORDERS
  - Close to 10% of patients w/ Graves & 14% of those w/ Hashimoto thyroiditis have co-existing autoimmune conditions
  - **RHEUMATOID ARTHRITIS is the most common associated autoimmune disorder**
  - Others: Pernicious anemia, SLE, Addison Disease, Celiac Disease, Vitiligo
- **DIAGNOSIS**: Diffuse increased uptake w/ Radioactive Iodine Uptake (RAIU)



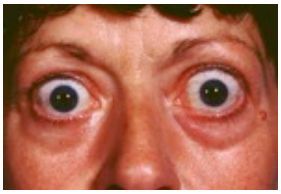
Diffuse, symmetrically enlarged, beefy-red Thyroid Gland

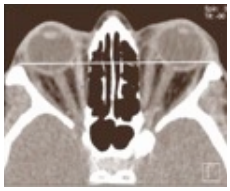


**HYPERPLASTIC FOLLICLES** w/ tall epithelial cells & **scalloped edges** – *scalloping is result of active reabsorption of thyroid hormone (hyperactivity of the gland)*
Flat Follicular Cells = Inactive; **Tall Follicular Cells = Overactive**

### **GRAVES' OPTHALMOPATHY** (EXOPTHALMOS – Bug eyed)

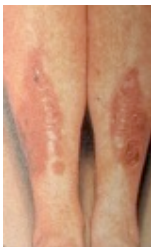
- Volume of both extra-ocular muscles & retro-orbital connective & adipose tissue is increased due to inflammation & accumulation of hydrophilic **GAGs**, mainly ***hyaluronic acid***
- Pathogenesis is not due to hyperthyroidism, but is **AUTOIMMUNE**. ***Thus, reducing TH secretion DOES NOT lead to improvement of Graves' ophthalmopathy/exophthalmos.***
  - Soft tissues in the orbit express TSH-R; Anti-TSH-R AutoAb trigger inflammatory reaction
  - T lymphocytes secrete cytokines IGF-γ & TNF-α that stimulate fibroblasts to produce GAG
  - Accumulation of GAG results in swelling of orbital soft tissues & extra-ocular muscles, producing exophthalmos & other ocular complications
- **SMOKING** increases the risk
- **GRAVES' DERMOPATHY/PRETIBIAL MYXEDEMA** has the same pathogenesis





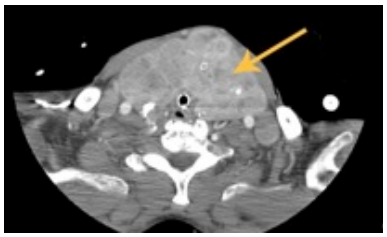
### **GRAVES' DERMOPATHY** (PRETIBIAL MYXEDEMA)

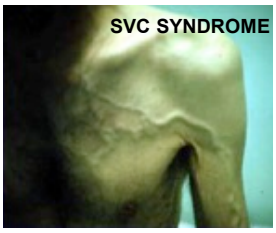
- Waxy, discolored induration of the skin on the anterior aspects of the legs, extending to dorsal surface of feet
- Accompanied by *burning sensation & itching*
- Due to accumulation of mucin in the dermis & subcutis



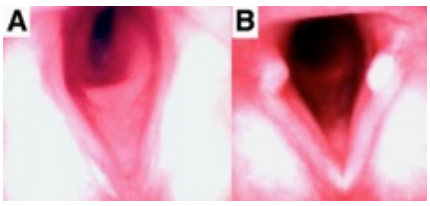
# GOITER: Non-Toxic (Euthyroid), Toxic (Hyperthyroid), Nodular (Hot or Cold)

- Enlargement of the thyroid gland due to hypertrophy & hyperplasia of follicular cells
- Most Common Manifestation of Thyroid Disease
- Compensatory phenomenon caused by **impaired synthesis of thyroid hormone** – *Compensatory response is usually sufficient to establish a euthyroid state, but most severe cases lead to hypothyroidism*
  - **Most Frequent Cause: IODINE DEFICIENCY** – *Without iodine, the thyroid cannot make TH. TSH will increase due to lack of negative FB leading to hyperplasia of the thyroid.*
- SIGNS & SYMPTOMS due to **mass effect** & compression on neck/mediastinal organs: *dysphagia* (esophagus), *breathing difficulty* (trachea), *SVC syndrome* (collateral circulation leads to distention of veins in neck/chest wall)
- 2 Types: Diffuse Non-Toxic (simple) & Multinodular






**A:** Tracheal narrowing due to goiter
**B:** Trachea after thyroidectomy



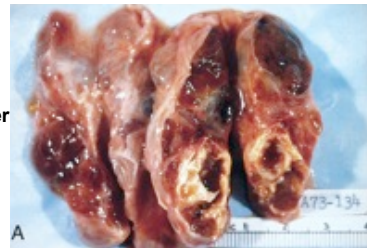

## 1. DIFFUSE NON-TOXIC (SIMPLE) GOITER

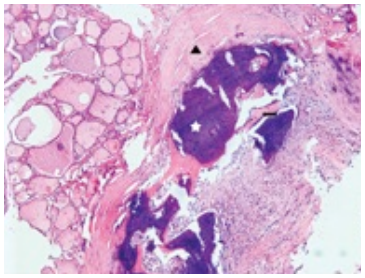
- ***Diffusely*** enlarged without nodules
- Most patients are EUTHYROID
- **ENDEMIC GOITER** is the most frequent – *Caused by **iodine deficiency** in regions of the world w/ low levels of iodine in water, soil, & food*
- SPORADIC GOITER is often idiopathic, but few cases are caused by ingestion of goitrogens or hereditary defects in thyroid synthesis
  - **Known Goitrogens:** vegetables of the Cruciferae family – cabbage, brussel sprouts, cauliflower, turnips, ***cassava root***

## 2. MULTINODULAR GOITER

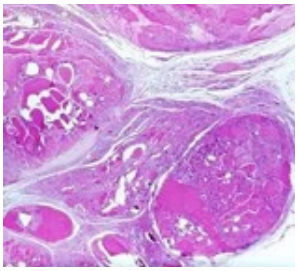
- Multilobulated, ***asymmetrically*** enlarged thyroid gland (up to 2kg)
- Develop from long-standing simple goiters through episodes of **hyperplasia** & involution
- Nodules can be polyclonal or monoclonal (autonomous growth)
- Follicles & vessels rupture leading to **scarring, calcification, hemosiderin deposition, & cysts**
- 10% develop a **hyper-functioning, autonomous nodule: *Toxic multinodular goiter*** or ***Plummer Syndrome*** *(Solitary Toxic Adenoma)*
  - "*Thyrotoxicosis due to autonomous nodule development in long-standing goiter is Plummer Syndrome, not Graves Disease*"

**Nodular appearance of multinodular goiter w/ patchy scarring & cystic changes**

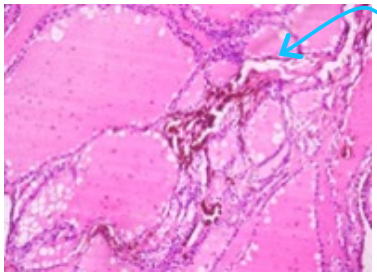




**Scarring & Calcification**



**Hyperplastic Nodules**



**HEMOSIDERIN**

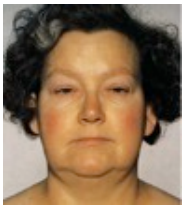
# HYPOTHYROIDISM

- Insufficient production of thyroid hormone
- PRIMARY: due to injury/dysfunction of the thyroid gland; ↑**TSH**
- SECONDARY: due to hypothalamic/pituitary injury; ↓**TSH**
- **CAUSES in Industrialized Countries:**
  - **HASHIMOTO THYROIDITIS** is the most common cause of **HYPOTHYROIDISM** in the US (95% of cases)
  - 2nd most common cause – **Therapeutic Ablation of the Thyroid**
- More common in **FEMALES** (F:M ratio is 10:1)
- **CLINICAL MANIFESTATIONS:** Fatigue, weight gain, cold intolerance, *constipation*, SOB, hair thinning (both hyper & hypo), cramping, menstrual irregularities, **Carpal tunnel syndrome,** slow deep-tendon reflexes, ***enlargement of thyroid gland (goiter) if due to Hashimoto Thyroiditis***
- **LABORATORY FINDINGS**
  - ↑ TSH in most cases
  - **TSH level is the most sensitive screening test for Hypothyroidism**
  - ↓ Circulating free $T_4$ & $T_3$
  - ↑ Total & LDL cholesterol

## HYPOTHYROIDISM IN OLD PATIENTS

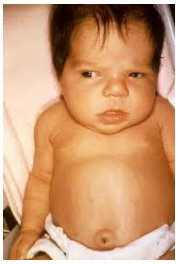
- Older patients may be misdiagnosed w/ dementia or depression
- DEMENTIA: progressive & irreversible cognitive decline caused by loss of neurons in regions playing key role in cognition
  - **3 Most Common Causes of Dementia:** Alzheimer disease, Dementia w/ Lewy bodies, Vascular dementia (multi-infarct dementia)

## MYXEDEMA CRISIS: Hypothyroidism



- Severe, prolonged hypothyroidism which may lead to coma
- **CLINICAL PRESENTATION:** dull face, swollen eyes, *doughy skin texture* from accumulation of mucopolysaccharides, thinned hair, thickened tongue, enlarged heart, ileus (paralysis of the bowel)
- **MEDICAL EMERGENCY:** Without prompt treatment, patients become hypothermic & comatose

## CRETINISM: Hypothyroidism of Neonates/Infants



- Due to ***congenital hypothyroidism (CH)***
- **CAUSE:** iodine deficiency in areas w/ low levels of iodine in soil, water, food supply
- **CLINICAL PRESENTATION:** impaired skeletal & CNS development
  - *Severe MR, short stature, coarse facial features, macroglossia, umbilical hernia*
- **PATHOGENESIS**
  - Maternal Hypothyroidism: Maternal $T_3$/$T_4$ are essential for fetal brain development
  - Impairment in fetal brain development is more severe if maternal thyroid insufficiency occurs early during pregnancy before the fetal thyroid gland develops
- **PREVENTION:** Screening for maternal hypothyroidism by measuring Blood TSH

### OTHER FORMS OF CONGENITAL HYPOTHYROIDISM

- **Most Common form of CH: Agenesis or hypoplasia of thyroid gland (85%)**
- Hereditary forms (15%) caused by genetic defects involving: iodine transport, organification of iodine, iodotyrosine coupling to form $T_3$/$T_4$, germ line mutations of TSH-R gene – *All lead to impaired synthesis of TH & present w/ goiter & hypothyroidism (dishormonogetic goiter)*
- **PREVENTION:** Screening newborns

### NEWBORN SCREENING FOR CONGENITAL HYPOTHYROIDISM

- Most neonates born w/ CH have no detectable physical signs
- Delayed diagnosis leads to severe MR
- Neonatal screening is preformed by measuring **blood $T_4$ following by TSH *if $T_4$ is below 10th percentile***
  - $T_4$ is more sensitive, TSH is more specific
- In most clinical settings, blood is obtained by a heel prick 24 hours after birth

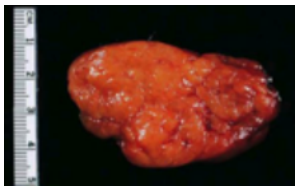
# THYROIDITIS

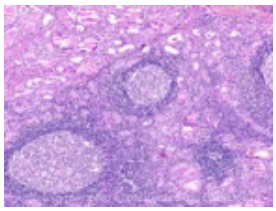
*Hashimoto, Subacute Granulomatous (DeQuervain), Subacute Lymphocytic (Painless), Riedel*

## 1. HASHIMOTO THYROIDITIS: Hypothyroidism

> ***Note**: Initial **hyper**thyroidism due to breakdown of follicle cells releasing TH, but with further destruction of the gland it progresses to **hypo**thyroidism.*

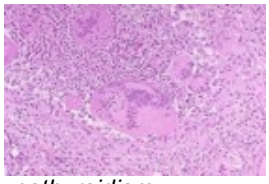
- **"CHRONIC LYMPHOCYTIC THYROIDITIS"**
- **Autoimmune disease against the thyroid gland** (associated w/ HLA-DR5)
- **Most Common cause of PRIMARY HYPOTHYROIDISM in industrialized countries**
- Most common in **40-60 y/o WOMEN**
- **CLINICAL PRESENTATION:** *hypothyroidism & a symmetrically enlarged thyroid*
- **PATHOGENESIS:** Circulating AutoAb against thyroid Ag (Thyroglobulin, *thyroid peroxidase*, TSH)
  - ***Type IV Hypersensitivity Reaction – DTH***
  - Breakdown of peripheral tolerance to thyroid AutoAg results in progressive autoimmune destruction of thyrocytes by infiltrating cytotoxic T cells, locally releasing cytokines, or by Ab-mediated cytotoxicity
- Strong **genetic component**, similar to Graves disease
- **GROSS:** *Diffusely enlarged thyroid gland*
- **HISTOPATHOLOGY**
  - **Lymphoid follicles** – dense lymphocyte infiltrate w/ prominent germinal centers
  - **HURTHLE CELLS** – a metaplastic response of follicular cells to **chronic inflammation**
  - **Atrophy of follicles** w/ sparse residual follicles & diffuse lymphocytic infiltration (Late Stage)
- **DIAGNOSIS**: Serum antibodies to **THYROID PEROXIDASE (TPO)**



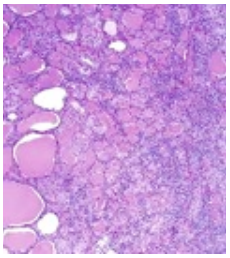
## 2. SUBACUTE GRANULOMATOUS/DeQUERVAIN THYROIDITIS: Transient Dysfunction

- Autoimmune process triggered by ***VIRAL INFECTIONS*** (**Mumps**, measles, adenovirus, **Coxsackie** (follows URI)
- Often in **Females 40-50 y/o**
- Most frequent in the **SUMMER**
- Most Common cause of **Painful Thyroid Gland**
- **CLINICAL PRESENTATION:** ***TENDER THYROID***, *PAINFUL dysphagia, flu-like S/S*
- **HISTOPATHOLOGY:** **GRANULOMAS** w/ multinucleated giant cells & some destruction of thyroid follicles
- Self-limiting within 2 months, without sequelae – *Does not progress to chronic thyroiditis & hypothyroidism*
- **TREATMENT**: β-blockers & NSAIDs



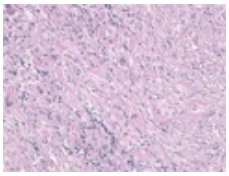
## 3. SUBACUTE LYMPHOCYTIC (PAINLESS) THYROIDITIS: Transient Thyroid Dysfunction

- Uncommon
- Probably of **autoimmune** pathogenesis
- Considered a less aggressive variant of Hashimoto thyroiditis
- **Most common in POST-PARTUM WOMEN**
- **PRESENTATION:** *enlarged thyroid* and/or *hyperthyroidism* (due to destruction of the gland)
- **HISTOPATHOLOGY:** Dense lymphocytic infiltration **WITHOUT** germinal centers or Hurthle cells; there is limited destruction of thyroid follicles w/ release of TH into circulation
- Self-limiting within a couple of months w/out sequalae



## 4. RIEDEL THYROIDITIS: Scarring of Thyroid & Surrounding Neck Structures

- **Rare**; *chronic inflammation with extensive fibrosis extending to surrounding structures*
- One of the manifestations of **IgG4-related disease**
- Most often in **Young Females**
- **PRESENTATION:** "hard as wood, non-tender thyroid"**;** *airway obstruction, dysphonia, hoarseness, hypothyroidism, hypoparathyroidism, dysphagia, stridor from tracheal compression*
- **HISTOPATHOLOGY:** extensive **scarring** extending into surrounding structures – fibrous tissue w/ deposition of **abundant collagen** (eosinophilic acellular bands)
- *Tx: Tamoxifen & corticosteroids*



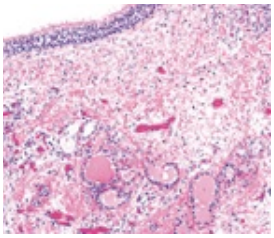
> *Hard, non-tender thyroid + involvement of local structures*
> **DDx:** Riedel Thyroiditis or Anaplastic Carcinoma
> **Riedel Thyroiditis** – **Young** & **Anaplastic Carcinoma** – **Elderly**

# NEOPLASMS OF THE THYROID

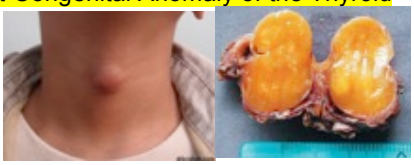
## THYROGLOSSAL DUCT

- The thyroid gland develops from the floor of the pharynx at the base of the tongue at a point later indicated by the foramen cecum - @ 3-4 weeks gestastion
- The thyroid descends in front of the primitive pharynx gut as a bilobed diverticulum along the ***thyroglossal duct***
- It migrates to the base of the neck, passing anterior to the hyoid bone
- During migration, the thyroid remains connected to the tongue by a narrow canal, the thyroglossal duct

## THYROGLOSSAL CYST



- Any part of the thyroglossal duct may persist & give rise to a fistula or a cyst
- Presents as *anterior neck mass*
- **MIDLINE** location
- Most Common *clinically significant* Congenital Anomaly of the Thyroid



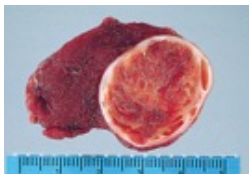
## THYROID NODULES

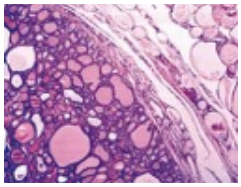
- Incidence: 5% in the general population
- **BENIGN 95%,** Malignant 5%
- ***MALIGNANT TUMORS:** *solitary*, in **younger male patients**, history of **prior radiation**, **COLD** on RAIU test

"**C**" for **C**old – **C**oncerning for **C**ancer

## FOLLICULAR ADENOMA

- **COMMON, BENIGN tumor of thyroid originating from follicular epithelium**
- Usually detected on palpation during **routine physical examination** – *painless*
- Vast majority are ***non-functional*** (aka they do not synthesize or release increased quantities of TH)
  - A small subset of follicular adenomas are ***functioning:*** **Toxic Adenomas**
- NOT A PRECURSOR OF THYROID CARCINOMA!!
- **TYPICAL GROSS APPEARANCE:** Well-circumscribed follicles, ENCAPSULATED (fibrous tissue), cut surface similar to normal thyroid parenchyma
- **HISTOPATHOLOGY:** *similar to follicular carcinoma* – differential based on evaluation of **capsular invasion** in thyroidectomy specimen, indicative of follicular carcinoma;
- **TREATMENT:** Surgical resection is curative
- **Clinical Vignette**: *35 y/o female is prepped for a hemithyroidectomy because of a painless, palpable neck mass. Histological findings demonstrate a single large nodule on the superior pole of the left lobe, which on frozen sections shows benign colloid follicles. The nodule is surrounded by bands of fibrous tissue. What is the most likely diagnosis?*





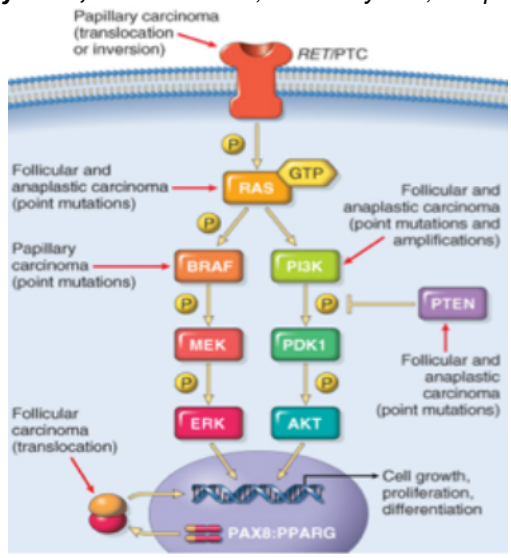
***Differentiating Follicular Carcinoma from Follicular Adenoma requires histologic evidence of capsular or blood vessel invasion, or documented metastasis. **Follicular Adenomas** have a fibrous capsule that circumferentially surrounds the neoplastic follicles & no capsular invasion is seen. **Follicular Carcinomas** demonstrate capsular invasion that may be minimal or widespread. The presence of vascular invasion is also a feature of carcinomas.*

## TOXIC (Functioning) FOLLICULAR ADENOMA

- Harbor somatic **GOF** mutations of the **TSH-R signaling pathway**, usually TSHR & GNAS, that cause follicular cells to secrete thyroid hormone ***independent of TSH stimulation***
  - Same mutations in Toxic Multinodular Goiter
  - *TSHR & GNAS are rare in follicular carcinoma, consistent w/ the fact that toxic adenomas & toxic multinodular goiter are NOT pre-malignant*
- Manifest w/ *hyperthyroidism*
- In contrast to non-functional follicular adenomas, toxic adenomas will show up as a **HOT** nodule RAIU because these adenomas are highly active & secreting TH

# THYROID CARCINOMA

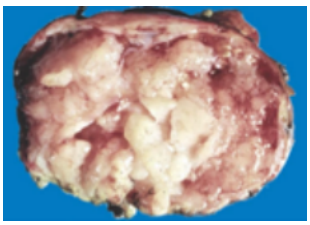
***Papillary: 80%,*** *Follicular: 15%, Medullary: 4%, Anaplastic: 1%*

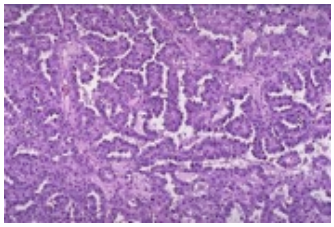


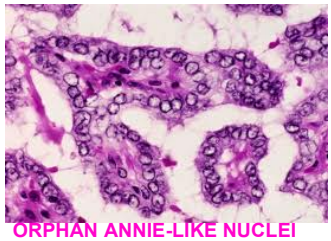

## PAPILLARY CARCINOMAS

- Most Common type of **Thyroid Carcinoma** (75-85%), accounting for the majority of all thyroid cancers
- *Malignant neoplasm characterized by the formation of numerous, irregular,* ***finger-like projections*** *(papillary!) of fibrous stroma that are covered w/ a surface layer of neoplastic epithelial cells*
- Most common between ages of **25-50** & associated w/ **exposure ionizing radiation in childhood**
  - *High incidence w/ Gardner Syndrome*
- **PRESENTATION**: *Asymptomatic* palpable nodule, **COLD** nodule on RAIU
- **PATHOGENESIS**
  - GOF mutations involves genes encoding the RET or NTRK1 RTKs; or genes in the serine/threonine kinase BRAF within the MAPK pathway
- **LYMPHATIC spread** to cervical **Lymph Nodes**
- **MICROSCOPIC: ORPHAN ANNIE-LIKE NUCLEI, PSAMMOMA BODIES**
- EXCELLENT PROGNOSIS even in the presence of nodal involvement – *95% survival at 10 years*

"**P**" for **P**apillary –for **P**sammoma





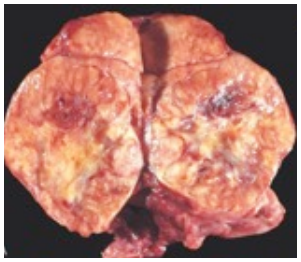


**ORPHAN ANNIE-LIKE NUCLEI**
*White clearing in center of nuclei*

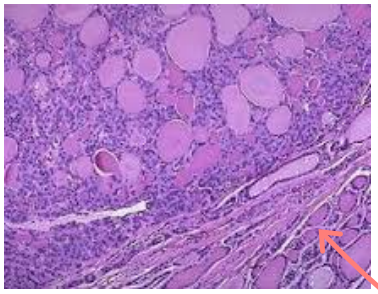
**PSAMMOMA BODIES**
*Concentric, layered calcification*

## FOLLICULAR CARCINOMAS

- 2nd most common type of Thyroid Carcinoma
- **PRESENTATION**: *Slow growing* palpable nodule, **COLD** on RAIU
- **PATHOGENESIS**
  - Mutations that activate RAS or $PI_3K$/AKT arm of the RTK signaling pathway
- **HEMATOGENOUS (VASCULAR) SPREAD** – *different from most carcinomas*; metastases to bone, lungs, etc.
- Follicular carcinomas lack the nuclear features (Orphan Annie-like) of Papillary Carcinoma & psammoma bodies are not present
- *50% survival at 10 years*



Cut surface of a **Follicular Carcinoma** w/ substantial replacement of the lobe of the thyroid. The tumor has a **light-tan appearance** & contains small foci of **hemorrhage**.

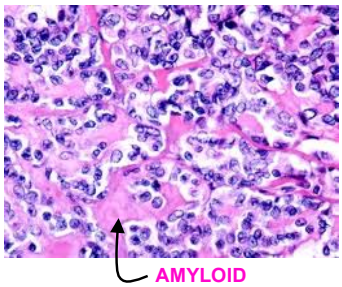


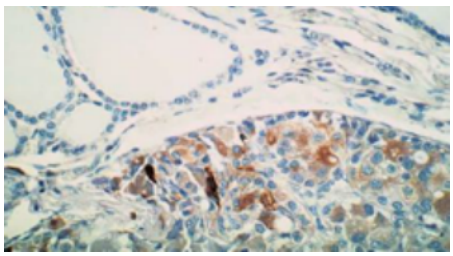
Follicular architecture is similar to normal thyroid gland & follicular adenomas, but there is evidence of **CAPSULAR INVASION**

## MEDULLARY CARCINOMA

- Originates from C cells (aka parafollicular cells of the thyroid)
  - C cells secrete Calcitonin
- Deposition of **AMYLOID** in the tumor
  - Amyloid is derived from Calcitonin secreted by the tumor cells
- **DIAGNOSIS & SCREENING:** ELEVATED SERUM CALCITONIN → *Hypocalcemia*
  - Immunohistochemistry for calcitonin is used
- **Most cases are Sporadic (80%)**, remaining cases are associated with MEN2A *(parathyroid involvement, thyroid involvement, pheochromocytoma)* & MEN2B *(pheochromocytoma, thyroid involvement, neuroglioma, marfanoid)*
- *65% survival at 10 years*
- **Clinical Vignette:** *40 y/o M c/o "lump in his neck." Physical exam yields a solitary, firm thyroid nodule on the left side. The nodule does not enhance during imaging. Lab studies demonstrated normal TSH, $T_3$, & $T_4$ levels but elevated calcitonin. Examination of biopsy showed neoplastic cells that most closely relate to... Parafollicular cells*

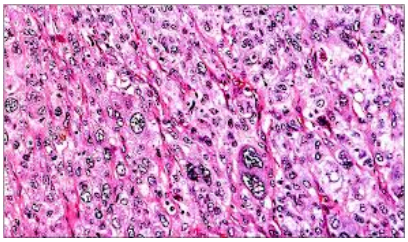
***Remember**: Calcitonin "tones down" serum $Ca^{2+}$*



Immuno stain for **Calcitonin**

## ANAPLASTIC CARCINOMA



- < 5% of cases
- Undifferentiated, highly aggression tumor
- Mean age is **65 years (elderly)**
- *Rapidly enlarging, bulging neck mass invading surround structures*
- Originates from de-differentiation of less malignant neoplasms
- POOR PROGNOSIS – *Almost always fatal*

*Hard, non-tender thyroid + involvement of local structures*
**DDx:** Riedel Thyroiditis or Anaplastic Carcinoma
**Riedel Thyroiditis** – **Young** & **Anaplastic Carcinoma** – **Elderly**