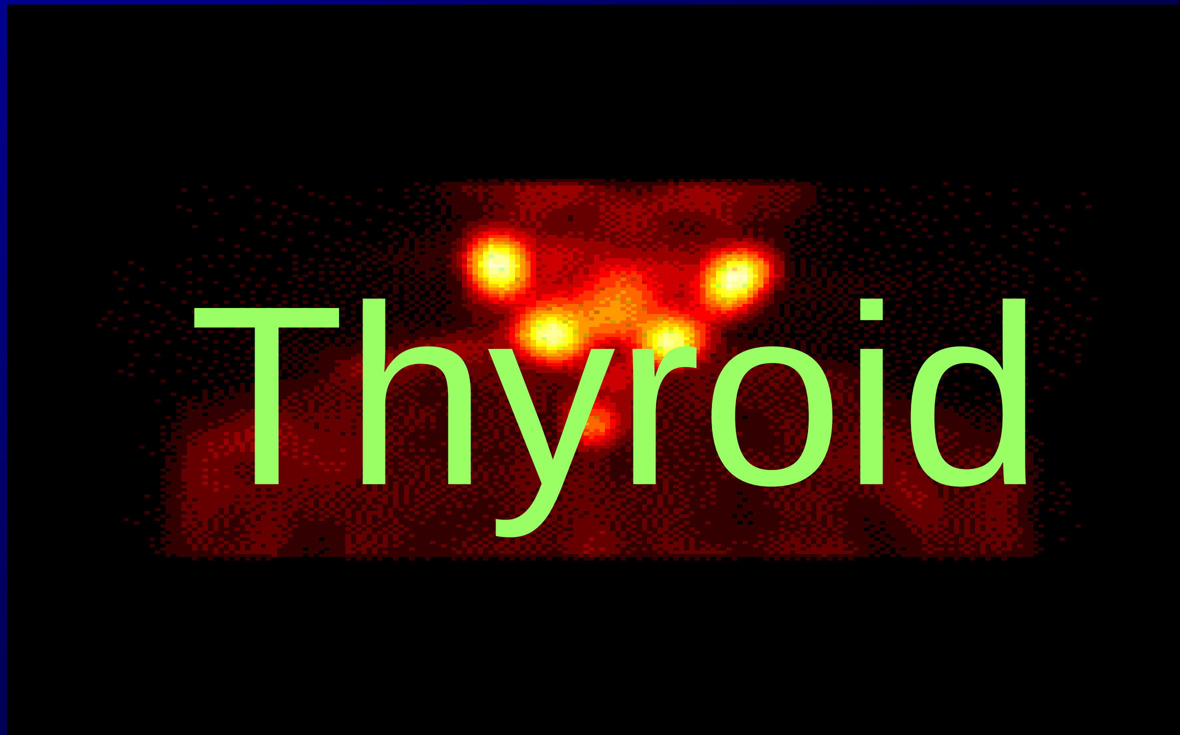


Tarek Mahdy

Ass Professor of Endocrine And Bariatric Surgery

Mansoura Faculty Of Medicine

Mansoura - Egypt

The Thyroid Gland

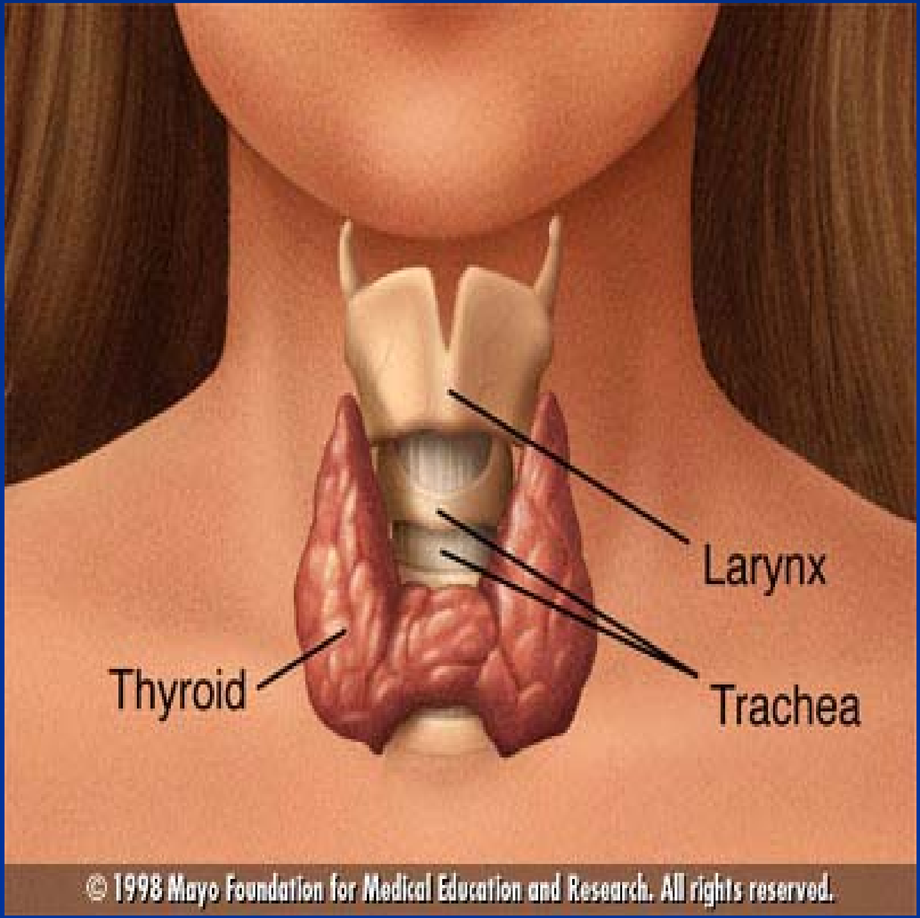
Named after the thyroid cartilage

(Greek: Shield-shaped)

The Thyroid Gland

- Vercelloni 1711: "*a bag of worms*" whose eggs pass into the esophagus for digestive purposes
- Parry 1825: "*a vascular shunt*" to cushion the brain from sudden increases in blood flow

Thyroid Embryology

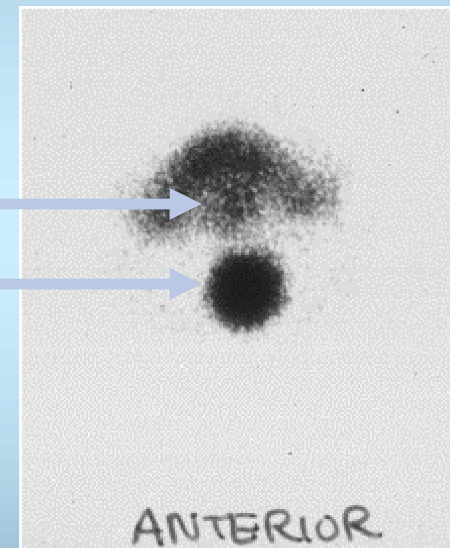


- Medial portion of thyroid gland
  - Arises frome the endodermal tissue of the base of tongue posteriorly, the foramen cecum - lack of migration results in a retrolingual mass
  - Attached to tongue by the thyroglossal duct - lack of atrophy after thyroid descent results in midline cyst formation (thyroglossal duct cyst)
  - Descent occurs about fifth week of fetal life - remnants may persist along track of descent
- Lateral lobes of thyroid gland
  - Derived from a portion of ultimobranchial body, part of the fifth branchial pouch from which C cells are also derived (calcitonin secreting cells)

Lingual Thyroid (failure of descent)

Verification that lingual mass is thyroid by its ability to trap I^{123}

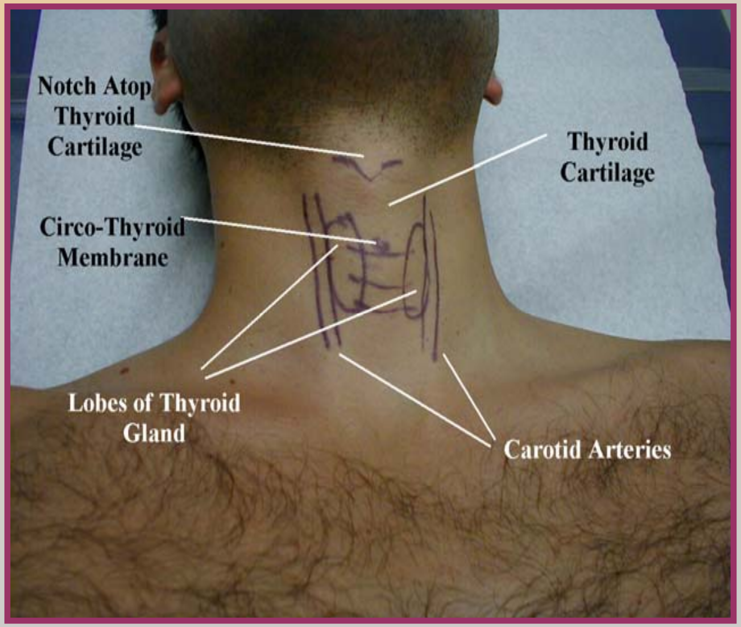
Lingual thyroid
Chin marker



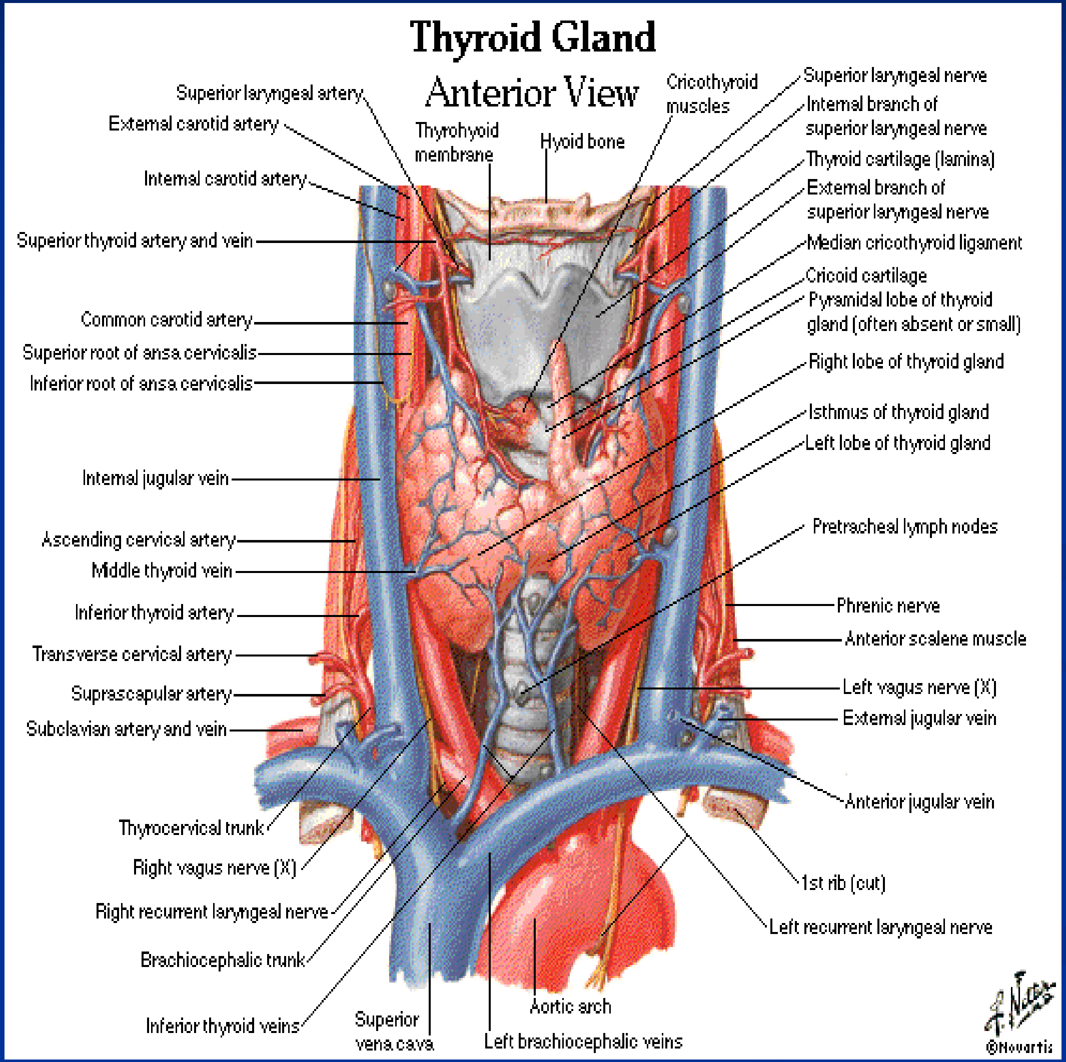
Significance: **May be only thyroid tissue in body (~70% of time), removal resulting in hypothyroidism; treatment consists of TSH suppression to shrink size**

Anatomy, physiology and pathology of the thyroid gland

Anatomy


Notch Atop Thyroid Cartilage
Thyroid Cartilage
Circo-Thyroid Membrane
Lobes of Thyroid Gland
Carotid Arteries

Thyroid Anatomy

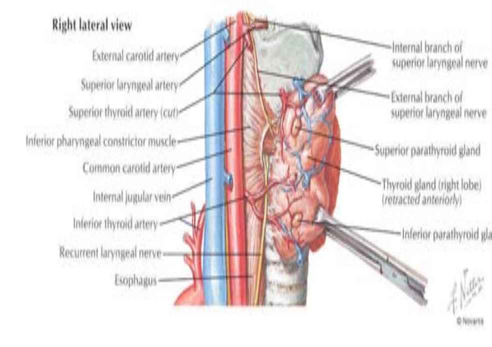


Brownish-red and soft during life Usually weighs about 25-30g (larger in women)
Surrounded by a thin, fibrous capsule of connective tissue
External to this is a “false capsule” formed by pretracheal fascia

Right and left lobes
United by a narrow isthmus, which extends across the trachea anterior to second and third tracheal cartilages

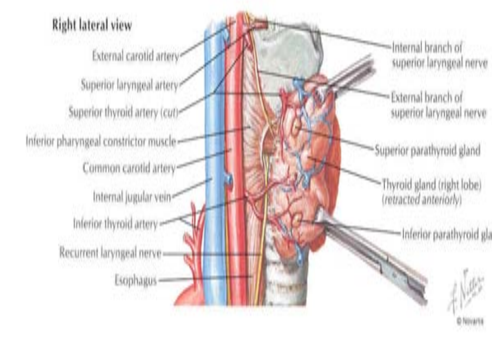
In some people a third “pyramidal lobe” exists, ascending from the isthmus towards hyoid bone

Position and relations



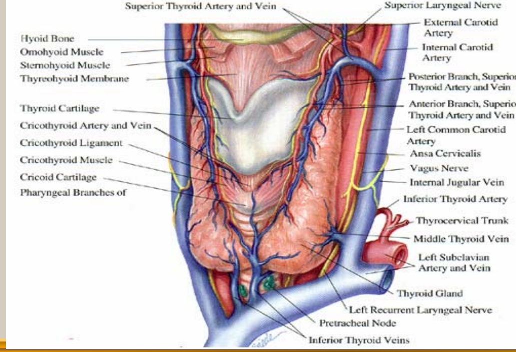
- Clasps anterior and lateral surface of ***pharynx, larynx, oesophagus and trachea*** “like a shield”
- Lies deep to ***sternothyroid*** and ***sternohyoid*** muscles
- ***Parathyroid glands*** usually lie between posterior border of thyroid gland and its sheath (usually 2 on each side of the thyroid), often just lateral to anastomosis between vessel joining superior and inferior thyroid arteries
- ***Internal jugular vein*** and ***common carotid artery*** lie postero-lateral to thyroid

Position and relations



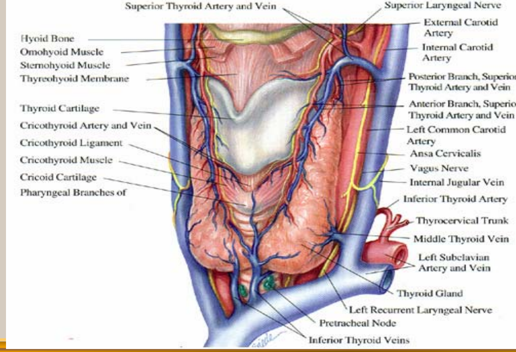
- ***Recurrent laryngeal nerve*** is an important structure lying between trachea and thyroid
  - may be injured during thyroid surgery → ipsilateral VC paralysis, hoarse voice
- Each lobe
  - pear-shaped and ~5cm long
  - extends inferiorly on each side of trachea (and oesophagus), often to level of 6th tracheal cartilage
- Attached to arch of cricoid cartilage and to oblique line of thyroid cartilage
  - moves up and down with swallowing and oscillates during speaking

Arterial supply



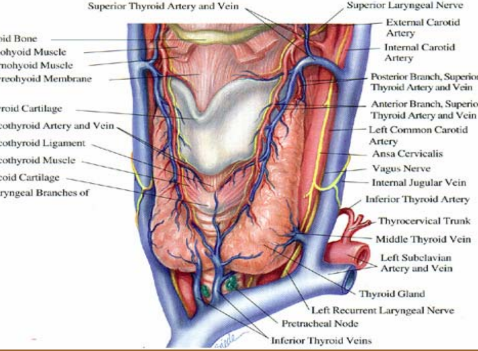
- highly vascular
- main supply from ***superior and inferior thyroid arteries***
  - lie between capsule and pretracheal fascia (false capsule)
- all thyroid arteries anastomose with one another on and in the substance of the thyroid, but little anastomosis across the median plane (except for branches of superior thyroid artery)

Arterial supply



- superior thyroid artery
  - first branch of ECA
  - descends to superior pole of gland, pierces pretracheal fascia then divides into 2-3 branches
- inferior thyroid artery
  - branch of thyro-cervical trunk
  - runs superomedially posterior to carotid sheath
  - reaches posterior aspect of gland
  - divides into several branches which pierce pretracheal fascia to supply inferior pole of thyroid gland
  - intimate relationship with recurrent laryngeal nerve
  - in ~10% of people the thyroid ima artery arises from aorta, brachiocephalic trunk or ICA, ascends anterior to trachea to supply the isthmus

Venous drainage

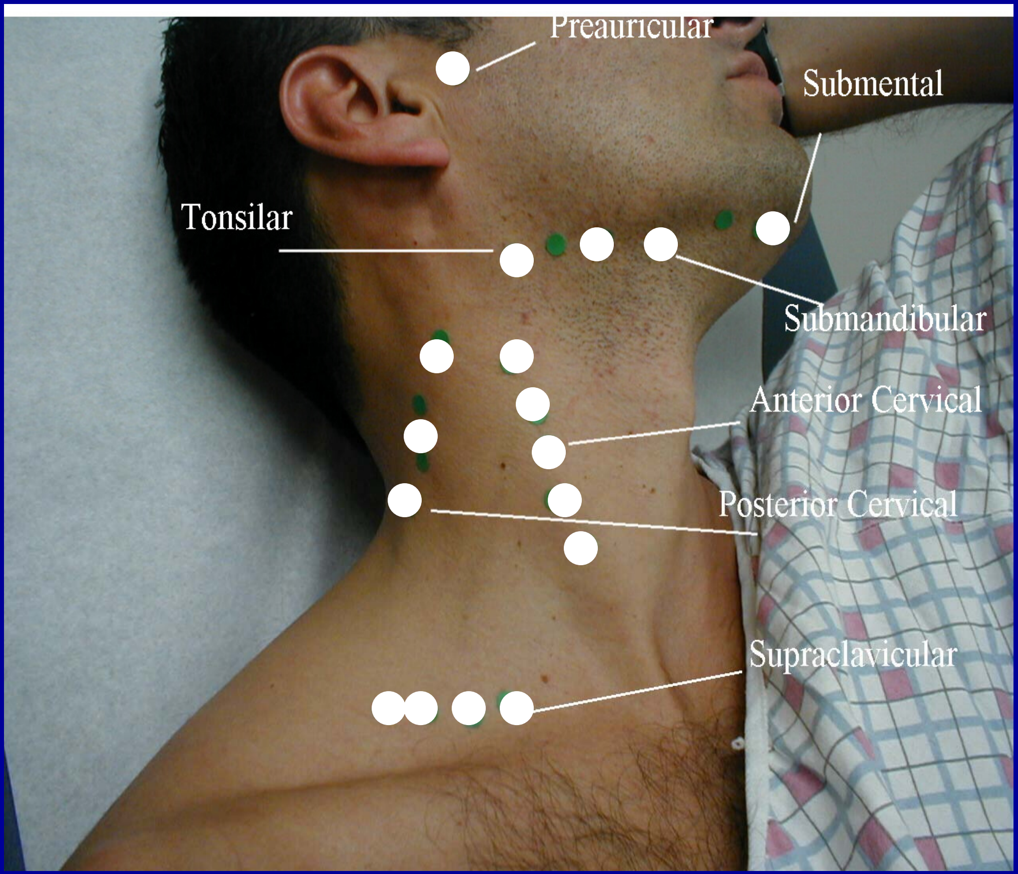


- usually 3 pairs of veins drain venous plexus on anterior surface of thyroid
  - superior thyroid veins drain superior poles
  - middle thyroid veins drain lateral parts
    - superior and middle thyroid veins empty into internal jugular veins
  - inferior thyroid veins drain inferior poles
    - empty into brachio-cephalic veins
    - often unite to form a single vein that drains into one or other brachio-cephalic vein

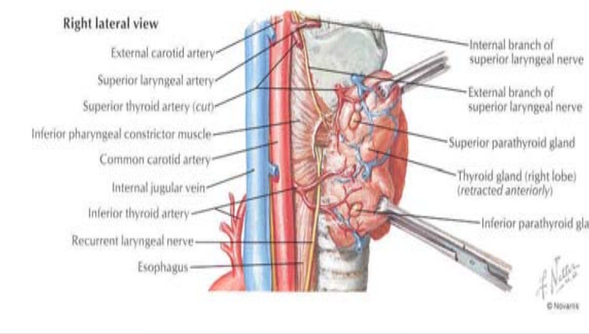
Lymphatic drainage

- lymphatics run in the interlobular connective tissue, often around arteries
- communicate with a capsular network of lymph vessels
- pass to prelaryngeal LN’s → pretracheal and paratracheal LN’s
- lateral lymphatic vessels along superior thyroid veins pass to deep cervical LN’s
- some drainage directly into brachio-cephalic LN’s or directly into thoracic duct

Lymph nodes of the neck

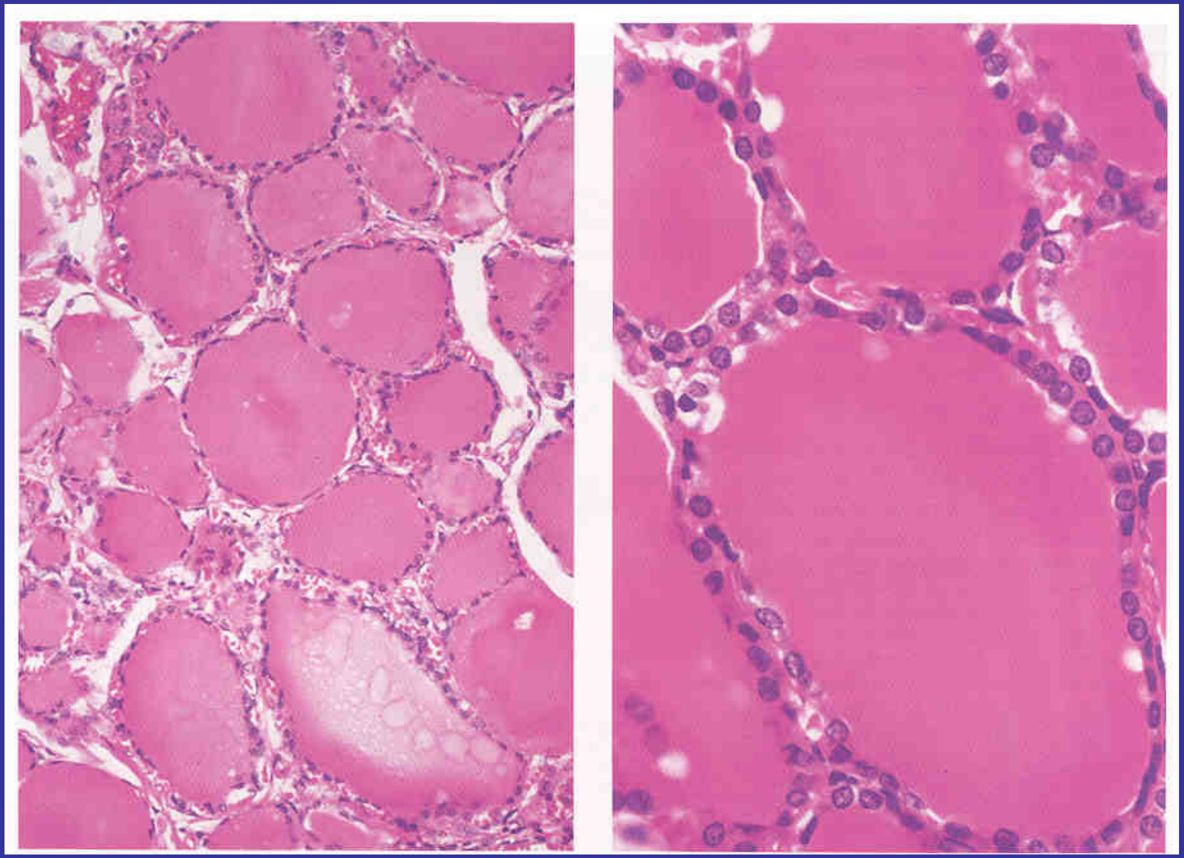


Innervation



- nerves derived from superior, middle and inferior cervical sympathetic ganglia
  - reach thyroid through cardiac and laryngeal branches of vagus nerve which accompany arterial supply
- postganglionic fibres and vasomotor – indirect action on thyroid by regulating blood vessels

Histology

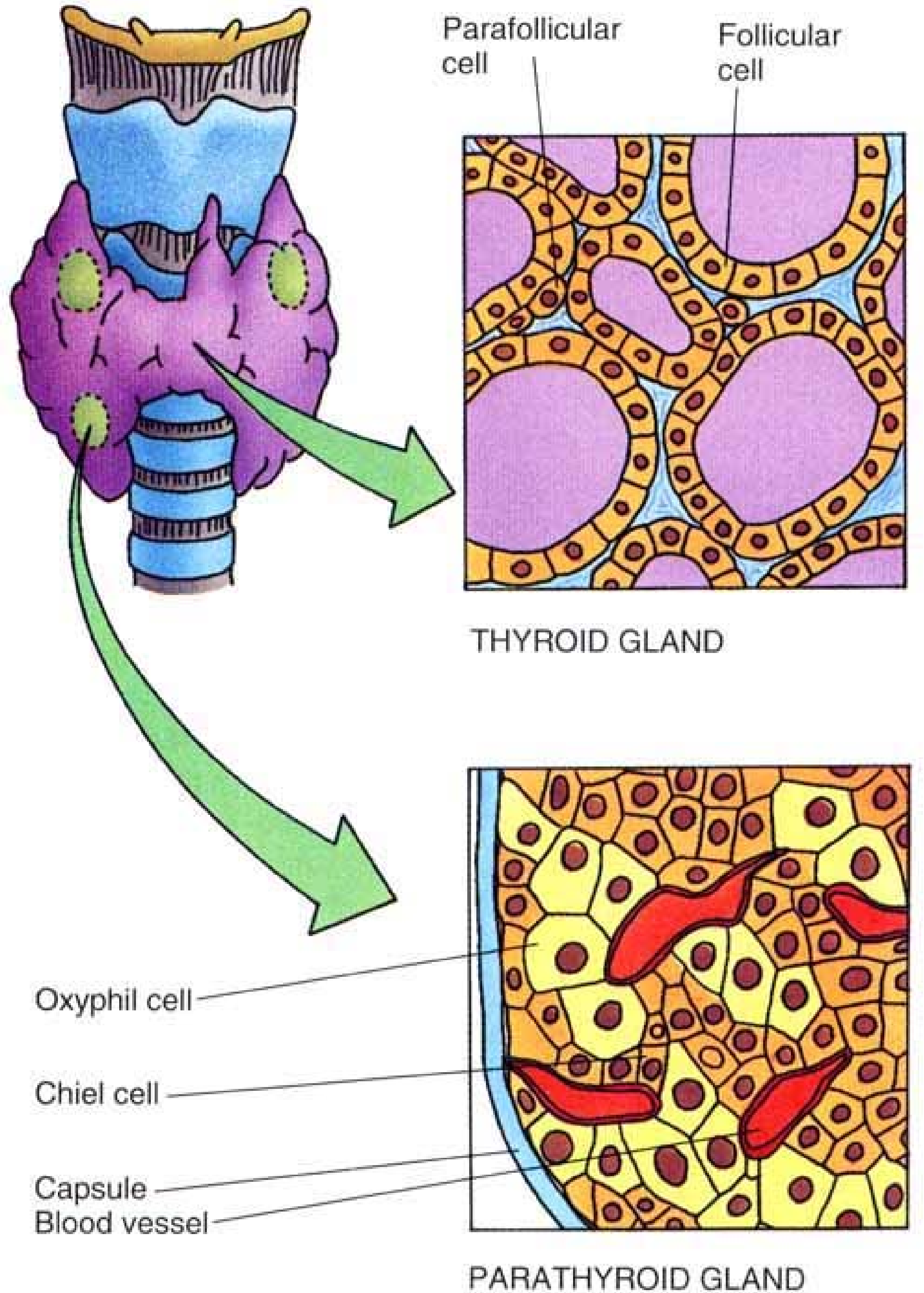


The thyroid gland is composed of 2 lobes connected by an isthmus.

It is surrounded by a dense irregular collagenous connective tissue capsule, in which (posteriorly) the parathyroid glands are embedded.

The thyroid gland is subdivided by capsular septa into lobules containing follicles.

These septa also serve as conduits for blood vessels, lymphatic vessels, & nerves

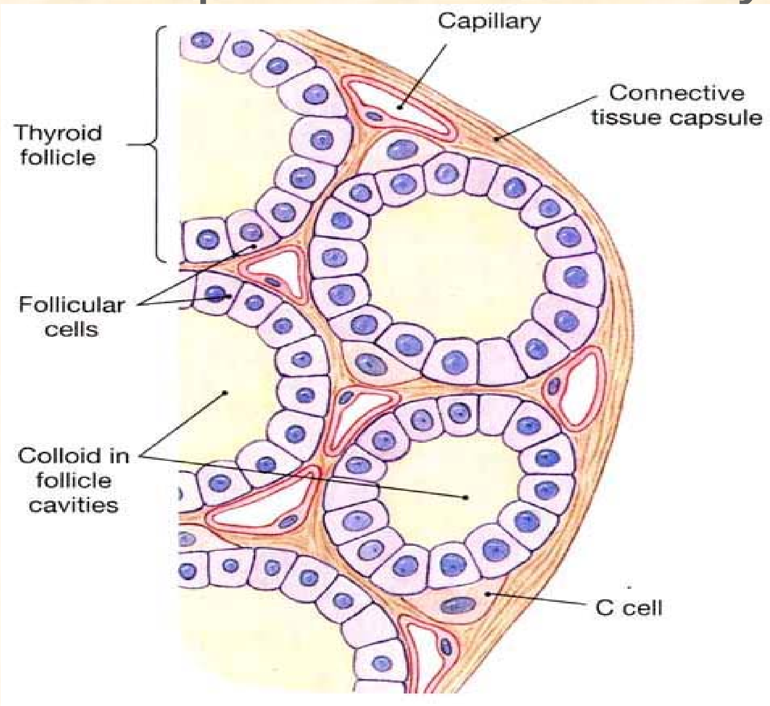


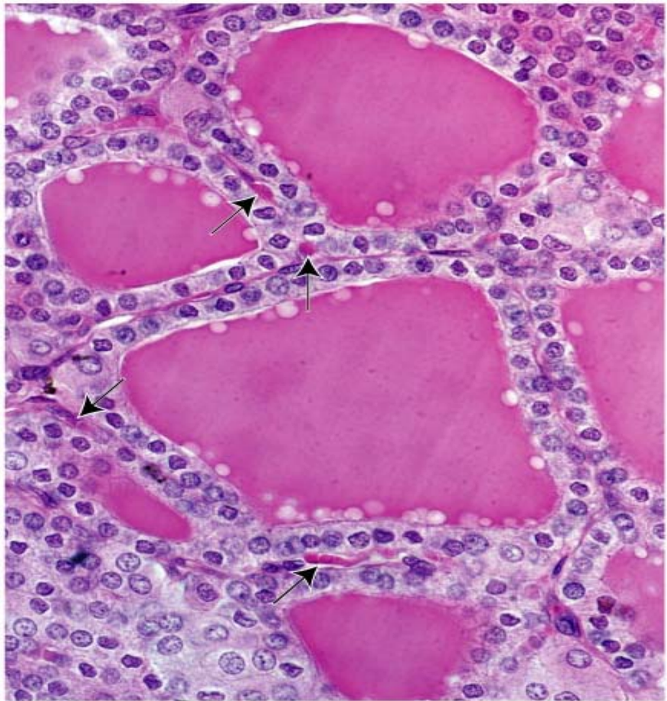
Thyroid Follicles

- **Thyroid follicles** are spherical structures filled with **colloid**, a viscous gel consisting mostly of **iodinated thyroglobulin**.
  - Thyroid follicles are enveloped by a layer of epithelial cells, called **follicular cells**, which in turn are surrounded by **parafollicular cells**. These 2 parenchymal cell types rest on a basal lamina, which separates them from the abundant network of **fenestrated capillaries** in the connective tissue.
  - **Function**. Thyroid follciles synthesize & store thyroid hormones.

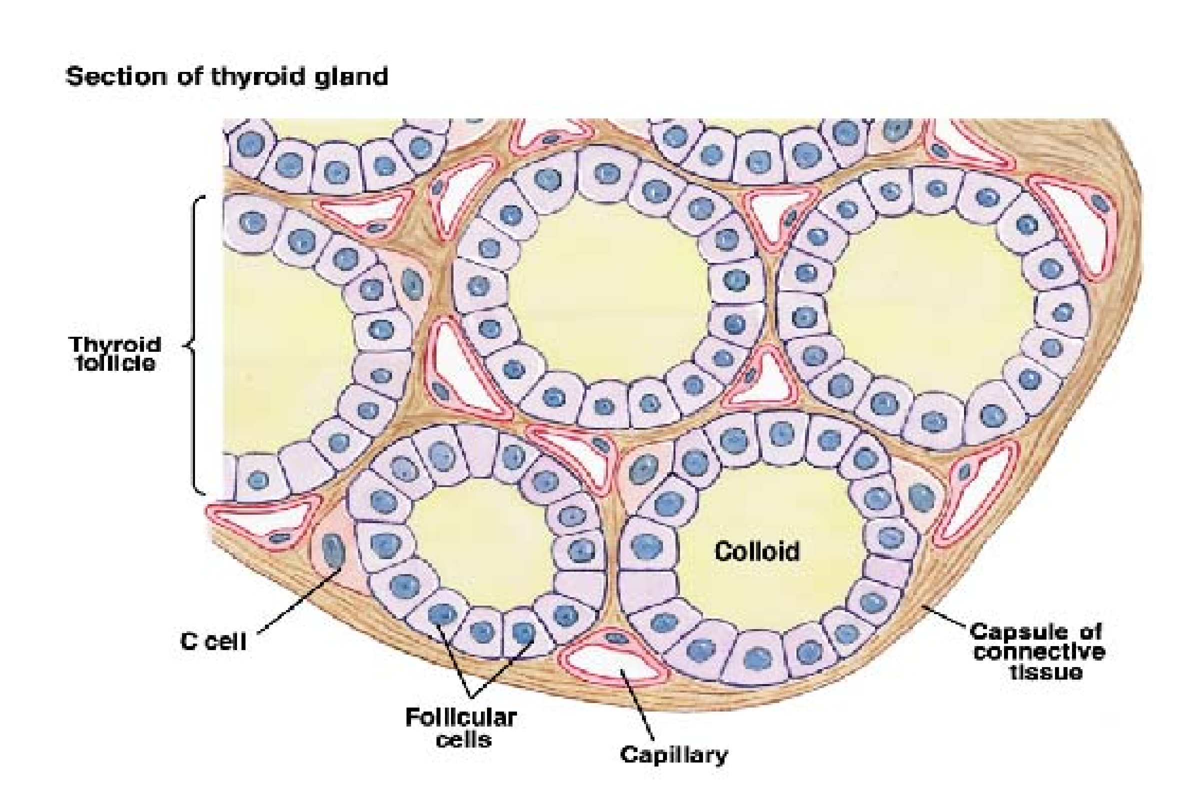
Follicular Cells

- Follicular cells are normally cuboidal in shape but become columnar when stimulated & squamous when inactive.
- Follicular cells contain many small **apical vesicles**, involved in transport & release of thyroglobulin & into the colloid.





Follicles: the Functional Units of the Thyroid Gland



Follicles Are the Sites Where Key Thyroid Elements Function:

- Thyroglobulin (Tg)
- Tyrosine
- Iodine
- Thyroxine (T_4)
- Triiodotyrosine (T_3)

Follicular Cells

- **Synthesis** & **release** of the thyroid hormones **throxine** (**T_4**) & **triiodothyronine** (**T_3**)
  - Thyroglobulin is synthesized like other secretory proteins.
  - Circulating iodide is actively transported into the cytosol, where a thyroid peroxidase oxidizes it & iodinates tyrosine residues on the thyroglobulin molecule; iodination occurs mostly at the apical plasma membrane.
  - A rearrangement of the iodinated tyrosine residues of thyroglobulin in the colloid produces the iodothyronines T_4 & T_3.

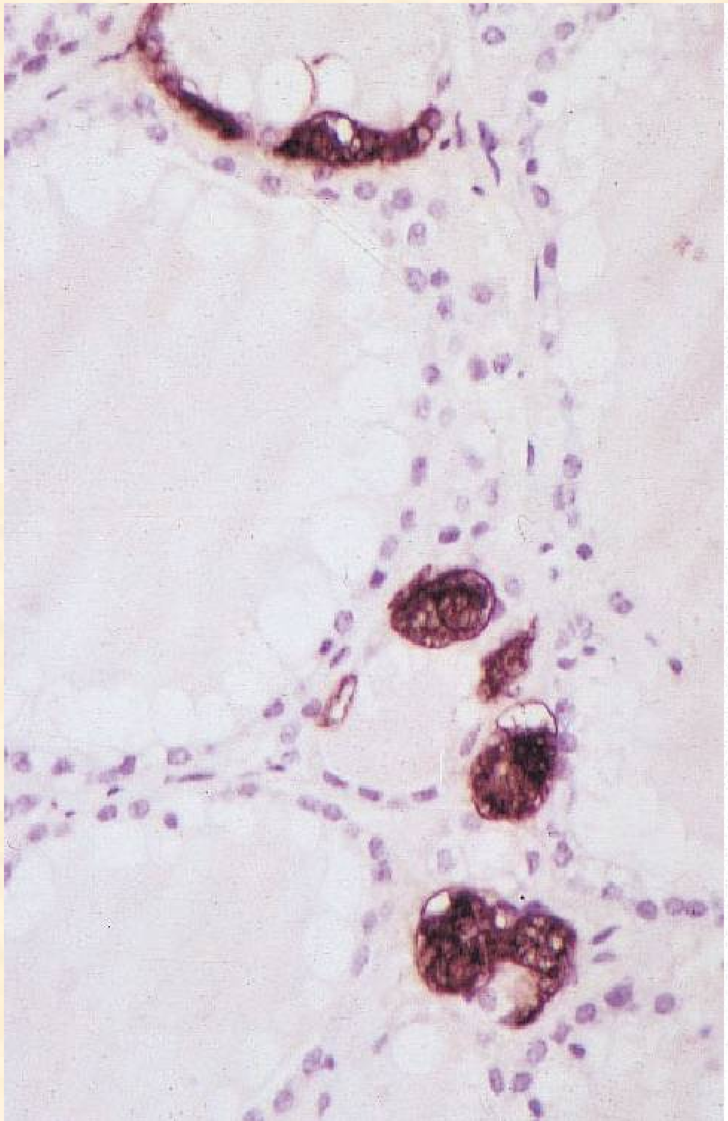
Follicular Cells

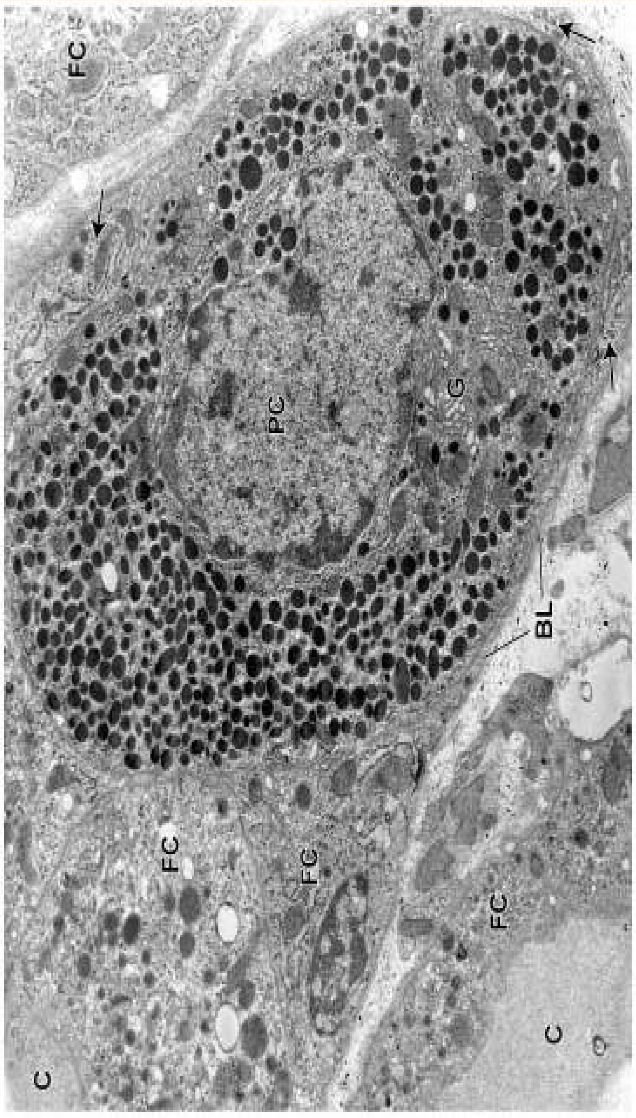
- Binding of thyroid-stimulating hormone to receptors on the basal surface stimulates follicular cells to become columnar & to form apical pseudopods, which engulf colloid by endocytosis.
- After the colloid droplets fuse with lysosomes, controlled hydrolysis of iodinated thyroglobulin liberates T_3 & T_4 into the cytosol.
- These hormones move basally & are released basally into the bloodstream & lymphatic vessels.

These processes are promoted by **TSH**, which binds to G-protein-linked receptors on the basal surface of follicular cells.

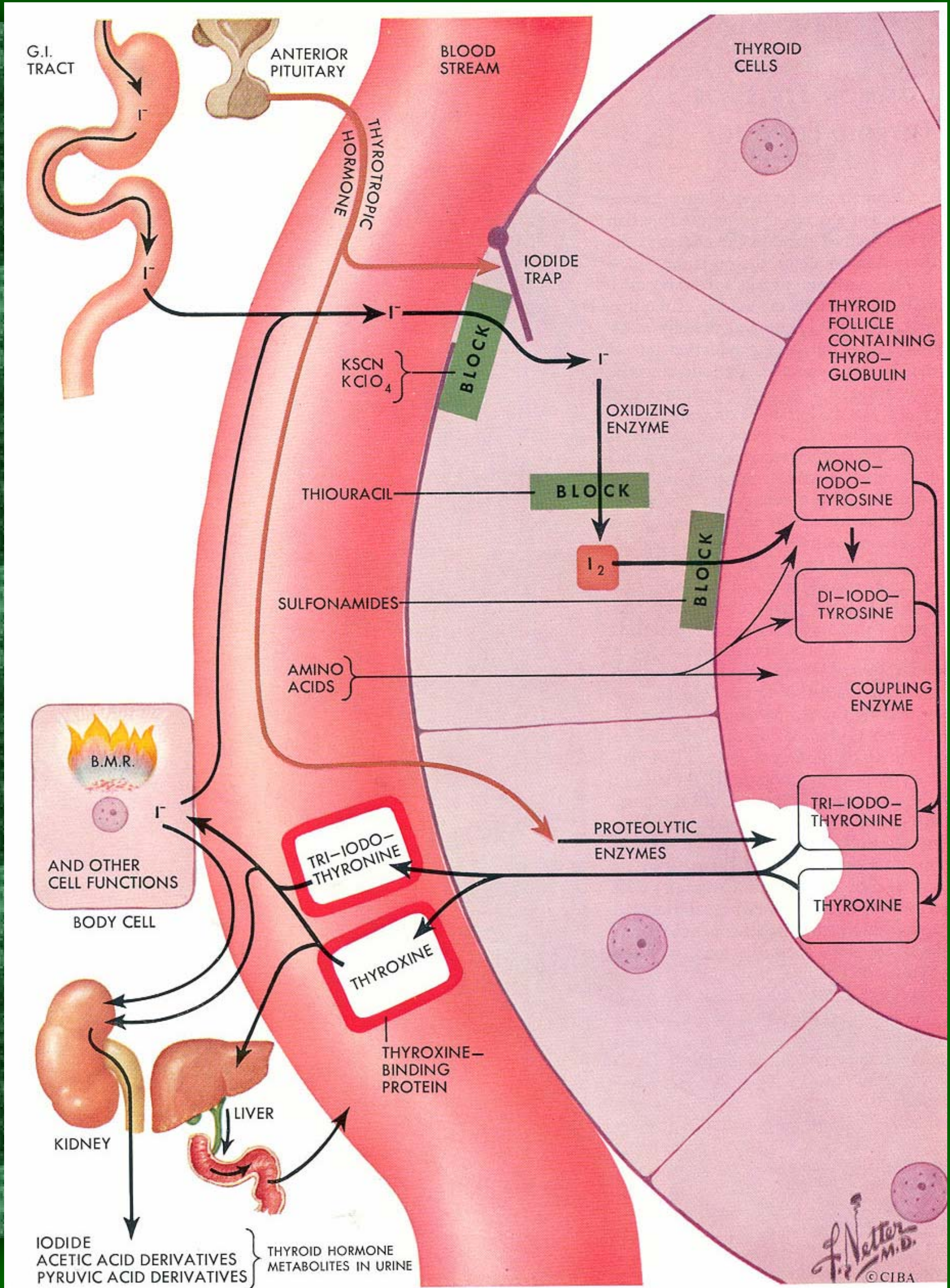
Parafollicular Cells

- **Parafollicular cells** are also called **clear** (**C**) **cells** because they stain less intensely than thyroid follicular cells.
    - They synthesize & release **calcitonin**, a polypeptide hormone, in response to high blood calcium levels.





Thyroid Physiology



The Thyroid Produces and Secretes 2 Metabolic Hormones

- Two principal hormones
  - Thyroxine (T_4) and triiodothyronine (T_3)
    - Required for homeostasis of all cells
    - Influence cell differentiation, growth, and metabolism
    - Considered the major metabolic hormones because they target virtually every tissue

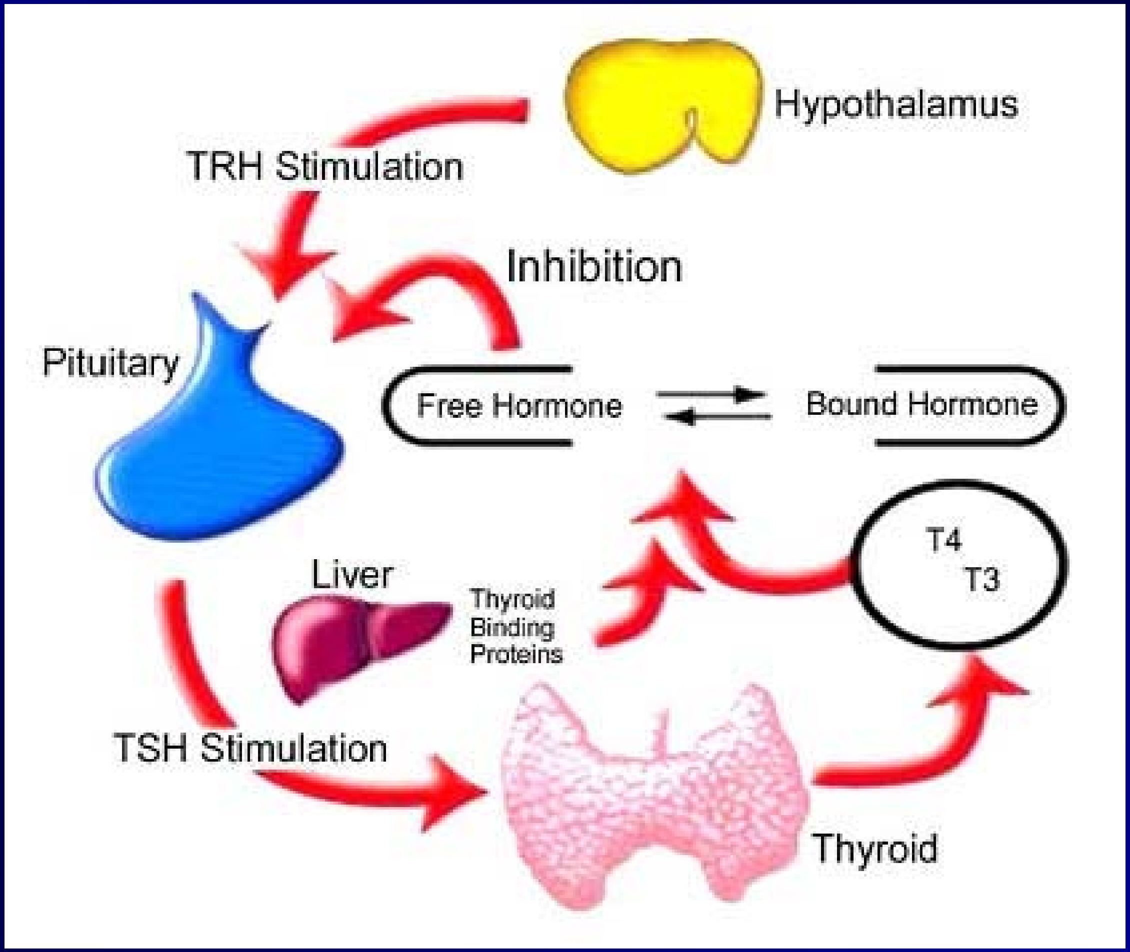
TRH

- Produced by Hypothalamus
- Release is pulsatile, circadian
- Downregulated by T_3
- Travels through portal venous system to adenohypophysis
- Stimulates TSH formation

Thyroid-Stimulating Hormone (TSH)

- Upregulated by TRH
- Downregulated by T4, T3
- Travels through portal venous system to cavernous sinus, body.
- Stimulates several processes
  - Iodine uptake
  - Colloid endocytosis
  - Growth of thyroid gland
- Produced by Adenohypophysis Thyrotrophs

Hypothalamic-Pituitary-Thyroid Axis Negative Feedback Mechanism



Biosynthesis of T_4 and T_3

The process includes

- Dietary iodine (I) ingestion
- Active transport and uptake of iodide (I^-) by thyroid gland
- Oxidation of I^- and iodination of thyroglobulin (Tg) tyrosine residues
- Coupling of iodotyrosine residues (MIT and DIT) to form T_4 and T_3
- Proteolysis of Tg with release of T_4 and T_3 into the circulation

Iodine Sources

- Available through certain foods (eg, seafood, bread, dairy products), iodized salt, or dietary supplements, as a trace mineral
- The recommended minimum intake is 150 μg/day

Active Transport and I^- Uptake by the Thyroid

- Dietary iodine reaches the circulation as iodide anion (I^-)
- The thyroid gland transports I^- to the sites of hormone synthesis
- I^- accumulation in the thyroid is an active transport process that is stimulated by TSH

Oxidation of I^- and Iodination of Thyroglobulin (Tg) Tyrosyl Residues

- I^- must be oxidized to be able to iodinate tyrosyl residues of Tg
- Iodination of the tyrosyl residues then forms monoiodotyrosine (MIT) and diiodotyrosine (DIT), which are then coupled to form either T_3 or T_4
- Both reactions are catalyzed by TPO

Thyroperoxidase (TPO)

- TPO catalyzes the oxidation steps involved in I^- activation, iodination of Tg tyrosyl residues, and coupling of iodotyrosyl residues
- TPO has binding sites for I^- and tyrosine
- TPO uses H_2O_2 as the oxidant to activate I^- to hypoiodate (OI^-), the iodinating species

Proteolysis of Tg With Release of T_4 and T_3

- T_4 and T_3 are synthesized and stored within the Tg molecule
- Proteolysis is an essential step for releasing the hormones
- To liberate T_4 and T_3, Tg is resorbed into the follicular cells in the form of colloid droplets, which fuse with lysosomes to form phagolysosomes
- Tg is then hydrolyzed to T_4 and T_3, which are then secreted into the circulation

Conversion of T_4 to T_3 in Peripheral Tissues

Production of T_4 and T_3

- T_4 is the primary secretory product of the thyroid gland, which is the only source of T_4
- The thyroid secretes approximately 70-90 μg of T_4 per day
- T_3 is derived from 2 processes
  - The total daily production rate of T_3 is about 15-30 μg
  - About 80% of circulating T_3 comes from deiodination of T_4 in peripheral tissues
  - About 20% comes from direct thyroid secretion

T_4: A Prohormone for T_3

- T_4 is biologically inactive in target tissues until converted to T_3
  - Activation occurs with 5' iodination of the outer ring of T_4
- T_3 then becomes the biologically active hormone responsible for the majority of thyroid hormone effects

Sites of T_4 Conversion

- The liver is the major extrathyroidal T_4 conversion site for production of T_3
- Some T_4 to T_3 conversion also occurs in the kidney and other tissues

T_4 Disposition

- Normal disposition of T_4
  - About 41% is converted to T_3
  - 38% is converted to reverse T_3 (rT_3), which is metabolically inactive
  - 21% is metabolized via other pathways, such as conjugation in the liver and excretion in the bile
- Normal circulating concentrations
  - T_4 4.5-11 μg/dL
  - T_3 60-180 ng/dL (~100-fold less than T_4)

Hormonal Transport

Carriers for Circulating Thyroid Hormones

- More than 99% of circulating T_4 and T_3 is bound to plasma carrier proteins
  - Thyroxine-binding globulin (TBG), binds about 75%
  - Transthyretin (TTR), also called thyroxine-binding prealbumin (TBPA), binds about 10%-15%
  - Albumin binds about 7%
  - High-density lipoproteins (HDL), binds about 3%
- Carrier proteins can be affected by physiologic changes, drugs, and disease

Free Hormone Concept

- Only unbound (free) hormone has metabolic activity and physiologic effects
  - Free hormone is a tiny percentage of total hormone in plasma (about 0.03% T_4; 0.3% T_3)
- Total hormone concentration
  - Normally is kept proportional to the concentration of carrier proteins
  - Is kept appropriate to maintain a constant free hormone level

Changes in TBG Concentration Determine Binding and Influence T_4 and T_3 Levels

- Increased TBG
  - Total serum T_4 and T_3 levels increase
  - Free T_4 (FT_4), and free T_3 (FT_3) concentrations remain unchanged
- Decreased TBG
  - Total serum T_4 and T_3 levels decrease
  - FT_4 and FT_3 levels remain unchanged

Drugs and Conditions That Increase Serum T_4 and T_3 Levels by Increasing TBG

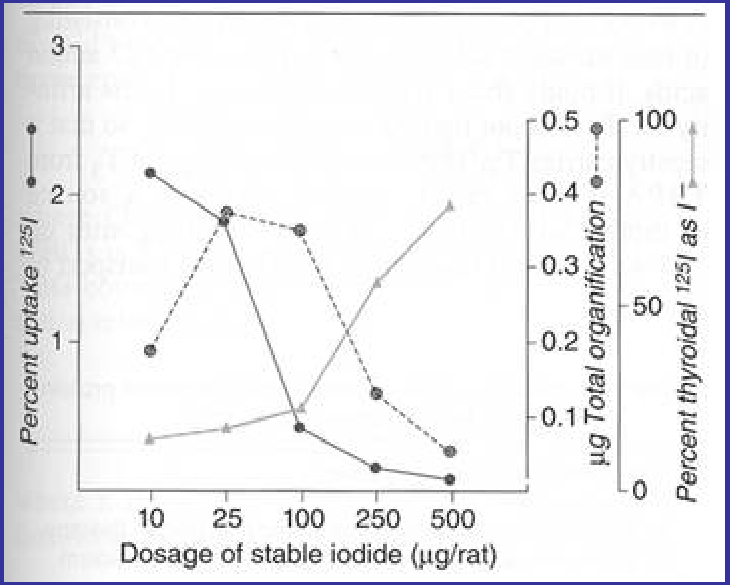
- Drugs that increase TBG
  - Oral contraceptives and other sources of estrogen
  - Methadone
  - Clofibrate
  - 5-Fluorouracil
  - Heroin
  - Tamoxifen
- Conditions that increase TBG
  - Pregnancy
  - Infectious/chronic active hepatitis
  - HIV infection
  - Biliary cirrhosis
  - Acute intermittent porphyria
  - Genetic factors

Drugs and Conditions That Decrease Serum T_4 and T_3 by Decreasing TBG Levels or Binding of Hormone to TBG

- Drugs that decrease serum T_4 and T_3
  - Glucocorticoids
  - Androgens
  - L-Asparaginase
  - Salicylates
  - Mefenamic acid
  - Antiseizure medications, eg, phenytoin, carbama-zepine
  - Furosemide
- Conditions that decrease serum T_4 and T_3
  - Genetic factors
  - Acute and chronic illness

Wolff-Chaikoff Effect

- Increasing doses of I^- increase hormone synthesis initially
- Higher doses cause cessation of hormone formation.
- This effect is countered by the Iodide leak from normal thyroid tissue.
- Patients with autoimmune thyroiditis may fail to adapt and become hypothyroid.

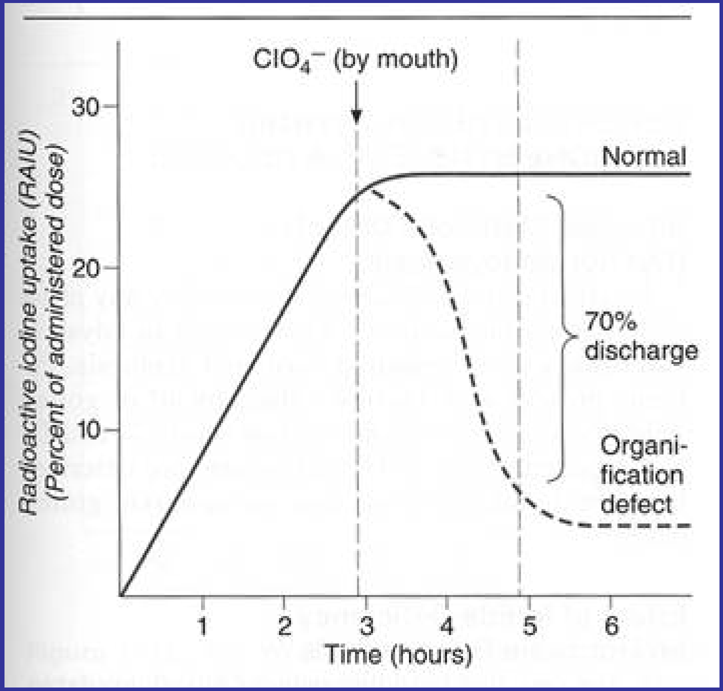


Jod-Basedow Effect

- Opposite of the Wolff-Chaikoff effect
- Excessive iodine loads induce <u>hyper</u>thyroidism
- Observed in hyperthyroid disease processes
  - Graves' disease
  - Toxic multinodular goiter
  - Toxic adenoma
- This effect may lead to symptomatic thyrotoxicosis in patients who receive large iodine doses from
  - Dietary changes
  - Contrast administration
  - Iodine containing medication (Amiodarone)

Perchlorate

- ClO_4^- ion inhibits the Na^+ / I^- transport protein.
- Normal individuals show no leak of I^{123} after ClO_4^- due to organification of I^- to MIT / DIT
- Patients with organification defects show loss of RAIU.
- Used in diagnosis of Pendred syndrome



Thyroid Hormone Action

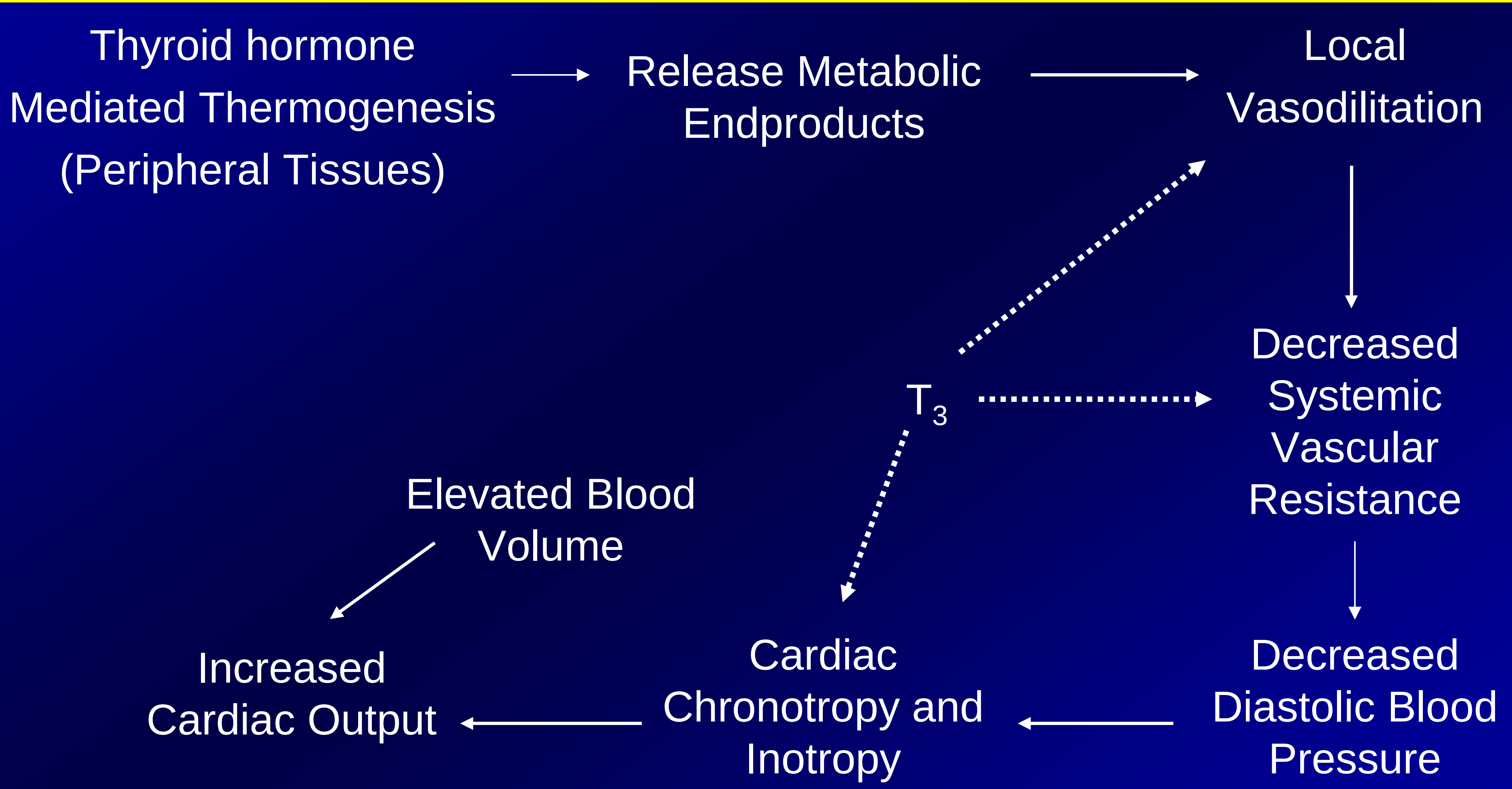
Thyroid Hormone Plays a Major Role in Growth and Development

- Thyroid hormone initiates or sustains differentiation and growth
  - Stimulates formation of proteins, which exert trophic effects on tissues
  - Is essential for normal brain development
- Essential for childhood growth
  - Untreated congenital hypothyroidism or chronic hypothyroidism during childhood can result in incomplete development and mental retardation

Thyroid Hormones and the Central Nervous System (CNS)

- Thyroid hormones are essential for neural development and maturation and function of the CNS
- Decreased thyroid hormone concentrations may lead to alterations in cognitive function
  - Patients with hypothyroidism may develop impairment of attention, slowed motor function, and poor memory
  - Thyroid-replacement therapy may improve cognitive function when hypothyroidism is present

Thyroid Hormone Influences Cardiovascular Hemodynamics



Laragh JH, et al. *Endocrine Mechanisms in Hypertension.* Vol. 2. New York, NY: Raven Press;1989.

Thyroid Hormone Influences the Female Reproductive System

- Normal thyroid hormone function is important for reproductive function
  - Hypothyroidism may be associated with menstrual disorders, infertility, risk of miscarriage, and other complications of pregnancy

Doufas AG, et al. *Ann N Y Acad Sci*. 2000;900:65-76.
Glinoer D. *Trends Endocrinol Metab.* 1998; 9:403-411.
Glinoer D. *Endocr Rev.* 1997;18:404-433.

Thyroid Hormone is Critical for Normal Bone Growth and Development

- T_3 is an important regulator of skeletal maturation at the growth plate
  - T_3 regulates the expression of factors and other contributors to linear growth directly in the growth plate
  - T_3 also may participate in osteoblast differentiation and proliferation, and chondrocyte maturation leading to bone ossification

Thyroid Hormone Regulates Mitochondrial Activity

- T_3 is considered the major regulator of mitochondrial activity
  - A potent T_3-dependent transcription factor of the mitochondrial genome induces early stimulation of transcription and increases transcription factor (TFA) expression
  - T_3 stimulates oxygen consumption by the mitochondria

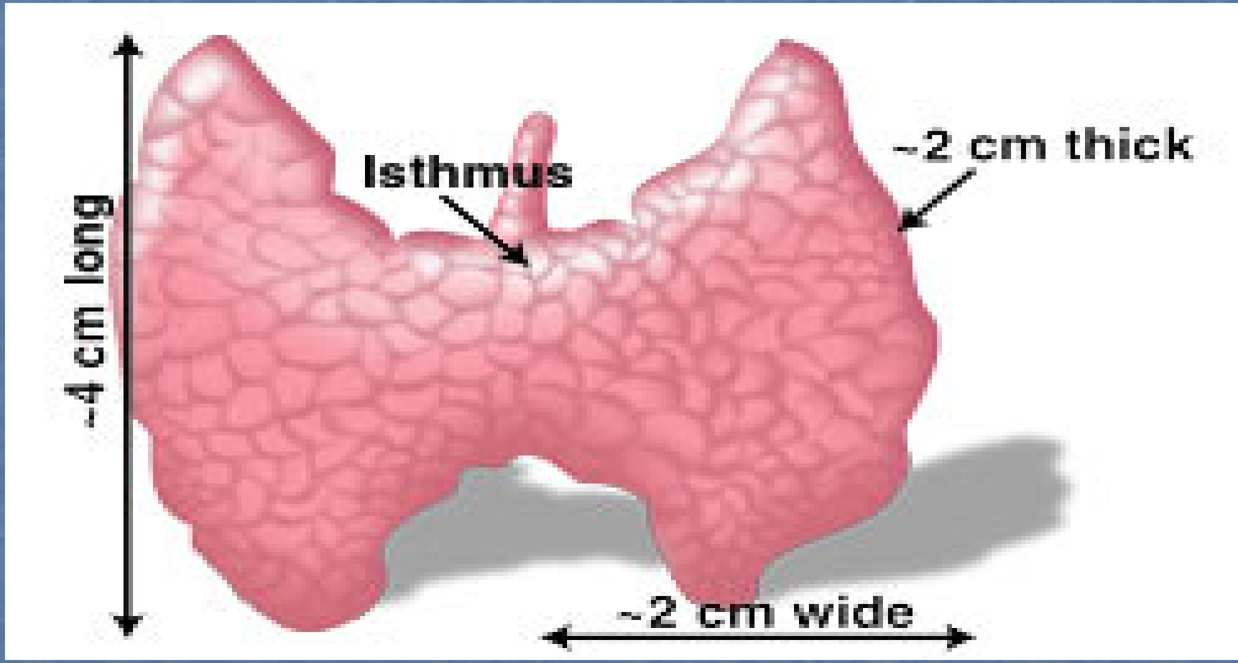
Thyroid Hormones Stimulate Metabolic Activities in Most Tissues

- Thyroid hormones (specifically T_3) regulate rate of overall body metabolism
  - T_3 increases basal metabolic rate
- Calorigenic effects
  - T_3 increases oxygen consumption by most peripheral tissues
  - Increases body heat production

Metabolic Effects of T_3

- Stimulates lipolysis and release of free fatty acids and glycerol
- Induces expression of lipogenic enzymes
- Effects cholesterol metabolism
- Stimulates metabolism of cholesterol to bile acids
- Facilitates rapid removal of LDL from plasma
- Generally stimulates all aspects of carbohydrate metabolism and the pathway for protein degradation

Evaluation Of Thyroid



History

- Age
- Gender
- Exposure to Radiation
- Signs/symptoms of hyper- / hypo-thyroidism
- Rapid change in size
  - With ***pain*** may indicate hemorrhage into nodule
  - Without pain may be bad sign

History

- Gardner Syndrome (familial adenomatous polyposis)
  - Association found with thyroid ca
  - Mostly in young women (94%) (RR 160)
  - Thyroid ca preceded dx of Garners 30% of time
- Cowden Syndrome
  - Mucocutaneous hamartomas, keratoses,fibrocystic breast changes & GI polyps
  - Found to have association with thyroid ca (8/26 patients in one series)

History

- Familial h/o medullary thyroid carcinoma
  - Familial MTC vs MEN II
- Family hx of other thyroid ca
- H/o Hashimoto's thyroiditis (lymphoma)

History

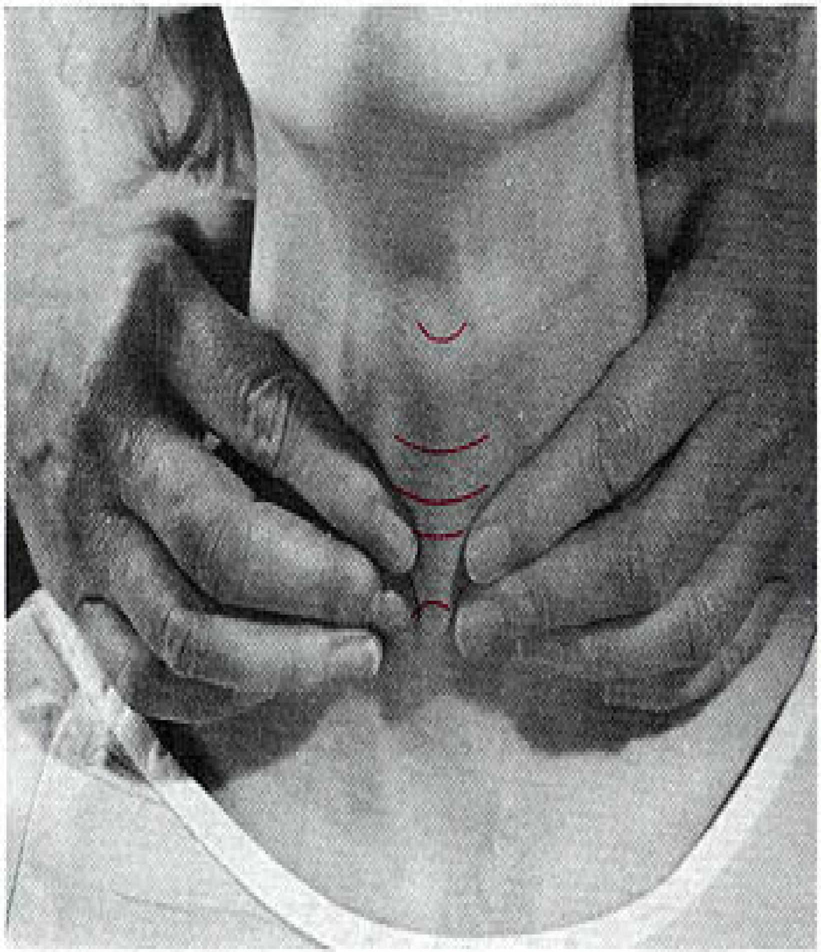
- History elements suggestive of malignancy:
  - Progressive enlargement
  - Hoarseness
  - Dysphagia
  - Dyspnea
  - High-risk (fam hx, radiation)
- Not very sensitive / specific

Disorders of the Thyroid Gland

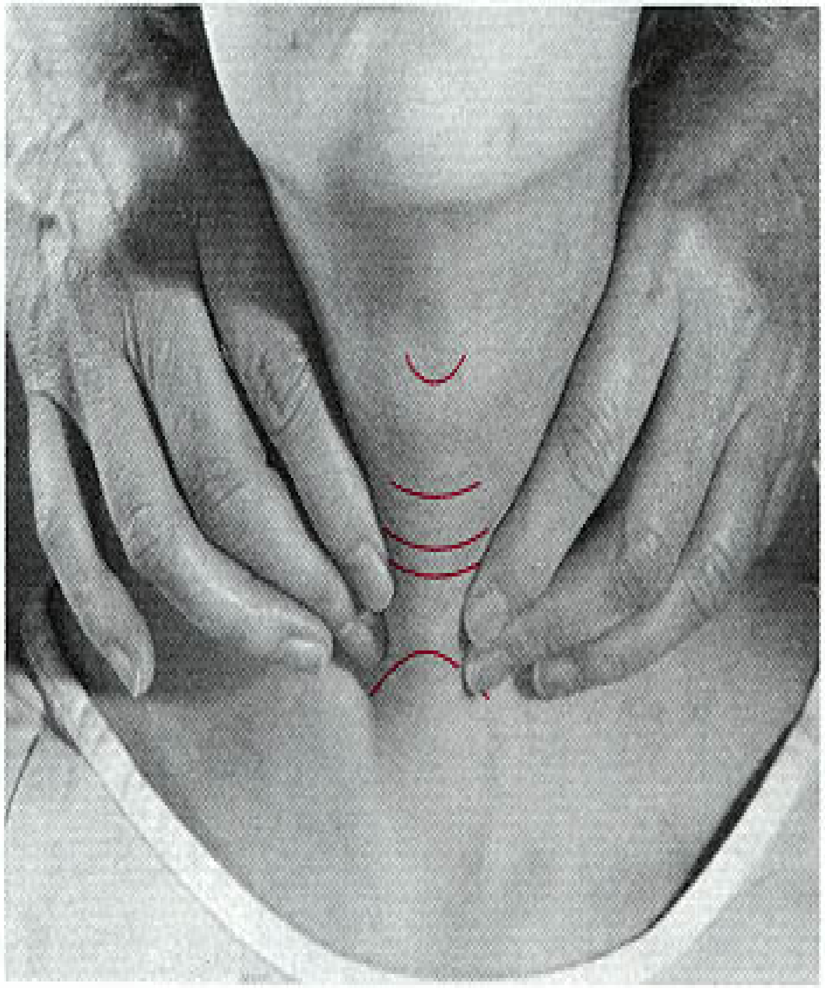
Physical Examination of the Thyroid Gland

- Inspection
  - Glass of water for swallowing
- Palpation
  - Anteriorly
  - From behind

Each lobe measures : vertical dimension – 2 cm
horizontal dimension – 1 cm

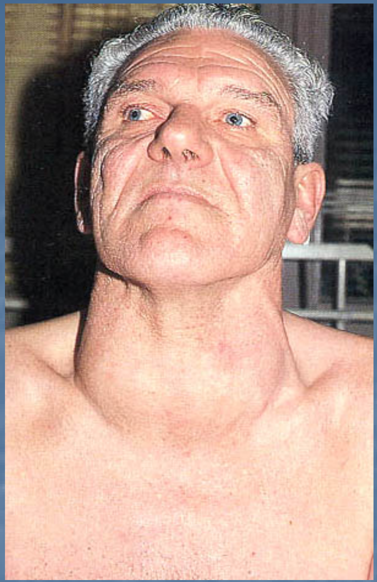


FEELING THE ISTHMUS



FEELING THE LATERAL LOBES

Thyroid Palpation



- Texture – soft / firm / hard
- Surface – smooth / seedy / lumpy
- Shape – diffuse / nodular
- Presence of regional adenopathy

Physical

- Complete Head & Neck exam
- Vocal cord mobility (?Strobe)
- Palpation thyroid
- Cervical lymphadenopathy
- Ophthalmopathy

Physical

- Physical findings suggestive of malignancy:
  - Fixation
  - Adenopathy
  - Fixed cord
  - Induration
  - Stridor
- Not very sensitive / specific

Graves Ophthalmopathy

Neck Bruising

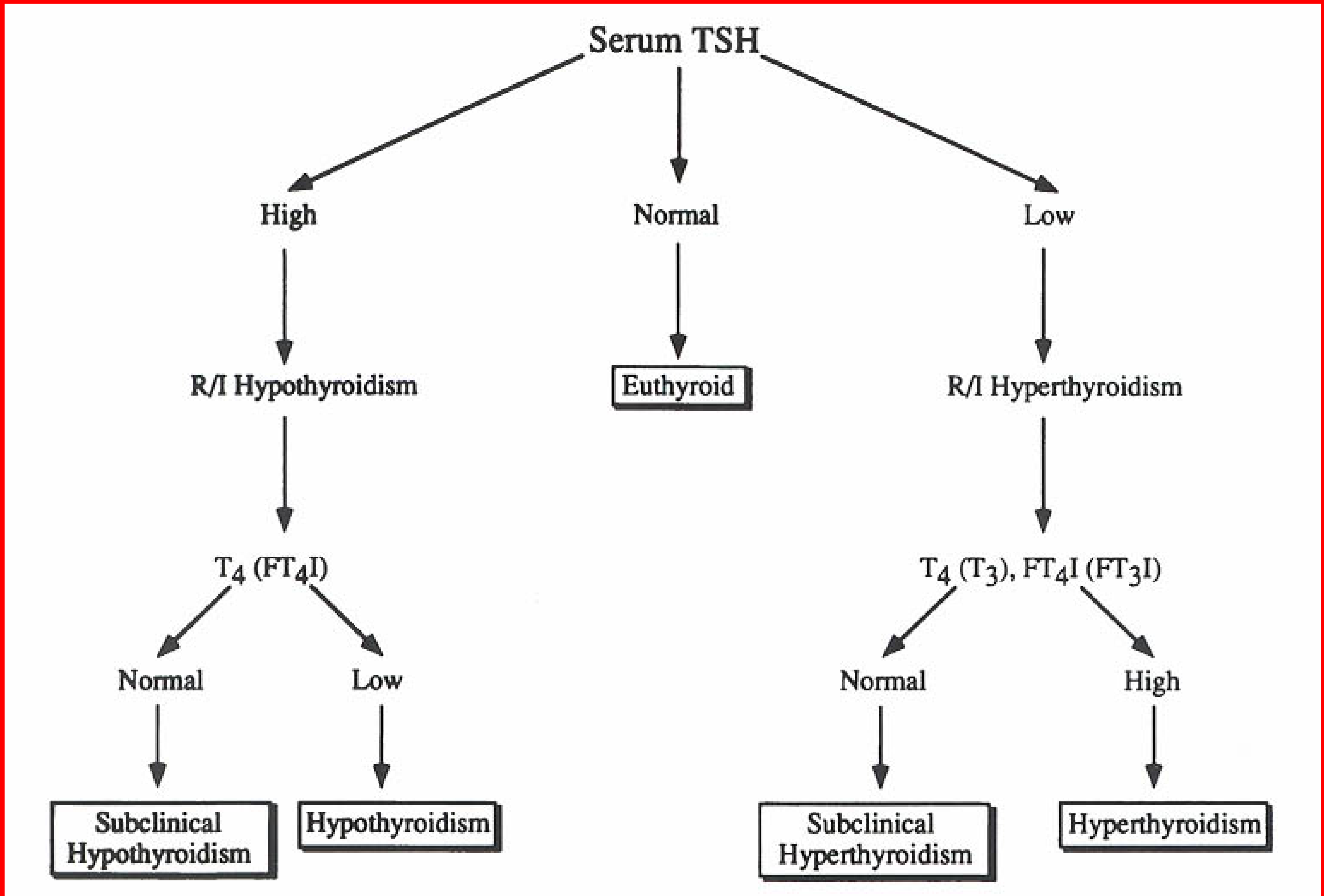
- Suggests hemorrhage into nodule

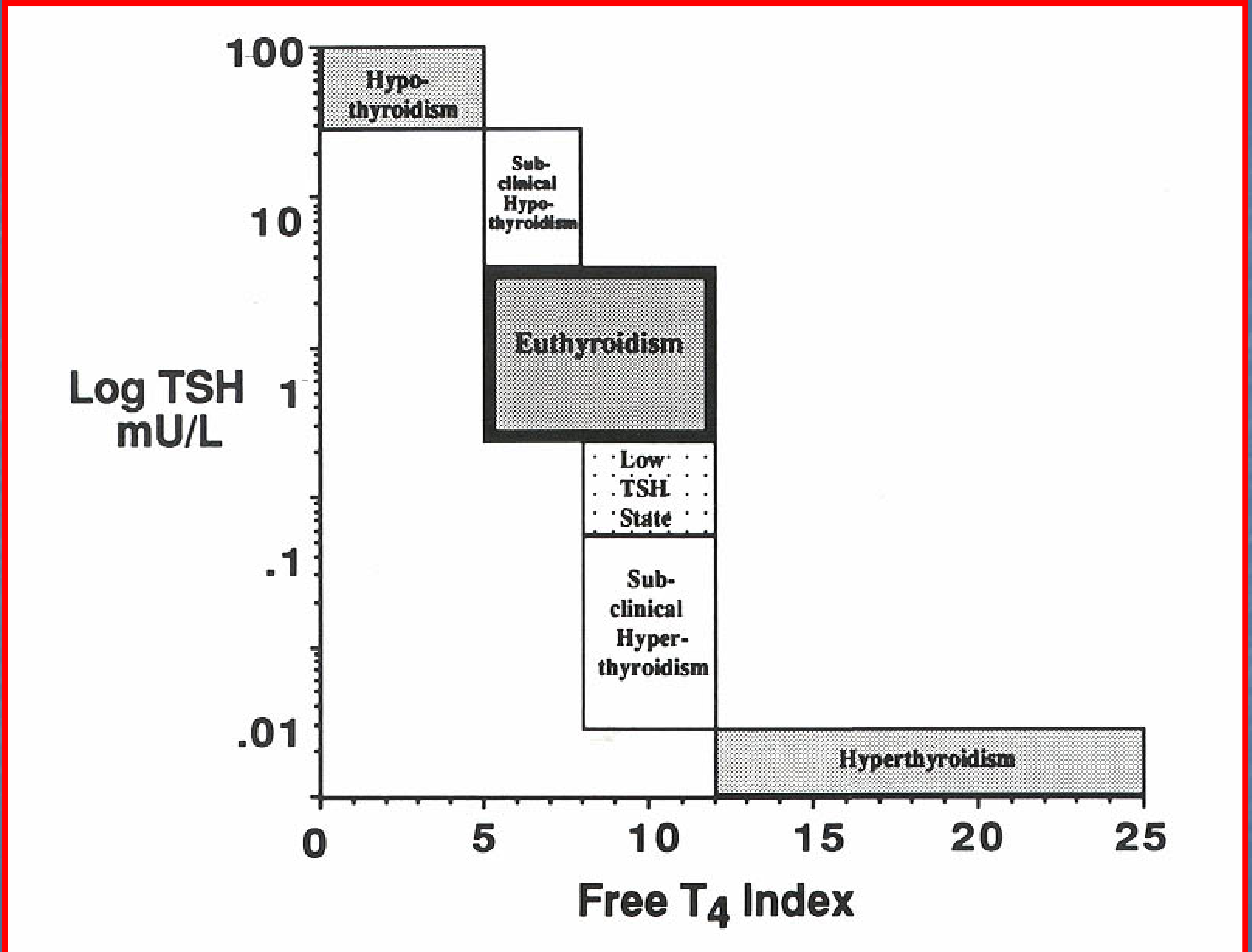
Lingual Thyroid

Workup

Serum Testing

- TSH – first-line serum test
  - Identifies subclinical thyrotoxicosis
- T4, T3
- Calcium
- Thyroglobulin
  - Post-treatment good to detect recurrence
- Calcitonin – only in cases of medullary
- Antibodies – Hashimoto's
- RET proto-oncogene


Serum TSH
High
Normal
Low
R/I Hypothyroidism
Euthyroid
R/I Hyperthyroidism
T_4 (FT_4I)
T_4 (T_3), FT_4I (FT_3I)
Normal
Low
Normal
High
Subclinical Hypothyroidism
Hypothyroidism
Subclinical Hyperthyroidism
Hyperthyroidism



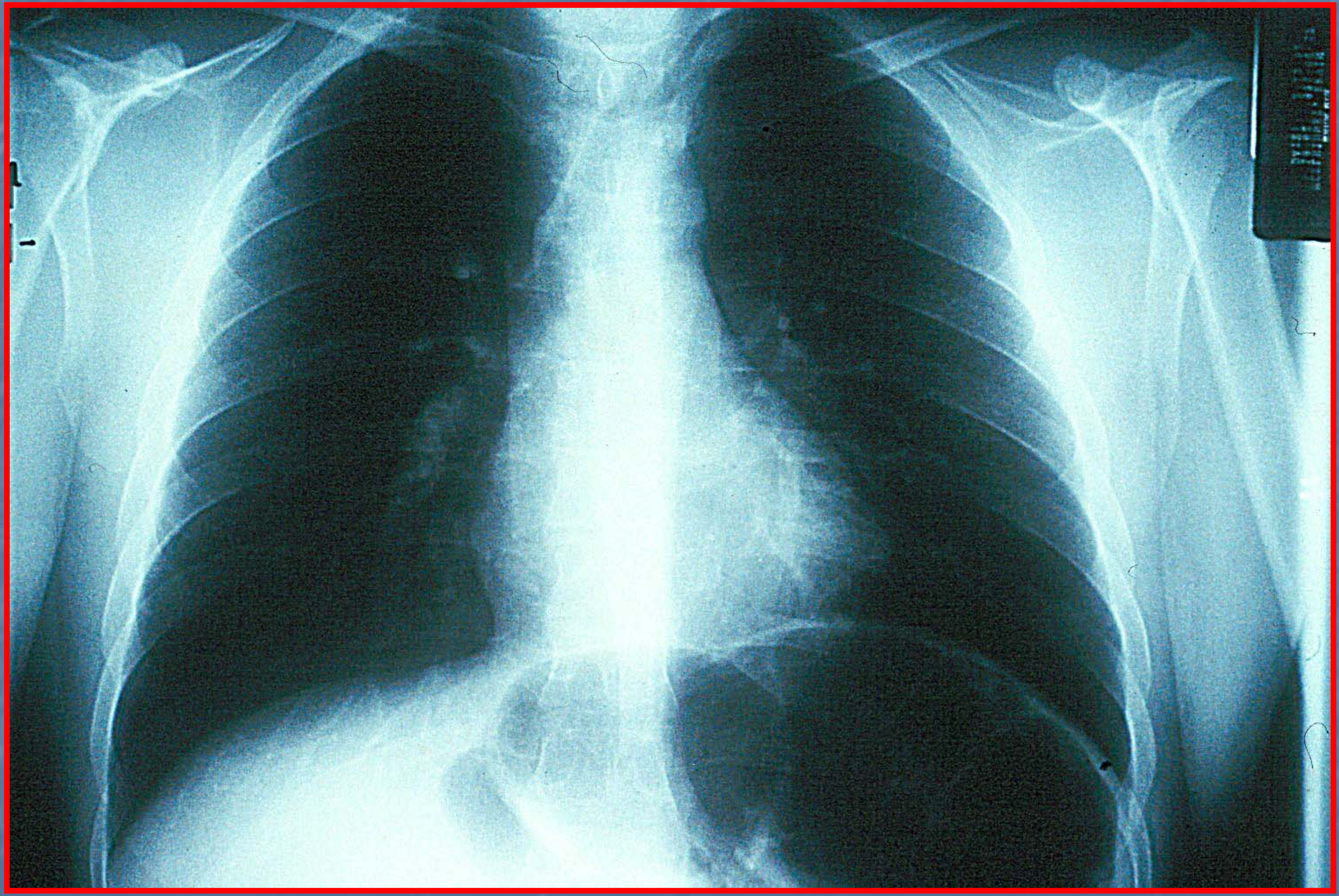
100
10
1
.1
.01
Log TSH mU/L
Hypo-thyroidism
Sub-clinical Hypo-thyroidism
Euthyroidism
Low TSH State
Sub-clinical Hyper-thyroidism
Hyperthyroidism
0
5
10
15
20
25
Free T4 Index

Imaging

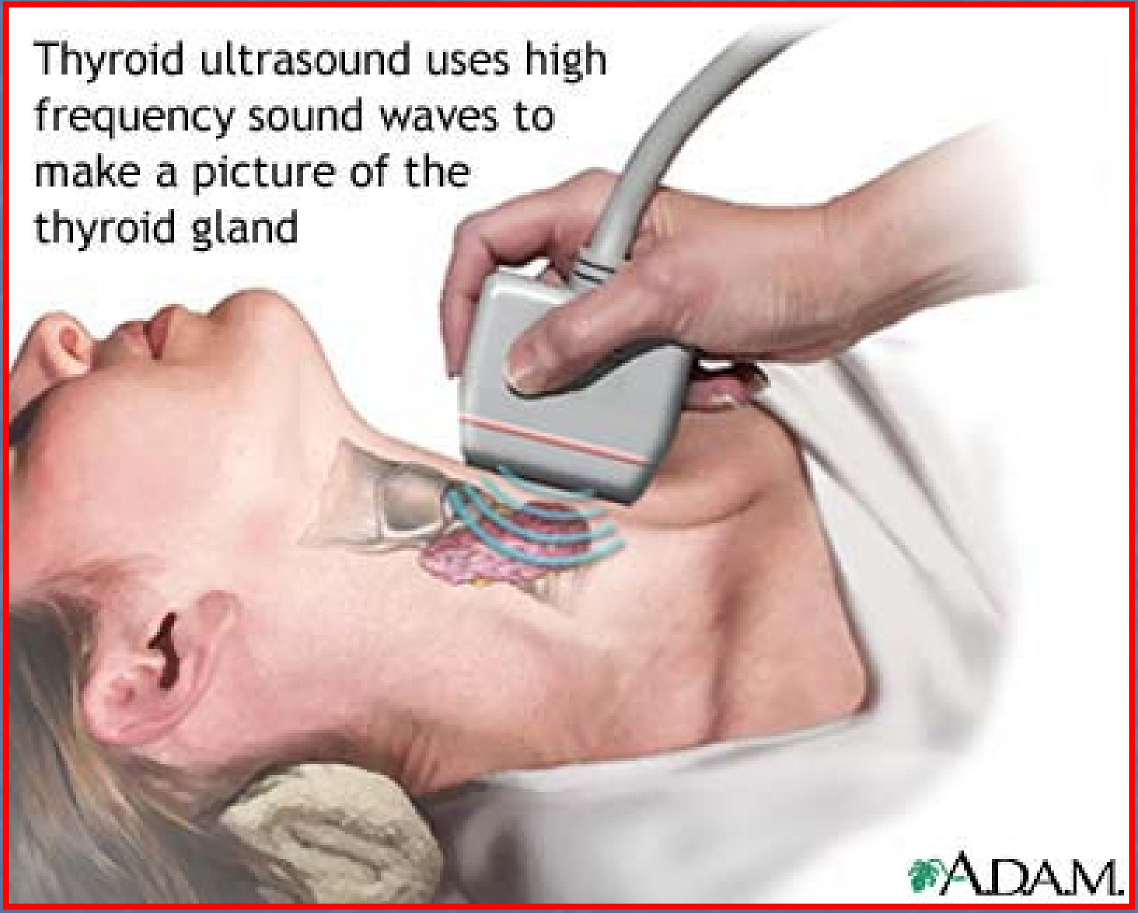
Plain Films

- Not routinely ordered
- May show:
  - Tracheal deviation
  - Pulmonary metastasis
  - Calcifications (suggests papillary or medullary)

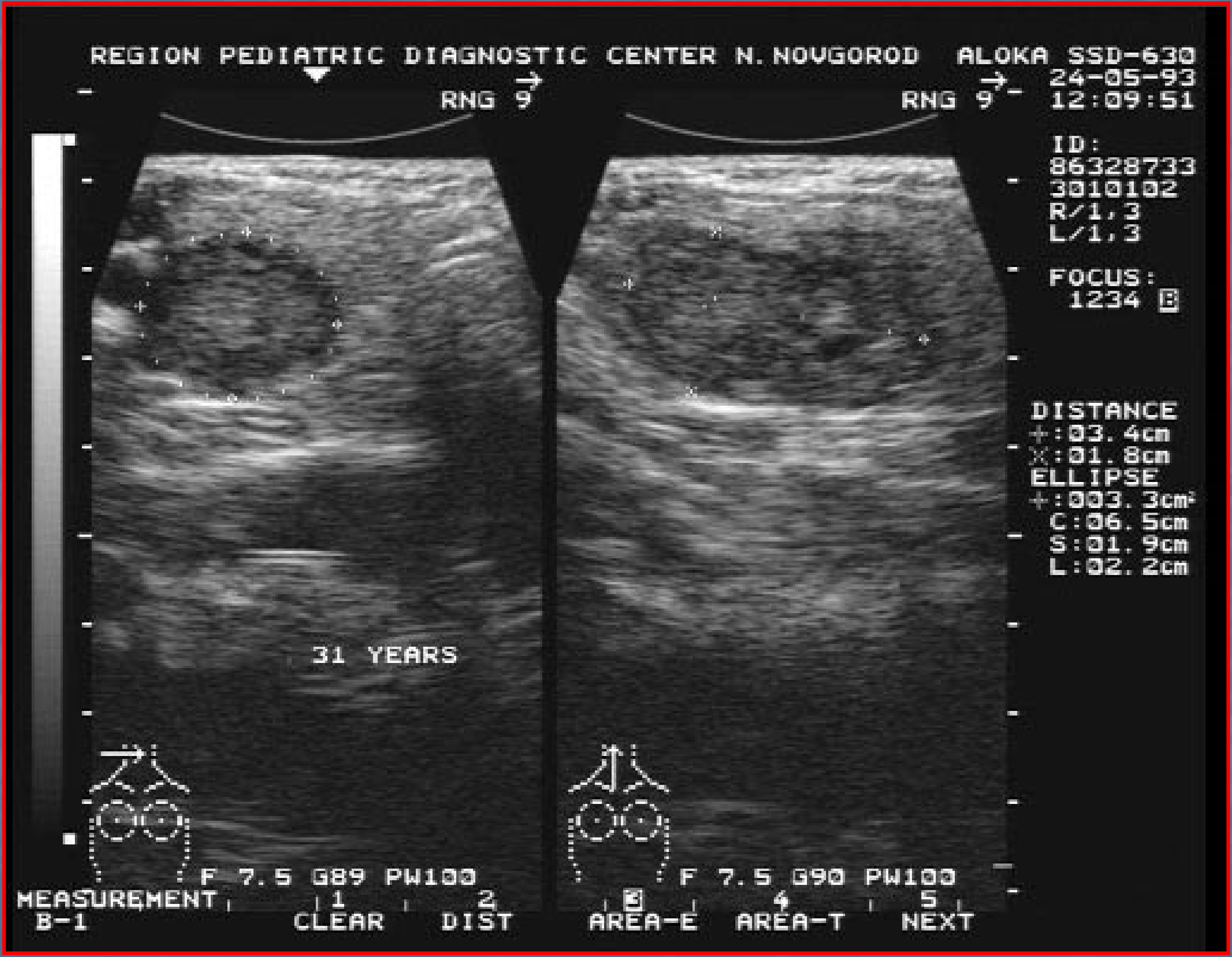
Tracheal Deviation



Thyroid ultrasound



Thyroid ultrasound



Ultrasonography

- Thyroid vs. non-thyroid
  - Good screen for thyroid presence in children
- Cystic vs. solid
- Localization for FNA or injection
- Serial exam of nodule size
  - 2-3 mm lower end of resolution
- May distinguish solitary nodule from multinodular goiter
  - Dominant nodule risks no different

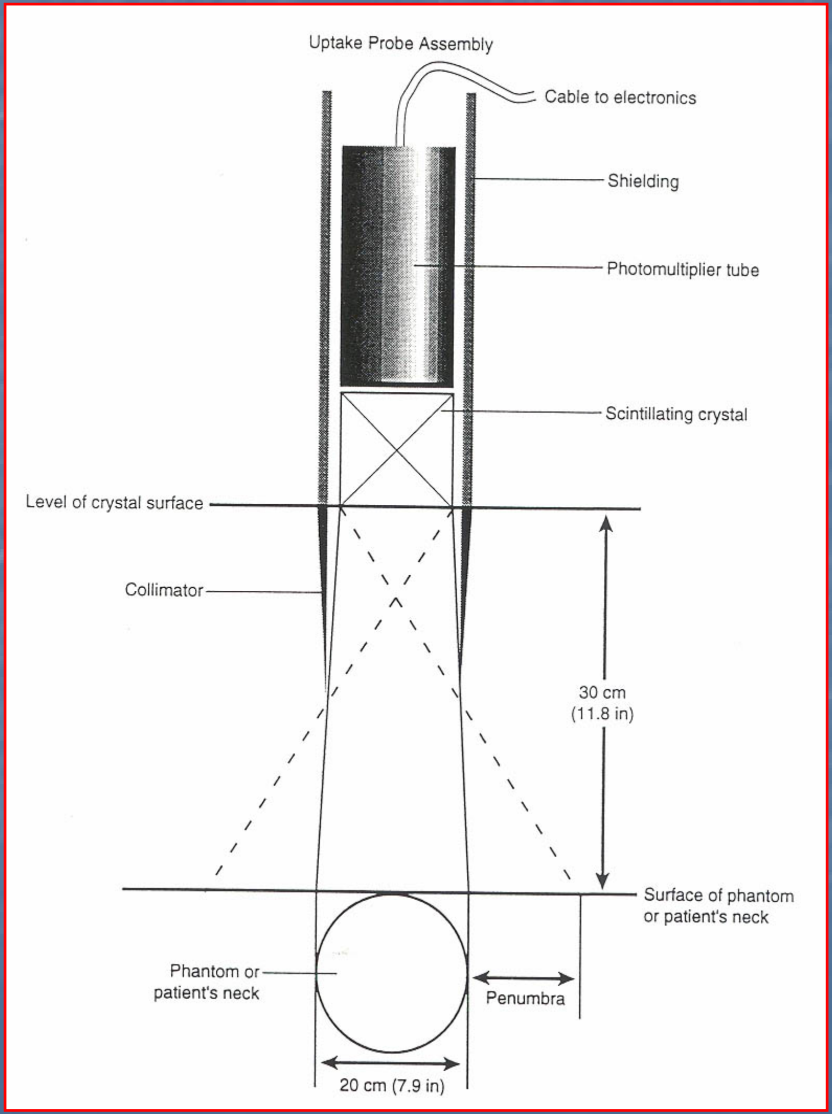
Ultrasonography

- Findings suggestive of malignancy:
  - Presence of halo
  - Irregular border
  - Presence of cystic components
  - Presence of calcifications
  - Heterogeneous echo pattern
  - Extrathyroidal extension
- No findings are definitive

Nuclear Medicine

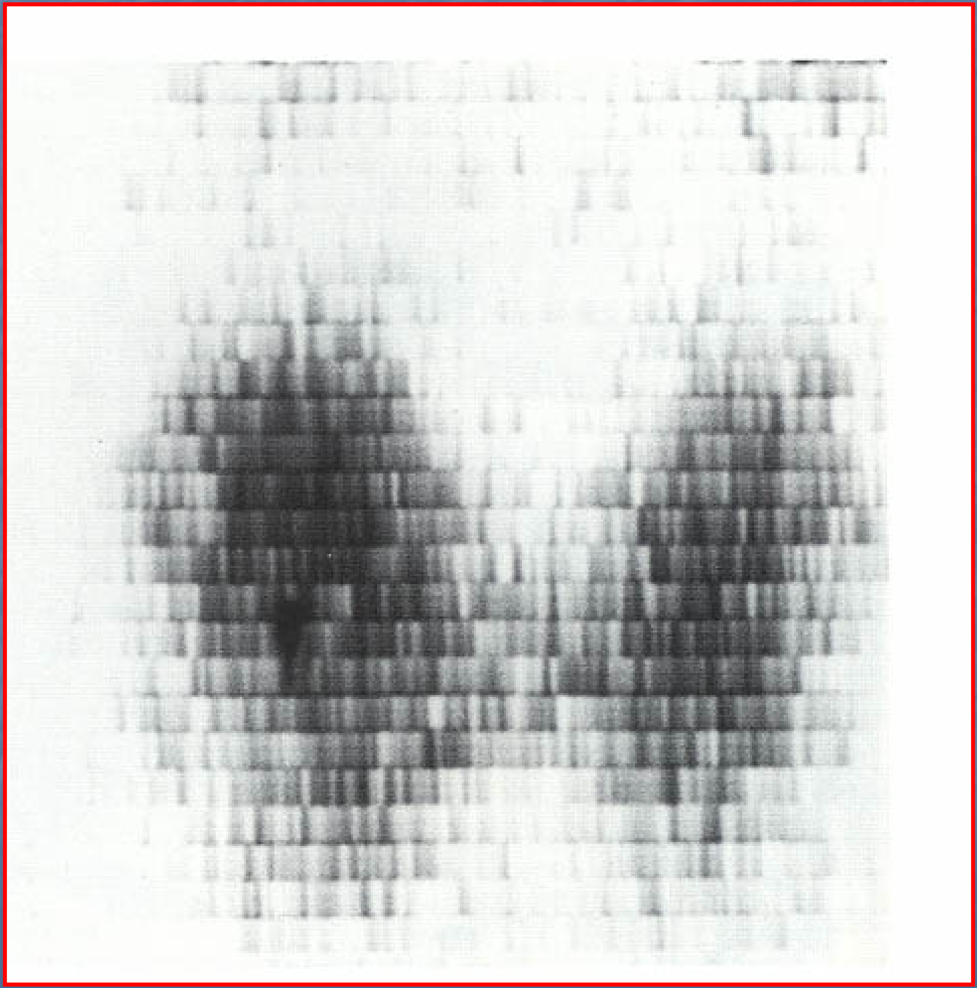
- Concept
- Uses
  - Metabolic studies
  - Imaging
- Iodine is taken up by gland and *organified*
- Technetium trapped but not organified
- Usually only for papillary and follicular
- Rectilinear scanner (historical interest) vs. scintillation camera

Nuclear Medicine



Rectilinear Scan

- Provided life-size images
- Not common today



Nuclear Medicine

- Radioisotopes:
  - I-131
  - I-123
  - I-125
  - Tc-99m
  - Thallium-201
  - Gallium 67

Nuclear Medicine

- Technetium 99m
  - Most commonly used isotope (some authors)
  - 99m: “m” refers to metastable nuclide
    - Decay product of Molybdenum-99
    - Long half-life before decaying into Tc-99
  - Administered as pertechnate ($TcO4^-$)
  - Images can be obtained quickly
    - “One-Stop” evaluation
  - Hot nodules need f/u Iodine scan
    - Discordant nodules higher risk of malignancy

Nuclear Medicine

- Iodine
  - 127 – only stable isotope of iodine
  - 123 – cyclotron product
    - Half-life 13.3 hr
    - Expensive, limited availability
    - Low radiation-exposure to patient
  - 131 – fission product
    - Half-life 8 days
    - Cheap, widely available
    - Better for mets (diagnostic and therapeutic) (high radiation exposure)
  - 125 – no longer used
    - Long half-life (60 days); high radiation exposure with poor visualization

Radioactive iodine uptake and scan

- Radio labeled Iodine (I-123) is given to the patient which is actively trapped and concentrated by the thyroid gland.
- It can assess:
  - ✓ Function → Uptake
  - ✓ Morphology → Scan

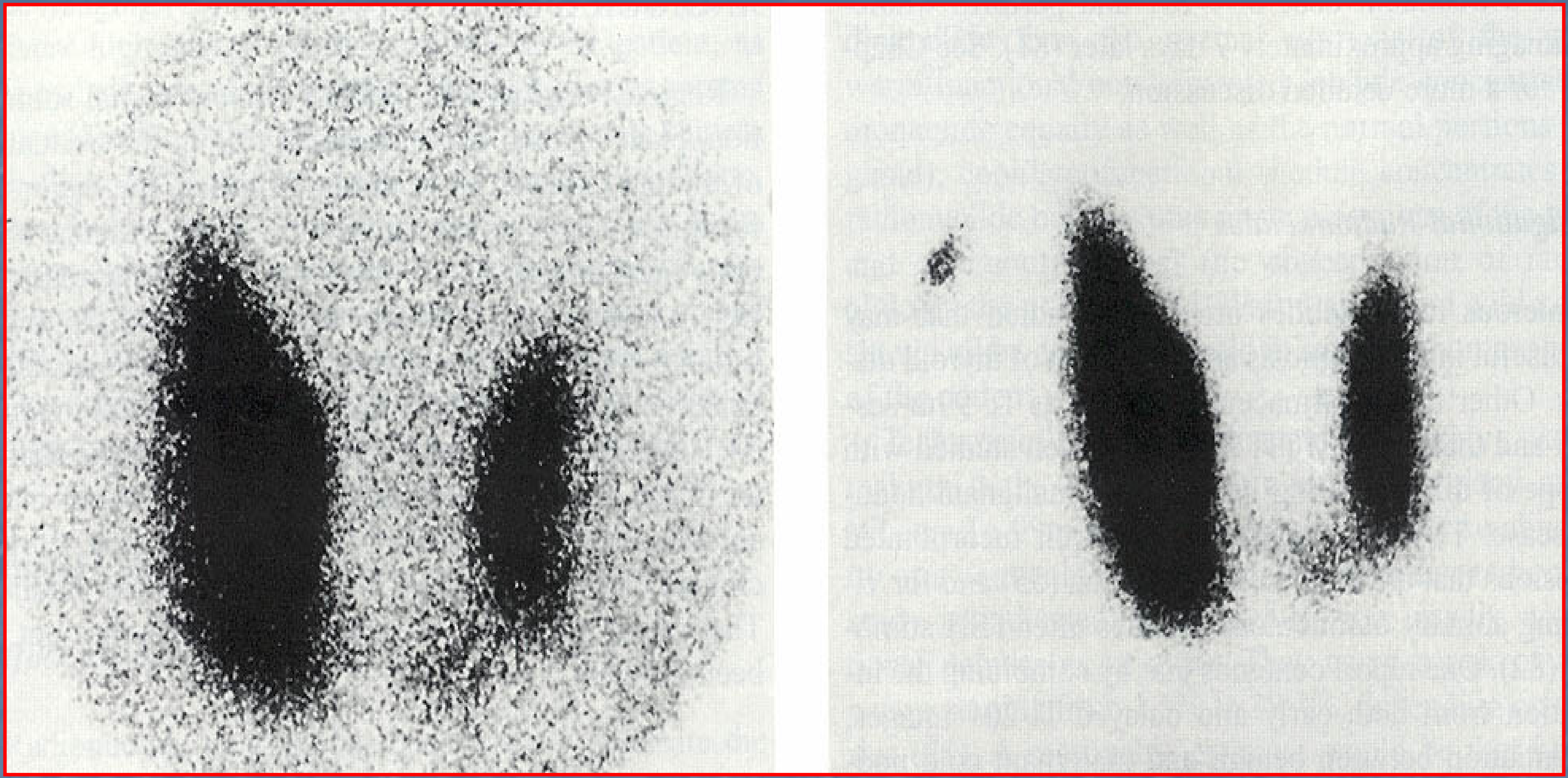
Radioactive iodine "uptake"

- Uptake:

-Measurements of % of the administered dose localizing to the gland at a fixed time.

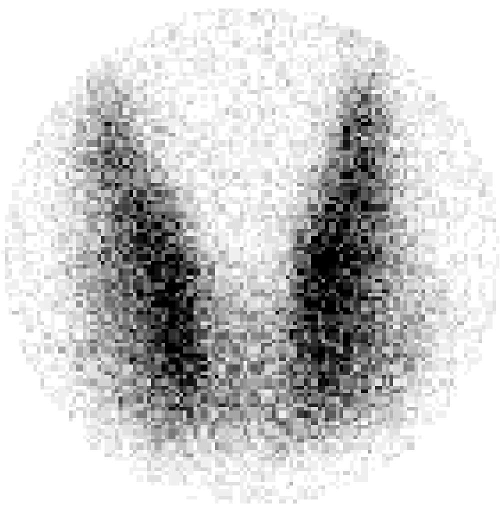
-Reflects gland function.

-Normal 24 hour uptake is ~10 to 30%.

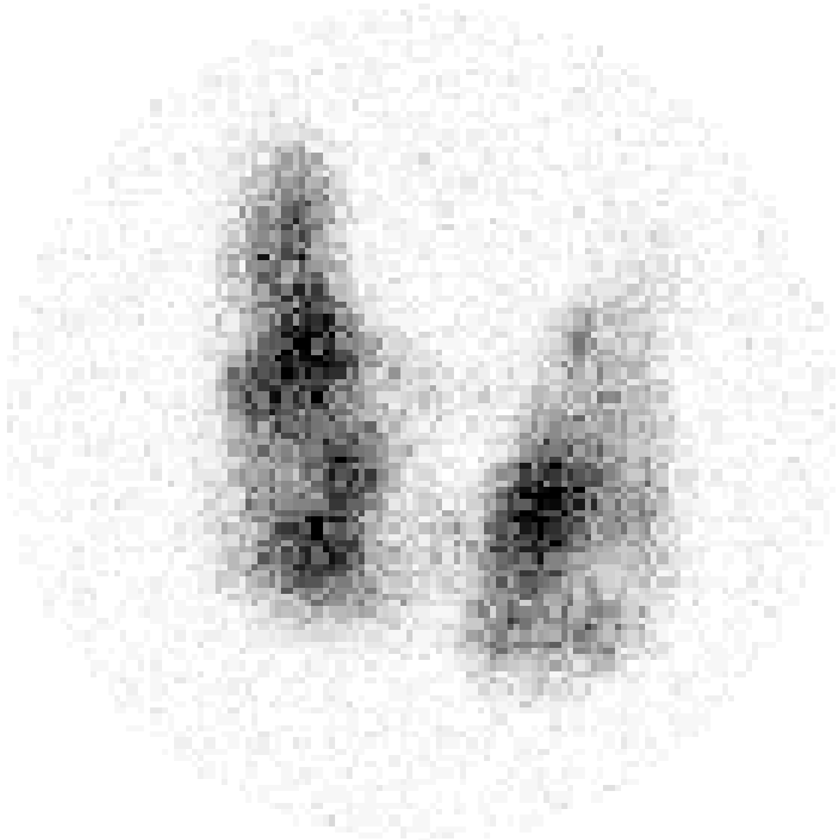


- Tc-99m versus I-123

Radioactive iodine "scan"



Normal Thyroid Scan

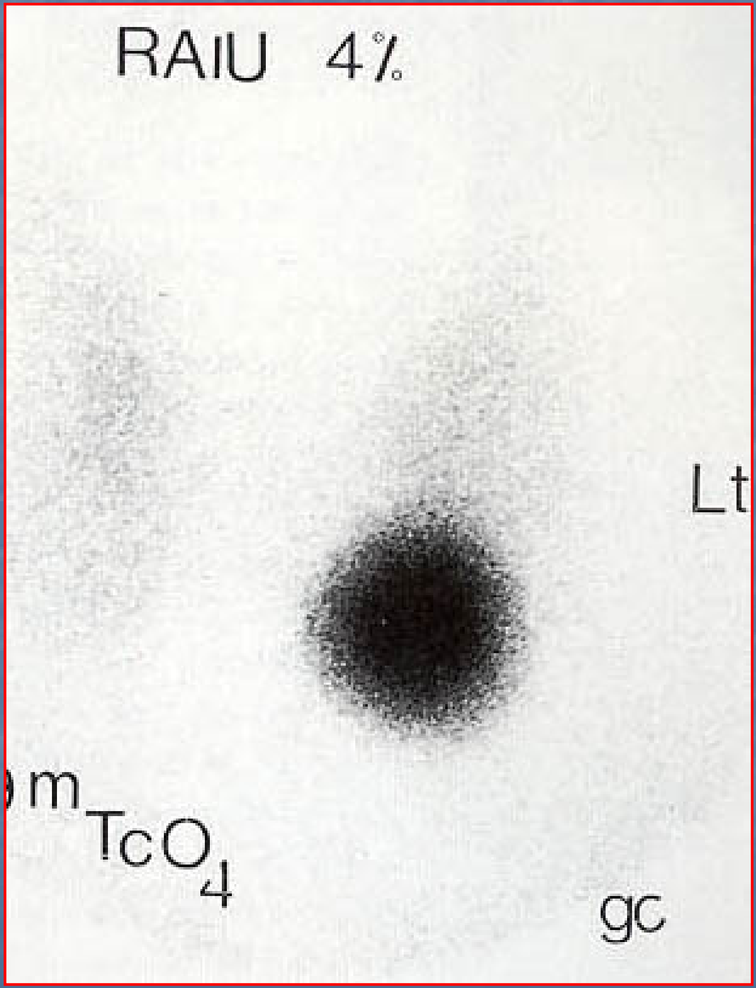


Nodular Thyroid

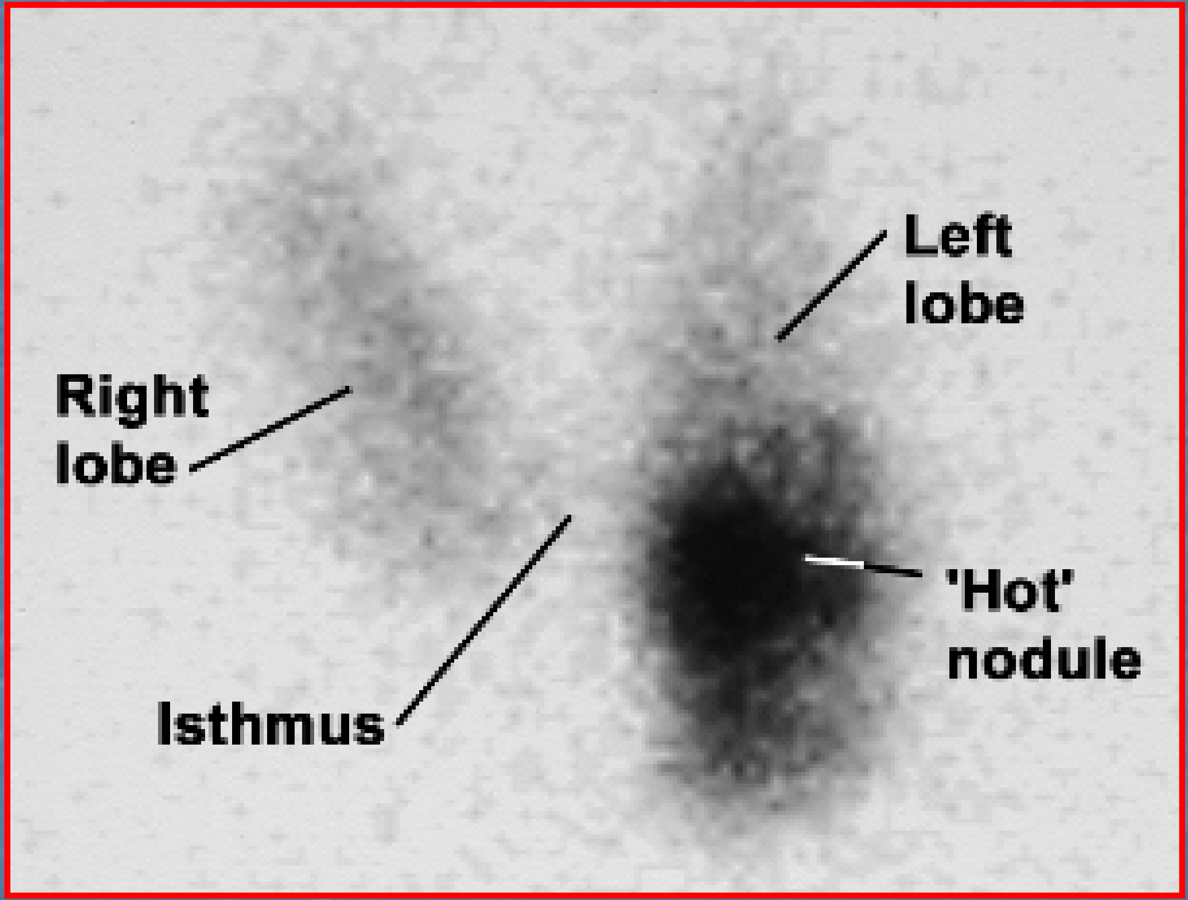
Combining "uptake" and "scan"

Any nodules can be "Hot", "Warm", or "Cold" depending on the intensity of the uptake.

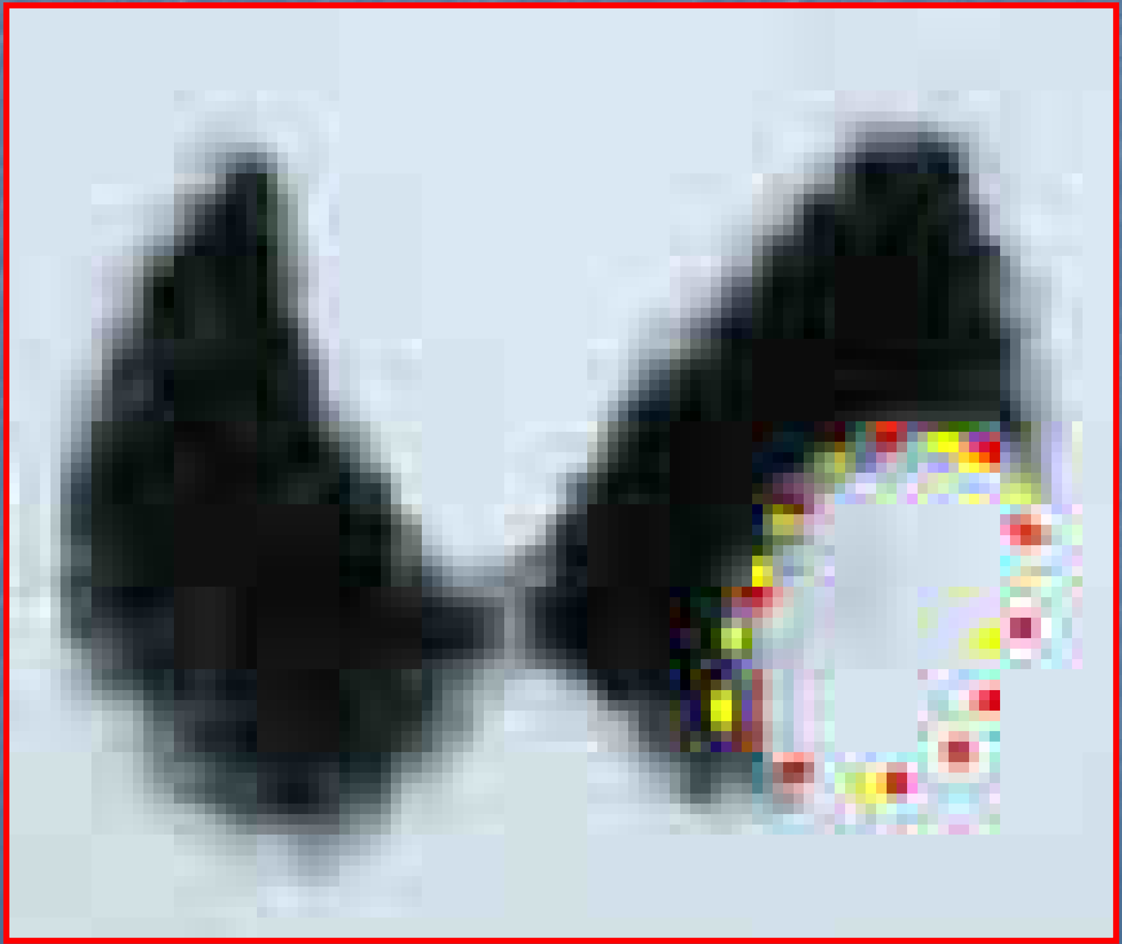
Hot Nodule



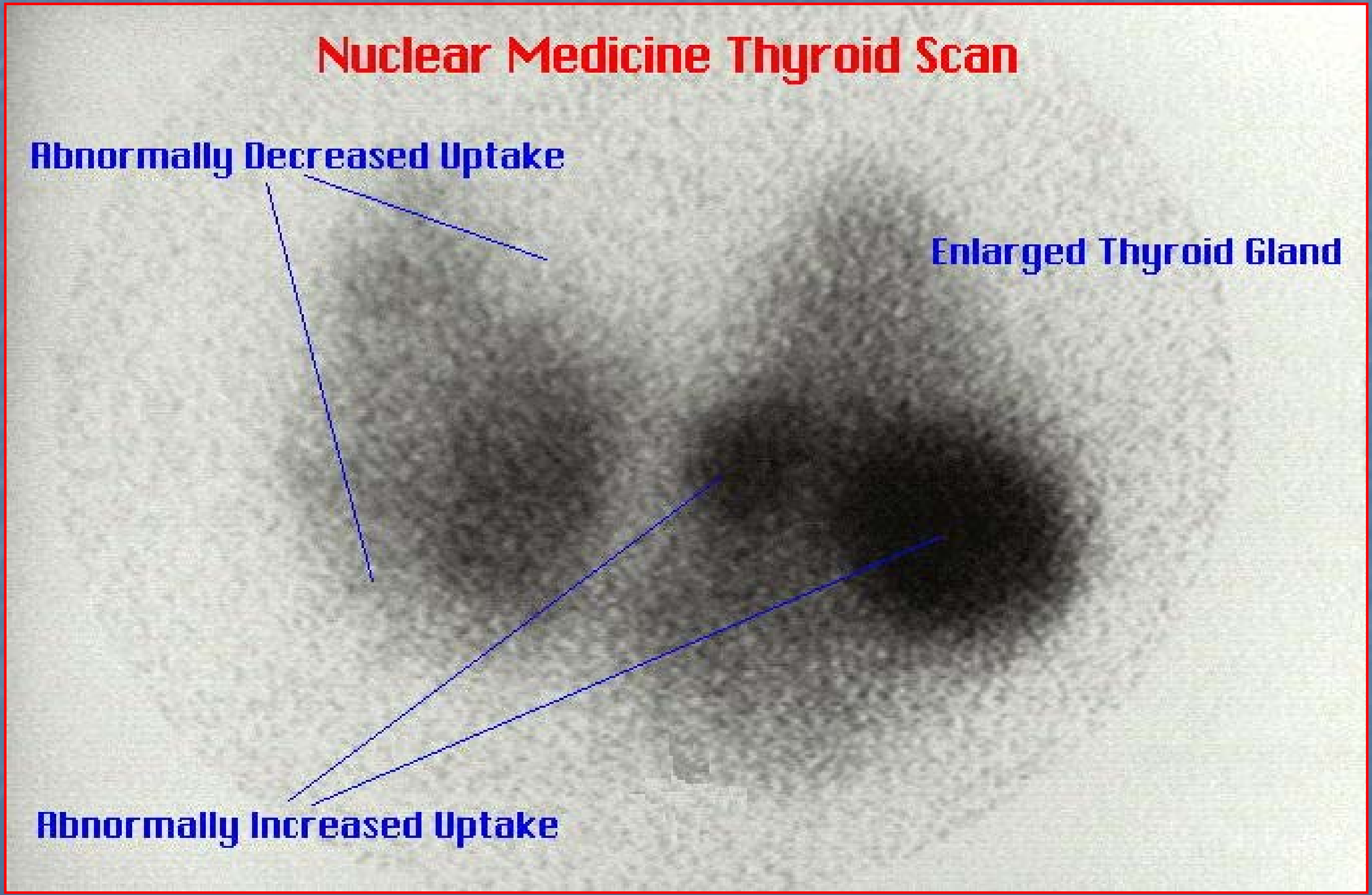
Hot nodule



Cold nodule



Multinodular Goiter



Radioactive iodine uptake and scan

- "Hot" nodules (autonomously functioning thyroid nodules) are usually not malignant, for practical purposes.
- "Cold" nodules (either hypofunctioning or nonfunctioning) can be malignant in approximately 5-8% of cases.

Nuclear Medicine

- Thallium-201
  - Expensive, role poorly defined
  - Can detect (but not treat) mets
  - Not trapped or organified – mechanism unclear
    - Potassium analogue
  - Potential advantages:
    - Not necessary to be off thyroid replacement
    - Patients with large body iodine pool (ex: recent CT with contrast) or hypofunctioning gland
    - Can sometimes image medullary

Nuclear Medicine

- Gallium-67
  - Generally lights up inflammation
    - Hashimoto's
  - Uses in thyroid imaging limited
    - Anaplastic
    - Lymphoma

Nuclear Medicine

- Other imaging agents
  - Tc-99m sestamibi
  - Tc-99m pentavalent DMSA
  - Radioiodinated MIBG
    - Developed for medullary (APUD derivative)
  - Radiolabeled monoclonal antibodies

Nuclear Medicine

- Hurthle-cell neoplasms
  - Better imaged with Technetium sestamibi
    - Concentrates in mitochondira
  - Poorly imaged with iodine

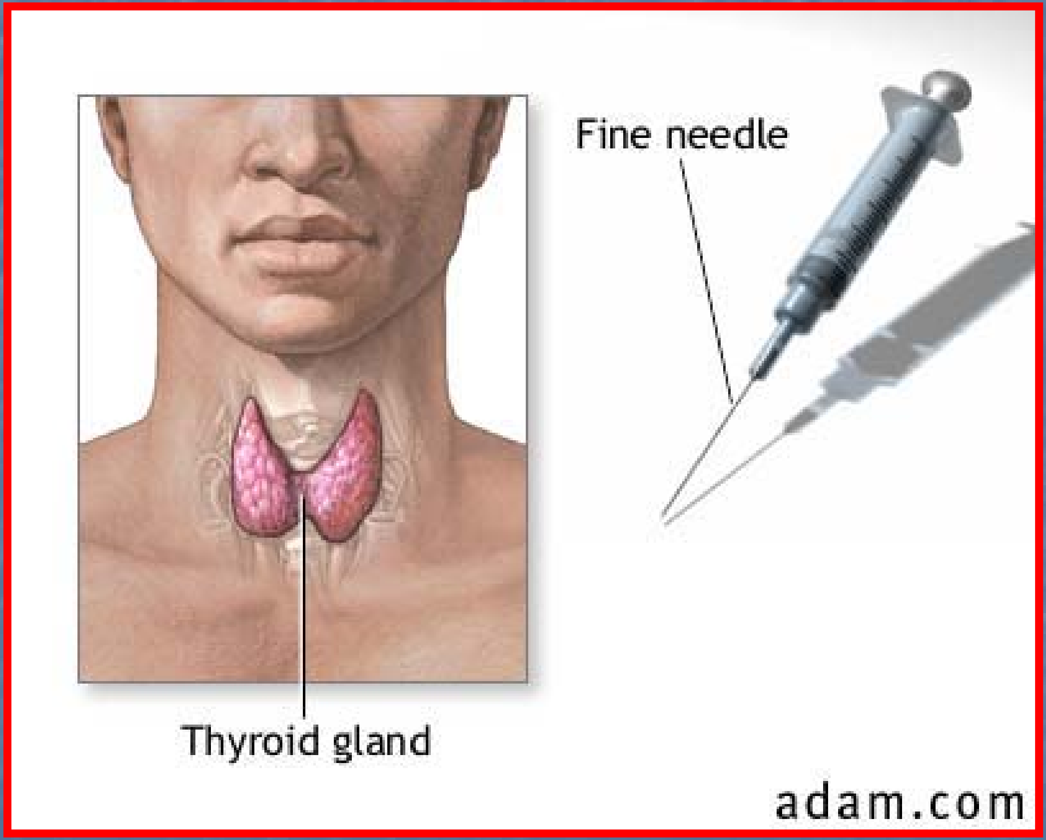
Other Imaging Modalities

- CT
  - Keep in mind iodine in contrast
- MRI
- PET

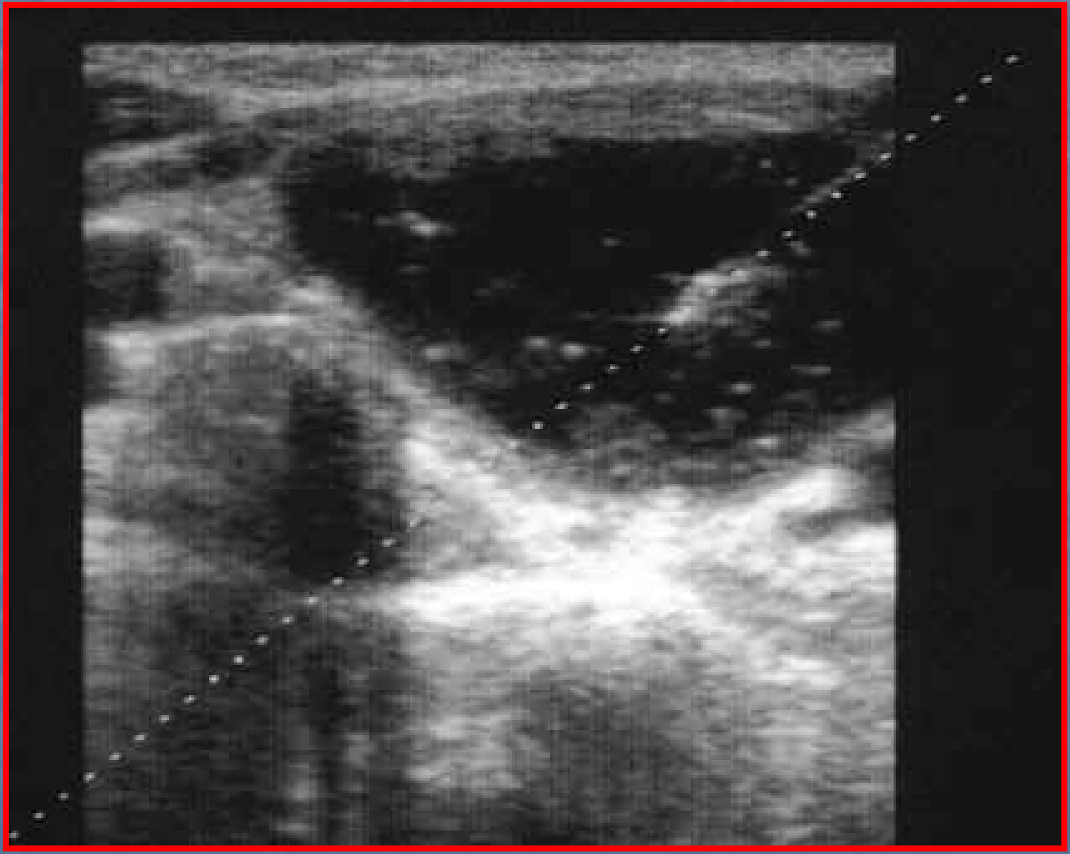
- Not first-line, but may be adjunctive

MRI

Fine Needle Aspiration (FNA)



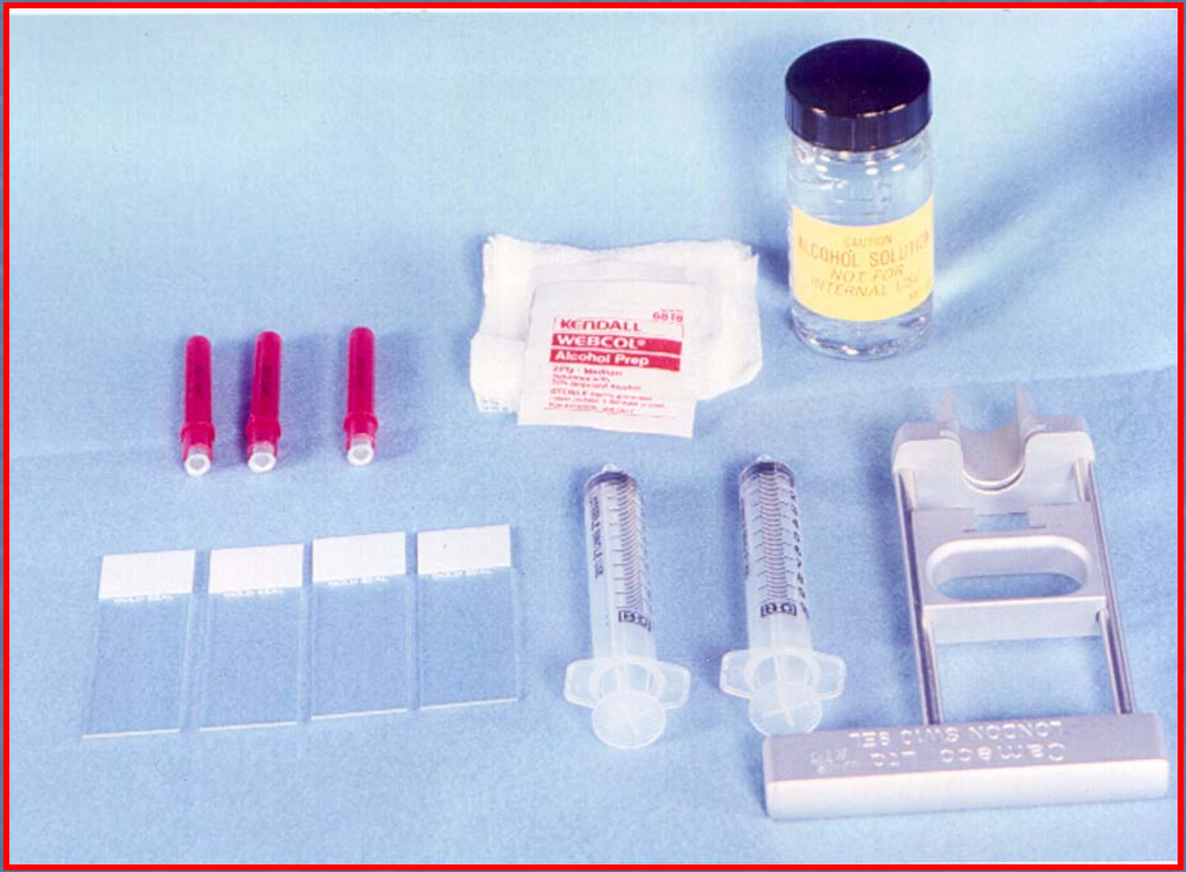
US Guided FNA



Fine-Needle Aspiration Biopsy

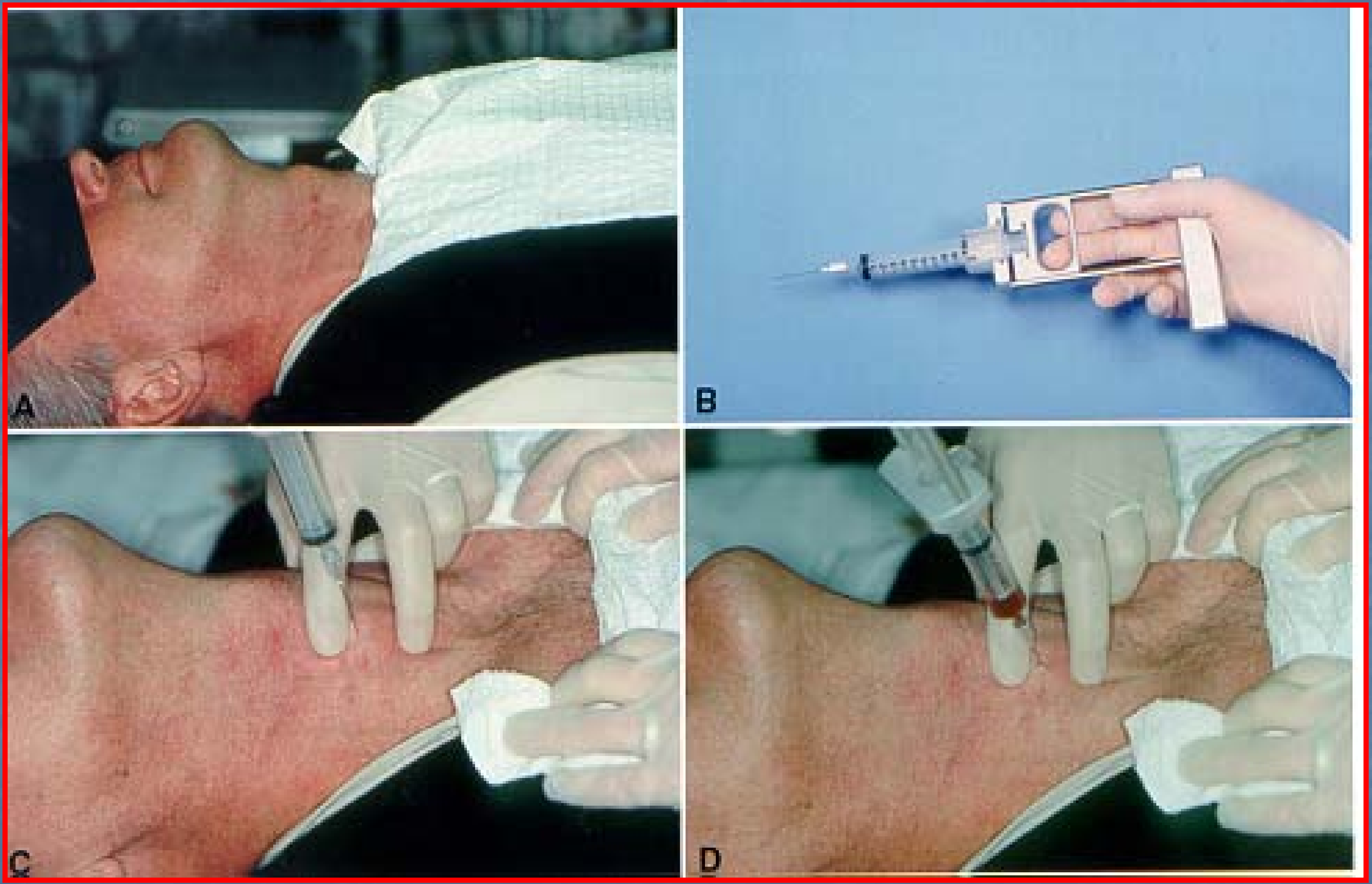
- Technique:
  - 25-gauge needle
  - Multiple passes
  - Ideally from periphery of lesion
  - Reaspirate after fluid drawn
  - Immediately smeared and fixed
  - Papanicolaou stain common

Fine-needle aspiration (FNA) biopsy



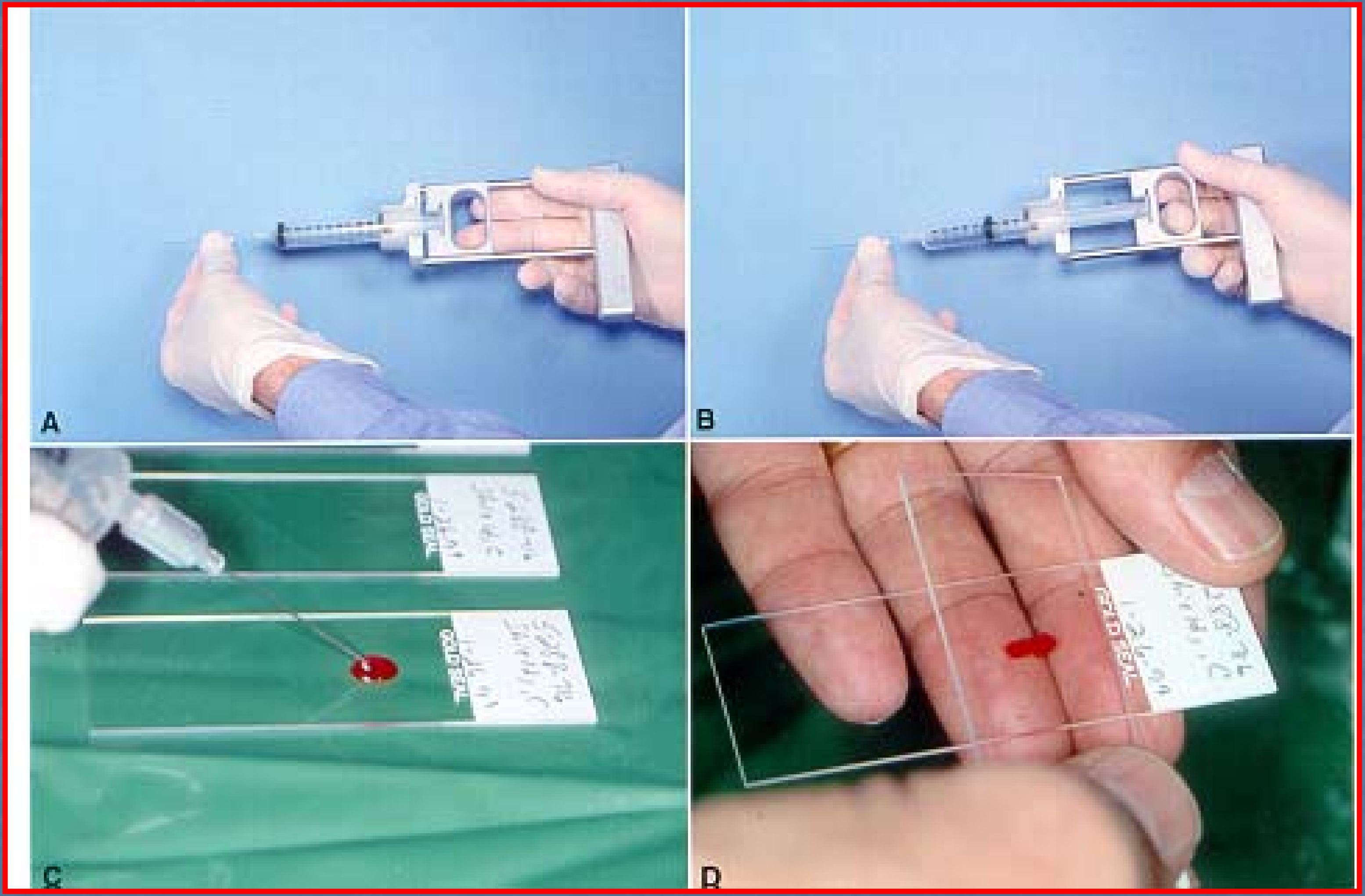
Source: Thyroid Disease Manager

FNA biopsy



Source: Thyroid Disease Manager

FNA biopsy



Source: Thyroid Disease Manager

FNA results

- Inadequate specimen
- Adequate specimen
  - Benign
  - Malignant
  - Suspicious

Fine-Needle Aspiration Biopsy

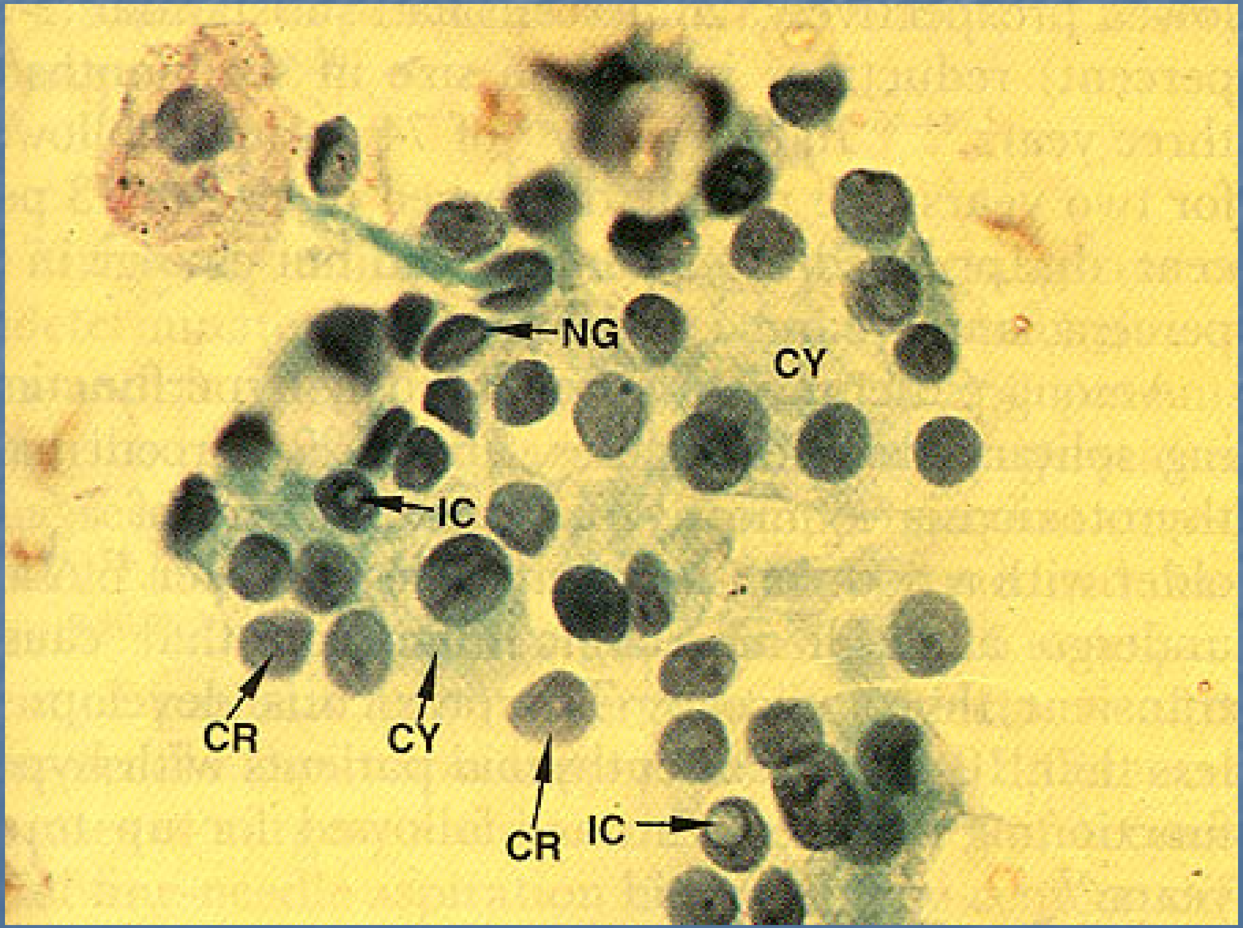
- Emerged in 1970s – has become standard first-line test for diagnosis
- Concept
- Results comparable to large-needle biopsy, less complications
- Safe, efficacious, cost-effective
- Allow preop diagnosis and therefore planning
- Some use for sclerosing nodules

Fine-Needle Aspiration Biopsy

- Problems:
  - Sampling error
    - Small (<1 cm)
    - Large (>4 cm)
  - Hashimoto's versus lymphoma
  - Follicular neoplasms
  - Fluid-only cysts
  - Somewhat dependent on skill of cytopathologist

FNA of Papillary Ca

- NG: nuclear grooves
- IC: intranuclear inclusions



Tarek Mahdy

Ass Professor of Endocrine And Bariatric Surgery

Mansoura Faculty Of Medicine

Mansoura - Egypt

Disorders of the Thyroid Gland

- **Abnormal thyroid function**
  - Hypothyroidism
  - Hyperthyroidism

- **Thyroid enlargement**

  Structural Thyroid Disease

Abnormal thyroid function

- Hypothyroidism
- Hyperthyroidism

Hypothyroidism

- Hypothyroidism is a disorder with multiple causes in which the thyroid fails to secrete an adequate amount of thyroid hormone
  - The most common thyroid disorder
  - Usually caused by primary thyroid gland failure
  - Also may result from diminished stimulation of the thyroid gland by TSH

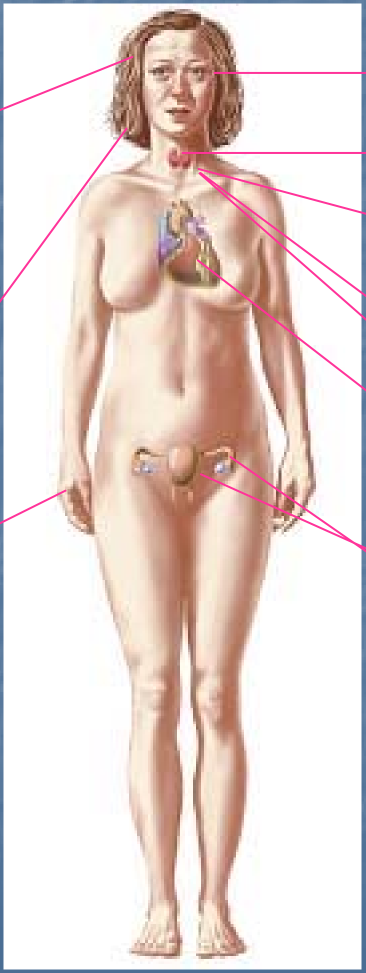
Hyperthyroidism

- Hyperthyroidism refers to excess synthesis and secretion of thyroid hormones by the thyroid gland, which results in accelerated metabolism in peripheral tissues

Typical Thyroid Hormone Levels in Thyroid Disease

	TSH	T_4	T_3
Hypothyroidism	High	Low	Low
Hyperthyroidism	Low	High	High

Clinical Features of Hypothyroidism



Tiredness

Forgetfulness/Slower Thinking

Moodiness/ Irritability

Depression

Inability to Concentrate

Thinning Hair/Hair Loss

Loss of Body Hair

Dry, Patchy Skin

Weight Gain

Cold Intolerance

Elevated Cholesterol

Family History of Thyroid Disease or Diabetes

Puffy Eyes

Enlarged Thyroid (Goiter)

Hoarseness/ Deepening of Voice

Persistent Dry or Sore Throat

Difficulty Swallowing

Slower Heartbeat

Menstrual Irregularities/ Heavy Period

Infertility

Constipation

Muscle Weakness/ Cramps

Hypothyroidism

Hypothyroid Face

Notice the apathetic facies, bilateral ptosis, and absent eyebrows

Faces of Clinical Hypothyroidism

Hypothyroidism

Clinical Presentations

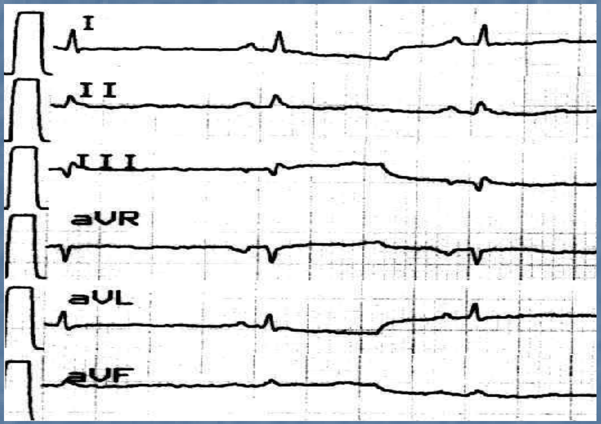
- Easy fatigability
- Coldness
- Weight gain
- Constipation
- Menstrual irregularities
- Muscle crumps
- Hair loss
- Difficulty concentrating

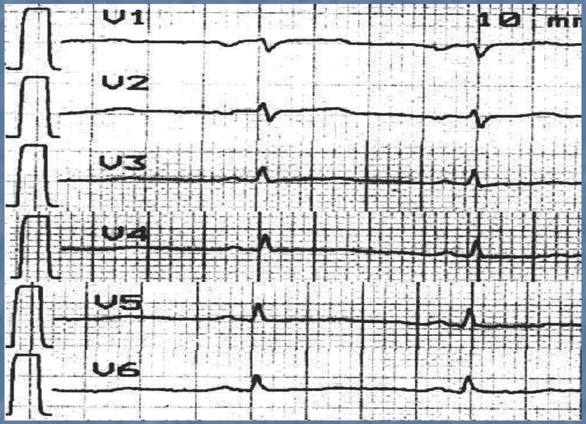
Clinical Findings

- Skin – cool, rough, dry
  yellowish color
  (carotenemia)
- Face – puffy
- Voice – hoarse
- Reflexes – slow
- Bradycardia
- Peripheral nonpitting edema

Hypothyroidism

- CVS :
  - Impaired muscular contraction
  - EKG - bradycardia, low voltage of QRS complexes and P and T waves





  - Echo - cardiac enlargement, pericardial effusion

Hypothyroidism

- Pulmonary function :
  - Respirations – shallow and slow
  - Impaired ventilatory response to hypercapnia
- Anemia :
  - Impaired Hb synthesis
  - Iron and folate deficiency
  - Pernicious anemia
- Renal function :
  - Decreased GFR
  - Impaired ability to excrete water load

Hypothyroidism

- Neuromuscular system :
  - Muscle crumps and weakness
  - Paresthesias
  - Carpal tunnel syndrome
- CNS symptoms :
  - Lethargy
  - Inability to concentrate
  - Depression

Hypothyroidism

Diagnostic Studies

- Thyroid function tests
  - TSH, fT_4, TT_3
- Thyroid autoantibodies
  - Anti TPO, Anti Tg
- Ultrasonography
  - Enlarged thyroid gland with a diffusely hypoechogenic pattern
- Other Laboratory Studies: Elevated cholesterol and TG, anemia, elevated CPK

Causes of Hypothyroidism

- **Primary ($fT_4 \downarrow$; TSH $\uparrow$)**
  - **Autoimmune (Hashimoto's) thyroiditis**
  - Iatrogenic: ^{131}I treatment, ionizing external irradiation, subtotal or total thyroidectomy
  - Drugs: Amiodarone, Lithium, Interferon-α, Interleukin-2
  - Congenital: absent or ectopic thyroid gland, dyshormonogenesis, TSH-R mutation
  - Iodine deficiency
  - Infiltrative disorders: amyloidosis, sarcoidosis, hemochromatosis, scleroderma, cystinosis

Causes of Hypothyroidism

- **Central - Hypothalamic-pituitary dysfunction**
  ($fT_4\downarrow$; TSH N / $\downarrow$)
  - Tumors
  - Pituitary surgery or irradiation
  - Infiltrative disorders
  - Trauma
  - Genetic forms of CPHD or isolated TSH deficiency
- **Transient (fT_4 N / $\downarrow$ / $\uparrow$; TSH $\uparrow$ / N / $\downarrow$)**
  - Silent thyroiditis including post-partum thyroiditis

Autoimmune (Hashimoto's) Thyroiditis

- Prevalence
  - 5% - 15% of women
  - 1% - 5% of men
- Sex ratio (F:M) - 8-9:1
- Diagnostic criteria
  - Positive test for thyroid autoantibodies
  - Presence of lymphocytic infiltration of thyroid
  - Goiter
  - Thyroid functions: 50%-75% - euthyroid
    25%-50% - subclinucal hypothyroidism
    5%-10% - overt hypothyroidism

Autoimmune (Hashimioto's) Thyroiditis

Associations with other diseases

IDDM (Insulin dependent diabetes mellitus)

Autoimmune polyendocrinopathy diseases

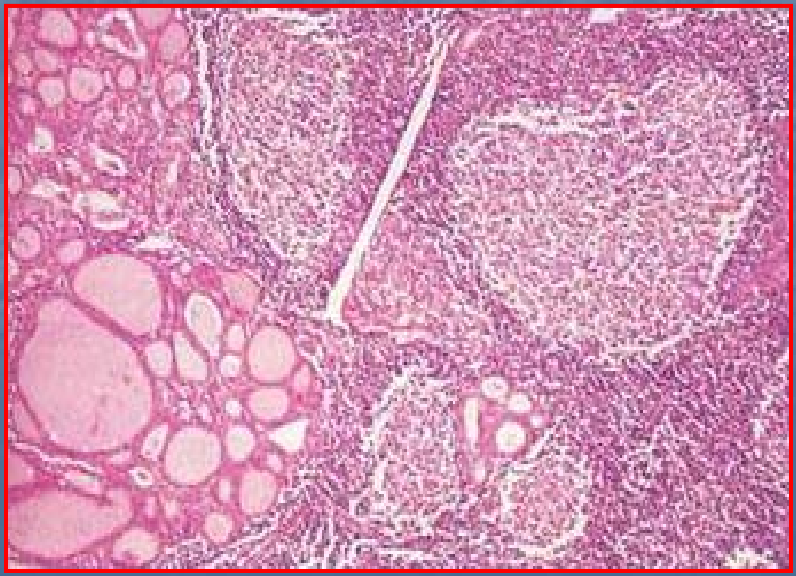
- Type 1: mococutaneous candidiadis, hypoparathyroidism, Addison's disease, alopecia, primary hypogonadism ...
- Type 2: Addison's disease, thyroiditis, IDDM ...

Pernicious anemia
Addison's disease
Myasthenia gravis
Vitiligo
Celiac disease

Turner syndrome (50%)
Down syndrome (20%)
Klienfelter syndrome

Hashimoto's
(Chronic, Lymphocytic)

- Most common cause of hypothyroidism
- Usually non-tender and asymptomatic
- Bossalated



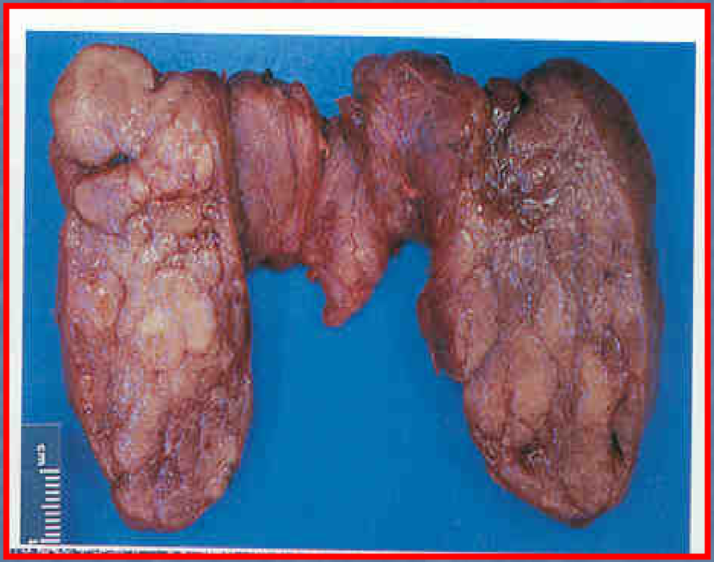
Antibodies in Hashimoto's

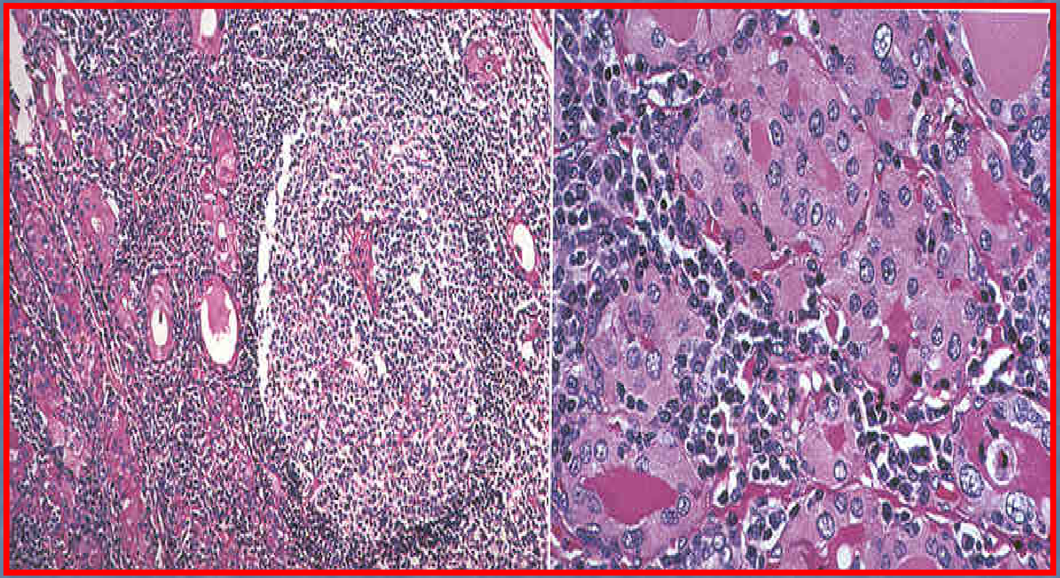
- Antimicrosomal abys
  - Against peroxidase
- Antithyroglobulin abys
  - Against thyroglobulin
- Autoantibodies against TSH receptor
  - Net effect is prevent TSH stimulation of gland

Hashimoto's Thyroiditis

- ***Treatment***
  - **Levothyroxine if hypothyroid**
  - **Triiodothyronine (for myxedema coma)**
  - **Thyroid suppression (levothyroxine) to decrease goiter size**
  - **Surgery for compression or pain or suspicious of malignant**

Gross and Microscopic Pathology of Chronic Thyroiditis

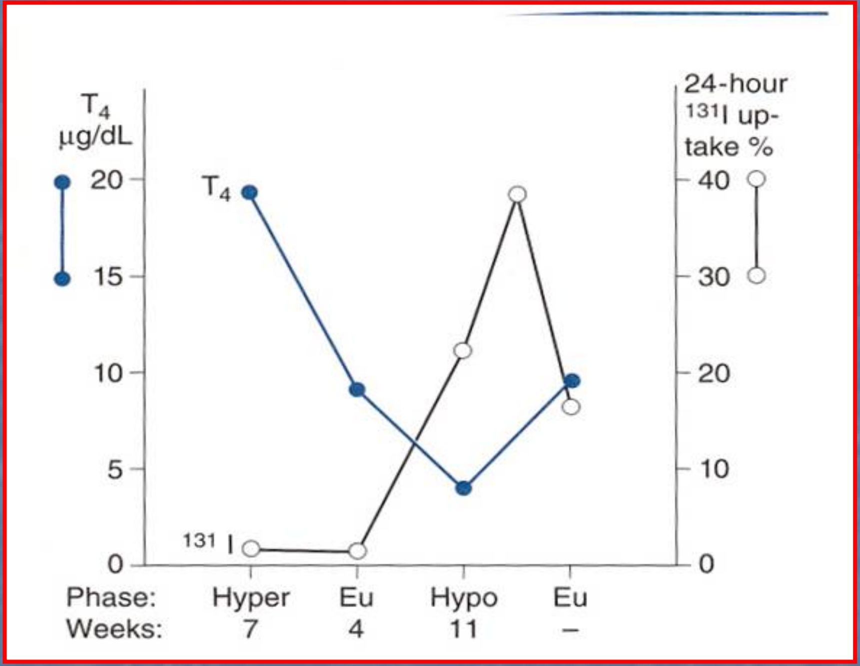




Subacute Thyroiditis

DeQuervain's, Granulomatous

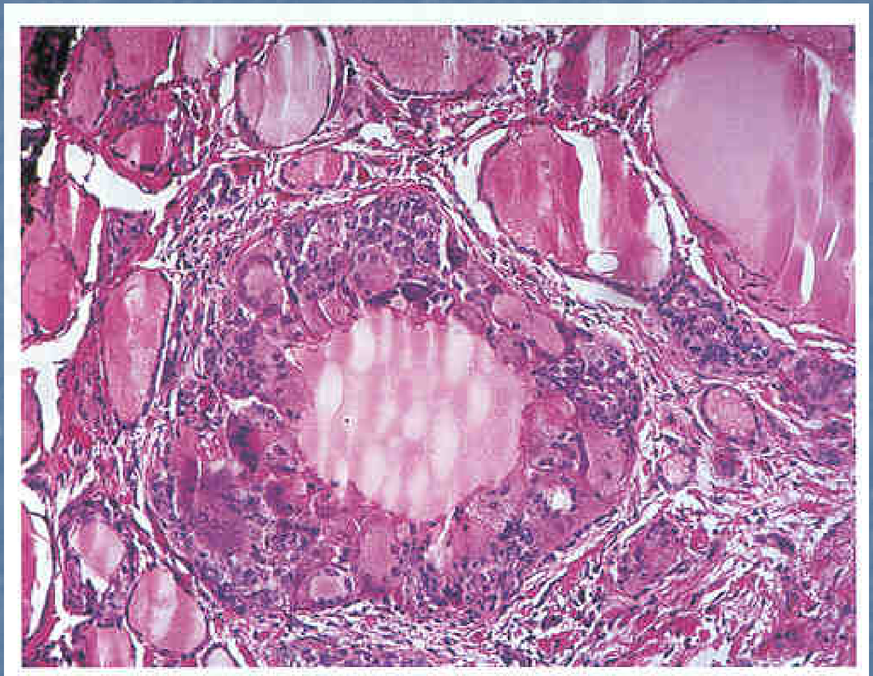
- Most common cause of painful thyroiditis
- Often follows a URI
- FNA may reveal multinuleated giant cells or granulomatous change.
- Course
  - Pain and thyrotoxicosis (3-6 weeks)
  - Asymptomatic euthyroidism
  - Hypothyroid period (weeks to months)
  - Recovery (complete in 95% after 4-6 months)



Subacute Thyroiditis

- Diagnosis
  - Elevated ESR
  - Anemia (normochromic, normocytic)
  - Low TSH, Elevated T4 > T3, Low anti-TPO/Tgb
  - Low RAI uptake (same as silent thyroiditis)
- Treatment
  - NSAID's and salicylates.
  - Oral steroids in severe cases
  - Beta blockers for symptoms of hyperthyroidism, Iopanoic acid for severe symptoms
  - PTU not indicated since excess hormone results from leak instead of hyperfunction
  - Symptoms can recur requiring repeat treatment
  - Graves' disease may occasionally develop as a late sequellae

Histopathology of Subacute Thyroiditis



Silent Thyroiditis

- Silent thyroiditis is termed painless Subacute Thyroiditis Clinical
  - Hyperthyroid symptoms at presentation
  - Progression to euthyroidism followed by hypothyroidism for up to 1 year.
  - Hypothyroidism generally resolves
- Diagnosis
  - May be confused with post-partum Graves' relapse
- Treatment
  - Beta blockers during toxic phase
  - No anti-thyroid medication indicated
  - Iopanoic acid (Telopaque) for severe hyperthyroidism
  - Thyroid hormone during hypothyroid phase. Must withdraw in 6 months to check for resolution.

Postpartum Thyroiditis

- Underlying autoimmune thyroid disease
- Up to 5% of women 3-6 months after pregnancy
- Transient
- Goiter - painless, small, non-tender, firm, diffuse
- Hyperthyroidism followed by hypothyroidism and resolution within 12 weeks
- Positive antithyroid antibodies; Thyroid scan – no uptake

Postpartum Thyroiditis

- May occur in 5% of women with no known thyroid disease
- Clinically
  - 44% hypothyroid
  - 33% thyrotoxicosis
  - 33% thyrotoxicosis followed by hypothyroidism
  - Treatment
    - Thyrotoxic phase – not necessary
    - Hypothyroid phase – levothyroxine

Acute Thyroiditis

- Causes
  - 68% Bacterial (S. aureus, S. pyogenes)
  - 15% Fungal
  - 9% Mycobacterial
- May occur secondary to
  - Pyriform sinus fistulae
  - Pharyngeal space infections
  - Persistent Thyroglossal remnants
  - Thyroid surgery wound infections (rare)
- More common in HIV

Acute Thyroiditis

- Diagnosis
  - Warm, tender, enlarged thyroid
  - FNA to drain abscess, obtain culture
  - RAIU normal (versus decreased in DeQuervain's)
  - CT or US if infected TGDC suspected
- Treatment
  - High mortality without prompt treatment
  - IV Antibiotics
    - Nafcillin / Gentamycin or Rocephin for empiric therapy
  - Search for pyriform fistulae (BA swallow, endoscopy)
  - Recovery is usually complete

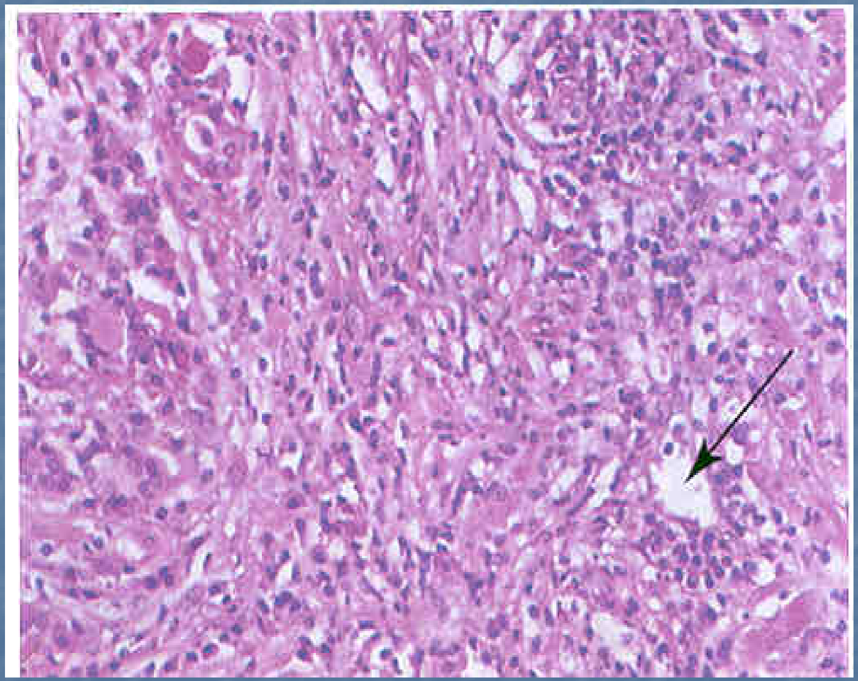
Riedel's Thyroiditis

- Rare disease involving fibrosis of the thyroid gland

- Diagnosis
  - Thyroid antibodies are present in 2/3
  - Painless goiter **"woody"**
  - Open biopsy often needed to diagnose
  - Associated with focal sclerosis syndromes (retroperitoneal, mediastinal, retroorbital, and sclerosing cholangitis)

- Treatment
  - Resection for compressive symptoms
  - Chemotherapy with Tamoxifen, Methotrexate, or steroids may be effective
  - Thyroid hormone only for symptoms of hypothyroidism

Histopathology of Riedel's Thyroiditis



Hypothyroidism

Treatment

- Overt hypothyroidism

  Thyroxine 1.6 mcg/kg/day (100-150 mcg/day)

  (elderly patients – lower dose)

  Adjustment: on the basis of TSH levels

- Sub-clinical / mild hypothyroidism

  Thyroxine

  - Symptoms attributable to hypothyroidism
  - TSH > 8 – 10 mU/L
  - Strongly positive thyroid autoantibodies
  - Goiter

  Surveillance – TSH measurements q 6mo

- Euthyroid goiter and positive thyroid autoantibodies

  Thyroxine

Hypothyroidism

Toxic Effects of Levothyroxine Therapy

- Cardiac symptoms
  (Paroxysmal atrial tachycardia or fibrillation)
- Restlessness and insomnia
- Tremor
- Excessive warmth
- Osteopenia

Hypothyroidism

Course and Prognosis

Treatment of hypothyroidism

Thyroxine - aiming to normalise the serum TSH concentration

Before

After

NB - always check for angina and perform an ecg

Hypothyroidism

Complications

- Myxedema and heart disease
- Neuropsychiatric disease – myxedema madness
- Myxedema coma
- Thyroid lymphoma or carcinoma

Myxedema
Long-standing *hypo*thyroidism

- Stress & starvation decrease thyroid function
  - provoked by sedatives, opioids, illness

- Periorbital edema, facial puffiness, masklike affect
  - also, intense cold intolerance, profound lethargy

- **Can progress coma: *a medical emergency***
  - Monitor vital signs & LOC
  - Respiratory support
  - Cardiac monitoring
  - Administer medications IV (Thyroid hormone)

Myxedema Characteristics

- Described as;
- Face is expression less when at rest, puffy, pale, heavy
- Skin of the face is parchment-like.
- In spite of the swelling it may be traced with fine wrinkles,
- Swelling sometimes gives face a round or moonlike appearance
- When spoken to, usually responds with a smile, which spreads after a latent period very slowly over the face.

Myxedema Coma

- The progression of *hypo*thyroid if remained
  - Decreasing mental ability
  - Cardio vascular collapse
  - Severe electrolyte imbalance
  - Cerebral hypoxia (elevated CO_2 levels)
  - Comatose
  - Severe hypothermia

- Monitor airway, breathing, circulation

Sick Euthyroid Syndrome

- Background – Acute and severe illness
  No underlying thyroid disease

- Pathogenesis – Release of cytokines

- Thyroid function tests – reduced TT_3 and fT_3
  increased rT_3
  normal TSH and fT_4

An adaptive state in order to limit catabolism

Mild Thyroid Failure

Definition of Mild Thyroid Failure

- Elevated TSH level (>4.0 μIU/mL)
- Normal total or free serum T_4 and T_3 levels
- Few or no signs or symptoms of hypothyroidism

Causes of Mild Thyroid Failure

- Exogenous factors
  - Levothyroxine underreplacement
  - Medications, such as lithium, cytokines, or iodine-containing agents (eg, amiodarone)
  - Antithyroid medications
  - ^{131}I therapy or thyroidectomy
- Endogenous factors
  - Previous subacute or silent thyroiditis
  - Hashimoto thyroiditis

Prevalence and Incidence of Mild Thyroid Failure

- Prevalence
  - 4% to 10% in large population screening surveys
  - Increases with increasing age
  - Is more common in women than in men
- Incidence
  - 2.1% to 3.8% per year in thyroid antibody-positive patients
  - 0.3% per year in thyroid antibody-negative patients

McDermott MT, et al. *J Clin Endocrinol Metab*. 2001;86:4585-4590.

Caraccio N, et al. *J Clin Endocrinol Metab*. 2002;87:1533-1538.

Biondi B, et al. *Ann Intern Med*. 2002;137:904-914.

Populations at Risk for Mild Thyroid Failure

- Women
- Prior history of Graves disease or postpartum thyroid dysfunction
- Elderly
- Other autoimmune disease
- Family history of
  - Thyroid disease
  - Pernicious anemia
  - Type 1 Diabetes mellitus

Caraccio N, et al. *J Clin Endocrinol Metab*. 2002;87:1533-1538.

Carmel R, et al. *Arch Intern Med*. 1982;142:1465-1469.

Perros P, et al. *Diabetes Med*. 1995;12:622-627.

Mild Thyroid Failure Affects Cardiac Function

- Cardiac function is subtly impaired in patients with mild thyroid failure
- Abnormalities can include
  - Subtle abnormalities in systolic time intervals and myocardial contractility
  - Diastolic dysfunction at rest or with exercise
  - Reduction of exercise-related stroke volume, cardiac index, and maximal aortic flow velocity
- The clinical significance of the changes is unclear

McDermott MT, et al. *J Clin Endocrinol Metab*. 2001;86:4585-4590.
Braverman LE, Utiger RD, eds. *The Thyroid: A Fundamental and Clinical Text*. 8th ed. Philadelphia, Pa: Lippincott, Williams & Wilkins; 2000:1004.

Mild Thyroid Failure May Increase Cardiovascular Disease Risk

- Mild thyroid failure has been evaluated as a cardiovascular risk factor associated with
  - Increased serum levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels
  - Reduced high-density lipoprotein cholesterol (HDL-C) levels
  - Increased prevalence of aortic atherosclerosis
  - Increased incidence of myocardial infarction

Four Stages in the Development of Hypothyroidism

Stage	FT$_4$	FT$_3$	Consensus for Treatment
Earliest	Normal	Within population reference range	None
Second	Normal	High (5-10 μIU/mL)	Controversial
Third	Normal	High (>10 μIU/mL)	Treat with LT$_4$*
Fourth	Low	High (>10 μIU/mL)	Uniform: Treat with LT$_4$

* Treat if patient falls into predefined categories.

Chu J, et al. *J Clin Endocrinol Metab. 2*001;86:4591-4599.

The Rate of Progression of Mild Thyroid Failure to Overt Hypothyroidism

- Mild thyroid failure is a common disorder that frequently progresses to overt hypothyroidism
  - Progression has been reported in about 3% to 18% of affected patients per year
  - Progression may take years or may rapidly occur
  - The rate is greater if TSH is higher or if there are positive antithyroid antibodies
  - The rate may also be greater in patients who were previously treated with radioiodine or surgery



Hyperthyroidism





Causes of Hyperthyroidism

Most common causes

- Graves disease
- Toxic multinodular goiter
- Autonomously functioning nodule

Rarer causes

- Thyroiditis or other causes of destruction
- Thyrotoxicosis factitia
- Iodine excess (Jod-Basedow phenomenon)
- Struma ovarii
- Secondary causes (TSH or ßHCG)

Causes of Thyrotoxicosis

Primary Hyperthyroidism

- **Diffuse toxic goiter (Graves' disease) – 60%-80%**

- Hashitoxicosis – hyperthyroid phase
- Toxic multinodular goiter
- Toxic adenoma
- Activating mutation of TSH receptor
- Ovarian struma
- Iodine excess

Causes of Thyrotoxicosis

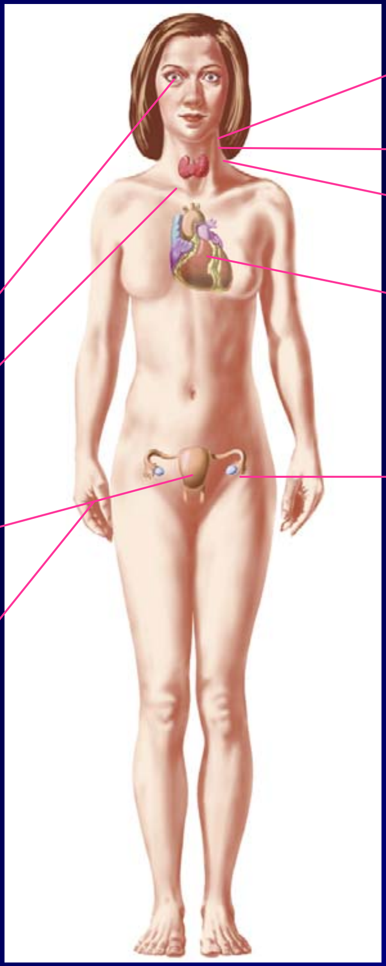
Secondary Hyperthyroidsm

- TSH secreting pituitary adenoma
- Pituitary resistance to T_3 and T_4
- Chorionic gonadotropin-secreting tumors (hydatiform mole)
- Gestational thyrotoxicosis

Thyrotoxicosis without Hyperthyroidism

- Subacute thyroiditis
- Silent thyroiditis
- Thyrotoxicosis factitia

Signs and Symptoms of Hyperthyroidism



Nervousness/Tremor

Mental Disturbances/
Irritability

Difficulty Sleeping

Bulging Eyes/Unblinking Stare/
Vision Changes

Enlarged Thyroid (Goiter)

Menstrual Irregularities/
Light Period

Frequent Bowel Movements

Warm, Moist Palms

First-Trimester Miscarriage/
Excessive Vomiting in Pregnancy

Hoarseness/
Deepening of Voice

Persistent Dry or Sore Throat

Difficulty Swallowing

Palpitations/
Tachycardia

Impaired Fertility

Weight Loss or Gain

Heat Intolerance

Increased Sweating

Sudden Paralysis

Family History of
Thyroid Disease
or Diabetes

Thyrotoxicosis

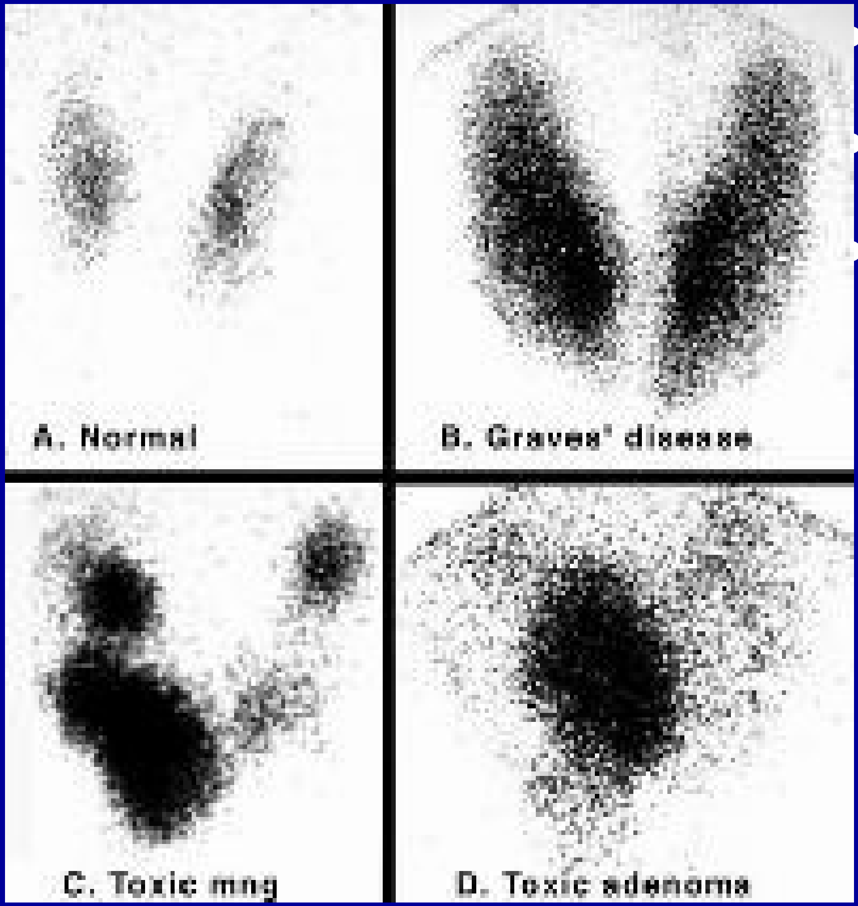
Symptoms

- Palpitations
- Nervousness
- Easy fatigability
- Excessive sweating
- Intolerance to heat
- Diarrhea
- Weight loss / gain (5%)
- Oligomenorrhea
- Atypical symptoms:
  - Hypokalemic periodic paralysis
  - Pruritus
  - Atrial fibrillation
  - Apathetic hyperthyroidism

Signs

- Goiter
- Thyrotoxic eye signs
- Tachycardia
- Tremor
- Warm, moist skin
- Muscle weakness/ loss of muscle mass
- Thickening of the pre-tibial skin
- Onycholysis
- Clubbing
- Gynecomastia

Diagnosis of Graves Disease



- TSH ↓, free T4 ↑
- Thyroid auto antibodies
- Nuclear thyroid scintigraphy (I_{123}, Te_{99})

Graves Disease

- Autoimmune disorder
- Ab^{s} directed against TSH receptor with intrinsic activity. Thyroid and fibroblasts
- Responsible for 60-80% of Thyrotoxicosis
- More common in women

Graves' Disease

- Autoimmune with over activity of thyroid gland
- HLA-DR3 association
- Defect in suppressor T cells
- B cells synthesize thyroid-stimulating immunoglobulin (TSI)
  - Autoantibody against TSH receptor
  - Gland becomes over stimulated and loses negative feedback to T_3 and T_4

Graves' Disease

- Goiter
- Thyrotoxicosis
- Exophthalmos
- pretibial myxedema
- Thyroid acropachy
- Thyroid stimulating immunoglobulins

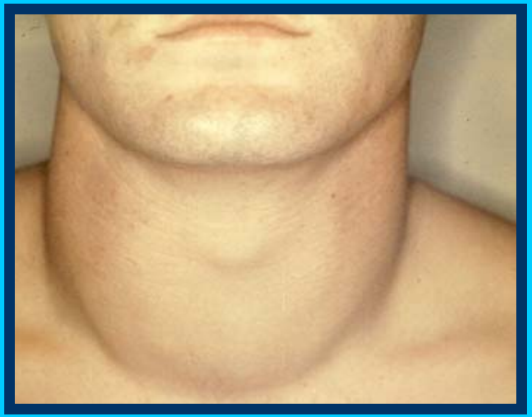
Graves' Disease

Associations with other diseases

- IDDM (Insulin dependent diabetes mellitus)
- Addison's disease
- Vitiligo
- Pernicious anemia
- Myasthenia gravis
- Celiac disease
- Other autoimmune diseases associated with the HLA-DR3 haplotype

Clinical Characteristics of Goiter in Graves' Disease

- Diffuse increase in thyroid gland size
- Soft to slightly firm
- Non-nodular
- Bruit and/or thrill
- Mobile
- Non-tender
- Without prominent adenopathy



Graves' Gross and Microscopic Pathology

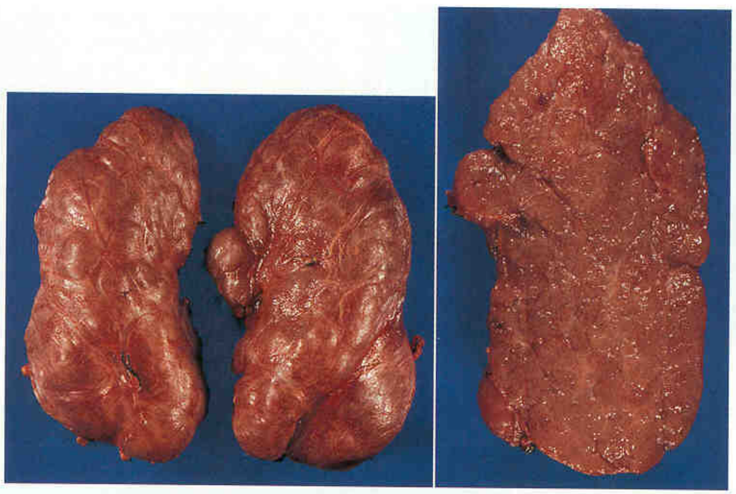
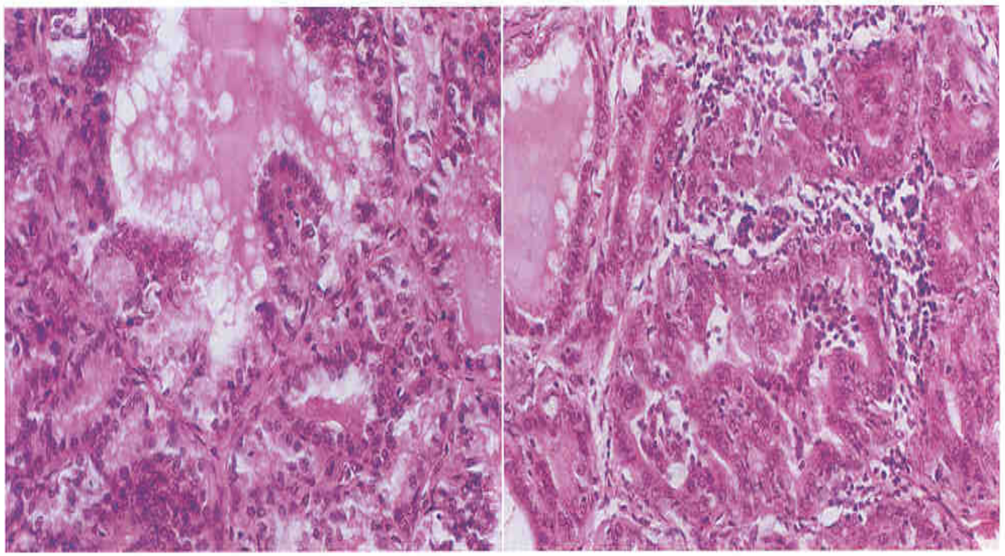


Fig. 10-13. Graves disease. A, The thyroid gland is symmetrically enlarged. B, On cut section the thyroid gland appears moist and hyperemic and lacks normal colloidal appearance.



Graves' Ophthalmopathy

- **Class one:** spasm of upper lids with thyrotoxicosis
- **Class two:** periorbital edema and chemosis
- **Class three:** proptosis
- **Class four:** extraocular muscle involvement
- **Class five:** corneal involvement
- **Class six:** loss of vision due to optic nerve involvement

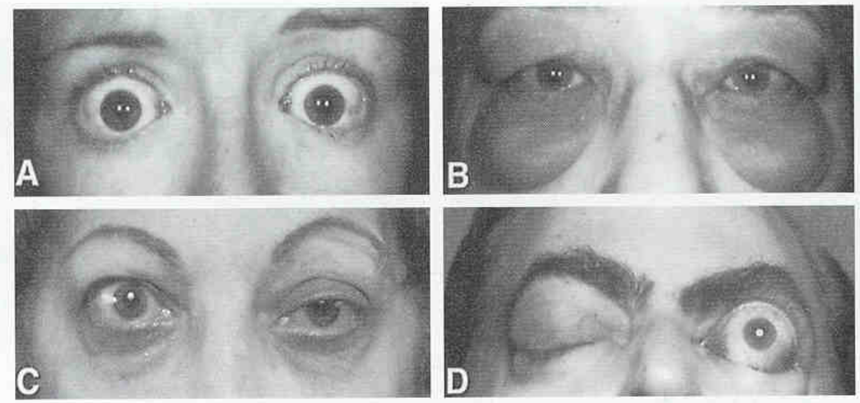
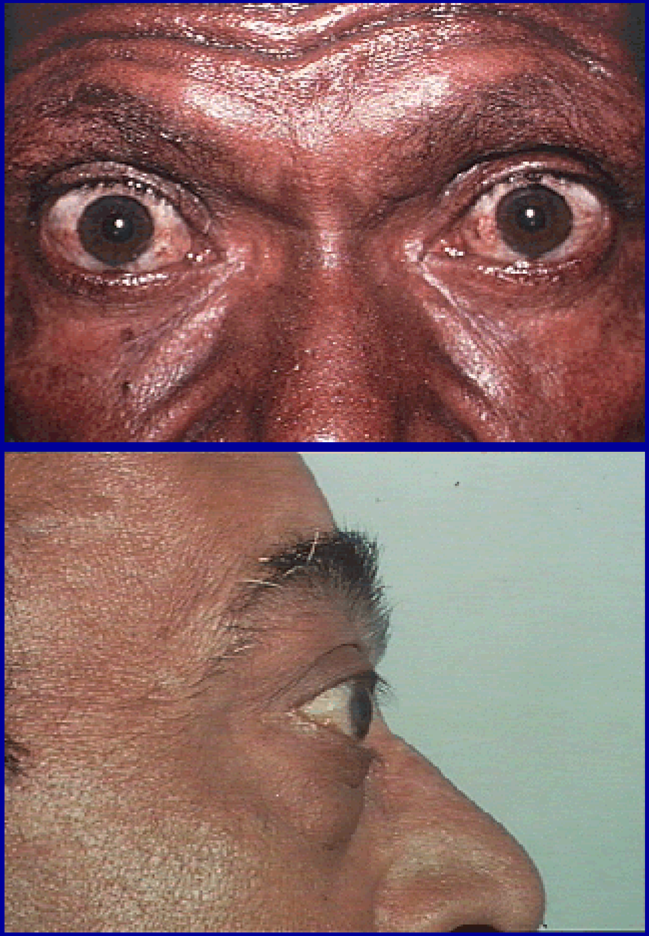


FIG. 29.16. Clinical presentations of Graves' ophthalmopathy. **A:** Retraction of both upper eyelids. **B:** Severe periorbital edema. **C:** Predominantly unilateral involvement. **D:** Spontaneous subluxation of a severely proptotic left eye.

Graves Disease Eye Signs



N - no signs or symptoms

O – only signs (lid retraction or lag) no symptoms

S – soft tissue involvement (peri-orbital oedema)

P – proptosis (>22 mm)(Hertl's test)

E – extra ocular muscle involvement (diplopia)

C – corneal involvement (keratitis)

S – sight loss (compression of the optic nerve)

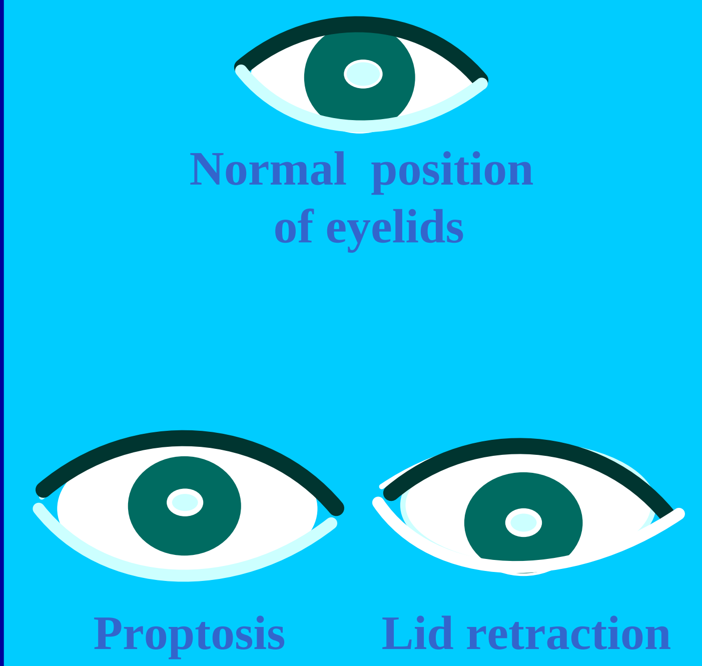
Clinical Characteristics of Exophthalmos

- Proptosis
- Corneal Damage
- Periorbital edema
- Chemosis
- Conjunctival injection
- Extraocular muscle impairment
- Optic neuropathy

Clinical Differentiation of Lid Retraction from Proptosis

- **Measurement using prisms or special ruler (exophthalmometer)**

  OR with sclera seen above iris :
- **Observing position of lower lid (sclera seen below iris = proptosis, lid intersects iris = lid retraction)**



Lid Lag in Thyrotoxicosis

Normal **Lid Lag**

Graves Disease Other Manifestations

- Pretibial mixoedema
- Thyroid acropachy
- Onycholysis

Graves'…Dermopathy

Clinical Characteristics of Localized Myxedema

- Raised surface
- Thick, leathery consistency
- Nodularity, sometimes
- Sharply demarcated margins
- Prominent hair follicles
- Usually over pretibial area
- Non-tender

Graves' Disease - Localized Myxedema

Margins sharply demarcated

Nodularity

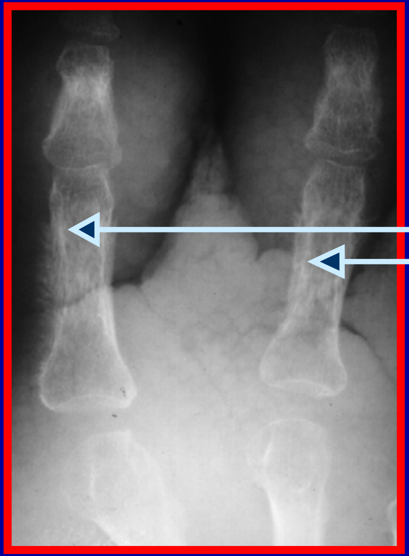
Thickened skin

Margins sharply demarcated

Thyroid Acropachy

- Clubbing of fingers
- Painless
- Periosteal bone formation and periosteal proliferation
- Soft tissue swelling that is pigmented and hyperkeratotic

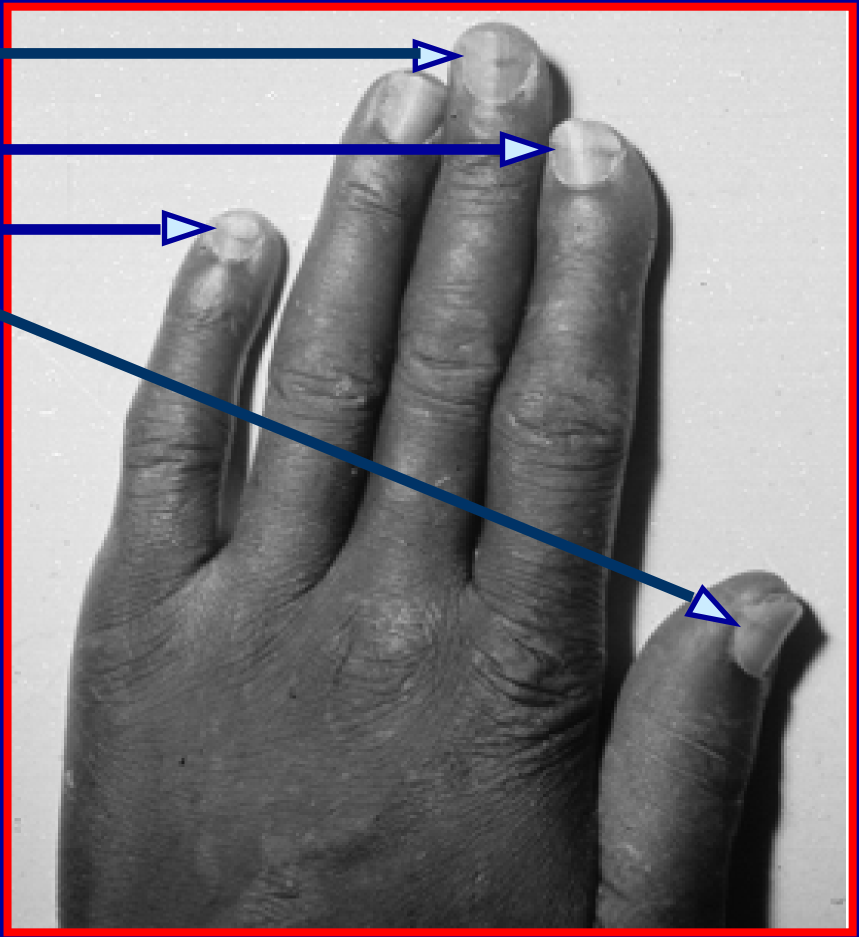
Clubbing of fingers



Periosteal bone formation and periosteal proliferation

Onycholysis of Thyrotoxicosis

Distal separation of the nail plate from nail bed (Plummer's nails)

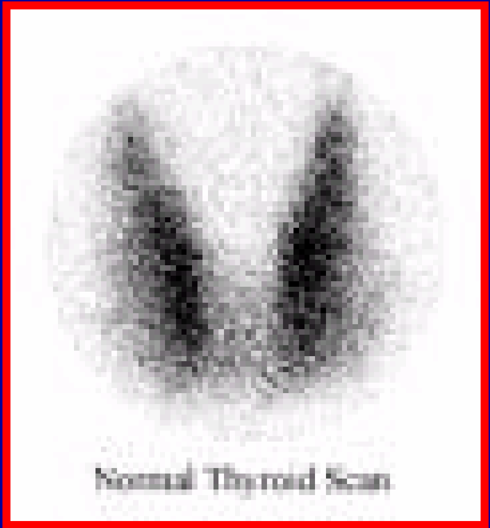


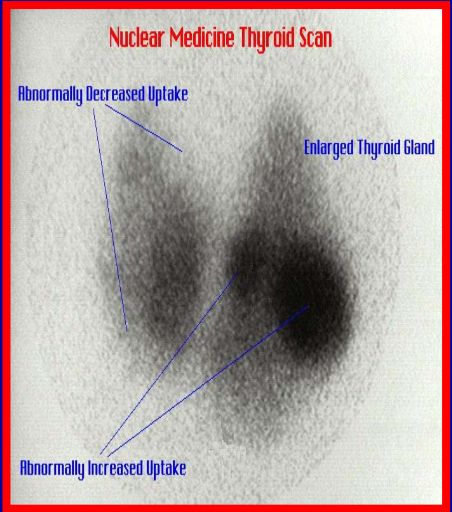
Thyrotoxicosis

Diagnostic Studies

- Thyroid function tests:
  - TSH - suppressed
  - fT_4 and/or TT_3 / fT_3 - elevated
- TSI
- Antithyroid antibodies
- Thyroid scan

Thyrotoxicosis – Thyroid Scan





Thyrotoxicosis

Increased Uptake

- Graves' disease
- Toxic adenoma
- Toxic multinodular goiter
- Hashitoxicosis
- TSH producing pituitary tumor

Decreased Uptake

- Subacute thyroiditis
- Painless thyroiditis
- Iodine induced hyperthyroidism
- Thyroid hormone therapy

Graves' Disease

Treatment

- Symptomathic treatment
  (Beta-adrenergic blocking agents)
- Antithyroid drug therapy
- Radioiodine therapy
- Surgical therapy

Graves' Disease

Antithyroid Drug Therapy - Thionamides

(Carbimazole, Mercaptizole, Propylthiouracil)

- Inhibit the synthesis of thyroid hormones (suppression of TPO ; interference with T4 $\rightarrow$ T3)

- Method of therapy
  - Titration regimen
  - "Block-replace" regimen

Antithyroid Drug Therapy - Thionamides

(Carbimazole, Mercaptizole, Propylthiouracil)

Side effects

- Minor (5%) – rash, urticaria, arthralgia, abnormalities of smell and taste, increased liver enzymes, fever, lymphadenopathy

- Major (<1%) – agranulocytosis, thrombocytopenia, DIC, hepatitis, vasculitis, nephrotic syndrome, SLE-like syndrome

Considerations with Thionamides

- Both PTU and Methimazole may be used in pregnancy
- PTU and Methimazole are considered safe in breastfeeding
  - Methimazole appears in higher concentrations
- Watch for agranulocytosis
  - Fever
  - Sore throat

Thionamides Cont…

- Measure FT_4 and FTI every 2-4 weeks and titrate accordingly
- Goal is high normal range
- 90% see improvement in 2-4 weeks

Graves' Disease

Surgical treatment

- Subtotal thyroidectomy

- Preoperative preparation

  antiyhroid drugs

  Inderal

  lugol"s iodoine

Surgery
Subtotal Thyroidectomy

- ***Complications***
  - Laryngeal nerve damage
  - Hemorrhage
  - Hypo calcemia –Tetany (tingling) usually in & around mouth. Does pt c/o numbness?
  - Resp distress
  - Dehiscence

Thyroidectomy
Post-operative Management

- Maintain patent airway
  - monitor respirations, color, O2 saturation
  - tracheostomy kit, O2, Suctioning- at bedside

- Monitor for complications
  - hemorrhage
    - Check VS
    - check back of neck & supraclavicular hollows
  - tetany (laryngospasm and seizures) – does pt deny numbness
  - injury to laryngeal nerve – can pt speak clearly

- Decrease strain on suture line, HOB up

Thyroidectomy
Post-op Management-continued

Monitor for complications

Tetany - from accidental removal of parathyroid (monitor calcium levels, assess for tingling, twitching, muscle cramps)

- Chvostek's sign: contraction of facial muscles in response to light tap over facial nerve in front of the ear
- Trousseau's sign: inflate BP cuff above systolic pressure. Carpal spasms occur within 3 minutes if hypocalcemia is present
- Treatment: Calcium Gluconate IV,

Thyroid storm (Monitor vital signs for tachycardia & hyperthermia)

Injury to laryngeal nerve (bedside trach)

Decrease strain on suture line

- Semi-fowlers position
- No hyperextension of neck

Thyroid Storm

- Medical Emergency
- Occurs in ~ 1% of pregnant pts with hyperthyroidism
- Diagnostic signs and symptoms:
  - Fever
  - Tachycardia
  - Altered mental status
  - Vomiting and diarrhea
  - Cardiac arrhythmia

Thyrotoxicosis and Thyroid Storm

- Acute thyrotoxicosis: beta-blockers, barbiturates, cholestyramine
- Thyroid storm: manage aggressively with beta-blockers, calcium channel blockers, PTU, methimazole, sodium iodide, digitalis or diuretics for heart failure, fluid and electrolyte management

Iodine 131

- Contraindicated in pregnancy
- Avoid pregnancy for 4 months after ^{131}I treatment
- Avoid breastfeeding for 120 days after ^{131}I treatment
- Gestational age key when counseling pregnant women exposed to ^{131}I

Graves' Disease

Radioactive Iodine Treatment

Side-effects

- Worsening of ophthalmopathy
- Hypothyroidism
- Radiation thyroiditis

Exophthalmos
Medical Management

Eye Care

- Continuous eye care is required until condition resolves.
- Blinking & closing eyelid helps move tears across eye and into drainage channels.
- Tears are continuously produced to maintain moisture in the eye, remove metabolic waste products & environmental debris (dust, ash, etc) keep the eyes outer surface smooth, & deliver nutrients to underlying tissues.

Exophthalmos
Medical Management

<u>Corneal protection</u>

- with anartificial tears solution (keep eye moist & debris out),
- sunglasses (help protect from injury & < dryness by < exposure to wind),
- an eye patch at night(heavy lubricant placed in eye, eyelid taped shut to < dryness & risk for injury

Graves' Disease

Course and Prognosis

- 45%-55% - Remission and exacerbation over a protracted period of time
- 30%-40% - Euthyroidism
- 15% - Hypothyroidism

Graves' ophthalmopathy is independent on thyroid status

Toxic Nodular Goiter

- Develops from multinodular goiter
- Nodules become autonomous
- Plummer’s disease
- Cardiac symptoms

Treatment

Antithyroid drug therapy

Surgery

Toxic Adenoma

- Thyrotoxicosis
  - Hyperfunctioning nodules <2 cm rarely lead to thyrotoxicosis
  - Most nodules leading to thyrotoxicosis are >3 cm.

- Treatment Indications
  - Post-menopausal female
    - Due to increased risk of bone loss
  - Patients over 60
    - Due to high risk of atrial fibrillation
  - Adenomas greater than 3 cm (?)

Toxic Adenoma

- Treatments
  - **Antithyroid medications**
    - **Not used due to complications of long-term treatment**
  - **Radioiodine**
    - **Cure rate > 80% (20 mCi I131)**
    - **Hypothyroidism risk 5% - 10%**
    - **Second dose of I131 needed in 10% - 20%**
    - **Patients who are symptomatically toxic may require control with thionamide medications before RAI to reduce risk of worsening toxicity.**

Toxic Adenoma

- Surgery
  - Preferred for children and adolescents
  - Preferred for very large nodules when high I131 doses needed
  - Low risk of hypothyroidism
- Ethanol Injection
  - Rarely done in the US
  - May achieve cure in 80%

Differential Diagnosis of a Painful Thyroid

Disorder	Frequency
Subacute granulomatous thyroiditis	Most common
Hemorrhage into a goiter, tumor or cyst with or without demonstrable trauma	Less common
Acute suppurative thyroiditis	<1%
Anaplastic (inflammatory) thyroid carcinoma	<1%
Hashimoto's thyroiditis	<1%
TB, atypical TB, amyloidosis	<1%
Metastatic carcinoma	<1%

Structural Thyroid Disease

Benign Thyroid Disease

- **Benign Simple Conditions**
  - Diffuse (Physiological , colloid)
  - Nodular Goiter (Multi , Solitary)
- **Benign Toxic Conditions**
  - Toxic Multinodular Goiter
  - Graves' Disease
  - Toxic Adenoma
- **Inflammatory Conditions**
  - Chronic (Hashimoto's) Thyroiditis
  - Subacute (De Quervain's) Thyroiditis
  - Riedel's Thyroiditis

History

- <u>Goiter</u>
  - Fist described in China in 2700 BC
- <u>Thyroid Function</u>
  - Roman physicians – thyroid enlargement is a sign of puberty

Surgical advances

- 500 AD
  - **Abdul Kasan Kelebis Abis** performed the first goiter excision in Baghdad.
  - Procedure: unknown

History of Thyroid Surgery

- 1870's-80's – **Billroth** – emerges as leader in thyroid surgery (Vienna)
  - Mortality 8%
  - Shows need for RLN preservation
  - Defines need for parathyroid preservation (von Eiselberg)
  - Emphasis on speed

History of Thyroid Surgery

- **Kocher** – emerges as leader in thyroid surgery (Bern)
  - Mortality:
    - 1889 – 2.4%
    - 1900 – 0.18%
  - Emphasis on meticulous technique
  - Performed 5000 cases by death in 1917
  - Awarded 1909 Nobel Prize for efforts

History of Thyroid Surgery

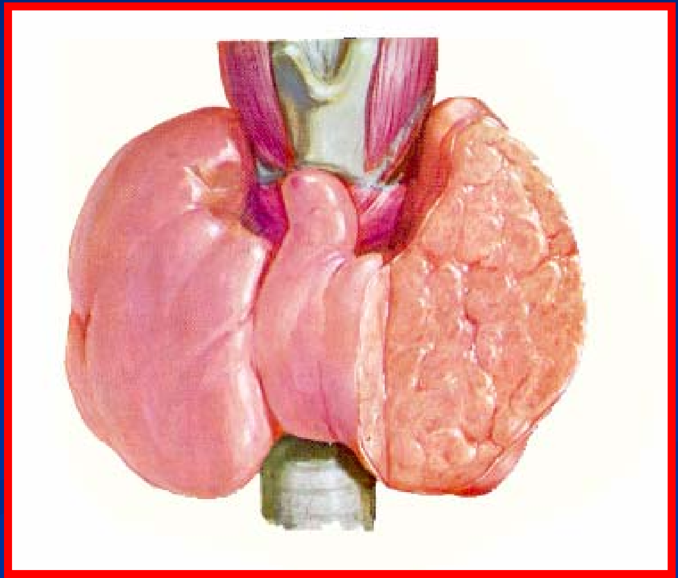
- **Halstead**
  - Studied under Kocher and Billroth
  - Returned to US 1880
  - Worked at Hopkins with Cushing, Osler, Welch
  - Laid groundwork for thyroid specialists Mayo, Lahey, Crile

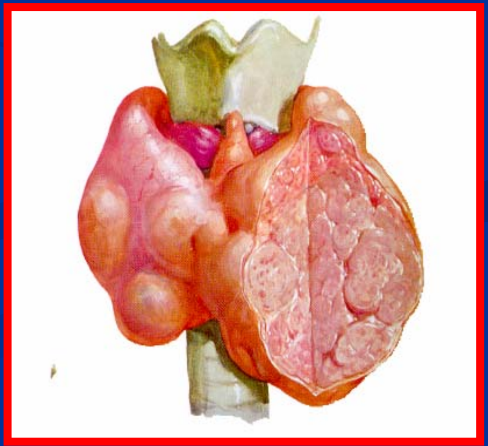
Goiter

- Goiter: Chronic enlargement of the thyroid gland not due to neoplasm
- Endemic goiter
  - Areas where > 5% of children 6-12 years of age have goiter
  - Common in China and central Africa
- Sporadic goiter
  - Areas where < 5% of children 6-12 years of age have goiter
  - *Multinodular goiter* in sporatic areas often denotes the presence of multiple nodules rather than gross gland enlargement
- Familial

Simple Goiter

- Physiological
- Colloid
- Nodular





Enlarged Thyroid Gland - Goiter

Diffuse

- Physiological
- Simple/Colloid goiter
- Iodine deficiency
- Endemic – > 5% of the population in the endemic region

  (iodine deficiency or exposure to environmental goitrogens)
- Biosynthetic defects

Nodular

- Single Or multiple

A woman in Viet Nam, 1970

A woman in Switzerland,1874



Simple Goiter

Etiology

- Physiological
  - Increase demand
- Pathological
-
  - Defects In Synthesis
    - Dyshormonegenesis
    - Goitergens

      Lithium , ca++ ,vit A, Fluride, Antithyroid , PASA , Iodine excess

      Vegetables----Brassica family (cabbage, turnips, cauliflower, rape)

- **Iodine Deficiency**
  - Intake
  - Absorption

Pathogenesis

- Hyperplasia , Hypertrophy
- Involution
- Hyperinvolution excess iodide(Colloid)
- Active & Inactive lobule
- Hage , Necrosis
- Nodular Goiter

clinical picture

- **Swelling**
- **pressure symptom**
  - Trachea , Esophagus , Recurrent laryngeal nerve , carotid
- **complication**
  - cystic degeneration
  - Hemorrhage
  - calcification
  - 2^{nd} toxic goiter
  - Reterosternal goiter
  - malignant

Tracheal Compression

Retrosternal Goiter

Diagnostic tools

- History and examination
- Thyroid function tests
  - T3, T4, TSH
- Tumour markers
  - Thyroglobulin
  - Anti-TG antibodies
- Iodine-123 or 131 scan
- Ultrasound
- Biopsy

MNG

- Cancer screening in MNG
  - Longstanding MNG has a risk of malignancy identical to solitary nodules (<5%)
  - MNG with nodules < 1.5 cm may be followed clinically
  - MNG with non-functioning nodules > 4cm should be excised
    - No FNA needed due to poor sensitivity
    - Incidence of cancer (up to 40%)
  - FNA in MNG
    - Sensitivity 85% - 95%
    - Specificity 95%
    - Negative FNA can be followed with annual US
    - Insufficient FNA's should be repeated
    - Incoclusive FNA or papillary cytology warrants excision
  - Hyperfunctioning nodules may mimic follicular neoplasm on FNA

Diffuse Goiter

- Treatment options
    - Iodoine (Salt , Oil)
    - Thyroid hormones therapy

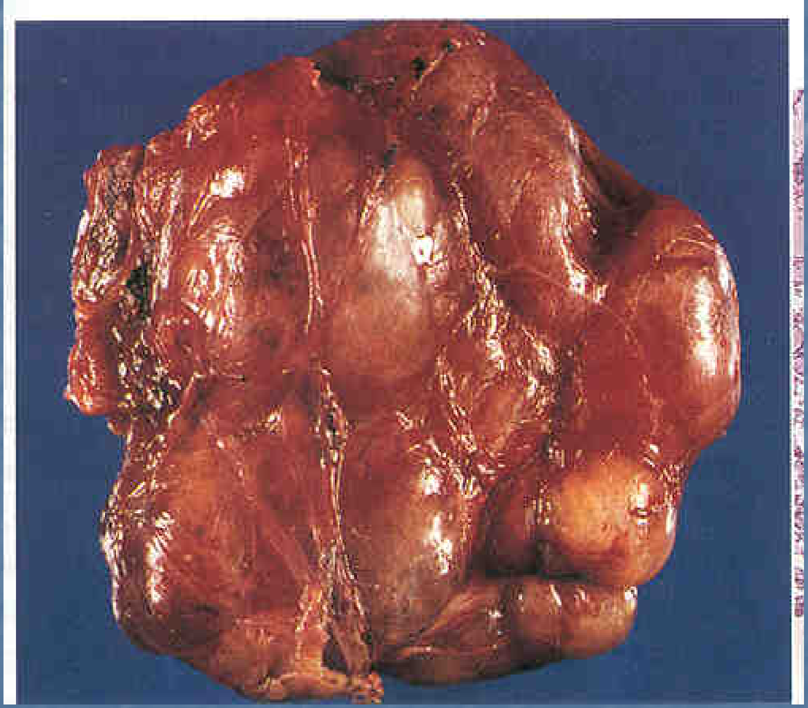
MNG Goiter

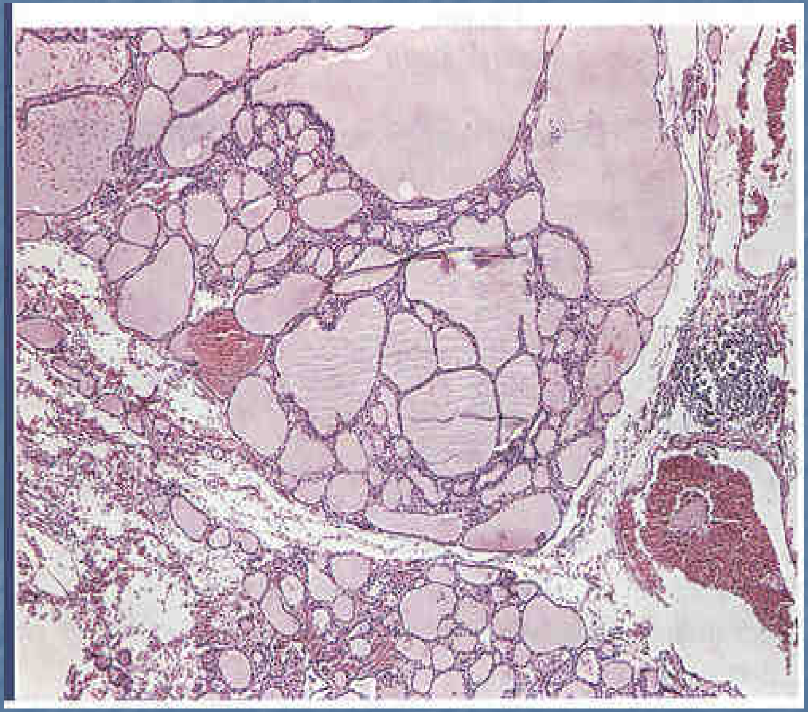
- Treatment options (no compressive symptoms)
  - **US follow-up to monitor for progression**
  - **Thyroid hormone therapy**
    - May be used for progressive growth
    - May reduce gland volume up to 50%
    - Goiter regrowth occurs rapidly following therapy cessation
  - **Surgery**
    - Suspicious neck lymphadenopathy
    - History of radiation to the cervical region
    - Rapid enlargement of nodules
    - Papillary histology
    - Microfollicular histology (?)

Non-Toxic Goiter

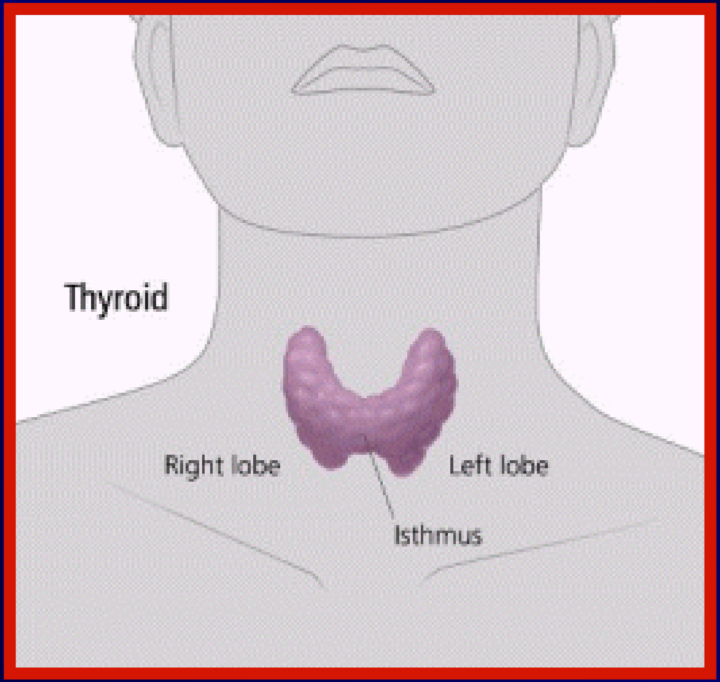
- Treatment options (compressive symptoms)
  - RAI ablation
    - Volume reduction 33% - 66% in 80% of patients
    - Improvement of dysphagia or dyspnea in 70% - 90%
    - Post RAI hypothyroidism 60% in 8 years
    - Post RAI Graves' disease 10%
    - Post RAI lifetime cancer risk 1.6%
  - Surgery
    - Most commonly recommended treatment for healthy individuals

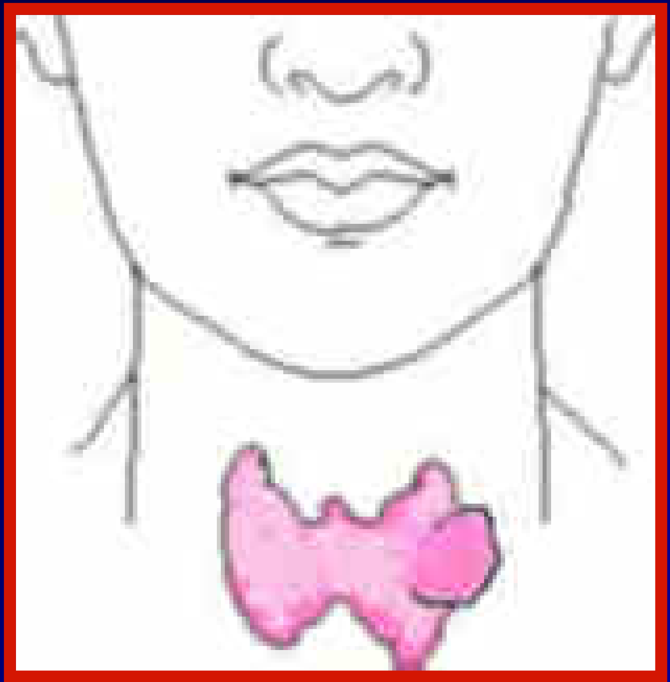
Gross and Microscopic Pathology Multinodular Goiter





THYROID CANCER



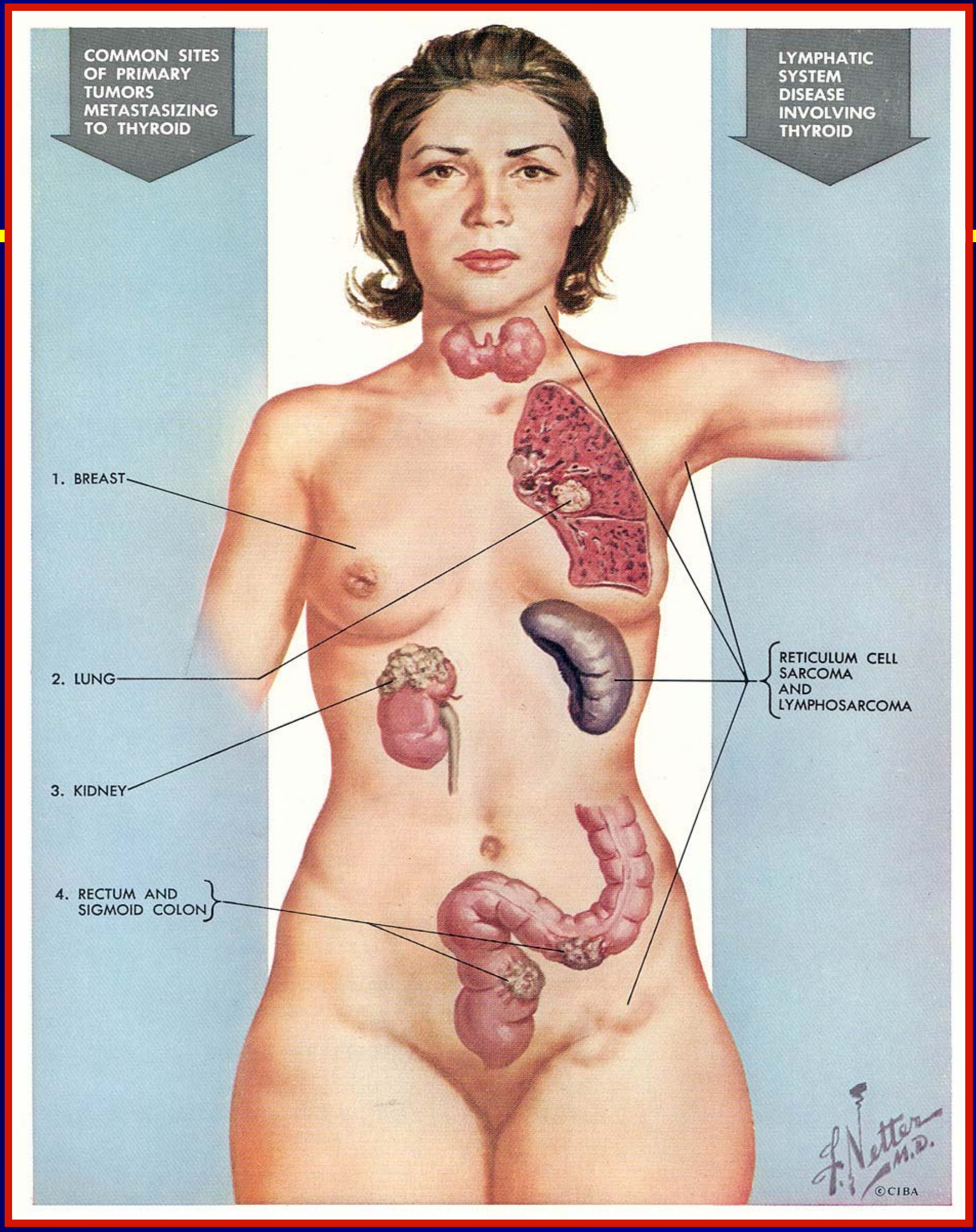


Classification of Malignant Thyroid Neoplasm

- **Papillary carcinoma**
  - Tall cell
  - Diffuse sclerosing
  - Follicular variant
  - Encapsulated
- **Follicular carcinoma**
  - Overtly invasive
  - Minimally invasive
- **Hurthle cell carcinoma**
- **Anaplastic carcinoma**
  - Giant cell
  - Small cell
- **Medullary Carcinoma**
- **Miscellaneous**
  - Sarcoma
  - Lymphoma
  - Squamous cell carcinoma
  - Mucoepidermoid carcinoma
  - Clear cell tumors
  - Plasma cell tumors
  - Metastatic
    - Direct extention
    - Kidney
    - Colon
    - Melanoma

Thyroid Mets

- Breast
- Lung
- Renal
- GI
- Melanoma



Well-Differentiated Thyroid Carcinomas (WDTC) - Papillary, Follicular, and Hurthle cell

- **Pathogenesis - unknown**
- Papillary has been associated with the RET proto-oncogene but no definitive link has been proven (Geopfert, 1998)
- Certain clinical factors increase the likelihood of developing thyroid cancer
  - Irradiation - papillary carcinoma
  - Prolonged elevation of TSH (iodine deficiency) - follicular carcinoma (Goldman, 1996)
    - relationship not seen with papillary carcinoma
    - mechanism is not known

RISK FACTORS

Radiation exposure

External: Treatment for benign conditions
Treatment for malignancies
Nuclear weapons/accidents

Internal: Medical treatment with I131
Diagnostic tests with I131
Environmental- nuclear weapons

Other factors

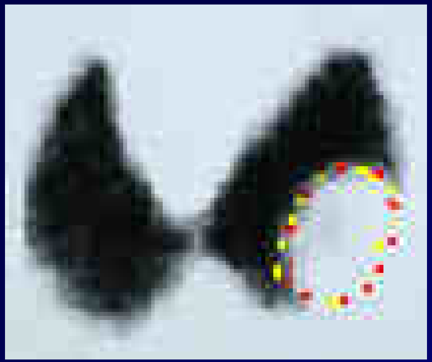
Diet- Iodine deficiency, goitrogens
Hormonal factors- female gender predominance
Benign thyroid disease
Alcohol

SIGNS AND SYMPTOMS

- Lump / Nodule In Neck
- Hoarseness
- Swollen Lymph Node
- Difficulty Swallowing
- Difficulty Breathing
- Pain In Throat / Neck

DIAGNOSIS

1. Physical Examination
2. TSH Level
3. Thyroid Scan
4. Ultrasound
5. Fine Needle Biopsy
6. Coarse Needle Biopsy
7. Surgical Biopsy



COLD NODULE

WDTC - Papillary Carcinoma

- **60%-80% of all thyroid cancers (Geopfert, 1998, Merino, 1991)**
- **Histologic subtypes**
  - **Follicular variant**
  - **Tall cell**
  - **Columnar cell**
  - **Diffuse sclerosing**
  - **Encapsulated**
- **Prognosis is 80% survival at 10 years (Goldman, 1996)**
- **Females > Males**
- **Mean age of 35 years (Mazzaferri, 1994)**

WDTC - Papillary Carcinoma
(continued…)

- Lymph node involvement is common
  - Major route of metastasis is lymphatic
  - 46%-90% of patients have lymph node involvement (Goepfert, 1998, Scheumann, 1984, De Jong, 1993)
  - Clinically undetectable lymph node involvement does not worsen prognosis (Harwood, 1978)

WDTC - Papillary Carcinoma (Continued...)

- **Microcarcinomas - a manifestation of papillary carcinoma**
  - **Definition - papillary carcinoms smaller than 1.0 cm**
  - **Most are found incidentally at autopsy**
  - **Usually clinically silent**
  - **Most agree that the morbidity and mortality from microcarcinoma is minimal and near that of the normal population**
  - **One study showed a 1.3% mortality rate (Hay, 1990)**

WDTC - Papillary Carcinoma
(continued…)

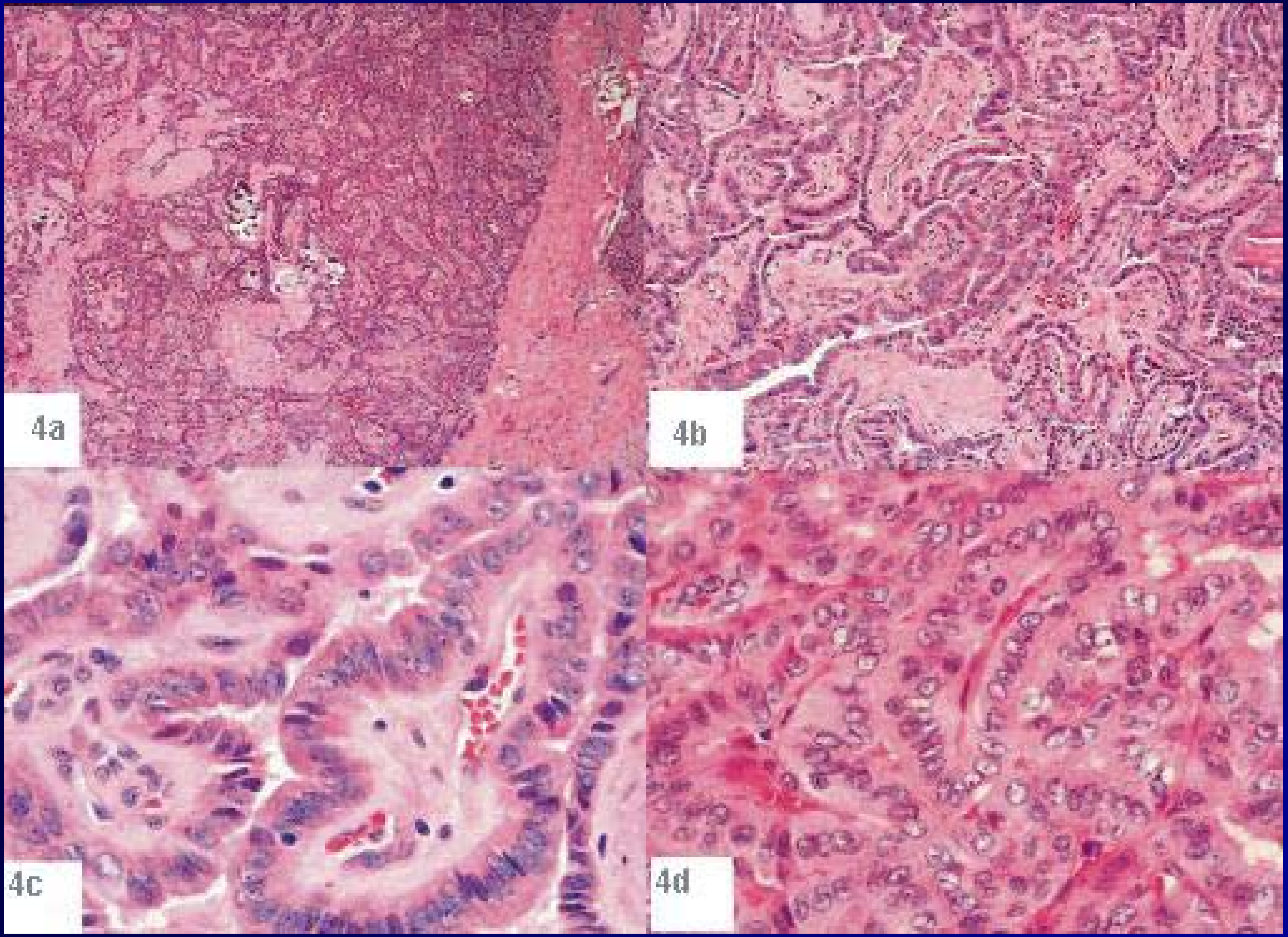
- **Pathology**
  - **Gross - vary considerably in size**

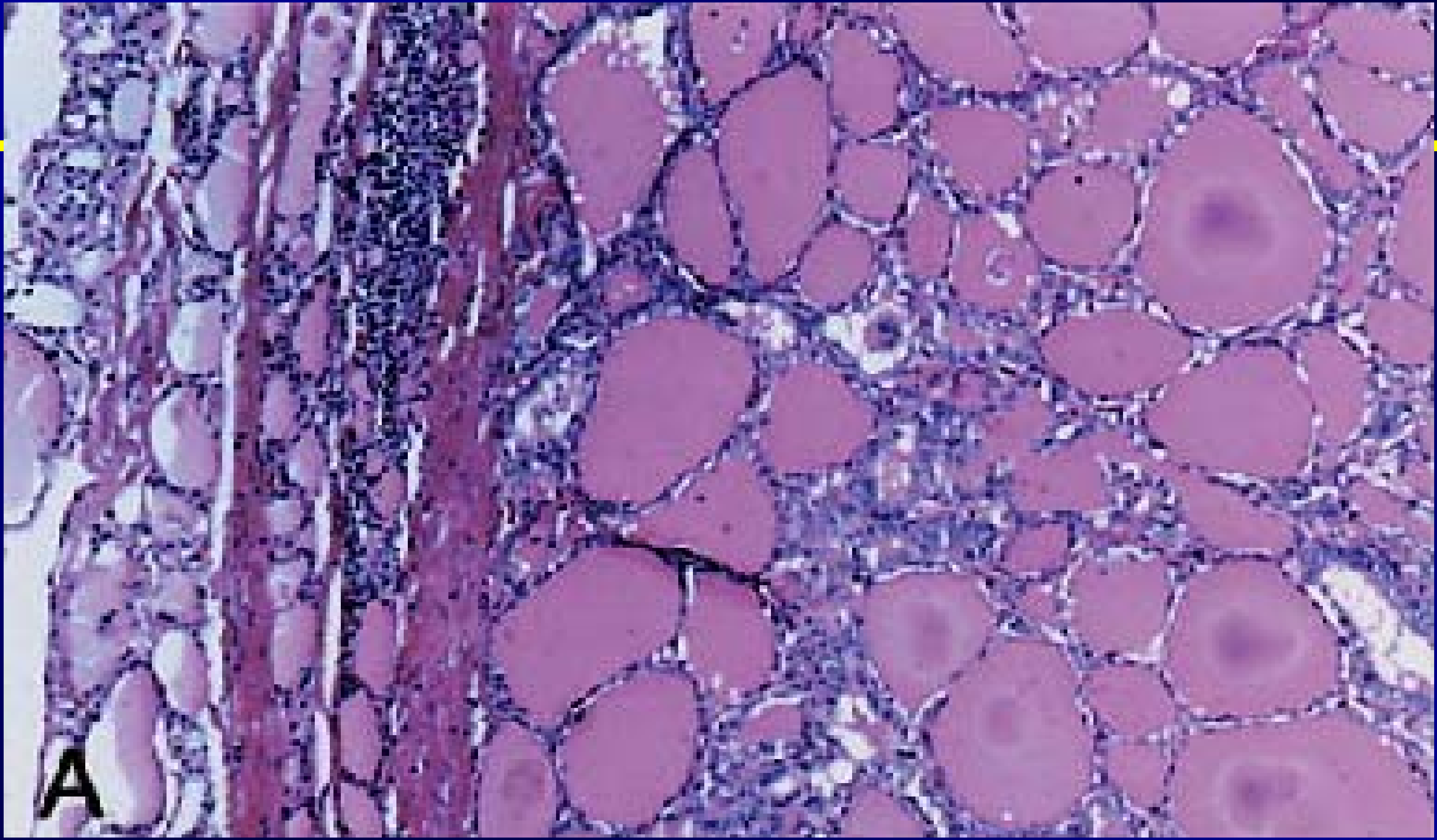
    - often multi-focal

    - unencapsulated but often have a pseudocapsule
  - **Histology - closely packed papillae with little colloid - *psammoma bodies***

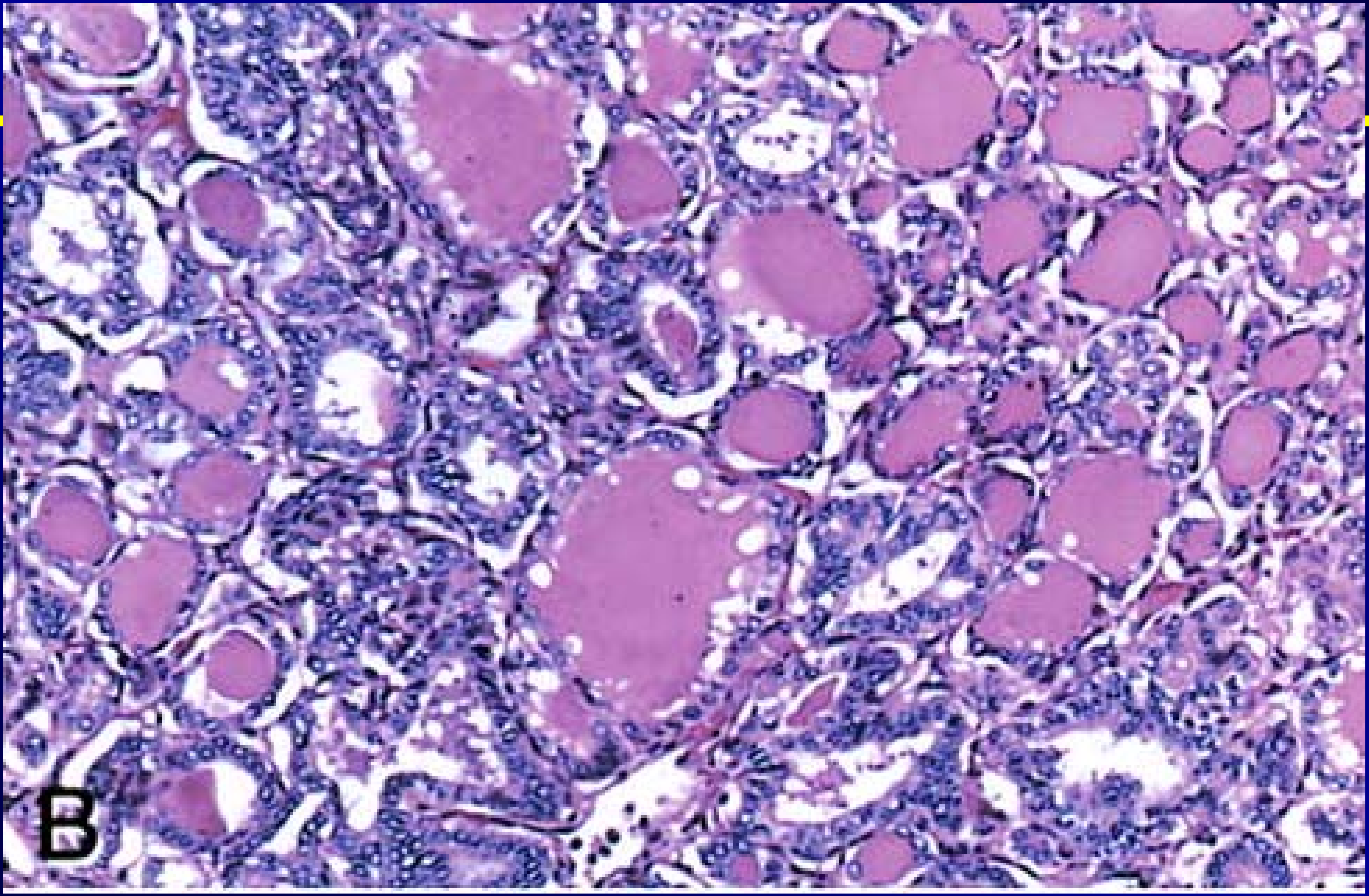
    - nuclei are oval or elongated, pale staining with ground glass appearanc - *Orphan Annie cells*

Papillary Thyroid Carcinoma

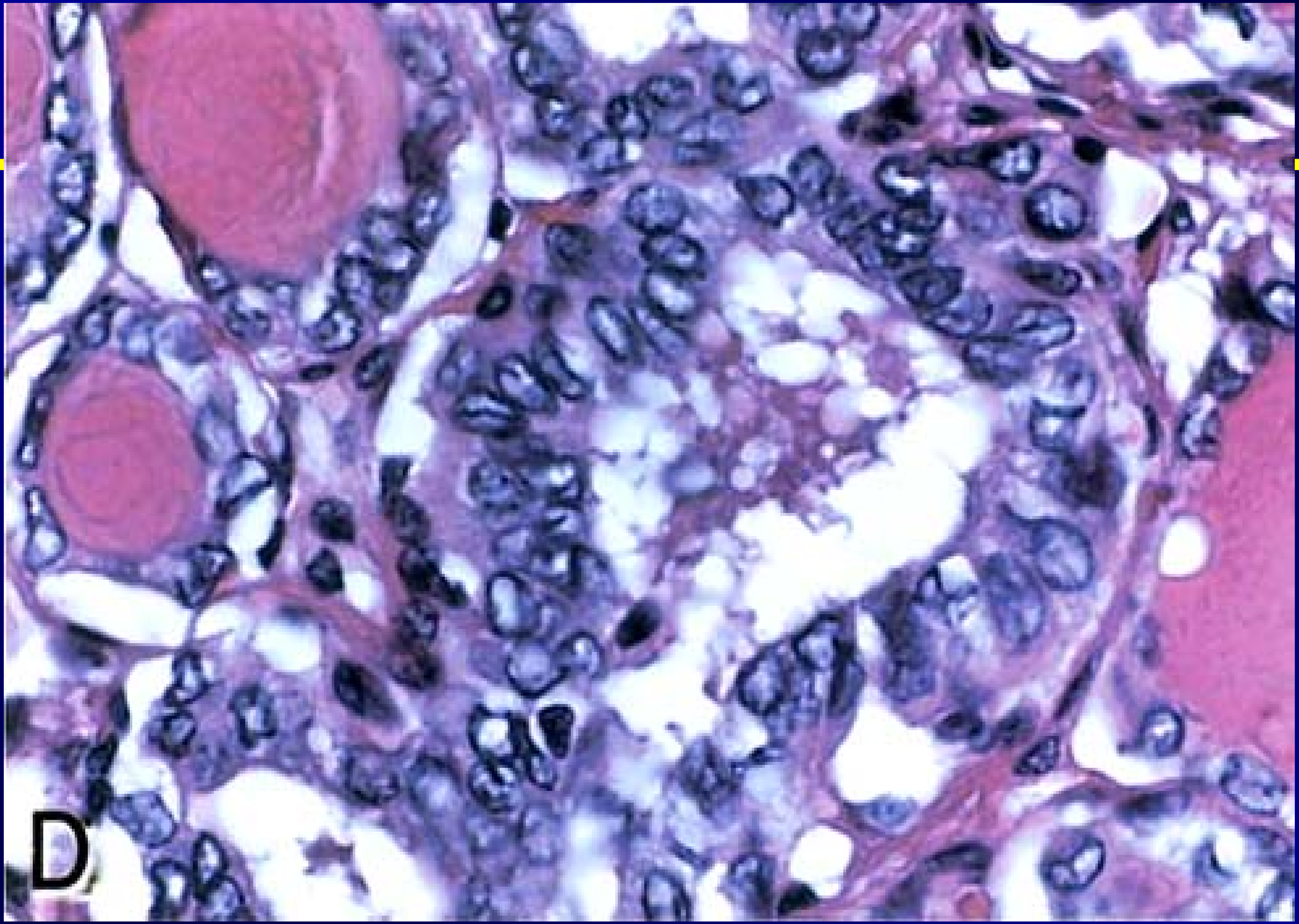




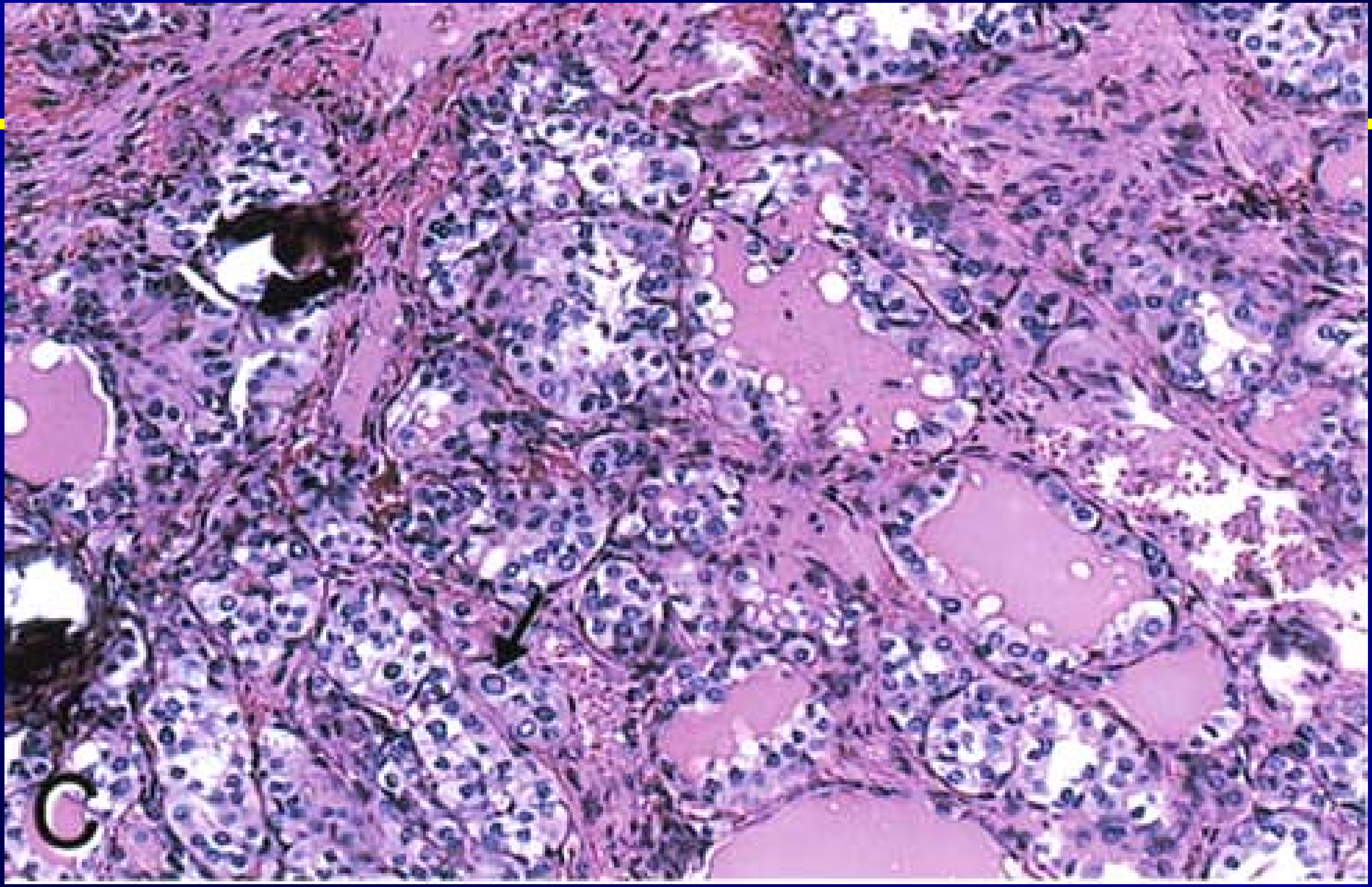
dark staining colloid in the FVPCA on right



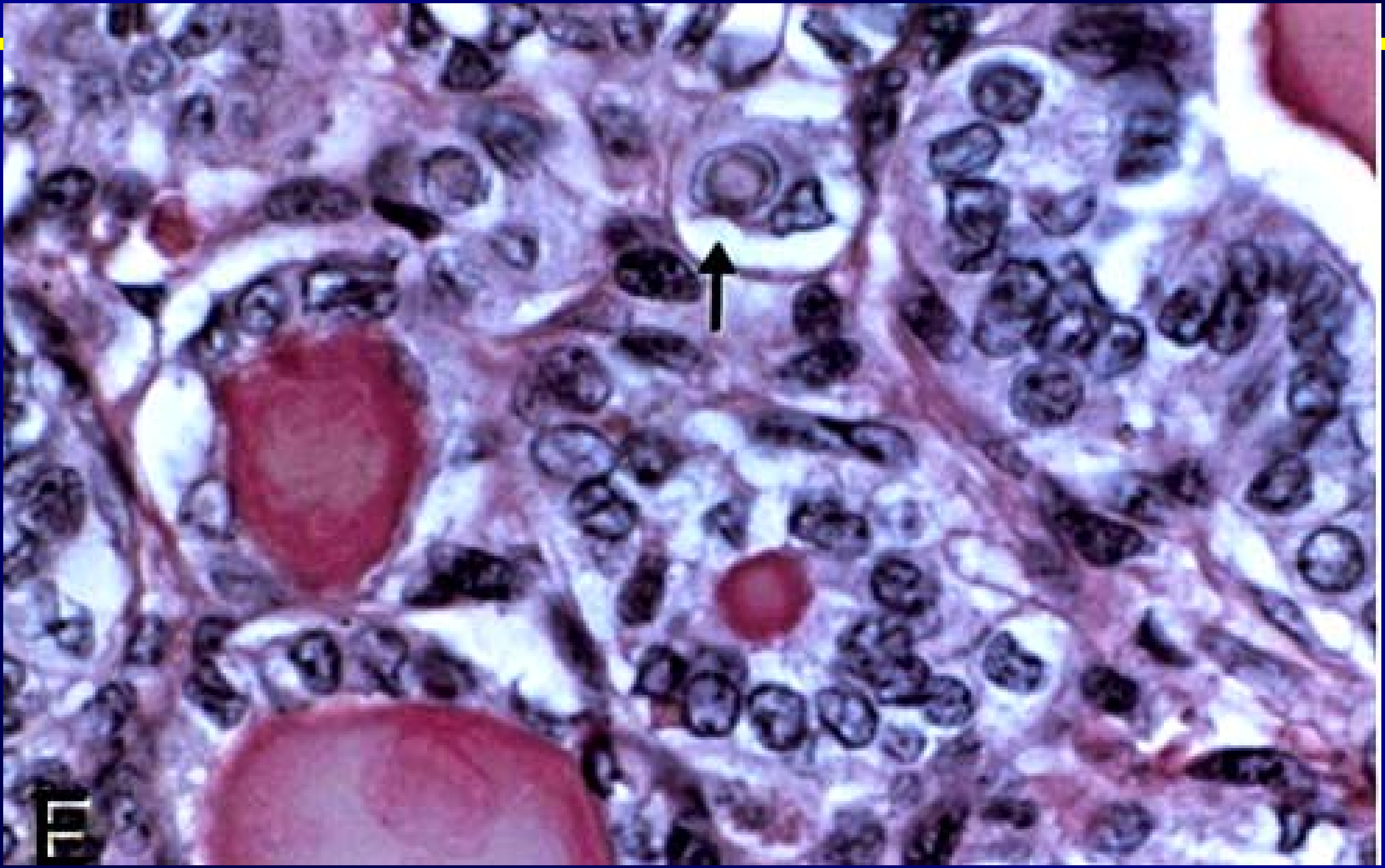
nuclear clearing / colloid scalloping / irregularly shaped follicles



irregularly shaped, overlapping nuclei with clearing and grooving



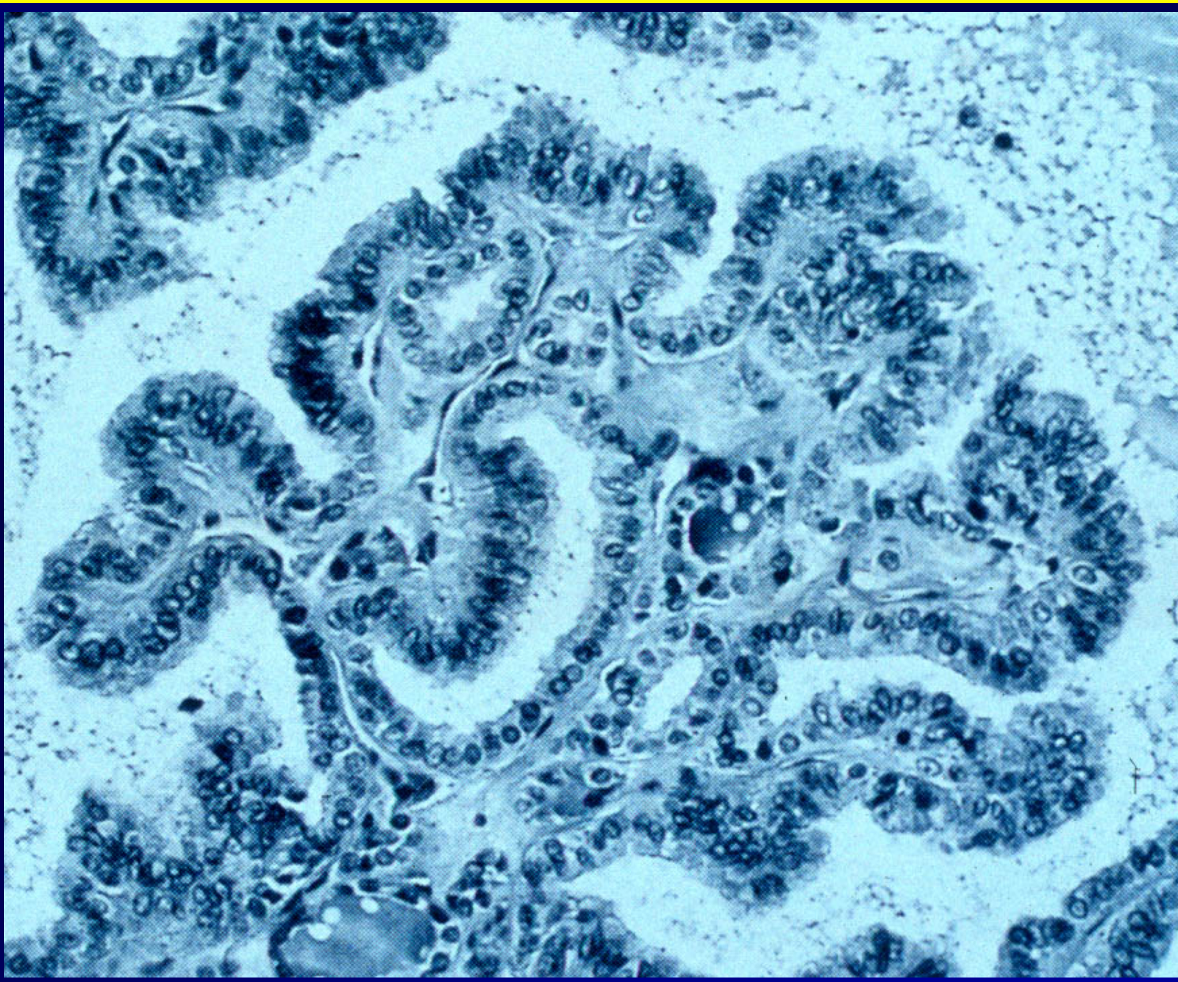
psammoma bodies / ground glass nuclei / nuclear pseudoinclusion



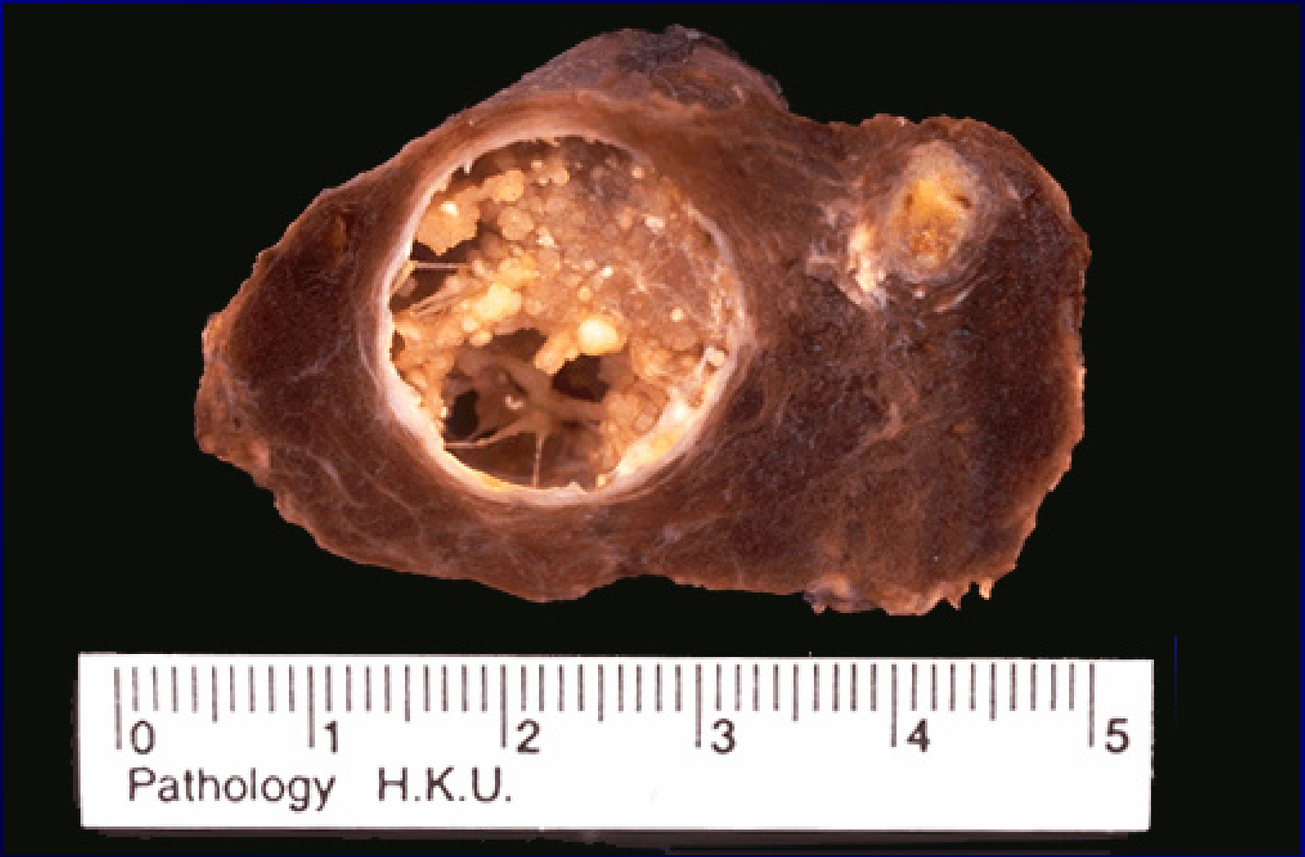
nuclear pseudoinclusion

Papillary Carcinoma

- "Orphan Annie" nuclei
- Psamomma bodies



Papillary carcinoma



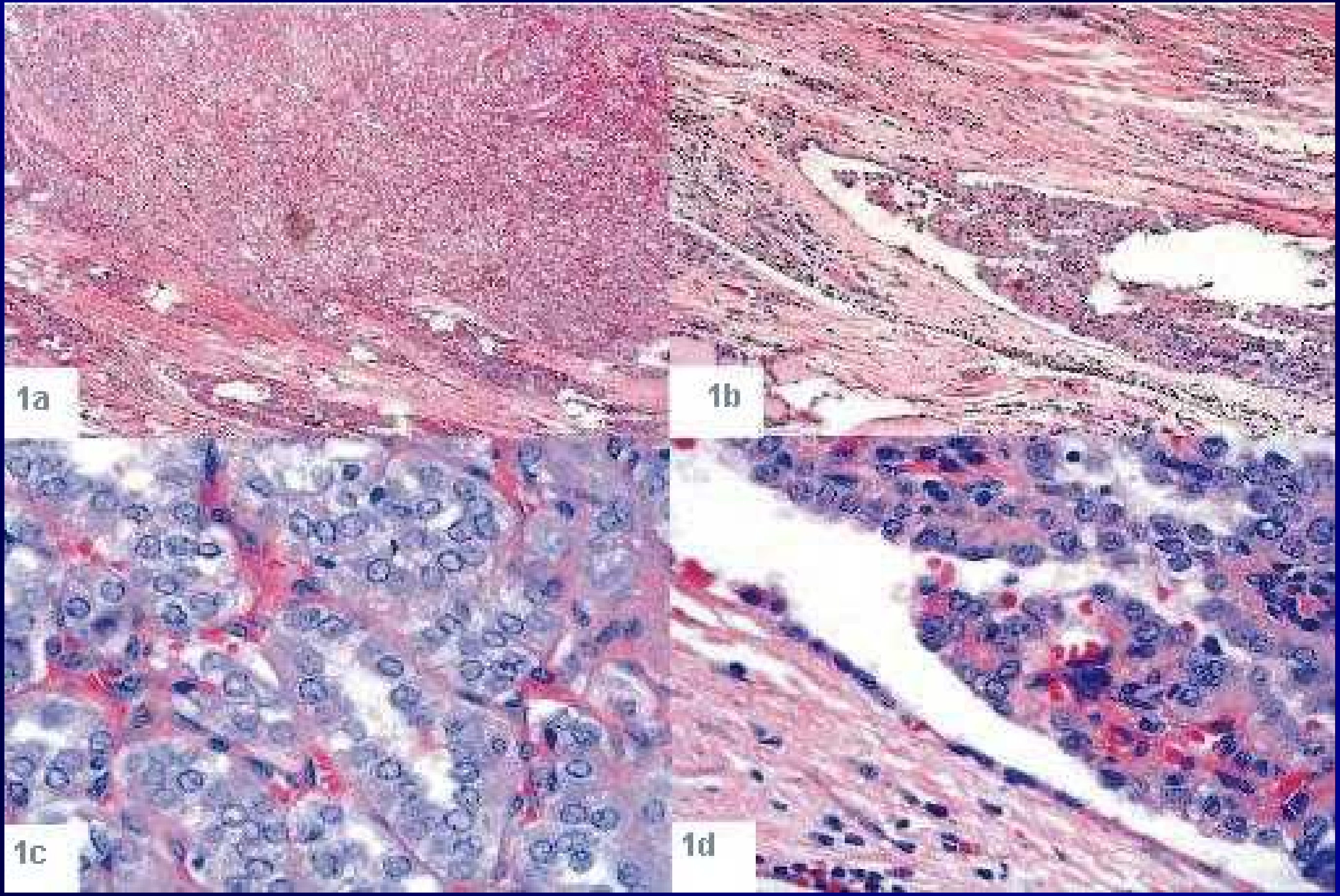
WDTC - Follicular Carcinoma

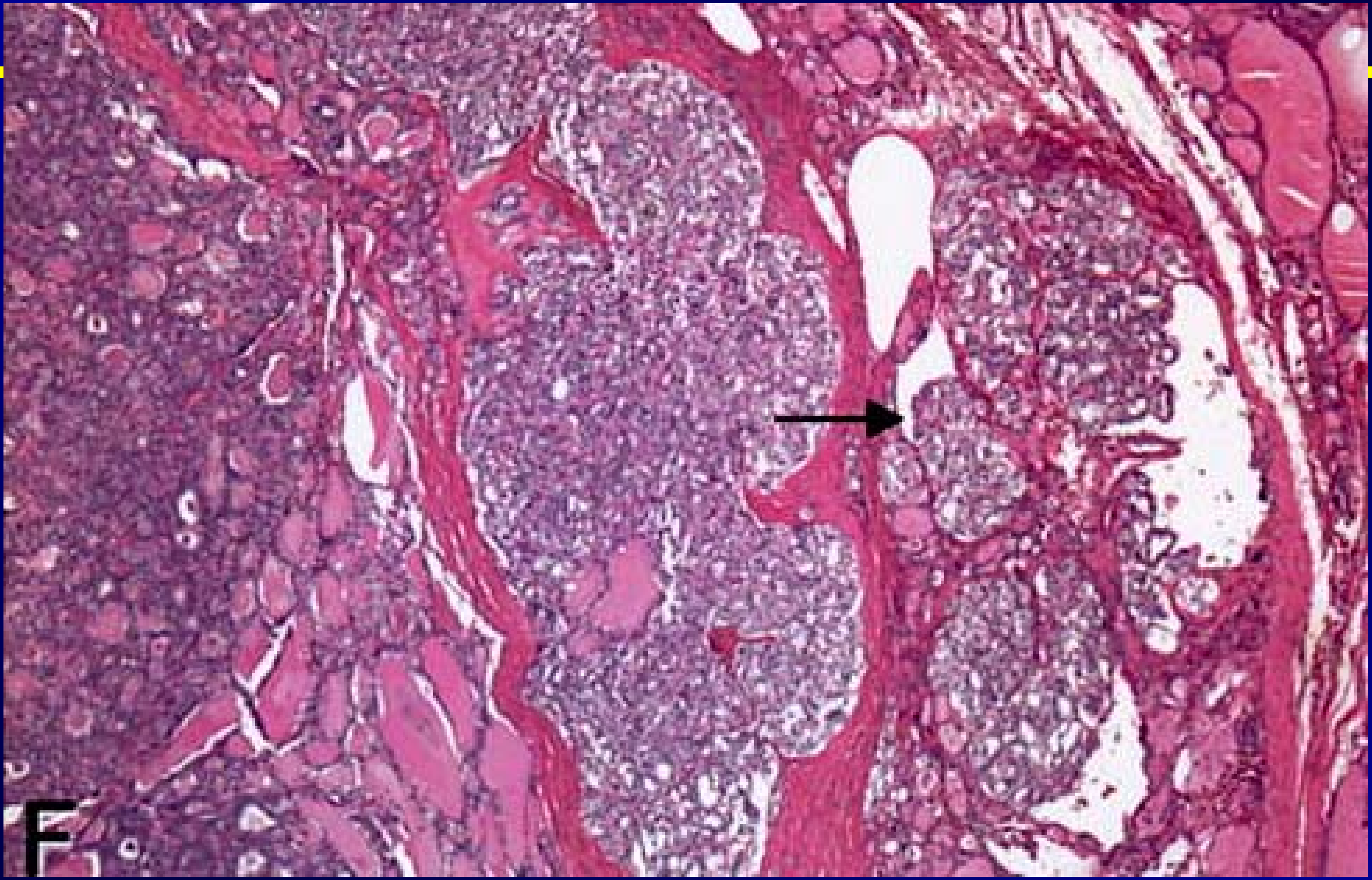
- **20% of all thyroid malignancies**
- **Women > Men (2:1 - 4:1) (Davis, 1992, De Souza, 1993)**
- **Mean age of 39 years (Mazzaferri, 1994)**
- **Prognosis - 60% survive to 10 years (Geopfert, 1994)**
- **Metastasis - angioinvasion and hematogenous spread**
    - **15% present with distant metastases to bone and lung**
- **Lymphatic involvement is seen in 13% (Goldman, 1996)**

WDTC - Follicular Carcinoma
(Continued…)

- **Pathology**
  - **Gross - encapsulated, solitary**
  - **Histology - very well-differentiated (distinction between follicular adenoma and carcinomaid difficult)**
    - **- Definitive diagnosis - evidence of vascular and capsular invasion**
  - **FNA and frozen section cannot accurately distinquish between benign and malignant lesions**

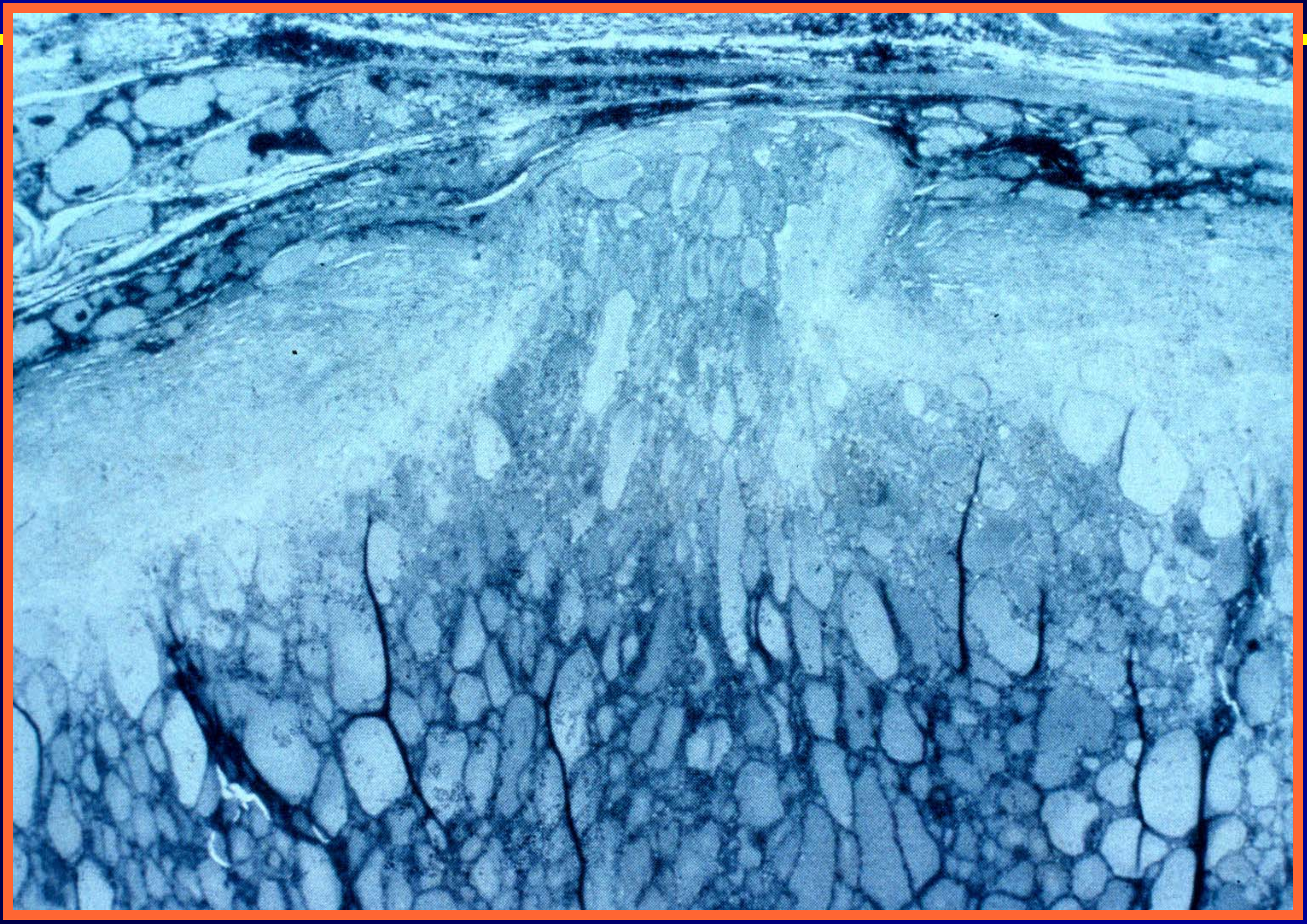
Follicular Thyroid Carcinoma





capsular invasion / suspicious vascular invasion

Follicular Carcinoma



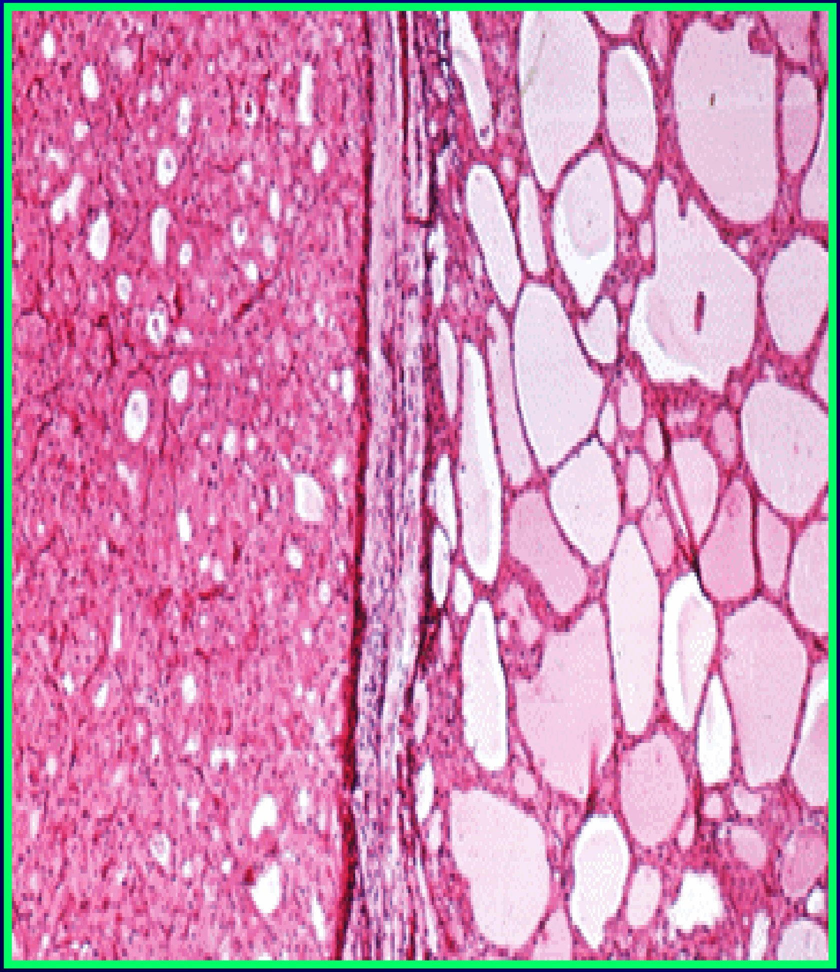
WDTC - Hurthle Cell Carcinoma

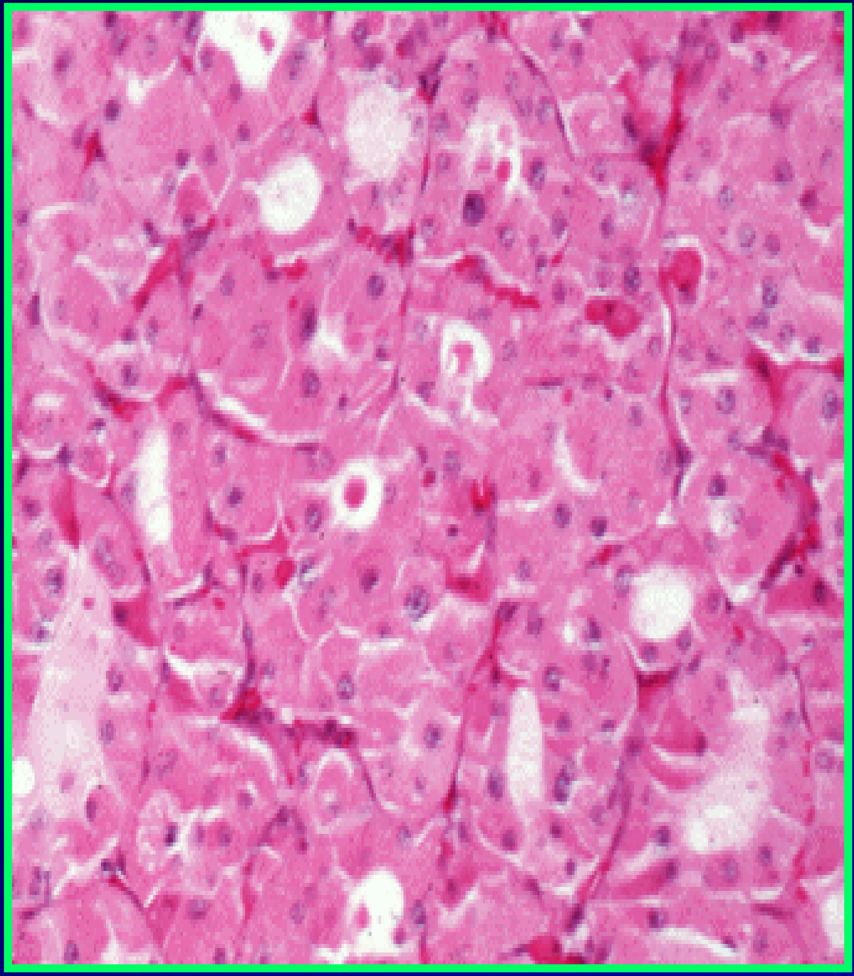
- **Variant of follicular carcinoma**
- **First described by Askanazy**
  - **“Large, polygonal, eosinophilic thyroid follicular cells with abundant granular cytoplasm and numerous mitochondria” (Goldman, 1996)**
- **Definition (Hurthle cell neoplasm) - an encapsulated group of follicular cells with at least a 75% Hurthle cell component**
- **Carcinoma requires evidence of vascular and capsular invasion**

WDTC - Hurthle Cell Carcinoma
(Continued…)

- **Women > Men**
- **Lymphatic spread seen in 30% of patients (Goldman, 1996)**
- **Distant metastases to bone and lung is seen in 15% at the time of presentation**

WDTC - Hurthle Cell Carcinoma



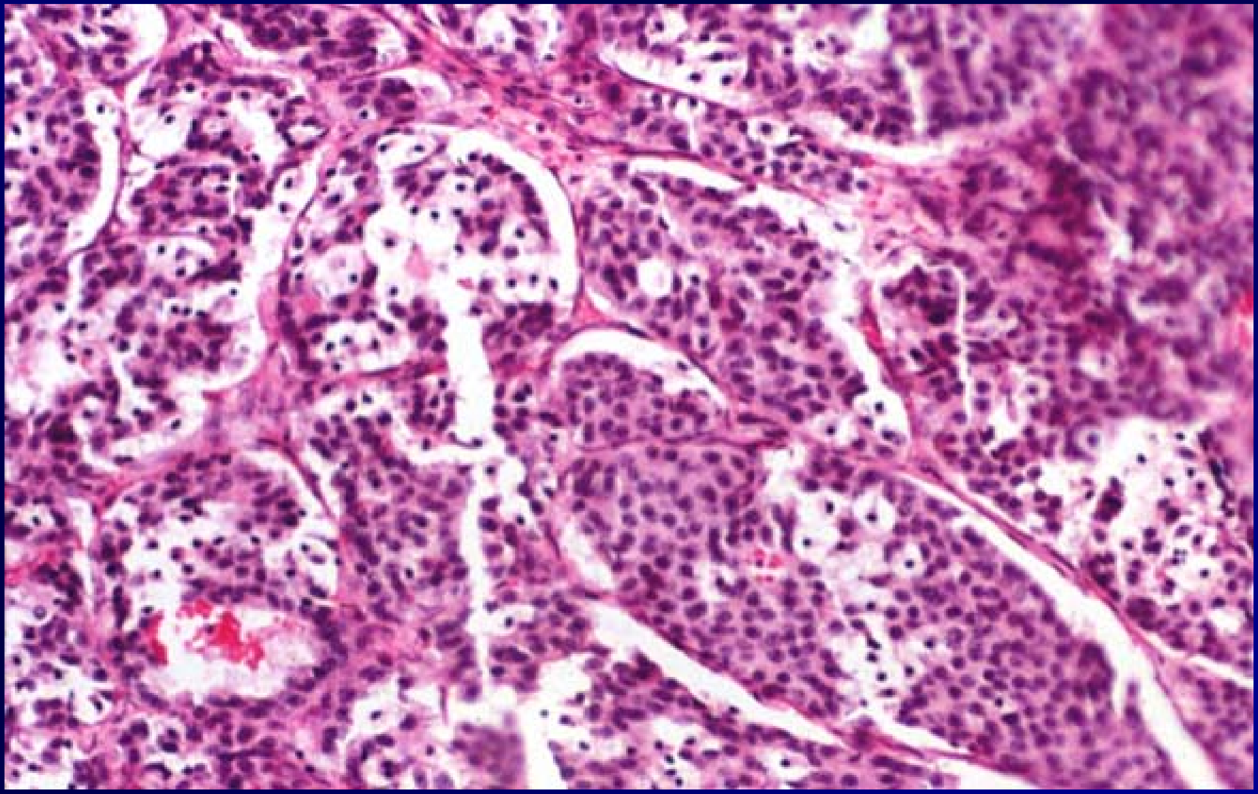


Medullary Thyroid Carcinoma

- **10% of all thyroid malignancies**
- **1000 new cases in the U.S. each year**
- **Arises from the parafollicular cell or C-cells of the thyroid gland**
  - **derivatives of neural crest cells of the branchial arches**
  - **secrete calcitonin which plays a role in calcium metabolism**

Medullary Thyroid Carcinoma (MTC)

- **Tumor of the para-follicular cells (C cells)**
- **Tumor markers: calcitonin and CEA**



Medullary Thyroid Carcinoma
(Continued…)

- **Developes in 4 clinical settings:**
  - **Sporadic MTC (SMTC)**
  - **Familial MTC (FMTC)**
  - **Multiple endocrine neoplasia IIa (MEN IIa)**
  - **Multiple endocrine neoplasia IIb (MEN IIb)**

Medullary Thyroid Carcinoma
(continued…)

- ***Sporadic MTC:***
  - **70%-80% of all MTCs Mean age of 50 years (Russell, 1983)**
  - **75% 15 year survival (Alexander, 1991)**
  - **Unilateral and Unifocal (70%)**
  - **Slightly more aggressive than FMTC and MEN IIa**
  - **74% have extrathyroid involvement at presentation (Russell, 1983)**

Medullary Thyroid Carcinoma
(Continued…)

- ***Familial MTC:***
  - **Autosomal dominant transmission**
  - **Not associated with any other endocrinopathies**
  - **Mean age of 43**
  - **Multifocal and bilateral**
  - **Has the best prognosis of all types of MTC**
  - **100% 15 year survival**

Medullary Thyroid Carcinoma
(continued…)

- ***Multiple endocrine neoplasia IIa (Sipple's Syndrome):***
  - **MTC, Pheochromocytoma, parathyroid hyperplasia**
  - **Autosomal dominant transmission**
  - **Mean age of 27**
  - **100% develop MTC (Cance, 1985)**
  - **85%-90% survival at 15 years (Alexander, 1991, Brunt, 1987)**

Medullary Thyroid Carcinoma
(continued…)

- ***Multiple endocrine neoplasia IIb (Wermer's Syndrome, MEN III, mucosal syndrome):***
  - **Pheochromocytoma, multiple mucosal neuromas, marfanoid body habitus**
  - **90% develop MTC by the age of 20**
  - **Most aggressive type of MTC**
  - **15 year survival is <40%-50%**

Medullary Thyroid Carcinoma
(continued…)

- **Diagnosis**
  - **Labs: 1) basal and pentagastrin stimulated serum calcitonin levels (>300 pg/ml)**

    2) serum calcium

    3) 24 hour urinary catecholamines (metanephrines, VMA, nor-metanephrines)

    4) carcinoembryonic antigen (CEA)
  - **Fine-needle aspiration**
  - **Genetic testing of all first degree relatives**
    - **RET proto-oncogene**

Anaplastic Carcinoma

- Highly lethal form of thyroid cancer
- Median survival <8 months (Jereb, 1975, Junor, 1992)
- 1%-10% of all thyroid cancers (Leeper, 1985, LiVolsi, 1987)
- Affects the elderly (30% of thyroid cancers in patients >70 years) (Sou, 1996)
- Mean age of 60 years (Junor, 1992)
- 53% have previous benign thyroid disease (Demeter, 1991)
- 47% have previous history of WDTC (Demeter, 1991)

Anaplastic Carcinoma of the Thyroid

- **Pathology**
  - Classified as large cell or small cell
  - Large cell is more common and has a worse prognosis
  - Histology - sheets of very poorly differentiated cells

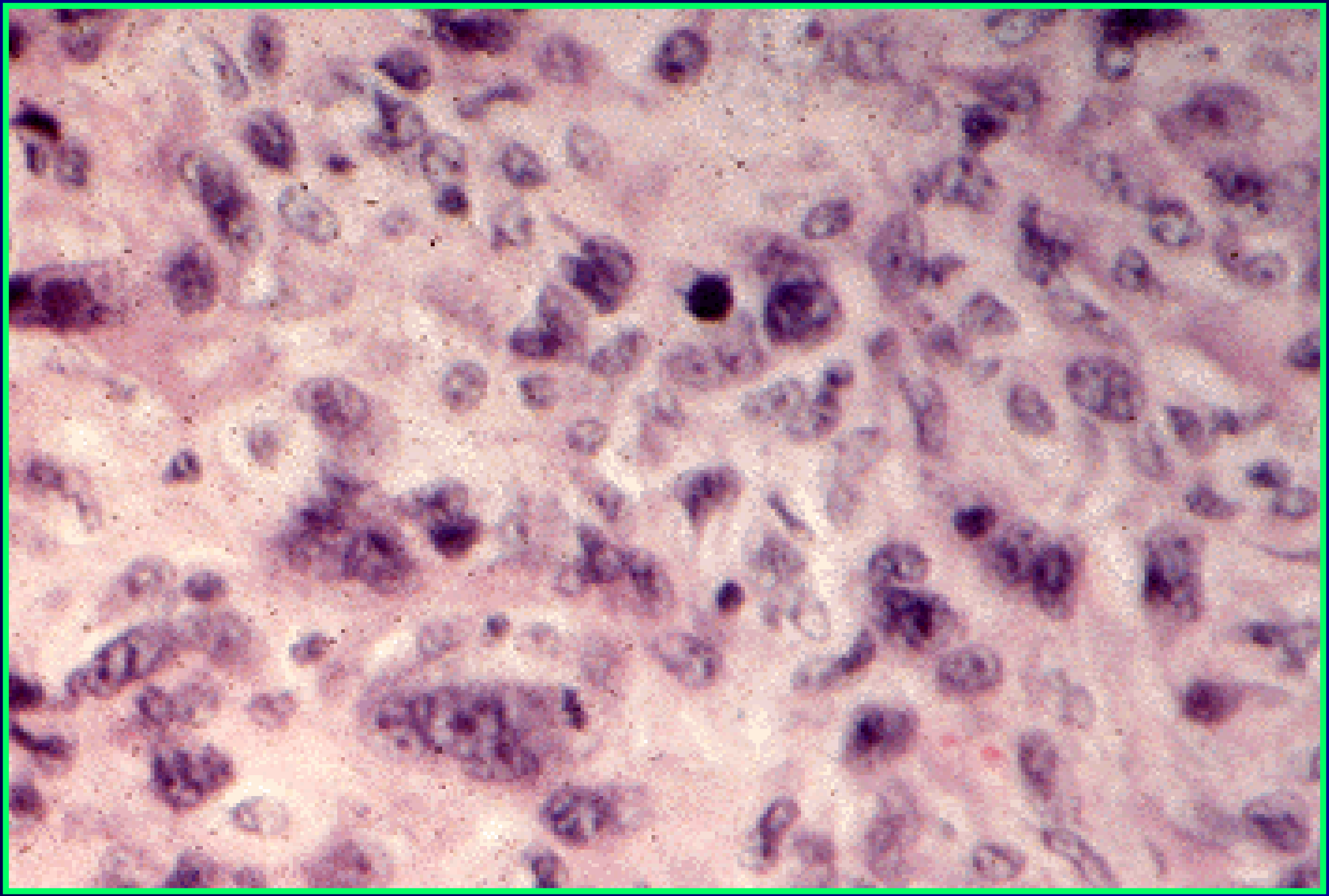
    little cytoplasm

    numerous mitoses

    necrosis

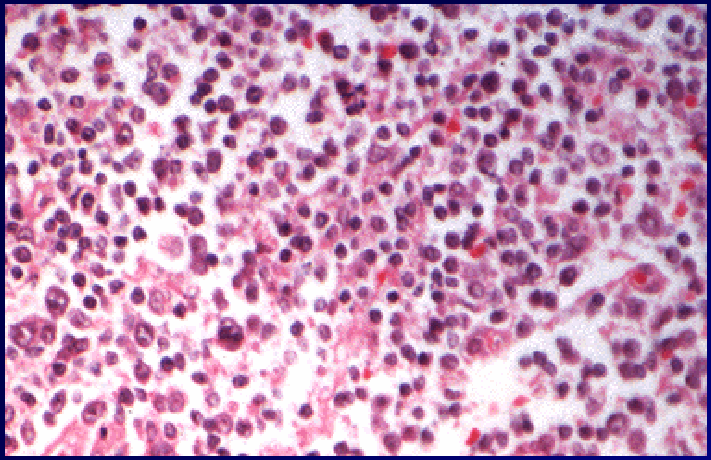
    extrathyroidal invasion

ANAPLASTIC THYROID CANCER



Primary Thyroid Lymphoma

- A rare type of thyroid cancer
  - Affects fewer than 1 in 2 million people
- Constitutes 5% of thyroid malignancies



Large Cell Lymphoma of the Thyroid

Primary Thyroid Lymphoma Characteristics and Diagnosis

- Develops in the setting of pre-existing lymphocytic thyroiditis
- Often diagnosed because of airway obstruction symptoms
- Tumors are firm, fleshy, and usually pale

THYROID CANCER STAGING

THE TNM STAGES OF THYROID CANCER

There are 4 main **T stages** for thyroid cancer

- T1 – Tumor entirely in thyroid and <1cm across in any direction
- T2 – Tumor entirely in thyroid and >1cm but <4cm in any direction
- T3 – Tumor entirely in thyroid and >4cm across in any direction
- T4 – Cancer has grown outside the covering of the thyroid gland.

There are 2 possible stages of lymph **Node** involvement.

- NO - No lymph nodes containing cancer cells
- N1 - Lymph nodes containing cancer cells
- N1a – LN w/ cancer cells on one side of the neck (same side as cancer)
- N1b – LN w/ cancer cells anywhere else (other side of the neck or in chest)

There are 2 possible stages of cancer spread **Metastasis**.

- M0 - Cancer has not spread
- M1 – Cancer has spread

Staging system for papillary and follicular thyroid carcinoma

(American Joint committee on Cancer, TNM system)

Stage	Age <45 yr	Age >/=45 yr
I	M0	T1
II	M1	T2-3
III	….	T4 or N1
IV	….	M1

- T: size (T1 <1cm, T2 1cm - <4cm, T3 >4cm, T4 direct extension or invasion through the thyroid capsule)
- N: lymph node
- M: distant metastases

PAPILLARY & FOLLICULAR STAGING

Stage	<45 yo	>45 yo	Local Recur	Distant Recur	Mortality
1	Any T Any N M0	T1 N0 M0	5.5%	2.8%	1.8%
2	Any T Any N M1	T2,3 N0 M0	7%	7%	11.6%
3		T4, N0, M0 Any T, N, M	27%	13.5%	37.8%
4		Any T, N, M1	10%	100%	90%

ANAPLASTIC STAGING

- There is no number staging system used
- All is stage IV: Any T, Any N, Any M
- This is because there is a high risk of the cancer spreading.
- Treatment dependent on whether the cancer is only in neck and may be able to be completely removed
- Level of fitness for treatments such as surgery or radiotherapy

MEDULLARY STAGING

- Stage 1 – Cancer < 1 cm across
  T1, N0, M0
- Stage 2 – Cancer 1 – 4 cm across
  T2, 3, 4; N0, M0
- Stage 3 – There is spread to lymph node
  Any T, N1, M0
- Stage 4 – There is spread to distant part of body
  Any T, Any N, M1

Staging system for medullary and anaplastic thyroid carcinoma

(American Joint committee on Cancer,TNM system)

Stage	Medullary	Anaplastic
I	T1	….
II	T2-4	….
III	N1	….
IV	M1	Any

- **T: size (T1 <1cm, T2 1cm - <4cm, T3 >4cm, T4 direct extension or invasion through the thyroid capsule)**
- **N: lymph node**
- **M: distant metastases**

General management scheme for papillary and follicular thyroid cancer

- **Thyroidectomy**
- **(Selective lymph node dissection)**
- **Post-op radioactive iodine ablation therapy**
- **TSH suppression therapy**
- **Periodic surveillance for recurrence and metastasis:**

  -Blood test: thyroglobulin level

  -Imaging studies: Radioactive iodine whole body scan, neck ultrasound, CXR, CT, PET CT, bone scan.

Management

- Surgery is the definitive management of thyroid cancer, excluding most cases of ATC and lymphoma
- Types of operations:
  - lobectomy with isthmusectomy - minimal operation required
    for a potentially malignant
    thyroid nodule
  - total thyroidectomy - removal of all thyroid tissue

Management (WDTC) - Papillary and Follicular

Subtotal *vs.* total thyroidectomy

Arguments for Total Thyroidectomy

- **Radioactive iodine** may be used to detect and treat residual normal thyroid tissue and local or distant metastases
- **Serum thyroglobulin** level is a more sensitive marker for persistent or recurrent disease when all normal thyroid tissue is removed
- In up to 85% of papillary cancer, **microscopic foci** are present in the contralateral lobe. Total thyroidectomy removes these possible sites of recurrence

Arguments for Total Thyroidectomy

- Recurrence develops in 7% of contralateral lobes (1/3 die)
- Risk (though very low [1%]) of dedifferentiation into anaplastic thyroid cancer is reduced
- Survival is improved if papillary cancer greater than 1.5cm or follicular greater than 1cm
- Need for reoperative surgery associated with higher risk is lower

Arguments against total thyroidectomy

- Total thyroidectomy may be associated with higher complication rate than lobectomy
- 50% of recurrences can be controlled with surgery
- Fewer than 5% of recurrences occur in the thyroid bed

Arguments against total thyroidectomy

- **Tumor multicentricity has little clinical significance**
- **Prognosis of low risk patients (age, grade, extent, size) is excellent regardless of extent of resection**

Indications for total thyroidectomy

- 1) Patients older than 40 years with papillary or follicular carcinoma
- 2) Anyone with a thyroid nodule with a history of irradiation
- 3) Patients with bilateral disease

Management (WDTC) - Papillary and Follicular

- **Managing lymphatic involvement**
  - pericapsular and tracheoesophageal nodes should be dissected and removed in all patients undergoing thyroidectomy for malignancy
  - Overt nodal involvement requires exploration of mediastinal and lateral neck
  - if any cervical nodes are clinically palpable or identified by MR or CT imaging as being suspicious a neck dissection should be done Prophylactic neck dissections are not done (Gluckman)

Radioactive iodine ablation

- **Advantages:**
  - It may destroy microscopic cancer cells.
  - Subsequent detection of persistent or recurrent disease by radioiodine scanning is facilitated.
  - The sensitivity of serum thyroglobulin measurements is improved.

PAPILLARY & FOLLICULAR FOLLOW UP

- Radioactive Iodine (Administration)
- Scan At 4-6 Weeks Postop
- Repeat Scan At 6-12 Months After Ablation
- Repeat Scan At 1 Year Then...
- Every 2 Years Thereafter

THS suppression therapy

- Patient after thyroidectomy is given thyroid hormone not only for physiological replacement, but also to suppress TSH as TSH can stimulate growth of thyroid cells.

- TSH level should ***not*** be “mid normal” range for patients with thyroid cancer.

THS suppression therapy

- TSH level needs to be subnormal or suppressed, depending on the aggressiveness of the disease.
- The degree of TSH suppression needs to be tailored to each patient.

Target TSH Suppression in Patients With Thyroid Cancer

Optimal TSH

	Low to Undetectable	Suppressed but Detectable	Low Normal
TSH, mIU/L	<0.1	0.1 to 0.4	0.5 to 1
Patients	• Persistent or recurrent disease • High-risk patients	• Most patients with no evidence of disease	• Very low-risk patients • Long-term survivors

Management (WDTC) - Hurthle Cell Carcinoma

- Total thyroidectomy is recommended because:
  - 1) Lesions are often Multifocal
  - 2) They are more aggressive than WDTCs
  - 3) Most do not concentrate iodine

Management - Hurthle Cell Carcinoma

- Postoperative management
  - Thyroid suppression
  - Measure serum thyroglobulin every 6 months
  - Postoperative radioactive iodine is usually not effective (10% concentrate iodine) (Clark, 1994)

Management of Medullary Thyroid Carcinoma

- Recommended surgical management
    - total thyroidectomy
    - central lymph node dissection
    - lateral jugular sampling
        - if suspicious nodes - modified radical neck dissection
- If patient has MEN syndrome
    - remove pheochromocytoma before thyroid surgery

Management of Medullary Thyroid Carcinoma

- Postoperative management
  - disease surveillance
    - –serial calcitonin and CEA
      - –2 weeks postop
      - –3/month for one year, then…
      - –biannually

Management of Medullary Thyroid Carcinoma

- If persistent elevated CEA or calcitonin, CT scan for residual disease (50% of pts)
- Aggressive neck dissection advocated by many if persistent disease
- Consider laparotomy for possible liver mets
- Prolonged survival with significant symptoms not uncommon with widely metastatic disease

Management of Medullary Thyroid Carcinoma

- Familial cases positive for *RET* proto-oncogene mutation
- If positive family history, then genetic testing
- If MEN IIA or FMTC then total thyroidectomy and central lymph node dissection between ages of 5-6 years
- If MEN IIB then total thyroidectomy and central node dissection ages 6mos - 3 years
- SURGERY IS ONLY EFFECTIVE THERAPY

Incidentaloma/Micrometastatic Disease

- **Lesions detected by imaging or found after surgery for unrelated indication**
- **Thyroid nodules common in population (4-10% have palpable nodules any given time)**
- **Female/male incidence 6.4 / 1.6%**
- **12% detected by palpation vs. 45% by imaging**
- **Lesions less than 1 cm-observe**
- **Lesions 1-2cm “gray zone”**
- **Lesions > 2cm are NOT INCIDENTAL**

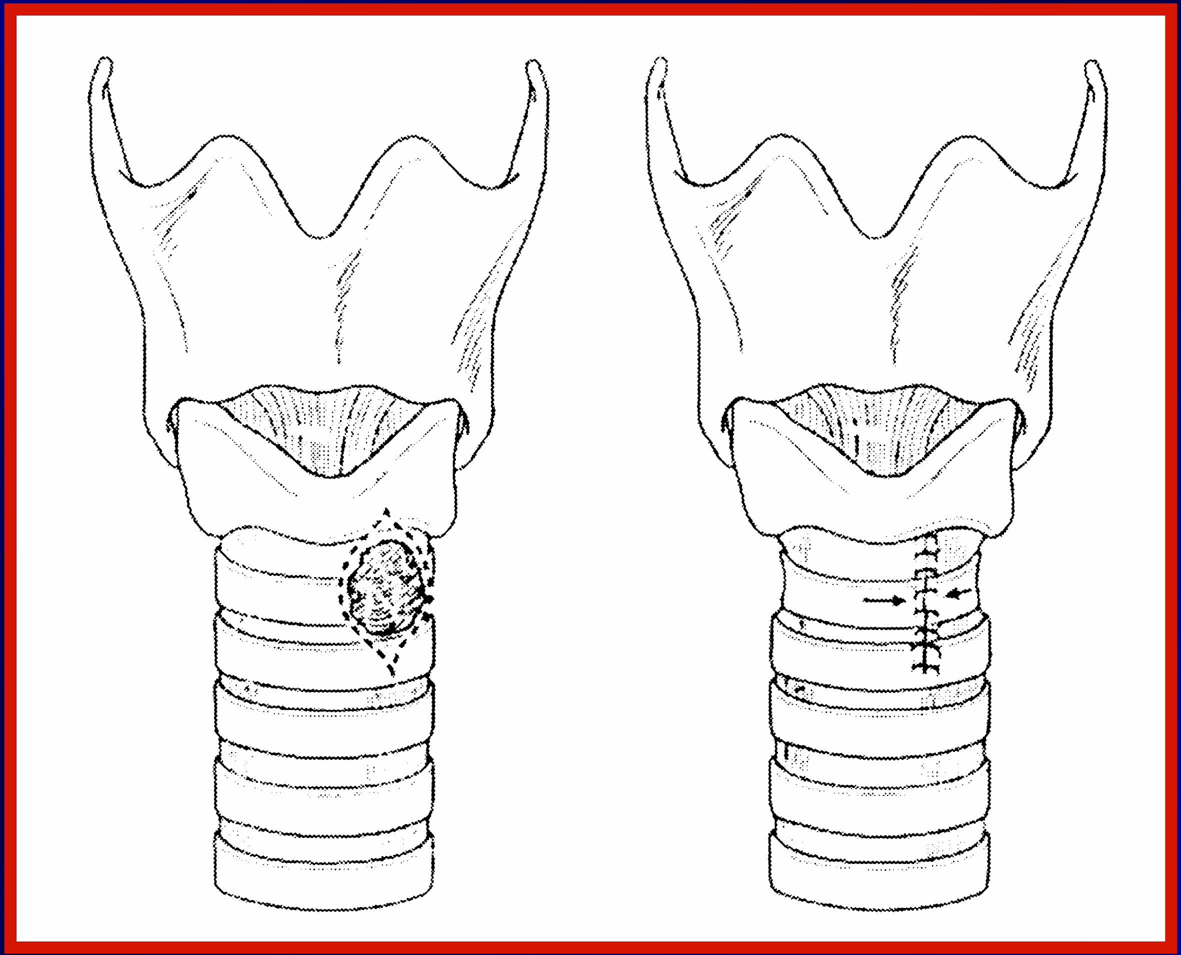
Incidentaloma/Micrometastatic Disease

- **Consider suspicious features:**
  - **Increased vascularity**
  - **Irregular margin**
  - **Central microcalcification**
  - **Cervical adenopathy**

Anaplastic Carcinoma
(Management)

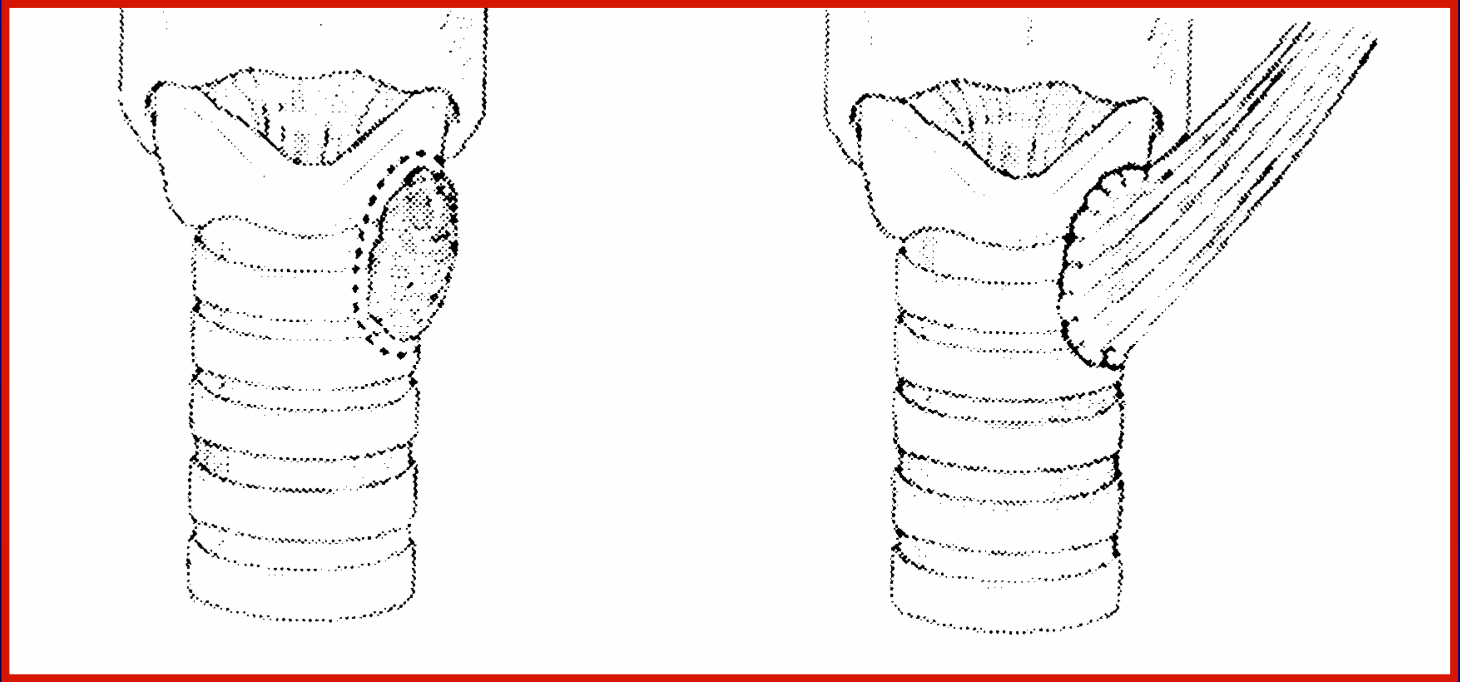
- **Most have extensive extrathyroidal involvement at the time of diagnosis**
  - **surgery is limited to biopsy and tracheostomy**
- **Current standard of care is:**
  - **maximum surgical debulking, possible**
  - **adjuvant radiotherapy and chemotherapy (Jereb and Sweeney, 1996)**

Local Invasion of the Neck



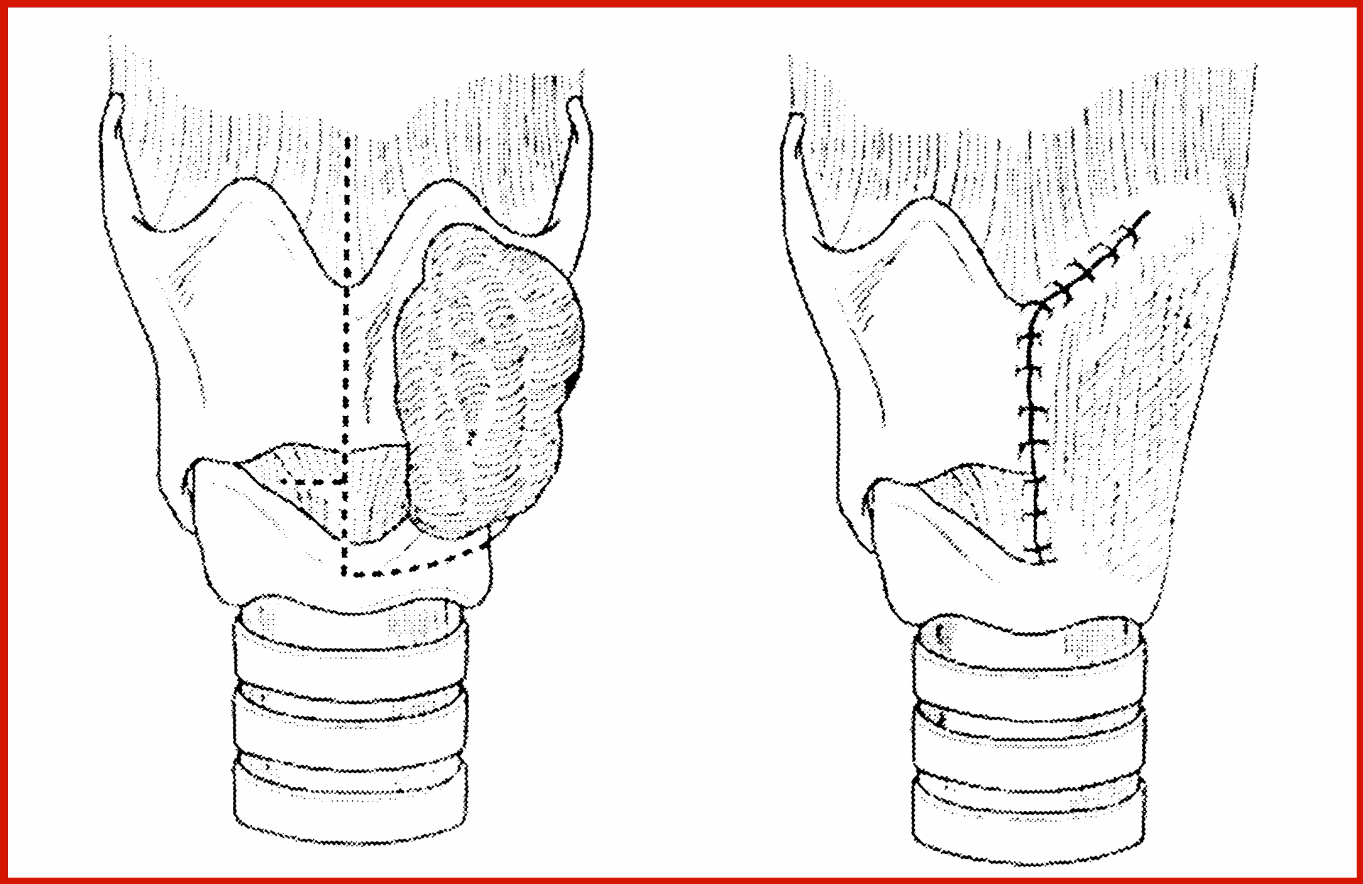
Tracheal resection repaired primarily

Local Invasion of the Neck



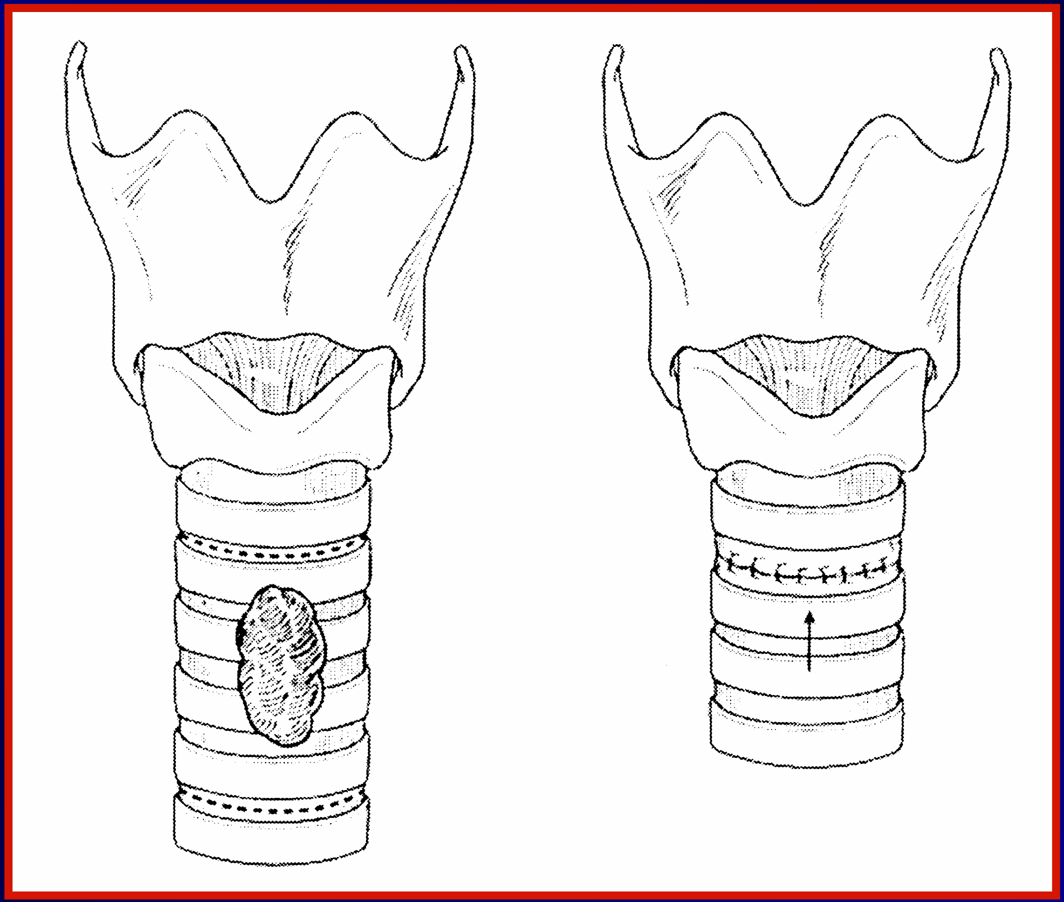
Crycoid invasion with local muscle flap reconstruction

Local Invasion of the Neck



Vertical hemilaryngectomy

Local Invasion of the Neck



Circumferential tracheal resection with primary anastomosis

Thyroid Tumor

Postoperative Complications

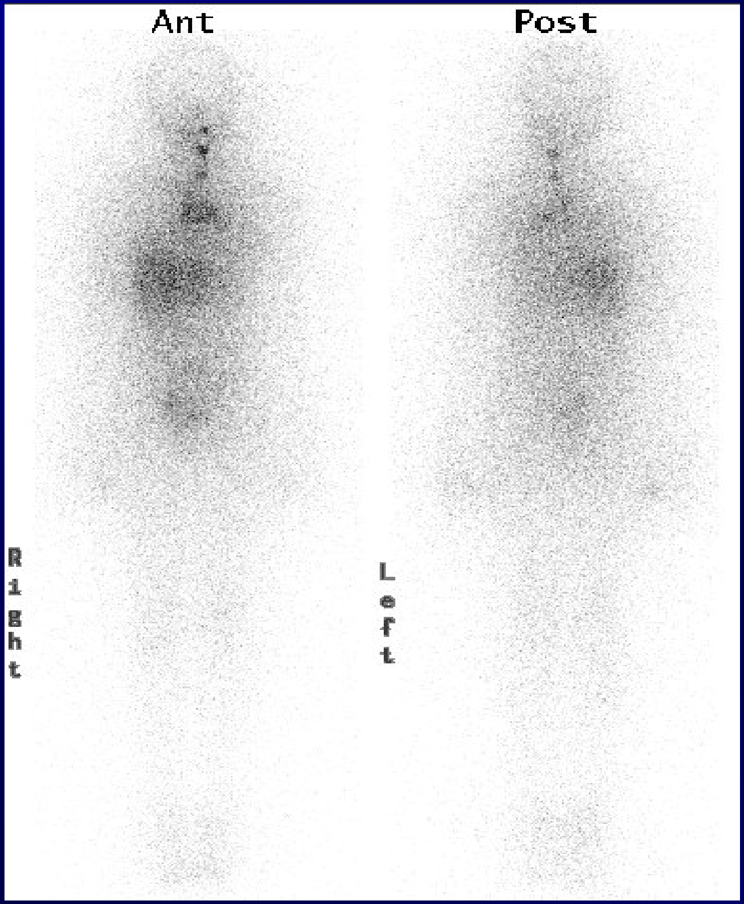
- **Postoperative hypocalcaemia (transient / permanent hypoparathyroidism)**
- **Recurrent laryngeal nerve dysfunction (vocal cords paralysis)**
- **Postoperative bleeding**
- **Postoperative infection**

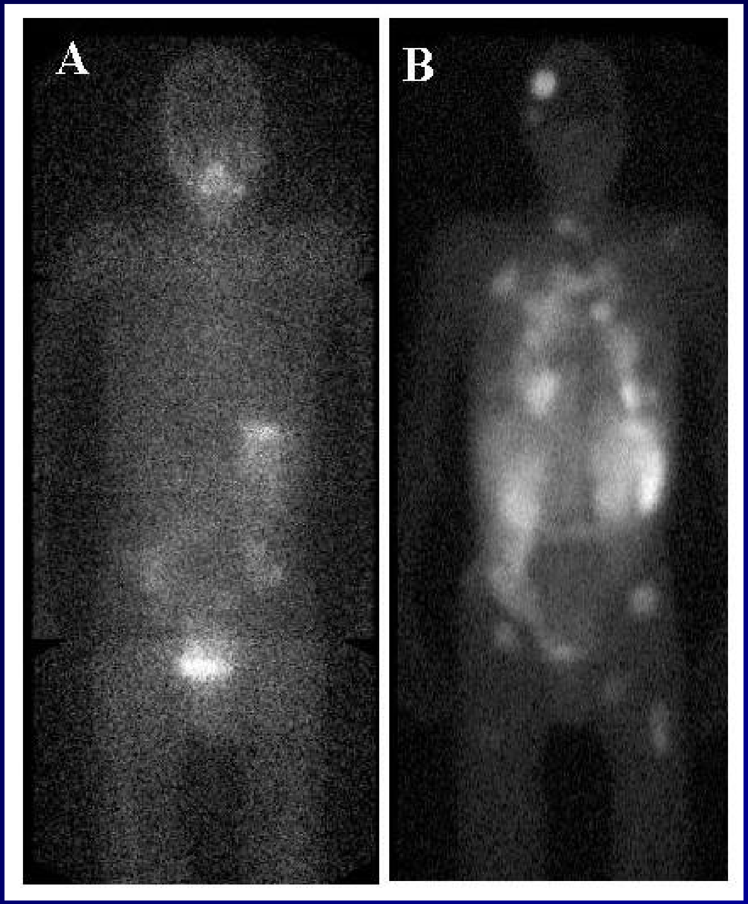
Thyroid Tumor

Monitoring of Differentiated Carcinoma

- Follow up at intervals of 6 -12 months throughout the patient's life
- To evaluate effectiveness of TSH suppression
  - Serum TSH (< 0.1 mU/L)
- To evaluate presence of recurrence
  - Serum thyroglobulin (< 1ng/ml)
- To evaluate presence and location of recurrence
  - Chest X-ray (CT) and cervical ultrasound
  - I^{131} total-body scanning

I^{131} Total Body Scan





PROGNOSIS

- **Prognostic schemes:**
  - **AMES (Lahey Clinic, Burlington, MA)**
  - **GAMES (Memorial Sloan-Kettering Cancer Center, NY)**
  - **AGES (Mayo Clinic, Rochester, MN)**

- AMES scoring (PAPILLARY & FOLLICULAR CANCER)
  - **A** **Age of patient when tumor discovered**
  - **M** **Metastases of the tumor (other than Neck LN**
  - **E** **Extent of primary tumor**
  - **S** **Size of tumor (>5 cm, or about 2 inches)**

PROGNOSIS

The patients are categorized into:

- ***Low risk group*** - men younger than 40 years and women younger than 50 years regardless of histologic type (intrathyroid papillary & follicular) – No distant mets & size <5cm - recurrence rate -11%; death rate - 4%

- ***Intermediate risk group*** - Men older than 40 years and women older than 50 years who have papillary carcinoma - size <5cm - recurrence rate - 29%; death rate - 21%

- ***High risk group*** - Men older than 40 years and women older than 50 years who have follicular carcinoma - with distant mets, size >5cm - recurrence rate - 40%; death rate - 36%

PROGNOSIS

- MAICS Scoring (PAPILLARY THYROID CANCER)

A mathematical calculation developed by the Mayo Clinic for staging. It is known to be the most accurate predictor of a patient's outcome with papillary thyroid cancer

(M = Metastasis, A = Age, I = Invasion, C = Completeness of Resection, S = Size)

MAICS Score		20 year Survival
<6	=	99%
6-7	=	89%
7-8	=	56%
>8	=	24%

THANK YOU!!

Evaluation of a Thyroid Nodule

Thyroid Nodule

- Prevalence: 4% - 7%
- Diagnosis of single thyroid nodule:
  - Malignant thyroid disease 5 - 7 %
  - Benign follicular neoplasms 13 - 15%
  - Benign colloid nodule 32 - 36 %
  - Benign cyst 18 - 20 %
  - Hashimoto thyroiditis 20 - 24 %

Thyroid Nodule

Diagnostic Work–Up

- Clinical history and physical examination

Clinical History & Physical Examination

(suspicion of Benign disease)

- Autoimmune thyroid disease
- Family history of benign thyroid nodule
- Pain or tenderness
- Soft, smooth, mobile nodule

Clinical History & Physical Examination

(suspicion of malignant disease)

- Age < 20 years ; > 60 years
- Gender – male
- Exposure to irradiation
- Hoarseness and dysphagia
- Rapid growth
- Firm, irregular and fixed nodule
- Cervical lymphadenopathy

Diagnostic Work–Up

- Clinical history and physical examination
- Laboratory assessment

Laboratory Assessment

- Thyroid function tests: TSH, fT_4, TT_3
- Serum thyroid antibodies
- Tumor markers: calcitonin
  (in patients with family history of medullary thyroid carcinoma, or MEN type 2).

Diagnostic Work–Up

- Clinical history and physical examination
- Laboratory assessment
- Imaging –
  - Ultrasound
  - Radionuclide scanning
  - (CT, MRI)

Ultrasound

- Size
- Solitary or multiple
- Cystic, solid or mixed
- Hypoechoic or hyperechoic
- Calcifications
- Increased nodular flow
- Lymph nodes
- Trachea

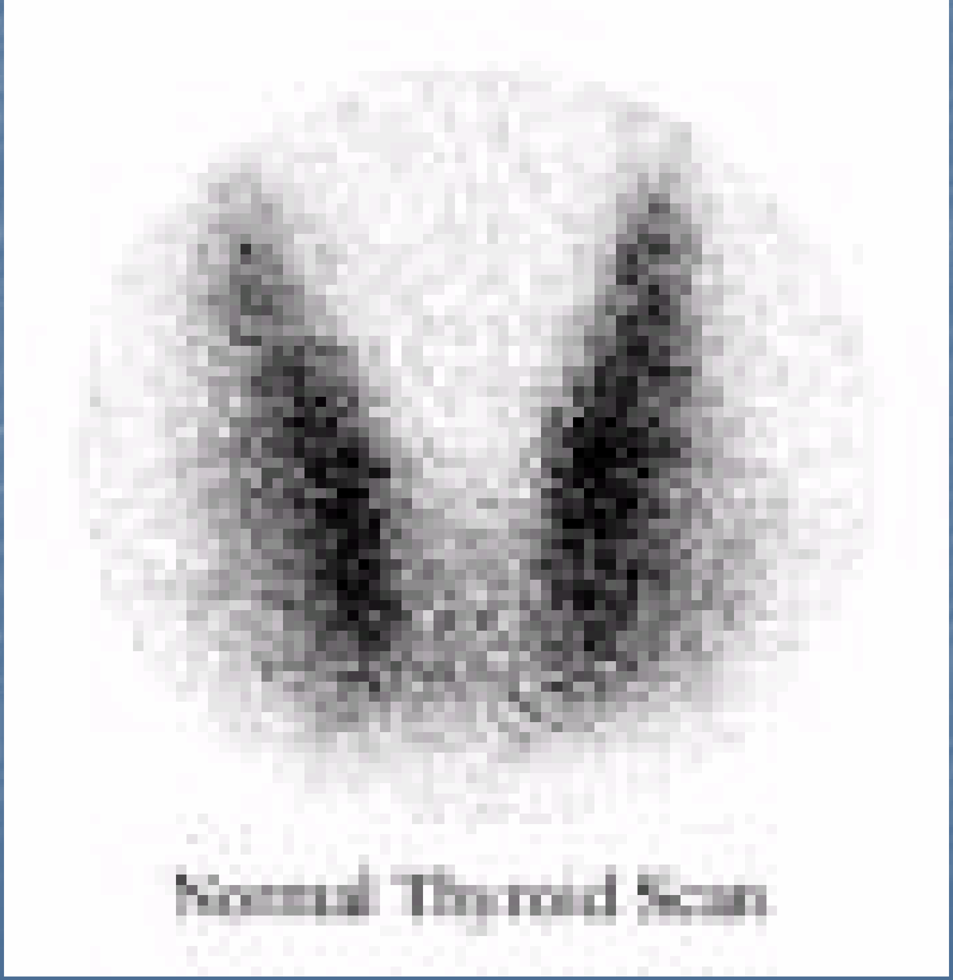
- Detect non-palpable nodules

Solitary Thyroid Nodule

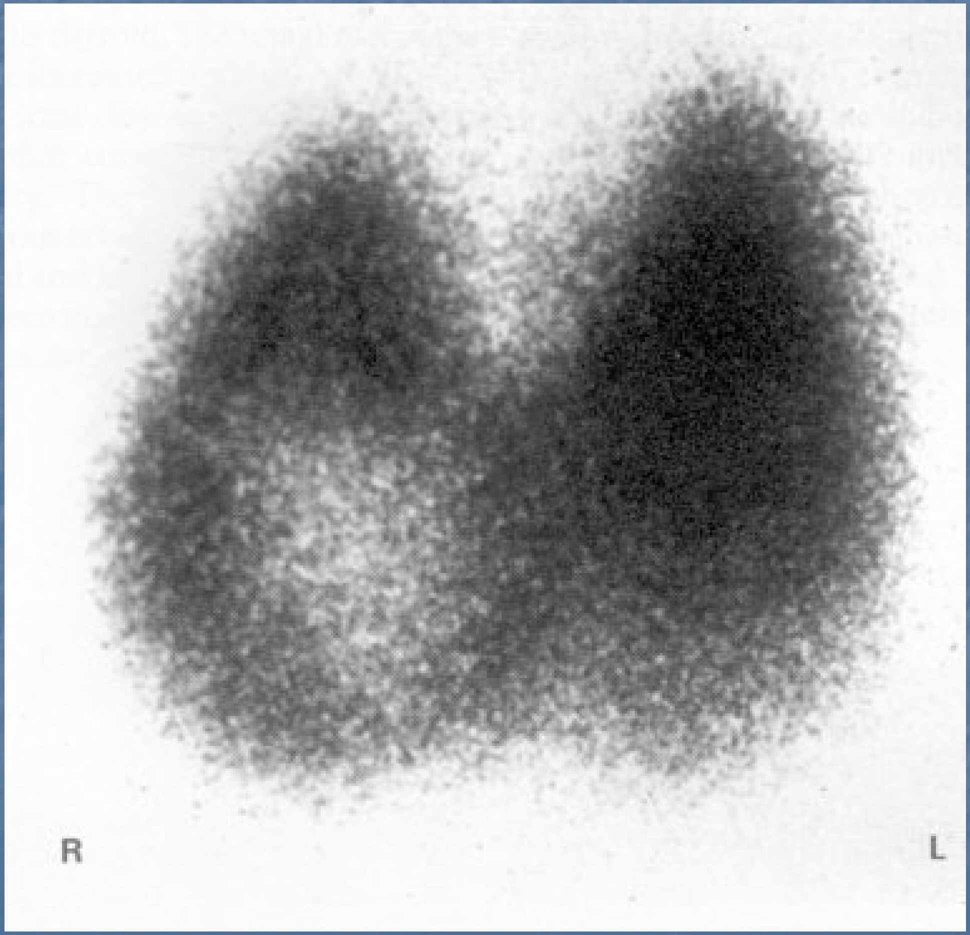
Radionuclide Scanning (Technetium)

- “Hot” nodule – 10%, nearly always benign
- “Warm” nodule
- “Cold” nodule – Has a 5% risk of being malignant

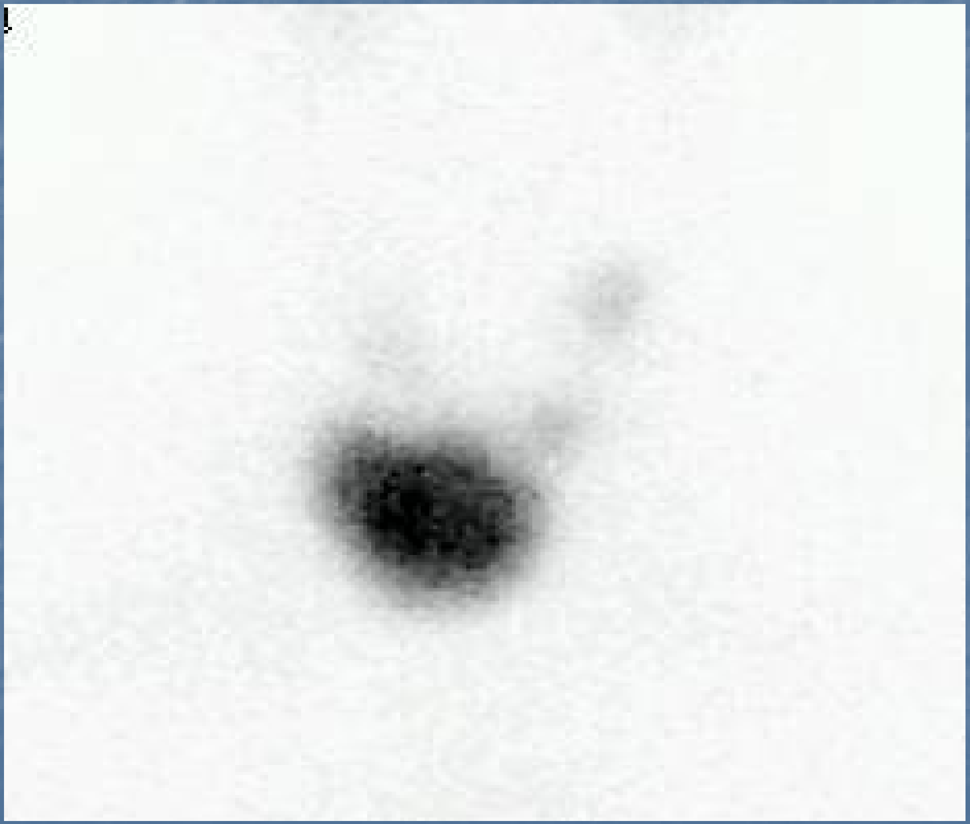
Thyroid Scan - Normal



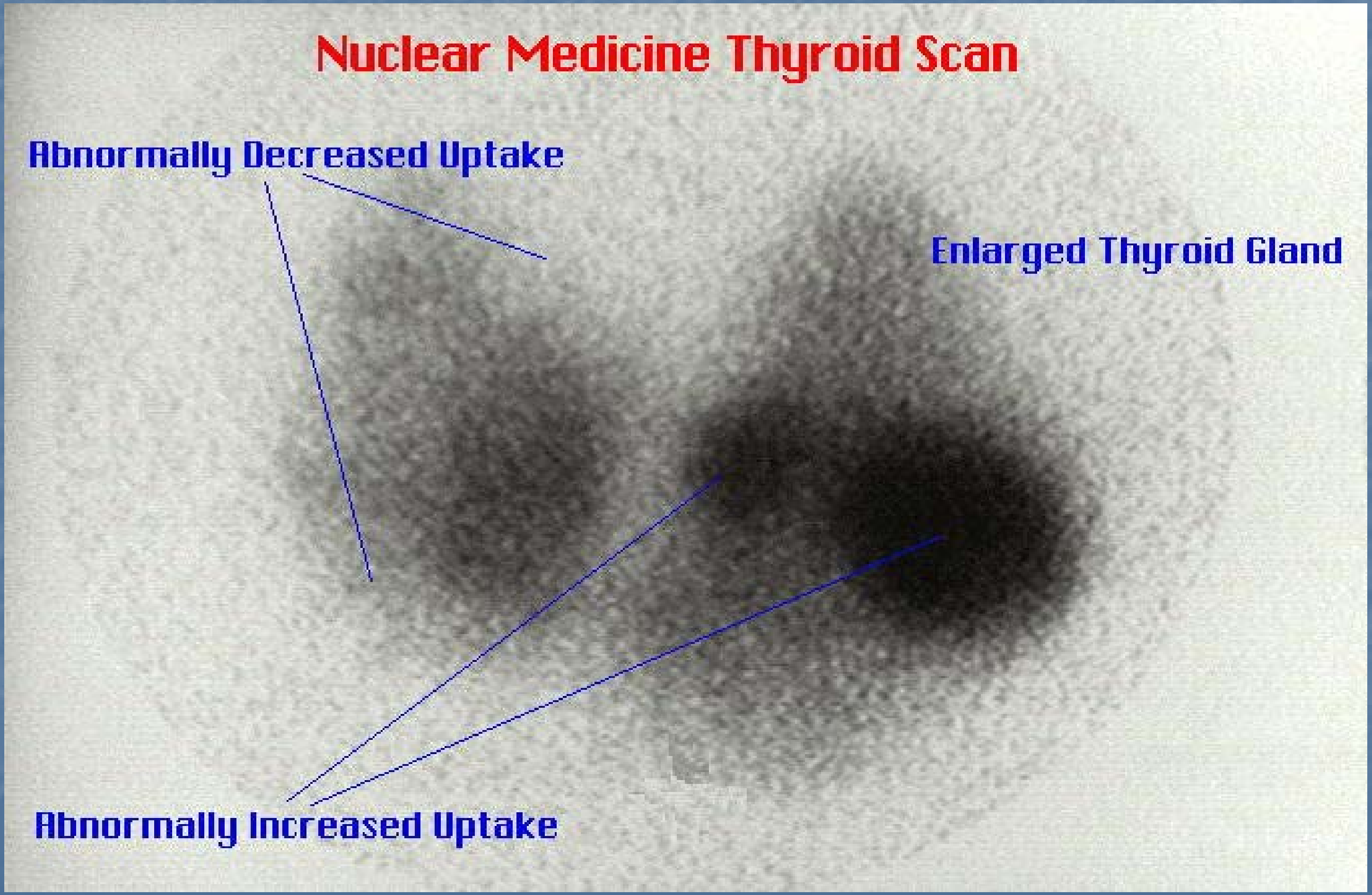
Thyroid Scan - Cold Nodule



Thyroid Scan - “Hot” Nodule



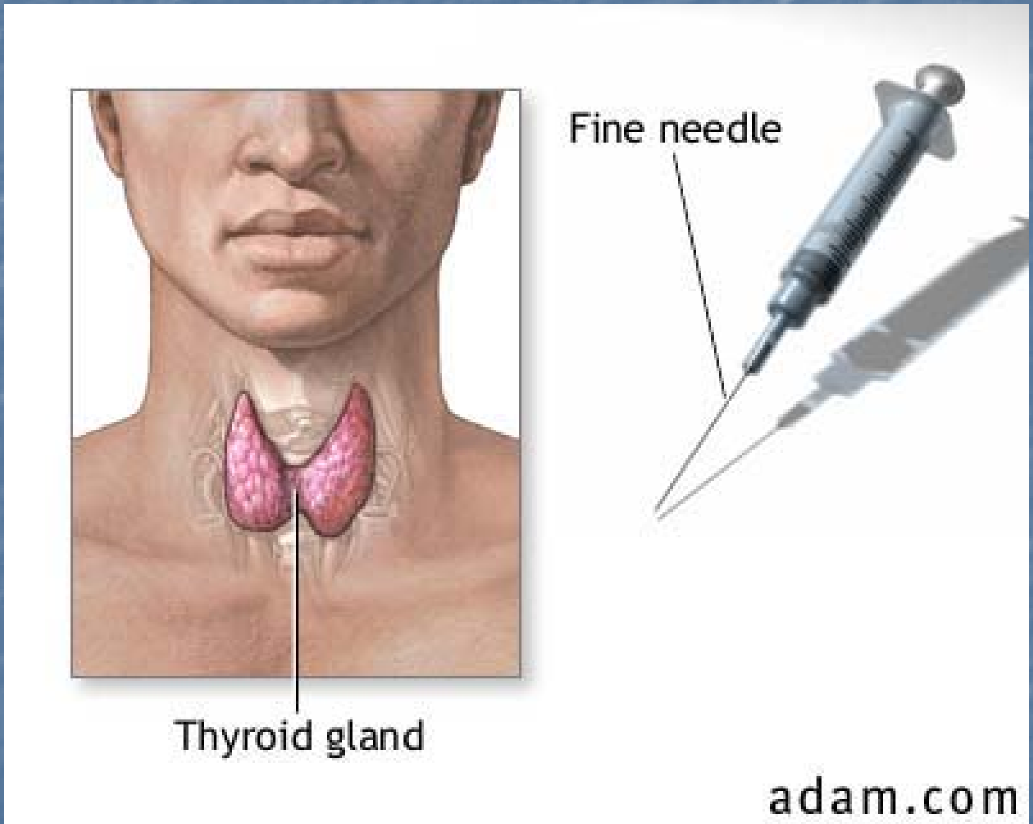
Thyroid Scan – Multinodular Goiter



Diagnostic Work–Up

- Clinical history and physical examination
- Laboratory assessment
- Imaging –
  - Ultrasound
  - Radionuclide scanning
  - (CT, MRI)
- FNA biopsy

Fine Needle Aspiration (FNA)



FNA results

- Inadequate specimen
- Adequate specimen
  - Benign
  - Malignant
  - Suspicious

Benign thyroid nodules

- Differential diagnosis

  -Thyroid adenoma

  -Multinodular goiter

  -Hashimoto’s thyroiditis

  -Subacute thyroiditis

  -Thyroid cyst

Malignant thyroid nodules

- Differential diagnosis

  -Papillary thyroid CA (75-85%)

  -Follicular thyroid CA (10-20%)

  -Medullary thyroid CA (5%)

  -Anaplastic thyroid CA (rare)

  -Lymphoma (rare)

  -Squamous cell carcinoma (rare)

Historical Red Flags

- Male
- Extremes of age (<20 or >65)
- Rapid Growth
- Symptoms of local invasion (hoarseness, dysphagia, neck pain)
- History of radiation to the head or neck
- Family history of Thyroid Cancer or Polyposis

Thyroid Nodules

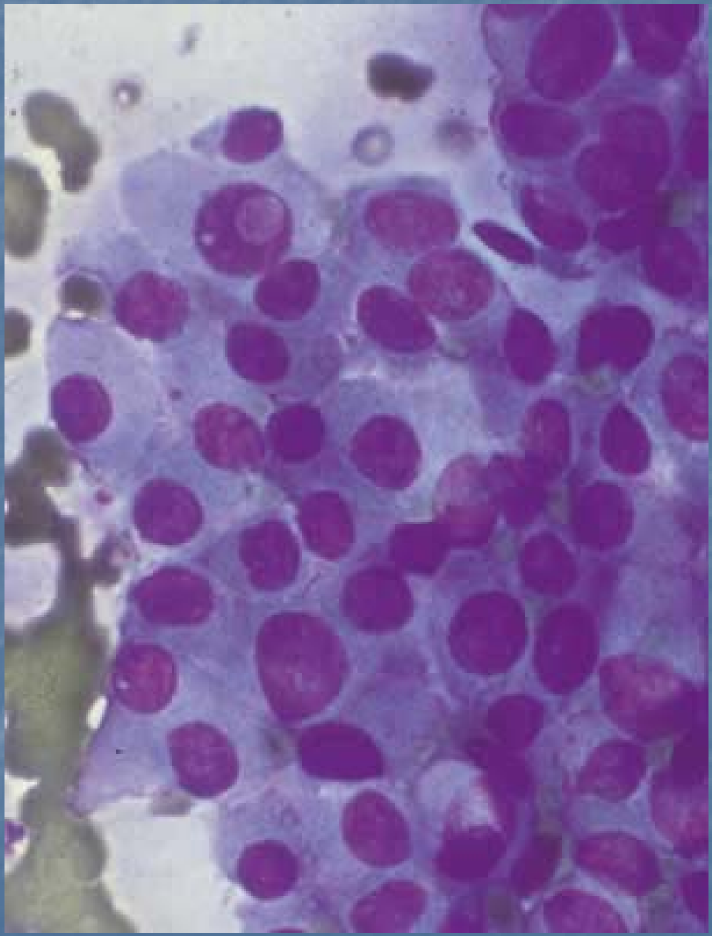
- FNA Results:
  - Suspicious--------Surgery
  - Negative----------6 month follow up
  - Indeterminant---repeat the FNA, if still indeterminant, surgery recommended

Suspicious nodules

- Not enough evidence to conclude that the lesion is benign or malignant.
- Follicular carcinoma may be indistinguishable from follicular adenoma on FNA.

→If the FNA result is a follicular lesion, that nodule needs to be surgically removed for diagnostic purpose.

FNA – Papillary Thyroid Carcinoma



Thyroid Nodule

FNA Biopsy

- Benign - 70%
- Malignant - 5%
- Suspicious
- Insufficient

Thyroid Nodule

Diagnostic Work–Up

- Clinical history and physical examination
- Laboratory assessment
- Imaging –
  - Ultrasound
  - Radionuclide scanning
  - (CT, MRI)
- FNA biopsy
- TSH suppressive therapy (?)

Thyroid Nodules

- Non-toxic Solitary Nodules
  - Indications for treatment
    - Compressive Symptoms
    - Growth of Nodule
    - Recurrence of cystic nodule after aspiration
    - Other
  - Unilateral lobectomy-preferred therapy
  - Aspiration
  - Suppression (SOR=C, LOE=3)
    - 6-12 month trial
    - Premenstrual women, post-menopausal on HRT, men
    - Cochrane review pending

Thyroid Nodules

- Non-toxic Multinodular Goiter
  - Indications for treatment: Same

Therapy	Advantages	Disadvantages
Surgery	Rapid Decompression and Pathological Interpretation	Hypoparathyroid or Hypothyroid, Recurrent Laryngeal Nerve Damage
Thyroxine	Easiest Option	Effectiveness unclear, bone mineral density decrease, Cardiac effects
I^{131}	Very effective	Slower decompression, thyroiditis, thyroid dysfunction, ? Risk CA

Thyroid Nodules

- Toxic Solitary or Multinodular Goiter
  - Indications: Overtly Hyperthyroid or Young/Old at risk for cardiac disease or osteoporosis

Therapy	Advantages	Disadvantages
I^{131}	Highly effective for reversal of hyperthyroidism, 90%	Gradual effect, 10% hypothyroid, ? Increased risk for CA
Surgery	Rapid reversal of hyperthyroidism, Pathology	Surgical Morbidity and Mortality, 10-20% hypothyroidism
Anti-thyroid Drugs	Easiest Option	Lifelong treatment and Adverse effects

Special Populations

- Pregnant/Breastfeeding
  - Hyperthyroidism
    - Risks: Fetal Loss, severe pre-eclampsia, preterm delivery, heart failure, LBW neonate
    - Anti-thyroid drugs preferred treatment
    - No I^{131}
    - Neonates can get immune mediated hypothyroidism and hyperthyroidism in Mothers with Graves Disease

Special Populations

- Pregnant/Breastfeeding
  - Hypothyroidism:
    - Risks: pre-eclampsia, LBW neonates
    - Check TSH each trimester
    - May need to increase thyroxine dose
  - Nodules:
    - Manage same as non-pregnant, but up to 40% may be malignant
    - Surgery in 2nd trimester is preferred treatment

Special Populations

- Pregnant/Breastfeeding
  - Hyperemesis Gravidarum associated with biochemical hyperthyroidism but rarely with clinical symptoms
  - No treatment required

Special Populations

- Children
  - Hyperthyroidism:
    - I^{131} typically not used
  - Hypothyroidism:
    - Larger replacement dose often needed
    - Neonates screened to decrease risk of cretinism
  - Nodules:
    - 14-40% malignant

Special Populations

- Elderly
  - General Comments:
    - Symptoms much more subtle, similar to normal aging
    - More sensitive to adverse and therapeutic effects of medicines
  - Hyperthyroidism:
    - Multinodular goiter more common in elderly
    - 10-15% with Apathetic Hyperthyroidism

Special Populations

- Elderly
  - Hypothyroidism:
    - Fewer classic symptoms
    - Treating sub-clinical disease likely more harm than good
  - Nodules:
    - Again...more common to have toxic multinodular goiter as cause of hyperthyroidism

Conclusions

Management

- **Incidentally discovered small thyroid nodule**
  - Clinical and ultrasonographic follow-up

- **Benign thyroid nodule**
  - Careful follow - up at periodic intervals
  - Repeated ultrasonography and FNA biopsy when the nodule enlarges or becomes suspicious

Conclusions

Management

- **Cystic lesion**
  - Complete cyst disappearance :
    A benign lesion
  - Suspicious or insufficient FNAB findings :
    Thyroid lobectomy

Conclusions

Management

- **Autonomously functioning “hot” nodule**

  Thyroid lobectomy, RAI therapy

- **Malignant thyroid nodule**

  Total or near total thyroidectomy

- **Suspicious thyroid nodule**

  Thyroid lobectomy

  (followed by total or near total thyroidectomy)

TFT's in Pregnancy and Disease

Maternal	TSH	FT4	FTI	TT4	TT3	RT3U
Pregnancy	No change	No change	No change	↑	↑	↓
Hyperthyroid	↓	↑	↑	↑	↑ or no change	↑
Hypothyroid	↑	↓	↓	↓	↓or no change	↓

Table 1, ACOG Practice Bulletin
Number 37, August 2002

Fetal Effects of Hyperthyroidism

- Treatment is key
- Less than adequate treatment may result in:
  - Increase in preterm deliveries
  - LBW
  - Possible fetal loss

Risks with Immune Mediated Thyroid Dysfunction

- Antibodies cross placenta
  - In Graves'
    - TBII
    - TSI
- In Graves'...1-5% of neonates have hyperthyroidism or neonatal Graves caused by maternal TSI
- Incidence low due to balance of antibodies with thioamide treatment

Neonatal Graves'

- Maternal abys cleared after thioamides
  - Results in delayed presentation
- Neonates of women Tx with ^{131}I or surgery at higher risk for developing Neonatal Grave's disease

Fetal Effects of Hypothyroidism

- Incidence of congenital hypothyroidism 1/4000
  - 5% of those identified clinically at birth
- High incidence of LBW
  - Preterm delivery
  - Preeclampsia
  - Placental abruption
- Unclear relationship between hypothyroidism and IUGR independent of other complications

Iodine Deficient Hypothyroidism

- Risk of congenital cretinism
- Treatment with iodine in 1st and 2nd trimesters significantly reduces abnormalities of cretinism

Cretinism

- Growth failure
- Mental Retardation
- Neuropsychologic deficits

Levothyroxine in Pregnancy

- Same for the nonpregnant pt
- Goal is to normalize TSH
- Adjust dose at 4 week intervals
- Should check TSH levels every trimester in pts with hypothyroidism

Other Obstetrical and Thyroid Conditions

- Hyperemesis Gravidarum
- Gestational Trophoblastic Disease
- Thyroid Storm
- Thyroid CA
- Postpartum Thyroiditis

Hyperemesis Gravidarum

- Associated with biochemical hyperthyroidism, but not clinical
- Routine screening and treatment not recommended

Gestational Trophoblastic Disease

- Clinical hyperthyroidism in ~7% of complete hydatidiform moles
- Treat with *B*-blockers if hyperthyroidism is suspected
  - If no Tx, surgery may precipitate thyroid storm