July 15, 2025

9.00-11.30am

9.00-10.30am	25 min	Basic Pathology of Thyroid Disease	อ.ถิรพล
	60 min	Thyrotoxicosis	อ.สิรินาถ
	5 min	Q&A	
10.30-11.30am	30 min	Hypothyroidism and Thyroid nodule	อ.ธาดา
	15 min	Thyroid function test	อ.สุดารัตน์
	10 min	Role of Anatomical Pathologist in Clinical Practice	อ.ถิรพล
	5 min	Q&A	

Mahidol University
Faculty of Medicine
Siriraj Hospital

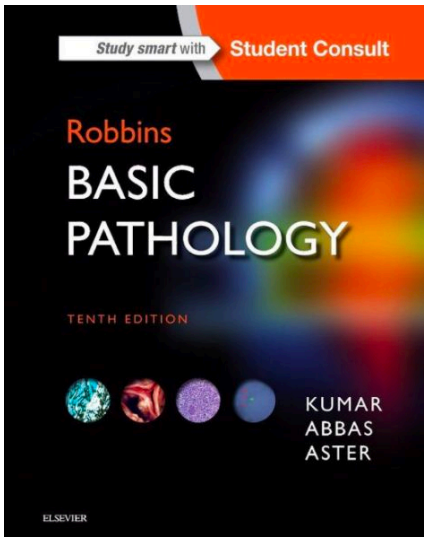
Diseases of Thyroid Gland

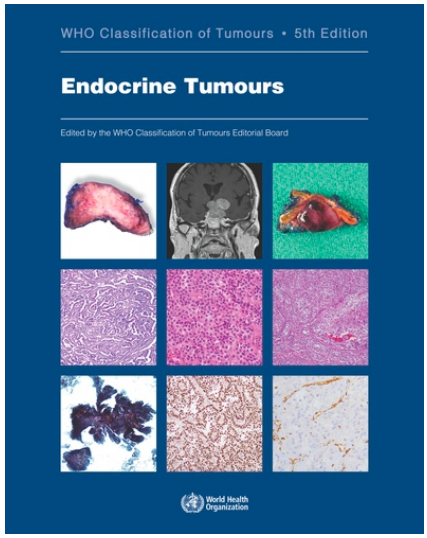
July 15, 2025
The 3rd-year medical student

Assist. Prof.Thiraphon Boonyaarunnate, M.D.

Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University

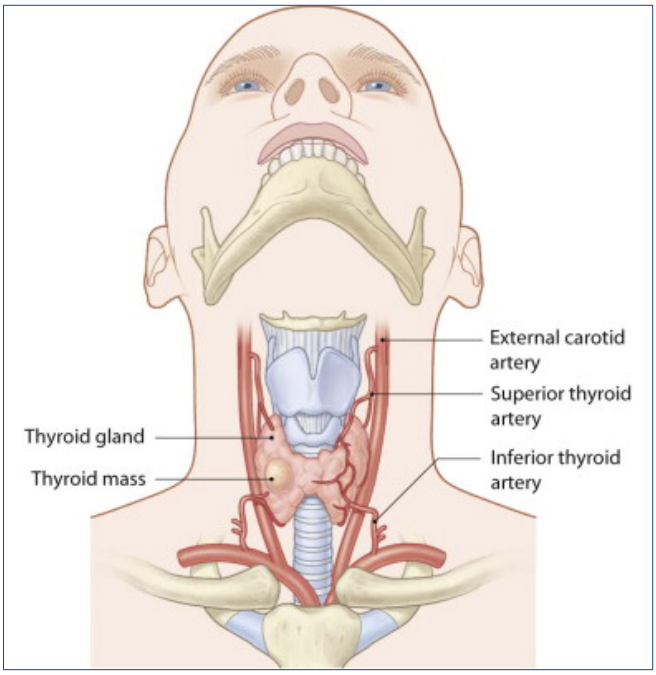
Referenes





Thyroid gland

- Weight 15-25 grams
- Midline part of neck
- Anterior and below to larynx
- Butterfly shape: Right and left lobe, isthmus, and pyramidal lobe



Atlas of Clinical Gross Anatomy, 2nd ed, 2013.

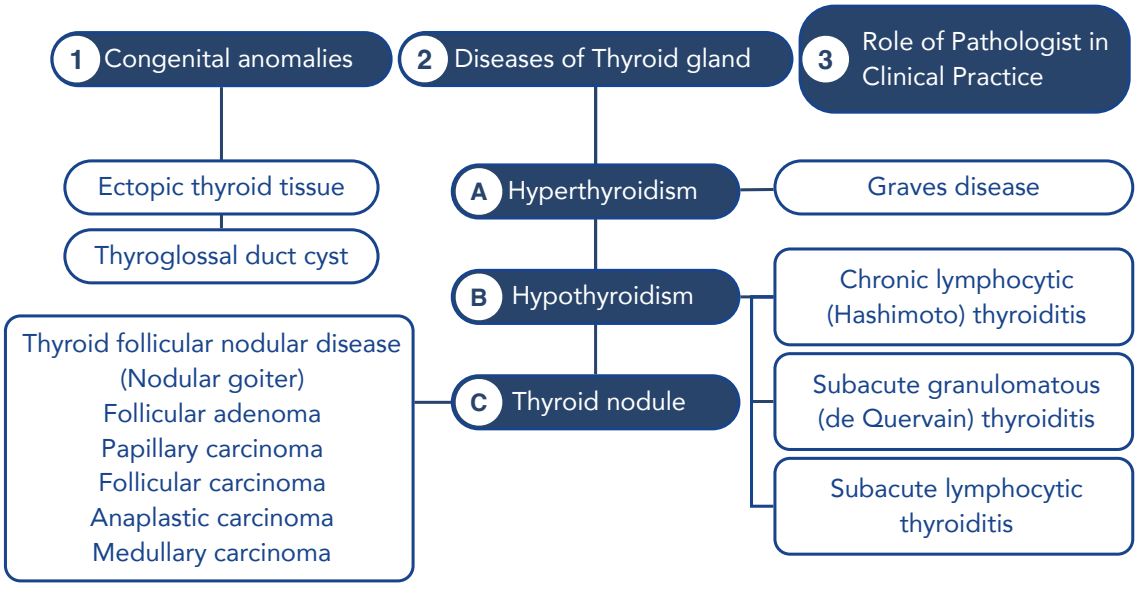
Netter F, Machado C. The Netter collection of medical illustrations. 2nd ed. Philadelphia: Elsevier Saunders; 2011.

Thyroid gland

- Follicle
- Thyroglobulin: the iodinated precursor protein of active thyroid hormone
- Follicular cells:
  - Tri-iodothyronine (T3)
  - Thyroxine (T4)
- Parafollicular cells or C cells:
  - Calcitonin

Kumar V, Abbas A, Aster J. Robbins Basic Pathology. 10th ed. Saint Louis: Elsevier; 2017.

Diseases of Thyroid gland

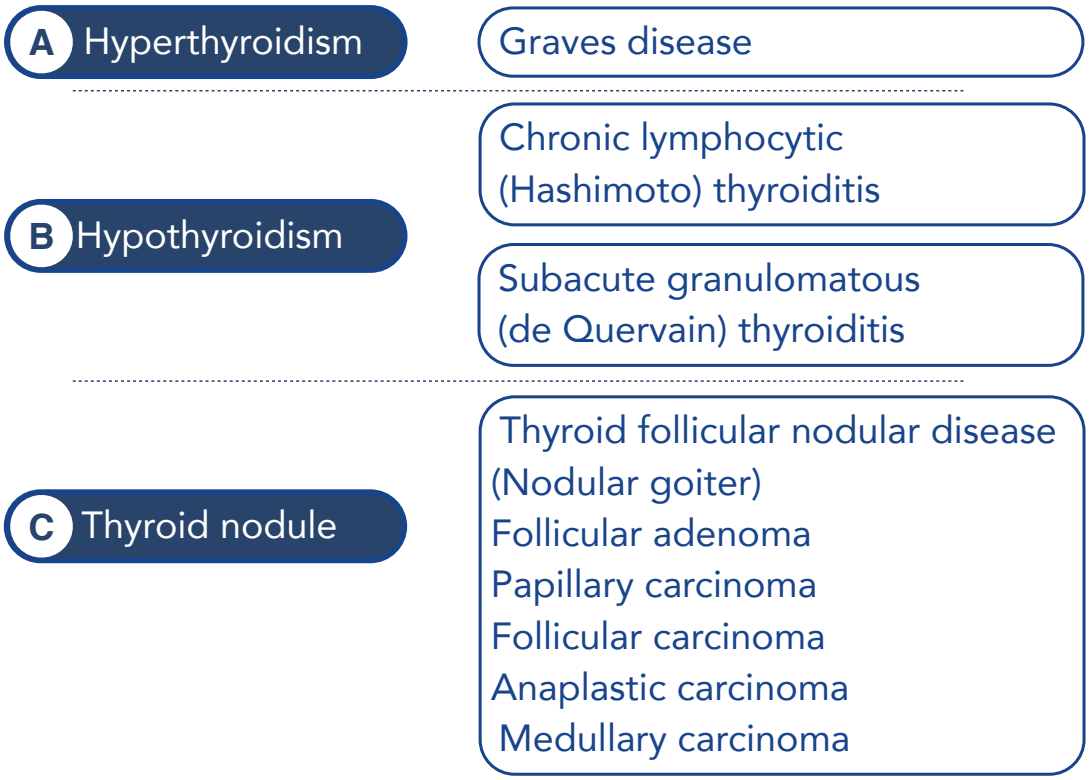


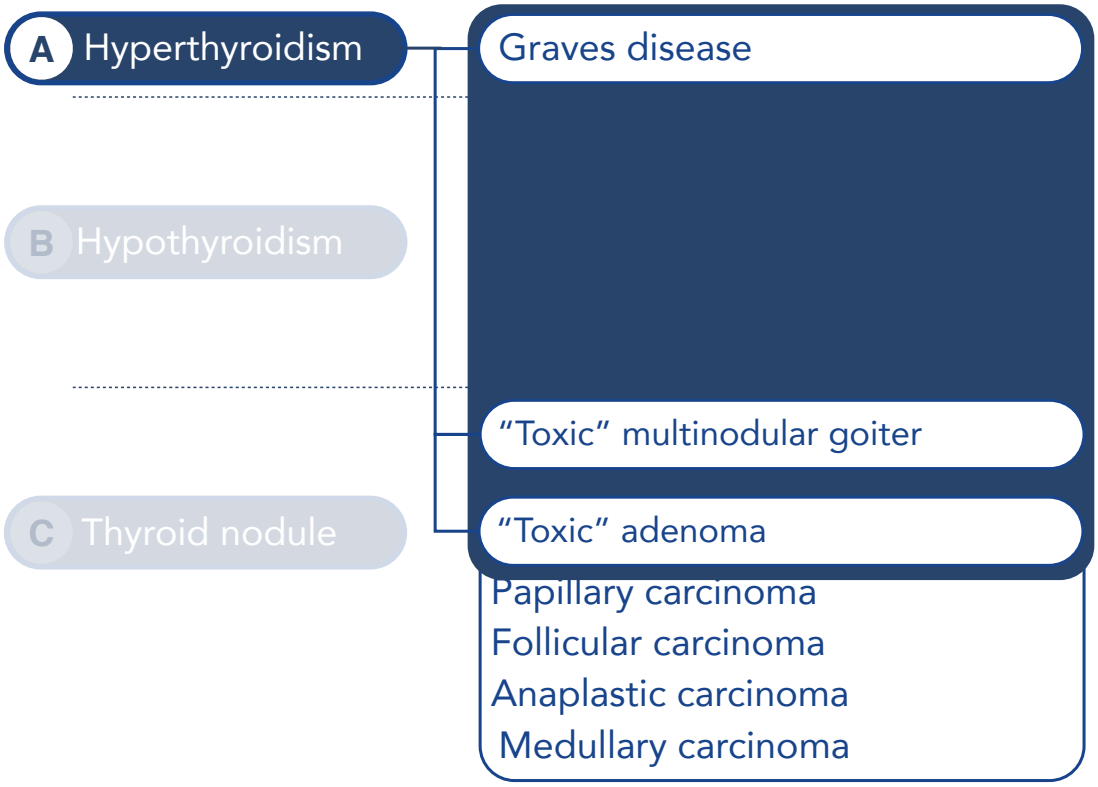
1.1 Ectopic thyroid tissue

- Thyroid tissue in area out side region of thyroid gland
- Failure to descend during development
  - Lingual thyroid (based of tongue)
  - Sublingual
  - Prelaryngeal

1.2 Thyroglossal duct cyst

Etiology	Persistence of thyroglossal duct (failure to involute completely)
Clinical	Anterior midline of neck
Macro	Cystic mass with mucous/clear fluid content
Micro	Straitified squamous epithelium and/or pseudostratified ciliated columnar epithelium Thyroid follicles in the cystic wall


A Hyperthyroidism
Graves disease
Chronic lymphocytic (Hashimoto) thyroiditis
B Hypothyroidism
Subacute granulomatous (de Quervain) thyroiditis
C Thyroid nodule
Thyroid follicular nodular disease (Nodular goiter)
Follicular adenoma
Papillary carcinoma
Follicular carcinoma
Anaplastic carcinoma
Medullary carcinoma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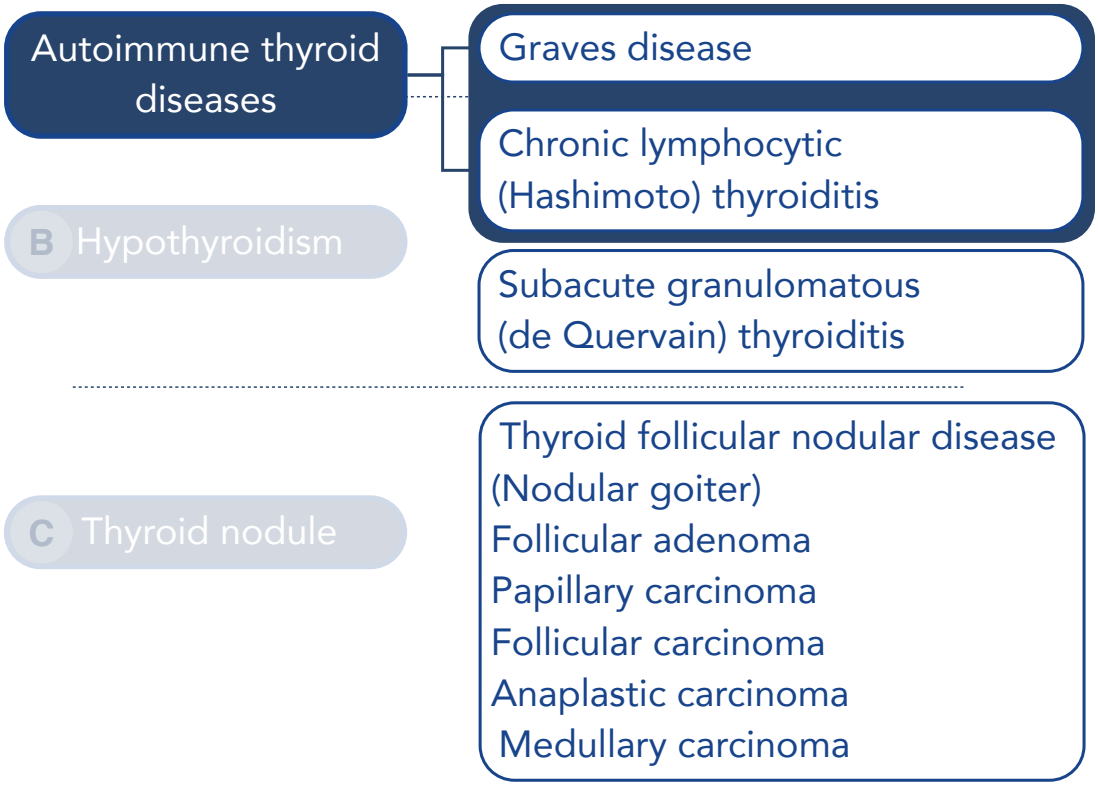

A1 Graves disease

- The most common cause of endogenous hyperthyroidism
- Female age 20-40
- Triad of manifestations:
  - Thyrotoxicosis by hyperfunction of thyroid gland, hypertrophy and hyperplasia of thyroid gland
  - Ophthalmopathy: exophthalmos
  - Infiltrative dermopathy: Pretibial myxedema

A1 Graves ophthalmopathy

- Infiltrative ophthalmopathy characteristic of Graves disease

1. Infiltration of retro-orbital space by T-cells
2. Inflammatory edema
3. Accumulation of extracellular matrix
4. Fat infiltration

A1 Pathogenesis

Autoantibodies against the TSH receptor

- Thyroid-stimulating immunoglobulin
  - Mimic action of TSH: increased release of thyroid hormone
- Thyroid growth-stimulating immunoglobulin
  - Proliferation of thyroid follicular epitheliums
- TSH-binding inhibitor immunoglobulins ✤
  - Prevent TSH from binding to its receptor

A1 Graves disease

- Diffuse symmetrical enlargement
- Smooth, soft and intact capsule

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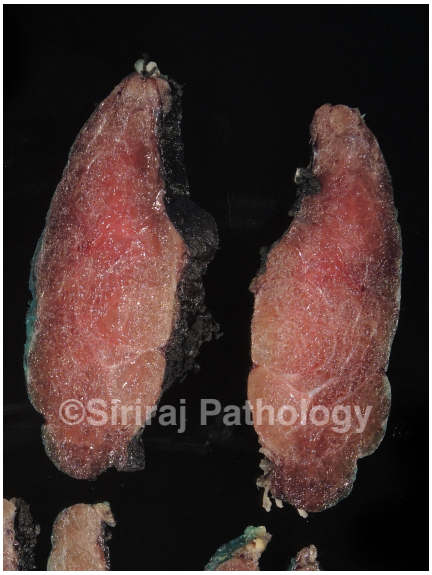
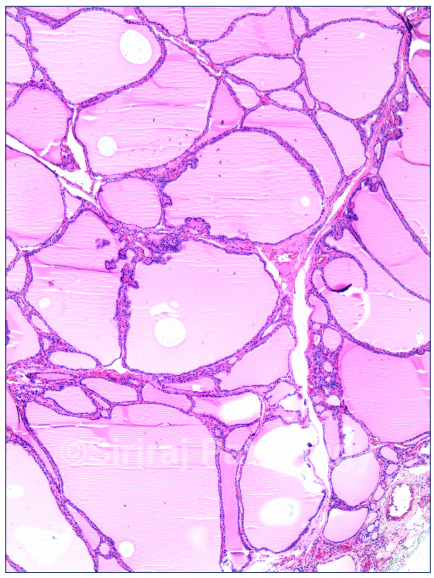
- Diffuse symmetrical enlargement
- Smooth, soft and intact capsule



A1 Graves disease

- Diffuse hypertrophy and hyperplasia
- Tall, columnar, crowded
- Small papillae
- Lymphoid infiltration, plasma cells, germinal centres
- Scalloped margins of colloid



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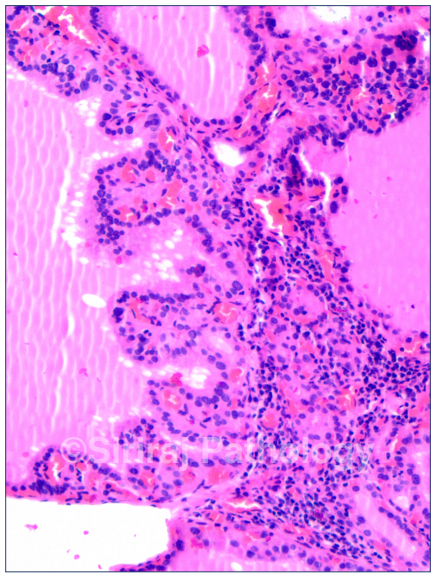
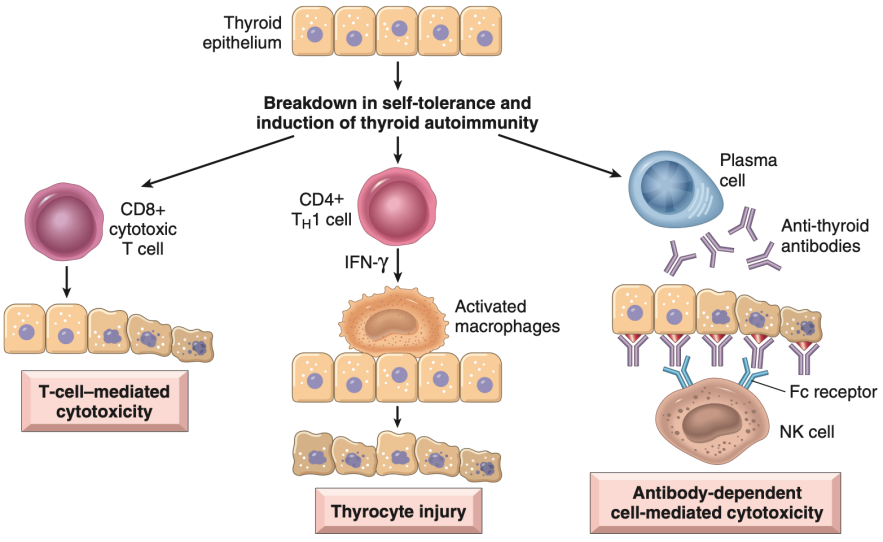


B1 Hashimoto thyroiditis

- The most common cause of hypothyroidism in areas of the world where iodine levels are sufficient.
- Woman > man (10:1 - 20:1), age 45-65
- Painless enlargement
- Transient thyrotoxicosis, initially
- Hypothyroidism gradually develops

B1 Pathogenesis



Kumar V, Abbas A, Aster J. Robbins Basic Pathology. 10th ed. Saintt Louis: Elsevier; 2017.

B1 Pathogenesis

- CD8+ cytotoxic T-cell - mediated killing of thyroid epithelial cells
- Cytokine-mediated cell death (IFN-γ): recruit and activate macrophages to damage follicles
- Binding of anti-thyroid antibodies (anti-thyroglobulin , anti-thyroid peroxidase antibodies)

B1 Hashimoto thyroiditis

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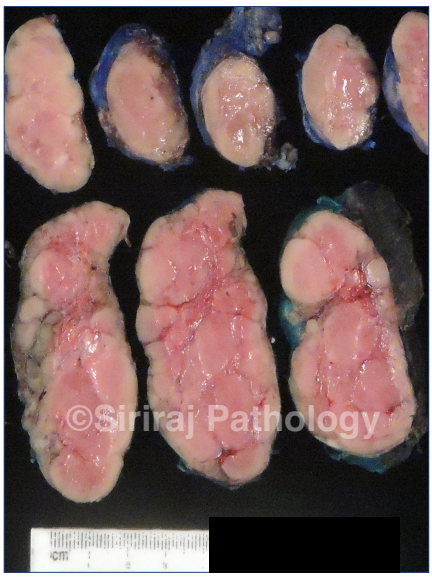
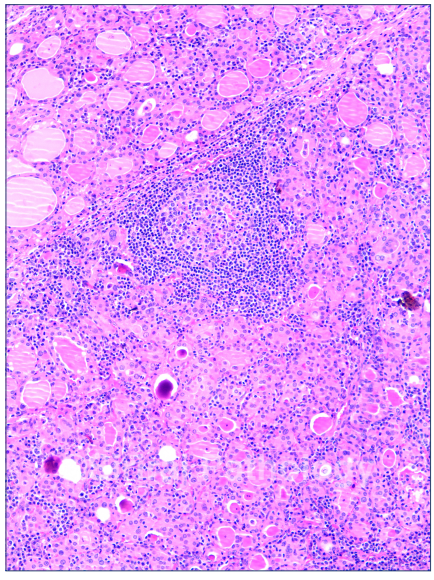


B1 Hashimoto thyroiditis

- Parenchymal infiltration by small lymphocytes, plasma cells and germinal centres
- Oncocytes (Hurthle or oxyphil cells)
- Increased risk for the development of B-cell non-Hodgkin lymphoma



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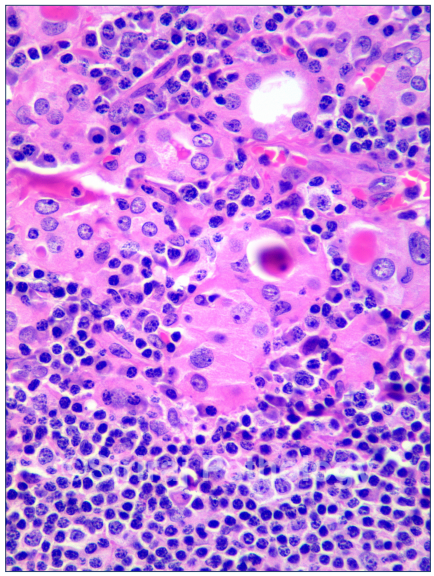


B2 De Quervain thyroiditis

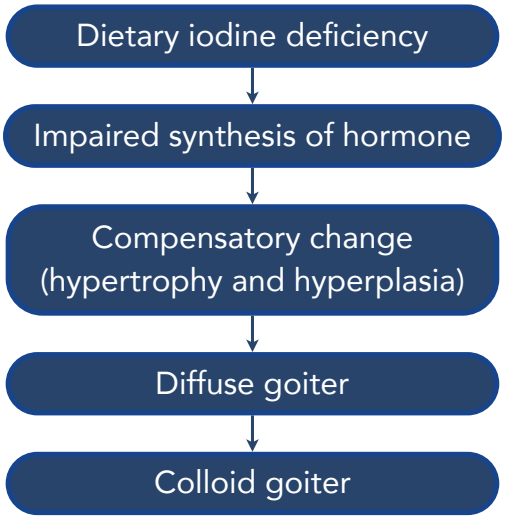
- Women > men
- 30-50 years old
- Viral infection or an inflammatory process triggered by viral infections
- A history of upper respiratory infection before the onset of thyroiditis
- Self remission (6-8weeks)

B2 De Quervain thyroiditis

- Unilateral or bilateral enlargement with firm consistency
- Disruption of follicles with neutrophil infiltration
- Replaced overtime by plasma, lymphocyte and macrophages
- Granulomatous reaction to extravasated colloid
- Resolution and Fibrosis

C1 Diffuse and nodular goiter

- Endemic goiter
- Sporadic goiter
  - Female > Male
  - Puberty/young adult
  - Calcium and vegetables (e.g., cabbage, cauliflower)
  - Dyshormonogenetic goiter (inherited enzymatic defects)



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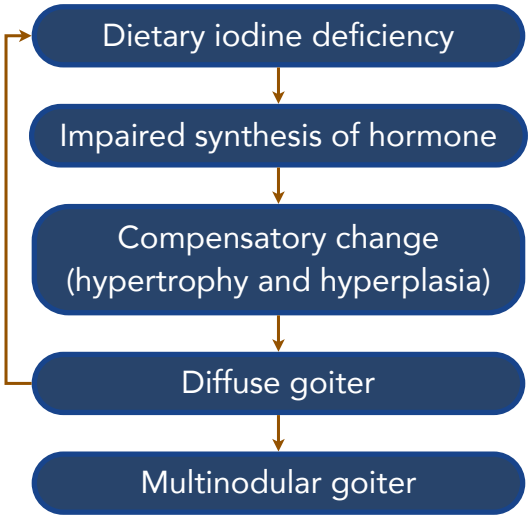

C1 Thyroid follicular nodular disease

- Multilobulated, asymmetrically enlarged gland
- Brown gelatinous colloid
- Fibrosis, haemorrhage, calcification and cystic change
- **Thyroid follicular nodular disease** (The WHO Classification of endocrine and neuroendocrine tumours, 5th ed, 2022)

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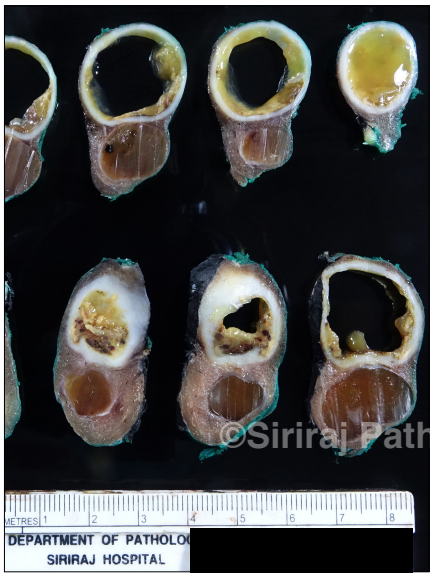

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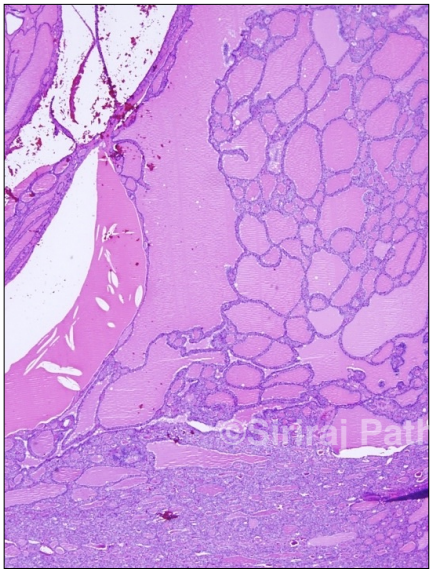
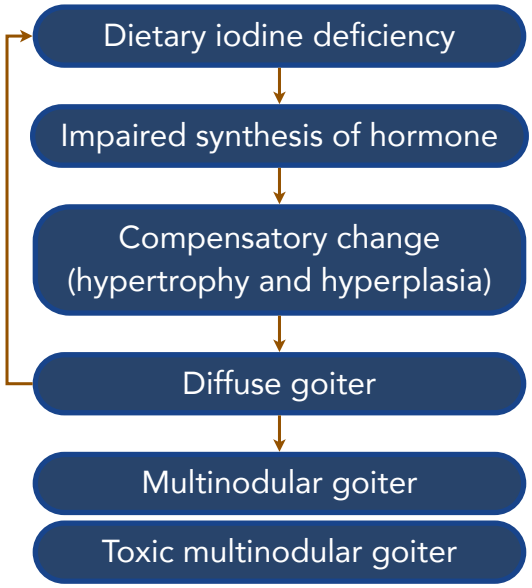
C1 Thyroid follicular nodular disease

- Colloid-rich follicles
- Flattened inactive epithelium



C1 Thyroid follicular nodular disease

- Mass effect (cosmetic problem, airway obstruction, dysphagia)
- Minority develops autonomous nodule (Toxic multinodular goiter or Plummer syndrome)
- The incidence of malignancy in long-standing MNG is low (<5 %).



C Thyroid nodule

Several clinical clues to nature of a thyroid nodule

1. Solitary nodule
2. Young (<20yrs) or old (>70yrs)
3. Male
4. Radiation exposure
5. Cold nodule

C Thyroid nodule

- Morphologic evaluation of a thyroid nodule
  - Fine needle aspiration
  - Surgically resection thyroid tissue

C2 Thyroid neoplasm

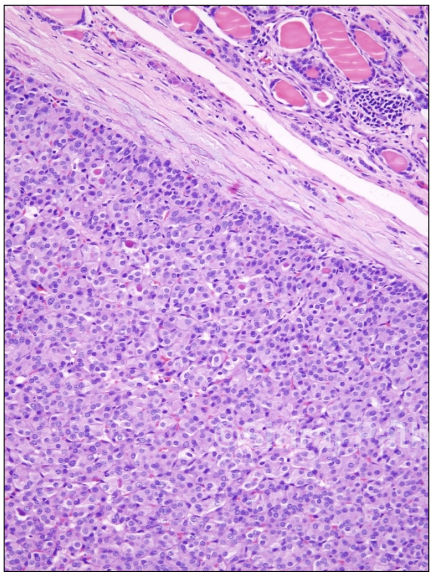
- Benign
  - Follicular adenoma
- Malignant
  - Papillary carcinoma
  - Follicular carcinoma
  - Anaplastic carcinoma
  - Medullary carcinoma

C2.1 Follicular adenoma

- Solitary, spherical, well-defined mass with intact capsule
- Compressing the adjacent thyroid tissue

C2.1 Follicular adenoma

- Uniformed microfollicles
- Endocrine atypia
- An intact well-formed capsule



C2 Thyroid carcinoma

Papillary carcinoma	>85%
Follicular carcinoma	5-15%
Anaplastic carcinoma	<5%
Medullary carcinoma	5%

Kumar V, Abbas A, Aster J. Robbins Basic Pathology. 10th ed. Saintt Louis: Elsevier; 2017.

C2.2 Papillary carcinoma

- Solitary/multifoci
- Well-circumscribed, uncapsulated or infiltrative

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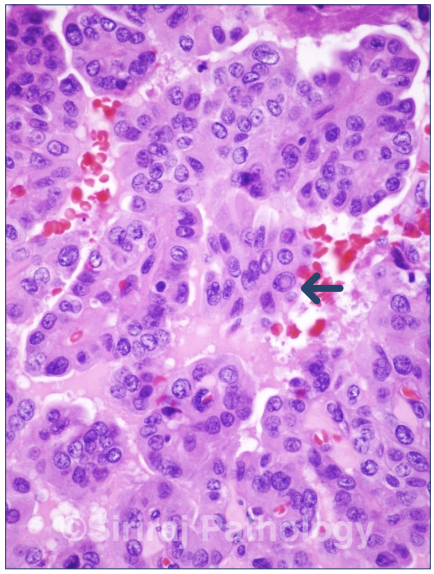
- Well-circumscribed, uncapsulated or infiltrative

C2.2 Papillary carcinoma

- Optically clear nuclei (ground-glass or Orphan Annie eye)
- Intranuclear grooves
- Intranuclear cytoplasmic pseudoinclusion
- Psammoma bodies
- Branching papillae with fibrovascular core



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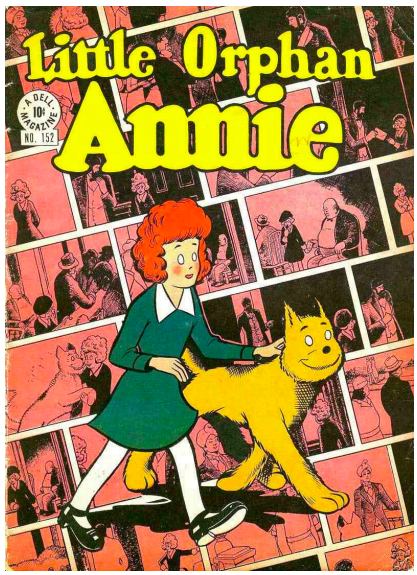


https://www.cbr.com/comic-book-legends-revealed-331/

C2.2 Papillary carcinoma

- The nuclear features are sufficient for diagnosis without papillary architecture.
- Lymphatic dissemination
- Nonfunctional tumor

C2.3 Follicular carcinoma

- Female:Male = 3:1
- 40-60 years of age
- More frequent in areas with dietary iodine deficiency
- Rare hyperfunction

C2.3 Follicular carcinoma

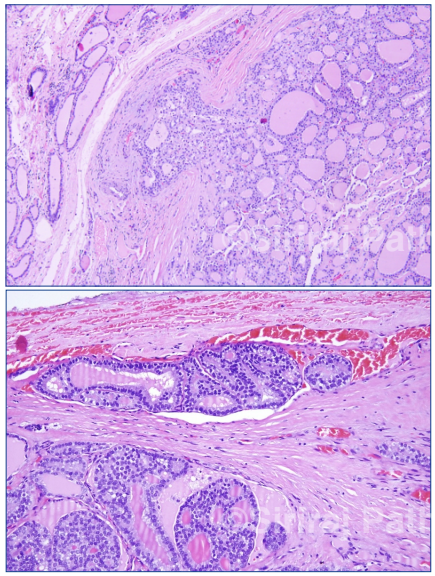
- Minimally invasive (capsular invasion only)
- Encapsulated angioinvasive
- Widely invasive

Baloch ZW, Asa SL, Barletta JA, Ghossein RA, Juhlin CC, Jung CK, LiVolsi VA, Papotti MG, Sobrinho-Simões M, Tallini G, Mete O. Overview of the 2022 WHO Classification of Thyroid Neoplasms. Endocr Pathol. 2022 Mar;33(1):27-63.

C2.3 Follicular carcinoma

- Minimally invasive (capsular invasion only)
- Encapsulated angioinvasive
- Widely invasive

- Requires extensive histologic sampling of the tumor capsule
- Hematogenous dissemination (lung, bone, liver)



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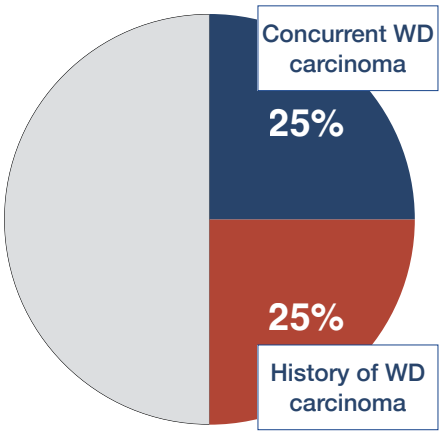
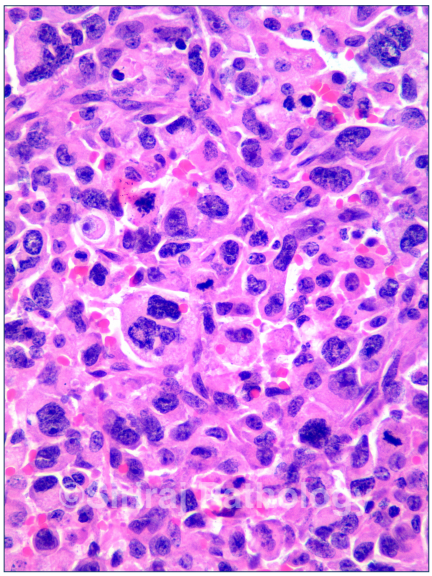
C2.4 Anaplastic carcinoma

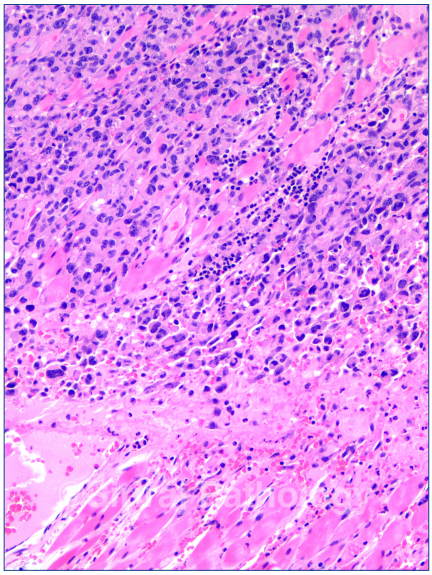
- The mortality rate approaching 100%
- Mean age of 65 years



C2.4 Anaplastic carcinoma



C2.4 Anaplastic carcinoma



C2.5 Medullary carcinoma

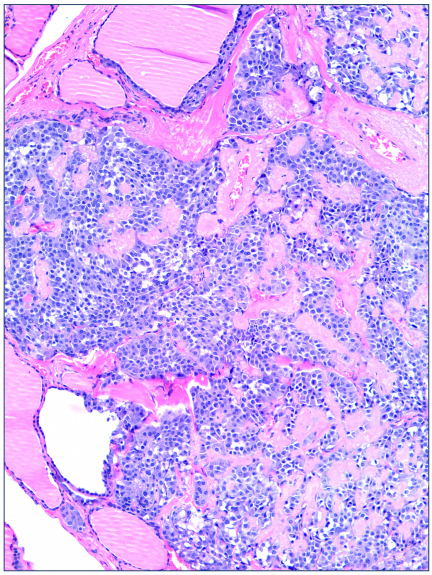
- Neuroendocrine tumor
- Functional tumor: Calcitonin
- Mutations in RET receptor tyrosine kinase

C2.5 Medullary carcinoma

- 70% Sporadic:
  - Adult (40-50 years of age)
- 30% Familial
  - MEN 2A or 2B
  - Familial
  - Children

C2.5 Medullary carcinoma

- Familial type
  - Multicentricity
  - Multicentric C cell hyperplasia
- Nest, trabecular, follicles
- Polygonal to spindle-shaped cells
- Amyloid deposits



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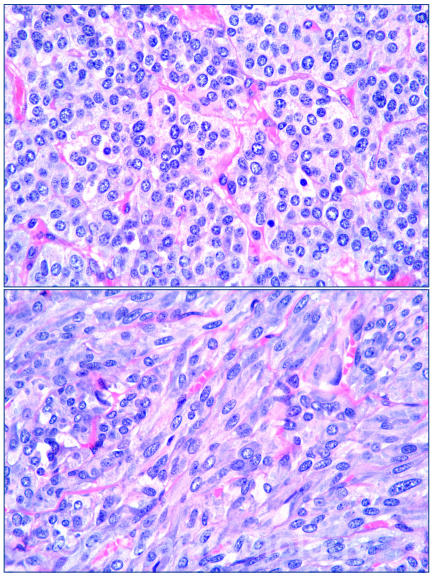

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- Follicular adenoma
- Papillary carcinoma
- Follicular carcinoma
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END

Role of pathologist in Clinical Practice

Cytology Specimen

Fine Needle Aspiration, FNA

Surgical Specimen

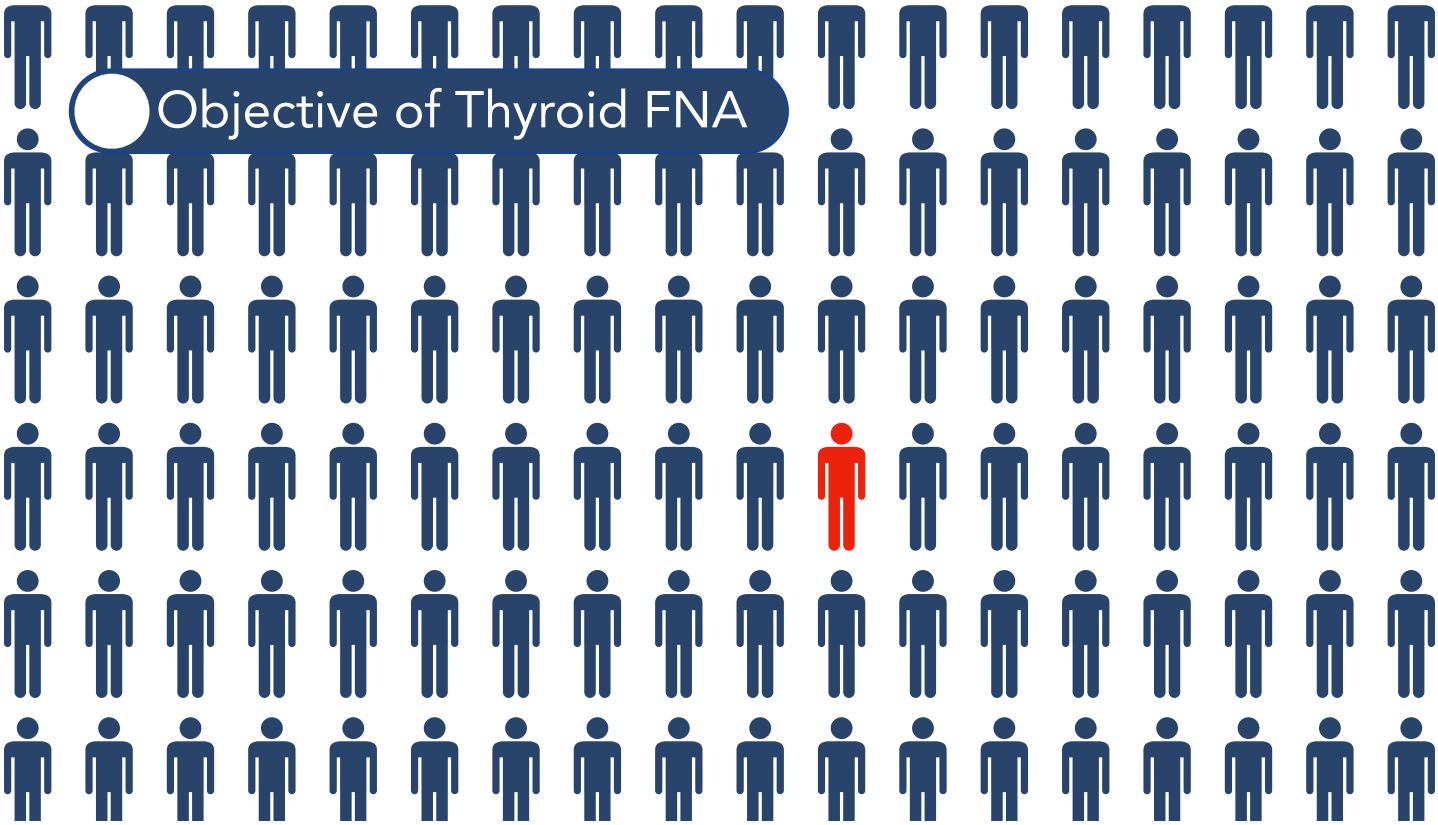
Lobectomy
Subtotal thyroidectomy
Total thyroidectomy

Thyroid nodule

Clinical manifestation

Radiologic findings

Fine Needle Aspiration


Objective of Thyroid FNA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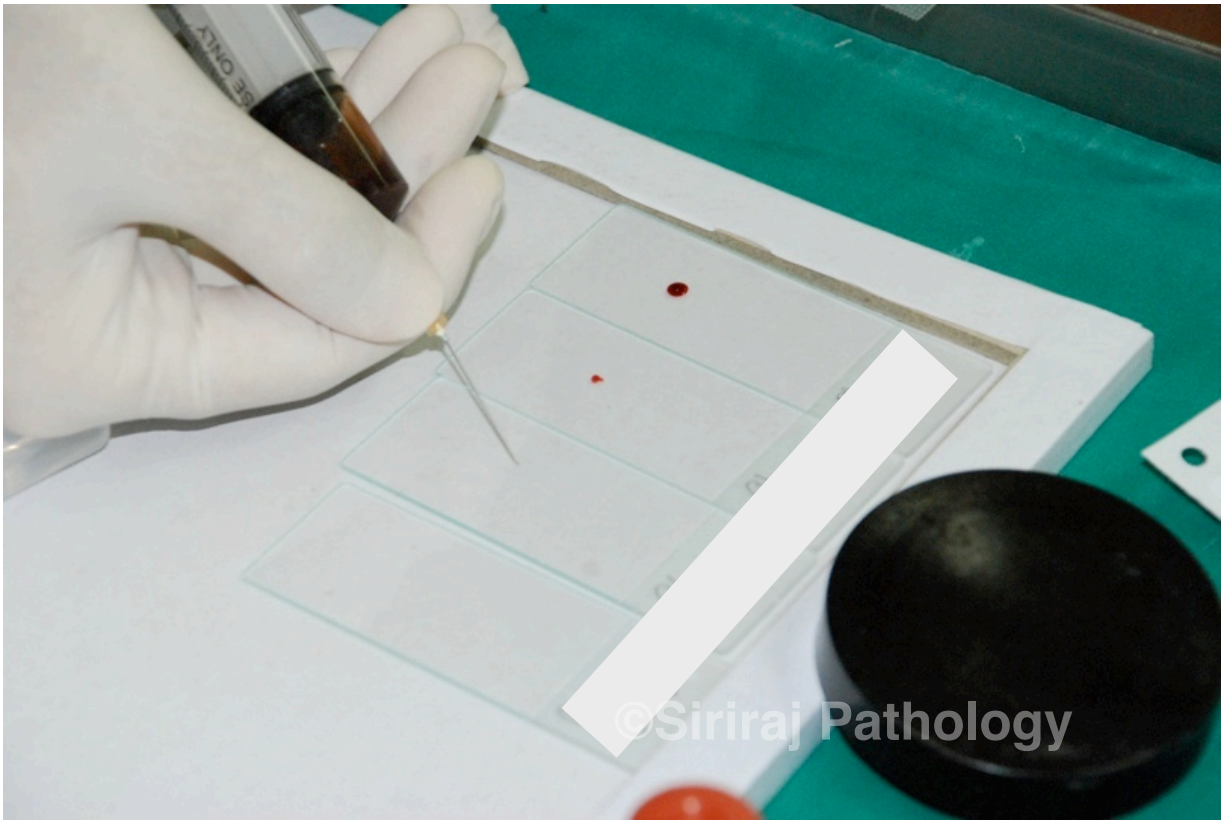
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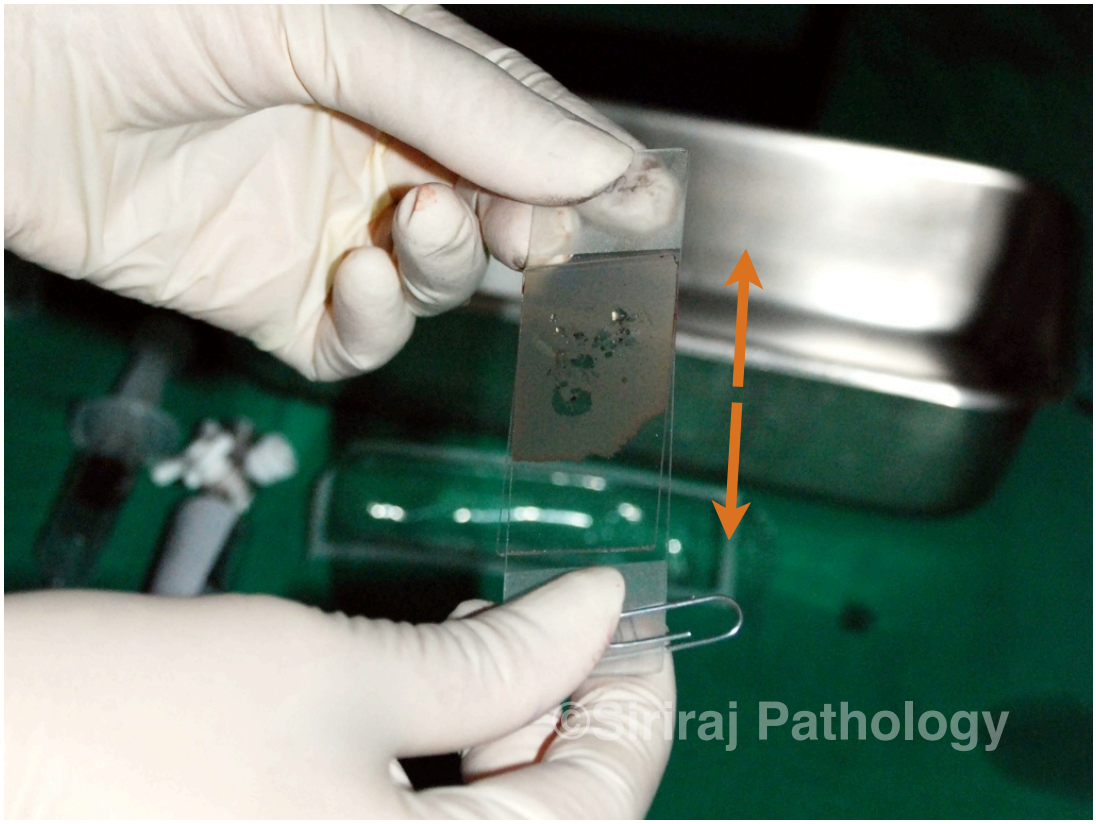
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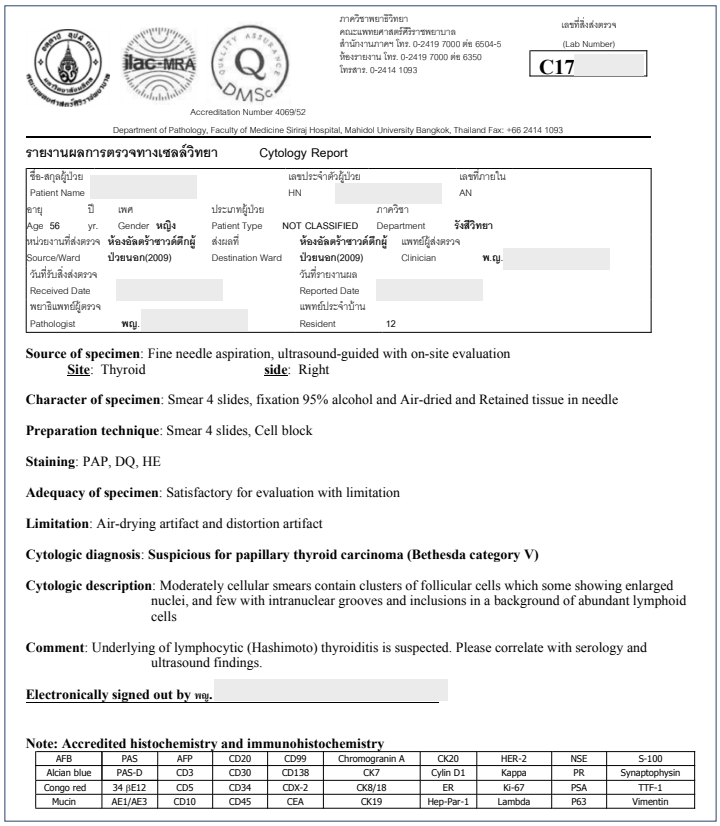
95% alcohol-fixed smear
95%ALC
CYTO
Air-dry smear
©Siriraj Pathology

The Bethesda System for Reporting Thyroid Cytopathology, 3rd edition

- Nondiagnostic
- Benign
- Atypia of Undetermined Significance (AUS)
- Follicular Neoplasm (FN)
- Suspicious for Malignancy (SFM)
- Malignancy



ภาควิชาพยาธิวิทยา
คณะแพทยศาสตร์ศิริราชพยาบาล
สำนักงานภาคฯ โทร. 0-2419 7000 ต่อ 6504-5
ห้องรายงาน โทร. 0-2419 7000 ต่อ 6350
โทรสาร. 0-2414 1093

เลขที่สิ่งส่งตรวจ
(Lab Number)
C17

Accreditation Number 4069/52

Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University Bangkok, Thailand Fax: +66 2414 1093

รายงานผลการตรวจทางเซลล์วิทยา Cytology Report

ชื่อ-สกุลผู้ป่วย Patient Name		เลขประจำตัวผู้ป่วย HN		เลขที่ภายใน AN	
อายุ Age 56 ปี yr.	เพศ Gender หญิง	ประเภทผู้ป่วย Patient Type	NOT CLASSIFIED	ภาควิชา Department	รังสีวิทยา
หน่วยงานที่ส่งตรวจ Source/Ward	ห้องอัลตร้าซาวด์ตึกผู้ป่วยนอก(2009)	ส่งผลที่ Destination Ward	ห้องอัลตร้าซาวด์ตึกผู้ป่วยนอก(2009)	แพทย์ผู้ส่งตรวจ Clinician	พ.ญ.
วันที่รับสิ่งส่งตรวจ Received Date		วันที่รายงานผล Reported Date			
พยาธิแพทย์ผู้ตรวจ Pathologist	พญ.	แพทย์ประจำบ้าน Resident	12		

Source of specimen: Fine needle aspiration, ultrasound-guided with on-site evaluation
Site: Thyroid **side**: Right

Character of specimen: Smear 4 slides, fixation 95% alcohol and Air-dried and Retained tissue in needle

Preparation technique: Smear 4 slides, Cell block

Staining: PAP, DQ, HE

Adequacy of specimen: Satisfactory for evaluation with limitation

Limitation: Air-drying artifact and distortion artifact

Cytologic diagnosis: **Suspicious for papillary thyroid carcinoma (Bethesda category V)**

Cytologic description: Moderately cellular smears contain clusters of follicular cells which some showing enlarged nuclei, and few with intranuclear grooves and inclusions in a background of abundant lymphoid cells

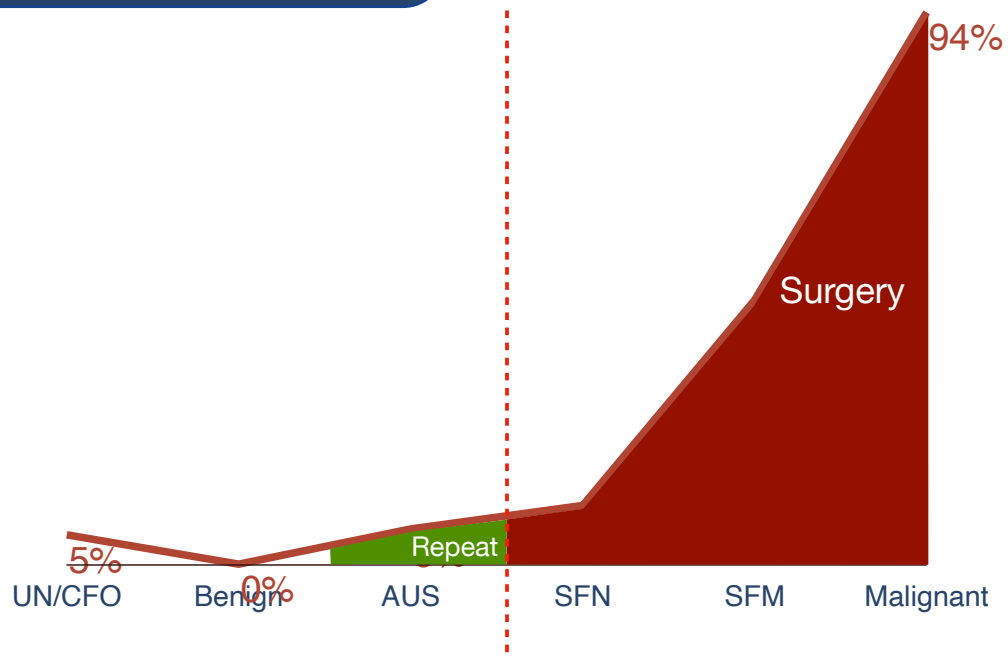
Comment: Underlying of lymphocytic (Hashimoto) thyroiditis is suspected. Please correlate with serology and ultrasound findings.

Electronically signed out by พญ.

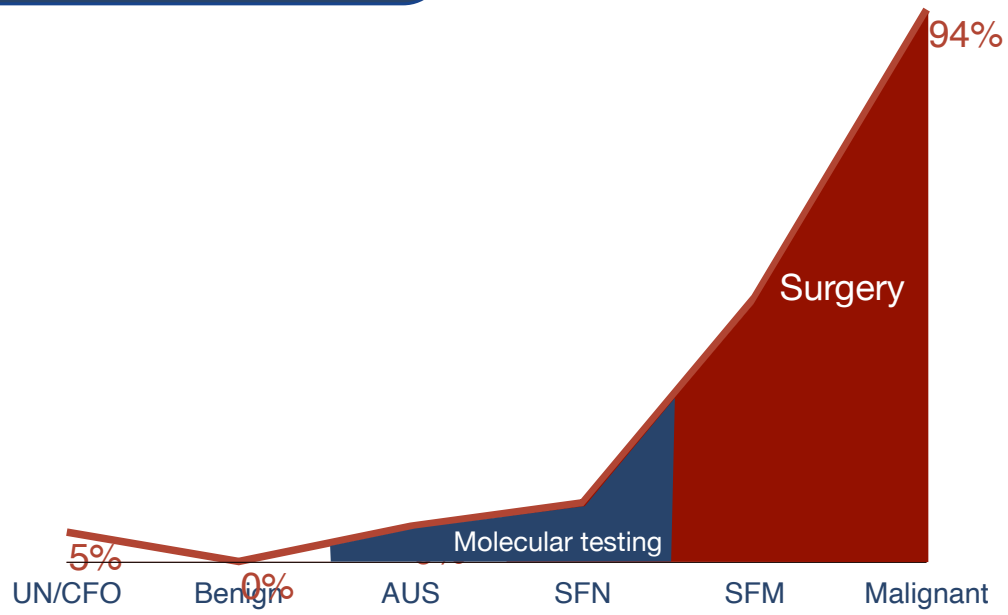
Note: Accredited histochemistry and immunohistochemistry

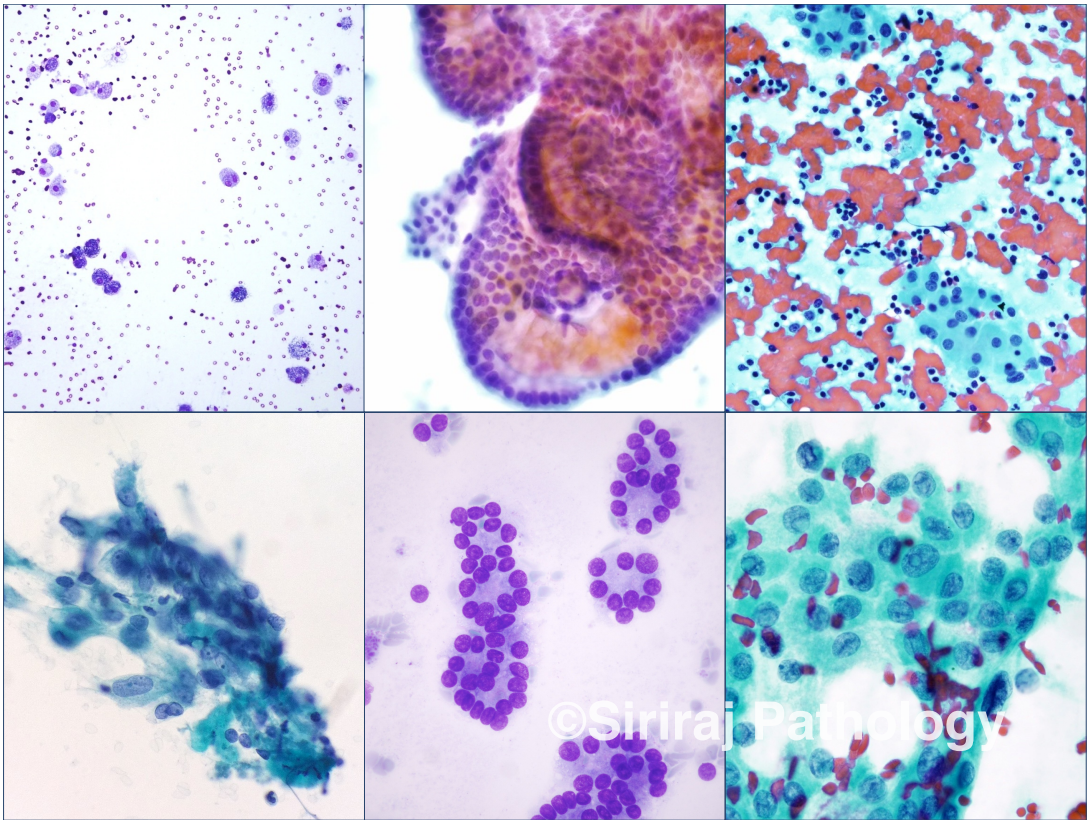
AFB	PAS	AFP	CD20	CD99	Chromogranin A	CK20	HER-2	NSE	S-100
Alcian blue	PAS-D	CD3	CD30	CD138	CK7	Cylin D1	Kappa	PR	Synaptophysin
Congo red	34 βE12	CD5	CD34	CDX-2	CK8/18	ER	Ki-67	PSA	TTF-1
Mucin	AE1/AE3	CD10	CD45	CEA	CK19	Hep-Par-1	Lambda	P63	Vimentin

Risk of Malignancy



Risk of Malignancy

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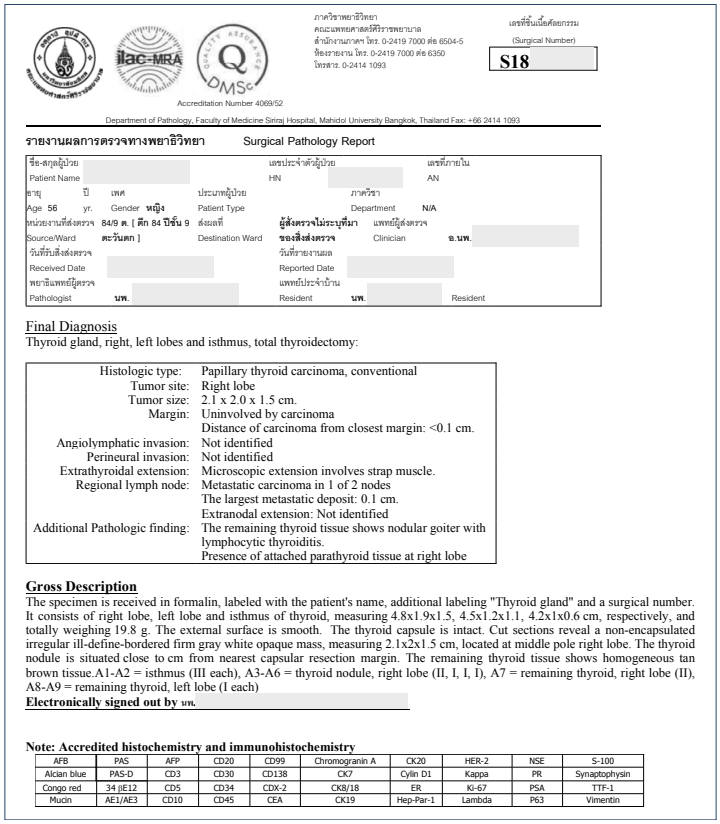


ภาควิชาพยาธิวิทยา
คณะแพทยศาสตร์ศิริราชพยาบาล
สำนักงานภาคฯ โทร. 0-2419 7000 ต่อ 6504-5
ห้องงานงาน โทร. 0-2419 7000 ต่อ 6350
โทรสาร. 0-2414 1093

เลขที่ชิ้นเนื้อศัลยกรรม
(Surgical Number)
S18

Accreditation Number 4069/52

Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University Bangkok, Thailand Fax: +66 2414 1093

รายงานผลการตรวจทางพยาธิวิทยา Surgical Pathology Report

ชื่อ-สกุลผู้ป่วย Patient Name			เลขประจำตัวผู้ป่วย HN		เลขที่ภายใน AN
อายุ Age 56 yr.	เพศ Gender **หญิง**		ประเภทผู้ป่วย Patient Type		ภาควิชา Department N/A
หน่วยงานที่ส่งตรวจ Source/Ward **ตะวันตก]**	84/9 ศ. [ศึก 84 ปีชั้น 9		ส่งผลที่ Destination Ward	**ผู้สั่งตรวจไม่ระบุที่มา ของสิ่งส่งตรวจ**	แพทย์ผู้ส่งตรวจ Clinician **อ.นพ.**
วันที่รับสิ่งส่งตรวจ Received Date			วันที่รายงานผล Reported Date		
พยาธิแพทย์ผู้ตรวจ Pathologist **นพ.**			แพทย์ประจำบ้าน Resident **นพ.**		Resident

Final Diagnosis
Thyroid gland, right, left lobes and isthmus, total thyroidectomy:

Histologic type:	Papillary thyroid carcinoma, conventional
Tumor site:	Right lobe
Tumor size:	2.1 x 2.0 x 1.5 cm.
Margin:	Uninvolved by carcinoma Distance of carcinoma from closest margin: <0.1 cm.
Angiolymphatic invasion:	Not identified
Perineural invasion:	Not identified
Extrathyroidal extension:	Microscopic extension involves strap muscle.
Regional lymph node:	Metastatic carcinoma in 1 of 2 nodes The largest metastatic deposit: 0.1 cm. Extranodal extension: Not identified
Additional Pathologic finding:	The remaining thyroid tissue shows nodular goiter with lymphocytic thyroiditis. Presence of attached parathyroid tissue at right lobe

Gross Description
The specimen is received in formalin, labeled with the patient's name, additional labeling "Thyroid gland" and a surgical number. It consists of right lobe, left lobe and isthmus of thyroid, measuring 4.8x1.9x1.5, 4.5x1.2x1.1, 4.2x1x0.6 cm, respectively, and totally weighing 19.8 g. The external surface is smooth. The thyroid capsule is intact. Cut sections reveal a non-encapsulated irregular ill-define-bordered firm gray white opaque mass, measuring 2.1x2x1.5 cm, located at middle pole right lobe. The thyroid nodule is situated close to cm from nearest capsular resection margin. The remaining thyroid tissue shows homogeneous tan brown tissue.A1-A2 = isthmus (III each), A3-A6 = thyroid nodule, right lobe (II, I, I, I), A7 = remaining thyroid, right lobe (II), A8-A9 = remaining thyroid, left lobe (I each)
Electronically signed out by นพ.

Note: Accredited histochemistry and immunohistochemistry

AFB	PAS	AFP	CD20	CD99	Chromogranin A	CK20	HER-2	NSE	S-100
Alcian blue	PAS-D	CD3	CD30	CD138	CK7	Cylin D1	Kappa	PR	Synaptophysin
Congo red	34 βE12	CD5	CD34	CDX-2	CK8/18	ER	Ki-67	PSA	TTF-1
Mucin	AE1/AE3	CD10	CD45	CEA	CK19	Hep-Par-1	Lambda	P63	Vimentin

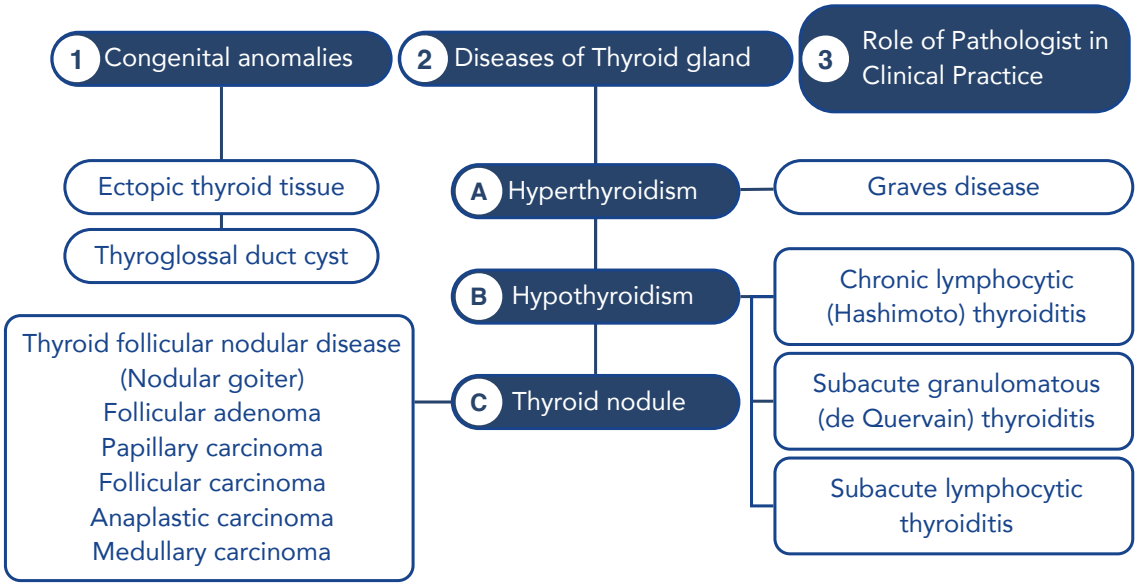
TABLE 3. A CLINICALLY BASED APPROACH TO STAGING IN DIFFERENTIATED THYROID CANCER USING THE EIGHTH EDITION AJCC/TNM UPDATE

	Distant metastasis	*Gross ETE present?*	*Structures involved with gross ETE*	*T category*	*N category*	*Stage*
<55 years	No	Yes or no	Any or none	Any	Any	I
	Yes	Yes or no	Any or none	Any	Any	II
≥55 years	No	No	None	≤4 cm (T1–2)	N0/Nx	I
					N1a/N1b	II
				>4 cm (T3a)	N0/Nx/N1a/N1b	II
		Yes	Only strap muscle (T3b)	Any	Any	II
			Subcutaneous, larynx, trachea, esophagus, recurrent laryngeal nerve (T4a)	Any	Any	III
			Prevertebral fascia, encasing major vessels (T4b)	Any	Any	IVA
	Yes	Yes or no	Any or none	Any	Any	IVB

The expected 10-year DSS estimates presented in this table are approximate figures based on a review of previously published retrospective studies evaluating the AJCC staging system and/or the prognostic importance of critical clinical features (age, gross extrathyroidal extension, cervical lymph node metastases, and distant metastases).

END

Diseases of Thyroid gland



มหาวิทยาลัยมหิดล
คณะแพทยศาสตร์ศิริราชพยาบาล

SIENDO
Faculty of Medicine Siriraj Hospital

Diseases of Thyroid Gland

Sirinart Sirinvaravong, MD
Division of Endocrinology and Metabolism
Department of Medicine
Faculty of Medicine Siriraj Hospital

Outline

1. Physiology of thyroid
2. Evaluation of thyroid function
3. Thyrotoxicosis & Hyperthyroidism
4. Hypothyroidism
5. Thyroid nodules

Objectives

At the end of this session, students should be able to

1. Explain pathophysiology of ***common causes of thyrotoxicosis***
2. Recognize and explain the symptoms and signs of thyrotoxicosis
3. Explain the appropriate investigation for thyrotoxicosis and able to determine the etiology
4. Explain the concept of the management of thyrotoxicosis

Outline

1. **Physiology of thyroid**
2. Evaluation of thyroid function
3. Thyrotoxicosis & Hyperthyroidism
4. Hypothyroidism
5. Thyroid nodules

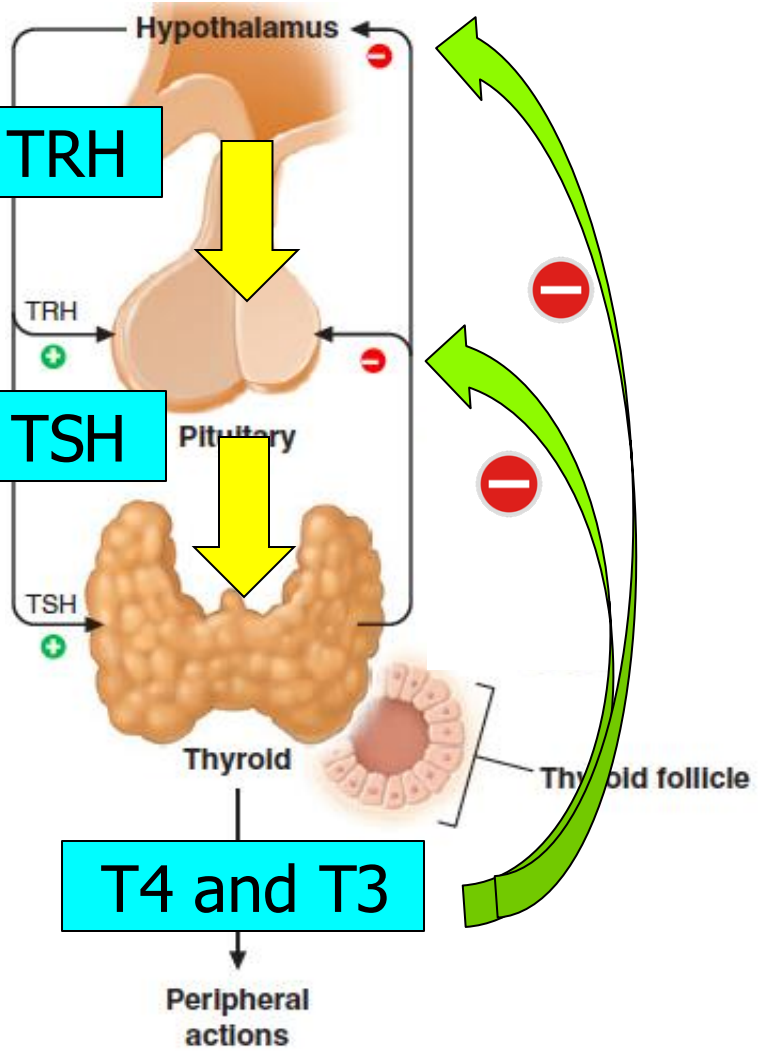
Hypothalamic-Pituitary-Thyroid Axis

Thyrotropin-releasing hormone

TRH

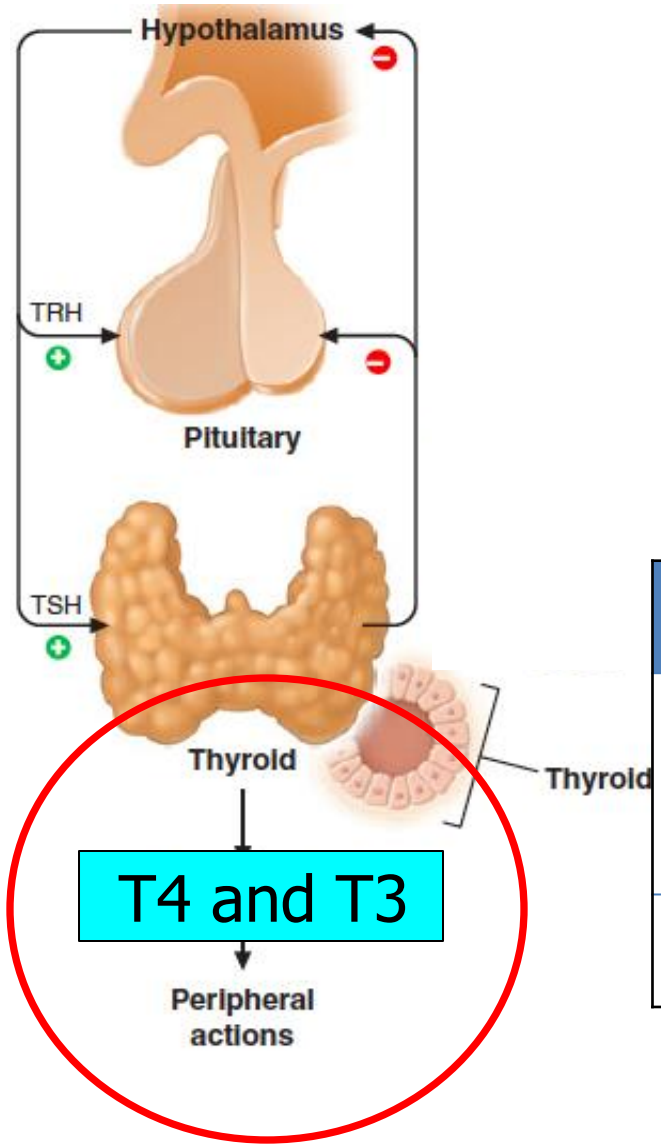
Thyroid stimulating hormone

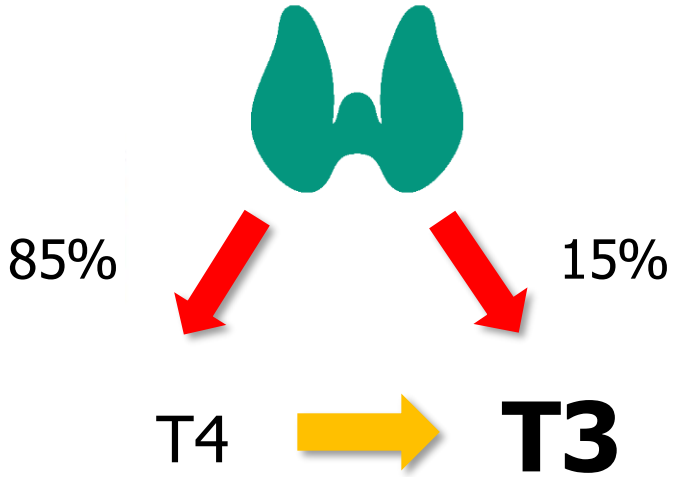
TSH



Harrison Textbook of Endocrinology, 2nd Edition

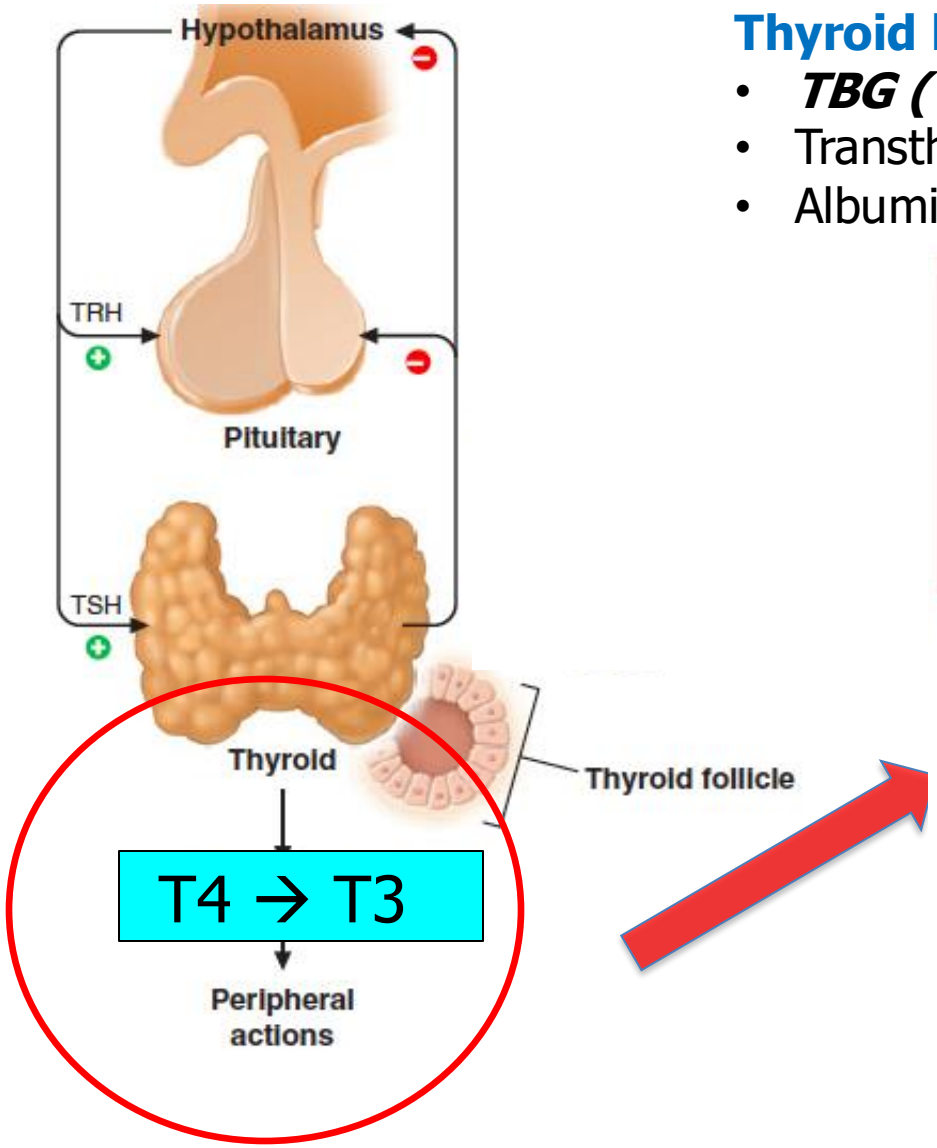
Thyroid Hormone Synthesis





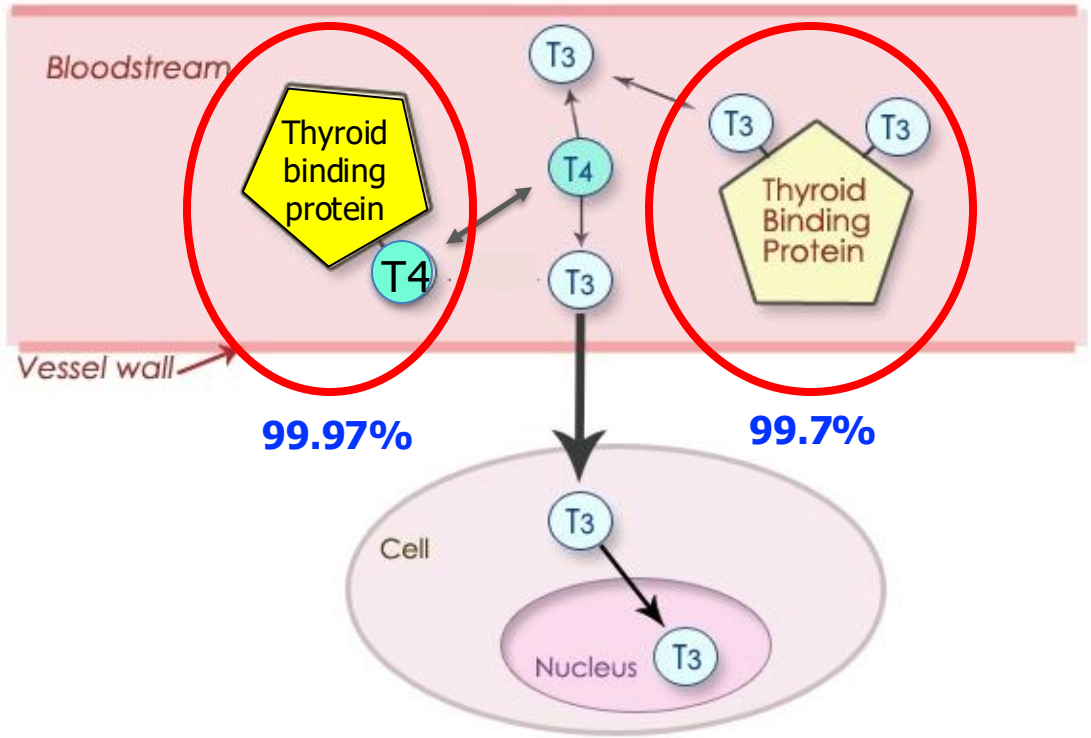
	T4	T3
Source	Thyroid gland	• 15% Thyroid gland • 85% peripheral conversion of T4 → T3
Half life	7 days	1 day

Thyroid Hormone Transport



Thyroid hormone binding proteins

- ***TBG (Thyroxine binding globulin)*** 70-80%
- Transthyretin (prealbumin)
- Albumin

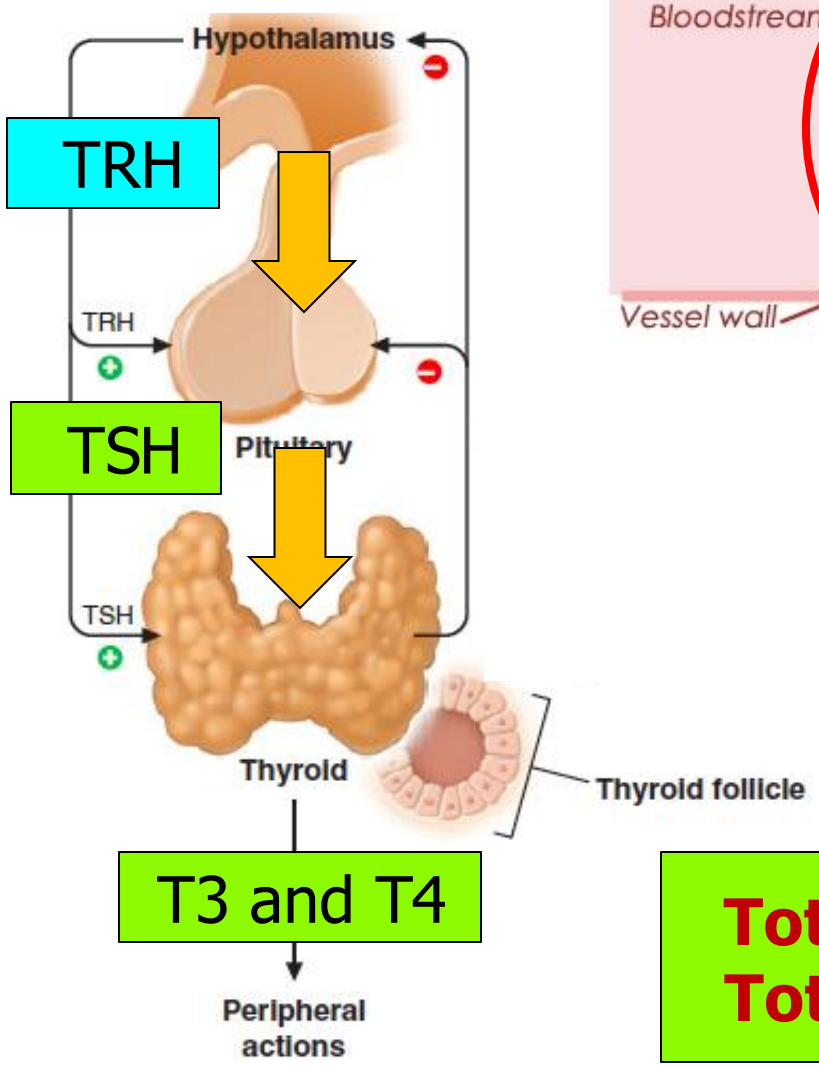


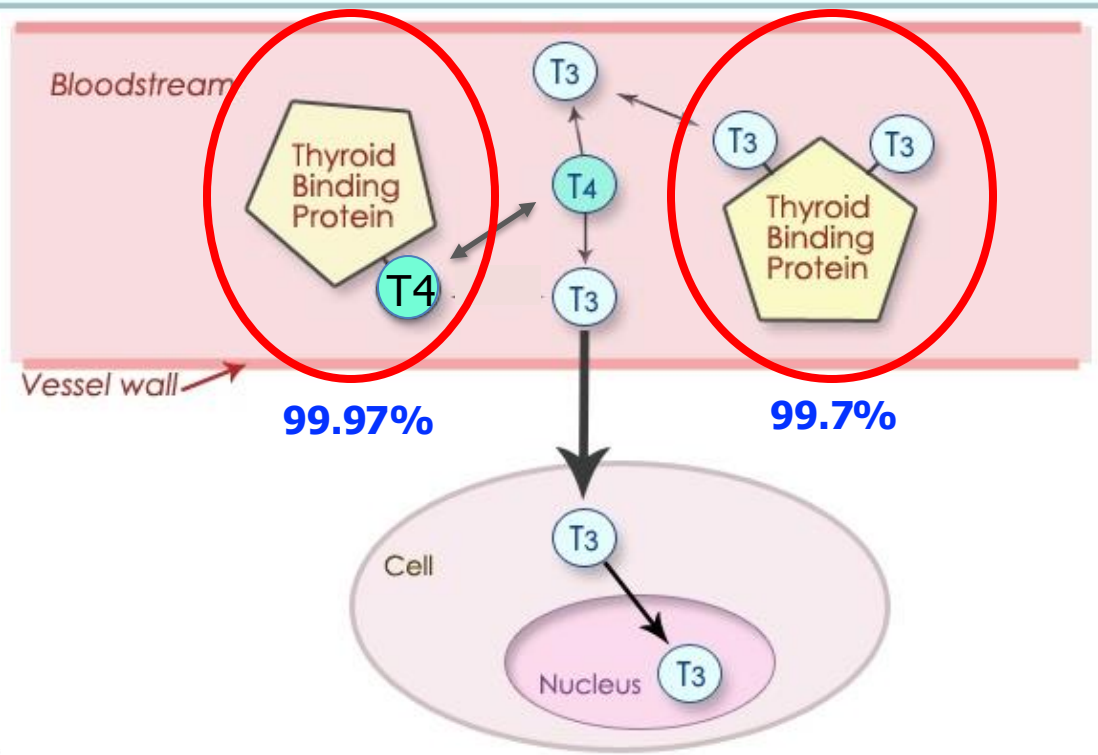
Harrison Textbook of Endocrinology, 2nd Edition

Outline

1. Physiology of thyroid
2. **Evaluation of thyroid function**
3. Thyrotoxicosis & Hyperthyroidism
4. Hypothyroidism
5. Thyroid nodules

Evaluation of thyroid function





Total T3 = **free T3** + THBP•T3
Total T4 = **free T4** + THBP•T4

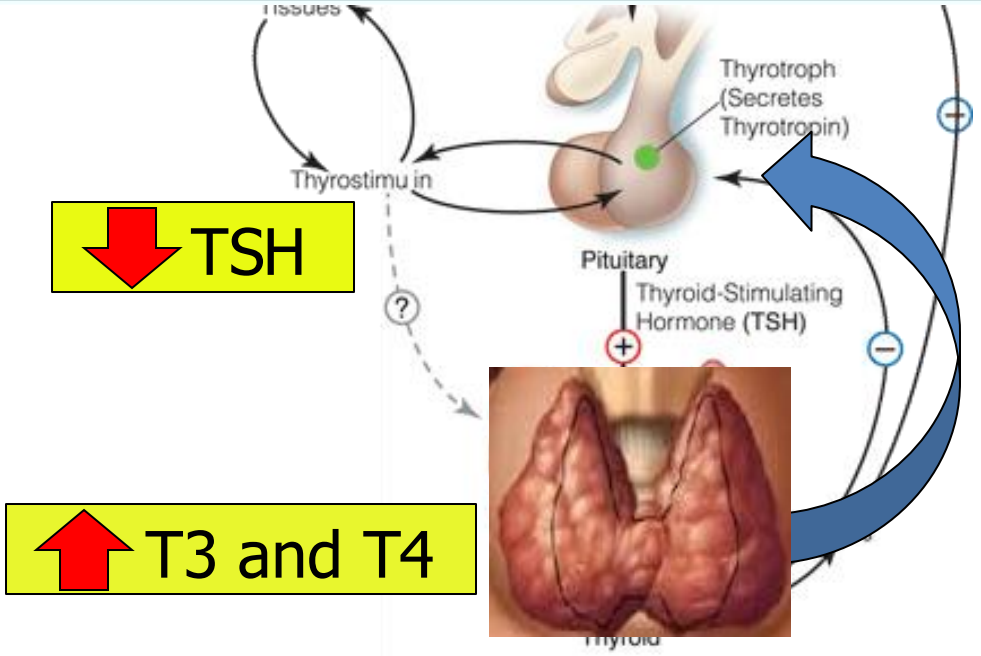
THBP: Thyroid hormone binding proteins

Evaluation of thyroid function

Tests and interpretation

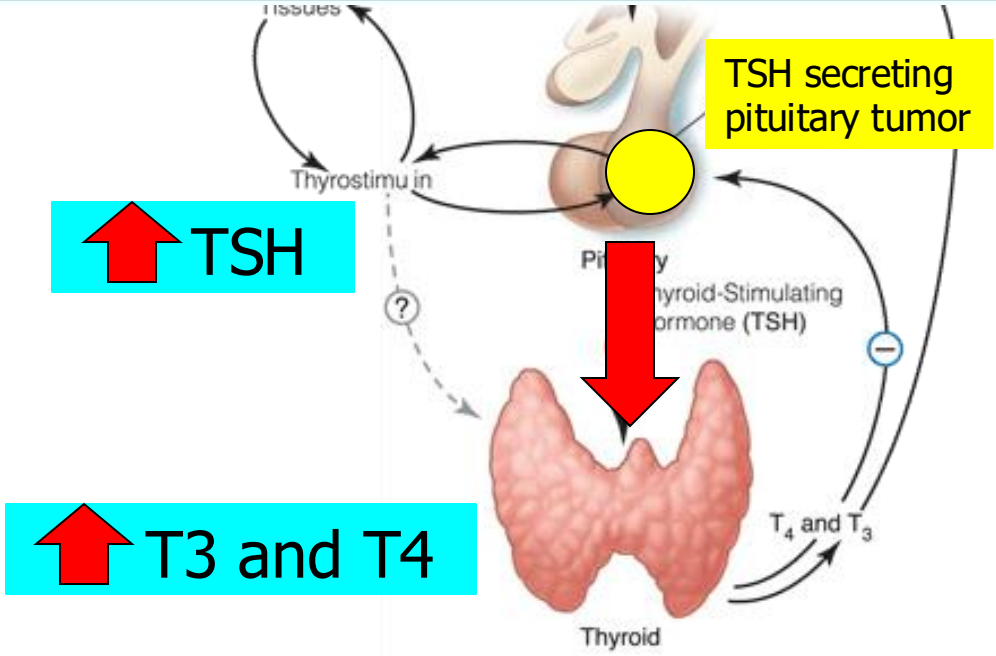
- TSH
- T4 (free T4, total T4)
- T3 (free T3, total T3)

Evaluation of thyroid function



	T3, Free T3	T4, Free T4	TSH
Thyrotoxicosis	↑	↑	↓
T3 toxicosis	↑	↔	↓
T4 toxicosis	↔	↑	↓

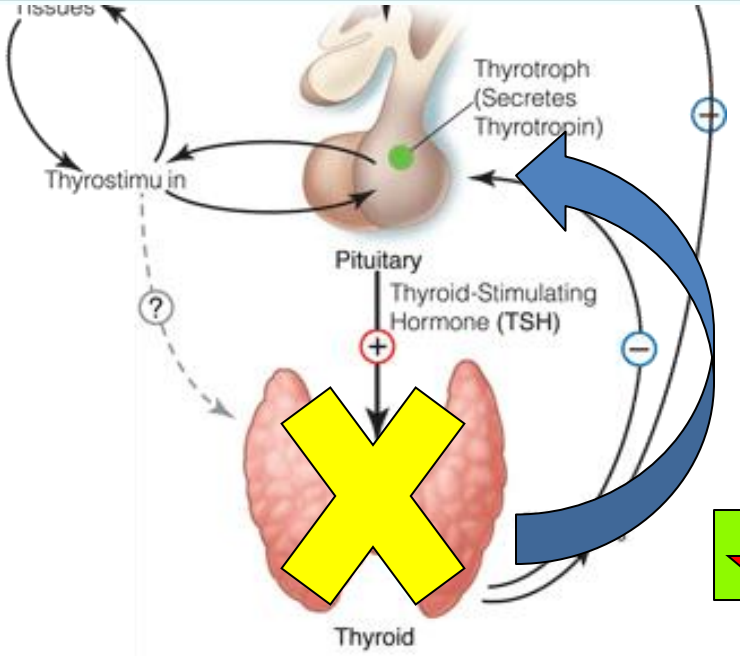
Evaluation of thyroid function



	T3, Free T3	T4, Free T4	TSH
Central hyperthyroidism	↑	↑	↑ ↔

Inappropriately normal TSH

Evaluation of thyroid function

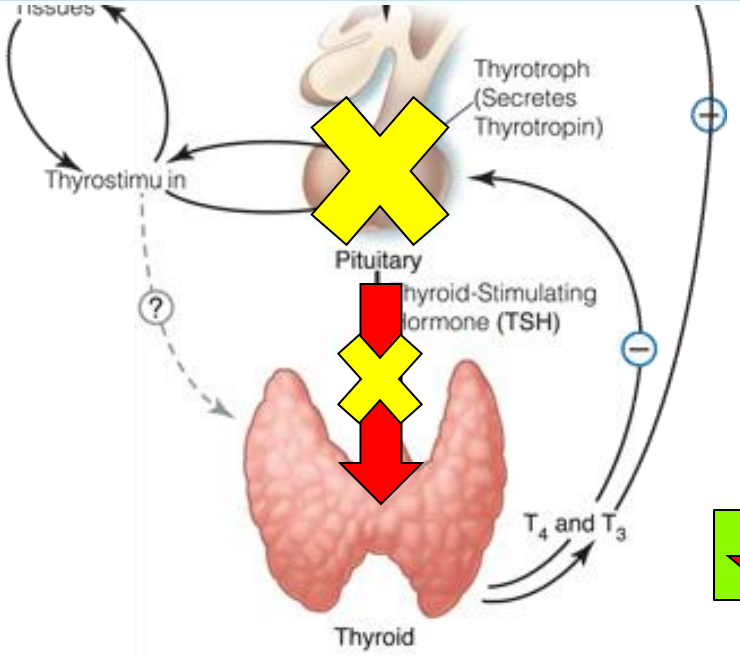


TSH ↑

T3 and T4 ↓

	T3, Free T3	T4, Free T4	TSH
Primary hypothyroidism	↓	↓	↑

Evaluation of thyroid function



TSH

T3 and T4

	T3, Free T3	T4, Free T4	TSH
Primary hypothyroidism	↓	↓	↑
Central hypothyroidism	↓	↓	↓ ↔ ↑

Biologically inactive TSH

Total and Free T

Total T3 = TBG•T3 + free T3
Total T4 = TBG•T4 + free T4

- Total T = bound form + free form (free T)

- **TBG**
- Transthyretin
- Albumin

99.9% bound to plasma proteins

0.1% active

- **Conditions that alter TBG alter total T**
- (In general) NO effect on free T → NO effect on TSH
- Only free thyroid hormone is biologically active and exerts negative feedback control to pituitary gland

Conditions altering serum TBG

TBG excess

- **Pregnancy**
- Chronic active hepatitis
- Drugs
  - Estrogen
  - Clofibrate
  - Tamoxifen
  - Perphenazine

⇔ TSH
⇔ FT4, FT3
↑ T4, T3

TBG deficiency

- Nephrotic syndrome
- Severe liver failure
- Drugs
  - Androgen
  - Corticosteroids
- Malnutrition

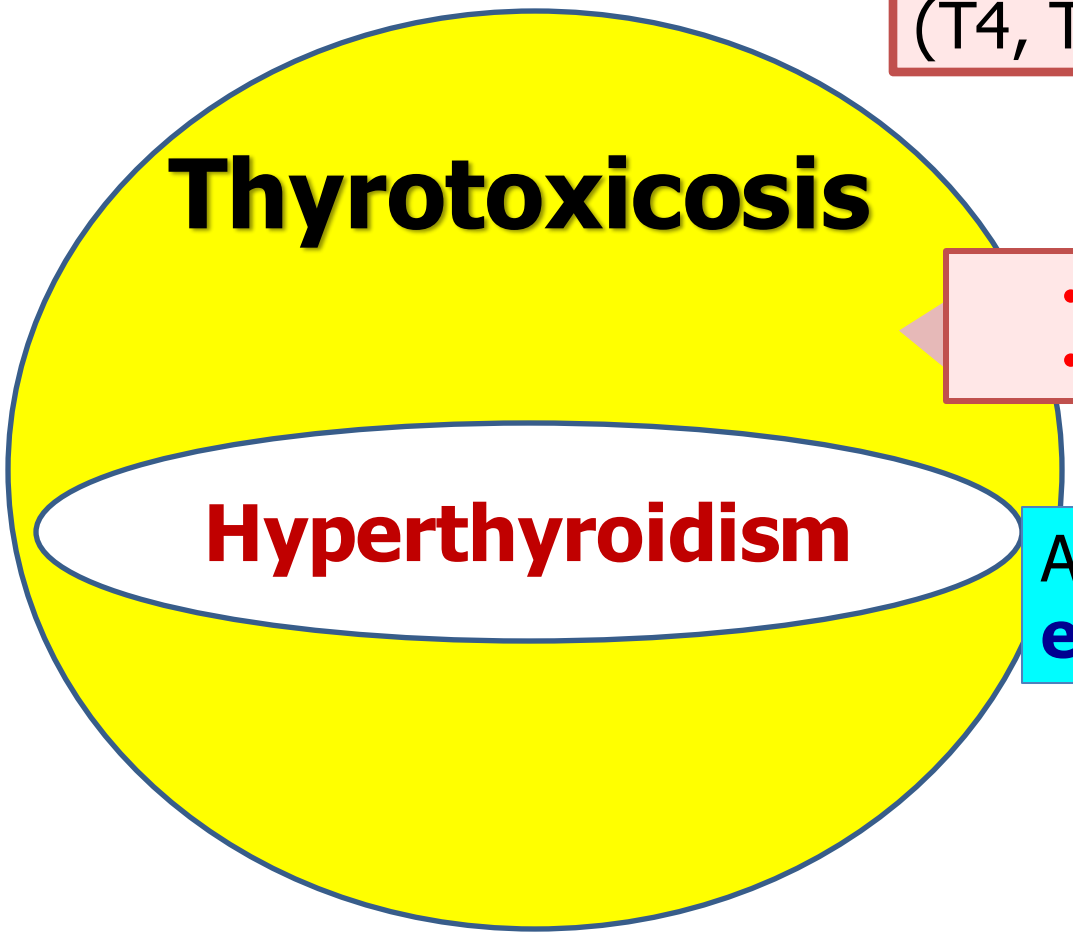
⇔ TSH
⇔ FT4, FT3
↓ T4, T3

Outline

1. Physiology of thyroid
2. Evaluation of thyroid function
3. **Thyrotoxicosis & Hyperthyroidism**

Definition

State of thyroid hormone excess (T4, T3 or both) of **any etiology**



- Thyroiditis
- Thyrotoxicosis factitia

A form of thyrotoxicosis due to **excessive thyroid gland function**

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

AACE, Endocr Pract. 2011

Clinical manifestation of thyrotoxicosis

Symptoms

- weight loss with increased appetite
- heat intolerance
- sweating
- hand tremor
- palpitation
- agitation, irritability, insomnia
- fatigue and weakness
- frequent bowel movement
- abnormal menstruation → oligomenorrhea
- apathetic thyrotoxicosis (especially in the elderly)

Clinical manifestation of thyrotoxicosis

Signs

Thyroid exam

- Variable findings
- Diffuse goiter: Graves' disease
- Nodular: Toxic MNG, adenoma

Cardiovascular

- Sinus tachycardia
- Bounding pulse/widened pulse pressure
- Atrial fibrillation (esp. in the patients > 50 years of age)

Neurological/musculoskeletal

- Tremor
- Hyperreflexia
- Proximal myopathy (without fasciculation)

Clinical manifestation of thyrotoxicosis

Signs

- **Dermatologic**
  - Warm/moist skin
  - Onycholysis
  - Diffuse alopecia

- **Ophthalmologic**
  - Stare
  - Lid retraction
  - Lid lag

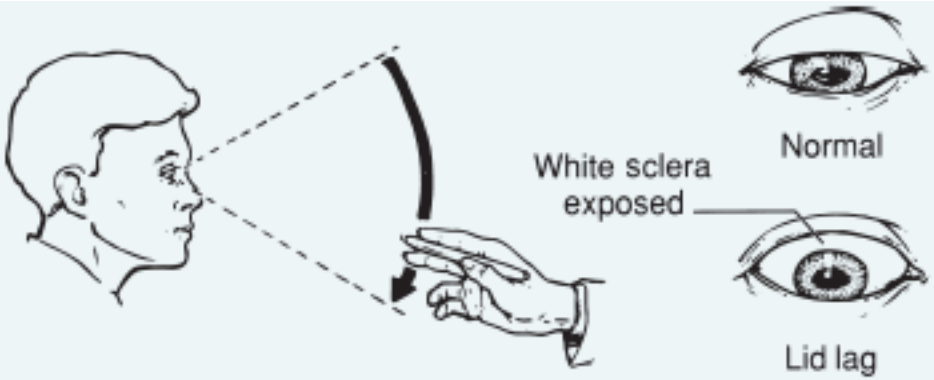
http://orthopedic.com.sg/patients-guide/foot-ankle-pain/onycholysis
Clin Ophthalmol. 2009; 3: 543–551.

Clinical manifestation of thyrotoxicosis

Signs

- **Dermatologic**
  - Warm/moist skin
  - Onycholysis
  - Diffuse alopecia

- **Ophthalmologic**
  - Stare
  - Lid retraction
  - Lid lag



Source: Richard F. LeBlond, Donald D. Brown, Manish Suneja, Joseph F. Szot: *DeGowin's Diagnostic Examination*, 10th Edition:
www.accessmedicine.com

http://orthopedic.com.sg/patients-guide/foot-ankle-pain/onycholysis

Clin Ophthalmol. 2009; 3: 543–551.

Which labs should be obtained in patients with symptoms and signs of thyrotoxicosis?

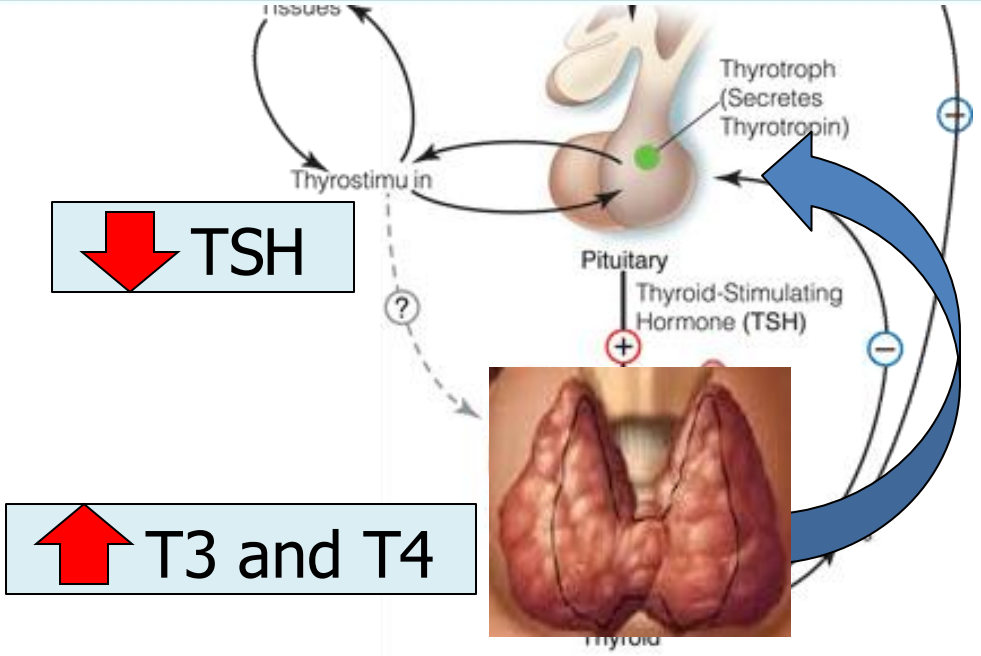
A. TSH only

B. TSH, FT4

C. TSH, FT3

D. TSH, FT4, FT3

Evaluation of thyroid function



	T3, Free T3	T4, Free T4	TSH
Thyrotoxicosis	↑	↑	↓
T3 toxicosis	↑	↔	↓
T4 toxicosis	↔	↑	↓

Biochemical evaluation

- **TSH** → *Single best or initial test of thyroid function*
- Strong suspicion of thyrotoxicosis:

  TSH + FT4 +FT3

	T3, Free T3	T4, Free T4	TSH
Thyrotoxicosis	↑	↑	↓
T3 toxicosis	↑	↔	↓
T4 toxicosis	↔	↑	↓

Biochemical evaluation

- **TSH** → *Single best or initial test of thyroid function*
- Strong suspicion of thyrotoxicosis:

  TSH + FT4 +FT3

- **FT4** is preferred over T4 (as it is not affected by alteration of TBG)

- (Historically) **T3** was preferred over FT3 (FT3 assay was less widely validated due to small amount of FT3 in the circulation)

T3: 80-200 ng/dL
FT3: 2.4-4.2 pg/mL

Causes of thyrotoxicosis

With hyperthyroidism	Without hyperthyroidism
• Graves' disease	• Thyroiditis
• Toxic multinodular goiter (MNG) / Toxic adenoma	• Thyrotoxicosis factitia
• TSH producing pituitary tumor	

AACE, Endocr Pract. 2011

Determination of etiology

Thyrotoxicosis WITH hyperthyroidism

- Graves' disease
- Toxic multinodular goiter (MNG) / Toxic adenoma
- TSH producing pituitary tumor

AACE, Endocr Pract. 2011

Graves' disease

Robert James Graves

1835 "...three cases of violent and long palpitations in females, in each of which the same peculiarity presented ...enlargement of the thyroid gland, ..."

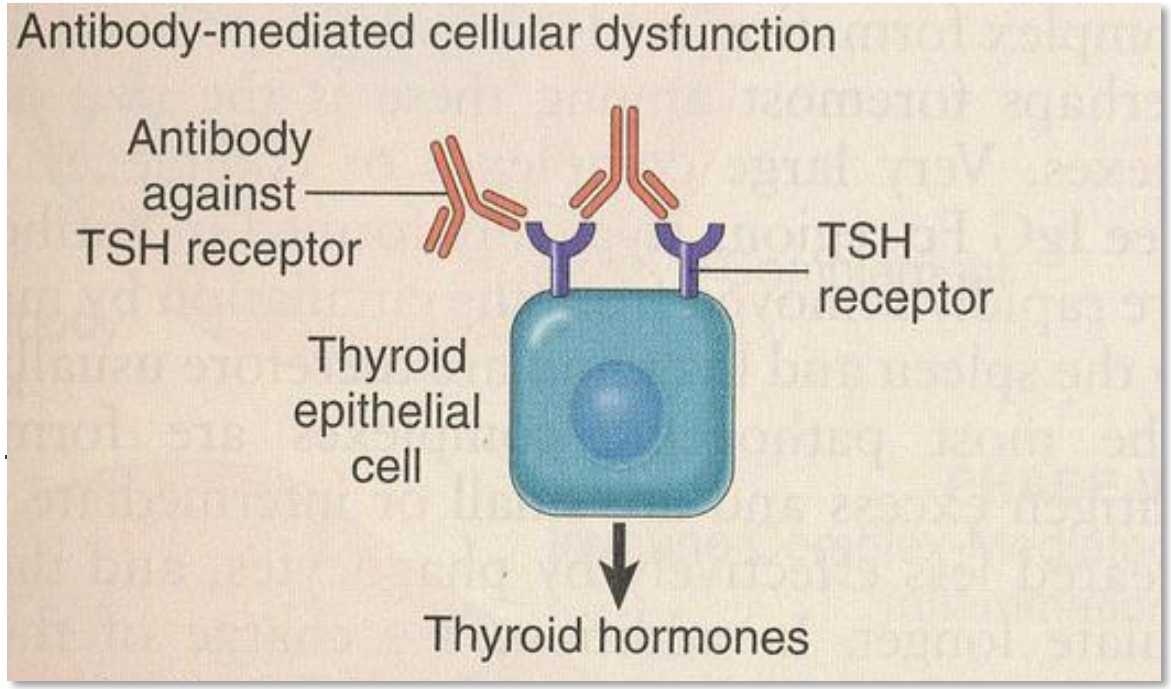
De Groot Endocrinology: Adult and pediatric, 7th edition

Graves' disease

- Most common cause of thyrotoxicosis (60–80% of cases)
- Female-to-male ratio is 7–10:1
- Typical age range: 20-40 years

Graves' disease

- Autoimmune condition
  - Caused by anti-TSH receptor antibodies directed against TSH receptor



These antibodies bind to and activate the TSH receptor, causing autonomous production of thyroid hormone

http://cms-histologyproject1-group13.wikispaces.com/Endocrine+System+-+Group+13

Graves' disease

How to diagnose Graves' disease?

History and Physical exam

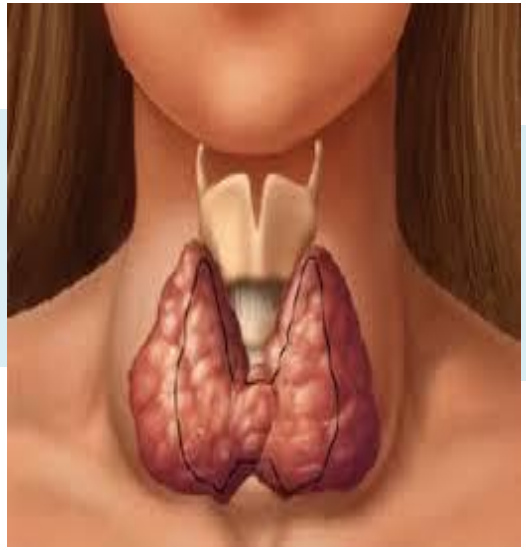
- Symptoms and signs of thyrotoxicosis
- Specific (pathognomonic) signs of Graves' disease

Investigation

- Lab
- Others (if needed)

Graves' disease

Graves' Ophthalmopathy (orbitopathy)



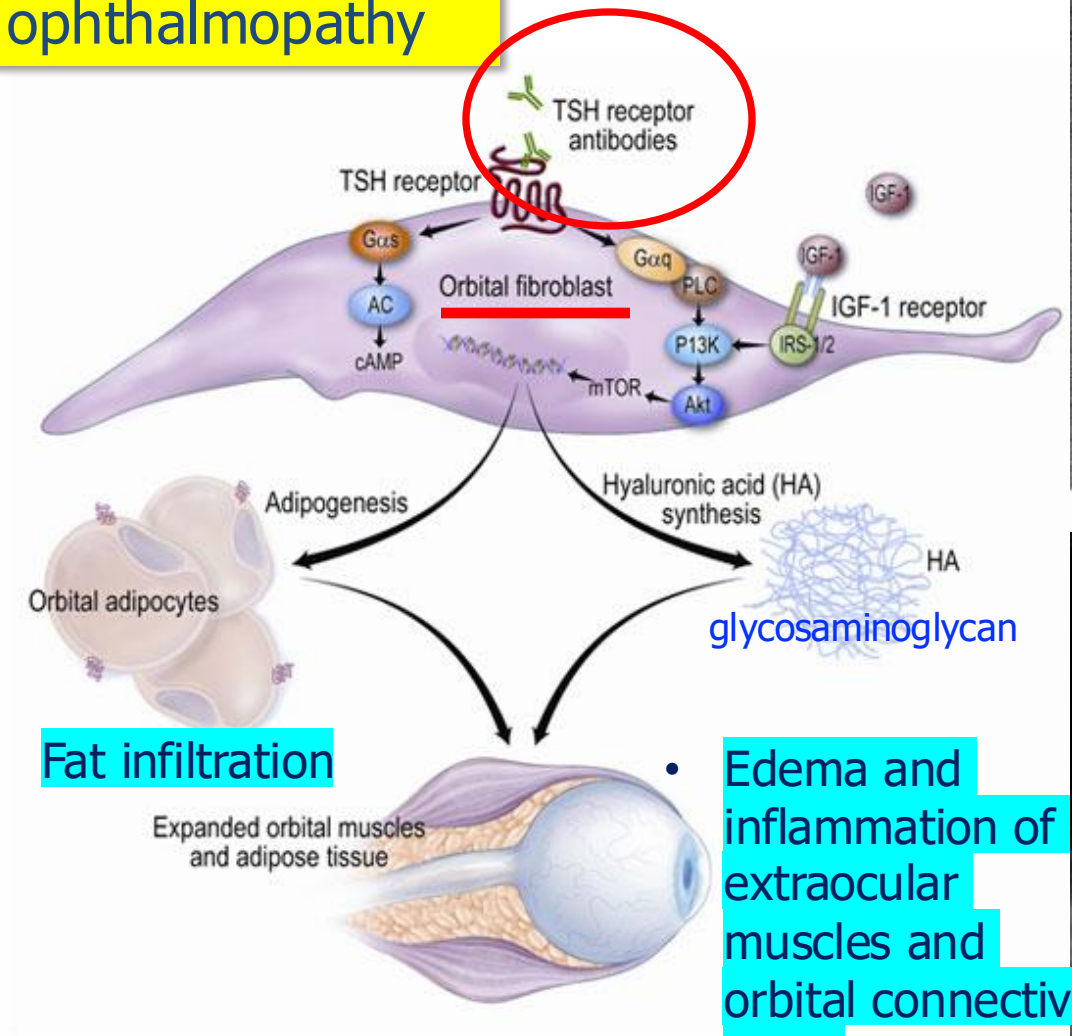
Thyroid bruit

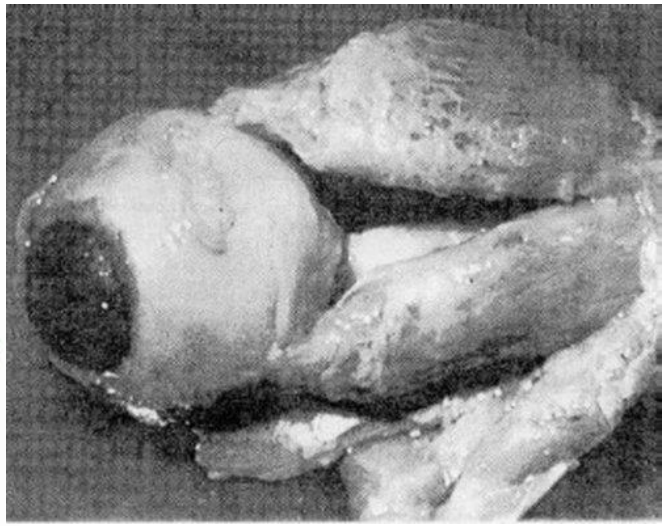
Graves' Dermopathy (pretibial myxedema)

Graves' acropachy

Specific sign of Graves' disease

Graves' ophthalmopathy





- Fat infiltration
- Edema and inflammation of extraocular muscles and orbital connective tissue

Williams Textbook of Endocrinology, 13th Edition

Eye signs in thyrotoxicosis

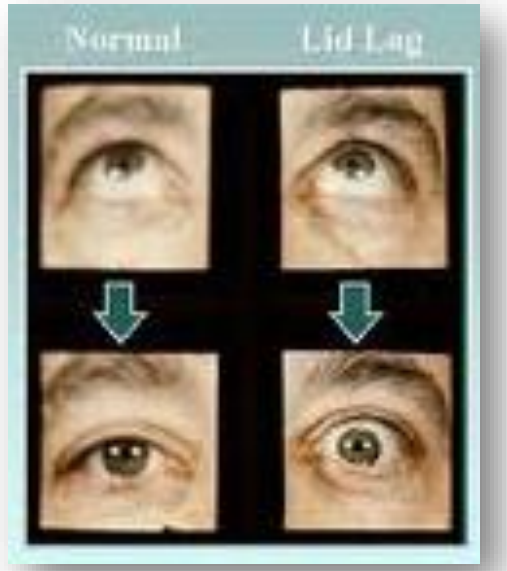
Graves ophthalmopathy

Exophthalmos

Pathognomonic signs of Graves' disease

Sympathetic overactivity

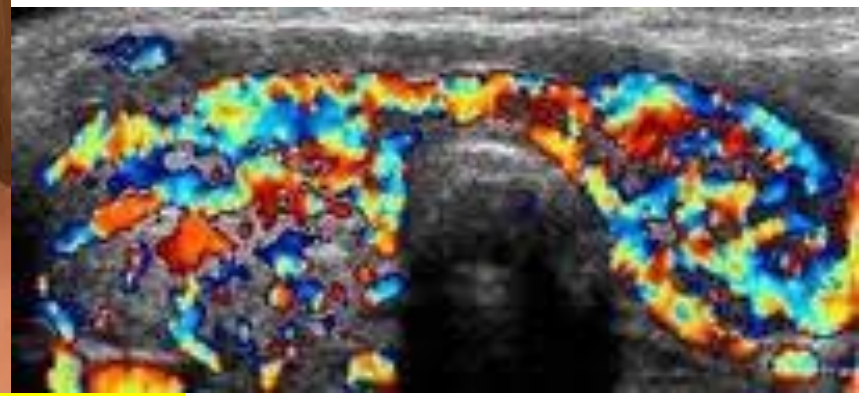
Lid retraction



Lid lag

Not specific for Graves' disease
Seen in all forms of thyrotoxicosis, regardless of the underlying cause

Specific signs of Graves' disease



Thyroid bruit

Specific signs of Graves' disease

Graves' dermopathy

- Hyperpigmented, non-pitting induration of the skin
- Occurs in <5%
- Almost always occur in the presence of moderate or severe ophthalmopathy

Graves' acropachy

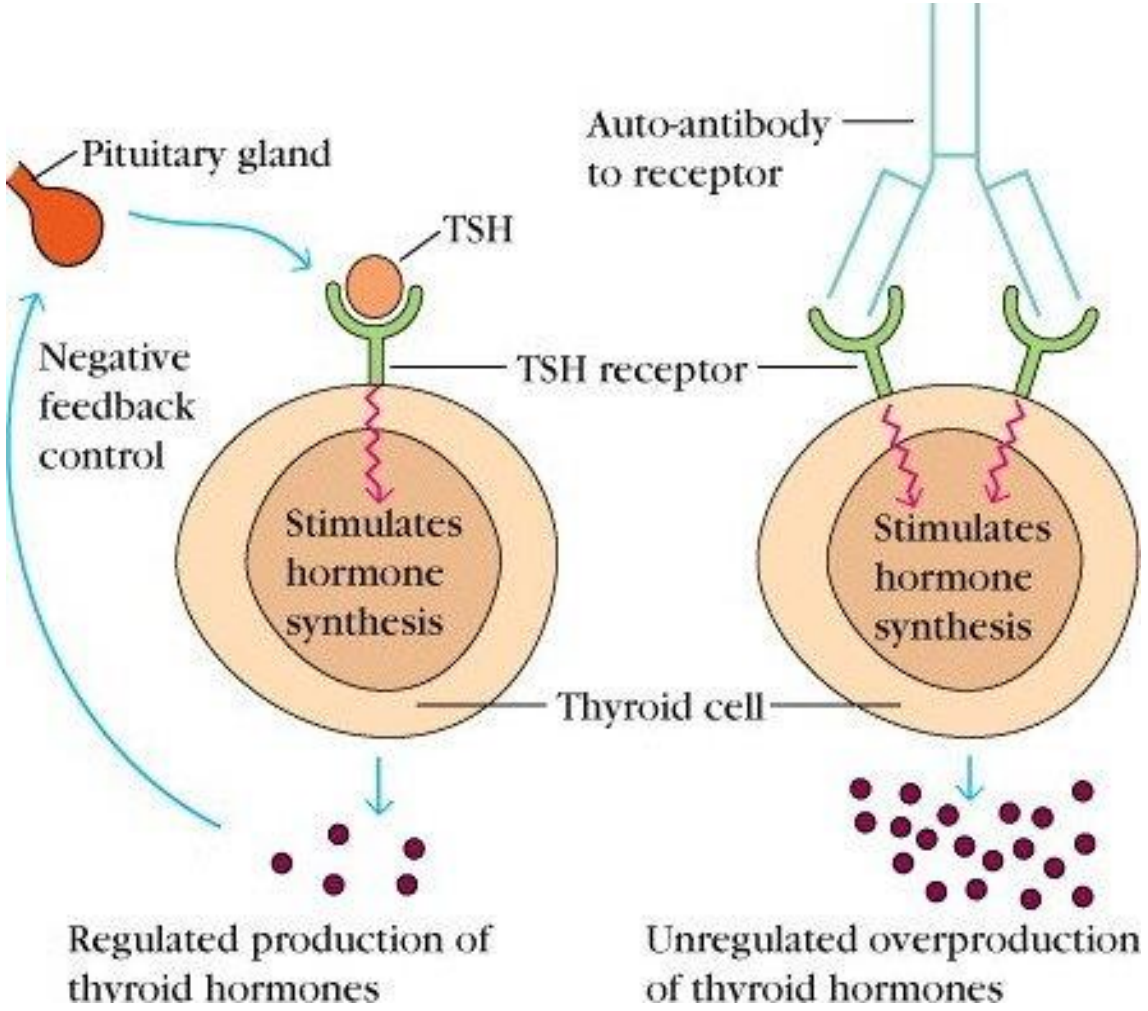
- Refers to a form of clubbing found in <1% of patients with Graves' disease
- It is so strongly associated with thyroid dermopathy

Graves' disease

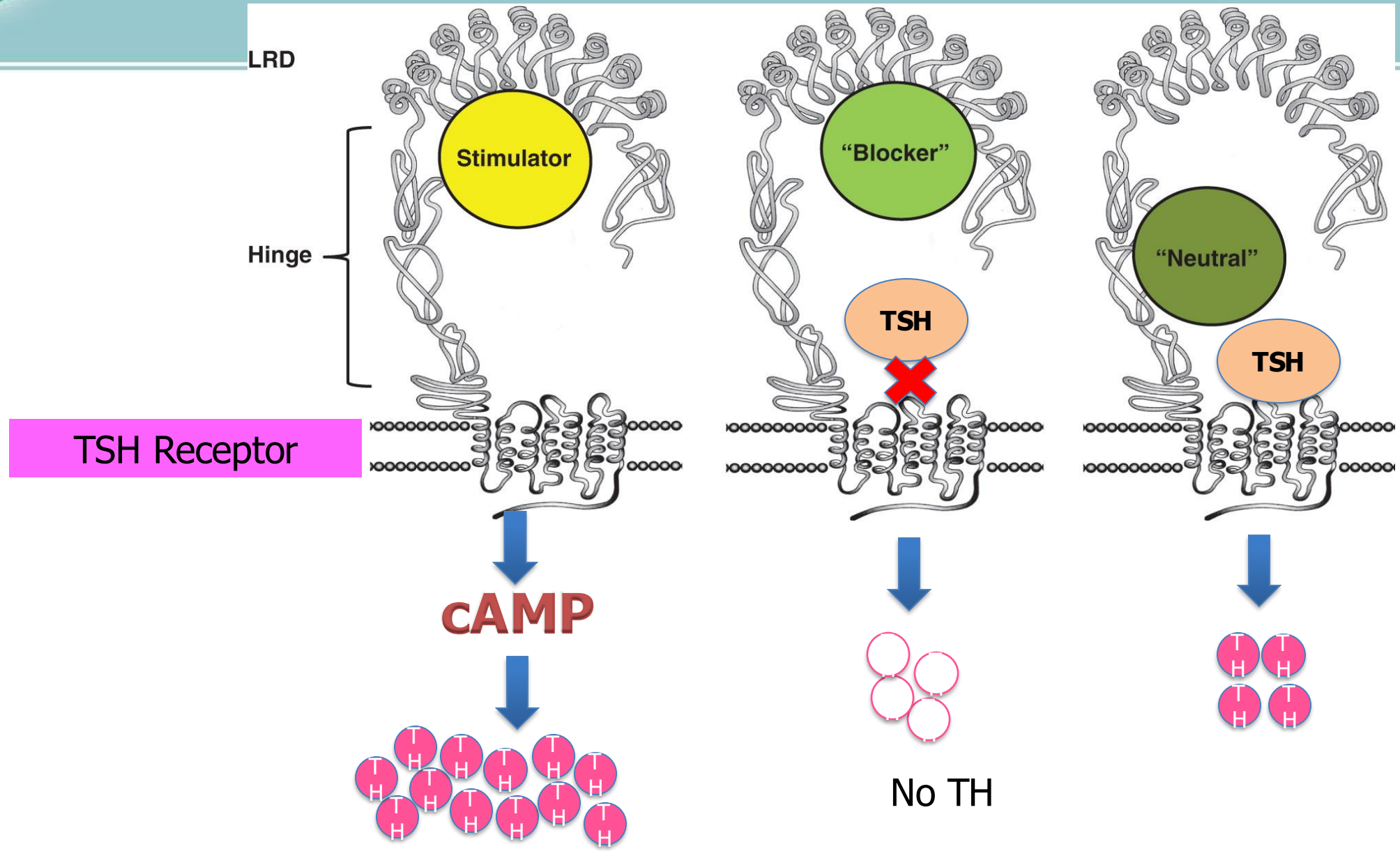
Labs

- ↓ TSH, ↑ free T4, ↑ free T3
- Positive anti-TSH receptor antibody: TSI (thyroid stimulating immunoglobulin) or TBII (thyroid binding inhibitory immunoglobulin)
- TPO Ab or Tg Ab may be positive

TSH receptor antibody



http://www.thyroid.com.au



Adapted from: Terry F Davies; Rauf Latif; Expert Opinion on Therapeutic Targets 2015, 19, 835-847.

Prevalence of thyroid autoantibodies

Group	TSH receptor Ab (TRAb) (%)	Tg-Ab (%)	TPO-Ab (%)
General population	0	5-20	8-27
Patients with Graves' disease	80-95	50-70	50-80
Patients with autoimmune thyroiditis	10-20	80-90	90-100
Relative of patients	0	40-50	40-50
Patients with IDDM	0	40	40
Pregnant women	0	14	14

TRAb assay

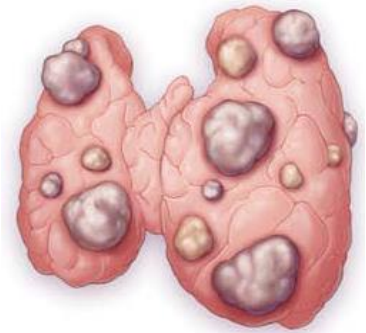
- Sensitivity for GD = 96-97%
- Specificity for GD = 99%

1. Salvatore D CR, Kopp PA, Larsen PR. Thyroid Pathophysiology and Diagnostic Evaluation. In: Melmed S KR, Rosen C, Auchus R, Goldfine A, editor. Williams Textbook of Endocrinology. 14 ed. Philadelphia, PA: Elsevier; 2019.
2. Autoimmunity Reviews, 2012-12-01

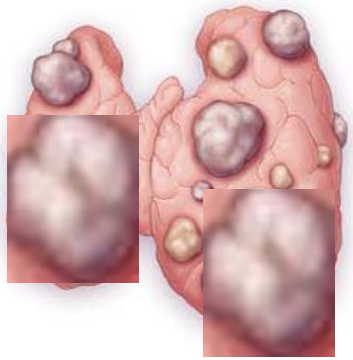
Toxic adenoma
Toxic multinodular goiter

"Not an autoimmune process"

Toxic MNG

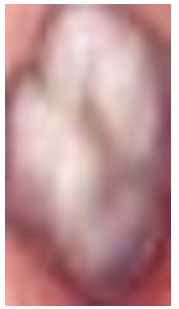


TSH-R mutation →



Toxic adenoma

TSH-R mutation →



Courtesy Dr. Taweesak Wannachalee

Toxic adenoma
Toxic multinodular goiter

- Symptoms and signs of thyrotoxicosis
- Thyroid exam: **palpable nodule(s)**
- Labs
  - ↓ TSH, ↑ free T4, ↑ free T3
  - Negative anti-TSH receptor antibody
  - Negative TPO Ab or Tg Ab

Determination of etiology

Thyrotoxicosis WITHOUT hyperthyroidism

- Thyroiditis
- Thyrotoxicosis factitia

AACE, Endocr Pract. 2011

Thyroiditis

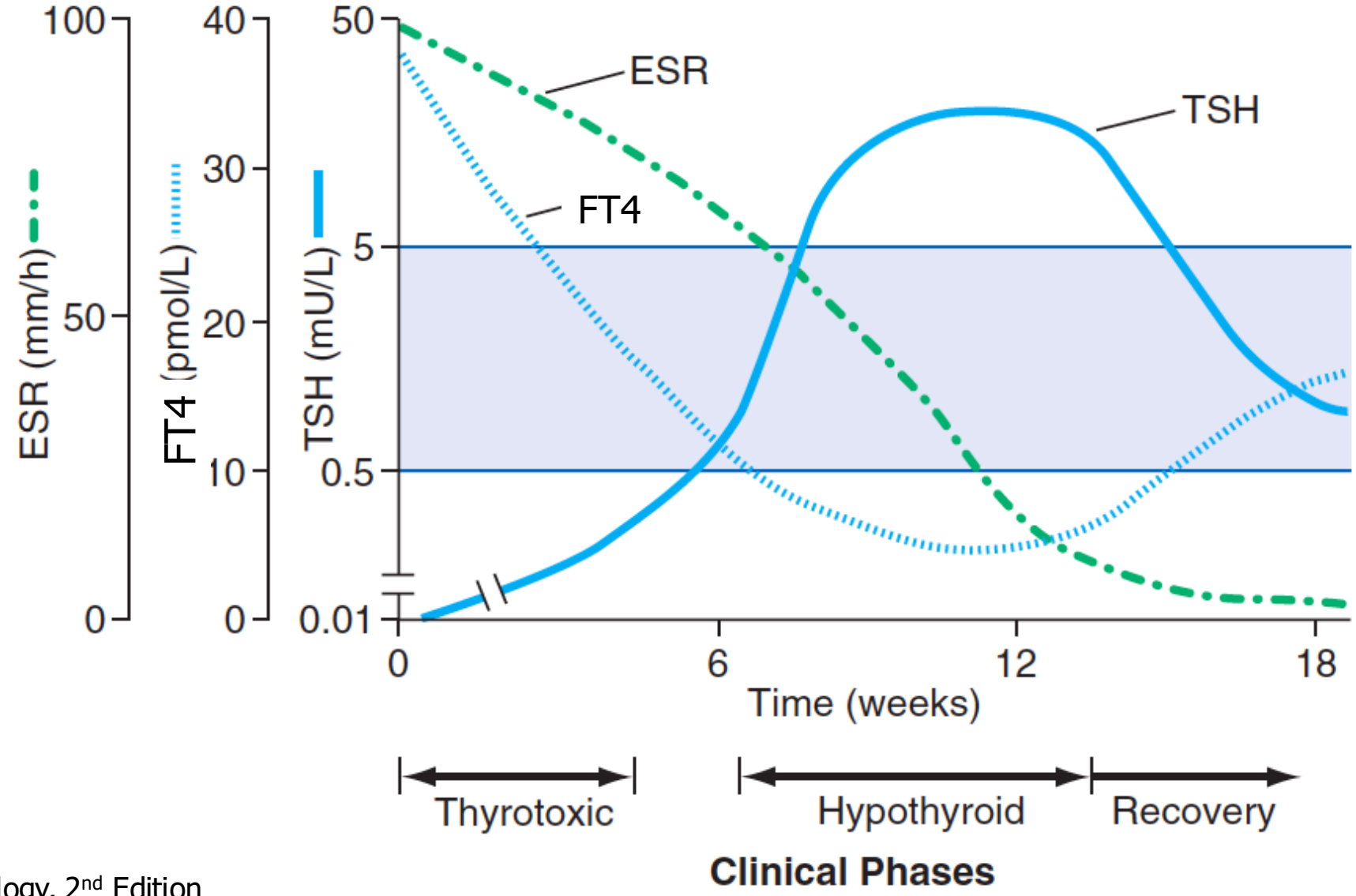
Inflammation or destruction of thyroid gland → Release of preformed thyroid hormone

- Acute infectious thyroiditis
- **Subacute (painful, DeQuervain, granulomatous)**
- **Autoimmune (painless, postpartum, silent)**
- Drug-induced (amiodarone, lithium, tyrosine kinase inhibitor, immune checkpoint inhibitor)
- Radiation-induced/ trauma

Thyroiditis

	Painful (Subacute)	Painless (Silent)
Etiology	Viral	Autoimmune
Symptoms	Neck pain +/- fever Preceded by malaise, URI	No pain 3-6 months postpartum → Postpartum thyroiditis
Physical exam	Painful, slightly enlarged thyroid (firm consistency)	Painless, slightly enlarged thyroid (firm consistency)
Labs	↓TSH, ↑free T4, ↔ or ↑free T3	
	↑ ESR	↔ ESR
Treatment	NSAIDS, glucocorticoid, β-blocker	Symptomatic Rx: β-blocker

Clinical course of thyroiditis



Harrison Endocrinology, 2nd Edition

Thyrotoxicosis Factitia

- Thyroxine ingestion
  - Overdose for treatment of hypothyroidism
    - By mistake
  - Psychiatric disorder (Munchausen syndrome)
- Symptoms and signs of thyrotoxicosis
- Thyroid gland – **not palpable**

HOW TO APPROACH THYROTOXICOSIS ?

Symptoms and signs of thyrotoxicosis

↓ TSH & ↑ FT3,FT4

Thyrotoxicosis **with** hyperthyroidism	Thyrotoxicosis **without** hyperthyroidism
• Graves' disease • Toxic multinodular goiter (MNG) • Toxic adenoma	• Thyroiditis • Thyroxine ingestion

Differentiation of causes of thyrotoxicosis

Clinical

- ✓Duration of symptoms
- ✓Physical exam: thyroid gland, other features

Imaging studies

- ✓RAI uptake
- ✓Thyroid scan

Differentiation of causes of thyrotoxicosis

Etiology	Symptoms	Goiter	Other features
With hyperthyroidism			
Graves' disease	> 3 months	Diffuse enlargement (20% absent)	Thyroid bruits Ophthalmopathy, dermopathy, acropachy
Toxic MNG	> 3 months	Nodules	
Toxic adenoma	> 3 months	Single nodule (>3 cm)	Contralateral thyroid lobe – not palpable
Without hyperthyroidism			
Thyroiditis	< 3 months	Firm and mildly enlarged (+/- pain)	Subacute – painful
Exogenous T4	variable	absent	

Differentiation of causes of thyrotoxicosis

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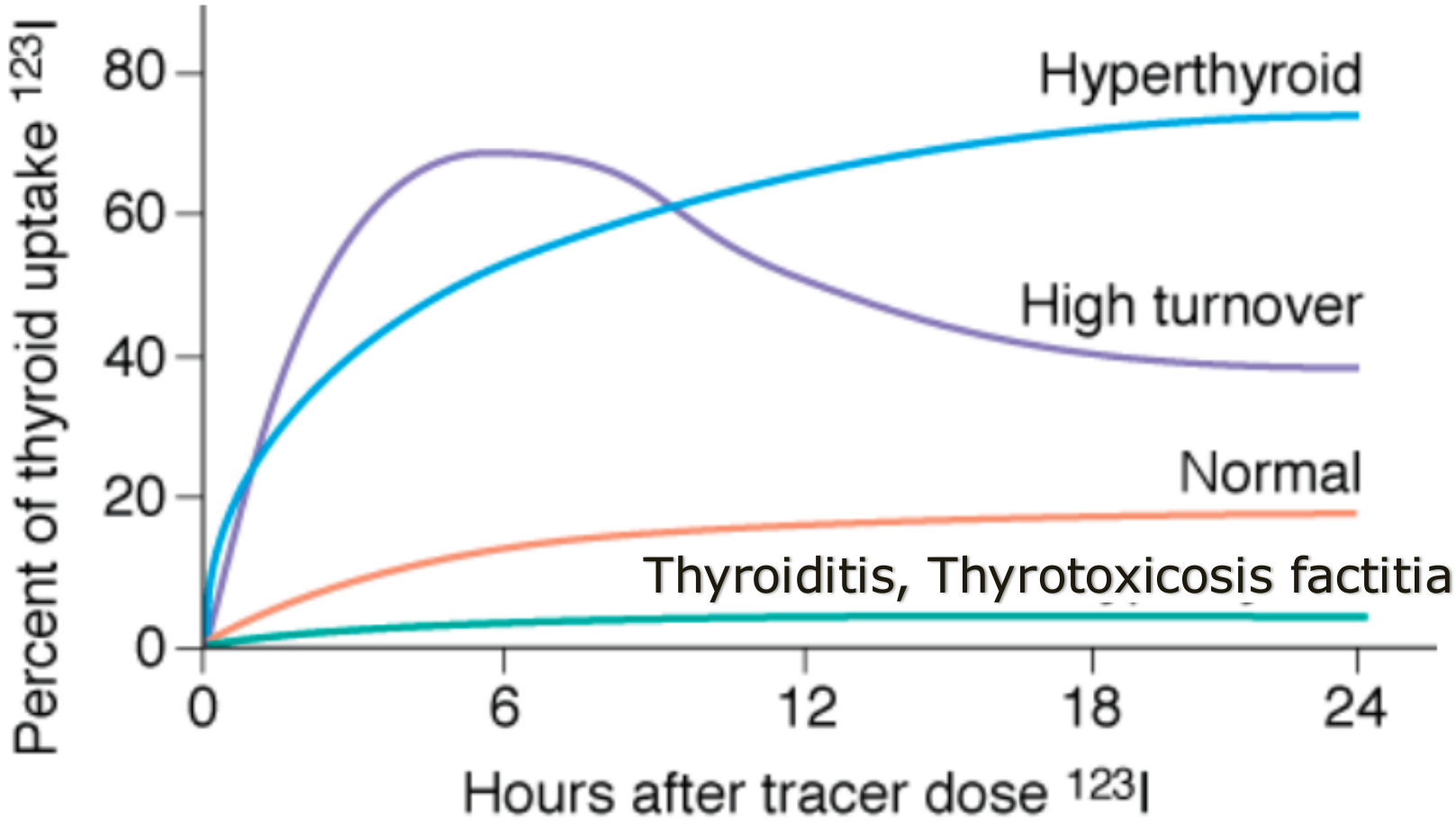
Exogenous T4	variable	absent	

Radioactive iodine (RAI) uptake

- ^{123}I or ^{131}I is given orally
- Radioactivity over the thyroid gland is quantified with a scintillation counter at 4-6 hours and at 24 hours
- Not useful if performed after administration of iv iodinated contrast

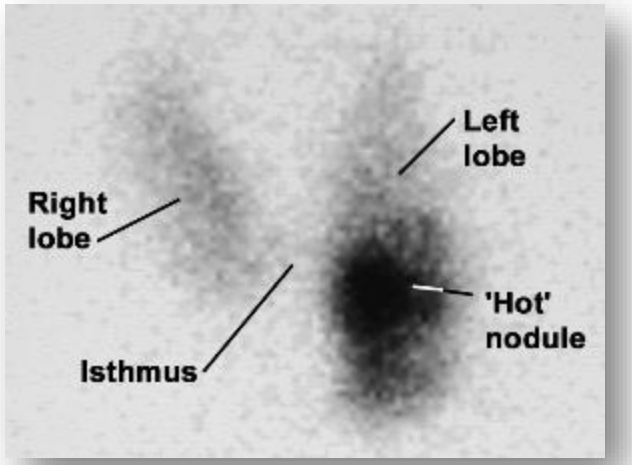
Radioactive iodine (RAI) uptake

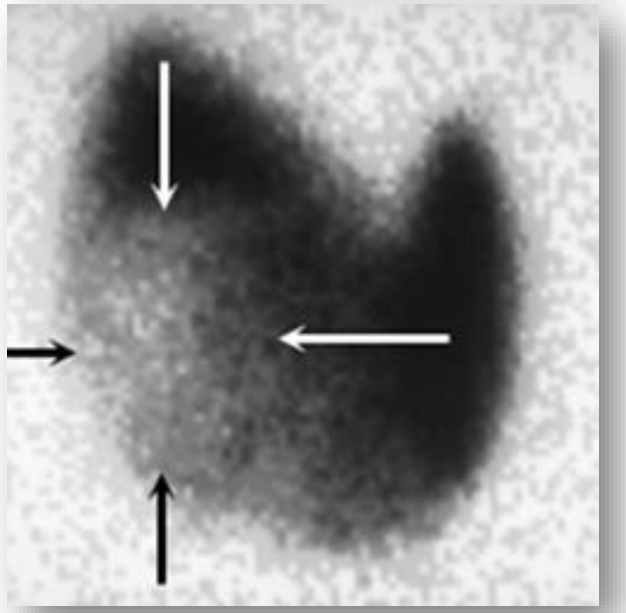


Source: Gardner DG, Shoback D: *Greenspan's Basic & Clinical Endocrinology, 9th Edition:* www.accessmedicine.com

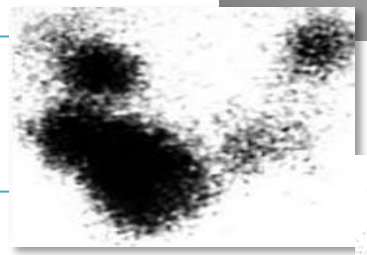
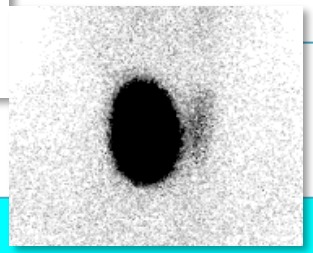
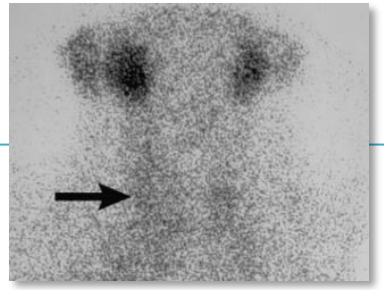
Radionuclide Thyroid scan

- ^{123}I, ^{131}I or ^{99m}Tc pertechnetate
- Images can be obtained with either rectilinear scanner or gamma camera
- Provides information about the size and shape of thyroid gland and the distribution of tracer activity within the gland
- Helps to determine whether nodules are functional or non-functional





Differentiation of causes of thyrotoxicosis

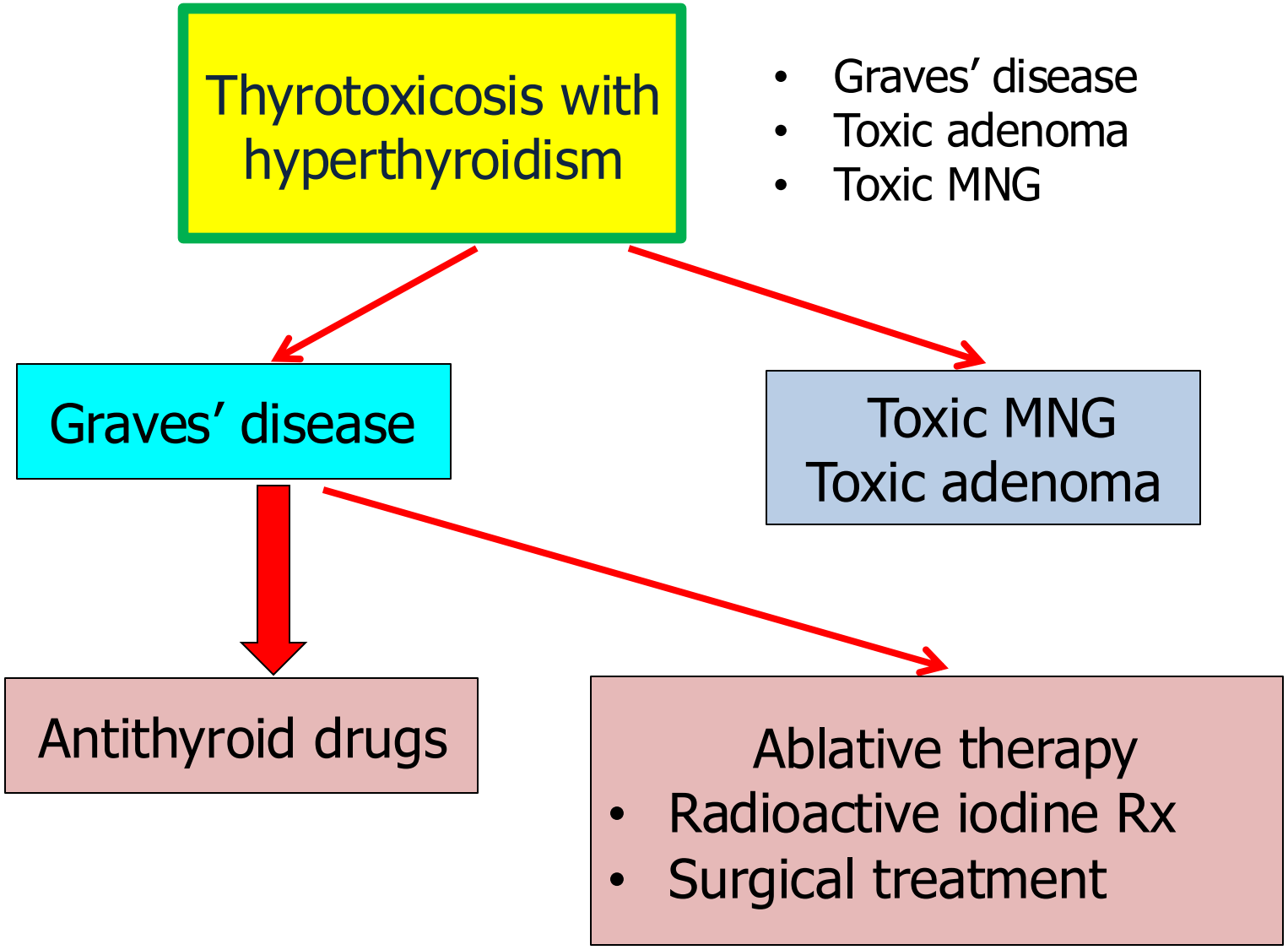
Etiology	RAI uptake	Thyroid scan
With hyperthyroidism		
Graves' disease	High	
Toxic MNG	Normal to high	
Toxic adenoma	Normal to high	
Without hyperthyroidism		
Thyroiditis	Low	
Exogenous T4	Low	

Management of thyrotoxicosis

Which of the followings is/are the treatment modalities for Graves' disease ?

A. Antithyroid drugs
B. Radioactive iodine ablation
C. Total thyroidectomy
D. All of the above
E. None of the above

Management of Thyrotoxicosis

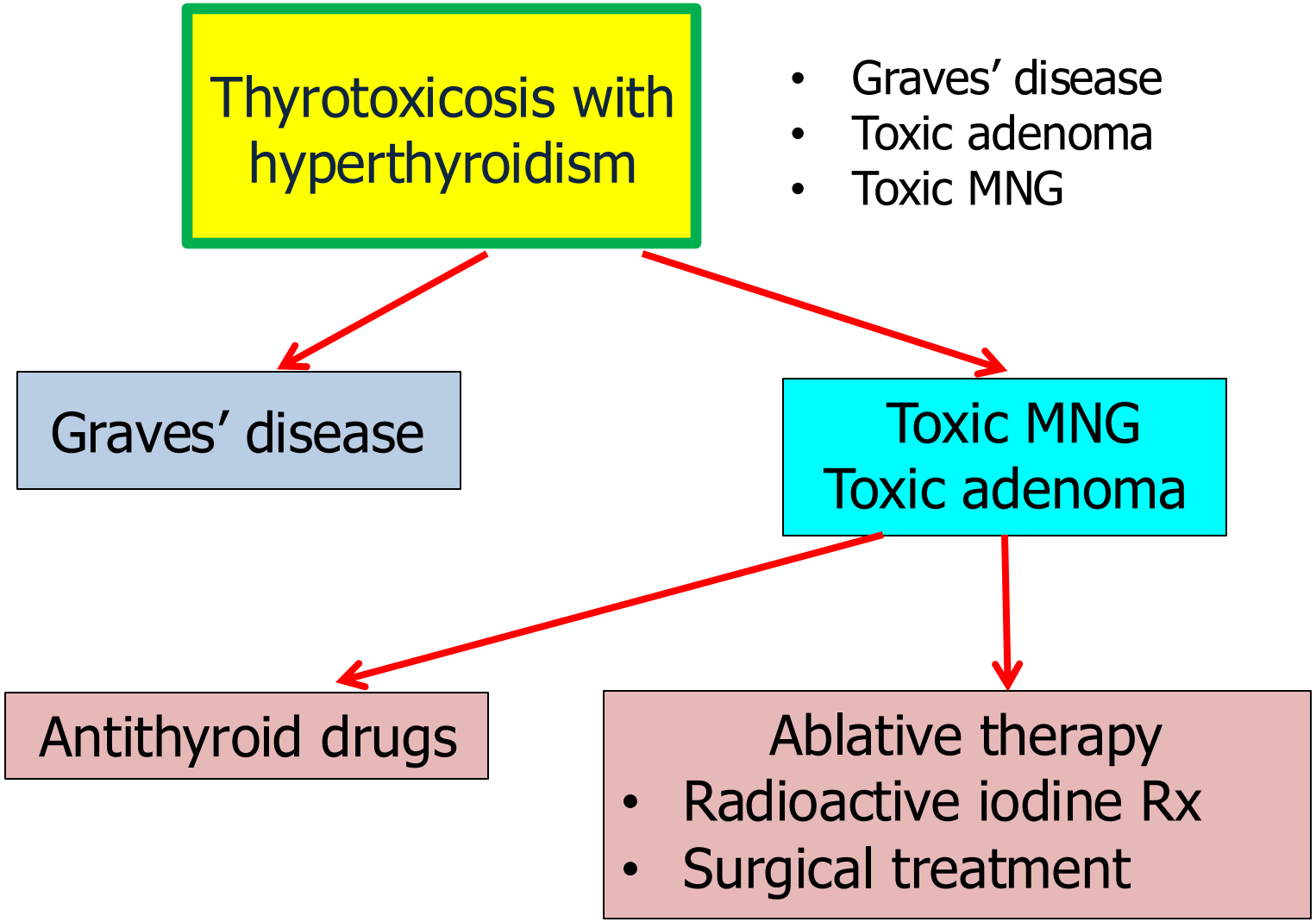


Graves' disease treatment

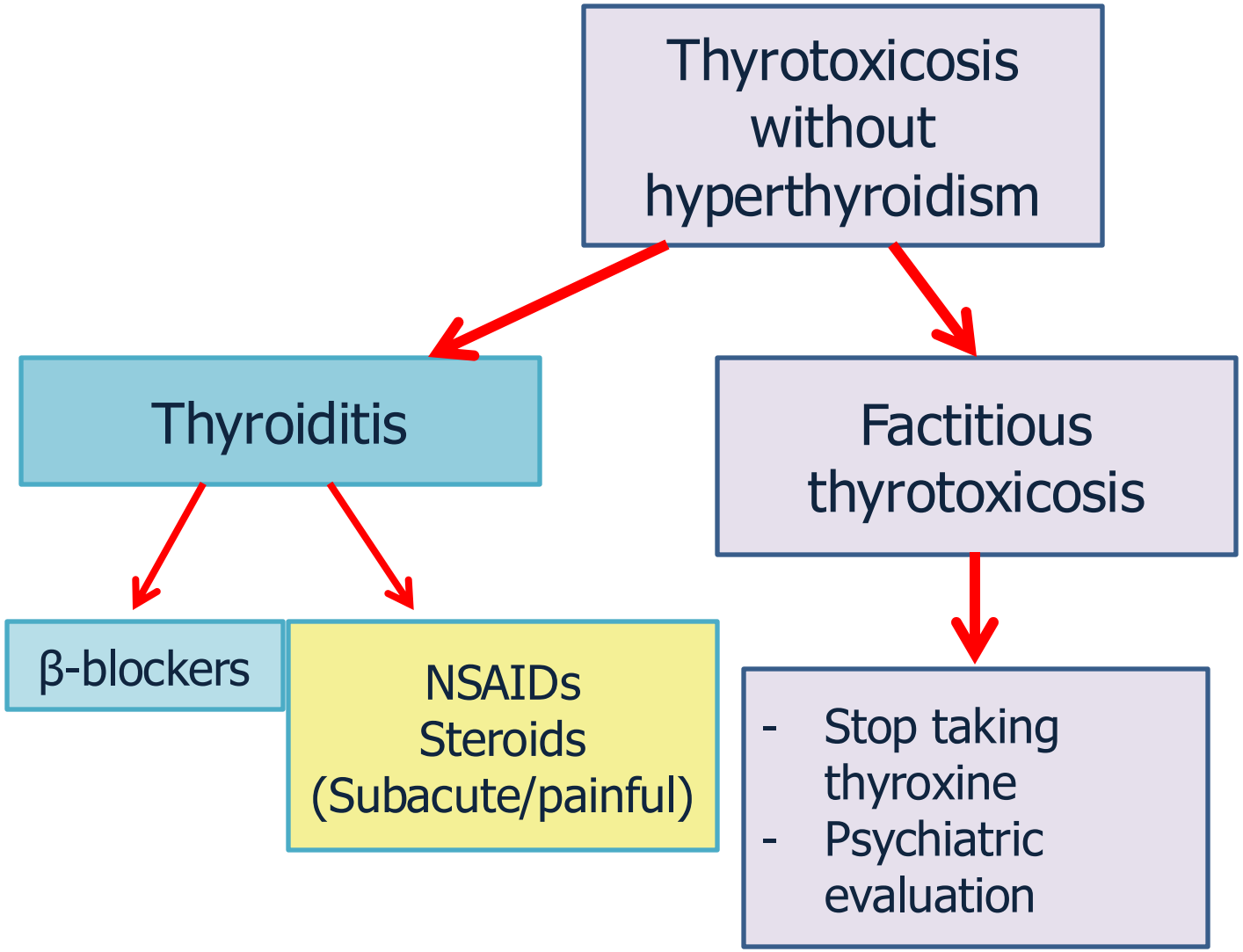
Treatment option	Advantages	Disadvantages
ATD	- Chance of permanent remission (~35%)	• Side effectsof ATDs • Long duration (12-18 months) • High recurrence risk
Radioactive iodine treatment	- Simplicity - Low recurrence risk	• Risk of orbitopathy • Lifelong LT4 needed • Possible small increase in cancer risk
Thyroidectomy	- Rapidity - Almost no recurrence	• Low but unavoidable morbidity • Lifelong LT4 needed

Williams Textbook of Endocrinology, 14th edition 2020

Management of Thyrotoxicosis



Management of Thyrotoxicosis



Thank you for your attention

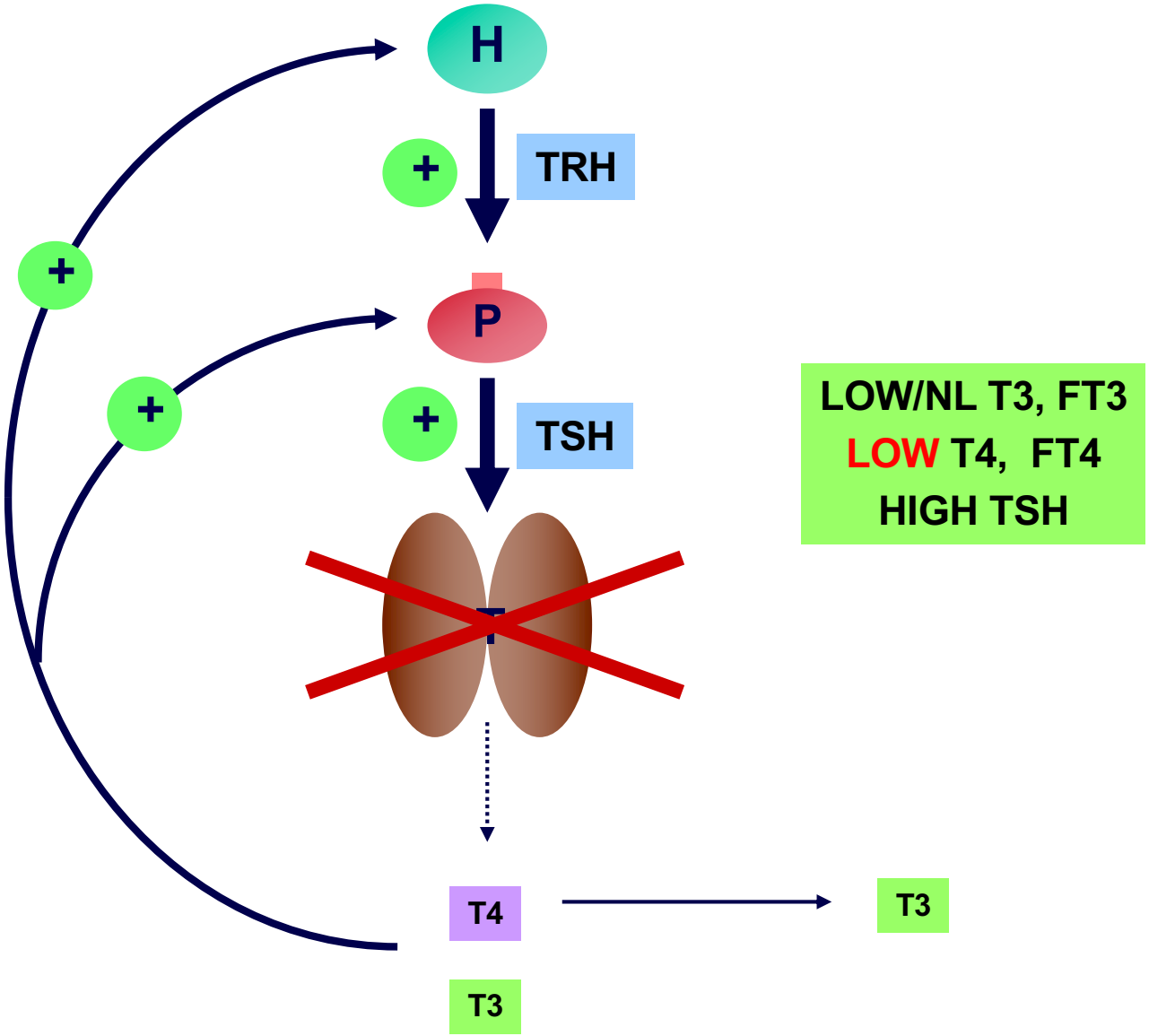
sirinart.oh@gmail.com

HYPOTHYROIDISM

Tada Kunavisarut

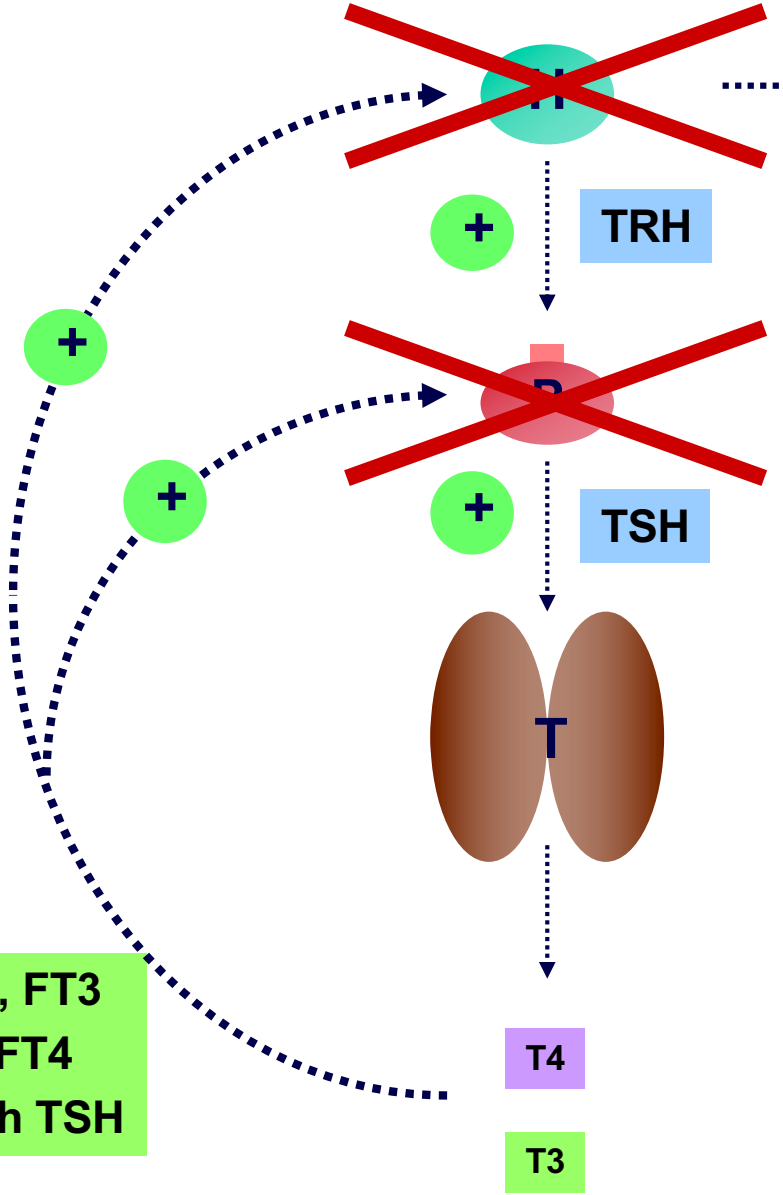
Division of Endocrinology & Metabolism

HYPOTHYROIDISM: PRIMARY



LOW/NL T3, FT3
LOW T4, FT4
HIGH TSH

HYPOTHYROIDISM: CENTRAL



LOW/NL T3, FT3
LOW T4, FT4
LOW/NL/High TSH

HYPOPITUITARISM
LOW GH
LOW FSH/LH
LOW ACTH

GH DEFICIENCY
LOW GH

HYPOGONADISM
LOW ESTROGEN
LOW TESTOSTERONE

ADRENAL INSUFFICIENCY
LOW CORTISOL

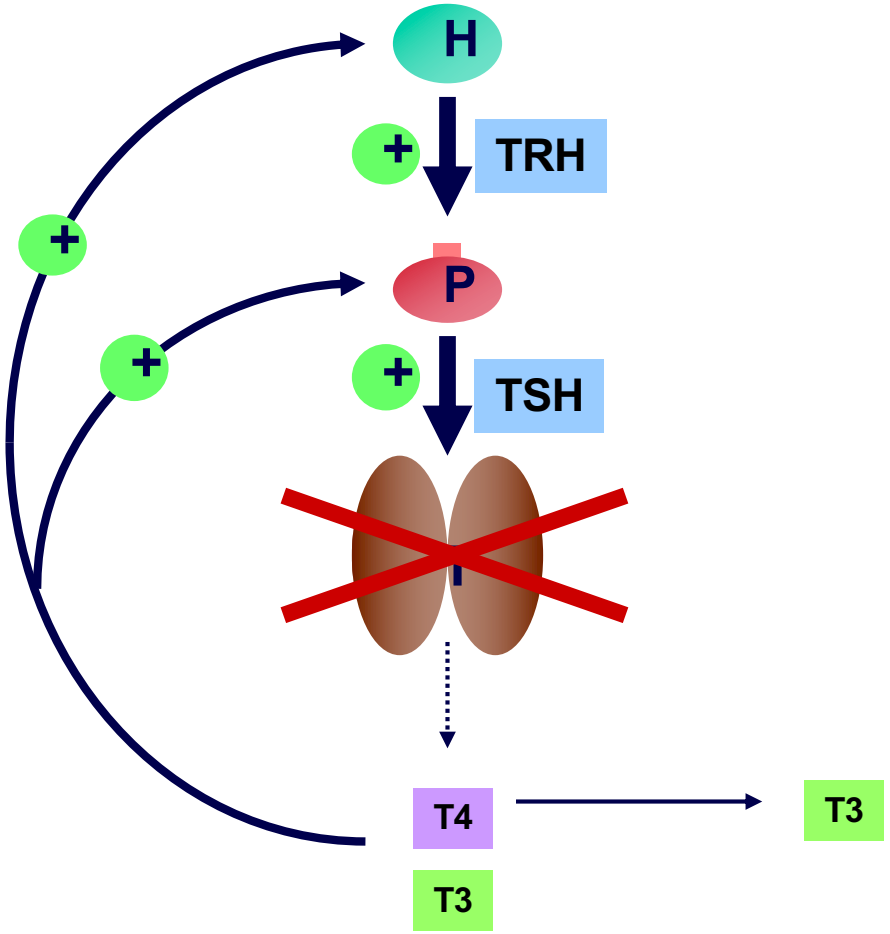
HYPOTHYROIDISM: PRIMARY VS. CENTRAL

PRIMARY

LOW/NL T3, FT3

LOW T4, FT4

HIGH TSH

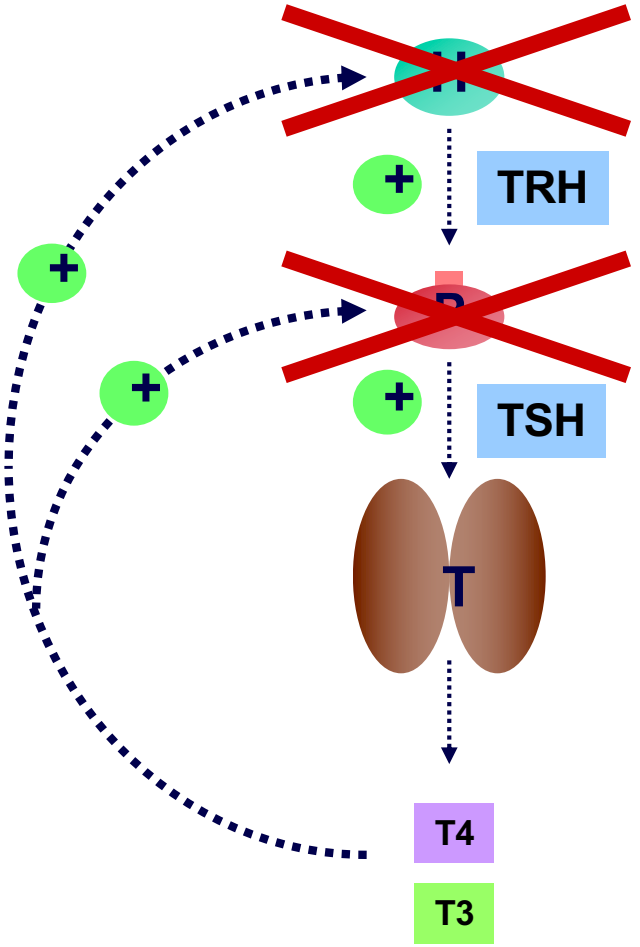


CENTRAL

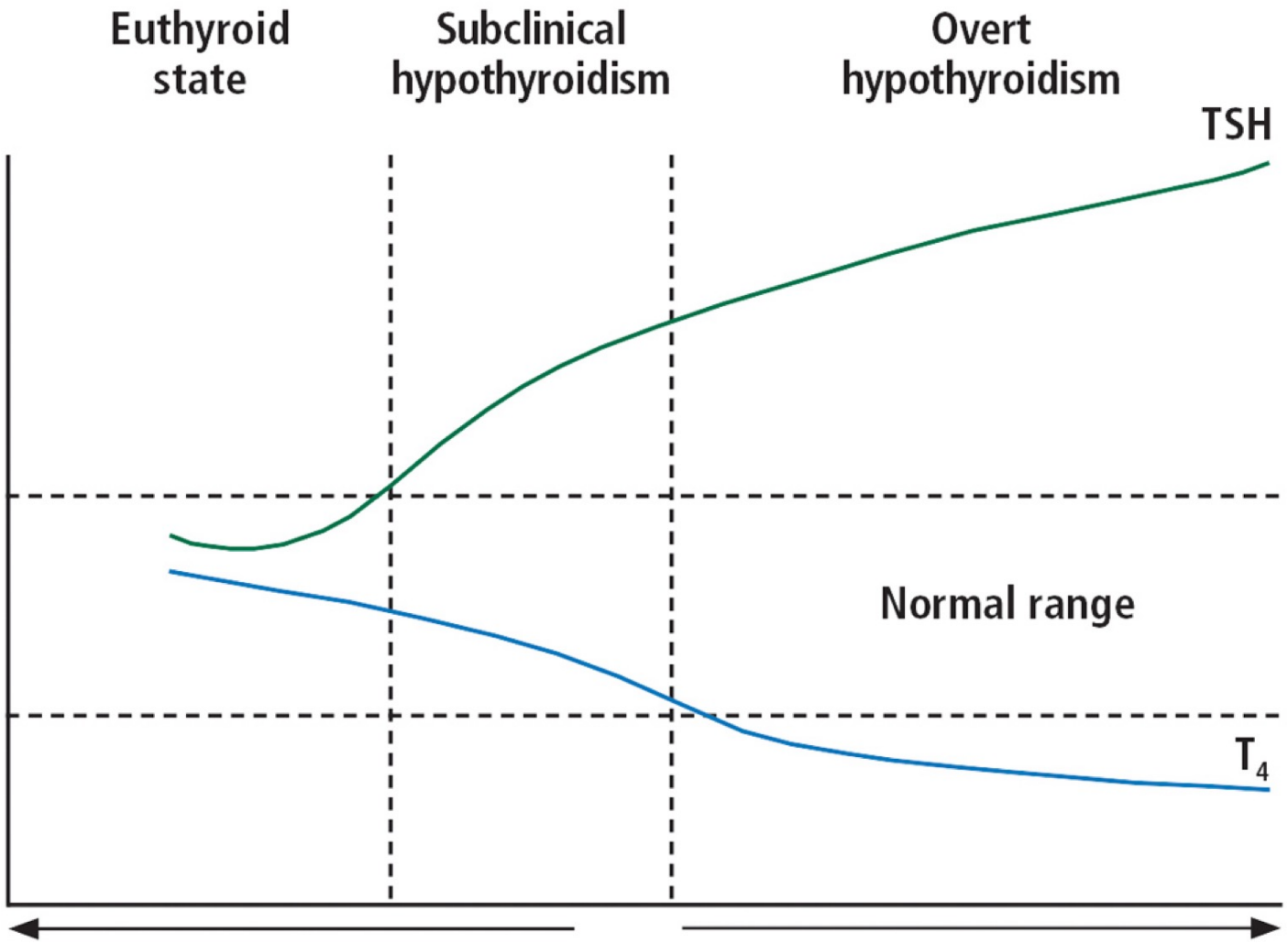
LOW/NL T3, FT3

LOW T4, FT4

LOW/NL/HIGH TSH



DEVELOPMENT OF 1° HYPOTYROIDISM



Lancet 2012; 379: 1142-54

HYPOTHYROIDISM
COMMON CLINICAL MANIFESTATIONS

SYMPTOMS

- Fatique
- Lethargy
- Sleepiness
- Mental impairment
- Depression
- Cold intolerance
- Decreased perspiration
- Weight gain
- Decreased appetite
- Constipation
- Arthralgia
- Paresthesia

SIGNS

- Slow movement
- Slow speech
- Hoarseness
- Bradycardia
- Dry skin
- Nonpitting edema (myxedema)
- Hyporeflexia
- Delayed relaxation of reflex
- Menstrual disturbance
- Pericardial effusion
- Pleural effusion

HYPOTHYROIDISM
COMMON CAUSES

PRIMARY

- Chronic autoimmune thyroiditis (Hashimoto Thyroiditis)
- Thyroidectomy: total, subtotal
- Radioiodine therapy (I-131)
- Drugs: ATD, iodine, lithium
- Others: infiltrative diseases, neck irradiation

CENTRAL

- Pituitary/hypothalamic tumor
- Surgery and radiation Rx of pituitary-hypothalamic tumor
- Sheehan syndrome

confirm Diagnosis

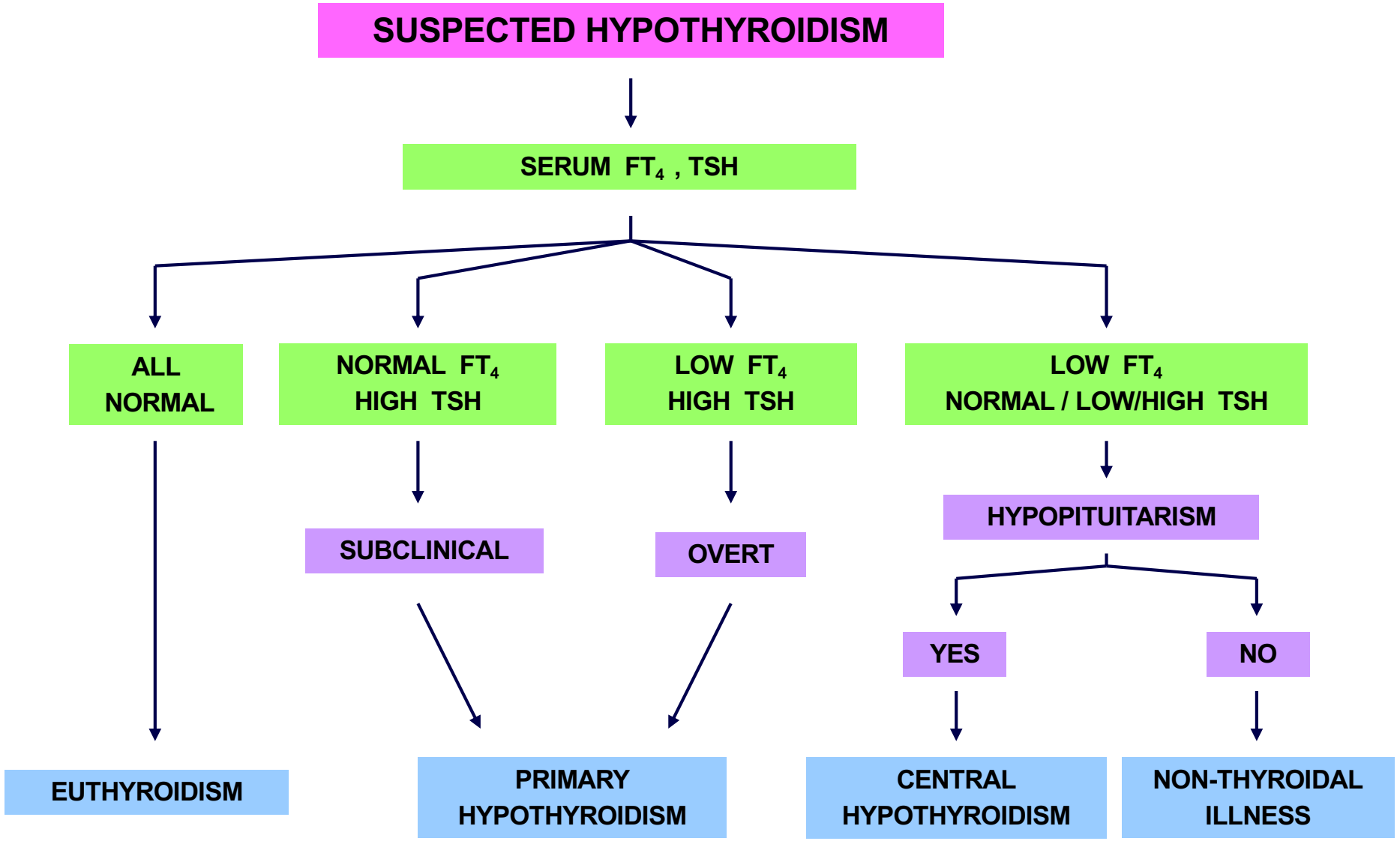
- use FT4 and TSH
- T3 not useful

Interpretation of TFTs

FreeT4	TSH	Condition
↓	↑	Primary hypothyroidism
↓	↓ ↑* ↔	Central hypothyroidism
↔	↑	Subclinical hypothyroidism

*usually not more than 7mIU/L ATA/AACE guideline 2012

DIAGNOSIS OF HYPOTHYROIDISM



HYPOTHYROIDISM
THYROID HORMNE REPLACEMENT

- Use only thyroxine (T4) 60 min before breakfast or 3 hours after dinner; empty stomach
- Starting dose:

  Coronary artery disease: 12.5-25 μg/day (ATA 2014)

  Young age: 1.6 μg/kg/day

  Age> 50 years: 50 ug/day (ATA 2012)

  Subclinical hypothyroid (TSH<10mIU/L: 25-50 ug/day
- 4-6 weeks after start Rx: Dose adjustment (12.5-25 ug/day) (ATA 2014)

HYPOTHYROIDISM
THYROID HORMNE REPLACEMENT (TARGET)

PRIMARY

Target: Keep serum TSH within normal range

SECONDARY

- Target: Keep serum FT4 at mid-normal range to upper limit
- Replace glucocorticoid before thyroxine

CIRCUMSTANCES ASSOCIATED WITH INCREASED THYROXINE REQUIREMENT

- Pregnancy
- Reduced absorption
  - Mucosal diseases
  - Short bowel
  - Sucralfate
  - Aluminum hydroxide
  - Proton pump inhibitors
  - Ferrous sulfate
  - Calcium
  - Cholestyramine (5 hrs apart)
- Increased clearance
  - Rifampicin
  - Carbamazepine
  - Phenytoin

* Need 4 hours apart

Common pitfalls in management of hypothyroidism

1. Diagnose low T3 as hypothyroidism
2. Forget about central hypothyroidism (L-thyroxine Rx may lead to adrenal crisis)
3. Prescribe L-thyroxine after meal
4. Don’t recognize medications that interfere thyroxine absorption and metabolism
5. Follow up FT4 and TSH at inappropriate interval
6. Start high dose L-thyroxine in CAD patients
7. Rely on TSH in central hypothyroidism

THYROID NODULE

SINGLE NODULE

MULTIPLE NODULES

Thyroid nodule

answer 2 questions:

1. hyperfunctioning nodule?
2. malignant nodule?

Hyperfunctioning?

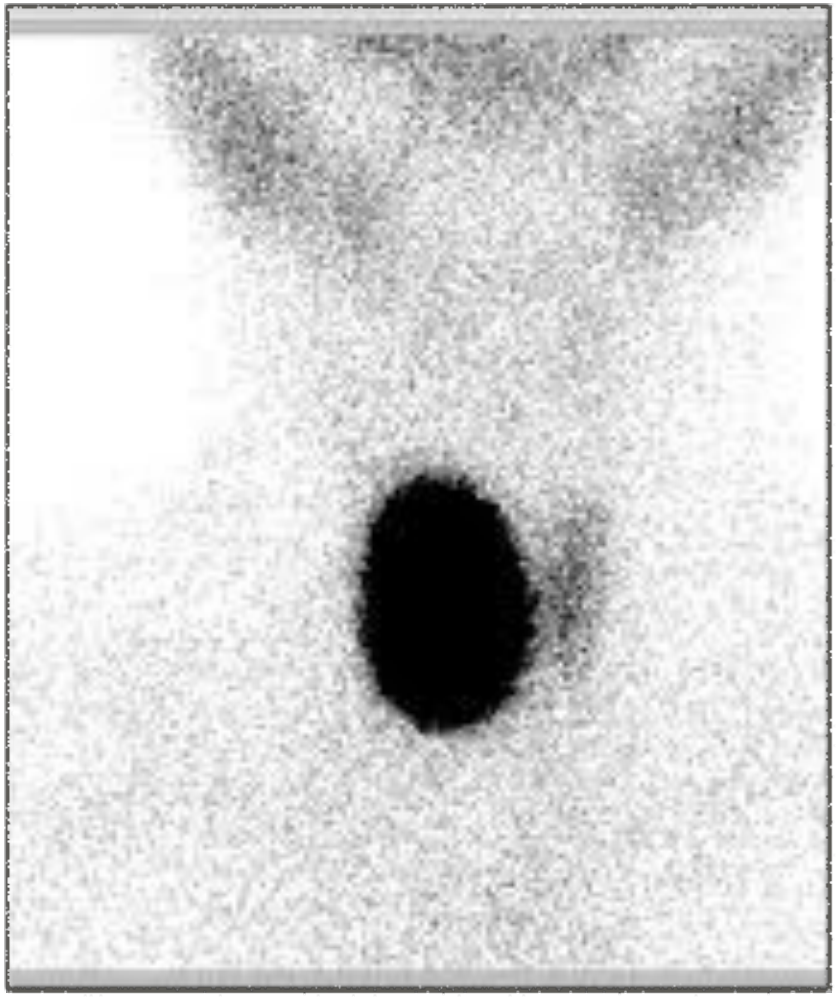
- weight loss despite normal or increased appetite
- heat intolerance
- palpitations/ tremor
- increased perspiration
- new onset AF
- apathetic thyrotoxicosis (weakness and asthenia=loss of strength and energy)

physical examination

- toxic adenoma: usually size more than 3 cms to cause symptom
- unable to palpate other part of thyroid gland (suppress normal gland)
- confirm by thyroid scan

toxic adenoma (scan)

- increase uptake at the nodule
- decrease uptake other part of thyroid gland



Investigation

- TSH in every thyroid nodule patient because of subclinical disease
- If TSH is normal or elevated: FNA
- If TSH normal or elevated: No need to do thyroid scan
- If TSH is suppressed: thyroid scan
- Hyperfunctioning nodule usually not malignant (No need FNA)

THYROID NODULES SPECTRUM

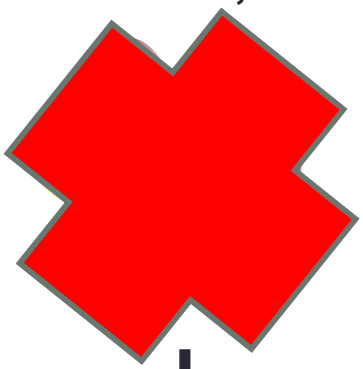
Hot nodule

Cold nodule

SOLITARY

NONFUNCTIONING

TSH N,H

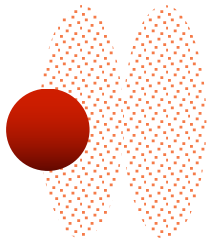


EU/HYPOTHYROIDISM

CANCER ↑

FUNCTIONING

TSH Low



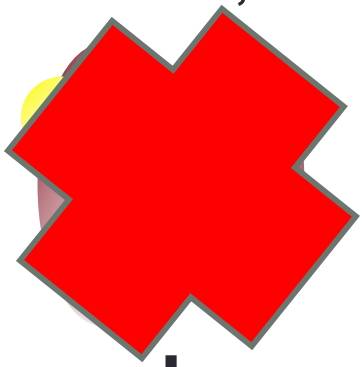
HYPER THYROIDISM

CANCER ↓

MULTINODULAR

NONFUNCTIONING

TSH N,H

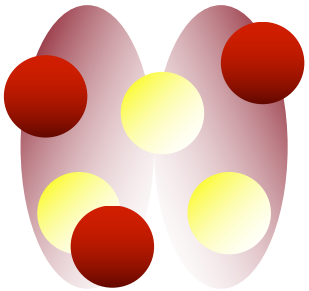


EU/HYPOTHYROIDISM

CANCER ↑

FUNCTIONING

TSH Low



HYPER THYROIDISM

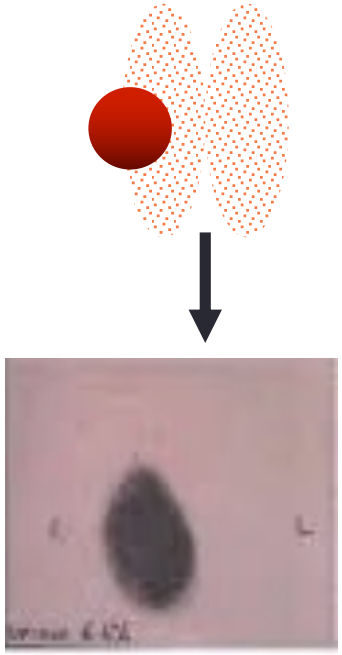
CANCER IN **COLD** ↑

SINGLE THYROID NODULE
SPECTRUM

NONFUNCTIONING

COLD NODULE
CANCER ↑

FUNCTIONING



HOT NODULE
CANCER ↓

2.Malignant?

History:

- History of head and neck RT
- growing nodule
- age <14 or >70 years
- Male
- Family history of MTC or PTC

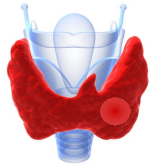
(Ultrasonography)

Physical examination:

- cervical lymphadenopathy
- firm and hard nodule
- fixed nodule
- persistent dysphonia, dysphagia or dyspnea

AACE/ETA guideline 2010

THYROID NODULES
EVALUATION OF MALIGNANCY RISK



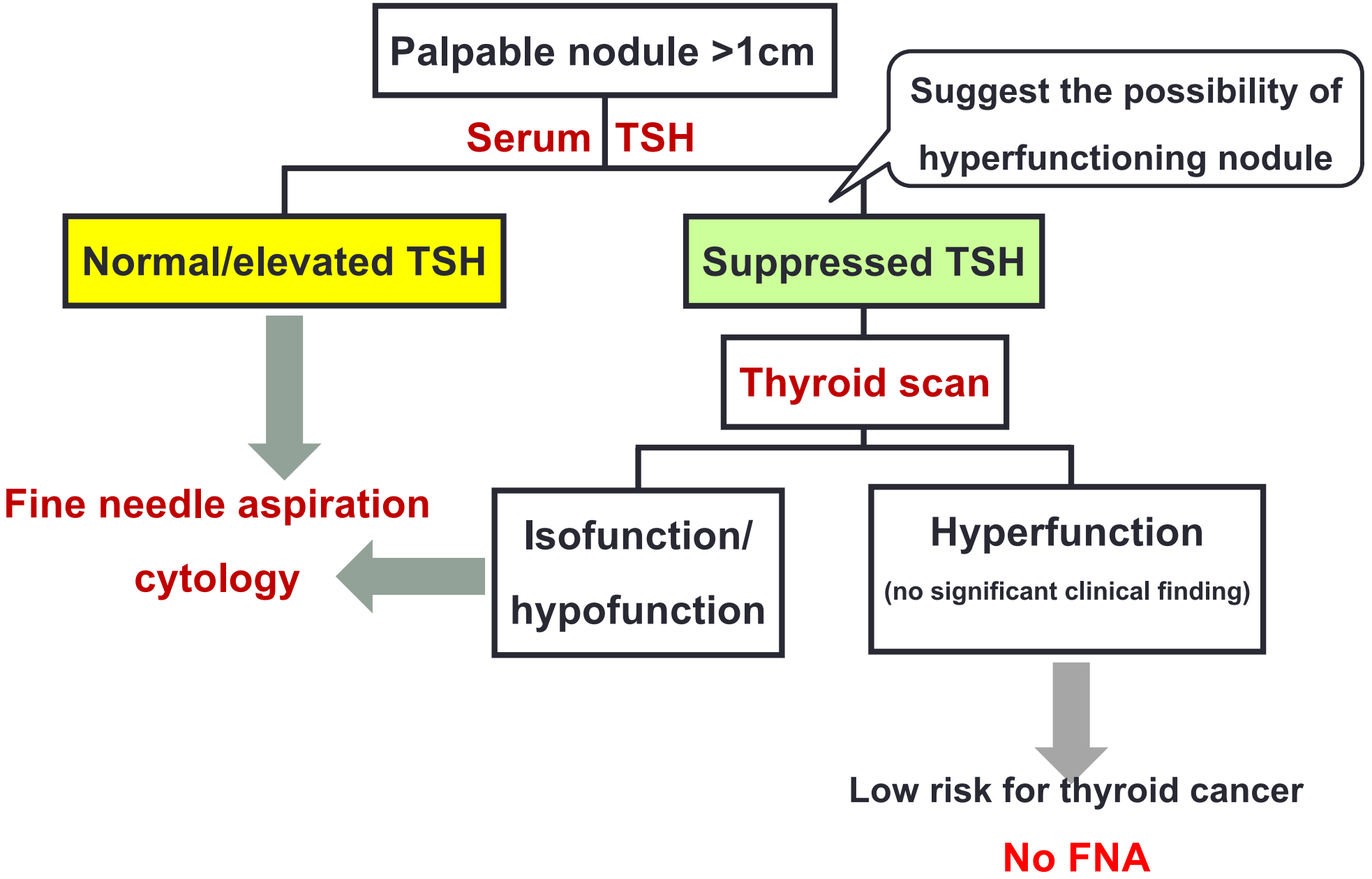
COMMONLY USED METHODS

- Symptoms
- Physical examination
- TSH
- Thyroid scan (^{99m}Tc, ^{131}I) when low TSH
- Ultrasonography
- FNA with cytology: palpation, U/S guided

Risk of malignancy and Management of thyroid nodule

Categories	Risk of malignancy % (Range)	Usual Rx
Non-diagnostic	**13** (5-20)	U/S guided FNA
Benign	**4** (2-7)	Follow up (clinical and U/S)
Atypia of undetermined significance (Nuclear/ Other)	**22**(13-30)	repeat FNA
Follicular neoplasm	**30**(23-34)	Diagnostic lobectomy
suspicious for malignancy	**74**(67-83)	Surgery
Malignant	**97**(97-100)	

Thyroid 2023 *DOI:10.1089/thy.2023.0141*


Palpable nodule >1cm
Serum TSH
Suggest the possibility of hyperfunctioning nodule
Normal/elevated TSH
Suppressed TSH
Thyroid scan
Fine needle aspiration cytology
Isofunction/ hypofunction
Hyperfunction
(no significant clinical finding)
Low risk for thyroid cancer
No FNA

Common pitfalls thyroid nodule management

1. Don’t send TSH at diagnosis
2. Don’t do thyroid scan when suppressed TSH
3. Rely on response after L-thyroxine suppression

   (L-thyroxine may decrease in size of gland (not nodule)

เอกสารอ่านเพิ่มเติม

1. อายุรศาสตร์ทันยุค 2561 เรื่อง Hypothyroidism
2. American thyroid association Guidelines

   2014: Hypothyroidism

   2015: Thyroid nodule

Thyroid function test

Sudarat Piyophirapong, M.D.

Objective

1. สามารถบอกหลักการควบคุมการทำงานของต่อมไร้ท่อในส่วนที่เกี่ยวข้องกับการตรวจทางห้องปฏิบัติการ และปัจจัยที่ต้องระวังในการแปลผล

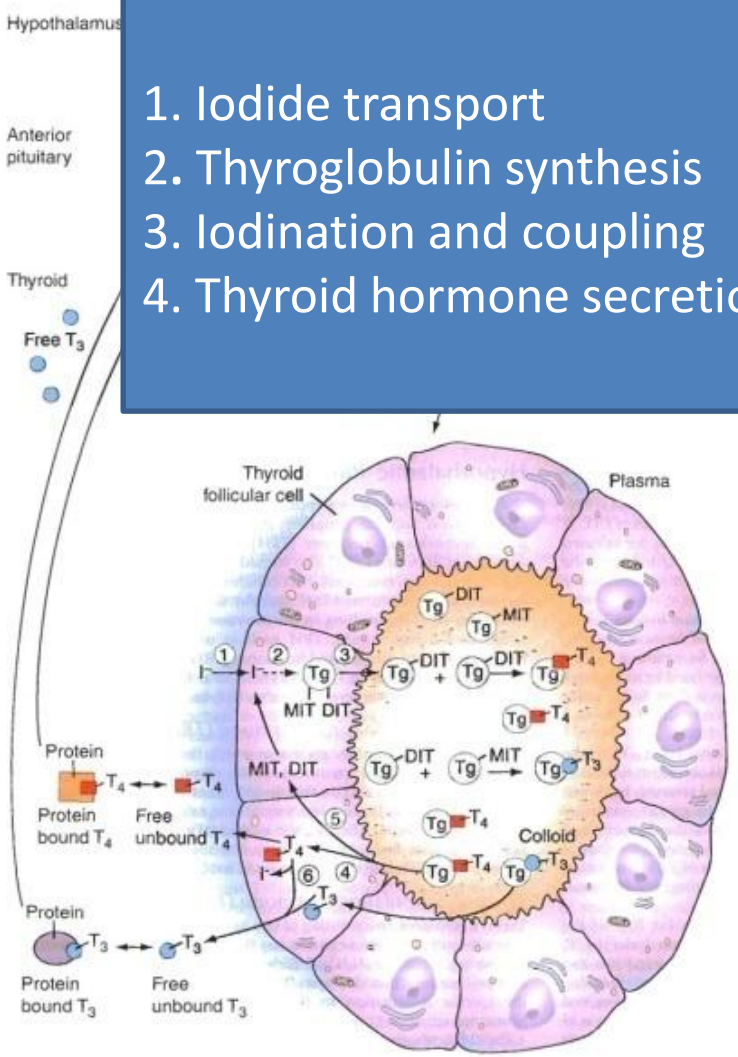
2. ใช้การตรวจทางห้องปฏิบัติการพยาธิวิทยาคลินิกเพื่อช่วยในการตรวจคัดกรองหรือวินิจฉัยภาวะ primary hyperthyroidism และ primary hypothyroidism

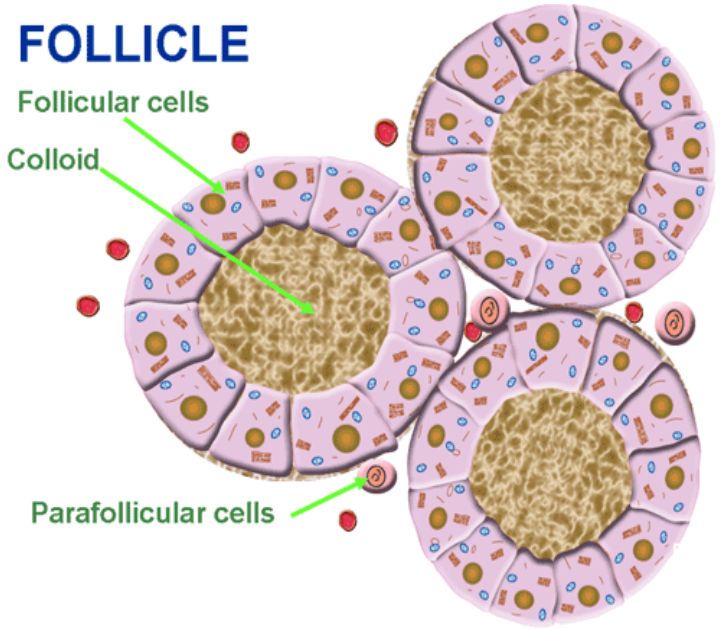
Scope: laboratory investigation

- Thyroid function tests
  - TSH and thyroid hormones assays
- Thyroid autoantibodies

Thyroid hormone synthesis

1. Iodide transport
2. Thyroglobulin synthesis
3. Iodination and coupling
4. Thyroid hormone secretion





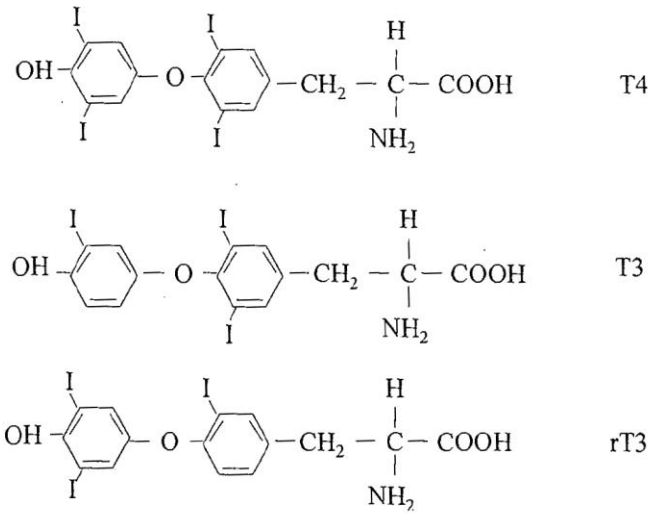
100% of circulating T_4 is of thyroid origin.

20% of T_3 is of thyroid origin;
80% of T_3 is produced enzymatically in nonthyroidal tissues by 5' monodeiodination of T_4.

Figure from *Henry's Clinical Diagnosis and Management by Laboratory Methods, 24th ed., p 397.*

Deiodination of thyroid hormones

- Thyroxine (T_4) contains 4 iodine atoms
- Deiodination leads to production of potent hormone,triiodothyronine(T_3) or inactive hormone,reverse T_3(rT_3)

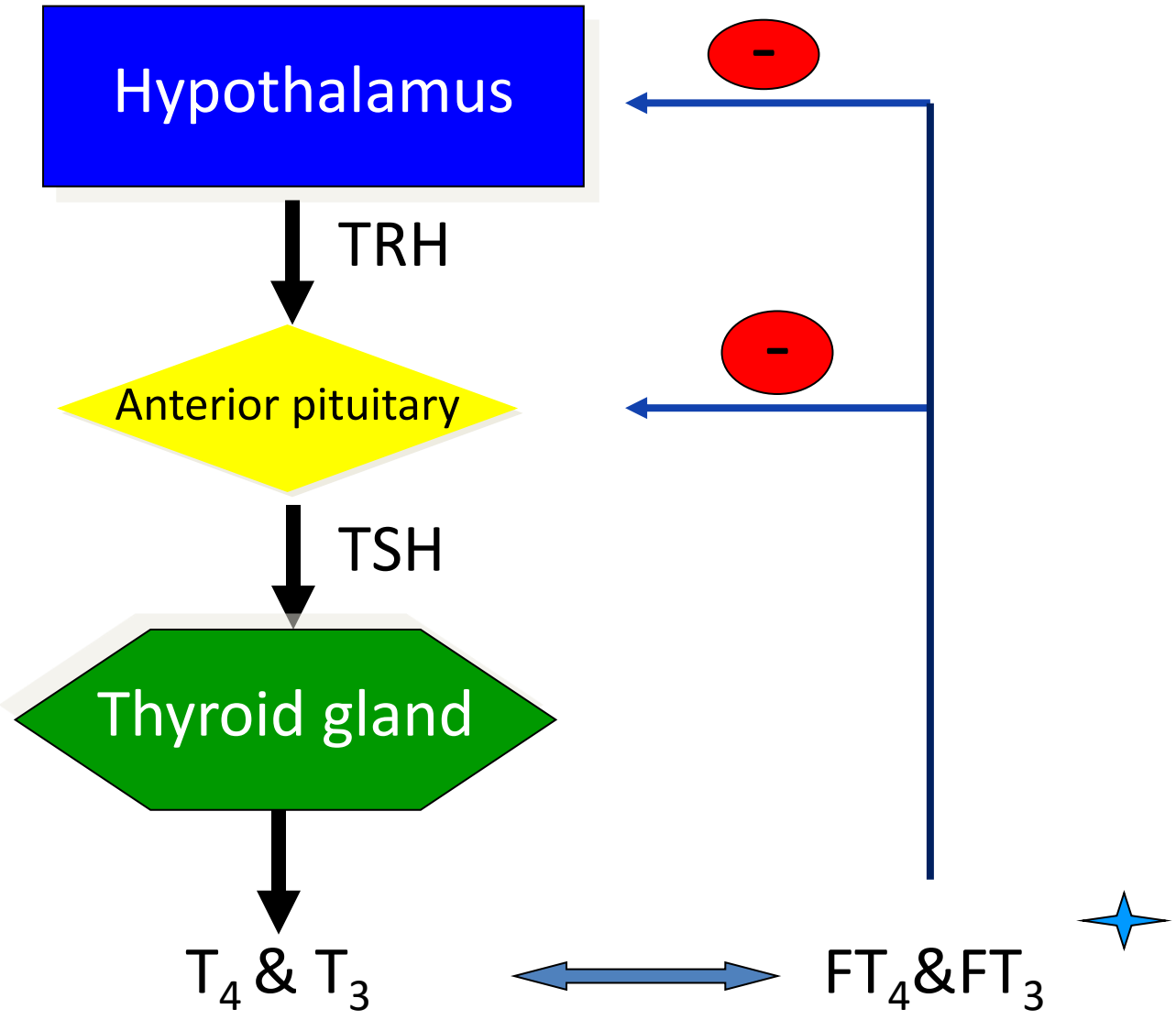


Comparison of T_4 and T_3 in plasma

	Total hormone (µg/dL)	Free hormone Percentage of total	Free hormone (ng/dL)	$T_{1/2}$ in blood (days)
T_4	8	0.03%	~2.24	6.5
T_3	0.15	0.3%	~0.4	1.5

From Harper's illustrated biochemistry, 32nd ed. ,Chapter 41; p 26.

Hypothalamic-pituitary-thyroid axis



TSH Measurement

- First-line assay on screening of thyroid dysfunction
  - TSH will be abnormal months or years earlier than the free thyroid hormones.

- TSH for screening of thyroid dysfunction
  - Hypothalamic-pituitary function is intact and normal.
  - The patient is stable (i.e., the patient had no recent therapy for hyperthyroidism or hypothyroidism)

TSH Measurement

- TSH
  - TSH immunoassays based on assay sensitivity
    - The American Thyroid Association (ATA) recommendations
      - Third-generation TSH assays should be able to quantitate TSH in the 0.010–0.020 mIU/L range on an interassay basis with a coefficient of variation of 20% or less (functional sensitivity)

- TSH results within the reference interval usually exclude thyroid dysfunction
- Typical of frank Graves' thyrotoxicosis
  - Profound TSH suppression (TSH $\leq$0.01 mIU/L)
- Subclinical primary hyperthyroidism and some cases of nonthyroidal illness
  - Mild to moderate TSH suppression

TSH: reference range 0.27-4.2 mIU/L

Nonthyroidal illness or euthyroid sick syndrome

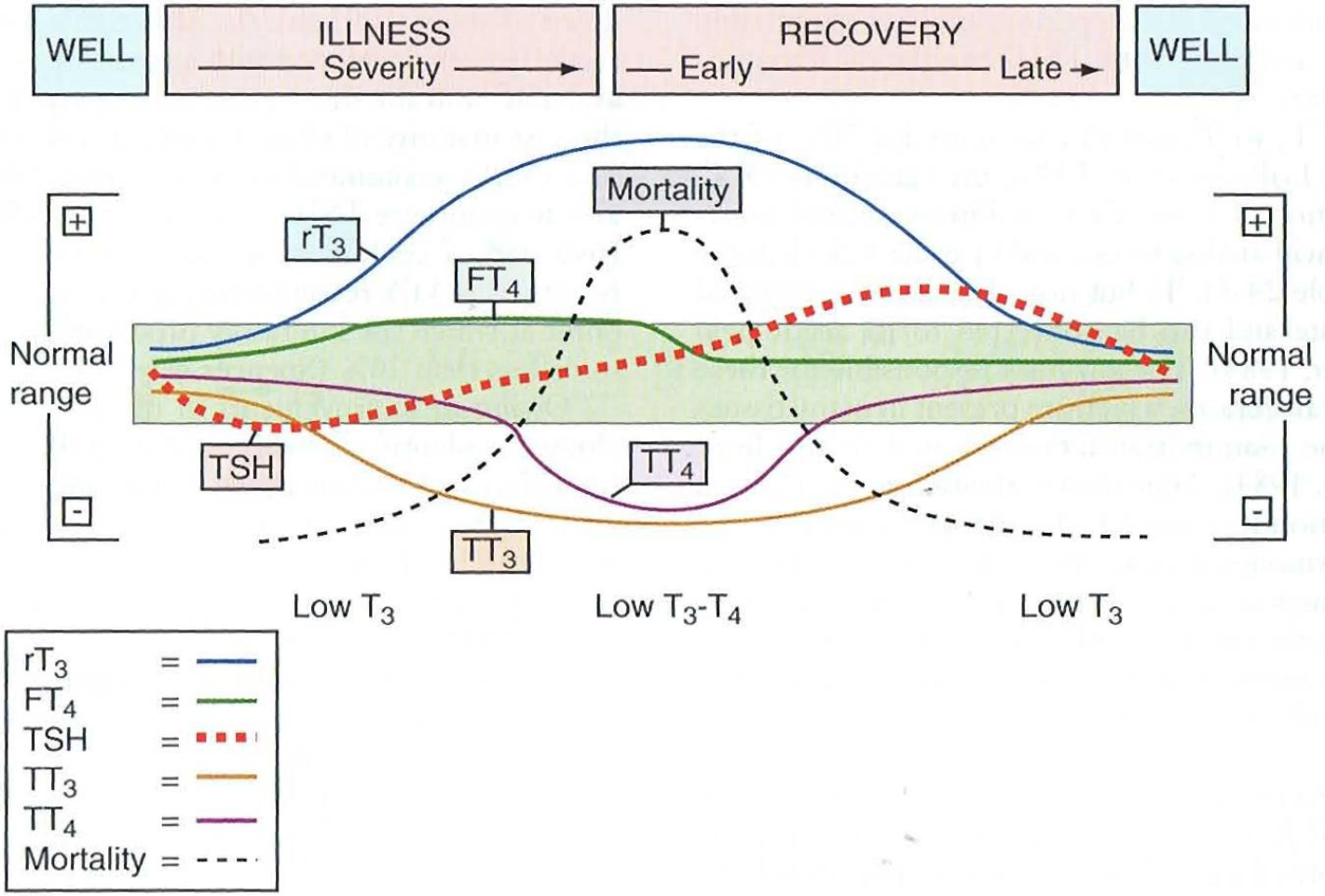


Figure from Henry's Clinical Diagnosis and managenent by laboratory methods,23rd edition , p374

TSH Measurement

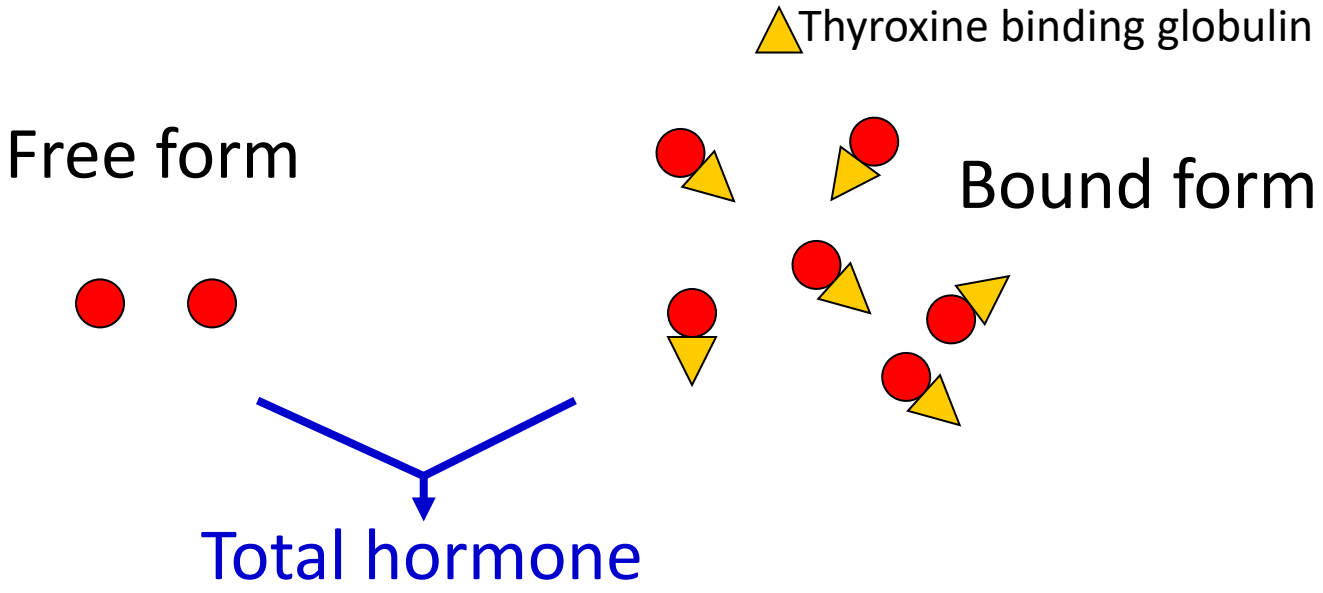
- Monitoring the treatment
  - Replacement therapy by thyroid hormone
    - Normal level of TSH is the goal.
  - Suppressive dose for malignant thyroid disease

Note: Return of TSH to normal is slow.

- during the early treatment of hyperthyroidism → TSH may be prolonged for several months
- after changes in the dose of thyroxine due to hypothyroidism treatment →may be prolonged for first few weeks.

Thyroid Hormone Measurements

- Measurable thyroid hormones
  - Total T_4 (TT_4), free T_4 (FT_4)
  - Total T_3 (TT_3), free T_3 (FT_3)



Considerable points for interpretation of results

– Some hormones have plasma transport proteins

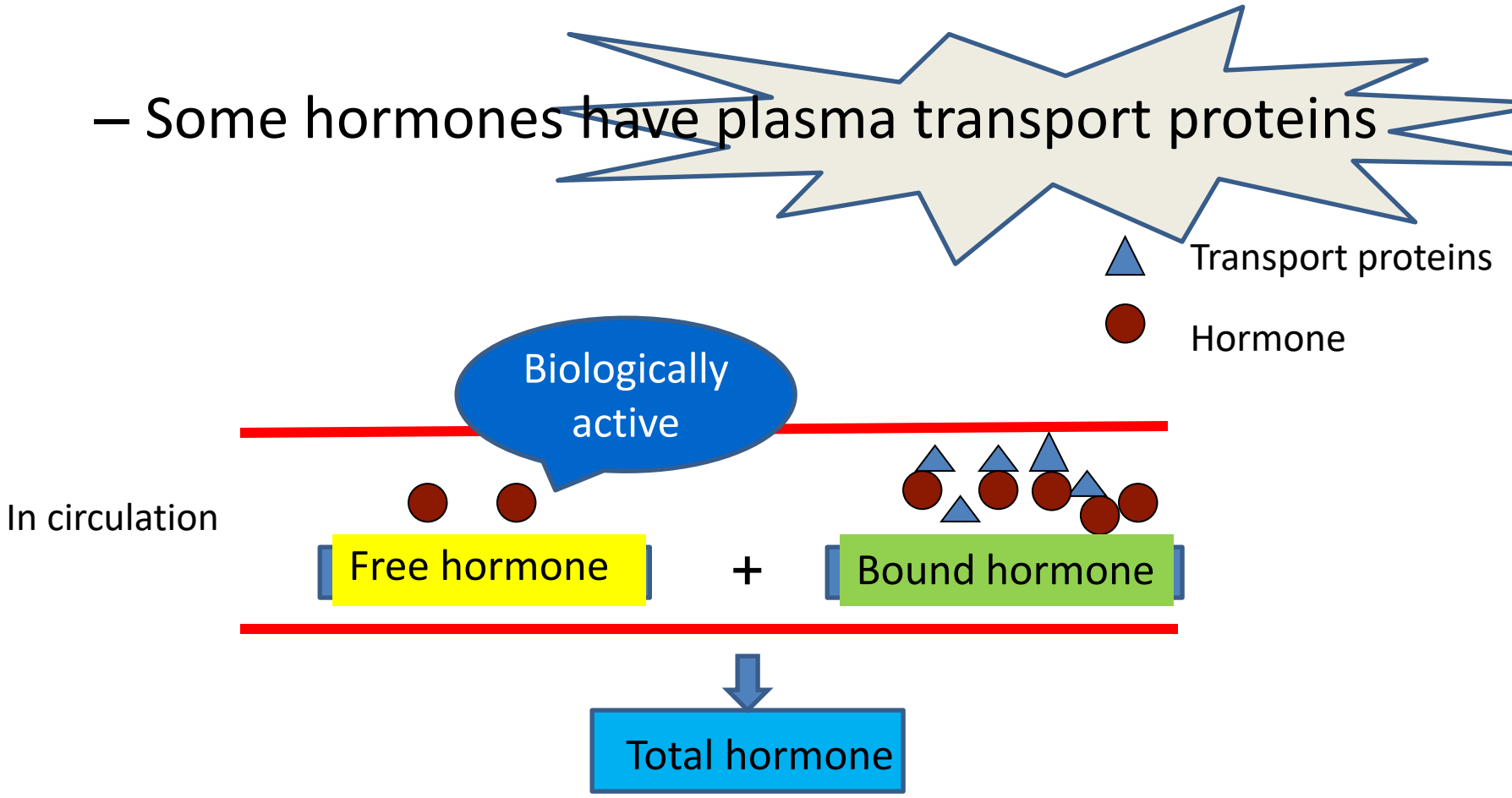


TABLE 24-7

Some Causes of Alterations in Thyroxine-Binding Globulin

Increases	Decreases
Drugs	Drugs
Clofibrate	Androgens
Estrogens, oral contraceptives	Glucocorticoids
5-Fluorouracil	Genetic
Heroin	Complete deficiency
Methadone	Partial deficiency
Genetic	Liver failure
Acute or chronic active hepatitis	Malnutrition
Pregnancy	Nephrotic syndrome
Idiopathic	Idiopathic

From Henry's Clinical Diagnosis and Management by Laboratory Methods, 23rd ed.

Total T_4, Total T_3 measurements

- Total T_4, Total T_3
  - These assays are specific and suffer little interference.
  - Changes in thyroid hormone-binding protein concentrations may affect total T_4 and T_3 concentrations.

  - During pregnancy, estrogen increases →elevation of TBG concentration → increase in total T_4 and T_3 reference range to approximately 1.5 times of nonpregnancy upper reference range by 16 weeks gestation.

Free T_4 measurement

- free T_4 generally correlates with the severity of the hormone excess or deficiency

- Free T_4 is used along with TSH assay to diagnose thyroid dysfunction.

- Free T_4 is more useful than total T_4 especially in the state of altered binding protein amounts.

Free thyroid hormone measurements

- Direct method : physical separation of free T_4 or free T_3 from its binding proteins.
  - The gold standard method is a Equilibrium Dialysis coupled with Tandem Mass Spectrometry (ED/ MS-MS).

- Indirect method : free thyroid hormone measurements are usually measured by immunoassay on automated instrument.

Total T_3 measurements

T3 thyrotoxicosis

- Total T_3 is helpful in the diagnosis of hyperthyroidism, especially in patients with no or minimal elevation of T_4.

- not useful in patients with suspecting hypothyroidism because serum T_3 is normal in 15-30% of hypothyroid patients.

Free T_3 measurement

- About 0.3% 0f T_3 circulates as free T_3.
- In general, free T_3 correlate well with total T_3.
- Test selection can be based on factors such as
  - Bias, precision, technical convenient, turn around time, commercial availability, cost

- *In general, total T_3 is as efficient as free T_3 except in the state of altered binding protein amounts.*

Clinical use of thyroid function test

- Screening for primary thyroid dysfunction
  TSH
- Diagnosis
  hypothyroidism → free T_4 & TSH
  hyperthyroidism → free T_4 ,T_3 & TSH
- Monitoring thyroid hormone therapy
  TSH
- Monitoring treatment of hyperthyroidism
  free T_4,T_3.
  (TSH may remain subnormal for several months. during the early treatment of hyperthyroidism)

Thyroid autoantibodies

- Autoantibodies against constituents of thyroid gland may occur in some normal subjects and in autoimmune thyroid diseases.
  - Anti-thyroid peroxidase antibodies (Anti-TPO)
  - Anti-thyroglobulin antibodies (Anti-Tg)
  - TSH receptor antibodies (TRAbs)

Prevalence of thyroid autoantibodies

Group	TSHr Ab (%)	Anti-Tg (%)	Anti-TPO (%)
General population	0%	5-20%	8-27%
Graves' disease	80-95%	50-70%	50-80%
Hashimoto thyroiditis	10-20%	80-90%	90-100%

Thyroid autoantibodies

– TSH receptor antibody

is not need except diagnosis of hyperthyroidism is unclear such as:

- Unilateral exophthalmos or no exophthalmos
- Apathetic or masked hyperthyroidism in elderly patients
- Predict outcome of Graves' patient treated with drug therapy
- Predict neonatal Graves' disease

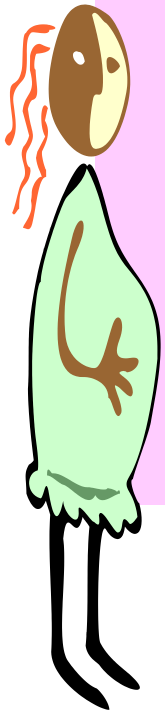
Thyroid antibodies

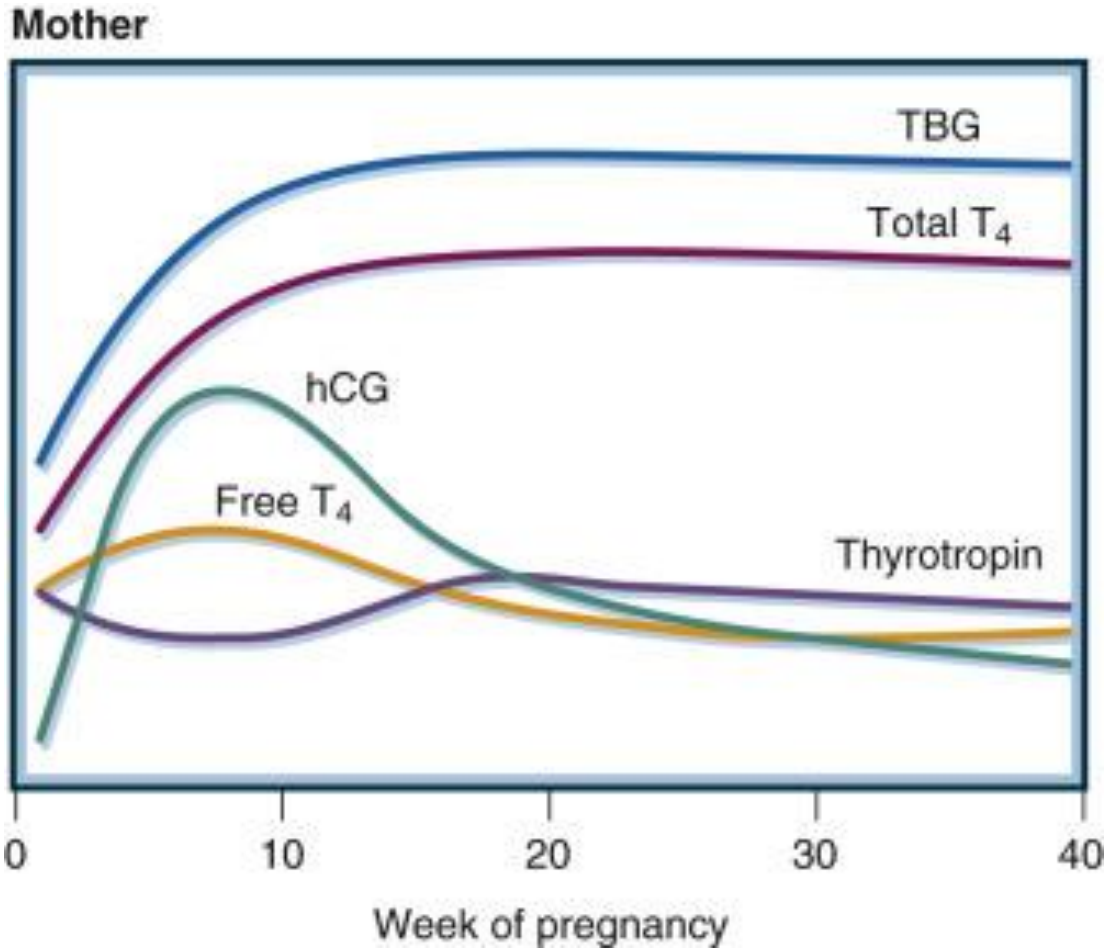
- Thyroid antibodies (anti-TPO, anti-Tg) are often present in autoimmune thyroid diseases

- Anti-thyroglobulin (anti-Tg)
  - Differentiated thyroid cancer , Tg Ab are measured whenever serum Tg is ordered.

Pre-analytical factors

- Age : reference range depend on age
- Pregnancy
  - Increased estrogen : :
    →increased TBG →increased Total T_4 and T_3
  - In 1st trimester of pregnancy
    →increase β subunit-HCG → increase FT_4
    →decreased TSH





From Williams textbook of Endocrinology, 2016 Figure 11-12

Pre-analytical factors

- Medications

Estrogen → TBG elevation → increased Total T_4,T_3

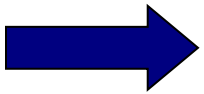
Glucocorticoids, Dopamine → inhibit TSH secretion → decreased TSH

- Drugs that increase TBG : raloxifene, tamoxifen, mitotane, fluorouracil, methadone, heroin
- Drugs that decrease TBG : androgen, chronic glucocorticoid therapy, nicotinic acid

- Medications

Furosemide,
Salicylate

displace thyroid hormone from binding protein



increased
free T_4
free T_3

Deiodination of thyroid hormones

- Impaired $T_4 \rightarrow T_3$ conversion
  - Systemic illness or acute trauma
  - Medications :

    propylthiouracil

    propanolol

    glucocorticoids

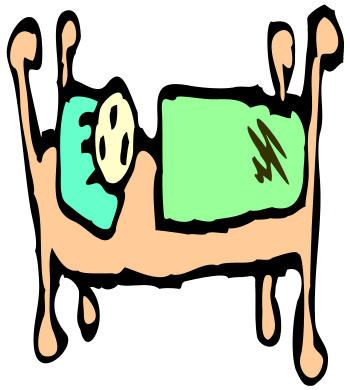
Pre-analytical factors

- Nonthyroidal illness

  – May caused abnormal thyroid function tests

  – **มักพบ TSH ต่ำหรือปกติ T_4 ปกติหรือต่ำ ร่วมกับ T_3 ต่ำ**

  – **ในระยะฟื้นตัว TSH** จะกลับสู่ระดับปกติหรือ สูงกว่าปกติเล็กน้อยแล้วค่อยๆลดสู่ระดับปกติ



Nonthyroidal illness or euthyroid sick syndrome

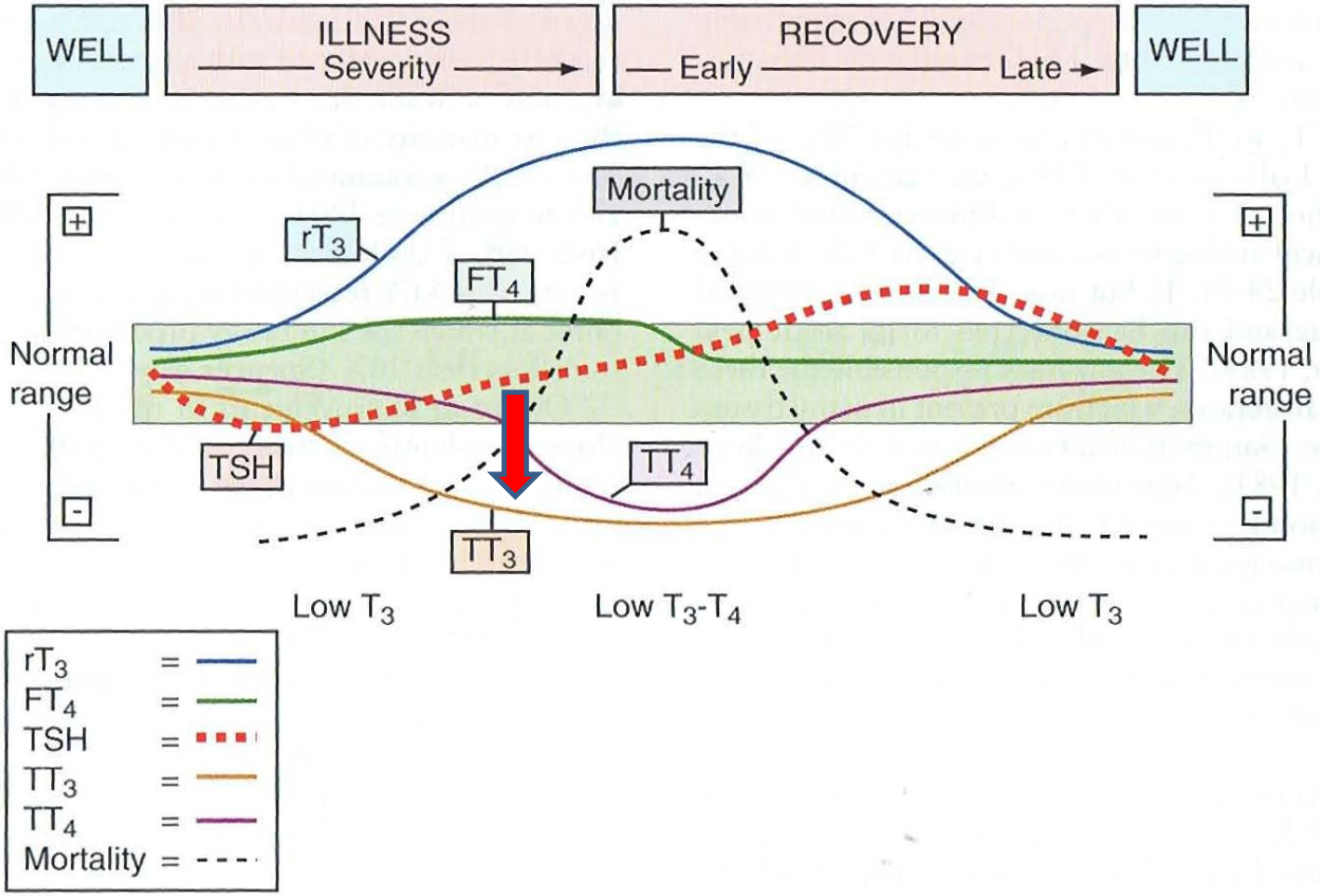


Figure from Henry's Clinical Diagnosis and managenent by laboratory methods,23rd edition , p374

TFT results appear discordant with clinical picture or contradict each other

Analytical interference

- Specimen
  - Heterophile antibodies (errorneous results caused by anti-mouse antibodies)
  - T_4 or T_3 autoantibodies
  - Abnormal variant of binding protein : familial dysalbuminemic hyperthyroxinemia
  - Antibody to streptavidin or ruthenium
  - Biotin

Diagnosis of endocrine disease

Clinical evaluation ★

+

Use of laboratory tests for diagnosis & management

Do not use only laboratory result interpretation

for

diagnosis

RATIONAL LAB USE

นึกถึงพยาธิวิทยาคลินิก

TSH

- First-line assay on screening of thyroid dysfunction
- Monitoring and adjustment of therapy for primary hypothyroidism
- Monitoring TSH suppression therapy for thyroid cancer

RATIONAL LAB USE

นึกถึงพยาธิวิทยาคลินิก

TSH inappropriate use

- Within several weeks of a change in thyroxine dose
- During early stages (several months) of treatment of hyperthyroidism

RATIONAL LAB USE

นึกถึงพยาธิวิทยาคลินิก

- Free T_4 is used along with TSH assay to diagnose thyroid dysfunction.
- T_3 is helpful in the diagnosis of hyperthyroidism, especially in patients with no elevation of T_4.
- T_3 is not useful in diagnose patients with suspecting hypothyroidism

RATIONAL LAB USE

นึกถึงพยาธิวิทยาคลินิก

TSH receptor antibodies

is not need to make diagnosis of Graves' disease **except diagnosis of hyperthyroidism is unclear**. Its primary use is in pregnant woman with a history of Graves' disease to **predict neonatal Graves' disease**