มหาวิทยาลัยมหิดล
คณะแพทยศาสตร์ศิริราชพยาบาล

SIENDO
Faculty of Medicine Siriraj Hospital

Diseases of Thyroid Gland

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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

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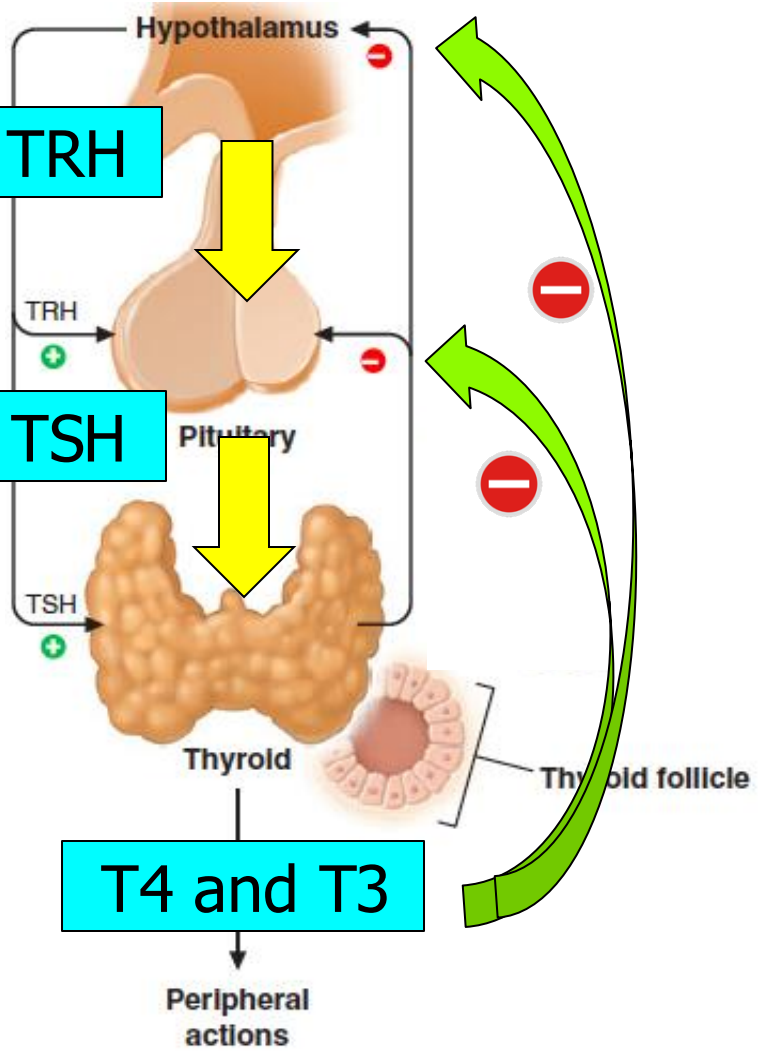
Hypothalamic-Pituitary-Thyroid Axis

Thyrotropin-releasing hormone

TRH

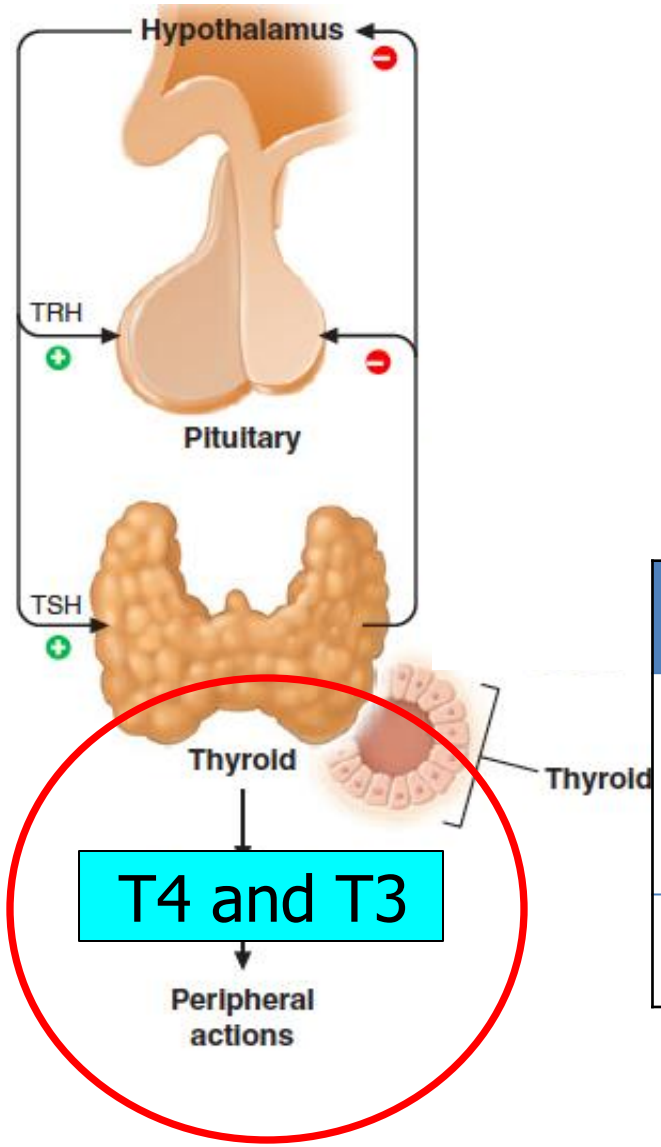
Thyroid stimulating hormone

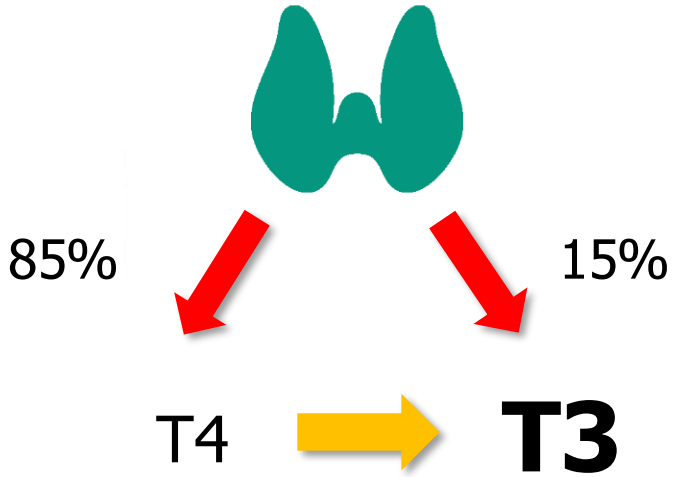
TSH



Harrison Textbook of Endocrinology, 2nd Edition

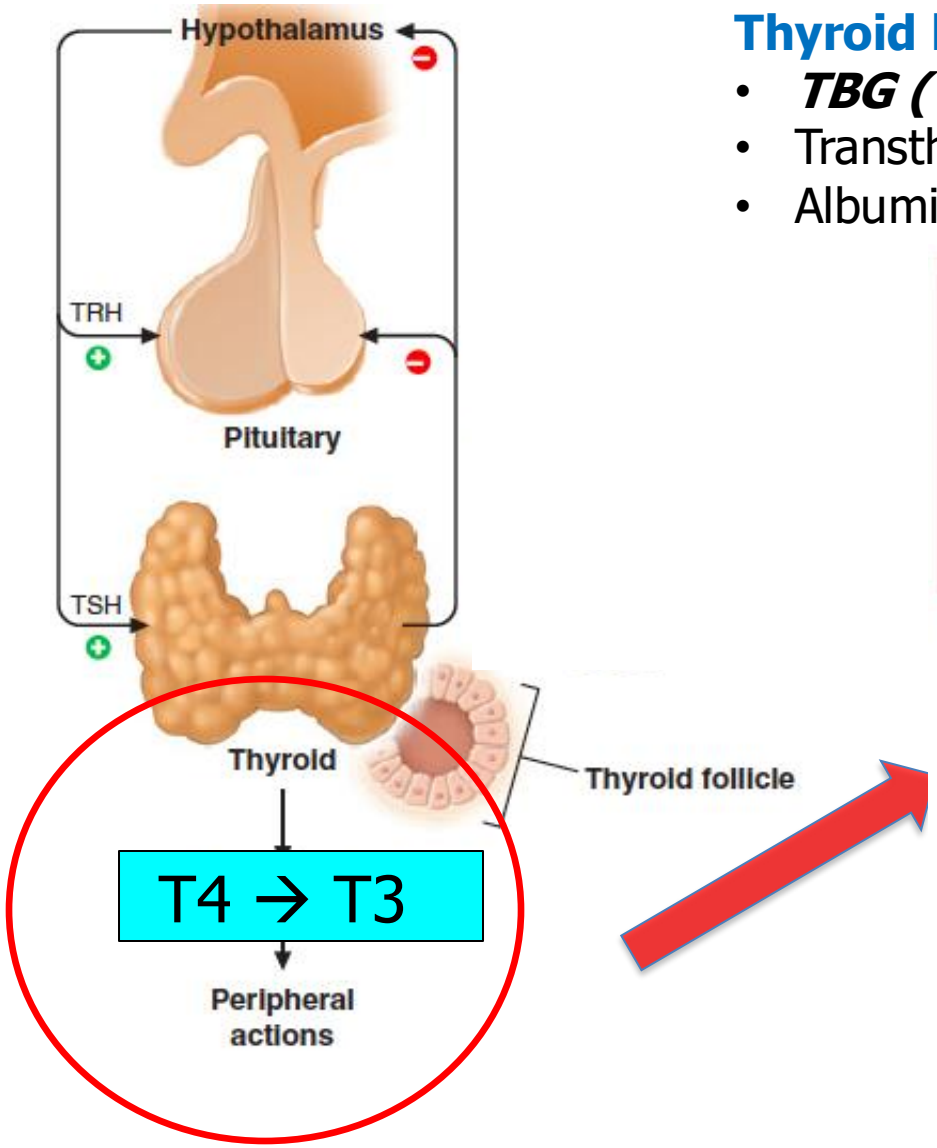
Thyroid Hormone Synthesis





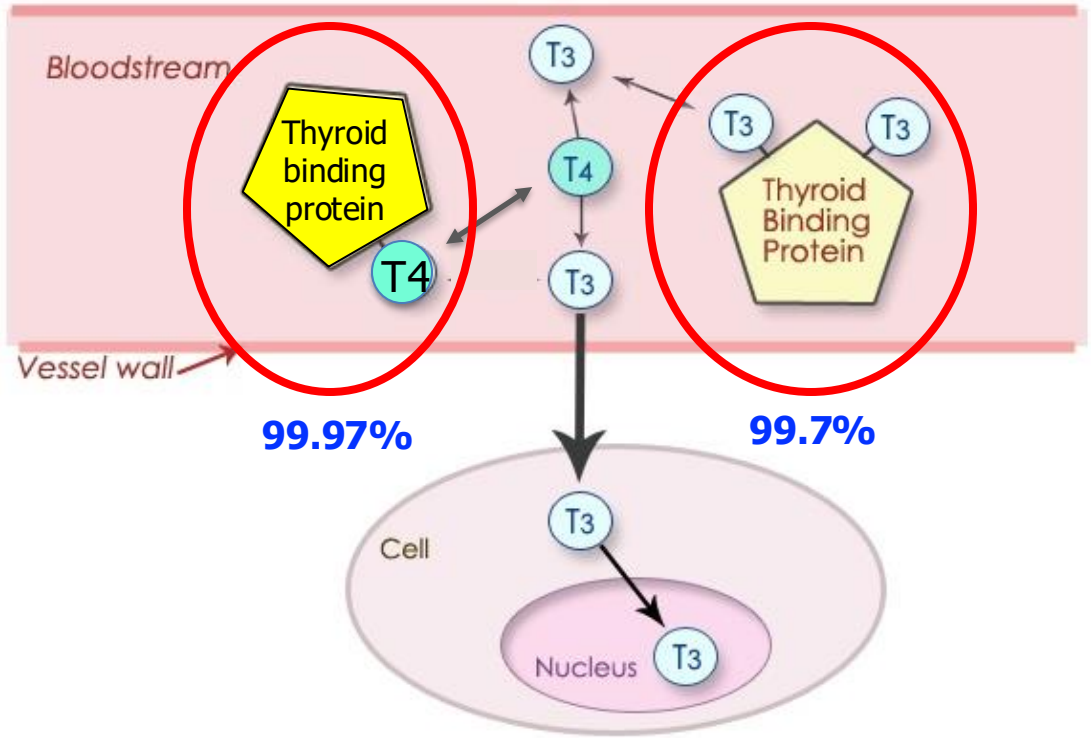
	T4	T3
Source	Thyroid gland	• 15% Thyroid gland • 85% peripheral conversion of T4 → T3
Half life	7 days	1 day

Thyroid Hormone Transport



Thyroid hormone binding proteins

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



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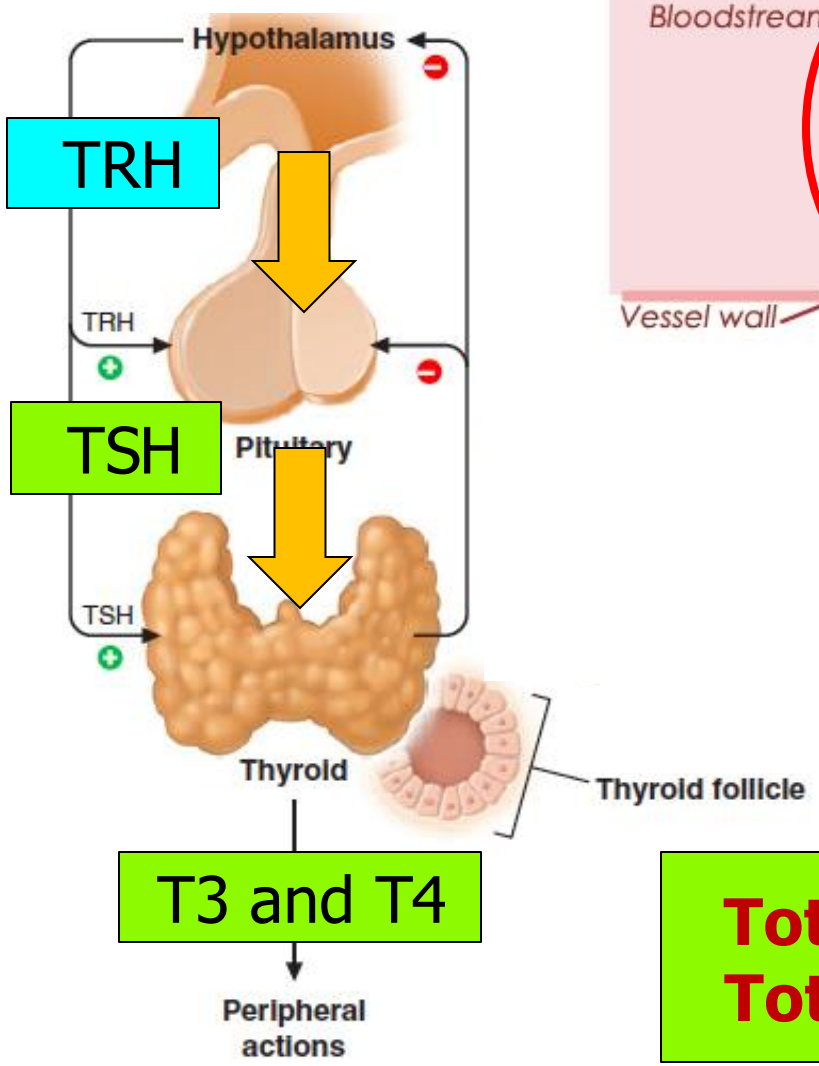
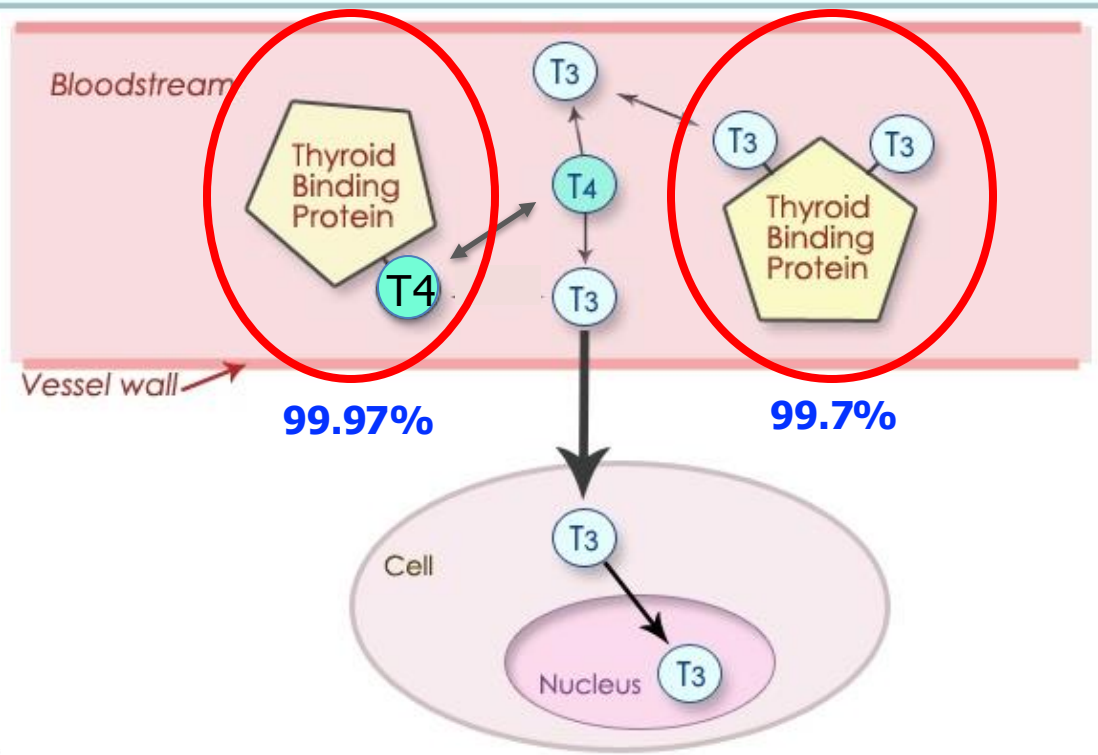
Evaluation of thyroid function





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

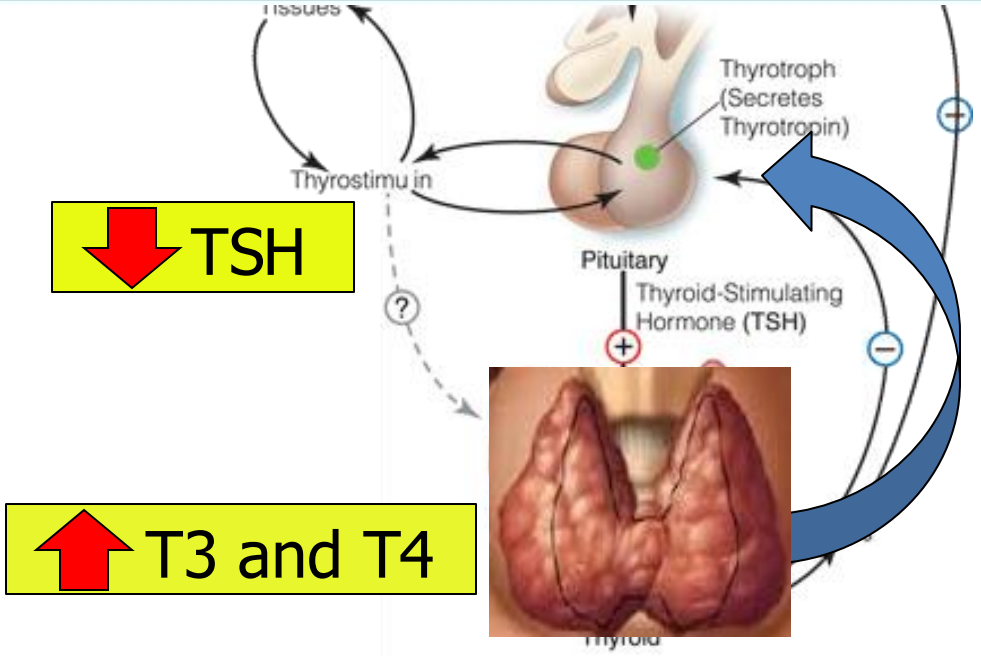
THBP: Thyroid hormone binding proteins

Evaluation of thyroid function

Tests and interpretation

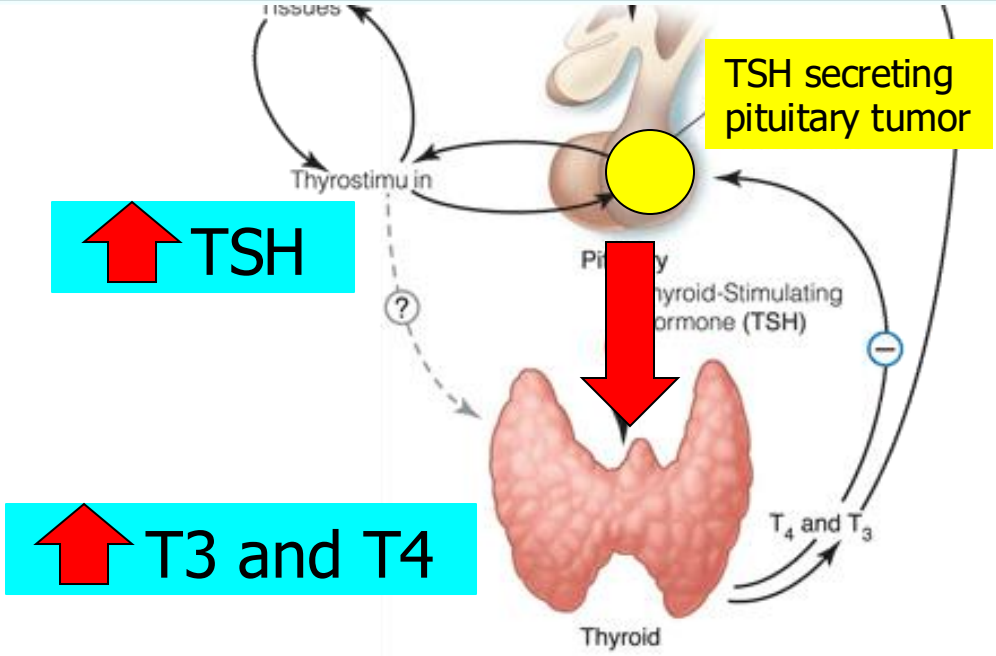
- TSH
- T4 (free T4, total T4)
- T3 (free T3, total T3)

Evaluation of thyroid function



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

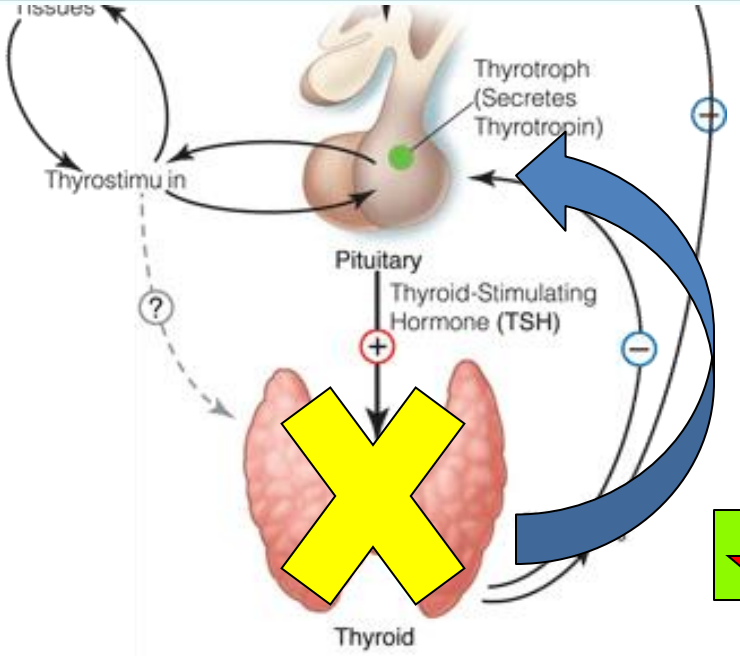
Evaluation of thyroid function



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

Inappropriately normal TSH

Evaluation of thyroid function

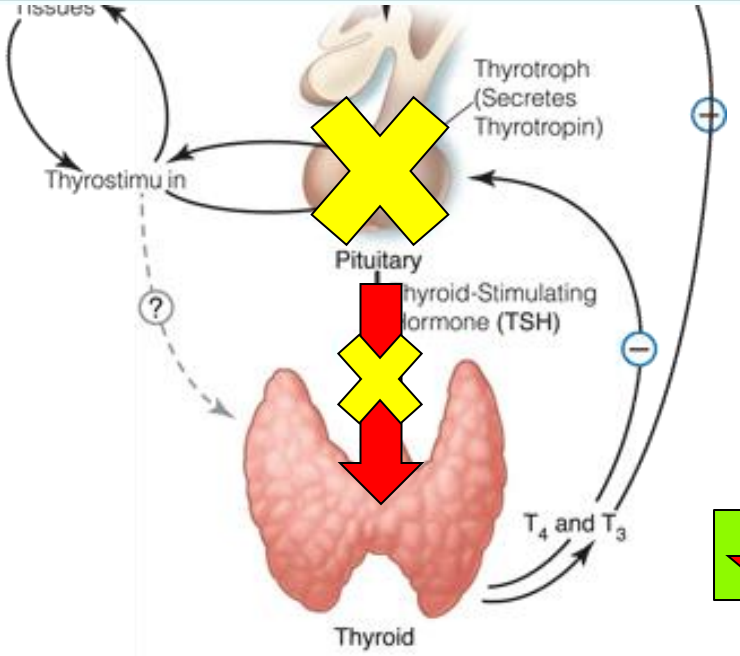


TSH ↑

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

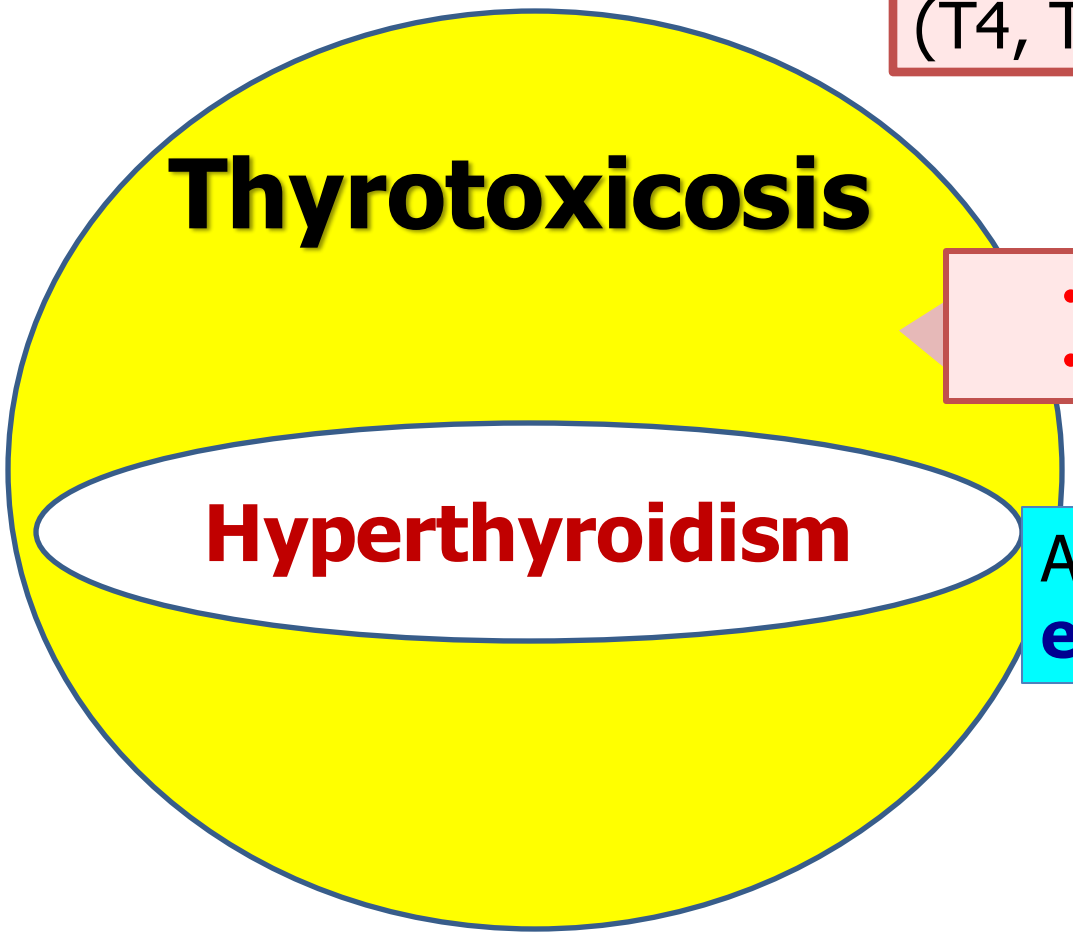
⇔ TSH
⇔ FT4, FT3
↓ T4, T3

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
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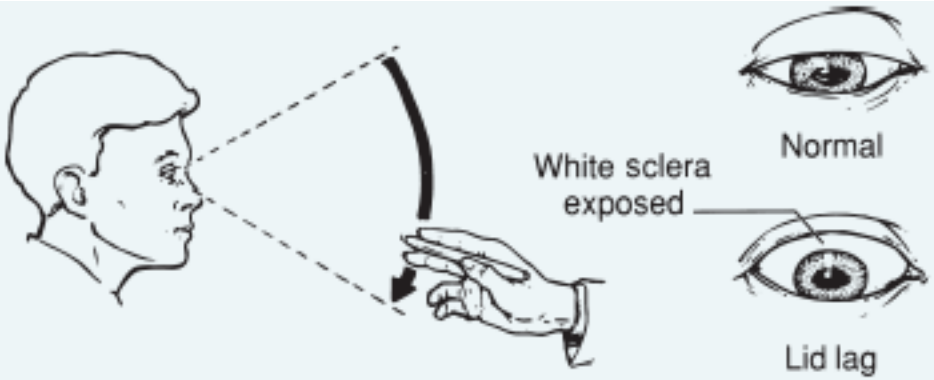
  - Lid lag



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?

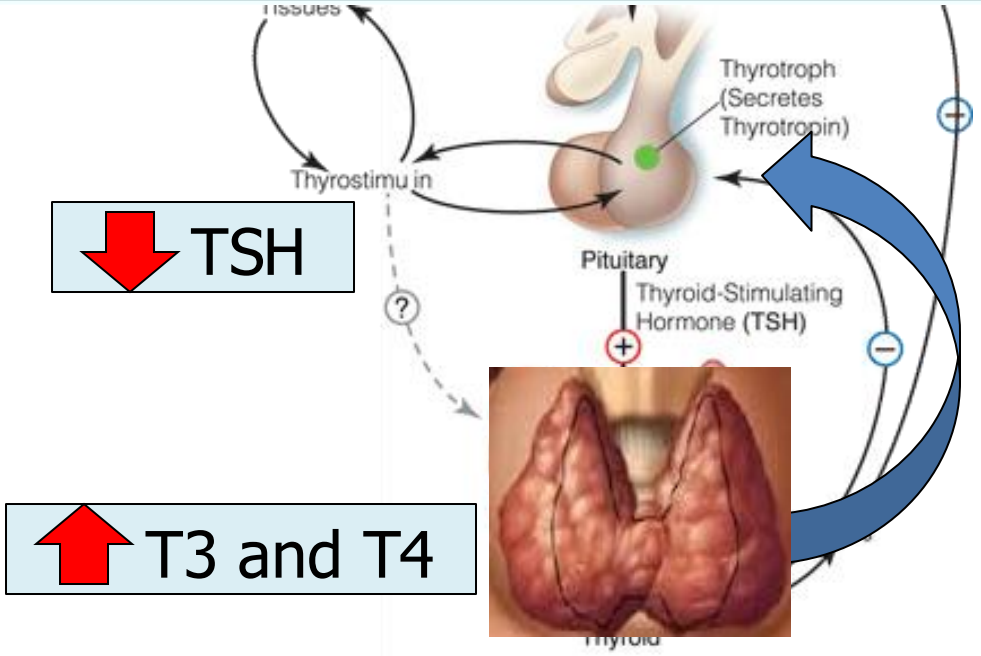
A. TSH only

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, ..."

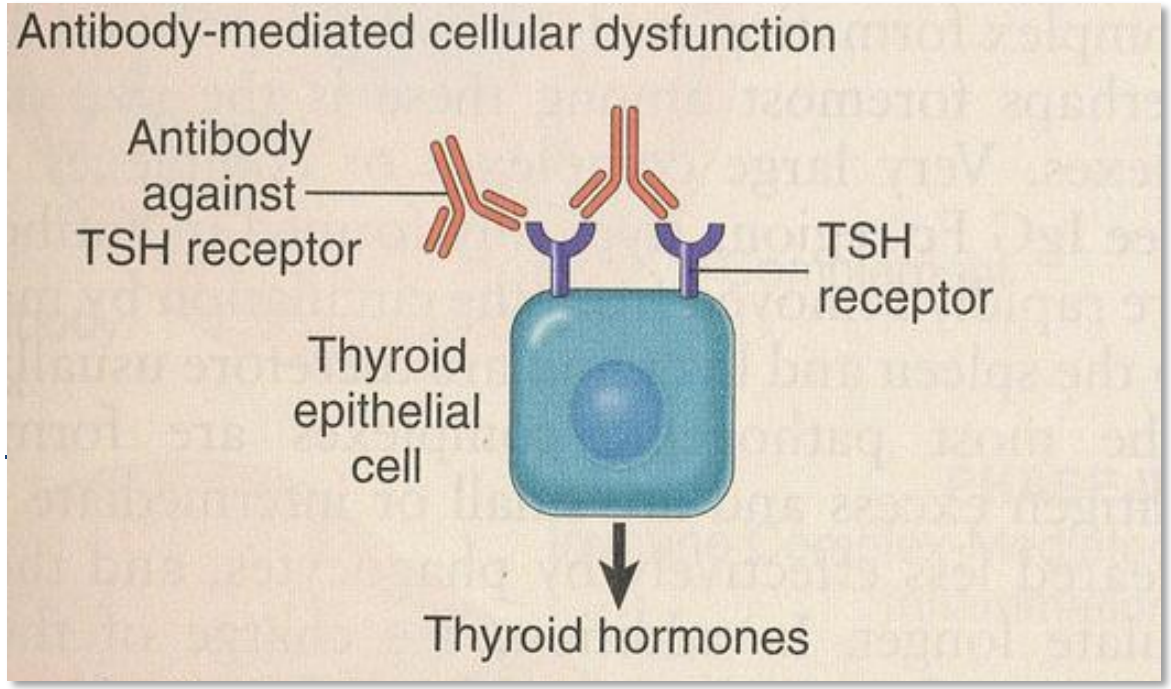
De Groot Endocrinology: Adult and pediatric, 7th edition

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

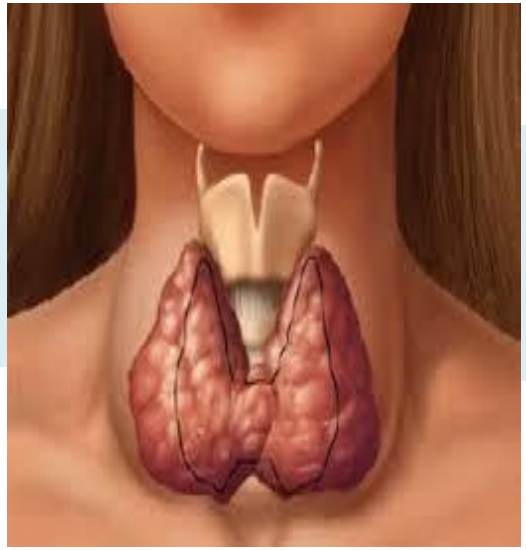
- Symptoms and signs of thyrotoxicosis
- Specific (pathognomonic) signs of Graves' disease

Investigation

- Lab
- Others (if needed)

Graves' disease

Graves' Ophthalmopathy (orbitopathy)



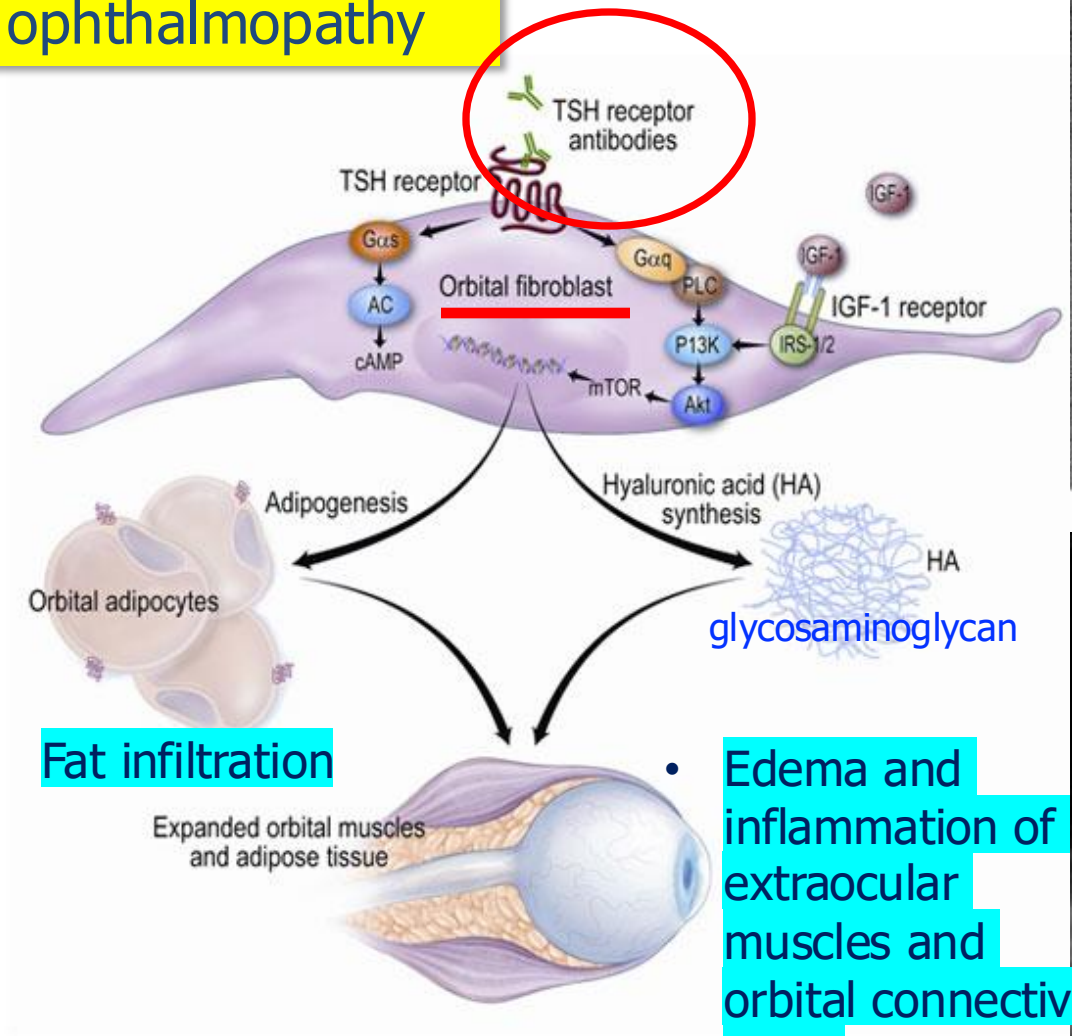
Thyroid bruit

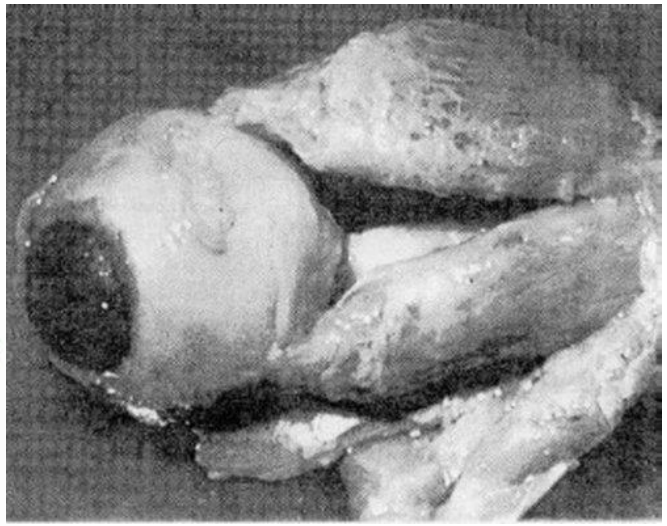
Graves' Dermopathy (pretibial myxedema)

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

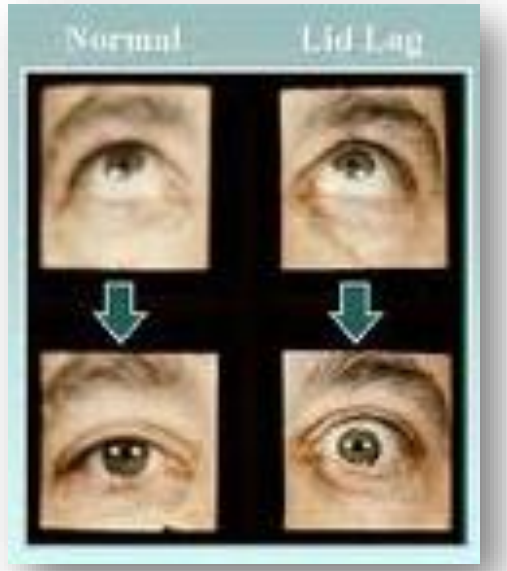
Graves ophthalmopathy

Exophthalmos

Pathognomonic signs of Graves' disease

Sympathetic overactivity

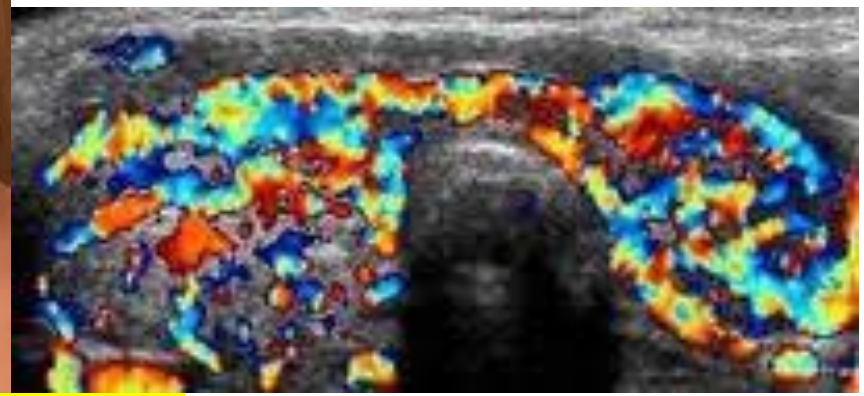
Lid retraction



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

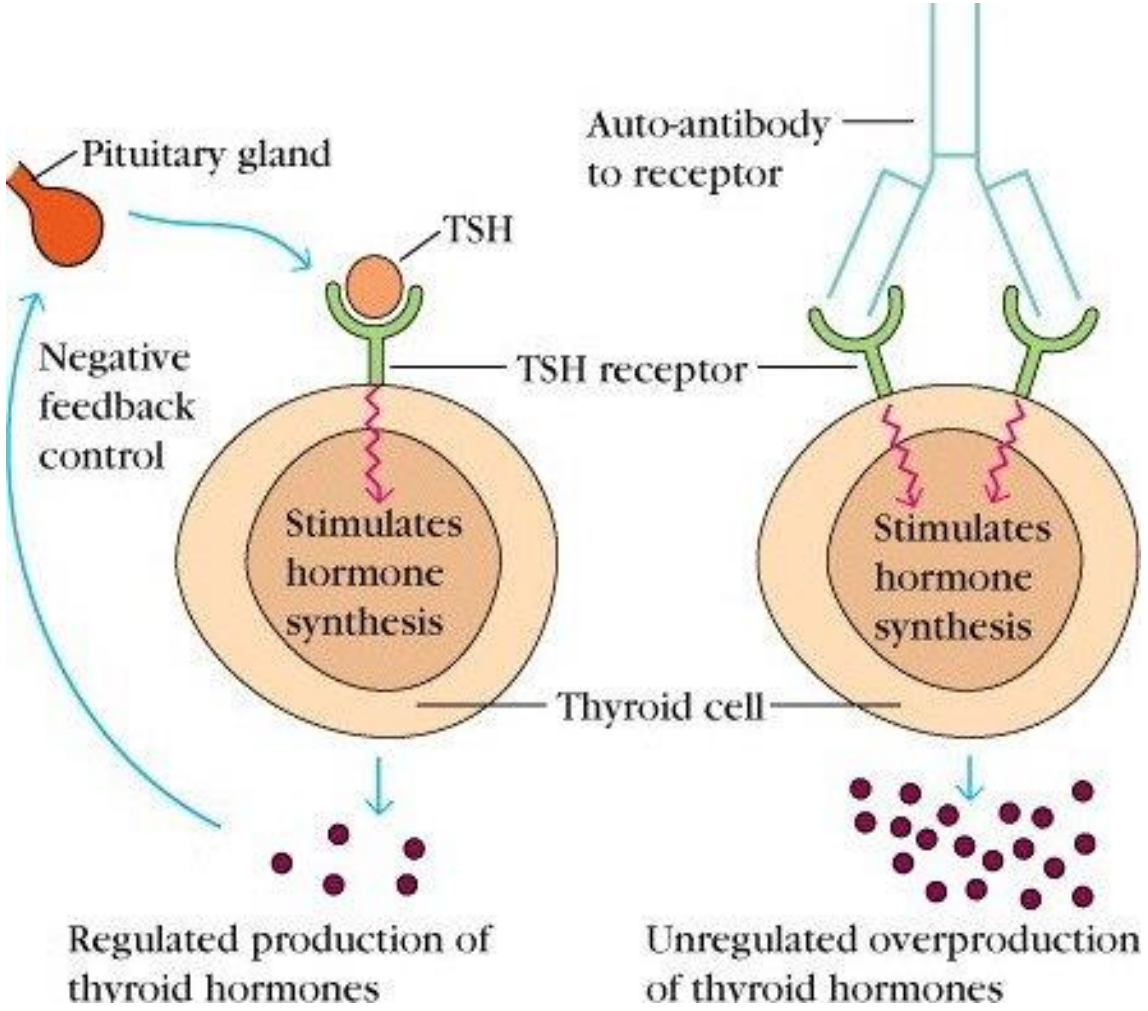
- Refers to a form of clubbing found in <1% of patients with Graves' disease
- It is so strongly associated with thyroid dermopathy

Graves' disease

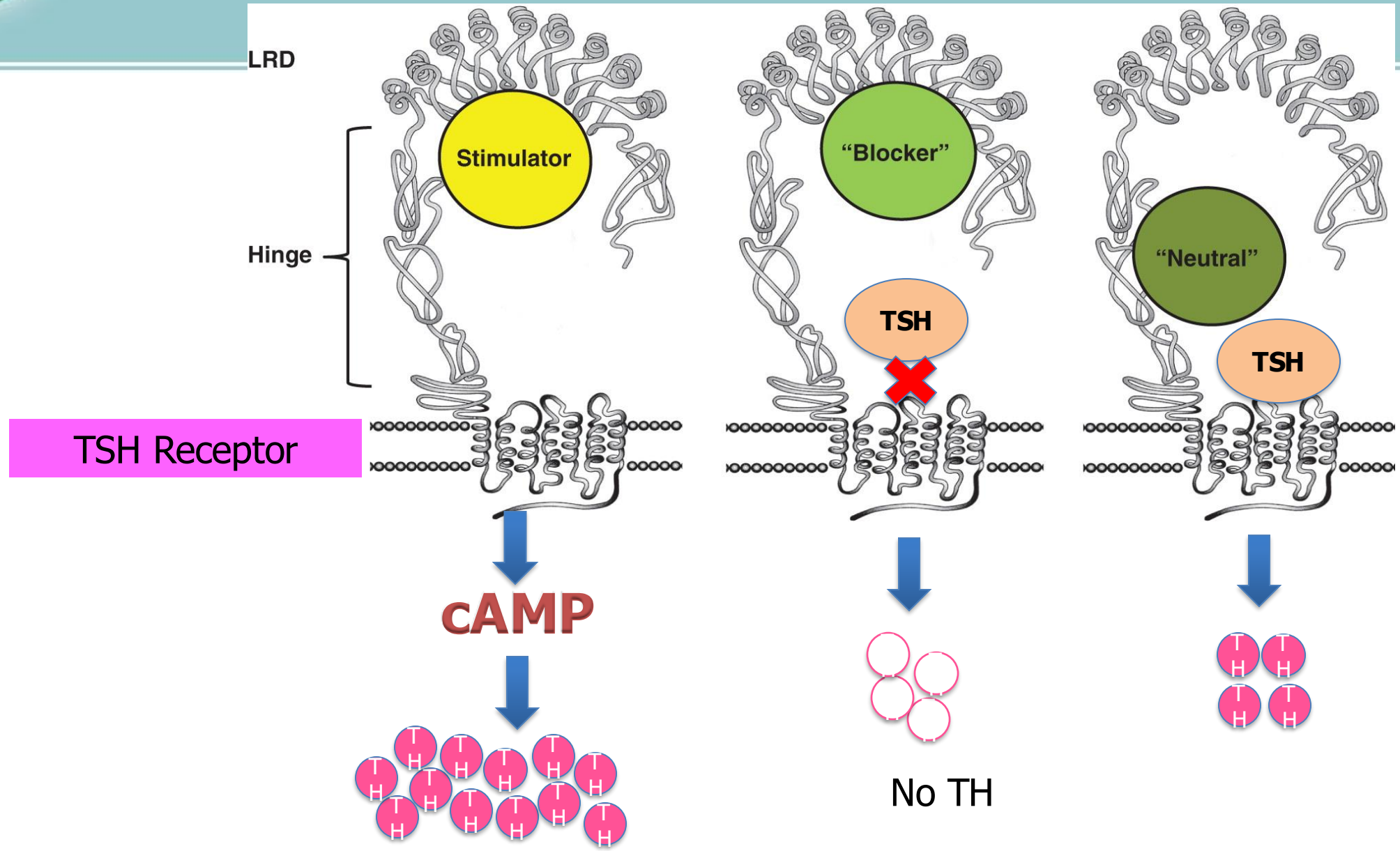
Labs

- ↓ 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

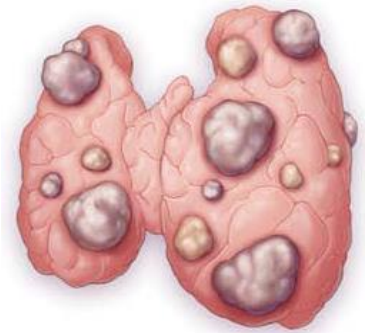
- Sensitivity for GD = 96-97%
- Specificity for GD = 99%

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

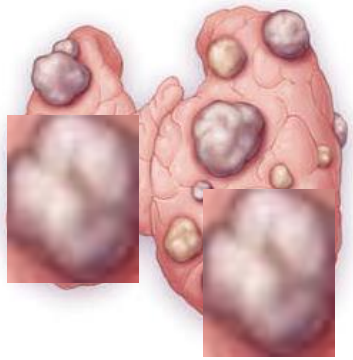
Toxic adenoma
Toxic multinodular goiter

"Not an autoimmune process"

Toxic MNG

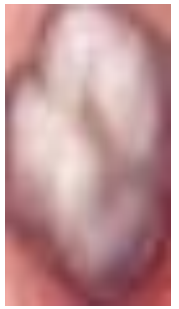


TSH-R mutation →



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

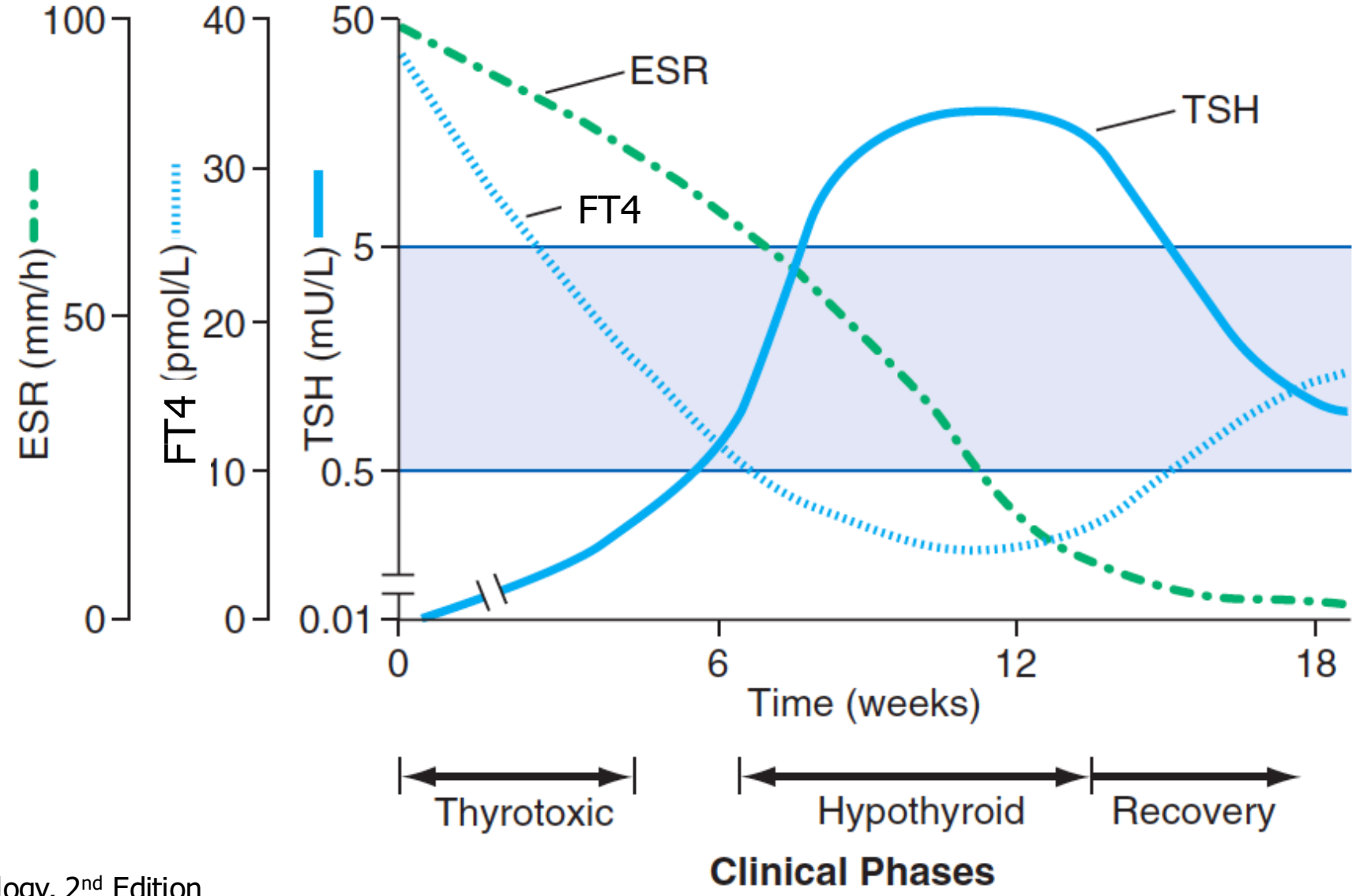
Inflammation or destruction of thyroid gland → Release of preformed thyroid hormone

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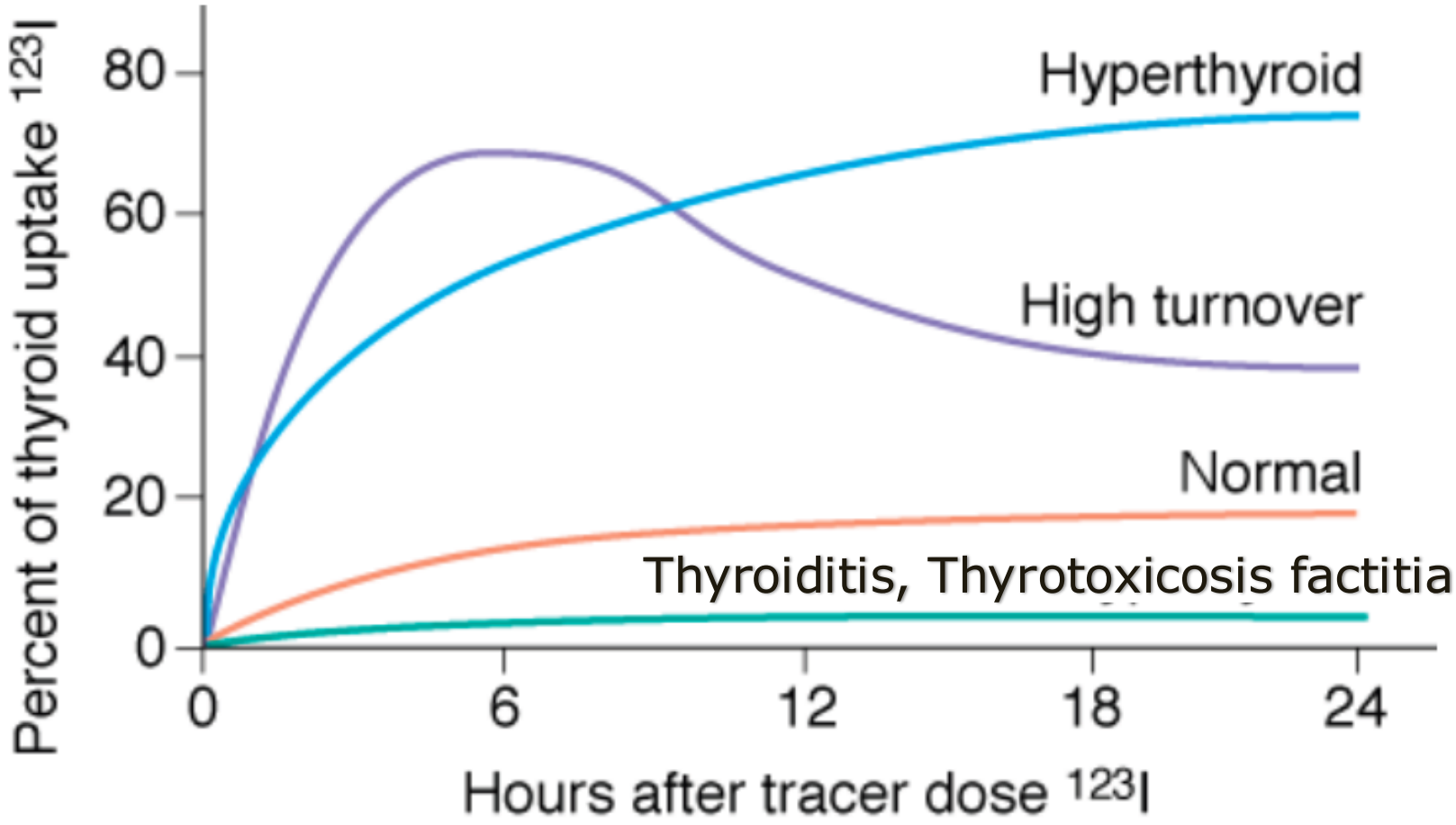
With hyperthyroidism			
Graves' disease	> 3 months	Diffuse enlargement (20% absent)	Thyroid bruits Ophthalmopathy, dermopathy, acropachy
Toxic MNG	> 3 months	Nodules	
Toxic adenoma	> 3 months	Single nodule (>3 cm)	Contralateral thyroid lobe – not palpable
Without hyperthyroidism			
Thyroiditis	< 3 months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

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

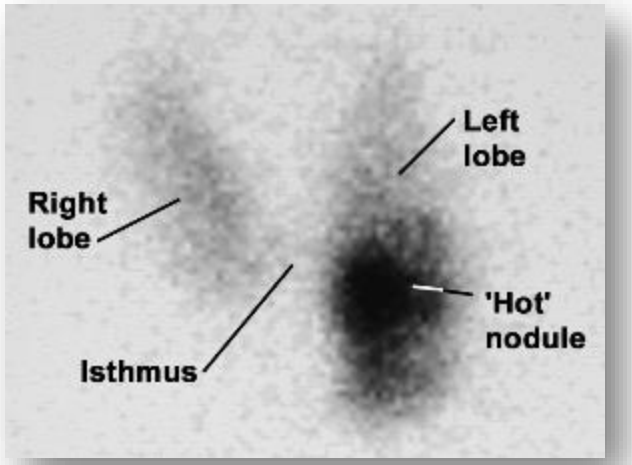
Radioactive iodine (RAI) uptake

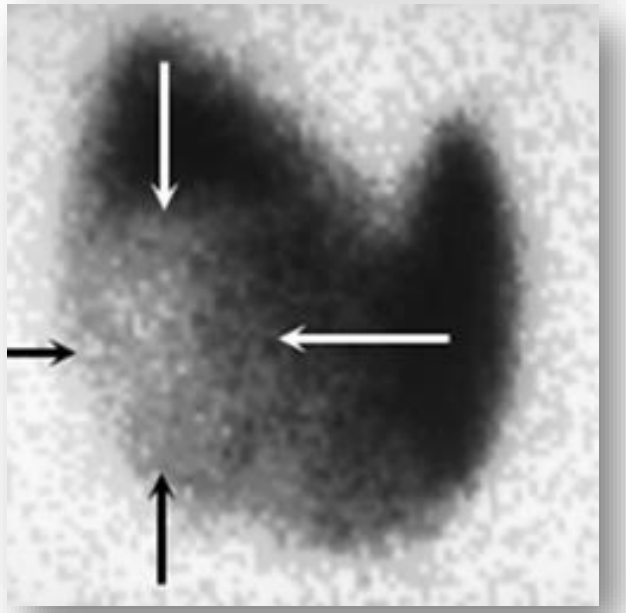


Source: Gardner DG, Shoback D: *Greenspan's Basic & Clinical Endocrinology, 9th Edition:* www.accessmedicine.com

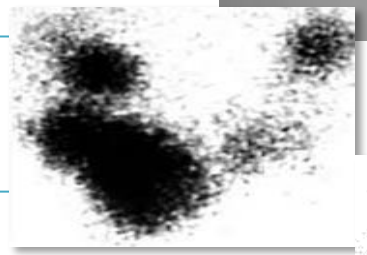
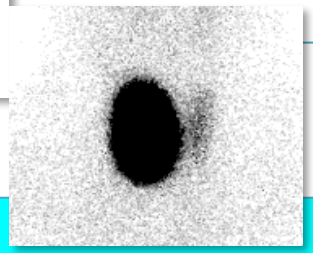
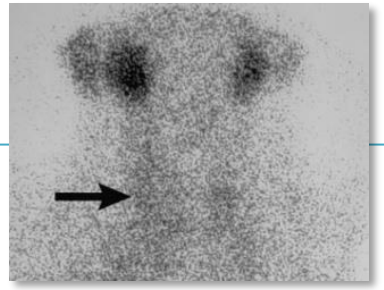
Radionuclide Thyroid scan

- ^{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

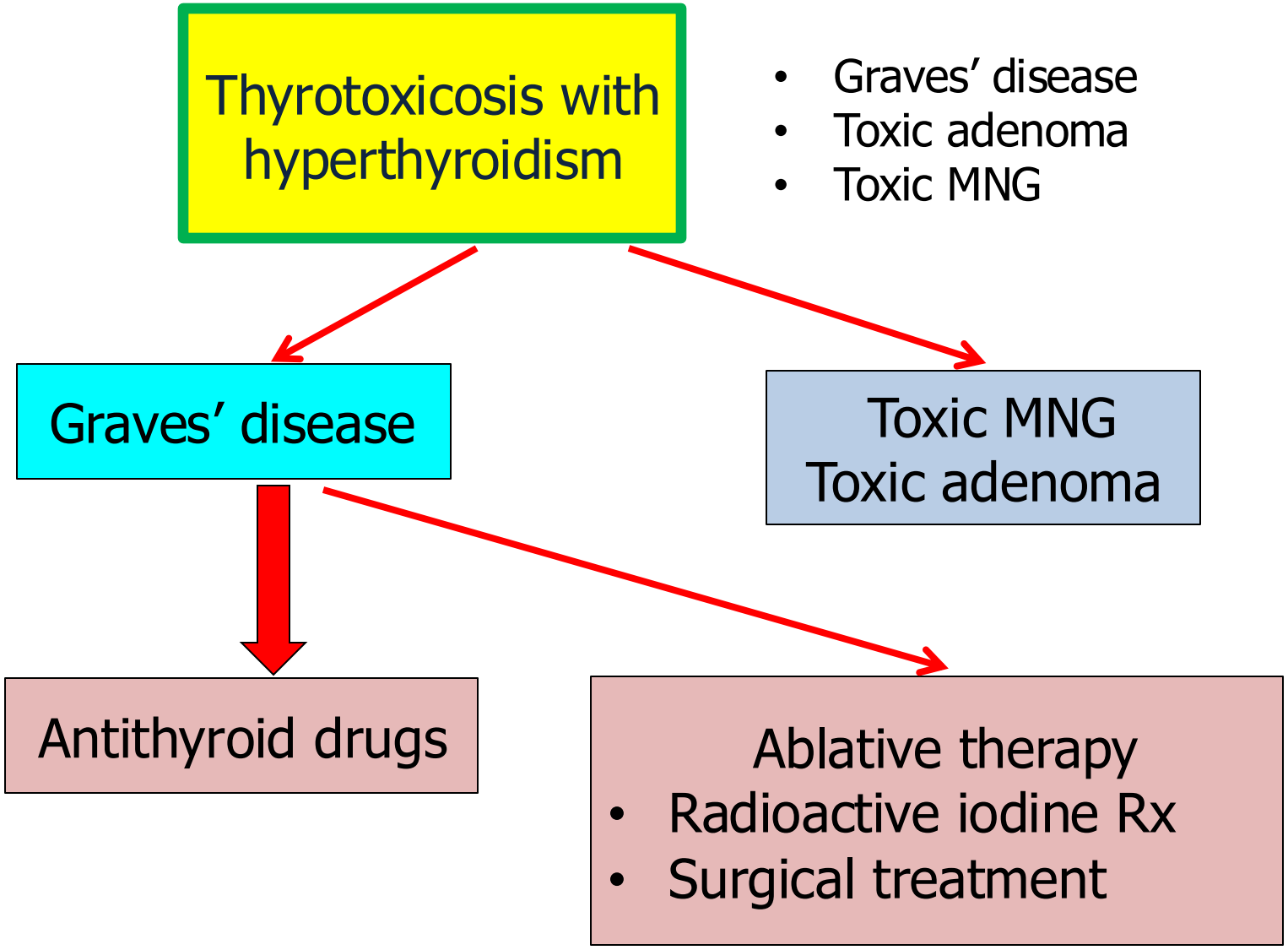
Etiology	RAI uptake	Thyroid scan
With hyperthyroidism		
Graves' disease	High	
Toxic MNG	Normal to high	
Toxic adenoma	Normal to high	
Without hyperthyroidism		
Thyroiditis	Low	
Exogenous T4	Low	

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

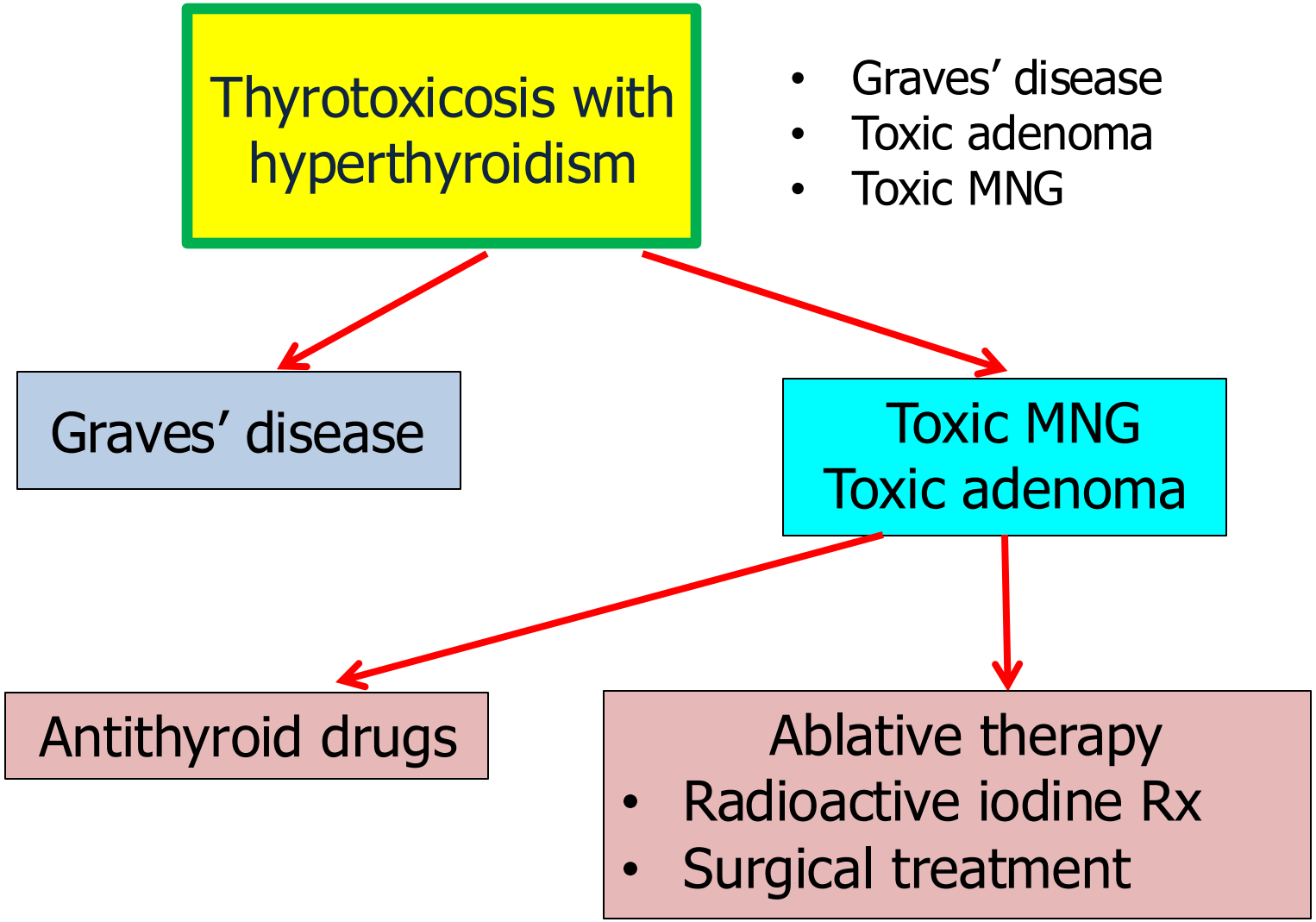


Graves' disease treatment

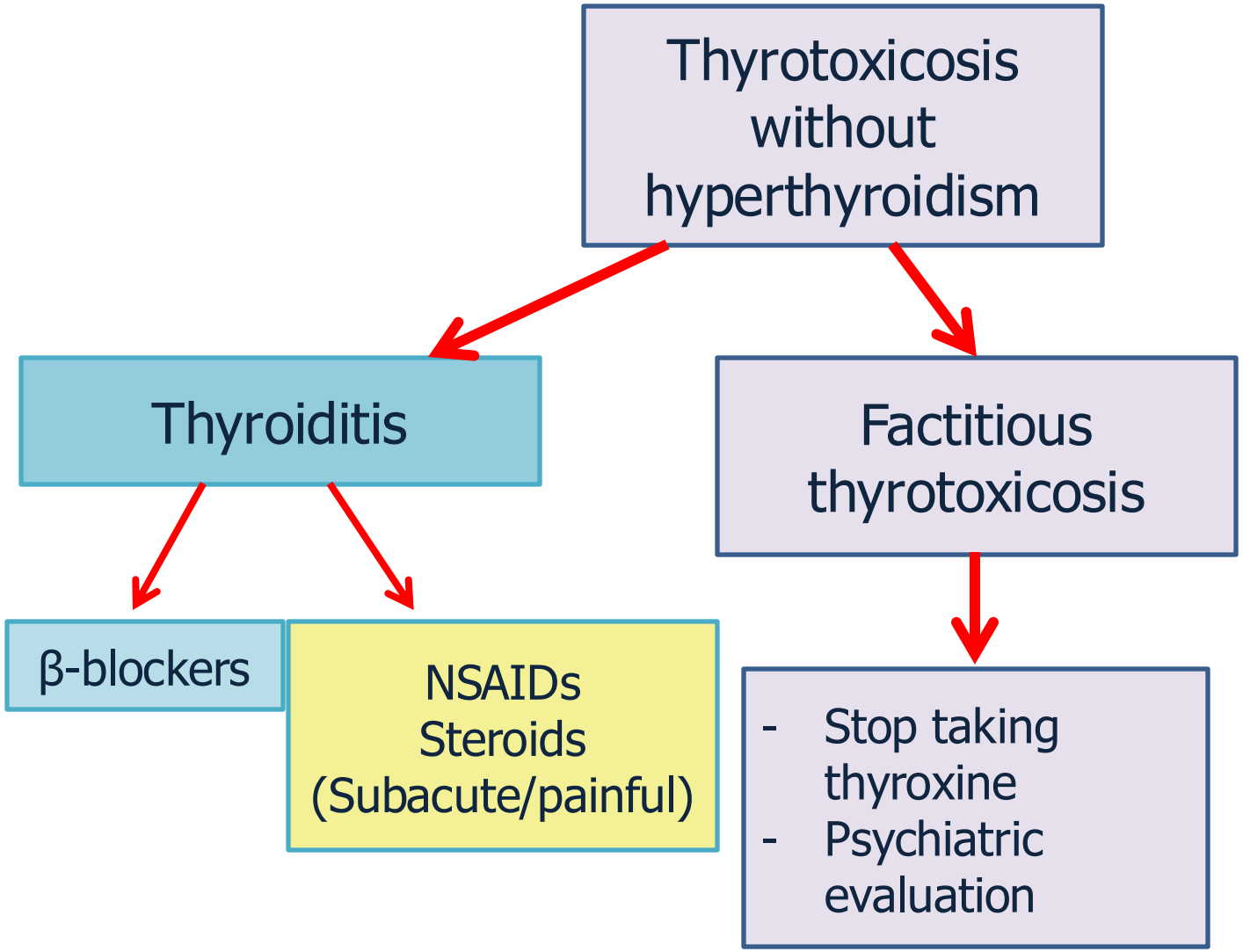
Treatment option	Advantages	Disadvantages
ATD	- Chance of permanent remission (~35%)	• Side effectsof ATDs • Long duration (12-18 months) • High recurrence risk
Radioactive iodine treatment	- Simplicity - Low recurrence risk	• Risk of orbitopathy • Lifelong LT4 needed • Possible small increase in cancer 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

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