

The Investigations of the Thyroid gland

Essential for understanding this presentation:

- 1) **Anatomy:** The Thyroid Gland and it's surroundings
- 2) **Biochemistry:** Hormones produced by the Thyroid Gland
- 3) **Physiology:** Function of the hormones produced by the Thyroid Gland

First then can one start on a journey to investigate abnormal functions of the Thyroid gland

The Investigations of the Thyroid Gland

Objectives:

- 1) Describe the mechanisms of endocrine **hypofunction** and **hyperfunction**.
- 2) Differentiate among **primary**, **secondary** and **tertiary** endocrine disorders.

The Investigations of the Thyroid Gland

*Discuss - based on the normal physiology - the **rationale** behind*

3) **Symptoms** of a dysfunctional Thyroid Gland.

4) The **investigations** the Thyroid Gland.

The Investigations of the Thyroid Gland

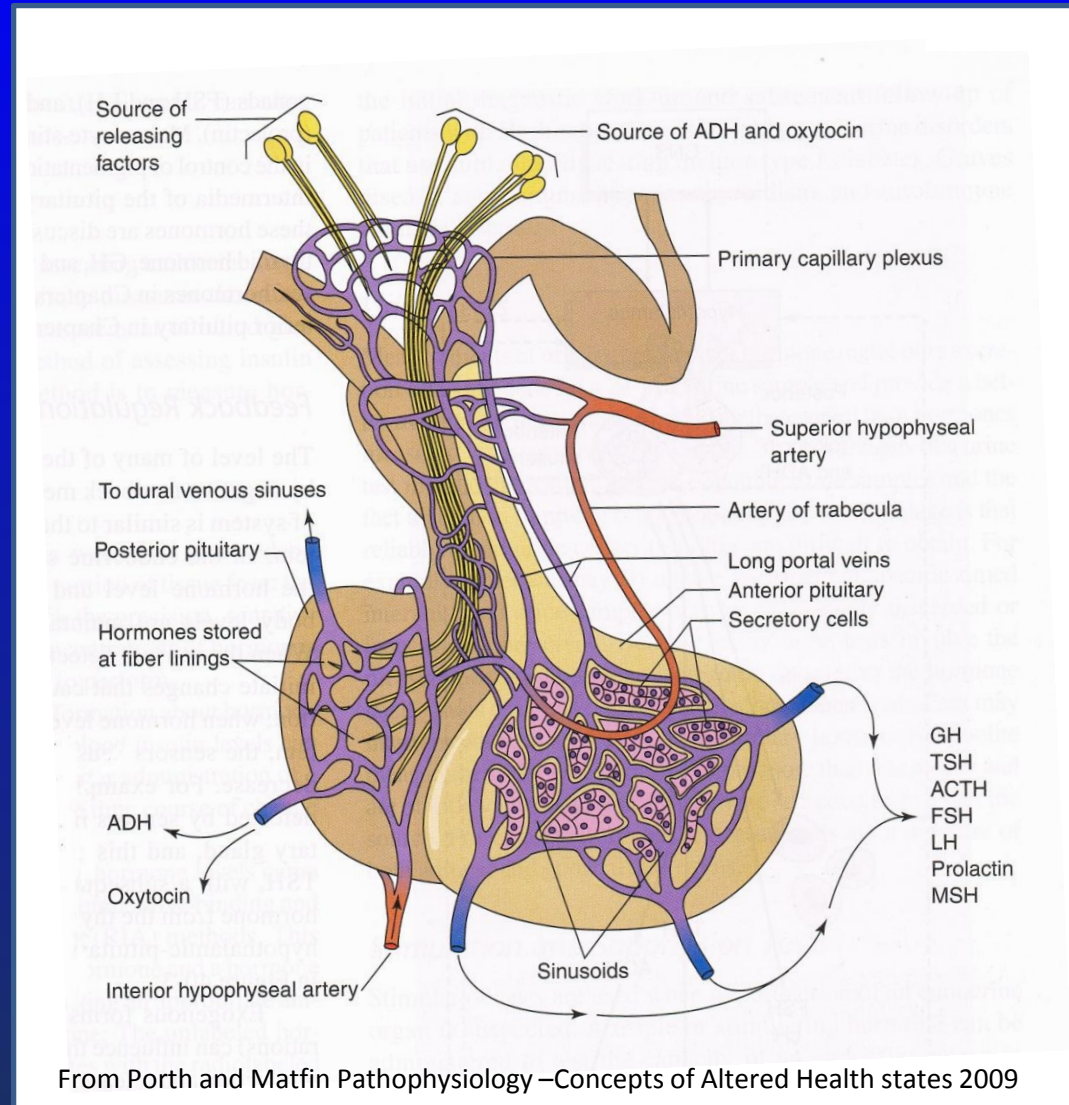
Essential for understanding the investigations

- 1) **Anatomy:**
- 2) **Biochemistry:**
- 3) **Physiology:**
- 4) **Diseases**

Essential anatomy

Connections to/from
hypothalamus (nerve
and vessels) to the
Thyroid gland

The *hypophyseal*
portal system



Posterior → Anterior

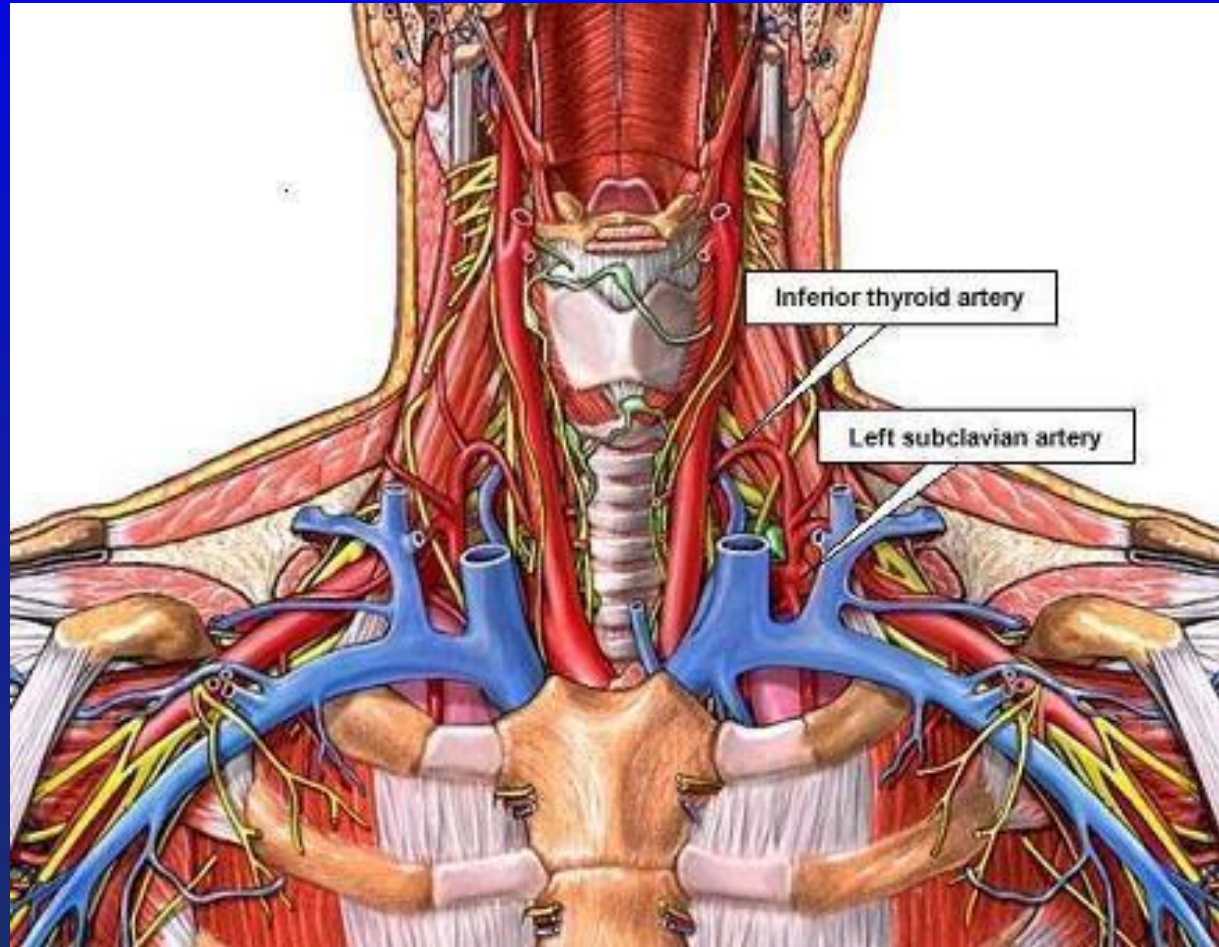
Essential anatomy

Relations

Trachea

Muscles

Main Arteries



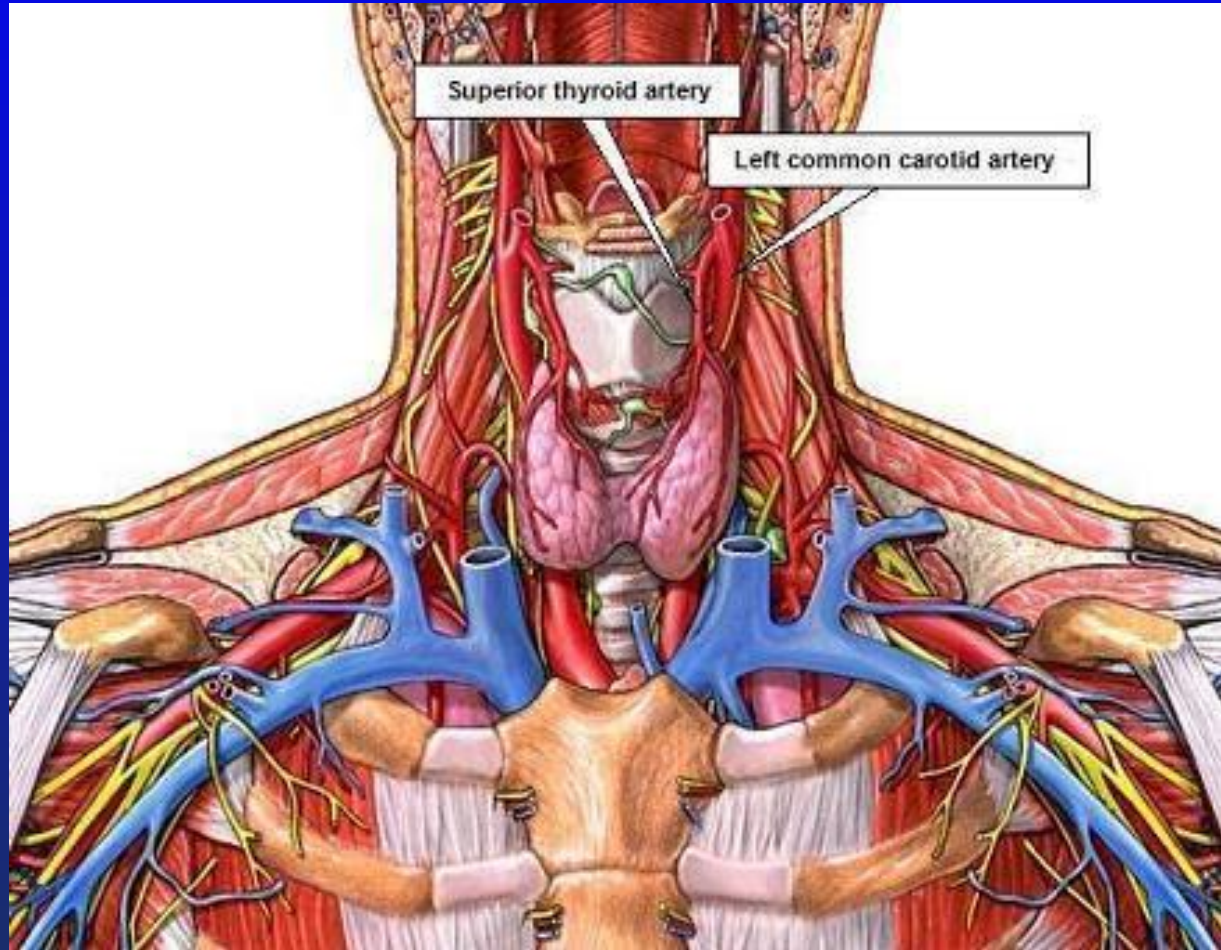
http://fitsweb.uchc.edu/student/selectives/Luzietti/Thyroid_anatomy.htm

Anterior

Essential anatomy

Relations

Main Arteries



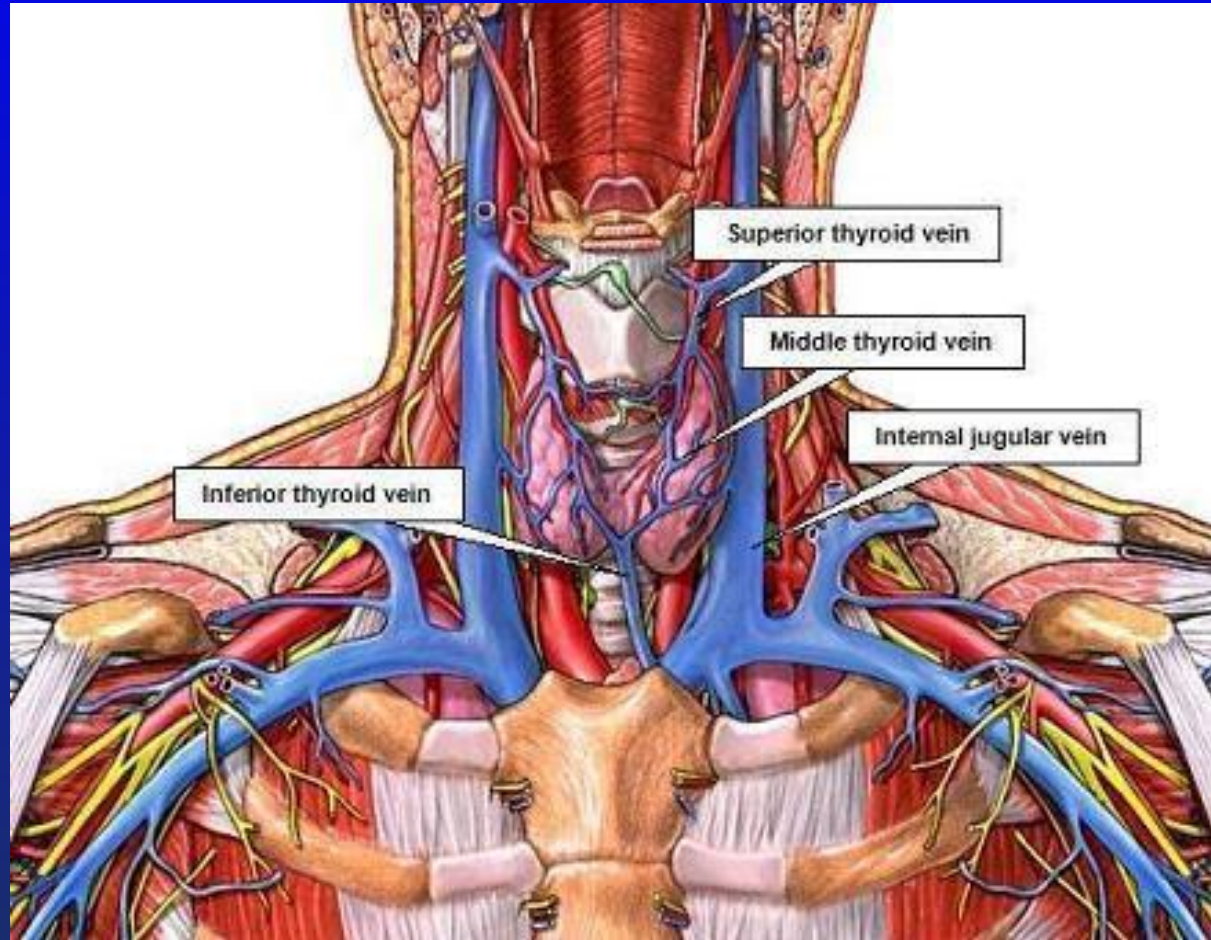
http://fitsweb.uchc.edu/student/selectives/Luzietti/Thyroid_anatomy.htm

Anterior

Essential anatomy

Relations

Main veins



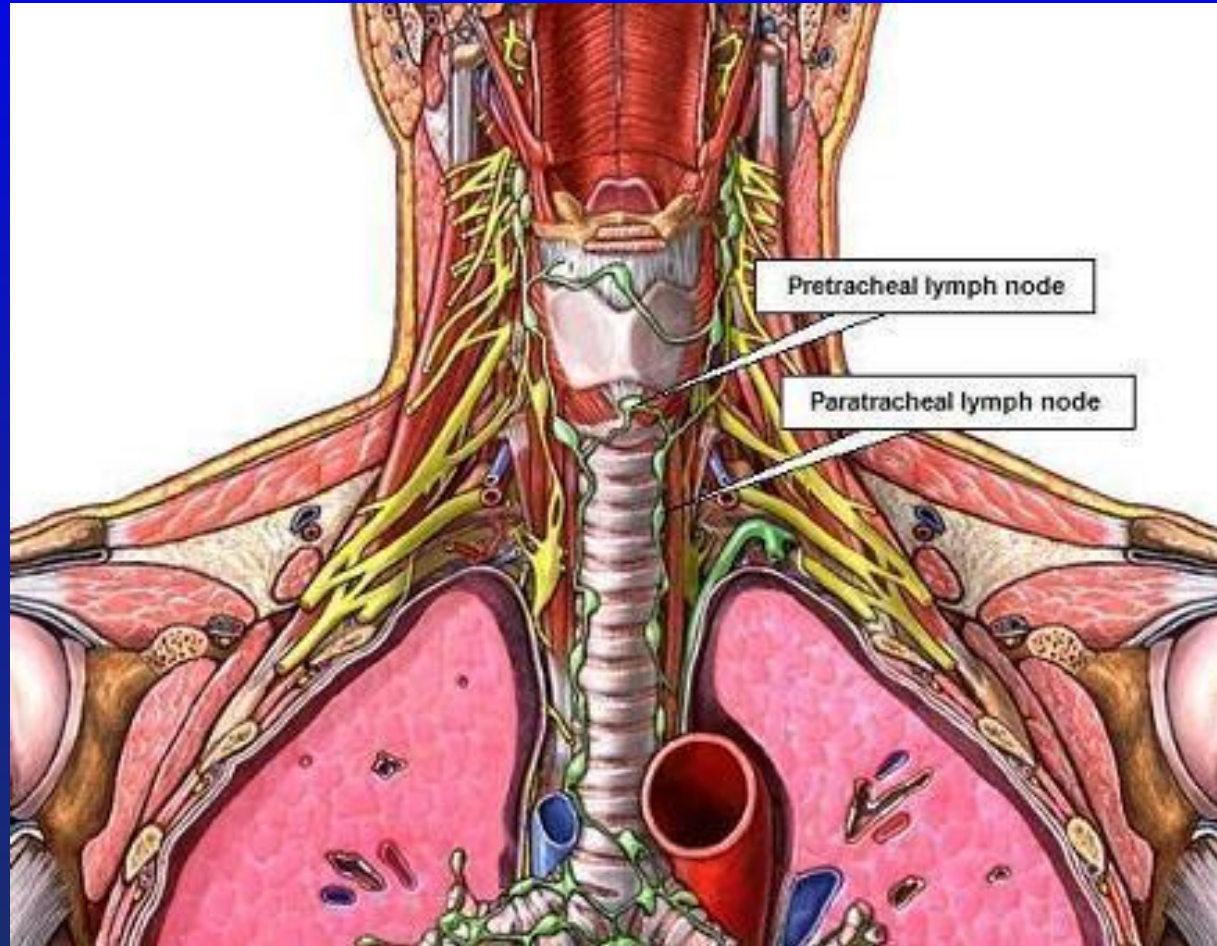
http://fitsweb.uchc.edu/student/selectives/Luzietti/Thyroid_anatomy.htm

Anterior

Essential anatomy

Relations

Lymph drainage



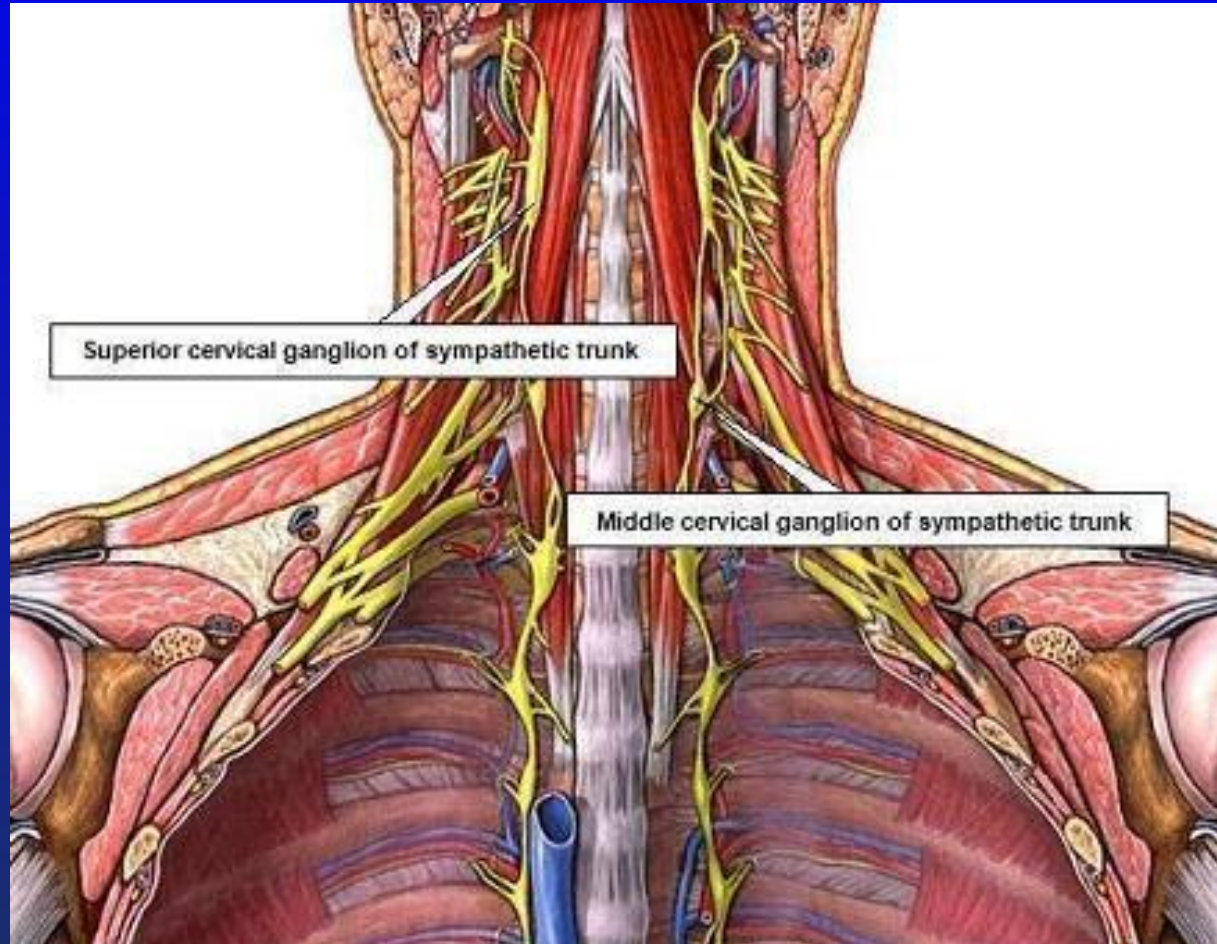
http://fitsweb.uchc.edu/student/selectives/Luzietti/Thyroid_anatomy.htm

Anterior

Essential anatomy

Relations

Nerves



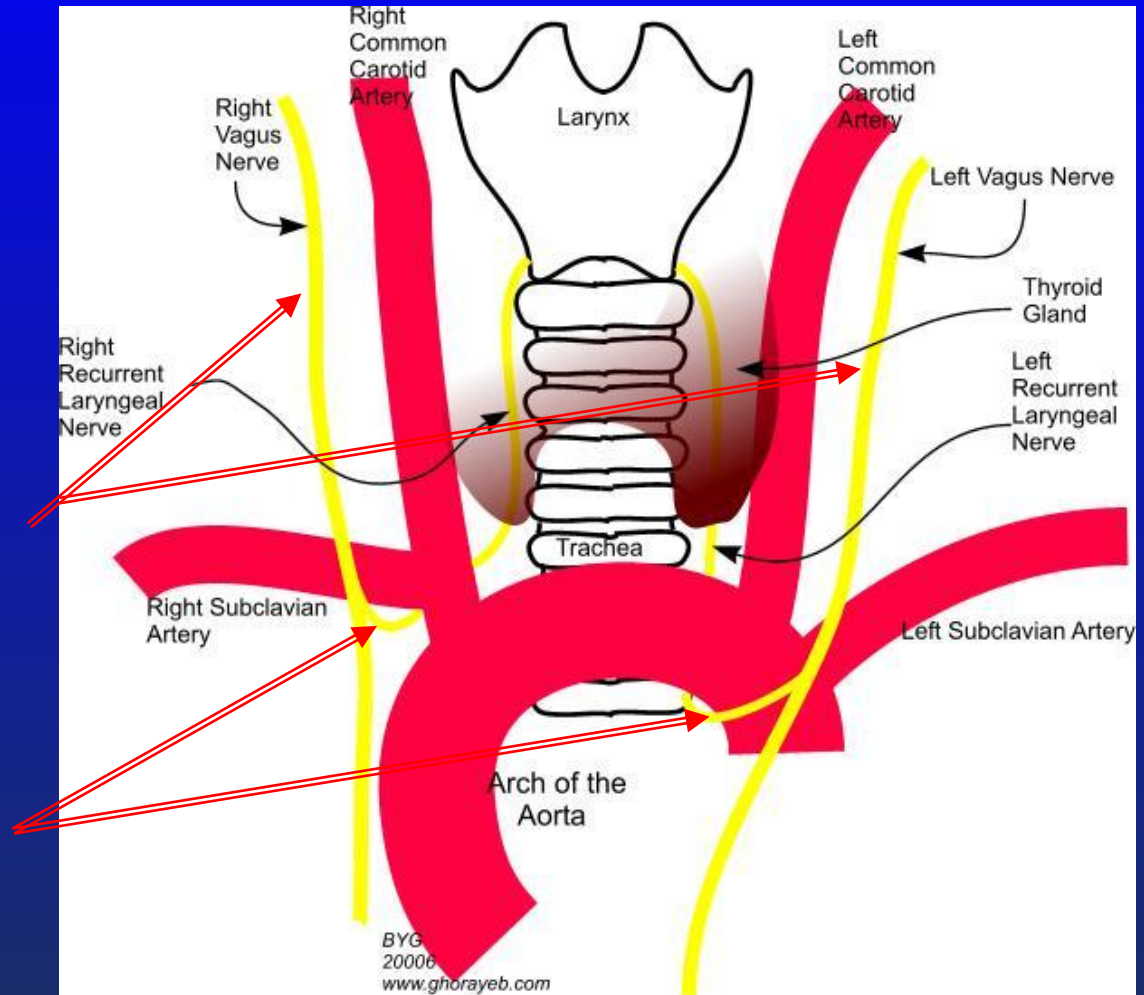
http://fitsweb.uchc.edu/student/selectives/Luzietti/Thyroid_anatomy.htm

Anterior

Essential anatomy

Which
nerves are
missing?

Vagus Nerves
Recurrent
Laryngeal
Nerves

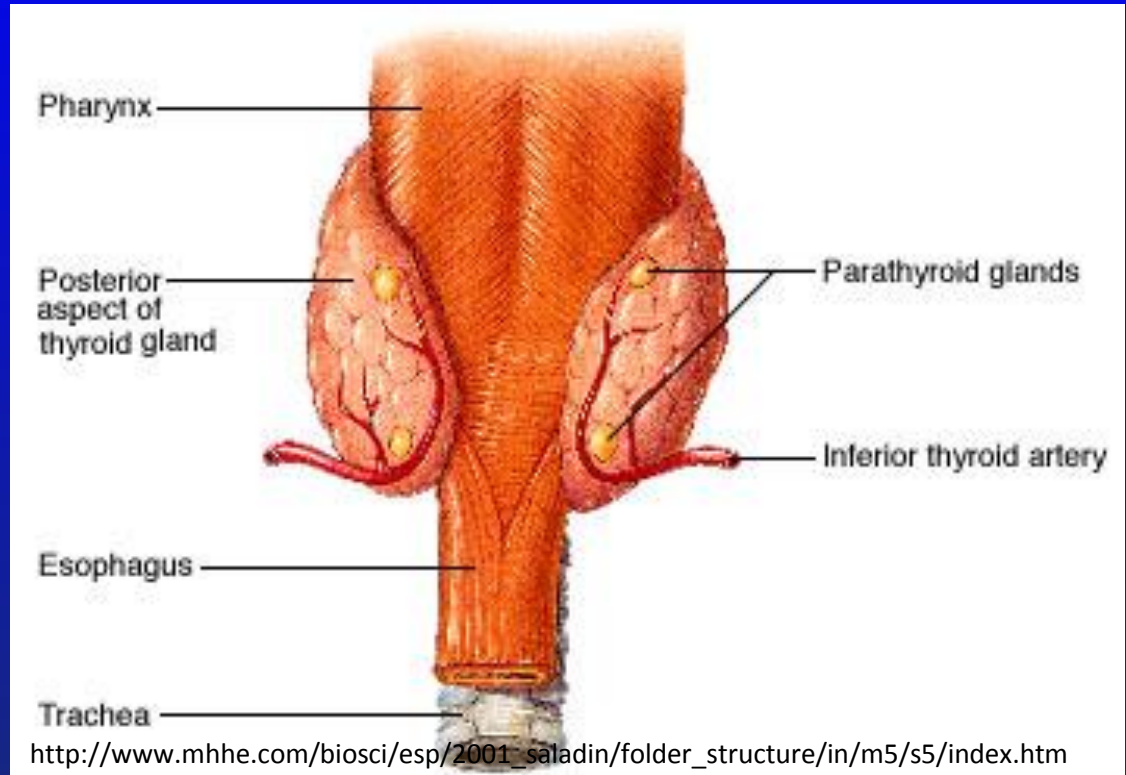


Always double check that you have it all

Essential anatomy

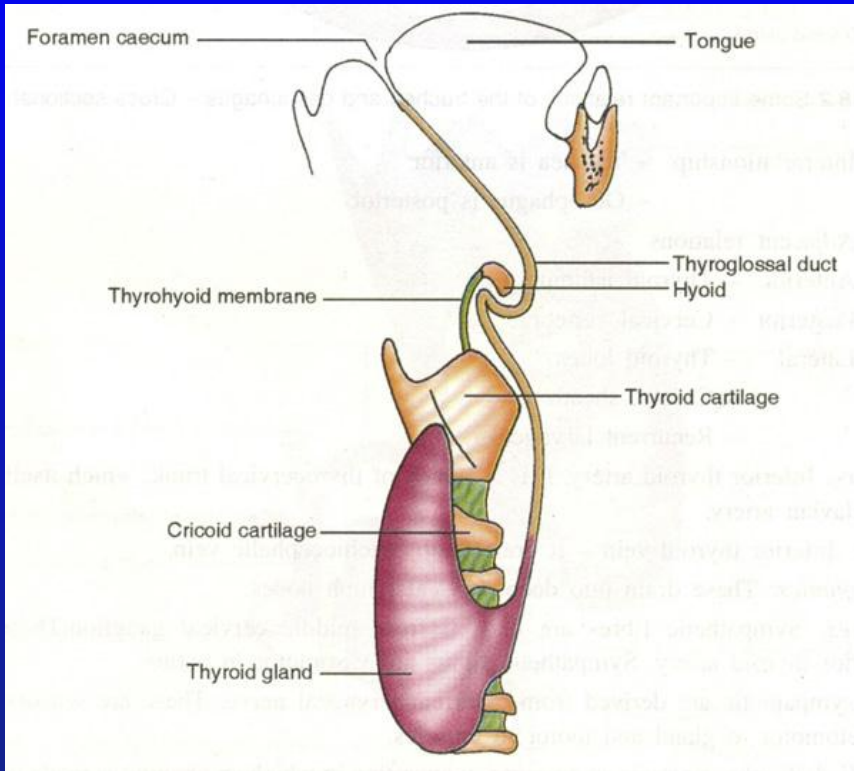
Any other
glands close
by?

Parathyroid
gland



Posterior view

Essential anatomy - Development



Why is it
important?

Aberrant tissue

The thyroid gland begins to develop as a median thickening of endoderm on the floor of the pharynx between the first and second pharyngeal pouches. This area later invaginates to form the median diverticulum, which appears in the later half of the fourth week. This thyroid diverticulum grows further, becoming a solid cellular cord called the thyroglossal duct. The duct grows caudally and bifurcates to give rise to the thyroid lobes and the isthmus.

The Investigations of the Thyroid Gland

Essential for understanding the investigations

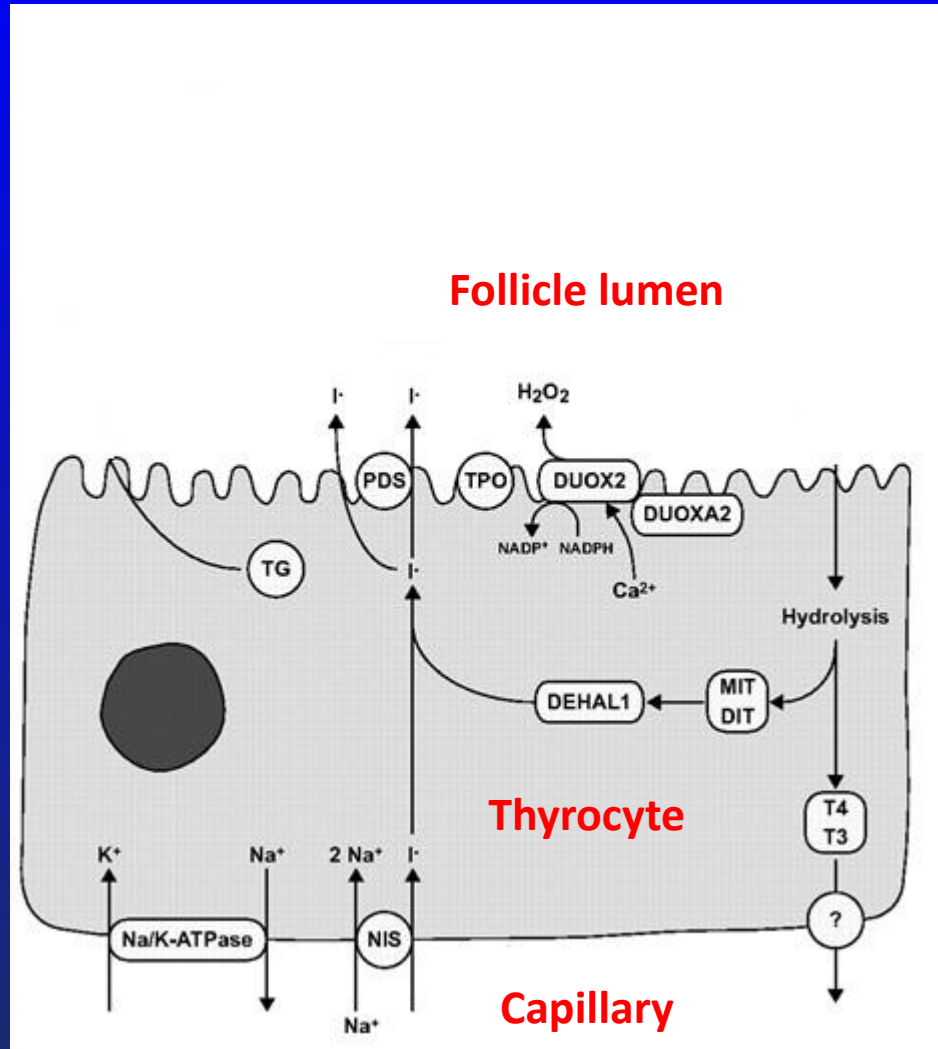
1) **Anatomy:**

2) **Biochemistry:**

3) **Physiology:**

4) **Diseases**

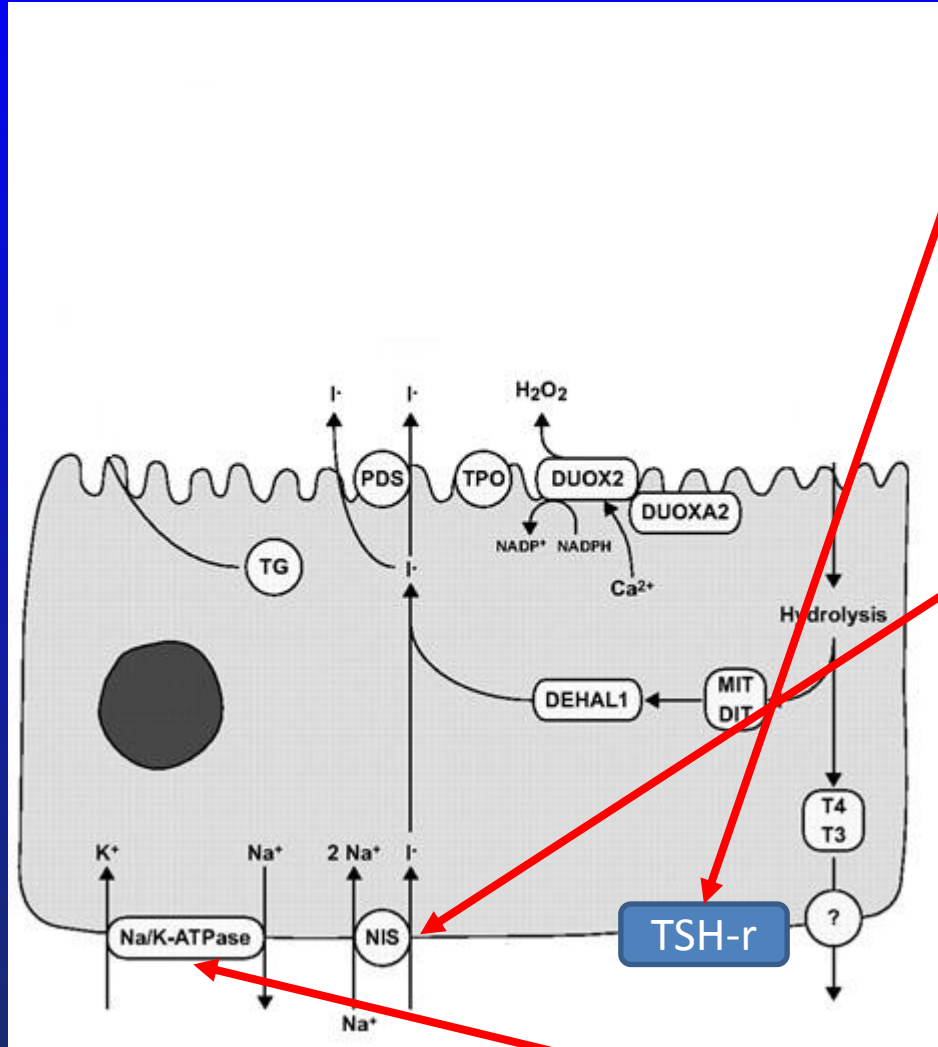
Essential biochemistry



Orientation

Bizhanova A , Kopp P Endocrinology 2009;150:1084-1090

Essential biochemistry



Bizhanova A , Kopp P Endocrinology 2009;150:1084-1090

TSH signaling via the TSH receptor controls thyroid hormone synthesis, Uptake of iodide into the thyrocytes is mediated by an intrinsic membrane glycoprotein, the **sodium-iodide symporter** (NIS), which actively cotransports two Na⁺ per each iodide anion.

NIS is dependent on the Na gradient created by the Na/K-ATPase

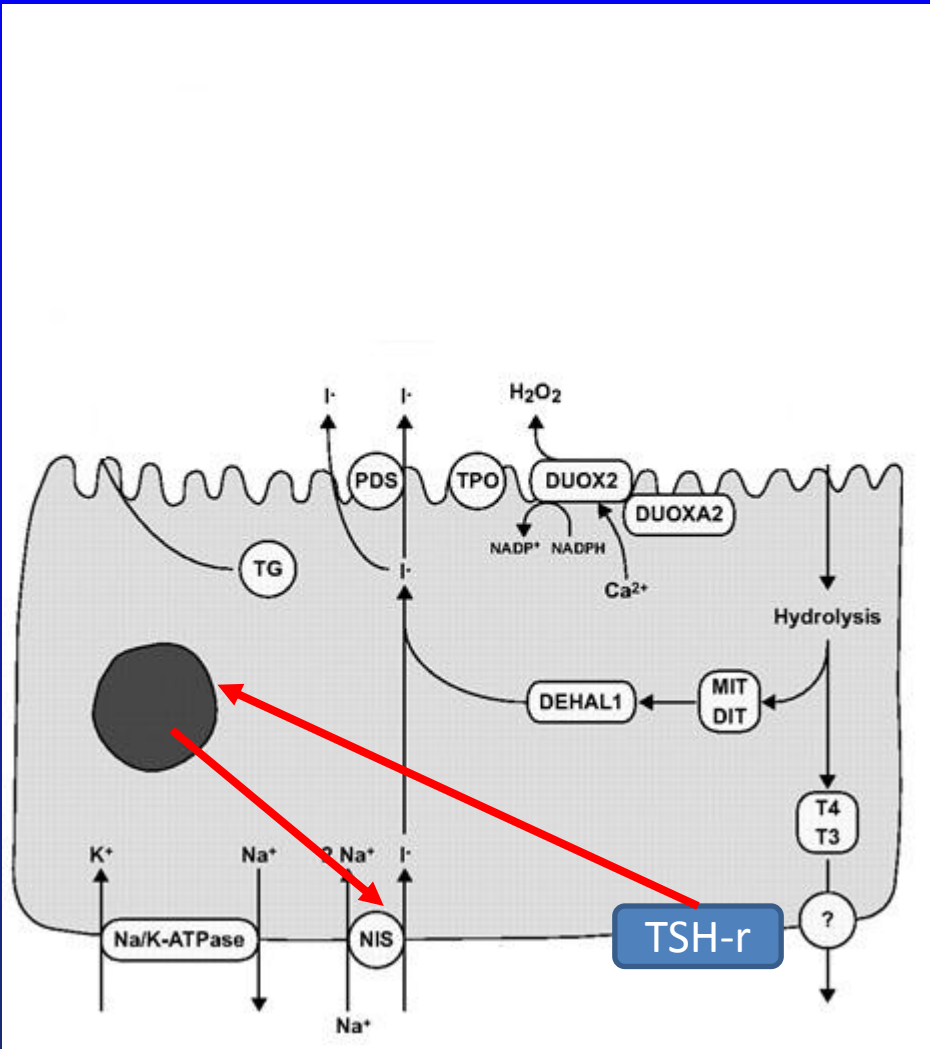
Essential biochemistry

TSH can increase expression of NIS in the basolateral membrane of thyrocytes.

Transcription

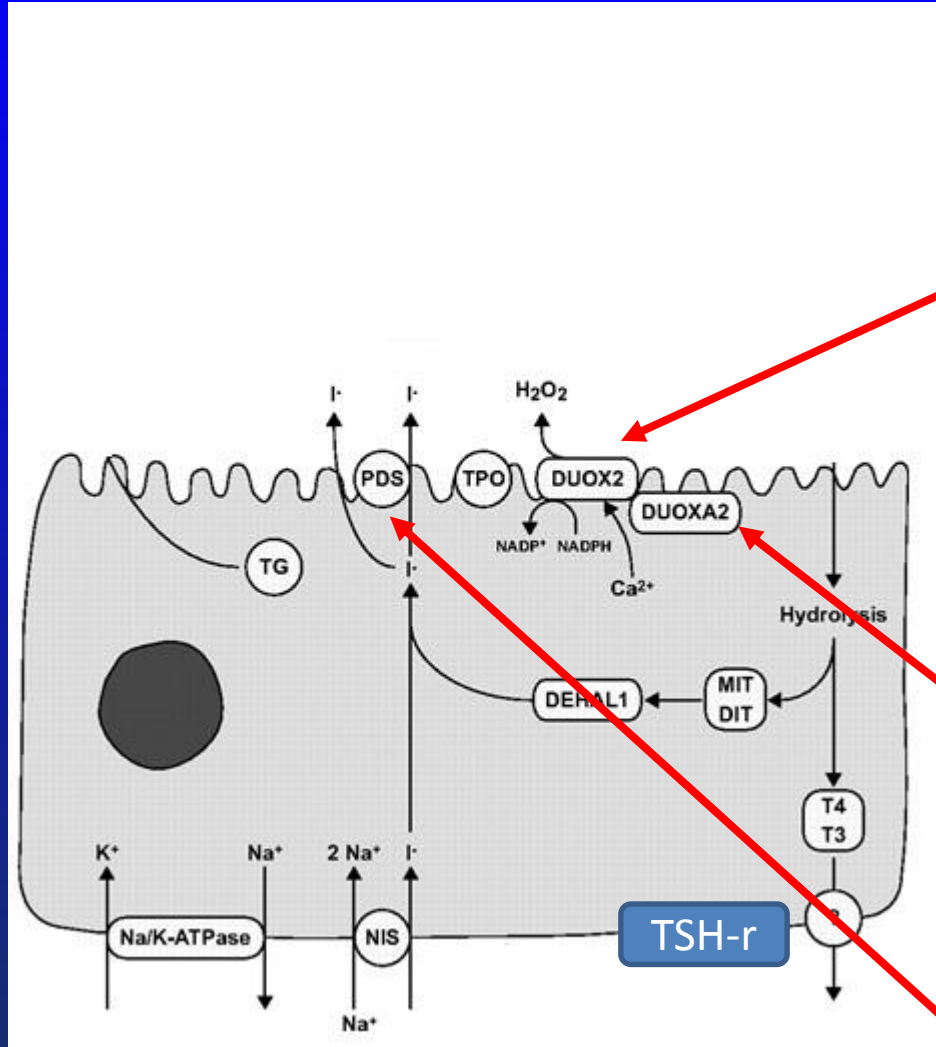
m-RNA

Protein synthesis



Bizhanova A , Kopp P Endocrinology 2009;150:1084-1090

Essential biochemistry



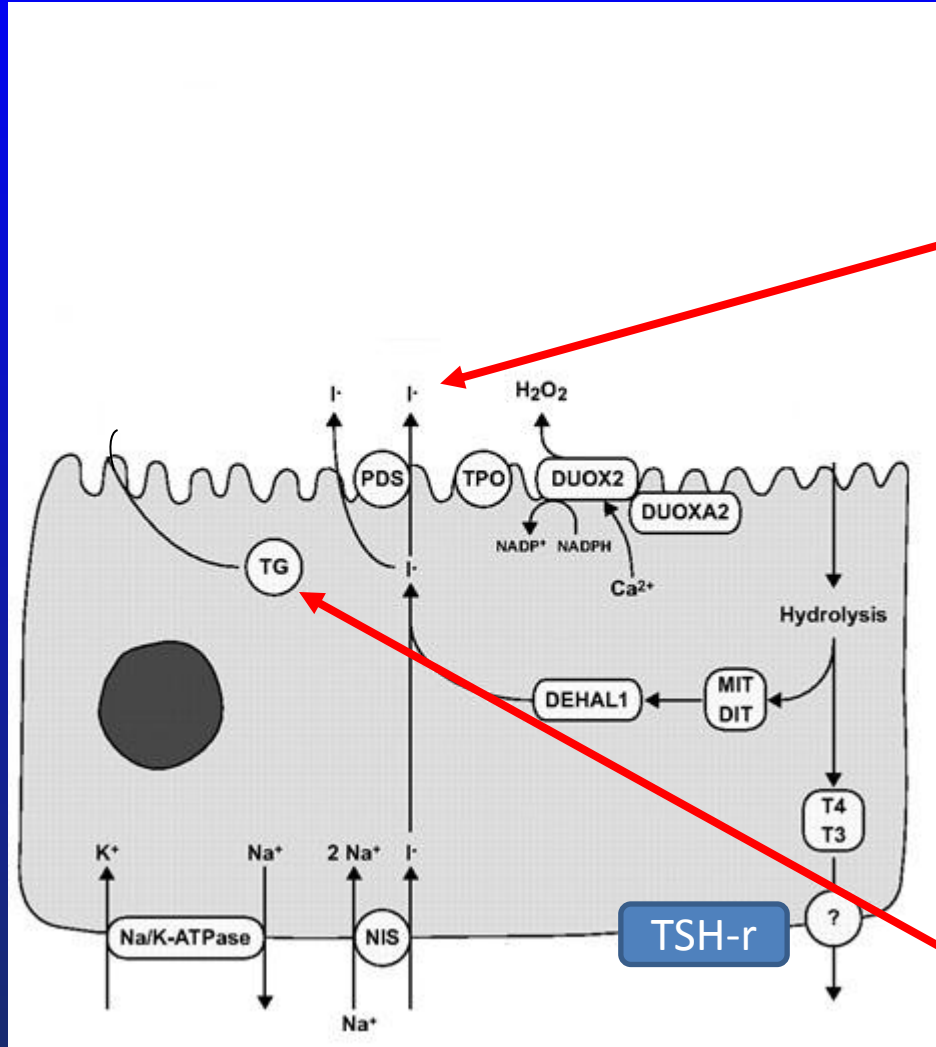
Bizhanova A , Kopp P Endocrinology 2009;150:1084-1090

H₂O₂ is produced by the calcium- and reduced nicotinamide adenine dinucleotide phosphate-dependent (NADPH) enzyme DUOX2.

DUOX2 requires a specific maturation factor, DUOXA2

At the apical membrane, iodide efflux is, in part, mediated by **pendrin** (PDS/SLC26A4)

Essential biochemistry

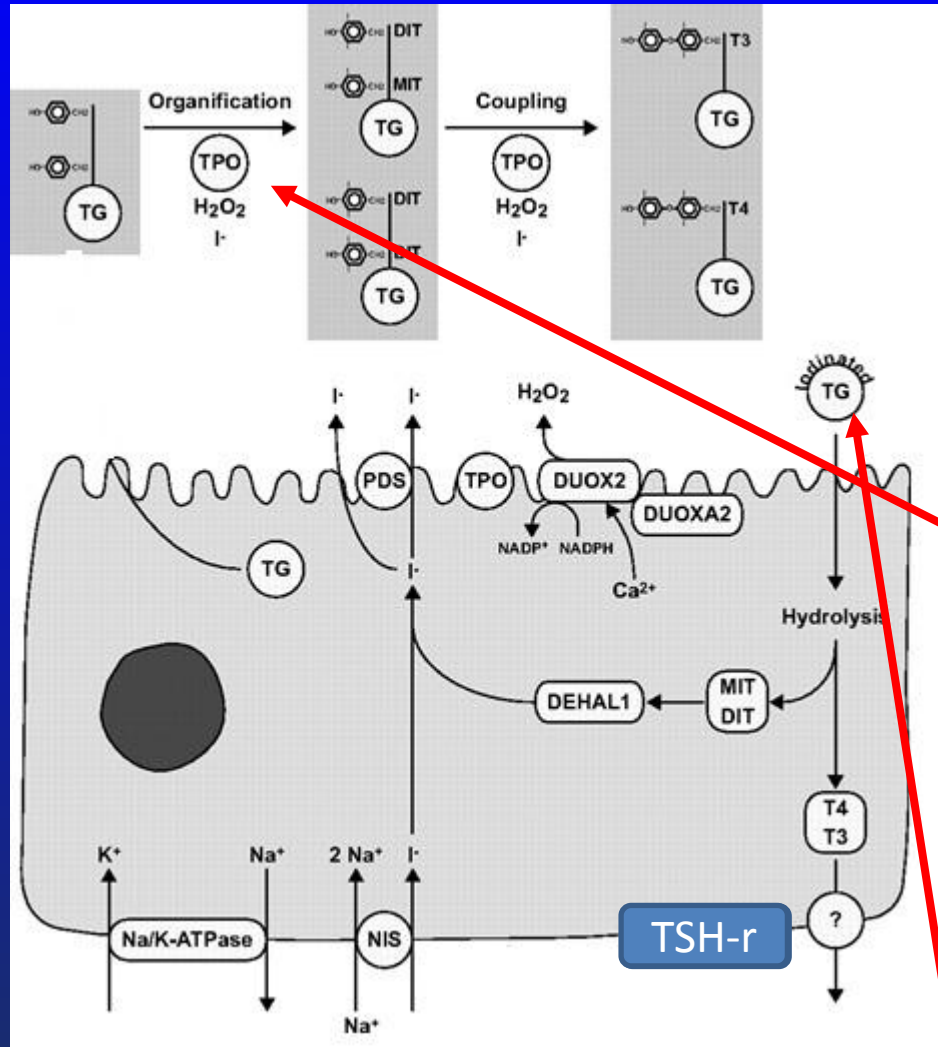


Bizhanova A , Kopp P Endocrinology 2009;150:1084-1090

H₂O₂ At the cell-colloid interface, iodide is oxidized by **TPO** (t_hyroid p_eroxidase or thyroperoxidase) in the presence of H₂O₂

Thyroglobulin (TG), which is secreted into the follicular lumen, serves as matrix for synthesis of T₄ and T₃.

Essential biochemistry



Bizhanova A , Kopp P Endocrinology 2009;150:1084-1090

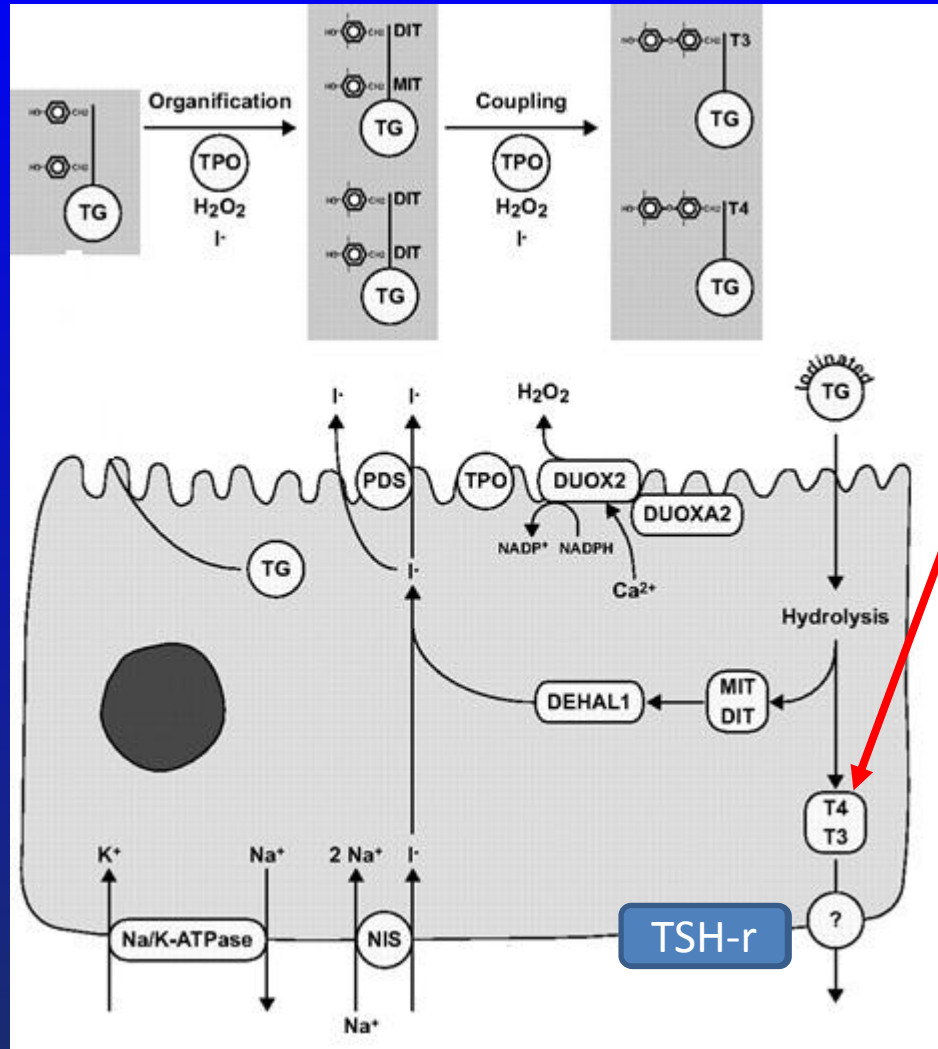
TG secreted into the follicular lumen, serves as matrix for synthesis of T4 and T3.

TPO catalyzes iodination of selected tyrosyl residues (organification), which results in the formation of MIT and DIT.

Two iodotyrosines are coupled to form either T4 or T3 (catalyzed by TPO).

Iodinated thyroglobulin is stored as colloid in the follicular lumen.

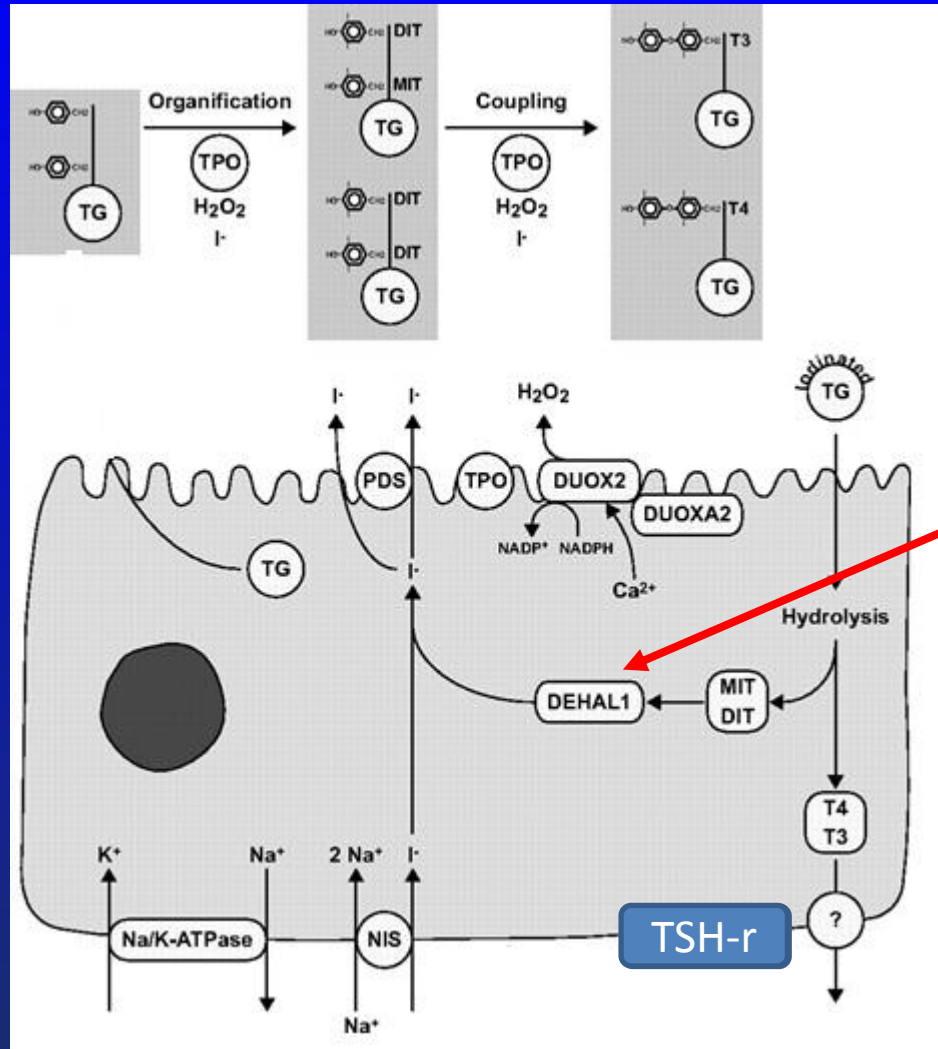
Essential biochemistry



Bizhanova A , Kopp P Endocrinology 2009;150:1084-1090

Iodinated thyroglobulin is stored as colloid in the follicular lumen. Upon a demand for thyroid hormone secretion, thyroglobulin is internalized into the follicular cell by pinocytosis and digested in lysosomes, which generates **T4 and T3** that are released into the bloodstream through unknown mechanisms.

Essential biochemistry

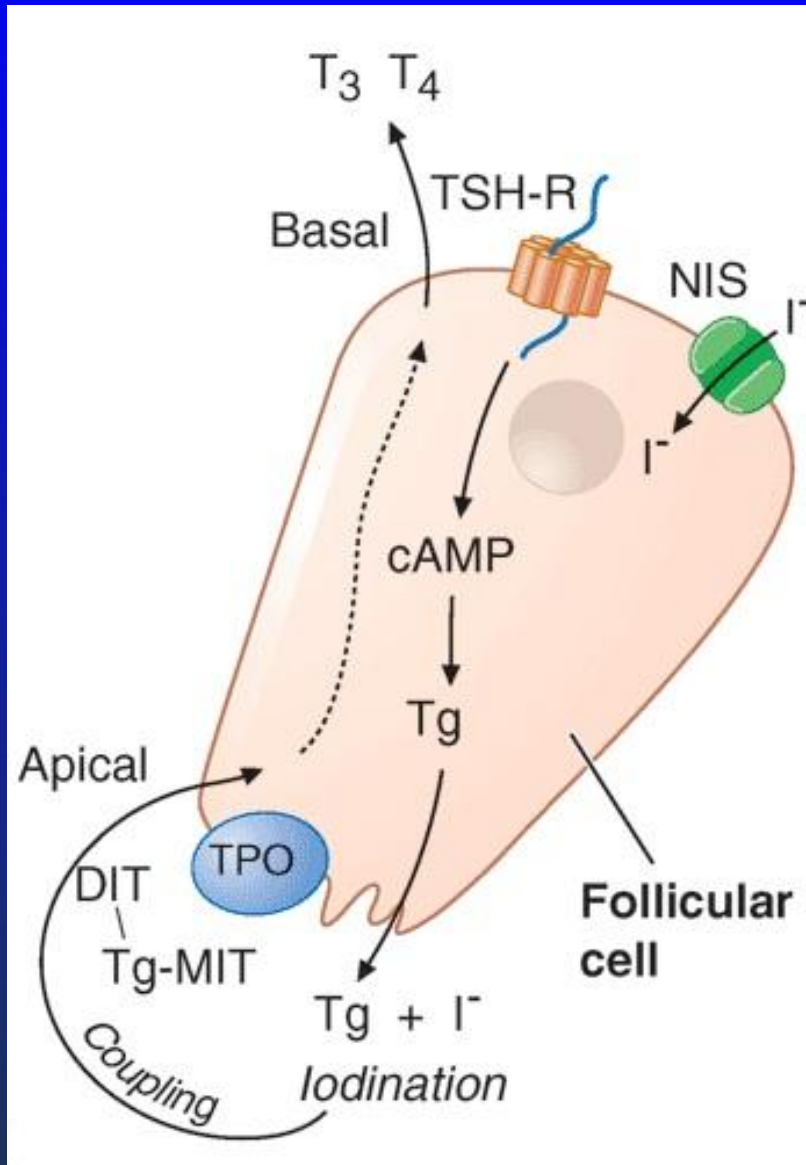


The unused MIT and DIT are retained in the cell and deiodinated by the iodotyrosine dehalogenase 1 (DEHAL1).

The released iodide is recycled for thyroid hormone synthesis.

Bizhanova A , Kopp P Endocrinology 2009;150:1084-1090

Essential biochemistry



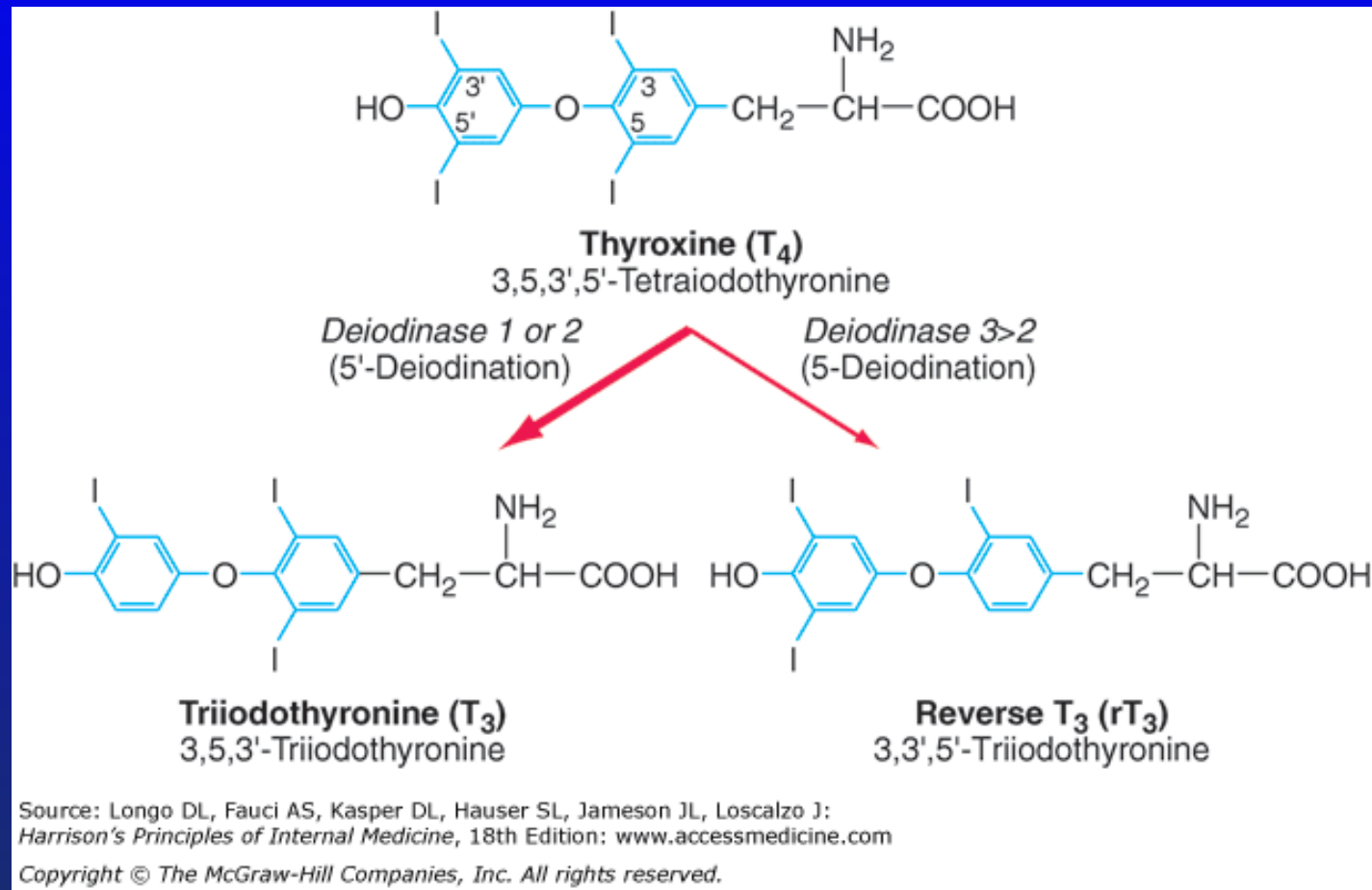
What does this figure show?

Basically the same as the previous 8 slides

Other growth factors simulates TSH:

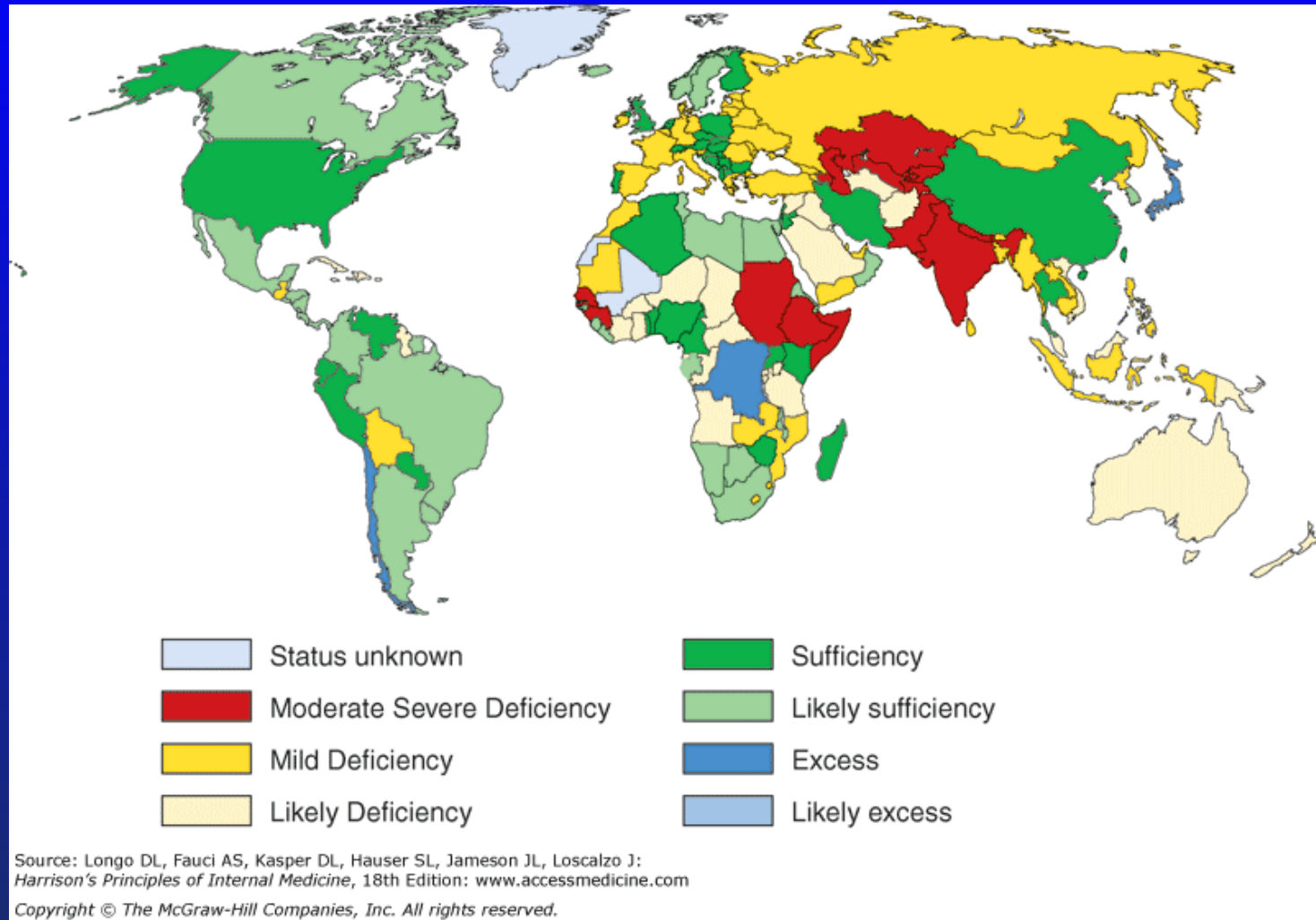
- 1 Insulin-like growth factor I (IGF-1)
- 2 Epidermal growth factor
- 3 Transforming growth factor β
- 4 Endothelins

T₃ converted to T₄



Reverse T₃ is inactive

Iodine in the world



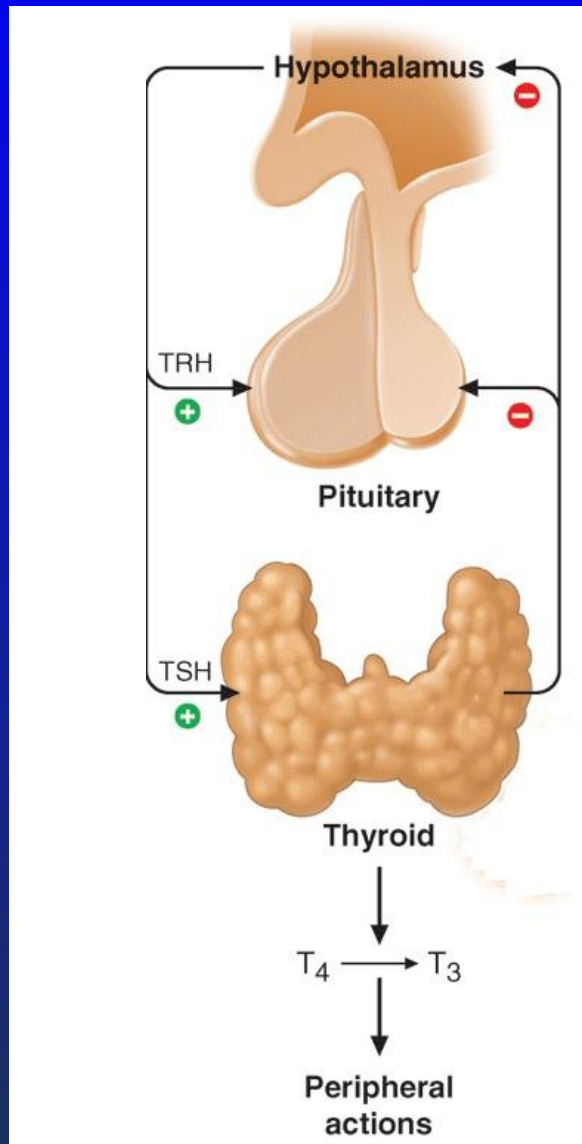
World health implications

The Investigations of the Thyroid Gland

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The Investigations of the Thyroid Gland



The T₃ and T₄ feedback

Don't forget the Pituitary gland feedback

The Investigations of the Thyroid Gland

The T_3 and T_4 are protein bound

99.8% of T_4

99.7% of T_3

The binding proteins are:

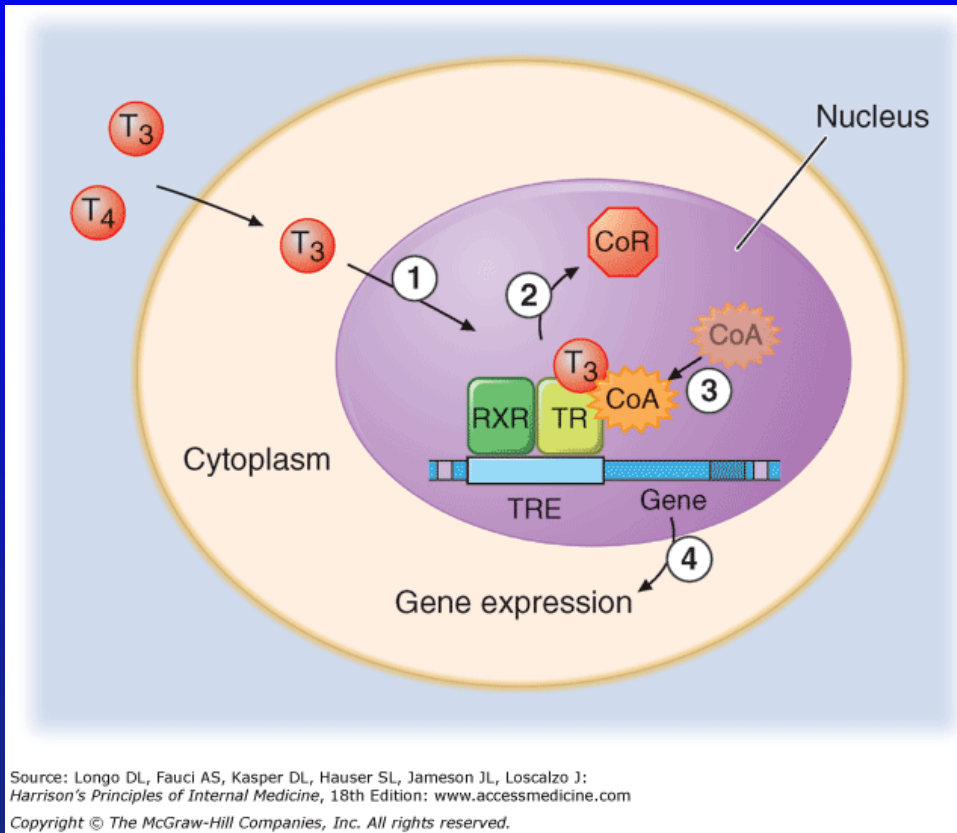
- **Thyroxine-binding globulin (TBG)**
- **Transthyretin (TTR)** *formerly known as thyroxine-binding pre-albumin (TBPA)*
- **Albumin**

The Investigations of the Thyroid Gland

Hormone property	T ₄	T ₃
Serum Concentration total hormone	8 µg/dL	0.14 µg/dL
Fraction of total hormone in free form	0.02%	0.3%
Free (unbound) hormone	21 x 10 ⁻¹² M	6 x 10 ⁻¹² M
Half-life	7 d	0.75 d
Fraction directly from the thyroid	100%	20%
Production rate, including peripheral conversion	90 µg/d	32 µg/d
Intracellular hormone fraction	~ 20%	~ 70%
Relative metabolic potency	0.3	1
Receptor binding	10 ⁻¹⁰ M	10 ⁻¹¹ M

From Harrison's principles of Internal Medicine 18th edition

Mechanism of thyroid hormone receptor action



The thyroid hormone receptor (TR) and retinoid X receptor (RXR) form heterodimers that bind specifically to thyroid hormone response elements (TRE) in the promoter regions of target genes.

In the absence of hormone, TR binds co-repressor (CoR) proteins that silence gene expression.

The numbers refer to a series of ordered reactions that occur in response to thyroid hormone:

- (1) T₄ or T₃ enters the nucleus;
- (2) T₃ binding dissociates CoR from TR;
- (3) Coactivators (CoA) are recruited to the T₃-bound receptor;
- (4) Gene expression is altered.

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Hyper - & Hypo-functions

In principle only two things can go wrong:

Increased production (over production) of hormones: Hyper.....dism

Decreased production (under production) of hormones: Hypo.....dism

Of cause there can be many underlying causes:
Tumor, starvation, infections

Hormone prioritizing

Hor-mone	Function (Stimulates)	Releasing factors	Hypo function	Hyper – Function	Priority
ACTH	Adrenal cortical hormone	CRH	Second. Adrenal hypofunction	Cushing disease	1
MSH	Melanocytes	CRH		Skin pigmentation	1?
TSH	Thyroid hormone	TRH	Second. Hypothyroidism	Second. Hyperthyroidism	2
FSH	F: Ovulation, M: Sperm	GnRH	Infertility	Precocious puberty	3
LH	Corpus luteum	GnRH	Sec. hypogonadism		4
GH	Growth	GHRH	Short stature	Acromegaly or gigantism	5
PRL	Breast feeding		Lactation failure	Amenorrhoea Galactorrhoea	6?
ADH	Water reabsorb	neurogenic	Diabetes insipidus	Hyponatraemia	
Oxytocin	uterine contractions	neurogenic	decreased bone density and fat ?		

Mnemonic: **Go Look For The Adenoma**

Meaning first goes GH then LH Last ATCH

The Investigations of the Thyroid Gland

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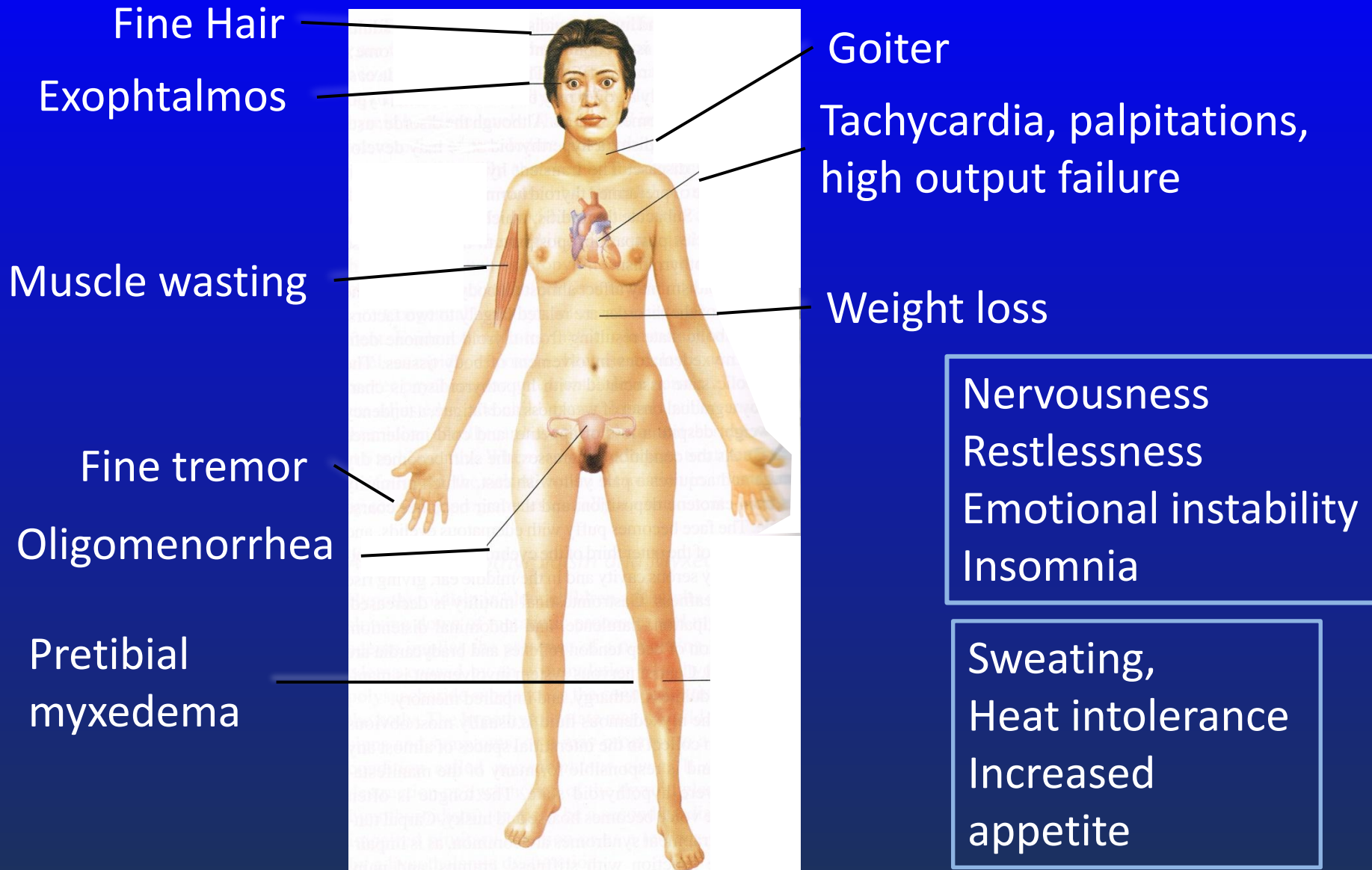
2) **Biochemistry:**

3) **Physiology:**

4) **Diseases**

Diagnose

Hyperthyroidism



From Porth and Matfin Pathophysiology –Concepts of Altered Health states 2009

Hyperthyroidism

	Total T4	Total T3	Free T4	Free T3	TBG	TSH
	Normal	Normal	normal	normal	normal	normal

Diagnose ?

Hyperthyroidism

	Total T4	Total T3	Free T4	Free T3	TBG	TSH
Euthyroid	Normal	Normal	normal	normal	normal	normal
	^	^	^	^	normal	v

Diagnose ?

^ = high

v = low

Hyperthyroidism

	Total T4	Total T3	Free T4	Free T3	TBG	TSH
Euthyroid	Normal	Normal	normal	normal	normal	normal
Hyperthyroid	^	^	^	^	normal	∇ if primary
						^

Diagnose ?

^ = high

∇ = low

Hyperthyroidism

	Total T4	Total T3	Free T4	Free T3	TBG	TSH
Euthyroid	Normal	Normal	normal	normal	normal	normal
Hyperthyroid	^	^	^	^	normal	∇ if primary ^ if Secondary
	Normal	^	normal	^	normal	∇

Diagnose ?

^ = high

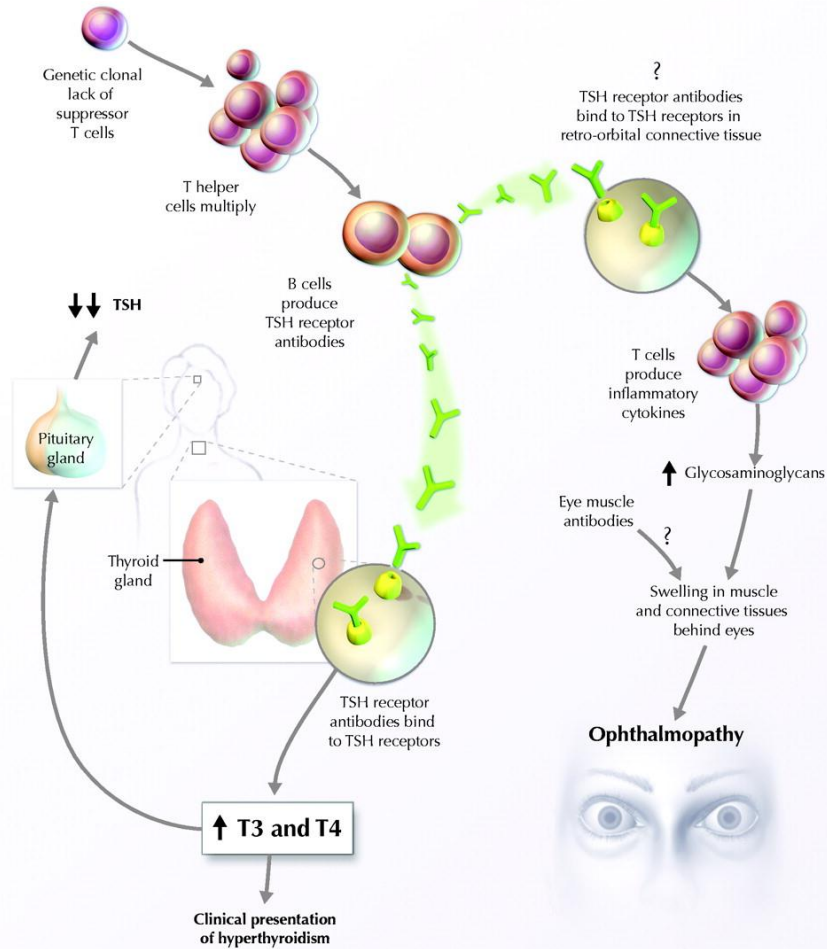
∇ = low

Hyperthyroidism

	Total T4	Total T3	Free T4	Free T3	TBG	TSH
Euthyroid	Normal	Normal	normal	normal	normal	normal
Hyperthyroid	^	^	^	^	normal	∇ if primary ^ if Secondary
T3 toxicosis	Normal	^	normal	^	normal	∇
Hypothyroid	∇	∇	∇	∇	normal	^ if primary ∇ if secondary
TBG excess	^	^	normal	normal	^	Normal
TBG deficiency	∇	∇	normal	normal	∇	Normal
T4 displacement by drugs	∇	normal	Normal or ∇	normal	normal	Normal

Hyperthyroidism

Graves Disease

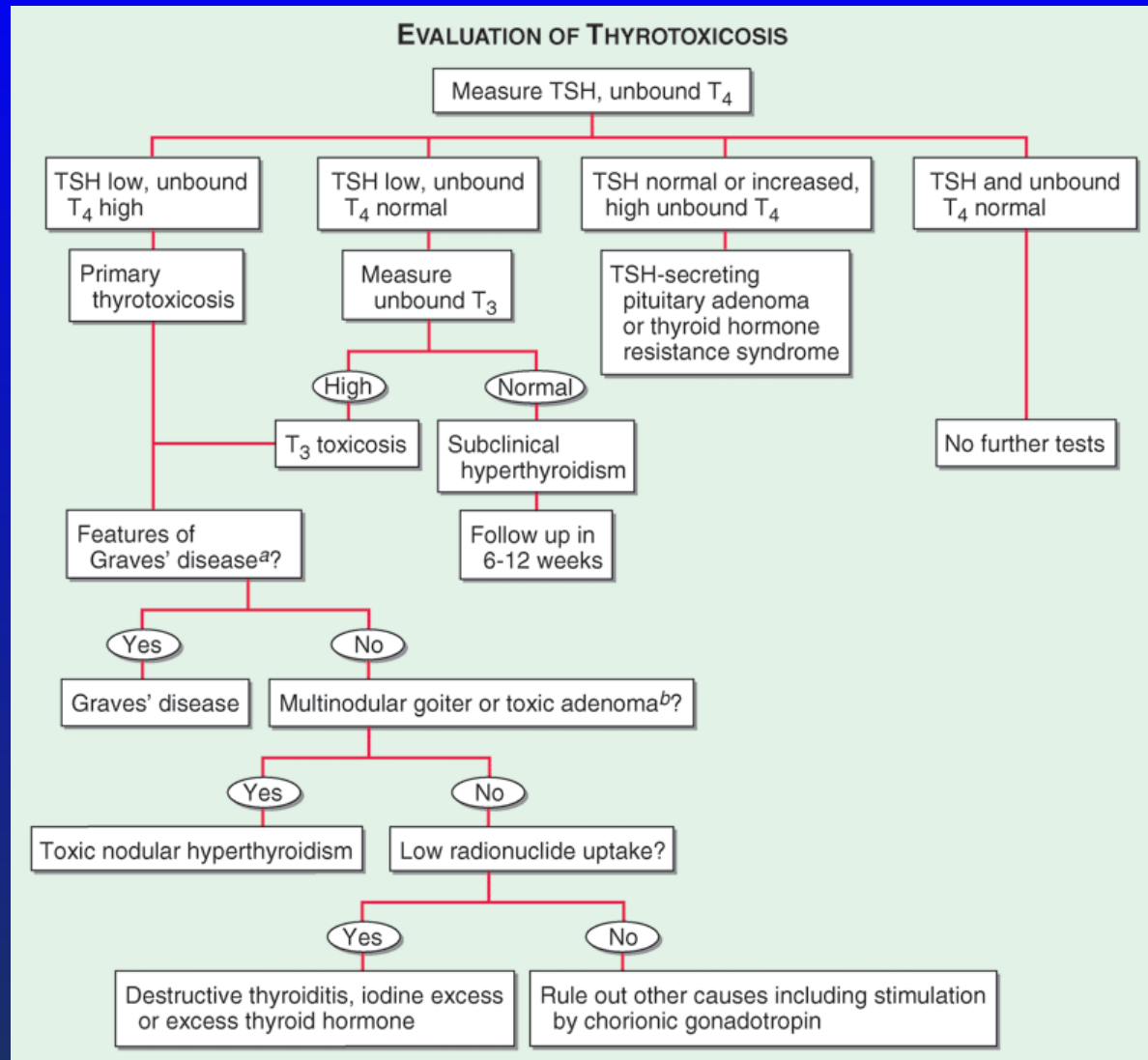


Ginsberg J CMAJ 2003;168:575-585



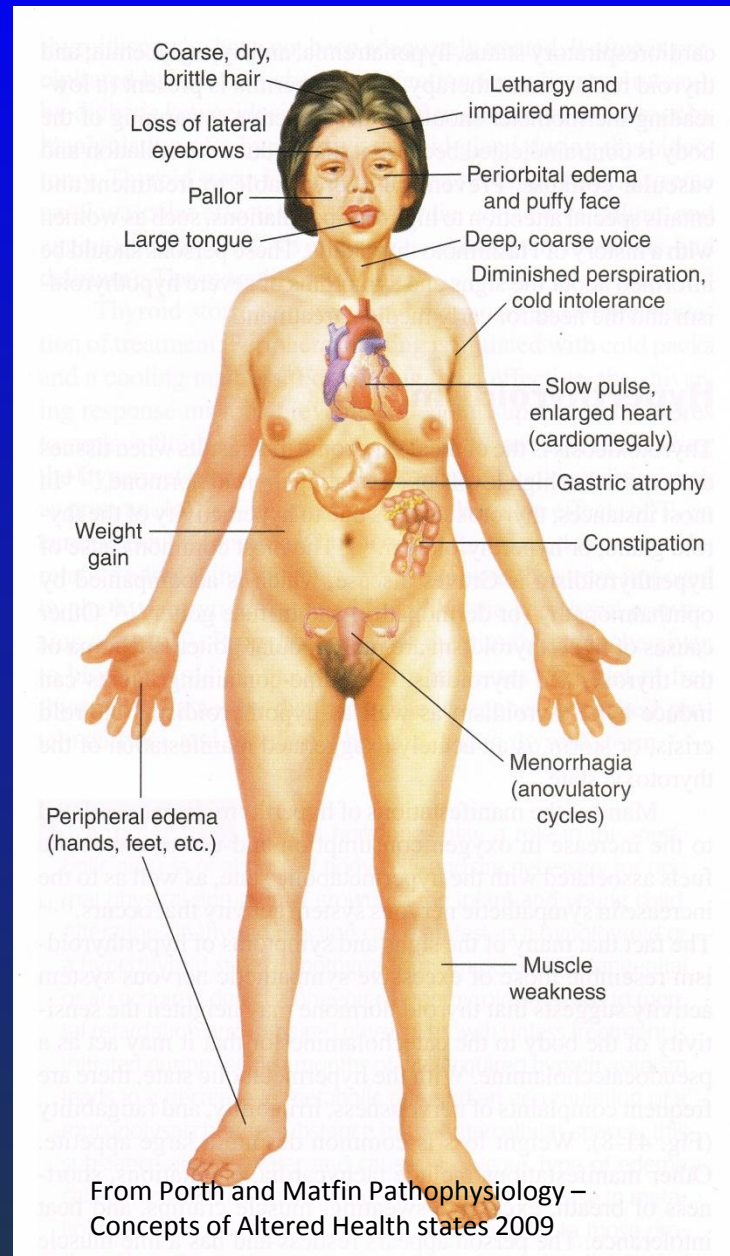
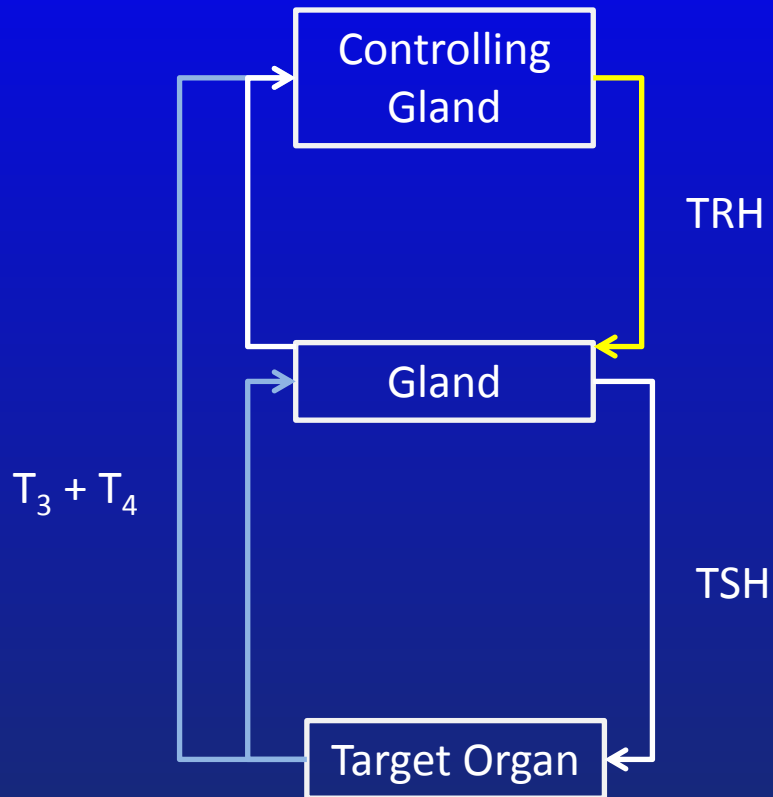
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Hyperthyroidism



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J:
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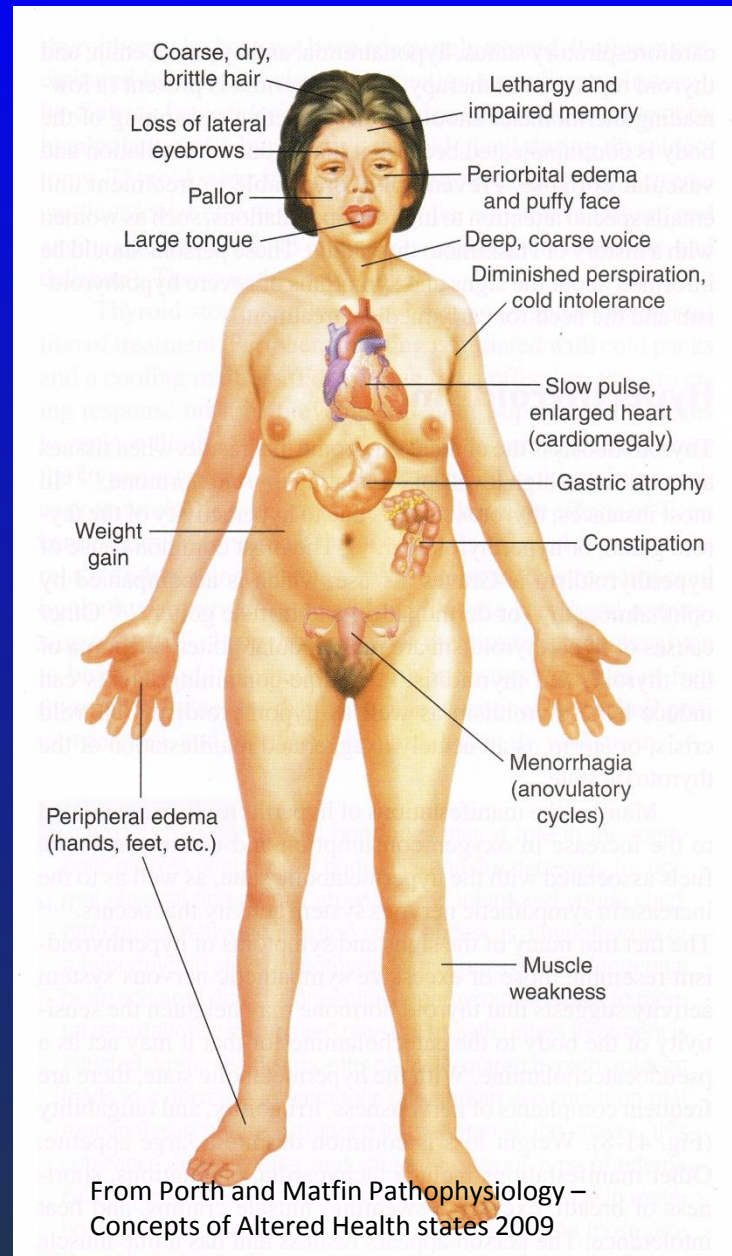
Hypothyroidism



Hypothyroidism



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From Porth and Matfin Pathophysiology –
 Concepts of Altered Health states 2009

Hypothyroidism

TSH	T3 T4	TRH	Conclusion
Slightly elevated	normal	Normal	

Diagnose ?

Hypothyroidism

TSH	T3 T4	TRH	Conclusion
Slightly elevated	normal	Normal	Compensated hypothyroidism Test for antiTBO and antiTg
Raised	Low fT4	Normal/ elevated	

Diagnose ?

Hypothyroidism

TSH	T3 T4	TRH	Conclusion
Slightly elevated	normal	Normal	Compensated hypothyroidism Test for antiTBO and antiTg
Raised	Low fT4	Normal/ elevated	Primary hypothyroidism Test for antiTBO and antiTg
Low	Low fT4	low	

Diagnose ?

Hypothyroidism

TSH	T3 T4	TRH	Conclusion
Slightly elevated	normal	Normal	Compensated hypothyroidism Test for antiTBO and antiTg
Raised	Low fT4	Normal/ elevated	Primary hypothyroidism Test for antiTBO and antiTg
Low	Low fT4	low	Tertiary hypothyroidism
Low	Low fT4	High	

Diagnose ?

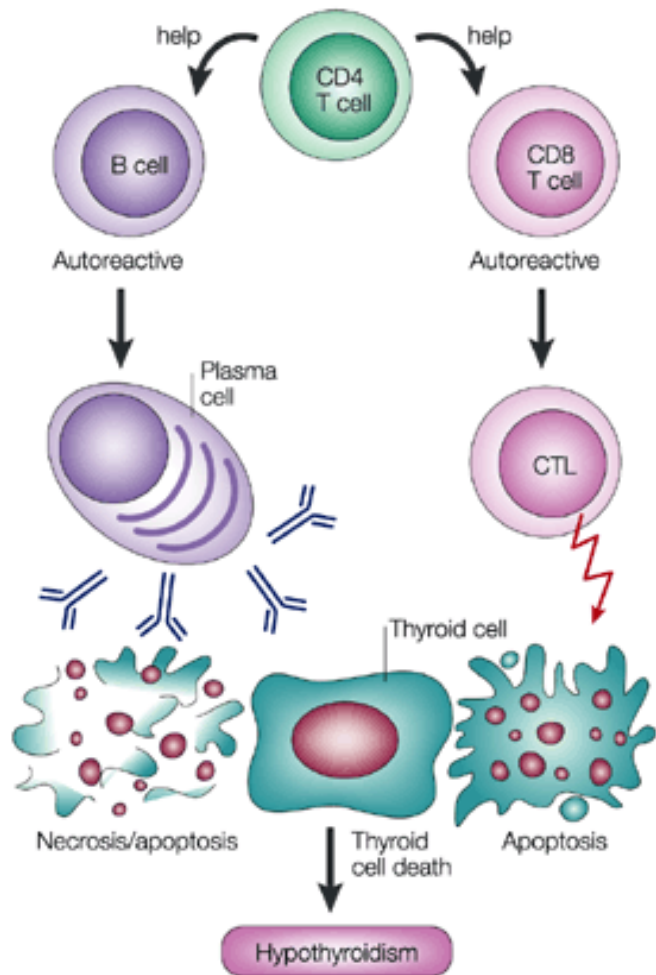
Hypothyroidism

TSH	T3 T4	TRH	Conclusion
Slightly elevated	normal	Normal	Compensated hypothyroidism Test for antiTBO and antiTg
Raised	Low fT4	Normal/ elevated	Primary hypothyroidism Test for antiTBO and antiTg
Low	Low fT4	low	Tertiary hypothyroidism
Low	Low fT4	High	Secondary hypothyroidism
Raised	Raised/ normal	Normal	

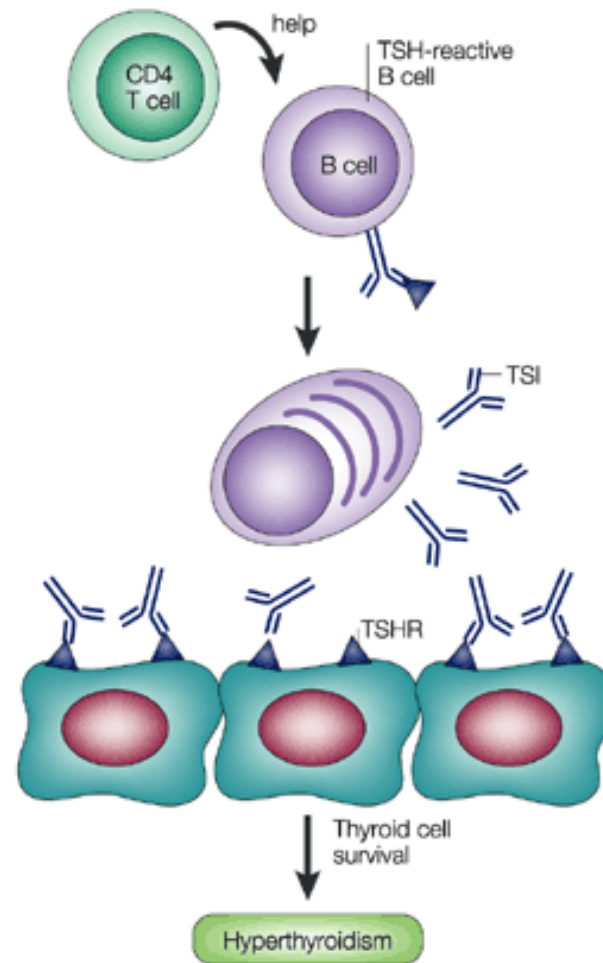
Diagnose ?

Hashimoto's thyroiditis

a Hashimoto's thyroiditis



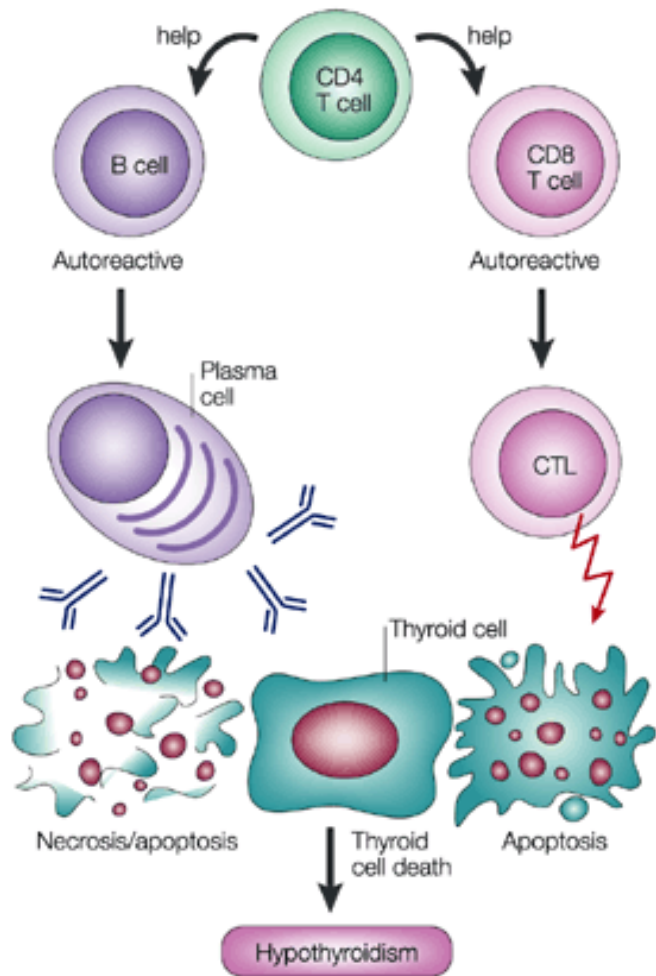
b Graves' disease



Nature Reviews | Immunology

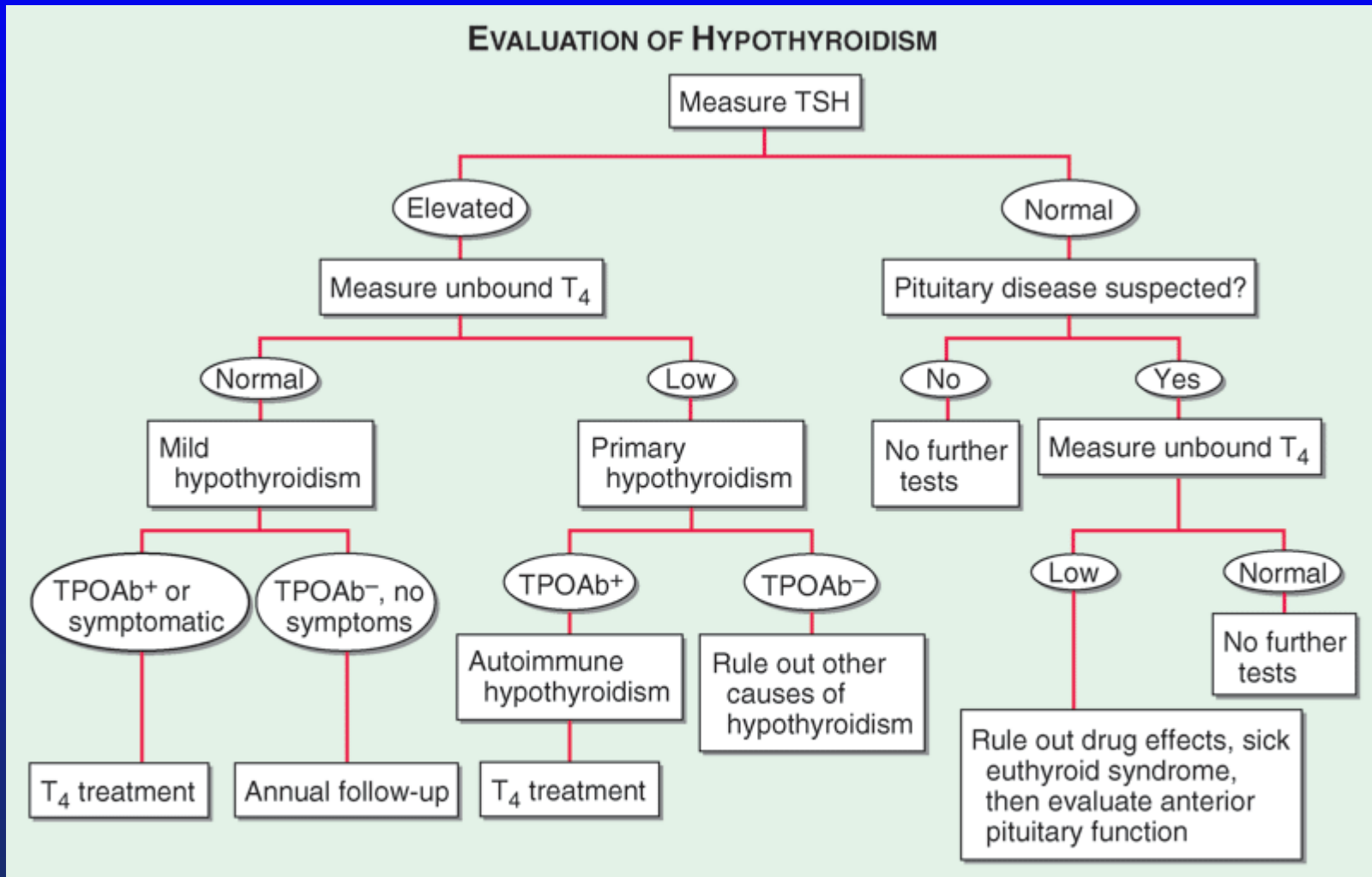
Hashimoto's thyroiditis

a Hashimoto's thyroiditis



Antibodies most likely directed against TBO

Hypothyroidism



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J:
Harrison's Principles of Internal Medicine, 18th Edition: www.accessmedicine.com
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Thyroid Nodule

