Production of Thyroid Hormones Molecular Biology and Pathophysiology

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Natural Thyroid Toolkit

NATURAL THYROID TOOLKIT

Jeffrey Dach MD was originally board certified in diagnostic and interventional radiology, and worked 25 years as a hospital based physician. Dr. Dach retired from hospital based medicine 20 years ago and opened an outpatient clinic specializing in natural thyroid and bioidentical hormones. This book, Natural Thyroid Toolkit, represents 20 years of experience using natural thyroid in the out-patient setting.

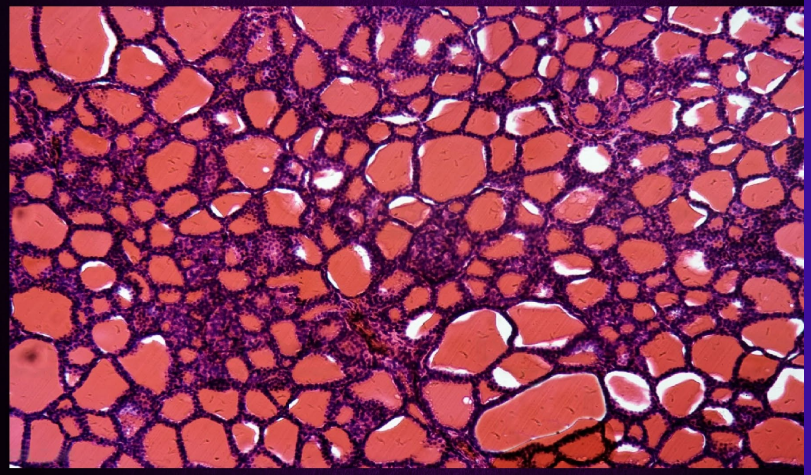
Dr. Dach is the author of ***Heart Book,*** published in 2018, and ***Cracking Cancer Toolkit*** published in 2020.

Author's web site:
www.jeffreydachmd.com

NATURAL THYROID TOOLKIT JEFFREY DACH MD

NATURAL THYROID TOOLKIT

Hashimoto's, Graves,' Iodine, Levothyroxine and Natural Desiccated Thyroid



JEFFREY DACH MD

Radio-Nuclide Scans of Benign Thyroid Disorders

Radio-Isotopes Imaged Under Gamma Camera

I-123

Technetium 99-M

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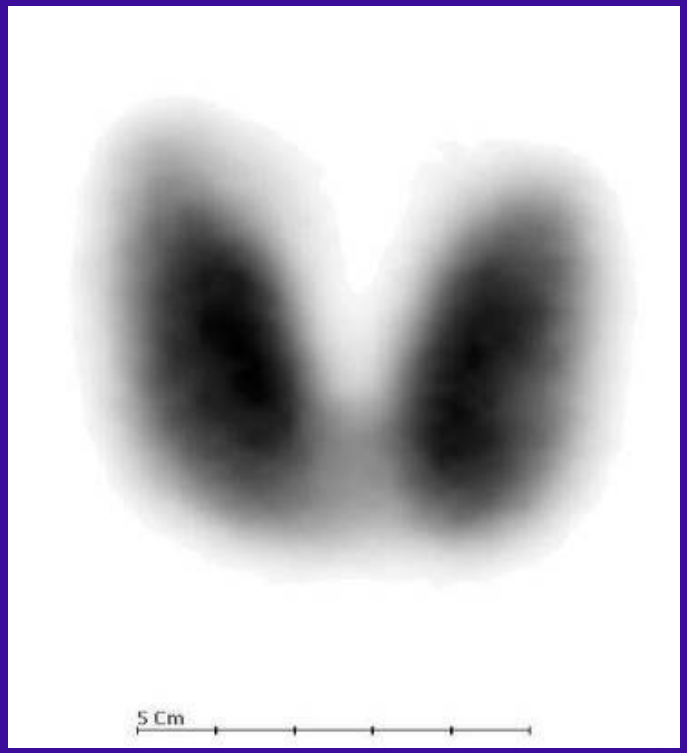
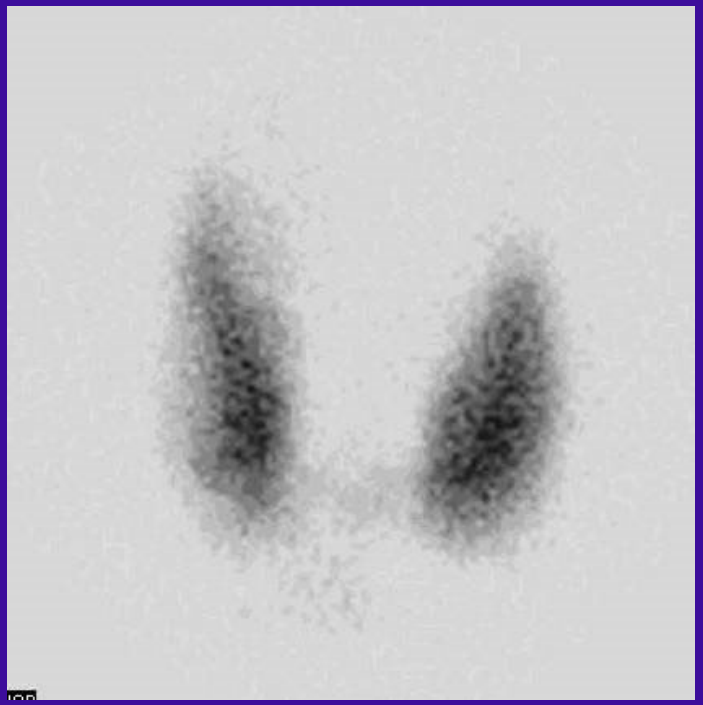
Graves' vs. Normal Thyroid





Graves'

Normal

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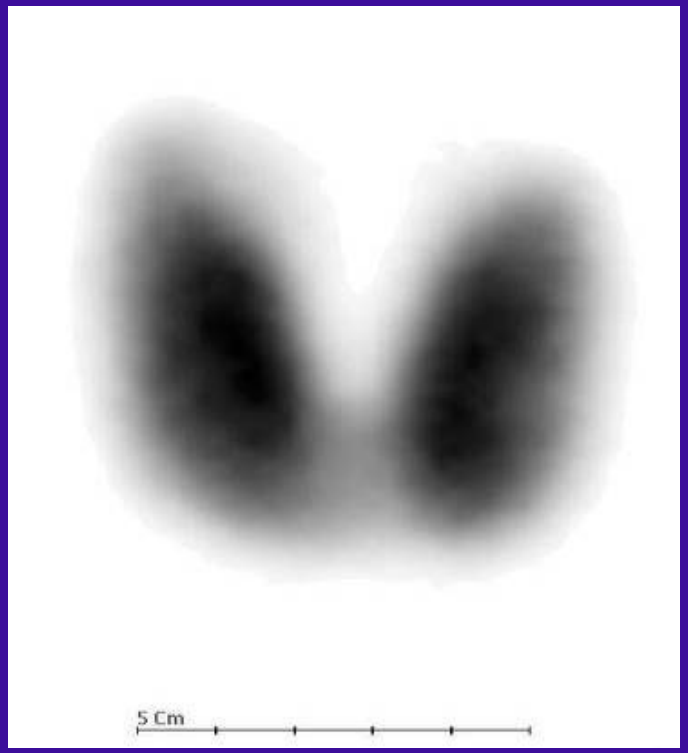
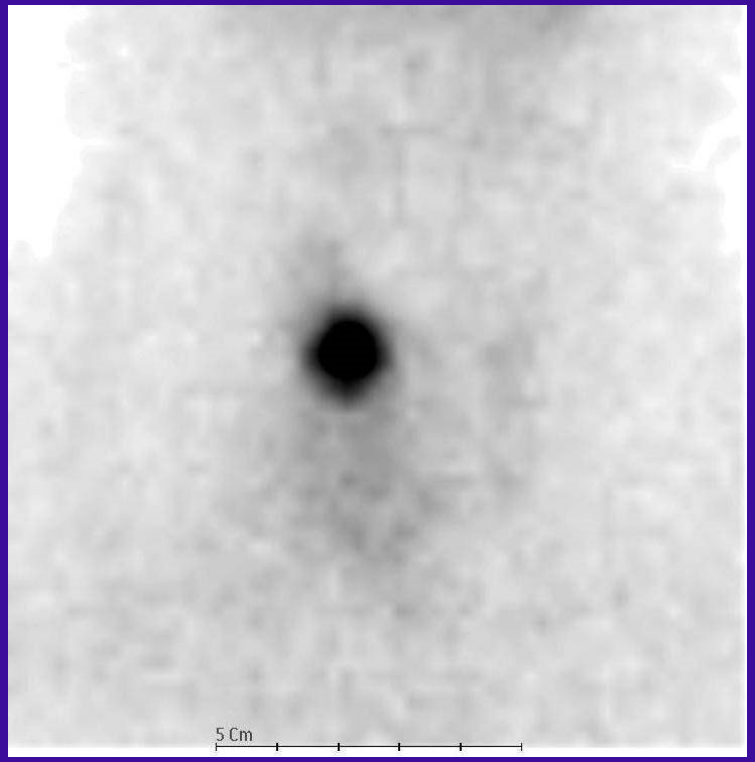
Graves' vs. Autonomous Nodule



Graves'



Autonomous Nodule

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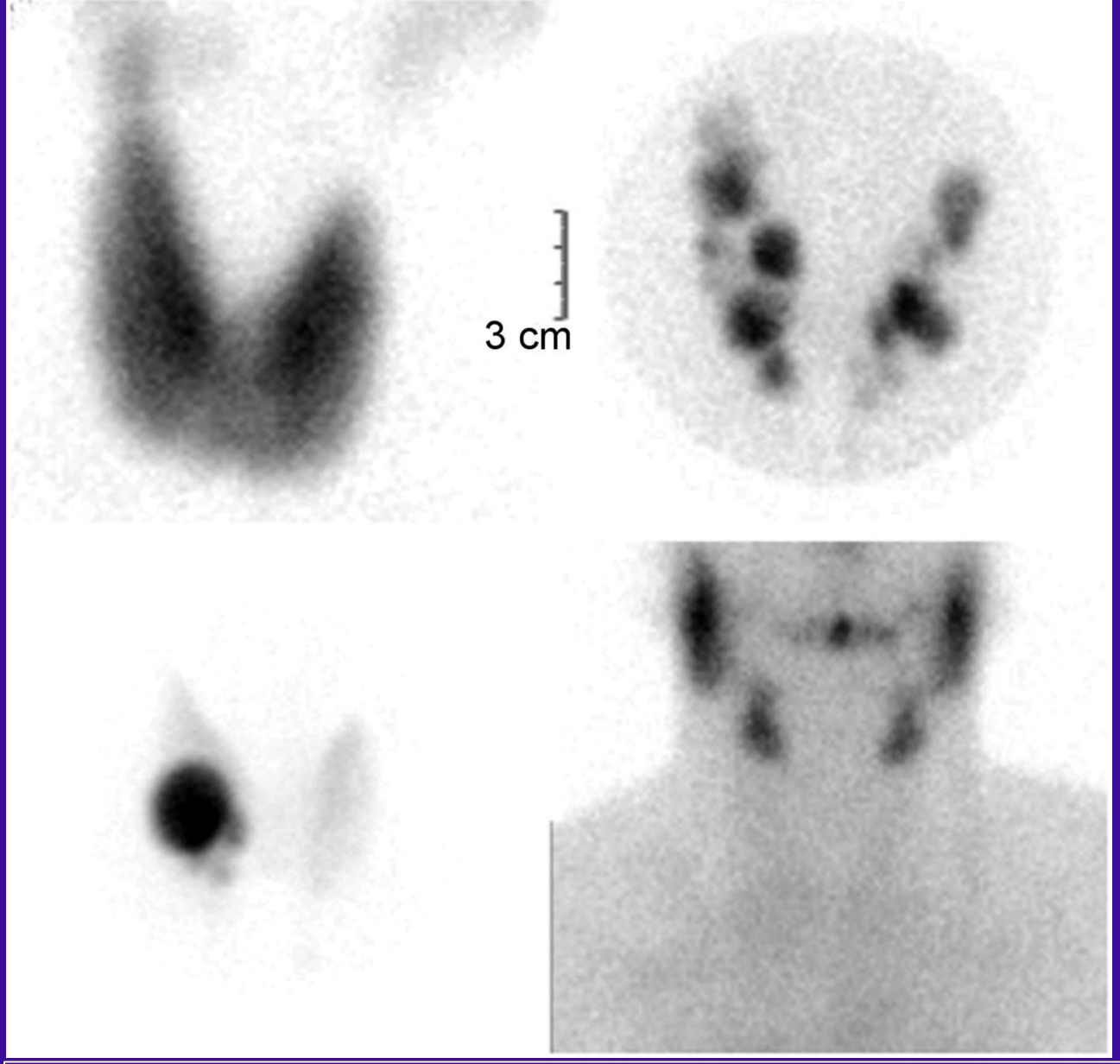
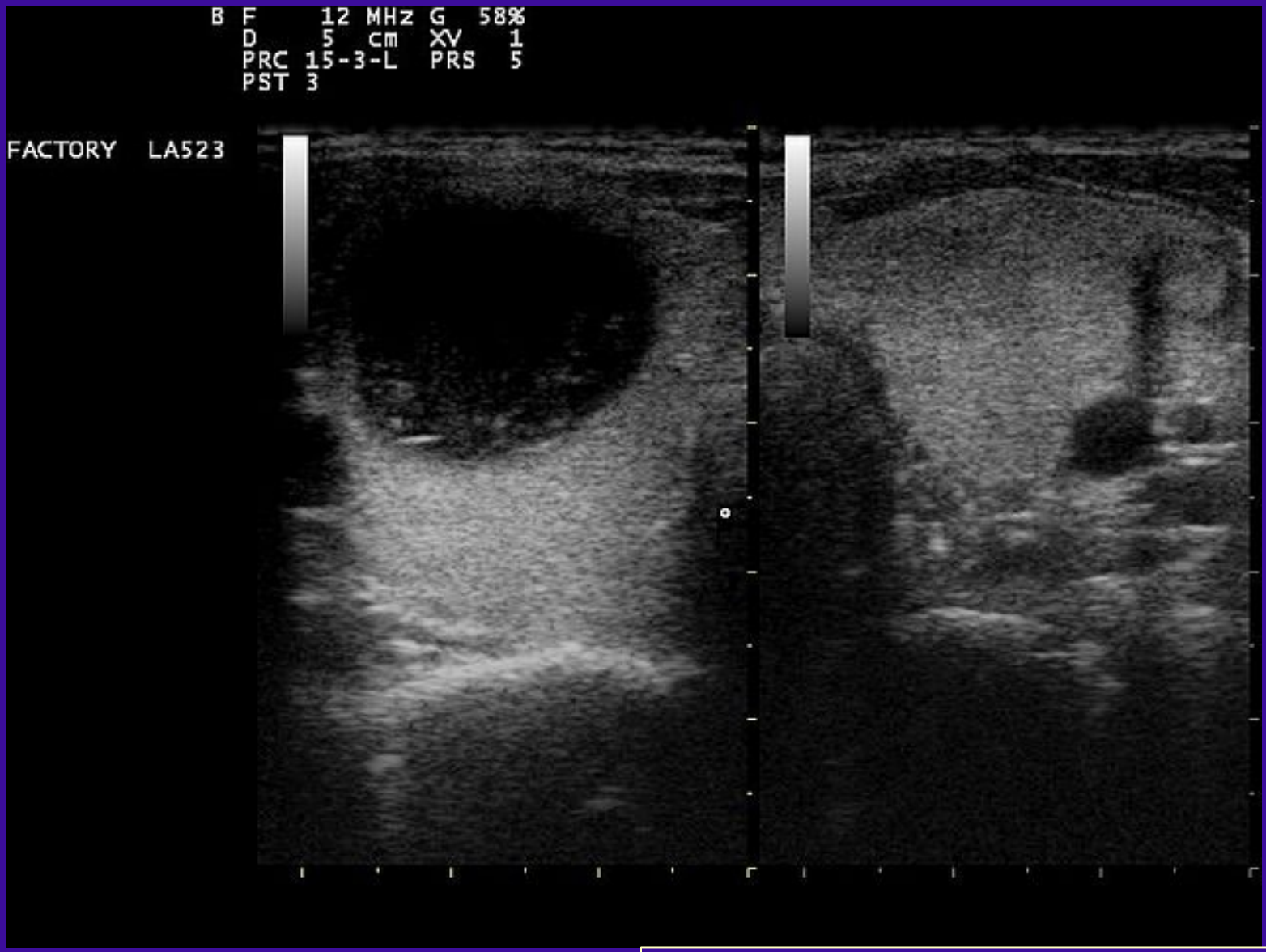


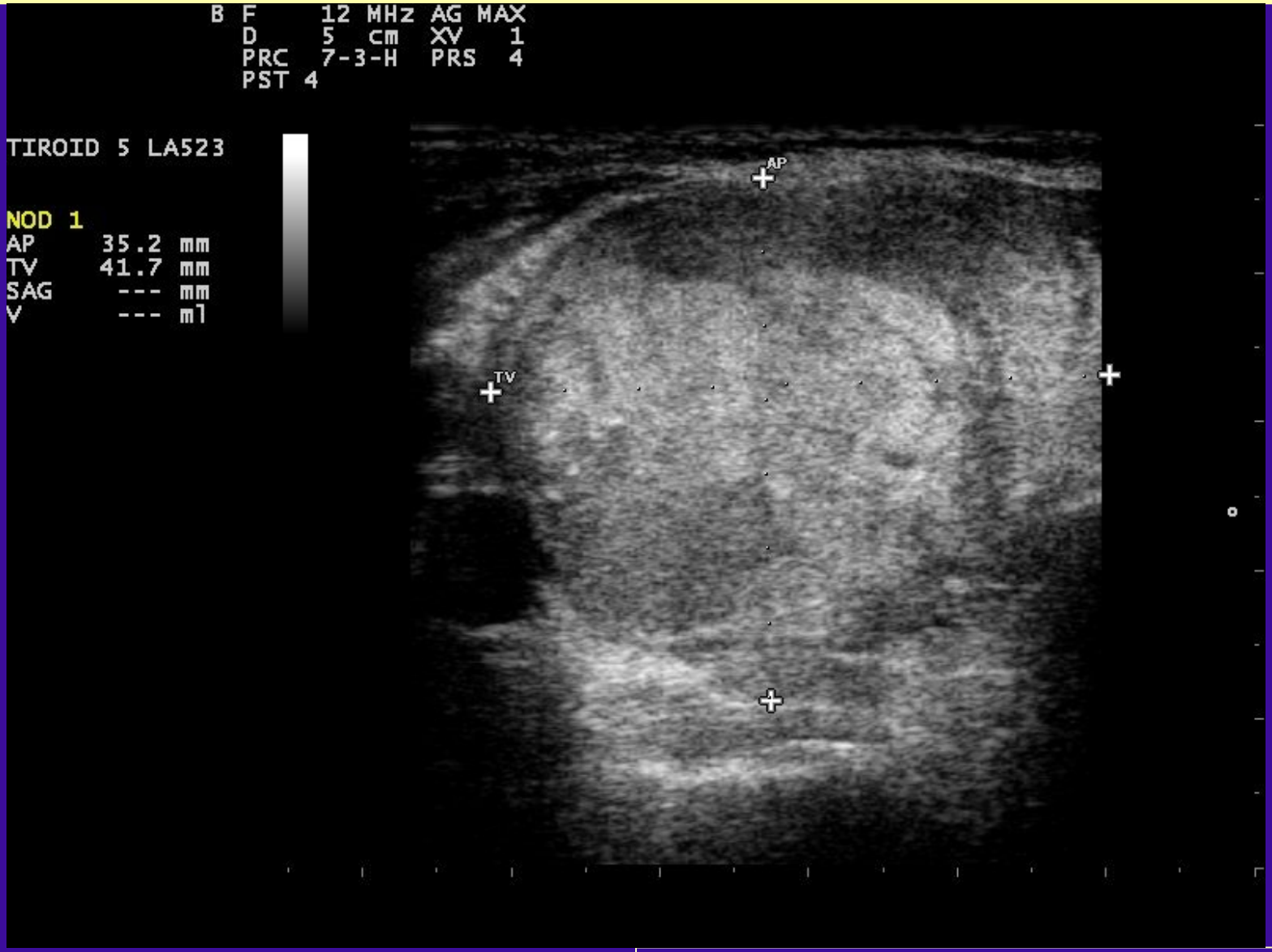
Upper L: NL
Upper R: Multinodular Goiter
Lower Left: Autonomous Nodule
Lower R: Thyroiditis

Mariani, Giuliano, et al. "The role of nuclear medicine in the clinical management of benign thyroid disorders, part 1: hyperthyroidism." Journal of Nuclear Medicine 62.3 (2021): 304-312.

Thyroid Ultrasound - Cyst



Thyroid Ultrasound - Nodule



References – Chapter 33
The Thyroid Nodule Epidemic

(1) Cronan, John J. "Thyroid Nodules: Is It Time to Turn Off the US Machines?" Radiology 247.3 (2008): 602-604.

(2) Ross, Douglas S. "Nonpalpable Thyroid Nodules—Managing an Epidemic." J of Clin Endo & Metaboli87.5 (2002): 1938-1940.

(3) Heller, Keith S. "Do All Cancers Need to Be Treated? the 2006 Hayes Martin Lecture." Archives of Otolaryngology 133.7 (2007): 639-643.

(4) Harach, H. Rubén, et al. "Occult Papillary Carcinoma of The Thyroid. A “Normal” Finding in Finland. A Systematic Autopsy Study." Cancer 56.3 (1985): 531-538.

(5) Harach, H. R., E. Saravia Day, and S. B. Zusman. "Occult Papillary Microcarcinoma of The Thyroid--A Potential Pitfall of Fine Needle Aspiration Cytology?" J of Clini Path 44.3 (1991): 205-207.

Hypothyroidism

Before

After

Symptoms of Hypothyroidism

- Chronic Fatigue
- Constipation
- Weight Gain
- Cognitive Dysfunction
- Depression/Mood
- Cold Intolerance
- Hair Loss
- Weak, Brittle Nails
- Dry Skin

- Muscle aches
- Iregular Menstrual Bleeding
- Heavy Bleeding
- Infertility
- Cardiomyopathy
- High Cholesterol
- Hoarseness
- Psychiatric Disorder

El-Shafie, Kawther T. "Clinical presentation of hypothyroidism." Journal of Family and Community Medicine 10.1 (2003): 55-58.

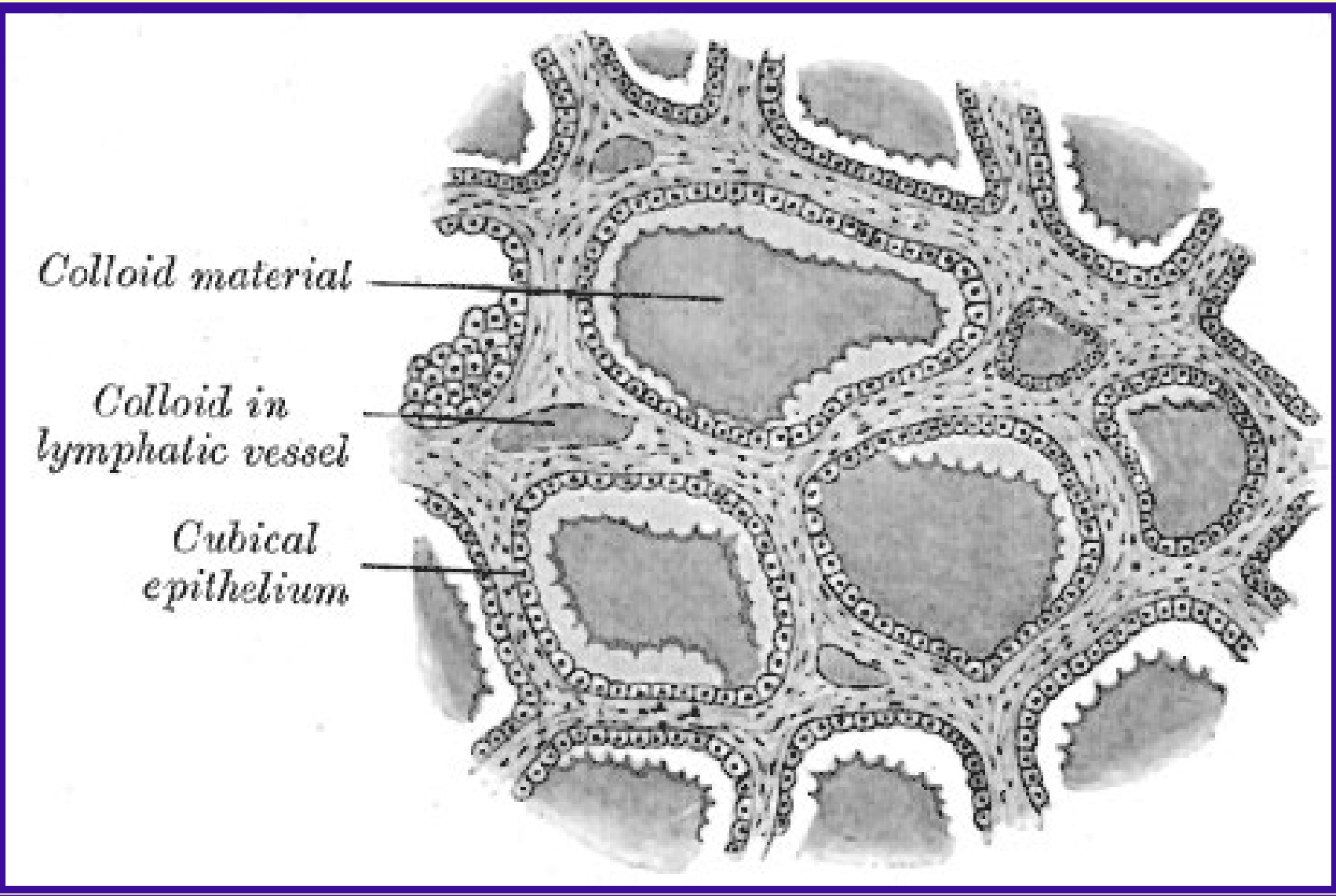
Clinical Signs of Hypothyroidism

- Hypothermia
- Low Body Temp.
- Myxedema
- Periorbital Edema
- Delayed Reflexes
- Loss of scalp hair
- Thinning of eyebrows
- Weak, Brittle, Nails

- Goiter
- Bradycardia
- Decreased sweating
- Abdominal distension
- Macroglossia
- Myxedema
- Dependent edema

Jabbari, Ali, et al. "Common signs and symptoms in hypothyroidism in central part of Iran." Pakistan Journal of Medical Sciences 24.1 (2008): 44.

Production of Thyroid Hormone



Gray's Anatomy Author: Henry Vandyke Carter Anatomy of the Human Body Publisher Lea & Febiger 1918 Henry Gray (1827–1861)

Thyroid Follicles - Microscopic View

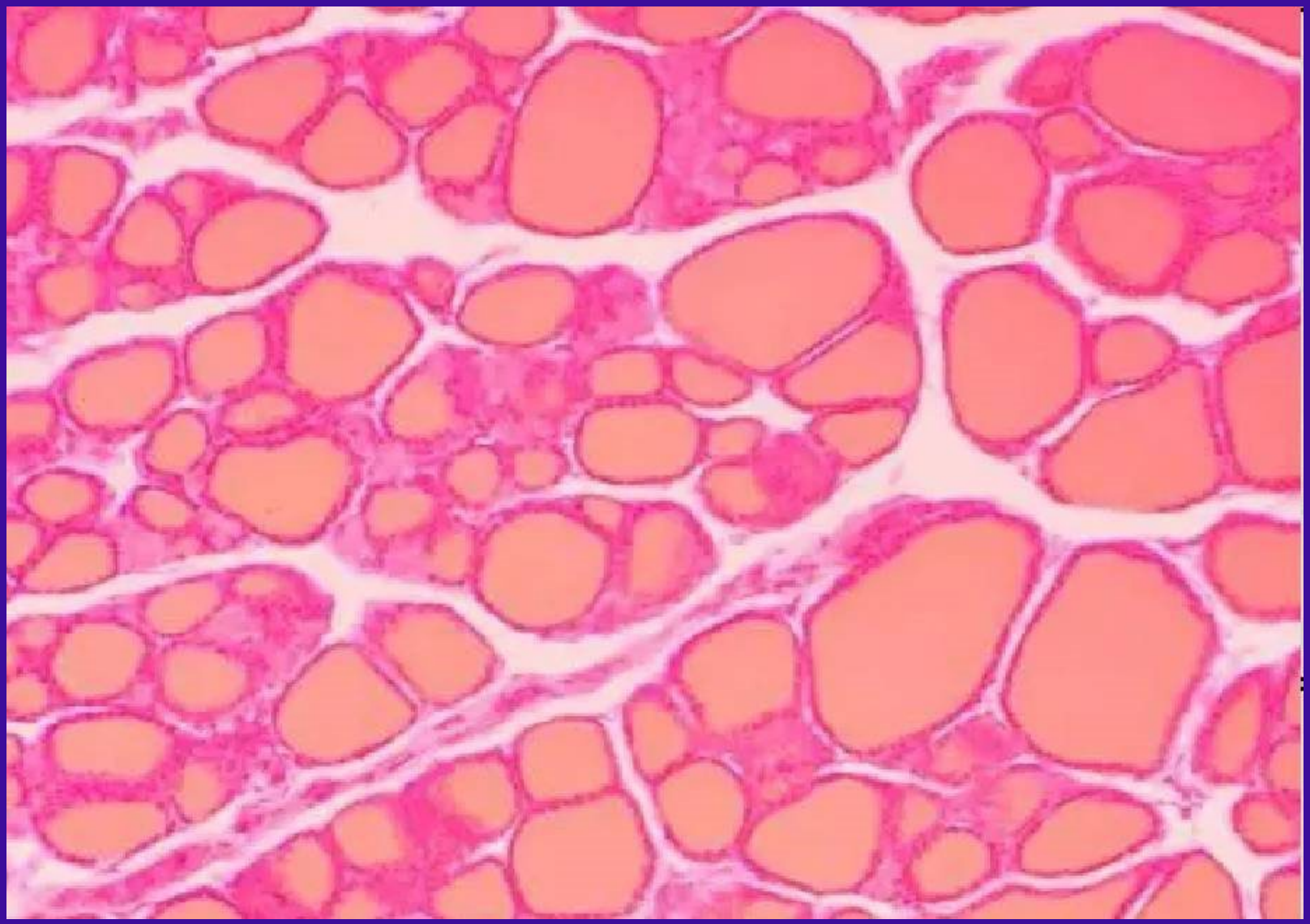
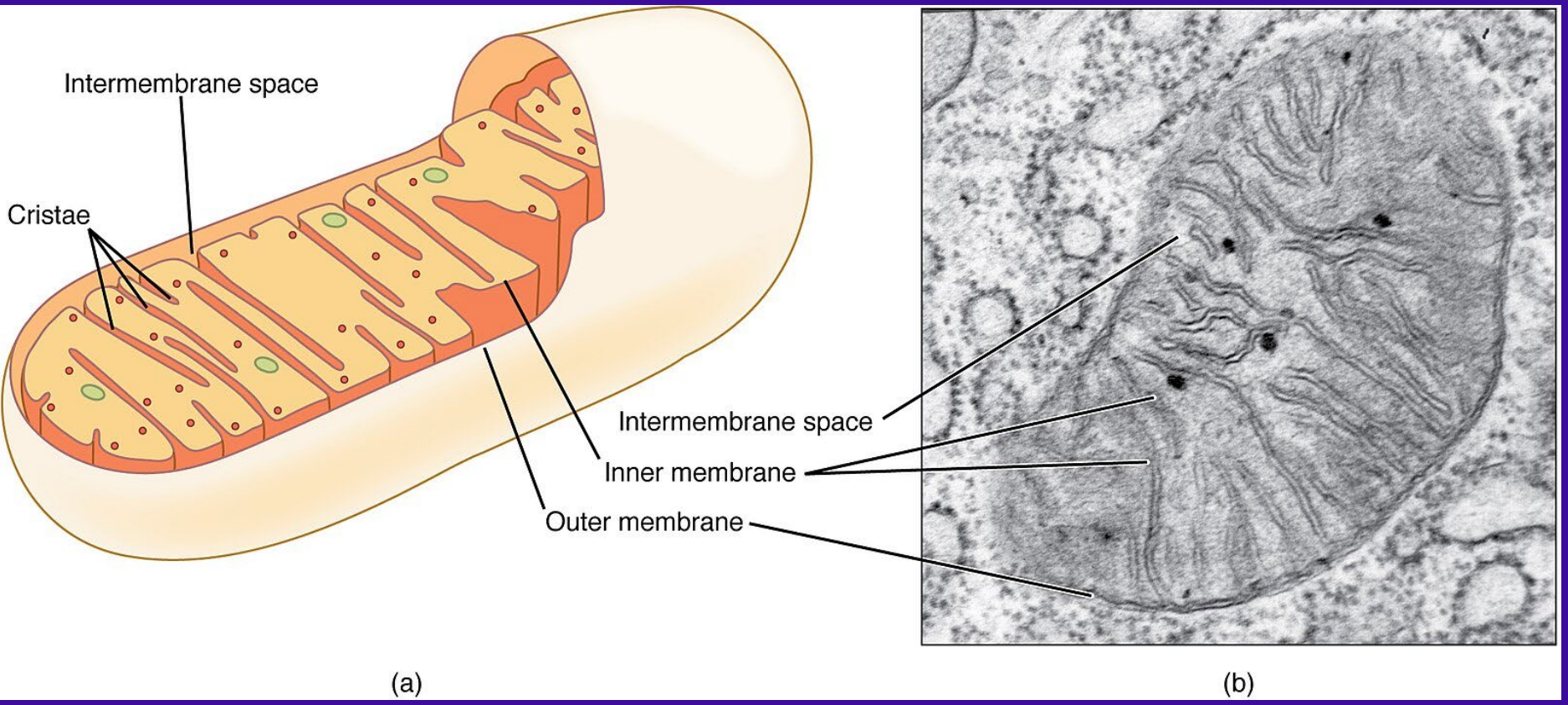


Image: thyroid follicle section under light microscope March 2017
Author :Panzer VI-II Courtesy Wikimedia Commons

Action of Thyroid Hormone on Mitochondria



Electron Microscope Image of Mitochondria Courtesy of Wikimedia Commons Version 8.25 from the Textbook OpenStax Anatomy and Physiologys CC 4.0

Action of Thyroid Hormones

Thyroid Hormone stimulates mitochondrial biogenesis, increasing mitochondrial size and number. Almost all components of the mitochondrial respiratory chain are affected by thyroid hormones.

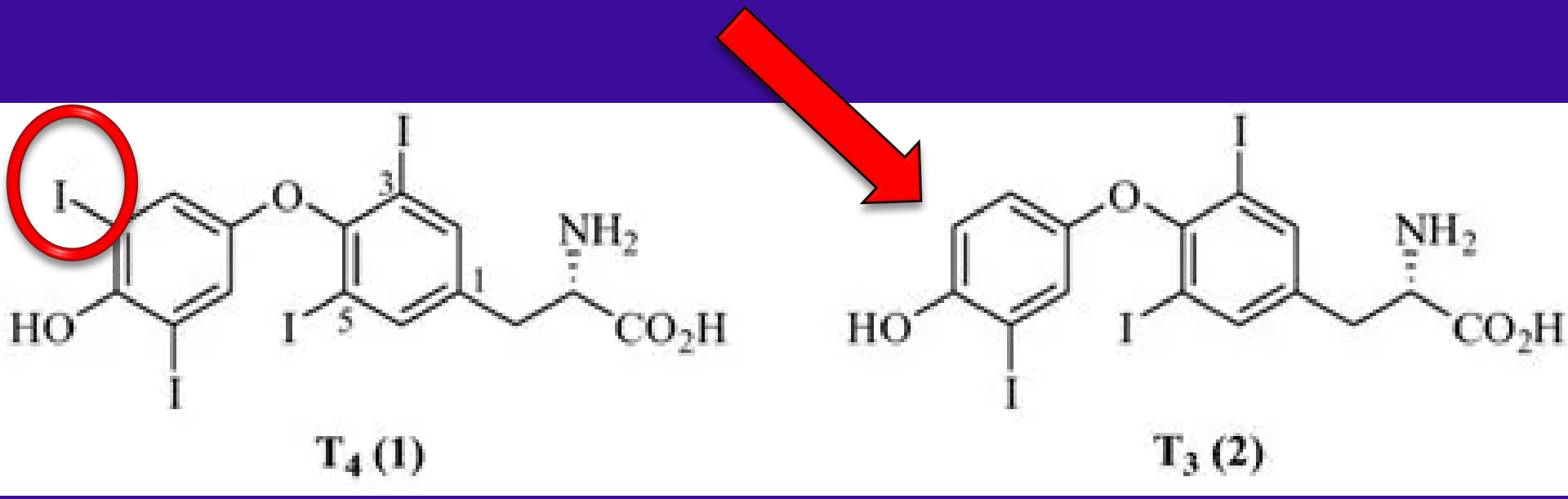
Cioffi, Federica, et al. “Bioenergetic Aspects of Mitochondrial Actions of Thyroid Hormones.” Cells 11.6 (2022): 997.
Vidali, Silvia, et al. "Thyroid hormones enhance mitochondrial function in human epidermis." Journal of Investigative Dermatology 136.10 (2016): 2003-2012.

Action of Thyroid Hormones Mitochondriogenesis

Thyroid hormone stimulates mitochondriogenesis and augments cellular oxidative capacity.
Thyroid hormone induces substantial modifications in mitochondrial inner membrane protein and lipid compositions.

Harper, Mary-Ellen, and Erin L. Seifert. “Thyroid hormone effects on mitochondrial energetics.” Thyroid 18.2 (2008): 145-156.

Production of Thyroid Hormone

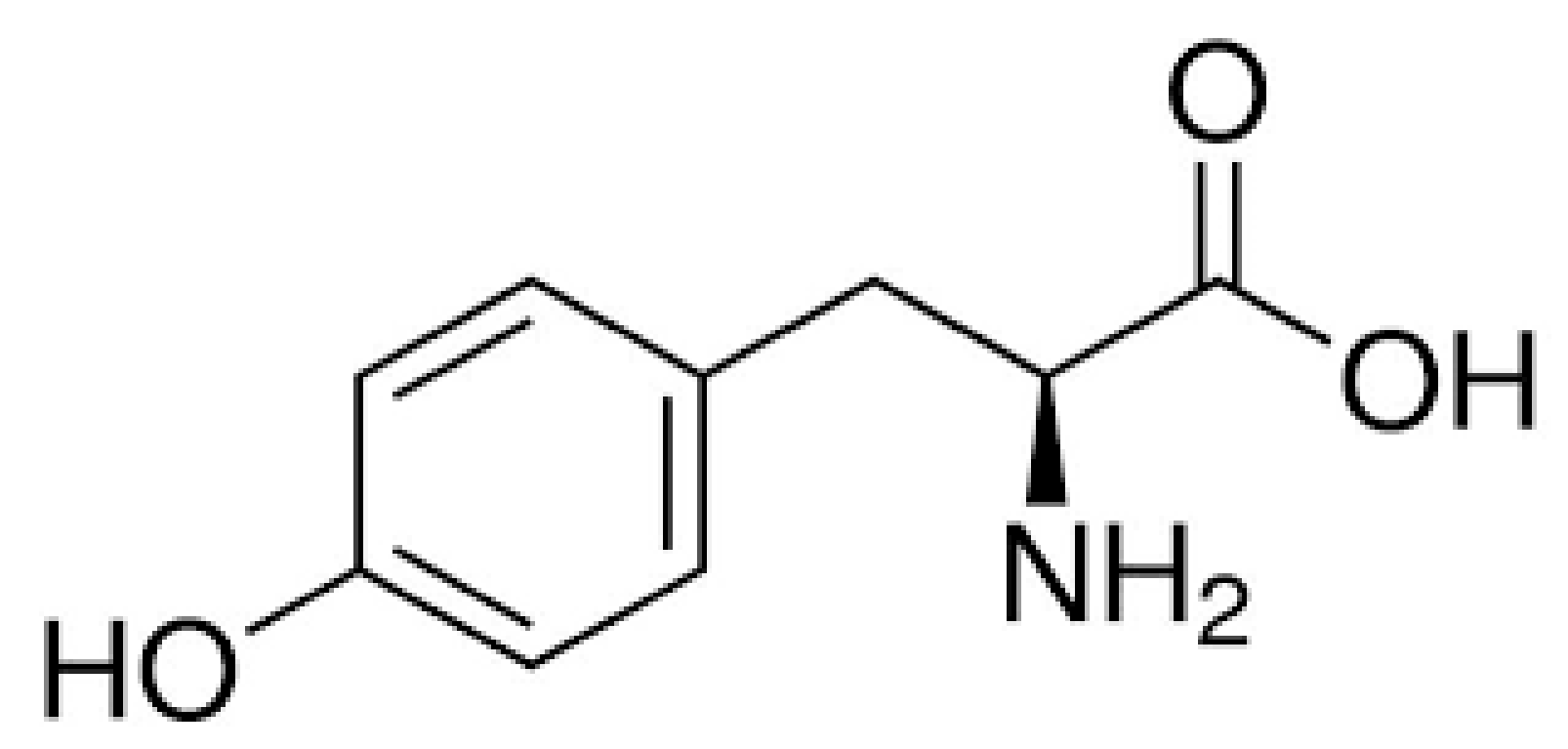


T4

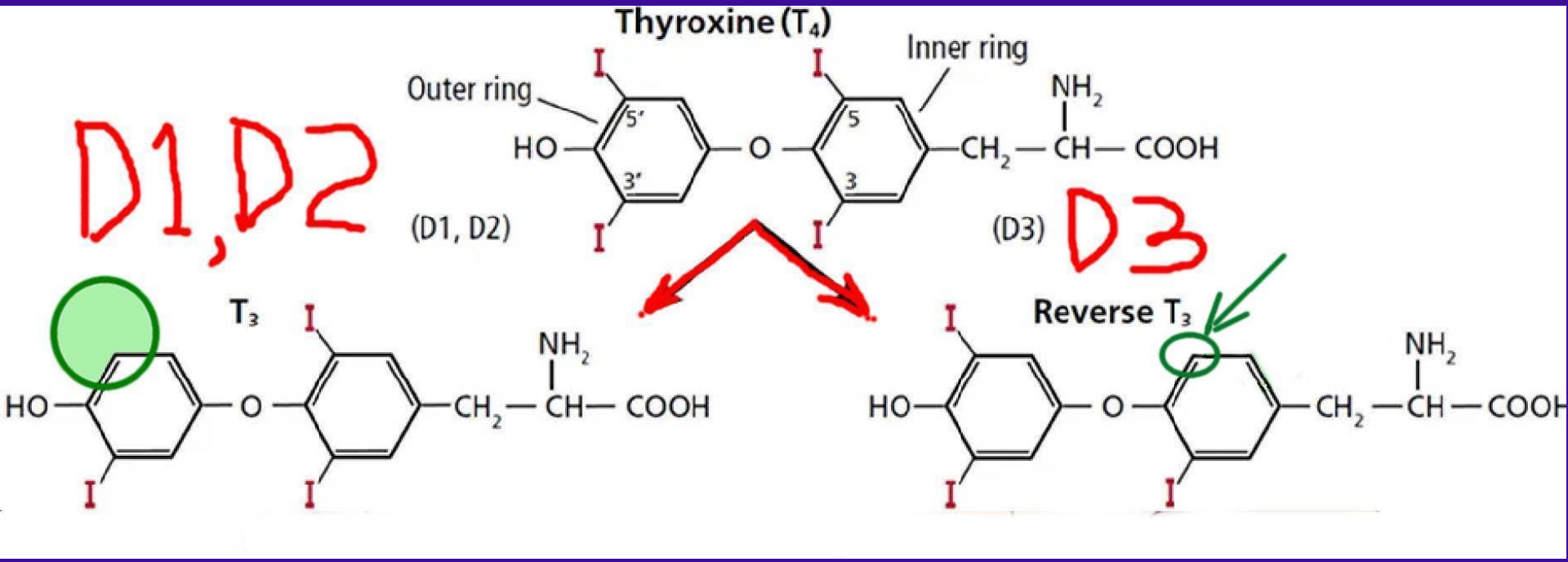
T3

Courtesy of de Castro, Guilherme Vieira, et al. “Synthesis of Analogues of Thyroid Hormones: Nuclear Receptor Modulators.” Orbital: The Electronic Journal of Chemistry 7.3 (2015): 282-291.(57)

Tyrosine



Production of Thyroid Hormone Reverse T3/ D2/D2/D3



T3

Reverse T3

Gomes-Lima, Cristiane, Leonard Wartofsky, and Kenneth Burman. "Can Reverse T3 Assay Be Employed to Guide T4 vs. T4/T3 Therapy in Hypothyroidism?." Frontiers in Endocrinology 10 (2019): 856.ourtesy of de Castro,

De-Iodinase Enzymes Converts T4 to T3

- **Type One Deiodinase** - responsible for most of T3 in the bloodstream. Located on cell membrane. Also converts T4 to T3 within Thyroid. Inhibited by PTU and Propranolol.
- **Type Two Deiodinase** – Converts T4 to T3 within the cells. Located near the nucleus.
- **Type Three Deiodinase-** Converts T4 to Reverse T3 (rT3), the inactive form, A protective mechanism. rT3 is high in Graves' disease, low in hypothyroidism.
- Deiodinase is a selenium based enzyme. Selenium deficiency impairs function.

Bianco, A, et al. "Biochemistry, Cellular and Molecular Biology, and Physiological Roles of the Iodothyronine Selenodeiodinases." Endo Rev 23.1 (2002): 38-89.

Five Steps - Production of Thyroid Hormone

1. Synthesis of Thyroglobulin
2. Uptake of Iodide (I-) by the Sodium Iodide Symporter (NIS).
3. Iodination of Thyroglobulin (TPO, H2O2)
4. Storage of Organified Thyroglobulin.
5. Release of thyroid hormone into circulation:

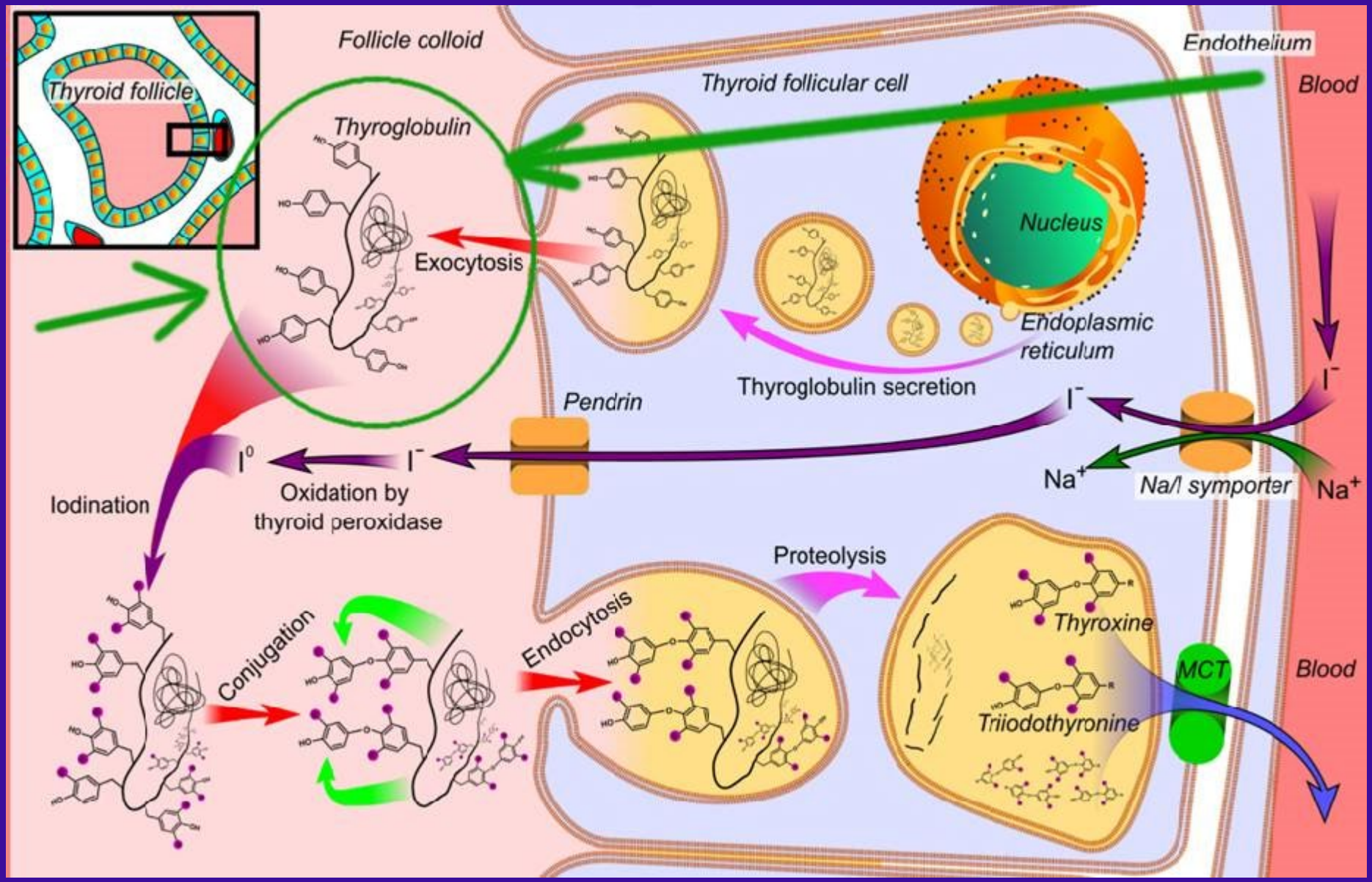
Shahid, Muhammad A., Muhammad A. Ashraf, and Sandeep Sharma. “Physiology, thyroid hormone.” StatPearls [Internet]. StatPearls Publishing, 2022.

Step One – Synthesis of Thyroglobulin

- Thyroglobulin (TG) is the precursor to thyroid hormone.
- TG is secreted by exocytosis and stored in the follicle.
- Initially, thyroglobulin does not contain iodine. However, over time, the thyrocyte attaches iodine to the thyroglogulin in a process called organification.

Shahid, Muhammad A., Muhammad A. Ashraf, and Sandeep Sharma. “Physiology, thyroid hormone.” StatPearls [Internet]. StatPearls Publishing, 2022.

Production of Thyroglobulin - Green Arrow

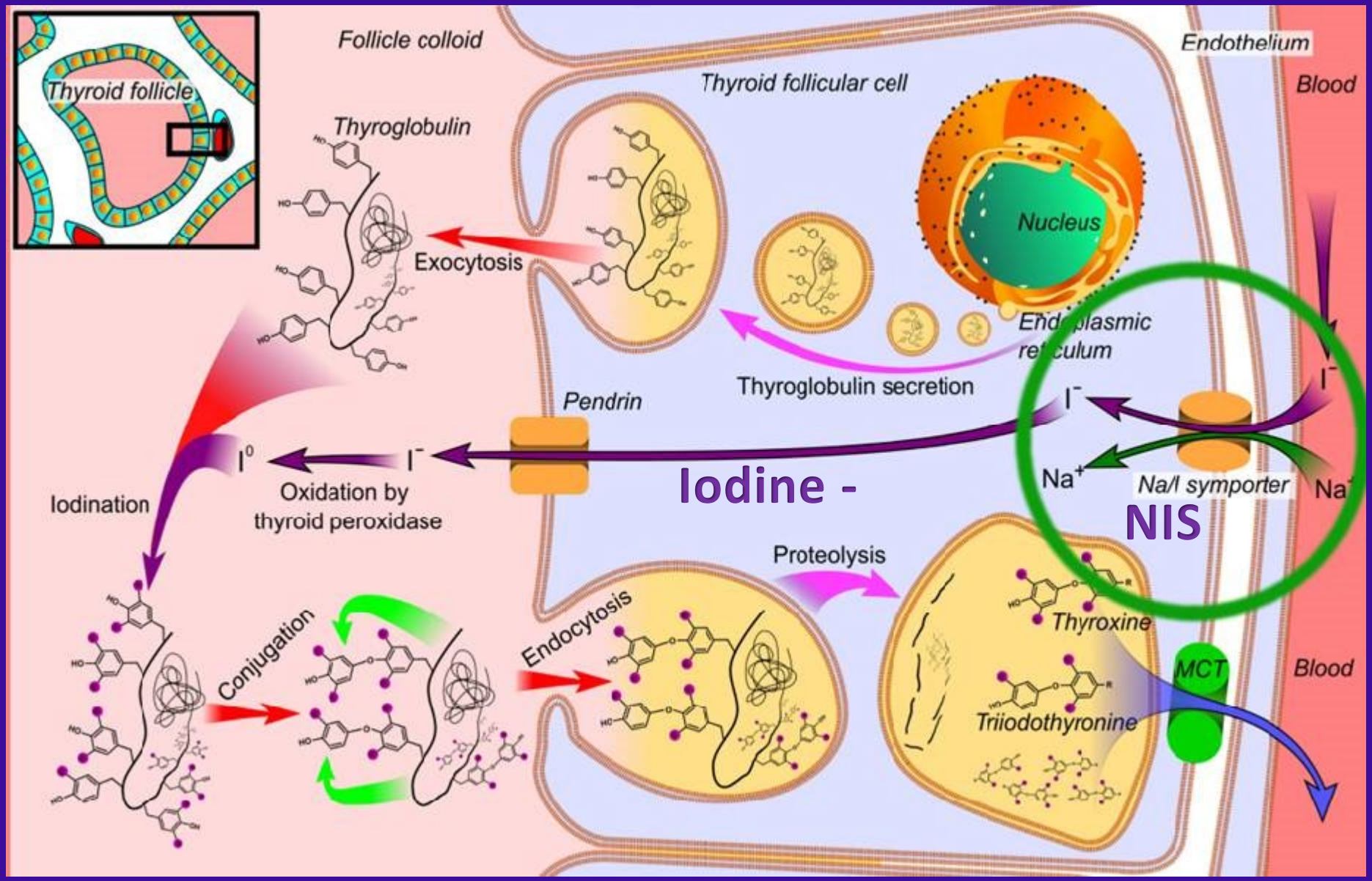


Step Two – Uptake of Iodide by NIS

- NIS is a protein pump within the basolateral membrane of the thyrocyte.
- TSH increases activity of NIS, NaI-Symporter, the active transport of iodide into the thyrocyte.
- The NIS creates concentrations 20 to 50 times greater than blood stream.
- In Grave's this ratio is >100 times higher due to TSH Receptor stimulation by TSI/ TRAb Abs.
- NIS also present: Stomach, salivary gland, breast, extraocular muscle tissue.

Ajjan, R. A., et al. "Regulation and tissue distribution of the human sodium iodide symporter gene." Clin endocrinology 49.4 (1998): 517-523.
Ravera, Silvia, et al. "The sodium/iodide symporter (NIS): molecular physiology and preclinical and clinical applications." Ann review of physiology 79 (2017): 261.

Uptake of Iodine -Sodium Iodide Transporter NIS



Step Three – Iodination of Thyroglobulin

- Iodination of Thyroglobulin into thyroid hormone (organification) is carried out by TPO Thyroperoxidase enzyme, an iron containing molecule with a porphyrin ring structure similar to hemoglobin.
- TPO is secreted into the follicular lumen at the thyrocyte apex villous membrane, and has three functions:
- 1) oxidation of iodide (I-) to iodine (I2).
- 2) organification of iodine (attachment of iodine(I2) to thyroglobulin).
- 3) coupling together of two Tyrosine residues.

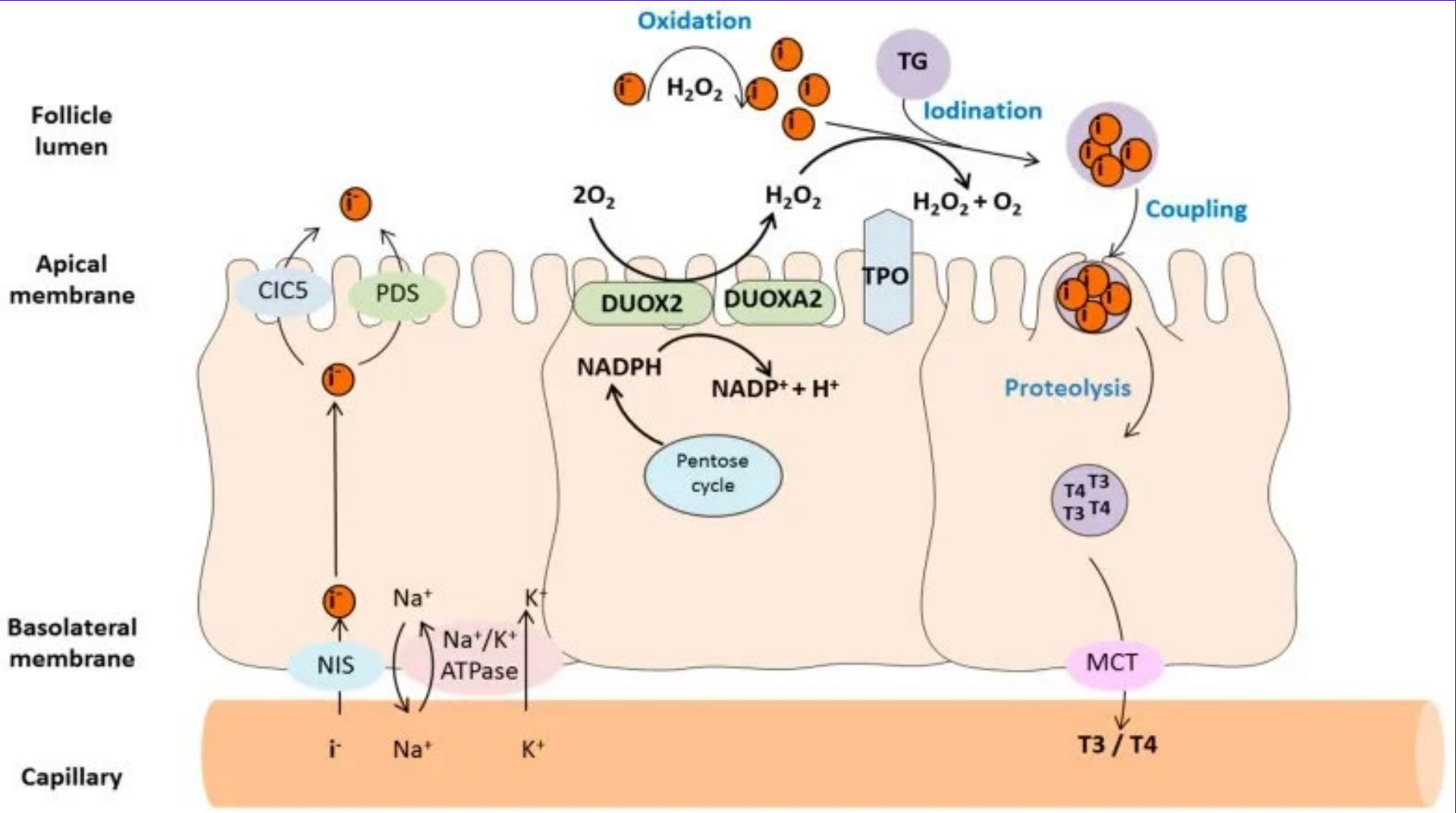
Shahid, Muhammad A., Muhammad A. Ashraf, and Sandeep Sharma. “Physiology, thyroid hormone.” StatPearls [Internet]. StatPearls Publishing, 2022.

Step Three – Iodination/Organification of Thyroglobulin

- **TPO uses H202:** to oxidize iodide (I-) to iodine (I2).
- **DUOX enzyme:** generates H202 within villous apex of thyrocyte. Excess H202 is DAMAGING.
  Oxidation: Iodide, a negative ion (I-), is oxidized to molecular iodine (I2) by TPO enzyme using H202 as substrate at micro-villous surface of the apical membrane of the thyrocyte.
- **Organification:** Iodine(I2) attaches to Tyrosine residues of Thyroglobulin, generating monoiodotyrosine (MIT, one iodine) and diiodotyrosine (DIT, two iodines)
- **Coupling Reaction**: Iodinated Tyrosines are coupled by TPO making T3 and T4.

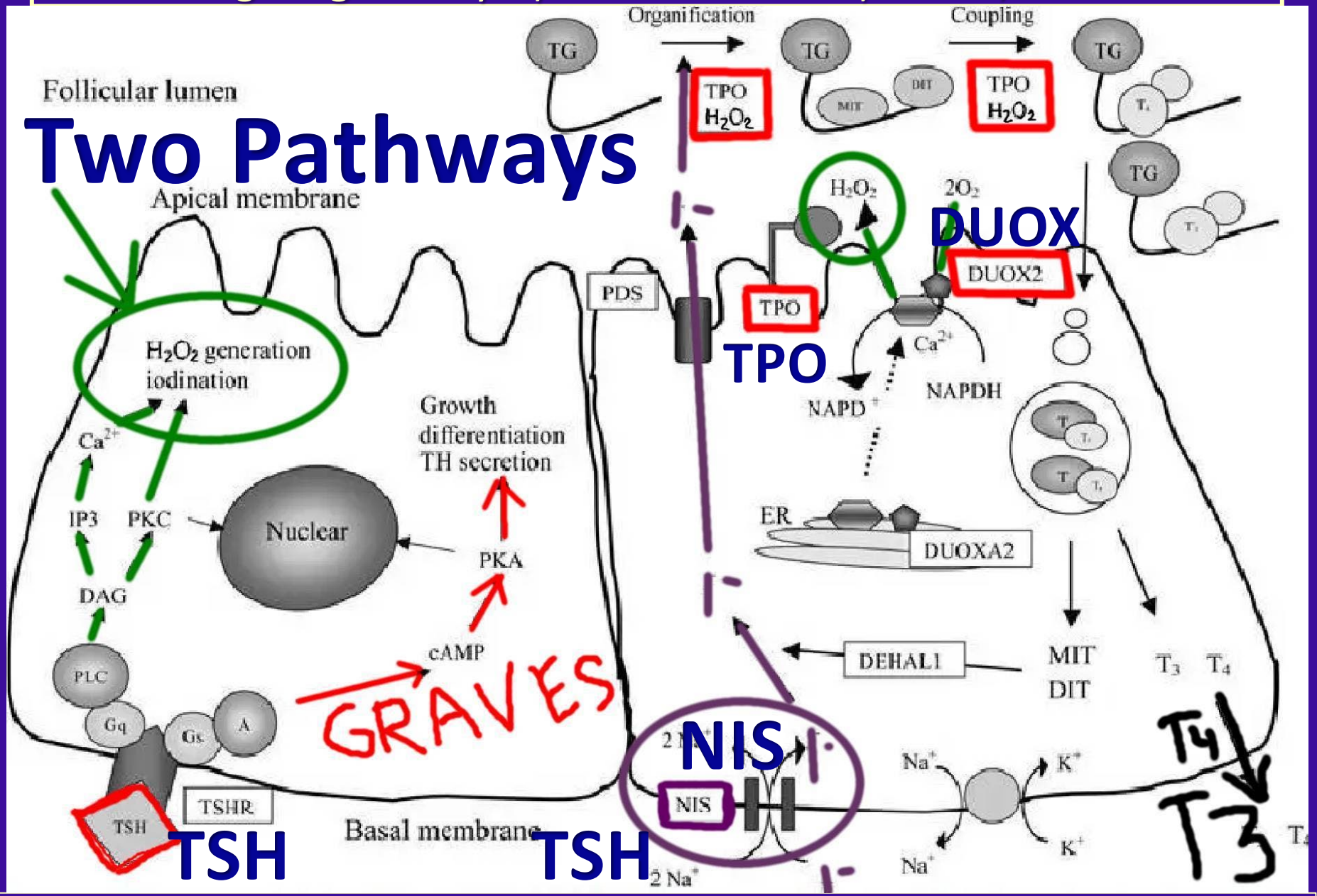
Shahid, Muhammad A., Muhammad A. Ashraf, and Sandeep Sharma. “Physiology, thyroid hormone.” StatPearls [Internet]. StatPearls Publishing, 2022.

Hydrogen Peroxide Generation



Thyroid Hormone Synthesis Courtesy of Szanto 2019 Fig 3. Szanto, Ildiko, Marc Pusztaszeri, and Maria Mavromati. “H2O2 metabolism in normal thyroid cells and in thyroid tumorigenesis: focus on NADPH oxidases.” Antioxidants 8.5 (2019): 126.

TSH: 2 Signaling Pathways 1) H202 Generation 2) Growth, TH secretion



Thyroid Hormone Synthesis Courtesy of Szanto 2019 Fig 3. Szanto, Ildiko, Marc Pusztaszeri, and Maria Mavromati. "H2O2 metabolism in normal thyroid cells and in thyroid tumorigenesis: focus on NADPH oxidases." Antioxidants 8.5 (2019): 126.

Nuclear Reactor - Hydrogen Peroxide Generation

- H2O2…in thyroid cells, is a signal, a mitogen, a mutagen, a carcinogen, and a killer…It is proposed that various pathologies can be explained, at least in part, by overproduction and lack of degradation of H2O2 (tumorigenesis, **myxedematous cretinism**, and thyroiditis) and by failure of the H2O2 generation or its positive control system (congenital hypothyroidism)… end quote Dr. Song. 2007

Song, Yue, "Roles of Hydrogen Peroxide in Thyroid Physiology and Disease." J of Clin Endo & Metab 92.10 (2007): 3764-3773.

TSH stimulates Hydrogen Peroxide Generation/ Mutageneisis

- TSH stimulates H2O2 Generation, Graves' Abs (TSI, TRAB) Do Not.
- The important generation of H2O2 in thyroid cells might account for mutagenesis, and so might the generation of nodules in the thyroid.
- This would also explain in part why more nodules are found in iodine-deficient areas…
- This Explains why no Nodules in Graves'.
- Oncologists Suppress TSH in Post Thyroidectomy Cancer Pts. Turns off H202 and Mutagenesis

Song, Yue, et al. "Roles of Hydrogen Peroxide in Thyroid Physiology and Disease." The Journal of Clinical Endocrinology & Metabolism 92.10 (2007): 3764-3773.

Hydrogen Peroxide Over-Production
Iodine and Selenium Deficiency

- "**Myxedematous endemic cretinism** [Zaire, Africa] is caused by thyroid destruction after birth, has been linked to low iodine supply in early life, leading to intense stimulation [by elevated TSH] and presumably H2O2 generation, to passage from low O2 to high O2 at birth, to selenium deficiency, and thus to decreases in GSH peroxidase and thioredoxinreductase activity and to dietary thiocyanate…" Dr. Song, 2007.

Song, Yue, et al. "Roles of Hydrogen Peroxide in Thyroid Physiology and Disease." The Journal of Clinical Endocrinology & Metabolism 92.10 (2007): 3764-3773.

Nuclear Meltdown - References for Myxedematous Endemic Cretinism [Zaire, Africa]

(1) Vanderpas, Jean B., et al. "Iodine and Selenium Deficiency Associated with Cretinism in Northern Zaire." The American Journal of Clinical Nutrition 52.6 (1990): 1087-1093.

(2) Vanderpas, Jean-Baptiste, et al. "Iodine and Selenium Deficiency in Northern Zaire." The American Journal of Clinical Nutrition 56.5 (1992): 957-958.

(3) Contempre, Bernard, et al. “Effects of Selenium Deficiency on Thyroid Necrosis, Fibrosis and Proliferation: A Possible Role in Myxoedematous Cretinism.” European Journal of Endocrinology 133.1 (1995): 99-109.

(4) Contempre, Bernard, et al. "Selenium Deficiency Aggravates the Necrotizing Effects of a High Iodide Dose in Iodine-Deficient Rats." Endocrinology 132.4 (1993): 1866-1868.

Hydrogen Peroxide Generation/ Selenum Deficiency/ Hashimoto's Auto-Immune Thyroiditis

- Interestingly, a similar scenario has been proposed for the physiopathology of thyroiditis [both Painless and Auto-immune].
- Selenium dietary supplementation has therefore been proposed for prevention and treatment of thyroiditis and has indeed alleviated it. (20)

Song, Yue, et al. "Roles of Hydrogen Peroxide in Thyroid Physiology and Disease." The Journal of Clinical Endocrinology & Metabolism 92.10 (2007): 3764-3773.

References - Selenium for Hashimoto's

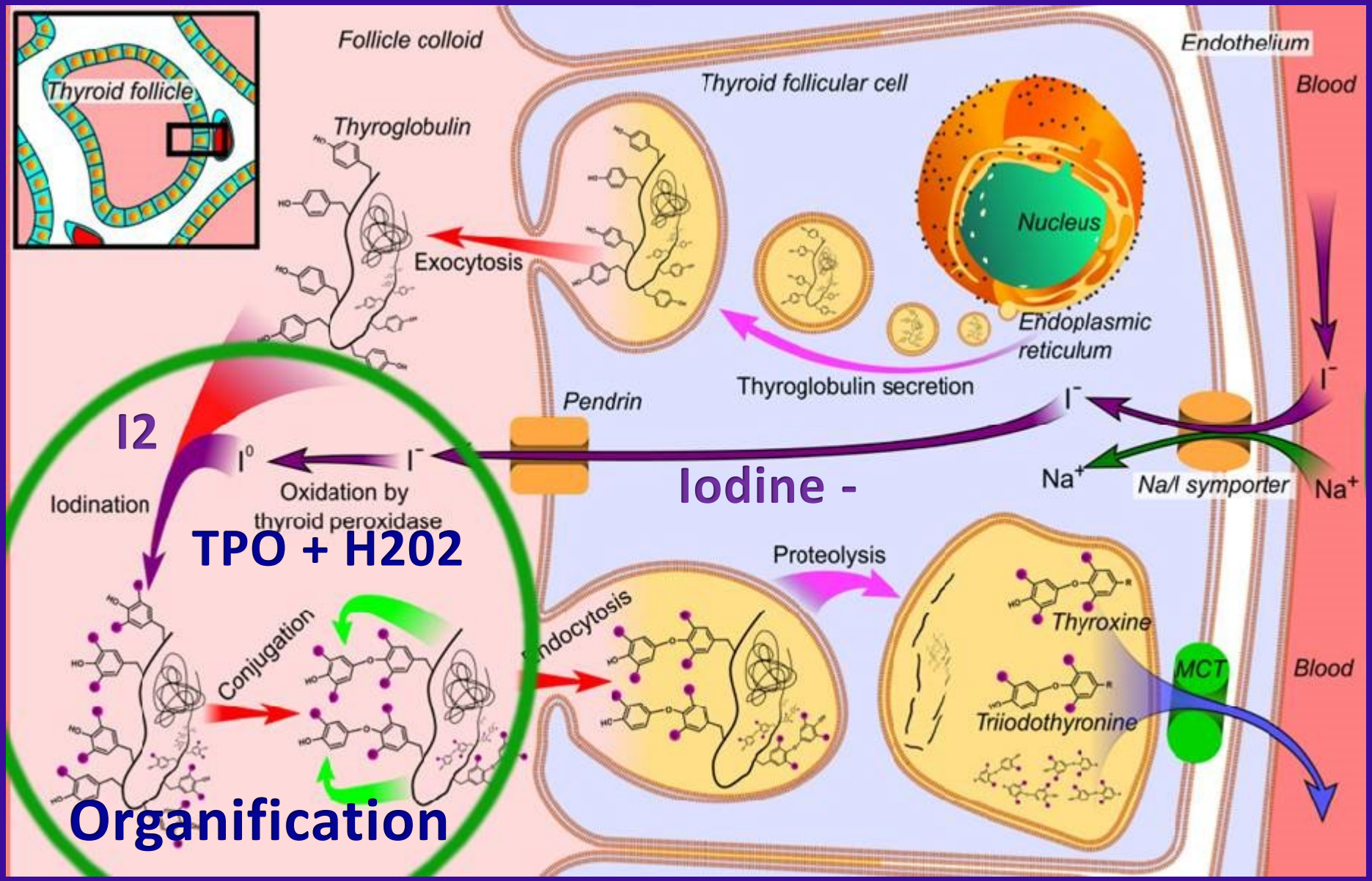
(1) Drutel, Anne, et al. "Selenium and the Thyroid Gland: More Good News for Clinicians." Clinical Endocrinology 78.2 (2013): 155-164.

(2) Wichman, Johanna, et al. "Selenium Supplementation Significantly Reduces Thyroid Autoantibody Levels in Patients with Chronic Autoimmune Thyroiditis" Thyroid 26.12 (2016): 1681-1692.

(3) Giammanco, Marco, et al."Selenium: A Cure for Autoimmune Thyroiditis." Endocrine, Metabolic & Immune Disorders-Drug Targets 21.8 (2021): 1377-1378.

(4) Vasiliu, Ioana, et al. "Protective Role of Selenium on Thyroid Morphology in Iodine-Induced Autoimmune Thyroiditis in Wistar Rats." Experimental and therapeutic medicine 20.4 (2020): 3425-3437.

Organification of Thyroglobulin

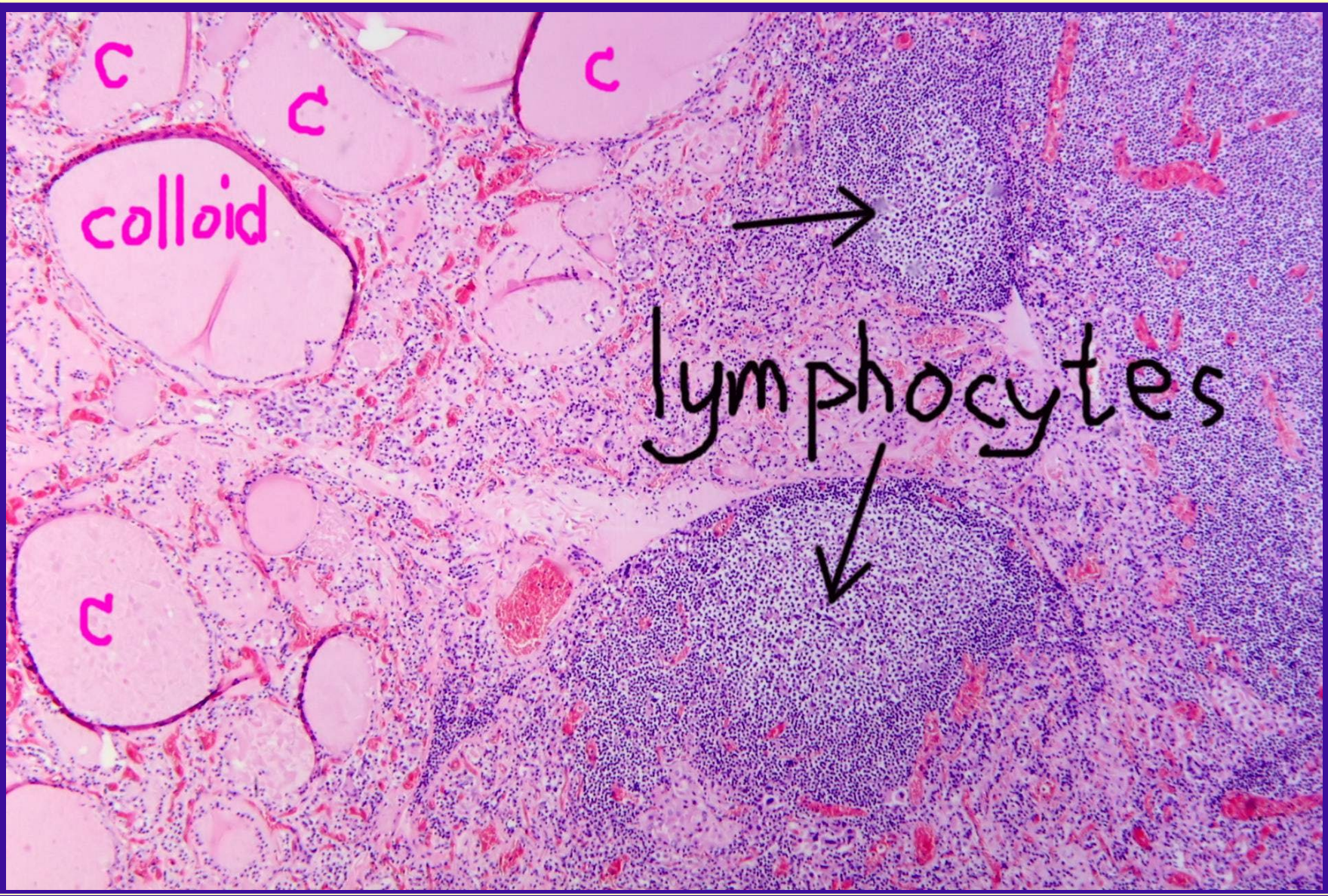


Defective Organification of Thyroglobulin

- **Organification Defect:** In Hashimoto's Thyroiditis **TPO** fails to organify Thyroglobulin.
- **Antibodies** to **TPO and Thyroglobulin**, and Infiltration of Immune Cells.
- **Hashimoto's Patients:** high I- washout, and low iodine content of thyroid glands due to **Suppression of Thyroid Function – Hypothyroidsim**
- **Methimazole:** Blocks TPO

Shahid, Muhammad A., Muhammad A. Ashraf, and Sandeep Sharma. "Physiology, thyroid hormone." StatPearls [Internet]. StatPearls Publishing, 2022.

Hashimoto’s – Lymphocytic infiltration



Hashimoto's thyroiditis with lymphoid infiltration. Autoantibodies against thyroid peroxidase and thyroglobulin were elevated Author : Patho, CC 3.0 Wikimedia Commons

Step Four – Storage

- Thyroid hormones (T3 and T4) are stored in the follicular lumen bound to thyroglobulin as colloid, a combination of free and iodinated thyroglobulin.
- Colloid is stored in the central area of the follicle.

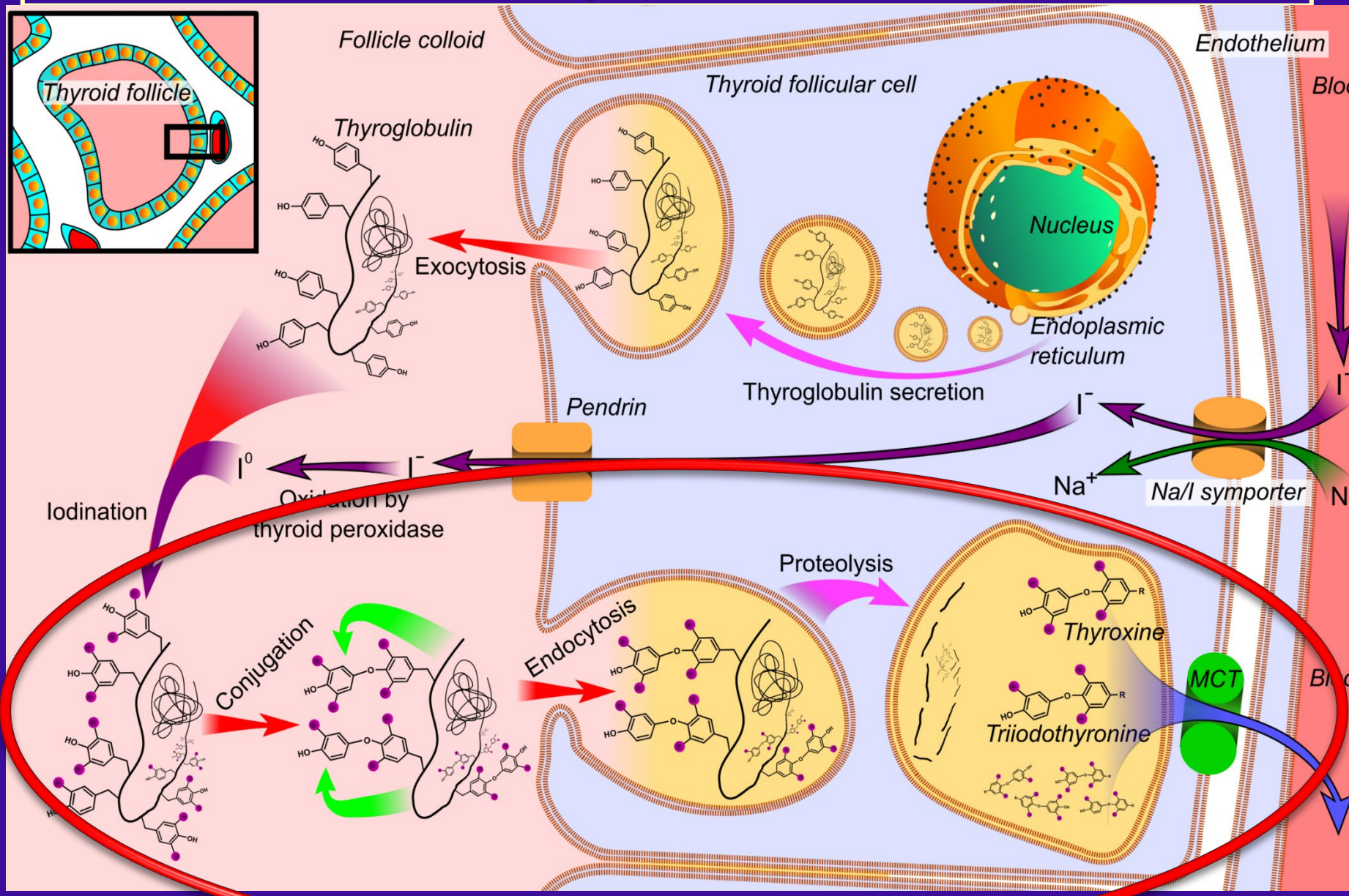
Shahid, Muhammad A., Muhammad A. Ashraf, and Sandeep Sharma. “Physiology, thyroid hormone.” StatPearls [Internet]. StatPearls Publishing, 2022.

Step Five – Release of thyroid hormone into circulation

- Iodinated thyroglobulin is taken up at the apex of the thyrocytes within vesicles via endocytosis, and travels back towards the basal membrane.
- While in transit, vesicles are fused with lysosomes, acid and proteolytic enzymes digest the thyroglobulin, freeing the T3 and T4, released at the basolateral membrane into the capillary blood stream in ratio of 12:1 (T4:T3).
- Final plasma ratio is 4:1 from D1 activity.
- Any extra iodine is salvaged and returned to the intracellular iodine pool.

Shahid, Muhammad A., Muhammad A. Ashraf, and Sandeep Sharma. “Physiology, thyroid hormone.” StatPearls [Internet]. StatPearls Publishing, 2022.

Production of Thyroid Hormone-Release



Features of Hashimoto's Thyroiditis

- Elevated TPO and Thyroglobulin antibodies.
- TPO and Thyroglob proteins are in close proximity to the H202 generating system called DUOX (dual oxidase system) at the apical villous membrane.
- Damage caused by excess H202 to these proteins creates antigenicity and autoimmunity.
- Thyroiditis, microscopic examination of the thyroid shows lymphocytic infiltration within the thyroid gland.
- Thus, the auto-immunity is represented by both antibody (B cell) and cellular immunity (T cell).

Song, Yue, et al. "Roles of hydrogen peroxide in thyroid physiology and disease." The Journal of Clinical Endocrinology & Metabolism 92.10 (2007): 3764-3773..
Murphy, Robyn, Caroline Turek, and Leigh Arseneau. "The role of iodine deficiency and subsequent repletion in autoimmune thyroid disease and thyroid cancer." Journal of Restorative Medicine 5.1 (2016): 32.

Wolff-Chaikoff Effect – Iodide Inhibits its Organification.

- This is the inhibition of hydrogen peroxide (H2O2) generation caused by iodide (I-) itself.
- **Excess iodide** inhibits organification because of reduced availability of H202 at the apical membrane.
- **Hashimoto's/Graves':** These patients are more sensitive to the inhibitory effect of iodine excess on thyroid function. Loss of Autoregulation.
- **Normal healthy people:** After a few days, they escape from the inhibitory effects of iodide. TSH returns to normal. This is the "Escape from the Wolff-Chaikoff Effect". The mechanism for escape is generation of iodolactones, and reduction in NIS activity and NIS mRNA.

Markou, K., et al. "Iodine-induced hypothyroidism." Thyroid 11.5 (2001): 501-510.

Hypothyroidism From High Iodide Intake in Hashimoto's Patients – Dr. Tajiri

- Patients with reversible hypothyroidism had focal lymphocytic thyroiditis changes in the thyroid biopsy specimen
- Patients with irreversible hypothyroidism had more severe destruction of the thyroid gland.
- Excess Iodine Downregulates the NIS.
- Excess Iodine Inhibits H202 Generation (DUOX).
- Excess Iodine Inhibits TPO, and Organification.
- Useful in Treating Grave's Hyperthyroidism (Japan)

Tajiri, Junichi, et al. "Studies of hypothyroidism in patients with high iodine intake." The J of Clin Endo & Metab, 1986.

Normally, Iodine Inhibits H202 Generation, In Iodine Deficiency (Hi TSH) - Iodine Stimulates H202 Generation

- Wolf Chaikoff Effect…Iodine Inhibits H202 Generation- Post-transcriptional change of the DUOX molecule by KI appears to be responsible for the decreased H2O2 generation.
- When Animal is Iodine Depleted, Iodine will Paradoxically Stimulate H202 production.
- Thus, abnormality of thyroid H2O2 generation in response to high iodide may play a role in the development of Hashimoto's thyroiditis in susceptible individuals.

Ohye, Hidemi, and Masahiro Sugawara. "Dual oxidase, hydrogen peroxide and thyroid diseases." Experimental biology and medicine 235.4 (2010): 424-433.

Methimazole - Thyroid Blocking Drug

- Methimazole (MMI), irreversibly binds to and blocks function of the TPO enzyme, thus inhibiting organification of iodine.
- Inability to organify bears a similarity to Hashimotos' Thyroiditis which also has organification defect.
- In addition, Methimazole inhibits the DUOX enzyme, thus inhibiting hydrogen peroxide formation, a beneficial feature which prevents excess hydrogen peroxide damage to the thyrocytes.

Abdi, Hengameh, Atieh Amouzegar, and Fereidoun Azizi. "Antithyroid drugs." Iranian journal of pharmaceutical research: IJPR 18.Suppl1 (2019): 1.

Methimazole - Thyroid Blocking Drug

- MMI is 10 times more potent than PTU (Propylthiouracil) in blocking thyroid function.
- MMI partially inhibits the DUOX enzyme which generates hydrogen peroxide.
- **Adverse Effects:** Agranulocytosis is serious and can induce fatal immunosuppression.
- **MMI** does not block the D1 Deiodinase enzyme which converts T4 to T3, as does PTU, corticosteroids and **Beta Blocker (propranolol).**
- M**ethimazole** (MMI) does not block release of thyroid hormone from the thyroid gland. However, both KI and Lithium block release of thyroid hormone from the thyroid gland.

El Sheikh, M., and A. M. McGregor. "Antithyroid drugs: their mechanism of action and clinical use." Pharmacotherapeutics of the thyroid gland. Berlin, Heidelberg: Springer Berlin Heidelberg, 1997. 189-206.

Laboratory Studies

	Lab Range (Quest Adults)
TSH	0.40–4.50 mIU/L
Free T3	230–420 pg/dL
Free T4	0.8-1.8 ng/dL
Reverse T3	8 to 25 ng/dL
TPO Abs	<9 IU/mL
Thyroglob Abs	≤1 IU/mL
TRAb	≤2.00 IU/L
TSI	0.00-0.55 IU/L

Quest Diagnostics

FreeT3 and Free T4 are Superior

- "Because of their higher diagnostic performance, free T3 (FT3) and free T4 (FT4) measurements have superseded total (free + bound) hormone determination." Endquote Dr. Sapin, 2003

Sapin, R., and J. L. Schlienger. "Thyroxine (T4) and Tri-Iodothyronine (T3) Determinations: Techniques and Value in the Assessment of Thyroid Function." Annales De Biologie Clinique. Vol. 61. No. 4. 2003.

Hashimotos' Thyroiditis

Patient	
TSH	7.2 mIU/L
Free T3	230 pg/dL
Free T4	0.8 ng/dL
rT3	8 ng/dL
TPO Abs	>900 IU/mL
Thyroglob Abs	420 IU/mL
TRAb	NL
TSI	NL

Normal Lab Range	
TSH	0.40–4.50 mIU/L
Free T3	230–420 pg/dL
Free T4	0.8-1.8 ng/dL
rT3	8 to 25 ng/dL
TPO Abs	<9 IU/mL
Thyroglob Abs	≤1 IU/mL
TRAb	≤2.00 IU/L
TSI	0.00-0.55 IU/L

Note: Labs are done **FASTING**, Early AM at LAB.
Hold Thyroid Meds in AM before Blood Draw.

Hashi-Toxicosis/ PainlessThyroiditis

	Patient	Lab Range
TSH	**0.01** mIU/L	0.40–4.50 mIU/L
Free T3	**530** pg/dL	230–420 pg/dL
Free T4	**2.5** ng/dL	.8-1.8 ng/dL
rT3	**27** ng/dL	8 to 25 ng/dL
TPO Abs	>**900** IU/mL	<9 IU/mL
Thyroglob Abs	**420** IU/mL	≤1 IU/mL
TRAb	NL	≤2.00 IU/L
TSI	NL	0.00-0.55 IU/L

I-123 scan: Very Reduced Uptake, Under 3 percent
Endemic Myxedematous Cretinism in Zaire, Africa (selenium def)
Amiodorane Induced Thyroiditis.

Toxic Nodular Goiter/ (Aut Nod)

	Patient
TSH	**.01** mIU/L
Free T3	**530** pg/dL
Free T4	**2.5** ng/dL
rT3	**27** ng/dL
TPO Abs	**NL**
Thyroglob Abs	**NL**
TRAb	NL
TSI	NL

	Lab Range
TSH	0.40–4.50 mIU/L
Free T3	230–420 pg/dL
Free T4	.8-1.8 ng/dL
rT3	8 to 25 ng/dL
TPO Abs	<9 IU/mL
Thyroglob Abs	≤1 IU/mL
TRAb	≤2.00 IU/L
TSI	0.00-0.55 IU/L

I-123 scan: Typical Appearance of Solitary or Multiple Noudles

Graves' Hyperthyroidism

	Patient	Lab Range
TSH	**.01** mIU/L	0.40–4.50 mIU/L
Free T3	**1200** pg/dL	230–420 pg/dL
Free T4	**7.3** ng/dL	.8-1.8 ng/dL
rT3	**35** ng/dL	8 to 25 ng/dL
TPO Abs	**560** IU/mL	<9 IU/mL
Thyroglob Abs	<1 IU/mL	≤1 IU/mL
TRAb	**42** IU/L	≤2.00 IU/L
TSI	**87** IU/L	0.00-0.55 IU/L

I-123 scan: Smoothly Enlarged Gland with Increased 6 hr Uptake

How to Start NDT

Tablet size	
30 mg tab	half grain
60 mg tab	one grain
120 mg tab	2 grains
180 mg tab	3 grains

T3/T4
30 mg 4.5 mcgT3/19 mcg T4
60 mg 9 mcg T3/ 38 mcg T4
120 mg 18 mcgT3/78mcgT4
180 mg 27mcgT3/ 114mcg T4

Start with 30 mg tablet x one week, then 30 mg BID X 6 weeks, recheck labs, adjust dosage

Ask the patient to hold the thyroid pill if symptoms of **thyroid excess:** Tachycardia (at rest), palpitations, anxiety, insomnia, loose stools. (Similar to Graves')

Levothyroxine

T3 half Life is 24 hours	T4 Half Life is one week.

1. **Levothyroxine: T4-Only** Medication.
2. **NDT**: both T3 and T4.
3. One grain (60mg) NDT = 100 mcg Levo
4. Levothyroxine tablet sizes: 25, 50 mcg, 75 mcg, 100 mcg, 125 mcg, 150 mcg.
5. NDT is SAFER because symptoms of thyroid excess dissipate after 6 hours, for T4-only, it may take a week.

What Are Symptoms of Thyroid Excess ?

- Nervous System Activation.
- Effect is Additive with Stimulants Caffeine, Amphetamines.
- Tachycardia at Rest.
- Anxiety, Panic Attacks.
- Insomnia.
- Loose Stools.

Kravets, Igor. "Hyperthyroidism: diagnosis and treatment." American family physician 93.5 (2016): 363-370.

Symptoms of Thyroid Excess
NDT is Safer the Levothyroxine

- Shorter Half Life of T3 – 6 hours
- Longer Half Life of T4 - One Week
- For NDT (T3/T4): symptoms of thyroid excess dissipate after 6 hours.
- For Levothyroxine (T4-only), symptoms of thyroid excess persist for a week or so.

Labs Before Starting Levothyroxine

Before Starting Levo	Patient	Lab Range
TSH	**8.4** mIU/L	0.40–4.50 mIU/L
Free T3	not done	230–420 pg/dL
Free T4	**0.6** ng/dL	0.8-1.8 ng/dL
rT3	not done	8 to 25 ng/dL

Typical Hypothyroid Pattern

After Starting Levothyroxine

Levothyroxine 125 mcg/d		
Patient		
TSH	**1.46**	mIU/L
Free T3	**240**	pg/dL
Free T4	**1.4**	ng/dL
rT3	**22**	ng/dl

Lab Range	
Lab Range	
TSH	0.40–4.50 mIU/L
Free T3	230–420 pg/dL
Free T4	0.8-1.8 ng/dL
rT3	8 to 25 ng/dL

Note: Lower Free T3 and Higher FT4 and RT3 indicates reduced conversion of T4 to T3 by the Diodinase system

After Switching to NDT

Levo 125 mcg/d	
Patient	
TSH	1.46 mIU/L
Free T3	240 pg/dL
Free T4	1.4 ng/dL
rT3	22 ng/dl

NDT 120 mg (2 gr)	
Patient	
TSH	0.26 mIU/L
Free T3	340 pg/dL
Free T4	1.0 ng/dL
rT3	14 ng/dl

Labs have normalized after NDT (T3/T4)

Reverse - T3 Useful or Waste of Time?

- "Reverse T3 is physiologically relevant to thyroid economy. However, its clinical use as a biochemical parameter of thyroid function is very limited. Currently, no evidence supports the use of rT3 [reverse T3] to monitor levothyroxine therapy, either given alone or in combination with liothyronine [generic Cytomel]". (Quote from: Gomes-Lima, 2019.)

Gomes-Lima, Cristiane, Leonard Wartofsky, and Kenneth Burman. "Can Reverse T3 Assay Be Employed to Guide T4 vs. T4/T3 Therapy in Hypothyroidism?." Frontiers in Endocrinology 10 (2019): 856.

De-Iodinase Enzymes Converts T4 to T3

- Dr. Alan B. McDaniel, (2021):
- "the ratio of tT3/ RT3 is the most accurate measure of the actual thyroid hormone function in the body,"
- Dr. Shimada (2019):
- "Serum rT3 level was a more sensitive parameter than serum T4 or T3 for evaluating thyroid dysfunction….."

MacDonald, Alan B. Diagnose and Treat Hypothyroidism Part 3: New Endocrinology Townsend Letter, 2021.
Shimada, T. "The Conversion of Thyroxine to Triiodothyronine (T3) or to Reverse T3 In Patients with Thyroid Dysfunction." Nihon Naibunpi Gakkai Zasshi 60.3 (1984): 195-206

Reverse T3 is Helpful - References

1) Shimada, T. “The Conversion of Thyroxine to Triiodothyronine (T3) or to Reverse T3 In Patients with Thyroid Dysfunction.” Nihon Naibunpi Gakkai Zasshi 60.3 (1984): 195-206

2) MacDonald, Alan B. Diagnose and Treat Hypothyroidism. Pt 3: Townsend Letter, 2021.

3) Friedman, T. et al. Reverse T3 in Patients with Hypothyroidism, Helpful or a Waste of Time?.” J Endo Soc 4.Supp_1 (2020): SUN-410.

4) Wilson, Julian Bryant et al. “Reverse T3 in Patients With Hypothyroidism, Helpful or a Waste of Time?.” J of the Endo Soc 5.Supp_1 (2021): A952-A952.

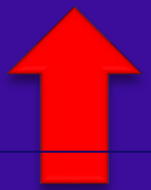
Using Reverse T3 to Monitor Dosage

Decrease Dosage

Patient	Lab Range
TSH	.01 mIU/L
Free T3	440 pg/dL
Free T4	1.8 ng/dL
rT3	24 ng/dL

Lab Range

	Lab Range
TSH	0.40–4.50 mIU/L
Free T3	230–420 pg/dL
Free T4	.8-1.8 ng/dL
rT3	8 to 25 ng/dL



High rT3

Reverse - T3 to Monitor Dosage

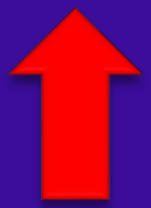
Increase Dosage

Patient	Lab Range
TSH	4.7 mIU/L
Free T3	240 pg/dL
Free T4	0.7 ng/dL
rT3	8 ng/dL

Low rT3

Lab Range

	Lab Range
TSH	0.40–4.50 mIU/L
Free T3	230–420 pg/dL
Free T4	.8-1.8 ng/dL
rT3	8 to 25 ng/dL



MECHANISM- Why T4-Only (Levothyroxine) Doesn't Work for 20 % of Patients

Anonymous Comment on Message Board

- Good old levo' nearly killed me. Gave me euthyroid blood tests but my body was crumbling. Stopped taking it. Felt better. T4 doesn't work for all.

Peterson, Sarah J., et al. "An Online Survey of Hypothyroid Patients Demonstrates **Prominent Dissatisfaction**." Thyroid 28.6 (2018): 707-721.

Stevens EW, Leung AM. "A Patient Survey of Hypothyroid Individuals Demonstrates **Dissatisfaction** with Treatment and With Managing Physicians." Clin Thyroidol. 2018; 30:175-178.

McAninch, Elizabeth A., and Antonio C. Bianco. "The swinging pendulum in treatment for hypothyroidism: from (and toward?) combination therapy." Frontiers in Endocrinology (2019): 446.

D2 Centrally in the Pituitary is Different from D2 in Periphery

- **Peripheral Tissues:** D2 is inhibited by T4 as a safety mechanism to protect cells from local hyperthyroidism. T4 is not converted to T3. Result: Peripheral Hypothyroidism.
- **Centrally:** D2 in the hypothalamus and pituitary is different, relatively insensitive to T4 inhibition. The abundant T4 in circulation is promptly converted to intracellular T3, which then suppresses the TSH to low levels.

De Castro, Joao Pedro Werneck, et al. “Differences in Hypothalamic Type 2 Deiodinase Ubiquitination Explain Localized Sensitivity to Thyroxine.” The Journal of Clinical Investigation 125.2 (2015): 769.

Only Combined T3/T4 Ensures Euthyroidism in All Tissues

- Dr. Hector Escobar-Morreale writes in 1996:

  "Only the combined treatment with thyroxine [T4] and triiodothyronine [T3} ensures euthyroidism in all tissues of the thyroidectomized rat."

Escobar-Morreale, Héctor F., et al. "Only the combined treatment with thyroxine and triiodothyronine ensures euthyroidism in all tissues of the thyroidectomized rat." Endocrinology 137.6 (1996): 2490-2502.

TSH Suppression
Benefits and Adverse Effects

- TSH Suppression Commonly Used for Post-Thyroidectomy Cancer Patients.
- “Women with differentiated thyroid cancer who had long-term (7 +/- 3 years) T4 therapy and suppressed TSH levels had no evidence of lower Bone Mineral Density.” (Chen, 2004)

Chen, Cheng-Hsiung, et al. "Bone Mineral Density in Women Receiving Thyroxine Suppressive Therapy for Differentiated Thyroid Carcinoma." J Formos Med Assoc. 2004 Jun;103(6):442-7. PMID: 15278189.

SUMMARY SLIDE

- H2O2 over-production or lack of degradation can explain most thyroid disorders.
- TSH Suppression Turns-Off H202.
- No Adverse Effects from TSH Suppression.
- NDT (T3/T4) is Superior to T4-only (Levothyroxine).
- rT3 is the most sensitive indicator of Thyroid Function.

Natural Thyroid Toolkit Available on Amazon

NATURAL THYROID TOOLKIT

Jeffrey Dach MD was originally board certified in diagnostic and interventional radiology, and worked 25 years as a hospital based physician. Dr. Dach retired from hospital based medicine 20 years ago and opened an outpatient clinic specializing in natural thyroid and bioidentical hormones. This book, Natural Thyroid Toolkit, represents 20 years of experience using natural thyroid in the out-patient setting.

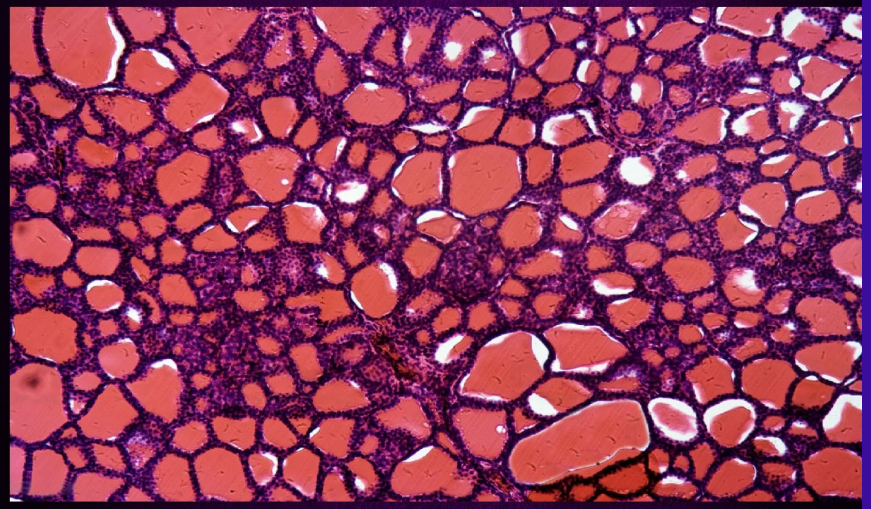
Dr. Dach is the author of ***Heart Book,*** published in 2018, and ***Cracking Cancer Toolkit*** published in 2020.

Author's web site:
www.jeffreydachmd.com

NATURAL THYROID TOOLKIT JEFFREY DACH MD

NATURAL THYROID TOOLKIT

Hashimoto's, Graves,' Iodine, Levothyroxine and Natural Desiccated Thyroid



JEFFREY DACH MD

Financial Dislosure

I receive royalties from the sale of my book: Natural Thyroid Toolkit,
No other financial interests to disclose.

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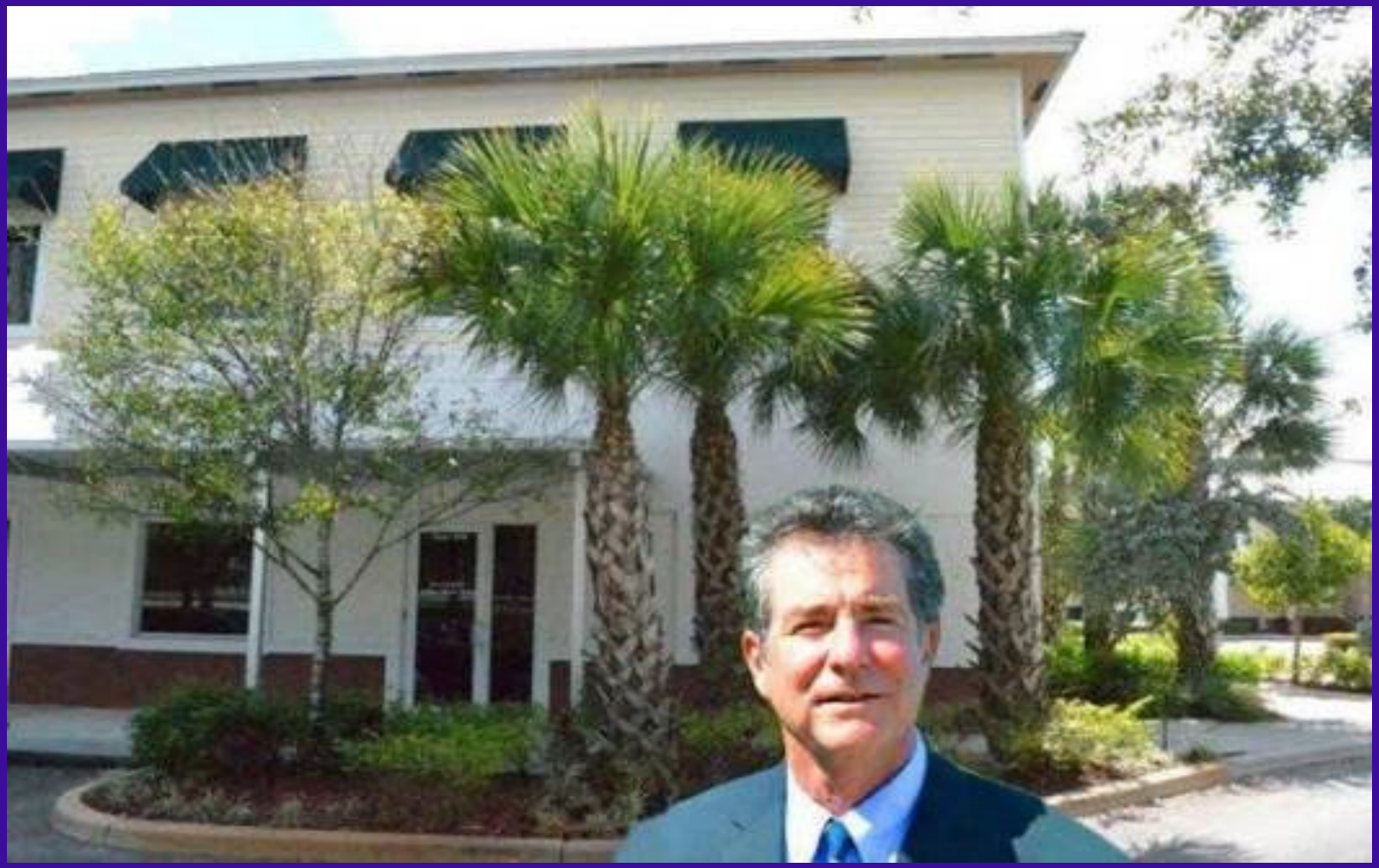
Thank You – Any Questions?



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