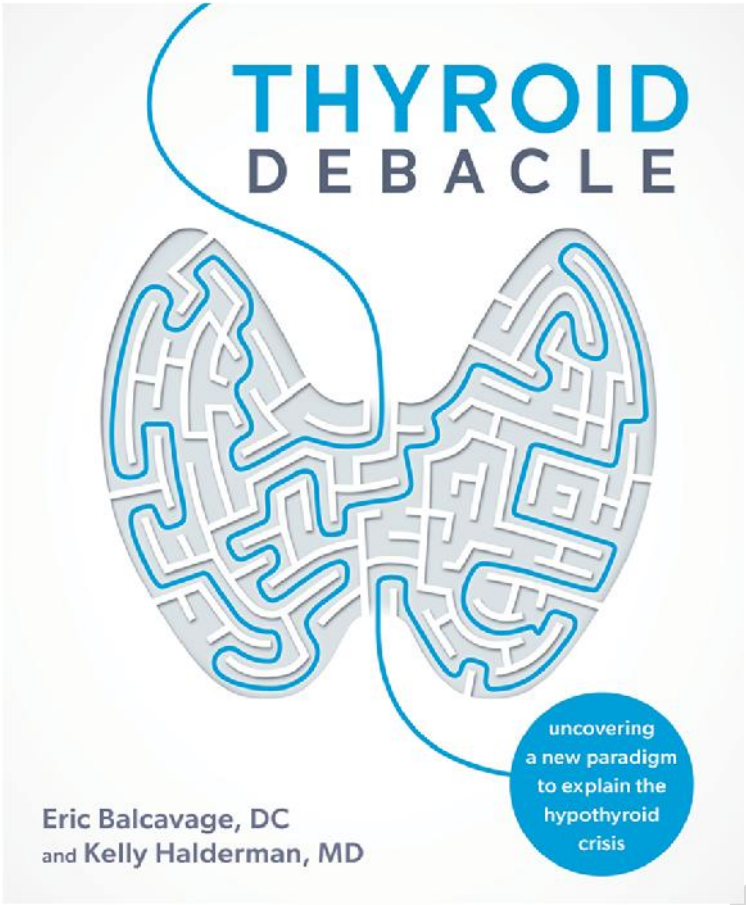
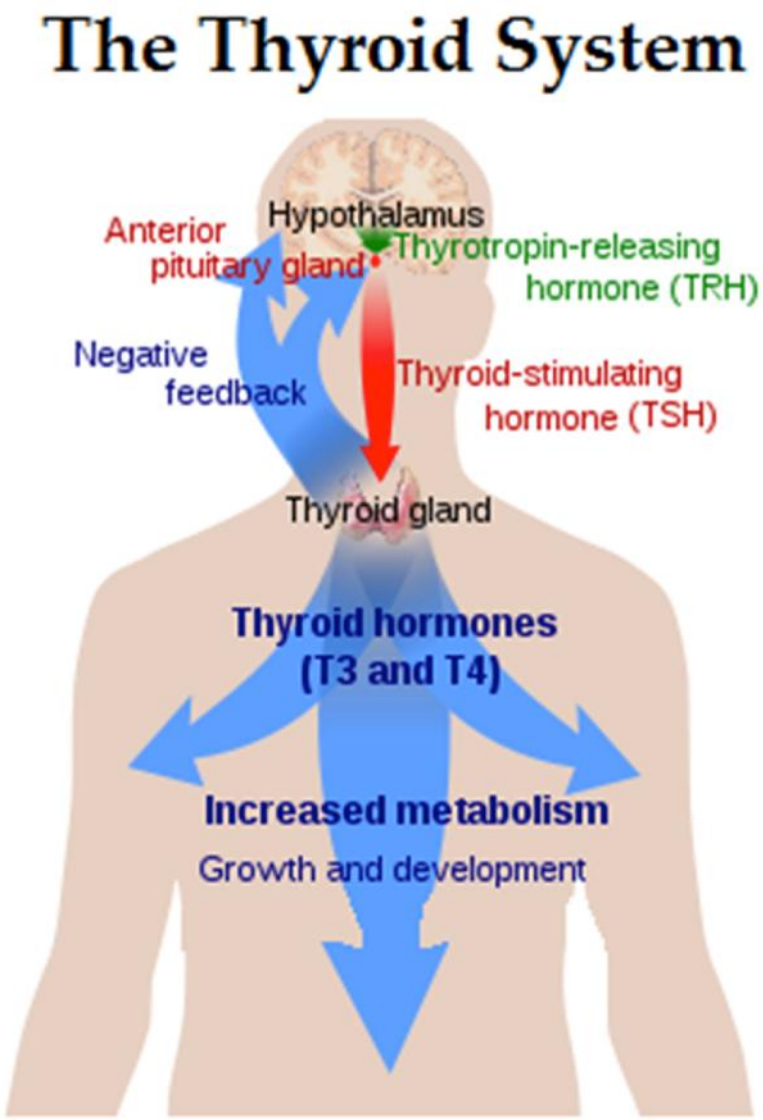


Cellular Hypothyroidism

The Undiagnosed Epidemic

Dr Eric Balcavage

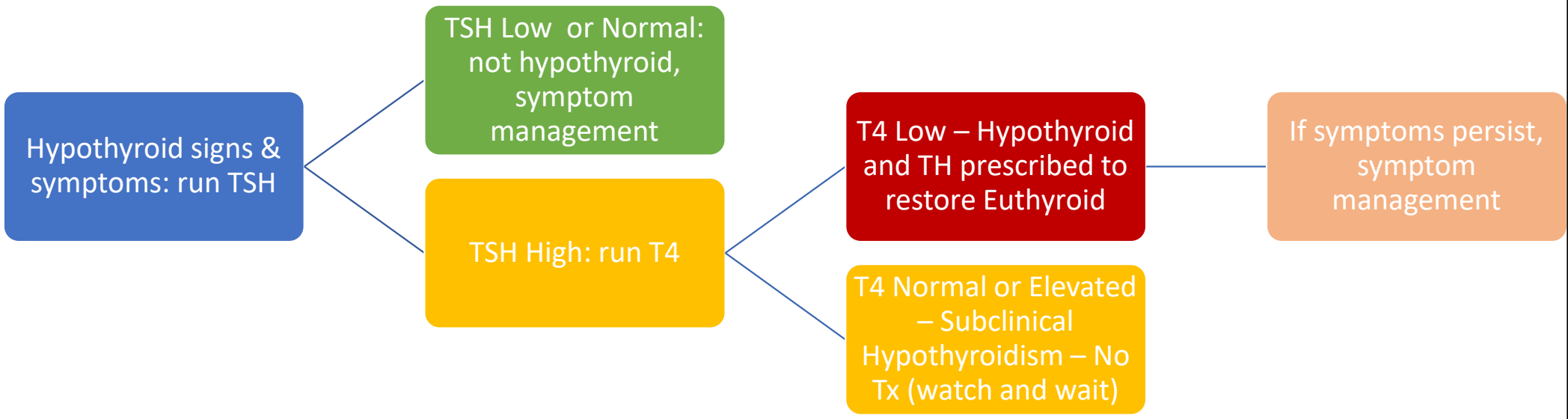
Allopathic Paradigm of Hypothyroidism



It's All About the Gland – Linear Model

- The body sends signals to brain to increase or decrease thyroid hormone production
- Hypothalamus releases TRH
- Pituitary releases TSH
- Thyroid releases T4 & T3
- T4 & T3 diffuses into cells
- T4 converted to T3
- T3 binds to nuclear receptors
- Cellular metabolism
- When cells have sufficient hormone, process is turned off

The Allopathic Model



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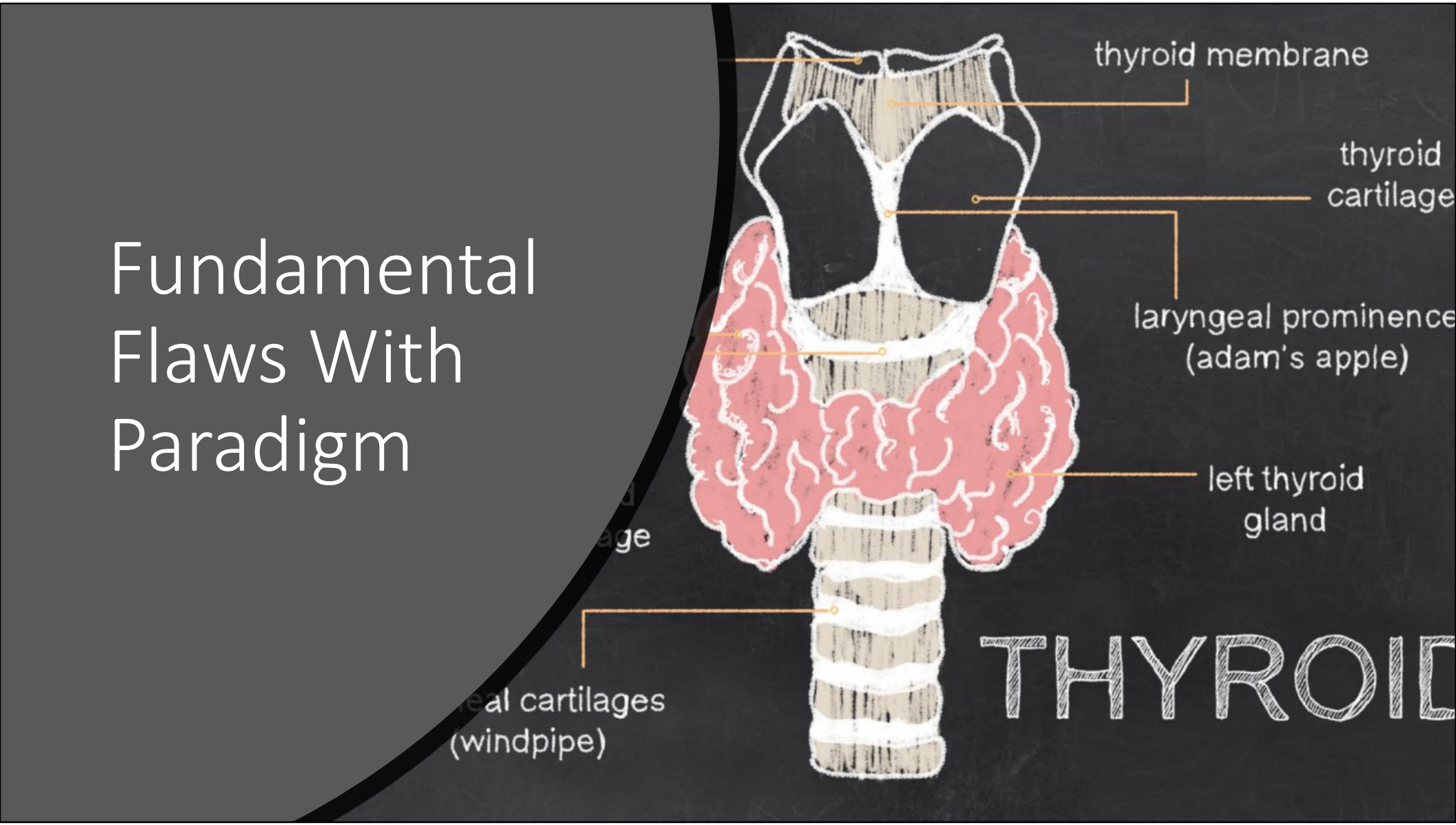
Thyroid. 2018 Jun;28(6):707-721. doi: 10.1089/thy.2017.0681. Epub 2018 Apr 5.

An Online Survey of Hypothyroid Patients Demonstrates Prominent Dissatisfaction.

Peterson SJ[1], Cappola AR[2], Castro MR[3], Dayan CM[4], Farwell AP[5], Hennessey JV[6], Kopp PA[7], Ross DS[8], Samuels MH[9], Sawka AM[10], Taylor PN[4], Jonklaas J[11], Bianco AC[1].

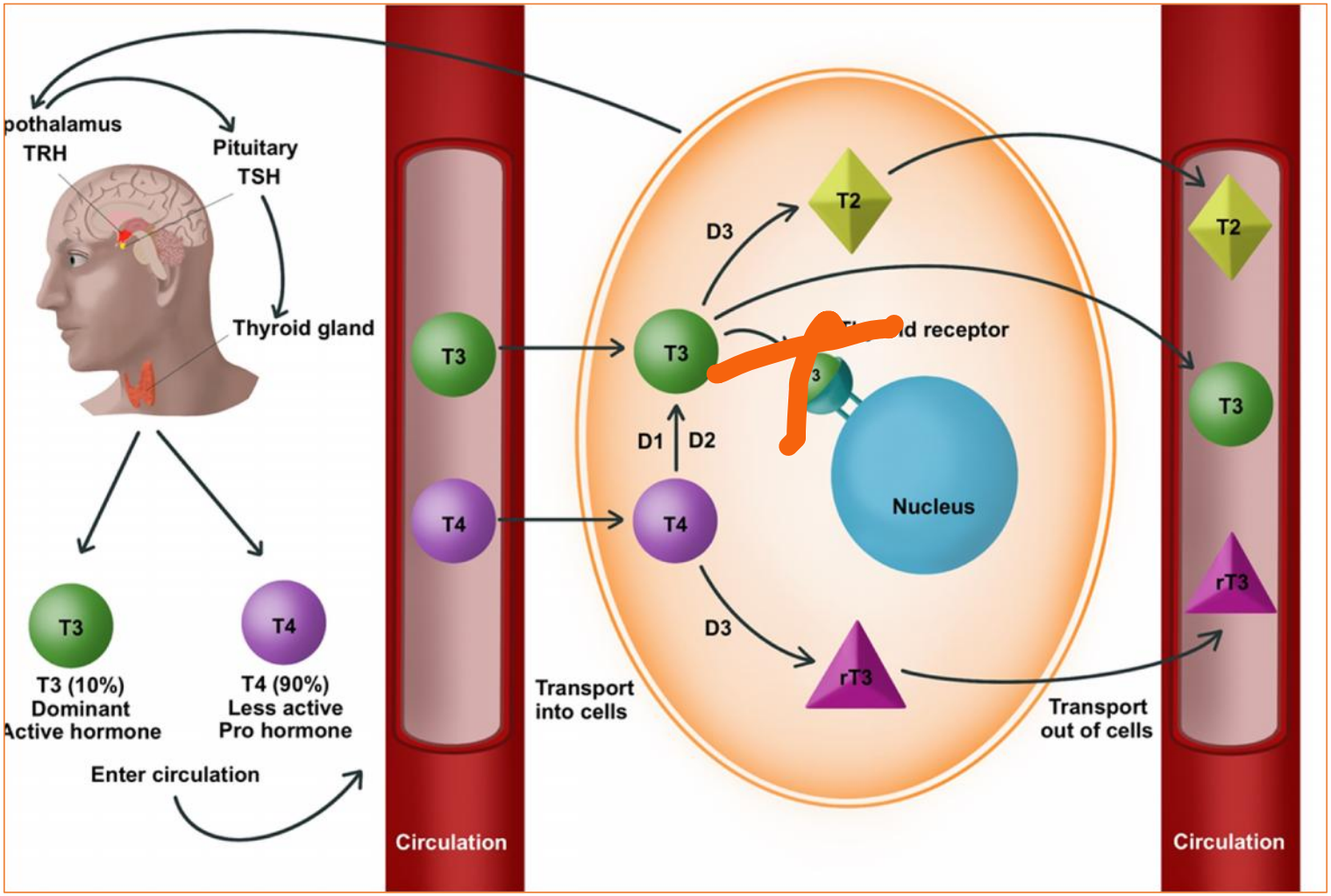
Fundamental Flaws With Paradigm



Fundamental Flaws

It assumes that hypothyroid symptoms only occur when the gland is dysfunctional

But, hypothyroid symptoms are the result of low thyroid hormone in the peripheral tissues



What Causes Hypothyroid Symptoms?

-

Reduced T3 reaching receptors

Fundamental Flaws

It assumes that TSH is a valid marker of thyroid hormone status in all cells

"Current guidelines for the diagnosis and management of thyroid dysfunction focus primarily on the measurement of TSH, as the most sensitive and specific marker of systemic thyroid status, with test results interpreted according to defined reference ranges."

"However, serum TSH has several limitations, and "normal" levels are not necessarily indicative of tissue-specific thyroid hormone status."

Razvi S, Bhana S, Mrabeti S. Challenges in Interpreting Thyroid Stimulating Hormone Results in the Diagnosis of Thyroid Dysfunction. J Thyroid Res. 2019;2019:4106816. Published 2019 Sep 22. doi:10.1155/2019/4106816

Fundamental Flaws

It assumes that TSH is a valid marker of thyroid hormone status in all cells

- *"While TSH-based diagnostic interpretation may be inexpensive (at least at the beginning of the decision-making process) it is over-simplifying and involves considerable risks of both false positive and false negative results."*
- *"The stable situation in equilibrium permits the use of TSH measurement for diagnostic purposes in thyroid disease. However, concentrations of TSH and thyroid hormones may be altered in other physiological and pathological situations in the absence of any dysfunction of the thyrotropic control system or any of its elements"*

Thyroid Allostasis–Adaptive Responses of Thyrotropic Feedback Control to Conditions of Strain, Stress, and Developmental Programming Front. Endocrinol., 20 July 2017 | https://doi.org/10.3389/fendo.2017.00163

Fundamental Flaws

It assumes that hypothyroidism begins when TSH rises above lab range and T4 drops below lab range

"Destruction of the thyroid gland >90% leads to hypothyroidism."

Fröhlich E, Wahl R. Thyroid Autoimmunity: Role of Anti-thyroid Antibodies in Thyroid and Extra-Thyroidal Diseases. Front Immunol. 2017;8:521. Published 2017 May 9. doi:10.3389/fimmu.2017.00521

Fundamental Flaws

It assumes that hypothyroidism is primarily caused by a mistake or loss of control of the immune system

Multiple papers now indicate Hypothyroidism is a protective mechanism

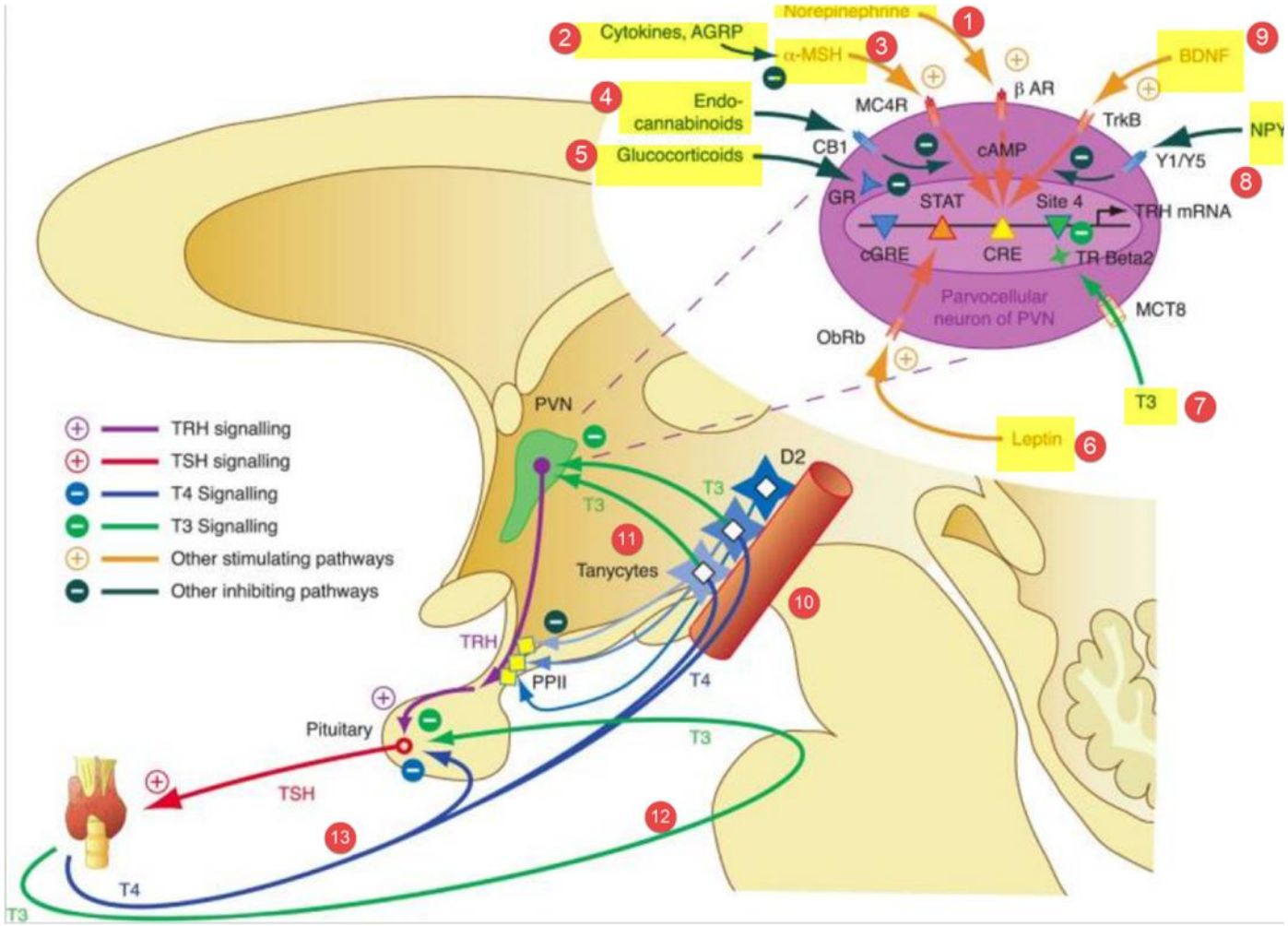
Krashin E, Piekiełko-Witkowska A, Ellis M, Ashur-Fabian O. Thyroid Hormones and Cancer: A Comprehensive Review of Preclinical and Clinical Studies. Front Endocrinol (Lausanne). 2019;10:59. Published 2019 Feb 13. doi:10.3389/fendo.2019.00059

Sahin T, Oral A, Turker F, Kocak E. Can hypothyroidism be a protective factor for hepatocellular carcinoma in cirrhosis?. Medicine (Baltimore). 2020;99(11):e19492. doi:10.1097/MD.0000000000019492

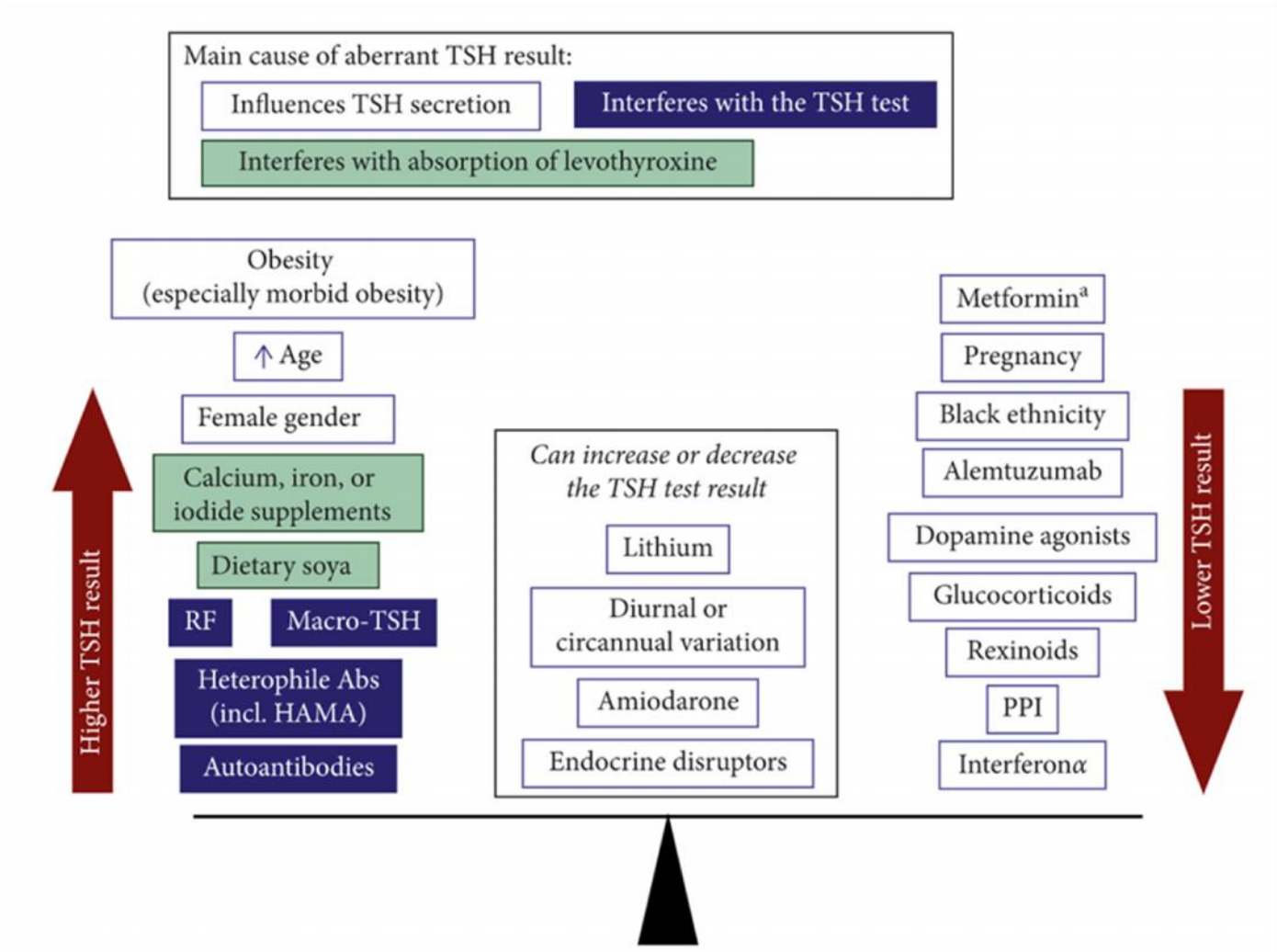
Fundamental Flaws

It assumes that TSH is the best and sometimes only test needed to evaluate thyroid physiology.

But literature shows TSH can be influenced by many factors



Chatzitomaris A, Hoermann R, Midgley JE, et al. Thyroid Allostasis-Adaptive Responses of Thyrotropic Feedback Control to Conditions of Strain, Stress, and Developmental Programming. Front Endocrinol (Lausanne). 2017;8:163. Published 2017 Jul 20. doi:10.3389/fendo.2017.00163



Razvi S, Bhana S, Mrabeti S. Challenges in Interpreting Thyroid Stimulating Hormone Results in the Diagnosis of Thyroid Dysfunction. J Thyroid Res. 2019;2019:4106816. Published 2019 Sep 22. doi:10.1155/2019/4106816

Fundamental Flaws

It assumes that biochemical euthyroidism (normalization of TSH) equates to cellular euthyroidism

But literature shows that is often not the case

"A large number of hypothyroid patients, receiving adequate doses of thyroxine supplementation, continue to complain of dissatisfaction and varied symptoms. This review discuses the concept of tissue hypothyroidism and suggests methods of measuring it, while calling for improvements in the medical management of hypothyroidism."

Why are our hypothyroid patients unhappy? Is tissue hypothyroidism the answer?

Indian J Endocrinol Metab. 2011 Jul; 15(Suppl2): S95–S98.

"Many patients complain of persistent psychological symptoms after treatment. Others state that they do not feel normal. Some patients report inadequate weight loss or continuous weight gain in spite of normal TSH levels. Many patients also feel that their treating physicians are "unsympathetic and dismissive of their symptoms."

Why are our hypothyroid patients unhappy? Is tissue hypothyroidism the answer?

Indian J Endocrinol Metab. 2011 Jul; 15(Suppl2): S95–S98.

"Patients' wellbeing does not seem to correlate with "biochemical wellbeing".

""Instead in, hypothyroid patients, doses are titrated to normalize serum TSH"

because in this model …. *"A normal TSH implies that the hypothalamo-pituitary axis is in satisfactory control."*

Why are our hypothyroid patients unhappy? Is tissue hypothyroidism the answer?

Indian J Endocrinol Metab. 2011 Jul; 15(Suppl2): S95–S98.

THE INTERNATIONAL JOURNAL OF
CLINICAL PRACTICE

REVIEW ARTICLE | Open Access

Current evide
with levothyrc
therapy versu

James V. Hennessey,

First published:30 Janu

Review | Open Access | Published: 17 January 2018

Management of hypothyroidism with combination thyroxine (T4) and triiodothyronine (T3) hormone rep review of sugges

Colin Dayan & Vijay Panicker

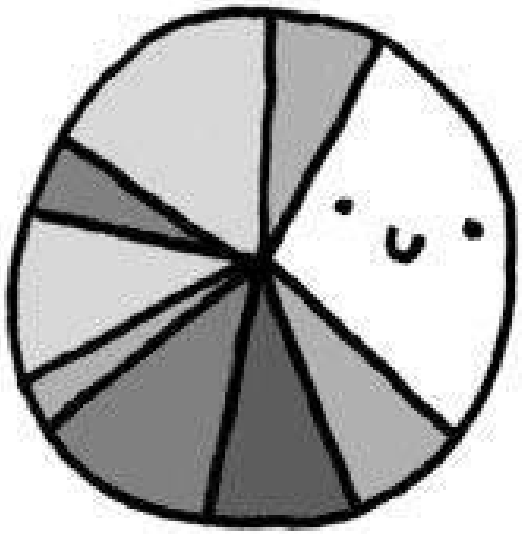
Thyroid Research **11**, Article num

16k Accesses | **9** Citations | 10

frontiers in Endocrinology

Predicting Optimal Combination LT4 + LT3 Therapy for Hypothyroidism Based on Residual Thyroid Function

Joseph DiStefano, III and Jacqueline Jonklaas



THIS PIE CHART IS COMPLETELY INACCURATE.

BUT AWW, LOOK AT ITS LITTLE FACE.

GEMMA CORRELL

What Allopathic Medicine wants.

Biochemical Euthyroidism

(Lab normal TSH)

VS

What Your Patient wants.

Cellular Euthyroidism

(optimal thyroid physiology)


Time for a New Paradigm

New Paradigm

- Symptoms we associate with thyroid physiology occur as a result of cellular events
- Thyroid hormone production is ONE part of thyroid physiology, not THE part.
- Thyroid hormones are transported into cells through “active” transport, not simple diffusion
- The fate of thyroid hormone is not pre-determined by glandular production, but by cellular forces.
- T4 can be converted into more active T3 OR inactive rT3 based on cell signaling.
- T3 can be directly used by most cells, but most prefer to control T4 – T3 conversion internally

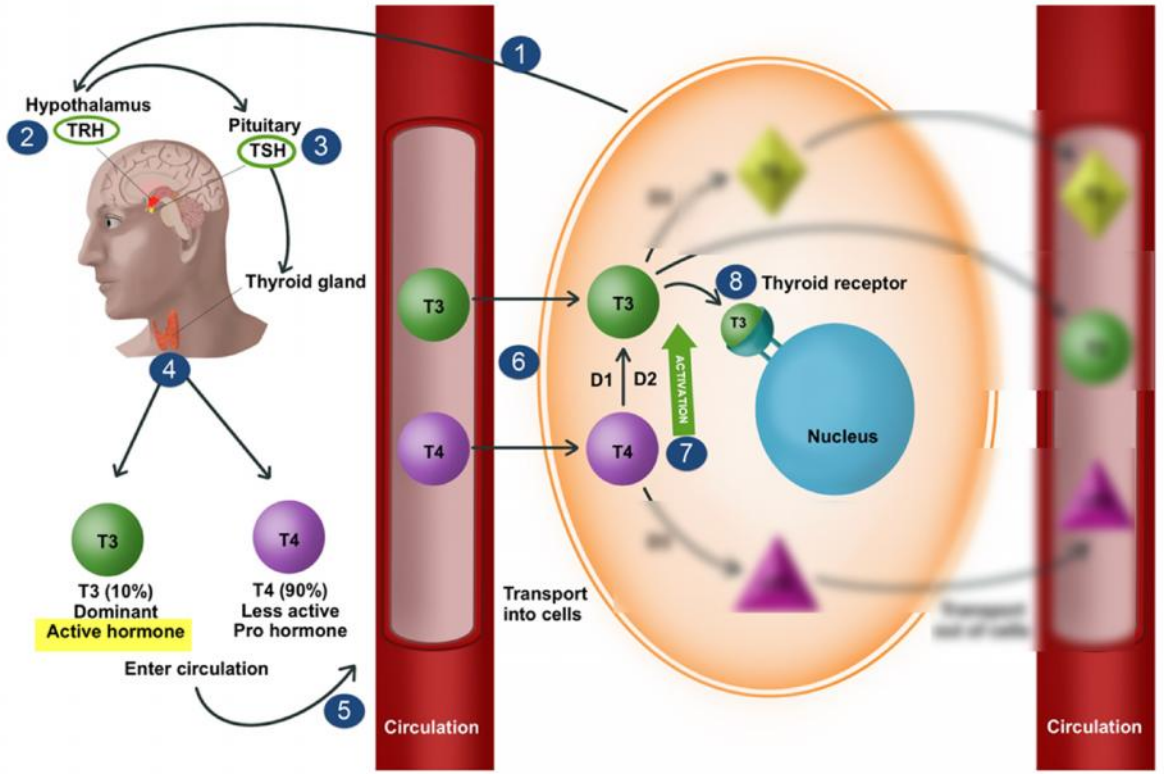
New Paradigm

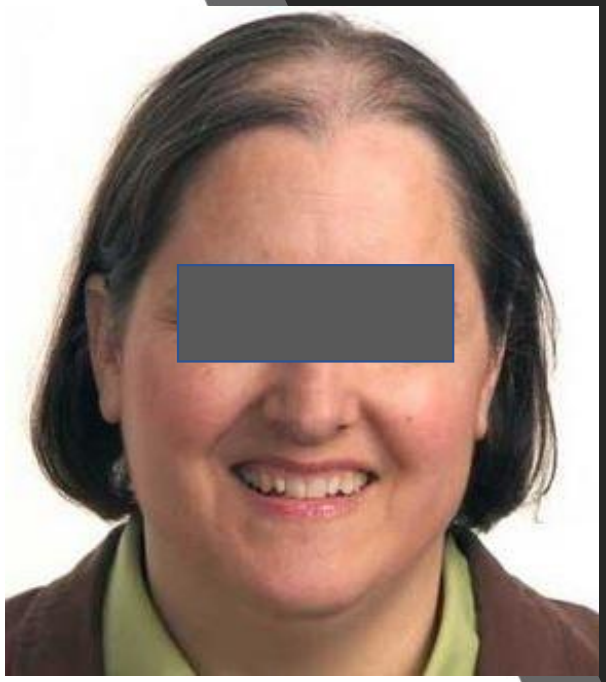
- The body fights to maintain serum T3 levels – often at the expense of peripheral tissues
- T4/T3 in blood does not always correlate with cellular levels.
- TSH does NOT represent the thyroid hormone status of all cells, especially during times of allostasis
- TH transporters, deiodinases, and receptors vary from tissue to tissue
- TH can have both genomic and non-genomic actions

New Paradigm

- Thyroid hormone physiology is adaptive not static
- In most cases changes in thyroid hormone physiology and the resulting symptoms are not abnormal “mistakes” but adaptations to protect
- Bringing TSH into lab range does NOT mean we’ve achieved Euthyroidism
- Thyroid physiology has two regulating mechanisms:
  - Homeostatic
  - Allostatic

"Normal" Thyroid Physiology = Sufficient T3 binds to cell receptors - No Hypothyroid Symptoms

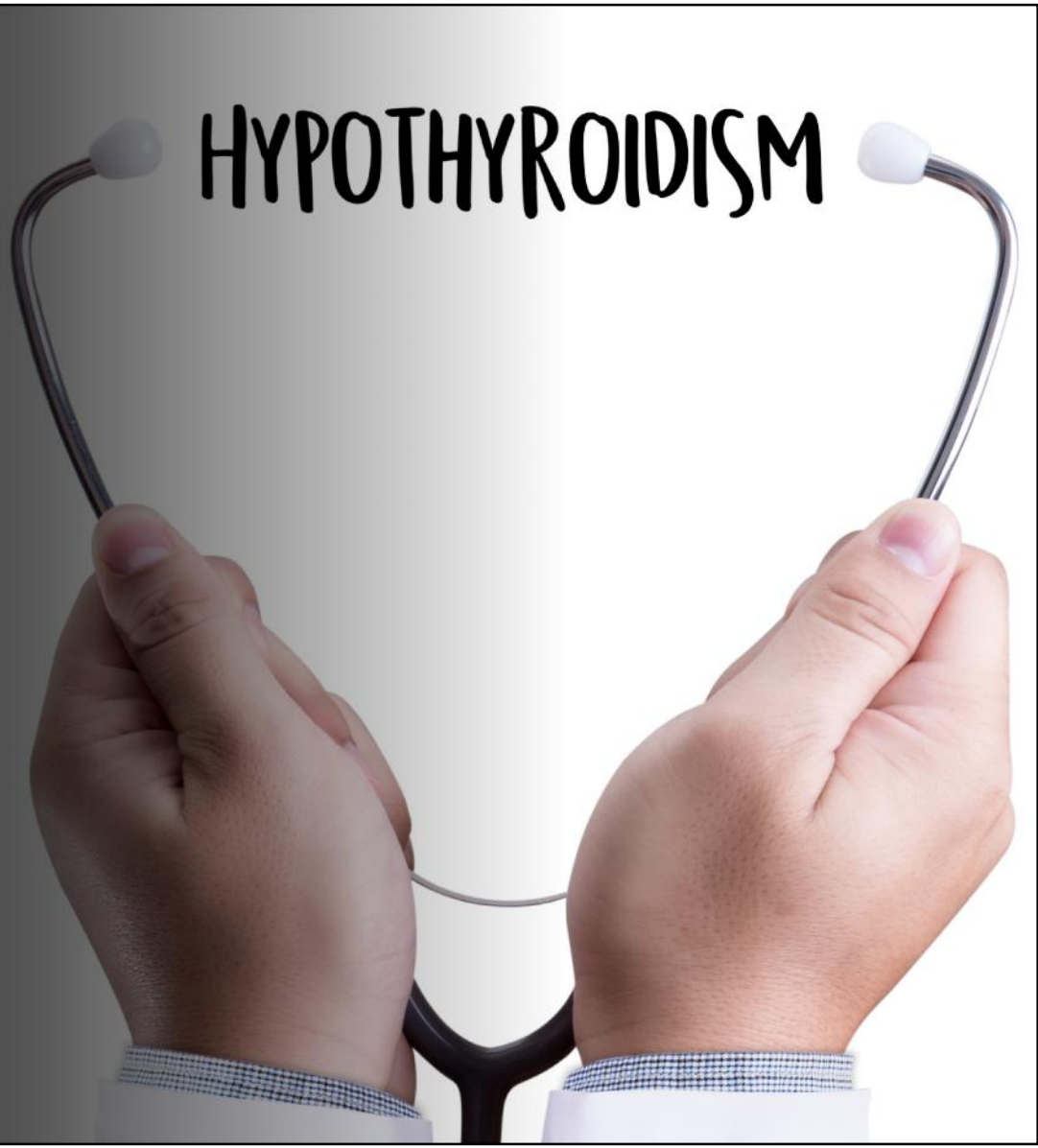




Hypothyroid Signs & Symptoms

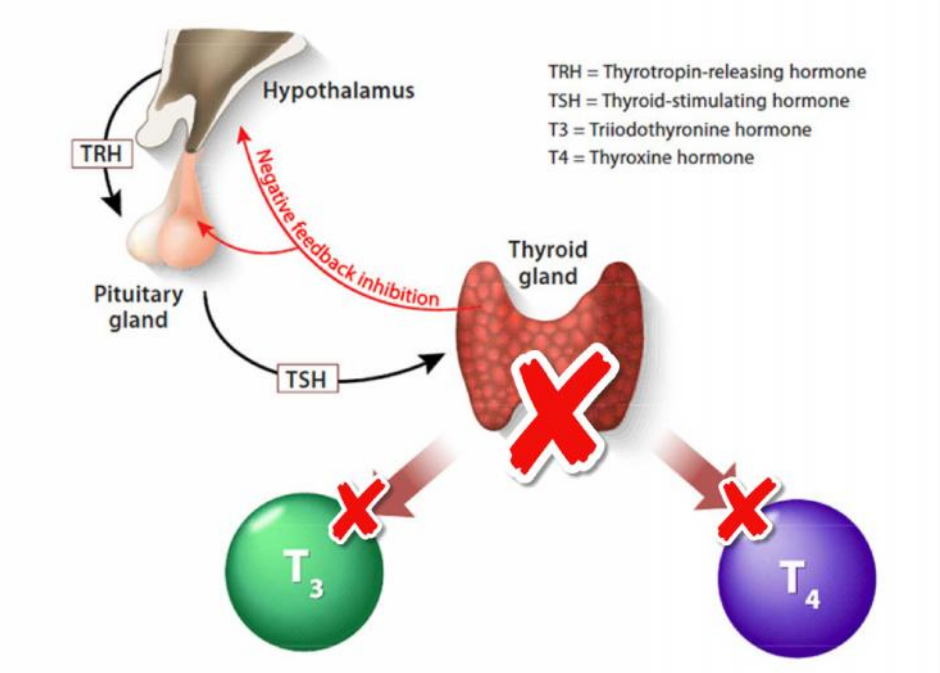
- Thinning Hair & Eyebrows
- Dry skin
- Weight Gain
- Fatigue
- Cold Sensitivity
- Constipation
- Puffy Face
- Muscle aches & pains
- Muscle weakness
- Elevated cholesterol
- Irregular Cycle
- Low Libido
- Reduced Heart Rate
- Brain Fog
- Gas, bloating & reflux
- Reduce memory

When Does Hypothyroidism Start?



Glandular Hypothyroidism
vs
Cellular / Tissue Hypothyroidism

Glandular Hypothyroidism



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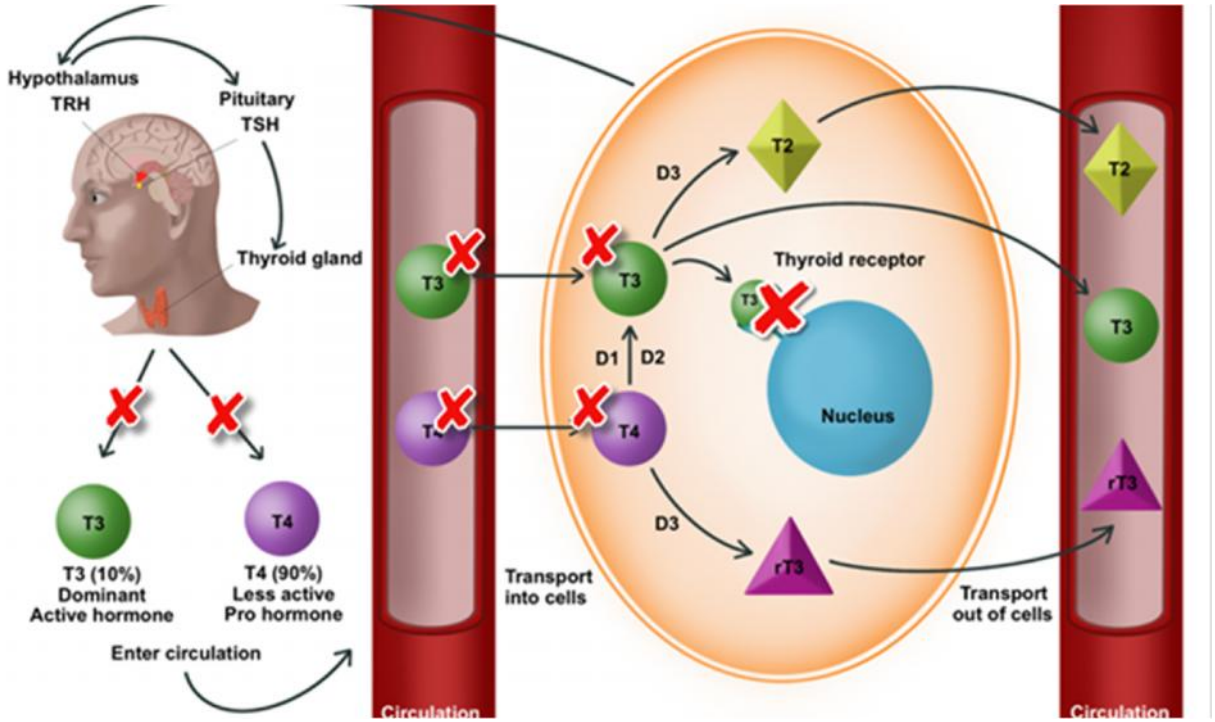
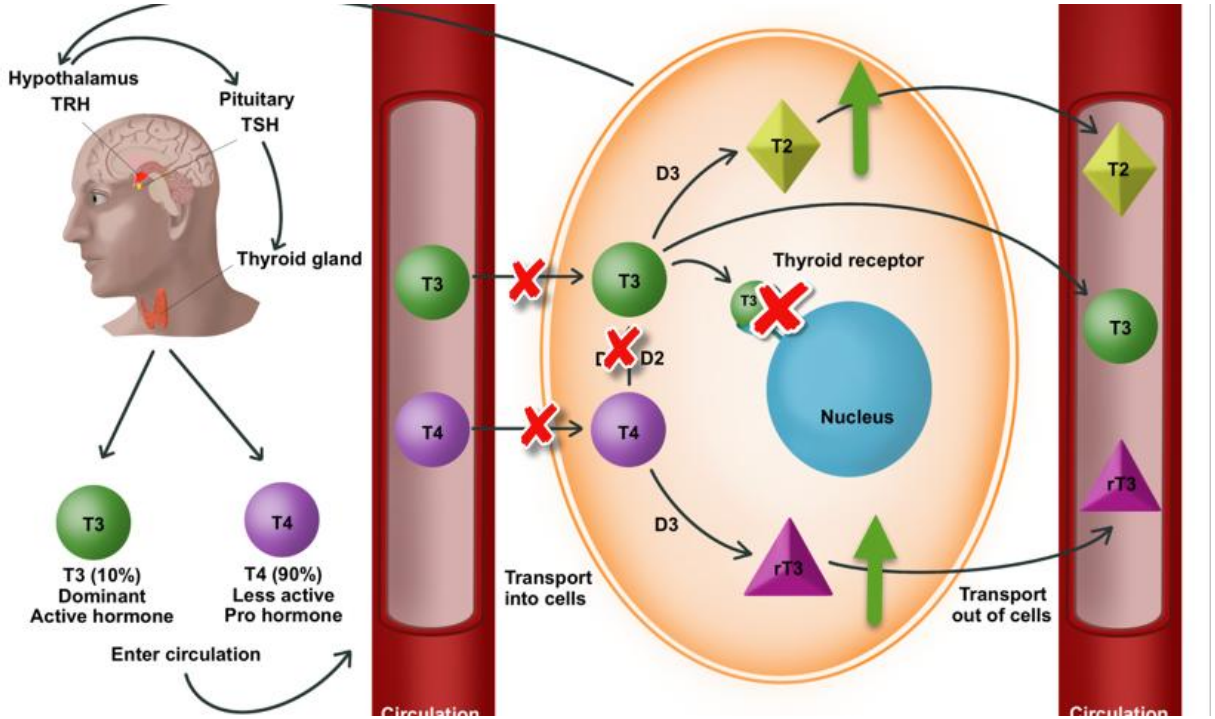


Glandular Hypothyroidism

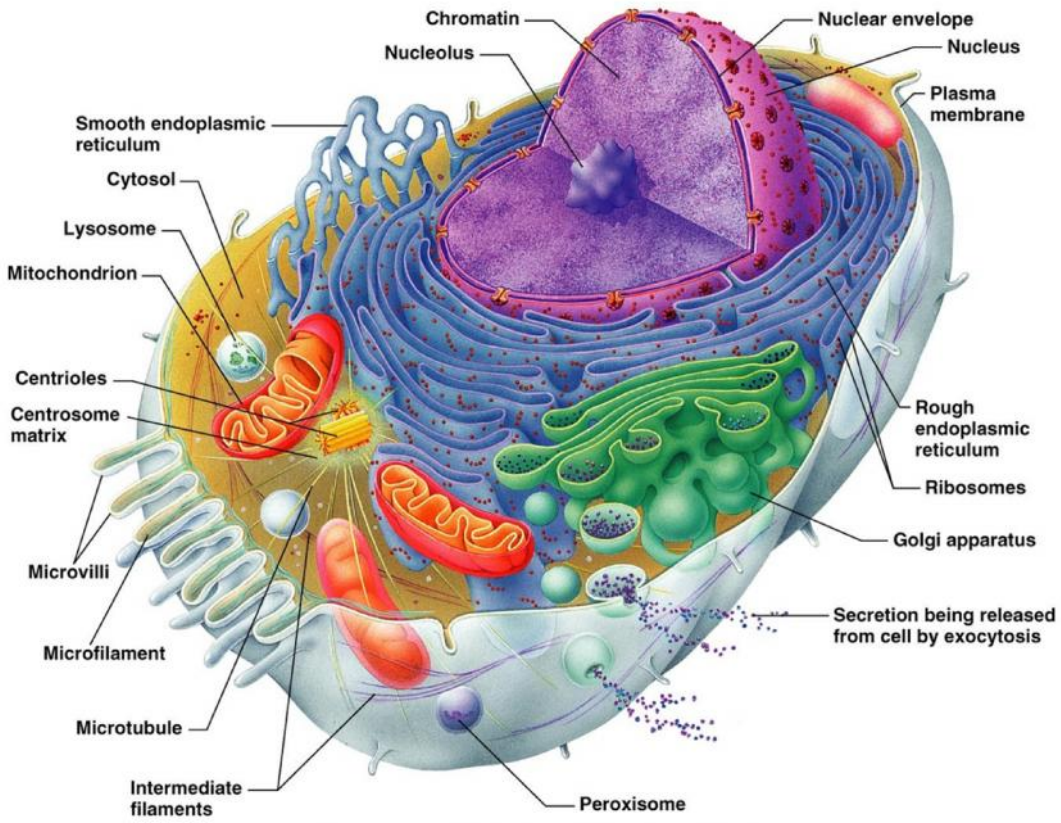
- Elevated TSH
- Low T4
- Hypothyroid symptoms



Cellular / Tissue Hypothyroidism

- Normal TSH, Normal T4
- Medical Dx = not hypothyroid
- Hypothyroid symptoms

Hypothyroidism is a Cellular Event!



Tissue Hypothyroidism aka Cellular Hypothyroidism aka Non-Thyroidal Illness Syndrome

The concept of tissue hypothyroidism, or hypothyroidism at the cellular level, has been proposed over two decades ago, to explain the clinical paradox of symptoms, in spite of biochemical euthyroidism with "optimal" thyroxine dosage. The lack of an agreed upon, simple gold standard tool for the measurement of tissue thyroid function has slowed research in this field. However, the large number of patients who complain of symptoms suggestive of "tissue hypothyroidism" warrants a detailed study of this aspect of thyroidology.

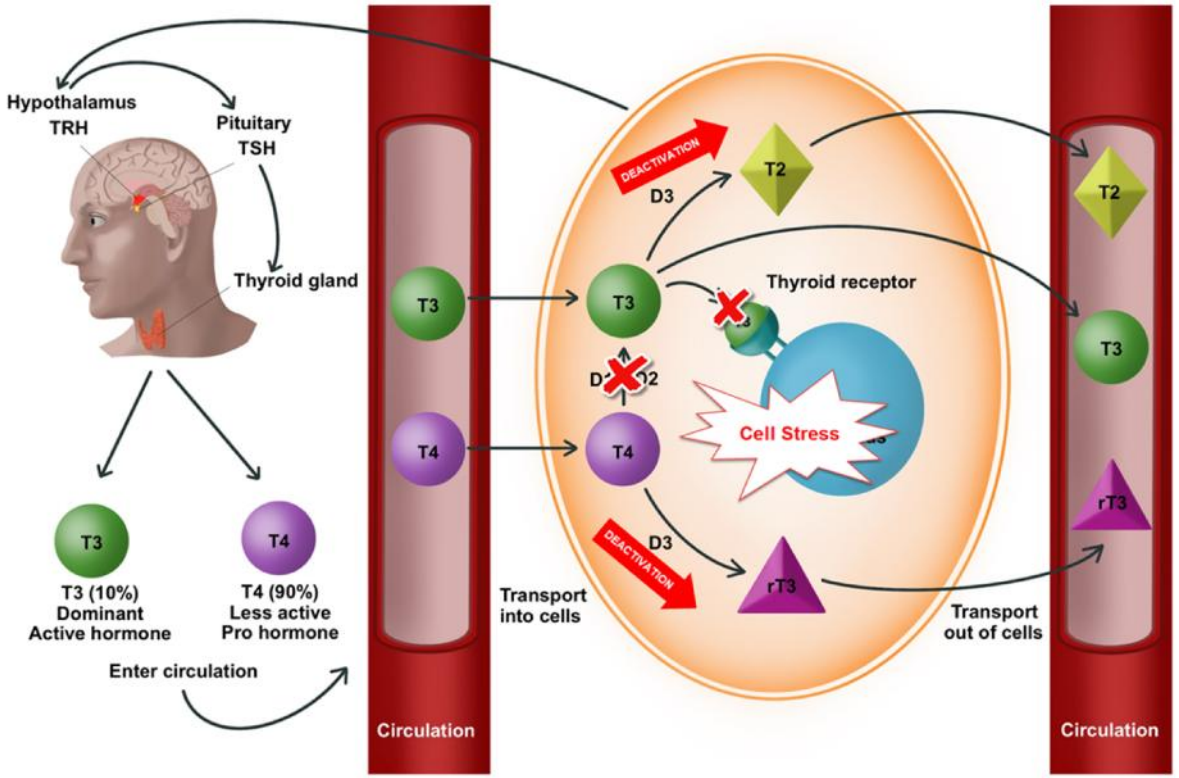
Kalra S, Khandelwal SK. Why are our hypothyroid patients unhappy? Is tissue hypothyroidism the answer? Indian Journal of Endocrinology and Metabolism. 2011;15(Suppl2):S95-S98. doi:10.4103/2230-8210.83333.

What causes cellular / tissue hypothyroidism?

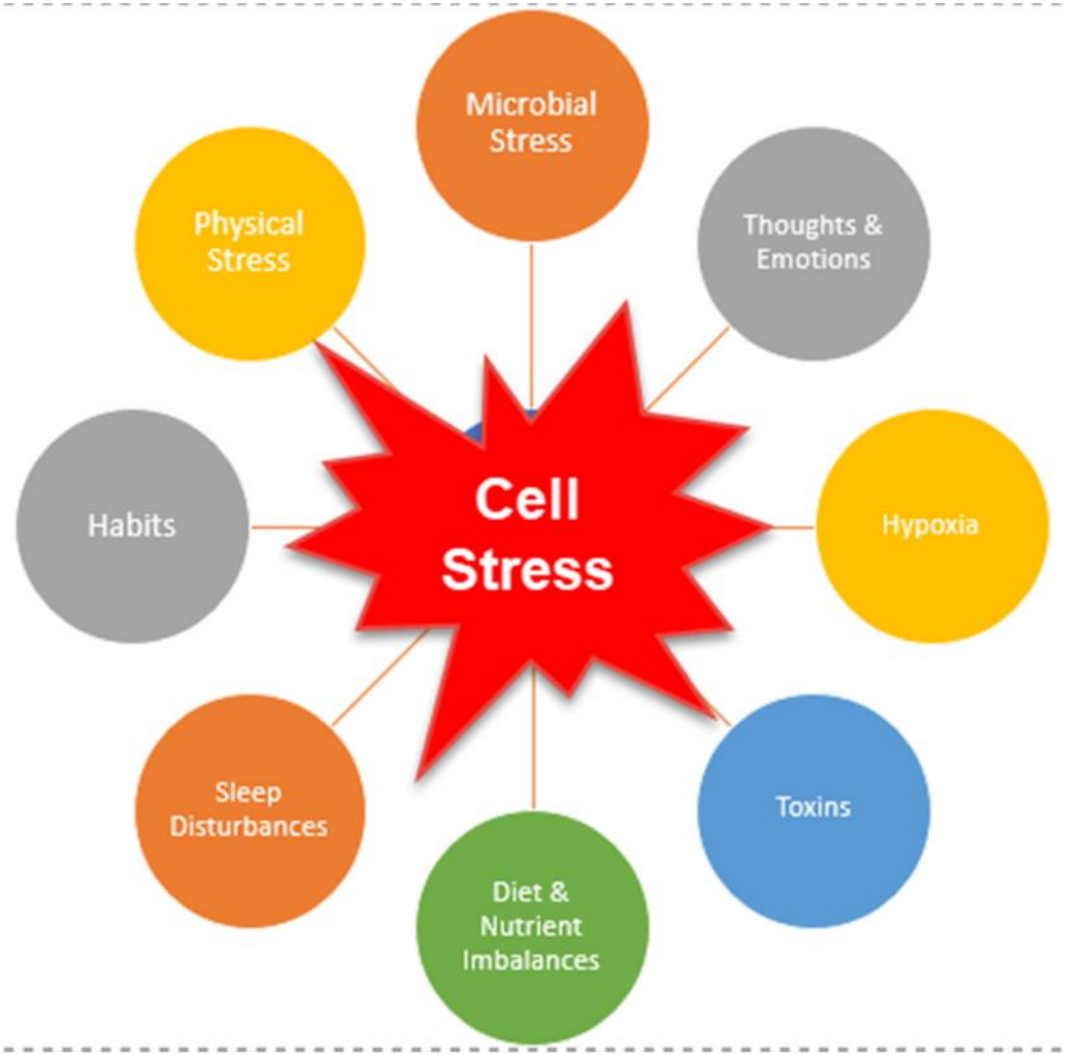
-

Excessive

Cellular Stress!



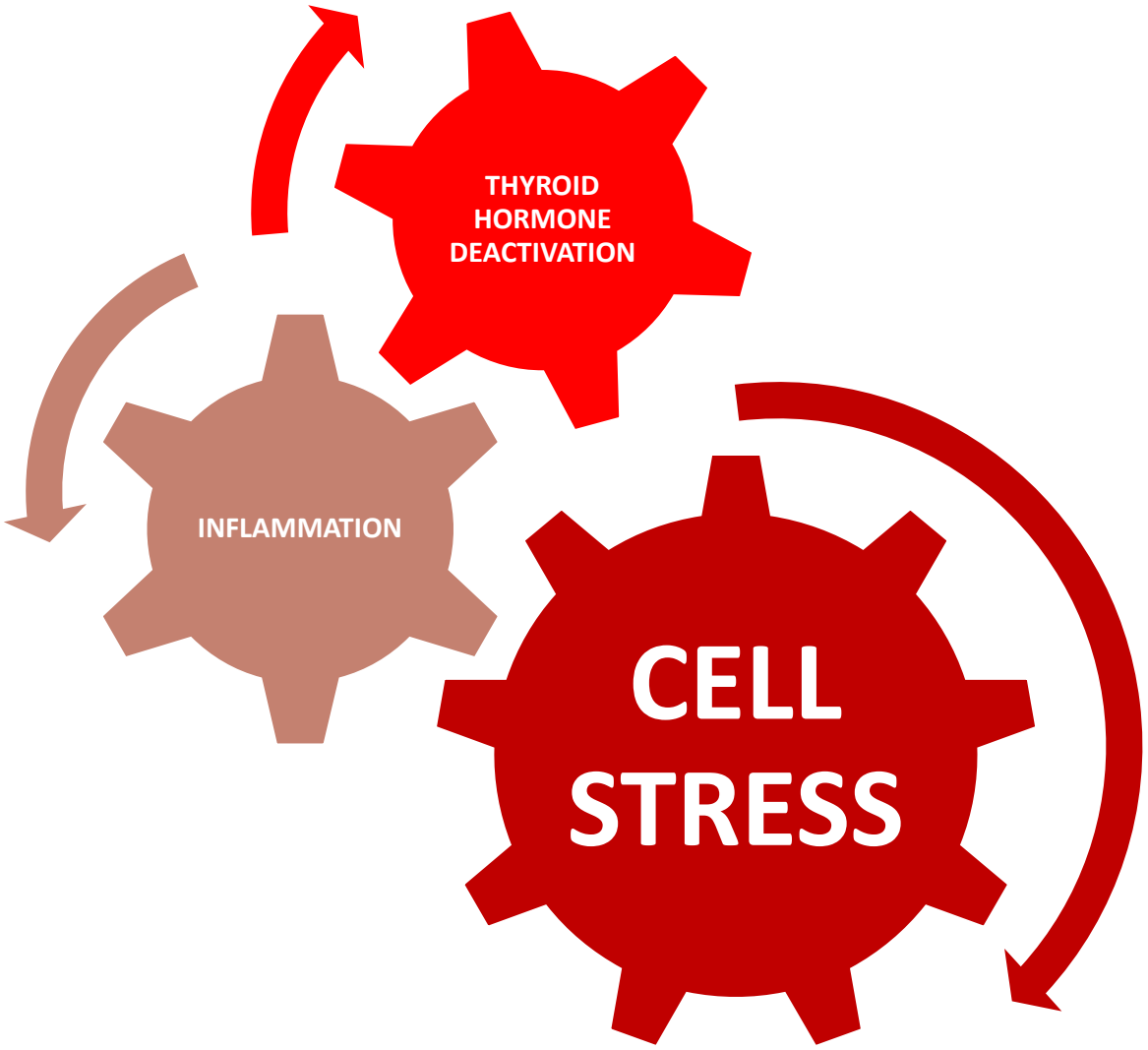
What Causes Excessive Cellular Stress?



Excessive cellular stress is perceived as a threat!

-

Inflammation and thyroid hormone deactivation are the "normal" response to a threat.



The Cell Danger Response

ELSEVIER

Mitochondrion

Volume 16, May 2014, Pages 7-17

Metabolic features of the cell danger response

Robert K. Naviaux

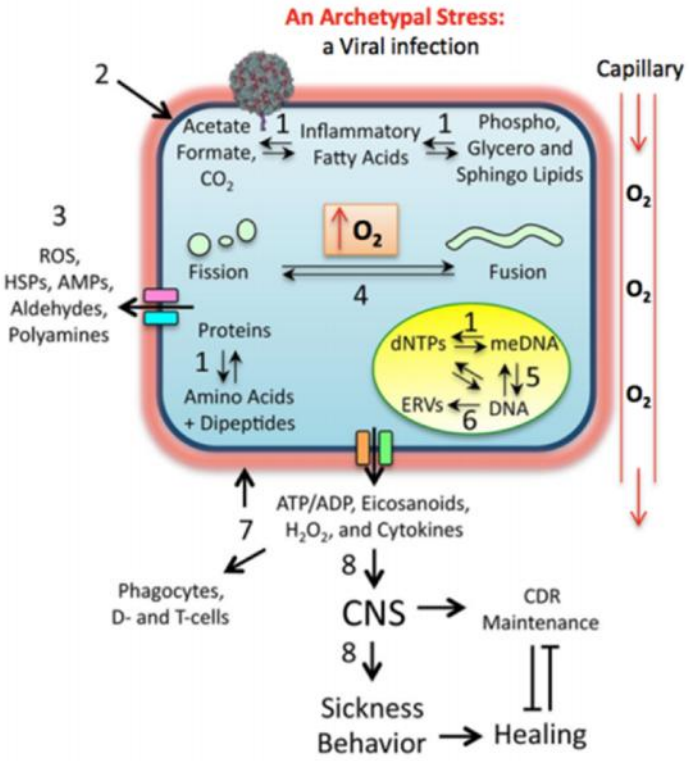
Show more

https://doi.org/10.1016/j.mito.2013.08.006

The Cell Danger Response (CDR)

"Is the evolutionarily conserved metabolic response that protects cells and hosts from harm. It is triggered by encounters with chemical, physical, or biological threats that exceed the cellular capacity for homeostasis. The resulting metabolic mismatch between available resources and functional capacity produces a cascade of changes in cellular electron flow, oxygen consumption, redox, membrane fluidity, lipid dynamics, bioenergetics, carbon and sulfur resource allocation, protein folding and aggregation, vitamin availability, metal homeostasis, indole, pterin, 1-carbon and polyamine metabolism, and polymer formation."

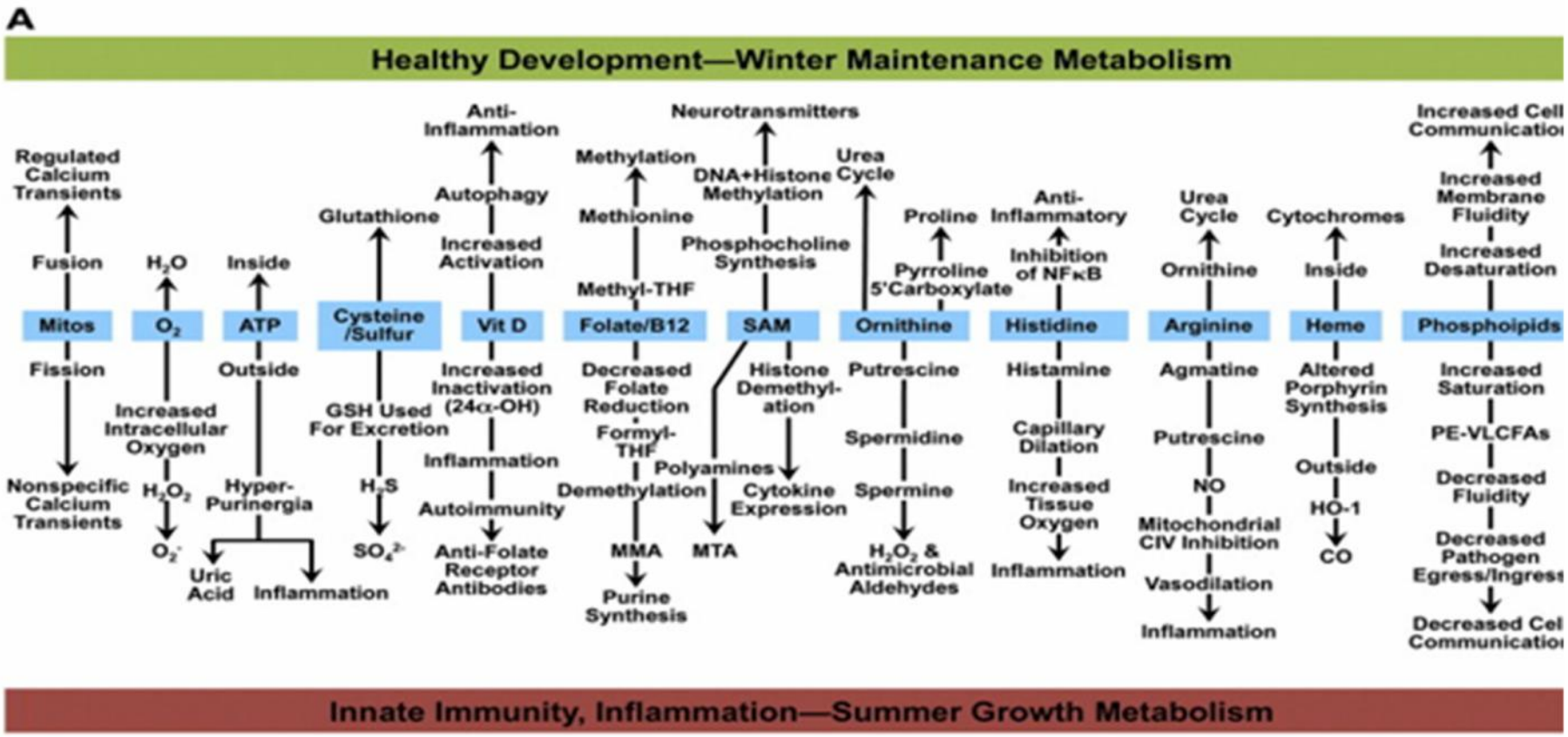
What is the Cell Danger Response (CDR)?



The CDR is a Coordinated, Multisystem, "Metabolic Reflex" Caused by an Electron Steal

0. Decrease oxygen consumption → increase dissolved O_2 concentration
1. Shift from polymer to monomer synthesis (ΔG; FA, AA, Dipeptides, NTs)
2. Stiffen cell membranes, lipid rafts
3. Release anti-viral and anti-microbial chemicals
4. Increase mitochondrial fission and autophagy & unfolded protein response
5. Change DNA and histone methylation—chromatin structure
6. Mobilize endogenous retroviruses, LINEs, and SVAs
7. Warn neighboring cells and call in effector cells—the "purinergic halo"
8. Alter host **behavior** to prevent spread of disease to kin

From Naviaux RK. Metabolic Features of the Cell Danger Response. *Mitochondrion*, 2014.


A
Healthy Development—Winter Maintenance Metabolism
Regulated Calcium Transients
Fusion
Mitos
Fission
Nonspecific Calcium Transients
H2O
O2
Increased Intracellular Oxygen
H2O2
O2-
Uric Acid
Inside
ATP
Outside
Hyper-Purinergia
Inflammation
Glutathione
Cysteine /Sulfur
GSH Used For Excretion
H2S
SO4 2-
Anti-Inflammation
Autophagy
Increased Activation
Vit D
Increased Inactivation (24α-OH)
Inflammation
Autoimmunity
Anti-Folate Receptor Antibodies
Methylation
Methionine
Methyl-THF
Folate/B12
Decreased Folate Reduction
Formyl-THF
Demethylation
MMA
Purine Synthesis
Neurotransmitters
DNA+Histone Methylation
Phosphocholine Synthesis
SAM
Histone Demethyl-ation
Polyamines
Cytokine Expression
MTA
Urea Cycle
Proline
Pyrroline 5'Carboxylate
Ornithine
Putrescine
Spermidine
Spermine
H2O2 & Antimicrobial Aldehydes
Anti-Inflammatory
Inhibition of NFκB
Histidine
Histamine
Capillary Dilation
Increased Tissue Oxygen
Inflammation
Urea Cycle
Ornithine
Arginine
Agmatine
Putrescine
NO
Mitochondrial CIV Inhibition
Vasodilation
Inflammation
Cytochromes
Inside
Heme
Altered Porphyrin Synthesis
Outside
HO-1
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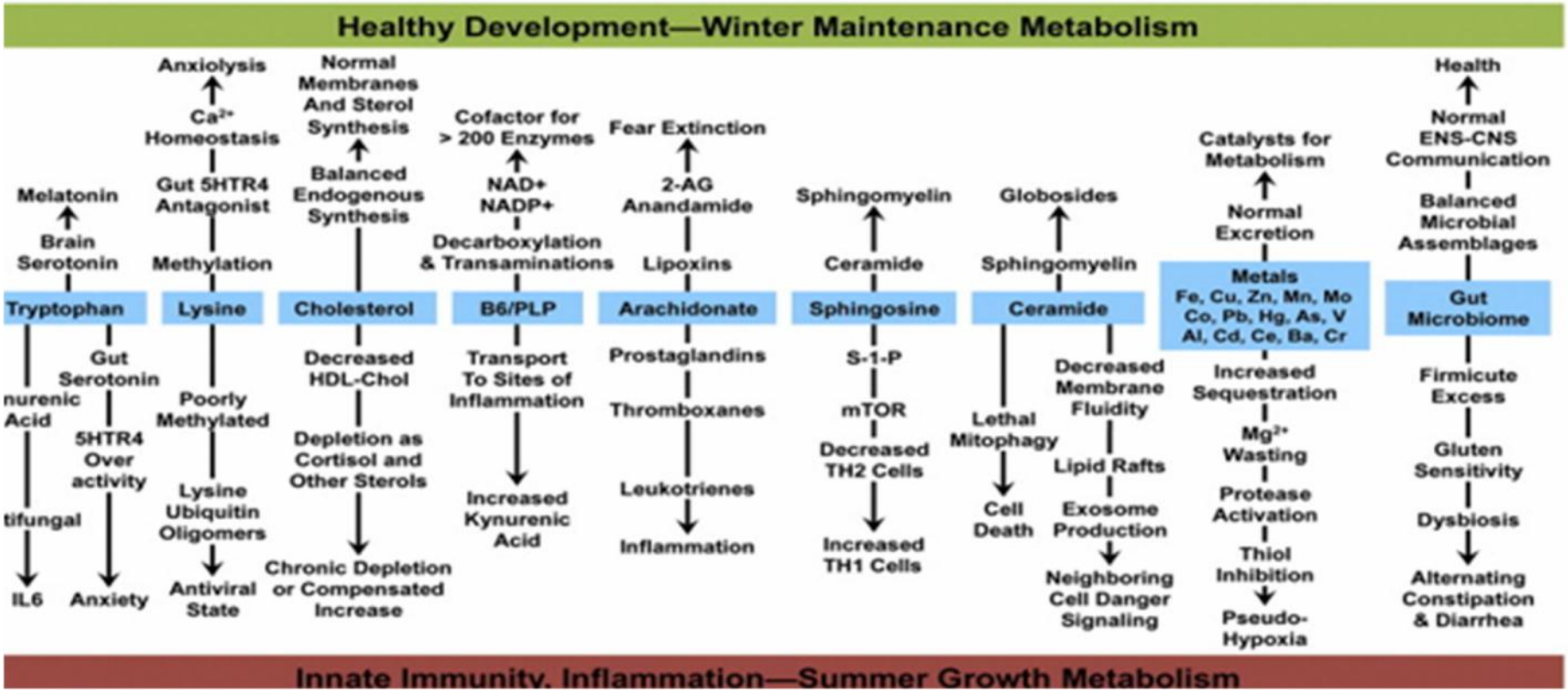
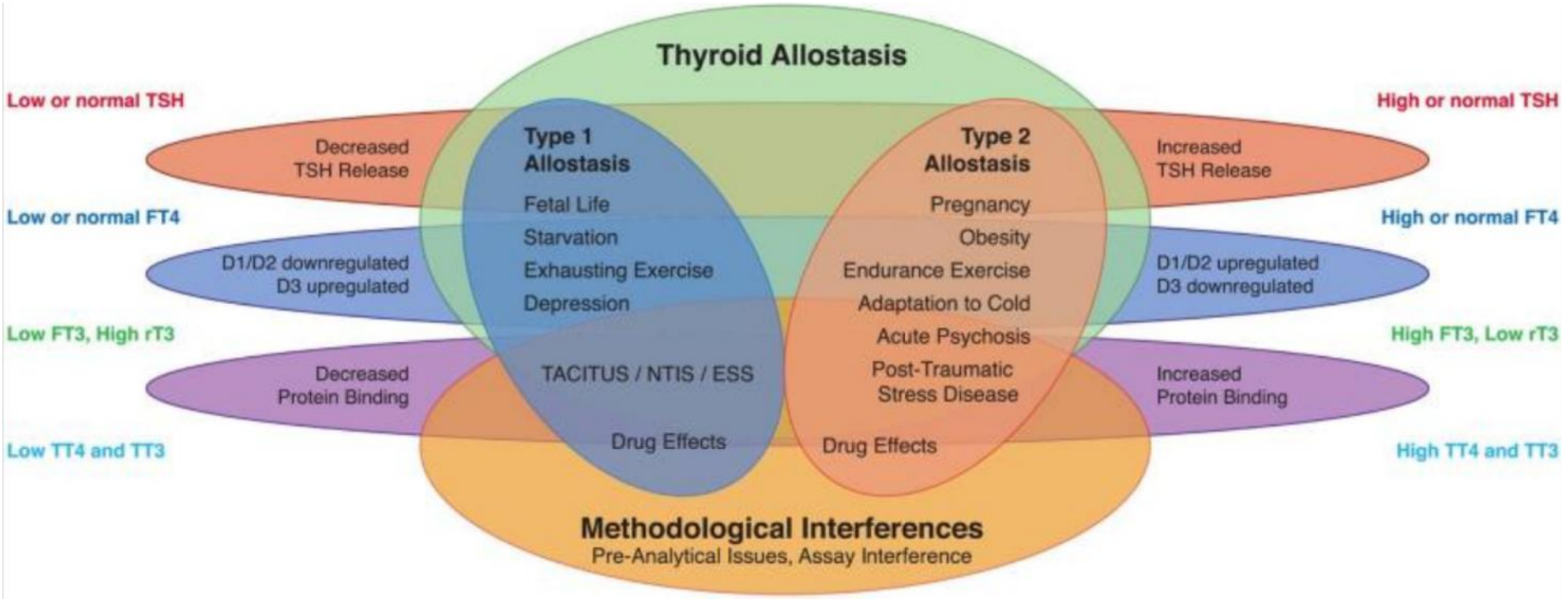
Increased Cell Communicatio
Increased Membrane Fluidity
Increased Desaturation
Phospholipids
Increased Saturation
PE-VLCFAs
Decreased Fluidity
Decreased Pathogen Egress/Ingress
Decreased Cel Communicatio
Innate Immunity, Inflammation—Summer Growth Metabolism


Healthy Development—Winter Maintenance Metabolism
Anxiolysis
Ca2+ Homeostasis
Gut 5HTR4 Antagonist
Methylation
Normal Membranes And Sterol Synthesis
Balanced Endogenous Synthesis
Cofactor for > 200 Enzymes
NAD+ NADP+
Decarboxylation & Transaminations
Fear Extinction
2-AG Anandamide
Lipoxins
Sphingomyelin
Ceramide
Sphingosine
S-1-P
mTOR
Decreased TH2 Cells
Increased TH1 Cells
Globosides
Sphingomyelin
Ceramide
Lethal Mitophagy
Cell Death
Decreased Membrane Fluidity
Lipid Rafts
Exosome Production
Neighboring Cell Danger Signaling
Catalysts for Metabolism
Normal Excretion
Metals
Fe, Cu, Zn, Mn, Mo
Co, Pb, Hg, As, V
Al, Cd, Ce, Ba, Cr
Increased Sequestration
Mg2+ Wasting
Protease Activation
Thiol Inhibition
Pseudo-Hypoxia
Health
Normal ENS-CNS Communication
Balanced Microbial Assemblages
Gut Microbiome
Firmicute Excess
Gluten Sensitivity
Dysbiosis
Alternating Constipation & Diarrhea
Melatonin
Brain Serotonin
Tryptophan
nurenic Acid
tifungal
IL6
Gut Serotonin
5HTR4 Over activity
Anxiety
Lysine
Poorly Methylated
Lysine Ubiquitin Oligomers
Antiviral State
Cholesterol
Decreased HDL-Chol
Depletion as Cortisol and Other Sterols
Chronic Depletion or Compensated Increase
B6/PLP
Transport To Sites of Inflammation
Increased Kynurenic Acid
Arachidonate
Prostaglandins
Thromboxanes
Leukotrienes
Inflammation
Innate Immunity, Inflammation—Summer Growth Metabolism



Thyroid Allostasis–Adaptive Responses of Thyrotropic Feedback Control to Conditions of Strain, Stress, and Developmental Programming https://www.frontiersin.org/articles/10.3389/fendo.2017.00163/full

Homeostasis

The tendency of organisms to auto-regulate and maintain their internal environment in a stable state.

Allostasis

An adaptive state to shift energy and resources to adapt to stressors, the allostatic load, to allow for survival, yet result in chronic signs, symptoms, and development of disease

Thyroid Allostasis: The process by which thyroid hormone physiology changes and adapts to stress / strain to try to return the body to homeostasis

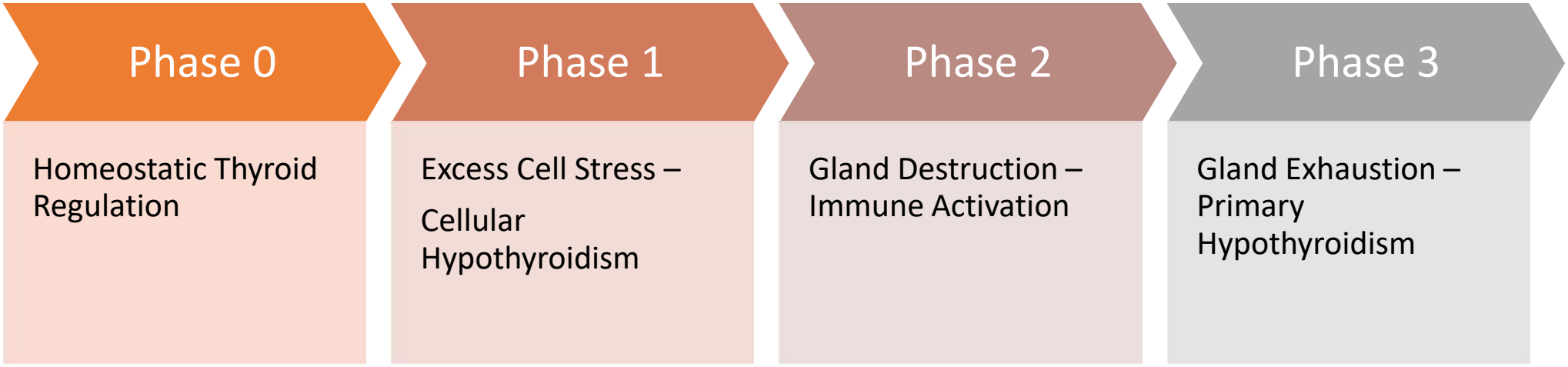
Alterations in cellular thyroid physiology can trigger hypothyroid symptoms

Consider:

- Hypothyroid signs and symptoms often exist **before** Primary Hypothyroidism is diagnosed
- Immune damage on the gland occurs **before** Primary Hypothyroidism is diagnosed
- Greater than 90% gland destruction occurs **before** Primary Hypothyroidism is diagnosed

Hypothyroidism occurs in the cells and tissues first.

Hypothyroid Spectrum



How Does a Thyroid Physiology Problem Develop?

1. Excessive cellular stress
   - Cell Danger Response
   - Shift from thyroid homeostasis to thyroid Allostasis = Cellular hypothyroidism
   - Release of DAMPs and PAMPs
2. Gland destruction
   - Thyroid cells perceive danger signals
   - Thyroid cell self-destruction and immune signaling
   - Subclinical Hypothyroidism
3. Glandular Exhaustion – overt glandular hypothyroidism = Primary Hypothyroidism

How Does a Thyroid Physiology Problem Develop?

Phase 1: Excessive Cellular Stress

- Cell Danger Response
- Shift from thyroid homeostasis to thyroid Allostasis = Cellular hypothyroidism
- Release of DAMPs and PAMPs

How Does a Thyroid Physiology Problem Develop?

Phase 2: Gland Destruction

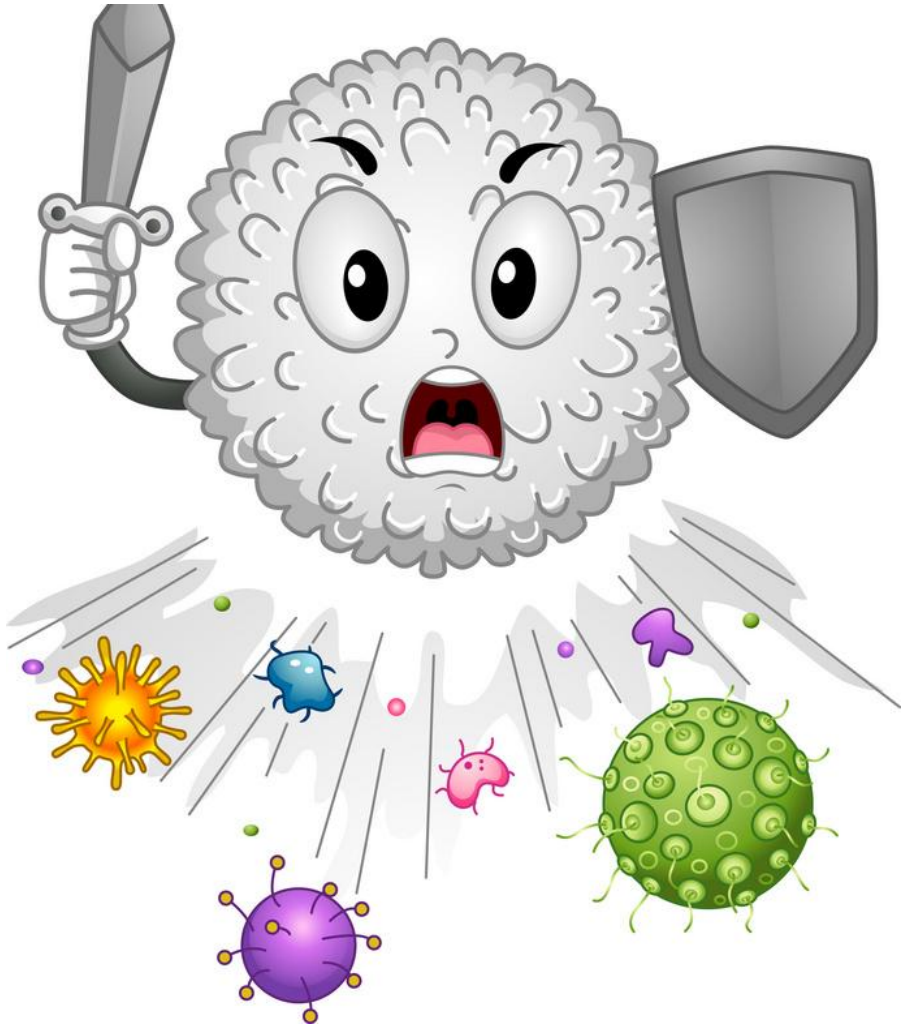
- Thyroid cells perceive danger signals
- Thyroid cell self-destruction and immune signaling
- Thyroiditis / Hashimoto's Thyroiditis
- Subclinical Hypothyroidism

How Does a Thyroid Physiology Problem Develop?

Phase 3: Glandular Exhaustion

- >90% gland destruction
- Overt glandular hypothyroidism = Primary Hypothyroidism

Deactivation of thyroid hormones in your cells is a Protective Mechanism to some type of cellular stress



How do we evaluate for Cellular Hypothyroidism?

Comprehensive Health History

- Does the patient have symptoms consistent with hypothyroidism?
- Is there a family history of hypothyroidism?
- Has the person ever been diagnosed with hypothyroidism in the past?
- Has the patient been on thyroid medication in the past?
- Is the patient on thyroid medication and still have symptoms?
- Is there a history of fluctuating TSH levels?

How do we evaluate for Cellular Hypothyroidism?

Comprehensive Thyroid Panel

- Full panel: TSH, T4, T3, fT4, fT3, T3U, rT3, Thyroid Ab
- TSH is not a valid marker of cellular thyroid physiology during stressed states
  - TSH is really measure of Hypothalamic T3
  - Transport mechanisms, deiodinases, and receptors are different in central system than peripheral tissues
  - Hypothalamus is much more sensitive to small shifts in thyroid hormone
  - TSH levels can be depressed in inflammatory and stressed states

How do we evaluate for Cellular Hypothyroidism?

1. Comprehensive Thyroid Panel
2. rT3 > 18
3. T3/rT3 < 10
4. fT3/rT3 < .20

How do we evaluate for Cellular Hypothyroidism?

Other lab tests that might indicate Cellular hypothyroidism:

- CRP > 1
- Increased glucose, Insulin, insulin resistance
- Elevated cholesterol
- Elevated lipid peroxides (OAT)
- Elevate cortisol, low metabolized cortisol (DUTCH)
- Low stomach acid / Hypochlorhydria (low protein and globulin)
- Elevated Uric Acid

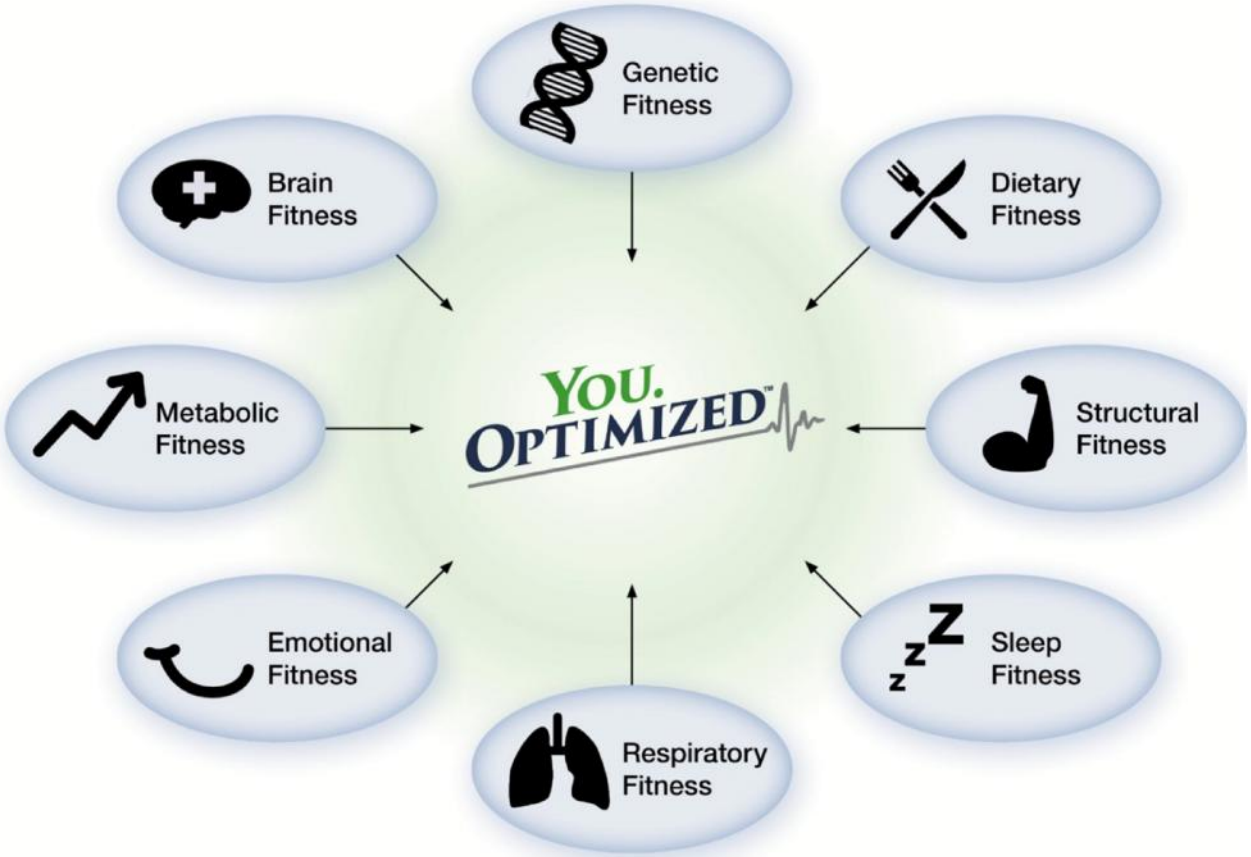
How do we evaluate for Cellular Hypothyroidism?

Other lab tests that might indicate Cellular hypothyroidism:

- Homocysteine
- 8 OHdG
- Low WBC
- Elevated CoQ10
- Anemia patterns
- Compromised methylation

Strategic Thyroid Solution

- Identify cell stressors and remove or reduce
- Identify tissues and systems that have become compromised and support shift in recovery from allostasis to homeostasis via modifications in diet, lifestyle and supplemental protocols
- Monitor and manage health vs disease



How do we support these patients?

Address the foundation – Fitness factors

Why does all this matter?

When we look at hypothyroidism as a cellular process first:

- We can intervene earlier
- We can start to address cause before pathology
- All thyroid tests matter as well as diet, lifestyle and environment
- Treatment becomes strategic vs dolling out a standard prescription
- We can actually improve a person's health vs managing their disease

References:

1. Razvi S, Bhana S, Mrabeti S. Challenges in Interpreting Thyroid Stimulating Hormone Results in the Diagnosis of Thyroid Dysfunction. J Thyroid Res. 2019;2019:4106816. Published 2019 Sep 22. doi:10.1155/2019/4106816

2. The deiodinases and the control of intracellular thyroid hormone signaling during cellular differentiation. https://doi.org/10.1016/j.bbagen.2012.05.007

3. Cellular Stress Responses: Cell Survival and Cell Death https://www.hindawi.com/journals/ijcb/2010/214074/

4. Thyroid Hormones and the Metabolic Syndrome https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3821514/

5. The kinetics of thyroid hormone transporters and their role in non-thyroidal illness and starvation. https://www.ncbi.nlm.nih.gov/pubmed/17574011

6. Why Can Insulin Resistance Be a Natural Consequence of Thyroid Dysfunction? http://dx.doi.org/10.4061/2011/152850

7. Plasma membrane transport of thyroid hormones and its role in thyroid hormone metabolism and bioavailability. Endocr Rev. 2001 Aug;22(4):451-76. https://www.ncbi.nlm.nih.gov/pubmed/11493579

8. Novel insights into thyroid hormones from the study of common genetic variation https://www.ncbi.nlm.nih.gov/pubmed/19352319#

9. Sodium selenite supplementation does not fully restore oxidative stress-induced deiodinase dysfunction: Implications for the nonthyroidal illness syndrome https://doi.org/10.1016/j.redox.2015.09.002

10. Why are our hypothyroid patients unhappy? Is tissue hypothyroidism the answer? Indian J Endocrinol Metab. 2011 Jul; 15(Suppl2): S95–S98. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3169863/#sec1-6title

11. Neuronal Hypoxia Induces Hsp40-Mediated Nuclear Import of Type 3 Deiodinase As an Adaptive Mechanism to Reduce Cellular Metabolism https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3752066/

12. Deiodinases: implications of the local control of thyroid hormone action J Clin Invest. 2006 Oct 2; 116(10): 2571–2579 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1578599/

13. Extra-Thyroidal Factors Impacting Thyroid Hormone Homeostasis: A Review http://www.ingentaconnect.com/content/aarm/jrm/2015/00000004/00000001/art00006

References:

13. Cellular Stress Responses: Cell Survival and Cell Death http://dx.doi.org/10.1155/2010/214074
14. Thyroid hormone action in mitochondria. https://www.ncbi.nlm.nih.gov/pubmed/11174855
15. Thyroid Hormone Stimulation of Autophagy Is Essential for Mitochondrial Biogenesis and Activity in Skeletal Muscle. https://www.ncbi.nlm.nih.gov/pubmed/26562261
16. Thyroid Hormones, Oxidative Stress, and Inflammation Volume 2016 (2016), Article ID 6757154, 12 pages http://dx.doi.org/10.1155/2016/6757154
17. Interaction of the endocrine system with inflammation: a function of energy and volume regulation https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3978663/
18. Homocysteine, hypothyroidism, and effect of thyroid hormone replacement. https://www.ncbi.nlm.nih.gov/pubmed/10646653
19. Homocysteine, folate and cobalamin levels in hypothyroid women before and after treatment. https://www.ncbi.nlm.nih.gov/pubmed/17464093
20. Hyperthyroid and Hypothyroid Status Was Strongly Associated with Gout and Weakly Associated with Hyperuricemia https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4259336/
21. Homeostatic Control of the Thyroid–Pituitary Axis: Perspectives for Diagnosis and Treatment https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4653296/
22. Thyroid Allostasis–Adaptive Responses of Thyrotropic Feedback Control to Conditions of Strain, Stress, and Developmental Programming Front. Endocrinol., 20 July 2017 | https://doi.org/10.3389/fendo.2017.00163
23. Demonstration of innate immune responses in the thyroid gland: potential to sense danger and a possible trigger for autoimmune reactions. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3610444/pdf/thy.2011.0480.pdf

References:

24. Thyroid Autoimmunity: Role of Anti-thyroid Antibodies in Thyroid and Extra-Thyroidal Diseases https://www.frontiersin.org/articles/10.3389/fimmu.2017.00521/full

25. Thyroid hormone induction of mitochondrial activity is coupled to mitophagy via ROS-AMPKULK1 signaling https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4590606/pdf/kaup-11-08-1061849.pdf

26. Role of the Iodothyronine Deiodinases in the Physiology and Pathophysiology of Thyroid Hormone Action https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3673746/pdf/etj-0001-0232.pdf

27. Pitfalls in the measurement and interpretation of thyroid function tests https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3857600/pdf/main.pdf

28. Why are our hypothyroid patients unhappy? Is tissue hypothyroidism the answer? https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3169863/#!po=19.2308

29. New insights into thyroid hormone action. https://www.ncbi.nlm.nih.gov/pubmed/28174093

30. Defending plasma T3 is a biological priority https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4699302/pdf/nihms746217.pdf

31. Recent Advances in Thyroid Hormone Regulation: Toward a New Paradigm for Optimal Diagnosis and Treatment https://www.frontiersin.org/articles/10.3389/fendo.2017.00364/full

32. Metabolic features of the cell danger response https://www.sciencedirect.com/science/article/pii/S1567724913002390