THYROID DISEASE: THE REST OF THE STORY

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TOO FREQUENTLY THE JOURNEY TO HEALTH IS FRAUGHT WITH DIFFICULTIES.

TRY A DIFFERENT RIDE: WELCOME TO ENDOCRINE AIRLINES

- For some, the ride will be long and bumpy, before you reach your desired destination.
- Unfortunately this journey allows no refunds or cancellations.
- We hope you all have a comfortable flight, upgrades in your travel arrangements, and a rewarding travel experience.
- So fasten your seatbelts, open your window shades, get ready to wrap your mind around new and exotic experiences, and prepare for take off.

OUR JOURNEY: WHAT WE WILL COVER

- **Basic understanding of the physiology of thyroid function—how the thyroid works. Fundamental in understanding thyroid treatment.**
- **Thyroid testing—how we can assess the thyroid. What thyroid tests, and what other tests should be ordered and what they tell us.**
- **Thyroid disorders—understanding what goes wrong:**
  - Hypothyroid—under active—what causes the high incidence of Hashimoto's thyroiditis, an auto-immune disease

OUR JOURNEY: DESTINATION

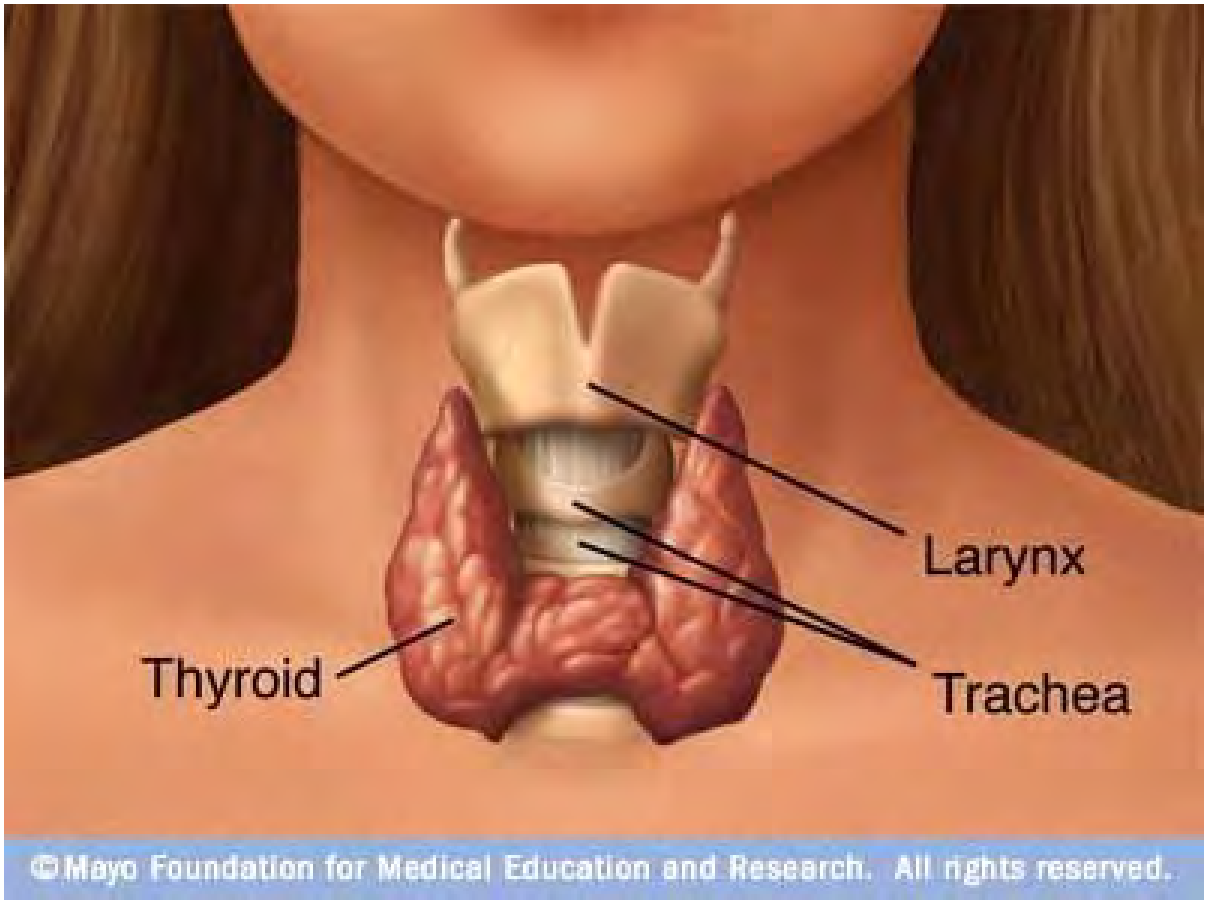
- **Managing and Healing Hashimoto's Thyroiditis**—important treatment considerations:
  - Addressing Causes: nutrition, inflammation, allergies, toxins, medications, and more.
  - Gluten/wheat allergy : celiac and non-celiac
- **The matrix**: Relationship between the endocrine systems—they are all intertwined with the thyroid:
  - Pituitary and Adrenals
  - Sex hormones
  - Insulin glucose

CONTROVERSIES: THYROID PROBLEMS PRESENT ONE OF THE AREAS IN MEDICINE WITH THE MOST CONTROVERSY, CONTENTION AND DISPARATE INFORMATION.

- What tests should I get to investigate and manage thyroid problems?
- What treatment, if any, should I receive for Hashimoto's Thyroiditis?
- Which form of thyroid hormone should I take? Synthyroid? Armour? T3 and T4?
- What is functional hypothyroidism? Should it be treated? What about sub-clinical hypothyroidism?
- What should I eat if I have Hashimoto's Thyroiditis?
  - Should I take iodine supplements?
  - Can I eat soy foods?
  - Should I eliminate wheat/gluten?

ANATOMY OF THE THYROID GLAND

- Located in the anterior (front of) the neck.
- Shaped like a shield
- Normally can not be palpated (felt)



THYROID:PATHWAY OF ACTION:

LIKE A RELAY RACE WITH A BATON BEING PASSED FROM BRAIN TO BODY ORGANS.

Hypothalamus (A structure at the base of the brain): Communicates between the nervous system and the endocrine (hormone) system

|

Thyroid Releasing Hormone (TRH)

|

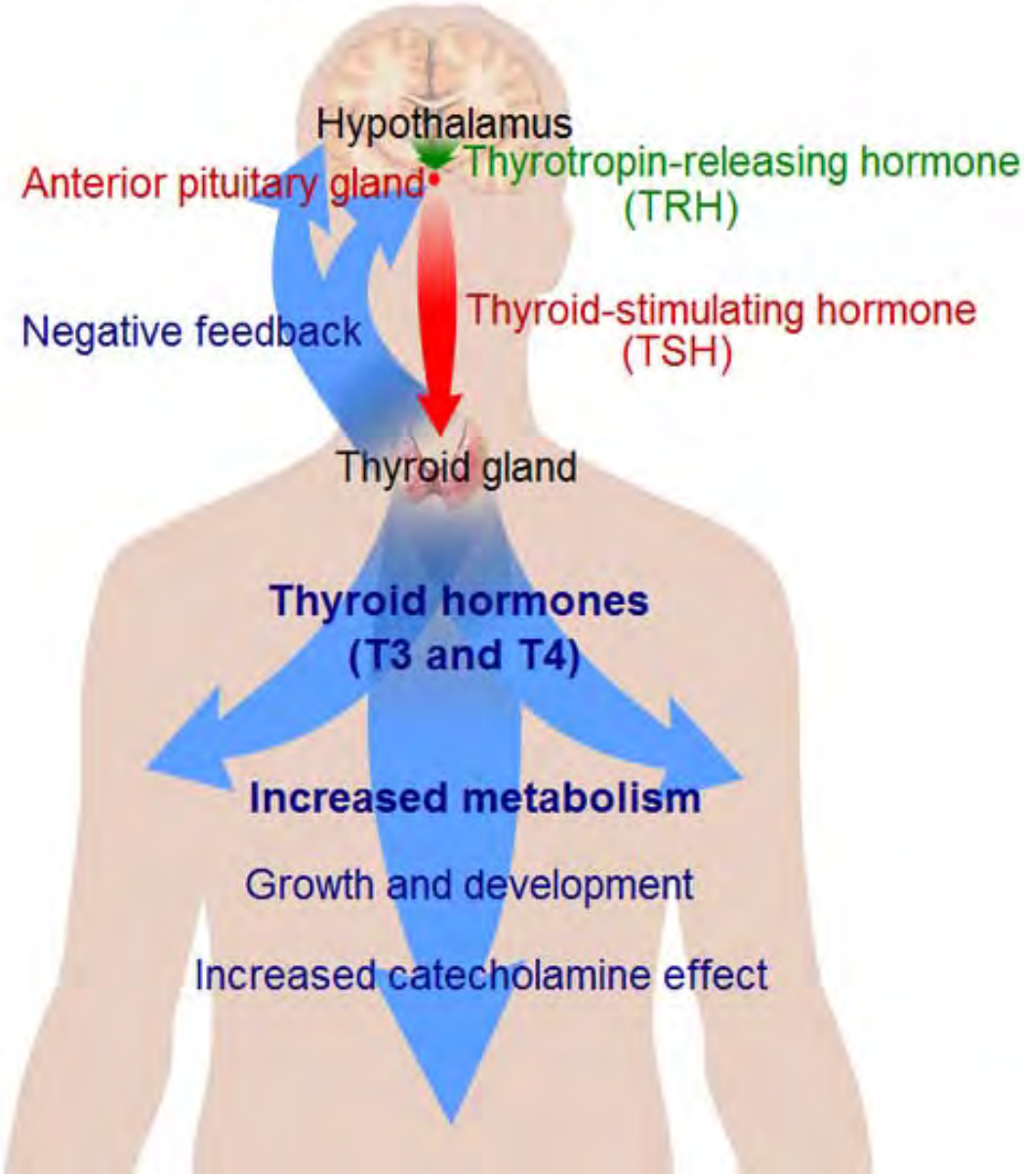
Pituitary Gland (just below the hypothyroid) “the master gland”

|

Thyroid Stimulating Hormone (TSH)

(TSH depends on pituitary function and the levels of T3 and T4. It does not reflect auto-immune problems or whether the thyroid hormones are working normally in the body.)

Thyroid system



THYROID PATHWAY OF ACTION: TSH STIMULATES THE THYROID TO PRODUCE T3 AND T4

Thyroid stimulating hormone

V

Thyroid

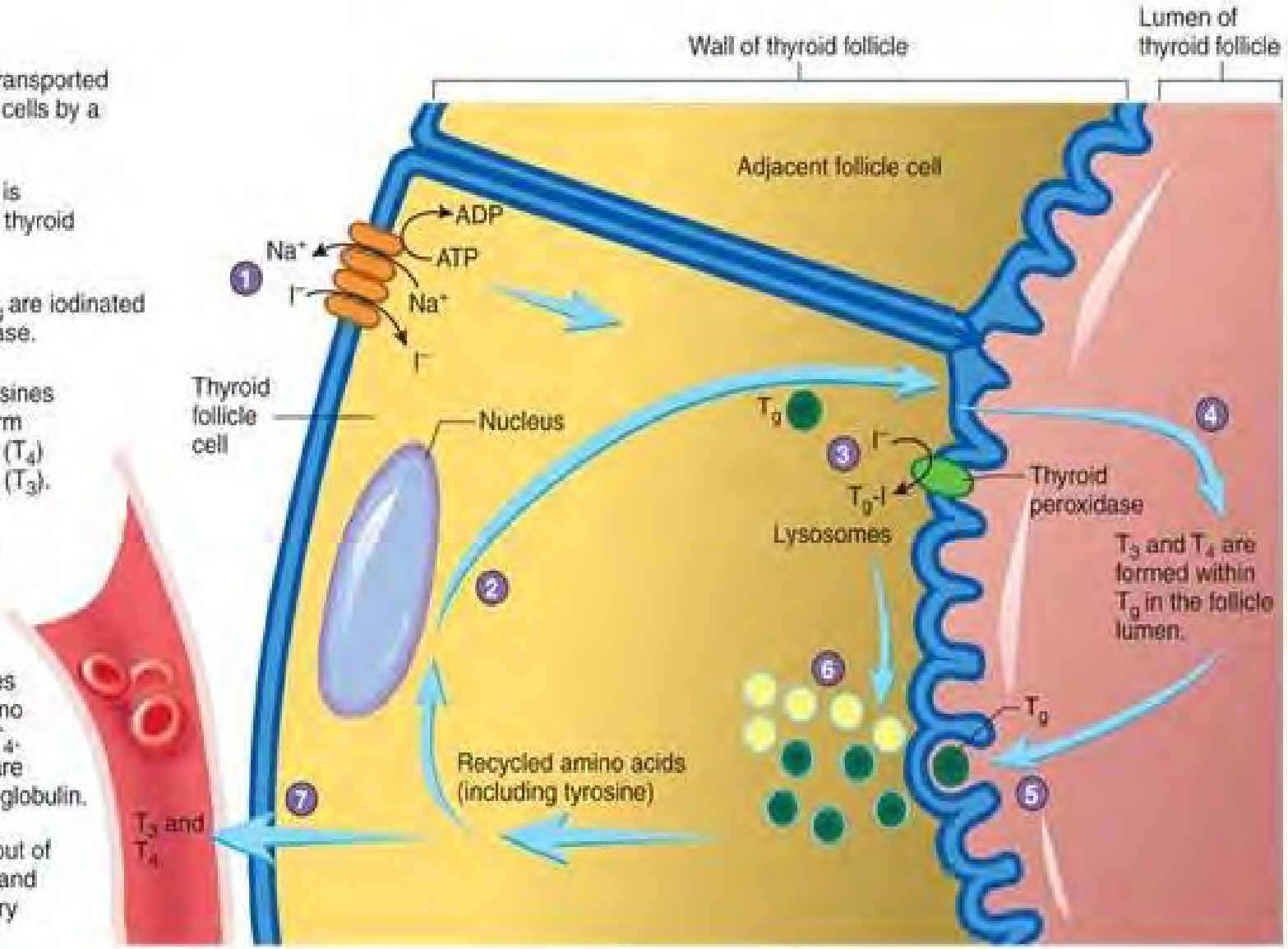
/ \

T4 (93%) T3 (7%)

(Most—almost 99% of the thyroid hormones are bound to proteins—albumin and thyroid binding globulin)

T4 is largely inactive. T3 is the active hormone, “the heavy lifter.”

1. Iodide is actively transported into thyroid follicle cells by a Na^+/I symporter.
2. Thyroglobulin (T_g) is synthesized in the thyroid follicle cell.
3. Tyrosines within T_g are iodinated by thyroid peroxidase.
4. Two iodinated tyrosines within T_g join to form tetraiodothyronine (T_4) or triiodothyronine (T_3).
5. Endocytosis of T_g into the thyroid follicle cells.
6. T_g is digested by lysosomal enzymes into individual amino acids and T_3 and T_4. The amino acids are recycled into thyroglobulin.
7. T_3 and T_4 diffuse out of the thyroid follicle and enter the circulatory system.



THYROID PATHWAY OF ACTION: THE ADVENTURES AND MISADVENTURES OF T4

T4 (thyroxine)

/ \

Liver (60%) Other organs (40%)

Heart, muscle, nerves, intestine

/ | \ |

T3 (20%) Reverse T3 (20%) T3S and T3AC inactive (20%) T3

|

Gastrointestinal Tract

(this step depends on

healthy bowel bacteria)

|

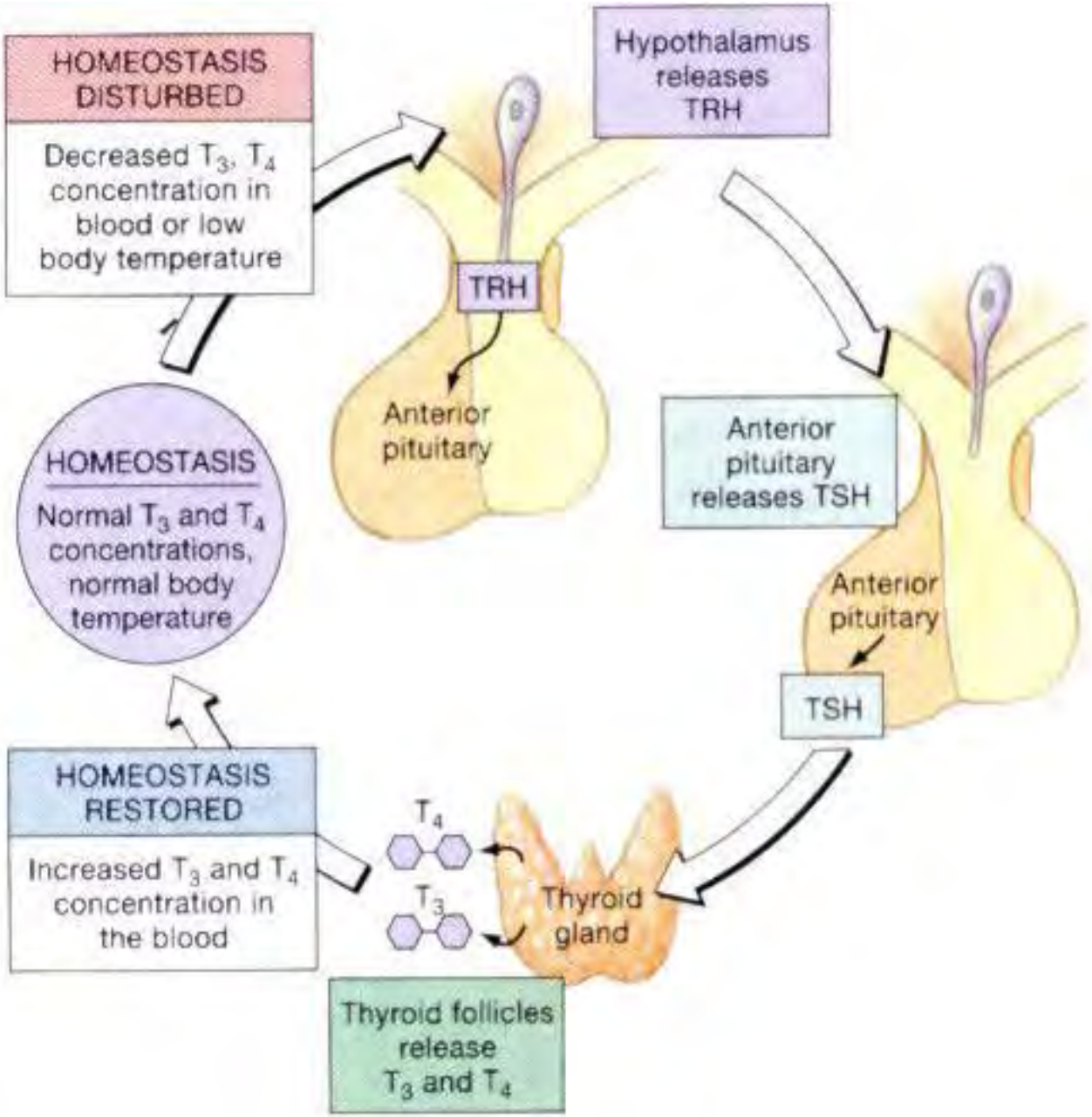
Active T3

SUMMARY: BOUND AND UNBOUND THYROID HORMONES

- **Mainly T4**: 93% of the hormones that the thyroid gland secretes are T4 (which has 4 molecules of iodine)
- **Conversion:** T4 is converted to T3 (which has 3 iodine molecules) by an enzyme called tetra-iodo-thyronine-5-dehydrogenase in the liver and other organs.
- **Bound and Free**:
  - T3 and T4 are mostly **bound to proteins** in the bloodstream. (Albumin and thyroid binding globulin)
  - The unbound T3 and T4 are called **"free T3" and "free T4".**
  - **Cash at hand:** the total T3 is like wealth that is stored in your total financial portfolio, and the free T3 is like cash available to you immediately from your checking account.

T3, REVERSE (DUD) T3, AND T4

- **Active Hormone**: The free T3 is the actual active hormone that can bind to and activate thyroid in all your body's organs.
- **Inactive Hormone:** The Liver converts some T4 to Reverse T3, which is inactive, but can bind to thyroid receptors and **not** activate them.
- **Activation by colon bacteria:** The liver produces some inactive forms of T3 that depend on healthy gut flora to convert them to active T3
- **Action of T3**: T3 binds to the nucleus of cells and switches genetic triggers on and off.
- **Feedback Loop:** T3 and T4 receptors in the hypothalamus mediate production of Thyroid Releasing hormone (TRH) and consequent production of Thyroid Stimulating Hormone (TSH) in the pituitary. This is the feedback loop that controls thyroid secretion.


HOMEOSTASIS DISTURBED
Decreased T_3, T_4 concentration in blood or low body temperature
Hypothalamus releases TRH
TRH
Anterior pituitary
Anterior pituitary releases TSH
Anterior pituitary
TSH
Thyroid gland
T_4
T_3
Thyroid follicles release T_3 and T_4
HOMEOSTASIS RESTORED
Increased T_3 and T_4 concentration in the blood
HOMEOSTASIS
Normal T_3 and T_4 concentrations, normal body temperature

LABORATORY TESTING

- Assessing thyroid function requires a full set of thyroid tests including
- TSH
- T3, free T3, T4, free T4, Reverse T3, and
- thyroid auto-antibodies, and
- If appropriate assessment of adrenal function, sex hormones, and glycemic function (insulin/glucose).
- If needed, nutritional testing: Vitamin D, Red Blood Cell (RBC) Selenium, Red Blood Cell (RBC) Zinc.

LABORATORY TESTING: WHAT SPECIMEN TO TEST?

Blood vs. Urine vs. Saliva

- Blood is easily available.
- Blood tests are covered by insurance.
- Blood is easier then 24-hour urine.
- Blood has more documentation then saliva or urine.

- Blood levels have been shown to be consistent markers

LABORATORY TESTING: WHAT SPECIFIC TESTS TO ORDER?

- TSH: Third-generation **"highly sensitive"** assay: Sensitivity to 0.02 mIU/mL
- Remember:
  - Testing TSH indicates only pituitary production
  - Pituitary hormone levels alone are not sufficient to measure the function of the gland they regulate
- **What is normal?**
  - Upper limit: went from **~10 to~4.5 mIU/mL** in past 20 years
  - **0.3-3.0 uIU/ml** (2003, The American College of Clinical Endocrinologists)
  - **0.27-4.2 uIU/ml.** Martha Jefferson Clinical Lab

TSH: A SENSITIVE BUT CRANKY TEST

- Sensitivity of TSH:
  - log-linear relationship with circulating thyroid hormone levels (**a 2-fold change in free thyroxine will produce a 100-fold change in TSH).**
  - Considered a necessary test for diagnosis of mild thyroid failure when the peripheral thyroid hormone levels are within normal laboratory range
    - because the individual range for peripheral thyroid hormones is narrower than the population reference laboratory range;
    - therefore, a slight reduction within the normal range will result in elevation of serum TSH above the normal range.
- Other reasons for Elevated TSH
  - Circadian rhythm: higher in PM
  - Stress hormone (along with cortisol, adrenalin, etc)

TSH CONTROVERSY: WHAT IS NORMAL?

In 2003, The American College of Clinical Endocrinologists recommended a new reference range of **Normal TSH: 0.3–3.0 uIU/ml**

- Hossein Gharib, MD, FACE, and president of AACE at the time:"**The prevalence of undiagnosed thyroid disease in the United States is shockingly high…The new TSH range from the ACCE guidelines gives physicians the information they need to diagnose mild thyroid disease before it can lead to more serious effects on a patient's health - such as elevated cholesterol, heart disease, osteoporosis, infertility, and depression.“**
- **“ The AACE believes the new range will result in proper diagnosis for millions of Americans who suffer from a mild thyroid disorder, but have gone untreated until now.”**
- **However, most labs and clinicians have not adopted these new recommendations,** The reference range for TSH tests is still approximately **Normal TSH: 0.5 to 5.0 uIU/ml.**
- **And debate continues.**

American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidis and hypothyroidism. Endocr Pract, 2002. 8(6): p. 457-69.

TSH CONTROVERSY
WHAT IS "CLINICAL" AND WHAT IS "SUBCLINICAL" HYPOTHYROID?

Customary diagnostic criteria

- **"Clinical Hypothyroid":** A high serum thyrotropin (TSH) concentration and a low serum free thyroxine (T4) concentration
- **"Subclinical Hypothyroid":** A normal free T4 in the presence of an elevated TSH
- **Hyperthyroidism**: High TSH and High T4

T3, TOTAL AND FREE. T4, TOTAL AND FREE REVERSE T3

- **T3 measures total T3**
  - **T3 uptake is an indirect measurement of T3, commonly used in a thyroid screening panel, and less accurate than direct measurement of T3**
- **T4 measures total T4.**
- **Free T3 measures T3 not bound to protein.**
- **Similarly Free T4 measures T4 not bound to protein.**
- **Reverse T3 measures an inactive form of T3. (More about this later)**

BIOCHEMICAL INDIVIDUALITY: ONE SIZE DOES NOT FIT ALL

- “Our data indicate that the distinction between subclinical and overt thyroid disease (abnormal serum TSH and abnormal T(4) and/or T(3)) is somewhat arbitrary. For the same degree of thyroid function abnormality, the diagnosis depends to a considerable extent on the position of the patient's normal set point for T(4) and T(3) within the laboratory reference range.”
- “*Test results within laboratory reference limits is not necessarily normal for an individual.”*
- Anderson et. al., "Narrow Individual Variations in the Serum T4 and T3 inNormal Subjects: A Clue to the Understanding of Subclinical ThyroidDisease," *Journal of Clinical Endocrinology and Metabolism, 2002:87(3):*1068-1072

BIOCHEMICAL INDIVIDUALITY

- **Just because a test result is somewhere within the laboratory reference range does not necessarily mean it is optimal for that individual.**

"Why do you call it a thyroid 'problem' when it's giving me an excuse for the 20 pounds I gained this year???"

THYROID AUTO-ANTIBODIES

- When our immune system starts to produce antibodies that attack our thyroid tissue;
- Two antibodies are commonly tested:
  - Thyroid peroxidase antibody (TPO)
  - Thyroglobulin Antibodies (TBG)
- They may be normal between flares of Hashimoto's, so testing at more than one occasion is useful.
- Following the level of antibodies can provide a handle on the activity of the disease.

ADDITIONAL LABORATORY EVALUATION FOR THYROID DISEASE

Assess adrenal hormones

- Blood and/or Saliva DHEA
- Saliva cortisol levels—4 timed specimens

Investigate gluten antibodies

- Serum Gliadin IgA and IgG
- Saliva or stool anti-gliadin IgA

Celiac testing

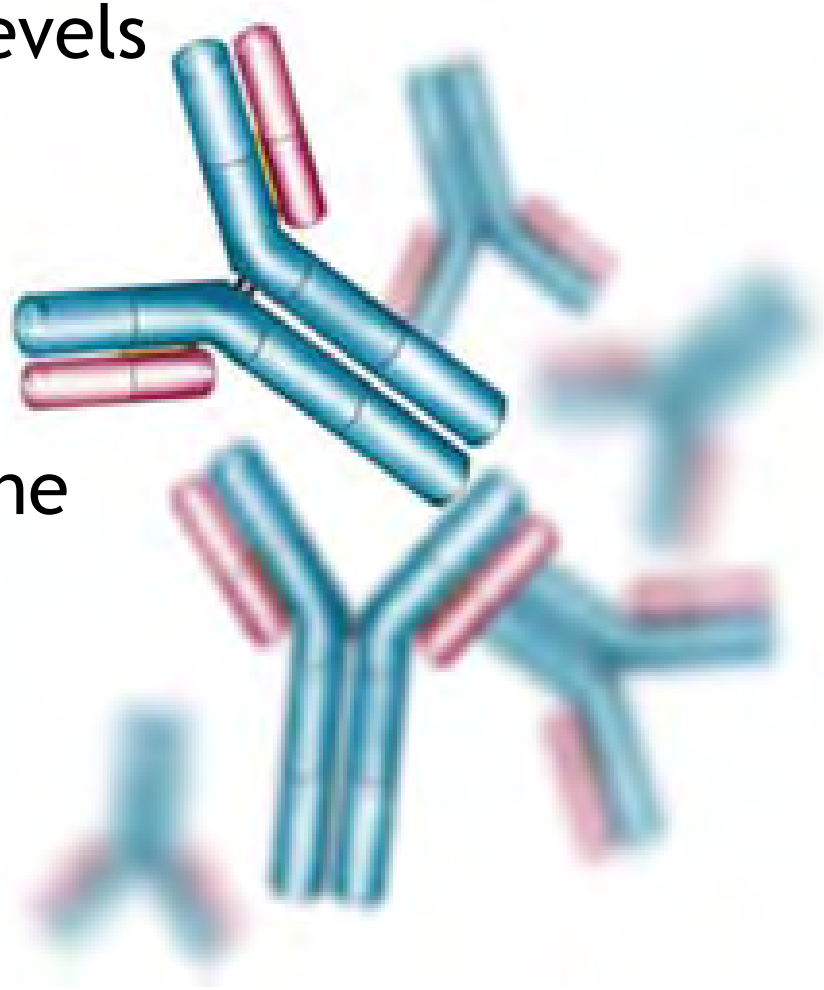
- Anti-endomesial antibody
- Anti-trans glutaminase antibody
- Total IgA

B12 DEFICIENCY—A COMMON COMPANION TO HASHIMOTO'S THYROIDITIS

- Also known as pernicious anemia
- Diagnosis is by
  - **Low B12**
  - **Elevated methylmalonic acid** (inability to convert methylmalonyl CoA to succinyl CoA)
  - **Elevated homocystine** (inability to convert homocystine to methionine) and
  - Antibodies against parietal cells occur in 85% of patients
    - Also occur in 10% of healthy people, and with other auto-immune diseases.
  - Antibodies against intrinsic factor are found in 50% of people with pernicious anemia,
    - but rarely found in healthy people or in other disorders.

SUMMARY: WHAT TO TEST AT BASELINE

- Thyroid hormone levels
  - T3 total and free
  - T4 total and free
  - Reverse T3
- Pituitary: Thyroid Stimulating Hormone (TSH)
- Thyroid Antibodies
  - TPO Antibodies
  - Anti-TG Antibodies



REFERENCE RANGE & OPTIMAL RANGE

Optimal Range	Standard Reference Range
TSH: 0.4-2 mIU/L	(rr .4-5.5)
Free T4: 1.4-1.8 ng/dL	(rr .8-1.8)
Free T3: 300-420 pg/dl	(rr 230-420)
Free T3 0.3-.42 ng/dl	(rr .23-.42)
Total T3: 120-181 ng/dL	(rr 76-181)
RT3: 11-20 ng/dL (rr 11-31)	(rr 11-31)
T3/RT3:	
McDaniel 10-12	
Woliner: >6	
Thyroid Antibodies:	
negative	

THYROID TESTING: SUMMARY OTHER TESTS THAT MAY BE USEFUL

- Other hormone systems:
  - Adrenal hormones: Salivary cortisol. Salivary or serum DHEA
  - Glycemic function: Insulin and blood sugar fasting and/or 2 hours after meal
  - Sex hormones: estrogens, testosterone, progesterone, Sex hormone binding globulin
- Identifying allergic and digestive causes of auto-immune disease:
  - Stool test to Assess digestive function and intestinal wall impermeability
  - IgG and IgA food antibodies, apart from gluten.

HYPOTHYROIDISM

- How common is hypothyroidism?
- What do we know that causes the thyroid to go awry?
- How do we recognize it clinically?
- What do we test for?
- How do we treat this?
- Hypothyroidism (Hashimoto's Thyroiditis)
- Subclinical Hypothyroidism
- Functional hypothyroidism (low thyroid symptoms with normal lab tests)

THYROID DISEASE BY THE NUMBERS

- Very Common: 5-10% of population
  - **27 Million:** The number of Americans estimated to suffer from Thyroid Disease.
  - **13 Million:** The number of Americans estimated to suffer from Thyroid Disease…but remain undiagnosed.

- Mostly women:
  - **8 out of 10:** patients with Thyroid Disease are women.
  - 15% of women over age 50
    - American Association of Clinical Endocrinologists (AACE)

IT IS ESTIMATED THAT ONE OUT OF EVERY SEVEN ADULTS IN THE UNITED STATES HAS A LOW FUNCTIONING THYROID

American Thyroid Association Website. http://www.thyroid.org/patients/brochures/Hypothyroidism%20_web_booklet.pdf.

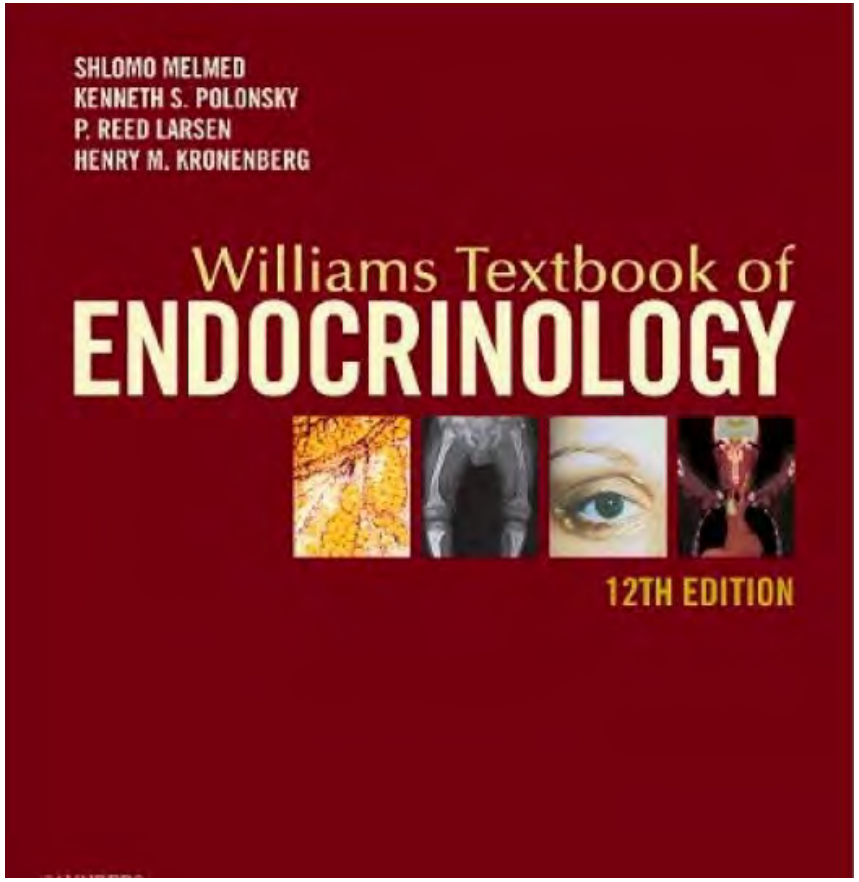
COLORADO STATE FAIR STUDY

- 25,862 people at the Colorado Fair
  - 9.5% had TSH values >5.01 mU/L
  - 2.2% percent had TSH <0.3 mU/L
- Only 60 percent of people taking thyroid medication had TSH levels in the normal range (>0.3 and<5.01 mU/L)
- Canaris GJ, et. al. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000;160(4):526.

ALL BODY ORGAN SYSTEMS HAVE THYROID RECEPTORS.

"Hypothyroidism can affect all organ systems. These manifestations are largely independent of the underlying disorder but are a **function of the degree of hormone deficiency."**

- Melmed S, Polonsky KS, Larsen PR, Kronenberg HM. *Williams Textbook of Endocrinology*. Elsevier Saunders: Philadelphia, PA . 2011.



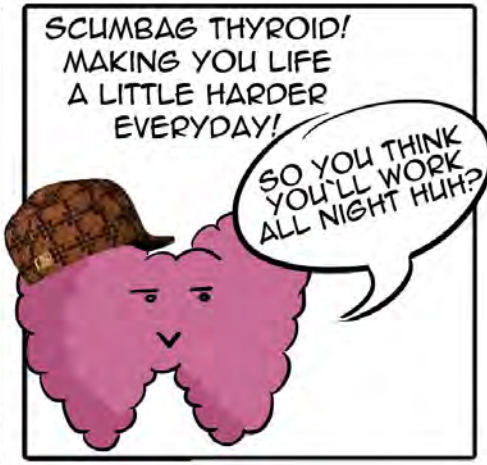
WHAT ARE THE EFFECTS OF SUBOPTIMAL THYROID FUNCTION?

- **Fatigue (mental and physical)**
  - Decreased mitochondrial energy production
- **Weight gain (or loss)**
- **Cold hands and feet. Cold intolerance**
- **Cardiovascular dysfunction**
  - - Dyslipidemias (Body less able to burn fat)
  - - Atherogenesis
- **Glucose intolerance/insulin resistance**
- **Women**
  - Menstrual irregularities
  - Poor pregnancy outcomes
- **Men: low libido, infertility, erectile dysfunction**


EATING NOTHING AND GOING FAT...

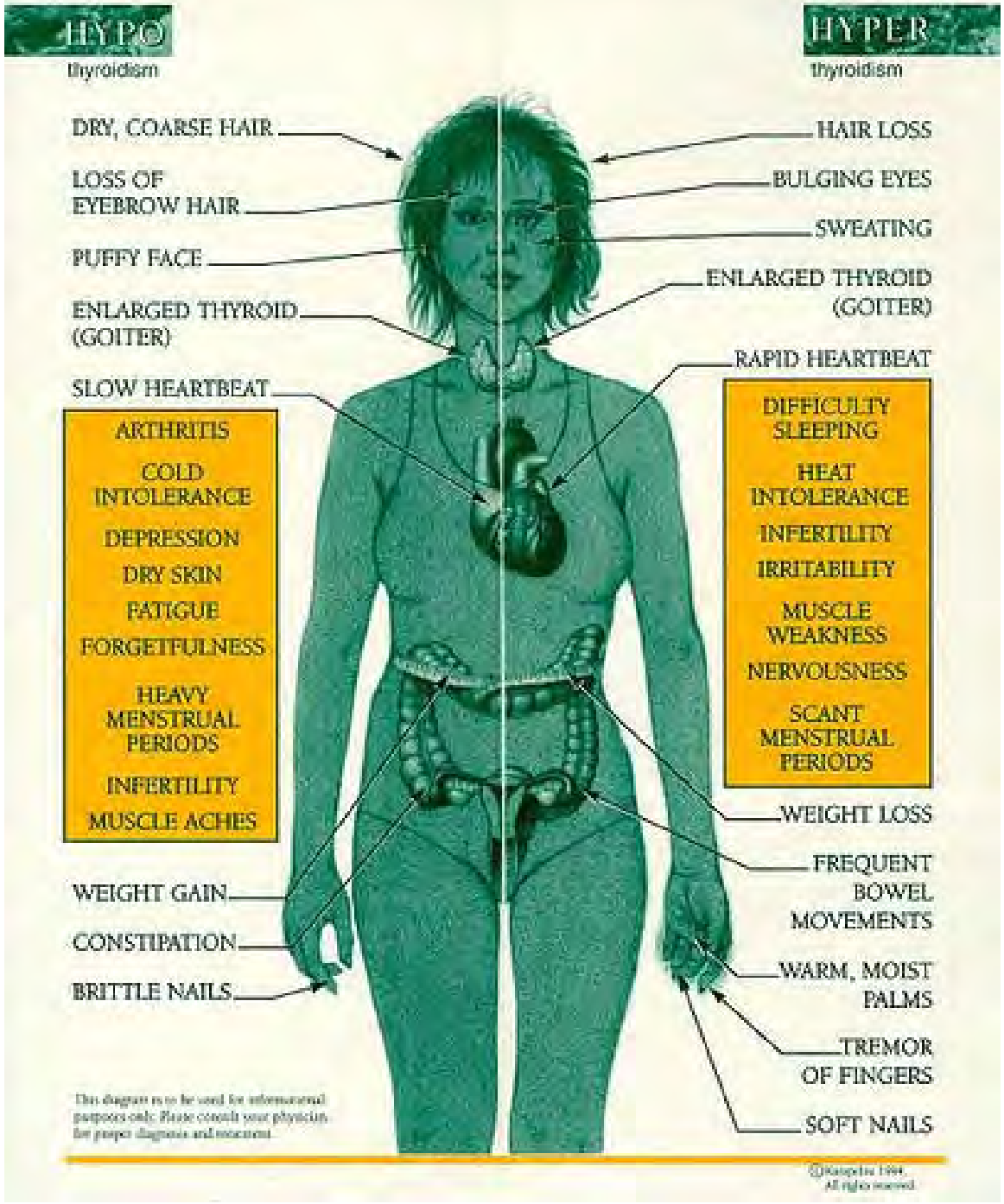

FEELING SLEEPY ALL DAY LONG...


FEELING TERRIBLE COLD NO MATTER WHAT


SCUMBAG THYROID! MAKING YOU LIFE A LITTLE HARDER EVERYDAY!
SO YOU THINK YOU'LL WORK ALL NIGHT HUH?

WHAT ARE THE EFFECTS OF SUBOPTIMAL THYROID FUNCTION?

- Decreased digestion and absorption, generally slowing of the GI tract. Constipation. (Vicious cycle)
- Muscle pain/cramps. Morning stiffness. Joint pain
- Low grade inflammation. Increased susceptibility to infection.
- Sensitivity and susceptibility to toxins
- Skin changes: dryness. Dry brittle hair. Hair loss. Edema.
- Headaches and migraines
- Depression
- Decreased cognitive function


HYPO
thyroidism
HYPER
thyroidism
DRY, COARSE HAIR
LOSS OF EYEBROW HAIR
PUFFY FACE
ENLARGED THYROID (GOITER)
SLOW HEARTBEAT
ARTHRITIS
COLD INTOLERANCE
DEPRESSION
DRY SKIN
FATIGUE
FORGETFULNESS
HEAVY MENSTRUAL PERIODS
INFERTILITY
MUSCLE ACHES
WEIGHT GAIN
CONSTIPATION
BRITTLE NAILS
HAIR LOSS
BULGING EYES
SWEATING
ENLARGED THYROID (GOITER)
RAPID HEARTBEAT
DIFFICULTY SLEEPING
HEAT INTOLERANCE
INFERTILITY
IRRITABILITY
MUSCLE WEAKNESS
NERVOUSNESS
SCANT MENSTRUAL PERIODS
WEIGHT LOSS
FREQUENT BOWEL MOVEMENTS
WARM, MOIST PALMS
TREMOR OF FINGERS
SOFT NAILS
This diagram is to be used for informational purposes only. Please consult your physician for proper diagnosis and treatment.
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IMPORTANT SIGNS (ON EXAM) OF LOW THYROID FUNCTION

- Dry skin, elbow keratosis, brittle nails
- Diffuse hair loss
- Puffy face, swollen eyelids; edema in legs, feet, hands
- Elevated cholesterol, generally LDL
- Easy bruising
- Prolonged Achilles tendon reflex
- Enlarged thyroid gland

ASSESSING METABOLIC RATE: BASAL BODY TEMPERATURE

- Shake down a thermometer to below 95 degrees and place it by the bed before going to sleep.
- Upon waking, place the thermometer under the armpit for 10 minutes.
- Remain resting.
- Record the temperature for at least 3 consecutive mornings, preferably at the same time of day.
- Note: Menstruating women should record where they are in their cycle as BBT increases with ovulation.

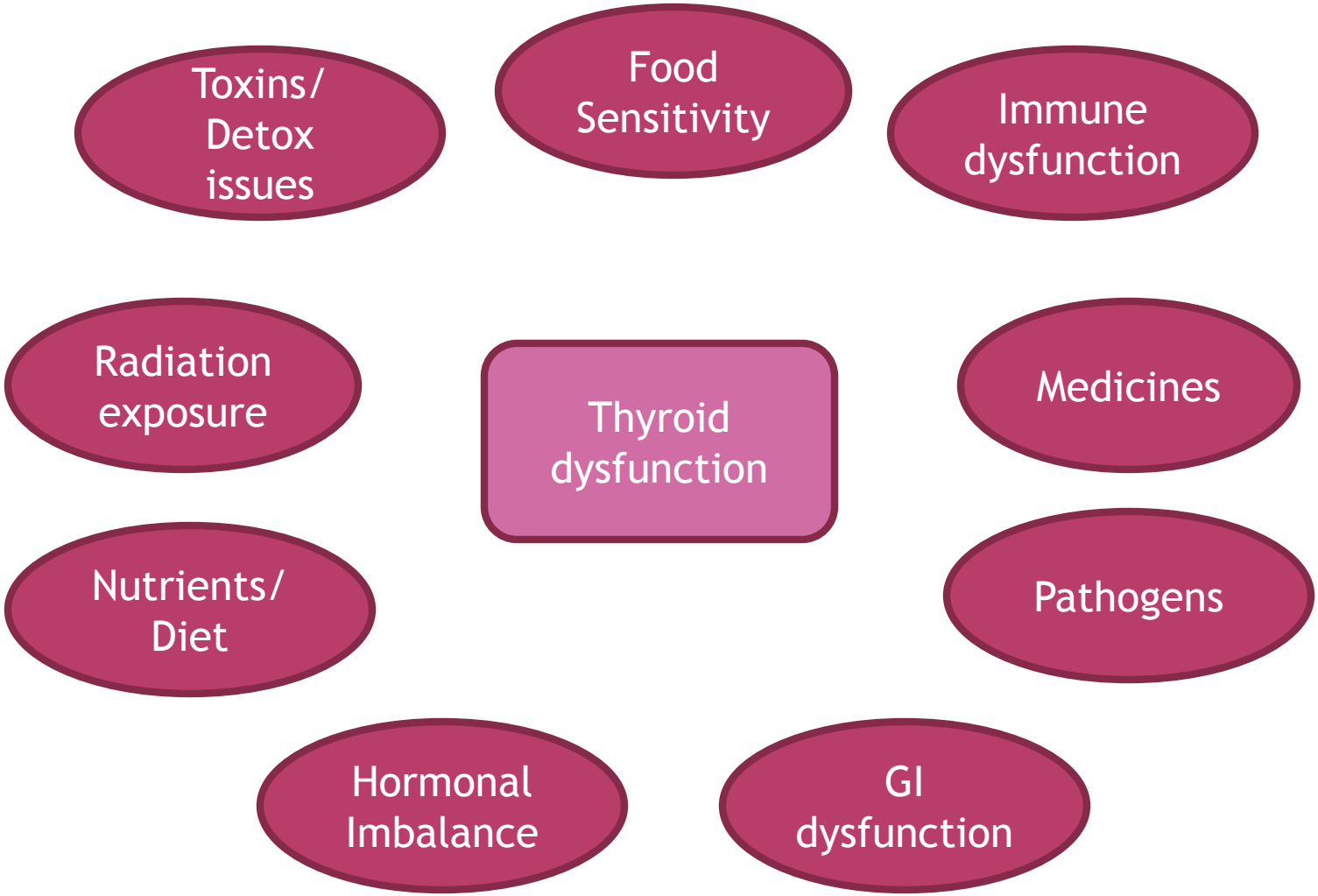
This is not well validated and I have found it to be of limited value.

HYPOTHYROIDISM (LOW THYROID FUNCTION)

Cause

- **Worldwide: most common cause is iodine deficiency**
- **In the US: 90% of hypothyroidism is caused by Hashimoto's thyroiditis. (Identified by Hakuro Hashimoto in 1912)**

CAUSES OF THYROID DYSFUNCTION



CONTRIBUTERS, TRIGGERS AND MEDIATORS OF HYPOTHYROIDISM

- Hashimoto's Thyroiditis—most common cause
- Other causes of underactive thyroid
  - Iodine deficiency
  - Radiation damage, from radioactive Iodine ablation, or therapeutic radiation
  - Drug toxicity
- Hypothyroid symptoms caused by other endocrine abnormalities:
  - Overconversion of T4 to T3, with resulting **resistance to thyroid hormone** (polycystic ovarian syndrome)
  - Elevated thyroid globulin (excess estrogen)
  - Over or under-active adrenals
  - Pituitary under-function
  - Insufficient progesterone/excess estrogen

INFLAMMATION AND THYROID

INFLAMMATION AND THYROID

- Anti-gliadin antibodies
  - Celiac disease
    - Celiac disease is defined generally as an autoimmune response to intestinal tissues upon gluten exposure, as well as overall activation of the immune system
    - Increased autoimmune response to thyroid and pancreas
  - Gluten sensitivity
    - basically defined as *any* immune response to gluten.
- Infections
  - ***Yersina enterocolitica***
  - Cold and flu viruses?
- Endogenous inflammatory compounds
  - cytokines

GLUTEN, CELIAC DISEASE, AND THYROID FUNCTION

- **Patients with celiac disease are at increased risk for developing thyroid disease with an overall 3- to 4-fold increase over non-celiac controls.**
  - Sategna-Guidetti C, et al. Prevalence of thyroid disorders in untreated adult celiac disease patients and effect of gluten withdrawal: an Italian multicenter study. Am J Gastroenterol. 2001 Mar;96(3):751-7.
  - Elfström P, Montgomery SM, Kämpe O, et. al. Risk of thyroid disease in individuals with celiac disease. J Clin Endocrinol Metab. 2008 Oct;93(10):3915-21.
- **Possible binding of antibodies to tTG (an enzyme found in the small bowel of active celiac patients) to thyroid tissue (cross-reaction).**
  - Naiyer AJ, Shah J, Hernandez L, et al. Tissue transglutaminase antibodies in individuals with celiac disease bind to thyroid follicles and extracellular matrix and may contribute to thyroid dysfunction. *Thyroid. Nov 2008;18(11):1171-1178.*

CELIAC PATIENTS: AFTER 1 YEAR ON A GLUTEN-FREE DIET

- Autoimmune thyroid disease with euthyroidism was present in 39 patients (16.2%) and eight controls (3.8%)
- In most patients who strictly followed a 1-yr gluten withdrawal (as confirmed by intestinal mucosa recovery), there was a normalization of subclinical hypothyroidism.
- Twenty-five percent of patients with euthyroid autoimmune disease shifted toward either a subclinical hyperthyroidism or subclinical hypothyroidism; in these subjects, dietary
  - Sategna-Guidetti C, et al. Prevalence of thyroid disorders in untreated adult celiac disease patients and effect of gluten withdrawal: an Italian multicenter study. Am J Gastroenterol. 2001 Mar;96(3):751-7.

GLUTEN SENSITIVITY AND THYROID

- Greater inflammatory load
- Cross-reactivity to thyroid protein (not proven)
- Many anecdotal reports of decreased anti-thyroid antibodies with complete gluten avoidance.

INFECTIONS, GRAVES', AND HASHIMOTO'S

- **1023 patients. 359 patients with Graves & 664 with Hashimoto's**
- **CONCLUSIONS:**
  - **The different month of birth seasonality in both Graves' and Hashimoto's points toward…a seasonal viral infection as the initial trigger in the perinatal period, the clinical disease resulting from further specific damage over time.**
    - Krassas GE, et al. Seasonality of month of birth of patients with Graves' and Hashimoto's diseases differ from that in the general population. Eur J Endocrinol. 2007 Jun;156(6):631-6.

BACTERIAL INFECTION

- **Higher incidence of *Yersina enterocolitica* antibodies in Graves' and Hashimoto's patients then in controls.**
- **Food borne (undercooked meat, unpasteurized milk, contaminated water) illness leading to fever, abdominal pain and diarrhea.**
  - Chatzipanagiotou, S., et al. Clinical Microbiology and Infection 2001:7 138-143
  - Corapcioglu, D., et al. Thyroid 2002:12 613-617
  - Arscott, P., et al. Journal of Clinical Endocrinology and Metabolism:1992:75 295-300

ADDITIONAL REFERENCES ON INFECTIONS AND THYROID DYSFUNCTION

- Duntas, LH: Environmental factors and autoimmune thyroiditis. *Nature Reviews Endocrinology 4, 454-460 (August 2008)*
- Desailloud and Hober: Viruses and thyroiditis: an update. *Virology Journal 2009, 6:51186/1743-422X-6-5*

INFLAMMATION AND SUPPRESSION OF THYROID FUNCTION IN FIBROMYALGIA PATIENTS

- **…high levels of inflammatory cytokines, have been associated with depressed levels of the active thyroid hormone T3 in fibromyalgia patients, suggesting these cytokines may down regulate the activity of the HPT axis.**
  - Riedel W, et al. Secretory pattern of GH, TSH, thyroid hormones, ACTH, cortisol, FSH, and LH in patients with fibromyalgia syndrome following systemic injection of the relevant hypothalamic-releasing hormones. Z Rheumatol. 1998;57 Suppl 2:81-7.

ENVIRONMENTAL POLLUTANTS

ENVIRONMENTAL POLLUTANTS

- At least 150 industrial chemicals have been shown to result in the reduction in TSH and/or T4.
  - Inhibition of iodide uptake by thyroid
  - Inhibition of thyroid synthesis via thyroperoxidase.
  - Binding of thryoxin transport protein in circulation.
  - Altered liver detoxification of T4/T3.
  - Alteration of deiodinase-thyroid metabolism.
  - Disruption of transport across cell membranes and receptors (TSH receptor).
  - Howdeshell KL. A model of the development of the brain as a construct of the thyroid system. Environ Health Perspect. 2002 Jun;110 Suppl 3:337-48.

Table 1. Mechanisms and Effects of Thyroid Disruptors[55,60]

Thyroid Disruptors	Mechanism	Effect
Perchlorates, thiocyanate, nitrate, bromates, phthalates	Blocking uptake of iodide into thyroid cell	Decreased synthesis of T3 and T4
Methimazole, amitrole, soy isoflavones, benzophenone 2	Blocking production of TPO in thyroid follicles	Decreased synthesis of T3 and T4
PCBs, pentachlorophenol, flame retardants, phthalates	Competitive binding to thyroid transport protein (TTR)	Possible effect on fetal brain T4 production
Dioxin, PBDE, chlordane	Altering transport across cell membrane	Increased biliary elimination of T3 and T4
Acetochlor (herbicide), PCBs	Enhanced hepatic metabolism	Increased biliary metabolism of T3 and T4
PCBs, triclosan, pentachlorophenol, dioxin, difuran	Inhibition of sulfation	Decreased sulfation of thyroid hormones leading to possible decrease of peripheral T3 synthesis
FD&C red dye #3, PCBs, octyl-methoxycinnamate	Inhibition of deiodinase activity	Decreased peripheral T3 synthesis
PCBs, bisphenol A, hexachlorobenzene, flame retardants	Altering binding to thyroid receptor	Altered thyroid hormone directed gene transcription
DDT, PCBs	Inhibiting TSH receptor	Decreased production of T3 and T4

OVER-CONVERSION OF T4 TO T3 AND DECREASED THYROID BINDING GLOBULIN

- Lab testing shows high T3
- Can occur with
  - Polycytic ovary syndrome (PCOS) in women
    - Insulin resistance and excess testosterone.
  - Diabetes with insulin dependence
- With excess T3, cells develop resistance to thyroid hormone, and the person experiences hypothyroid symptoms.
- Treatment:
  - Reversing insulin resistance with diet, supplements, and exercise
- Can also occur with use of testosterone supplementation
  - Treatment: Decreasing testosterone supplementation.

DRUGS THAT CAN TRIGGER THYROID ABNORMALITIES

- **Decrease TSH secretion**: Dopamine. Glucocorticoids. Octreotide (Sandostatin)
- **Decrease thyroid hormone secretion**: lithium, iodide, amiodarone
- **Decrease T4 absorption**: Colestipol, cholystyramine, aluminum hydroxide, iron, sucralfate.
- **Alter T4 and T3 transport by displacement from protein binding sites**: Furosemide (lasix), mefanamic acid (ponstel), salicylates (aspirin)
- **Up-regulate T4 and T3 metabolism by increasing hepatic detoxification**: Phenobarbital, rifampin, phentoin (dilantin), carbamazapine (tegretol)
- **Decrease T4 deiodinase activity**: propylthiouracil, aiodarone (cordorone), beta blockers.
  - NEJM. 333(25) 1688, Table 2. December 1993

THYROID BINDING GLOBULIN ELEVATION

- Associated with oral contraceptives or estrogen replacement therapy.
- Other drugs that have this effect: tamoxifen, heroin, methadone, chemotherapy agents: mitotane and fluorouracil
- High estrogen levels stimulate production of excess thyroid binding globulin (TBG)
- TBG binds T3 and T4, decreasing free T3 and T4, with less available to the cells.
- Treatment: Decreasing excess estrogen
  - Less supplementation
  - Nutritional support to increase detoxification of estrogens

HYPOTHYROIDISM SECONDARY TO PITUITARY HYPOFUNCTION

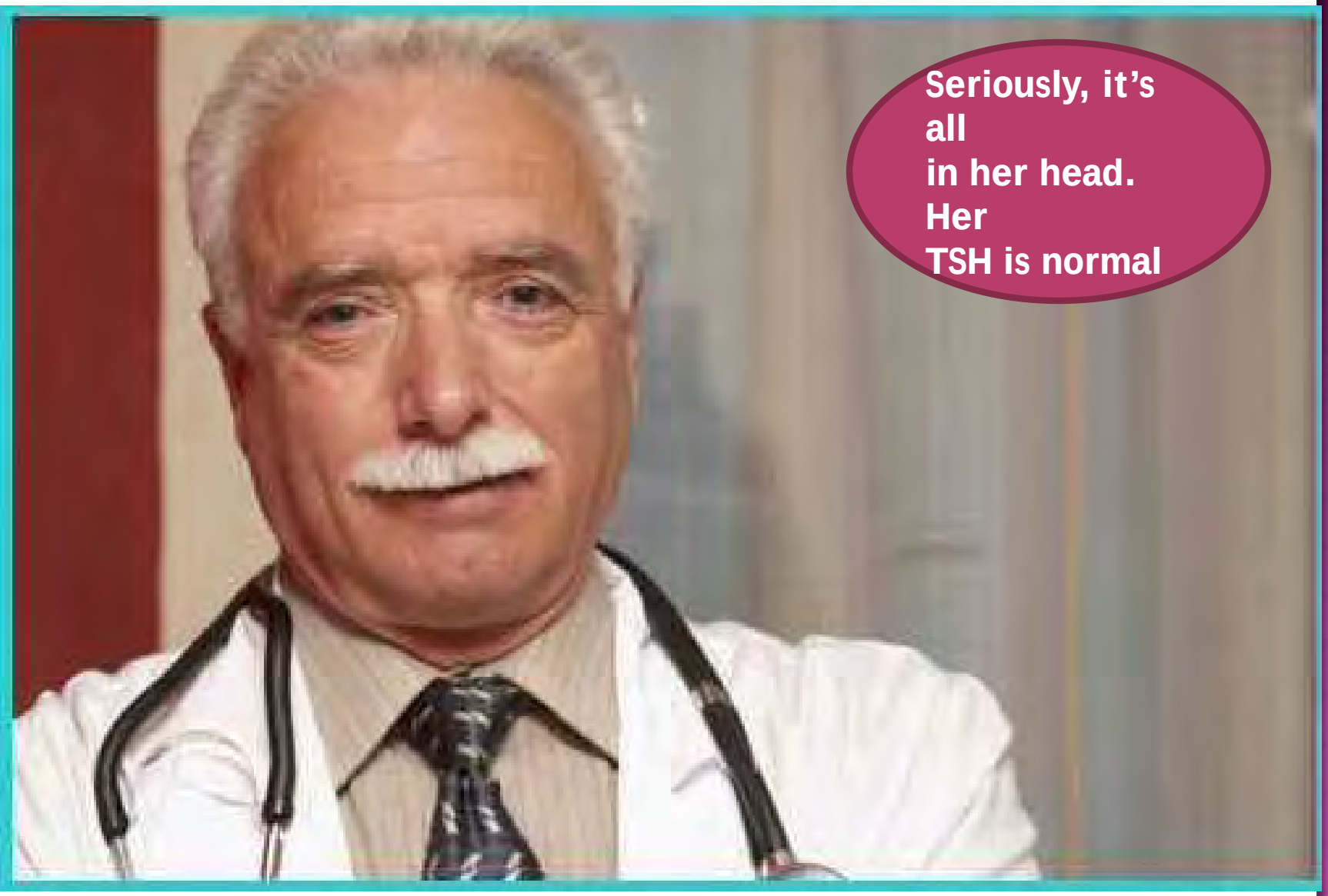
- Thyroid Stimulating Hormone will be low, although not as low as with hyperthyroidism.
- Common pattern for functional hypothyroidism.
- Chronic stress causes under-active response of release of TSH from the pituitary gland.
- Causes:
  - Chronic stress: busy lifestyle, poor diet, inadequate sleep, excess caffeine, chronic inflammation, chronic infections
  - Post-partum associated with depression
  - Inappropriate use of thyroid hormone supplementation, decreases sensitivity to thyroid hormone in pituitary as well as other organs.

TREATING HYPOTHYROIDISM: CONTROVERSIES

- What form of thyroid hormone to use?
  - Thyroxine (T4) **vs.**
  - Dessicated Porcine Thyroid (Armour Thyroid) and others **vs.**
  - Tri-iodothyronine (T3) with T4
- Evaluation of Thyroid function. What testing is needed?
- Subclinical Hypothyroid: To treat or not to treat?

VARIATIONS OF HYPOTHYROIDISM

- **Subclinical Hypothyroidism:**
  - Assymptomatic person **with mildly elevated TSH and normal T4.**
  - Frequently thyroid auto-antibodies present. (In conventional medicine this is also referred to as functional hypothyroidism. We will refer to it as subclinical hypothyroidism)
- **Symptomatic Hypothyroidism**, especially Hashimoto's Thyroiditis.
- **Functional hypothyroidism**: Clinical symptoms of hypothyroid with normal or low normal thyroid hormone tests.


Seriously, it's all
in her head. Her
TSH is normal

SUBCLINICAL HYPOTHYROIDISM: WHAT HAPPENS OVER TIME ?

- Natural course of Subclinical Hypothyroidism:
  - **progression** to clinically overt hypothyroidism,
    - 2.6% each year if thyroperoxidase (TPO) antibodies are absent and
    - 4.3% if they are present
  - **TSH level normalized in** 52% of those with a serum TSH of less than 10 mIU/L.
- Intervention with Gluten Free Diet
  - 2 studies of **celiac patients** with Hashimoto's show reversal. "In distinct cases, gluten withdrawal may single-handedly reverse the abnormality."
    - Am J Gastroenterol.2001 Mar;96(3):751-7.**Prevalence of thyroid disorders in untreated adult celiac disease patients and effect of gluten withdrawal: an Italian multicenter study.** Sategna-Guidetti C, Volta U, Ciacci C, Usai P, Carlino A, De Franceschi L, Camera A, Pelli A, Brossa C.
  - In non-Celiac patients, anecdotally, gluten free diet (and other interventions) lead to improvement and resolution of Hashimoto's Thyroiditis, if (dietary) treatment is started before significant damage has occurred to the thyroid gland.

TSH CONTROVERSY: PEOPLE WITH "SUBCLINICAL HYPOTHYROIDISM—TO TREAT OR NOT TO TREAT

- Subclinical hypothyroidism:
- Definition: **serum TSH level above the upper limit of** normal despite a normal serum free thyroxine concentration.
- Conventional recommendations:
  - Initiate levothyroxine replacement therapy for all patients with a TSH greater than 10 mIU/L, even if the free thyroxine concentration is within normal laboratory range
  - Treatment of patients with a serum TSH level between 5 and 10 mIU/L remains controversial.
- Strongest arguments for levothyroxine therapy (conventional treatment) are
  - the high risk of progression to overt hypothyroidism,
  - the possible improvement of quality of life,
  - and the possibility that SCH is a cardiovascular risk factor.
  - Recent evidence shows that any possible increased cardiovascular risk would be to persons younger than 70 years
- Conventional Treatment Protocols include
- hormone supplementation only
- no consideration of treatment of the precipitating factors with the goal of reversing the disease process.

THYROID HORMONE AND PROGESTERONE: RECIPROCITY

- Progesterone
  - Stimulates Thyroid peroxidase
    - Catalyst that produces T3 and T4 from thyroglobulin and iodine.
  - Sensitizes (improves signaling mechanism) of thyroid receptors.
  - Progesterone surge at ovulation stimulates thyroid activity and metabolism (temperature rise)
- Thyroid
  - Sensitize the body to progesterone.
  - Underactive thyroid will cause symptoms of progesterone deficiency.(heavy menstrual bleeding, mid cycle or PMS symptoms, depression, inability to lose weight, etc)

CONVENTIONAL CARE: TAKE THIS PILL!

- Replace thyroid hormone with synthetic T4 (thyroxine)
- Target TSH is 0.5-2.0microU/ml
- Monitor TSH or monitor TSH and free T4.
- Repeat these tests within 5-6 weeks after achieving steady dose. (1/2 life of T4 is 7-8 days)

SYNTHROID 50 MCG TABLET

This medicine is a white, round, partially scored tablet imprinted with "SYNTHROID" and "50".

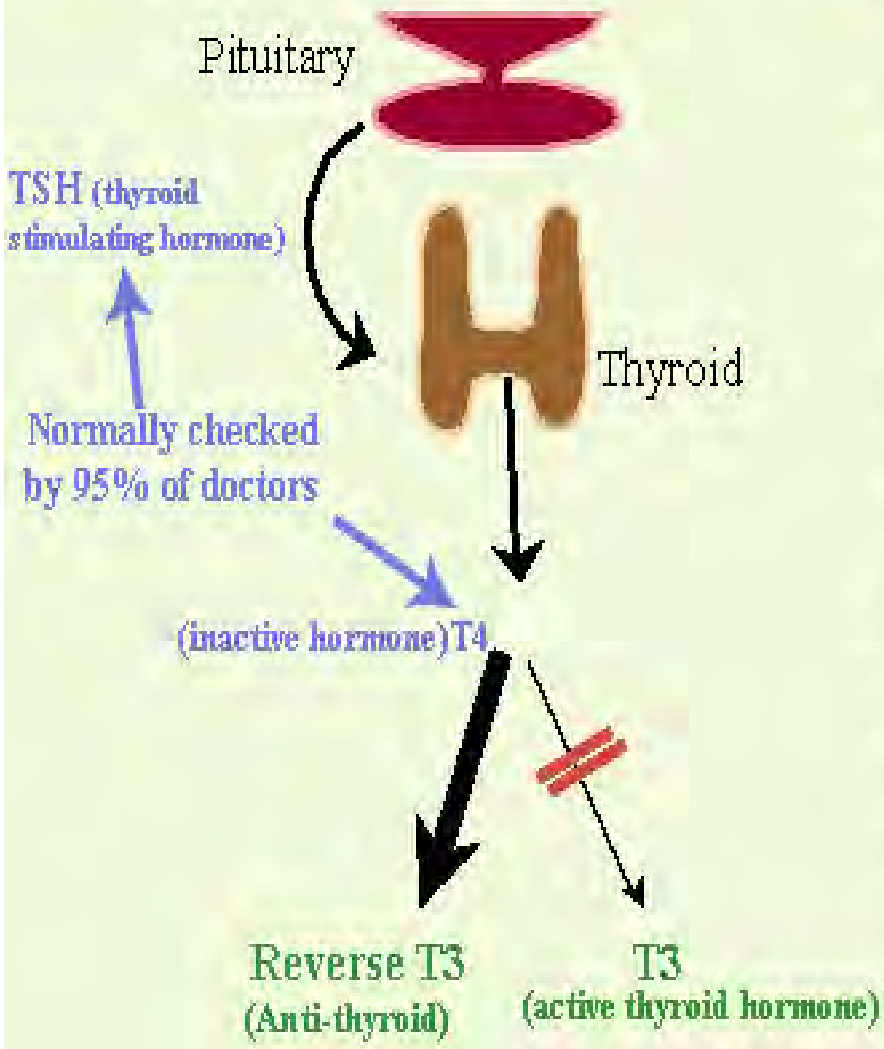
CONTROVERSY: WHAT FORM OF THYROID SHOULD BE PRESCRIBED ?

- Most endocrinologists and primary care doctors use exclusively T4 (levothyroxine -- 12 different brands).
- My experience: T4 works well for about 80% of people treated.
- For 20% of people treated, test results (TSH and T4) are in the desired range, but the person feels undertreated.
- Possible causes:
  - Poor conversion of T4 to T3 and/or
  - Excess production of reverse T3 (dud T3)
  - Abnormal adrenal, or other hormone function

SLUGGISH CONVERSION OF T4 TO T3

- Here, the body makes plenty of T4, but does not convert enough to T3
- Causes:
  - Chronic adrenal stress: elevated cortisol suppresses conversion of T4 to T3
  - Chronic infection or inflammation. Inflammatory cytokines decrease T4 to T3 conversion.

Thyroid Physiology



TSH and T4 can be perfect but poor T4 to T3 conversion and/or an increased T4 to reverse T3 formation can result in low thyroid.

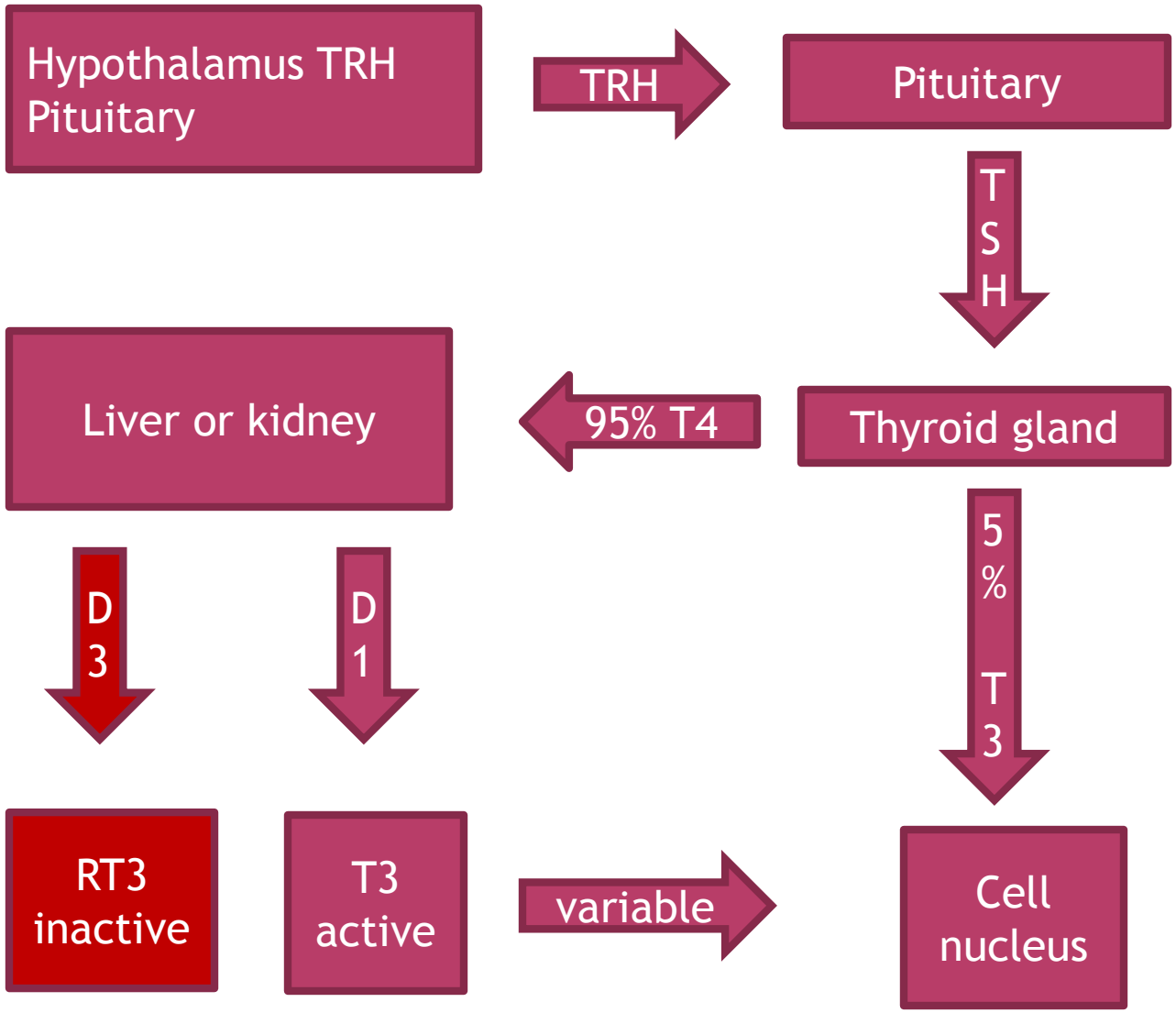
Optimization of the T3/reverse T3 ratio can be achieved with T3 supplementation (not T4).

One must also consider thyroid resistance as a mechanism of hypothyroidism with normal blood levels.

* Note that reverse T3 is a difficult assay for laboratories to do and most standard commercial labs will give inaccurate results. We have done numerous parallel studies in patients demonstrating this.

FORMATION OF REVERSE T3 ANOTHER OPTION FOR T4 METABOLISM:

- T4 can be metabolized by 5 (not prime)-deiodinase (D3).
  - Production of “regular T3” is with 5’-deiodinase (D1)
- A different iodine is removed from the other ring (the 5-locus), which converts it to RT3 (3,3',5' triiodothyronine).
- 95% of circulating RT3 is made this way.


Hypothalamus TRH
Pituitary
TRH
Pituitary
TSH
Liver or kidney
95% T4
Thyroid gland
D3
D1
5% T3
RT3 inactive
T3 active
variable
Cell nucleus

FUNCTION OF REVERSE T3:

- RT3 was discovered in 1975 and found incapable of increasing cell metabolism (unlike T4, T3, and T2). So RT3 has been considered “functionless,” and it has been assumed that RT3 is inactive.
- It was thought that RT3 was a “default” position into which unwanted T4 is dumped without increasing metabolism.
- But RT3 does seem to be useful when a slower metabolism is advantageous: life-threatening illness, injury, or starvation.

THEREFORE…

- **Converting T4 to T3 is optional.**
  - **The body determines whether it will convert T4 to T3 or RT3.**
- **RT3 is a protective/adaptive response during periods of significant stress. A slow metabolism is energy-efficient. This is another way the body can regulate energy use.**
  - **Example: RT3 lets a person live longer without food or water.**

ONE CAVEAT ABOUT REVERSE T3?

- Why are you braking?
- Sometimes you do want to STOP

RT3 AND IMPAIRED THYROID HORMONE METABOLISM

Stress, both physical and psychological, *blocks conversion of T4 to T3, causing higher RT3.*

Stressors include:

- School examinations
- Severe cold exposure
- Starvation
- Injuries
- Life-threatening conditions
- Operations
- Infections
- Cancer
- Heart attacks

Kelly GS. Peripheral metabolism of thyroid hormones: a review. Altern Med Rev. Aug 2000;5(4):306-33.

OTHER THAN STRESS, WHAT ARE D1 (5'-DEIODINASE) INHIBITORS, THAT SLOW THE CONVERSION OF T4-T3?

- Certain medications
- Selenium deficiency
- Inadequate protein, excess carbohydrates
- Chronic illness (cytokines, free radicals)
- Compromised liver or kidney function
- Cd, Hg, Pb, herbicides, pesticides
- Stress (emotional or physiological), ie., excess cortisol, catecholamines
- Excess estrogen

RT3 AND IMPAIRED THYROID FUNCTION

- **RT3 can effectively block cell metabolism (competitively with T3)**
- **Consequences:**
  - One can have excessive RT3 levels with potentially normal T3. (RT3 is measured as part of total T3 and part of free T3)
  - Since T4 may be available but converting to RT3, symptoms of hypothyroidism can develop with normal thyroid levels of TSH, T4 and total T3 levels.
  - This is why is can be essential to measure Reverse T3.

RT3 AND IMPAIRED THYROID HORMONE METABOLISM

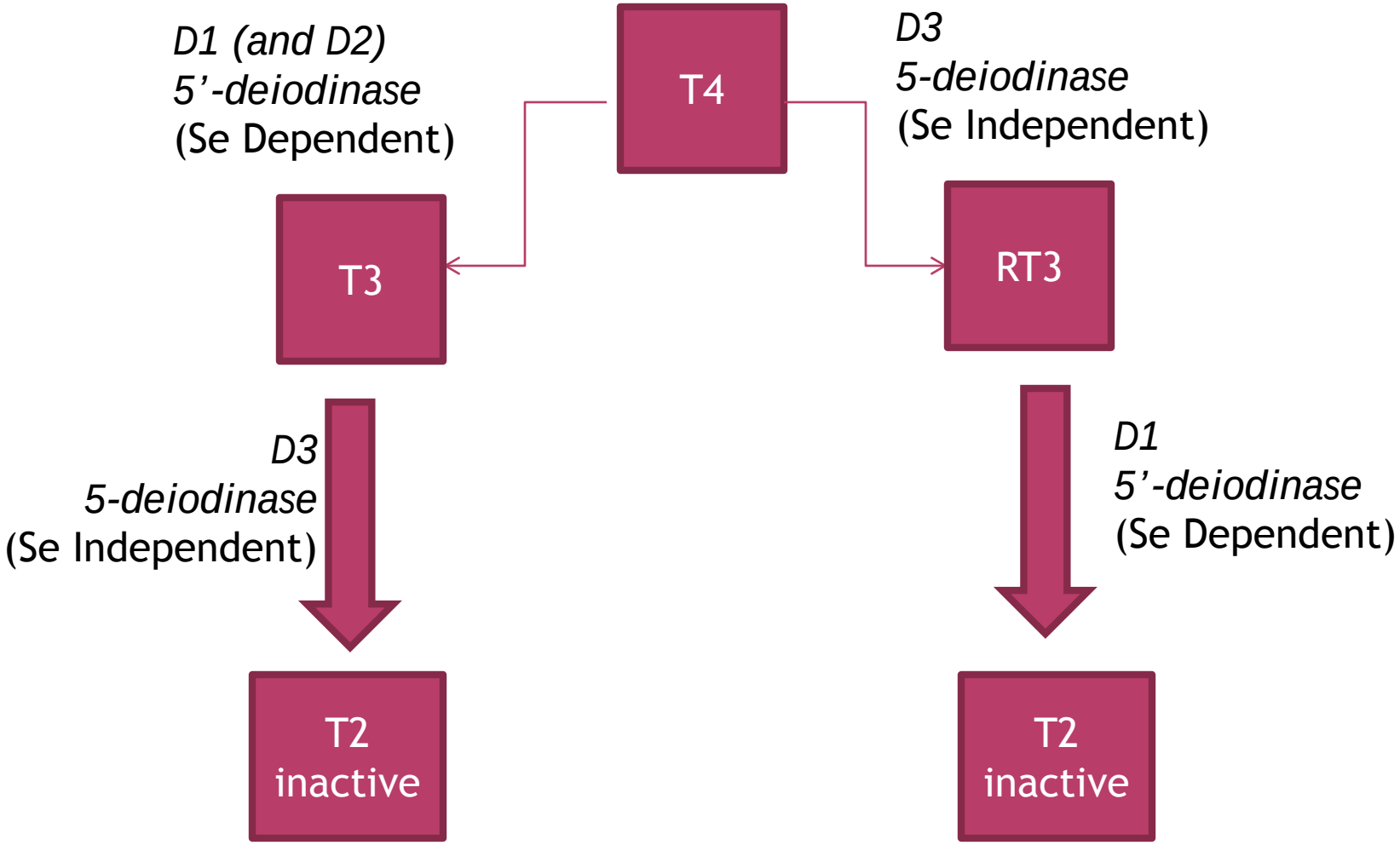
Excessive conversion of T4 to RT3

- **May cause failure of "classical" thyroid treatment using T4 resulting not in low T3 but *poor T3-RT3 ratio*.**
- **The "normal" amount of T3 produced is not adequate to overcome the inhibitory effects of RT3.**

RT3 AND IMPAIRED THYROID HORMONE METABOLISM

This concept has been overlooked because of:

- **Ignorance about RT3 function**
- **Dogma that T4 will always be converted adequately to T3**
- **Reliance on TSH as sole diagnostic criteria**



ROLE OF SELENIUM (SE) IN FORMATION AND DEGRADATION OF T3 AND REVERSE T3

Peeters, RP et. al. Reduced Activation and Increased Inactivation of Thyroid Hormone in Tissues of Critically Ill Patients J Clin Endocrinol Metab. 2005 Oct;90(10):5613-20.

DEIODINASE ENZYMES AND METABOLISM OF THYROID HORMONES

- D1:
  - **Selenium dependent**
  - Conversion of T4 to T3
  - Conversion of RT3 to inactive metabolite (T2)
- D3:
  - Conversion of T4 to RT3
  - Conversion of T3 to inactive metabolite (T2)
  - **Selenium independent**

TESTING TOTAL T3

- Free T3 is the most accurate measure of T3 but…
- Total T3 has been used as a measure of activity of T3 and RT3. Thus a surrogate marker of D1 and D3 activity is the TT3/RT3 ratio.
- There is significant literature looking at this ratio (TT3/RT3) in animals and severely ill patients.

WHAT SHOULD THAT RATIO BE?

- T3 should be about 10 times Reverse T3
  - Alan McDaniel, MD has developed a range for optimal function in sick ambulatory patients using his clinical experience. McDaniel, 14th Symposium on Functional Medicine, Florida 2007.
- Alternatively, if you subtract Reverse T3 from T3, the remainder is the active T3.

THEREFORE, THERE ARE TWO IMPORTANT REASONS TO GO BEYOND T4:

- **Is T4 converting to T3** and therefore (you assume) driving the metabolic machinery of the cell?
  - **To know, you must assess T3**
- **Has too much T4 been converted to Reverse T3 (RT3)** -- and therefore even with normal T3 serum levels there may be a metabolic block to its action?
  - **To know, you must assess RT3**

SELECTED REFERENCES ON TT3/RT3 RATIO

- Abdulrahman RM et. al. Sorafenib-induced hypothyroidism is associated with increased type 3 deiodination. J Clin Endocrinol Metab. 2010 Aug;95(8):3758-62. Epub 2010 May 19.
- Debaveye Y, et. al. Regulation of tissue iodothyronine deiodinase activity in a model of prolonged critical illness. Thyroid. 2008 May;18(5):551-60.
- Peeters, RP et. al. Reduced Activation and Increased Inactivation of Thyroid Hormone in Tissues of Critically Ill Patients J Clin Endo & Metabolism Vol. 88, No. 7 3202-3211J Clin Endocrinol Metab. 2005 Oct;90(10):5613-20. Epub 2005 Aug 2.
- den Brinker M et al, Euthyroid sick syndrome in meningococcal sepsis: the impact of peripheral thyroid hormone metabolism and binding proteins. J Clin Endocrinol Metab. 2005 Oct;90(10):5613-20. Epub 2005 Aug 2
- Calvey HD, et. al, A new prognostic index in surgery and parenteral feeding: the ratio of triiodothyronine in serum (T3/RT3 Clin Nutr. 1986 Aug;5(3):145-9.

ANOTHER CONTROVERSY: WHY TEST THYROID ANTIBODIES?

- Hashimoto's Thyroiditis is the most common autoimmune disease in the United States.
- It is the most common cause of hypothyroidism in the United States.
- It affects women four times more than men:
  - Up to 20% of menopausal women
  - Up to 24% of allergic women
  - 5–10% of postpartum women
- Thyroid auto-antibodies identify Hashimoto's thyroiditis (vs hypothyroidism from another cause)

TESTING THYROID ANTIBODIES

- Autoimmune Thyroiditis (AIT) can be tested with about 90% accuracy using RIA.
- Radioimmunoassay, or RIA, is a technique used in testing for the presence of proteins in the body, such as antibodies
  - Thyroid peroxidase antibody (TPO)
  - Thyroglobulin Antibodies (TBG)
  - Thyroid Stimulating Hormone Receptor Antibody (TRAb)
    - may either mimic the action of TSH and cause hyperthyroidism as observed in Graves' disease or alternatively,
    - antagonize the action of TSH and cause hypothyroidism

AUTOIMMUNE THYROID DISEASE

- Thyroid peroxidase antibody (Anti-TPO): attacks thyroid peroxidase, which is important in the production of thyroid hormones.
  - involved in the tissue destructive processes associated with Hashimoto's and atrophic thyroiditis.
  - appearance of TPOAb usually precedes the development of thyroid dysfunction.
- Thyroglobulin Antibodies (TgAb): attacks thyroglobulin, which is essential in the production of the T4 and T3 thyroid hormones.

WHY TEST THYROID ANTIBODIES?

2011 study showed that Thyroid antibodies correlate with increased symptoms (morbidity)

- All patients had normal TSH (mean between 1 and 2), some were on thyroid replacement.
- Women with high TPO antibodies had significantly higher incidence of dry hair, chronic fatigue*, “becoming easily fatigued”, chronic weakness, dysphasia*, irritability*, lack of concentration and chronic nervousness* and lower QOL on SF 36.
- TPO antibodies were highest in patients with six or more symptoms and those with the highest BMI.
- Higher TPO antibodies were also associated with early pregnancy loss, higher age at menopause, higher gravidity, and breast cancer.

- Ott J, Promberger R, Kober F, et al. Hashimoto’s Thyroiditis Affects Symptom Load and Quality of Life Unrelated to Hypothyroidism: A prospective Case-Control Study in Women Undergoing Thyroidectomy for Benign Goiter. Thyroid 2011;21(2):161-7.

TREATMENT: SUMMARY

- **Nutrition: Review nutrient needs for optimal function:**
  - **Production of T4 and T3**
  - **Conversion of T4 to T3**
- **Toxins: Eliminate or decrease toxins and medications that affect thyroid function.**

TREATMENT SUMMARY

- **Improve or minimize disease states that affect thyroid function.**
  - Assess for celiac disease and gluten allergy
  - Assess for infections and/or inflammatory conditions
- **Lifestyle: Decrease chronic stress.**
  - Regular sleep
  - Exercise
  - Meditation and other relaxation practices

THYROID REPLACEMENT THERAPY?

- "...the decision as to whether to initiate a trial of levothyroxine therapy is based more upon the 'art of medicine' at this time than the science.“
  - Wartofsky and Dickey, "Controversy in Clinical Endocrinology: The Evidence for a Narrower Thyrotropin Reference Range is Compelling," *Journal of Clinical Endocrinology and Metabolism 2005: 90(9)5483-5488.*

TREATMENT: THYROID REPLACEMENT THERAPY:

- Choices
  - Levothyroxine (T4)
  - Liothyronine (T3)
  - Dessicated Porcine thyroid: Armour® thyroid or others
    - Approximately 4 parts T4:1 part T3
  - Compounded synthetic thyroid replacement
    - Various ratios of T4 to T3

DESSICATED PORCINE THYROID: NOT LOVED BY ENDOCRINOLOGISTS

“It is much more important to know what sort of person has a disease, than what sort of disease a person has.”

-William Osler

SUMMARY: MANAGING AND HEALING HASHIMOTO'S THYROIDITIS

- Conventional model: take this pill
- **Functional model:**
  - Hashimoto's thyroiditis is an auto-immune disease .
  - Optimal treatment involves not only appropriate thyroid replacement therapy, but addressing the upstream causes,
  - Address lifestyle, environmental factors, diet, other hormonal imbalance, digestion, and immune (allergic) dyfunction.
    - **Particular attention to Gluten/wheat intolerance/allergy**

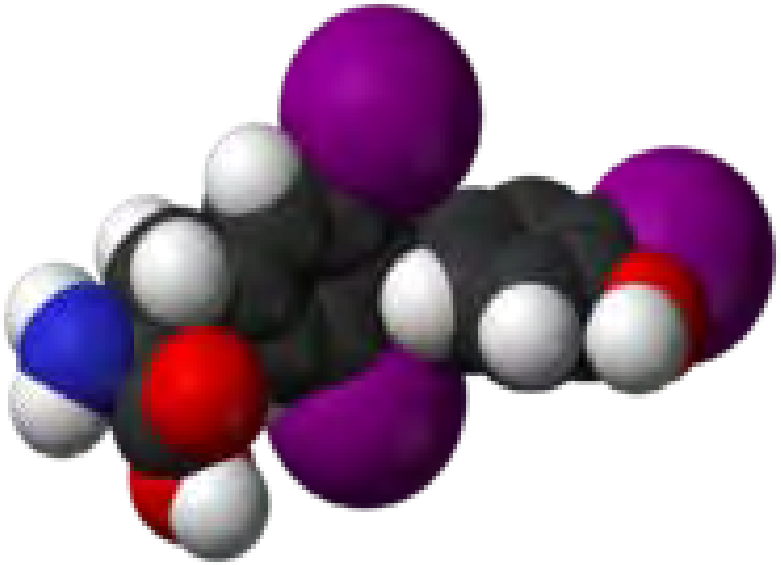
KEY NUTRIENTS TO CONSIDER IN THYROID DYSREGULATION

- Iodine
- Selenium
- Zinc
- Iron
- Vitamin D
- Vitamin A

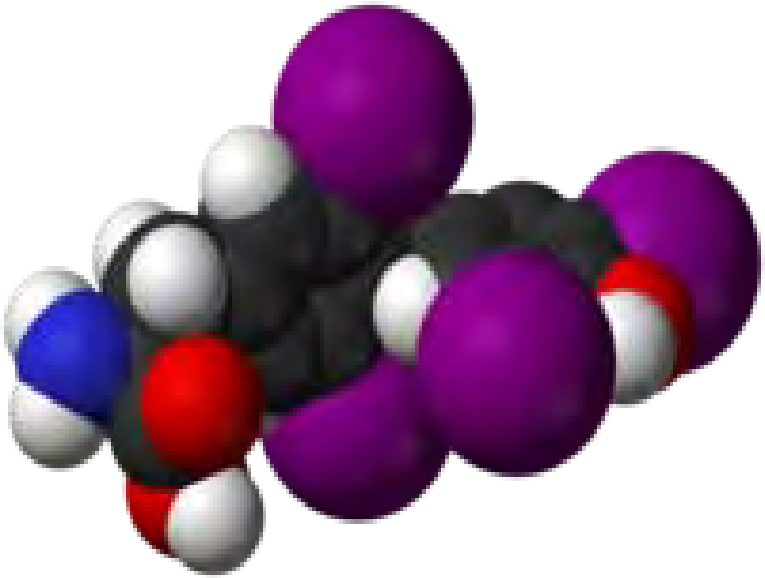
IODINE AND THYROID

- **Iodine accounts for 65% of the molecular weight of T4 and 59% of the T3**.
- 15–20 mg of iodine is concentrated in thyroid tissue and hormones, but 70% of the body's iodine is distributed in other tissues, including mammary glands, eyes, gastric mucosa, arterial walls, the cervix, and salivary glands. In the cells of these tissues, iodide enters directly by sodium-iodide symporter (NIS).
- **Iodine is not stored in the body and a little needs to be eaten daily.**

IODINE & THYROXIN

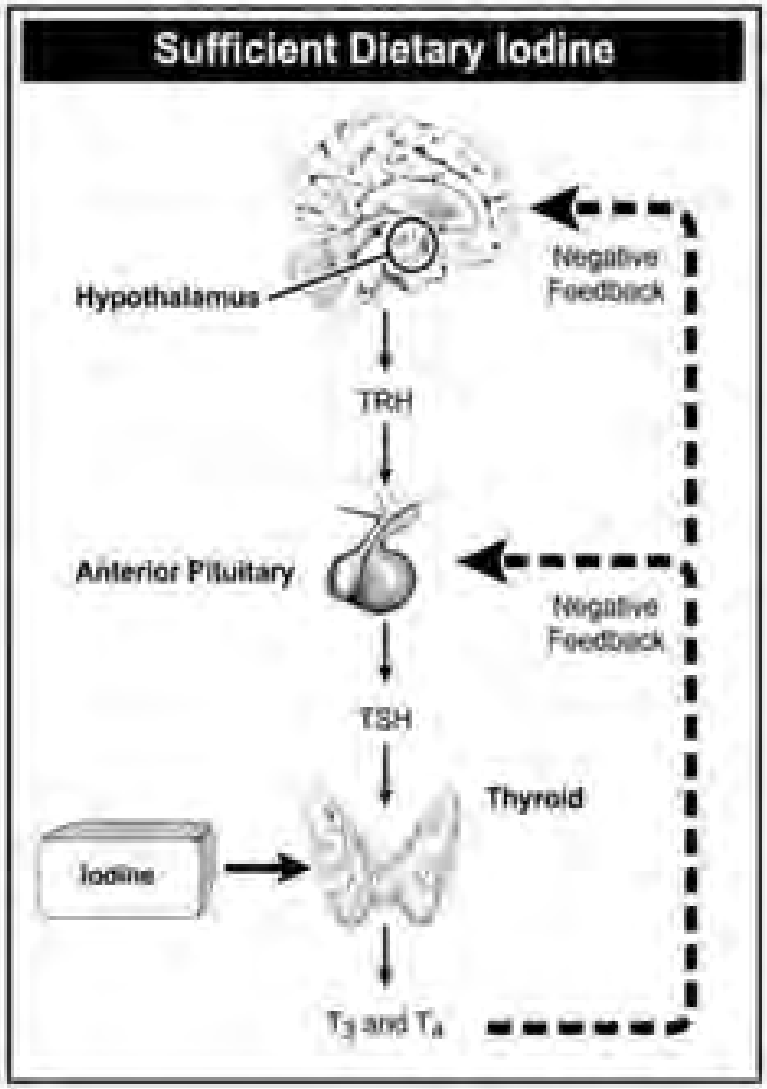


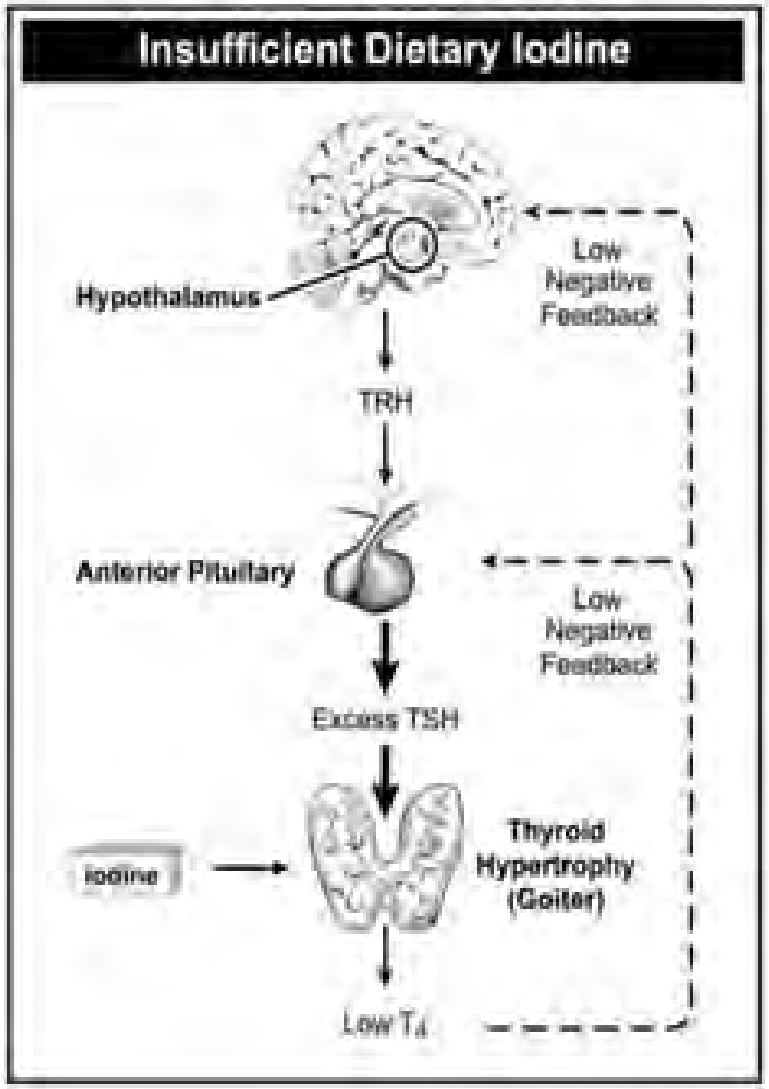
T3



T4

IODINE & THYROID

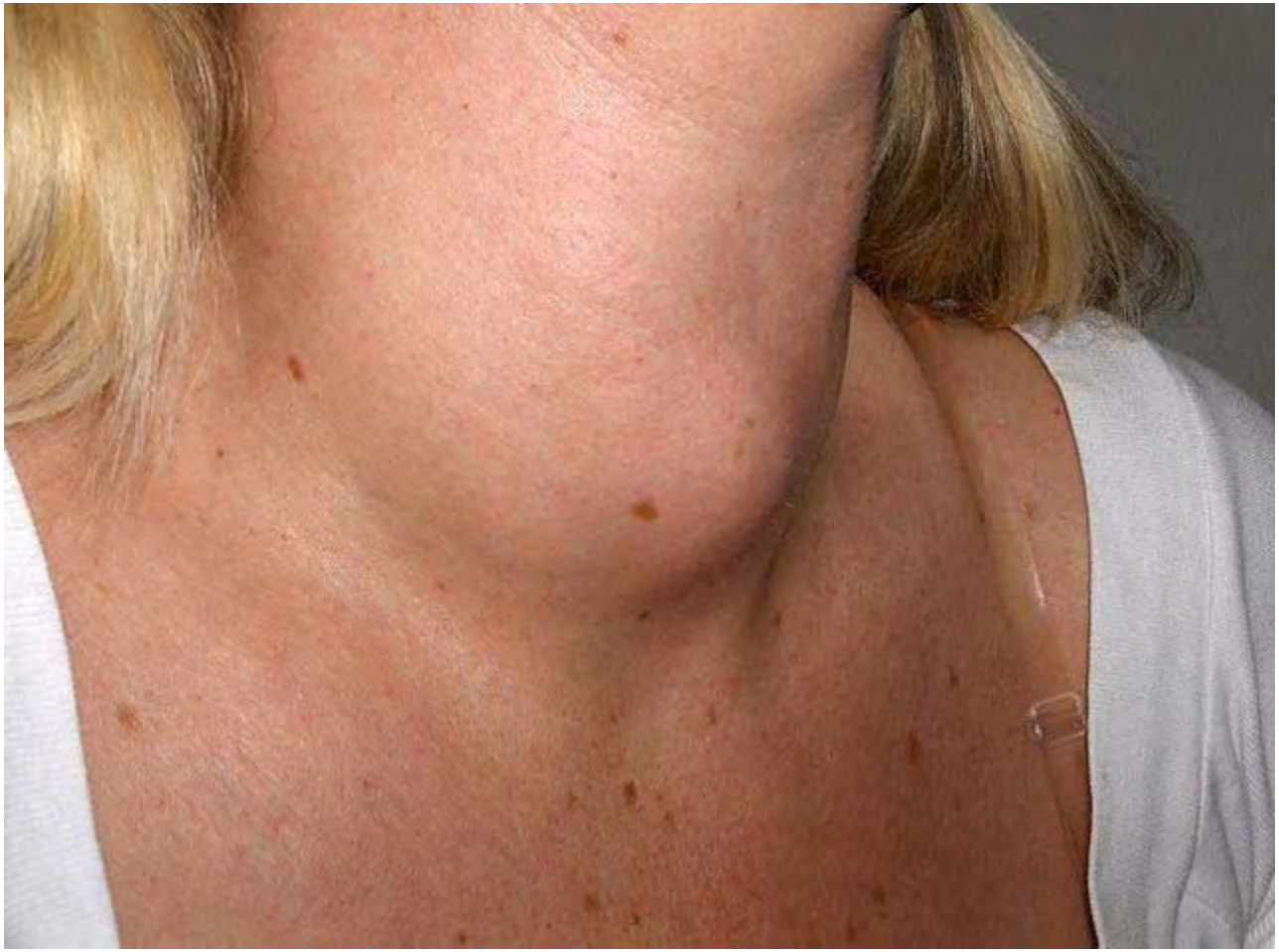


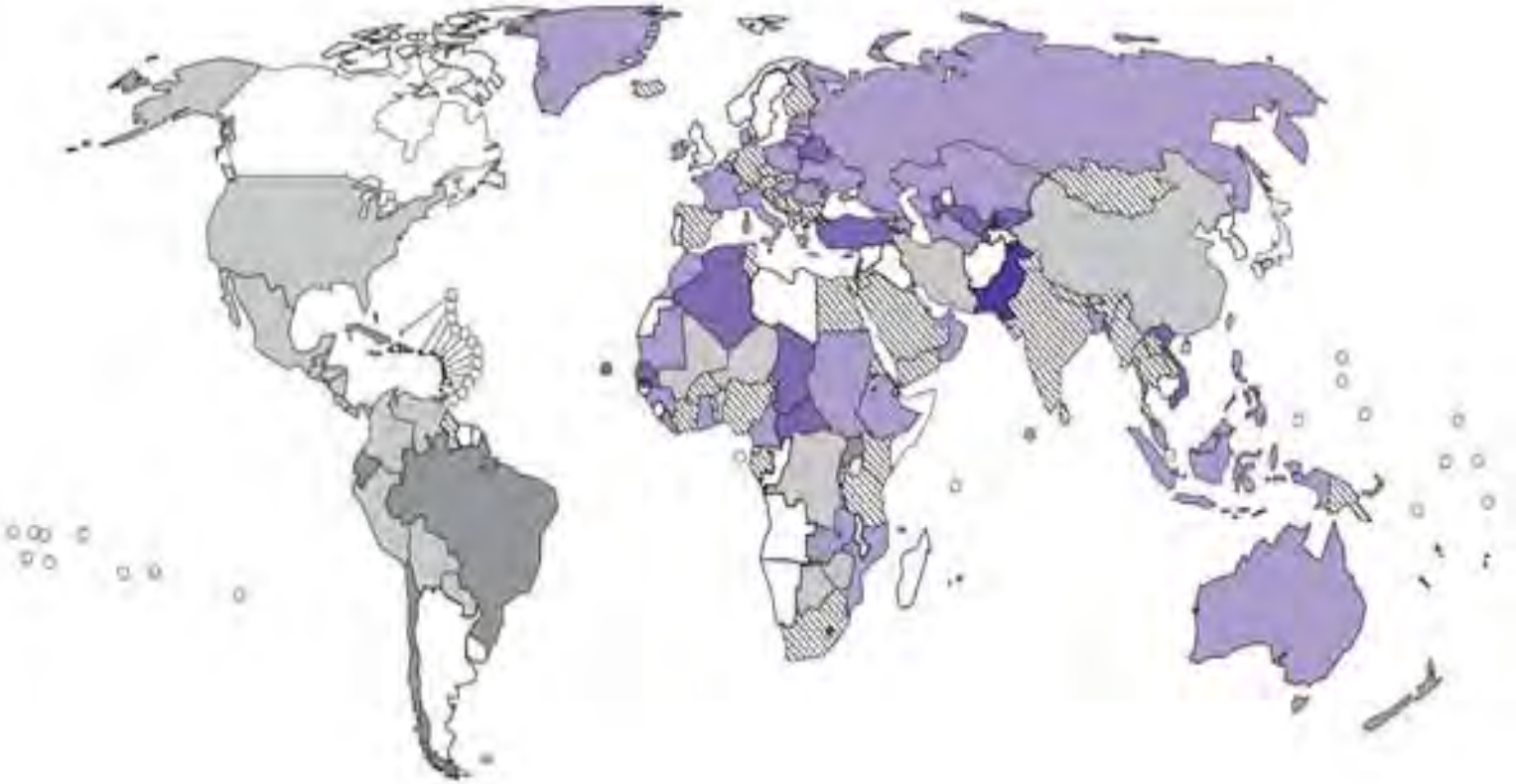


WHAT ARE IODINE DEFICIENCY SYMPTOMS?

- In areas where there is little iodine (inland areas with no seafood, areas where the iodine content of the soil is poor, and supplements such as iodized salt are lacking) **iodine deficiency gives rise to hypothyroidism, including goiter**.
- Worldwide, iodine deficiency is the leading cause of preventable mild to severe mental and growth retardation (called cretinism).
- **The addition of iodine to table salt has largely eliminated this problem** in many of the wealthier nations, but iodine deficiency remained a serious public health problem in the developing world.
- Australia, New Zealand, and certain areas of Europe (Germany) all experience iodine deficiency and resulting hypothyroidism.

GOITER AND THYROID NODULES





Severe iodine deficiency (<20 µg/l)

Moderate iodine deficiency (20–49 µg/l)

Mild iodine deficiency (50–99 µg/l)

Optimal (100–199 µg/l)

Risk of iodine-induced hyperthyroidism (200–299 µg/l)

Risk of adverse health consequences (>300 µg/l)

No data

World Health Organization 2003

INCREASE OF IODINE DEFICIENCY IN THE UNITED STATES

- The NHANES studies showed a decrease in mean urinary iodine excretion of 50% from the mid 1970s compared to the late 1980s/early 1990s. As of 2001-2, the level has stabilized.
- Monitoring of high-risk groups showed that 6.7% of pregnant women and 14.9% of women of childbearing age had a urine excretory level of less than the WHO threshold of iodine.
  - Hollowell JG, Staehling NW, Hannon WH, et al. 1998 J Clin Endocrinol Metab. 83:3401–3408. National Health and Nutrition Examination Survey IV NHANES (IV)

WHO IS AT RISK FOR IODINE DEFICIENCY?

- Deficits in Vegetarians and Vegans
  - **78 µg/l in vegans**
  - **172 µg/l in vegetarians**
  - **216 µg/l in subjects on a mixed diet**
- 25% of the vegetarians and 80% of the vegans suffer from iodine deficiency (iodine excretion value below 100 µg/l) compared to 9% in the persons on a mixed nutrition.
- Proposed link: Prevailing consumption of food of plant origin, **no intake of fish and other sea products, as well as reduced iodine intake in the form of sea salt**.
  - Krajoviova-Kudlakovaa, M., et al. Annals of Nutrition & Metabolism. 47(5):183-185, 2003.

DIETARY SOURCES OF IODINE

- In the early part of the 20th century, iodine deficiency was quite common in the United States and Canada.
- This problem was almost completely resolved by the use of iodized salt.
- In addition, iodine is now added to animal feed, which has increased the iodine content of commonly consumed foods, including cow's milk.

SOURCES OF IODINE

Food	Serving	Iodine (mcg)
Salt (iodized)	1 gram	77
Cod	3 ounces*	99
Shrimp	3 ounces	35
Fish sticks	2 fish sticks	35
Tuna, canned in oil	3 ounces (1/2 can)	17
Milk (cow's)	1 cup (8 fluid ounces)	56
Egg, boiled	1 large	12
Navy beans, cooked	1/2 cup	32
Potato with peel, baked	1 medium	60
Turkey breast, baked	3 ounces	34
Seaweed	1/4 ounce, dried	Variable; may be greater than 4,500 mcg (4.5 mg)

CAN I GET TOO MUCH IODINE?

- Double Edged Sword and Delicate Balance
- Diets both low and high in iodine are associated with hypothyroidism.
- **Studies that have shown that both low and high urinary iodine excretion are associated with hypothyroidism.**
- High intake of iodine also increases the risk of Hashimoto's thyroiditis.
  - Laurberg P, et al., Thyroid. 2001 May;11(5):457-69. Duarte GC, et al., J Pediatr Endocrinol Metab. 2009 Apr;22(4):327-34.

CAN I GET TOO MUCH IODINE?

- Acute iodine poisoning is rare. It usually occurs only with doses consisting of many grams. Symptoms of acute iodine poisoning include burning of the mouth, throat, and stomach; fever; nausea; vomiting; diarrhea; a weak pulse; and coma
- It is rare for diets of natural foods to supply more than 2,000 mcg of iodine/day, and most diets supply less than 1,000 mcg of iodine/day.
- People living in the northern coastal regions of Japan, whose diets contain large amounts of seaweed, have been found to have iodine intakes ranging from 50,000 to 80,000 mcg (50-80 mg) of iodine/day .
- It is estimated that men and women consume at most 300 mcg and 210 mcg of iodine per day, respectively. In general, even high intakes of iodine from food are well-tolerated by most people.

TOO MUCH IODINE: HYPOTHYROIDISM

- Excess consumption of iodine can actually inhibit the synthesis of thyroid hormones, leading to hypothyroidism.
- In iodine-sufficient adults, elevated TSH levels (a sign of hypothyroidism) have been found at iodine intakes between 1,700 and 1,800 mcg/day.
- This is the body's way of protecting and regulating itself, and involves a number of complex mechanisms.
- In order to minimize the risk of developing hypothyroidism, the Food and Nutrition Board (FNB) of the Institute of Medicine set a tolerable upper level of intake (UL) for iodine at 1,100 mcg/day for adults.
- In fact, large doses of iodide were used to treat hyperthyroidism before antithyroid drugs such as propylthiouracil and methimazole were developed.

TOO MUCH IODINE: HYPERTHYROIDISM

- Very high doses of iodine may also produce thyroid enlargement (goiter) due to increased TSH stimulation of the thyroid gland. Prolonged intakes of more than 18,000 mcg/day (18 mg/day) have been found to increase the incidence of goiter.

Excessive iodine intake may also cause hyperthyroidism, thyroid papillary cancer, and/or iodermia (a serious skin reaction).

TOO MUCH IODINE: HYPERTHYROIDISM

- "Iodine supplementation programs in iodine-deficient populations have been associated with an increased incidence of iodine-induced hyperthyroidism (IHH), mainly in older people and those with multinodular goiter.
- Iodine intakes of 150-200 mcg/day have been found to increase the incidence of IHH in iodine-deficient populations.
- **Iodine deficiency increases the risk of developing autonomous thyroid nodules that are unresponsive to the normal thyroid regulation system, resulting in hyperthyroidism after iodine supplementation."**

http://lpi.oregonstate.edu/infocenter/minerals/iodine/

IODINE: MY TAKE

- If you have been eating a low iodine diet, you may need a normal iodine intake to optimize your thyroid function.
  - Do not add large amounts of iodine; try adding just small amounts, as in a multi-vitamin supplement or as a small amount of sea vegetables (like a square of nori snack) daily
  - Stay under 150 mcg iodine daily
- If you are borderline hypothyroid do not take large amounts of supplemental iodine.
- If you have a family history of hyperthyroidism (Graves' disease) do not take large amounts of iodine from either diet or supplements.
- If you are already hypothyroid, be sure to get a normal amount of iodine, but avoid large doses of supplemental iodine.
- There may be certain medical reasons to increase iodine intake (such as fibrocystic breast disease). This should be discussed with your doctor.

SELENIUM & THYROID

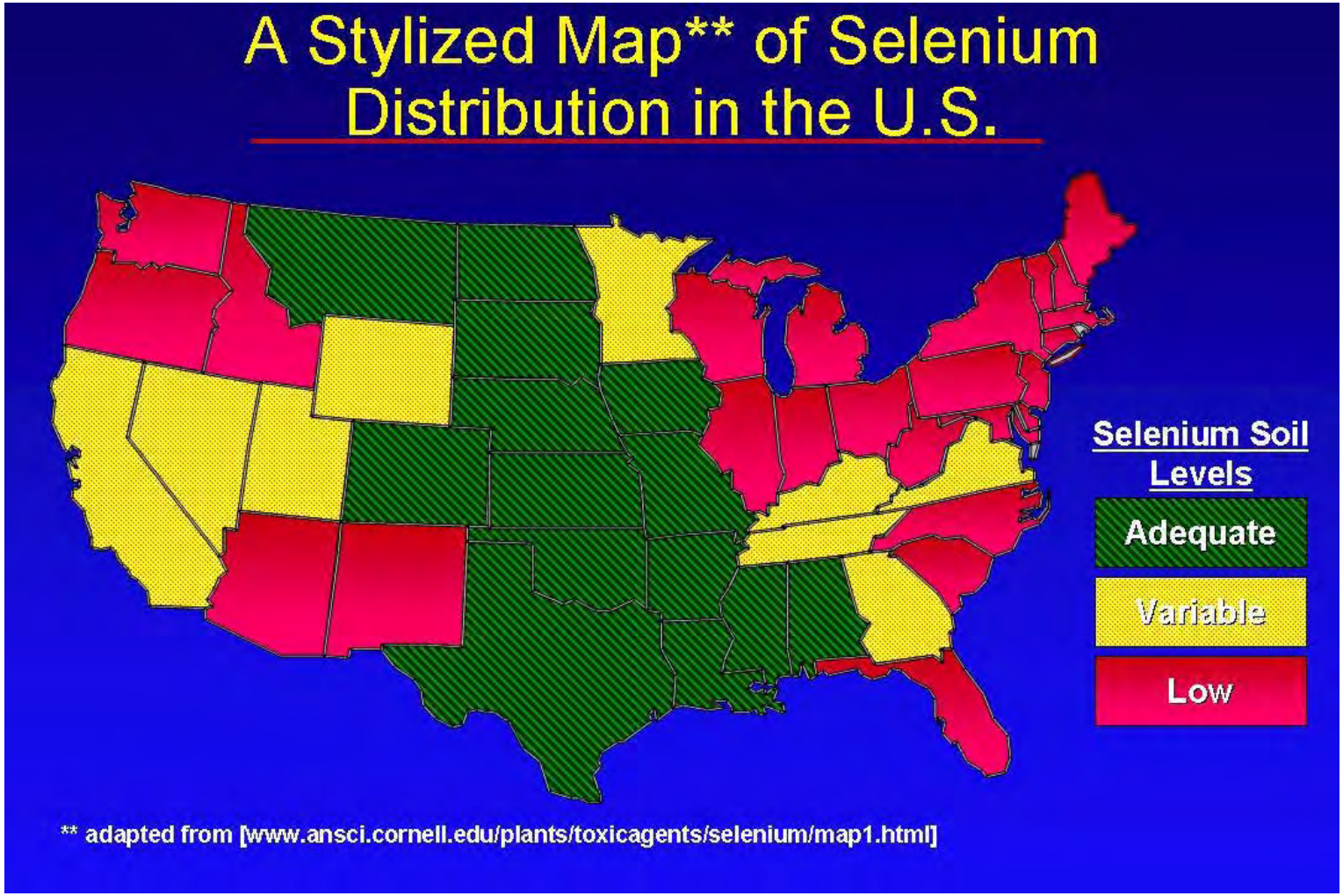
- The conversion of thyroxine (T4) to triiodthyronine (T3) requires the removal of an iodine molecule from T4. This reaction requires the mineral selenium.
- The iodine molecule that is removed gets returned to the body's pool of iodine and can be reused to make additional thyroid hormones.
- If your body is deficient in selenium, the conversion of T4 to T3 is slowed, and less iodine is available for the thryroid to use in making new hormones.

FOOD SOURCES OF SELENIUM

Food	Serving	Selenium (mcg)
Brazil nuts (from selenium-rich soil)	1 ounce (6 kernels)	544*
Shrimp	3 ounces (10-12)	34
Crab meat	3 ounces	41
Salmon	3 ounces	40
Halibut	3 ounces	40
Noodles, enriched	1 cup, cooked	38
Rice, brown	1 cup, cooked	19
Chicken (light meat)	3 ounces	13
Pork	3 ounces	35
Beef	3 ounces	16
Whole wheat bread	2 slices	23
Milk, skim	8 ounces (1 cup)	5
Walnuts, black	1 ounce, shelled	5

*Above the tolerable upper intake level (UL) of 400 mcg/day.

SNAP SHOT OF ONE KEY NUTRIENT



ADDITIONAL SELENIUM REFERENCES

- Toulis KA, et al. Selenium supplementation in the treatment of Hashimoto's thyroiditis: a systematic review and a meta-analysis. Thyroid. 2010 Oct;20(10):1163-73.
- Schomburg L. Treating Hashimoto's thyroiditis with selenium: no risks, just benefits? Thyroid. 2011 May;21(5):563-4.

ZINC & THYROID

- **Supplementation resulted in increased levels of serum free T3, reduced levels of rT3 and normalized TSH levels.**
- **This is the likely result of zincs role as cofactor for the thyroid receptor.**
- Nishiyama S, et al. Zinc supplementation alters thyroid hormone metabolism in disabled patients with zinc deficiency. J Am Coll Nutr. 1994 Feb;13(1):62-7.

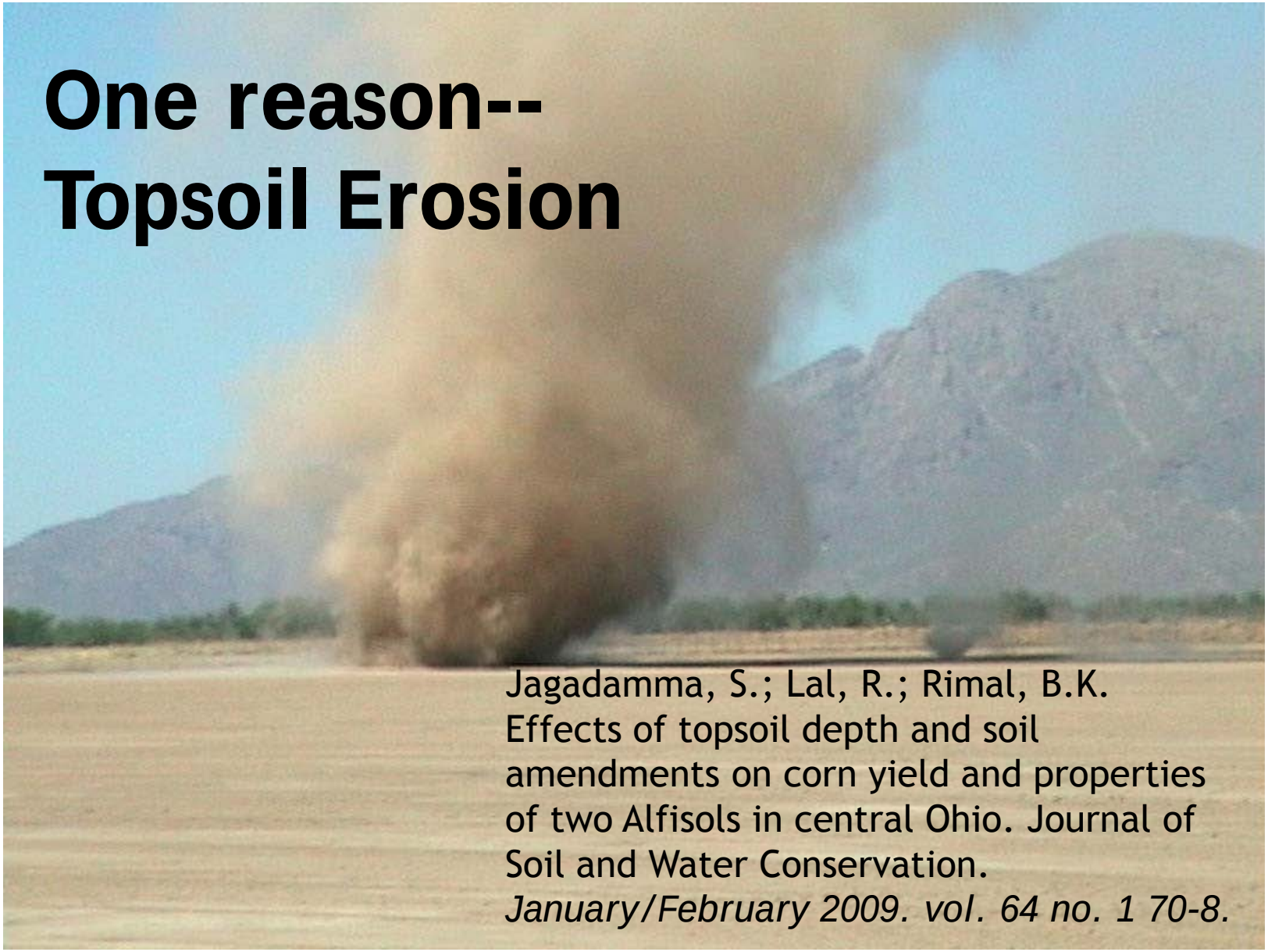
NUTRITIONAL INSUFFICIENCIES: SELENIUM AND ZINC

- **Low T3/T4 ratio may be related to impaired zinc and/or selenium status.**
- **Supplementation was associated with modest changes in thyroid hormones, with an earlier normalization of T4 and RT3 plasma levels.**
- Berger MM, et al. Influence of selenium supplements on the post-traumatic alterations of the thyroid axis: a placebo-controlled trial. Intensive Care Med. 2001 Jan;27(1):91-100.
- Olivieri O, et al. Selenium, zinc, and thyroid hormones in healthy subjects: low T3/T4 ratio in the elderly is related to impaired selenium status. Biol Trace Elem Res. 1996 Jan;51(1):31-41.

NUTRITIONAL INSUFFICIENCIES: IRON

- **Iron deficiency impairs thyroid hormone synthesis by reducing the activity of heme dependent thyroid peroxidase.**
- **Iron-deficiency anemia blunts, and iron supplementation improves, the efficacy of iodine supplementation.**
- Zimmermann MB, Köhrle J. The impact of iron and selenium deficiencies on iodine and thyroid metabolism: biochemistry and relevance to public health. Thyroid. 2002 Oct;12(10):867-78.

WHY SO MUCH MINERAL DEFICIENCY?



One reason--
Topsoil Erosion

Jagadamma, S.; Lal, R.; Rimal, B.K. Effects of topsoil depth and soil amendments on corn yield and properties of two Alfisols in central Ohio. Journal of Soil and Water Conservation. *January/February 2009. vol. 64 no. 1 70-8.*

NUTRITIONAL INSUFFICIENCIES: VITAMIN A

- **Factors that either produce vitamin A (retinol) insufficiency or prevent the conversion of vitamin A to retinoic acid may result in reduced thyroid nuclear signaling.**
- Feart C, et al. Aging affects the retinoic acid and the triiodothyronine nuclear receptor mRNA expression in human peripheral blood mononuclear cells. Eur J Endocrinol. 2005 Mar;152(3):449-58.

NUTRITIONAL INSUFFICIENCIES: VITAMIN D

- Vitamin D Link to Autoimmune Thyroid VDR gene polymorphism was found to associate with autoimmune thyroid diseases (AITDs).
- The prevalence of vitamin D deficiency was significantly higher in patients with AITDs compared with healthy individuals (72% versus 30.6%; $P<0.001$), as well as in patients with Hashimoto's thyroiditis compared to patients with non-AITDs (79% versus 52%; $P<0.05$).
- Significantly low levels of vitamin D were documented in patients with AITDs that were related to the presence of anti-thyroid antibodies and abnormal thyroid function tests, suggesting the involvement of vitamin D in the pathogenesis of AITDs and the advisability of supplementation.
- Kivity S,et al. Cell Mol Immunol.2011 May;8(3):243-7.

NUTRITIONAL INSUFFICIENCIES: VITAMIN D

- Follicular thyroid cancer and vitamin D
  - "Our study revealed that impaired vitamin D(3) metabolism may play an important role in thyroid follicular cell oncogenesis."
  - Stepien T, et al. Decreased 1-25 dihydroxyvitamin D3 concentration in peripheral blood serum of patients with thyroid cancer. Arch Med Res. 2010 Apr;41(3):190-4.

DIET: GOITROGENS

- Goitrogens are naturally-occurring substances that can interfere with function of the thyroid gland.
- Goitrogens get their name from the term "goiter," which means an enlargement of the thyroid gland.
- If the thyroid gland is having difficulty making thyroid hormone, it may enlarge as a way of trying to compensate for this inadequate hormone production.
- "Goitrogens," like circumstances that cause goiter, cause difficulty for the thyroid in making its hormone.

SOY & GOITROGENS

SOY & GOITROGENS

- While soy foods share many common ingredients, it is the isoflavones in soy that have been associated with decreased thyroid hormone output. Isoflavones are naturally-occurring substances that belong to the flavonoid family of nutrients.
- Isoflavones like genistein appear to reduce thyroid hormone output by blocking activity of an enzyme called *thyroid peroxidase*. This enzyme is responsible for adding iodine onto the thyroid hormones.

SOY & GOITROGENS

- **Animal studies show suppression…But…**
- Chang HC, Doerge DR. Dietary genistein inactivates rat thyroid peroxidase in vivo without an apparent hypothyroid effect. Toxicol Appl Pharmacol. 2000 Nov 1; 168(3):244-52.

SOY AND THYROID FUNCTION: HUMAN STUDY 1

- **18 postmenopausal women for 3 months each**
- **Three soy powders containing different levels of isoflavones**
  - **virtually none**
  - **a modest level [1mg/kg]**
  - **a high level [2mg/kg])**
- **Thyroid hormones assayed had only small changes between the groups, which authors suggested were so minor as to not be of physiologic importance.**
- Duncan, A.M., et al., Modest hormonal effects of soy isoflavones in postmenopausal women. J Clin Endocrinol Metab, 1999. 84(10): p. 3479-84.

SOY AND THYROID FUNCTION: HUMAN STUDY 2

- **73 postmenopausal women randomly divided into three groups and each given powders containing 40 g protein.**
- **The protein consumed for 6 months was from**
  - **casein from nonfat dry milk.**
  - **isolated soy protein containing 56 mg isoflavones, or**
  - **isolated soy protein containing 90 mg isoflavones**
- **Soy protein groups had minimal effects on thyroid function. "Intragroup differences were statistically indistinguishable at 6 months."**
- **The authors concluded that the changes were of such small magnitude that they were unlikely to be clinically important.**
- Persky, V.W., et al., Effect of soy protein on endogenous hormones in postmenopausal women. Am J Clin Nutr, 2002. 75(1): p. 145-53.

SOY AND THYROID FUNCTION: HUMAN STUDY 3

- **Randomized, double-blind, placebo-controlled study of the effect on thyroid function of a daily supplement containing 90 mg of total isoflavones per day vs. placebo in 38 postmenopausal women.**
- **TSH, T4, and T3 were measured at baseline and after 90 and 180 days.**
- **Intragroup differences for all three measures were statistically indistinguishable at 6 months, and levels were similar between the isoflavone supplement and placebo groups at each measurement.**
- Bruce B, Messina M, Spiller GA. Isoflavone supplements do not affect thyroid function in iodine-replete postmenopausal women. J Med Food. 2003;6: 309-316.

EVEN MORE RECENT… LONG TERM STUDY OF 3 YEARS:

- **"These data suggest that genistein aglycone intake does not significantly increase the risk of clinical or subclinical hypothyroidism at the dose of 54 mg/d."**
- Bitto A, Polito F, Atteritano, M et. al. Genistein Aglycone Does Not Affect Thyroid Function: Results from a Three-Year, Randomized, Double-Blind, Placebo-Controlled Trial. J Clin Endocrinol Metab 2010 Jun;95(6):3067-72.

BUT WAIT…

- **60 patients with subclinical hypothyroidism.**
- **Of those,6 female patients progressed into overt hypothyroidism after 16-mg isoflavone supplementation (cross over design).**
  - ***TSH values increased by 57% (8.0 vs. 13.1 mU/ liter; P 0.05), and fT4 values decreased by 25% (12 vs. 8.80 pmol/liter; P0.05).***
- **However… systolic and diastolic blood pressure, hsCRP and insulin resistance all decreased with that 16 mg isoflavone supplementation.**
- Manuchehri AM, Thatcher NJ, et. al, The effect of soy phytoestrogen supplementation on thyroid status and cardiovascular risk markers in patients with subclinical hypothyroidism: a randomized, double-blind, crossover study. J Clin Endocrinol Metab. 2011 May;96(5):1442-9.

SOY AND SYNTHROID: CASE REPORT

- **45-year-old woman who had hypothyroidism after a near-total thyroidectomy and radioactive iodine ablative therapy.**
- **Required unusually high oral doses of levothyroxine to achieve suppressive serum levels of free T4 and TSH.**
- **She had routinely been taking a "soy cocktail" protein supplement immediately after her levothyroxine.**
- **Separation of the intake of the soy protein cocktail from the levothyroxine resulted in attainment of suppressive serum levels of free T4 and TSH with use of lower doses of levothyroxine.**
- Bell DS, Ovalle F. Use of soy protein supplement and resultant need for increased dose of levothyroxine. Endocr Pract. 2001 May-Jun;7(3):193-4.

SOY AND THYROID: REVIEW

- **14 trials were assessed. With only one exception, either no effects or only very modest changes were noted in these trials.**
- **In contrast, some evidence suggests that soy foods, by inhibiting absorption, may increase the dose of thyroid hormone required by hypothyroid patients.**
- **In addition, there remains a theoretical concern based on in vitro and animal data that in individuals with compromised thyroid function and/or whose iodine intake is marginal soy foods may increase risk of developing clinical hypothyroidism.**
- **Therefore, it is important for soy food consumers to make sure their intake of iodine is adequate.**
- Messina M, Redmond G. Effects of soy protein and soybean isoflavones on thyroid function in healthy adults and hypothyroid patients: a review of the relevant literature. Thyroid. 2006 Mar;16(3):249-58.

SOY AND SEAWEED

Iodine deficiency greatly increases soy antithyroid effects, whereas iodine supplementation is protective. Small amounts of seaweed can help assure adequate iodine intake.

SOY AND SEAWEED

- Seaweeds and soy are two commonly eaten foods in Asia. Both have been reported to affect thyroid function, seaweed because of its iodine content and soy because of its goitrogenic effect.
- Twenty-five healthy postmenopausal women (mean age 58 years) completed a double-blinded randomized crossover study.
  - 475 mcg of iodine/day, (5 grams of seaweed in capsules) were consumed daily for 7 weeks.
  - A powdered soy protein isolate (Solae Co., St. Louis, MO), providing 2 mg of isoflavones/kg of body weight, was given daily during the last week of each treatment arm. On average, this provided 141.3 mg of isoflavones/day and 67.5 g of protein/day.
  - **Seaweed ingestion increased serum TSH (P < .0001) (1.69 +/- 0.22 vs. 2.19 +/- 0.22 muU/mL.**
  - **Soy supplementation did not affect thyroid end points.**
- Teas J, Braverman LE, Kurzer MS, Pino S, Hurley TG, Hebert JR. Seaweed and soy: companion foods in asian cuisine and their effects on thyroid function in American women. *J Med Food. Spring 2007;10(1):90-100.*

THE SOY/THYROID CONTROVERSY MY TAKE….

- **Concerns are based primarily on *in vitro research,* animal studies, and older reports of goiter in infants fed soy formula not fortified with iodine.**
- **It is reasonable to be cautious in people with borderline hypothyroidism, a history of thyroiditis, or on a poor diet that may be marginally deficient in iodine.**
- **Some people are likely "thyroid sensitive" to soy protein and/or its isoflavones.**
- **For the broad majority of individuals, normal dietary soy is unlikely to have any long-term negative effects on thyroid function.**
- **For people already on thyroid hormones, soy is unlikely to have long-term negative effects.**

CRUCIFEROUS VEGETABLES AND THYROID HORMONES

CRUCIFEROUS VEGETABLES AND THYROID

- A second category of foods associated with disrupted thyroid hormone production is the cruciferous food family.
- Foods belonging to this family are called "crucifers," and include broccoli, cauliflower, Brussels sprouts, cabbage, mustard, rutabagas, kohlrabi, and turnips.
- Isothiocyanates are the category of substances in crucifers that have been associated with decreased thyroid function.
  - Like the isoflavones, isothiocyanates appear to reduce thyroid function by blocking thyroid peroxidase, and also by disrupting messages that are sent across the membranes of thyroid cells.

CRUCIFEROUS VEGETABLES AND THYROID

- Two mechanisms
  - Compound called "goitrin" created by enzymes from "glucosinolates" has been found to interfere with thyroid hormone synthesis.
  - Another compound released from "indole glucosinolates" creates thiocyanate ions which can compete with iodine for uptake.
- Generally
  - Increased exposure to thiocyanate ions from cruciferous vegetable consumption or, more commonly, from cigarette smoking, does not appear to increase the risk of hypothyroidism unless accompanied by iodine deficiency.
  - One study in humans found that the consumption of 150 g/day (5 oz/day) of cooked Brussels sprouts for four weeks had no adverse effects on thyroid function.

TABLE I

Results of Studies on Antithyroid Potency of Various Foods in Man (Modified from Reference)[16]

Marked effect	Questionable effect	No effect	
Rutabaga	Grape	Beefsteak	Banana
Moderate effect	Celery	Bonita	squash
	Green pepper	Cheese	Corn
Turnip	Orange	Ice cream	Rice
Peach	Apricot	Lobster	Rye
Pear	Peanut	Sardines	Black
Strawberry	Pea	Shrimp	beans
Spinach	String bean	Mushrooms	Lima beans
Carrot	Walnut	Dates	Onion
	Filbert	Pineapple	Olive
	Honeydew	Broccoli	Almond
	Cabbage	Cauliflower	Apple
	Lettuce	Mustard	Blackberry
	Beet	Radish	Loganberry
	Oyster	Cucumber	Tangerine
	Milk		Banana
	Liver		Potato
	Clam		Tomato
	Grapefruit		

MONTE A. ***GREER, M.D. 1958.*** Downloaded from www.ajcn.org by guest on April 30, 2012

DIET: EXTREMES IN CALORIC INTAKE AFFECT THYROID FUNCTION

During caloric restriction

- Serum T3 concentrations decrease as a consequence of its reduced production rate from peripheral deiodination of T4.
- Serum RT3 concentrations markedly increase as a result of its decreased metabolic clearance rate.
- During caloric restriction and overfeeding serum T4 concentrations and its production and degradation are not modified.
  - Roti E, Minelli R, Salvi M. Thyroid hormone metabolism in obesity. Int J Obes Relat Metab Disord. 2000 Jun;24 Suppl 2:S113-5.

SUMMARY

- Understanding the chain of events and feedback loops in thyroid hormone production is important in selecting appropriate testing and treatment of thyroid disease.
- Assessing thyroid function requires a full set of thyroid tests including TSH, T3, free T3, T4, free T4, Reverse T3, and thyroid auto-antibodies, and if appropriate assessment of adrenal function, sex hormones, and glycemic function (insulin/glucose).
- Hashimoto's thyroiditis is an auto-immune disease . Optimal treatment involves not only appropriate thyroid replacement therapy, but addressing the upstream causes, especially gluten intolerance.
- A minority of people receiving T4 as Thyroid replacement therapy continue to show chemical and/or functional hypothyroidism, and require additional T3 or treatment with dessicated thyroid (which contains about 20% T3 and 80% T4).

SUMMARY

- Another frequent cause of lack of full response to therapy with T4 is decreased conversion of T4 to T3 with increased conversion of T4 to reverse T3. There are specific causes of increased Reverse T3 production including stress, inflammation, selenium deficiency and insufficient calories.
- Nutrient adequacy but not excess of iodine, selenium, zinc, Vitamin A and Vitamin D are necessary for optimal thyroid hormone function. Supplements may be important to provide these.
- For most people soy intake will not interfere with thyroid hormone function, if sufficient iodine is present in the diet. There are exceptions—some people with subclinical Hashimoto's thyroiditis.
- Cooking cruciferous vegetables is usually sufficient to inactivate goitrogens. If you have hypothyroidism, avoid large amounts of raw cruciferous vegetables.
- Avoid pollutants that interfere with thyroid function.