

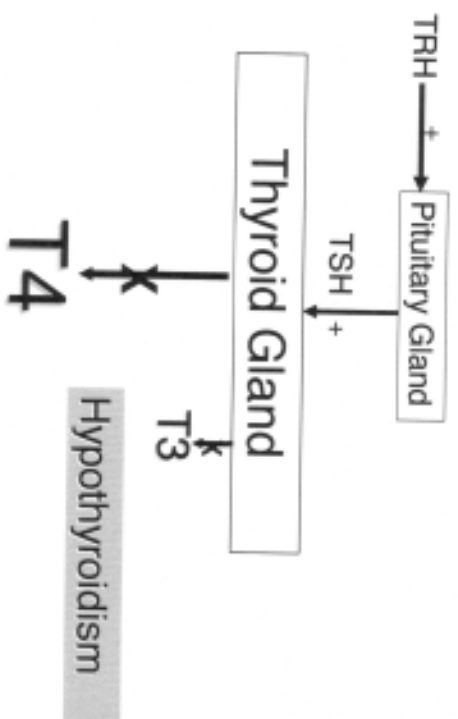
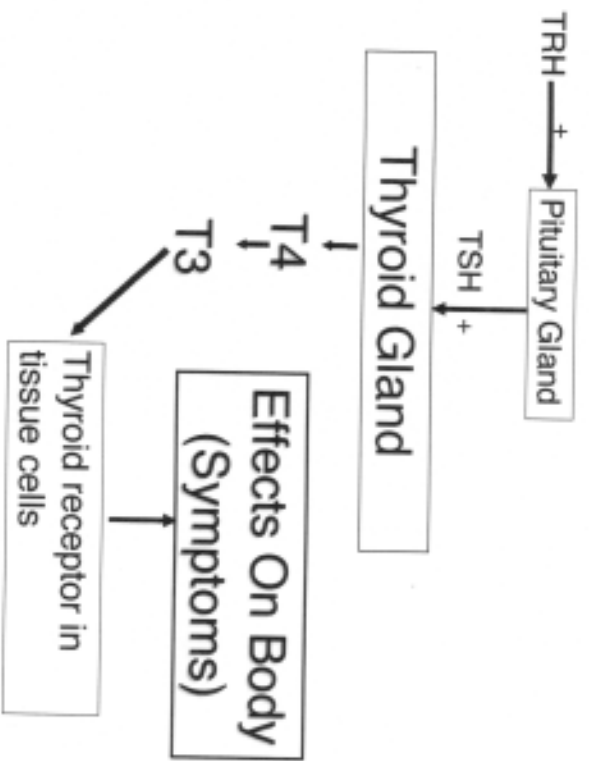
Hypothyroidism, Functional Hypothyroidism, and Functional Hypometabolism

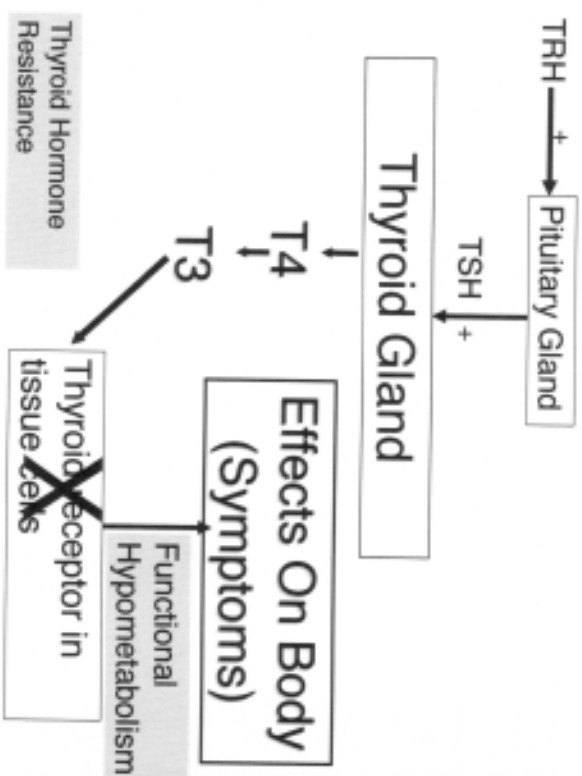
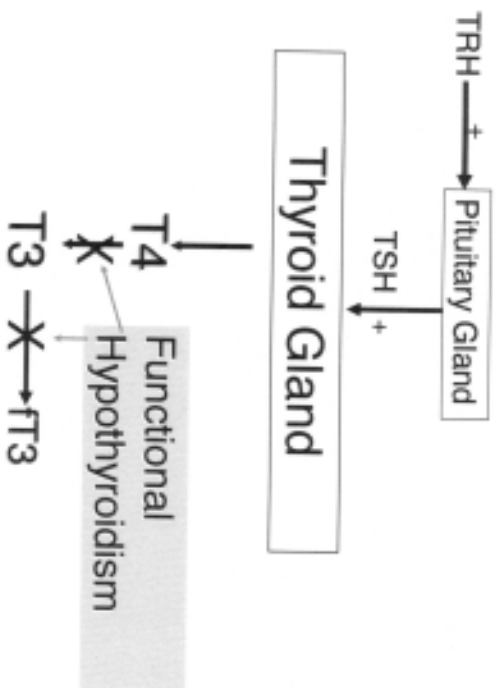
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Less Than Optimal Thyroid Function

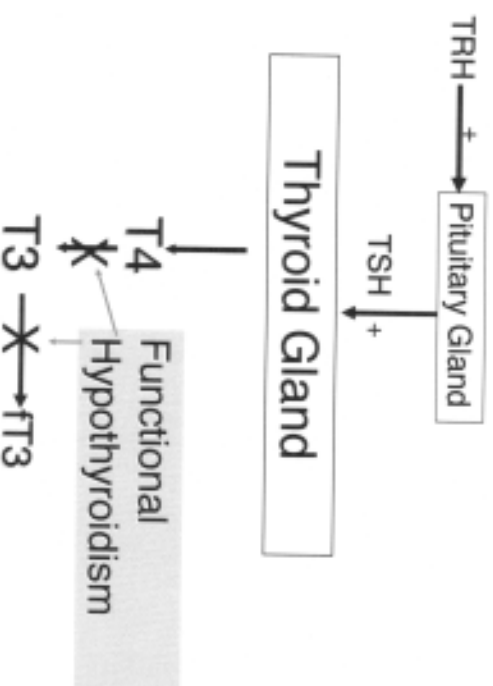
- A number of situations can contribute
 - Inadequate production of T₄
 - Poor conversion from T₄ to T₃
 - Problems with the cell's ability to take up T₃
 - Problems with receptor function
 - Problems with intracellular transport





Hypothyroidism

- Thyroid function decreases with age
 - Decrease production occurs at ages 45-50 in normal individuals
- Lack of components that make up thyroid hormones
 - Iodine
 - Tyrosine
- “Sluggish” thyroid – poor recovery following acute stress
- Thyroid Gland destruction
 - Autoimmune reaction, heavy metal toxicity



Causes of Functional Hypothyroidism

- Excessive binding through increased TBG
 - Estrogen
 - Pregnancy, OCs, ERT (especially oral)
 - Thyroid replacement therapy
 - Delayed response (typically 4 weeks-4 months)

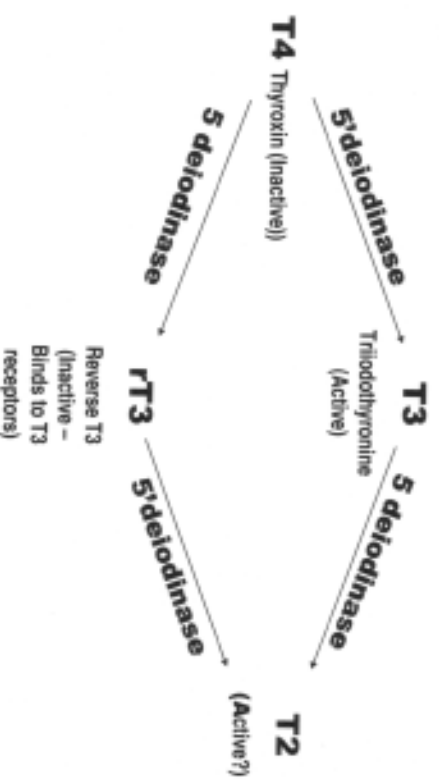
Binding of Thyroid Hormones

- More than 99% of circulating thyroid hormones are bound to serum proteins
 - Thyroxine-binding globulin (TBG)
 - Thyroxine-binding prealbumin (TBPA)
 - Albumin (TBA)
- T4 is more extensively bound than T3
 - 0.04% of total T4 is free
 - 0.4% of total T3 is free

Causes of Functional Hypothyroidism

- Imbalance of fT_3 and rT_3
 - Caused by decreased conversion of T_4 to the active T_3
 - T_4 therapy with imbalanced conversion worsens the situation

Normal T_4 Conversion to T_3 by the Enzyme $5'$ deiodinase.



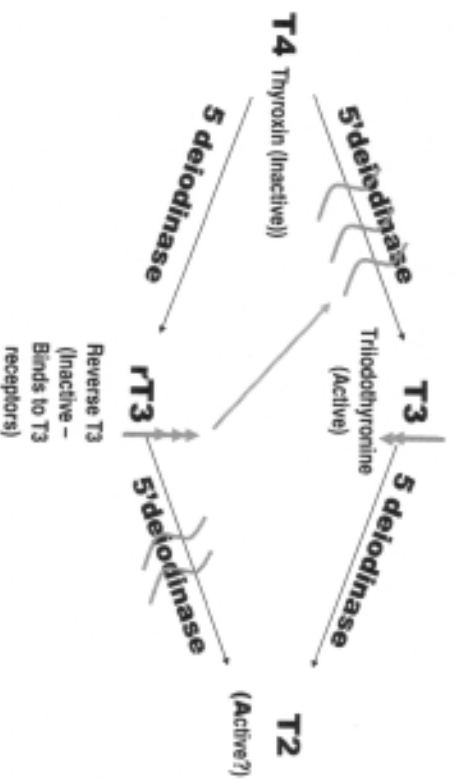
T4 to T3 Conversion

- Peripherally T4 is converted to equal parts T3 and reverse T3
- Remember as far as thyroid activities, the main hormone is T3
 - No T4 receptors have been identified in the body
 - Reported relative strengths determined by s.q. administration and measuring outcomes
 - Decreased conversion to T3 is almost always accompanied by an increased conversion to reverse T3
- Whenever T4 is administered, depending on proper conversion to T3 to obtain metabolic effects!

De-Iodinases

- D1 in liver & kidneys
 - Systemic T3 production
- D2 in muscle, & in brain & pituitary
 - Local T3 production
- D3 in brain
 - T4, T3 degradation
- Extrathyroidal T3 production is mediated primarily by type D2 normally
 - At low & normal T4, D2 predominates (muscle)
 - At high T4, D1 predominates

Inhibition of T4 Conversion to T3 by the Enzyme 5' deiodinase.



Factors That Inhibit T4 to T3 Conversion

Nutrient Deficiencies

- Selenium
- Chromium
- Iron
- Copper
- Vitamin A
- Vitamin B2
- Vitamin B6
- Vitamin B12
- Vitamin E
- Zinc
- Iodine

David Brownstein, MD (adaptation)

Factors That Inhibit T4 to T3 Conversion

- Stress -- excessive cortisol
- Inadequate production of adrenal hormones
- Halogen toxicity
- Anti-thyroid peroxidase antibodies
- Excess reverse T3
- Estrogen
- Obesity
- Liver and kidney disease
- Starvation

Factors That Inhibit T4 to T3 Conversion

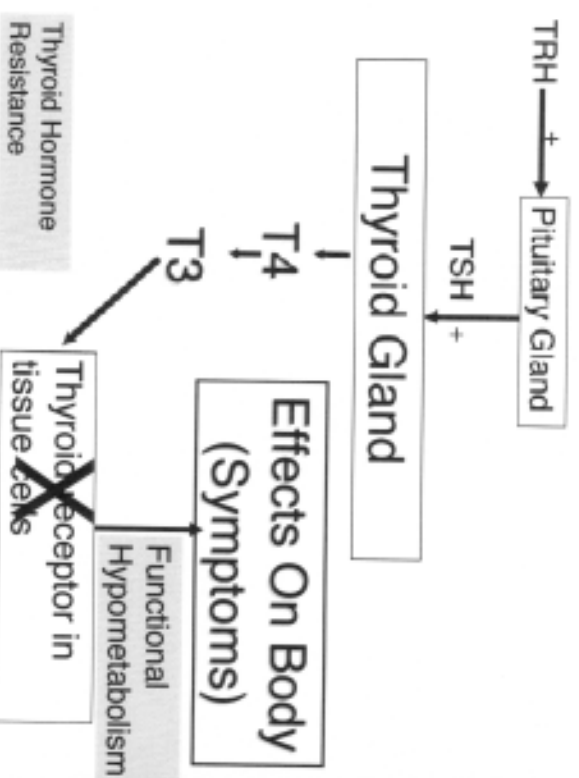
Medications

- | | |
|-----------------------------|------------------------|
| • SSRIs | • Glucocorticoids |
| • Opiates | • Beta Blockers |
| • Phenytoin | • Birth Control Pills |
| • Chemotherapy | • Estrogen Replacement |
| • Theophylline | • Estrogen Dominance |
| • Lithium | |
| • Fluoride supplementation | |
| • Iodinated Contrast Agents | |

David Brownstein, MD (adaptation)

Causes of Functional Hypothyroidism

- Nutritional deficiencies/excess
 - Iodine: to much or too little
 - Soy: excess decreases $T_4 \rightarrow T_3$, may increase autoimmune reactions in infants
- Thyroid antibodies
- Toxins



Functional Hypometabolism

(Thyroid Hormone Resistance)

- Thyroid levels are optimal in values and in relationship to each other, but symptoms persist
 - Adequate production & metabolism
- Thyroid receptor not responding to optimal thyroid levels
 - Target tissues of the body have reduced responsiveness to thyroid hormone

D.B.

Causes of Functional Hypometabolism

- Vitamin D level below optimal
 - Affects thyroid receptor response (Jeffrey Bland, PhD)
 - Low end of serum level range should be 32 (not 15)
 - Optimal range for thyroid receptor function is 50-70

Causes of Functional Hypothyroidism

- Impaired T3 transport
 - Low ferritin
 - Required for transport of T3 to nucleus of cell and utilization of hormone
 - Optimal level for thyroid function is 90-110
 - Chronic low cortisol
 - High reverse T3
 - High TPO
- Autoimmune antibodies

Causes of Functional Hypometabolism

- Genetic anomalies of thyroid hormone receptors
- Autoimmune (antibodies), oxidative, or toxic damage to thyroid-hormone receptors
 - (heavy metal toxicities)
- Competitive binding to thyroid-hormone receptors by pollutants, food additives, etc. (halogens, pesticides, perchlorate)

David Brownstein, MD (adaptation)

Causes of Functional Hypometabolism

- **Excessive competitor to T₃**
 - T₃ receptor forms a heterodimer with RXR
 - Progesterone, Vitamin D, and ω 3 fatty acids also form heterodimers with RXR
 - Excess of any can block signaling of the others

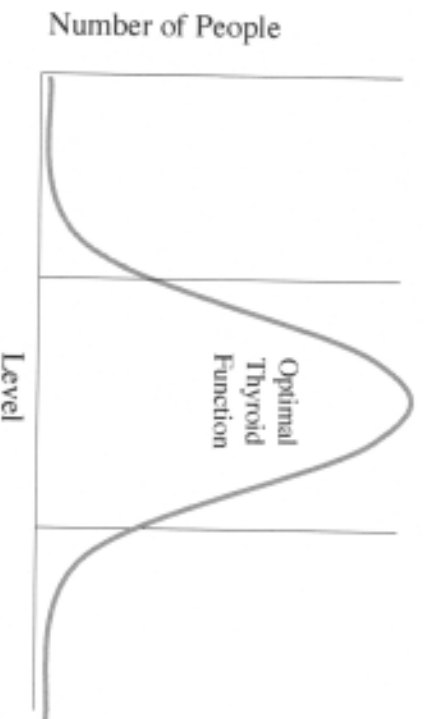
Causes of Functional Hypometabolism

- **Excess cortisol**
 - Inhibits T₄ to T₃ conversion
 - Suppresses TSH
 - Decreases thyroid receptor responsiveness
- **Low cortisol**
 - Decreases thyroid receptor responsiveness
 - May inhibit T₄ to T₃ conversion
 - Transport across the membrane is energy dependent & modified by cortisol
 - Cortisol regulates T₃ receptor density
 - May have to give cortisol to make thyroid supplementation work properly

- You must address adrenal dysfunction before fixing the thyroid function
 - High cortisol: causes excess catabolic action on muscles and bones
 - Low cortisol: adrenal insufficiency cannot meet the demands of increased metabolism
 - Hypoadrenalism is an absolute contraindication to thyroid replacement therapy

Considerations in Thyroid Testing

Optimal Thyroid Levels?



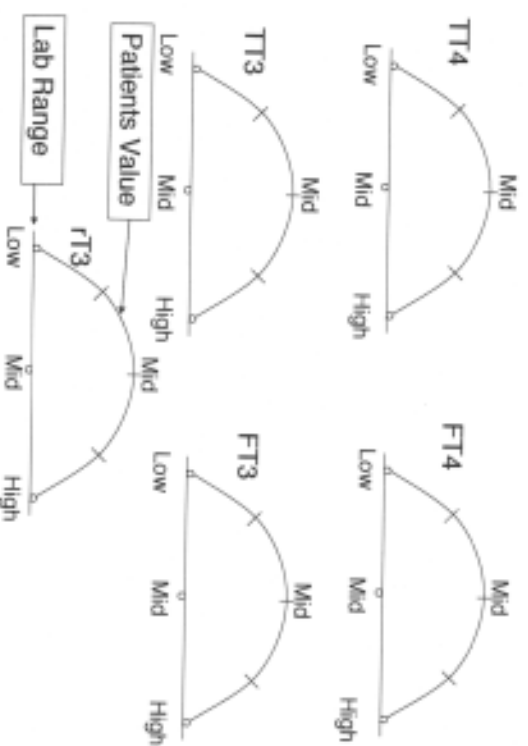
TSH

- Test designed as a screening tool only not diagnostic or therapeutic measurement
- Brain can be happy but peripheral tissue can be lacking
 - Different forms of 5'deiodinase enzyme
- The majority (>95%) of healthy euthyroid subjects have a serum TSH concentration below 2.5 mIU/L.
 - A serum TSH result between 0.5 and 2.0 is generally considered the therapeutic target for a standard T4 replacement dose for primary hypothyroidism
 - http://www.nacdb.org/impj/thyroid/t3c_thyroid.pdf

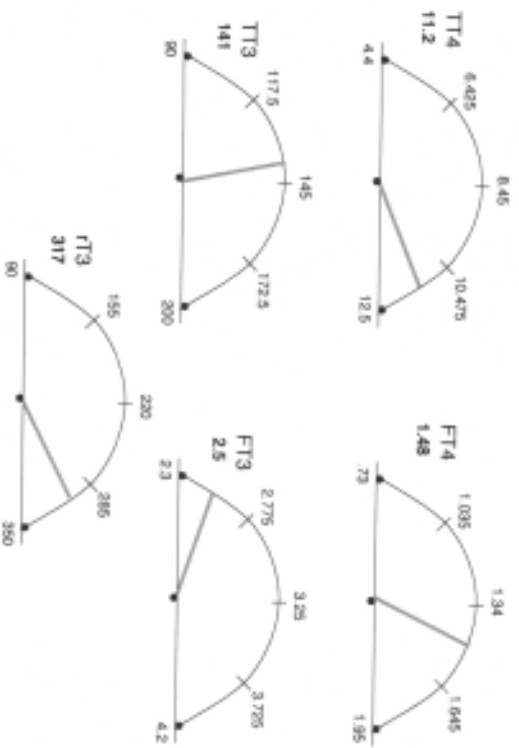
Thyroid "Panel"

- TSH, TT4, RT3U or T3U(T3 resin uptake), and Free Thyroxine Index (FT4I)
- Total T4
 - May be normal, but not enough converted to T3
- T3 resin Uptake
- Does not measure Free T3 levels
- Estimates the amount of unbound TBG.
 - How much binding sites are available
 - Low T3 uptake = lots of T3 - few empty binding sites and high T3 uptake = low T3 (lots of spaces available)
- Free Thyroxine Index (FT4I)
 - Calculation based on an estimate of serum free T4
 - Multiple T4 by T3 uptake
 - Calculated from total T4 and thyroid hormone binding ratio
- T3 uptake and FTI cheaper than measuring actual free T3 and rT3 hormone levels

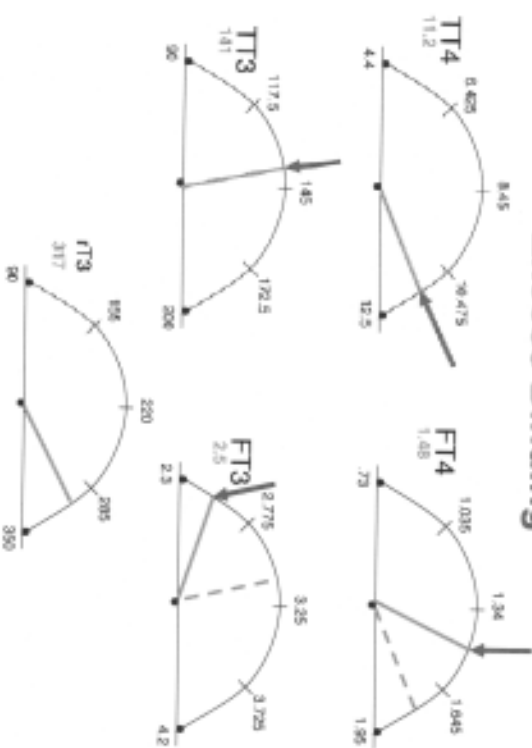
Thyroid Level Gradients



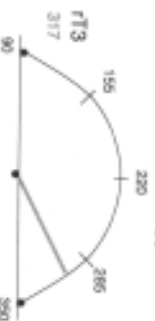
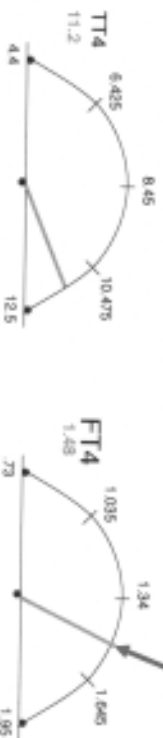
Thyroid Level Gradients Example



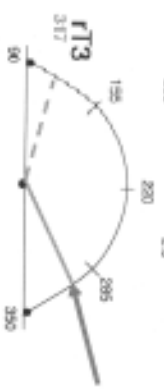
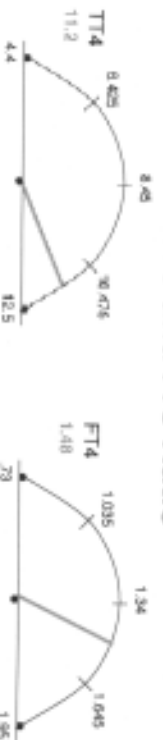
Excess Binding



Decreased Conversion of T4 to T3



FT3 and rT3 Ratio



Thyroid Testing

Initial Testing:

- Basal Body Temperature
- Patients < 45 yo and/or on thyroid replacement
 - TSH, TT4, fT4, TT3, fT3, TPO
 - Antibodies are the most frequent cause of thyroid conditions
- Patients with chronic symptoms, non-responsive to therapy
 - TSH, TT4, fT4, TT3, fT3, TPO, ferritin, Vitamin D, Iodine

Thyroid Testing

Follow-up testing

- fT4, fT3, TSH, TPO
 - Add ons - where previous testing indicates need to monitor:
 - Ferritin
 - Vitamin D
 - Iodine

Thyroid Replacement Therapy Options

Thyroid USP

- 1 Grain (60 mg) of Thyroid USP contains only 38 mcg of T₄ and 9 mcg of T₃
 - More than 99.9% of contents of thyroid USP are not the thyroid hormones T₃ and T₄
- Ratio of T₄:T₃ is 4.2:1, which is *not* physiological
- Ratio is fixed – doesn't allow for individual differences in metabolism or changes with time

Thyroid USP

- May also contain T₂, T₁, selenium, calcitonin
 - T₂ & T₁ may provide biological activity but overall contribution is considered minimal
 - The amounts are not identified, quantified, or standardized
- May contain lactose, sucrose, dextrose, starch or other "suitable" diluents

Compounded Thyroid

- Allows individualized ratio and strengths of T₄ and T₃ for every patient
 - Lower T₄ to T₃ ratio for patient not converting well
 - Ratio of ingredients can be adjusted based on levels and response – individualized to the patient
 - Correcting the problem(s) causing poor conversion should change the ratio of T₄:T₃ required
- Precisely compounded to optimize metabolism, symptom resolution, labs and body temperatures

Compounded Thyroid

- Compounded thyroid preparations allow for addition of adjunctive therapies
 - Hydrocortisol for proper thyroid utilization in adrenal dysfunction
 - Addition of selenium, zinc,
- Allow for varying doses at different times of the day based on individual responses
- Allow for gradual withdrawal of hydrocortisol

Compounded: The Best of Both Worlds

- Slow release T₃
 - Decreases side effects
 - Decreases suppression of thyroid gland & TSH
 - Can add nutrition and or hydrocortisone (cortisol)
- Combined T₄/T₃ in slow release capsule for increased ease in compliance and less cost
- Ratios individualized to the patient
- . Compounded thyroid preparations allow for addition of adjunctive therapies

Thank You

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THANKS

- Dr John Lee (of Australia)
- Dr David Brownstein
- Dr Allison McAllister
- Dr David Zava

- For education, insights and slides!

Thyroid Resources

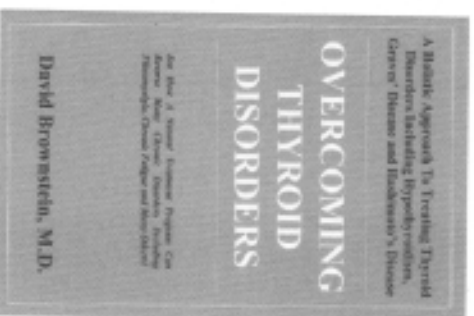
- www.thyroid.org.au
- www.drhowe.com
- www.thyrolink.com
- www.ThyroidPower.com
- www.endotext.com

Thyroid Books

LOW THYROID HORMONE—HOW
IT MAY BE AFFECTING YOUR BODY
AND PROOFS, POOL BY



Thyroid Books



Thyroid Books



BOX 4-3**Factors Altering Serum
TBG-Bound Hormone****Increased TBG Concentration**

High estrogen levels because of pregnancy
or oral contraceptives

Decreased TBG Concentration

Androgens, glucocorticoids
Malnutrition

Drugs Decreasing Binding

Phenytoin (Dilantin)
Salicylates

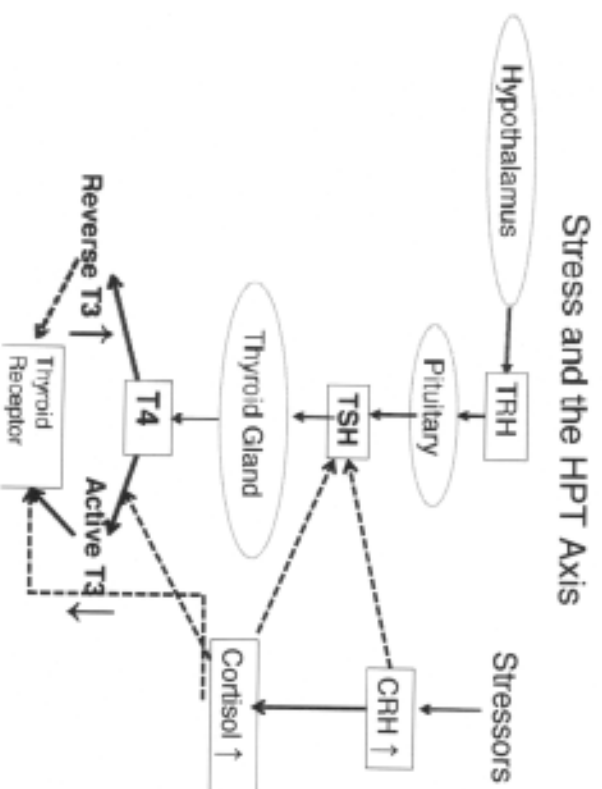
TBG, Thyroxine-binding globulin.

Factors That Increase Conversion of T₄ to T₃

- Selenium, zinc, chromium, potassium, iodine, iron, Vitamins A, B₂, E
- Growth hormone
- Testosterone, melatonin
- Insulin, glucagons
- Tyrosine
- High protein diet
- Ashwaganda

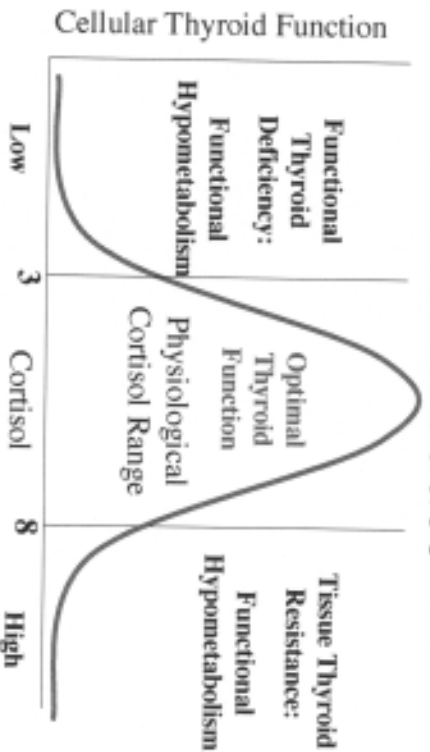
Factors That Inhibit T4 to T3 Conversion

- Aging
 - Alcohol
 - Alpha-Lipoic Acid *
 - Chemotherapy
 - Cigarette Smoking
 - Cruciferous Vegetables *
 - Diabetes
 - Fasting
 - Fluoride
 - Growth Hormone Deficiency
 - Hemochromatosis
 - Lead
 - Low Adrenal State
 - Mercury
 - Pesticides
 - Soy *
 - Stress
 - Surgery
 - Radiation
- *excessive amounts
- David Brownstein, MD



Normal Thyroid Function Requires Normal Adrenal Function

Optimal thyroid receptor function is at a saliva cortisol level of 3-8



TSH

- Despite the clinical sensitivity of TSH, a TSH-centered strategy has inherently two primary limitations. First, it assumes that hypothalamic-pituitary function is intact and normal. Second, it assumes that the patient's thyroid status is stable, i.e. the patient has had no recent therapy for hypo- or hyperthyroidism [Section-2 A1 and Figure 2] (19). If either of these criteria is not met, serum TSH results can be diagnostically misleading

- http://www.nacb.org/mtgthyroid2c_thyroid.pdf
- NACB: Laboratory Support for the Diagnosis and Monitoring of Thyroid Disease Laurence M. Demers, Ph.D., F.A.C.B. and Carole A. Spencer Ph.D., F.A.C.B.

Free T_3 and rT_3

- If the conversion of T_4 to FT_3 and rT_3 is normal, FT_3 and rT_3 should have about the same position on the clock.
- Even though rT_3 is within the normal range for this laboratory, it is in excess of FT_3 .
- Since FT_3 and rT_3 occupy the same receptor and FT_3 will activate the receptor and rT_3 will not, if the patient has excess rT_3 they will have symptoms of tissue hypometabolism despite all the laboratory tissue falling within the normal range.

Etiology and Correction of Excess rT_3

- Excess rT_3 will further inhibit conversion from T_4 to T_3
- Since rT_3 is derived from T_4 , you must lower T_4
- If the patient is on a T_4 preparation, give slow release T_3 and discontinued T_4 preparation (slowly over time to control TSH)
- If the patient is not on a T_4 preparation, still give slow release T_3
 - This will decrease TSH and the production of T_4 from the thyroid gland and its inappropriate conversion to rT_3

Etiology and Correction of Excess rT3

- Excess cortisol blocks T4 to T3 conversion and increases T4 to rT3
 - Check 4 point salivary levels of cortisol and correct appropriately
 - Correct the reasons for poor conversion – nutritional deficiencies, medications, etc
- Growth Hormone increases T3 production
 - Oral estrogen inhibits growth hormone; change to transdermal if appropriate
 - Modify lifestyle (exercise, sleep) and nutrition to increase natural growth hormone production

Etiology and Correction of Excess rT3

- The enzyme that converts T4 to rT3 is D3
- D3 is increased in tissue hypermetabolism and decreased in tissue hypometabolism*
- D3 is markedly induced by acidic and basic fibroblast growth factors as well as epidermal growth factor, platelet-derived growth factor, and cAMP analogs

*Endocrine Reviews 2/2002, 23(1):38-89

What's In Your Thyroid?

- 1 Grain (60 mg) of "natural" Thyroid USP contains 38 mcg of T4 and 9 mcg of T3
- T4 commercial products may contain lactose and have variable absorption problems
- T3 commercial products limited in strengths and only available in immediate release dosage form
- Levothyroxine Sodium USP (T4) Pentahydrate and Liothyronine Sodium USP (T3) are pure, bio-identical hormones

Commercial Thyroid USP

- Thyroid Desiccated USP
 - Derived from pork or beef
 - Armour® Thyroid
 - Porcine source
 - Thyroid USP (various manufacturers)
 - Thyroid Strong®
 - Thyrrar® (bovine)
 - S-P-T® (pork thyroid suspended in soybean oil)

Commercial T4

Levothyroxine Sodium (L-thyroxine, T4)

- Synthroid®, Levothyroid®, Levoxyl®, Eltroxin®
- Immediate release tablets and injections available
- No sustained release products
- Many tablets contain lactose which has may interfere with thyroid absorption

Commercial T4

- Absorption issues
 - Degree of oral T4 absorption is dependent on the product formulation as well as character of the intestinal contents
 - Studies have shown absorption varies from 48 to 80%
 - T4 commercial products may contain lactose, reported to interfere with thyroid absorption
 - Significant differences in absorption rates between "bioequivalent" products
 - Tablets may contain less than stated amount
 - Absorption increased by fasting.
 - Absorption decreased by low stomach acid
 - Absorption may be decreased with age

Commercial T3

- Liothyronine Sodium
 - Tri-iodothyronine Sodium, T3
 - Cytomel® tablets 5, 25 and 50 micrograms
 - Triostat® injection 10 mcg/ml
 - Liothyronine Sodium generic 25mcg tablets
- T3 commercial products very limited in strengths available and only available in immediate release dosage form

Iodine Content of Desiccated Thyroid

0.17-0.23% Iodine

1 grain of Desiccated Thyroid
contains: $0.20\% \times 60\text{mg} = \underline{120\mu\text{g}}$

Commercial Thyroid Preparations

- Liotrix
 - Thyrolar® tablets
 - Euthroid® tablets
 - A uniform mixture of synthetic T4 and T3 in a 4 to 1 ratio by weight
 - Manufacturers differed on approximate equivalents to 1 grain thyroid
 - Immediate release

What's In Your Thyroid?

- Compounded Thyroid
 - Levothyroxine Sodium USP (T4) Pentahydrate and Liothyronine Sodium USP (T3) bulk powders are pure, *bio-identical* hormones
 - Immediate release or slow release capsules
 - CoA (Certificates of Analysis) describe contents and purity of each lot

Thyroid Of Choice

- Liothyronine Sodium used most often
 - "Levothyroxine is the agent of choice, rather than a preparation containing tri-iodothyronine (T3), since T3 has a short half-life and requires multiple daily doses to maintain blood levels in the normal range"

*Adlin, V., *Subclinical Hypothyroidism: deciding when to treat*, Am Fam Physician 1998 Feb 15;57(4):776-80.

Before You Medicate with Thyroid

Considerations

- Poor thyroid function can lead to absorption problems and poor nutrient absorption can lead to poor thyroid function
- Hypothyroid skin may affect absorption of lipophilic substances (hormones)
- Gut problems may affect absorption of slow release preparations contain HPMC as well as nutrients
- No one size fits all
- Nothing works as well as the thyroid gland!
 - "Kick-start or 'wake-up' with iodine, Vitamin B-6 L-tyrosine, zinc, magnesium, glutamine

If You Medicate with T4

Considerations

- Patient feels better at 30 day follow up (TSH and T4 "look good"), but symptoms return over next few months
 - Adrenal insufficiency
 - Converting to improper ratio of rT3 to T3 and build up of rT3 occurs
 - Oral thyroid can increase TBG, and increase can take place over several months

Considerations for T3 SR Capsules

- Insoluble filler
 - Microcrystalline cellulose
- Capsule size #1 or larger
- Avoid lactose or calcium as fillers
- Fix the gut
- Quality assurance – potency testing

Considerations for Combined T4 and T3

- T4:T3 ratio is initially arbitrary
- Ratio an strengths adjusted based on
 - Symptoms
 - Body temperature
 - Levels and balance of free T4, free T3 and reverse T3 along with TSH
 - Retest in 60-90 days
- Monitor basal temperatures, lab work, physical exam signs and symptoms

- Most patients are symptomatic because they are converting an excessive amount of T4 into reverse T3.
- Ratios are modified as indicated by the combination of follow up symptom resolution, temperature log results and balance of free T4, free T3, rT3 and TSH in the blood.
- Some patients need T3 gradually released over 24 hours especially as the doses become higher to avoid side effects or to maximize a more even distribution of energy throughout the day and to avoid later afternoon or evening fatigue.

Common Associations with Hypothyroidism

- Iron deficiency
 - Ferritin levels need to be measured, not just iron
- Gluten intolerance
- Leaky Gut
- Chymotrysin deficiency
 - Antigenic challenge to GALT (Gut Associated Lymphoid Tissue)
- Carbohydrate craves and intolerances

John Lee 2004

Diagnosing Hypothyroidism

- History
 - Risks
 - Thyroid evaluation form
 - Signs and symptoms
- Physical exam – signs and symptoms
- Basal Body Temperature
- Laboratory Tests
- Blood tests
 - Serum
 - Blood spot (whole blood)
- Saliva

How To Check The Basal Body Temperature

- Shake thermometer down at night
- In A.M., take axillary temperature before arising for 10 minutes
- Menstruating women should take their temperatures on days 2-4 of cycle
- Normal axillary temperature is 97.8-98.2

Suggested Approaches for Autoimmune Thyroid Conditions

- Use enough thyroid hormones to keep $TSH \leq 1.0$
- Selenium 200-800 mcg daily
- Gluten-free diet for at least 60 days
- Rectify any iodine deficiency
- Remove aspartame, trans fats and processed whole foods from diet
- Magnesium
- Treat any underlying infections
- Correct any hormone imbalances, especially DHEA insufficiency and adrenal dysfunction
- Restore proper gut function
- Avoid Thyroid glandulars

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