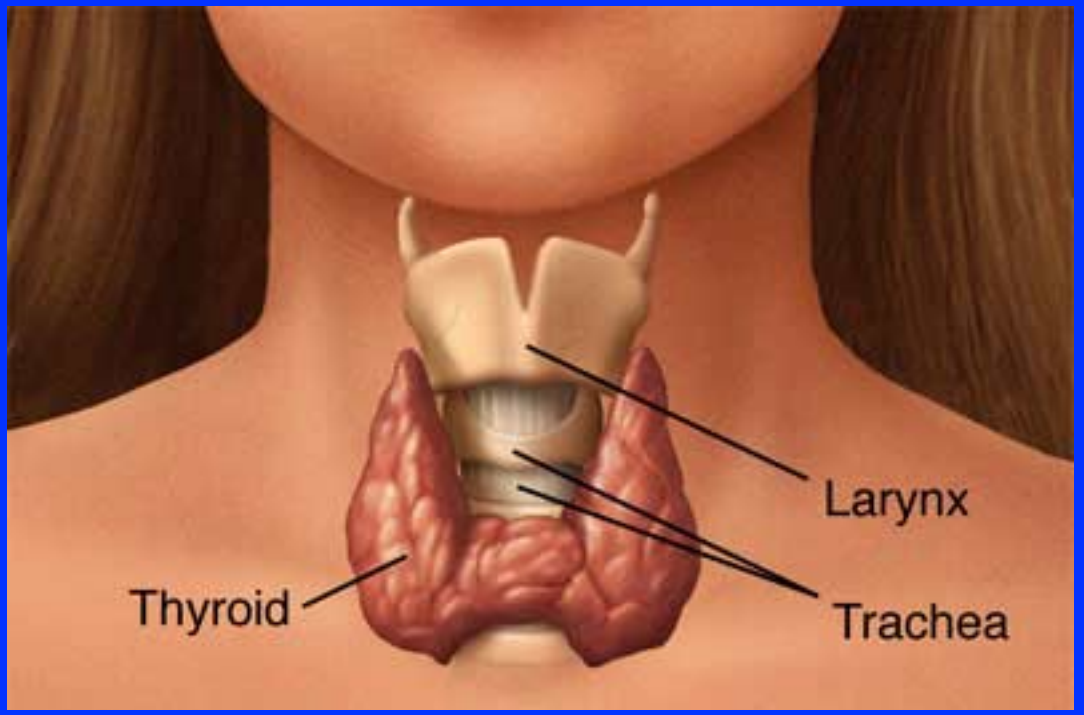
Managing Thyroid Disorders

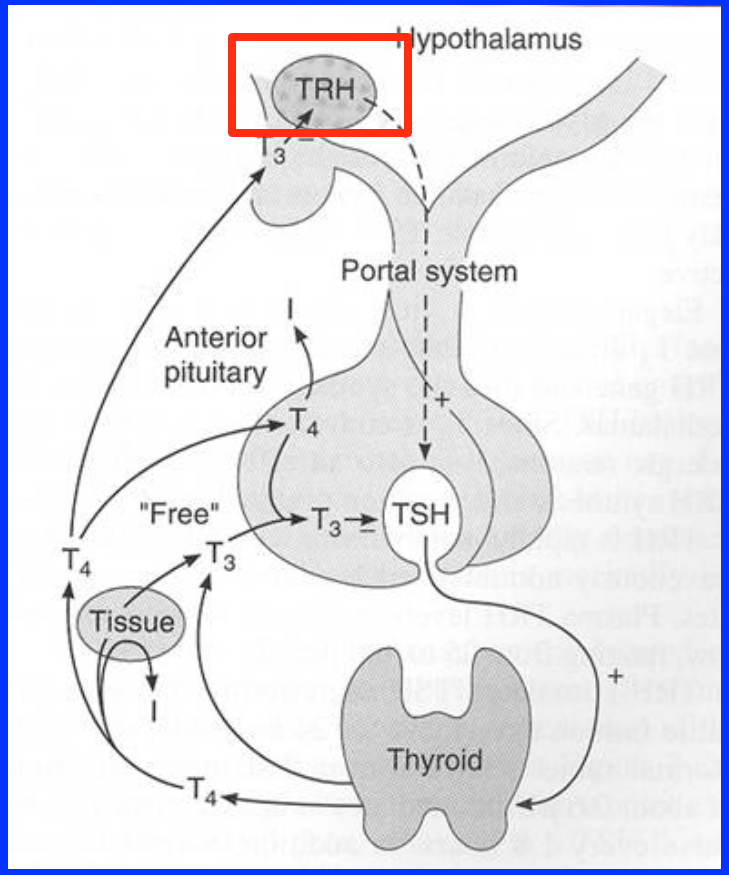


Adil Virani, BSc (Pharm), Pharm D, FCSHP

Outline

- Thyroid Hormone Control 101
- Treating Subclinical hypothyroidism
- Thyroid Disorders
- Goals of therapy
- Hypothyroidism treatments
  - Choice of therapies
- Hyperthyroidism treatments

Thyroid Hormone Control 101

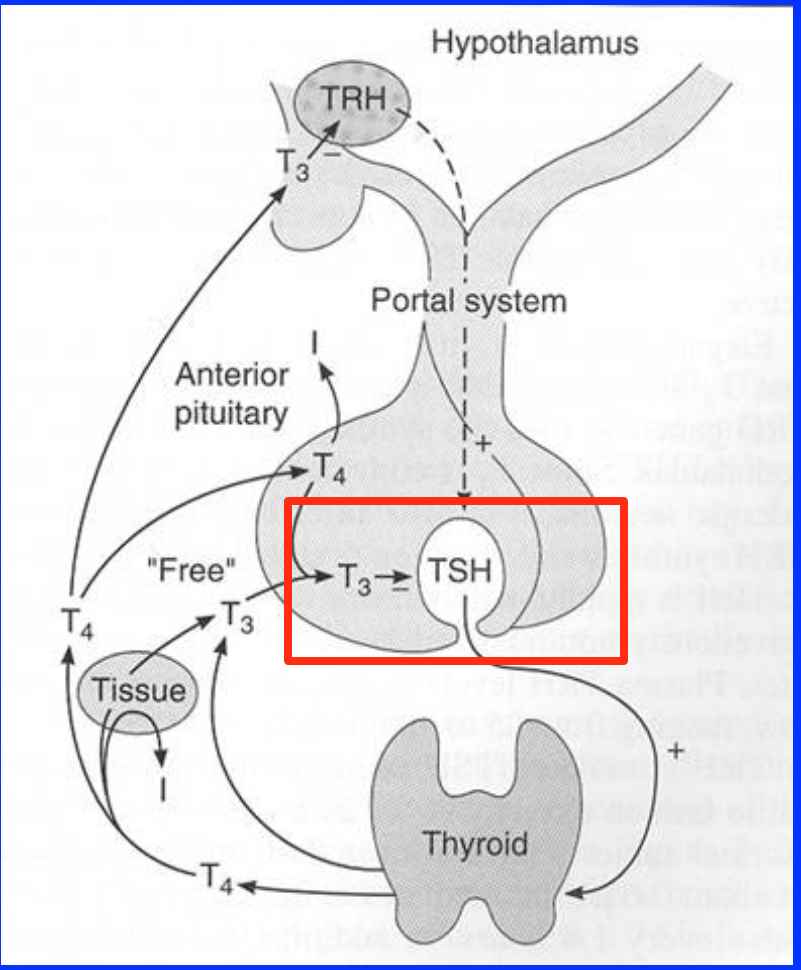


Thyroid Releasing Hormone (TRH)

- Produced by Hypothalamus
- Release is pulsatile, circadian
- Stimulates TSH formation
- Downregulated by T_3

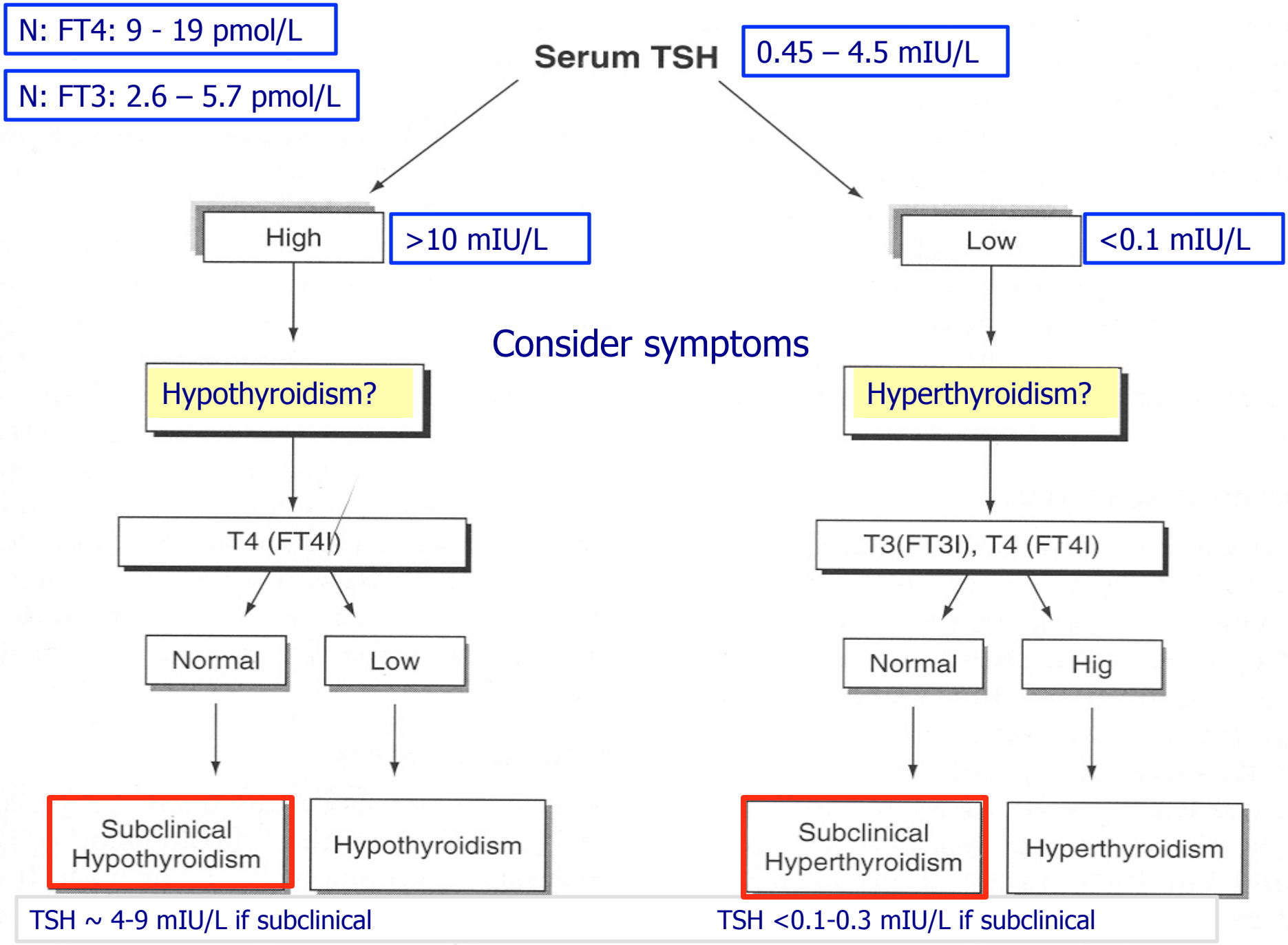
T3 = triiodothyronine; T4 = thyroxine

Thyroid Stimulating Hormone (TSH)



- Upregulated by TRH
- Downregulated by T_4, T_3
- Normal 0.45-4.5 mIU/L
- Best screening test for hypo/ hyperthyroidism (am blood draw)
- Stimulates several processes
  - Iodine uptake
  - Colloid endocytosis
  - Growth of thyroid gland

T3 = triiodothyronine; T4 = thyroxine


N: FT4: 9 - 19 pmol/L
N: FT3: 2.6 – 5.7 pmol/L
Serum TSH
0.45 – 4.5 mIU/L
High
>10 mIU/L
Low
<0.1 mIU/L
Consider symptoms
Hypothyroidism?
Hyperthyroidism?
T4 (FT4I)
T3(FT3I), T4 (FT4I)
Normal
Low
Normal
Hig
Subclinical Hypothyroidism
Hypothyroidism
Subclinical Hyperthyroidism
Hyperthyroidism
TSH ~ 4-9 mIU/L if subclinical
TSH <0.1-0.3 mIU/L if subclinical

Would you treat asymptomatic subclinical hypothyroidism?

- P: 75 yo female with TSH between 6-8 mIU/L and T4 = 13 umol/L (asymptomatic)
- I: T4
- C: Placebo
- O: Improved cognition, overall funcitoning

A Randomized Controlled Trial of the Effect of Thyroxine Replacement on Cognitive Function in Community-Living Elderly Subjects with Subclinical Hypothyroidism: The Birmingham Elderly Thyroid Study

J. Parle, L. Roberts, S. Wilson, H. Pattison, A. Roalfe, M. S. Haque, C. Heath, M. Sheppard, J. Franklyn, and F. D. R. Hobbs

College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham B152TT, United Kingdom

Context: Subclinical hypothyroidism (SCH) and cognitive dysfunction are both common in the elderly and have been linked. It is important to determine whether T_4 replacement therapy in SCH confers cognitive benefit.

Objective: Our objective was to determine whether administration of T_4 replacement to achieve biochemical euthyroidism in subjects with SCH improves cognitive function.

Design and Setting: We conducted a double-blind placebo-controlled randomized controlled trial in the context of United Kingdom primary care.

Patients: Ninety-four subjects aged 65 yr and over (57 females, 37 males) with SCH were recruited from a population of 147 identified by screening.

Thyroxine Replacement on Cognitive Function in Community-Living Elderly Subjects with Subclinical Hypothyroidism

- n=94, 75 y/o, 82% female, BP 145/80, TSH 6.6 (high), Free T_4 12.7 (normal)
- given T_4 or placebo
- at 6-12 months
  - T_4 - TSH was 4 (82% euthyroid), FT_4 =16
  - Placebo - TSH was 6 (35% euthyroid), FT_4 =13

"no significant changes in any of the measures of cognitive function over time and no between-group difference in cognitive scores at 6 and 12 months"

J Clin Endocrinol Metab 2010;95:3623–32

TABLE 1. RCTs of effects on cognitive function of thyroxine replacement in subclinical hypothyroidism

Author	Protocol	Cognitive function tests	Number of subjects	Age (yr)	Sampling frame	Entry criteria and TSH values	Results
Nystrom *et al.* (14)	Randomized to T_4 or placebo (50 μg for 2 wk, 100 μg for 2 wk, 150 μg for 22 wk), then crossed over	Identical forms test, Bingley's memory test, and reaction time to combined light and sound stimuli	20 females	51–73	Population, Sweden	Subclinical hypothyroidism. Mean TSH 7.7 (SD 3.7), range 2.9–16.3	4 of the 17 women improved on T_4
Jaeschke *et al.* (15)	Randomized to T_4 or placebo (25 μg for 1 month, 50 μg for 1 month, then dose titrated at monthly intervals against TSH to achieve biochemical euthyroidism); total length 40 wk	Composite psychomotor speed: subsuming word fluency, digit symbol substitution, and Trail Making; composite memory score: subsuming logical memory and word learning	37 (12 females, 6 males in active arm; 16 females, 3 males in placebo arm)	≥55 (mean 68 in both arms)	Not defined	Subclinical hypothyroidism; active arm (n = 18) mean TSH 12.1 (SD 6.8), range 6–32.4; placebo arm (n = 19) mean TSH 9.4 (SD 3.1), range 6–16.5	Composite psychomotor speed scores, NS; composite memory score improved in treatment group (mean change in z-score 0.58 (P = 0.01; 95% CI = 0.14–1.03)
Jorde *et al.* (17)	Randomized to T_4 or placebo in increasing doses (50 μg for 6 wk, 100 μg for 6 wk, then dose titrated at 3-monthly intervals according to TSH to achieve	Attention and working memory: digit span forward, digit span backward; seashore rhythm test; psychomotor/ cognitive speed: Trail Making Test A, Stroop test, parts 1 and 2, digit Symbol test; memory:	69 (17 females, 19 males in active arm; 15 females, 18 males in placebo arm)	29–75 (mean 61.6 in T_4 arm, 63 in placebo arm	Population study, Tromso, Norway	Subclinical hypothyroidism; active arm (n = 36) mean TSH 5.81 (SD 1.76); placebo arm (n = 33): mean TSH 5.32 (SD 1.25)	No significant differences in any tests

J Clin Endocrinol Metab, August 2010, 95(8):3623–3632

Subclinical thyroid disorders

No large randomised controlled trials in subclinical hyperthyroidism nor subclinical hypothyroidism have used robust clinical endpoints, particularly cardiovascular morbidity and mortality. Despite this absence of evidence, David Cooper and Bernadette Biondi (March 24, p 1142)[1] make rather strong recommendations favouring treatment in both situations, particularly for patients with concentrations of thyroid-stimulating hormone below 0·1 mU/L or above 5·0 mU/L.

Authors' reply

Bernard Goichot and Stéphane Vinzio state that we make "rather strong recommendations" favouring treatment of subclinical thyroid dysfunction. Our recommendations to treat were for patients with the most extreme degrees of subclinical hyperthyroidism and hypothyroidism (serum thyroid-stimulating hormone [TSH] <0·1 mU/L and >10 mU/L, respectively), and to "consider" individualised treatment for milder degrees of thyroid impairment, taking the patient's age and associated risk factors into account. Obviously, the treatment should not be worse than the disease. Goichot and Vinzio correctly point out that both mild subclinical hyperthyroidism and subclinical hypothyroidism represent risk factors for future comorbidity rather than diseases, although some patients do have mild symptoms, and subclinical hypothyroidism in pregnancy is clearly associated with many adverse outcomes.

TSH Screening

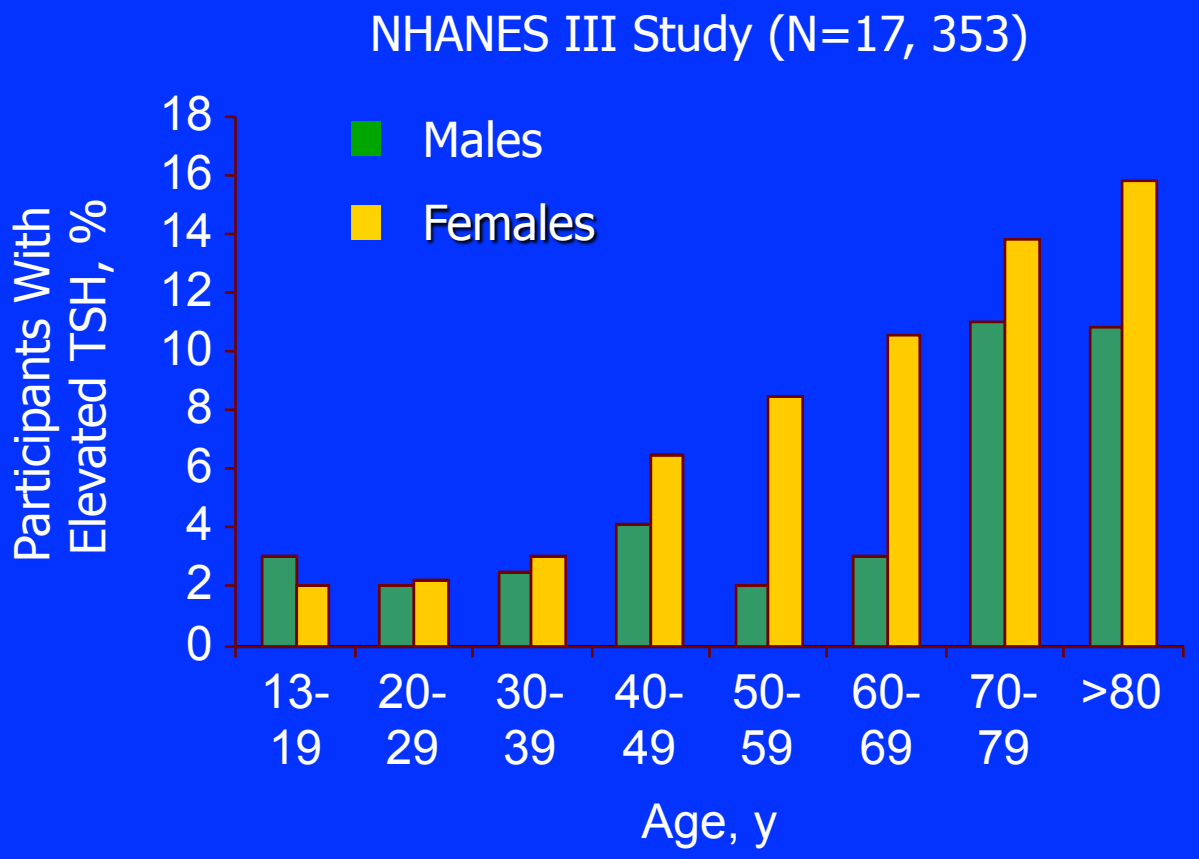
- High risk patients
  - Family history of thyroid disease
  - Thyroid disease signs and symptoms or thyroid surgery
  - Females older than 45 years old
  - Those with autoimmune disease (T1DM, RA, viiligo, Sjogren's syndrome)
  - Drugs (e.g., amiodarone, lithium)
  - Psychiatric diagnosis
  - Pernicious anemia
  - Neck radiation
  - Pregnancy or postpartum

TSH Screening Continuted

- Note: changes in TSH could be abnormal in people with hypothalamic or pituitary disease.
- TSH can be suppressed by some medications (corticosteroids, domperidone, metoclopramide, dopamine)

American Thyroid Association: thyroidguidelines.org.

Prevalence of Elevated Serum TSH by Decade of Age and Gender



- At <40 yrs old, prevalence is low and similar btwn genders
- At ≥40 yrs old, higher percentage of female patients and have elevated TSH levels

Hollowell JG, et al. *J Clin Endocrinol Metab*. 2002;87:489-499.

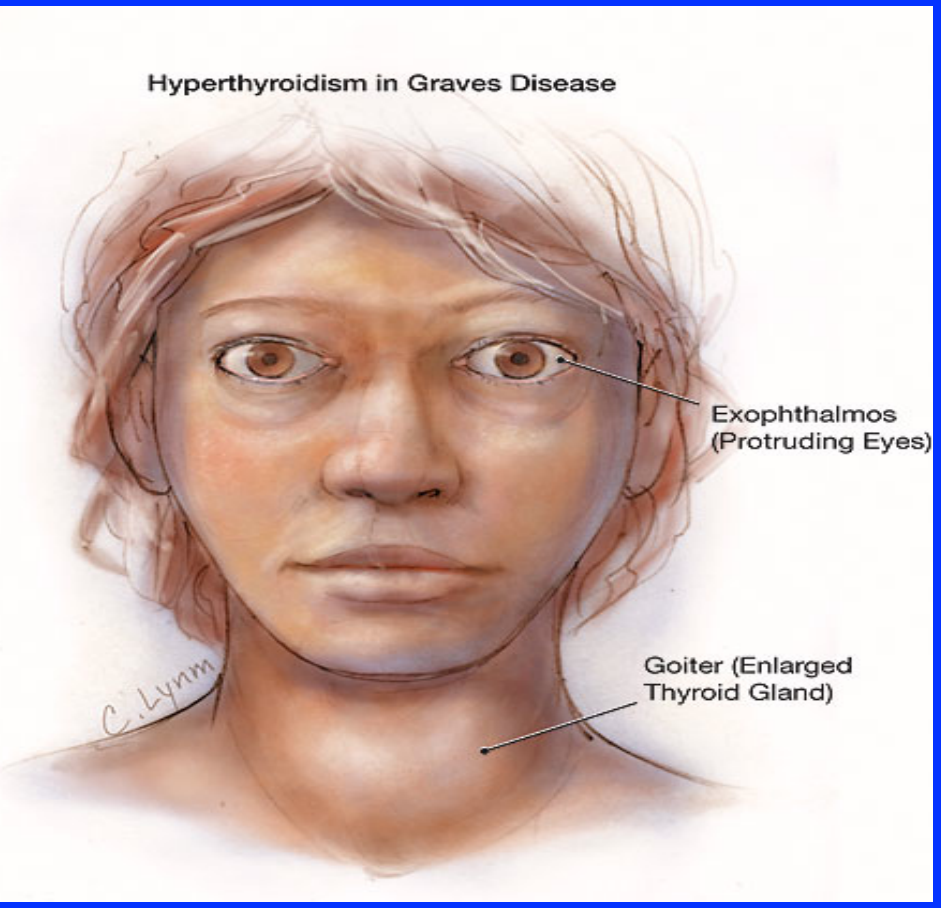
Common Thyroid Disorders

- Goiter: Chronic enlargement of the thyroid gland not due to neoplasm
  - Endemic (>5%), Sporadic (<5%), Familial goiter
  - Hashimoto's
    - May present with hypo, hyper, or euthyroid states
  - Graves' disease
    - Due to chronic stimulation of TSH receptor
  - Diet
    - Brassica (cabbage, turnips, cauliflower, broccoli), Cassava
  - Chronic excess Iodine (which leads to increased colloid formation and can prevent hormone release)
  - Medications
    - Lithium, amiodarone, sulfonylureas
  - Iodine deficiencies

Hypothyroidism

- Prevalence ~2% in females (0.1% in males)
- Symptoms – fatigue, cold intolerance, weight gain, poor concentration, constipation, emotional lability, menorrhagia
- Signs – Cool dry skin, swelling of face/hands/legs, slow reflexes, myxedema, decrease heart rate
- Newborn – Retardation, short stature, swelling of face/hands, possible deafness
- Types of Hypothyroidism
  - Primary – Thyroid gland failure
  - Secondary – Pituitary failure
  - Tertiary – Hypothalamic failure
  - Peripheral resistance

Hyperthyroidism



- Prevalence ~1% in females
- Symptoms:
  - tremor, nervousness
  - ophthalmophathy
  - heat intolerance
  - weight loss
  - diarrhea
  - weakness
  - perspiration
  - menstrual changes
- Signs:
  - increase Ca^{2+}
  - tachycardia
  - warm, smooth skin

Goals of Therapy

- Hypothyroidism
  - Resolve signs and symptoms
  - Restore thyroid hormones (thyroxine) to normal levels
  - Improve quality of life
- Hyperthyroidism
  - Resolve signs and symptoms
  - Restore a eumetabolic state
  - Improve quality of life

Singer PA, et al. *JAMA*. 1995;273:808-812.

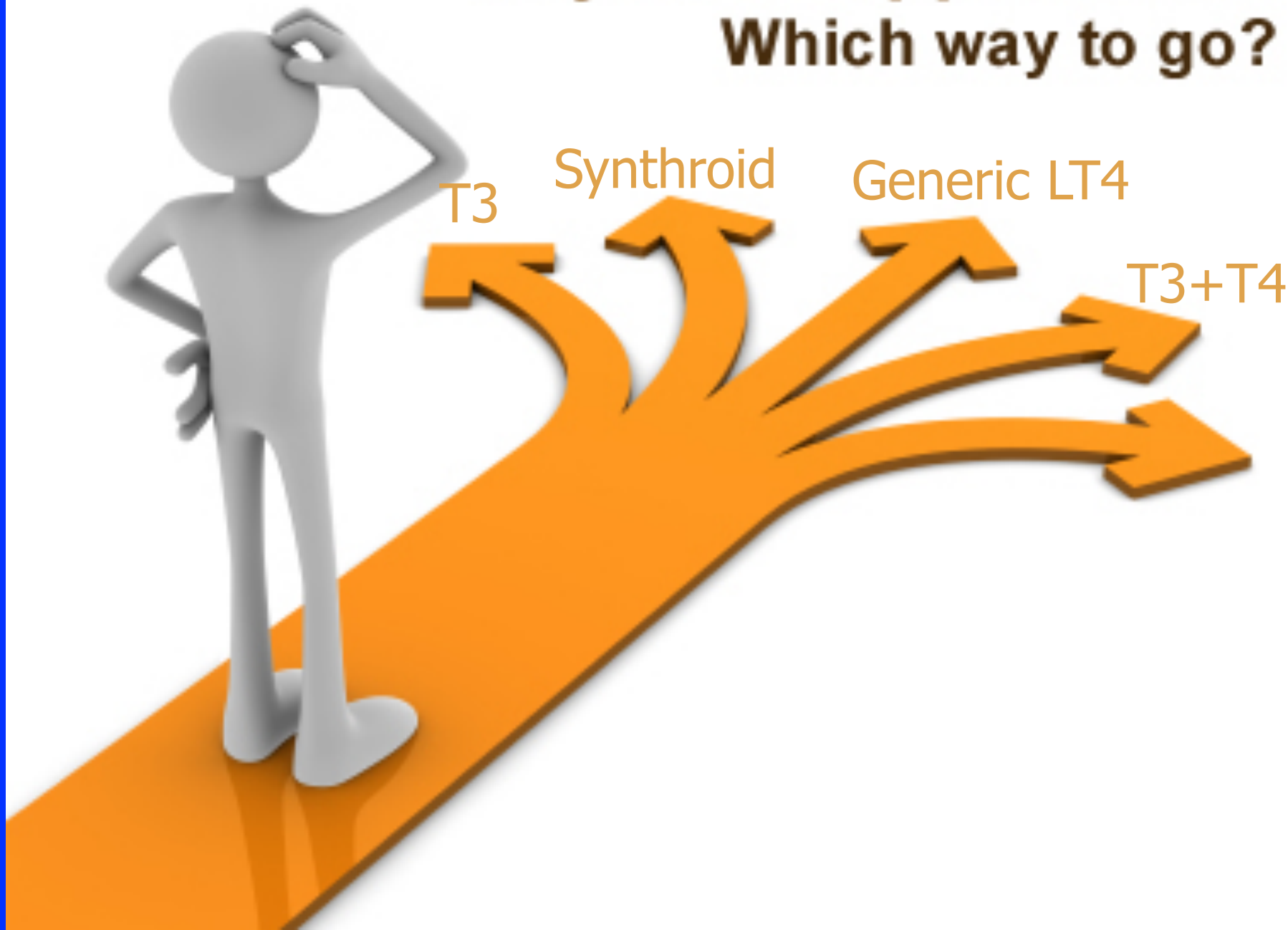
Treatment of Hyperthyroidism

- Antithyroid drugs
  - e.g., propylthiouracil (PTU), methimazole
  - Inhibit the synthesis of T_4 and T_3
- Surgical resection
  - Remove hyperplastic and adenomatous tissues
  - Restore normal thyroid function and, consequently, pituitary function
- Radioactive iodine therapy
  - radioactive iodine (^{131}I), taken up by functioning thyroid tissue can decrease thyroid hormone production
- Beta blockers to decrease symptoms

Braverman LE, et al. *Werner & Ingbar's The Thyroid. A Fundamental and Clinical Text*. 8th ed. 2000.

Thyroid Supplements

Which way to go?



Treatment of Hypothyroidism

- First line: levothyroxine (LT_4)
  - Chemically stable
  - T_4 converted to T_3 in periphery
    - Adults: about **1.7 μg/kg/d**
    - Children **up to 4.0 μg/kg/d**
    - Elderly **<1.0 μg/kg/d**

- Other therapies (T_3 or T_3 and T_4 mixtures)
  - Thyroid USP, liothyronine, liotrix, thyroglobulin
  - **No advantages vs levothyroxine**

Singer PA, et al. *JAMA*. 1995;273:808-812.
Endocr Pract. 2002;8:457-469.
Braverman LE, et al. *Werner & Ingbar's The Thyroid. A Fundamental and Clinical Text*. 8th ed. 2000.

Thyroxine-Triiodothyronine Combination Therapy Versus Thyroxine Monotherapy for Clinical Hypothyroidism: meta-analysis

- 11 studies - 1216 patients
- 5 weeks - 9 months
- Outcomes included: bodily pain, fatigue, anxiety, depression, insomnia, quality of life, adverse events - no difference
- no difference in biochemistry results

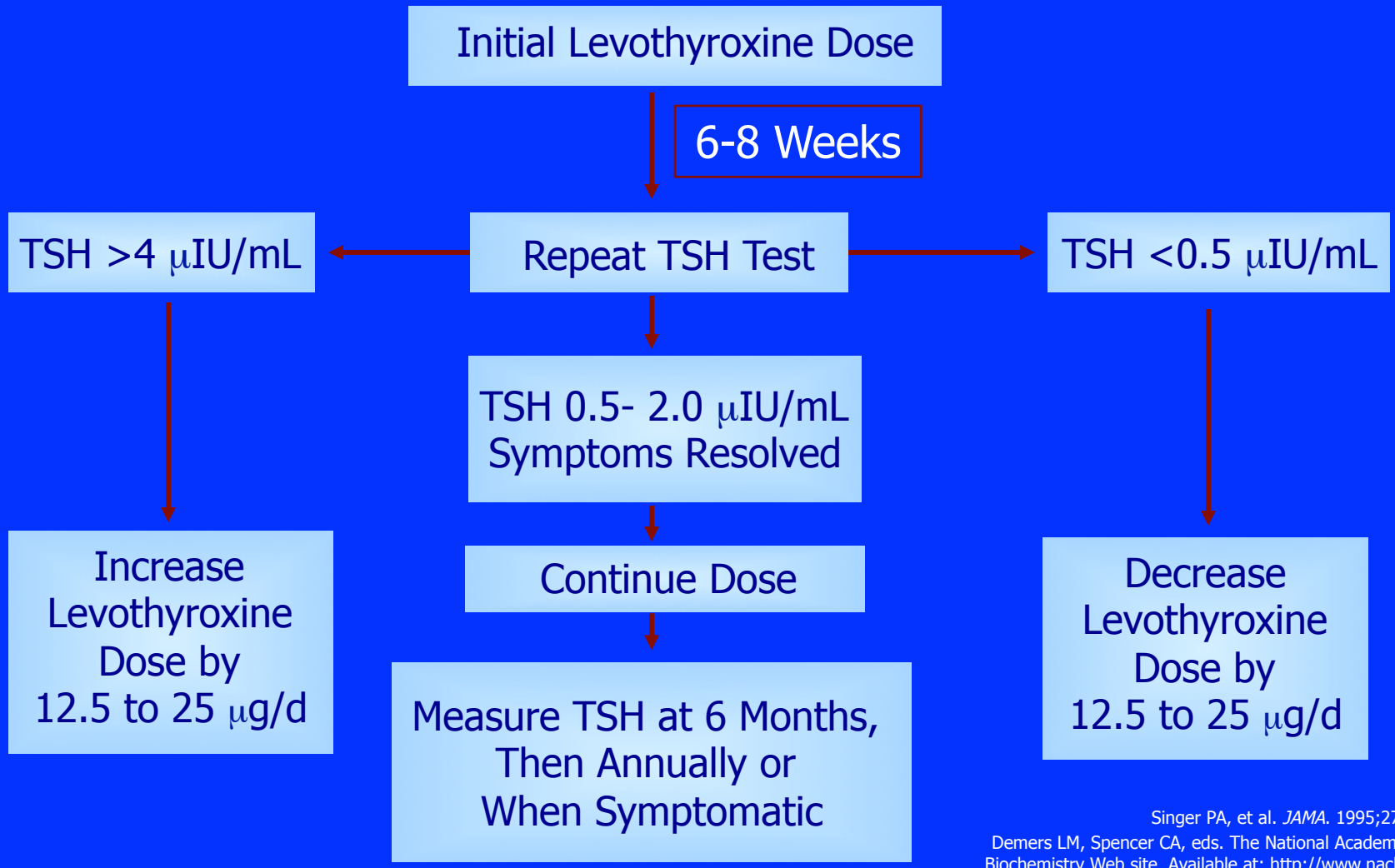
J Clin Endocrinol Metab 2006;91:2592–9

Desiccated Animal Thyroid Extract (DATE)

- DATE, which contains T_3 and T_4, is not recommended because it produces variable serum T_4 levels compared with pure thyroxine preparations and its potency varies widely from batch to batch.
- T_4 is converted to T_3 in the bloodstream making exogenous administration of T_3 products unnecessary.

Braverman LE, et al. *Werner & Ingbar's The Thyroid. A Fundamental and Clinical Text*. 8th ed. 2000.

Primary Hypothyroidism Treatment Algorithm



Singer PA, et al. *JAMA*. 1995;273:808-812.
Demers LM, Spencer CA, eds. The National Academy of Clinical Biochemistry Web site. Available at: http://www.nacb.org/lmpg/thyroid_lmpg.stm. Accessed Aug. 2007

Clinical Pearls

- When considering TFTs (TSH, T4, T3, antithyroid peroxidase (anti-TPO)), consider symptoms and correlate the previous 6-8 weeks
- Wait 6-8 wks after LT_4 dose change before rechecking TSH
- Total T_3 and T_4 not useful for surveillance (first check TSH alone)
- T_3 (Lyothyronine) is used primarily for the short term management of thyroid cancer (pts undergoing T4 withdrawal)

Factors that may reduce Levothyroxine effectiveness

- Compliance
- Malabsorption (e.g., short bowel syndrome, celiac dx, postjejunoileal bypass surgery)
- Drug interactions (Ca^{2+}, Fe^{2+}, antacids, cholestyramine, colestipol, sucralfate, carbamazepine, rifampin, lovastatin, sertraline)
- Other disorders (adrenal)

Iron Ingestion and Levothyroxine Therapy

Ferrous Sulfate Effect on TSH Levels in Patients With Hypothyroidism

Campbell NR, et al. *Ann Intern Med*. 1992;117:1010-1013.

Questions?