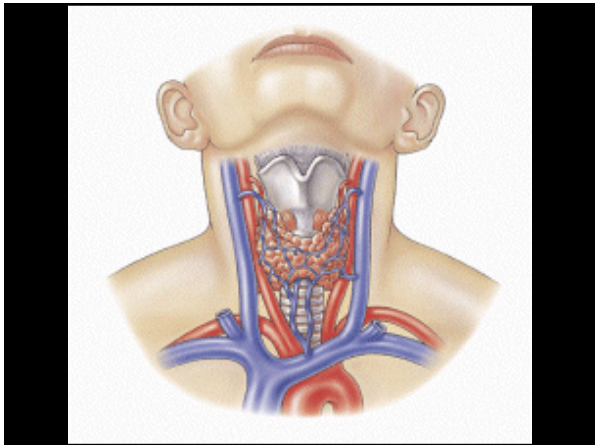


The Thyroid

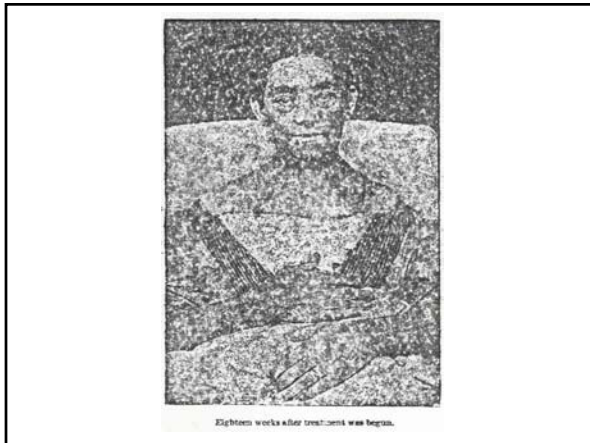
...an introduction

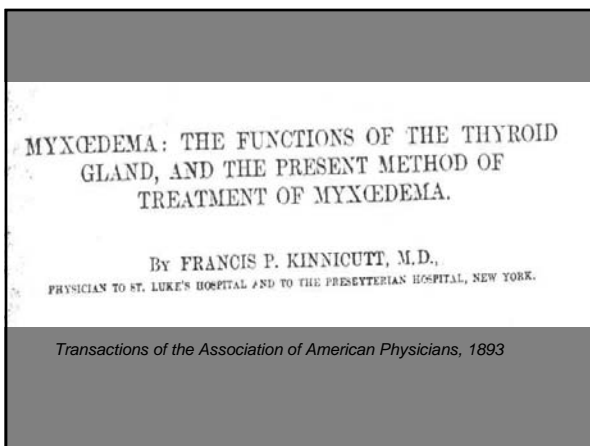




19th Century Thyroidology...

- **Dr. Kinnicutt's patient (1893)**
A cold, tired, constipated middle aged woman
Slow pulse rate
Low body temperature
- **From physiology... it was likely patient needed thyroid replacement**
How to give this?
∞ *It had never been done before!*
- **The search for thyroid extract...**





A 21st Century Counterpart

A patient

You are seeing a thirty eight year old woman who complains of being tired. She tells you she is cold all the time and is constipated and lethargic. She takes no medicines except vitamins and laxatives.

Her past history is unremarkable. A sister has diabetes. She has a nine year old son with mild intellectual impairment. She recalls something "about" her thyroid during her pregnancy.

Physical examination revealed a sluggish woman with BMI of 31 kg/m² and blood pressure was 110/66 mm Hg. Temperature was 96° F.

A patient (continued)...

She had prominent bags under her eyes and looked "puffy." Her thyroid gland could not be felt with certainty.

She had "hung up", slow deep tendon reflexes.

Laboratory studies:

FT₄: 0.3 ng/dL {0.9 - 1.7}

FT₃: 62 pg/dL {230 - 420}

TSH: 198 mIU/L {0.25 - 3.0}

Anti-TPO Antibodies: 1880 IU/mL {<35}

Total cholesterol 262 mg/dL {112 - 199}

LDL cholesterol 176 mg/dL {< 130}

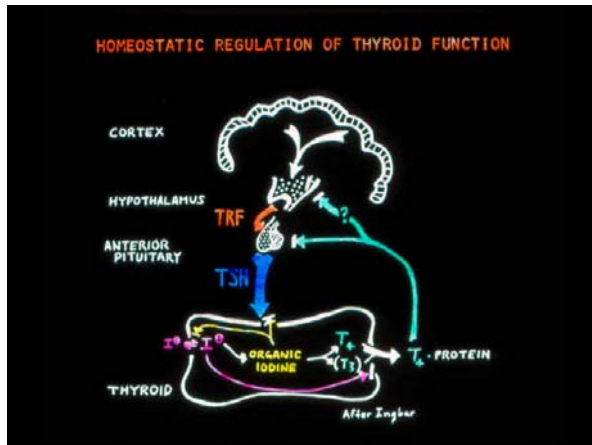
What is wrong with this woman?

What is the significance of her symptoms?

What do the physical findings mean?

What do the laboratory numbers mean?

How should she be treated?
...to be discussed



Thyroid Function

- Regulates basal metabolic rate
- Enhances cardiac contractility
- Enhances bowel motility
- Increases speed of muscle contraction
- Regulates LDL metabolism
- Myriad effects in the brain
- Synergizes with catecholamines
- Required for fetal neural growth and early development

The patient has hypothyroidism!

The low fT_4 , low fT_3 , and high TSH (thyrotropin) prove the diagnosis!

Like Dr. Kinnicutt's patient, she needs oral thyroid hormone replacement.

Hypothyroidism

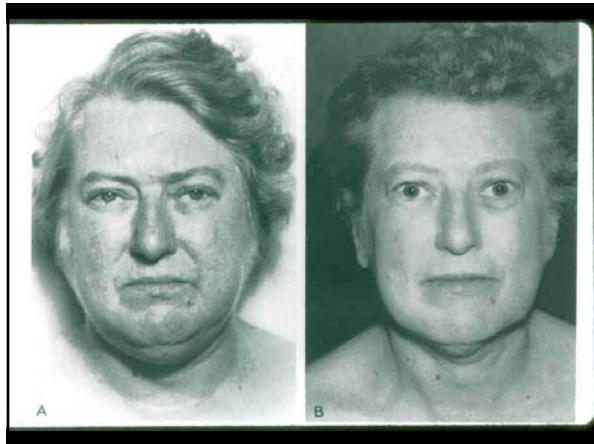
- **Common symptoms:** mild weight gain; depression; coldness, constipation, fatigue

n.b. These symptoms may (and very often DO) exist in absence of hypothyroidism!

- **Common physical signs:** thick hair; dry, cool skin; "hung-up" reflexes; bags under eyes
 - ∞ **In children:** cretinism; poor growth rate; deafness
- **Laboratory:** Low fT_4 , low fT_3
In "primary" hypothyroidism, TSH is high, LDL cholesterol is high
- **Treatment:** Oral thyroxine (T_4)

Hashimoto's Disease

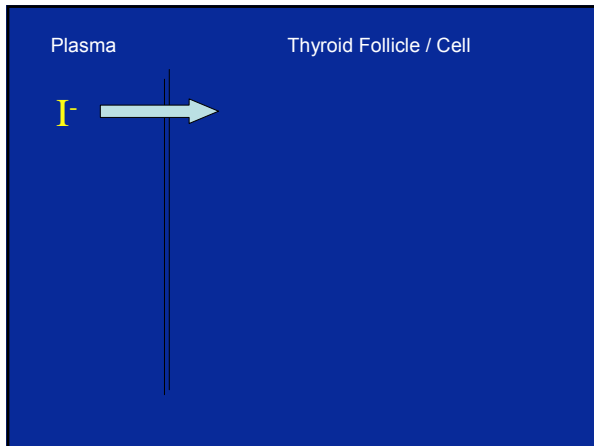
- Most common cause of hypothyroidism in North America
- Autoimmune (ass'd with anti-TPO Ab's)
- lymphocytic thyroiditis
- Women > Men, Runs in families
- May be "subclinical" for years

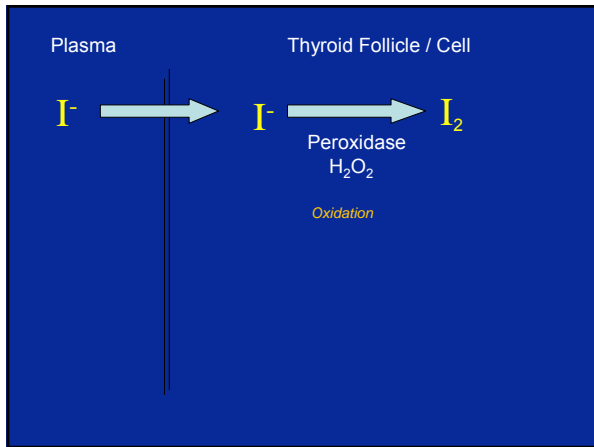


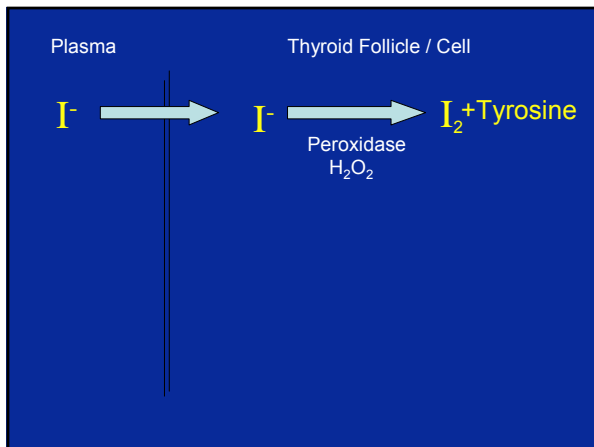
...about iodine metabolism...

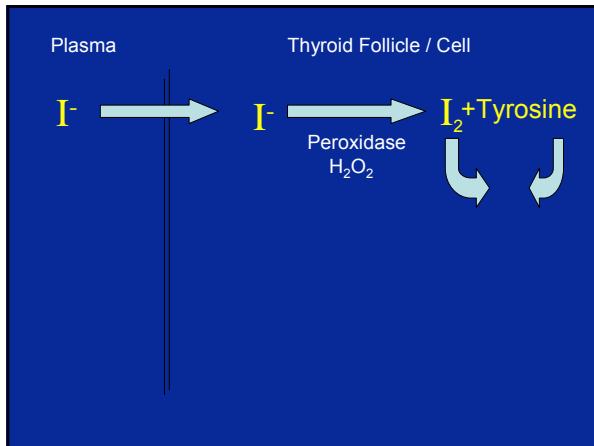
Iodine Metabolism

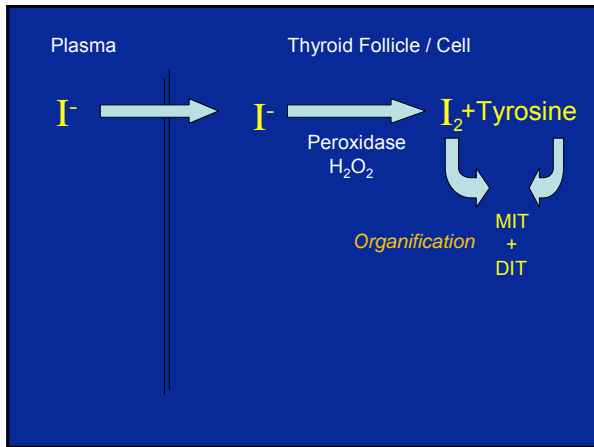
- Iodide intake in U.S.: ~ 300 -1000 $\mu\text{g}/\text{day}$ (salt, flour)
- I^- absorbed: 300 $\mu\text{g}/\text{day}$
- MDR: 75 $\mu\text{g}/\text{day}$
- Most Iodide is excreted in urine.
 - ¶ Nearly all the rest is taken up by the thyroid
 - 1) Uptake and oxidation
 - 2) Organified (bound to tyrosine in thyroglobulin)
 - 3) Tyrosine + $\text{I}^- \rightarrow \text{MIT} + \text{DIT}$
 - 4) MIT + DIT coupled to T_3 & T_4
 - ¶ Stored in colloid in gland, released as T_3 , T_4 , TG

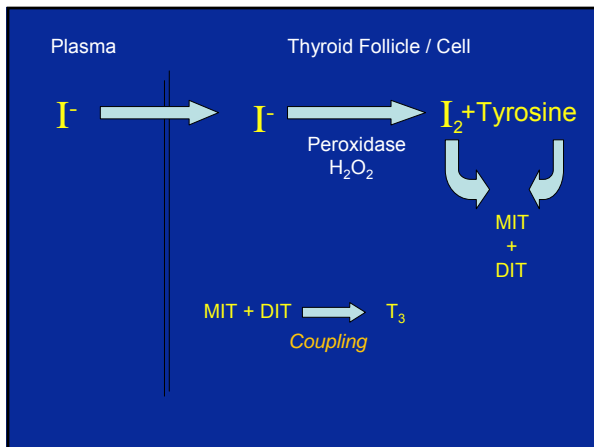


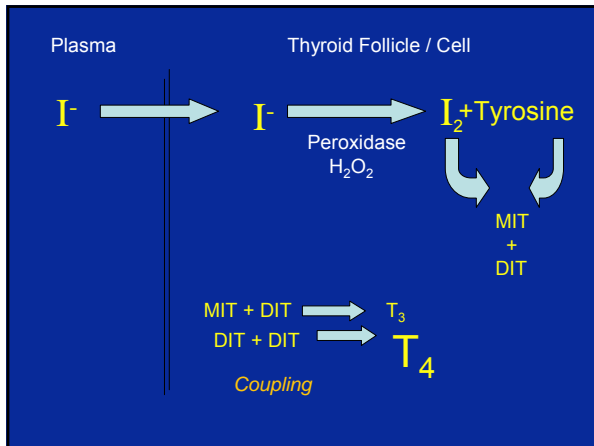


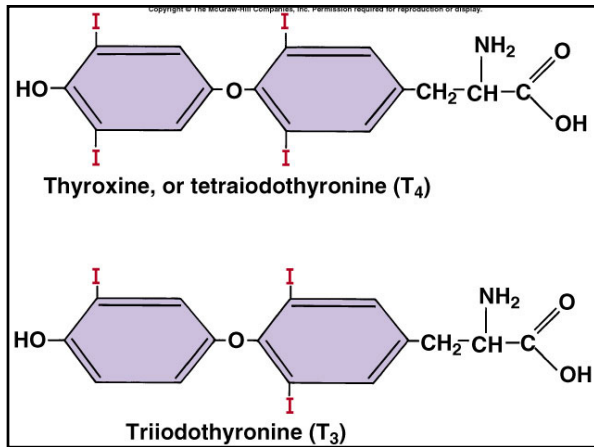


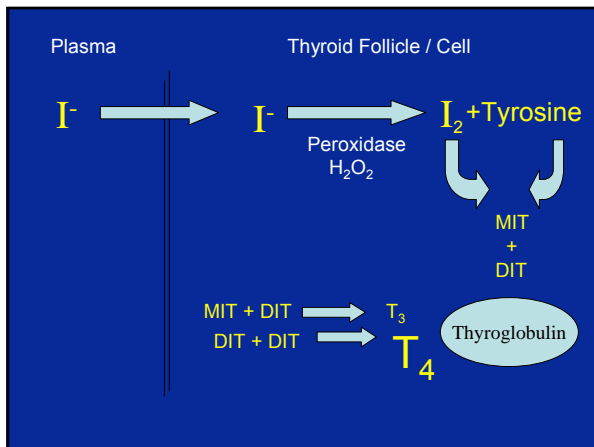


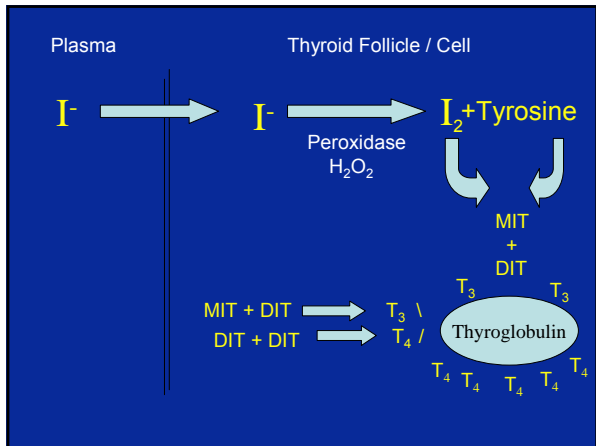


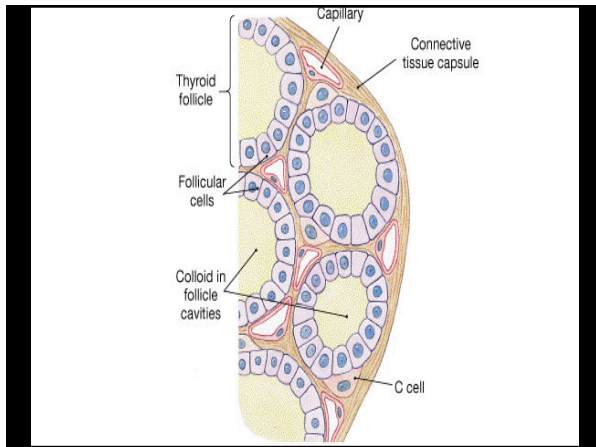


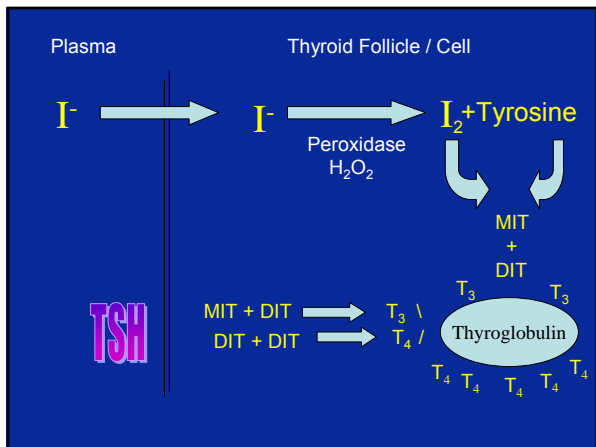


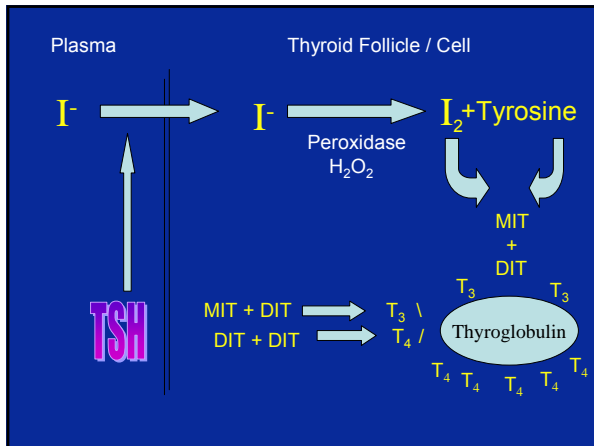


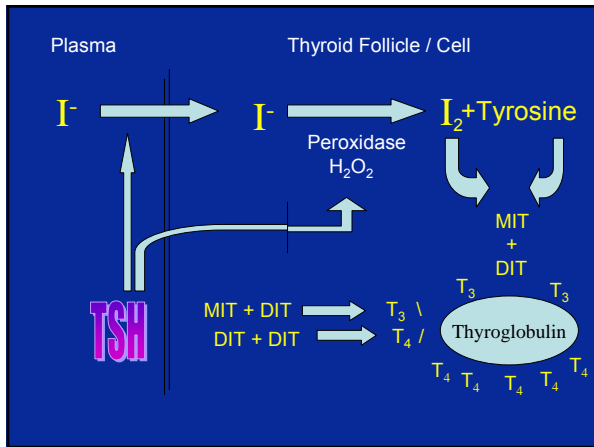


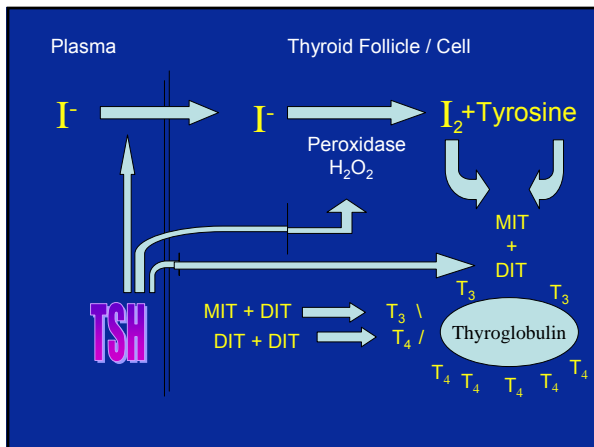


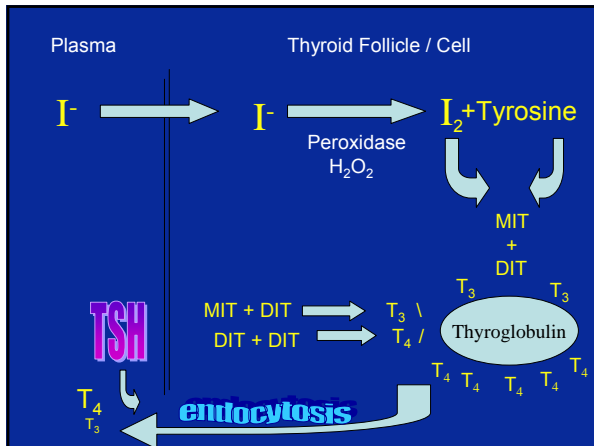


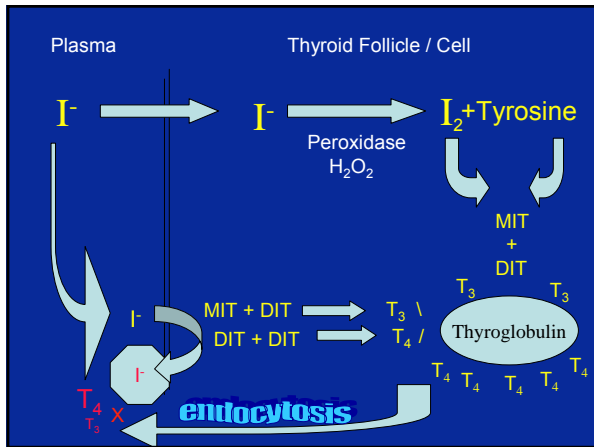




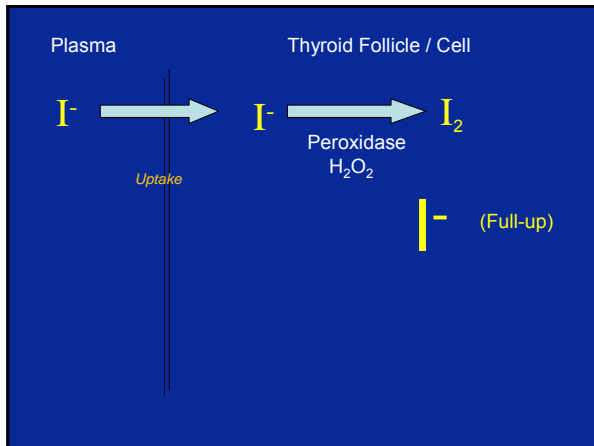


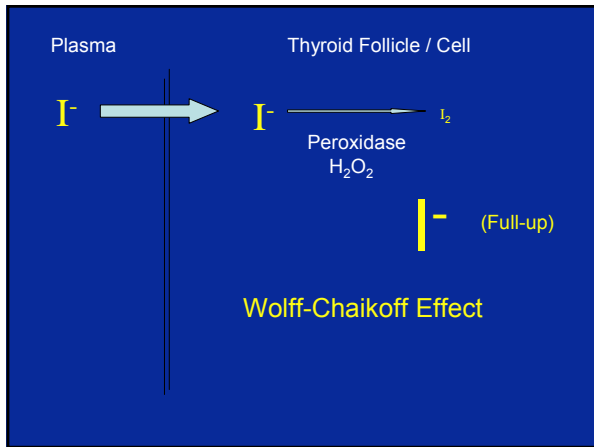


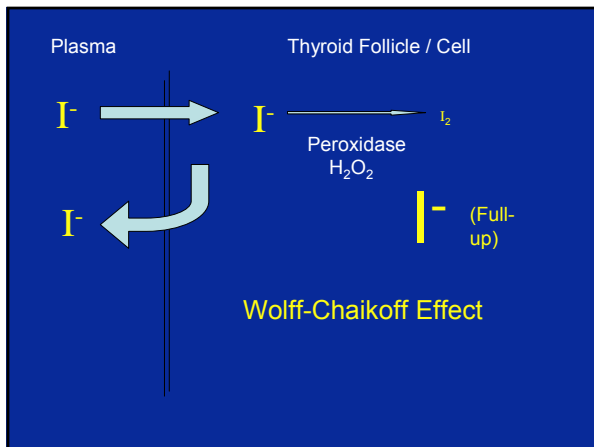




Iodine metabolism in thyroid disease



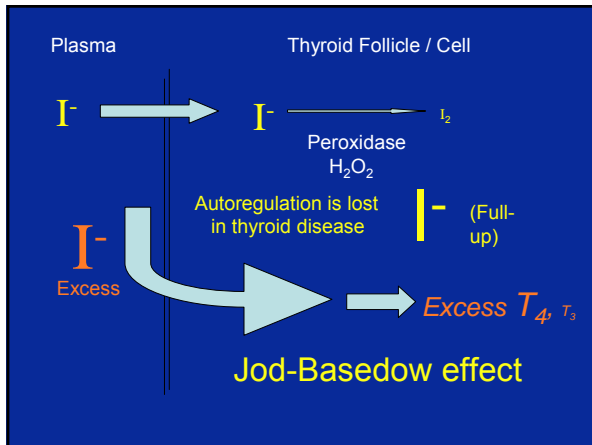




Wolff-Chaikoff Effect

With Normal Autoregulation:

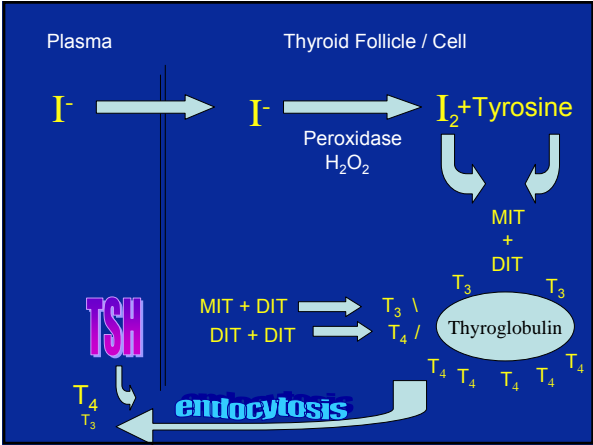
- When iodine is abundant, binding and organification of iodide increase TO A POINT
- Beyond that point, both functions diminish sharply
- Iodide blocks thyroid from making excess hormone

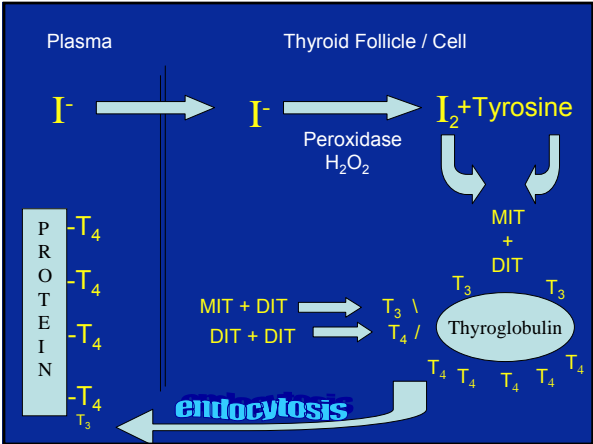


Jod-Basedow Effect

- In thyroid disease, normal Wolff- Chaikoff autoregulation may be lost.
- Thyroid cells lose
 - 1) ability to restrict importation of iodide
 - 2) ability to have hormone output blocked by iodide
- The higher the iodide load outside the thyrocyte, the greater the iodide imported.
- Thyroid hormone production parallels iodide intake even when iodide levels are very high.
- This may result in goiter, severe hyperthyroidism.
- Occurs in "hot" nodules, Graves' disease.

...on the transport of thyroid hormone in the circulation





DIFFERENCE BETWEEN FREE T₄ (fT₄) AND FREE T₃ (fT₃)

- Free T₄ (thyroxine)** 0.001% of total circulating T₄
- The more abundant of the two circulating hormones
 - Most closely reflects thyroid function status
 - § High in hyperthyroidism (~ 90-95%)
 - § Low in hypothyroidism
 - Equilibrates in 2-3 weeks after change in patient's thyroid status
 - A *pro-hormone*: T₄ is metabolically inactive; it must be converted to T₃ for hormone action
- Free T₃ (triiodothyronine)** 0.01% of total circulating T₃
- The active form of thyroid hormone
 - Virtually always indicates hyperthyroidism when elevated

Thyroid tests over the years

- Basal metabolic rate
- Protein bound iodine
 - Distorted by iodine load
- Protein bound hormone (Total T₄, Total T₃, "Uptake" tests)
 - ↓ Distorted by abnormal TBG, albumin
 - ↓ Largely obsolete (Serum protein dependent)
 - "Free thyroxine index": a mathematical "fix"
- Free T₄, free T₃
 - In current use

hormone)

- The most accurate reflector of thyroid status
- Patient must be in **steady state**
 - § Treating a patient (i.e., thyroidectomy, change in thyroxine dose, etc.) may lead to rough useful changes in fT₄ (and fT₃) in 2-3 weeks, but several weeks to (occasionally) months may be needed for TSH to be accurate
- TSH is *suppressed* in hyperthyroidism
 - § Exceptions exist
- TSH is *high* in hypothyroidism
 - § Exceptions exist

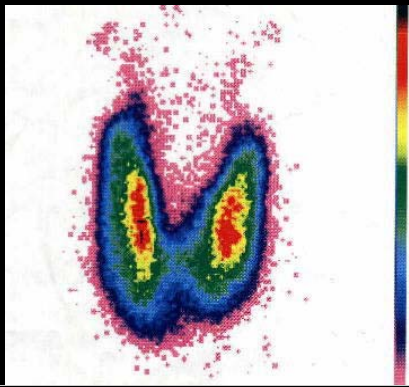
Radionuclide uptake and scanning

Functioning thyroid tissue takes up radioiodine.

§ Useful for

- Measuring isotope uptake
 - *Roughly* correlates with thyroid status
 - ∞ *NOT a substitute for chemical tests*
 - ∞ *May be blocked by non-radioactive iodide, filling binding sites*
- Looking for anatomical lesions (and cancer)
- Treatment of Graves' disease, "hot" nodules, most thyroid cancers

Normal Thyroid Scintiscan

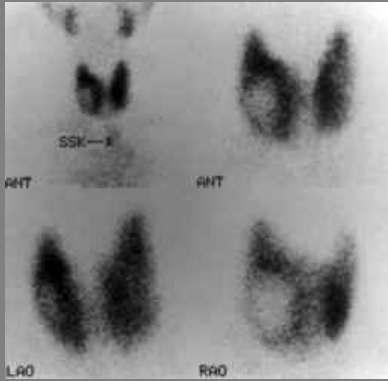


What is a thyroid nodule?

Hot Nodule



Follicular Carcinoma - Scintiscan



**A nodule is a lump
in the thyroid gland...**

Ultrasound-guided FNA



Caveats on thyroid nodules

- *May be single or multiple*
- *Cancer is uncommon, but nodules are common*
- *A multinodular gland is much LESS likely to harbor a cancer than a gland with a single nodule*
- *A single nodule in a young person, especially a young man, is likely to be cancer and should be biopsied*

Caveats on thyroid nodules

- *Nodules > 1.0 - 1.5 cm in diameter should be considered for FNAB*
- *Nodules > 3 - 4 cm in diameter should be considered as suspect and considered for removal*
- *Thyroid hormone therapy does NOT usually shrink them!*

The **worst** thyroid test...

SYMPTOMS!

Doctor, I'm...

- **VERY** tired **ALL** the time
- **Cold** all the time
- **Hot** all the time
- **Anxious; depressed; nervous**
- **Gaining** weight
- **Losing** weight (*rare*)
- **Losing** hair
- **Constipated**
- **Having** diarrhea
- **Etc....**

Symptoms may be useful, especially in **extreme** hyper- or hypothyroidism, but are very often **misleading** and **SHOULD NOT BE USED AS A PRIMARY GUIDE TO THERAPY.**

A DEFINITION OF THYROIDITIS

An inflammation of the thyroid gland caused by hereditary, autoimmune, and/or exogenous factors. It may be chronic or acute, painful or painless, producing a syndrome that may entirely remit and resolve, permanently or temporarily. It is commonly associated with hypothyroidism, but may be preceded by hyperthyroidism.

Spectrum of Autoimmune Thyroiditis

- Euthyroidism with (+) Antibodies (+/- palpable abn)
- Subclinical hypothyroidism (Ab's present in 95%)
- Clinical hypothyroidism (*goiter or atrophic*)
- Transient (silent) thyroiditis
- Postpartum thyroiditis
- Transient neonatal hypothyroidism (*maternal Ab's*)

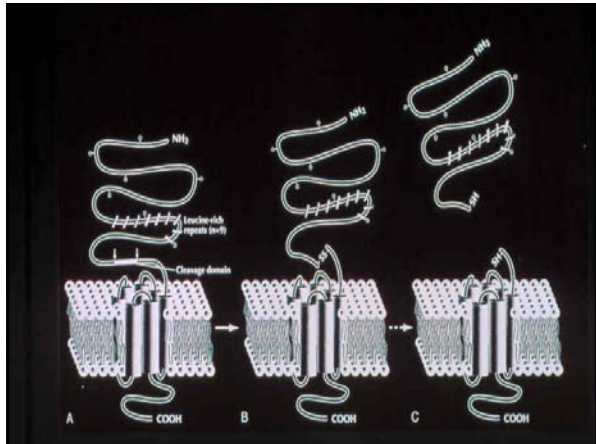
Also: Graves' disease...

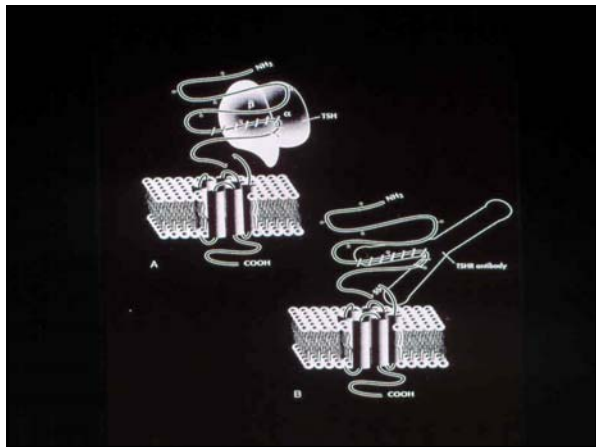
TSH RECEPTORS (MAJOR GRAVES' AUTOANTIGENS)
OCCUR IN 3 COEXISTING FORMS

- UNIT FIRST APPEARS ON THYROCYTE MEMBRANE AS INTACT HOLORECEPTOR
- THIS IS PROCESSED INTO A 2-SUBUNIT FORM
 - § SEPARATE ECTODOMAIN (ALPHA SUBUNIT)
 - § TRANSMEMBRANE (β -SUBUNIT) LINKED S-S
- SOME ALPHA SUBUNITS ARE SHED, LEAVING MEMBRANE-ANCHORED β -SUBUNITS THAT BIND TSH WITH HIGH AFFINITY

TSH RECEPTOR ANTIBODIES (TSHR)

- TSHR MAY BE ACTIVATED (NORMALLY) BY TSH
- TSHR MAY BE ACTIVATED BY TSHR ANTIBODY
 - ~ ANTIBODY BINDS TO ECTODOMAIN EPITOPES
 - § EITHER BLOCKS OR STIMULATES TSH ACTION
 - § GAIN-OF-FUNCTION MUTATIONS IN TRANSMEMBRANE LOOPS MAY INDUCE CONSTITUTIVE ACTIVITY
 - ↔ GRAVES DISEASE
 - § LOSS-OF-FUNCTION MUTATIONS MAY → HYPOTHYROIDISM
- TSHR MAY BE THE ORBITAL AUTOANTIGEN

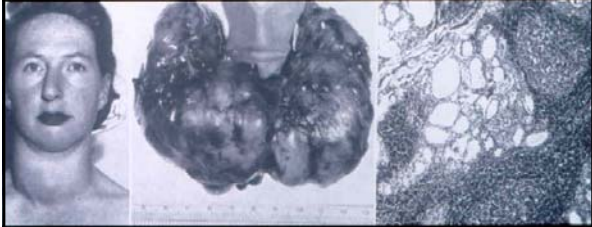




Goiter (Definition: any thyroid enlargement)

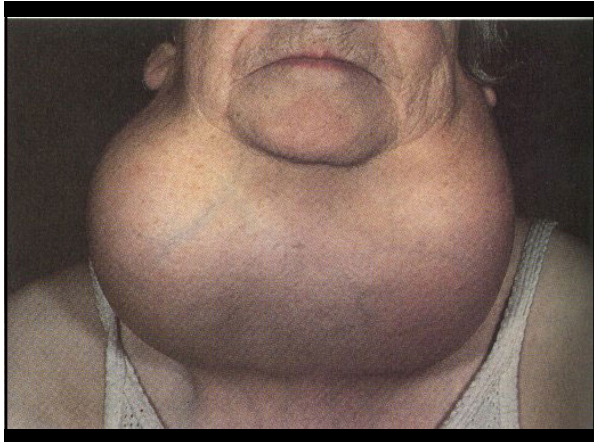
- Endemic goiter
 - † Low-iodide diet
 - † TSH excess (stimulates gland growth)
- Goiter in iodide-replete areas
 - † Hashimoto's thyroiditis
 - † Nodules, adenomas, cancer
 - † Subacute thyroiditis
 - † Resistance to thyroid hormone (genetic)
 - † Drugs

Nodular goiter in Hashimoto disease









Another Patient (Patient 2)

A 42 year old woman is seen because of several months of chronic anxiety and a weight loss of 3 kg. She had been previously well, but now complains of bad sleeping, episodic diarrhea, and a peculiar preference for dressing light and driving with the car windows wide open in the winter.

She has noticed "racing" of her heart while she tries to go to sleep.

She is taking no medications. She is not a smoker.

Review of systems reveals that she has trouble climbing stairs and getting out of her car. She has troublesome double vision when looking to the left.

Patient 2 (continued)

On physical examination she looked thin, somewhat emaciated. She could not easily sit still and was very fidgety.

She had a distinct stare. Pulse rate was 116/min; blood pressure was 146/56 mm Hg. BMI was 22 kg/m². She had velvety, moist skin. She had diplopia on looking to both right and left, and bilateral exophthalmos, R > L, with mild conjunctivitis. There was a diffuse, easily palpable goiter.

Her heart was hyperdynamic with a systolic murmur. She had very rapid and brisk deep tendon reflexes and severe proximal muscle weakness.



Patient 2 (continued)

Laboratory

fT₄: 6.7 ng/dL {0.9 - 1.7}
fT₃: 1026 pg/dL {230 - 420}
TSH: 0 mIU/L {0.25 - 3.0}

Nuclear Medicine

¹²³I uptake: 74% @ at 24 hours {10-26}
Scan: homogenous pattern

Causes of Hyperthyroidism

- Graves' disease
- Hashimoto disease ("Hashitoxicosis")
- Toxic nodule (s)
- Subacute thyroiditis
- Uncommon
 - ¶ Thyrotoxicosis factitia
 - ¶ Struma ovarii
 - ¶ Metastatic thyroid cancer
 - ¶ "Hamburger" thyrotoxicosis
 - ¶ TSH-secreting adenoma

Hyperthyroidism

Symptoms: Palpitations, Nervousness, Fatigue, Diarrhea, Sweating, Heat Intolerance, Weakness

Signs: Goiter (?), Tremor, Rapid Reflexes, Inability to sit still, Eye signs (if Graves' disease), Rapid reflexes, Fine hair and skin, Proximal Muscle Weakness, Arrhythmia

Laboratory:

- TSH (low or undetectable in primary hyperthyroidism)
- FT_4 (usually high)
- FT_3 (always high)
- RAI Uptake (usually elevated)
- Antibodies (may be high)

**A gallery of eyes
in Graves' disease**



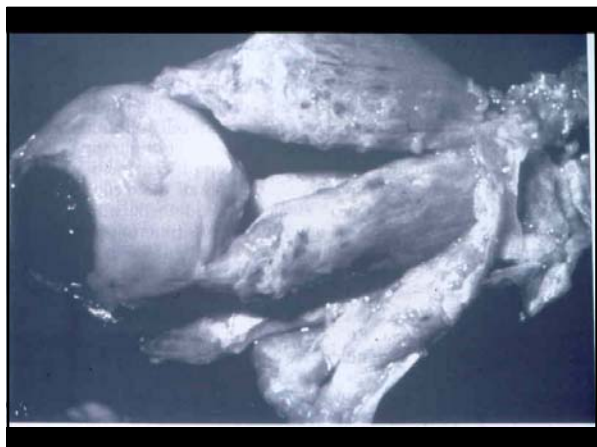












Graves' Disease

- Most common cause of hyperthyroidism
- Women much more commonly than men
- Diagnosis
 - † Clinical presentation
 - † Laboratory
 - † Radioisotope uptakes and imaging
- Management
 - † Surgery
 - † Radioiodine ablation
 - † Antithyroid drugs
 - † Beta blockers
 - † Iodides (short term use)

* Management of orbitopathy: a separate topic

One final patient...

A 20 year old nursing student is seen for a recent 20 lb weight loss. She tells you that she is under great stress, has recently broken up with her boy friend, and is doing poorly in school. Her heart pounds rapidly when she tries to sleep. She is very fidgety and nervous in the office and cries easily.

She has been previously well, has no family history of thyroid problem. She is not a smoker, drinker, or coffee drinker, and she denies use of medications.

One final patient...(continued)

On physical examination she is gaunt, anxious, and Has a pulse rate of 120/minute. Her hair is thin. She has no eye signs and her thyroid gland is not palpable.

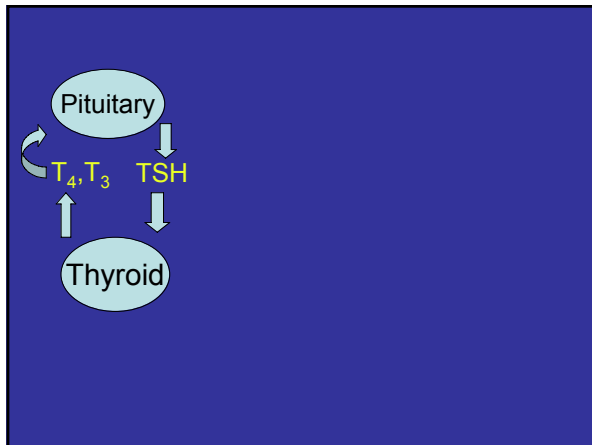
She is unable to get out of a chair without using her arms and has striking proximal muscle weakness.

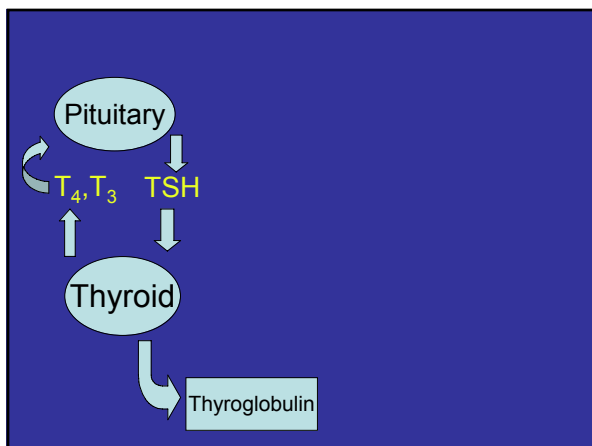
Laboratory: fT_4 : 7.3 ng/dL {0.9 - 1.7}
 fT_3 : 710 pg/dL {230 - 420}
TSH: 0 mIU/L {0.25 - 3.0}
Antithyroid antibodies:
Undetectable

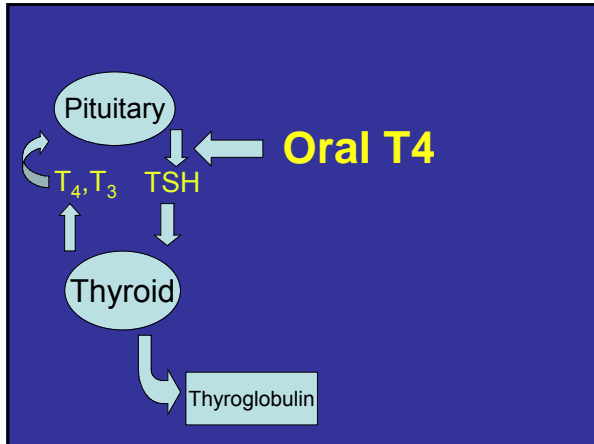
You suspect that this young woman is taking thyroid hormone by mouth and probably has *thyrotoxicosis factitia*.

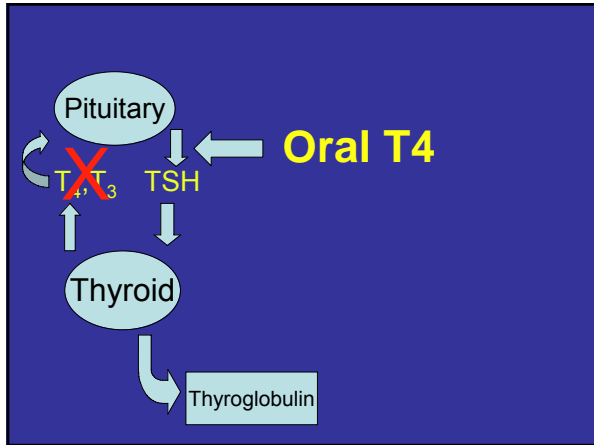
The absence of eye signs and goiter can occur in true Graves' disease but suggest otherwise.

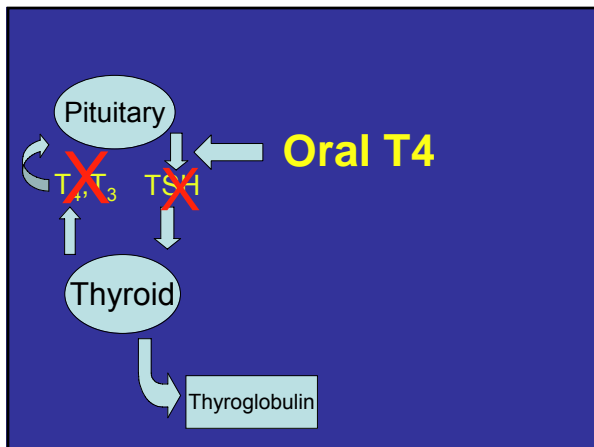
What test will confirm that she's been surreptitiously taking thyroid hormone?

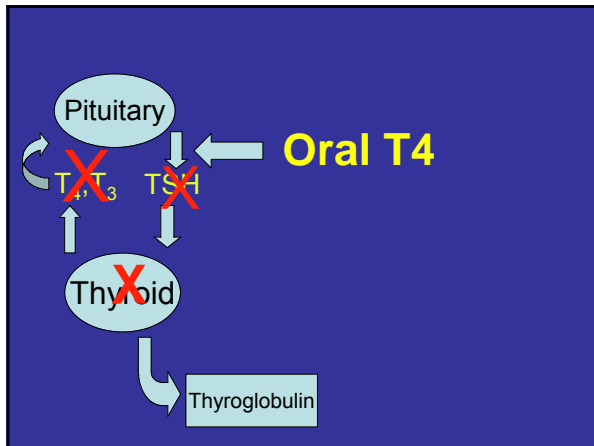


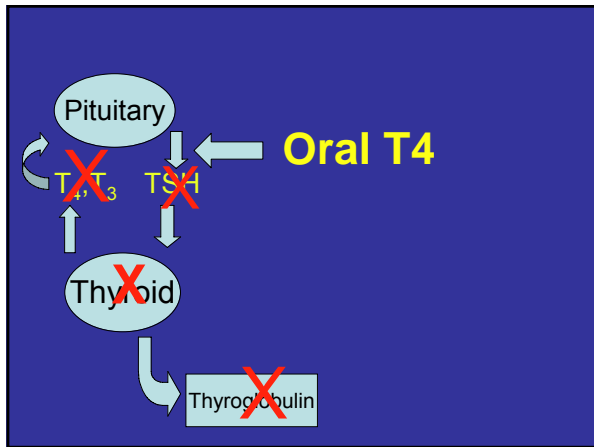












On testing: Thyroglobulin undetectable.
 Antithyroglobulin antibodies undetectable.

Conclusion: there is no endogenous thyroid tissue functioning in this patient. She's getting her thyroxine from a bottle!

ANOTHER CONCLUSION...

**The thyroid "arena" hosts
a LOT of crazy stuff!**
