Diagnosis and Therapy of Hyperthyroidism, with Emphasis on Graves' Disease

BENNETT S. GREENSPAN, MD, MS
PROFESSOR, DEPT. OF RADIOLOGY
MEDICAL COLLEGE OF GEORGIA/AUGUSTA UNIVERSITY

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Disclosures

- No financial disclosures.
- No FDA unapproved radiopharmaceuticals will be discussed.

OBJECTIVES

- 1. Be able to discuss the hypothalamic-pituitary-thyroid axis.
- 2. Understand the use of lab tests and nuclear medicine studies in the evaluation of hyperthyroidism.
- 3. Understand the use of I-131 in the treatment of hyperthyroidism.

The thyroid

- Normal thyroid: Hypothalamic-pituitary-thyroid axis, with negative feedback
- Hypothalamus: TRH (thyrotropin releasing hormone [TSH]) ->
- Pituitary: thyrotropin (TSH) ->
- Thyroid: thyroxine (T4) and triiodothyronine (T3)

Hypothalamic-Pituitary-Thyroid axis

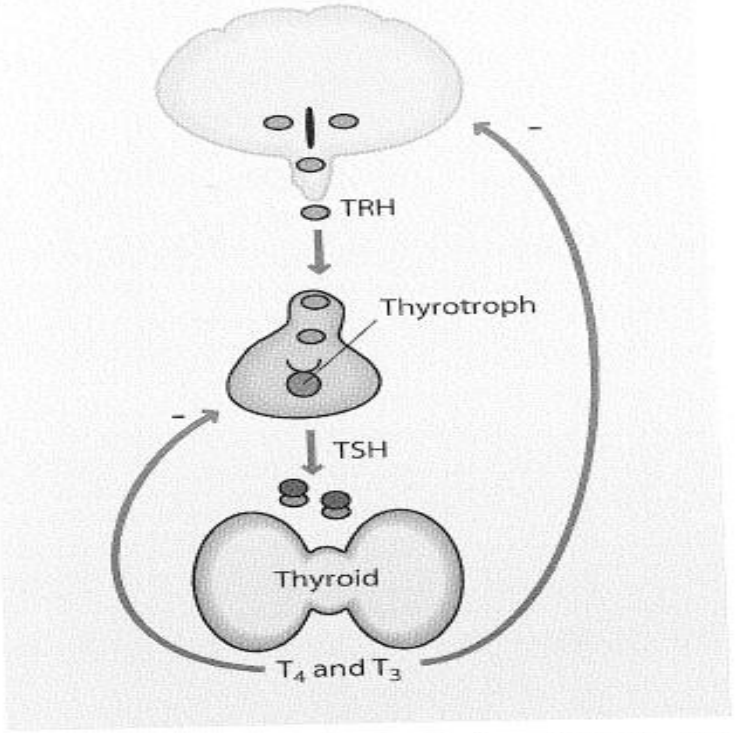


FIGURE 2.1. The hypothalamic–pituitary–thyroid axis. Thyrotropin-releasing hormone (TRH) is synthesized in the hypothalamus and secreted into the hypothalamic–pituitary portal venous system, in which it is carried to the pituitary, where it stimulates the synthesis and secretion of thyrotropin (TSH). TSH binds to its receptor in the thyroid gland, stimulating the synthesis and secretion of thyroxine (T_4) and triiodothyronine (T_3). Precise control of the axis is maintained by the inhibitory actions of T_4 and T_3 on both TRH and TSH secretion.

Normal thyroid gland

- The thyroid develops from a diverticulum of the pharynx, and also from mainly the second pharyngeal pouch. It consists of two lobes on either side of the larynx, connected by an isthmus.
- Contains endoderm-derived follicular cells, responsible for thyroid hormone production.
- Thyroid gland also contains parafollicular or C-cells, derived from ultimobranchial bodies. C-cells secrete calcitonin.

Thyroid gland

- The thyroid gland is the largest endocrine gland in the body.
- Question 1: What is the normal weight of the thyroid gland in adults?

Normal thyroid gland

- Answer: 10-20 grams
- Some references: 15-20 grams
- I like to consider it as 20 grams, 10 grams per lobe.

Iodine in Thyroid hormones

- Iodine (Iodide [I-] is the ionized form) is essential for synthesis of thyroid hormones, T3 and T4. Thyroid function depends on an adequate supply of iodine.
- Accumulation of I- in the thyroid is due to active transport, known as the sodium-iodide symporter (NIS).
- TSH regulates the NIS in the thyroid.

Iodine Uptake

- Question 2: When is maximal uptake of iodine by the thyroid?

Iodine Uptake

- Answer: Approximately 24 hours.

Iodine Uptake Curves

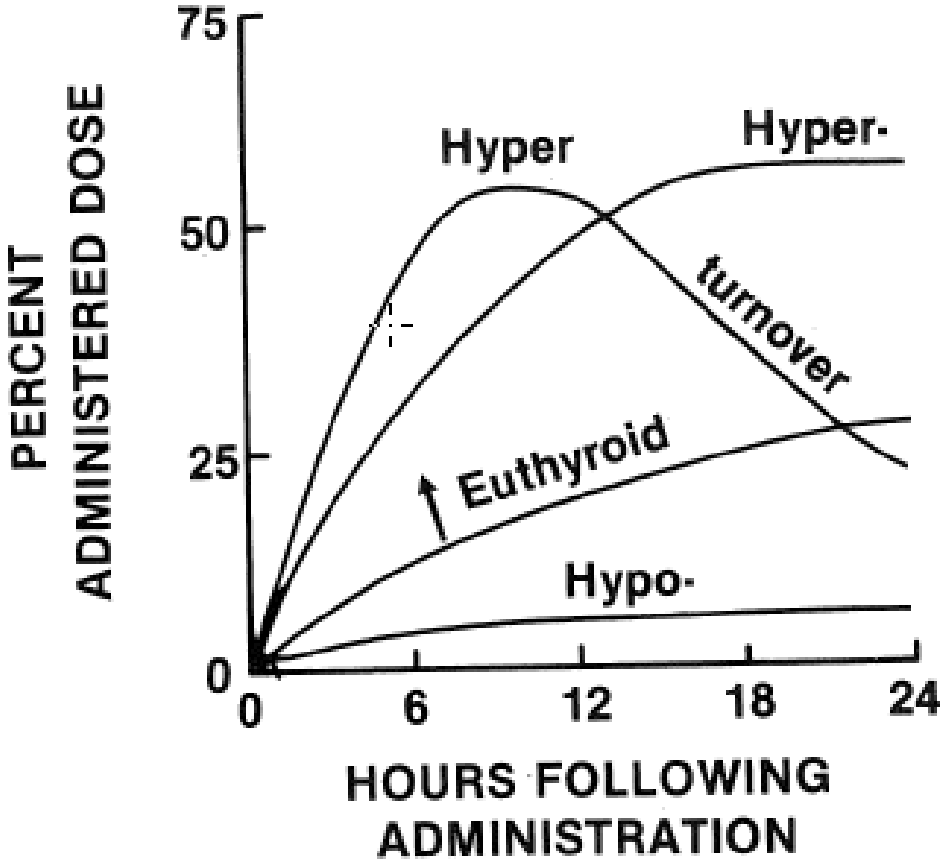


Figure 5. Characteristic curves of thyroid uptake of radioiodine after oral administration.

Thyroid hormone synthesis

- Thyroid hormone synthesis, storage and secretion is highly regulated, and is dependent on nutritional availability of iodine.

- Question 3: Thyroid iodide concentration is how much greater than serum iodide concentration?
- 5-10 times
- 20-40 times
- 50-100 times

Iodide in the Thyroid

- Answer: 20-40 times.

- Reference: Werner and Ingbar's The Thyroid Ninth Edition, Lewis E. Braverman and David S. Cooper Wolters Kluwer/Lippincott Williams & Wilkins 2013 Chapter 4B Thyroid Hormone Synthesis, p 48.

Thyroid hormone synthesis

- Drugs that interfere with thyroid hormone synthesis and metabolism
- Iodine trapping: thiocyanate, perchlorate
- Iodine uptake: PTU, Methimazole (Tapazole)
- Organification: propylthiouracil (PTU), methimazole (MMI) – also known as Tapazole
- Hormone synthesis: Iodine
- Hormone release: Lithium

Thyroid hormone synthesis

- Drugs and conditions that interfere with thyroid hormone synthesis and metabolism:
- Conversion of T4 to T3 – PTU, glucocorticoids, oragrafin, propranolol, amiodarone, fasting, significant illness, hepatic disease

Thyroglobulin

- Thyroglobulin (Tg) is a large glycoprotein dimer. It serves as the matrix for the synthesis of T4 and T3, and also as the storage form of the hormones and iodide.
- Tg is secreted into the lumen of thyroid follicles and is stored as colloid.

Thyroid function

- Some factors that control thyroid function:
- Thyrotropin (TSH)
- Intrinsic and extrinsic variables – cold and heat, altitude and hypoxia, and other environmental influences drugs, cytokines, iodine deficiency or excess, age, non-thyroidal illness.

Normal Thyroid

- Normal thyroid scan
- Indications:
- Thyroid function
- Thyroid nodules

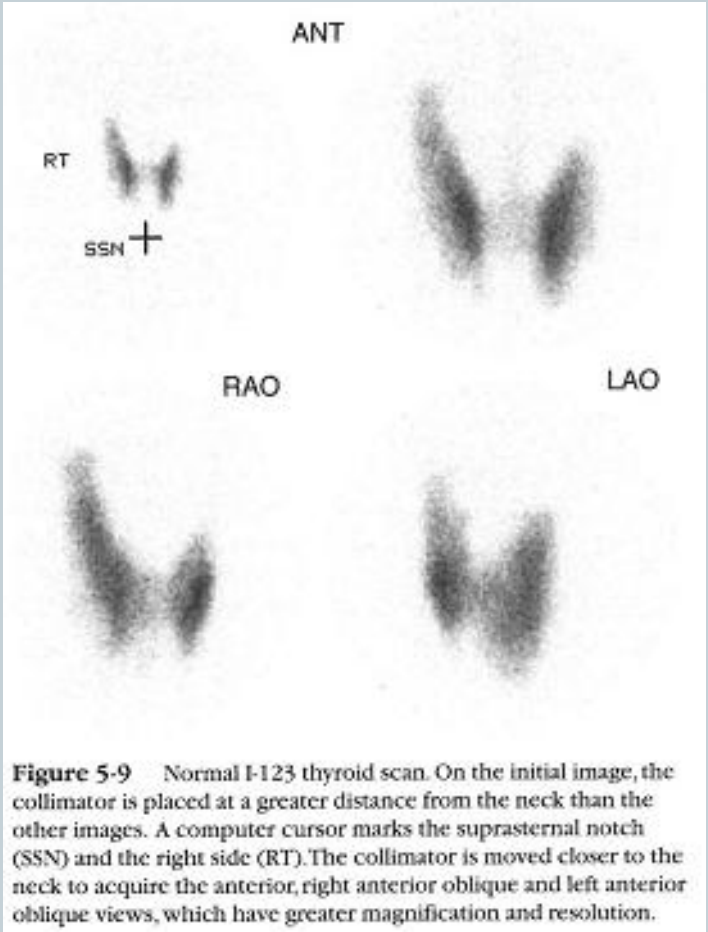


Figure 5-9 Normal I-123 thyroid scan. On the initial image, the collimator is placed at a greater distance from the neck than the other images. A computer cursor marks the suprasternal notch (SSN) and the right side (RT). The collimator is moved closer to the neck to acquire the anterior, right anterior oblique and left anterior oblique views, which have greater magnification and resolution.

Lab Tests in Hyperthyroidism

- Lab tests in the evaluation of hyperthyroidism:
- TSH
- Serum free thyroxine (T4) and free triiodothyronine (T3)
- Serum free T4 and free T3 indexes – indirect measurements that have been replaced by serum free T4 and free T3.
- Serum total T4 and T3 – useful in non-thyroidal illness.

Lab Tests - Hyperthyroidism

- Question 4: Which is the best single laboratory test for evaluation of hyperthyroidism, i.e., which is the most sensitive indicator?

- A. TSH
- B. free T4
- C. free T3

Lab tests - Hyperthyroidism

- Answer: TSH

Thyrotoxicosis/Hyperthyroidism

- Thyrotoxicosis – clinical syndrome of hypermetabolism and hyperactivity resulting from high serum T4 and/or T3.
- Hyperthyroidism – sustained increases in thyroid hormone biosynthesis and secretion.
- Thyrotoxicosis is not synonymous with hyperthyroidism; patients with thyrotoxicosis from thyroiditis or exogenous thyroid hormone administration do not have hyperthyroidism.

Causes of Thyrotoxicosis

- Common, associated with hyperthyroidism
- Graves' disease
- Intrinsic thyroid autonomy
  - Toxic adenoma (autonomous)
  - Toxic multinodular goiter

Causes of Thyrotoxicosis

- Uncommon, associated with hyperthyroidism:
- TSH-secreting tumor, thyrotropin-induced thyrotoxicosis
- Trophoblastic tumors
- Struma ovarii
- Metastatic follicular carcinoma

Causes of Thyrotoxicosis

- Common, not associated with hyperthyroidism
- Inflammatory disease
  - Silent (painless thyroiditis)
  - Subacute thyroiditis
  - Hashimoto's thyroiditis (Hashitoxicosis) – Hashimoto's thyroiditis is relatively common, and usually causes hypothyroidism; Hashitoxicosis is transient hyperthyroidism
- Extrathyroidal source of hormone
  - Exogenous thyroid hormone

Causes of Thyrotoxicosis

- Uncommon, Not associated with hyperthyroidism
- Iodine-induced (Jod-Basedow); includes amiodarone
- Lithium carbonate (long term therapy)

Thyrotoxicosis

- Common Clinical Symptoms:
- Nervousness, fatigue, weakness, irritability
- increased perspiration, heat intolerance,
- tremor, hyperactivity, palpitations,
- appetite change (usually increase), weight change (usually weight loss),
- menstrual disturbances.

Thyrotoxicosis

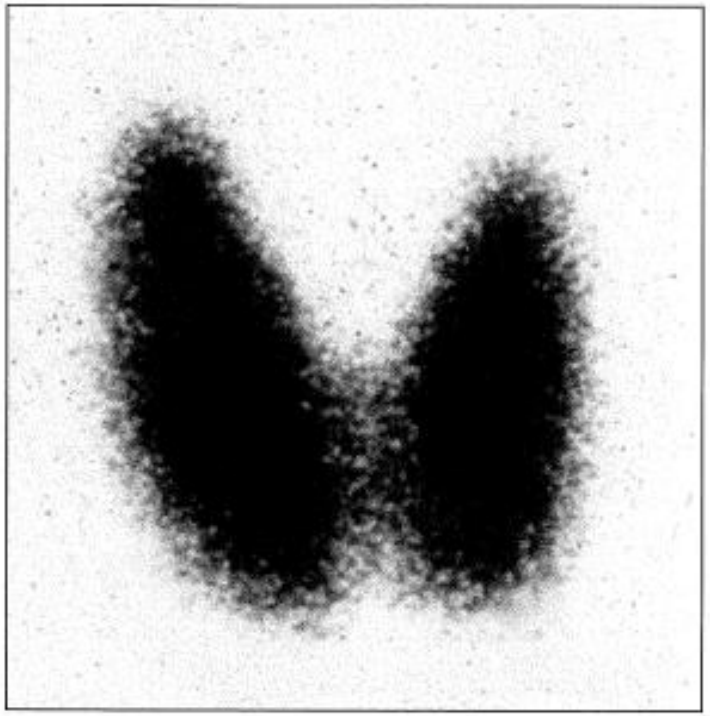
- Common Clinical Signs:
- Hyperactivity, tachycardia or atrial arrhythmia, systolic hypertension
- warm moist smooth skin
- Stare and eyelid retraction
- Tremor
- Hyperreflexia
- Muscle weakness

Hyperthyroidism – Graves' Disease

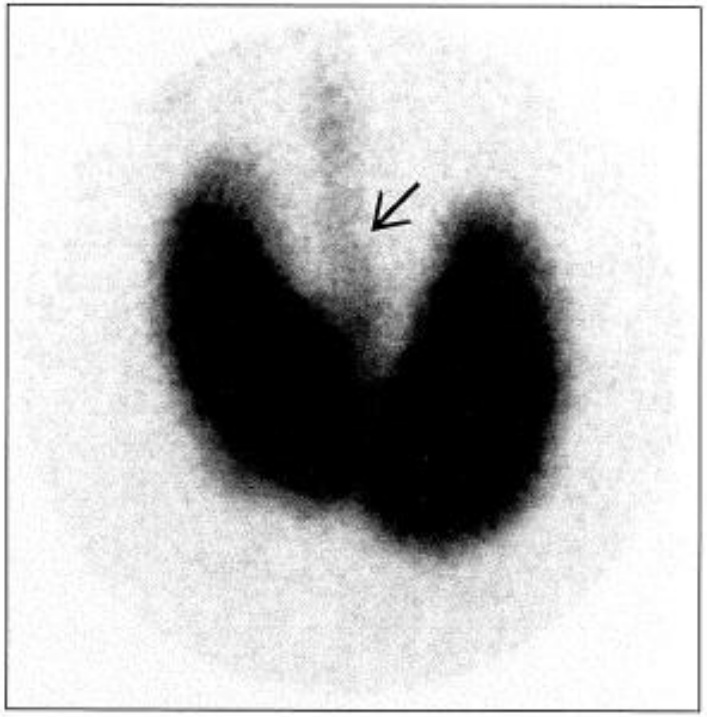
- Graves' disease: an autoimmune disease.
- Uniquely human autoimmune disease.
- Unique: stimulating autoantibodies to the TSH receptor are not just markers of the disease but are responsible for the hyperthyroidism
- Also autoantibodies to thyroglobulin and thyroid peroxidase, but these are less important.
- Thyroid enlargement and hyperfunction
  - Typical uptake 50-80+%

Graves' disease

GRAVES DISEASE



Anterior thyroid scan shows homogeneously increased thyroid uptake with smooth contours classic for Graves disease.



Anterior thyroid scan shows intense uptake in enlarged thyroid with prominent pyramidal lobe ⇒, a frequent finding in Graves disease.

Normal Thyroid

- Normal thyroid scan
- Indications:
- Thyroid function
- Thyroid nodules

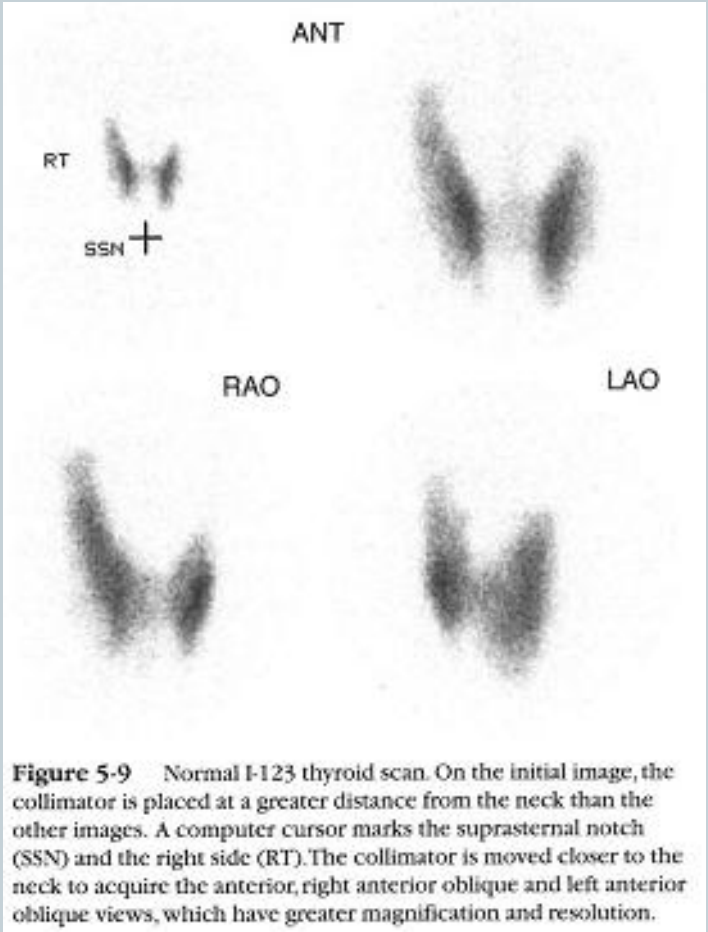
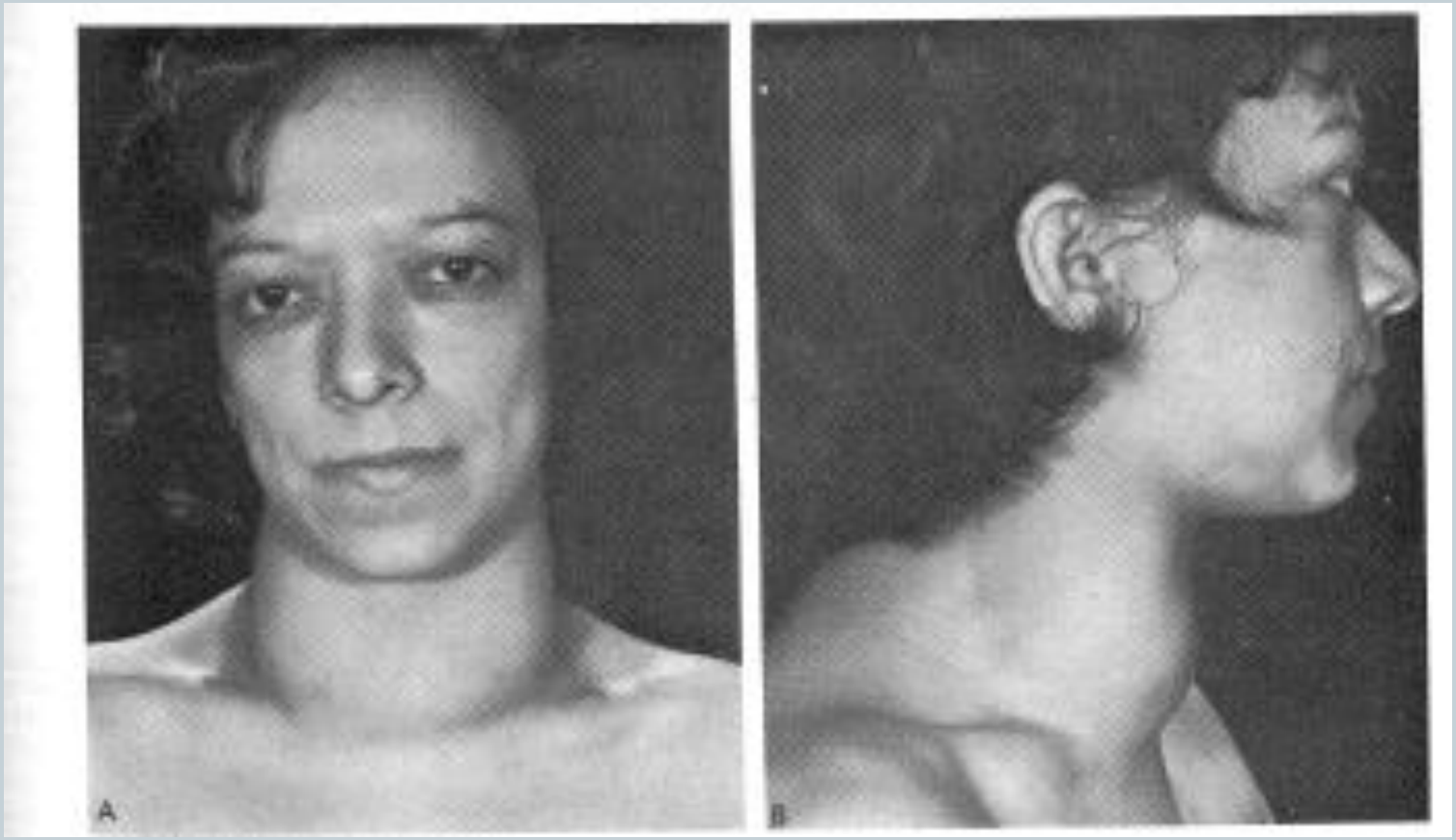


Figure 5-9 Normal I-123 thyroid scan. On the initial image, the collimator is placed at a greater distance from the neck than the other images. A computer cursor marks the suprasternal notch (SSN) and the right side (RT). The collimator is moved closer to the neck to acquire the anterior, right anterior oblique and left anterior oblique views, which have greater magnification and resolution.

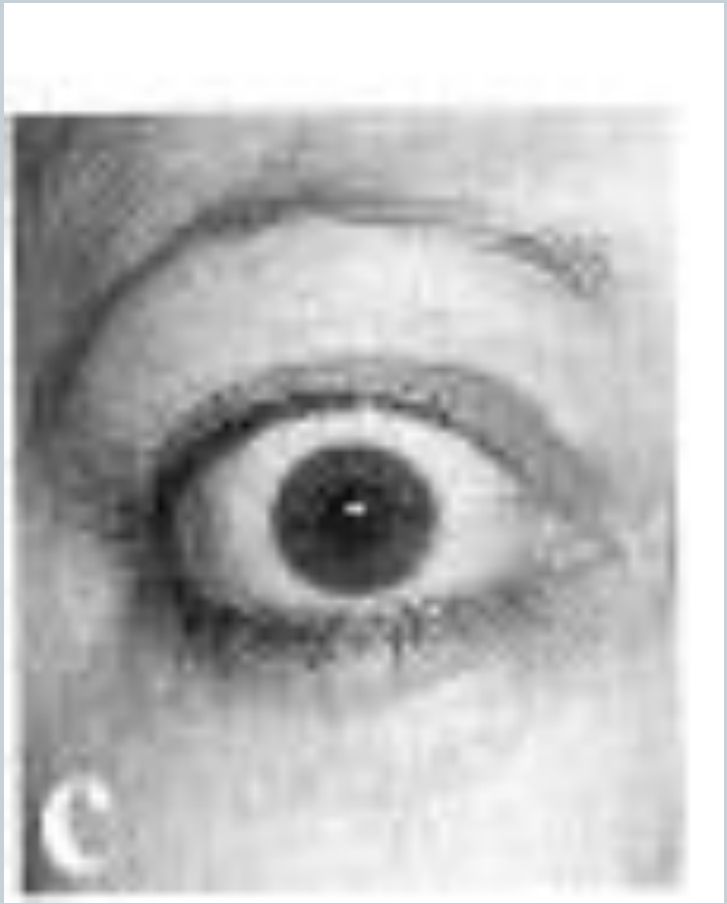
Hyperthyroidism – Graves' Disease

- Extra-thyroidal Manifestations of Graves' disease:
- Exophthalmos –due to retro-orbital deposition of mucopolysaccharides
- Exophthalmos in majority of cases is mild, moderate degree is relatively uncommon (10%), and severe degree is rare (3%)
- Pretibial myxedema – subcutaneous deposition of mucopolysaccharides in the legs

Graves' disease – neck swelling

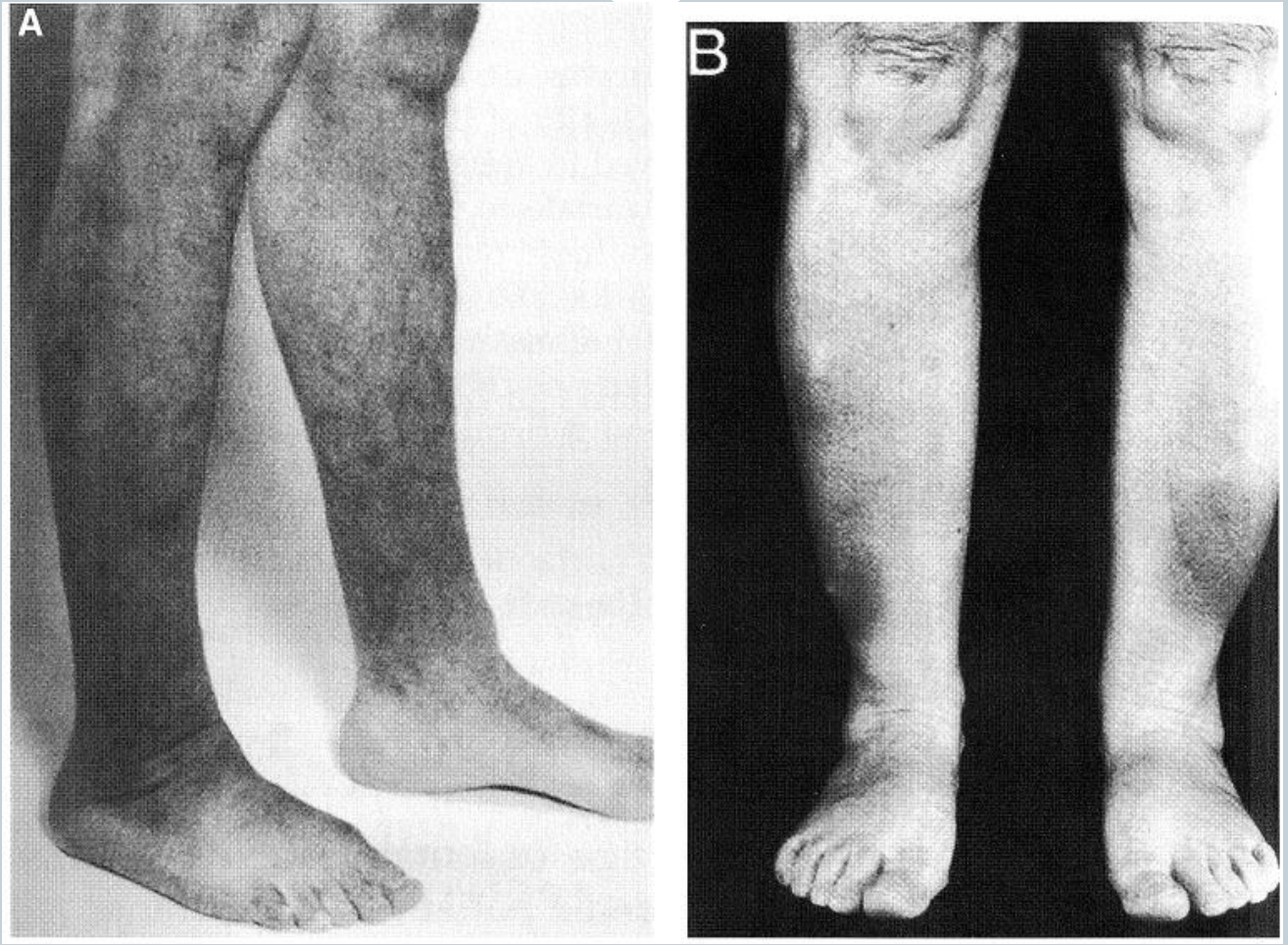


Graves ophthalmopathy – lid retraction



Graves' ophthalmopathy – lid swelling

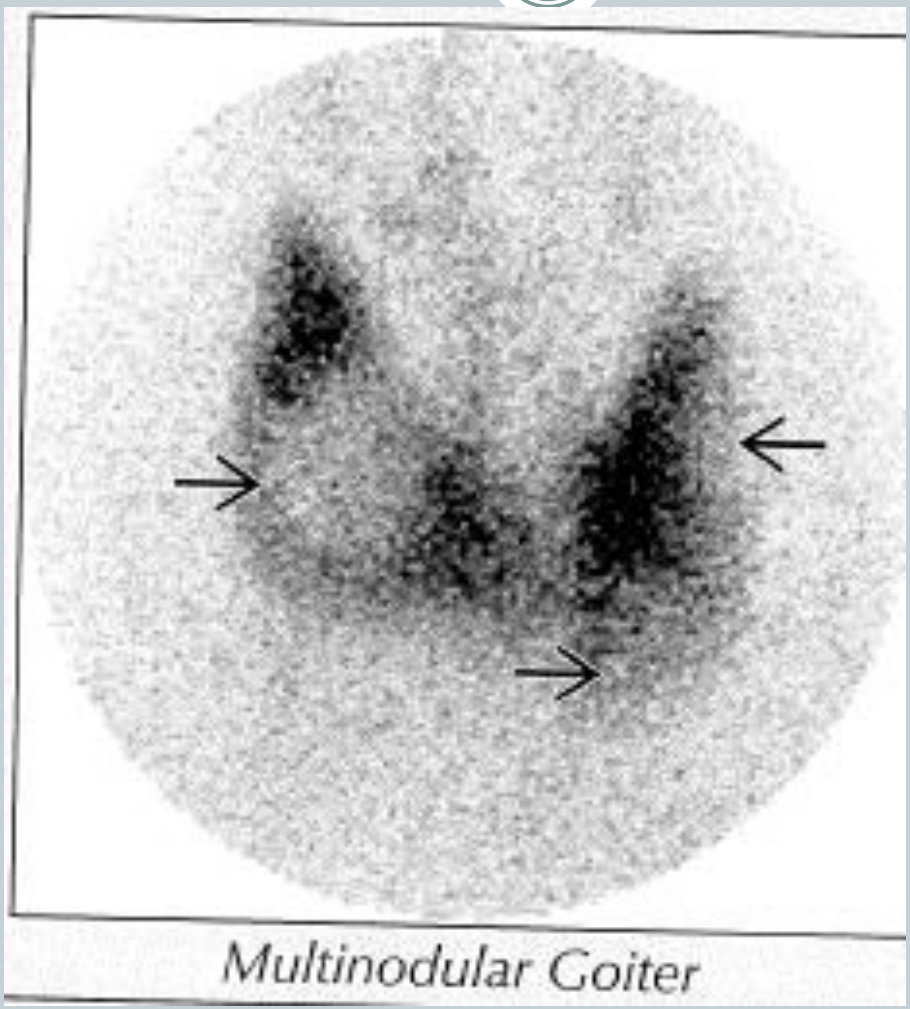
Graves' dermopathy
A. pretibial myxedema B. plaque form



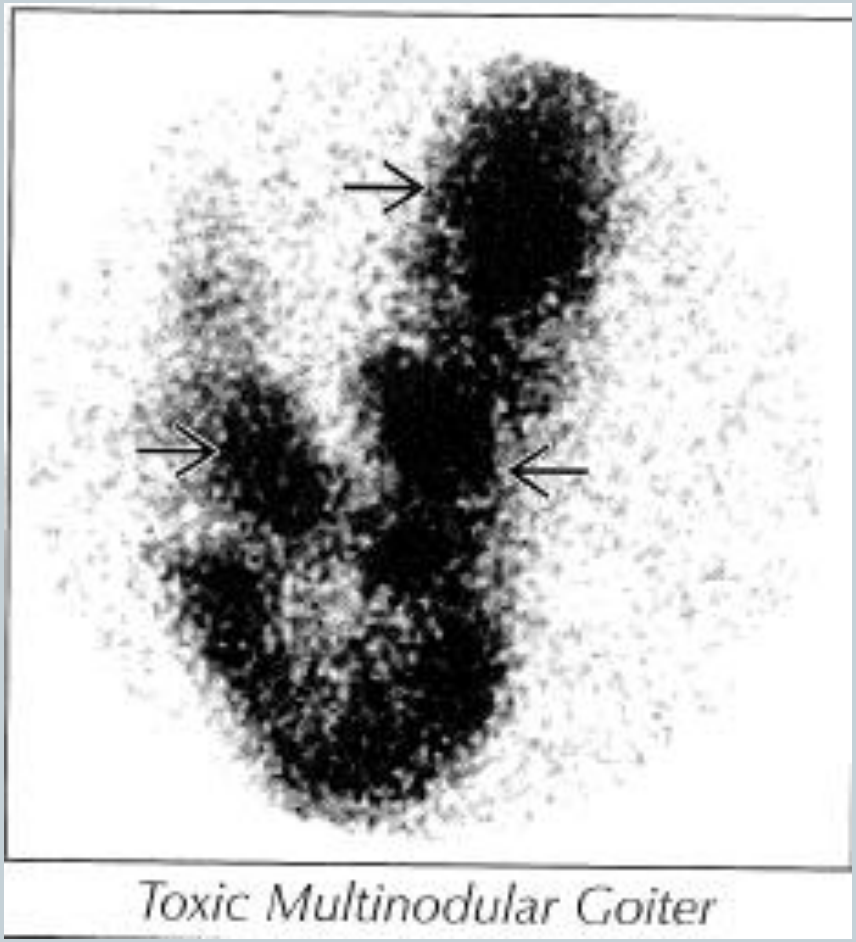
Hyperthyroidism – Graves' vs. TNG

- Graves' disease vs. Toxic Nodular Goiter (TNG)
- Graves' disease: diffuse, grows rapidly (weeks or months), rapidly developing hyperthyroidism, uniform follicles histologically and metabolically. Uptake generally 50-80%
- TNG: diffuse intially, becomes multinodular, grows slowly (years), hyperthyroidism develops slowly, heterogeneous follicle size and iodine turnover. Uptake 30-50%. May appear somewhat bizarre.

Multinodular Goiter



Multinodular Goiter

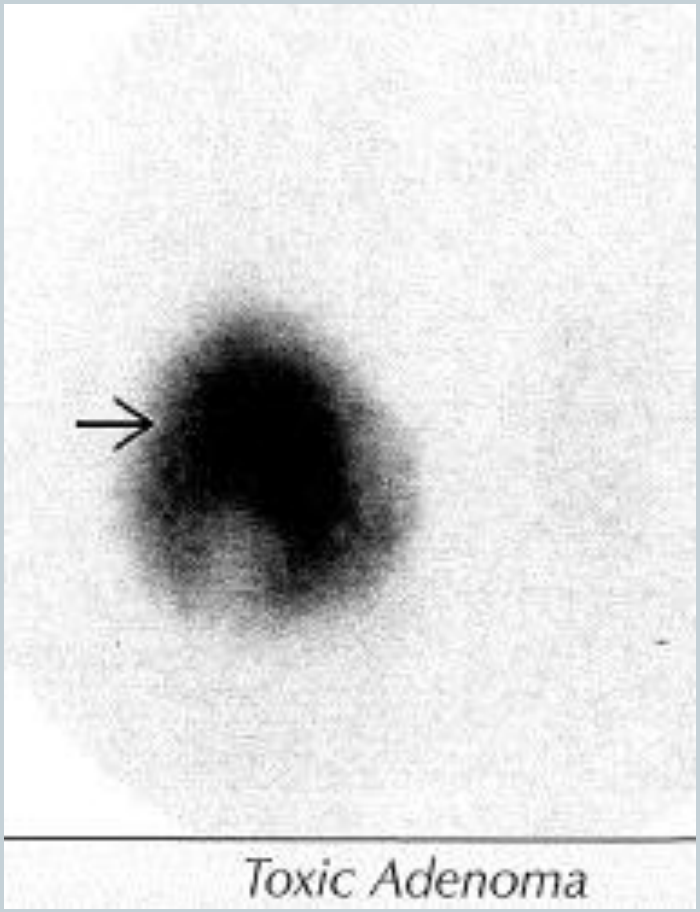


Toxic Multinodular Goiter

Toxic Adenoma

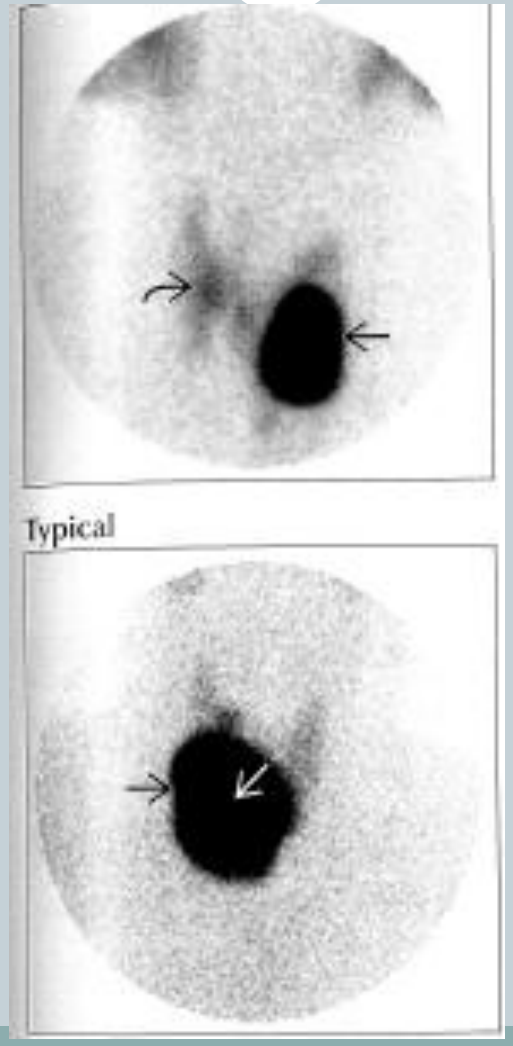
- Solitary nodule
- If autonomous, will begin to suppress the remainder of the thyroid gland.

Toxic Adenoma



Toxic Adenoma

Toxic Adenoma



Thyroiditis

- Thyroiditis – symptoms of hyperthyroidism, difficult to distinguish from Graves' disease on clinical grounds
- Easy to distinguish by uptake – typically 1-3%
- DO NOT treat thyroiditis with I-131!

Clinical Course of Subacute Thyroiditis

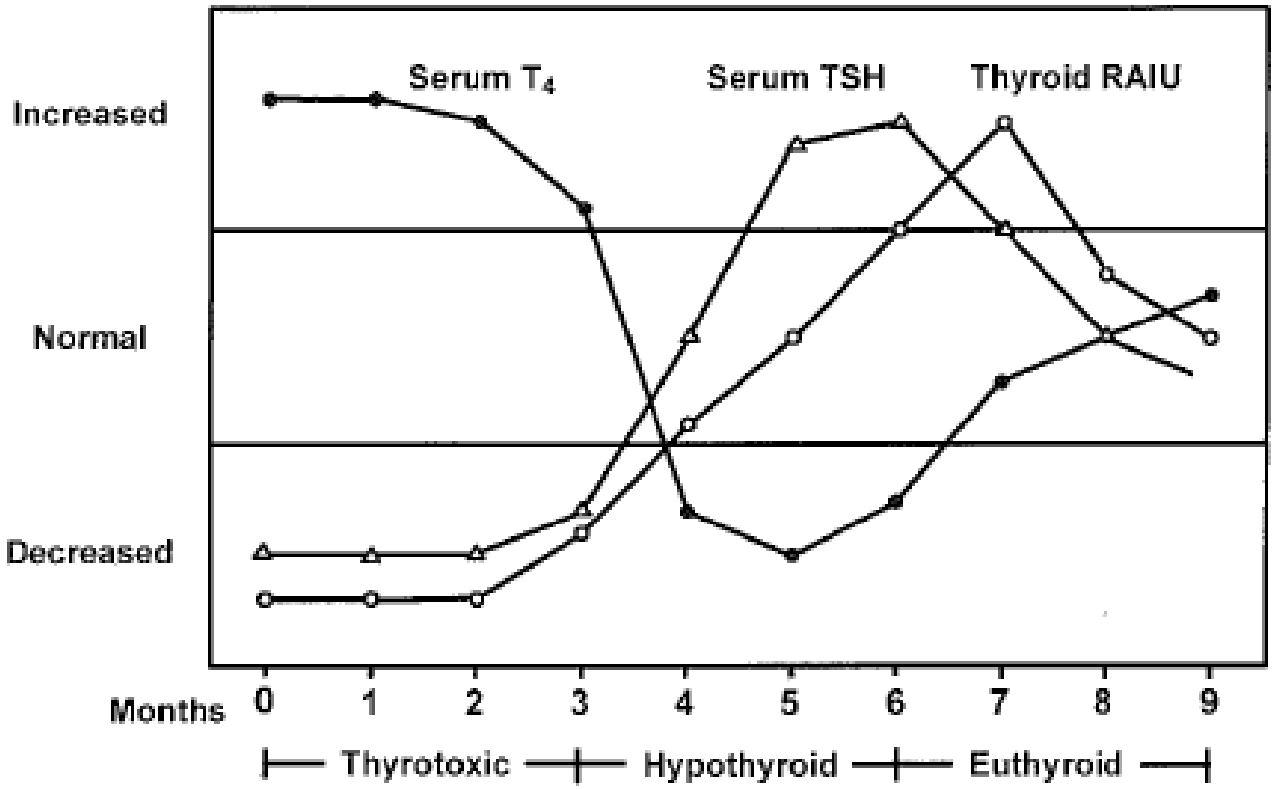
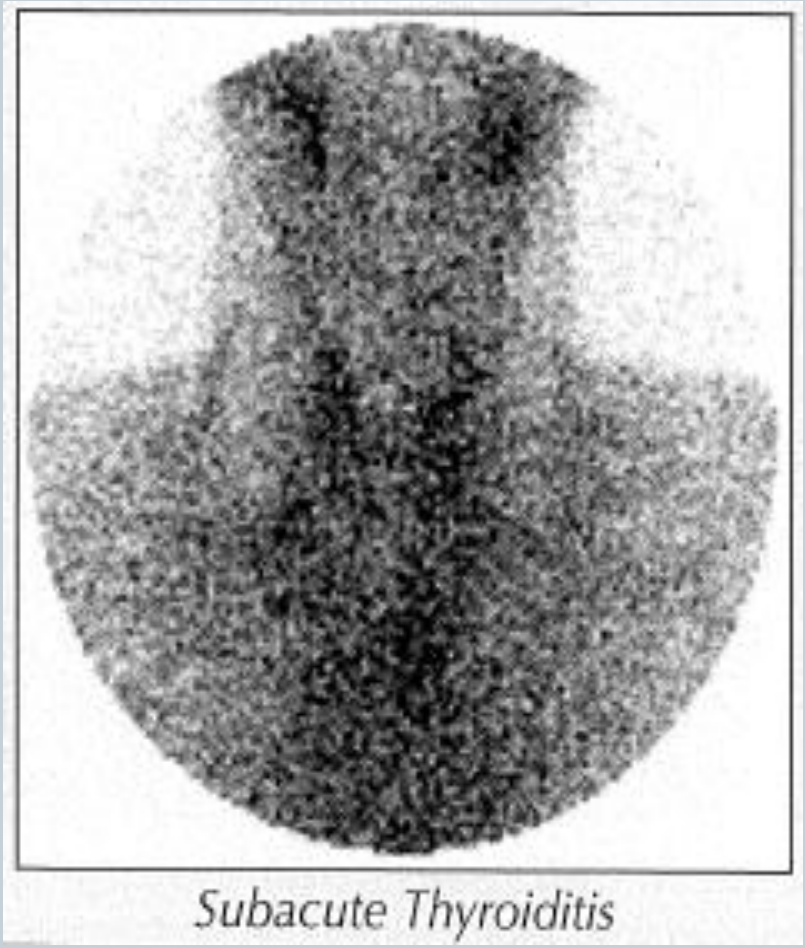


Figure 5-14 Clinical course of subacute thyroiditis. Typical evolving pattern of the serum T_4, TSH and %RAIU over 9 months, from initial presentation to resolution. When the patient initially presents, the T_4 is elevated and TSH and RAIU are suppressed. Once there is no more thyroid hormone to release, thyroid function may be poor due to inflammatory damage to the gland and the TSH and RAIU will rise. With time, most patients become euthyroid and the values normalize.

Thyroiditis



Subacute Thyroiditis

Treatment of Graves' Disease

- Antithyroid drugs:
- Propylthiouracil (PTU)
- Methimazole (MMI)

- Question 5: Which of those above inhibit synthesis of T4 and T3 in the thyroid?
- PTU
- MMI
- both
- neither

- Answer: Both PTU and MMI.

- Question 6: Which of these (PTU or MMI) blocks conversion of T4 to T3 in the thyroid and peripheral tissues?
- A. PTU
- B. MMI
- C. Both
- D. Neither

Treatment of Graves' Disease

- Answer:
- Only Propylthiouracil (PTU).

- Question 7: Which of the two, PTU or MMI, have immunosuppressive effects, as well as antithyroidal effects?

Hyperthyroidism

- Answer:
- Both PTU and MMI have immunosuppressive effects.

Treatment of Graves' Disease

- Antithyroid drugs, PTU and MMI
- Both are very effective (>= 90%) *initially* in controlling Graves' disease.
- Multiple potential side effects
- Common (1-5%): considered allergic reactions – fever, urticaria or other rashes, arthralgia, transient granulocytopenia.
- Major side effects are rare (<1%).

Antithyroid drugs

- Antithyroid drugs
- Major side effects – rare
- Include Agranulocytosis, aplastic anemia, thrombocytopenia, toxic hepatitis (PTU), cholestatic hepatitis (MMI), vasculitis, SLE-like syndrome

Antithyroid drugs – Graves' disease

- Antithyroid drugs
- Percentage of patients remaining in remission after discontinuation of antithyroid therapy:
  - Reaches about 50% at 18 months, with little change therafter.
  - Remission is defined as being euthyroid for at least 1 year after discontinuing therapy.
  - Remission occurs in approx. half the patients

Treatment for Graves' disease

- Treatment for Graves' disease
- Inorganic iodide
  - decreases T4 and T3 synthesis by inhibiting iodine oxidation and organification, i.e., blocks uptake.
  - Blocks release of T4 and T3 from the thyroid by inhibiting thyroglobulin proteolysis
  - Not a generally reliable method to control hyperthyroidism

Treatment for Graves' disease

- Treatment for Graves' disease
- Potassium perchlorate
  - Competitive inhibitor of iodide transport
  - Effective in combination with PTU or MMI for iodine-induced thyrotoxicosis
  - Not a primary therapy, due to side effects (aplastic anemia and gastric ulceration)

Treatment for Graves' disease

- Treatment for Graves' disease
- Beta-adrenergic antagonistic drugs
  - Useful adjuncts for alleviating symptoms
  - Propranolol, also atenolol, metoprolol

Treatment for Graves' disease

- Treatment for Graves' disease
- Radioiodine – I-131
  - Effective, safe, relatively inexpensive
  - Administered orally in a single dose
  - Rapidly and completely absorbed, and quickly concentrated, oxidized and organified by thyroid follicular cells
  - **ALWAYS** obtain uptake before I-131 therapy!
  - BOARD QUESTION (8): Approximately what dosage of I-131 is used for Graves' disease?
  - Answer: 10-15 mCi

Treatment for Graves' disease

- Treatment of Graves' disease
- Complications and potential risks of I-131
  - Hypothyroidism – some consider this a desired consequence rather than a complication
  - Pregnancy, or the possibility of pregnancy, is an ABSOLUTE contraindication to I-131 therapy.
  - At 10 weeks or later, fetal thyroid may be damaged – potentially can cause neonatal hypothyroidism or fetal demise
  - Patients who are breastfeeding must stop. Breastfeeding cannot be resumed for this infant post therapy, as I-131 is excreted in breast milk.

Treatment of Graves' Disease

- I-131
  - Postradioiodine worsening of thyroid function – occasionally seen, more common with TNG
  - In patients with severe thyrotoxicosis, elderly patients, and those with cardiac disease, pretreatment with PTU or MMI is prudent
  - Graves' ophthalmopathy may worsen, may be preventable by glucocorticoid therapy

I-131 Therapy

- Dose determination
- 1. Fixed dose method
- 2. Microcurie per gram method
- 3. Delivered radiation dose method

I-131 Therapy

- 1. Fixed-dose method
- 3-5 mCi: 60% become euthyroid within 3-4 months
- Second dose: 85% are euthyroid or hypothyroid
- Very poor method (in my opinion) – no relation to gland size, uptake, or severity of disease.
- Many patients remain hyperthyroid and require retreatment
- MCG approach: 30 mCi for Graves' disease – should cure all patients, but all will become hypothyroid.

I-131 Therapy

- 2. Microcurie per gram method
- Dose (uCi) = uCi/g selected X est. weight of gland (g) X 100/ % uptake at 24 hours
- 55-110 uCi/g delivers 5,000 to 10,000 rad (cGy) per gram
- Washington University: 120 uCi/g
- Walter Reed National Military Medical Center: 140 uCi/g

I-131 Therapy

- 3A. Delivered radiation dose method

- Dose (uCi) = cGy/g selected X est. gland weight (g) X 100 / % uptake at 24 hr X 90

- Dose (uCi) = cGy/g selected X est. gland weight (g) X 6.67 / T1/2 eff (days) X % uptake at 24 hours

I-131 Therapy

- 3B. Delivered Radiation Dose Method

- Dosage (uCi) = cGy X Tp X est. gland weight (g)

$$\frac{\text{cGy} \times \text{Tp} \times \text{est. gland weight (g)}}{\text{G-cGy/uCi I-131} \times \text{Teff} \times \text{Max Uptake}}$$

Ref: Carol Marcus, Ph.D., M.D. UCLA

I-131 Therapy

- 3B. Delivered Radiation Dose Method

- Dosage (uCi)= cGy X Tp X est. gland weight (g)

$$\frac{12{,}000 \quad 8d \quad \text{e.g. } 60\ g}{\text{G-cGy/uCi I-131} \times \text{Teff} \times \text{Max Uptake}} = 20\ mCi$$

$$\frac{}{120 \quad 4d \quad 0.6\ (\text{fractional} = 60\%)}$$

Ref: Carol Marcus, Ph.D., M.D. UCLA

I-131 Therapy

- 3B. Delivered Radiation Dose Method

- Dosage (uCi)= est. gland weight (g)

$$\frac{100 \times 2 \quad \text{e.g. 60 g}}{\text{Max Uptake}} = 20 \text{ mCi}$$

0.6 (fractional = 60%)

Ref: Carol Marcus, Ph.D., M.D. UCLA

I-131 Therapy

- Question 9: Which of the following has the greatest error?
- A. size (mass) of the gland
- B. determination of % uptake
- C. turnover rate

I-131 Therapy

- Answer:
- A. size of the gland – particularly if estimate is made by palpation

I-131 Therapy

- Dose determination (from Harbert):
- For young pts and pts with small glands, 7000 cGy/g = approx. 75 uCi per gram
- For pts with larger glands or more severe disease: 7500-10,000 cGy: 75-110 uCi/g
- TNG: 10,000-12,000 cGy (110-133 uCi/g)
- Pts with cardiac disease: 10,000-18,000 cGy (110-200 uCi/g)

I-131 Therapy

- Typical therapy dosages:
- Graves' Disease: Generally 10 – 15 mCi (my preference approx. 12 – 18 mCi)
- Autonomous nodules, 20-25 mCi
- Toxic multinodular goiter: 20-30 mCi

I-131 Therapy

- Begins to take effect in 2-3 weeks
- Maximal effect in 3-4 months –
- Which means, if patient needs retreatment, they must wait 4-6 months after the initial or previous therapy

I-131 Therapy

- Considerations:
- **ALWAYS** obtain uptake!
- Consider low iodine diet – not common
- **ALWAYS** check for possible pregnancy (and do not rely on the patient!)

I-131 Therapy

- Further considerations –
- Need informed consent
- Identify patient by *at least* two independent methods – name, DOB, SSN, address, referring physician, etc.
- Radiation safety precautions – time, distance, hygiene; give verbal and written instructions
- For outpatient therapy – patient must not pose a risk to family members or caregivers – exposure to others must be <500 mrem

I-131 Therapy

- Further considerations –
- Avoid medications that decrease I-131 uptake
- Iodinated contrast
- Iodine containing supplements, e.g., some cough medicines, seaweed (kelp)
- Thyroid hormone replacement
- Antithyroid medications -
  PTU -3-5 days, MMI – 5-7 days

I-131 Therapy

- Response to therapy
- Incidence of hypothyroidism
  - 4-7% after 1 year with 80 uCi/g, up to 20% with higher doses
  - 40% after intermediate doses, 70% after high doses after 10 years
  - Up to 90% in first year
  - After first year, continuing 2-3% per year

  Some consider hypothyroidism a desired effect, not a complication

I-131 Therapy

- Question 10: Which is a more serious problem?
- “under” treatment (not enough I-131), or
- “over” treatment (“too much” I-131).

Hyperthyroidism

- Answer-
- In my opinion, under treatment is a much more serious problem – patient still has the disease, an especially serious problem in the elderly, particularly with cardiac disease.
- “Over treatment” means the disease is cured, and hypothyroidism can be easily treated by replacement thyroxine*.
- * (Synthroid is best)

I-131 Therapy – Side Effects and Complications

- Early
- Nausea and vomiting
- Exacerbation of hyperthyroidism
- Thyroid storm
- Radiation thyroiditis

I-131 Therapy

- Complications
- Worsening of exophthalmos – rare, treated with steroids
- Slight decrease in bone marrow function (maximal at 4-5 weeks) – not clinically significant

Hyperthyroidism – Therapy with I-131

- Complications – Late
- Hypoparathyroidism – rare
- Hyperparathyroidism – rare, probably coincidental
- Calcitonin deficiency – rare, may be due to bystander effect
- Leukemia – no evidence of increased incidence over expected rate in treatment for hyperthyroidism

Therapy - TNG

- Therapy for Toxic Multinodular Goiter
- Antithyroid drugs are rarely the treatment of choice, except as preparation for I-131 therapy.

Toxic Adenoma

- Treatment of Toxic adenoma
  - I-131 is preferred over antithyroid drugs, as it will usually cure the hyperthyroidism
  - Post treatment hypothyroidism is less common than in Graves' disease, as I-131 is not concentrated by suppressed normal tissue.

I-131 therapy

- Late complications of I-131 therapy
- Carcinogenesis (theoretical)
  - Incidence of thyroid cancer one sixth that of patients who underwent surgery
  - No risk of thyroid cancer
  - No risk of lymphoma (incidence also below expectation)
  - No definite risk of any cancer type

I-131 Therapy - Summary

- I-131 therapy for Graves' Disease is simple and highly successful if done properly
- Very few complications

- REMEMBER:
- **ALWAYS** obtain thyroid uptake
- **ALWAYS** check for possible pregnancy