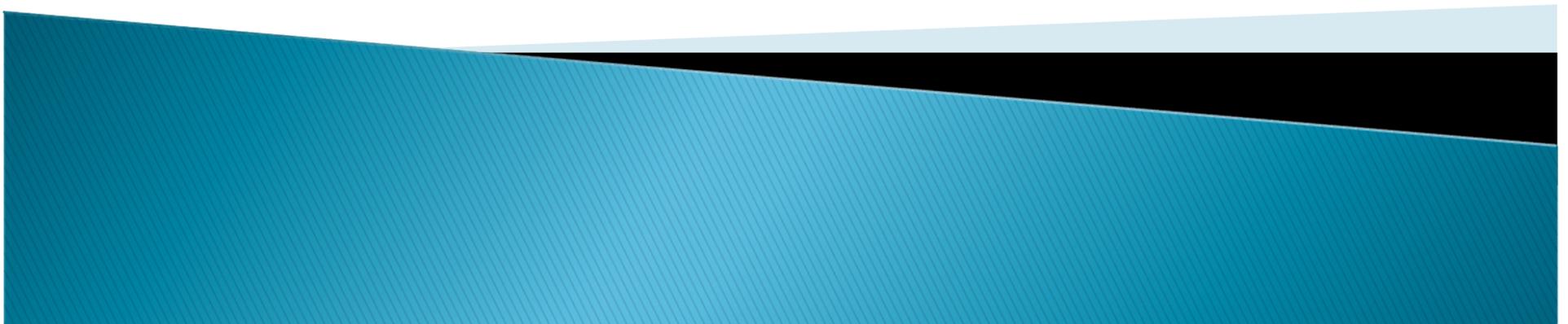


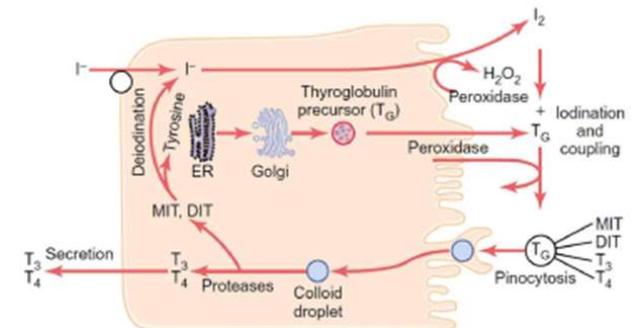
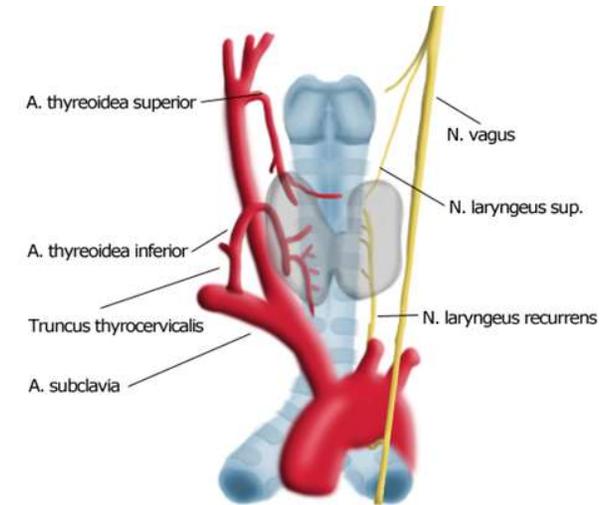
Nuclear Endocrinology

The Thyroid Gland
functional and morphological evaluation

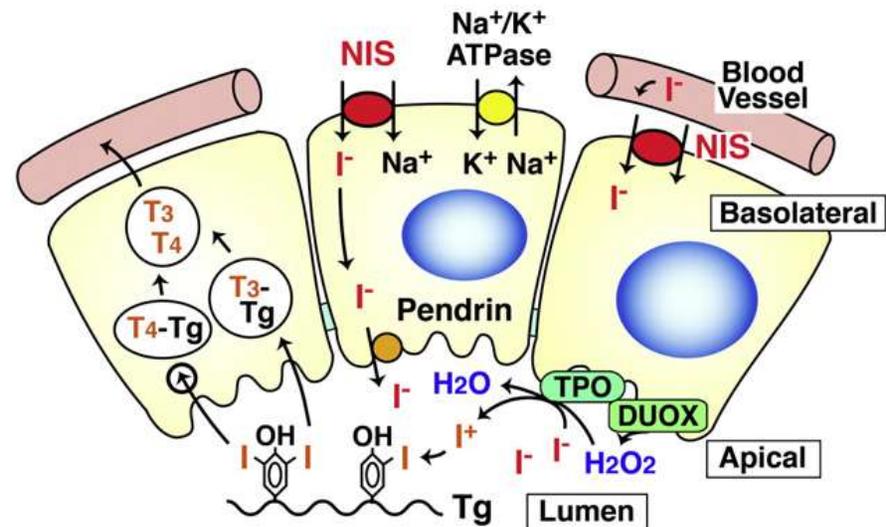


Embryology, Anatomy and Physiology

- The thyroid gland develops from the ventral wall of the pharynx and grows caudally from the base of the tongue to the level of the cricoid cartilage at the base of the neck during the first semester of gestation.
- A narrow isthmus unites the two lobes and sometimes a pyramidal lobe, representing the end of the thyroglossal duct, is present in the midline.
- The protein by which the thyroid concentrates iodide is the sodium/iodine symporter (NIS), on the basolateral membrane of the thyroid follicular cells.



- The expression of NIS is mainly dependent on TSH. Iodide is then translocated across the apical membrane into the colloid. The oxidation of iodide into iodine and organification of iodine in tyrosyl residues of the thyroglobulin molecule take place at the luminal surface of the apical membrane.
- The function of the thyroid gland includes the concentration of iodine, synthesis of thyroid hormones, storage of these hormones as part of the thyroglobulin (Tg) molecule in the colloid, and their secretion into the circulation.
- The concentration of iodide by the thyroid gland, synthesis, and release of thyroid hormones are under the regulatory control of the **hypothalamic–pituitary thyroid axis**. Thyroid stimulating hormone (TSH) from the pituitary plays the major role in regulating thyroid function and this, in turn, is under the control of hypothalamic thyrotropin releasing hormone (TRH) secretion.



Over 99% of circulating thyroid hormones are bound to plasma proteins, primarily thyroxine-binding globulin (TBG). Only the unbound fraction of thyroid hormone is metabolically active and, for this reason, accurate assays of free thyroid hormone, “free T4” and “free T3”, have been developed.

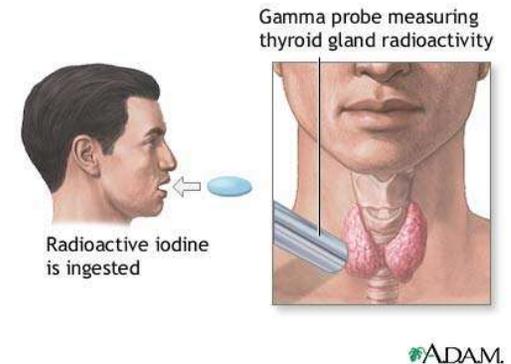
Radionuclides for Thyroid Imaging and Measurements

- **Iodine-131**–the first radiopharmaceutical that was used for thyroid scanning. ^{131}I is unfavorable for thyroid imaging. $T_{1/2}=8.1$ days, a relatively high-energy gamma ray (364 keV) and beta emissions.
- **Iodine-123** is a pure gamma emitter (gamma energy: 159 keV) with a $T_{1/2} = 13$ h. ^{123}I is trapped by functioning thyroid, organified and retained, thus allowing for a proper determination of the iodine uptake in the gland. *The activity commonly administered for imaging in adults is about 5–15 MBq either intravenously or orally (in this case fasting for 6 h before administration is recommended).*
- TcO_4^- ($T_{1/2}=6$ h, gamma energy: 140 keV) is not organified in the thyroid gland. Although TcO_4^- does not perfectly reflect the physiology of iodine, it has some practical advantages, lower cost and on-site daily availability. *For thyroid scanning, an activity of about 37–74 MBq is intravenously injected.*



Thyroid Uptake of Radioiodine

- Measurements of radioiodine uptake help in selecting the appropriate ^{131}I activity to be used for the treatment of hyperthyroidism.
- Thyroid uptake (RAIU) with ^{123}I is performed using either scintillation counting equipment or with the region of interest technique on a gamma camera. Correction for neck “background” (radioactivity in the neck outside the thyroid) must be performed.
- In a normal subject, thyroid uptake increases progressively and reaches a plateau at 24 h. Several factors may influence the normal radioiodine uptake, the most important being the daily iodine intake.



- Thyroid uptake values vary largely from one region to another. Usual values are: 8–20% at 3 h, and 20–45% at 24 h.
- Among the factors that reduce uptake are the use of iodine-containing medications (amiodarone, Lugol's solution, antitussive syrups, surface disinfectants such as povidone-iodine, etc.), antithyroid drugs (propylthiouracil, carbimazole, methimazole), other medications (sulfonamides, p-aminosalicylic acid, glucocorticoids, etc.), and administration of iodinated contrast agents. Thyroid hormones suppress TSH and therefore expression of NIS by the thyrocytes, reducing thyroid uptake. Intake of LT4 should be withheld for about 3 weeks before scintigraphy.



Patient preparation for thyroid scan and RIUT

- Ensuring cessation of iodine-containing foods, vitamin supplements and medicines before the scan for a minimum of 1–2 weeks.
- Ensuring cessation of the following drugs before the scan:
 - Thyroxine (2 week);
 - Liothyronine – needs to be ceased for 5 days;
 - Carbimazole; Propylthiouracil (3–5 days);
 - Amiodarone – an antiarrhythmic, contains high-dose iodine. This will affect scan results if used in the 3 months before the scan;
 - Lithium – affects uptake of the radiopharmaceutical. Cessation of lithium will depend on the clinical condition of the patient and risk versus benefit of carrying out the scan.
- Ensuring that no previous radiological procedure requiring the injection of iodine contrast medium has been carried out 8 weeks before the thyroid scan.



Radioactive Iodine Uptake Testing: Indications

Thyroid uptake is another measure of thyroid function. Measurement allows for the following:

1. Diagnosis of hyperthyroidism
2. Distinguishes other causes of thyrotoxicosis from hyperthyroidism
3. Provides data for calculation of a therapeutic dose of ^{131}I
4. Detects intrathyroidal defects in organification

Contraindications to radioactive iodine uptake (RAIU) testing include: Hypersensitivity reaction to iodine, Pregnancy, Breastfeeding, Severe Graves ophthalmopathy



Causes of increased iodine uptake include the following:

- Hyperthyroidism
- Iodine deficiency
- Recovery phase of subacute, silent, or postpartum thyroiditis
- Rebound after suppression of thyrotropin
- Rebound after withdrawal of antithyroid medication
- Lithium carbonate therapy
- Hashimoto thyroiditis
- Congenital defects of thyroid hormogenesis apart from trapping defect

Causes of decreased uptake include the following:

- Primary hypothyroidism
- Destructive thyroiditis (subacute thyroiditis, silent thyroiditis, postpartum thyroiditis)
- Post-thyroidectomy, ^{131}I treatment, or external neck radiation
- Central hypothyroidism
- Thyroid hormone
- Excess iodine
- Dietary variations and supplements
- Radiological contrast
- Amiodarone
- Topical iodine
- Medications other than those containing iodine (eg, antithyroid drugs, perchlorate, thiocyanate, sulphonamides, sulphonylurea, high-dose glucocorticosteroids)



Thyroid Scintigraphy

- Imaging with TcO_4^- should be done 20 min after intravenous injection (before leakage out of the thyroid).
- With ^{123}I , images are usually acquired 2–4 h after injection.
- An anterior image is standard and oblique images can be obtained
- Normal Thyroid Scintigraphy: The thyroid lobes appear as two elliptical columns slightly angled towards each other inferiorly. A slight degree of asymmetry is common and the right lobe is more often larger. The isthmus may or may not be visualized and the pyramidal lobe appears in 10% of patients.

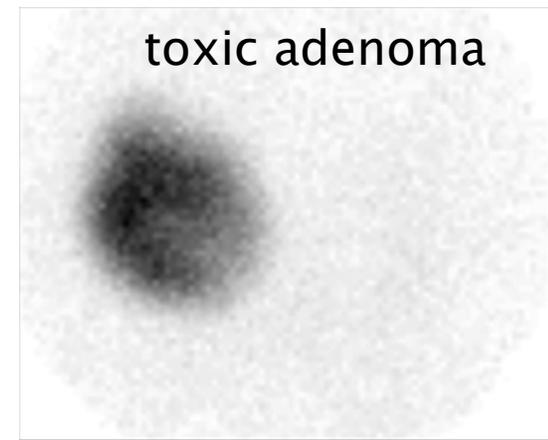
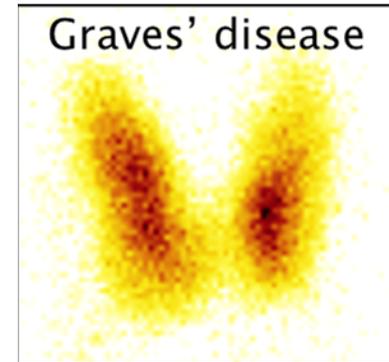


Indications

1. to differentiate causes of primary hyperthyroidism;
2. to evaluate functionality of a thyroid lesion found on clinical examination;
3. to evaluate functionality of a nodule/s found on other imaging tests;
4. Location of ectopic thyroid tissue (e.g., lingual, incomplete thyroid descent).
5. Evaluation of congenital hypothyroidism (total agenesis or hemiagenesis, dyshormonogenesis, incomplete thyroid descent).
6. Evaluation of a neck or substernal mass. Scintigraphy may be helpful to confirm that the mass is functioning thyroid tissue.
7. Differentiation of thyroiditis (i.e. viral, autoimmune) and factitious hyperthyroidism from Graves' disease and other forms of hyperthyroidism.



- **Graves' disease:** The typical scintigraphy pattern in a patient with a first episode of is an increased uptake with homogeneous distribution of the tracer
- Thyroid Autonomy is the second most frequent cause of hyperthyroidism. The probability of autonomy as the cause of hyperthyroidism increases with age, goiter volume and goiter nodularity, and is more frequent in iodine deficiency areas.
- Scintigraphy can show a “hot” nodule with suppression of the remainder of the gland, together with suppressed TSH (“toxic adenoma”).
- **Toxic multinodular goiter** is scintigraphically characterized by multiple hot nodules with suppression of the surrounding stroma and suppressed TSH.

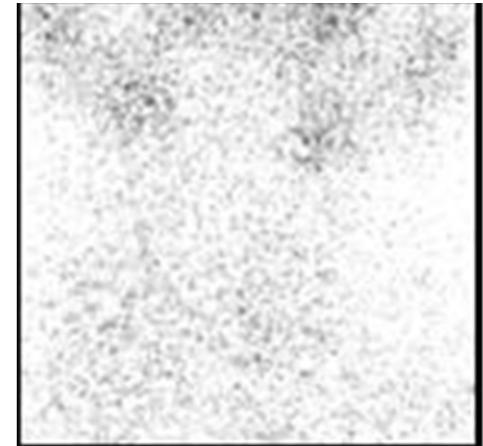


Toxic multinodular goiter



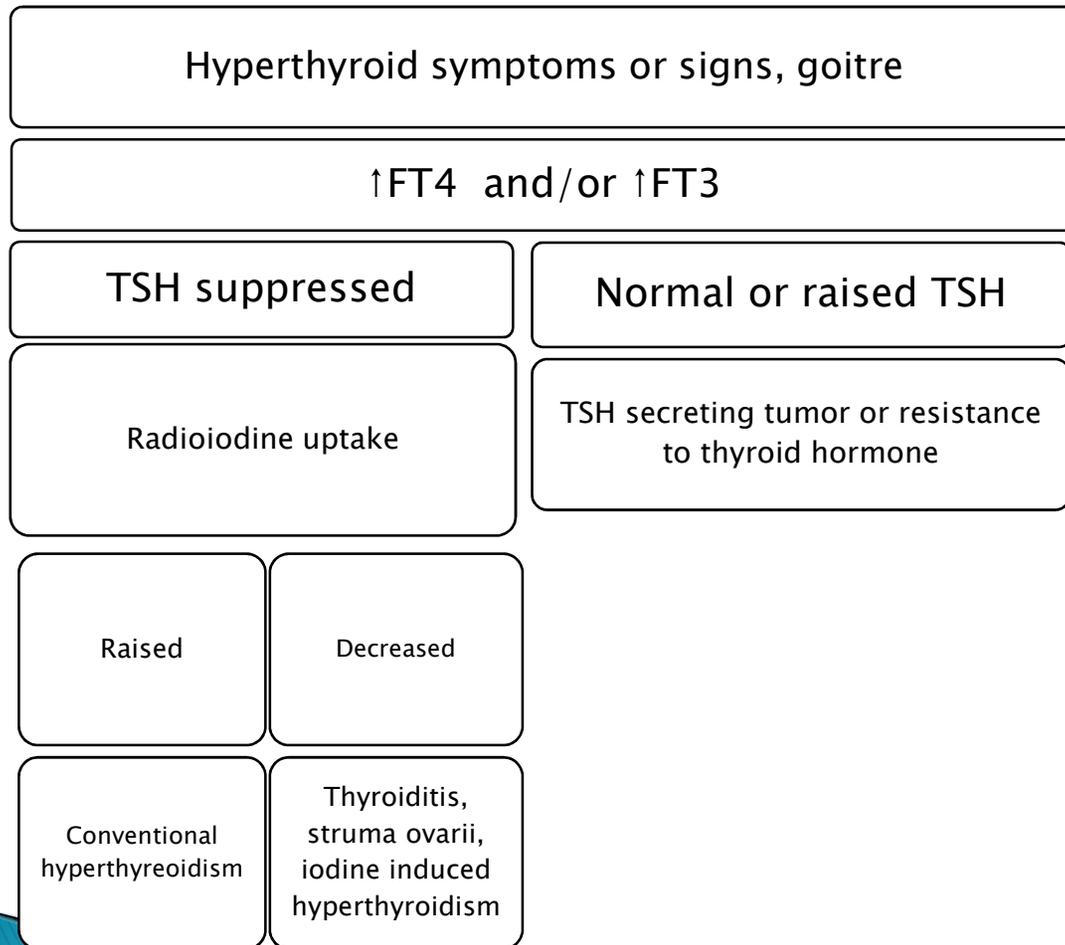
Subacute Thyroiditis

- is an inflammatory disease of the thyroid of presumed viral origin. The inflammatory process causes the release of much of the stored thyroid hormones, which results in mild and transient thyrotoxicosis, then – hypothyroid phase before the patient returns to euthyroidism.
- Clinical symptoms are a painful gland “sore throat” sometimes accompanied by fever. Pain can irradiate to the ear and jaw.
- TSH levels are suppressed at the initial phase with hyperthyroidism and increase in sedimentation rate and C–reactive protein.
- In the initial phase, scanning shows absent or markedly decreased uptake. If scanning has been delayed, the pattern is more that of heterogeneous uptake.



**Similar scan findings are seen in “silent thyroiditis” and “postpartum thyroiditis.”*

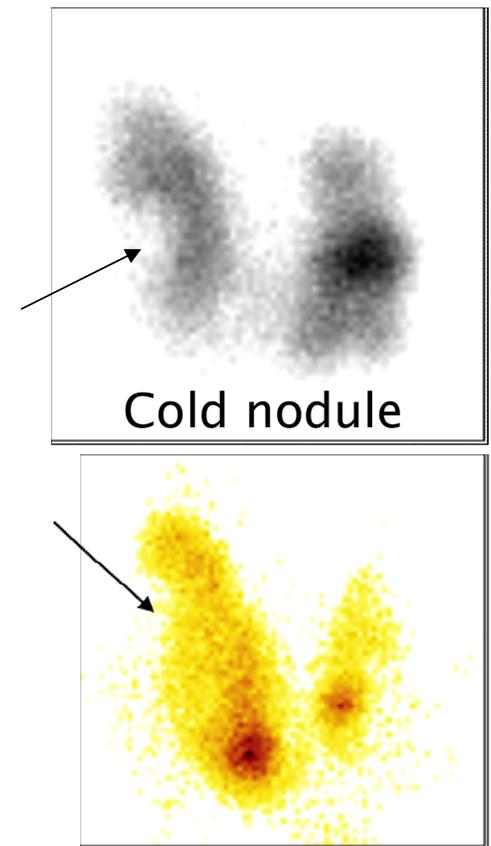
Distinguishes other causes of thyrotoxicosis from hyperthyroidism



When thyroid scanning in a patient with hyperthyroidism shows absence of uptake one should eliminate other causes such as iodine overload (iodinated contrast media, iodine-containing drugs such as amiodarone, etc.) and thyrotoxicosis factitia due to intake of thyroid hormones. Measurement of urinary iodine and Tg (very low in the case of thyrotoxicosis factitia) are helpful.

Solitary Thyroid Nodule

- The risk of thyroid cancer is about 10% for a palpable thyroid nodule. It increases in the case of a previous history of radiation exposure, among other factors.
- In the evaluation of patients with a palpable thyroid nodule (or with a non-palpable nodule larger than 1 cm), thyroid sonography and measurement of serum thyrotropin (TSH) are the initial steps.
- If serum TSH is subnormal, scintigraphy should be obtained to document whether the nodule is hot, iso-functioning, or non-functioning. Because “hot” nodules rarely harbor malignancy, no additional cytological evaluation is necessary. When the nodule is isofunctioning “warm” or non-functioning “cold” FNA should be performed.
- When TSH is normal or elevated one may go directly to FNA. However, if the cytology reading is “indeterminate,” a thyroid scan should be performed because a significant number of indeterminate readings are due to “follicular” benign lesions that appear as a functioning nodule.



Autoimmune Thyroiditis (AIT)

- AIT or Hashimoto's disease is characterized by a destructive lymphocytic infiltration of the thyroid gland with or without goiter. In most patients, antibodies against thyroid peroxidase (anti-TPO) can be observed.
- Subclinical or manifest hypothyroidism is present in 30–40% of patients. Initial transient hyperthyroidism (hashitoxicosis) can occur in 5–10% due to thyroid hormone release secondary to inflammation.
- The differential diagnosis between Graves' disease and hyperthyroid AIT can be difficult. Scintigraphy in AIT usually shows heterogeneous uptake, but is not very specific.



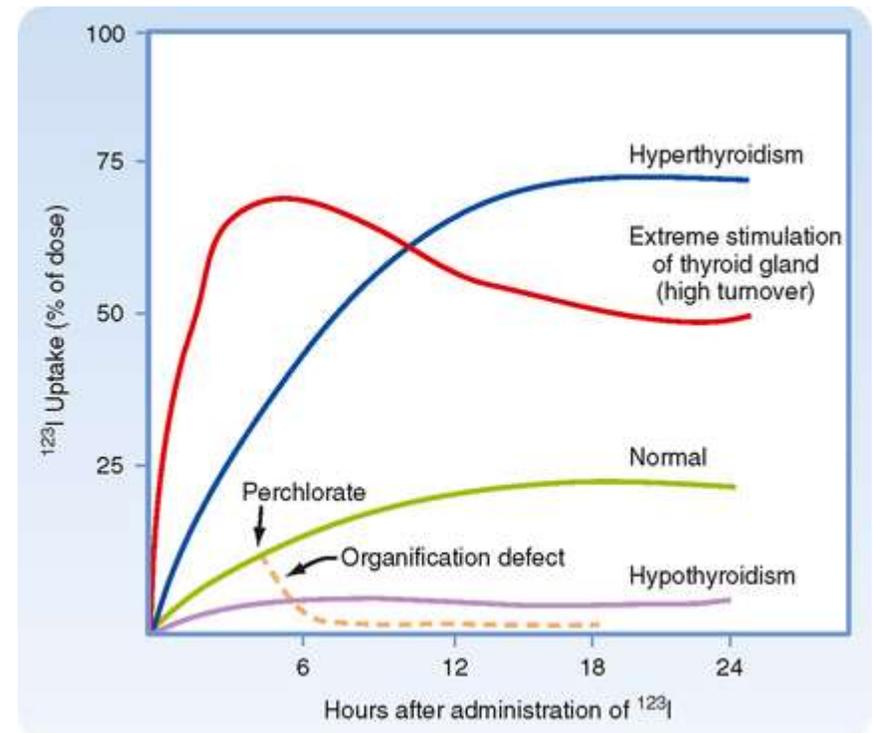
Neonatal Hypothyroidism

- Thyroid dysgenesis (agenesis, hypoplasia, ectopia) is the most common cause of neonatal hypothyroidism. Other causes are inherited disorders of the thyroid metabolism, such as iodine organification defect (peroxidase defect) and specific mutations of the genes coding for the NIS, thyroid peroxidase, thyroglobulin and pendrin.
- Thyroid scintigraphy is helpful for differential diagnosis.
- Scintigraphy can show ectopic tissue at the base of the tongue with no normal tissue in the neck (lingual thyroid), neither uptake in the neck nor ectopic tissue (agenesis of thyroid)



The Potassium Perchlorate Discharge Test

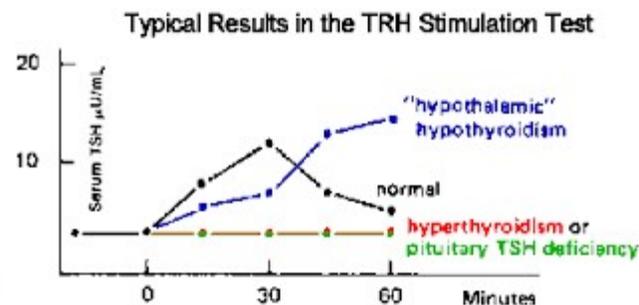
- In spite of the identification of specific mutations of the genes coding for thyroid peroxidase and pendrin, the discharge test has kept a role in establishing the diagnosis of neonatal hypothyroidism. This test is helpful for the differential diagnosis of newborns with a suspicion of Pendred's syndrome (congenital deafness, hypothyroidism by thyroidal organification defect and goiter).
- Potassium perchlorate prevents iodide from entering the thyroidal space by impairment of the NIS function.
- In a normal thyroid, the uptake of iodine will remain constant after perchlorate because organified and therefore non-dischargeable iodine cannot leave the follicular lumen. An organification defect is present if a reduction in the thyroidal uptake is noted after administration of potassium perchlorate.



In this procedure a regular RAIU test is performed initially, measuring thyroid counts at 3 h. Then potassium or sodium perchlorate, 0.5 in children and 1 g in adults, is given orally and a new thyroid uptake is determined 1 h to 2 h later

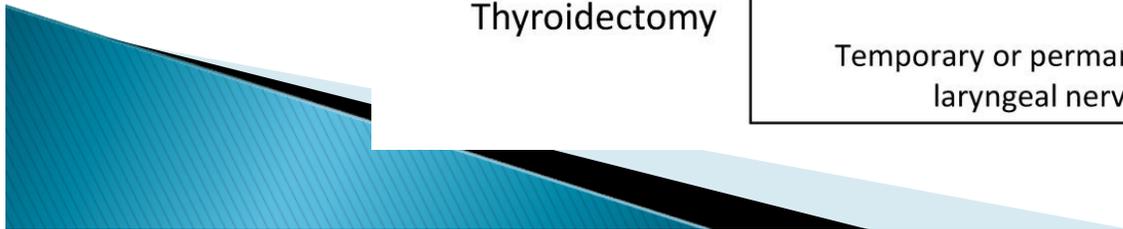
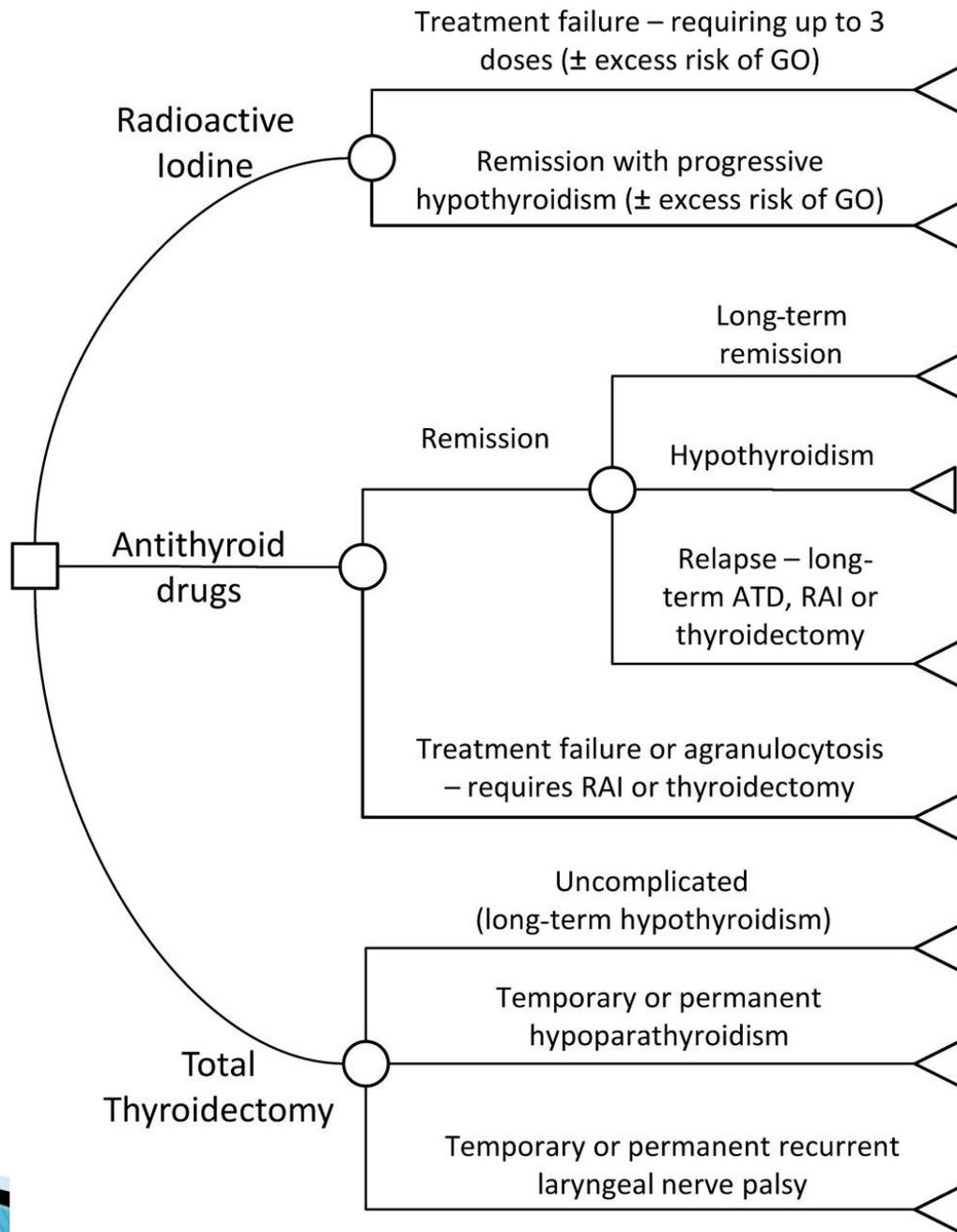
TRH Stimulation Test

- The TRH stimulation test is used to distinguish between pituitary or hypothalamic deficiency as the cause of secondary hypothyroidism and to evaluate cases of hyperthyroidism. The test is conducted by collecting blood specimens for TSH before and thirty minutes after intravenous administration of a test dose of TRH. The normal response is a substantial increase in TSH in the 30 minute specimen.
- In secondary hypothyroidism caused by pituitary insufficiency the TSH concentration in the thirty minute specimen will remain essentially unchanged. The TSH concentration in the thirty minute specimen will be noticeably increased in cases of hypothalamic insufficiency.
- In hyperthyroidism, the pituitary is suppressed by elevated thyroid hormone and there is no significant increase in TSH in the 30 minute specimen.



Hyperthyroidism

- is a clinical syndrome of tachycardia, weight loss, and hypermetabolism resulting from supraphysiological circulating levels of thyroid hormones, leading to suppression of TSH secretion. Most cases of hyperthyroidism are due to increased endogenous synthesis and secretion of thyroid hormones from the thyroid.
- Clinical assessment combined with circulating hormone and thyroid autoantibody measurements, thyroid scintigraphy, and RAIU usually allow identification of the various disease processes that may be responsible.
- Graves' disease (autoimmune diffuse toxic goiter) is due to the presence of thyroid-stimulating immunoglobulins and is associated with autoimmune exophthalmos and pretibial myxedema. Radioiodine uptake will usually be elevated at 3 hours and/or 24 hours, and the gland will reveal diffuse enlargement in most cases with increased thyroid activity and minimal background and salivary gland activity.
- The low RAIU (usually $\leq 5\%$) of hyperthyroid patients with subacute thyroiditis, postpartum thyroiditis, silent thyroiditis, and surreptitious thyroid hormone
- The thyroid scan should easily be able to distinguish toxic nodular goiters from Graves' disease. The clinical importance of this is that many patients with toxic nodular goiter will require a higher dose of ^{131}I for therapy than will Graves' disease patients.



Radioiodine Therapy of Hyperthyroidism

- Radioiodine was first used for the treatment of hyperthyroidism in 1941 and has since evolved to the treatment modality of choice for the majority of adult patients.
- Antithyroid drug therapy achieves a permanent remission in only 10–40% of patients, is used initially in many patients.
- Although subtotal thyroidectomy is effective and complications are rare, It is normally limited to patients in whom radioiodine is unsuitable, such as women who may be pregnant, or who have extremely large goiters with compressive symptoms.
- Radioiodine therapy is effective, practical, inexpensive, and available on an outpatient basis.
- **Prior to initiation of therapy** : the diagnosis must be confirmed by elevation FT4, FT3 levels and suppression TSH, an elevated RAIU
- The patient must be counseled prior to therapy regarding the advantages and disadvantages of alternative therapies. Because iodide readily crosses the placenta, ¹³¹I may not be administered during pregnancy so a pregnancy test is mandatory prior to administration

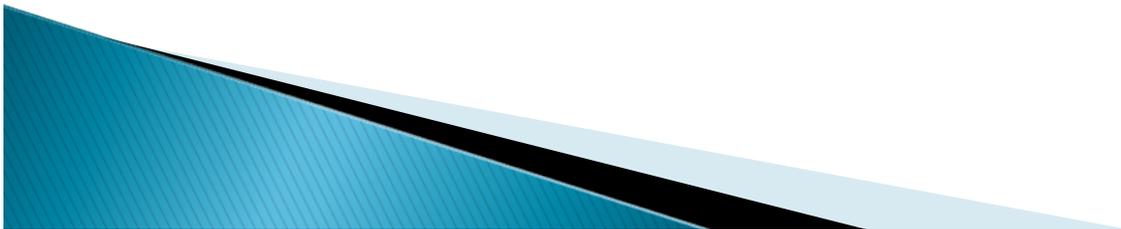


Radioiodine Therapy of Hyperthyroidism

- The effectiveness of radioiodine treatment for hyperthyroidism is due to radiation-induced cellular damage resulting from high-energy beta emission. The radiation dose to the thyroid is related to (1) the amount of radioiodine administered, (2) the fraction deposited in the gland (uptake), (3) the duration of retention by the thyroid (biologic half-life), and (4) the radiosensitivity of the irradiated tissue.
- The complications of radioiodine therapy include rare exacerbation of hyperthyroidism, possible exacerbation of existing Graves' orbitopathy, and post-therapeutic hypothyroidism. It is estimated that less than 10% of patients require retreatment, and this is rarely undertaken before 3-4 months following therapy



- A full thyroid blood test panel measures the levels of these hormones and antibodies blood:
- TSH (thyroid-stimulating hormone).
- T3 or free T3 (tri-iodothyronine).
- T4 or free T4 (thyroxine).
- TPO (thyroid peroxidase antibodies), also known as microsomal antibodies.
- TG (thyroglobulin).
- TGAb (thyroglobulin antibodies)
- TRAB



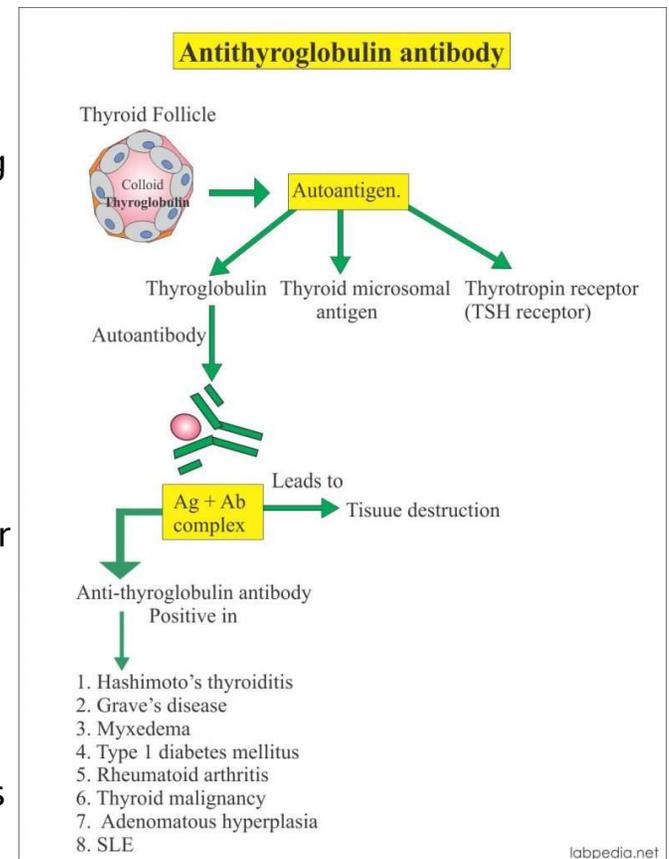
Serum thyroglobulin measurement

- Thyroglobulin (Tg) is a large glycoprotein it is produced only by normal thyrocytes or well-differentiated thyroid cancer (DTC) cells. Tg is usually measured in serum, but measurements can also be made in thyroid cyst fluids and materials obtained by fine needle biopsy of thyroid nodules. Serum Tg is elevated in patients with goiter and in most hyperthyroid conditions; a low serum Tg can be also an useful biomarker to confirm the diagnosis of thyrotoxicosis factitia and/or to investigate the ethiology of congenital hypothyroidism
- The primary use of serum Tg measurement is, however, as tumor marker for patients affected by DTC
- A strong correlation between serum Tg levels and the amount of DTC tissue has been reported (after thyroidectomy and radioiodine therapy)



Thyroid-related antibodies–TgAb

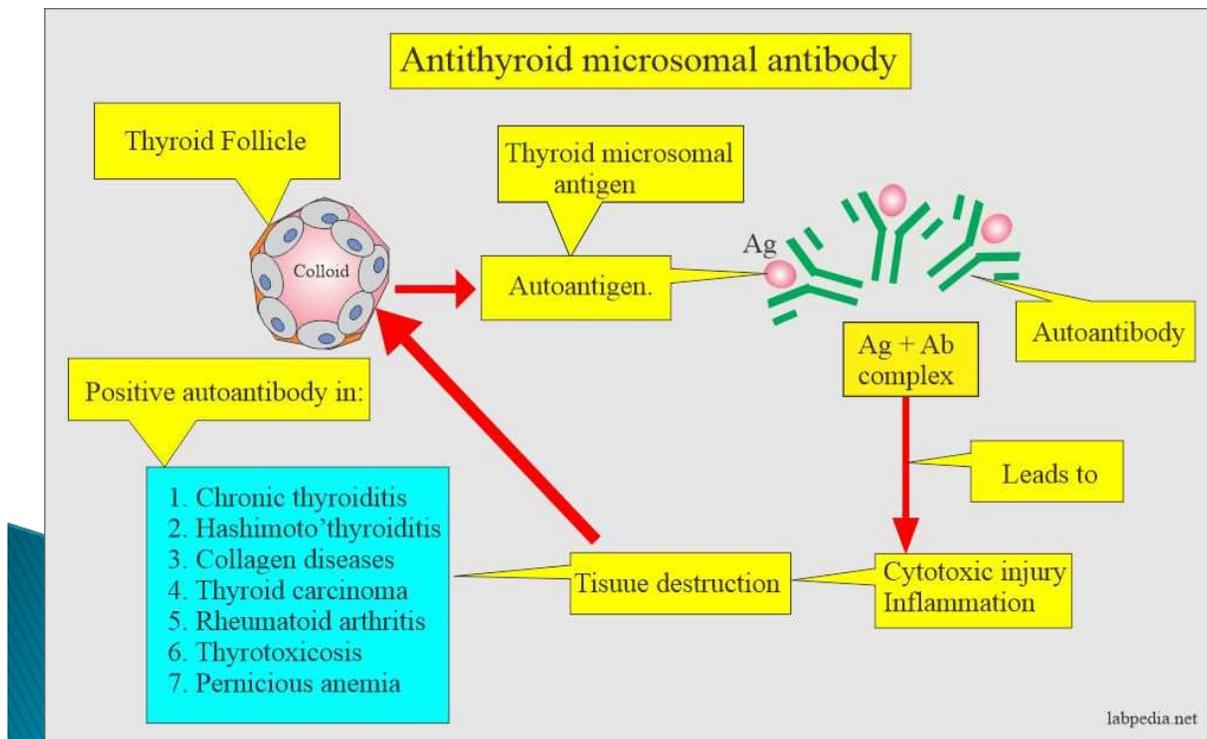
- **TgAb** itself does not cause thyroid cell destruction. Massive destruction of the thyroid gland induces structural changes in Tg, leading to antibody production against Tg. However, high Tg levels in blood do not necessarily induce antibody production. The TgAb level depends on antigen exposure time. TgAb levels may transiently rise postoperatively as an apparent immune reaction to released tissue particles after surgery, and they may rise after RIT. After total thyroidectomy and RIT, all antibodies disappeared progressively, with a median disappearance time for TgAb of about 3 years
- Follow-up measurements of TgAb levels are useful for detecting persistent or recurrent disease after total thyroidectomy and RI remnant ablation of DTC. High TgAb levels could cause Tg levels to be undetectable. Therefore, rising TgAb levels after initial treatment are evaluated as a ‘biochemical incomplete response,’ and these patients should be carefully monitored to detect recurrent or persistent disease.



20% of people with normal thyroid function have +TgAb

Thyroid-related antibodies–TPOAb

- It is one of the first thyroid antibodies identified. It was later discovered that this antibody targets Thyroid Peroxidase (TPO), and these antibodies are used to diagnose AITD. The production of thyroid hormones is carried out by the trans-membrane protein TPO, which is found in the apical membrane of thyrocytes, and antibodies to TPO lead to AITD
- anti-TPO antibodies from AITD patients can fix complement, destroy thyrocytes



Anti-TPO antibodies are detected in 90–95% of AITD patients, 80% of GD, and 10–15% of non-AITD patients. While anti-TPO antibodies may act cytotoxic on thyrocytes in HT they do not have an established role in GD.

TSH Receptor Ab (TRAb/TSHRAb)

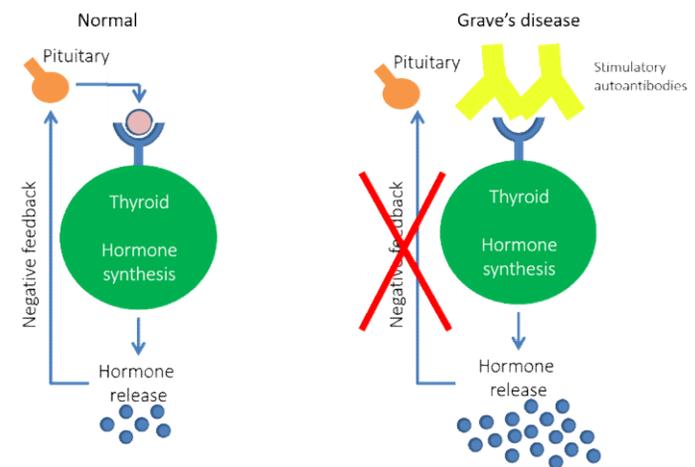
- in Grave's disease patient's blood.
- in other thyroid autoimmune diseases.

Their function is variable: In some cases, they may have a stimulatory effect. In some cases, they block the TSH-receptor site and decrease thyroid function.

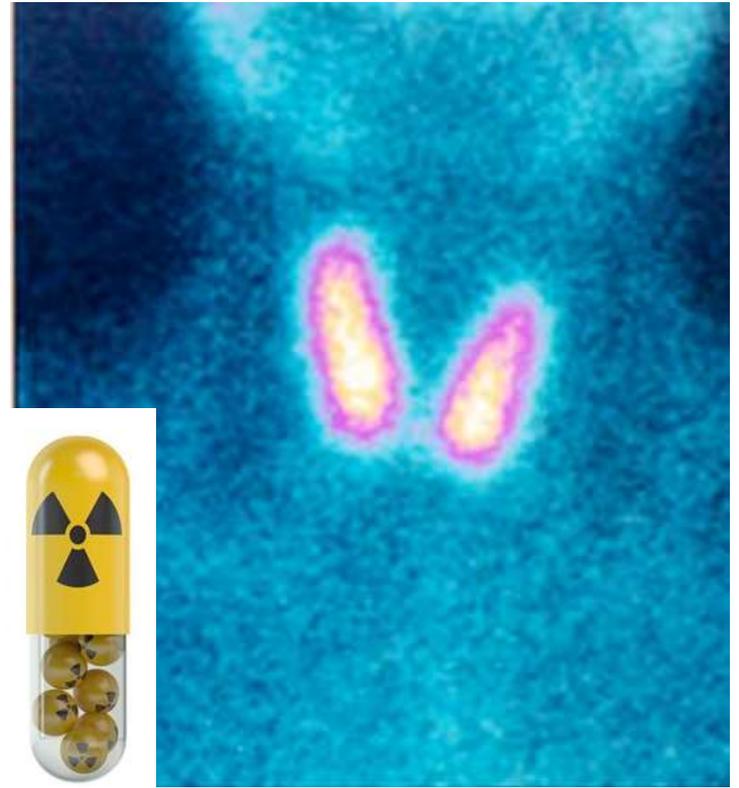
The conventional TRAb immunoassays measure not only thyroid-stimulating immunoglobulin but also thyroid-blocking immunoglobulins and neutral immunoglobulins.

TRAb titer was a good predictor of the final outcome ($p < 0.001$);

titer ≥ 46.5 UI/L could identify patients who had never achieved long-term remission with a sensitivity of 52% and a specificity of 78%.



Thank You
for Your
Attention!



Questions?