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M2 Thyroid Lecture Series

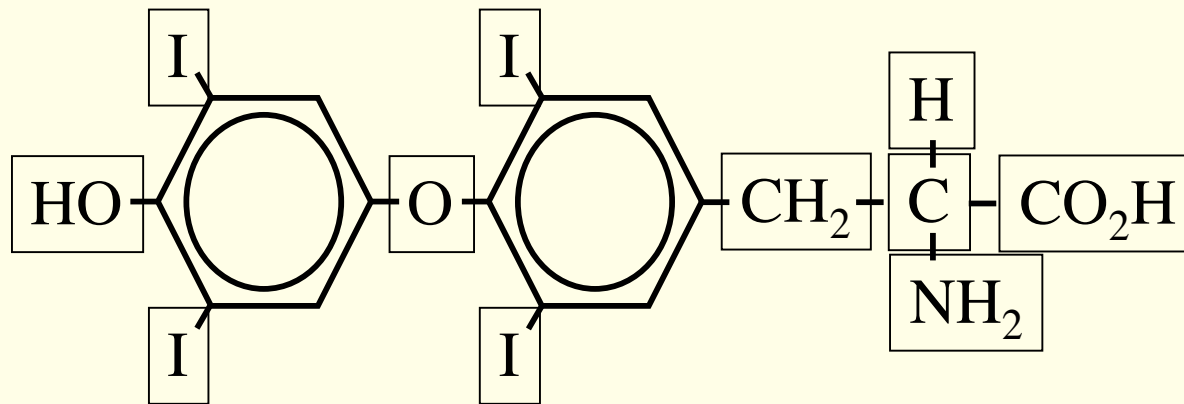
Robert Lash, MD

February 28, 2007

- Lecture 1: Regulation of Thyroid Follicular Cell Function
- Goals/Objectives
 - Understand the structure and metabolism of thyroid hormone
 - Understand the structure and function of the thyroid follicle
 - Understand homeostatic control of plasma thyroid hormone levels

Thyroxine (T4)

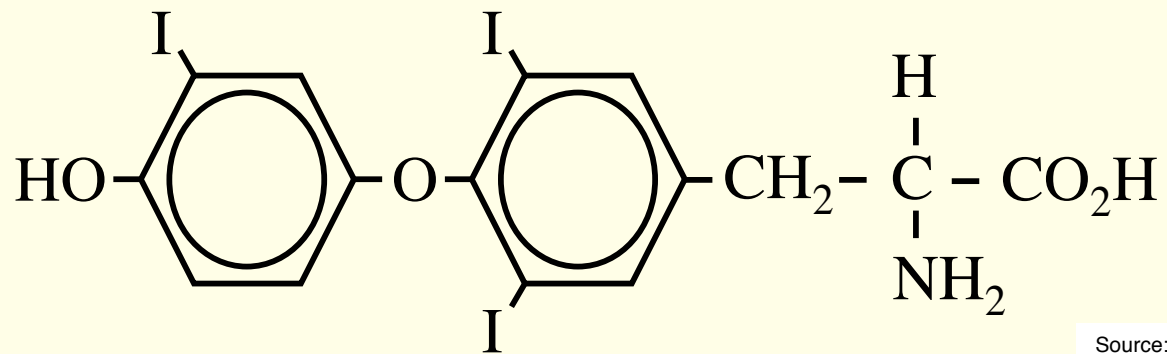
(3,5,3',5' tetraiodo-L-thyronine)



Source: Undetermined

- Derived entirely from the thyroid gland
- Is a pro-hormone

T3 (3,5,3' triiodo-L-thyronine)



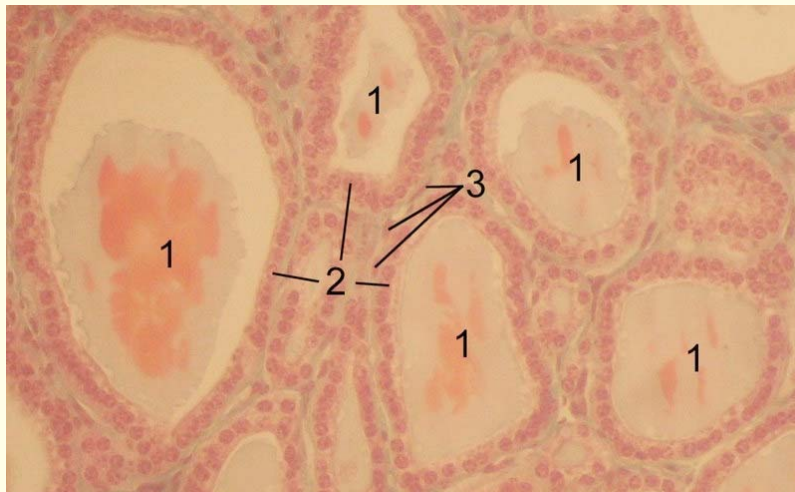
Source: Undetermined

- Is the biologically active thyroid hormone
- 20% of plasma T3 comes from thyroidal secretion
- 80% comes from T4 5'-deiodination in peripheral organs

Three Iodothyronine Deiodinases

- Types 1 and 2 deiodinases convert T4 to T3
 - D1 primarily in liver and kidney, supplies plasma T3
 - D2 in pituitary, brain, placenta, brown fat, muscle and thyroid; produces T3 for “local” use as well as plasma T3
- Type 3 deiodinase (D3) removes an inner ring iodine
 - Converts T4 to reverse T3, and T3 to T2
 - D3 inactivates thyroid hormone

Thyroid Follicle: Functional unit of the thyroid gland



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[BY: Uwe Gille](#)

Normal thyroid gland illustrating the histologic structure, including colloid-filled (C) follicles of varying size lined by cuboidal follicular cells

Thyroid hormone synthesis (1)

- Plasma iodide enters the thyroid cell through the sodium iodide symporter (NIS).
- Thyroglobulin (Tg), a large glycoprotein, is synthesized within the thyroid cell.
- Thyroid peroxidase (TPO) sits on the luminal membrane. It iodinates specific tyrosines in Tg, creating mono- and di-iodotyrosines.
- The iodotyrosines combine to form T3 and T4 within the Tg protein.

Thyroid hormone synthesis (2)

- Each mature Tg molecule contains ~3 T4's, but only 1 in 4 Tg's contains a T3 molecule.
- Colloid is largely composed of Tg, and is basically a storage depot of thyroid hormone.

Thyroid hormone synthesis (3)

- In response to TSH, pseudopodia form and endocytose colloid.
- In the cell, colloid droplets fuse with lysosomes and thyroid hormone is cleaved enzymatically from Tg.
- T4 and T3 are released into the circulation.
- TSH stimulates iodide trapping, as well as thyroid hormone synthesis and secretion.

Sodium Iodide Symporter (NIS)

- Co-transporters iodide and sodium
- 65 kDa protein with 13 putative trans-membrane domains
- Structurally similar to other Na⁺ cotransporters, e.g. Na⁺/glucose transporter
- Allows for use of radioiodine as a specific and effective agent in the diagnosis and therapy of multiple thyroid disorders

Endemic Goiter



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[BY: Hoorob](#)

Dietary Iodide: Thyroid function and endemic goiter

- Intake of >200 $\mu\text{g}/\text{d}$ is ideal. Less than 50 $\mu\text{g}/\text{d}$ impairs thyroid gland function and T_4 secretion, resulting in elevation of TSH and goiter (thyroid enlargement).
- “Endemic Goiter” implies $\geq 10\%$ of the population is affected.

Dietary Iodide: Thyroid function and endemic goiter

- Iodine deficiency is virtually non-existent in the US. However, worldwide it is the leading cause of goiter and hypothyroidism.

Endemic Cretinism



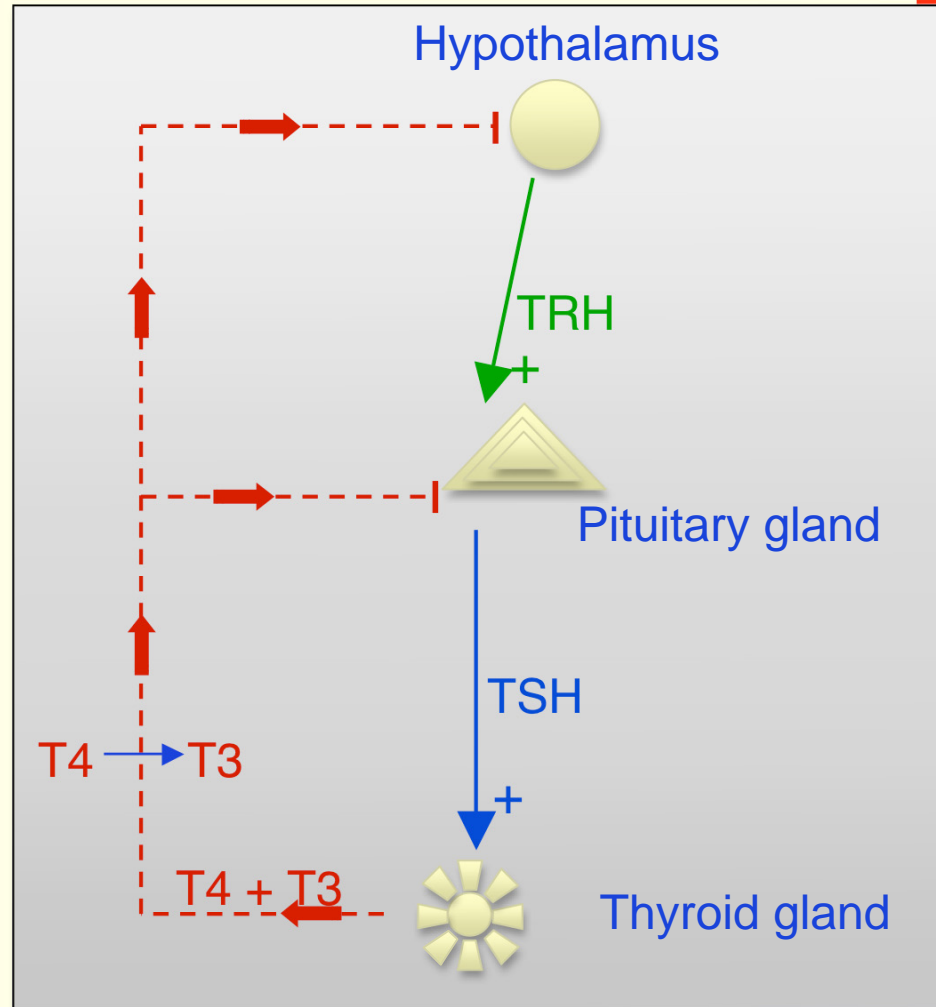
On the left, a euthyroid 6 year old Ubangi girl at the 50th height %ile (105 cm). On the right, a 17 year old girl with a height of 100 cm, mental retardation, myxedema and a TSH of 288 (normal 0.3-5.5).

Werner & Ingbar's The Thyroid, 8th Edition, page 744.

Endemic Cretinism

- Children born to women with endemic goiter
- Mental retardation, abnormalities of hearing, gait and posture, short stature
- Consequence of fetal/neonatal hypothyroidism, possibly with maternal hypothyroidism contributing
- Despite being readily preventable by iodized salt, mental retardation due to iodine deficiency is still common worldwide

Feedback regulation of thyroid function



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Thyrotropin (TSH; Thyroid Stimulating Hormone)

- 28 kDa glycoprotein dimer composed of non-covalently linked alpha and beta chains.
- The alpha chain is shared by TSH, FSH, LH and CG.
- The biological specificity of each glycoprotein hormone is conferred by the beta chain.

TSH: Mechanism of Action

- Binds to specific receptors on thyroid follicular cells.
- TSH receptors are members of the large family of G-protein coupled receptors.
- The major second messenger is cAMP, although activation of phospholipase C also may be involved.

Thyrotropin Releasing Hormone (TRH)

- A tripeptide: pyroGlutamate-histidine-proline-amide
- Synthesized from a 29 kDa precursor protein that contains 5 copies of TRH flanked by basic amino acids.
- A specific protease cleaves the precursor to yield TRH. The intervening peptides also may have hormonal function.

Plasma thyroid hormone binding proteins

- ~99.97% of plasma T4 and 99.7% of T3 are non-covalently bound to proteins.
- Thyroxine Binding Globulin (TBG) is the major binding protein for T4 and T3. TBG's affinity for T4 is ~10-fold greater than for T3.
 - Do not confuse TBG with thyroglobulin, the precursor protein from which T4 and T3 derive.

Plasma thyroid hormone binding proteins

- Transthyretin also carries some T4. Albumin carries small amounts of T4 and T3.
- TBG, transthyretin and albumin are made in the liver.

Importance of free versus protein-bound hormone

- Only free T4 and free T3 are biologically active and regulated by feedback loops.
- Therefore conditions that alter TBG levels alter total T4 and T3, but do not alter free T4 and free T3.
 - Pregnancy (elevated estrogen)
 - Acute hepatitis
 - Chronic liver failure

M2 Thyroid Lecture Series

Robert Lash, MD

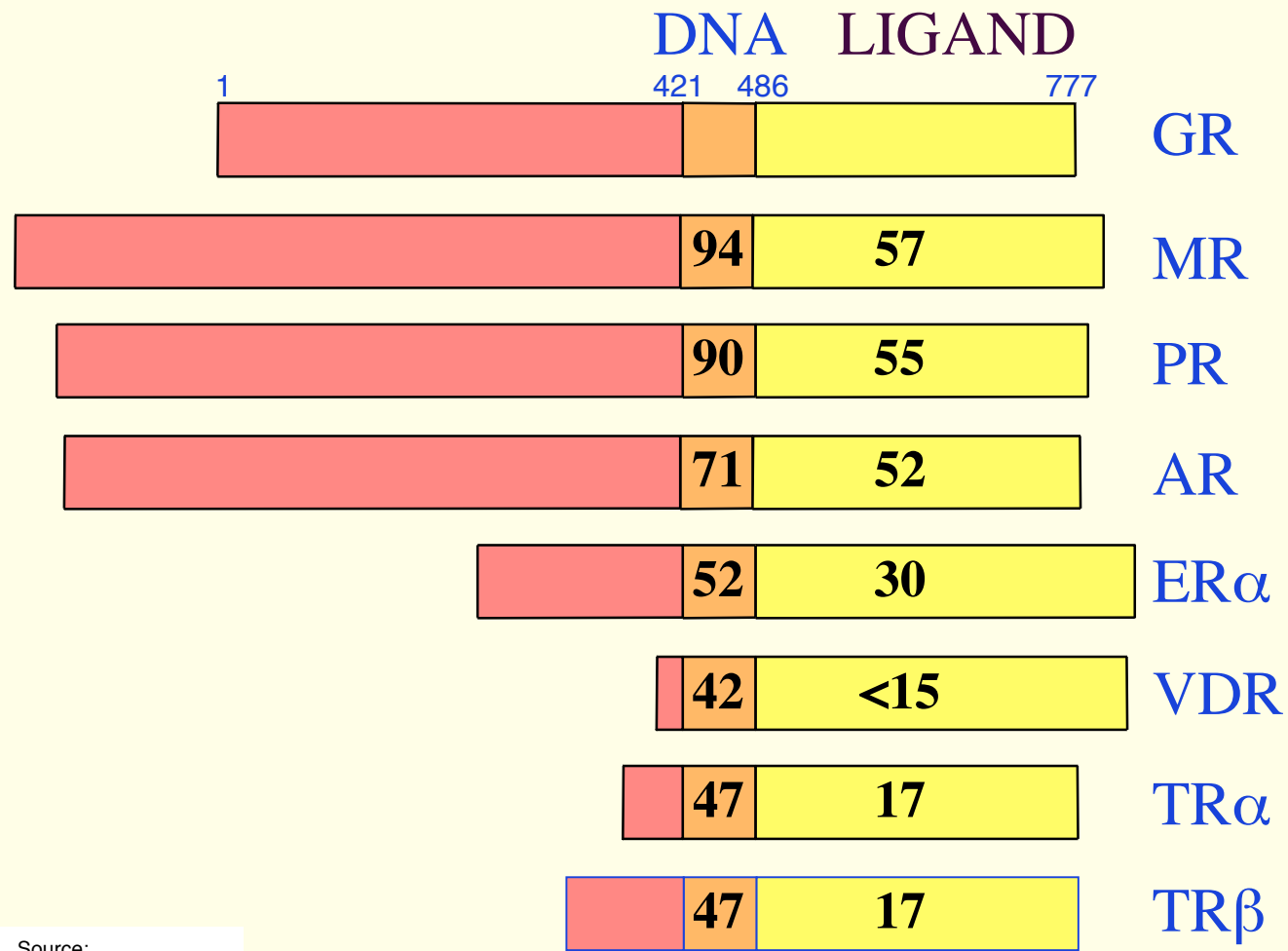
February 28, 2007

- Lecture 2: Actions and Pharmacology of Thyroid Hormones
- Goals/Objectives
 - Understand the molecular basis of thyroid hormone action and its relevance to clinical medicine
 - Understand the appropriate use of laboratory tests to evaluate thyroid function

Molecular basis of thyroid hormone action

- Thyroid hormone binds to nuclear receptor proteins.
- T3 binds with 10-fold greater affinity than T4.
- T3 receptors bind to specific DNA sequences (hormone response elements) generally located in the 5' flanking regions of target genes.

Nuclear Receptor Superfamily



Source:
Undetermined

Molecular basis of thyroid hormone action

- T3 receptors are related to receptors for steroids, retinoids and vitamin D.
- T3 receptors bind DNA as heterodimers with retinoid X receptors.
 - RXRs are nuclear receptors that dimerize with numerous members of this superfamily (RARs, VDR, PPARs and others), but not with steroid receptors.

Molecular basis of thyroid hormone action

- T3-occupied T3 receptors activate many genes and repress others (e.g. TRH, TSH).
- Unliganded T3 receptors are not “neutral” - they repress genes that are activated by T3, and activate genes that are repressed by T3.
- This may explain why hypothyroidism causes greater abnormalities than does the absence of T3 receptors (in mice).

How does T3 induce transcription?

- Unliganded TRs bind to a co-repressor complex which deacetylates histones, tightening chromatin structure and thereby impeding transcription.
- T3 binding causes a conformational change in the TR. Co-repressors fall off and co-activators now bind. These include histone acetyltransferases, which loosen chromatin to allow access to critical transcription factors.

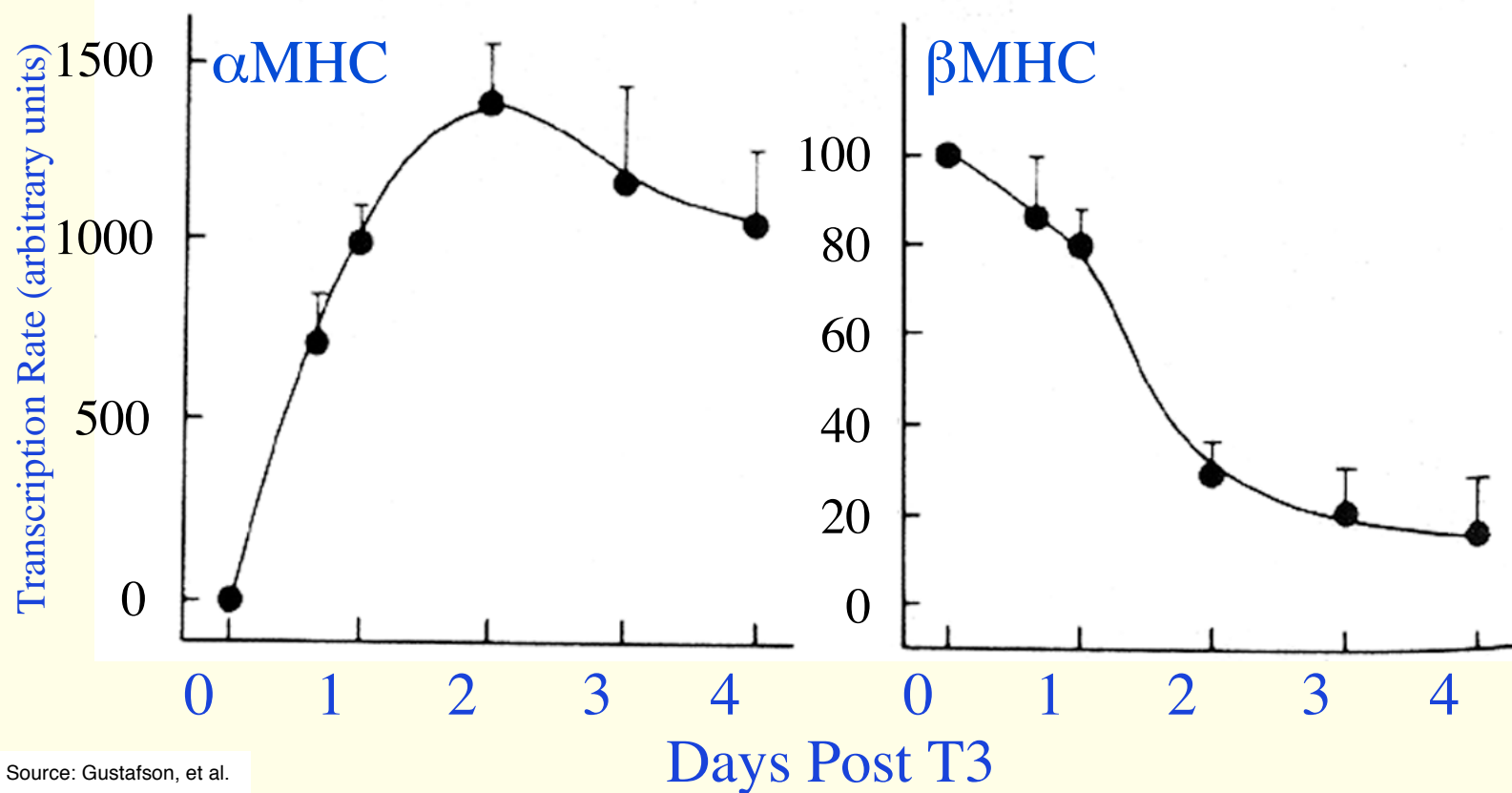
Mechanisms of gene regulation are similar for all nuclear receptors

- Co-activators are recruited by estradiol-occupied estrogen receptors, etc.
- Although unliganded steroid receptors do not bind co-repressors, receptor antagonists alter the receptor structure to recruit co-repressors (tamoxifen-bound estrogen receptor; RU486-bound progesterone receptor, etc.).
- Aberrant histone deacetylation underlies some cancers, and histone deacetylase inhibitors show promise as therapies.

Inotropic Action of T3

- Cardiac myosin is a hexamer that contains either α or β heavy chains.
- The velocity of cardiac contraction correlates with myosin ATPase activity, which is greater for MHC α than β .
- T3 induces transcription of MHC α and represses MHC β , thereby increasing ATPase activity and inotropy.

T3 Regulates MHC Transcription in Rats



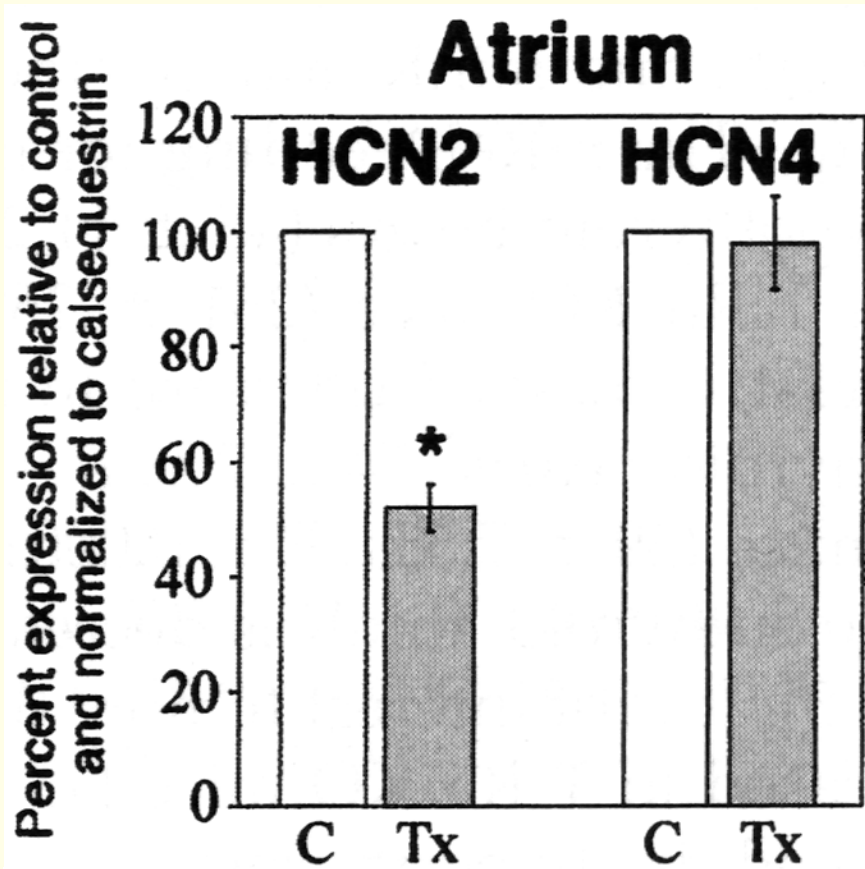
Source: Gustafson, et al.

TA Gustafson, et al. J. Biol. Chem. 262: 13316-22, 1987

Inotropic Action of T3 (2)

- Sarcoplasmic reticulum ATPase removes Ca^{++} from the cytosol during diastole, leading to myocardial relaxation.
- T3 induces transcription of this Ca ATPase, thus increasing the speed of relaxation.

Chronotropy: Atrial Pacemaker Channel HCN2 is Induced by T3



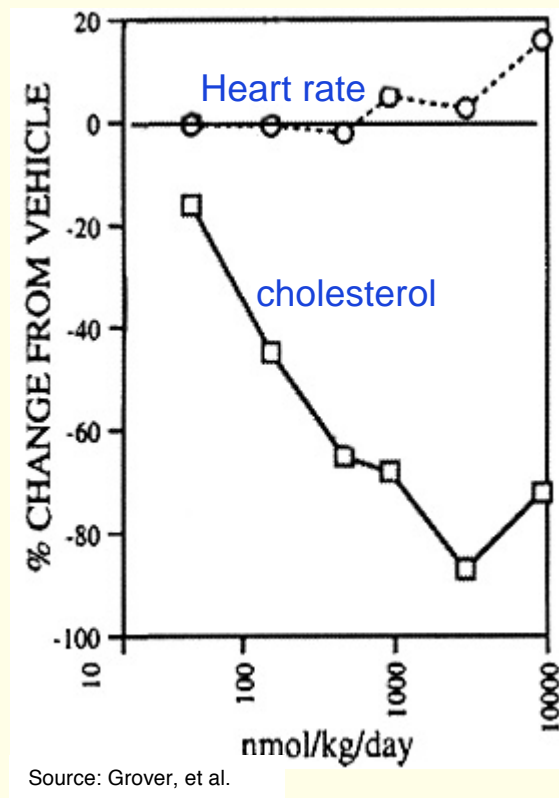
Source: Gloss, et al.

Atrial RNA from control (C) or hypothyroid (Tx) mice was assayed for HCN2 and HCN4 expression. Heart rates were 472 ± 26 (C) and 335 ± 21 (Tx) beats/min.

B Gloss, et al. Endocrinology 142: 544-550, 2001

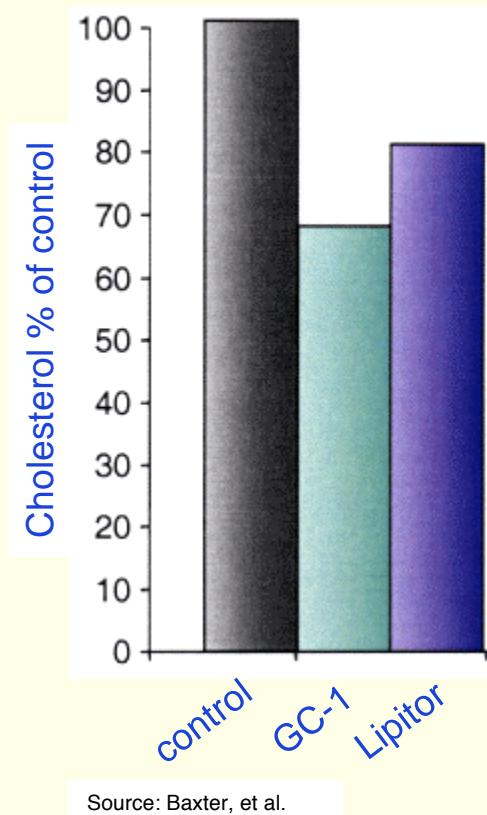
T3 Receptor β -specific ligands have potential as cholesterol lowering agents

GC-1 treatment of cholesterol-fed rats



GJ Grover, et al. Endocrinology 145:1656, 2004

GC-1 vs atorvastatin (Lipitor) treatment of monkeys



JD Baxter, et al. TEM 15:154, 2004

A mother wheeled her daughter in a stroller into clinic...



...and lifted the child onto the
examining table



What is this
girl's age?

T3 and Growth Hormone

- Humans and rodents with hypothyroidism have low growth hormone levels and do not grow as rapidly as normal.
- The rat growth hormone gene contains a T3 response element. How T3 regulates human growth hormone is uncertain.

Laboratory Evaluation of Thyroid Function

Serum Thyroxine (T4)

- Measure free T4, not total T4
 - Only free T4 is biologically active
 - Conditions that alter TBG alter total T4 but not free T4
 - Pregnancy raises total T4
 - Chronic liver failure lowers total T4
- High in hyperthyroidism
- Low in hypothyroidism

Serum Triiodothyronine (T3)

- High in hyperthyroidism
- Low in hypothyroidism
 - But generally not worth measuring in hypothyroidism because T3 is less sensitive and less specific than the decrease in free T4
- Not as influenced by changes in TBG as is T4, but measurement of free T3 is still preferable to total T3

Serum Thyrotropin (Thyroid Stimulating Hormone; TSH)

- Low in hyperthyroidism
 - Hyperthyroidism secondary to excess TSH secretion is too rare to be worth considering
- High in primary hypothyroidism; inappropriately “normal” or low in secondary and tertiary hypothyroidism
- Most sensitive screening test for hyperthyroidism and primary hypothyroidism
 - TSH within the normal range excludes these diagnoses

Antithyroid Antibodies

- Antimicrosomal antibodies - the antigen is TPO
- Antithyroglobulin antibodies
- Present in ~95% of Hashimoto's and ~60% of Graves' patients at the time of diagnosis
- Usually not very helpful in making a diagnosis or guiding therapy

Radioiodine Uptake

- Used to evaluate the cause of hyperthyroidism
 - High if the thyroid is hyperfunctioning e.g. Graves' disease
 - Low if thyroid hormone is leaking out of damaged thyroid cells (subacute thyroiditis) or the patient is taking excess exogenous thyroid hormone
- Used to calculate the dose of I-131 to treat hyperfunctioning thyroid tissue or cancer

Thyroid Scan (nuclear medicine)

- Primary use is to determine whether palpated nodules are functional or non-functional.
 - “Hot” nodules concentrate the radionuclide and are essentially always benign.
 - “Cold” nodules are usually benign but are sometimes malignant.
 - The majority, perhaps 90%, of palpable nodules are cold.

M2 Thyroid Lecture Series

Robert Lash, MD

March 1, 2007

- Lecture 3: Hyperthyroidism and the Non-thyroidal Illness Syndrome (Sick Euthyroid Syndrome)
- Goals/Objectives
 - Understand the etiology, epidemiology, clinical features and therapy of the various forms of hyperthyroidism
 - Understand the basis for and characteristics of the non-thyroidal illness syndrome

Graves' Disease: Epidemiology

- Most common cause of hyperthyroidism
- Female/Male ~10/1
- Peak onset 3rd-4th decade, but can occur at any age
- ~1-2% of women in the United States

Graves' Disease: An Autoimmune Disease

- Thyroid Stimulating Immunoglobulins (TSIs) bind to the TSH receptor and mimic the action of TSH.
- Underlying defect probably lies with T lymphocytes, perhaps CD8 cells.
- Increased risk of other autoimmune diseases.

Graves' Disease: Genetic Factors

- MHC class II antigen HLA-DR3 increases risk ~3 fold
- ~50% concordance in monozygotic twins, ~5% concordance in dizygotic twins

Hyperthyroidism: General Symptoms

Younger Patients

Nervousness

Diaphoresis

Heat intolerance

Palpitations; tachycardia

Insomnia

Weight loss

Hyperdefecation

Older Patients

Angina

Atrial fibrillation

Weakness

Cachexia

Hyperthyroidism: General Signs

- Goiter (symmetric in Graves' disease)
- Tremor
- Diaphoresis
- Tachycardia
- Rapid DTR relaxation
- Lid lag
- Systolic hypertension
- Atrial fibrillation

Graves' Disease

Ophthalmopathy



Dermopathy



Signs and symptoms specific for Graves' hyperthyroidism

- Graves' ophthalmopathy
- Graves' dermopathy (pretibial myxedema)
- Thyroid thrills or bruits
 - Increased thyroid blood flow causes turbulence

Graves' Ophthalmopathy

- Clinically evident in <50% of patients
- Exophthalmos
- Periorbital edema
- Extraocular muscle weakness
- Corneal ulceration
- Optic nerve damage (compression)

Graves' Ophthalmopathy: Symptoms

- Gritty, dry eyes
- Periorbital puffiness
- Diplopia
- Decreased vision

Graves' Ophthalmopathy: Pathogenesis

- Presumed autoimmune, likely due to shared antigens on thyroid and retroorbital tissue (possibly the TSH receptor).
- Extraocular muscles enlarge with edema, glycosaminoglycan deposition, mononuclear cell infiltrate, and fibrosis.

Graves' Ophthalmopathy

- Course independent of hyperthyroidism
- Generally not influenced by treatment of hyperthyroidism
- Therapy includes artificial tears, taping lids closed at night, glucocorticoids, orbital XRT, and decompression surgery

Graves' Dermopathy (Pretibial Myxedema)

- Violaceous induration of pretibial skin
- Glycosaminoglycan deposition
- Rare, generally accompanied by eye disease
- Usually asymptomatic
- Therapy typically topical glucocorticoids

Graves' Disease: Onycholysis

(separation of the distal margin of the nail plate from the nail bed)



Most commonly begins on the 4th digit of the hands (honest!)

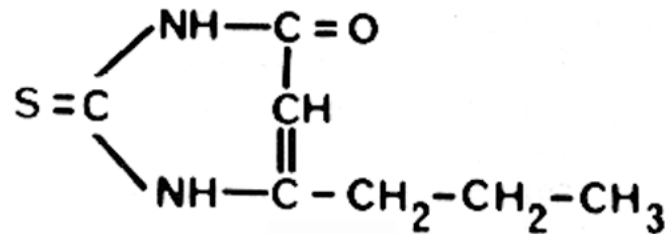
Graves' Disease: Laboratory Evaluation

- TSH low (always measure this)
- Free T4, free T3 elevated (measure one or both if TSH is low)
- Radioiodine uptake increased (excludes subacute thyroiditis and allows Rx with radioiodine)
- Thyroid stimulating antibodies present (could measure instead of RAIU)
- Antithyroid (anti-TPO and Tg) antibodies often present (generally don't measure)

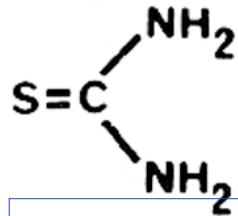
Graves' Disease: Medical Therapy

- Antithyroid drugs (thionamides)
 - Methimazole, Propylthiouracil (PTU)
- Beta adrenergic blockers
- Iodide

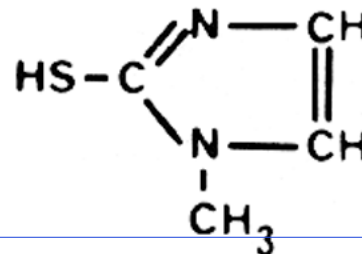
Antithyroid Drugs (thionamides)



Propylthiouracil



Thiourea



Methimazole

Antithyroid Drugs: Mechanism of Action

- Inhibit organification of iodine by TPO
- PTU (high dose) inhibits type 1 deiodinase
 - PTU is preferred in severe hyperthyroidism
 - In typical hyperthyroidism PTU and methimazole are equally good
- Do not influence the long term course of Graves' disease.
 - ~30% of Graves' patients undergo spontaneous remission within ~1 year of diagnosis. Patients treated with antithyroid drugs are hoping to be in the lucky 30%.

Antithyroid Drugs: Toxicity

- Common (1-5%)
 - Rash, urticaria, fever, arthralgias
- Rare
 - Agranulocytosis
 - Liver damage, vasculitis, lupus-like syndrome

Medical therapy of Graves' disease: Beta adrenergic blockers

- Improve sympathetic overdrive type symptoms
- Propranolol at high doses modestly inhibits T4 to T3 conversion (other β blockers don't)
- Do not lower serum T4 levels
- Usual contraindications apply

Medical therapy of Graves' disease: Iodide

- Rarely indicated
- Rapidly lowers serum T4 and T3 by blocking thyroidal secretion
- Can cause hyperthyroidism
 - Iodine can both cause and cure both hyperthyroidism and hypothyroidism!
- Blocks radioiodine uptake

Graves' Disease: Definitive Therapy

■ Radioiodine (I-131)

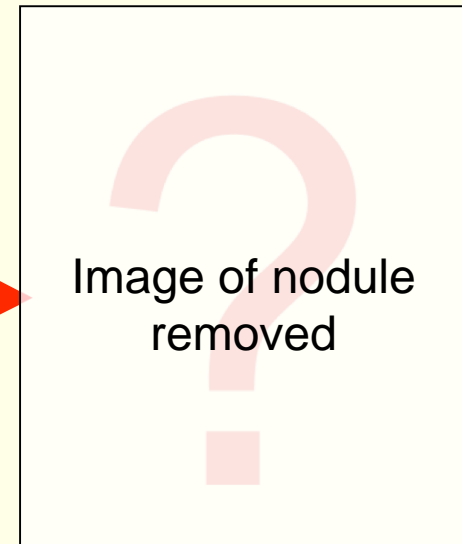
- Advantages: safe, outpatient, painless
- Disadvantages: slow, hypothyroidism, radiation

■ Surgery

- Advantages: rapid (but must pre-treat with antithyroid drugs or β -blockers), may not cause hypothyroidism
- Disadvantages: inpatient surgery, general anesthesia, complications (hypoparathyroidism, recurrent laryngeal nerve palsy)

Autonomously Functioning Adenoma (Hot Nodule)

Palpable nodule in
left lobe of thyroid
is “hot” by
radionuclide scan



Autonomously Functioning Adenoma (Hot Nodule)

- Less common cause of hyperthyroidism than Graves' disease
- In most patients, the nodule produces too little thyroid hormone to cause hyperthyroidism
- Generally must be >2.5 cm to cause clinical hyperthyroidism (“toxic adenoma”)
- Constitutively activating mutations of the TSH receptor are causative in many cases

TSH Receptor: Loss or gain of function mutations

Extracellular domain →

Cell membrane →

Intracellular domain →



Dark circles indicate activating mutations; Light circles indicate inactivating mutations.

J Van Sande, et al. JCEM 80:2577, 1995

Hyperthyroidism due to Toxic Adenomas (hot nodules)

- Labs are similar to Graves' disease except TSI and anti-thyroid Abs are negative.
- Spontaneous remissions are very rare.
- Thionamides will lower T4 and T3, but will not lead to cure.
- Therefore, preferred therapy is surgery or radioiodine.
 - The patient can be followed without therapy if she/he is euthyroid (normal TSH).

Multinodular Goiter (1)

- Thyroid has multiple nodules, some of which may be too small to palpate.
- Some of the nodules function autonomously.
- “Toxic” multinodular goiter signifies that the level of autonomous function is sufficient to cause hyperthyroidism.

Multinodular Goiter (2)

- Usually occurs in an older age group than Graves' disease.
- Generally the cause is not known, although some nodules have activating mutations of the TSH receptor.
- Treat with radioiodine or surgery, as spontaneous remissions do not occur.

Thyrotoxicosis by a totally different mechanism

- A 30 y.o. woman had a respiratory illness a week ago, and now c/o rapid heart beat, sweating and neck pain, especially noting tenderness to touch.
- This is typical of subacute thyroiditis.
- Leakage of thyroid hormone from damaged thyroid cells, rather than increased synthesis, is the cause of thyroid hormone excess.
 - Therefore, the radioiodine uptake is low.
- Resolves spontaneously after 2-3 months.
- Thyrotoxic phase may be followed by a hypothyroid phase, also lasting 2-3 months.

Subacute thyroiditis

- The thyrotoxic and/or hypothyroid phases may be asymptomatic.
- If needed, use beta blockers to treat the thyrotoxic phase.
- If needed, use levothyroxine to treat the hypothyroid phase.
- If needed, use NSAIDs for neck pain.
- This disease also is called subacute painful thyroiditis, De Quervain's thyroiditis, subacute granulomatous thyroiditis, and giant cell thyroiditis.

Painless Subacute thyroiditis

- Silent, or painless, subacute thyroiditis is similar in clinical course to painful subacute thyroiditis, except there is no neck pain.
- Autoimmune etiology with lymphocytes infiltrating the thyroid.
- Since a small, symmetric goiter is common, painless subacute thyroiditis must be distinguished from Graves' disease by laboratory testing.

Non-thyroidal Illness Syndrome

- Also called the sick euthyroid syndrome.
- Definition: decreased serum T3 (total and free) caused by non-thyroidal illness rather than thyroid dysfunction.
- TSH usually is normal but can be low in severe cases.
- T4 and free T4 usually are normal but can be low in very severe cases.

Non-thyroidal Illness Syndrome

- Occurs with virtually any acute or chronic illness, e.g. infections, myocardial infarction, chronic renal failure, surgery, trauma.
- Inhibition of 5' deiodinase causes the low serum T3.
- TSH secretion is “inappropriately” normal.
- Underlying mechanisms are poorly understood.

Non-thyroidal Illness Syndrome

- Prognosis: Full recovery when the non-thyroidal illness resolves.
- Therapy: It is currently felt that patients do not benefit from attempts to normalize serum T3 levels.
- It is important to know of this syndrome so as not to confuse it with secondary hypothyroidism.

M2 Thyroid Lecture Series

Ronald J. Koenig, MD, PhD
February 22, 2006

- Lecture 4: Hypothyroidism, thyroid nodules and thyroid cancer
- Goals/Objectives
 - Understand the etiology, epidemiology, clinical features and therapy of Hashimoto's thyroiditis
 - Understand the etiology, epidemiology, differential diagnosis, evaluation and therapy of thyroid nodules and cancer

Hashimoto's Thyroiditis: Epidemiology

- Most common cause of hypothyroidism in the United States.
- Female/male ~10/1.
- ~5% of females, increasing with age.

Hashimoto's Thyroiditis: An Autoimmune Disease

- Anti-TPO (microsomal) and anti-Tg Abs
- Intrathyroidal CD8 (cytotoxic) T cells
- Increased incidence of HLA-DR5
- Increased risk of other autoimmune diseases
 - Type 1 diabetes mellitus
 - Addison's disease (adrenal insufficiency)
 - Pernicious anemia
 - Etc.

Hypothyroidism: Symptoms

Fatigue

Lethargy

Weakness

Cold intolerance

Mental slowness

Depression

Dry skin

Constipation

Muscle cramps

Irregular menses

Infertility

Mild weight gain

Fluid retention

Hoarseness

Hypothyroidism: Signs

Goiter (primary
hypothyroidism only)

Bradycardia

Nonpitting edema

Dry skin

Delayed DTR relaxation

Hypertension

Slow speech

Slow movements

hoarseness

Hashimoto's Thyroiditis: Goiter

- Usually but not always present
- Generally firm, non-tender
- May be irregular or asymmetric

Hypothyroidism: Laboratory Evaluation

- Increased TSH is the most sensitive test
 - Primary hypothyroidism only
 - Always measure unless you know the patient has defective TSH secretion
- Decreased free T4
 - probably should measure at diagnosis if TSH high
- Decreased FT3
 - Less sensitive and less specific than decreased FT4 (don't measure)
- Anti-TPO and anti-Tg Abs (Hashimoto's)

Hypothyroidism: Therapy

- L-Thyroxine (levothyroxine; T4)
- Goals
 - Alleviate symptoms
 - Normalize TSH (primary hypothyroidism) or free T4 (secondary and tertiary hypothyroidism)

Relationship between hypothyroidism and freedom of speech

- <http://www.greenwillowtree.com/the-380/superb-thyroid-support%2C-low/Detail.bok>
- <http://www.alvidar.com/>
- <http://www.naturallydirect.net/thyroid-supplement.htm>
- <http://www.herbalremedies.com/hypothyroid.htm>
- http://www.usmedicalresearch.org/he_thy/
- http://www.cellucor.com/pages/index.php?pageName=product_details&id=5&set_session=yes&mwrc_session_code=Qg8VnwF3qlkkNbRquV9E

Thyroid Nodules

- ~5% of adults have thyroid nodules, with a 5:1 female:male ratio
- ~95% of thyroid nodules are benign
- The differential diagnosis is large, but the most important thing is to distinguish benign from malignant causes

Thyroid Nodules: Differential Diagnosis

Adenoma

Carcinoma

Cyst

Multinodular Goiter

Hashimoto's Thyroiditis

Subacute Thyroiditis

Prior thyroid surgery

Thyroid hemiagenesis

Metastasis

Lymphadenopathy

Thyroglossal duct cyst

Parathyroid cyst/adenoma

Cystic hygroma

Aneurysm

Bronchocele

Laryngocele

Thyroid Nodules: History

- Childhood Irradiation
- Age
- Gender (malignancy more likely in males)
- Duration and Growth (thyroid cancer can be very slow growing)
- Local symptoms (hoarseness worrisome)
- Hyper- or hypothyroidism (suggest benign)
- Family history (MEN2)

Thyroid Nodules: Physical Exam

- Size
- Fixation
- Consistency
- Adenopathy
- Vocal cord paralysis
- Multiple nodules (multinodular goiter) does not imply the nodules are benign

Thyroid Nodules: Laboratory Evaluation

- TSH
- Ultrasound
- Fine needle aspiration biopsy
- Radionuclide Scan (usually not needed)

Thyroid Nodules: why measure TSH?

- A low TSH suggests the nodule is “hot”, which would indicate it is benign but causing hyperthyroidism.
- A high TSH suggests hypothyroidism due to Hashimoto’s thyroiditis. The nodule may disappear with levothyroxine Rx to normalize TSH.
- However, TSH will be normal in most cases.

Thyroid Nodules: why ultrasound?

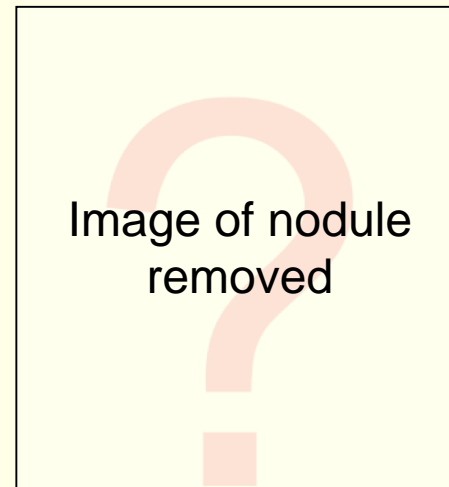
- Ultrasound provides objective confirmation of your physical exam (or refutes it).
- Ultrasound is the most accurate way to determine the size of a nodule, and hence is the best way to assess whether it is growing over time.
- Ultrasound cannot distinguish benign from malignant, but some ultrasound features are more common in malignant nodules.

Thyroid Nodules: Fine Needle Aspiration Biopsy

- Most accurate and cost effective means to predict whether a nodule is benign or malignant.
- However, well differentiated follicular carcinomas are difficult to distinguish from follicular adenomas.
- No serious morbidity.
- In patients with a normal TSH, nodules greater than ~1.0-1.5 cm are biopsied.

Non-functioning (Cold) Thyroid Nodule

Palpable nodule in
right lobe of thyroid
is “cold” by
radionuclide scan



Thyroid Nodules: Radionuclide Scan

- Hot nodules are virtually always benign.
- Cold nodules have ~5% risk of malignancy.
- Since ~90% of nodules in euthyroid patients are cold, a scan rarely permits one to rule out cancer.
- Therefore a scan is not usually a cost effective test in the evaluation of thyroid nodules in euthyroid individuals.
- Perform a scan if the TSH is low, to confirm the nodule is the cause.

Thyroid Nodules: Therapy

- Benign nodules:
 - Generally nothing
 - Sometimes T4
 - Occasionally surgery
- Malignant nodules
 - Surgery
 - T4 to suppress TSH
 - Radioiodine (I-131)

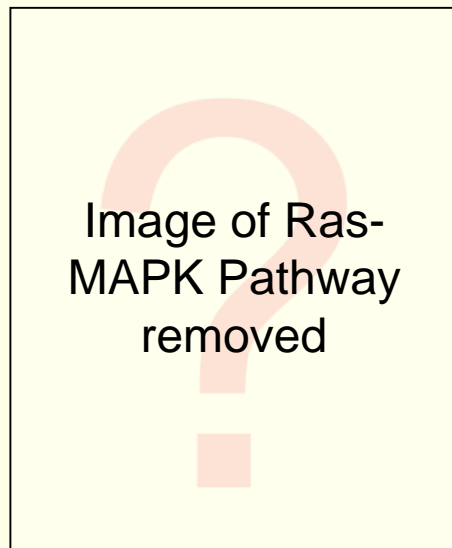
Thyroid Cancer

- Papillary
- Follicular
- Medullary
- Anaplastic
- Lymphoma
- Metastases

Papillary Thyroid Cancer

- Most common type
- Excellent prognosis
- Spreads first to local cervical lymph nodes; also can spread to lung and bone
- Therapy: surgery, T4, radioiodine
- Thyroglobulin is an excellent tumor marker

Papillary Thyroid Cancer: Ras-MAPK pathway activation



- BRAF V600E mutation in ~50% of cases
- RET/PTC chromosomal translocation in ~20% of cases
- Ras mutations in ~15% of cases

Importance of BRAF V600E mutation in papillary thyroid cancer

- Diagnosis: PCR of biopsy specimens may be useful.
- Prognosis: tumors tend to be more aggressive than other papillary cancers.
- Treatment: An experimental BRAF inhibitor is in a clinical trial for papillary thyroid cancer. There currently are no effective chemotherapeutic agents to treat thyroid cancers.

Papillary Thyroid Cancer: RET oncogene mutations

- ~20% of papillary cancers are caused by translocations involving the RET proto-oncogene.
- RET is a plasma membrane receptor with a cytoplasmic tyrosine kinase domain.

Papillary Thyroid Cancer: RET oncogene mutations

- RET is not normally expressed in thyroid follicular cells. A chromosomal inversion juxtaposes sequences of another gene (called PTC) with the tyrosine kinase domain of RET, resulting in inappropriate RET expression.
- Detection of RET rearrangements by PCR of thyroid biopsies and peripheral blood may become important diagnostic tests.

Thyroid Cancer and the Chernobyl Nuclear Accident

- The 1986 Chernobyl accident released a large amount of radioiodine into the atmosphere.
- New cases of thyroid cancer began to increase in 1990, and rose 50-fold by 1993.
- Virtually all cases are papillary cancer, and most have RET/PTC rearrangements.
- Most cases occurred in children <5 years of age at the time of the accident.

New cases of thyroid cancer in Belarus, 1986-1995

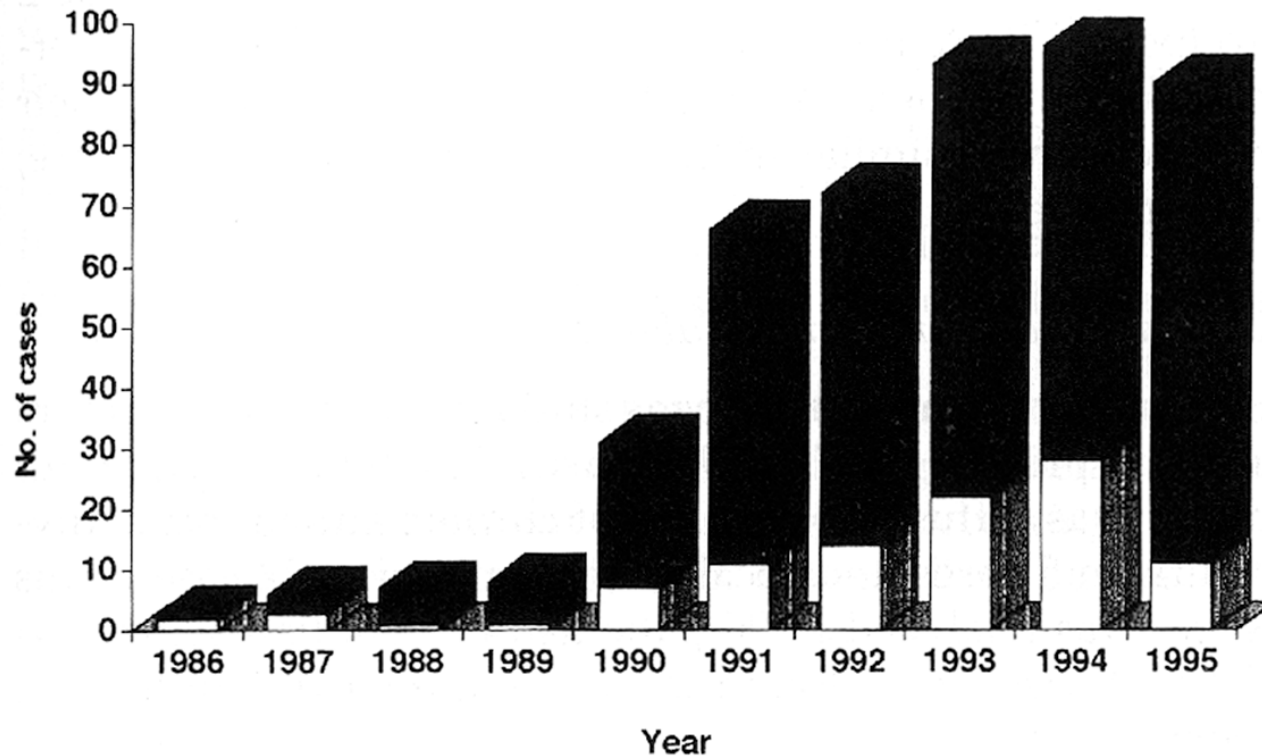


FIG. 2. New cases of childhood (■) and adolescent (□) thyroid carcinoma in Belarus, registered yearly from 1986 to 1995.

Source: Undetermined

Age of Belarus patients at the time of the accident

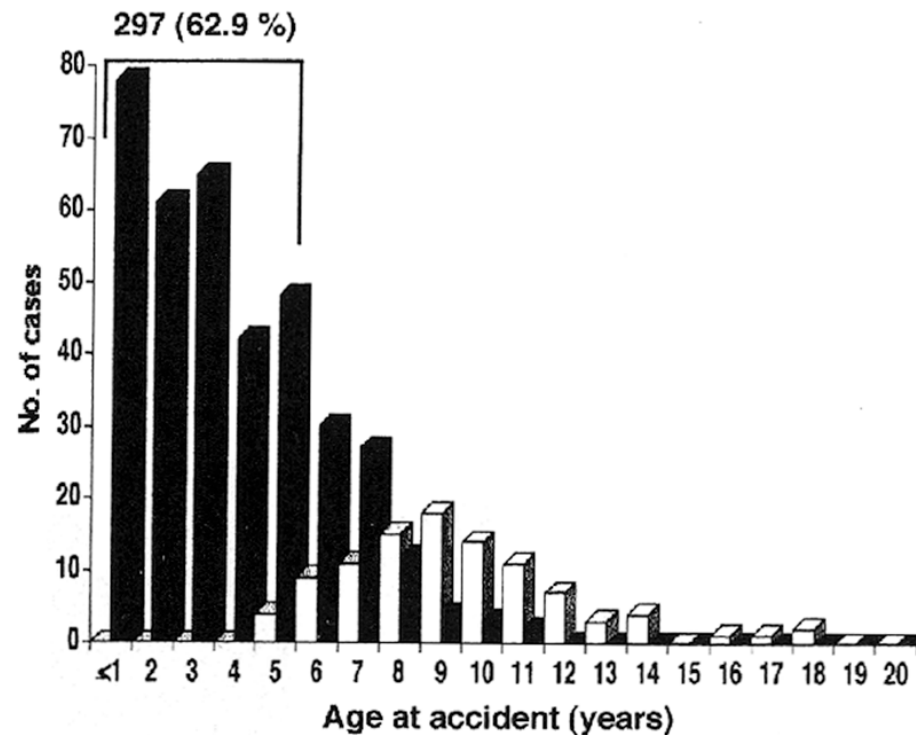


FIG. 3. Age distribution of Belarus thyroid cancer patients at the time of the accident (1986). The *black* column (■) and the *white* column (□) represent patients diagnosed during childhood and during adolescence, respectively.

Source: Undetermined

Thyroid Cancer from Nuclear Accidents

- May be preventable by ingestion of iodide (non-radioactive).
- The American Thyroid Association recommends that nuclear power plants stock NaI or KI for emergency administration to local residents.

Follicular Thyroid Cancer

- Less common than papillary
- Prognosis probably not quite as good as papillary, but still excellent
- Greater tendency than papillary to spread to lung and bone, with less to cervical lymph nodes
- Therapy: surgery, T4, radioiodine
- Thyroglobulin is an excellent tumor marker

Follicular Thyroid Cancer

- Often caused by a chromosomal translocation fusing the genes encoding Pax8 and PPAR γ .
- Pax8 is a transcription factor that controls the development of the thyroid and the expression of many thyroid specific genes.
- PPAR γ is a nuclear receptor (it is the target of the insulin sensitizing drugs thiazolidinediones).

Pax8/PPAR γ fusion protein and follicular thyroid cancer

- The mechanism of oncogenesis is unclear.
- PCR-based assays of thyroid biopsies and peripheral blood may become important diagnostic tests.
- Whether PPAR γ ligands (thiazolidinediones) affect follicular thyroid cancer is an important but unanswered question.

Medullary Thyroid Cancer

- Only ~5% of thyroid cancers
- Derived from parafollicular C cells, not follicular cells
- Calcitonin is an excellent tumor marker
- Can be sporadic or part of MEN2a or 2b
- Therapy - surgery (radioiodine ineffective)

Multiple Endocrine Neoplasia Type 1

- MEN 1

- Pituitary adenoma
- Parathyroid (usually 4 gland hyperplasia)
- Pancreas (gastrinoma, insulinoma)

Multiple Endocrine Neoplasia Type 2

■ MEN 2A

- Medullary carcinoma of the thyroid
- Parathyroid (usually 4 gland hyperplasia)
- Pheochromocytoma (usually bilateral)

■ MEN 2B

- Medullary carcinoma of the thyroid
- Pheochromocytoma (usually bilateral)
- Mucosal neuromas, Marfanoid habitus, ganglioneuromas

RET proto-oncogene

- RET point mutations (single amino acid changes) cause MEN2A and 2B.
- Similar RET mutations also are found in some sporadic medullary cancers. RET translocations cause some papillary cancers.
- RET mutations that cause thyroid cancer are gain of function mutations, and hence MEN2A and 2B are autosomal dominant.

RET Mutations in MEN2A and 2B

- MEN2A - RET mutations occur in extracellular domain cysteines.
 - Results in intermolecular RET dimerization, leading to inappropriate kinase activation.
- MEN2B - RET amino acid 918 is mutated from methionine to cysteine.
 - Mutation lies within the kinase domain and presumably alters enzyme specificity.
- Patients with medullary thyroid cancer and family members can be tested for RET mutations.

RET Mutations and MEN2A and 2B




Mutation of
extracellular domain
cysteine causes MEN2A

Mutation of amino acid
918 within the tyrosine
kinase domain causes
MEN2B



Straightforward Clinical Thyroid Cases



(You should be able to figure these out
from the lectures)

26 y.o. female c/o irregular periods,
insomnia, rapid heart beat and feeling hot

- What is the likely diagnosis?
- What should you look for on exam?
- What lab test(s) would you order?
- How would you treat the patient?

(Continued on next slide)

You make the diagnosis of Graves' disease and treat the patient with PTU

- How quickly will the drug work and why?
- Three weeks after starting the PTU, the patient develops fever and tachycardia. How should you proceed?

On routine exam, a 40 y.o. man is found to have a 2 cm thyroid nodule


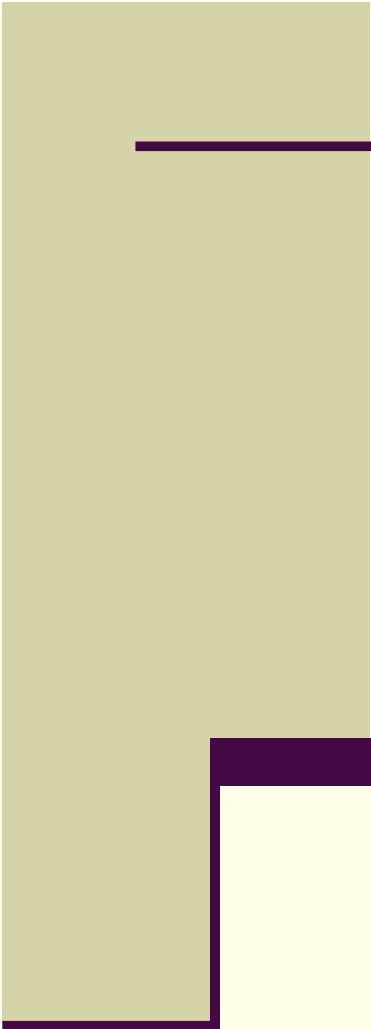
- What are the key points to ask in the history?
- What should you focus on in the exam?
- What is the differential diagnosis?
- How should the work up proceed?

A 56 y.o. woman c/o being tired and cold, and notes a 5 pound weight gain

- What is the likely diagnosis?
- What should you look for on exam?
- What lab test(s) would you order?
- How would you treat the patient?



Not so straight forward thyroid cases



(But you should be able to deduce the
answers from the lecture material)

Goiter is c/w hypothyroidism due to which of the following?

- Hashimoto's thyroiditis
- Inactivating mutation of TSH receptor
- Inactivating mutation of Iodide transporter
- Dietary Iodine deficiency
- X-Ray Rx of a brain tumor

A 55 y.o. man receives the antiarrhythmia drug amiodarone, which inhibits the type 1 deiodinase

- What would happen to the serum T4, T3 and TSH shortly after starting this drug?
- What would be the effect of chronic amiodarone on T4, T3 and TSH?
- How would you diagnose hypothyroidism or hyperthyroidism in this man?


A 25 y.o. hypothyroid woman has the following lab tests while taking thyroxine

- Free T4 1.90 (normal 0.73 - 1.79 ng/dl)
- TSH 0.6 (normal 0.3 - 5.5 mU/L)

- How do you interpret these results and what should you do?



Bonus Thyroid Cases

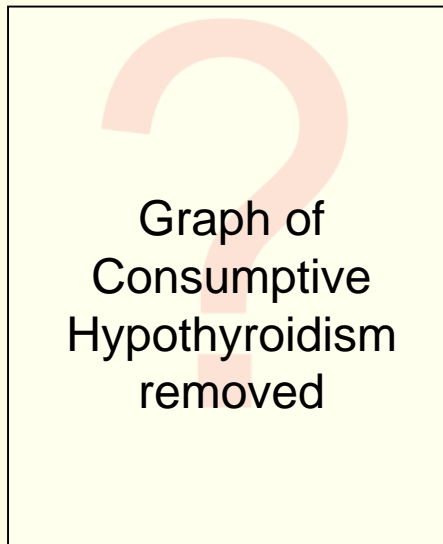


(Uncommon genetic thyroid diseases that teach us about thyroid function)

Consumptive Hypothyroidism

- A 6 wk old boy with a large hepatic hemangioma was found to have a TSH of 156 (normal 0.3-6.2 mU/L), and low T4 and T3 levels.
- Huge doses of intravenous T4 and T3 were required to normalize the TFTs.
- Why?

Consumptive Hypothyroidism



← Adult T3 production rate = 32 mcg/d

Consumptive Hypothyroidism is due to over-expression of type 3 Deiodinase (D3)

D3 RNA expression



H&E stain



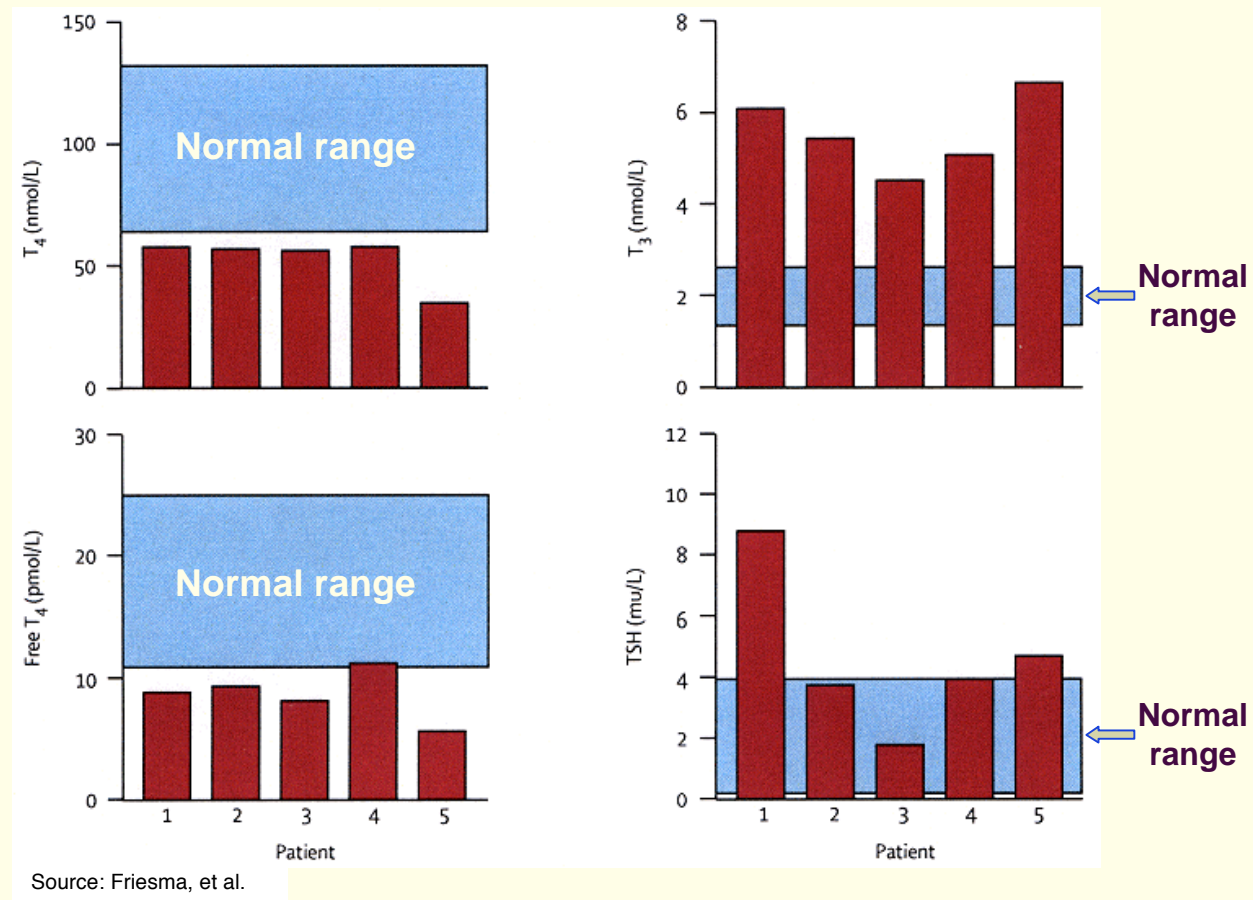
Consumptive hypothyroidism

- Hemangioma D3 degrades T4 and T3 so fast the thyroid cannot keep up.
- Demonstrates the role of D3 in regulating thyroid hormone levels.
- Infants with large hemangiomas could be at risk for mental retardation due to consumptive hypothyroidism, unless diagnosed and treated.

X-linked psychomotor retardation

- A boy with severe mental retardation and other neurological symptoms was found to have a TSH of 8.8 (normal 0.3-4.0) and a Total T3 of 6.1 (normal 1.4-2.7; free T3 was equally elevated).
- Several families with similar findings in boys have been described.
- What is the cause of this syndrome?

TFTs in X-linked psychomotor retardation



ECH Friesma, et al. Lancet 364:1435, 2004

X-linked psychomotor retardation

- The syndrome of X-linked psychomotor retardation, elevated serum T3 and elevated TSH was found to be due to mutations in the gene *MCT8*.
- *MCT8* was found to encode a thyroid hormone transporter highly expressed on the surface of neurons as well as several other cell types.

X-linked psychomotor retardation

- T3 does not simply diffuse into cells, but must enter through specific transporters.
- *MCT8* is one of several potential T3 and T4 transporters.
- Neuronal hypothyroidism may explain the phenotype of X-linked psychomotor retardation.