Thyroid gland tests

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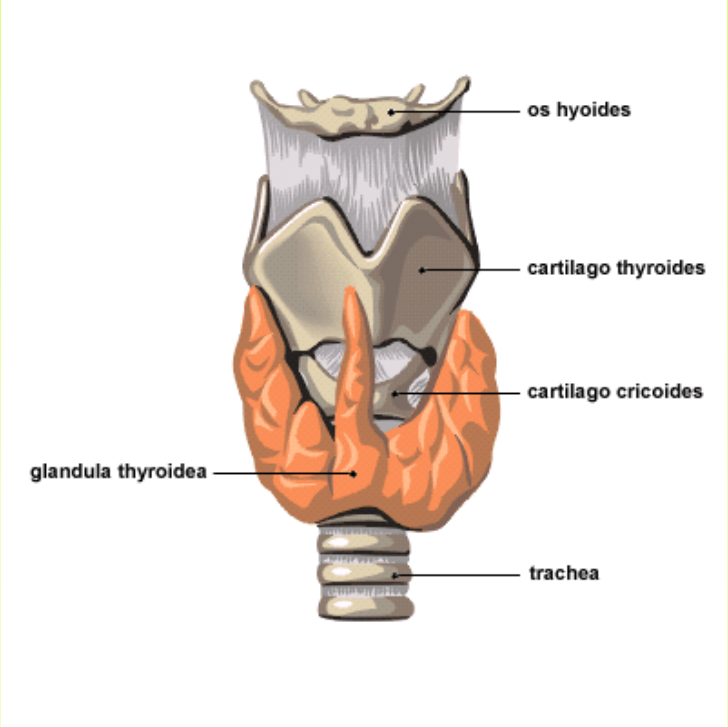
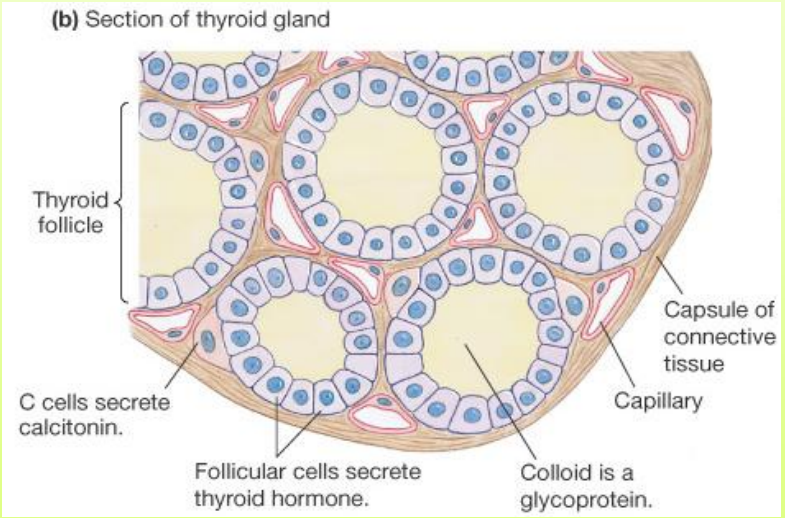
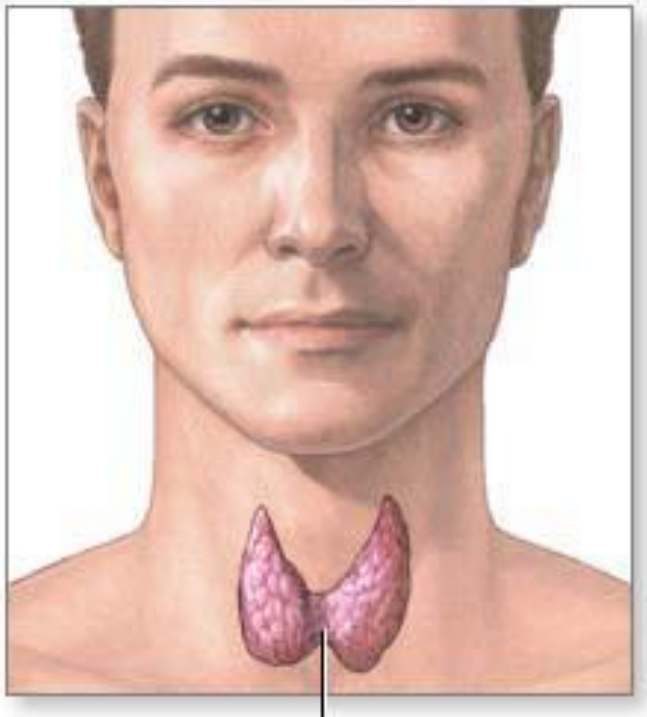
- In the development of the embryo (at 3-4 weeks gestational age), the **thyroid gland** appears as an epithelial proliferation in the floor of the pharynx at the base of the tongue. It descends in front of the pharyngeal gut as a bilobed diverticulum through the thyroglossal duct. Then it migrates to the base of the neck, passing in front of the hyoid bone.
- It is an endocrine gland in the neck, cosisting of **two lobes** connected by an **isthmus** (± **pyramidal lobe**)
- There are three primary features of the thyroid – **follicles, follicular cells and parafolicular cells**



- **Follicular cells**
  - when stimulated by thyroid stimulating hormone TSH, these secrete the thyroid hormones T3 and T4
  - these cells vary in shape (depending on how active they are)
- **Parafollicular cells**
  - originate from the neural crest and migrate during development into the thyroid gland
  - scattered among follicular cells and in spaces between the follicles
  - these cells secrete calcitonin and so they are also called C cells

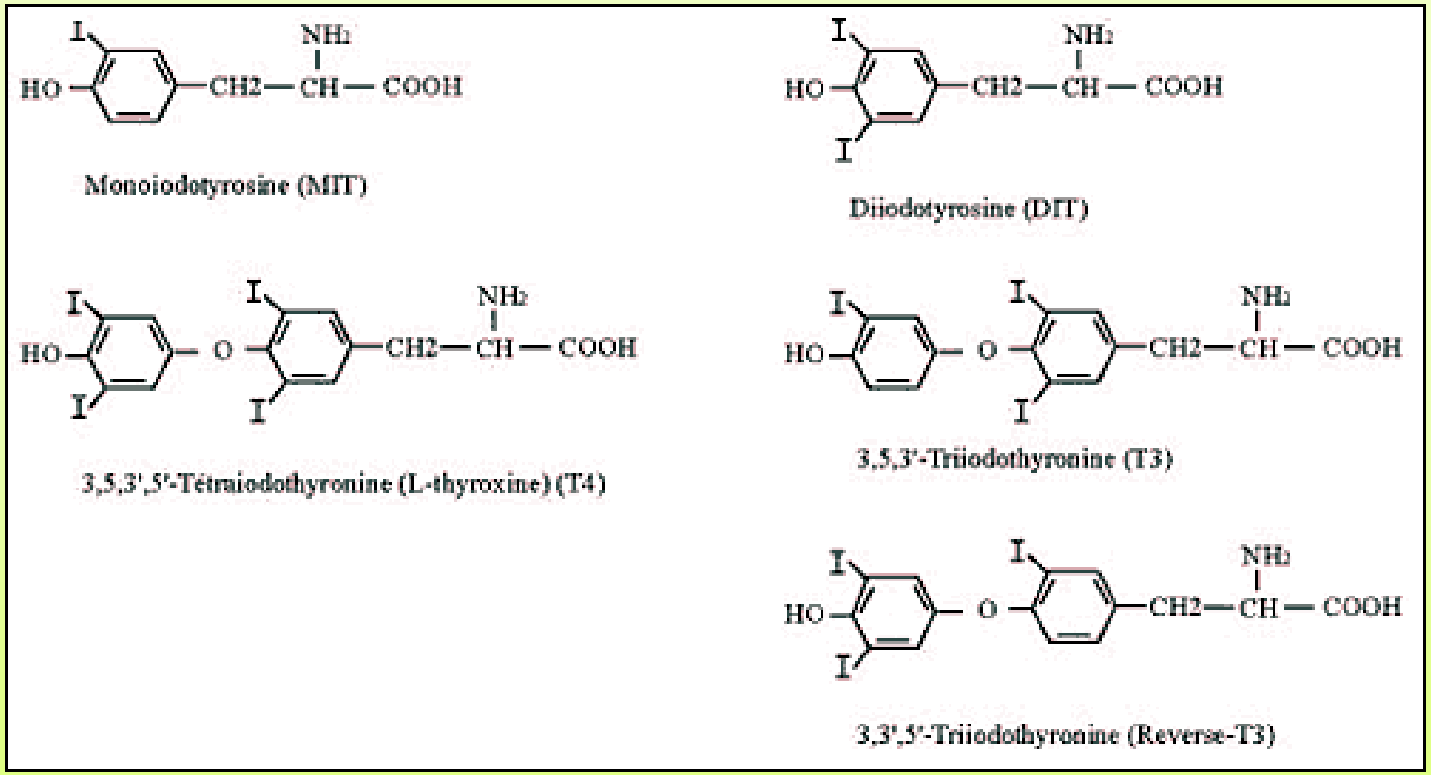




A.D.A.M.

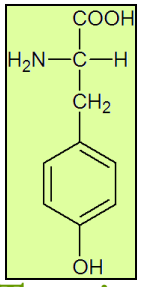
Thyroid hormones

- **triiodothyronine** (3,5,3’-triiodothyronine, **T3**),
  its prohormone, **thyroxine** (3,5,3’,5’-tetraiodothyronine, **T4**)
  and **reverse triiodothyronine** (3,3’,5’-triiodothyronine, reverse T3, or **rT3**)
- tyrosine-based hormones
- partially composed of iodine (a deficiency of iodine leads to decreased production of T3 and T4, enlarges the thyroid tissue and will cause the disease known as simple goitre)

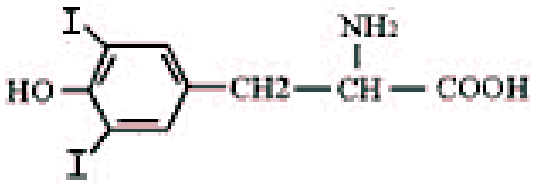


peptidic **MIT** + peptidic **DIT** → peptidic **T3** (eventually released as T3)
2 peptidic **DITs** → peptidic **T4** (eventually released as T4)
peptidic **DIT** + peptidic **MIT (in the opposite order)** → peptidic **r-T3** (eventually released as rT3)

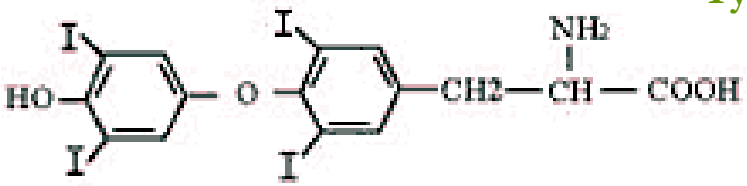
Monoiodotyrosine (MIT)



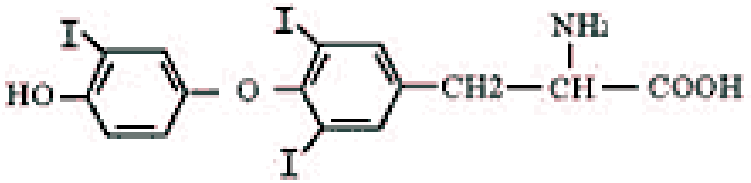
Tyrosine



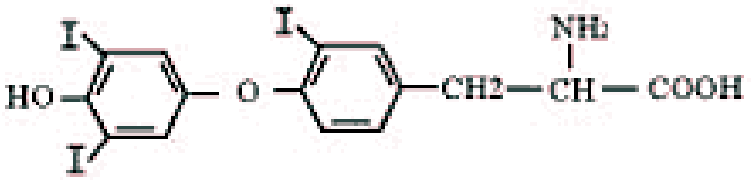
Diiodotyrosine (DIT)



3,5,3',5'-Tetraiodothyronine (L-thyroxine) (T4)



3,5,3'-Triiodothyronine (T3)



3,3',5'-Triiodothyronine (Reverse-T3)

- **the major form** of thyroid hormone **in the blood is thyroxine (T4),** which has a longer half-life than T3
- in humans, the ratio of T4, T3 and rT3 released **into the blood** is:
  - **90 % T4**
  - **9 % T3**
  - **0.9 % rT3**
- T4 is believed to be a prohormone and a reservoir for the most active and main thyroid hormone T3
- T4 is converted to the active **T3, which is three to five times more potent than T4,** within cells by **iodothyronine deiodinases (5'-iodinase)**
- **about 80 % of T3 is produced in the liver and other organs**, and only about 20 % of T3 is produced in the thyroid itself
- the levels of **rT3** increase in conditions such as euthyroid sick syndrome because **its clearance decreases** (the decreased clearance is possibly from lower 5'-deiodinase activity in the peripheral tissue or decreased liver uptake of rT3)

Plasma transport

- most of the thyroid hormone circulating in the blood is bound to transport proteins
- only a very small fraction of the circulating hormone is free (unbound) and biologically active, hence **measuring concentrations of free thyroid hormones is of great diagnostic value**
- when thyroid hormone is bound, it is not active, so the amount of free T3/T4 is what is important (for this reason, measuring total thyroxine in the blood can be misleading)

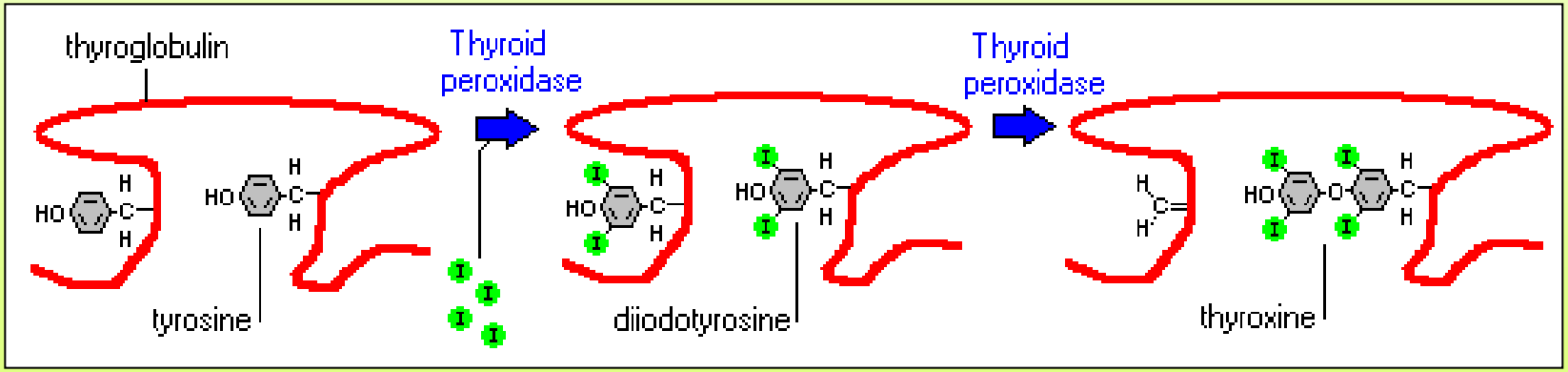
  - Thyroxine-binding globulin (TBG) 70 %
  - Transthyretin (TTR) (thyroxine-binding prealbumin, TBPA) 10-15 %
  - Albumin 15-20 %
  - Unbound T4 (free T4, fT4) 0.03 %
  - Unbound T3 (free T3, fT3) 0.3 %

Euthyroid sick syndrome (ESS)

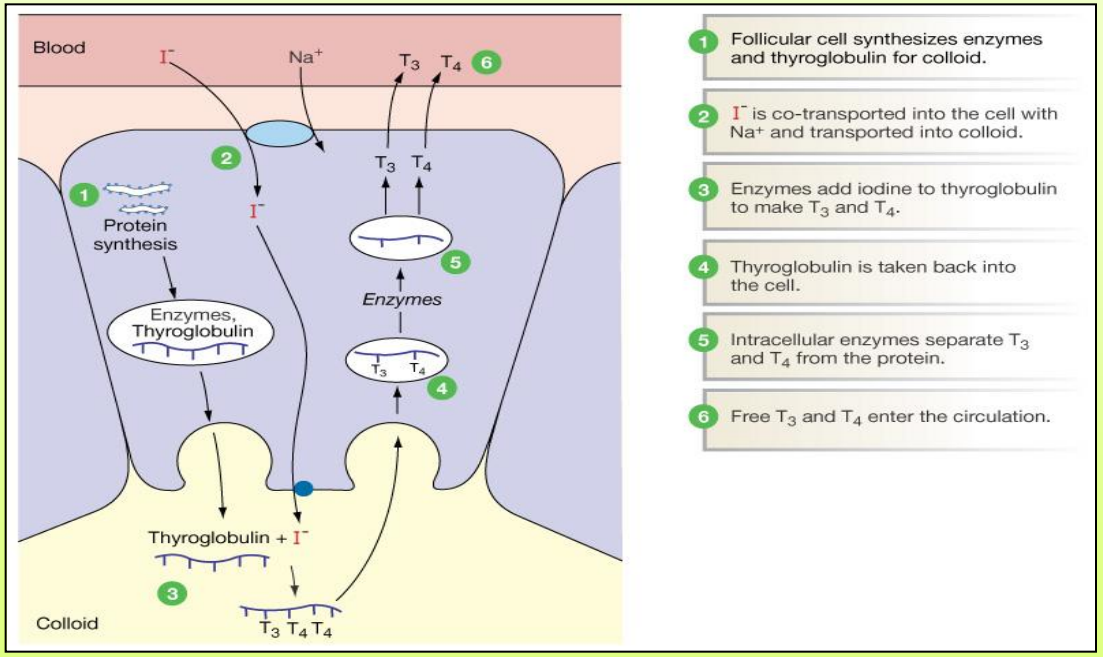
- **sick euthyroid syndrome** (**SES**),
  thyroid allostasis in critical illness, tumours, uremia and starvation (TACITUS), non-thyroidal illness syndrome (**NTIS**) or **low T3 low T4 syndrome**
- a state of **adaptation or dysregulation** of thyrotropic feedback control where the levels of T3 and/or T4 are at unusual levels, but the thyroid gland does not appear to be dysfunctional
- **often seen in** pneumonia, fasting, starvation, anorexia nervosa, sepsis, trauma, cardiopulmonary bypass, malignancy, stress, heart failure, hypothermia, myocardial infarction, chronic renal failure, cirrhosis, diabetic ketoacidosis or in other **critical illnesses**
- **a low total and free T3 levels with normal T4 and TSH levels** (in more severe disease lowering of fT4)
- **increased rT3 levels** signifying inhibition of 5'-deiodinase or reduced clearance of rT3
- **in critical illness the activity of 5'-deiodinase is downregulated, while 5-deiodinase activity is upregulated**

Thyroglobulin (Tg)

- a homodimeric protein (660 kDa) produced by the follicular cells (thyrocytes) of the thyroid and used entirely within the thyroid gland
- accounts for approximately half of the protein content of the thyroid gland
- each thyroglobulin molecule contains approximately 100-120 tyrosine residues, a small number of which (<20) are subject to iodination catalysed by **thyroperoxidase** in the follicular colloid (each Tg molecule forms only approximately 10 thyroid hormone molecules); the same enzyme then catalyses **"coupling" of one modified tyrosine with another**
- these iodinated bicyclic molecules are released by hydrolysis of this protein (T3 and T4 are the result)

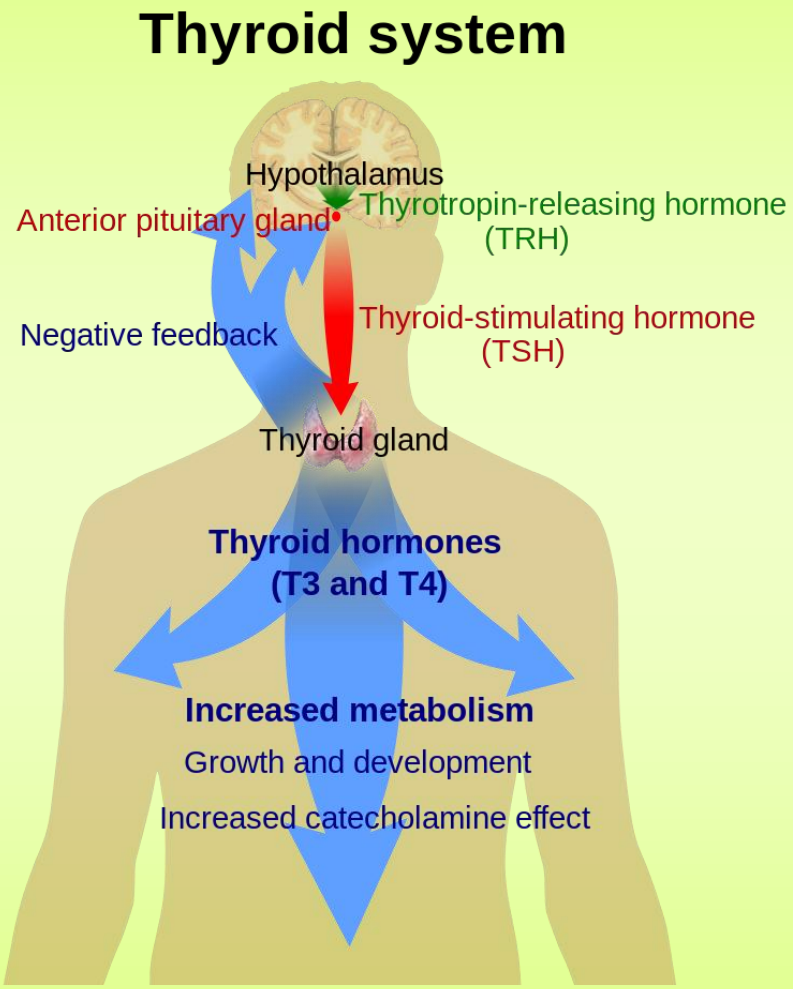


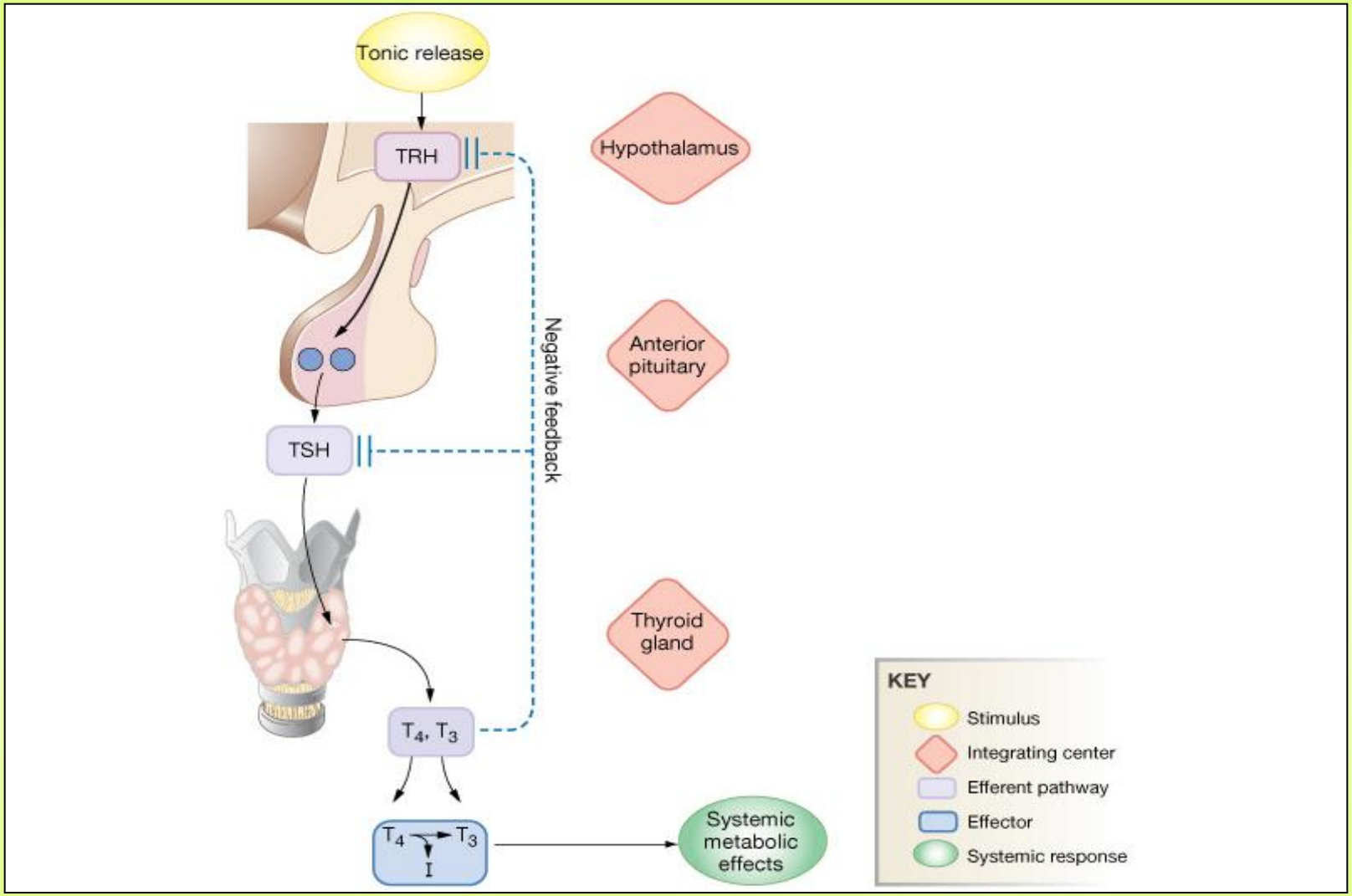
- **Iodide (I^-)** is actively absorbed from the bloodstream by a process called **<u>iodide trapping.</u>**
- Two ions of sodium are cotransported with an iodide ion (Na^+/I^- symport) from the basolateral side of the membrane into the cell and then concentrated in the thyroid follicles to about **thirty times its concentration in the blood.**
- Thyroperoxidase oxidizes two **I^- to form I_2** (iodide is non-reactive, the more reactive iodine is required for the next step).
- Tyrosine residues in thyroglobulin are iodinated by thyroperoxidase on their phenol rings, at one or both of the positions *ortho* to the phenolic hydroxyl group, yielding **monoiodotyrosine (MIT) and diiodotyrosine (DIT).**
- Coupling together of two fully iodinated tyrosine residues (also catalysed by thyroperoxidase) yields the peptidic (still peptide-bound) precursor of **<u>thyroxine</u>**, coupling one molecule of MIT and one molecule of DIT yields the comparable precursor of **<u>T3</u>**, coupling of DIT to MIT in the opposite order yields a biologically inactive substance, **<u>r-T3.</u>**
- TSH released from the adenohypophysis binds the TSH receptor on the basolateral membrane of the cell and stimulates the endocytosis of the colloid.
- The endocytosed vesicles fuse with the lysosomes of the follicular cell. The lysosomal enzymes cleave the T4 and T3, as well as the non-coupled tyrosine derivatives MIT and DIT from the iodinated thyroglobulin.



Thyroid hormones regulation

- thyroid hormones are produced by the follicular cells of the thyroid gland and are regulated by **TSH made by the thyrotropes of the anterior pituitary gland and TRH of hypothalamus**
- the effects of T4 are mediated via T3; T4 is converted to T3 in target tissues by **the selenium-dependent enzyme iodothyronine deiodinase**
- **when T3 and T4 serum concentrations are low, the production of TSH is increased, and, conversely, when T3 and T4 concentrations are high, TSH production is decreased → negative feedback loop**




Tonic release
TRH
Hypothalamus
Anterior pituitary
TSH
Negative feedback
Thyroid gland
T_4, T_3
T_4 → T_3
I
Systemic metabolic effects
KEY
Stimulus
Integrating center
Efferent pathway
Effector
Systemic response

Thyroid-stimulating hormone

- thyrotropin, thyrotropic hormone, TSH, or hTSH (human TSH)
- a glycoprotein hormone synthesized and secreted by thyrotrope cells in the anterior pituitary gland
- stimulates the thyroid gland to produce T4 and T3
- TSH is secreted throughout life but particularly reaches high levels during the periods of rapid growth and development
- the hypothalamus produces **thyrotropin-releasing hormone (TRH)** that stimulates the pituitary gland to produce TSH
- **somatostatin** is also produced by the hypothalamus, and has an **opposite effect** on the pituitary production of TSH, **decreasing or inhibiting its release**
- the concentration of thyroid hormones → **negative feedback loop**

- TSH (with a half life of about an hour) is released in a pulsatile manner resulting in both circadian and ultradian rhythms of its serum concentrations

Structure of TSH

- a glycoprotein consisting of two subunits, the alpha and the beta

- **the α (*alpha*) subunit**
  - nearly identical to that of human chorionic gonadotropin (hCG), luteinizing hormone (LH), and follicle-stimulating hormone (FSH)
  - thought to be the effector region responsible for stimulation of adenylate cyclase (involved the generation of cAMP)
  - the α chain has a 92-amino acid sequence

- **the β (*beta*) subunit**
  - **unique to TSH → determines its receptor specificity**
  - the β chain has a 118-amino acid sequence

TSH receptor

- is found mainly on thyroid follicular cells
- its stimulation increases T3 and T4 production and secretion
- **stimulating antibodies to the TSH receptor mimic TSH and cause Graves' disease**
- **hCG** shows some cross-reactivity to the TSH receptor and therefore **can stimulate production of thyroid hormones** → **in pregnancy**, prolonged high concentrations of hCG can produce **a transient condition termed gestational hyperthyroidism**

Membrane transport and mechanism of action

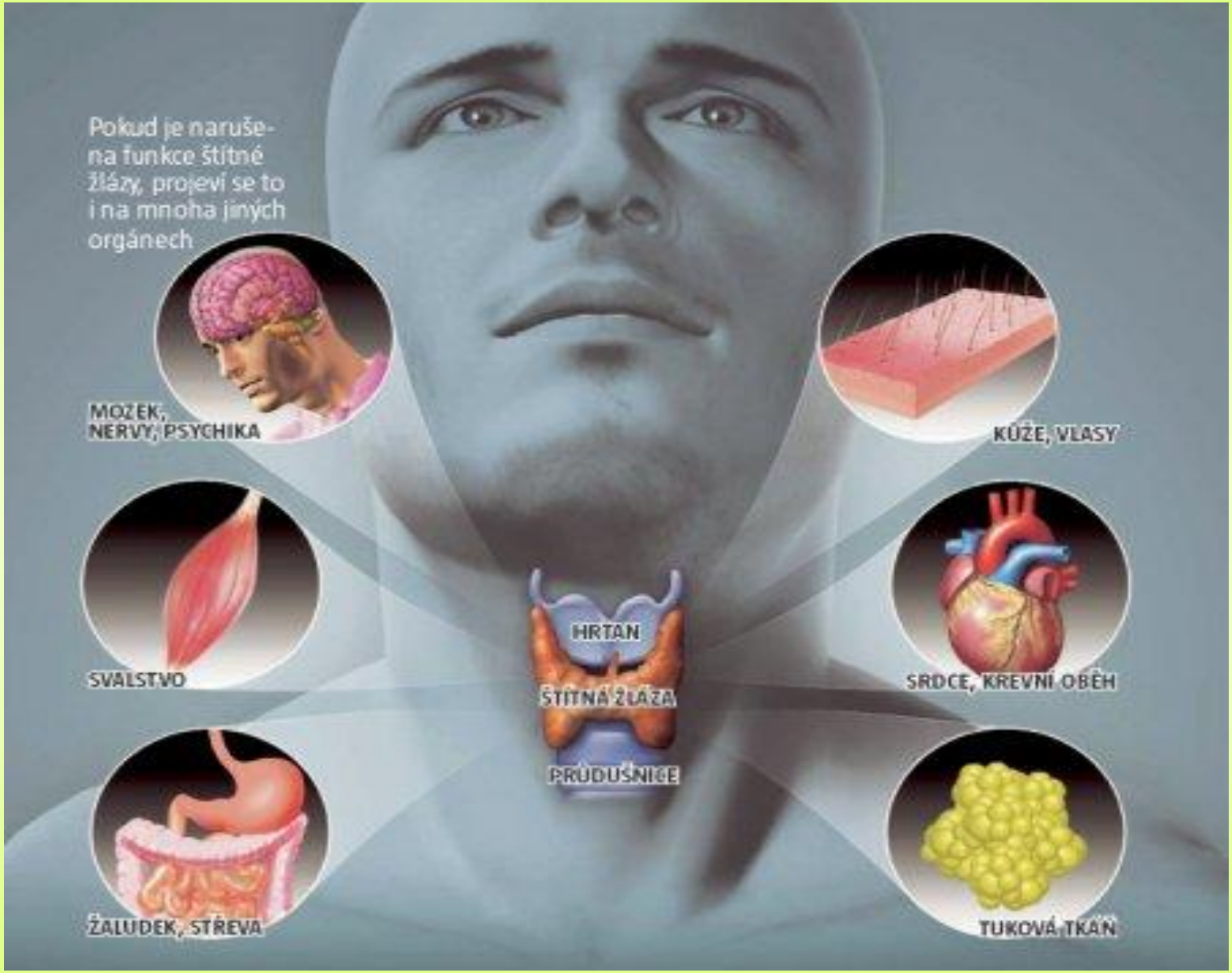
- contrary to common belief, **thyroid hormones cannot traverse cell membranes in a passive manner like other lipophilic substances**
- the iodine in *o*-position makes the phenolic OH-group more acidic, resulting in a negative charge at physiological pH
- **energy-dependent and genetically-regulated iodothyronine transporters have been identified** in humans, they guarantee that intracellular levels of thyroid hormones are higher than in blood plasma or interstitial fluids
- the thyroid hormones function via **nuclear receptors**
- these receptors, together with corepressor molecules, bind DNA regions called thyroid hormone response elements near genes, this ***receptor/corepressor/DNA complex*** can block gene transcription
- when T3 binds a thyroid hormone receptor (TR), it **induces a conformational change in the TR which displaces the corepressor from the receptor/DNA complex**, resulting in **recruitment of coactivator proteins and RNA polymerase, activating transcription of the gene** and the production of specific proteins
- additionally, the hormone binds to integrin αvβ3 on the cell membrane, thereby stimulating the sodium–hydrogen antiporter and processes such as formation of blood vessels and cell growth

Initiation of production in fetuses

- **thyrotropin-releasing hormone** is released from hypothalamus by 6 – 8 weeks of gestation
- **thyroid-stimulating hormone** secretion from fetal pituitary is evident by 12 weeks of gestation
- fetal production of **thyroxine** reaches a clinically significant level at 18–20 weeks
- fetal **triiodothyronine** remains low (less than 15 ng/dL) until 30 weeks of gestation, and increases to 50 ng/dL at term
- **fetal self-sufficiency of thyroid hormones protects the fetus against e.g. brain development abnormalities caused by maternal hypothyroidism**

Function of thyroid hormones

- act on nearly every cell in the body
- act to increase the basal metabolic rate, affect protein synthesis, help regulate long bone growth and neural maturation, potentiate brain development, increase cardiac output, heart and ventilation rate, thicken endometrium in females, and increase the body's sensitivity to catecholamines by permissiveness
- essential to proper development and differentiation of all cells of the human body
- regulate protein, fat, and carbohydrate metabolism, affecting how human cells use energetic compounds and leads to heat generation in humans
- stimulate vitamin metabolism
- numerous physiological and pathological stimuli influence thyroid hormone synthesis


Pokud je naruše-
na funkce štítné
žlázy, projeví se to
i na mnoha jiných
orgánech
MOZEK,
NERVY, PSYCHIKA
KŮŽE, VLASY
SVALSTVO
HRTAN
ŠTÍTNÁ ŽLÁZA
PRŮDUŠNICE
SRDCE, KREVNÍ OBĚH
ŽALUDEK, STŘEVA
TUKOVÁ TKÁŇ

Source of pathology	TSH level	Thyroid hormone level	Disease causing conditions
Hypothalamus/ pituitary	High	High	benign tumor of the pituitary (adenoma) or thyroid hormone resistance
Hypothalamus/ pituitary	Low	Low	secondary hypothyroidism or "central" hypothyroidism
Hyperthyroidism	Low	High	primary hyperthyroidism i.e. Graves' disease
Hypothyroidism	High	Low	congenital hypothyroidism, primary hypothyroidism i.e. Hashimoto's thyroiditis

Diseases

- **Goitre**
  - a swelling of the neck or larynx resulting from enlargement of the thyroid gland, mostly associated with a thyroid gland that is not functioning properly
- **Hypothyroidism**
  - an example is Hashimoto's thyroiditis
  - there is a deficiency of T4, T3, or both
- **Hyperthyroidism**
  - an example is Graves Disease
  - the clinical syndrome caused by an excess of circulating fT4, fT3, or both
- **Inflammation (thyroiditis)**
  - Hashimoto's thyroiditis, postpartum thyroiditis, subacute thyroiditis, silent thyroiditis, drug-induced thyroiditis, radiation-induced thyroiditis, acute thyroiditis, Riedel's thyroiditis
- **Tumors**
  - benign (follicular adenoma, papillary is very rare)
  - malignant (carcinoma…)

Goitre

Goitre

- a **goitre** (British English) or **goiter** (American English) (from the Latin *gutteria*)
- a swelling of the neck or larynx resulting from enlargement of the thyroid gland, mostly associated with a thyroid gland that is not functioning properly
- worldwide, over 90 % cases are caused by iodine deficiency
- more common among women (but this includes the many types of goitre caused by autoimmune problems)

- associated with hypothyroidism or hyperthyroidism, may be present with symptoms of the underlying disorder
- for **hyperthyroidism**, the most common symptoms are associated with adrenergic stimulation: tachycardia, palpitations, nervousness, tremor, increased blood pressure and heat intolerance; clinical manifestations are often related to hypermetabolism, excessive thyroid hormones, an increase in oxygen consumption, metabolic changes in protein metabolism, immunologic stimulation of diffuse goitre
- **hypothyroid** individuals may have weight gain despite poor appetite, cold intolerance, constipation and lethargy (these symptoms are often non-specific)

Causes of goitre

- iodine deficiency (usually seen in countries that do not use iodized salt)
- selenium deficiency
- Hashimoto's thyroiditis (in countries that use iodized salt, it is the most common cause)
- cyanide poisoning (in tropical countries where people eat the cyanide-rich cassava root as the staple food)
- pituitary disease
- Graves' disease
- thyroiditis (acute or chronic inflammation)
- thyroid cancer
- benign thyroid neoplasms
- thyroid hormone insensitivity….

Iodine deficiency

- a lack of the trace element iodine, an essential nutrient in the diet
- if there is a deficiency of dietary iodine, the thyroid will not be able to make thyroid hormone
- the lack of thyroid hormones will lead to **decreased negative feedback on the pituitary**, leading to **increased production of TSH**, which stimulates the thyroid to increase many biochemical processes; the cellular growth and proliferation can result in the characteristic swelling or hyperplasia of the thyroid gland, or goiter (***colloid goitre***)
- this has the effect of increasing the thyroid's ability to trap more iodide, compensating for the iodine deficiency and allowing it to produce adequate amounts of thyroid hormones
- in mild iodine deficiency, levels of T3 may be elevated in the presence of low levels of T4 (the body converts more of T4 to T3)

Iodine deficiency

- sometimes, it may result in an **endemic goiter** as well as cretinism due to untreated congenital hypothyroidism, which results in developmental delays and other health problems

- *cretinism is an old term for the state of mental and physical retardation resulting from untreated congenital hypothyroidism, usually due to iodine deficiency from birth because of low iodine levels in the soil and local food sources*

- **endemic goiter** = the prevalence in a population is **> 5 %,** and, in most cases, goiter can be treated with iodine supplementation
  (if goiter is untreated for around five years, however, iodine supplementation or thyroxine treatment may not reduce the size of the thyroid gland because the thyroid is permanently damaged)

Iodine deficiency

- an important public health issue, a preventable cause of intellectual disability (producing typical reductions in IQ of 10 to 15 IQ points)
- in areas where is little iodine in the diet, typically **remote inland areas** (where no marine foods are eaten), **in mountainous regions of the world** (where food is grown in iodine-poor soil)
- prevention includes adding small amounts of iodine to table salt (→***iodized salt***) or to other foodstuffs (flour, water and milk); seafood is also a well known source of iodine
- iodine deficiency resulting in goiter occurs in 187 million people globally as of 2010 (2.7 % of the population), it resulted in 2700 deaths in 2013 up from 2100 deaths in 1990
- **the recommended daily intake of iodine for adult women is 150-300 µg for maintenance of normal thyroid function; for men it is somewhat less at 150 µg**
- too high iodine intake (e.g.overdosage of iodine supplements) can have toxic side effects (→ hyperthyroidism and consequently high blood levels of thyroid hormones); extremely high single-dose iodine intake → a short-term suppression of thyroid function
- persons with pre-existing thyroid disease, elderly persons, fetuses and neonates…. are at a higher risk of experiencing iodine-induced thyroid abnormalities

Diagnosis of iodine deficiency

- signs and symptoms, possible risk factors mentioned above
- a 24-hour urine iodine collection
- approximately 90 % of ingested iodine is excreted in the urine
- **The standardized 24-hour test**
  - a 50 mg iodine load is given first, and 90 % of this load is expected to be recovered in the urine of the following 24 hours
  - recovery of less than 90 % is taken to mean high retention, that is, iodine deficiency
  - the recovery may, however, be well less than 90 % during pregnancy, and an intake of goitrogens can alter the test results
  - *it is well documented that over 90 % of a nutritional dose of iodine is excreted in urine, but not necessarily within the first 24 hours after ingestion*
- a random urine “iodine-to-creatinine ratio” can alternatively be used

- **The iodine skin test**
  - the skin is painted with an iodine solution
  - if the iodine patch disappears quickly, this is taken as a sign of iodine deficiency
  - *however, no accepted norms exist on the expected time interval for the patch to disappear, and in persons with dark skin color the disappearance of the patch may be difficult to assess*

Ioduria

- iodine urine concentration may be expressed in **µg/L**, or in relation with creatinine (**µg/g creatinine**), or also as 24h urine concentration (**µg/day**)
- it is usually recommended to measure ioduria in a urine sample taken either in the morning or at random (0.5-1 mL) in a specific group, and it is expressed as median ioduria in **µg/L**

- ioduria may be used to extrapolate daily iodine intake in the population using the estimated 24-h mean urinary volume and assuming an average iodine bioavailability of 92 % on the basis of the following formula:

Daily iodine intake = urinary iodine(µg/L) x 0.0235 x body weight(kg)

Using this formula, a median ioduria of 100 µg/L would correlate with an average mean intake of 150 µg

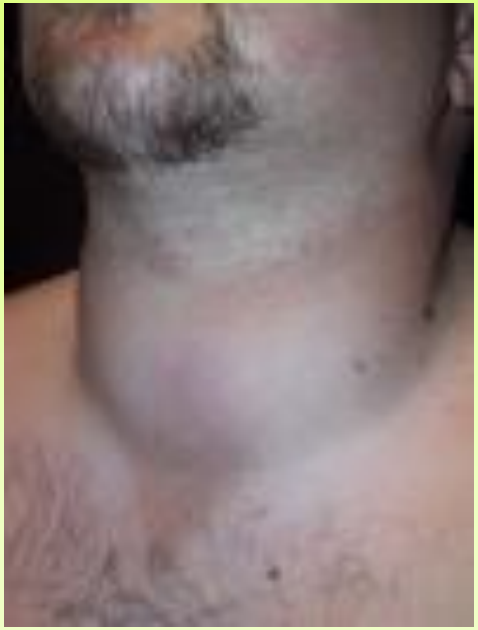
Ioduria levels (WHO specifications)

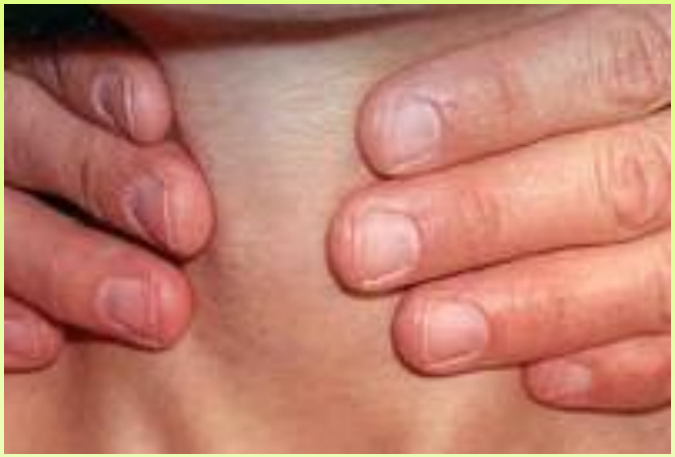
Ioduria (µg/L)	Category	Clinical cosequences
100 - 200	norm	-
50 - 99	mild insufficiency	risk of the goitre?
20 - 49	moderate insufficiency	risk of the goitre, thyroid dysfunction
< 20	serious insufficiency	……and risk of the cretenism

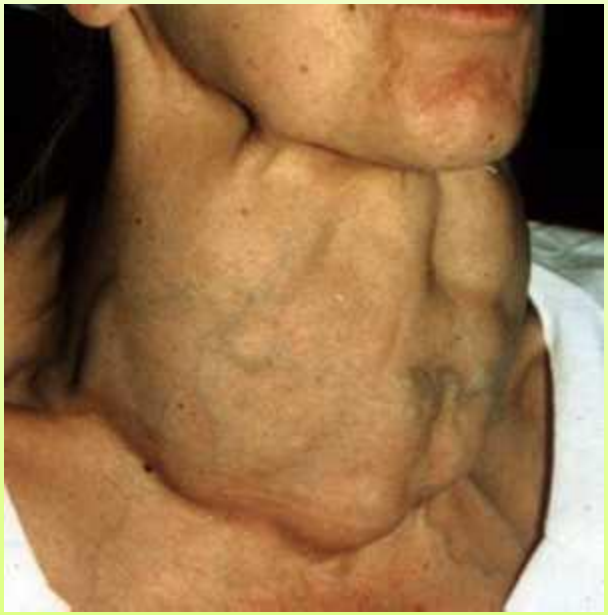
Classification of goitre

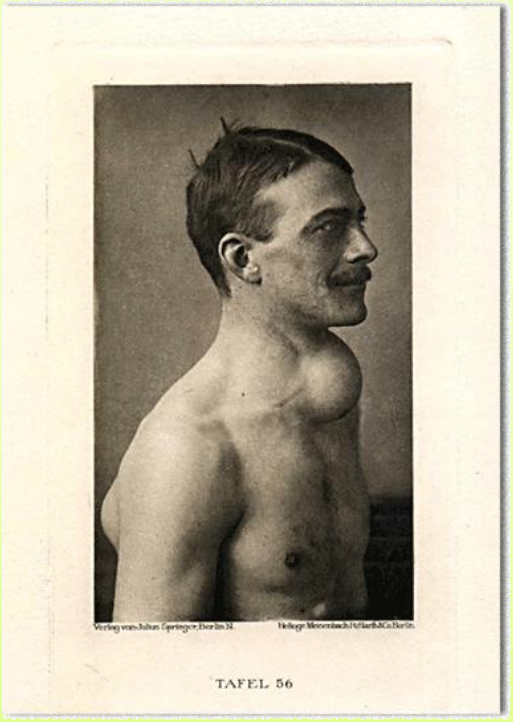
- **Growth pattern**
  - **Uninodular goitre:** can be either inactive or a toxic nodule
  - **Multinodular goitre:** can likewise be inactive or toxic (toxic multinodular goitre)
  - **Diffuse goitre:** the whole thyroid appearing to be enlarged

- **Size**
  - **Class I (palpation goitre):** in normal posture of the head, it cannot be seen; it is only found by palpation
  - **Class II:** the goitre is palpable and can be easily seen
  - **Class III:** the goitre is very large and is retrosternal; pressure results in compression marks





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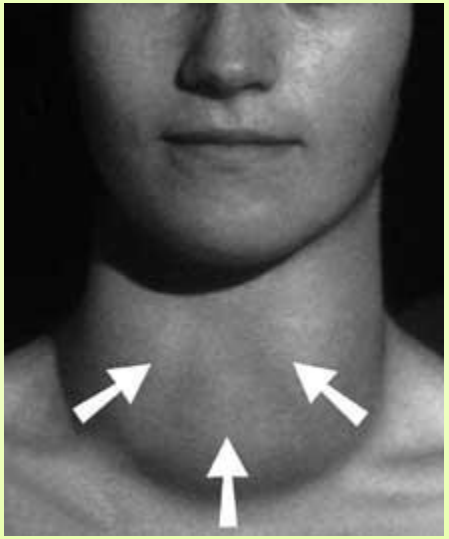


Pressure symptoms

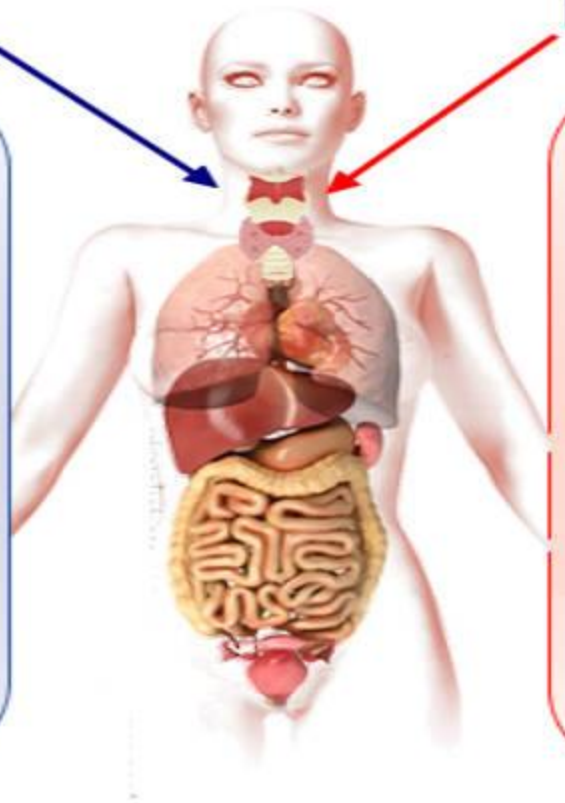
- enlarging gland produces pressure symptoms on the trachea and the esophagus
- discomfort, difficulty in swallowing, difficulty in breathing, cough, the feeling of a lump in the throat (and hoarseness)
- paralysis of the recurrent laryngeal nerve may occur when the nerve is stretched taut across the surface of an expanding goitre, but this event is rare
- symptoms suggesting obstruction of the trachea (cough, stridor and shortness of breath) may occur

(occasionally tenderness and a sudden increase in goitre size arise due to hemorrhage into a nodule)

THYROID DYSFUNCTION

HYPO THYROIDISM

- DRY HAIR
- PUFFY FACE
- SLOW HEARTBEAT
- WEIGHT GAIN
- CONSTIPATION
- BRITTLE NAILS
- ARTHRITIS
- COLD INTOLEREANCE
- DEPRESSION
- DRY SKIN
- FATIGUE
- MEMORY LOSS
- HEAVY MENSTRUAL PERIODS
- MUSCLE ACHES



HYPER THYROIDISM

- HAIR LOSS
- BULGING EYES
- SWEATING
- RAPID HEARTBEAT
- WEIGHT LOSS
- REGULAR GAS
- SOFT NAILS
- SLEEPING DIFFICULTIES
- HEAT INTOLERANCE
- INFERTILITY
- IRRITABILITY
- MUSCLE WEAKNESS
- NERVOUSNESS
- SCANT MENSTRUAL PERIODS

Hypothyroidism

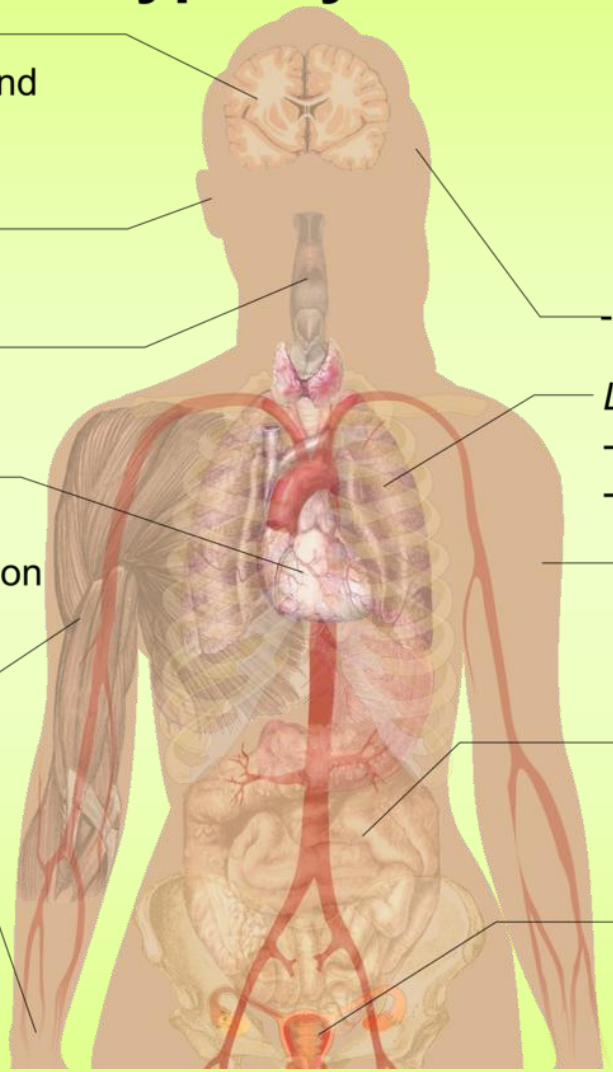
Hypothyroidism

- also called **underactive thyroid** or **low thyroid**
- a common disorder of the endocrine system in which the thyroid gland does not produce enough thyroid hormone
- the diagnosis can be **confirmed with blood tests measuring TSH** and thyroxine levels
- delayed relaxation after testing the ankle jerk reflex is a characteristic sign of hypothyroidism and is associated with the severity of the hormone deficit

- people with hypothyroidism often have no or only mild symptoms
- numerous symptoms and signs are associated with hypothyroidism (poor ability to tolerate cold, a feeling of tiredness, constipation, depression, weight gain, dry, coarse skin, swelling of the limbs, occasionally there may be swelling of the front part of the neck due to goitre)
- untreated hypothyroidism during pregnancy can lead to delays in growth and intellectual development in the baby, which is called cretinism

Signs and symptoms of

Hypothyroidism



Psychological
- Poor memory and concentration

- Poor hearing

Pharynx
- Hoarseness

Heart
- Slow pulse rate
- Pericardial effusion

Muscular
- Delayed reflex relaxation

Extremities
- Coldness
- Carpal tunnel syndrome

General
- Fatigue
- Feeling cold
- Weight gain with poor appetite

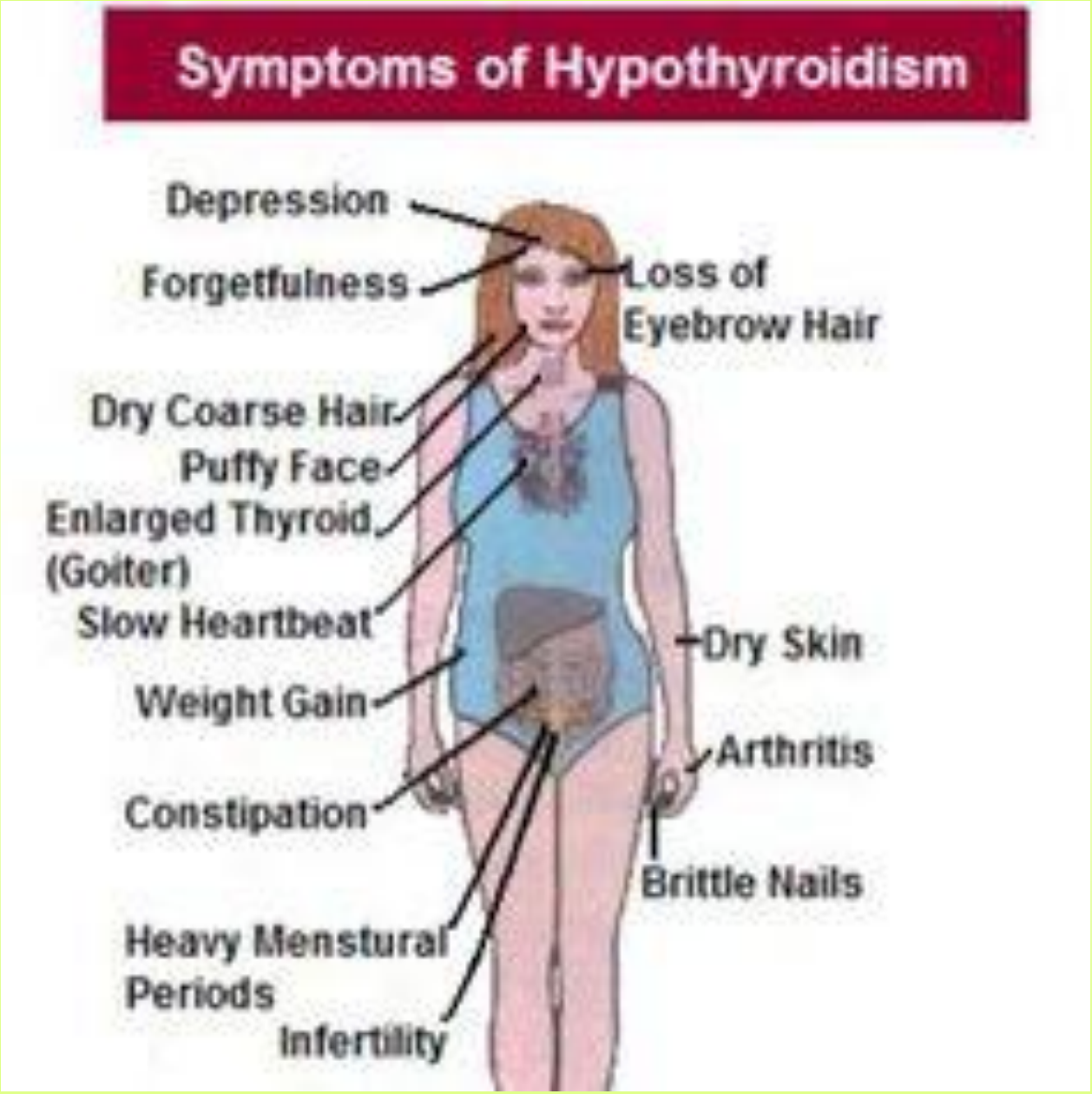
- Hair loss

Lungs
- Shortness of breath
- Pleural effusion

Skin
- Paresthesia
- Myxedema

Intestines
- Constipation
- Ascites

Reproductive system
- Menorrhagia


Symptoms of Hypothyroidism
Depression
Forgetfulness
Loss of Eyebrow Hair
Dry Coarse Hair
Puffy Face
Enlarged Thyroid (Goiter)
Slow Heartbeat
Weight Gain
Constipation
Heavy Menstural Periods
Infertility
Dry Skin
Arthritis
Brittle Nails

Hypothyroidism

- worldwide, **too little iodine in the diet** is the most common cause of hypothyroidism
- in countries with enough iodine in the diet, the most common cause is **the autoimmune condition Hashimoto's thyroiditis**
- less common causes: previous treatment with radioactive iodine, injury to the hypothalamus or the anterior pituitary gland, certain medications, a lack of a functioning thyroid at birth, previous thyroid surgery

- prevention at the population level = the universal salt iodization
- **worldwide about 1.5 milliard people are estimated to be iodine deficient**; however, it is unknown how often this results in hypothyroidism
- in the United States, hypothyroidism occurs in 0.3–0.4% of people
- **subclinical hypothyroidism, a milder form of hypothyroidism characterized by normal thyroxine levels and an elevated TSH level** (bellow 10 mIU/L), is thought to occur in 4.3–8.5% of people in the United States

- **more common in women than men** (in population-based studies, women were 7x more likely than men to have TSH levels above 10 mU/l)
- people over the age of 60 are more commonly affected

Causes of hypothyroidism

- inadequate function of the gland itself **(primary hypothyroidism)**
- inadequate stimulation by TSH from the pituitary gland **(secondary hypothyroidism)**
- inadequate release of TRH from the brain's hypothalamus **(tertiary hypothyroidism)**

- **primary hypothyroidism is about a thousandfold more common than central hypothyroidism**
- after women give birth, about 5 % develop **postpartum thyroiditis** which can occur up to nine months afterwards; this is characterized by a short period of hyperthyroidism followed by a period of hypothyroidism; 20–40 % remain permanently hypothyroid
- **autoimmune thyroiditis is often associated with other immune-mediated diseases** such as diabetes mellitus type 1, pernicious anemia, myasthenia gravis, celiac disease, rheumatoid arthritis and systemic lupus erythematosus; it may occur as part of autoimmune polyendocrine syndrome (type 1 and type 2)

Group	Causes
Primary hypothyroidism	Iodine deficiency, autoimmune thyroiditis, subacute granulomatous thyroiditis, subacute lymphocytic thyroiditis, postpartum thyroiditis, previous thyroidectomy, previous radioiodine treatment, previous external beam radiotherapy to the neck Medication: lithium-based mood stabilizers, amiodarone, interferon alpha, tyrosine kinase inhibitors such as sunitinib
Central hypothyroidism	Lesions compressing the pituitary (pituitary adenoma, craniopharyngioma, meningioma, glioma, metastasis…), surgery or radiation to the pituitary, drugs, injury, vascular disorders, autoimmune diseases (lymphocytic hypophysitis, polyglandular disorders), infiltrative diseases (iron overload due to hemochromatosis or thalassemia, neurosarcoidosis, Langerhans cell histiocytosis), particular inherited congenital disorders, and infections (tuberculosis, mycoses, syphilis)
Congenital hypothyroidism	Thyroid dysgenesis (75%), thyroid dyshormonogenesis (20%), maternal antibody or radioiodine transfer Syndromes: mutations (in *GNAS complex locus*, *PAX8*, *TTF-1/NKX2-1*, *TTF-2/FOXE1*), Pendred's syndrome (associated with sensorineural hearing loss) Transiently: due to maternal iodine deficiency or excess, anti-TSH receptor antibodies, certain congenital disorders, neonatal illness Central: pituitary dysfunction (idiopathic, septo-optic dysplasia, isolated TSH deficiency)

Hashimoto's thyroiditis

- **chronic lymphocytic thyroiditis** and **Hashimoto's disease**
- an autoimmune disease in which the thyroid gland is gradually destroyed
- affects about 5 % of the population
- it can occur in teens and young women, but typically begins between the ages of 30 and 50
- is about **seven times more common in women** than in men
- rates of disease appear to be increasing
- it was first described by the Japanese physician Hakaru Hashimoto in 1912, in 1957 it was recognized as an autoimmune disorder

- a combination of genetic and environmental risk factors
- a family history of this condition and having another autoimmune disease (celiac disease, type 1 diabetes, vitiligo, alopecia)
- preventable environmental factors (high iodine intake, selenium deficiency, infectious diseases and certain drugs)
- the genes implicated vary in different ethnic groups and the incidence is increased in people with chromosomal disorders, including Turner, Down, and Klinefelter syndromes
- **diagnosis is confirmed with blood tests for TSH (compensatory elevation), low fT4, fT3, and antithyroid antibodies**
- can be treated with levothyroxine (if hypothyroidism is not present some may recommend no treatment while others may treat to try to reduce the size of the goitre)

Hashimoto's thyroiditis

- early on there may be no symptoms, over time the thyroid may enlarge forming a painless goitre (which can be firm and lobulated but also nonpalpable), some people develop hypothyroidism with its accompanying signs and symptoms, after many years the thyroid typically shrinks in size
- **enlargement of the thyroid is due to infiltration of the thyroid with T lymphocytes and autoantibodies against specific thyroid antigens** (such as thyroid peroxidase, thyroglobulin) **and fibrosis** rather than tissue hypertrophy
- **antibodies against thyroid peroxidase** (TPO, TPOAb) **and/or thyroglobulin** (TgAb) cause gradual destruction of follicles in the thyroid gland (**the disease can be detected by looking for these antibodies in the blood**)
- activation of cytotoxic T-lymphocytes in response to cell-mediated immune response affected by helper T-lymphocytes is central to **thyrocyte destruction**
- a rare complication is thyroid lymphoma, generally the B-cell type, non-Hodgkin lymphoma

- the most common symptoms: fatigue, weight gain, pale or puffy face, feeling cold, joint and muscle pain, constipation, dry and thinning hair, heavy menstrual flow or irregular periods, depression, panic disorder, a slowed heart rate, and problems getting pregnant and maintaining pregnancy

Hypothyroidism in pregnancy

- **pregnancy leads to changes in thyroid hormone physiology; the gland is increased in size by 10 %, thyroid hormones production is increased by 50 %** (to provide enough thyroid hormone for the developing fetus and the expectant mother), **and iodine requirements are increased**
- **fT4 levels may be lower than anticipated due to increased binding to thyroid binding globulin** and decreased binding to albumin (they should either be corrected for the stage of pregnancy, or total thyroxine levels should be used instead for diagnosis); **TSH values may also be lower** (the normal range should be adjusted for the stage of pregnancy)
- many women have normal thyroid function but have immunological evidence of thyroid autoimmunity or are iodine deficient, and develop evidence of hypothyroidism before or after giving birth
- **even mild or subclinical hypothyroidism has been associated with impaired fertility and an increased risk of miscarriage** (determination of TPO antibodies may be considered as part of the assessment of recurrent miscarriage, but this recommendation is not universal)
- hypothyroidism in early pregnancy (even with limited or no symptoms), may increase the risk of **pre-eclampsia, offspring with lower intelligence, and the risk of infant death** around the time of birth
- subclinical hypothyroidism during pregnancy has also been associated with **gestational diabetes** and birth of the baby before 37 weeks of pregnancy

Congenital hypothyroidism

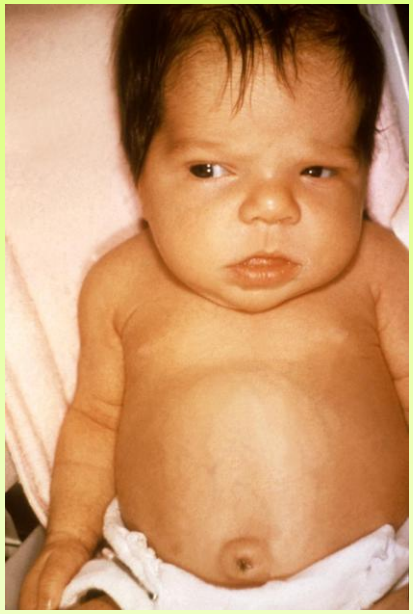
- a condition of thyroid hormone deficiency present at birth
- occurs with an incidence of 1: 3000 - 1: 4000 newborn infants
- association with **female sex** (2-4x more than in male) and gestational age >40 weeks
- **if untreated for several months after birth, it can lead to growth failure and permanent intellectual disability**
- treatment consists of a daily dose of thyroxine by mouth
- because the treatment is simple, effective, and inexpensive, **nearly all of the developed world practices newborn screening**
- newborns may show no symptoms, or may display mild symptoms that often go unrecognized as a problem: **excessive sleeping**, **reduced interest in nursing**, poor muscle tone, low or hoarse cry, infrequent bowel movements, exaggerated **jaundice**, and low body temperature
- if fetal deficiency was severe physical features may include **a larger anterior fontanel, persistence of a posterior fontanel, an umbilical hernia, and a large tongue**
- in the era before newborn screening, less than half of cases of severe hypothyroidism were recognized in the first month of life; as the months proceeded, these infants would grow poorly and be delayed in their development; by several years of age, they would display the recognizable facial and body features of cretinism with severe mental impairment (IQ below 80 in the majority)

Causes

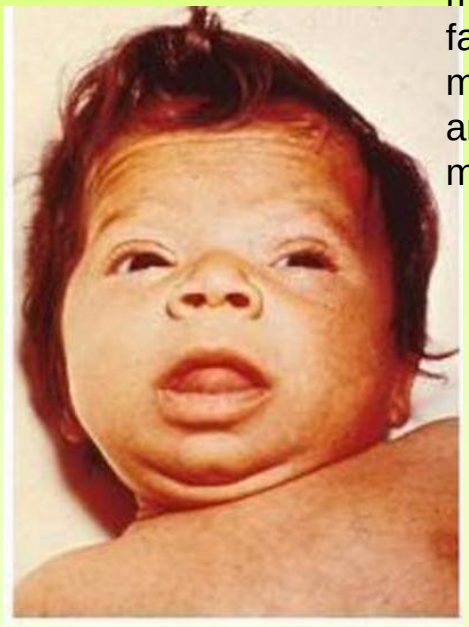
- iodine deficiency
- a defect of development of the thyroid gland itself, resulting in an absent (athyreosis) or underdeveloped (hypoplastic) gland
- in some instances, hypothyroidism detected by screening may be transient (one common cause of this is the presence of maternal antibodies that temporarily impair thyroid function for several weeks)
- genetic defects of T4 or T3 synthesis within a structurally normal gland
- TSH resistance, iodine trapping defect, organification defect, thyroglobulin, and iodotyrosine deiodinase deficiency…

The newborn screening program

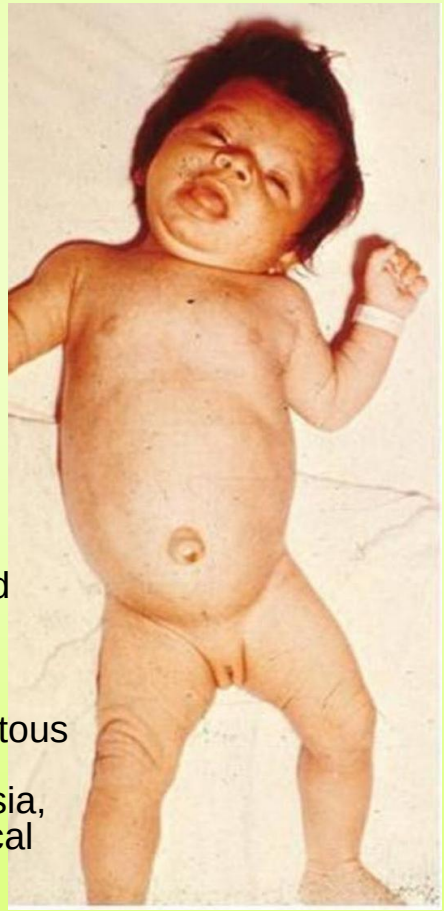
- based on **measurement of TSH** (or T4) **on the second or third day of life (Heel prick test)**
- TSH is high (or T4 low)
- most children correctly treated with thyroxine grow and develop normally in all respects
- in Czech Republic from 1985



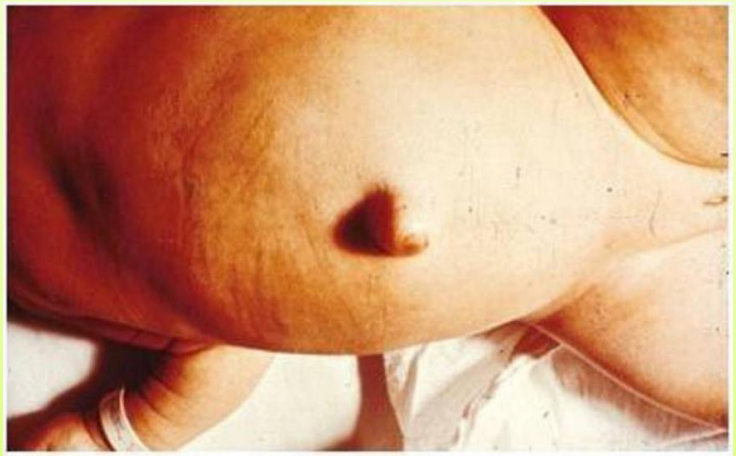
6 week old female with symptoms of jaundice



myxedematous facies, macroglossia, and skin mottling



3 month old infant with hypotonic posture, myxedematous facies, macroglossia, and umbilical hernia



abdominal distension and umbilical hernia

Screening of hypothyreosis in adult ?

- **widespread screening of the general population is a matter of debate**
- some organizations state that evidence **is insufficient to support routine screening**, while others recommend **either intermittent testing above a certain age in both sexes or only in women**
- targeted screening may be appropriate in a number of situations where hypothyroidism is common:
  - other autoimmune diseases
  - a strong family history of thyroid disease
  - those who have received radioiodine or other radiation therapy to the neck
  - those who have previously undergone thyroid surgery
  - those with an abnormal thyroid examination
  - those with psychiatric disorders
  - people taking amiodarone or lithium
  - those with a number of health conditions (such as certain heart and skin conditions)
- yearly thyroid function tests are recommended in people with Down syndrome (they are at higher risk of thyroid disease)
- the 2012 study *(Lepoutre et al.)* strongly recommends universal screening of thyroid levels for pregnant
- in 2015, the Endocrine Society clearly stated that it does recommend screening in pregnant women who are considered high-risk for thyroid autoimmune disease

Myxedema coma

- a rare but **life-threatening state of extreme hypothyroidism**
- it may occur in those who are known to have hypothyroidism when they develop another illness, but it can be the first presentation of hypothyroidism
- **very low body temperature without shivering, confusion, a slow heart rate and reduced breathing effort**
- there may be physical signs suggestive of hypothyroidism, such as skin changes or enlargement of the tongue

- very severe hypothyroidism and myxedema coma are associated with **low sodium levels** in the blood together with **elevations in antidiuretic hormone**, as well as **acute worsening of kidney function** due to a number of causes

Diagnosis

- **laboratory testing of TSH levels**
- a second TSH level is obtained several weeks later for confirmation
- free T4 levels are then often obtained
- measuring T3 is discouraged

TSH	**fT4**	**Interpretation**
Normal	Normal	Normal thyroid function
Elevated	Low	Overt hypothyroidism
Normal/low	Low	Central hypothyroidism
Elevated	Normal	Subclinical hypothyroidism

Diagnosis

- **mild elevations in creatine kinase and liver enzymes** in the blood
- **levels of cholesterol, low-density lipoprotein and lipoprotein(a) can be elevated**
- **typically return to normal when hypothyroidism has been fully treated**

- a diagnosis of hypothyroidism without any lumps or masses felt within the thyroid gland does not require thyroid imaging; however, if the thyroid feels abnormal, diagnostic imaging is then recommended
- **the presence of antibodies against thyroid peroxidase makes it more likely that thyroid nodules are caused by autoimmune thyroiditis**, but if there is any doubt, a needle biopsy may be required

Overt

- **TSH levels are high, fT4 and fT3 levels are low**
- TSH on multiple occasions of greater than 5 mIU/L, appropriate symptoms, and only a borderline low fT4
- TSH of greater than 10 mIU/L

Subclinical

- a milder form of hypothyroidism characterized by **an elevated serum TSH level, but with a normal serum free T4**
- most commonly caused by Hashimoto's thyroiditis
- **in adults it is diagnosed when TSH levels are greater than 5 mIU/L and less than 10mIU/L**
- the presentation is variable and classic signs and symptoms of hypothyroidism may not be observed
- of people with subclinical hypothyroidism, a proportion will develop overt hypothyroidism each year (in those with detectable antibodies against thyroid peroxidase, this occurs in 4.3%, while in those with no detectable antibodies, this occurs in 2.6%)

Treatment

- **<u>Levothyroxine</u>**
  - synthetic long-acting form of thyroxine

- **(Liothyronine)**
  - adding liothyronine (synthetic T3) to levothyroxine has been suggested as a measure to provide better symptom control
  - x this has not been confirmed by studies!!!

Hyperthyroidism

Hyperthyroidism

- the condition that occurs due to **excessive production of thyroid hormone** by the thyroid gland
- **Thyrotoxicosis** is the condition that occurs due to excessive thyroid hormone of any cause (it can be caused by the intake of thyroxine tablets or by an over-active thyroid) and therefore **includes hyperthyroidism** (some, however, use the terms interchangeably)
- a common disorder that affects approximately **2 % of women and 0.2 % of men**
- about half of these cases have obvious symptoms while the other half do not
- onset is commonly between 20 and 50 years of age, overall the disease is more common in those over the age of 60 years

Hyperthyroidism

- **signs and symptoms** vary between people and may include: irritability, muscle weakness, sleeping problems, a fast heartbeat, heat intolerance, diarrhea, enlargement of the thyroid, and weight loss
- symptoms are **typically less in the old and during pregnancy**
- an uncommon complication is **thyroid storm (thyrotoxic crisis)** in which an event such as an infection results in worsening symptoms such as confusion and a high temperature and often results in death
- **Graves' disease** is the cause of about 50 % to 80 % of the cases of hyperthyroidism in the United States
- **Other causes** include multinodular goiter, toxic adenoma, inflammation of the thyroid, eating too much iodine, and too much synthetic thyroid hormone
- a less common cause is a **pituitary adenoma**
- the diagnosis may be suspected based on signs and symptoms and confirmed with blood tests
- typically blood tests: **a low TSH, raised fT4 or fT3**

Hyperthyroidism in pregnancy

- recognizing and evaluating hyperthyroidism in pregnancy is a diagnostic challenge
- thyroid hormones are naturally elevated during pregnancy and hyperthyroidism must also be distinguished from gestational transient thyrotoxicosis
- high maternal fT4 levels during pregnancy have been associated with impaired brain developmental outcomes of the offspring

Causes of hyperthyroidism

- most often, **the entire gland is overproducing** thyroid hormone
- less commonly, a single nodule is responsible for the excess hormone secretion, called a **"hot" nodule**
- **thyroiditis** (inflammation of the thyroid) can also cause hyperthyroidism
- **functional thyroid tissue producing an excess of thyroid hormone occurs in a number of clinical conditions**:
  - **Graves' disease**
  - **toxic thyroid adenoma** (the most common etiology in Switzerland, 53 %)
  - **toxic multinodular goiter**
  - **thyroiditis** (Hashimoto's and subacute (de Quervain's) thyroiditis: **may be *initially* associated with secretion of excess thyroid hormone** but usually progress to gland dysfunction and hypothyroidism)
  - oral consumption of excess thyroid hormone tablets (surreptitious use, thyrotoxicosis), event of consumption of ground beef contaminated with thyroid tissue, and thus thyroid hormone (termed "hamburger hyperthyroidism")
  - Amiodarone (structurally similar to thyroxine) may cause either under- or overactivity of the thyroid
  - postpartum thyroiditis occurs in about 7% of women during the year after they give birth, typically has several phases, the first of which is hyperthyroidism
  - excess iodine consumption notably from algae
  - hypersecretion of TSH (almost always caused by a pituitary adenoma), accounts for much less than 1 % of hyperthyroidism cases

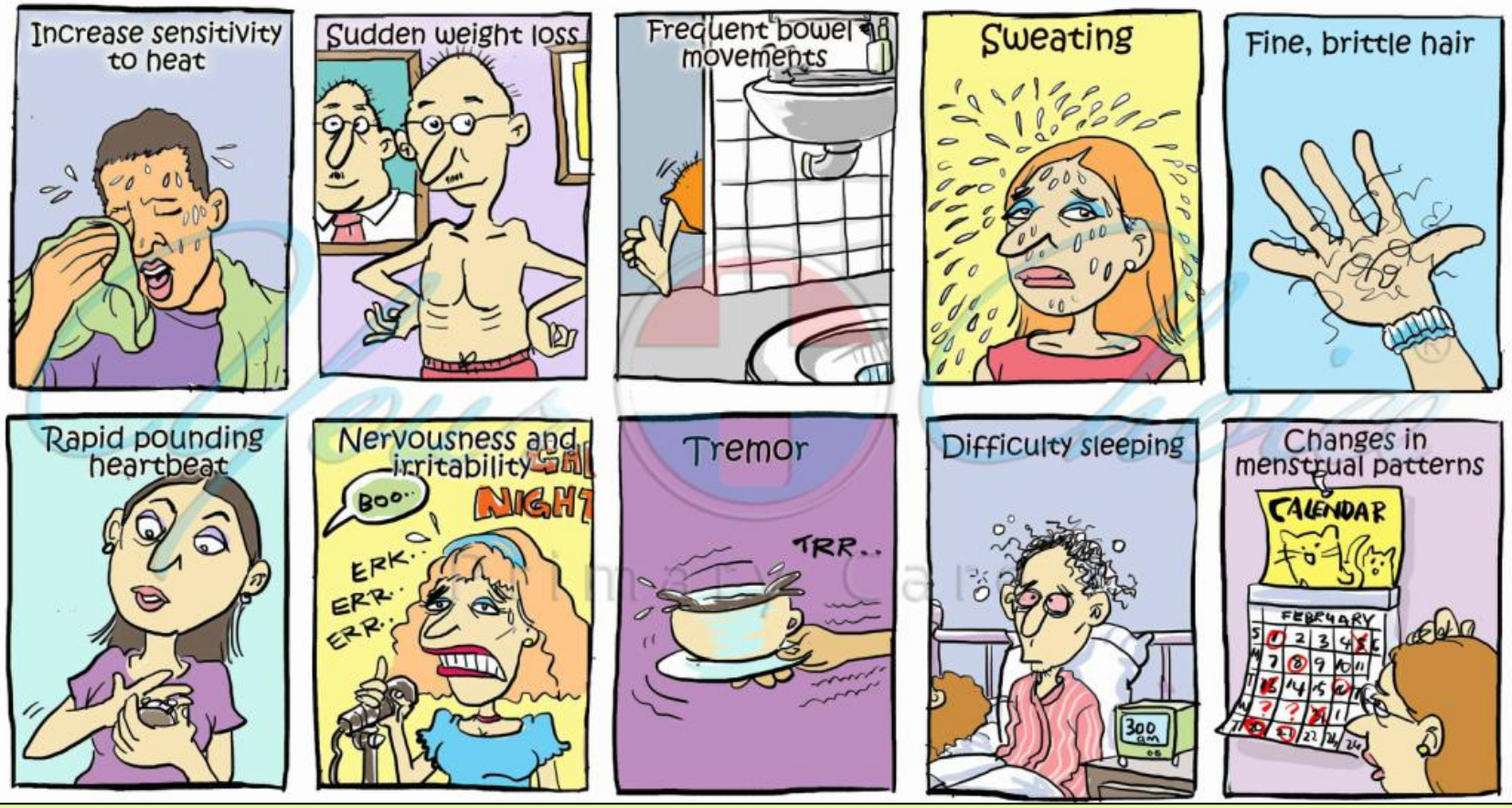
Signs and symptoms

- hyperthyroidism may be **asymptomatic** or present with **significant symptoms**
- **overstimulation of metabolism and exacerbation of the effect of the sympathetic nervous system:** nervousness, emotional lability, anxiety, difficulty sleeping, irritability, fatigue, hyperactivity, increased perspiration, heat intolerance, sweating, hair loss (fine brittle hair), palpitations and abnormal heart rhythms (atrial fibrillation), shortness of breath, hand tremors, thinning of the skin, and muscular weakness-especially in the upper arms and thighs, muscle aches, more frequent bowel movements and diarrhea, weight loss (despite a good appetite), vomiting, ***high blood sugar***, excessive urination, excessive thirst, loss of libido, gynecomastia and feminization, and, for women, lighten menstrual flow, less often menstrual periods, amenorrhea, ***a lower and sometimes unusually low serum cholesterol***

- long term untreated hyperthyroidism can lead to ***osteoporosis***

- these symptoms **may not be present often in the elderly**

HYPERTHYROIDISM



Subclinical hyperthyroidism

- a milder form of hyperthyroidism characterized **by low or undetectable serum TSH, but with a normal serum fT4**

- treatment of elderly persons having subclinical hyperthyroidism could reduce the incidence of atrial fibrillation
- there is also an increased risk of bone fractures (by 42%, there is insufficient evidence to say whether treatment with antithyroid medications would reduce that risk)

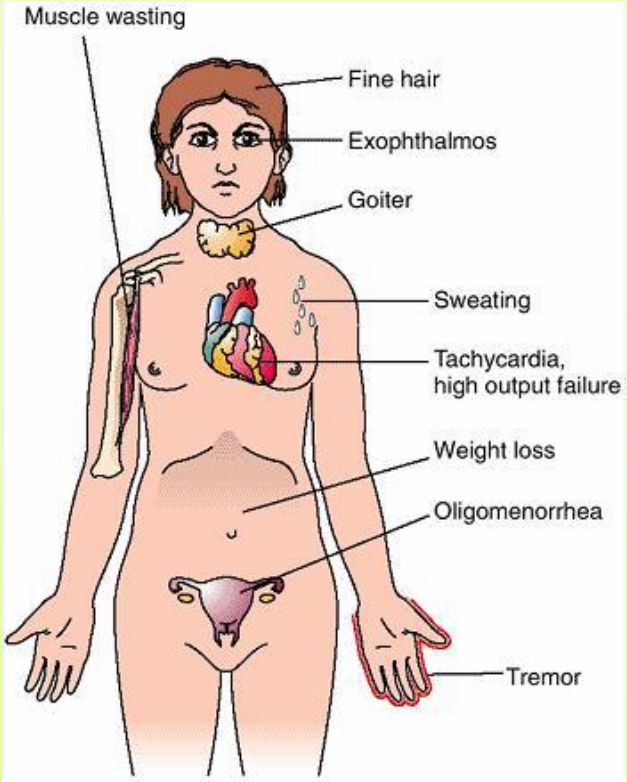
Graves-Basedow disease

- **Graves' disease, toxic diffuse goiter**
- an autoimmune disease
- frequently results in hyperthyroidism
- often results in an enlarged thyroid
- occurs **about 7.5 times more often in women** than men (it will develop in about 0.5% of males and 3% of females)
- often it starts between the ages of 40 and 60 but can begin at any age
- **the most common cause of hyperthyroidism** with 50-80 % worldwide, although this varies substantially with location (47% in Switzerland to 90 % in the USA, thought to be due to varying levels of iodine in the diet)
- named after Robert Graves who described it in 1835
- signs and symptoms of hyperthyroidism may include irritability, hyperactivity, muscle weakness, hand tremor, sleeping problems, a fast heartbeat, heat intolerance, diarrhea, weight loss, hair loss, excessive sweating, itching…
- other symptoms may include **thickening of the skin on the shins, known as pretibial myxedema, and eye bulging, a condition caused by Graves' ophthalmopathy** (about 25 % to 80 % of people with the condition develop eye problems)

- ophthalmopathy may cause the eyes to look enlarged because the eye muscles swell and push the eye forward
- some have swelling of the front of the neck from an enlarged thyroid **(usually diffusely and symmetric goitre)**
- exophthalmos (protrusion of the eyeball) occurs specifically and uniquely in hyperthyroidism caused by Graves' disease, this forward protrusion of the eyes is due to immune-mediated inflammation in the retro-orbital fat

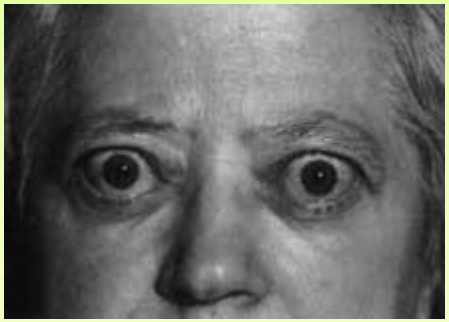
"Diagnostic" signs of Graves' disease are:

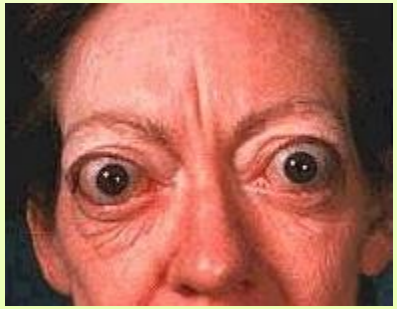
- **exophthalmos**
- **pretibial myxedema**

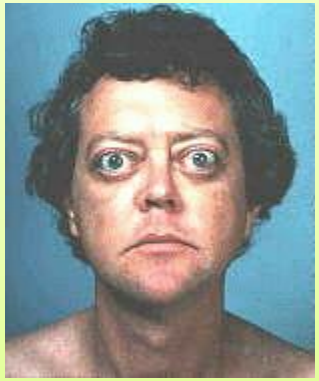


Graves-Basedow disease

diffusely goitre



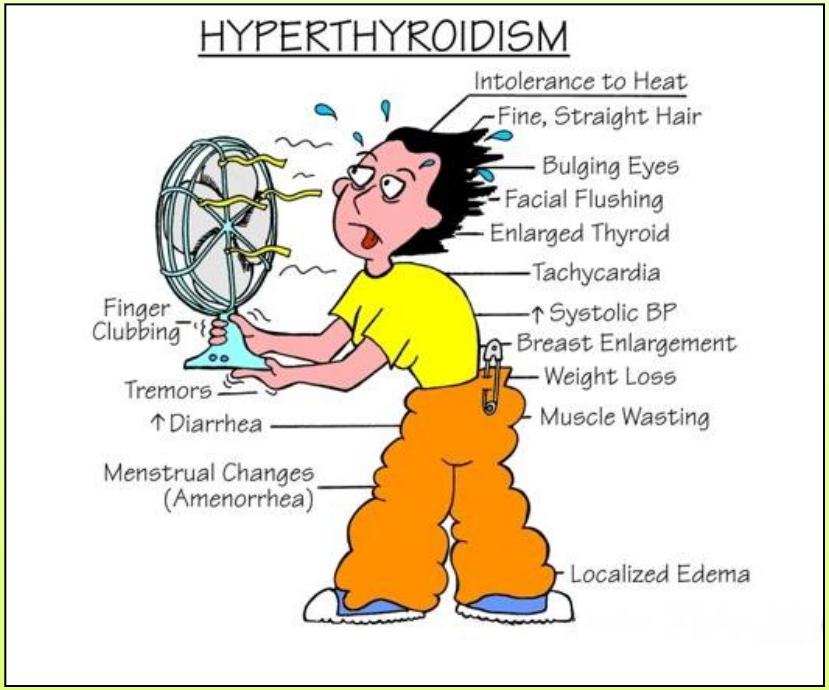




exophthalmos

Characteristic signs

- Rapid heart beat **(80 %)**
- Diffuse palpable goiter with audible bruit **(70 %)**
- Tremor **(40 %)**
- Exophthalmos (protuberance of one or both eyes), periorbital edema **(25 %)**
- Fatigue **(70 %),** weight loss **(60 %)** with increased appetite in young people and poor appetite in the elderly, and other symptoms of hyperthyroidism/thyrotoxicosis
- Heat intolerance **(55 %)**
- Tremulousness **(55 %)**
- Palpitations **(50 %)**



Graves-Basedow disease

- the exact cause is unclear (**probably combination of genetic and environmental factors**)
- a person is more likely to be affected if they have a **family member** with the disease (if one twin is affected there is a 30 % chance the other twin will also have the disease)
- the onset of disease may be **triggered by stress, infection, or giving birth**
- **a viral or bacterial infection may trigger antibodies** which cross-react with the human TSH receptor, a phenomenon known as **antigenic mimicry** (the bacterium *Yersinia enterocolitica* bears structural similarity with the human thyrotropin receptor and was hypothesized to contribute to the development of thyroid autoimmunity in genetically susceptible individuals)
- those with other **autoimmune diseases** such as type 1 diabetes and rheumatoid arthritis are more likely to be affected
- **smoking** increases the risk of disease and may worsen eye problems

Graves-Basedow disease

- **the disorder results from an antibody, called thyroid stimulating immunoglobulin (TSI), that has a similar effect to TSH**
- (antibodies to thyroglobulin and to the thyroid hormones T3 and T4 may also be produced)
- TSI recognizes and binds to the TSH receptor which chronically stimulates the **excessive production and secretion of T4 and T3**
- thyroxine receptors in the pituitary gland are activated by the surplus hormone, **suppressing additional release of TSH in a negative feedback loop**
- **the result is very high levels of circulating thyroid hormones and a low TSH level**
- radioactive iodine uptake, or thyroid ultrasound with Doppler can confirm a diagnosis
- *the infiltrative exophthalmos has been explained by postulating that the thyroid gland and the extraocular muscles share a common antigen which is recognized by the antibodies; antibodies binding to the extraocular muscles would cause swelling behind the eyeball*
- *the "orange peel" skin has been explained by the infiltration of antibodies under the skin, causing an inflammatory reaction and subsequent fibrous plaques*

Eye disease in Graves-Basedow

- Class 0: No signs or symptoms
- Class 1: Only signs (limited to upper lid retraction and stare, with or without lid lag)
- Class 2: Soft tissue involvement (oedema of conjunctivae and lids, conjunctival injection, etc.)
- Class 3: Proptosis
- Class 4: Extraocular muscle involvement (usually with diplopia)
- Class 5: Corneal involvement (primarily due to lagophthalmos)
- Class 6: Sight loss (due to optic nerve involvement)

Thyrotoxic crisis (thyroid storm)

- a rare but **severe and potentially life-threatening complication** of thyrotoxicosis characterized by **rapid and often irregular heart beat** (heart failure and myocardial infarction are encountered), **high fever** (often above 40°C), **vomiting, diarrhea, and mental agitation**
- symptoms may be unusual in the young, old, or pregnant
- it is a medical emergency and requires hospital care
- even with treatment, **death occurs in 20 % to 50 %**
- most episodes occur either in those with known hyperthyroidism whose treatment has been stopped or become ineffective, or in those with untreated mild hyperthyroidism who have developed an intercurrent illness (such as an infection)

Diagnosis of hyperthyroidism

- measuring serum TSH is typically the initial test
- **a low TSH** level typically indicates that the pituitary gland is being inhibited or "instructed" by the brain to cut back on stimulating the thyroid gland, having sensed **increased serum levels of fT4 and/or fT3**
- **in rare circumstances, a low TSH indicates primary failure of the pituitary, or temporary inhibition** of the pituitary due to another illness (euthyroid sick syndrome) and so **checking the fT4 and fT3 is still clinically useful**
- measuring specific antibodies, such as **anti-TSH-receptor antibodies (TSI) in Graves' disease**, or anti-thyroid peroxidase in Hashimoto's thyroiditis

Treatment

- **Radioiodine therapy** involves taking iodine-131 by mouth which is then concentrated in and destroys the thyroid over weeks to months (the resulting hypothyroidism is treated with synthetic thyroid hormone)
- **Thyrostatics** (carbimazole, methimazole, propylthiouracil) are believed to work by inhibiting the iodination of thyroglobulin by thyroperoxidase and, thus, the formation of T4;
  propylthiouracil also works outside the thyroid gland, preventing the conversion of T4 to the active form T3;
  medications such as beta blockers may control some symptoms
- **Surgery** to remove the thyroid may be used in those with very large thyroids or when cancer is a concern

- *People with autoimmune hyperthyroidism should not eat foods high in iodine, such as edible seaweed and kelps*

Thyroiditis

Thyroiditis

- acute
- subacute (de Quervain's)
- autoimmune thyroiditis (Hashimoto's thyroiditis)
- Riedel's thyroiditis

Acute thyroiditis

- **also known as acute infectious thyroiditis, suppurative thyroiditis**, **microbial inflammatory thyroiditis**, **pyrogenic thyroiditis, bacterial thyroiditis**
- the thyroid is normally very resistant to infection (due to a relatively high amount of iodine, high vascularity and lymphatic drainage to the region)
- a persistent fistula from the piriform sinus may make the left lobe of the thyroid susceptible to infection and abscess formation
- **most often caused by a bacterial infection** (but also by a fungal or parasitic infection, most commonly in an immunocompromised patients)
- **found in children** (the occurrence about 92%) and young adults between the ages of 20 and 40 (the occurence about 8%)
- men and women are each just as likely to get the disease
- **if left untreated, there is a 12 % mortality rate**
- pain, firmness, tenderness, redness or swelling in the anterior aspect of the neck, sudden fever, dysphagia and dysphonia
- **blood tests of thyroid functions (TSH, fT4, fT3) are usually normal**
- elevated white blood cell count and erythrocyte sedimentation rate
- ultrasonographic examination often shows the abscess or swelling in thyroid
- antibiotic treatment, surgical drainage or lobectomy

Subacute thyroiditis

- can be a cause of both thyrotoxicosis and hypothyroidism
- uncommon and can affect individuals of both sexes and people of all ages
- the most common form: **subacute granulomatous or de Quervain's thyroiditis**
  - a sudden and painful enlargement of the thyroid accompanied with fever, malaise and muscle aches
  - etiology: viral infection
  - there may be a genetic predisposition
  - fever and **symptoms of thyrotoxicosis (in two thirds of subjects), hypothyroidism is rare**
  - laboratory markers for thyroid inflammation and dysfunction typically peaked within one week of onset of illness
  - therapy: acetylsalicylic acid, antiflogistics, corticosteroids
- Other types:
  - Subacute lymphocytic thyroiditis (silent thyroiditis or painless thyroiditis, occur at any age and is more common in females)
  - Postpartum thyroiditis

  } **first phase is typically hyperthyroidism; then, the thyroid either returns to normal or develops hypothyroidism**

  - Palpation thyroiditis (the development of thyroid inflammation due to mechanical damage to thyroid follicles, initial transient hyperthyroidism)

Riedel's thyroiditis

- also called **Riedel's struma**
- **a chronic form of thyroiditis**
- now believed that it is one manifestation of a **systemic disease** that can affect many organ systems **called IgG4-related disease** (it is often a multi-organ disease affecting pancreas, liver, kidney, salivary and orbital tissues and retroperitoneum; the hallmarks are fibrosis and infiltration by IgG4 secreting plasma cells)
- **a replacement of the normal thyroid parenchyma by a dense fibrosis that invades adjacent structures of the neck and extends beyond the thyroid capsule**
- **the thyroid gland: stone-hard and fixed to adjacent structures**
- **the inflammatory process infiltrates muscles and causes symptoms of tracheal compression**
- rare, most seen in **women**
- **most patients remain euthyroid, but approximately 30% of patients become hypothyroid and very few patients are hyperthyroid**
- therapy usually consists of prednisolone, some cases may require surgery to relieve tracheal or esophageal obstruction (isthmectomy)

Thyroid cancer

Thyroid cancer

- a cancer originating from follicular or parafollicular (C) thyroid cells
- the follicular cells give rise to both well-differentiated cancers
  - **papillary thyroid cancer (PTC)** (75 % to 85 % of cases)
  - **follicular thyroid cancer (FTC)** (10 % to 20 % of cases)

  and poorly differentiated **anaplastic thyroid cancer (ATC)** (< 5% of cases)
- the C cell produces calcitonin and is the cell of origin for **medullary thyroid cancer (MTC)** (5 % to 8 % of cases)
- **3x more common in women** than in men (but according to European statistics, the overall relative 5-year survival rate is 85 % for females and 74 % for males)
- 5-year survival rates are 98.1% in the United States

- Others tumors
  - thyroid lymphoma
  - squamous cell thyroid carcinoma
  - sarcoma of thyroid

	5-year survival			
Thyroid cancer type	**Stage I**	**Stage II**	**Stage III**	**Stage IV**
Papillary	100%	100%	93%	51%
Follicular	100%	100%	71%	50%
Medullary	100%	98%	81%	28%
Anaplastic	(always stage IV)			7%

Thyroid cancer

- most often the first **symptom** is **a nodule** in the thyroid region of the neck
- many adults have small nodules in their thyroids, but under 5 % are found to be cancerous
- sometimes the first sign is an enlarged lymph node
- later symptoms are pain in the anterior region of the neck and changes in voice (due to an involvement of the recurrent laryngeal nerve)

- **usually found in a euthyroid patient**, but symptoms of hyperthyroidism or hypothyroidism may be associated with a large or metastatic well-differentiated tumor

- **thyroid nodules are of particular concern when they are found in those under the age of 20** (the presentation of benign nodules at this age is less likely)

- a number of environmental and genetic **predisposing factors**
  - environmental exposure to ionizing radiation from both natural background sources and artificial sources
  - exposure to mantlefield radiation for lymphoma
  - thyroiditis and other thyroid diseases
  - genetic causes include multiple endocrine neoplasia type 2 which markedly increases rates, particularly of the rarer medullary form of the disease

Diagnosis and therapy of thyroid cancer

- most commonly an **ultrasound** is performed to confirm the presence of a nodule
- measurement of **TSH and anti-thyroid antibodies** will help decide if there is a functional thyroid disease such as Hashimoto's thyroiditis present (a known cause of a benign nodular goiter)
- measurement of **calcitonin** is necessary to exclude the presence of medullary thyroid cancer
- to achieve a definitive diagnosis before deciding on treatment, **a fine needle aspiration cytology** test is usually performed
- once a diagnosis of thyroid cancer has been established, it is likely that a **total thyroidectomy** will be performed

- *the most effective management of aggressive thyroid cancers is total thyroidectomy followed by radioactive iodine ablation and TSH-suppression therapy, chemotherapy or radiotherapy may also be used in cases of distant metastases or advanced cancer stage*

Thyroglobulin as a tumor marker

- metabolism of thyroglobulin occurs in the liver and via thyroid gland recycling of the protein
- circulating thyroglobulin has a half-life of 65 hours
- **following thyroidectomy, it may take many weeks before thyroglobulin levels become undetectable**
- after thyroglobulin levels become undetectable (following thyroidectomy), **levels can be serially monitored**
- **a subsequent elevation** is an indication of **recurrence of papillary or follicular thyroid carcinoma**
- **thyroglobulin levels in the blood are mainly used as a tumor marker for papillary or follicular thyroid cancer**
- thyroglobulin is not produced by medullary or anaplastic thyroid carcinoma

- *thyroglobulin testing can be complicated by the presence of anti-thyroglobulin antibodies which are present in 1 in 10 normal individuals, and a greater percentage of patients with thyroid carcinoma; the presence of these antibodies can result in falsely low (or rarely falsely high) levels of thyroglobulin*

Calcitonin

- also known as thyrocalcitonin
- a 32-amino acid linear polypeptide hormone (3455 Da) that is **produced by the parafollicular cells (C-cells) of the thyroid**
- formed by the proteolytic cleavage of a larger preprocalcitonin (17kDa), which is the product of the CALC1 gene
- *(the CALC1 gene belongs to a superfamily of related protein hormone precursors including islet amyloid precursor protein, calcitonin gene-related peptide, and the precursor of adrenomedullin)*
- it belongs to the calcitonin-like protein family
- its structure comprises a single alpha helix
- alternative splicing of the gene coding for calcitonin produces a distantly related peptide of 37 amino acids, called calcitonin gene-related peptide (CGRP), beta type

The following are the amino acid sequences of salmon and human calcitonin

- **salmon:**

  Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro
- **human:**

  Cys-Gly-Asn-Leu-Ser-Thr-Cys-Met-Leu-Gly-Thr-Tyr-Thr-Gln-Asp-Phe-Asn-Lys-Phe-His-Thr-Phe-Pro-Gln-Thr-Ala-Ile-Gly-Val-Gly-Ala-Pro

compared to salmon calcitonin, human calcitonin differs at 16 residues

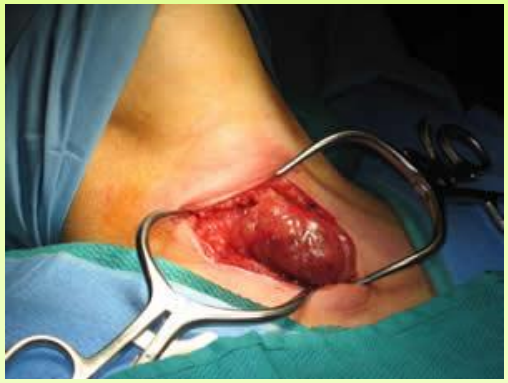
Calcitonin

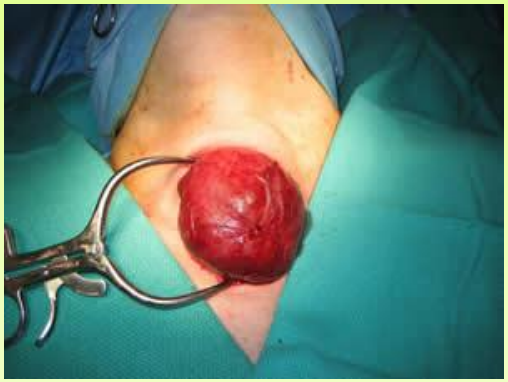
- participates in calcium (Ca^{2+}) and phosphorus metabolism
- in many ways, calcitonin counteracts parathyroid hormone (PTH)
- more specifically, **calcitonin lowers blood Ca^{2+}levels** in two ways:
  - major effect: inhibits osteoclast activity in bones
  - minor effect: inhibits renal tubular cell reabsorption of $Ca^{2+}$and phosphate, allowing them to be excreted in the urine (no physiological significance in humans, a short-lived effect because the kidneys become resistant to calcitonin)
- in its skeleton-preserving actions, **calcitonin protects against calcium loss from skeleton during periods of calcium mobilization**, such as **pregnancy** and, especially, **lactation**
- other effects are in **preventing postprandial hypercalcemia** resulting from absorption of Ca^{2+}
- **its function is usually not significant** in the regulation of normal calcium homeostasis
- calcitonin lowers blood calcium and phosphorus mainly through its inhibition of osteoclasts *(osteoblasts do not have calcitonin receptors and are therefore not directly affected by calcitonin levels; bone resorption and formation are coupled processes → calcitonin's inhibition of osteoclastic activity leads to decreased osteoblastic activity (as an indirect effect))*
- secretion of calcitonin is stimulated by:
  - an increase in serum [Ca^{2+}]
  - gastrin and pentagastrin

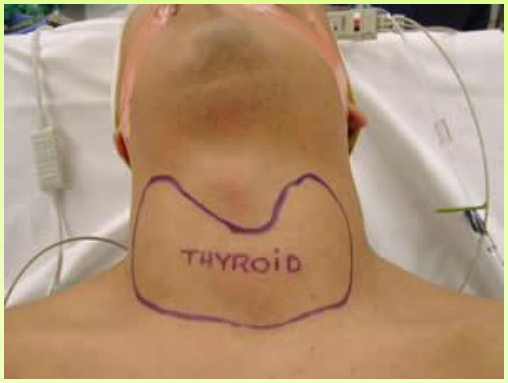
Medical significance of calcitonin

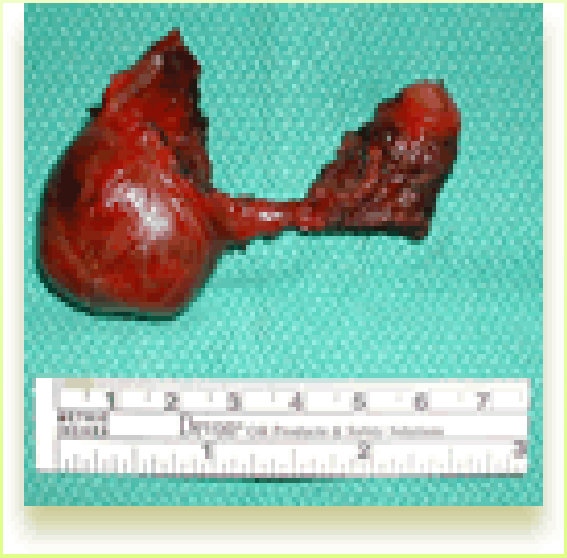
- **a malignancy of the parafollicular cells, medullary thyroid cancer, typically produces an elevated serum calcitonin level**

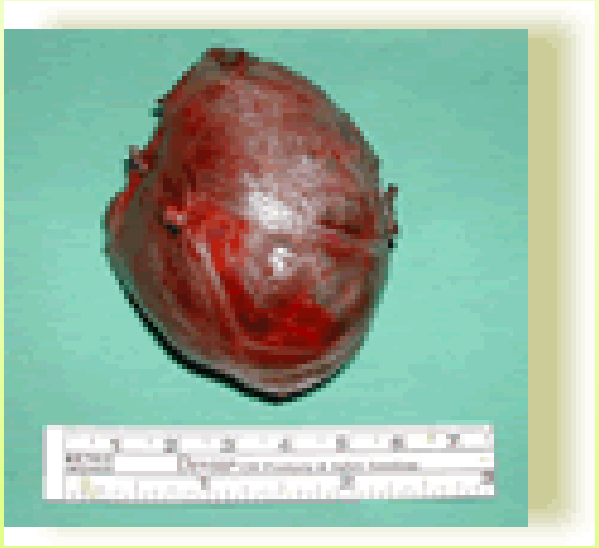
- **Salmon calcitonin is used for the treatment of:**
  - postmenopausal osteoporosis
  - hypercalcaemia
  - Paget's disease
  - bone metastases
  - phantom limb pain
  - a possible non-operative treatment for spinal stenosis?

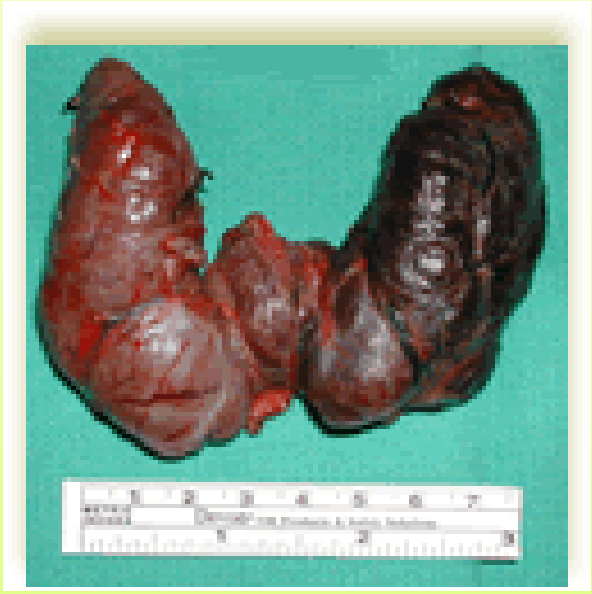





THYROID







Thyroid function tests

Thyroid function tests

TSH

- **generally increased in hypothyroidism and decreased in hyperthyroidism**
- **its measurement is the most sensitive test for thyroid hormone function**
- **the recommended screening tool for thyroid disease** (a better screening tool than fT4)
- the production of TSH is controlled by TRH
- TSH levels may be suppressed by excess fT3 or fT4 in the blood
- a low-normal TSH together with a low-normal T4 may signal central disease and a TSH to TRH pathology
- elevated reverse T3 together with low-normal TSH and low-normal T3, T4 values, which is regarded as indicative for euthyroid sick syndrome, may also have to be investigated for chronic subacute thyroiditis
- for hypothyroid patients on thyroxine, measurement of TSH alone is generally considered sufficient (an increase in TSH above the normal range indicates under-replacement, a significant reduction in TSH suggests over-treatment)
- for hyperthyroid patients, both TSH and fT4 are usually monitored

Thyroid function tests

total T4, total T3

- rarely measured, having been largely superseded by free T4 tests
- generally elevated in hyperthyroidism and decreased in hypothyroidism
- usually slightly elevated in pregnancy
- measured to see the bound and unbound levels
- less useful in cases where there could be protein abnormalities, the total hormones are less accurate due to the large amount of T4 and T3 that are bound

fT4, fT3

- **generally elevated in hyperthyroidism and decreased in hypothyroidism**

Carrier proteins

Thyroxine-binding globulin (TBG)

- an increased TBG results in an increased total T4 and total T3 without an actual increase in hormonal activity of thyroid hormones

Transthyretin (prealbumin)

Albumin

Autoantibodies

- **Antibodies against thyroid peroxidase** (anti-TPO, TPOAb)
- **Antibodies against thyroglobulin** (anti-Tg, TgAb)
- **Thyroid stimulating immunoglobulin (against TSH receptor)** (TSI, anti-TSHR, **TRAK**)

Thyroid hormone uptake (T uptake)

- a measure of the unbound thyroxine binding globulins in the blood, that is, the TBG that is unsaturated with thyroid hormone
- unsaturated TBG increases with decreased levels of thyroid hormones

Thyroid Hormone Binding Ratio (THBR)

- measures the "uptake" of T3 or T4 tracer by TBG
- this provides an indirect and ***reciprocal*** estimate of the **available** binding sites on TBG within the sample
- attempts to correct for changes in thyroid binding globulin due to liver disease, protein losing states, pregnancy or various drugs
- in patients with hyperthyroidism, there will be fewer available binding sites on TBG (due to the increased circulating T3 / T4) → increased THBR
- in patients with hypothyroidism, there will be more free binding sites on TBG (due to the decreased amount of circulating T3 / T4) → decreased THBR
- in general, **H**igh with **High** thyroid activity and **L**ow with **Low** thyroid activity

Free thyroxine index

- obtained by multiplying the total T4 with T uptake
- a more reliable indicator of thyroid status in the presence of abnormalities in plasma protein binding
- rarely used now that reliable fT4 and fT3 assays are routinely available
- elevated in hyperthyroidism and decreased in hypothyroidism

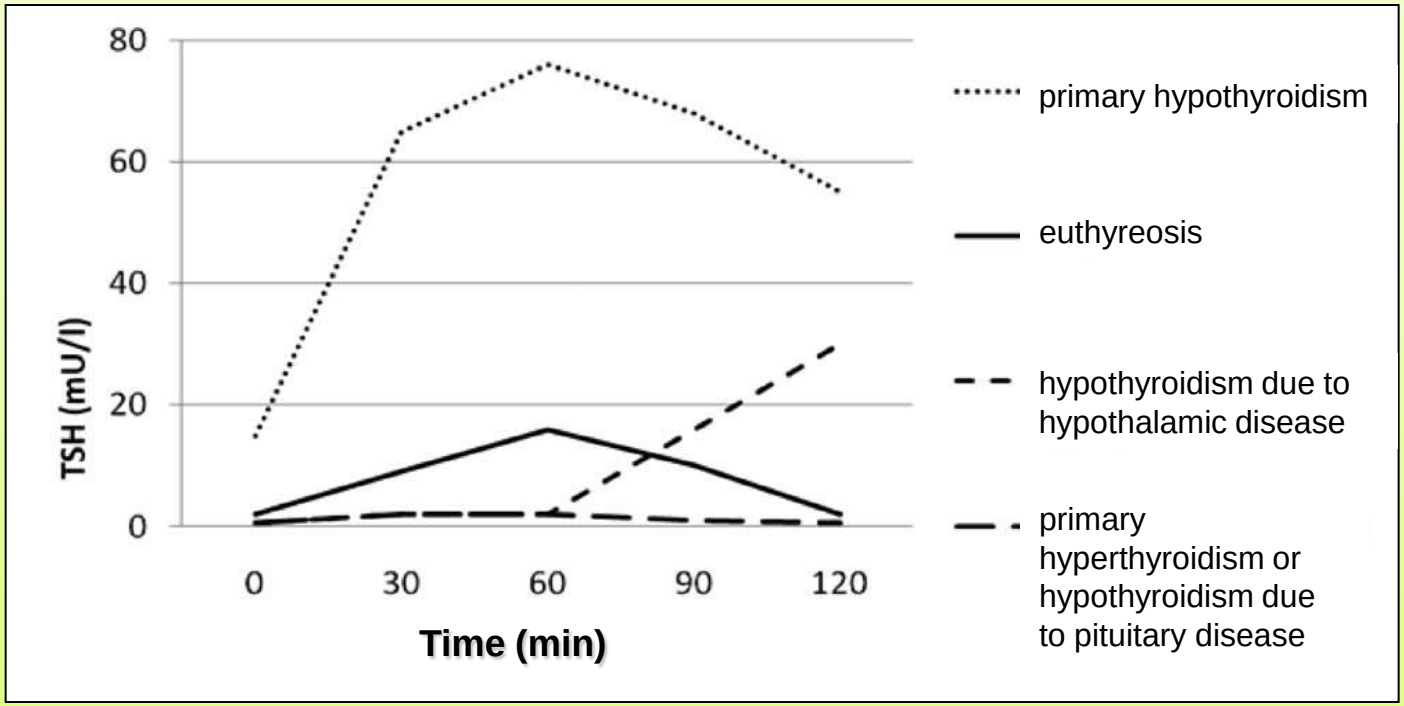
TRH stimulation test

- prior to the availability of sensitive TSH assays, TRH stimulation test was relied upon for confirming and assessing the degree of suppression in suspected hyperthyroidism
- this test **involves determining basal TSH levels** and **levels 15 to 30 minutes after an intravenous bolus of TRH**
- **normally, TSH would rise into the concentration range**

TRH stimulation test

- **Use and interpretation:**

  helpful in diagnosis in patients with confusing thyroid function tests
  - in **primary hyperthyroidism** TSH are low and TRH administration induces little or no change in TSH levels
  - in **hypothyroidism** due to end organ failure (**primary**), administration of TRH produces a prompt increase in TSH
  - in **hypothyroidism** due to pituitary disease (**secondary** hypothyroidism) administration of TRH does not produce an increase in TSH
  - in **hypothyroidism** due to hypothalamic disease (**tertiary** hypothyroidism), administration of TRH produces a delayed (60–120 minutes, rather than 15–30 minutes) increase in TSH

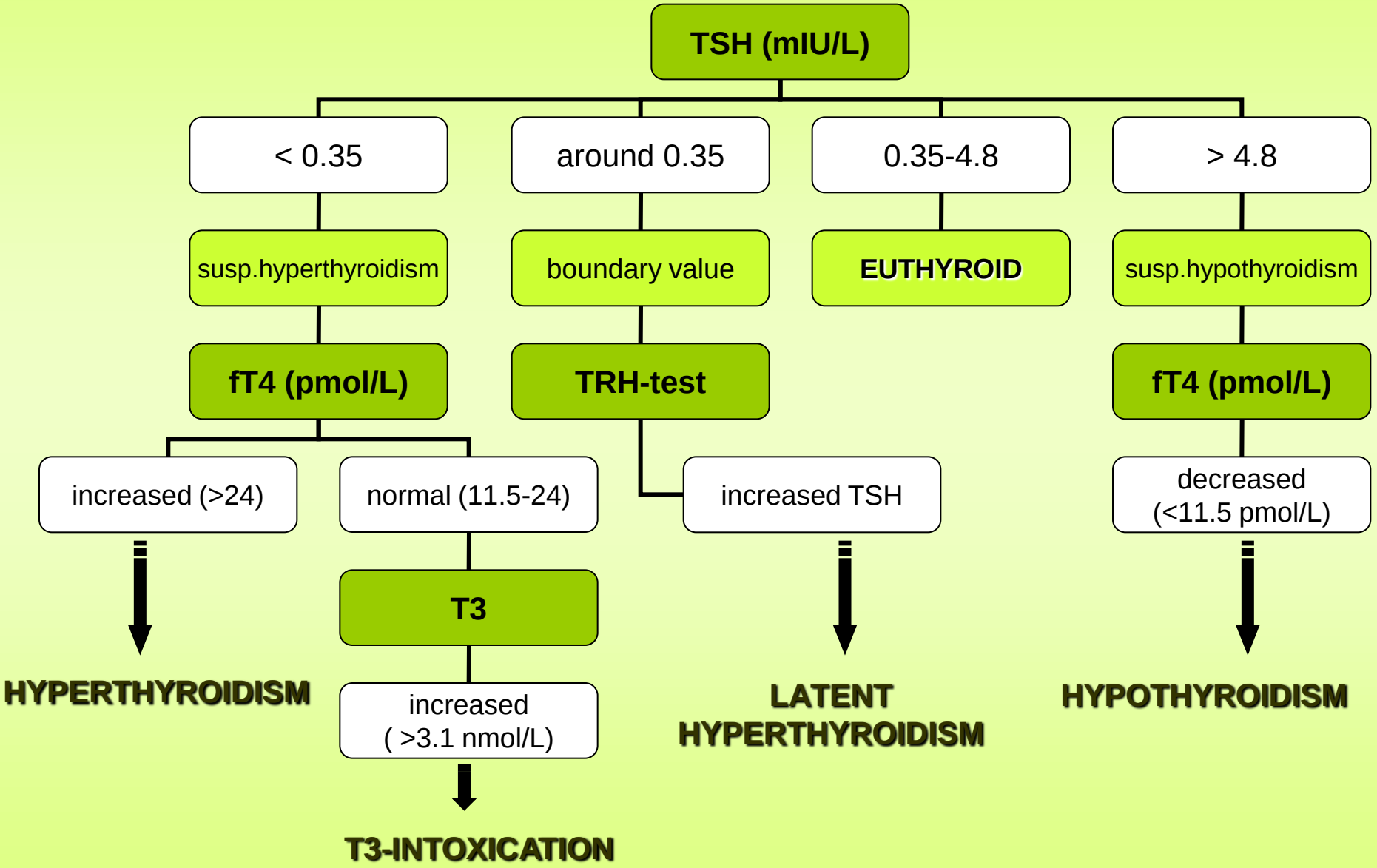


Reference range:

- Total T4: 50 – 150 nmol/L *(in US in **"ng/dl"…**)*
- Total T3: more than 15 years: 1.3-3.1 nmol/L
  1 year – 15 years: 1.25 – 3.6 nmol/L
  1 month – 1 year: 1.1 – 3.7 nmol/L
  0- 1 month: 0.55 – 3.2 nmol/L
- **fT4: more than 15 years: 11.5 – 24 pmol/L**
  1 year – 15 years: 12 – 27 pmol/L
  1 month – 1 year: 10 – 24 pmol/L
  0- 1 month: 14 – 32 pmol/L
- fT3: more than 15 years: 3.5 – 6.5 pmol/L
  0- 1 month: 3.3 – 10.5 pmol/L
- **TSH: more than 15 years: 0.35 – 4.8 mIU/L** (3-4,8 transient zone)
  1 year – 15 years: 0.34 – 5.5 mIU/L
  1 month – 1 year: 0.46 – 7.3 mIU/L
  0- 1 month: 0.59 – 13 mIU/L
- thyroglobulin: 0.1 – 85 µg/L

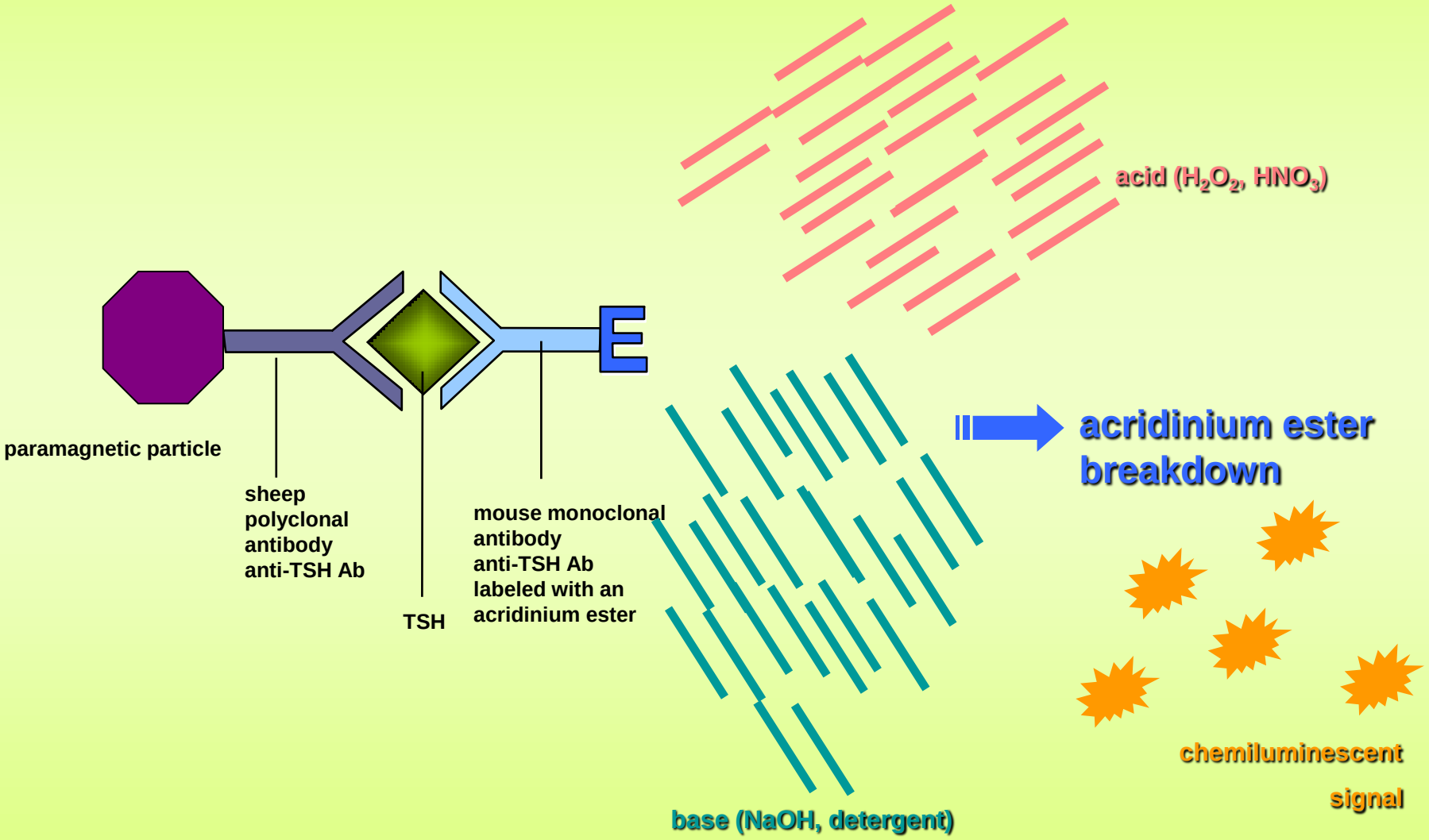
- calcitonin males: < 17 ng/L, females: < 8.9 ng/L (more than 3 years of age)
  under 6 months of age: < 40 ng/L
  6 months -3 years: < 17 ng/L

Examination algorithm

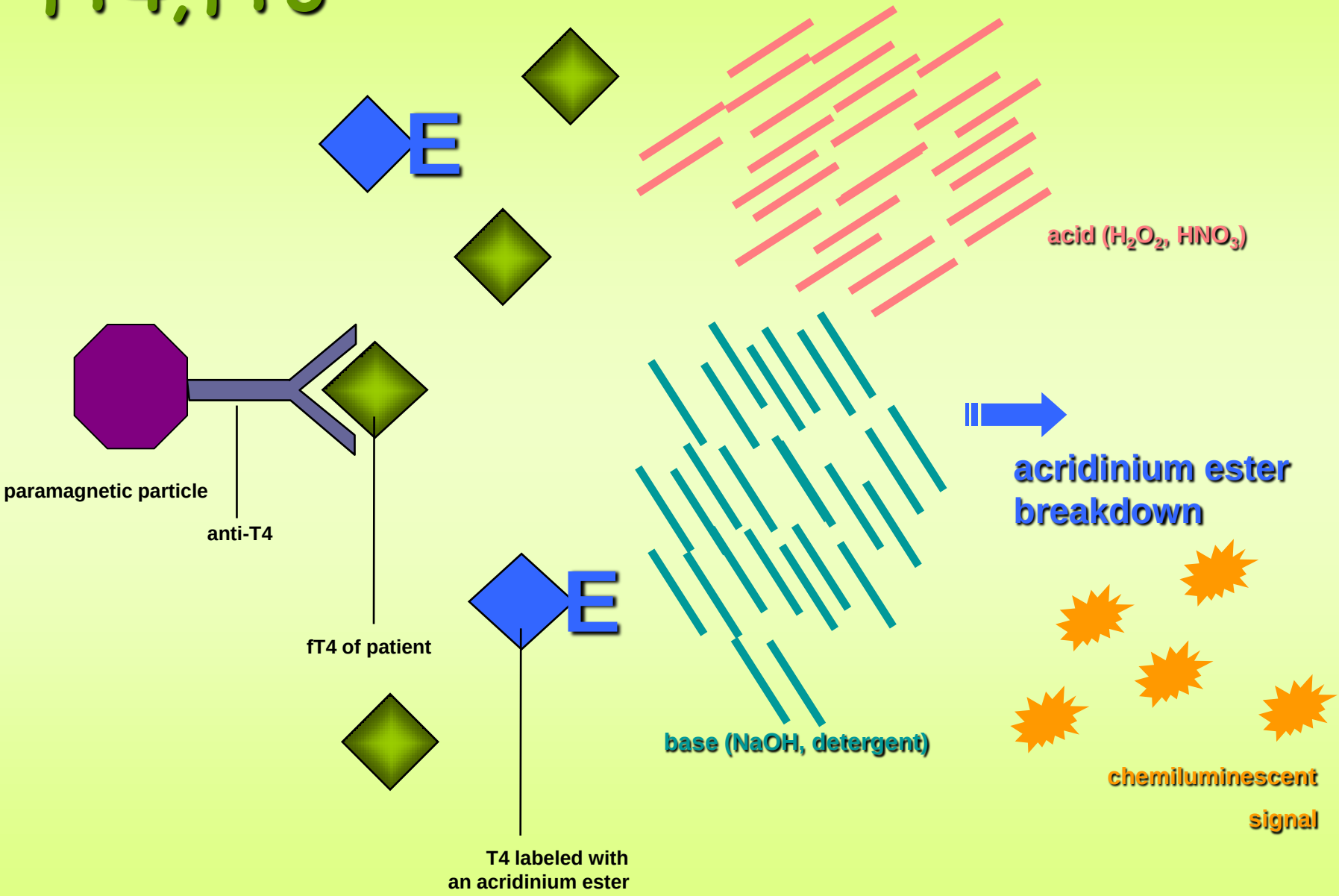


Methods of assessment

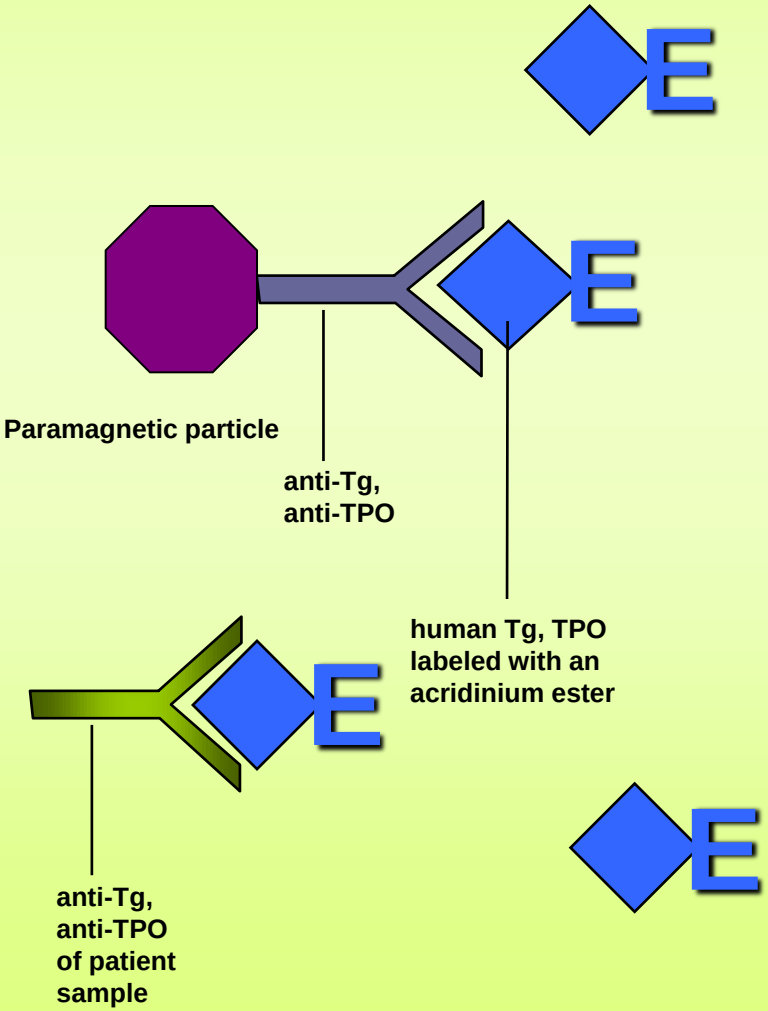
TSH

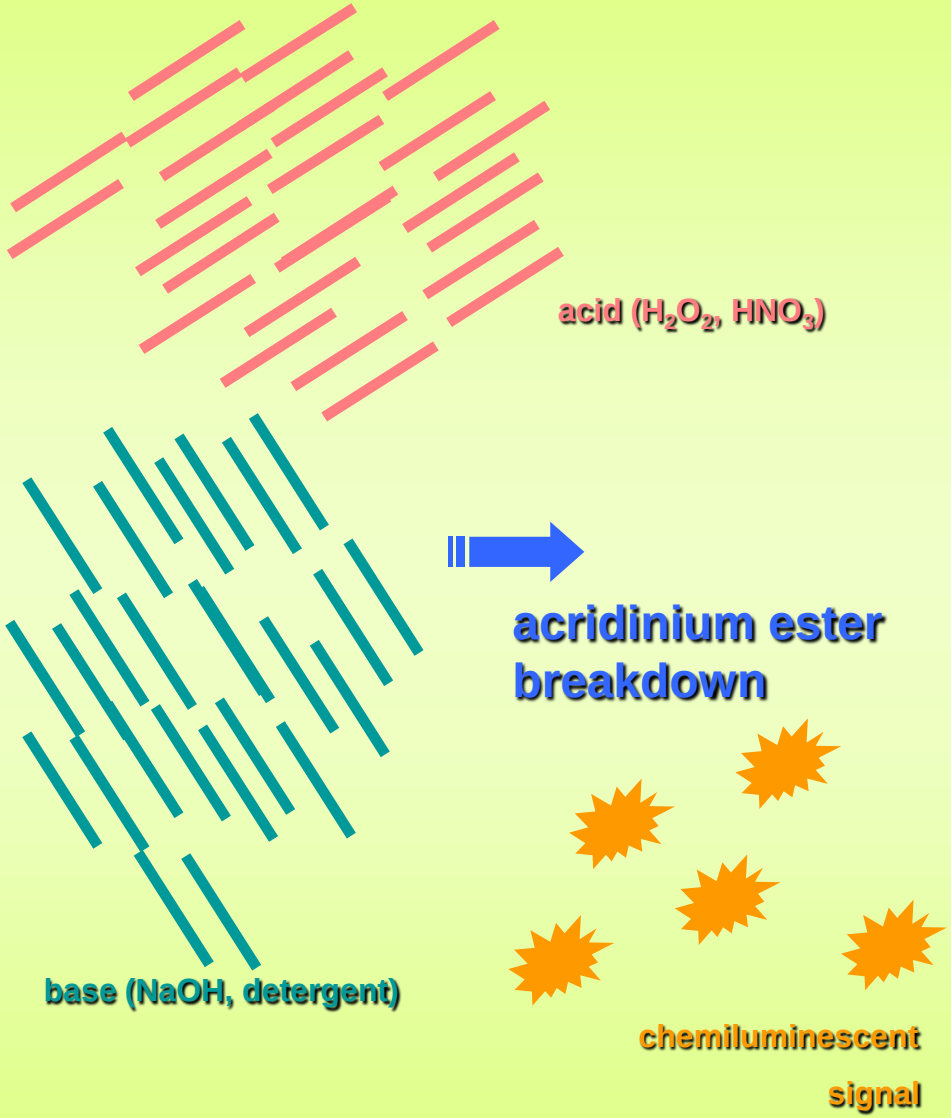

acid (H_2O_2, HNO_3)
E
paramagnetic particle
sheep polyclonal antibody anti-TSH Ab
TSH
mouse monoclonal antibody anti-TSH Ab labeled with an acridinium ester
acridinium ester breakdown
chemiluminescent signal
base (NaOH, detergent)

fT4, fT3


E
acid (H_2O_2, HNO_3)
paramagnetic particle
anti-T4
fT4 of patient
E
base (NaOH, detergent)
acridinium ester breakdown
chemiluminescent signal
T4 labeled with an acridinium ester

anti-Tg
anti-TPO





Anti-TSHR (TSI, TRAK)