Academic lectures for general medicine
Summer course 3rd year
Updated 2001- 2011

SPECIAL PATHOPHYSIOLOGY

ENDOCRINE SYSTEM 2

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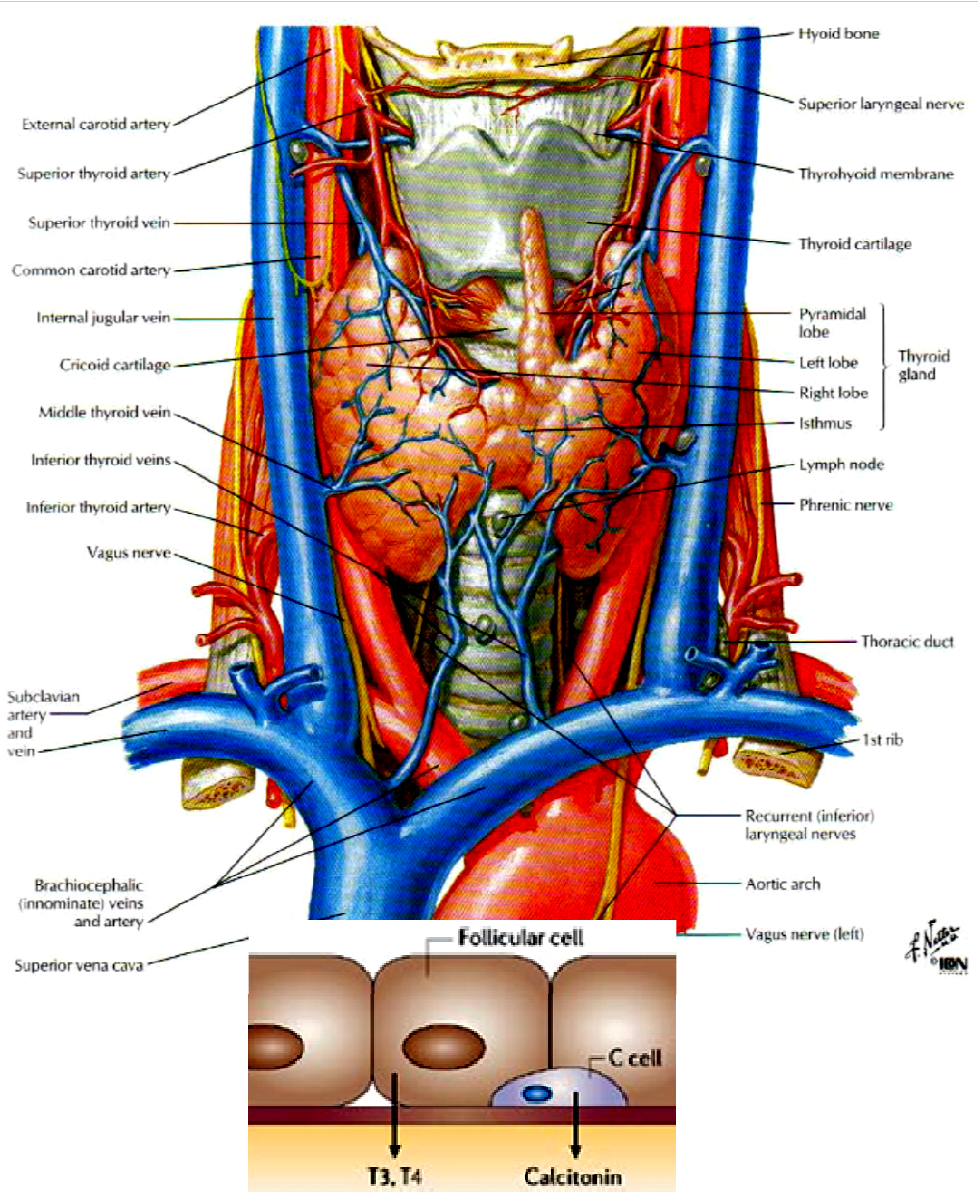
Thyroid gland

- Physiological review
- Hyperthyroidism
- Congenital hypothyreoidism
- Hypothyreoidism in adulthood
- Goiter
- Thyroid tumors

Thyroid gland – anatomy and physiology

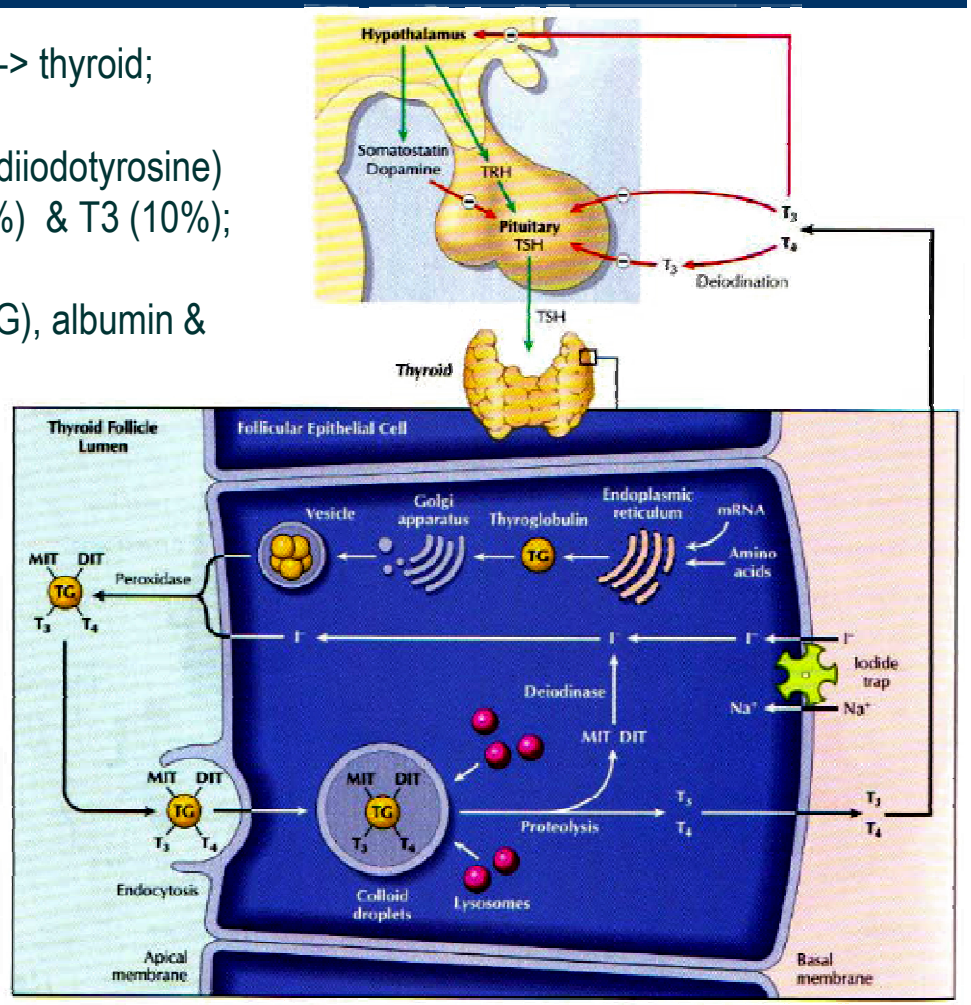
- **Largest endocrine organ in the body** synthetizing, storing, secreting thyroxine (T4) and triiodothyronine (T3) in response to TRH and TSH.
- **Butterfly-shaped organ** (weight 15–25 g) located at the base of the neck on the anterior surface of the trachea.
- **Lobules of spherical follicles** lined by cuboidal-to-flat follicular epithelial cells 50–500 um filled with colloid.
- C cells (produce calcitonin (at the junction of the upper and middle third of both thyroid lobes)

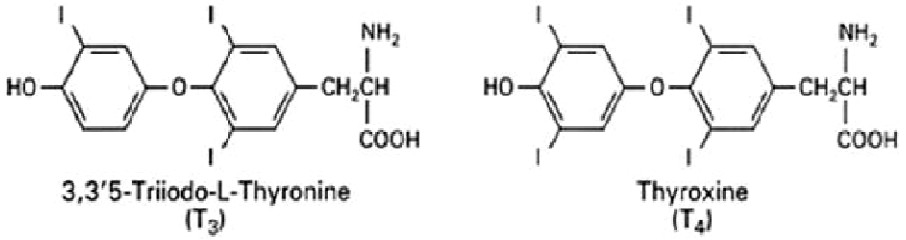


Thyroid gland (TG) – anatomy and physiology

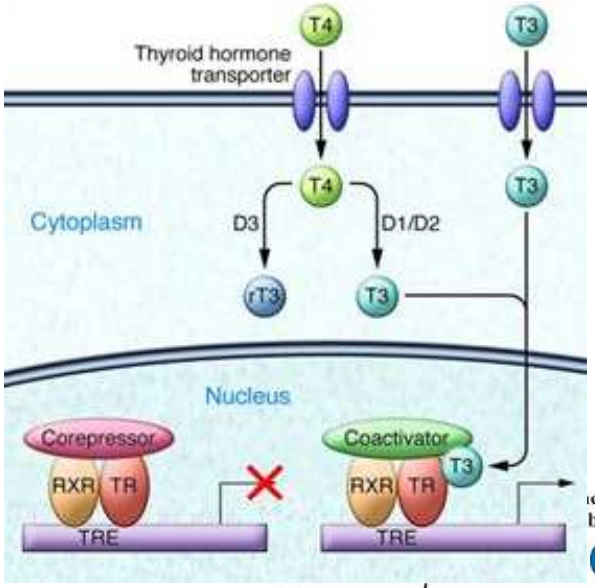
- Axis: hypothalamus (TRH) -> pituitary function (TSH) -> thyroid; iodine access important
- Iodination of tyrosine (MIT = monoiodotyrosine, DIT = diiodotyrosine)
- Coupling MIT + DIT together to form lipophilic T4 (90%) & T3 (10%); storing them bounds to TG
- Blood transport of T3 & T4 bound to transthyrenin (TBG), albumin & pre-albumin.

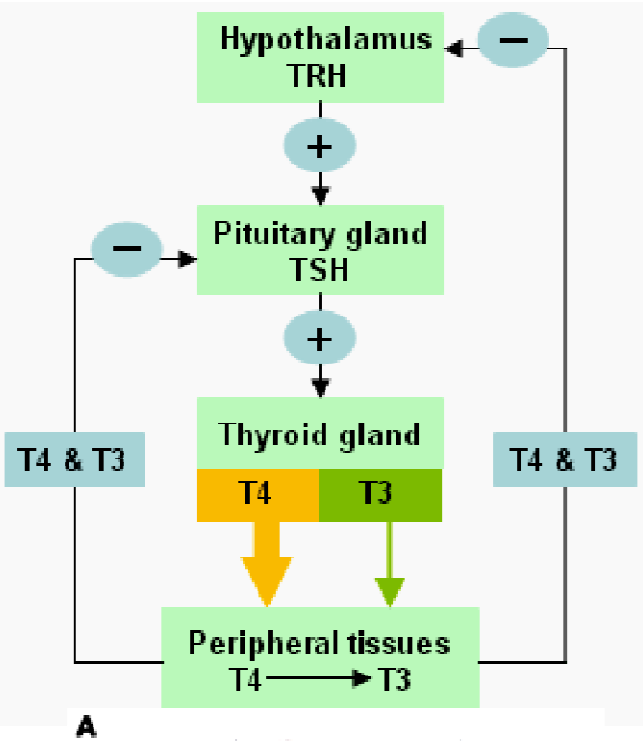
- Increase of basal metabolic rate
- Improves cardiac contractility
- Increases the gain of catecholamines
- Increases bowel motility
- Increases speed of muscle contraction
- Decreases cholesterol (LDL)
- Required for proper fetal neural growth

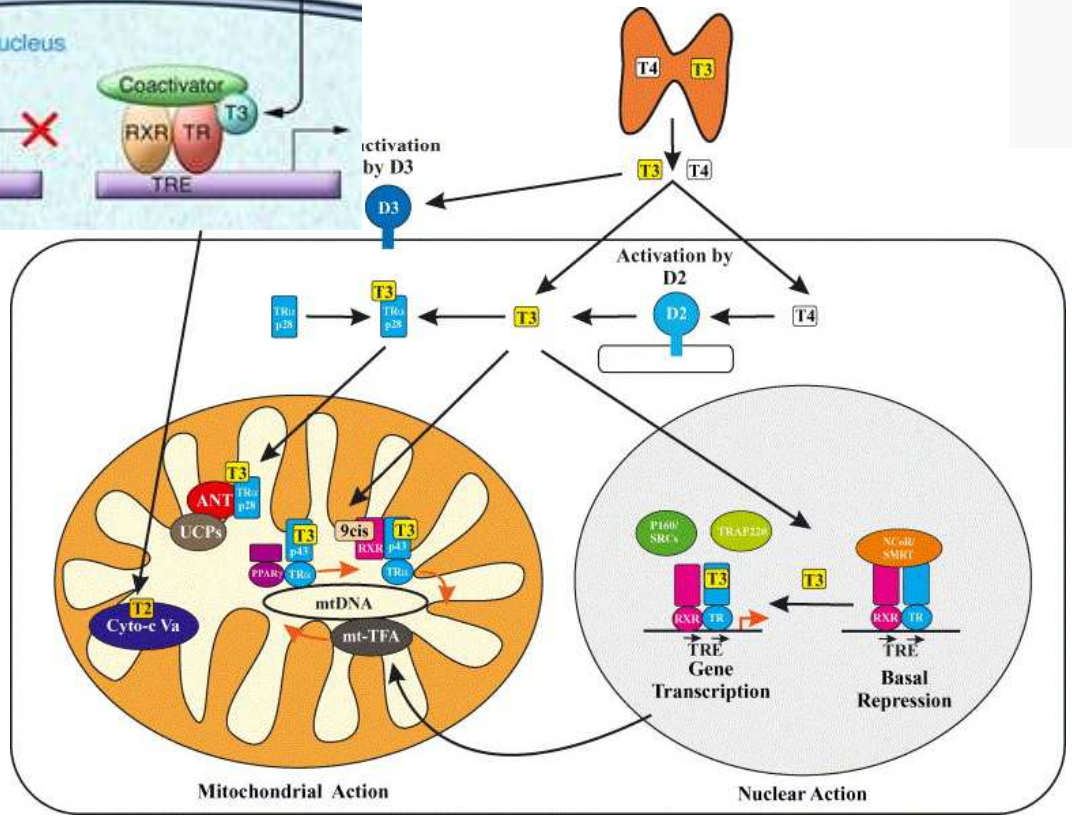


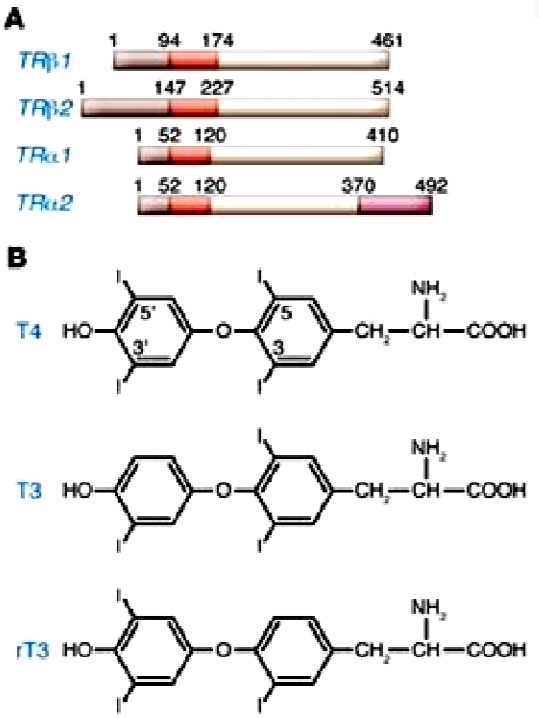


Celullar action of T3 and T4









Physiologic Effects of Thyroid Hormones

Target Tissue	Effect	Mechanism
Heart	Chronotropic	• Increase number and affinity of adrenergic receptors.
	Inotropic	• Enhance responses to circulating catecholamines. • Increase proportion of alpha-myosin heavy chain (with higher ATPase activity).
Adipose tissue	**Catabolic**	• Stimulate lipolysis
Muscle	**Catabolic**	• Increase protein breakdown.
Bone	**Developmental and metabolic**	• Promote normal growth and skeletal development; accelerate bone turnover.
Nervous system	**Developmental**	• Promote normal brain development.
Gut	Metabolic	• Increase rate of carbohydrate absorption.
Lipoprotein	Metabolic	• Stimulate formation of LDL receptors.
Other	Metabolic Calorigenic	• Stimulate oxygen consumption by metabolically active tissues (exceptions: adult brain, testes, uterus, lymph nodes, spleen, anterior pituitary). • Increase of metabolic rate.

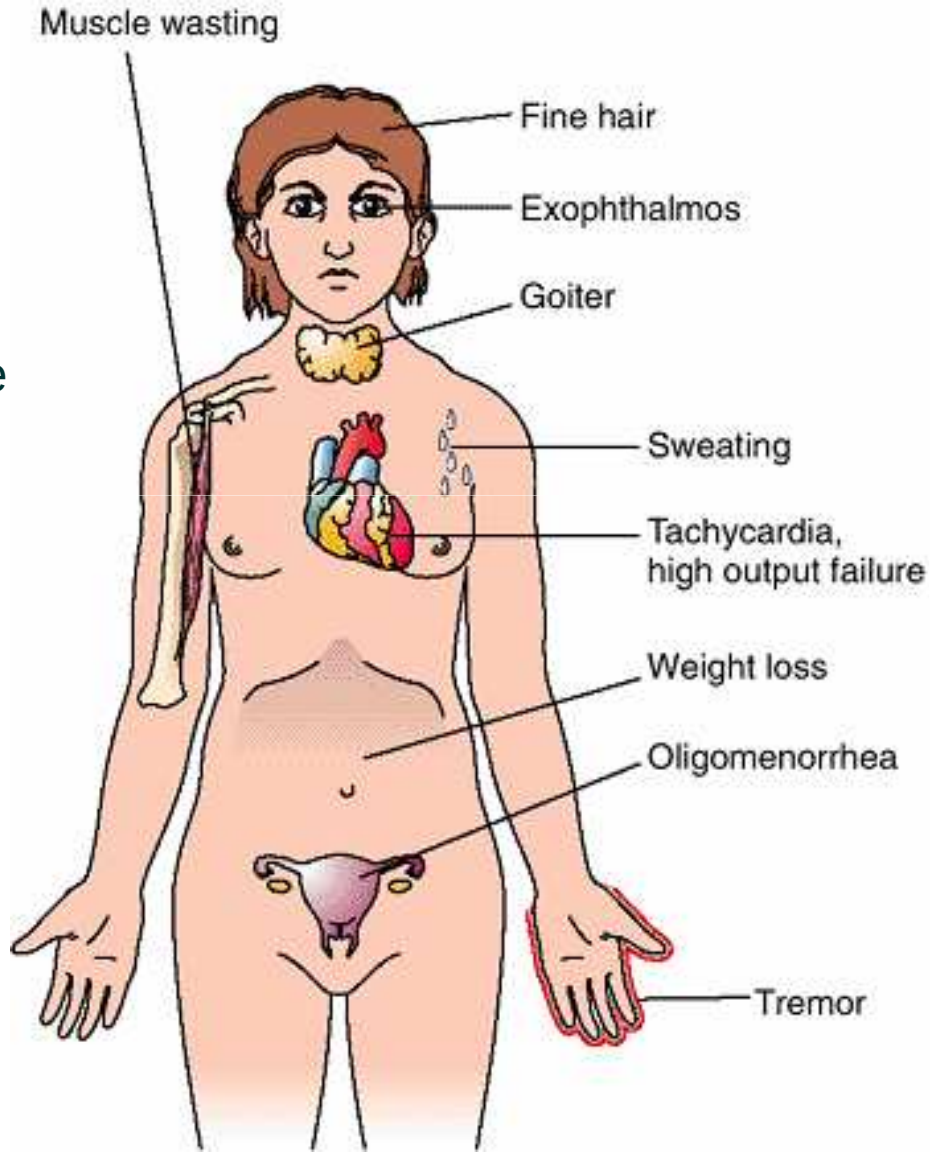
Hyperthyroidism

Hyperthyroidism: Causes

Etiologic Classification	Pathogenetic Mechanism
Thyroid hormone overproduction	
Graves' disease	Thyroid-stimulating hormone receptor-stimulating antibody (TSH-R [stim] Ab)
Toxic multinodular goiter	Autonomous hyperfunction
Follicular adenoma	Autonomous hyperfunction
Pituitary adenoma	TSH hypersecretion (rare)
Pituitary insensitivity	Resistance to thyroid hormone (rare)
Hypothalamic disease	Excess TRH production
Germ cell tumors: choriocarcinoma, hydatidiform mole	Human chorionic gonadotropin stimulation
Struma ovarii (ovarian teratoma)	Functioning thyroid elements
Metastatic follicular thyroid carcinoma	Functioning metastases
Thyroid gland destruction	
Lymphocytic thyroiditis	Release of stored hormone
Granulomatous (subacute) thyroiditis	Release of stored hormone
Hashimoto's thyroiditis	Transient release of stored hormone
Other	
Thyrotoxicosis medicamentosa, factitia	Ingestion of excessive exogenous thyroid hormone

Hypertyroidism - symptoms

- Alertness, emotional lability, nervousness, irritability, poor concentration
- Proximal **muscle weakness** (quadriceps, biceps), fatigability
- **Hyperkinesia**; rapid speech; fine tremor,
- **Tachycardia, palpitations**, widened pulse pressure, accentuated first heart sound;
- Dyspnea
- Voracious appetite, **weight loss**
- Hyperdefecation (increased frequency of bowel movements)
- **Sweating**, skin is fine, moist, warm;; onycholysis; Fine & abundant hair;
- **Exopthlamos**; periorbital edema, lid lag, proptosis, staring
- **Heat intolerance**



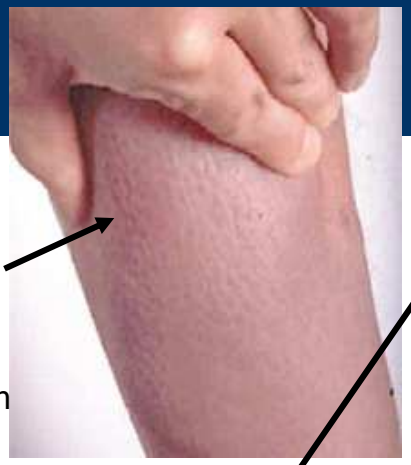
Clinical findings in hyperthyroidism

- **Symptoms**
  - Alertness, emotional lability, nervousness, irritability, poor concentration
  - Proximal muscle weakness (quadriceps), fatigability
  - Hyperkinesia, fine tremor, rapid speech,
  - Palpitations, tachycardia, atrial fibrillation (resistant to digitalis), widened pulse pressure, accentuated first heart sound; Dyspnea
  - Voracious appetite, weight loss,
  - Hyperdefecation (increased frequency of bowel movements)
  - Sweating, skin is fine, moist, warm; heat intolerance; fine & abundant hair; onycholysis
  - Periorbital edema, lid lag, proptosis, stare, chemosis

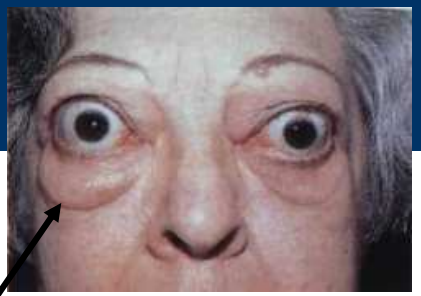
- **Laboratory findings**
  - Suppressed serum TSH level
  - Elevated serum free thyroxine, elevated serum total T4, elevated resin T3 or T4 uptake, elevated free thyroxine index
  - Increased radioiodine uptake by thyroid gland (some causes)
  - Increased basal metabolic rate (BMR)
  - Decreased serum cholesterol level

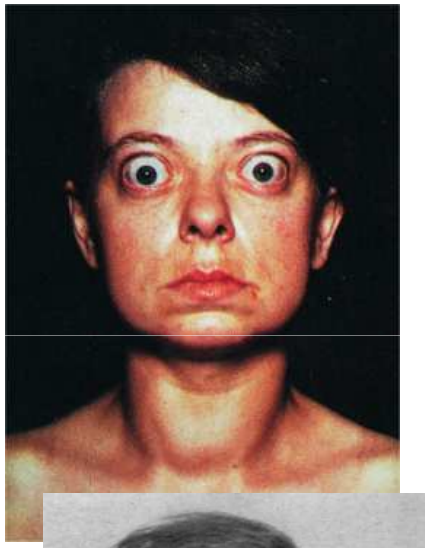
Graves disease

- Most common cause of hyperthyroidism
- anti-TSH receptor antibodies with uncontrolled stimulatory effect on thyroid
- **Dg:**
  - Symptoms of hyperthyroidism
  - Extreme ***exopthalmos*** and ***goiter***
  - ↓↓ TSH, n/↑ T_4, anti-TSH Ab
  - I^{123} increased uptake.
- Treatments
  - Pharm – Propothyouracil, Methimazole, Propranolol
  - Surgical – Subtotal Thyroidectomy
  - Radiation – RAI ablation [I^{131}(μCi/g) x weight / %RAIU]

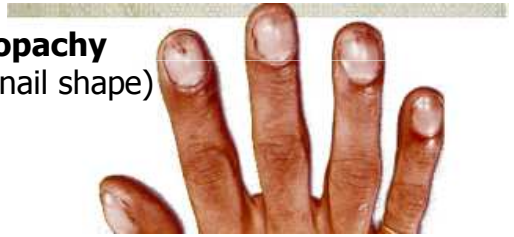


Graves' dermopathy - lumpy, reddish thickening of the skin (accumulation of proteins).

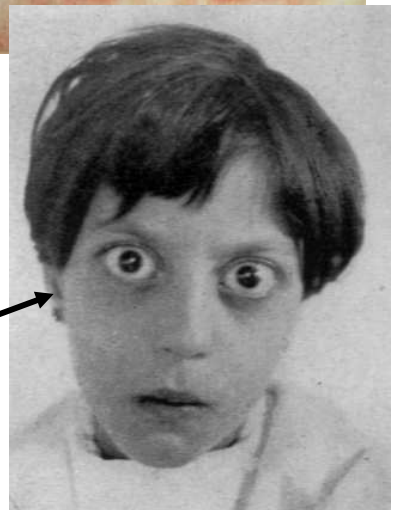




Exopthalmos, goiter



Graves' acropachy (watch glass nail shape)

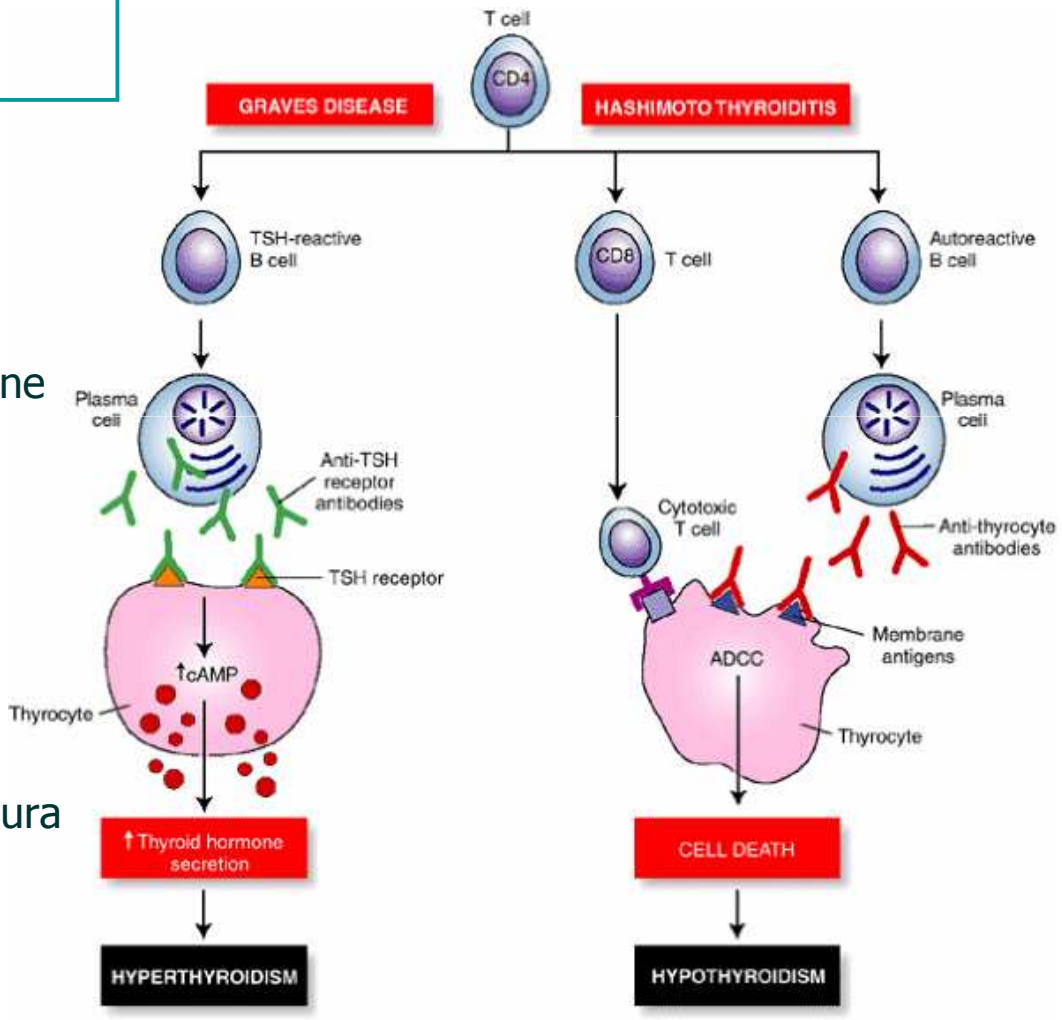


Exopthalmic goiter in 5y - old girl. Common in adults very rare in kids. Symptoms: nervousness, bulging of the eyes, tachycardia, underweight, enlarged thyroid

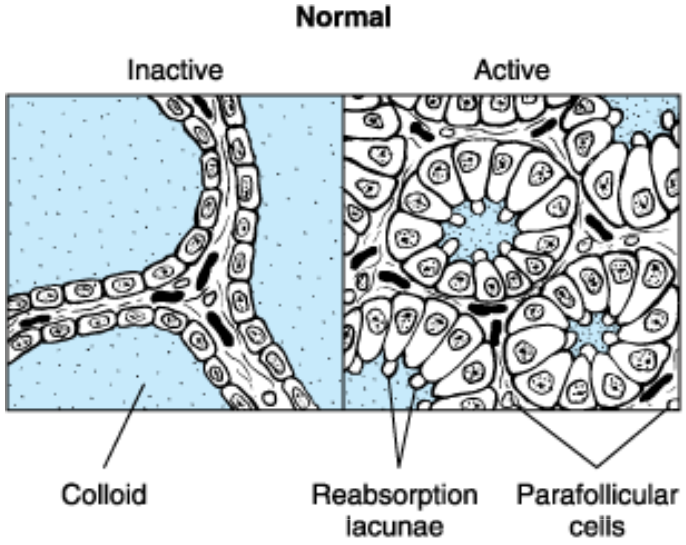
Graves' Disease and Hashimoto's Thyroiditis - Autoimmune Disorders Associated with them

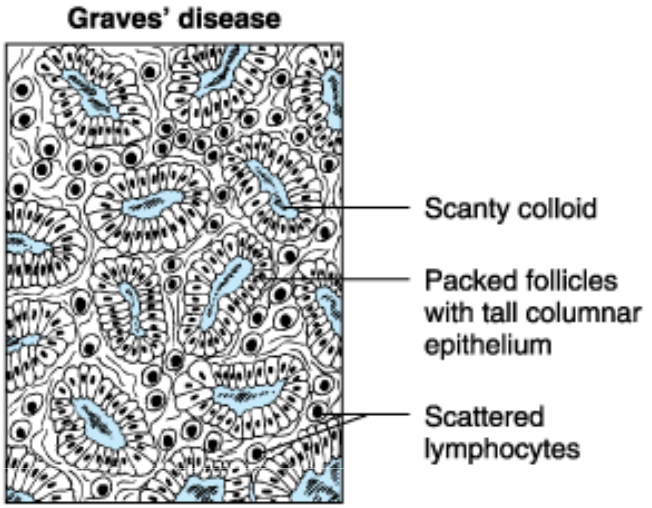
Autoimmune response against different epitopes in thymocytes may lead hyperthyroidism and hypothyroidism

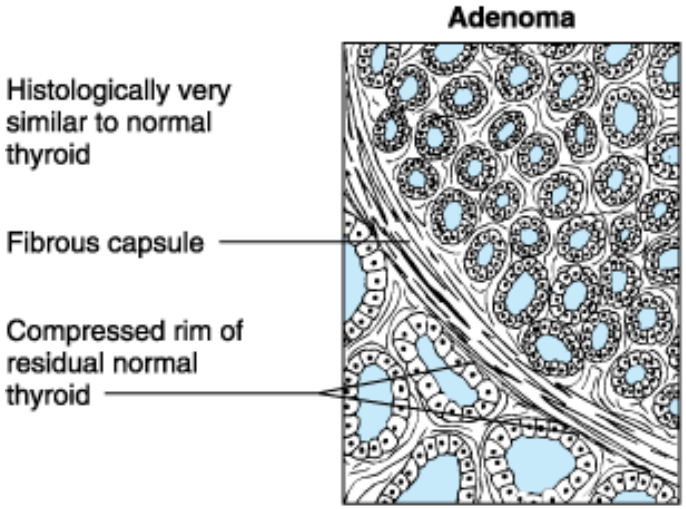
- **Endocrine disorders**
  - Diabetes mellitus
  - Hypoadrenalism,
  - autoimmune (Addison's disease)
  - Orchitis or oophoritis, autoimmune
  - Hypoparathyroidism, idiopathic
- **Nonendocrine disorders**
  - Pernicious anemia
  - Vitiligo
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
  - Immune thrombocytopenic purpura
  - Myasthenia gravis
  - Sjögren's syndrome
  - Primary biliary cirrhosis
  - Chronic active hepatitis

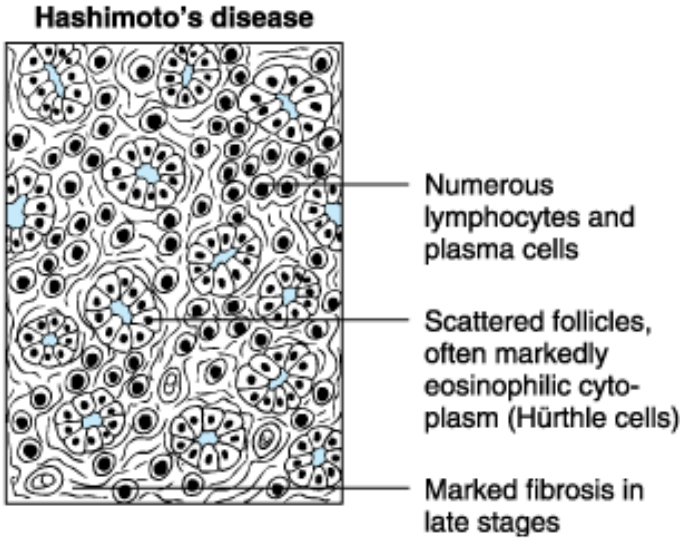


Graves' Disease and Hashimoto's Thyroiditis
Histological comparisons

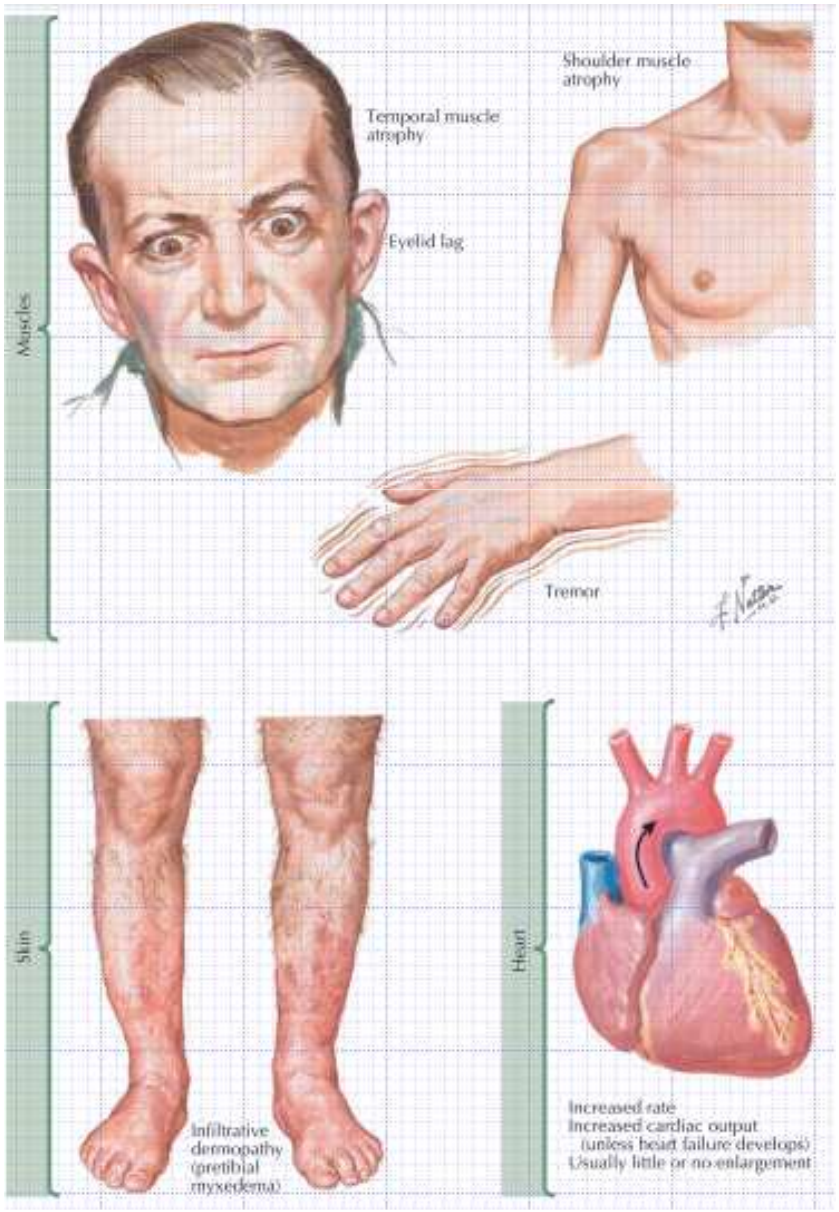


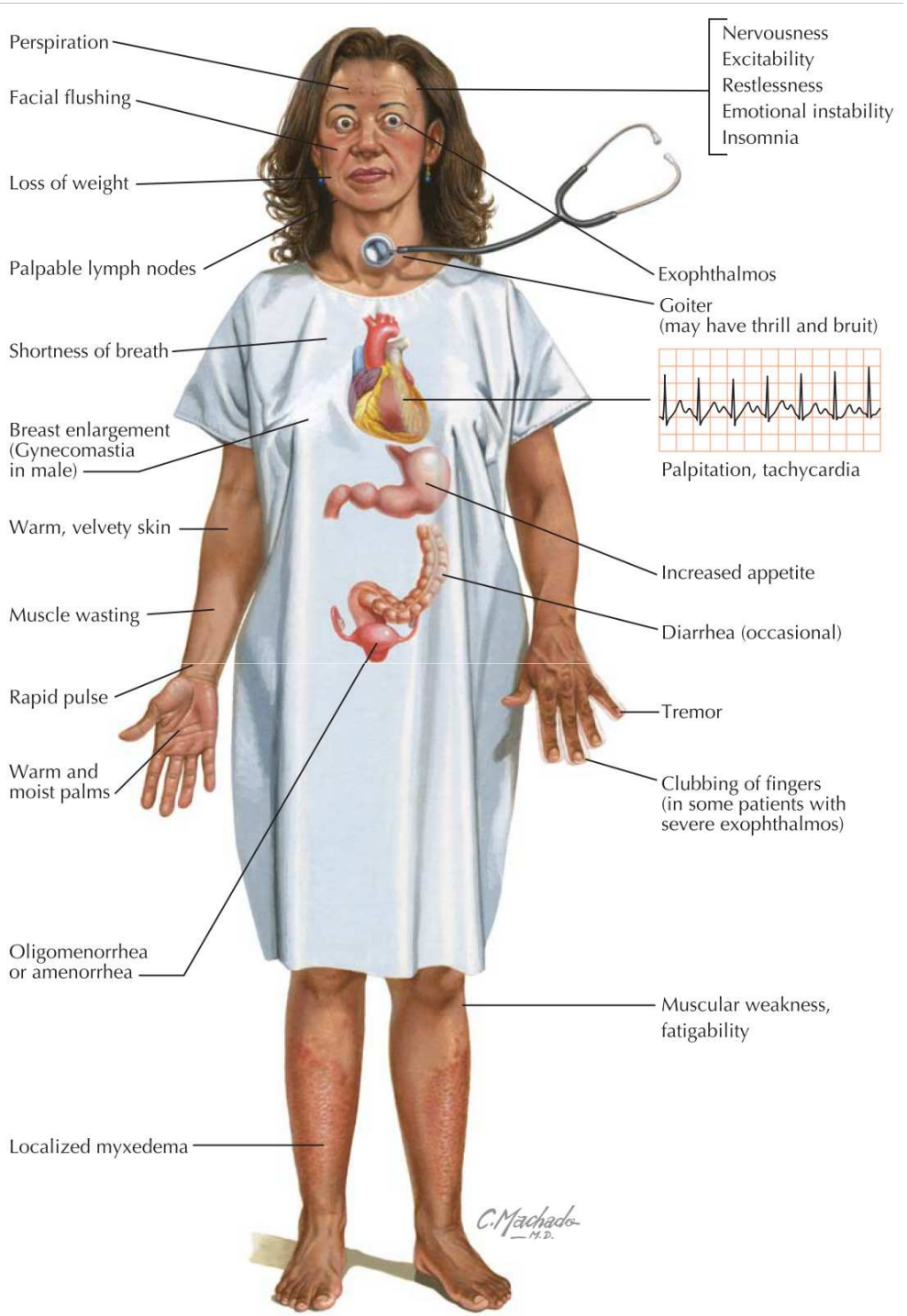


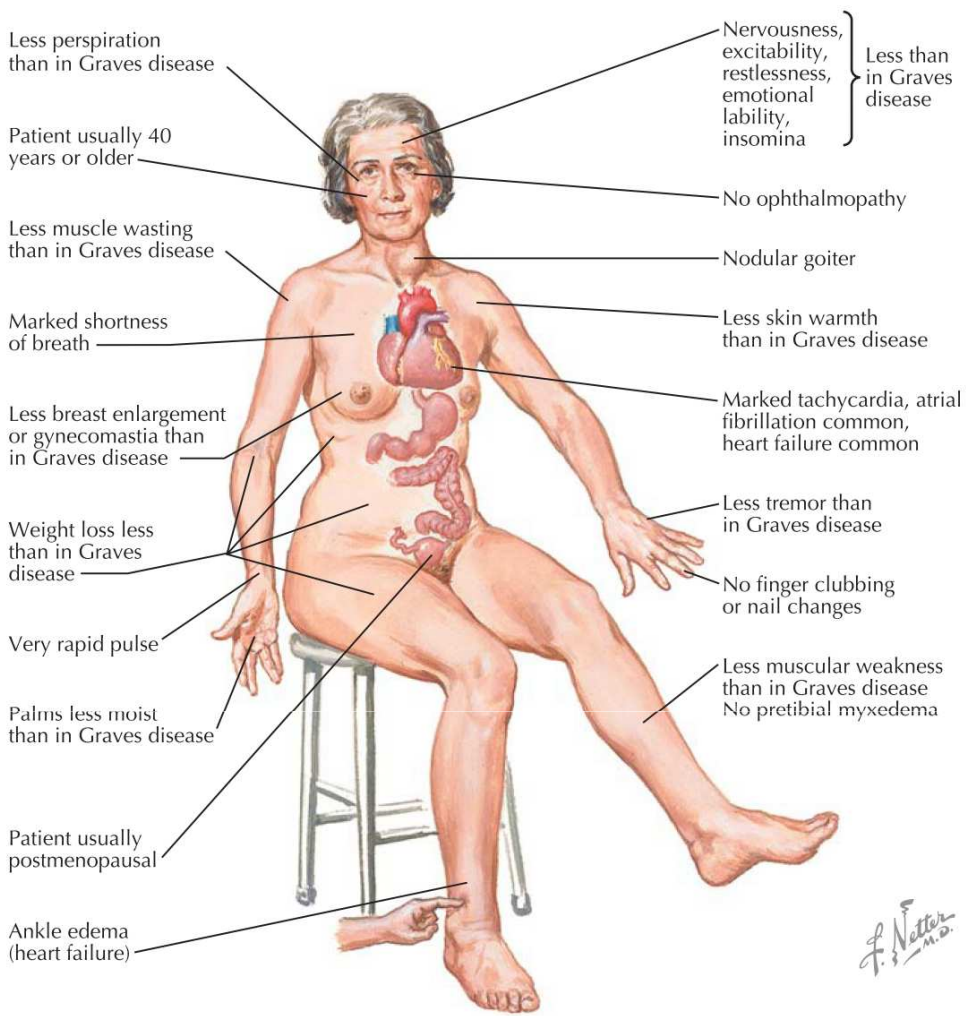




Graves disease

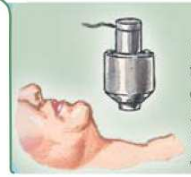






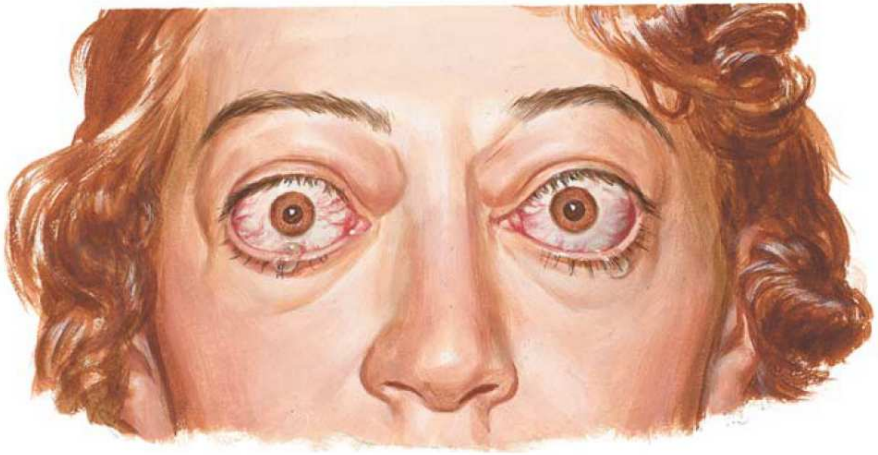
Laboratory findings

Basal metabolic rate
Moderately elevated (25%–30%)

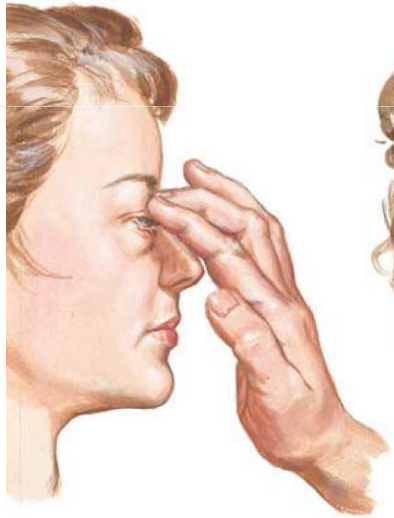


^{131}I uptake
Elevated less than in Graves disease (40%–55%) localized in functioning adenoma

Blood tests:
Decreased TSH
Increased free T_4
Increased total T_3
Undetectable TSH-receptor antibodies
Decreased total and HDL cholesterol
Increased sex hormone–binding globulin
Increased estradiol (in men and women)
Increased osteocalcin and bone-specific alkaline phosphatase

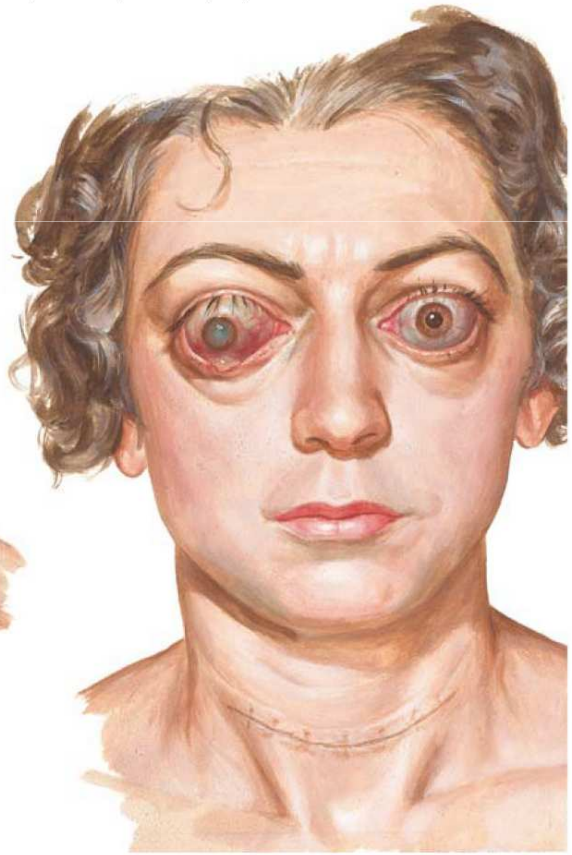


Moderately severe ophthalmopathy



Testing for resiliency

F. Netter M.D.



Severe progressive ophthalmopathy

Hypothyroidism

Hypothyroidism

Forms of hypothyroidism

- Primary – malfunction in thyroid gland
- Secondary – pituitary failure
- Tertiary – Hypothalamic failure
- Peripheral resistance – inresponsiveness of tissues to T3 &T4

- **Laboratory findings**
  - Increased **serum TSH level**
  - Decreased serum **free thyroxine**, decreased serum **total T4 and T3** decreased T3 or T4 uptake; decreased free thyroxine index
- Cause is determined by geography
- **Diagnosis**
  - Low FT4, High TSH (Primary, check for antibodies)
  - Low FT4, Low TSH (Secondary or Tertiary, TRH stimulation test, MRI)
- **Treatment**
  - Levothyroxine (T4) due to longer half life

SECONDARY CENTRAL (HYPOPITUITARY) HYPOTHYROIDISM
PIT-1 mutations : Deficiency of TSH, growth hormone, and prolactin
PROP-1 mutations: Deficiency of TSH, GH, prolactin, LH, FSH, ACTH
Thyrotropin-releasing hormone (TRH) deficiency; Isolated?
Multiple hypothalamic deficiencies (e.g., septo-optic dysplasia)
TRH unresponsiveness Mutations in TRH receptor
TSH deficiency - Mutations in β-chain
Multiple pituitary deficiencies (e.g., craniopharyngioma)
TSH unresponsiveness Gsα mutation (e.g., type IA)
Mutation in TSH receptor
PRIMARY HYPOTHYROIDISM (THYROID)
Defect of fetal thyroid development : Aplasia, hypoplasia, ectopia (dysgenesis)
Defect in thyroid hormone synthesis (e.g., goitrous hypothyroidism): Iodide transport defect, Thyroid peroxidase defect, Thyroid oxidase mutations: homozygotic permanent; heterozygotic - transient Thyroglobulin synthesis defect, Deiodination defect
Defect in thyroid hormone transport
Iodine deficiency (endemic goiter): Neurologic type, Myxedematous type
Maternal antibodies: Thyrotropin receptor–blocking antibody (TRBAb, thyrotropin-binding inhibitor immunoglobulin)
Maternal medications: Radioiodine, iodides; Propylthiouracil, methimazole; Amiodarone

1. Congenital hypothyroidism (CH)

- Df: thyroid hormone deficiency present at birth; if untreated for months lead to growth delay and permanent mental retardation (cretins).
- Oc: 1 from 4000 newborns has severe deficiency; 1 from 2300 have mild to partial !!! Nongoitrous CH "most prevalent inborn endocrine disorder"
- Et: in past endemic, now gen., dev. tox. (sporadic)
  - Environmental iodine deficiency (endemic in past);
  - Hypoplasia; Athyreosis
  - Toxic dammage: ? organochlorine insecticides, dioxin-like chemicals in the milk of mothers
  - Immuno-damage - maternal antibodies

Genetic:

- Defect of T4 and T3 synthesis in normal gland
- Deficiency of TSH, Resistance to TSH,
- Iodine trapping defect, thyroglobulin, and iodotyrosine deiodinase deficiency

Sy: CH goitrous (CHG) CH nonhoitrous (CHNG)

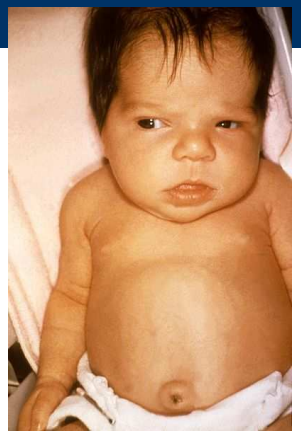
- **Mild to severe thyroid deficiency**
- No or only neglible effects after birth : excessive sleeping, reduced interest in nursing, poor muscle tone, low or hoarse cry, infrequent bowel movements, exaggerated jaundice, low body temperature.
- > ½ of cases of severe hypothyroidism were recognized in the first month of life. Poor delayed grow,
- After years untreated: recognizable facial and body features of cretinism. severe mental impairment, with an IQ < 80

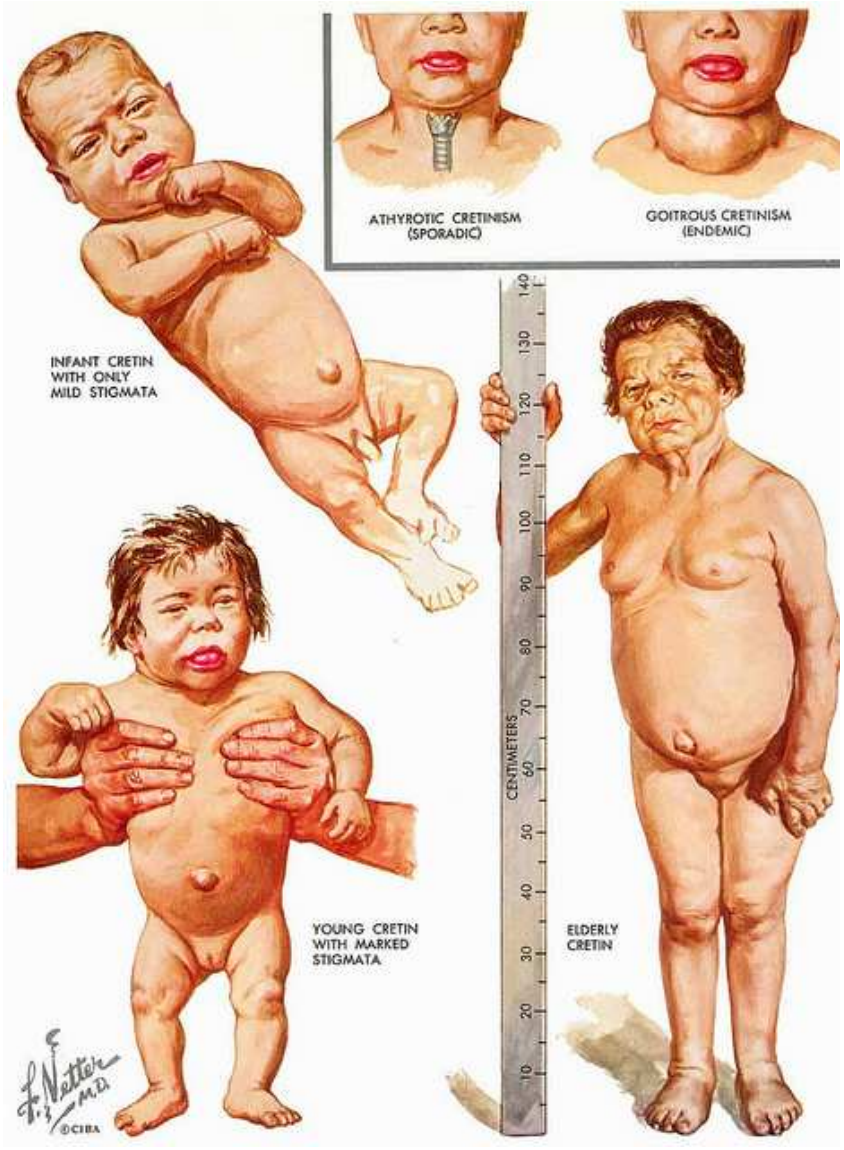
- **Very severe fetal deficiency (athyreosis):**
- Larger anterior fontanel, persistence of a posterior fontanel, umbilical hernia, large tongue (macroglossia).
- Growth retardation, short stature, short neck. swelling of face/hands,legs, cool skin, dry skin,
- Neurological retardation: slow reflexes, possible deafness

Type	Locus	Gene	Result
CHNG1	2q13	**TSH-R**; TSH receptor	TSH resistance
CHNG2	14q31.1	**PAX8;** Paired box gene; transcription factor; expression of thyroid-specific genes.	Thyroid dysgenesis
CHNG3	15q25.3	?	TSH resistance
CHNG4	1p13.2	**TSHB** (beta chain of heterodimeric TSH)	TSH resistance
CHNG5	5q35.1	**NKX2-5;** NK2 homeobox 5; Tissue specific gene expression	Thyroid dysgenesis

Cretinism

- 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 food sources

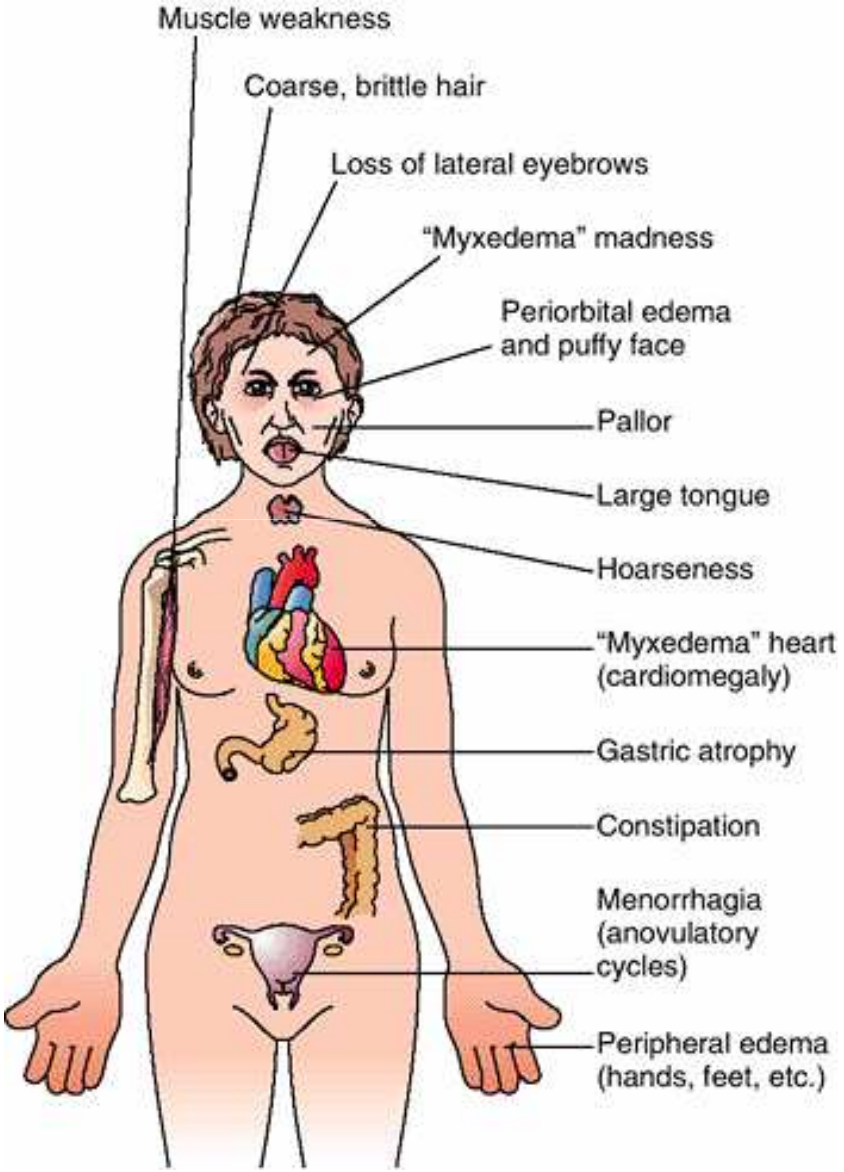




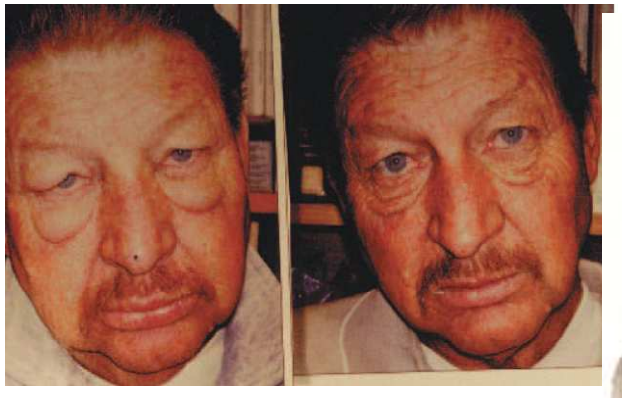
Endemic goitre and **cretinism** in Bolivia. The mother is goitrous but otherwise normal. The daughter is goitrous, mentally retarded, deaf mute, but of normal stature and clinically euthyroid.

2. Postpubertal hypothyroidism - myxedema

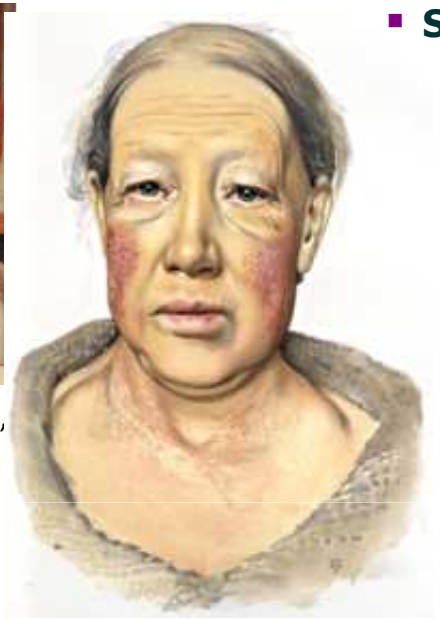
- **Decreased vigor**, lethargy, slow thinking, mental clouding, depression
- Fatigability, coldness, weight gain, constipation, low voice
- **Round puffy face**; periorbital edema, swelling of face/hands/legs, slow reflexes, myxedema
- Enlarged tongue, slow speech; hoarseness,
- Cold, dry, thick, scaling skin; Feeling cold, cold intolerance
- Dry, coarse, brittle thickened hair; hair loss; longitudinally ridged nails;
- **Loss of appetite**; weight gain, constipation
- Ascites; pericardial effusion; ankle edema
- Menorrhagia; diminished libido
- **Hypokinesia**; generalized muscle weakness; delayed relaxation of deep tendon reflexes
- Cardiac enlargement; bradycardia, indistinct heart sounds

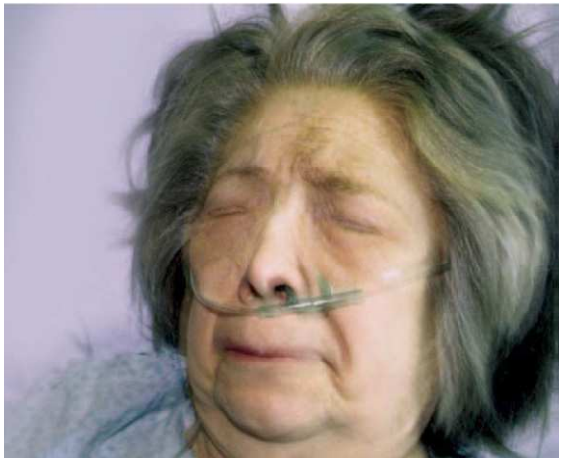


Postpubertal hypothyroidism - myxedema

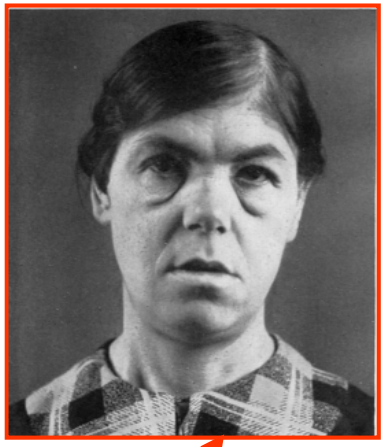


Myxedema: periorbital puffiness closing eyes, after thyroxine therapy (pericardial effusion).





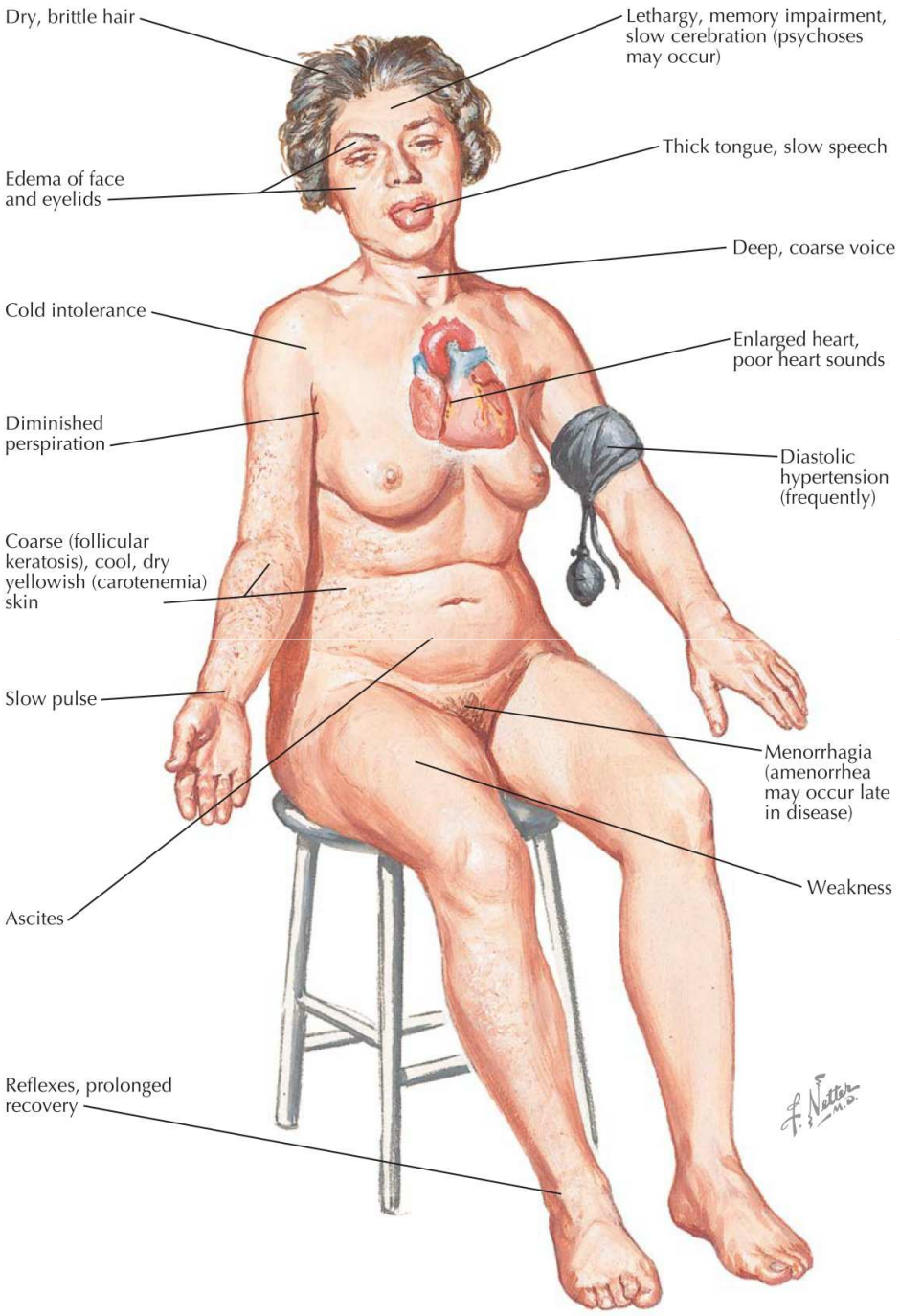
Myxedema, coarse hair, dry skin, pasty colored face: elderly woman stopped medication

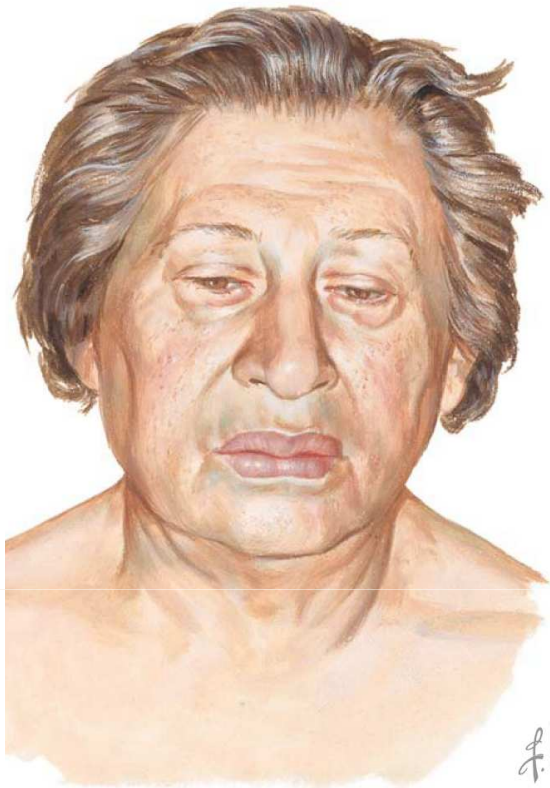


Post-operative myxedema. Basal metabolic rate 40%

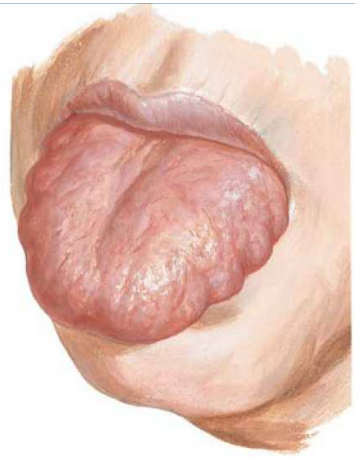
- **Symptoms**
  - Decreased vigor, **lethargy,** slow thinking, mental clouding, depression
  - **Round puffy face**; **periorbital edema**,
  - Enlarged tongue, slow speech; hoarseness,
  - **Cold, dry, thick, scaling skin**; dry, coarse, brittle thickened hair; hair loss; longitudinally ridged nails; feeling cold, cold intolerance
  - Loss of appetite; **weight gain**, constipation
  - **Ascites**; pericardial effusion; **ankle edema**
  - Menorrhagia; diminished libido
  - **Hypokinesia**; generalized muscle weakness; delayed relaxation of deep tendon reflexes
  - Cardiac enlargement; bradycardia, indistinct heart sounds

Thyroid





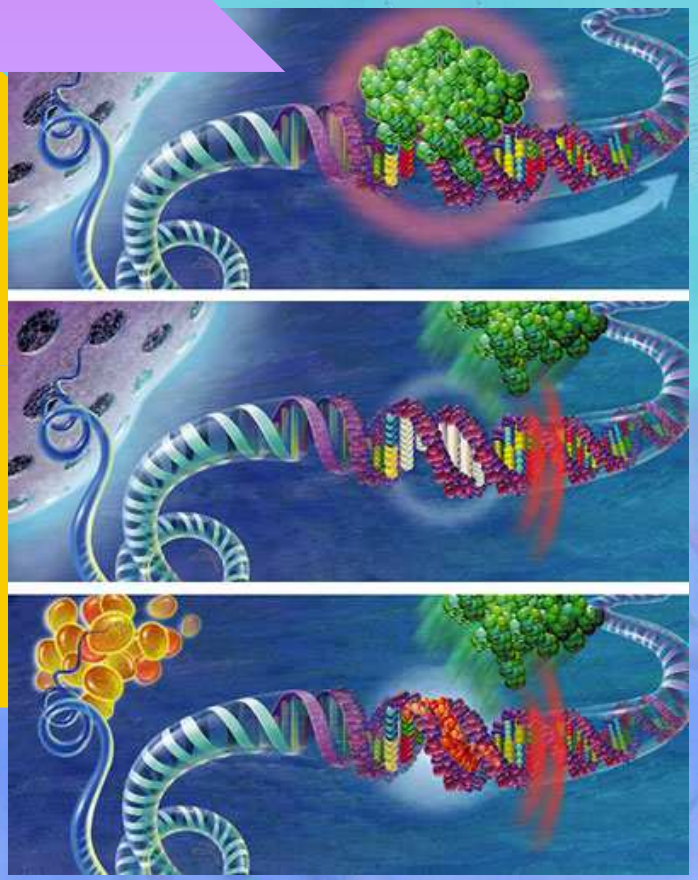
Characteristic facies in hypothyroidism: coarse features; thick lips; dry skin; puffy eyelids; dull, lethargic expression; coarse hair



Macroglossia, showing dental impressions

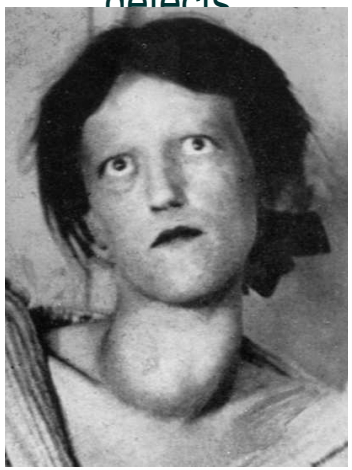
Pudgy hands; chipped nails; dry, wrinkled skin; hyperkeratosis of elbow

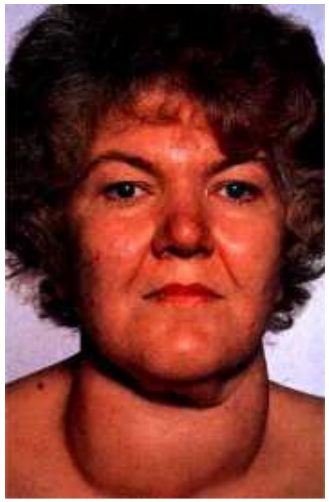
Goiter

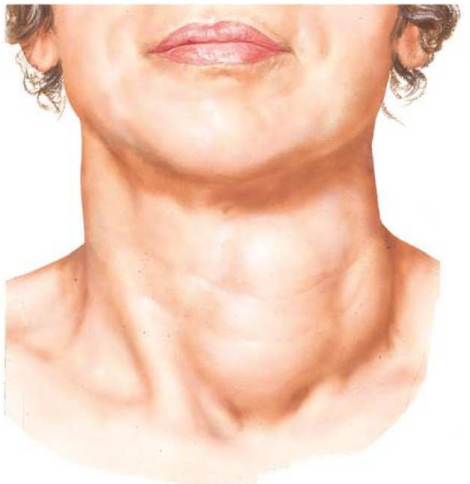


Goiter

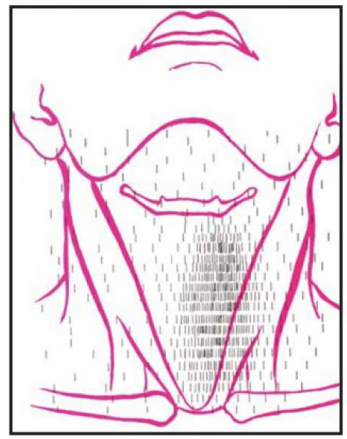
- **Endemic goiter**
  - Caused by dietary deficiency of Iodide
  - Increased TSH stimulates gland growth
  - Also results in cretinism
- **Goiter in developed countries**
  - Hashimoto's thryoiditis
  - Subacute thyroiditis
- **Other causes**
  - Excess Iodide (Amiodarone, Kelp, Lithium
  - Adenoma, Malignancy
  - Genetic / Familial hormone synthesis defects



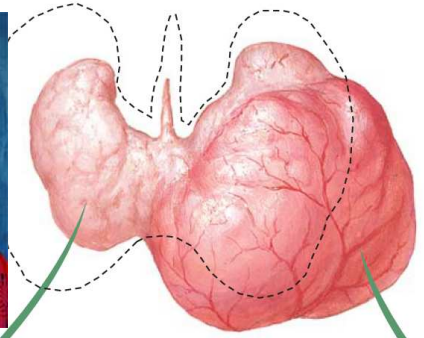


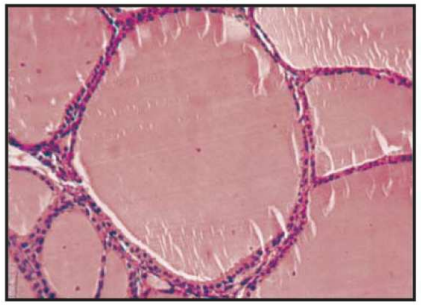


Hyperfunctioning adenoma

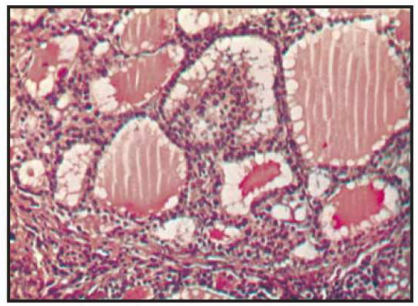


Scintigram





Remainder of gland—involution



Adenoma—hyperplasia

Etiology of goiter

I. Goiter associated with hypo & euthyroidism

- **Iodine turnover**
  - Iodine deficiency; defective transport
  - Iodine excess (secretion of hormone)
- **Hormone biosynthesis**
  - Defective organification of iodide : absence/ reduction ***of peroxidase***; abnormal peroxidase
  - Thyroglobulin (TG): synthesis of an ***abnormal TG*** impaired proteolysis of TG
  - Iodotyrosine : defective deiodination
  - Congenital disorders
- **Exogenous substances and drugs (hormone biosynthesis)**
  - Goitrogen in diet, drinking water or medication
  - Thioamides (propylthiouracil, methimazole, carbimazole), Thiocyanates (nitroprusside), Anilin derivatives (sulfonylureas, sulfonamides, aminosalicylic acid, phenylbutazone, aminoglutethimide)
  - Lithium (secretion of hormone)
- **Resistance**
  - Pituitary and peripheral resistance to thyroid hormone (receptor defects)

Etiologic factors of nontoxic goiter

Iodine deficiency
- Nutritional

Thyrotropin (TSH) receptor dysfunction
- TSH receptor mutations

Block of sodium-iodide symporter (NIS)
- Iodine
- Thiocyanate (e.g., millet, cassava)
- Perchlorate
- NIS gene mutations

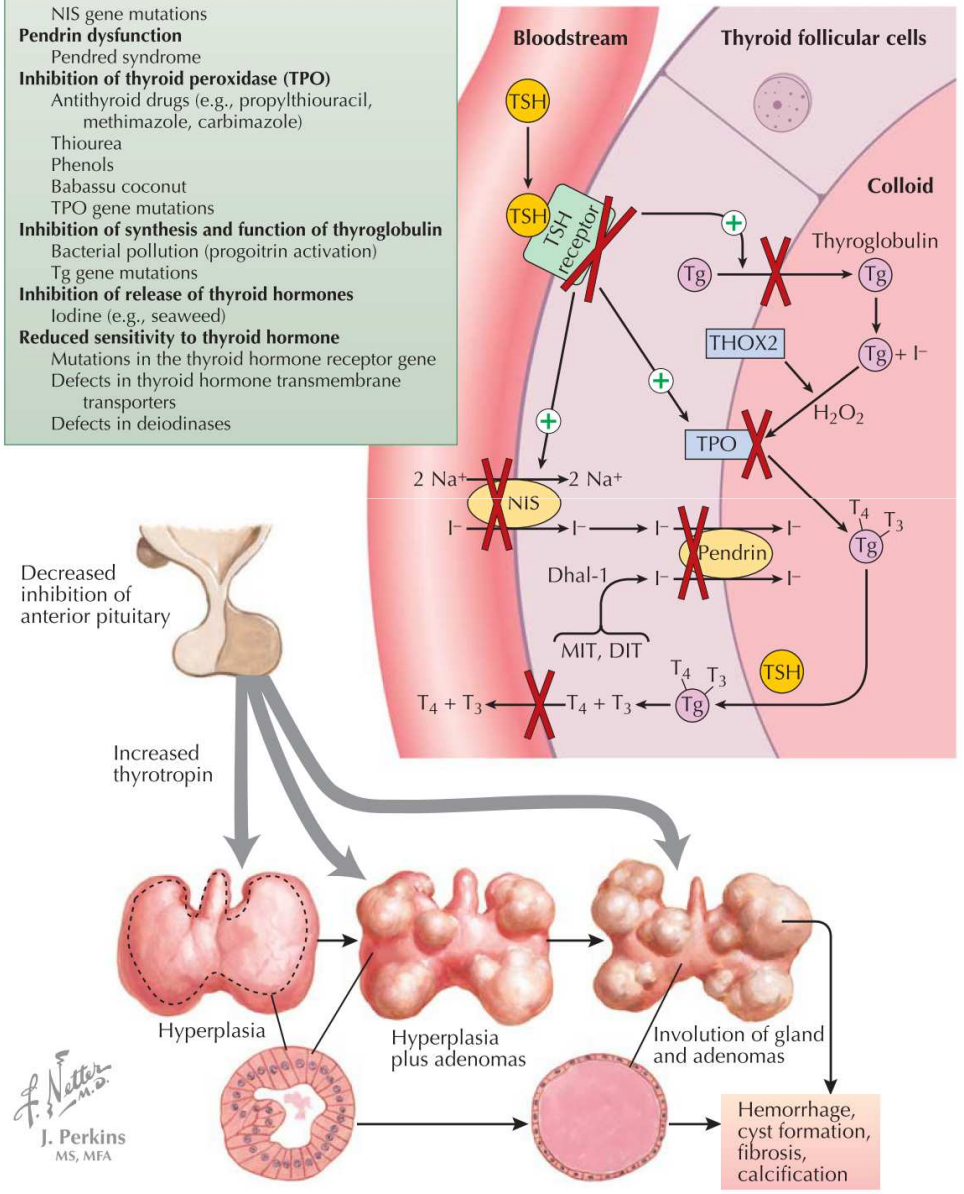
Pendrin dysfunction
- Pendred syndrome

Inhibition of thyroid peroxidase (TPO)
- Antithyroid drugs (e.g., propylthiouracil, methimazole, carbimazole)
- Thiourea
- Phenols
- Babassu coconut
- TPO gene mutations

Inhibition of synthesis and function of thyroglobulin
- Bacterial pollution (progoitrin activation)
- Tg gene mutations

Inhibition of release of thyroid hormones
- Iodine (e.g., seaweed)

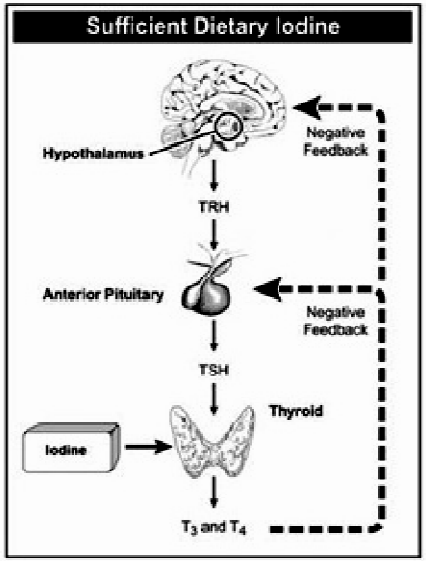
Reduced sensitivity to thyroid hormone
- Mutations in the thyroid hormone receptor gene
- Defects in thyroid hormone transmembrane transporters
- Defects in deiodinases

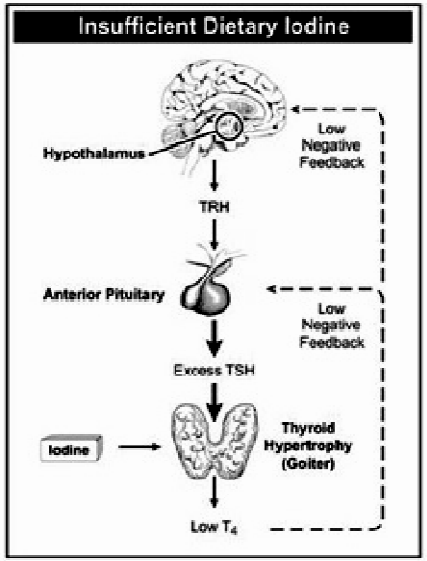


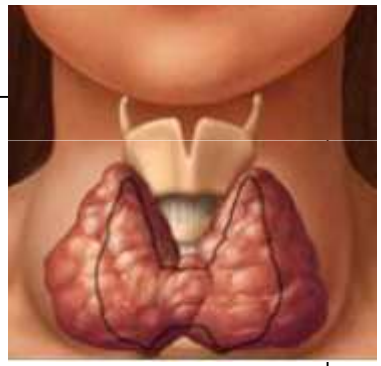
Goiter

II. Goiter associated with hyperthyroidism

- Graves' disease (TSH-R [stim] Ab stimulation of gland)
- Toxic multinodular goiter (Autonomous hyperfunction)
- Germ cell tumor (hCG stimulation of gland)
- Pituitary adenoma (TSH overproduction)
- Thyroiditis ("injury" due to infiltration, and edema)





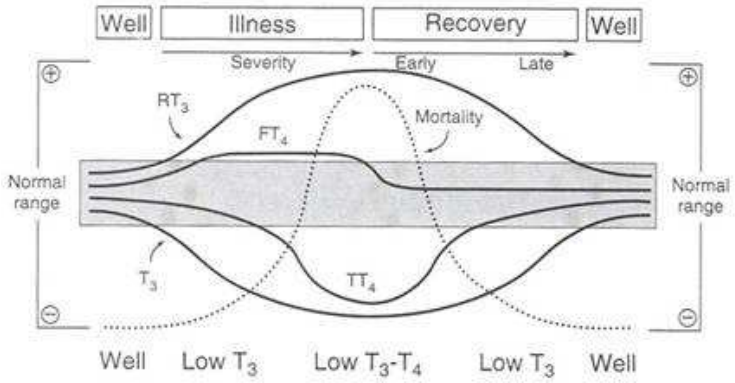


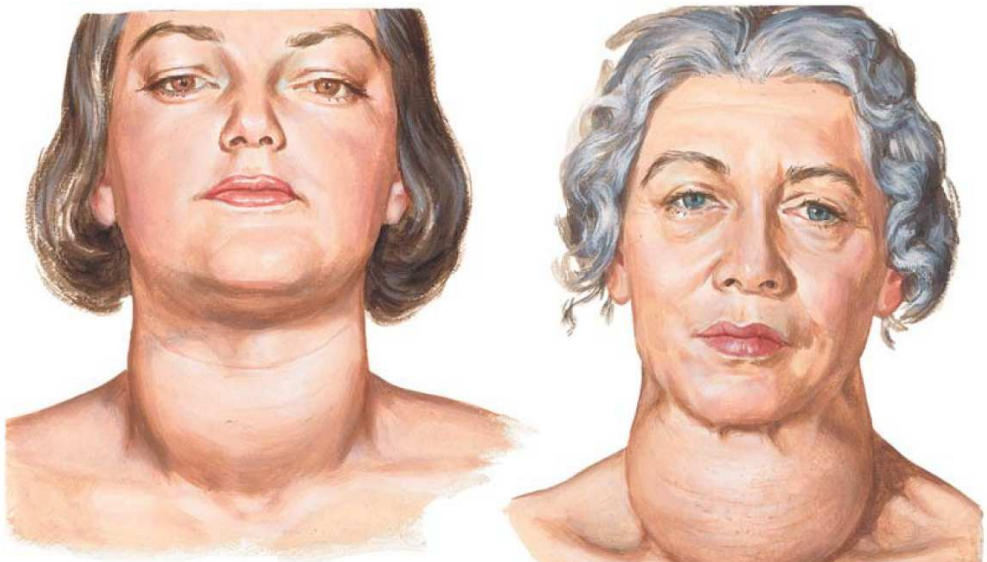
Thyroid storm

- **Causes**
  - Surgery, Radioactive Iodine, Therapy, Severe Illness
- **Diagnosis**
  - Clinical – tachycardia, hyperpyrexia, thyrotoxicosis symptoms
  - Labs (Low TSH, High T4, FT4)
- **Treatment**
  - Propranolol IV vs. Verapamil IV, Propylthiouracil, Methimazole
  - Sodium Iodide, Acetamenophen, cooling blankets
  - Plasmapheresis (rare), Surgical (rare)

Euthyroid goiter

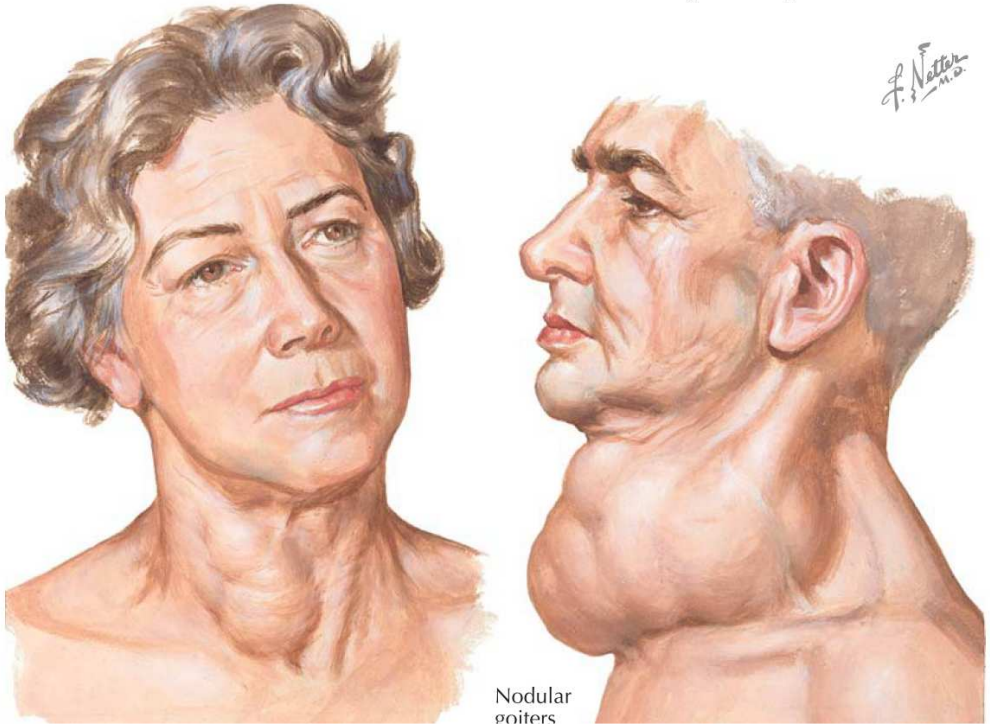
- Cause is an inactivation of 5'-deiodinase, resulting in conversion of FT_4 to rT_3.
- Occurs in critically ill patients; may occur with DM, malnutrition, iodine loads, or medications (Amiodarone, PTU, glucocorticoids)
- Treatment
  - Avoid above medications
  - Treat primary illness
  - T_3, T_4 not helpful





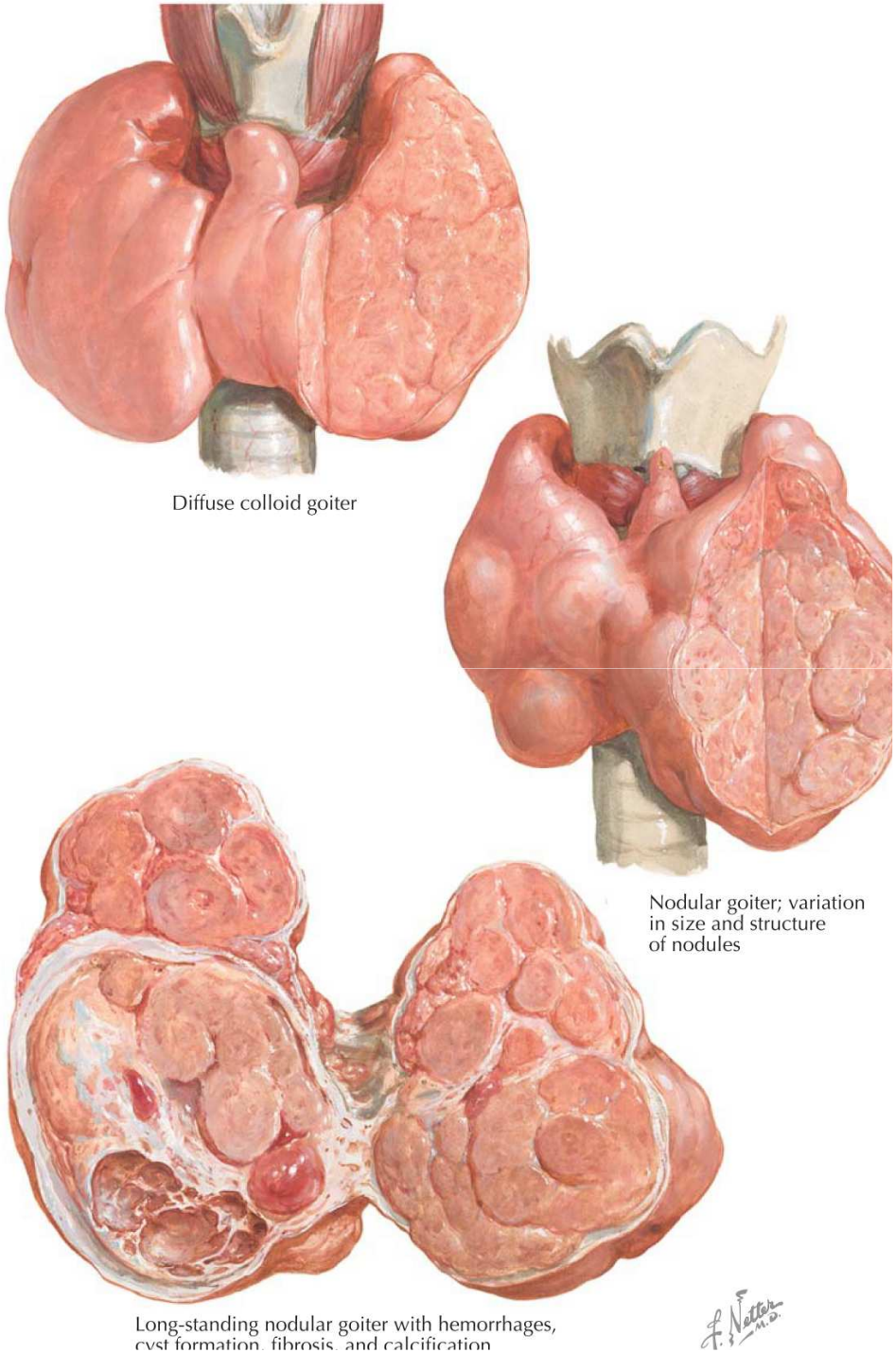
Moderate size nontoxic diffuse goiter

Large diffuse goiter



Nodular goiters

Goiter gross anatomy

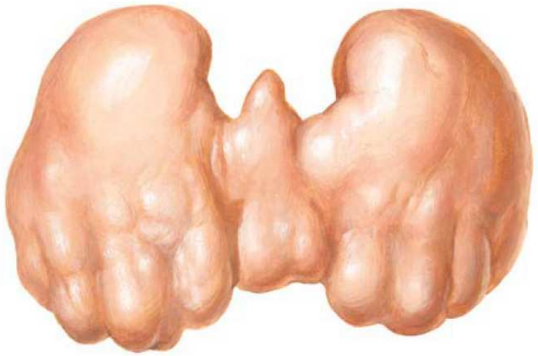


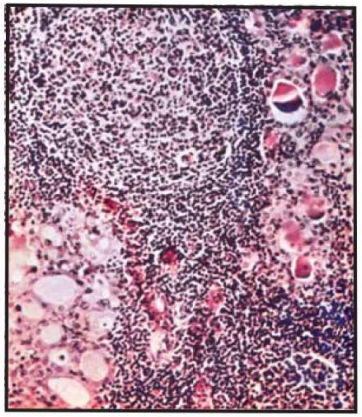
Diffuse colloid goiter

Nodular goiter; variation in size and structure of nodules

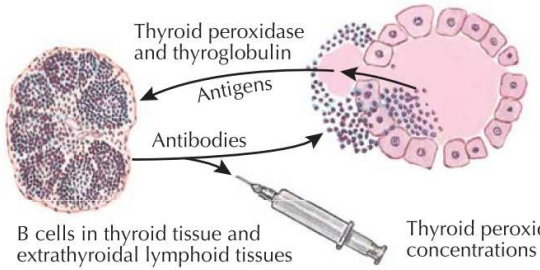
Long-standing nodular goiter with hemorrhages, cyst formation, fibrosis, and calcification

Hashimoto thyroiditis

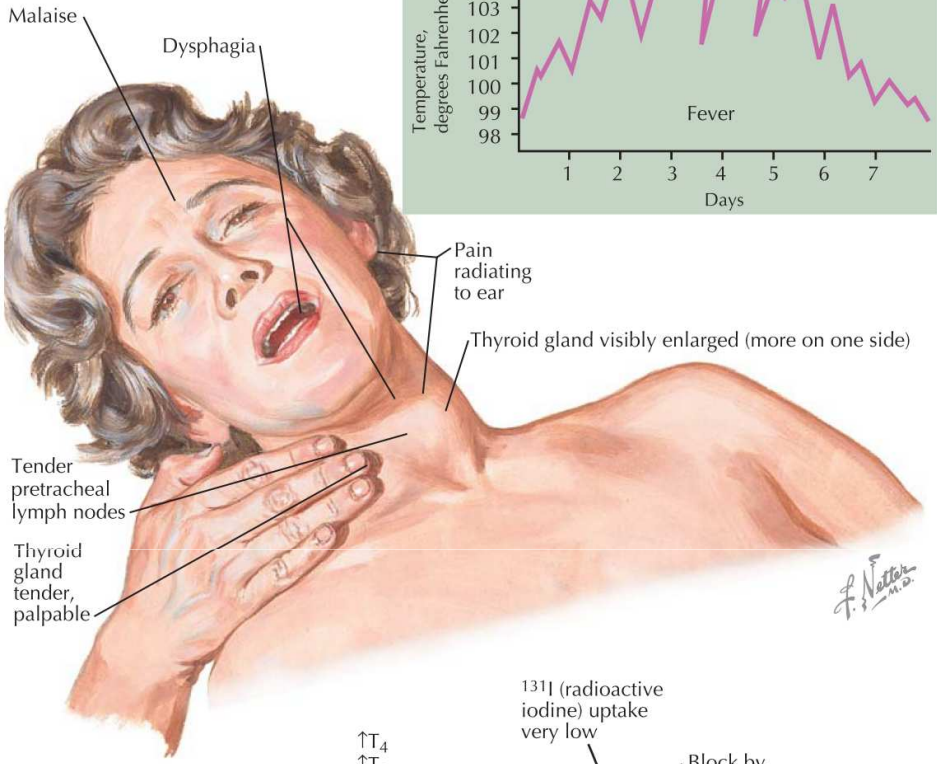




Microscopy of Hashimoto Thyroiditis
Mixture of hyperplastic and atrophic follicles with diffuse lymphocytic infiltration

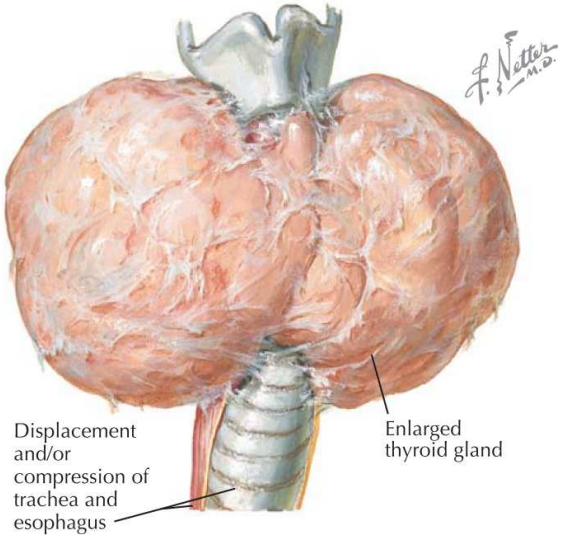


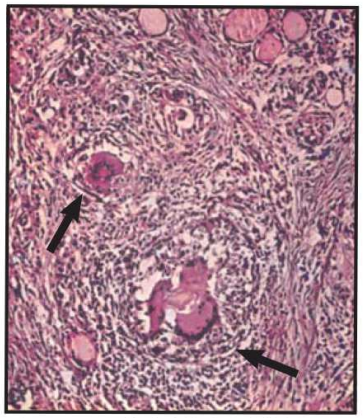
SUBACUTE THYROIDITIS



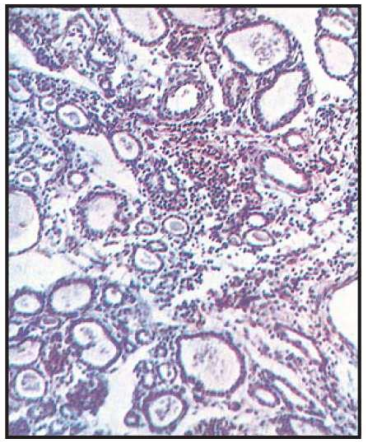
CHRONIC LYMPHOCYTIC THYROIDITIS AND FIBROUS THYROIDITIS

Riedel thyroiditis

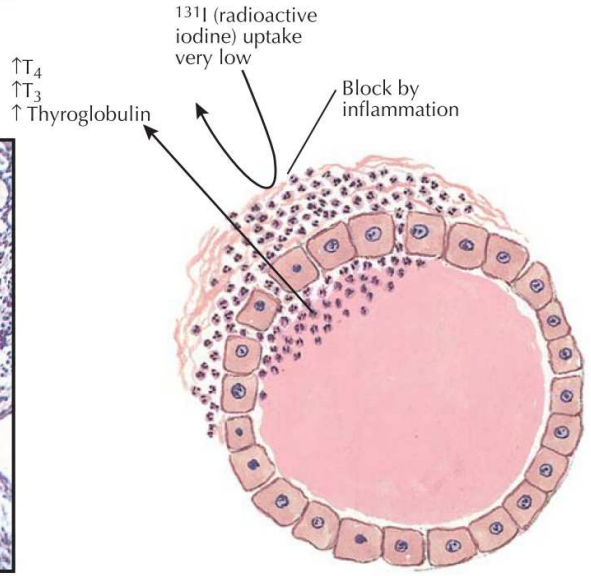


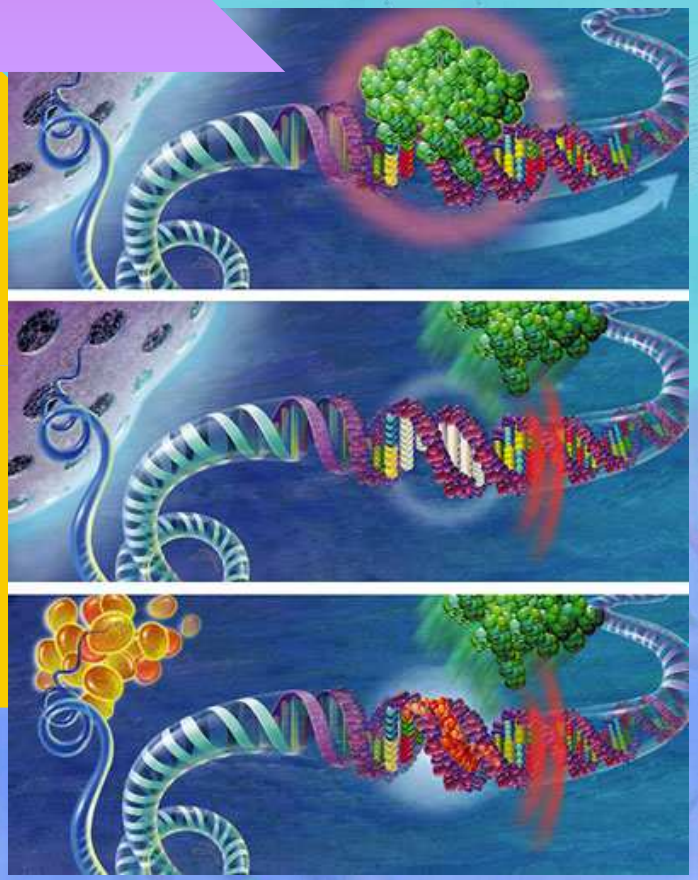


Microscopy of Riedel Thyroiditis
Macrophage and eosinophilic infiltration with atrophy of follicles (*arrows*) and marked diffuse fibrosis

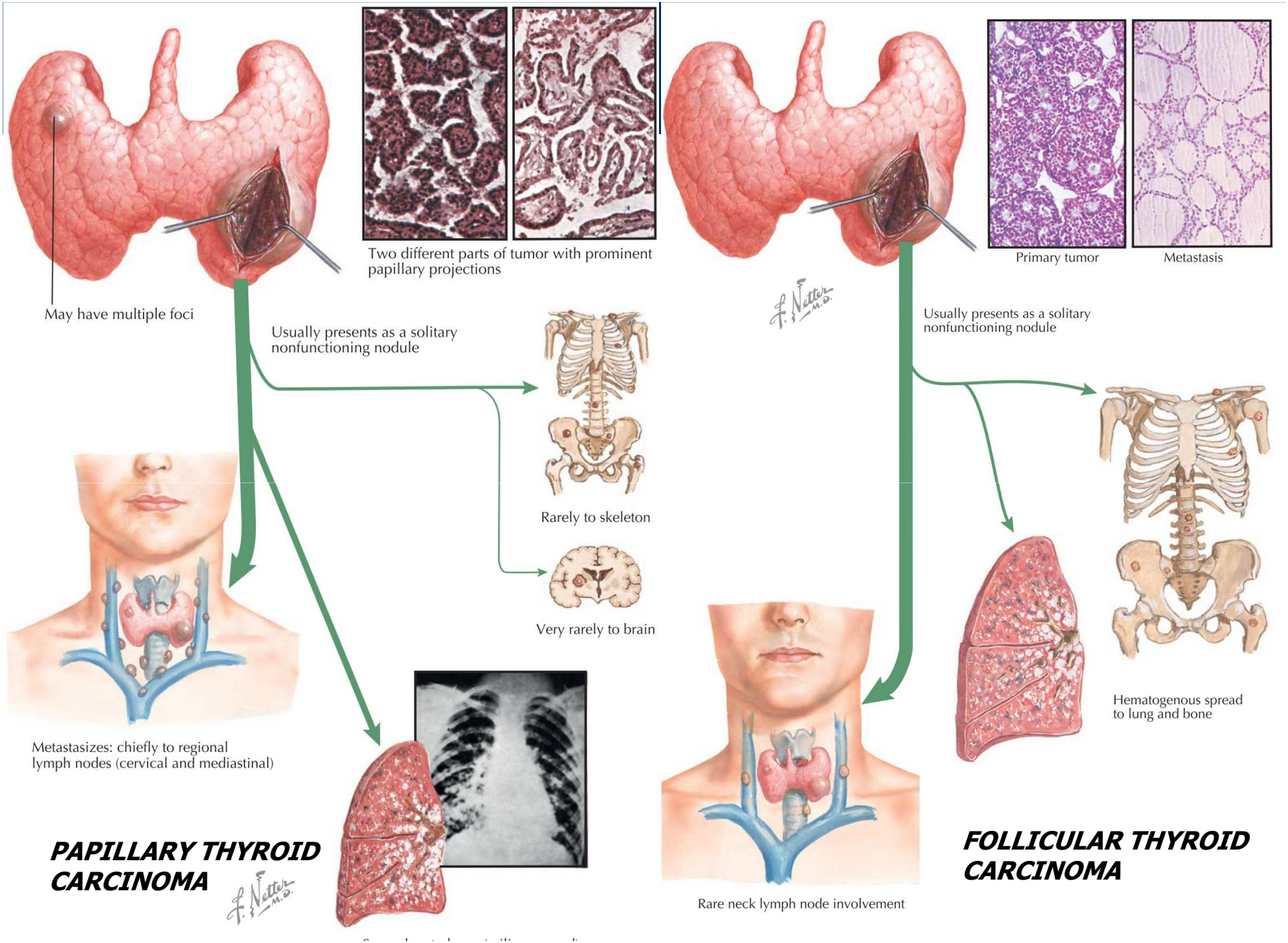


Diffuse infiltration of thyroid stroma

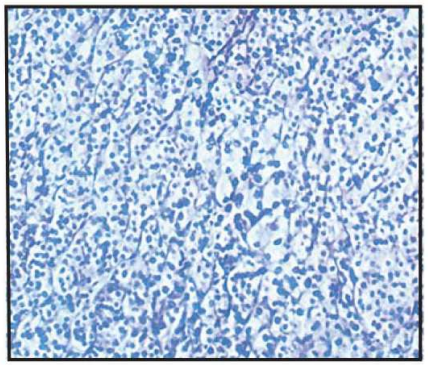


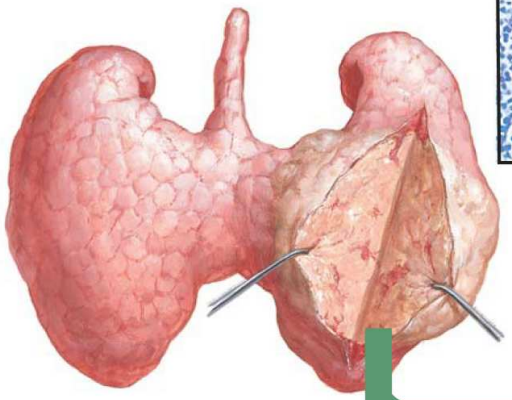


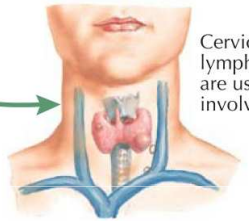
Thyroid gland neoplasms


May have multiple foci
Two different parts of tumor with prominent papillary projections
Usually presents as a solitary nonfunctioning nodule
Rarely to skeleton
Very rarely to brain
Metastasizes: chiefly to regional lymph nodes (cervical and mediastinal)
PAPILLARY THYROID CARCINOMA
Primary tumor
Metastasis
Usually presents as a solitary nonfunctioning nodule
Hematogenous spread to lung and bone
Rare neck lymph node involvement
FOLLICULAR THYROID CARCINOMA

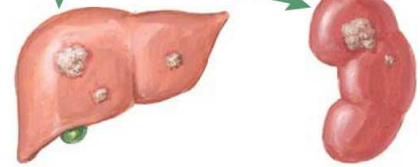
MEDULLARY THYROID CARCINOMA





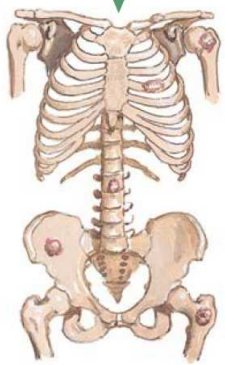


Cervical lymph nodes are usually involved



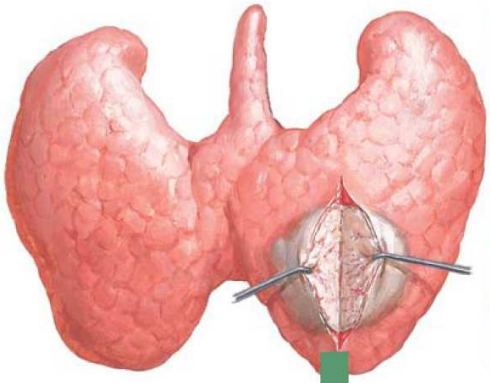
Liver Kidney

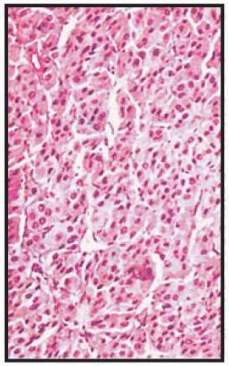
Less common sites of metastasis



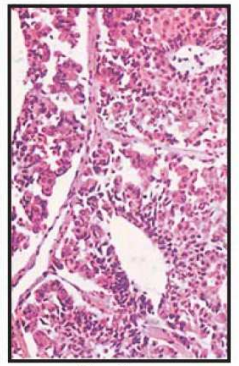
Lung (discrete nodules) Skeleton

Most common sites of metastasis

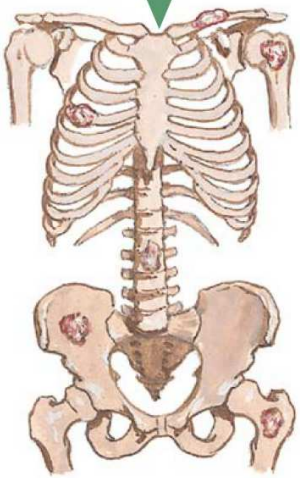




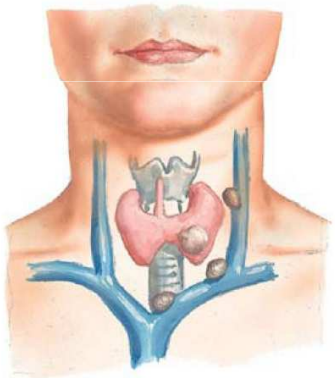
Trabecular



Plexiform



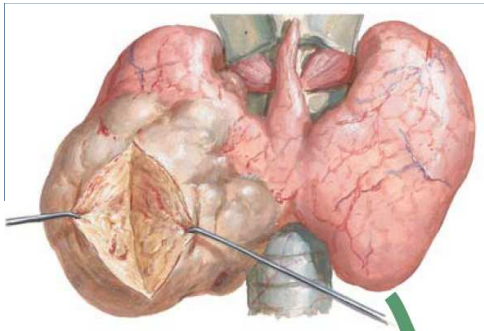
Metastasis chiefly to skeleton

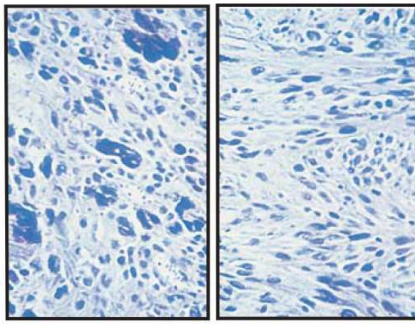


Secondarily to regional lymph nodes

and to lung (discrete nodule)

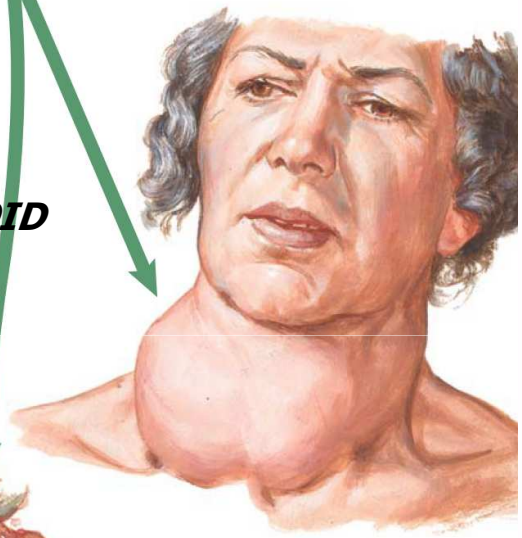
HüRTHLE CELL THYROID CARCINOMA



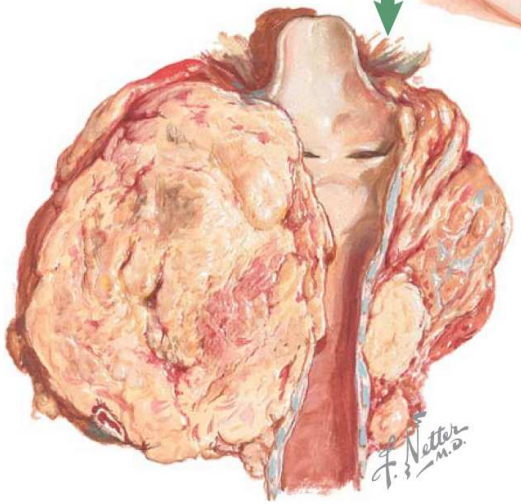


Giant cells Spindle cells

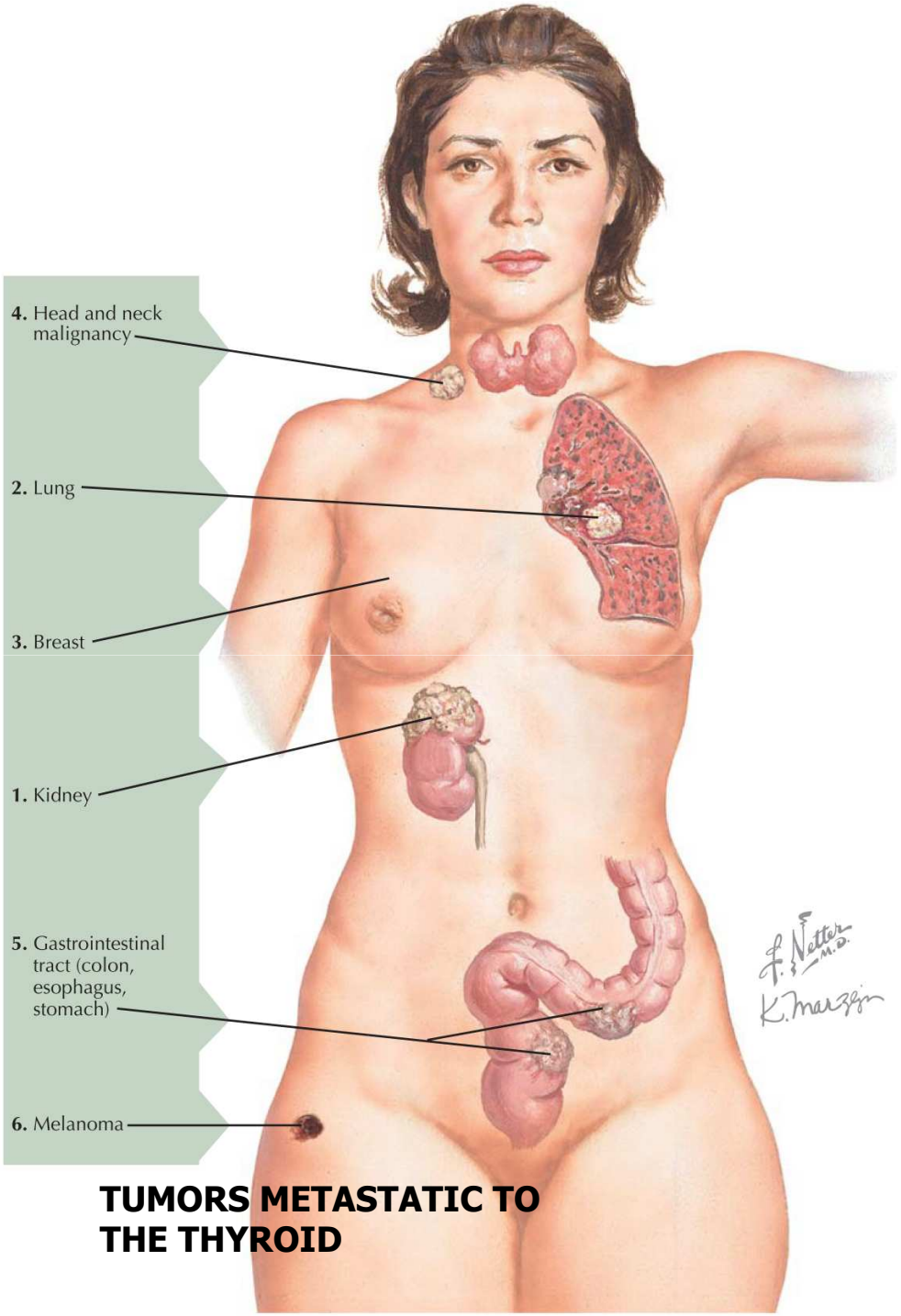
ANAPLASTIC THYROID CARCINOMA



Rapidly growing tender tumor of neck



Compression and invasion of trachea



TUMORS METASTATIC TO THE THYROID

Model of thyroid carcinogenesis

Risk factors (exposure to radiation) genomic instability through direct and indirect mechanisms,

early genetic alterations involve MAPK signalling pathway increases genomic instability, activation of RET or BRAF

later genetic alterations involve signalling pathways, cell-cycle regulators and various adhesion molecules.

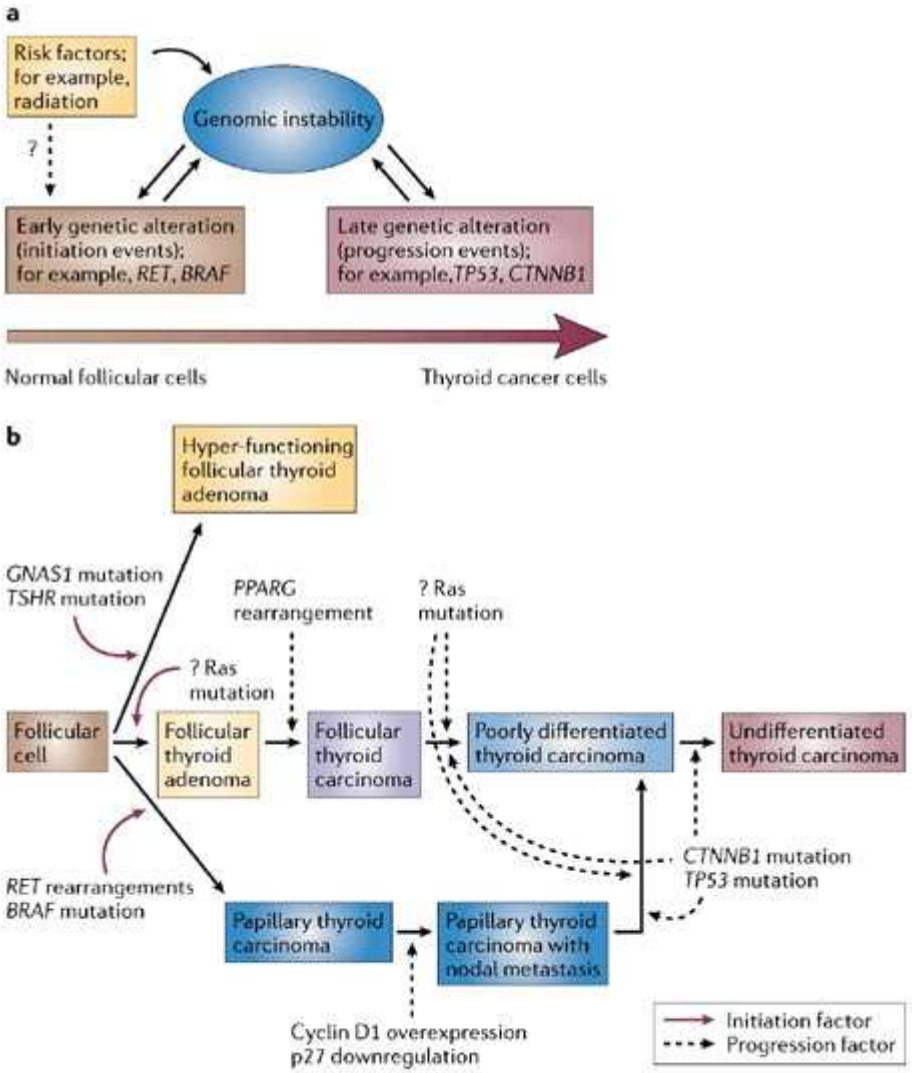
Accelerating the interactions between genomic instability and genetic alterations promotes progression from well-differentiated to undifferentiated thyroid carcinoma.

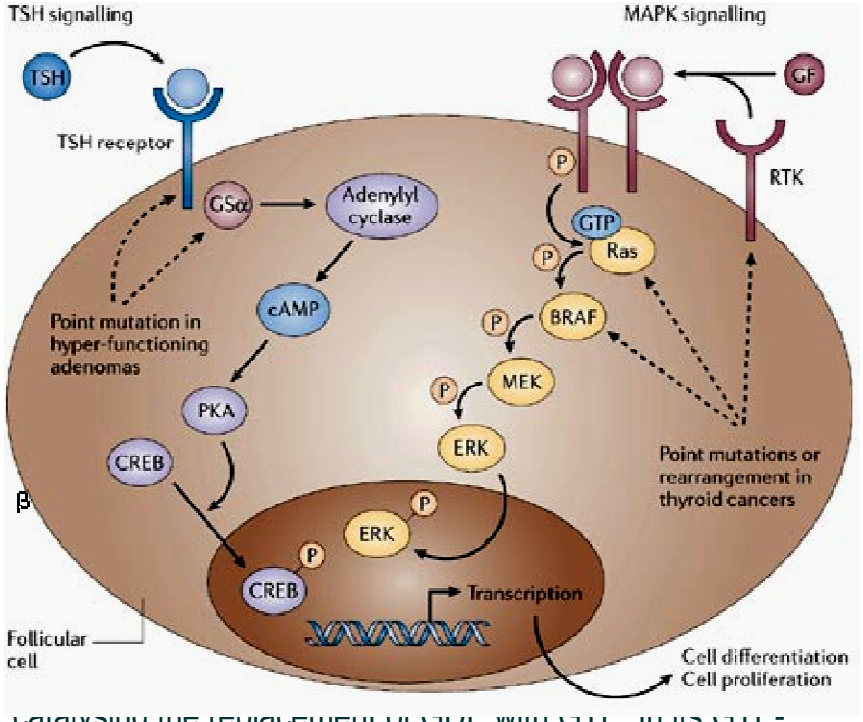
three distinct pathways are proposed for neoplastic proliferation of thyroid follicular cells, including hyper-functioning follicular thyroid adenoma (tumours that are almost always benign), follicular thyroid carcinoma and papillary thyroid carcinoma.

Underexpression of the cyclin-dependent-kinase inhibitor p27KIP1 and overexpression of cyclin D1 are strong predictors of lymph-node metastases in papillary thyroid carcinomas.

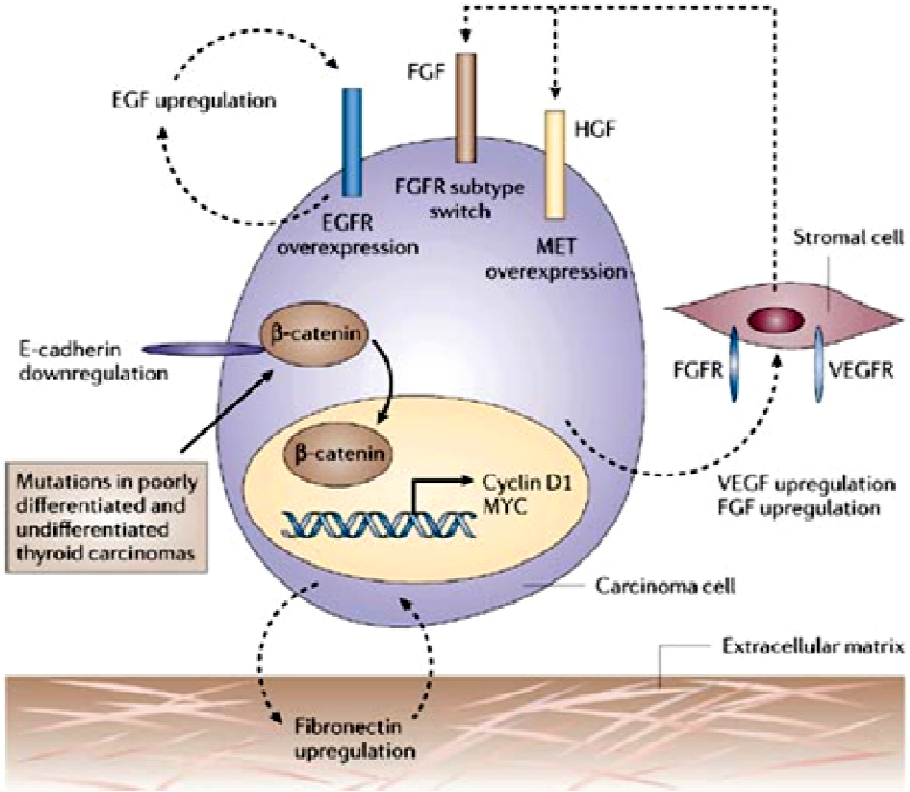
Most poorly differentiated and undifferentiated thyroid carcinomas are derived from pre-existing well-differentiated thyroid carcinoma through additional genetic events including catenin (*CTNNB1 gene*) nuclear accumulation and p53 inactivation, but *de novo* occurrence might also occur.

GNAS1, guanine nucleotide-binding -subunit 1; PPARG, peroxisome proliferation-activated receptor- ; TSHR, thyroid stimulating - hormone receptor.





catalysing the replacement of GDP with GTP. In its GTP-bound form, Ras activates the kinase activity of BRAF and its downstream signalling cascade. BRAF phosphorylates the mitogen-activated protein kinase (MAPK) kinase (MEK), which phosphorylates and activates extracellular-signal-regulated kinase (ERK). Activated ERK migrates to the nucleus where it phosphorylates and activates various transcription factors that are involved in cell proliferation and differentiation, such as MYC and ELK1.



Autocrine and paracrine growth-factor signalling has been implicated in thyroid carcinogenesis. Growth factors and their receptors that signal between stromal and endothelial/carcinoma cells include: fibroblast growth factor (FGF)–FGF receptor (FGFR), epidermal growth factor (EGF)–EGF receptor (EGFR), hepatocyte growth factor (HGF)–MET, and vascular endothelial growth factor (VEGF)–VEGF receptor (VEGFR). In normal endothelial cells, -catenin binds the cytoplasmic domain of E-cadherin as an adhesive component, mediating the Wnt signalling pathway. Defects in Wnt signalling occur in carcinoma cells, resulting in -catenin stabilization and translocation to the nucleus, and expression of cyclin D1 and MYC. Additionally, loss of E-cadherin is associated with increased invasion and cell motility. Fibronectin is upregulated at the protein and mRNA levels in papillary thyroid carcinoma, but its effect on tumour cell proliferation, adhesion and migration remains to be determined.

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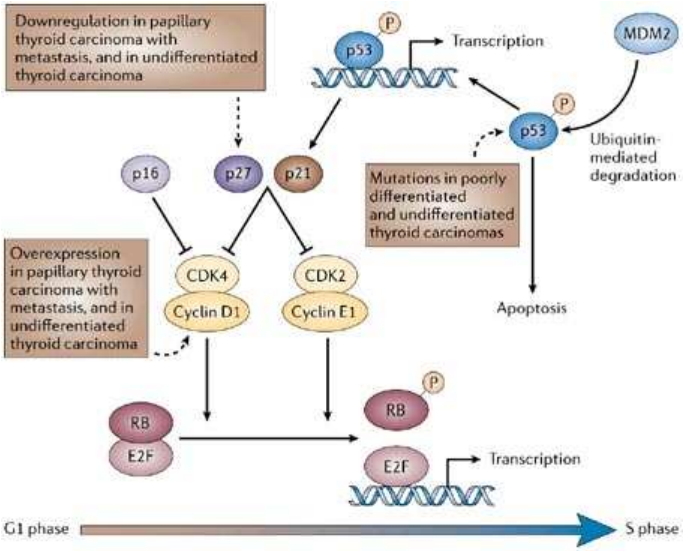
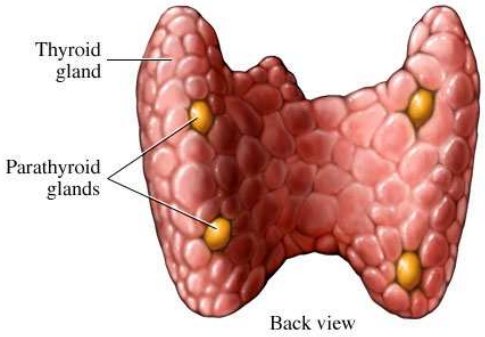
Cyclin D1 and cyclin E1 cooperate to control the G1 to S phase transition through interactions with retinoblastoma protein (RB). Cyclin D1 and cyclin E1 heterodimerize with cyclin-dependent kinases (CDKs) 4 and 2, respectively, to inactivate the tumour suppressor RB by phosphorylation. Active RB functions as a repressor of E2F transcription factors, whereas inactivation (phosphorylation) of RB allows E2F transcriptional activity. E2F activates the transcription of genes that are involved in the G1 to S phase transition, such as DNA polymerase and thymidine kinase. The CDK inhibitors p16INK4A, p21CIP1 and p27KIP1 impair the activity of cyclin–CDK complexes, thereby preventing phosphorylation of RB. The CDK inhibitors therefore function as tumour suppressors. The tumour suppressor p53 induces cell-cycle arrest by upregulating p21CIP1, which initiates apoptosis. The function of p53 is controlled by negative regulators, including MDM2. The MDM2 protein targets p53 for ubiquitin-mediated degradation, constituting a feedback loop to maintain a low concentration of p53 in the cells.




Thyroid gland
Parathyroid glands
Back view