Academic lectures for medical students – 3rd year
2005 - 2017

ENDOCRINE PATHOPHYSIOLOGY 1

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Basic terminology

- **Endocrine system** - system of secretory cells of mesodermal origin, which due to their secretion of biologically active substances with signaling functions – **hormones** into blood can influence vital processes in distant cells, tissues or organs of the body.
  - **Glands with inner secretion** (e.g. hypophysis, thyroid gland, parathyroid glands, supraren)
  - **Groups of cells** in organs, that obviously do other functions (e.g. hypothalamus, pancreas, ovaries, testis).
- **Hormone**
  - The substance produced by specialized gland and released into blood, transported by a blood to the tissues and organs, passes out and affects target cells
  - In broad view – biologically active product of one cell, which achieves pharmacological (or clinically relevant) effects in other cells – target cells, that are localized (in greater distances from production cells), hormone has to be transported in blood
- **Target cells (tissues)**
  - differ from others in that they posses the some kind of receptors for a given hormone

Intercellular signaling in brief

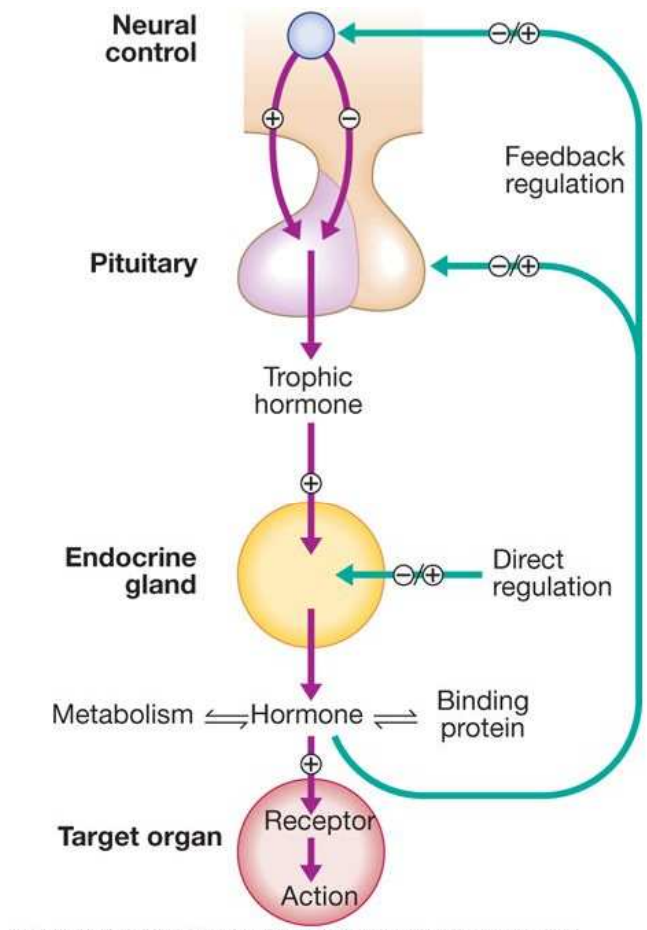
- **Endocrine signaling** – the way of chemical communication between two distant cells – signaling cell and target cells, that is conveyed via *blood.* If the production cell is neuron → *neuroendocrine signaling*
  - Note: There are dozens of mediators produced by cells and tissues in a endocrine way (into a blood) that are not a part of classical endocrine system
- **Signaling molecules** –substances produced /released in very small quantities (micro-, nano-moles) to target other cells (having specific receptors); they have no other significant role than signaling
  - *Classical hormones* – chemical substances released from specialized cells into blood and acting onto distant target cells
  - *Classical transmitters* – substances acting as chemical messengers in synapses of nervous cells or released from synapses into the surroundings to act on neighbor cells
  - *Cytokines* – substances of mostly peptide composition and pleotropic functions (many purposes) identified firstly in immunological cells (incl. interleukins, interferons, neurokines, lymphokines, monokines, chemokines, etc.)
  - *Eicosanoidsoids* - signaling molecules made by oxidation of arachidonic acid or other polyunsaturated fatty acids (PUFAs) that are, similar to arachidonic acid,
  - *Products of intermediary metabolism, nutrients* – may act on nuclear orphan receptors (e.g. oxysterols, glucose, fatty acids).

Regulations

- There are often hormonal **cascade regulations** and feed-backs.
- **Classical feed-backs:**
  - Effect by hormone (**very short feedback),**e.g. autocrine regulation or inner millieu changes back to production compartment (cells)
  - Effect by hormone over 1 etage **(short feed-back),** e.g. cortisol → ACTH (hypophysis)
  - Effect by hormone/ hormones – made effectors over 2 etages **(long feedback),** e.g. estrogenes, progesterone to regulate PRH or PIF (dopamine) in hypothalamus; or feedback of FFA or glucose level to regulate hypothalamic GRH → hypophyseal GH.
  - Hormone - made metabolic effectors, inner milieu changes (Na, K, Ca, glucose, pH, osmolarity etc.), effects on other hormons, mediators which show regular and clinically persistent feedbacks to initial cascade hornone regulation **(very-long feed backs)**

- **Types :**
- **Positive feedback -** maintains/ stimulates the production of the hormone
- **Negative feedback –** via dosis effect it inhibits further hormone production

Functional anatomy and physiology - repetitorium



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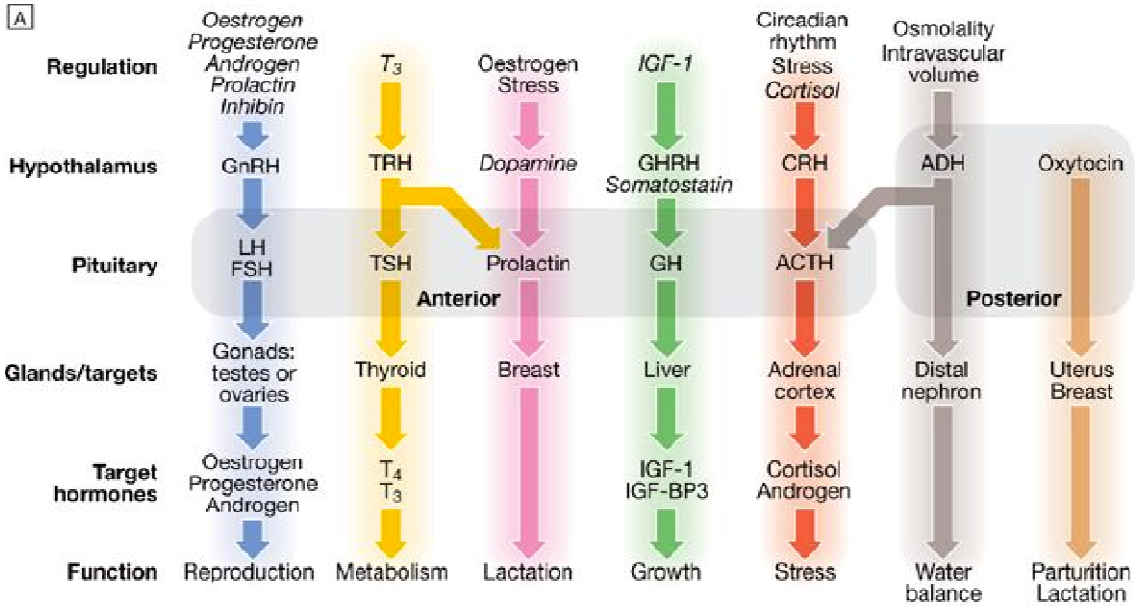
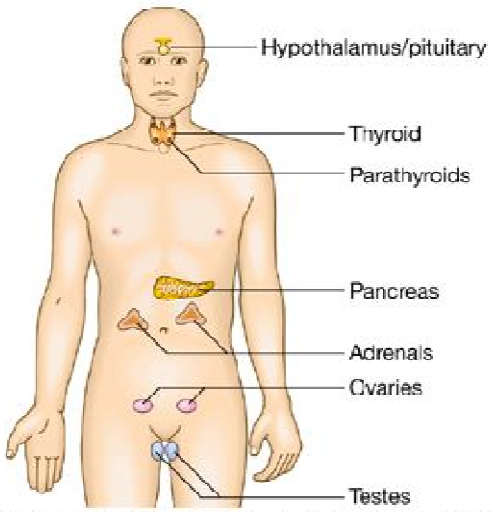
An archetypal endocrine axis. Regulation by negative feedback and direct control is shown along with the equilibrium between active circulating free hormone and bound or metabolised hormone.





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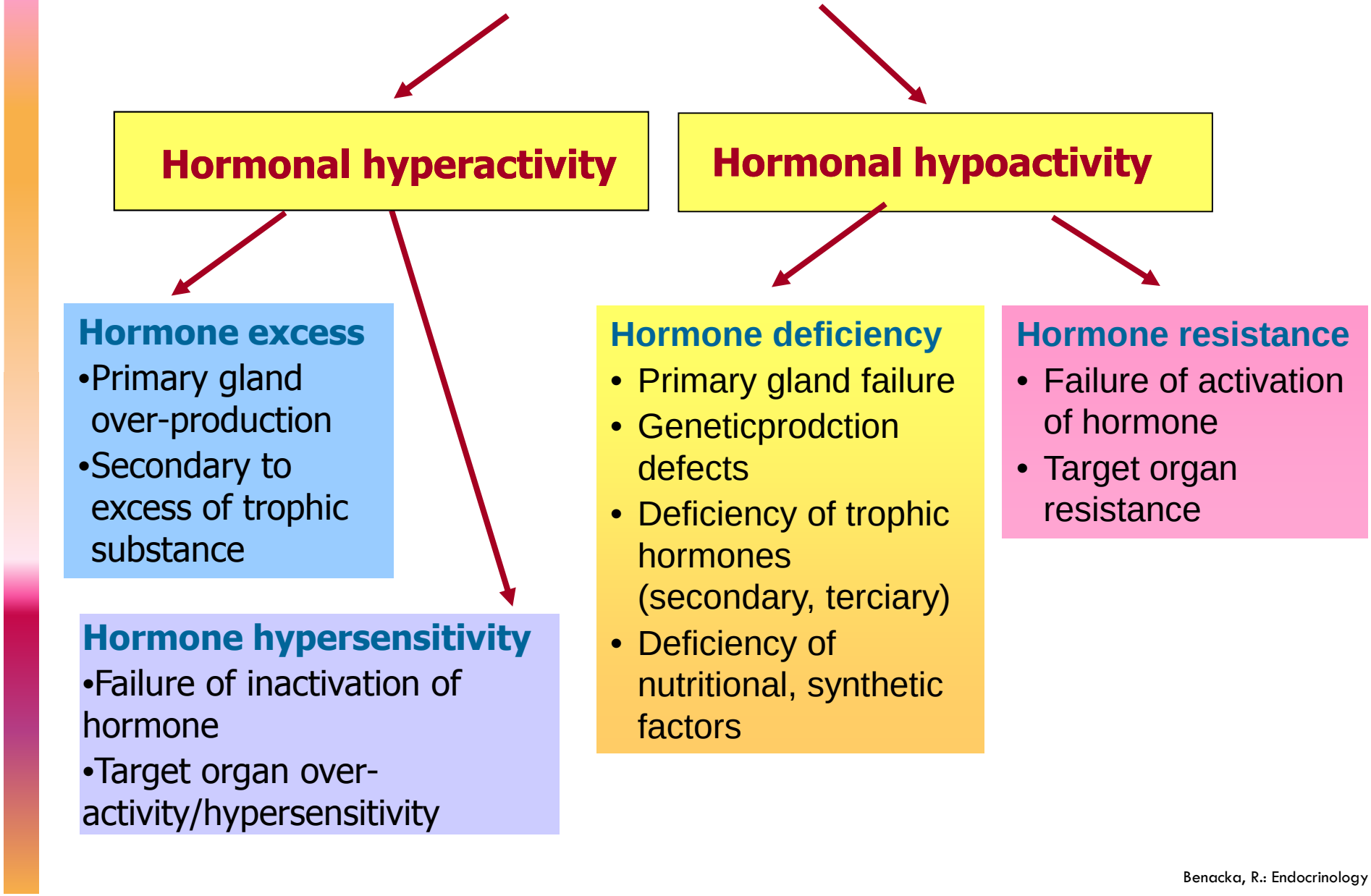
Examples of hormones by structure

Group	Hormones	Main resources
Derivatives of aminoacids	Adrenaline, Noradrenaline, Dopamine Thyroxin, Tri-iodthyronin (T3), Melatonin	Suprarenal medulla Thyroid gland, Epiphysis
Oligopeptides	Vasopressin, Oxytocin, Thyreoliberin (TRH)	Hypothalamus
Polypeptides	Glucagon Gonadoliberin, Somatostatin ACTH, Endorphins, MSH Calcitonin	Pancreas (alfa cells) Hypothalamus Adenohypophysis C-cells of thyroid gl.
Proteins	Insulin Somatotropin, Prolactin, Parathormone	Pancreas (beta cells) Hypothalamus Parathyroid glands
Glycoproteins	Follicular - stimulating hormone Luteinizing hormone, ACTH Thyrotropin (TSH)	Adenohypophysis Adenohypophysis Adenohypophysis
Steroids	Glucocorticosteroids (cortisol) Mineralocorticosteroids (aldosterone) Progestins (progesterone) Estrogens Androgens – testosterone, androstenedione	Suprarenal cortex Suprarenal cortex Yellow body, Placenta Ovaries, placenta Testicles (Supraren)

Classification of endocrine disease



Manifestations of endocrinopathies

Number of hormones involved:

- **Isolated dysfunction** – increased or decreased tissue effects of a single hormone
- **Multiple (combined) dysfunctions** – several hormones are involved (judging from both manifestations and plasma levels of hormones)

Type of disordered hormonal function:

- **hyperfunction disorders (syndromes)** – enhanced effects of hormone/ hormones in the body organ and tissues (e.g. hyperthyroidism, hyper(adreno)corticism; multiple hyperfuncions are in MEN syndromes)
- **hypofunction disorders (syndromes)** - lack of normal action od a diven hornone in target tissues (often assoc. with the overbalance of contraregulatory hormones)
- **mixed disorders** - hyperfunction of one/or few hormone(s) combined with hypofunction of another /others; e.g. pituitary adenoma overproducing one/two hormone(s) (prolactinoma (+ GH)) can devastate the rest of the gland

Terminological note:

- Decreased hormonal effect in target tissues does not mean necessarily hormone deficiency, nor decreased hormone levels in the blood (-emia) (e.g. hypocorticism is not the same as hypocortisolemia; diabetes is not the same as hypoinsulinemia)
- Hormone overactivity does not stem necessarily from hormone's hyperproduction in obvious locations

Non-specific presentations of endocrine disease

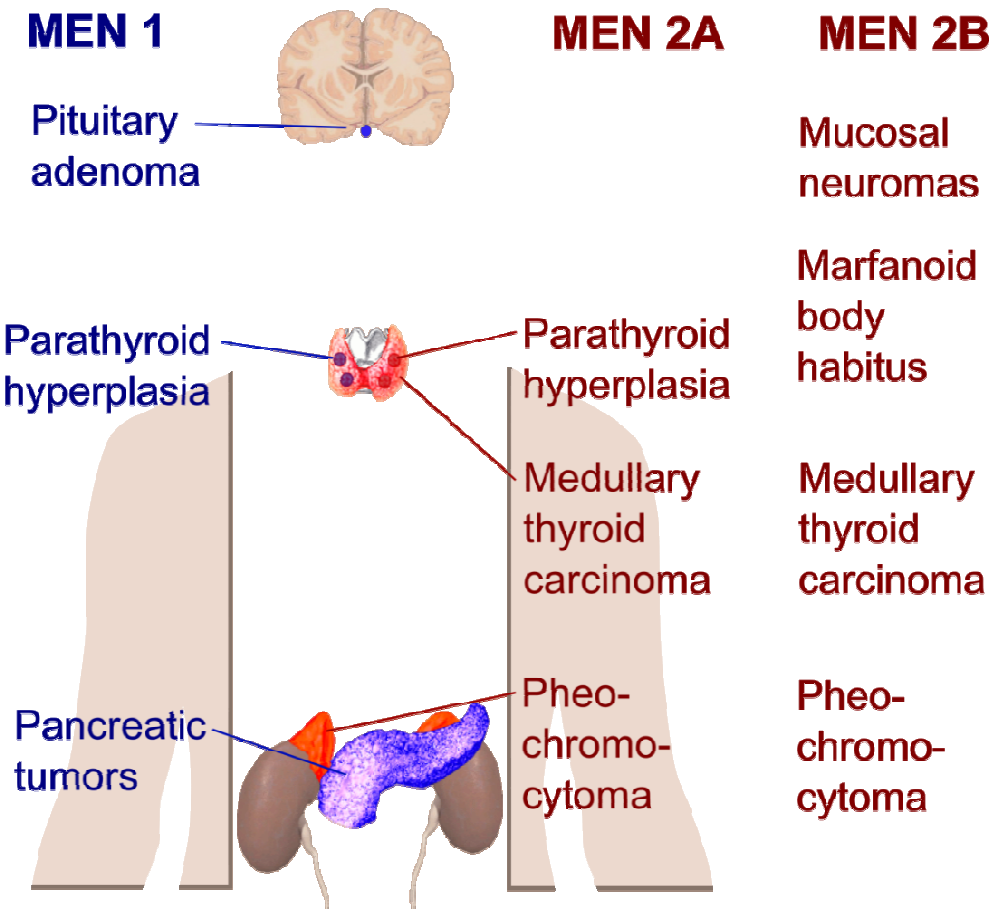
Symptom	Most likely endocrine disorder(s)
Lethargy and depression	Hypothyroidism, diabetes mellitus, hyperparathyroidism, hypogonadism, adrenal insufficiency, Cushing's syndrome
Weight gain	Hypothyroidism, Cushing's syndrome
Weight loss	Thyrotoxicosis, adrenal insufficiency, diabetes mellitus
Polyuria and polydipsia	Diabetes mellitus, diabetes insipidus, hyperparathyroidism, hypokalaemia (Conn's syndrome)
Heat intolerance	Thyrotoxicosis, menopause
Palpitations	Thyrotoxicosis, phaeochromocytoma
Headache	Acromegaly, pituitary tumour, phaeochromocytoma
Muscle weakness (usually proximal)	Thyrotoxicosis, Cushing's syndrome, hypokalaemia (e.g. Conn's syndrome), hyperparathyroidism, hypogonadism
Coarsening of features	Acromegaly, hypothyroidism

Combined hormonal hyperfunction

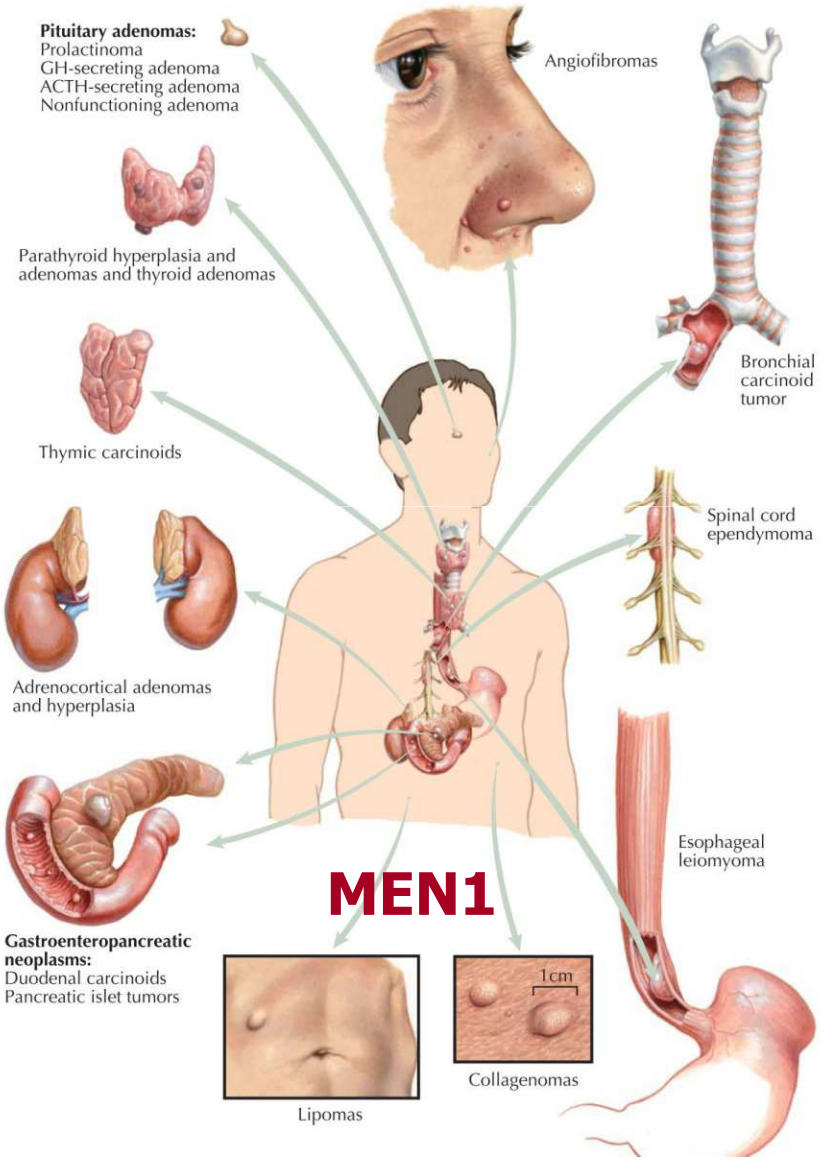
- **Multiple endocrine neoplasia (MEN)** rare AD – trasmitted hereditary disease – combined overpro-duction of several hormones

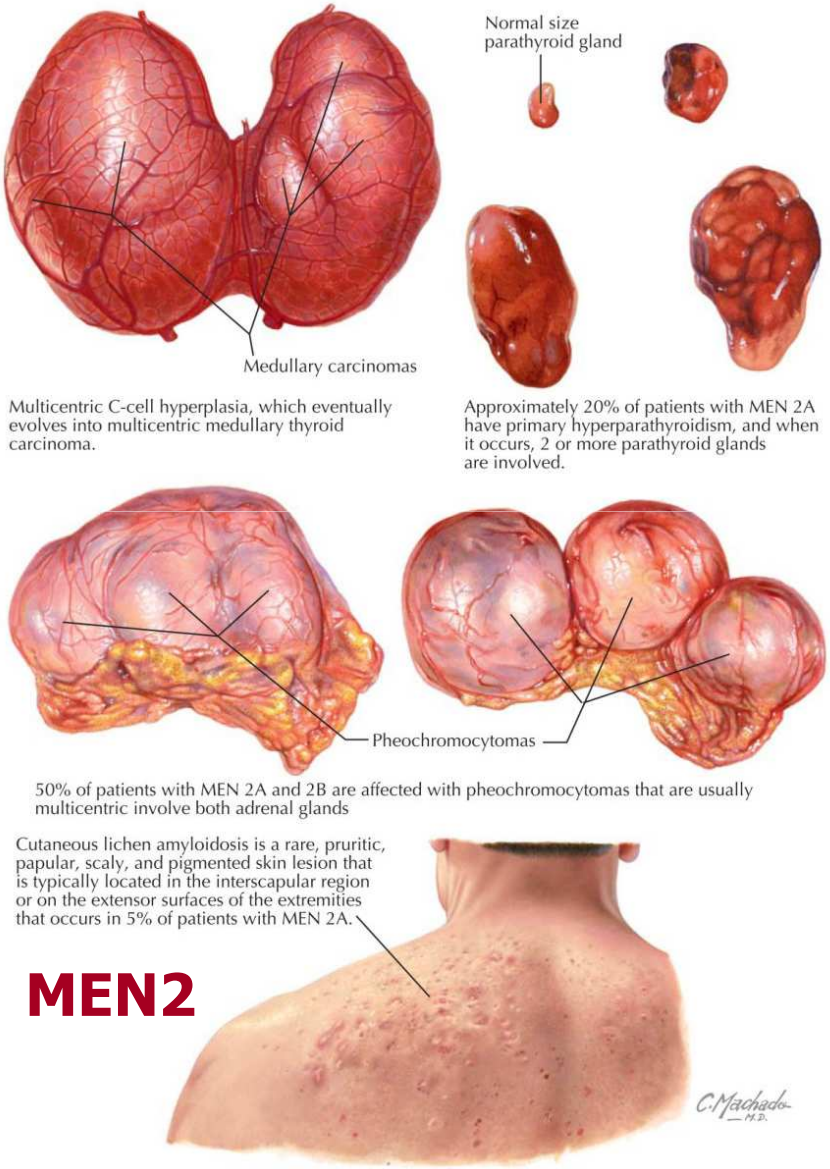
  - **MEN 1** – parathyroid adenoma (hyperplasia), pancreatic tumors (inzulinoma, gastrinoma), pituitary adenoma (+variably: suprarenal cportical adenoma, thyroid adenoma)
  - **MEN 2** – medullary carcinoma, pheochromocytoma + (2A: parathyroid adenoma; 2B: neuromas)
  - Include multiple tumors from **APUD cells** → gastinoma, pheochromocytoma, neuroblastoma.

APUD cells = group of apparently unrelated endocrine cells (Pearse,1962) secreting a low molecular weight polypeptide hormones (secretin, cholecystokinin, gastrin)



Multiple endocrine neoplasia





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Hormonal hyperfunction

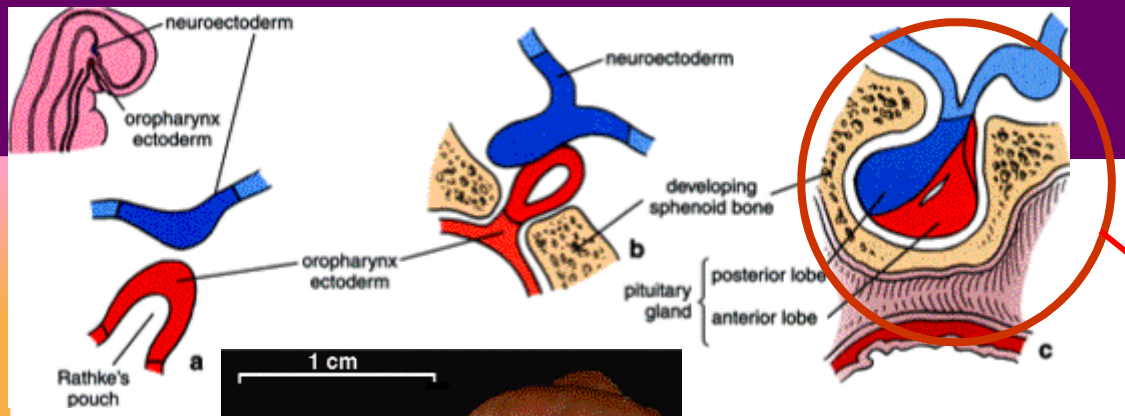
- **Hyperplasia/ hypertrophy of normal production cells**
- **Tumors** - nomotopic production (adenomas); paraneoplastic ectopic production,
  - **isolated overproduction** – in all endocrine glands
  - **combined hyperfunction** – e.g. hypophyseal tumors, MEN (multiple encocrine neoplasia)

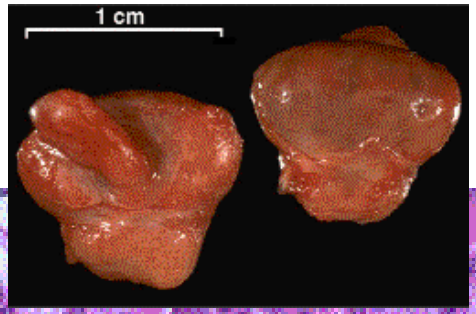
- **Ectopic hormone production** – mainly in bronchial carcinomas
  - parathormone, vazopresin (bronchial Ca),
  - calcitonin (bronchial Ca, mammary Ca),
  - corcotrophin ACTH (bronchial Ca)
  - somatotrophin (STH, GH) (bronchial Ca, mammary Ca),
  - prolactin (bronchial Ca,
  - human choriogonadotropin, HCG (teratomas, testicular, ovarial tumors),
  - HPL (ovarial, testicular tumors, Ca of lungs)
  - insulin-like growth factor (retroperitoneal fibromas, etc.),
  - erythropoetin (liver Ca, bronchial Ca).

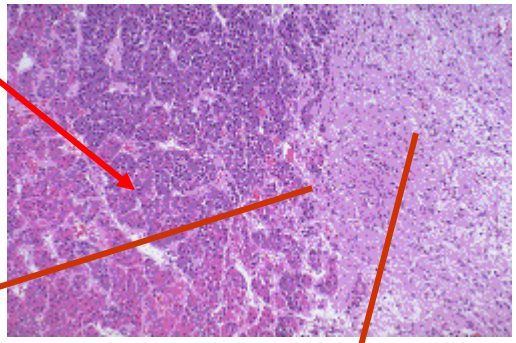
Pituitary gland

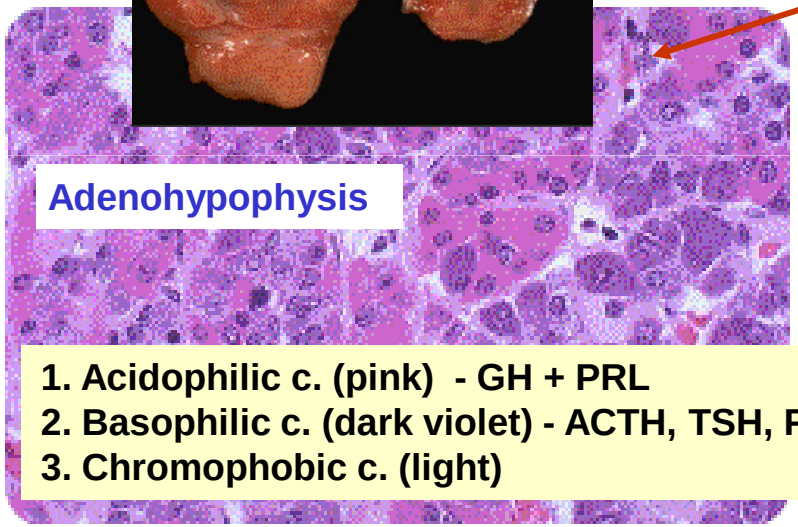
- Physiological review
- Hypopituitarisms

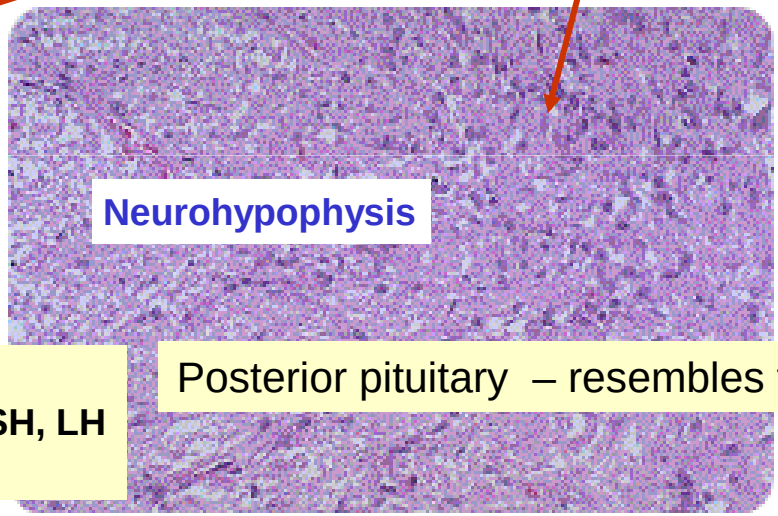
Pituitary histo-embryology







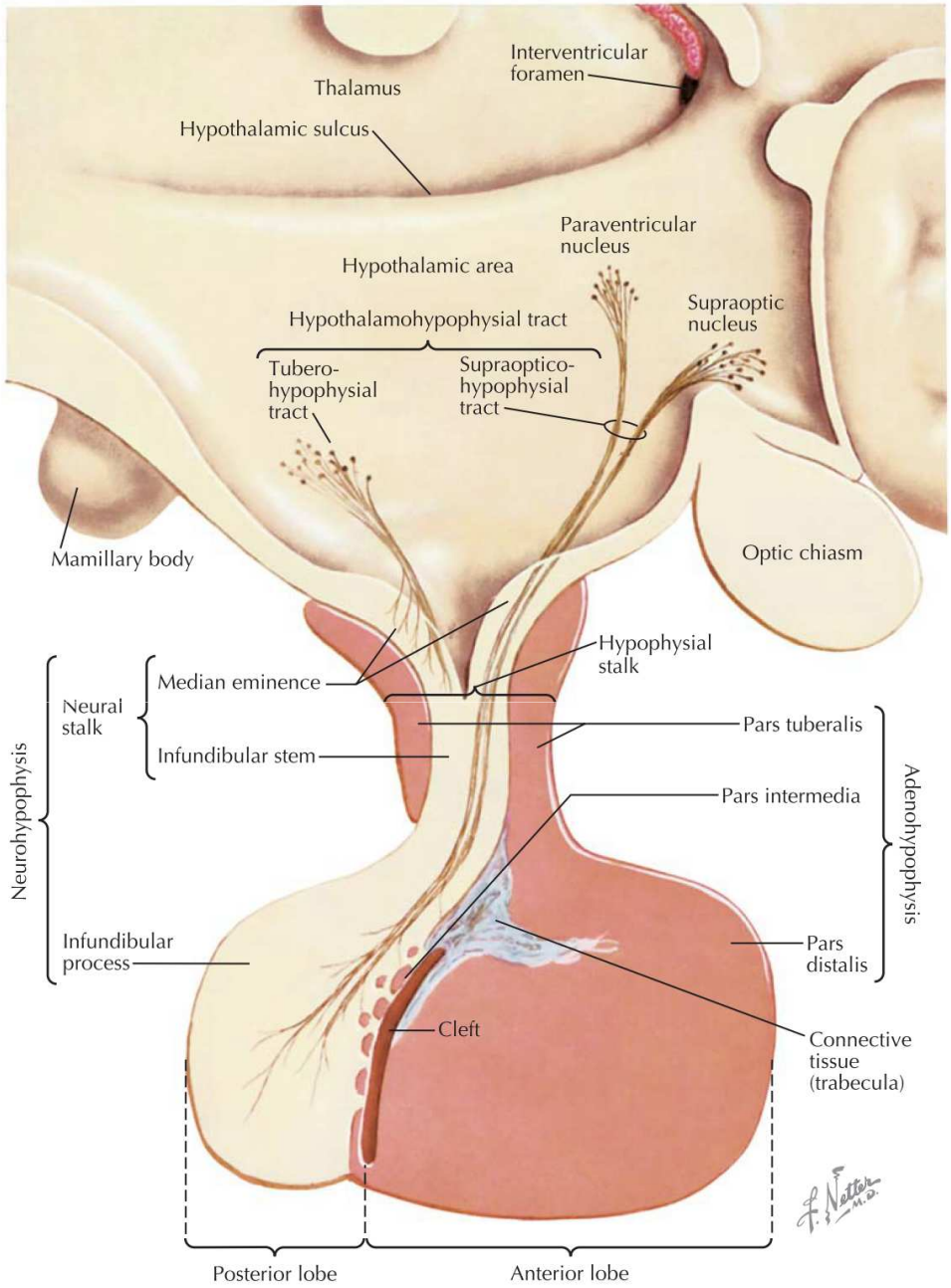


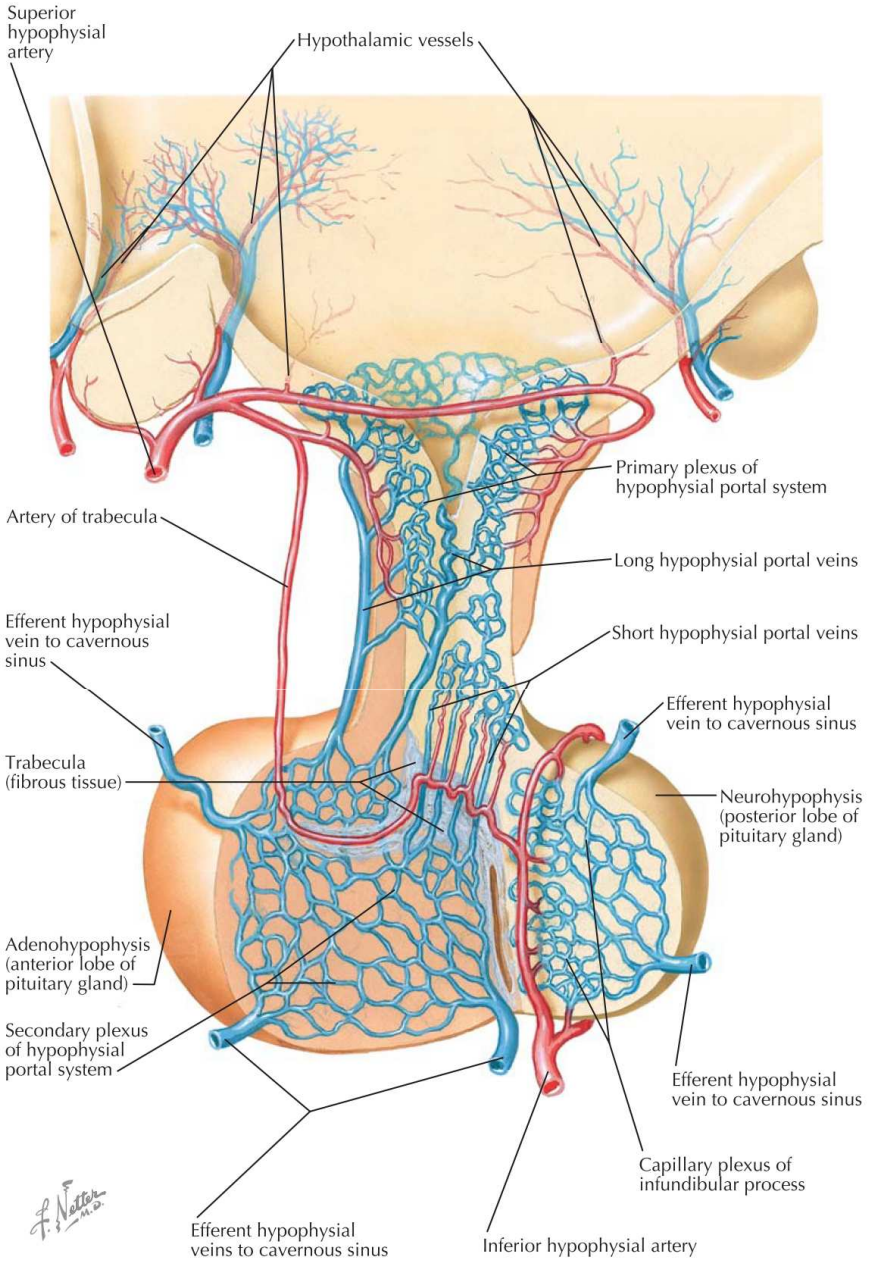


1. Acidophilic c. (pink) - GH + PRL
2. Basophilic c. (dark violet) - ACTH, TSH, FSH, LH
3. Chromophobic c. (light)

Posterior pituitary – resembles to NS

- Pituitary develops in the 3rd week of embryogenesis from interactions between the diencephalon part of the brain and the nasal cavity. Brain cells secrete → FGF-8, Wnt5a + BMP-4, Nasal cavity → BMP-2.
- Cells from the nasal cavity form Rathke's pouch (becomes independent of the nasal cavity, → develops into the anterior pituitary; the cells differentiate further into hormone-producing cells by transcription factors like HESX1, PROP1, POU1F1, LHX3, LHX4, TBX19, SOX2, SOX3. (each acts in particular cells).





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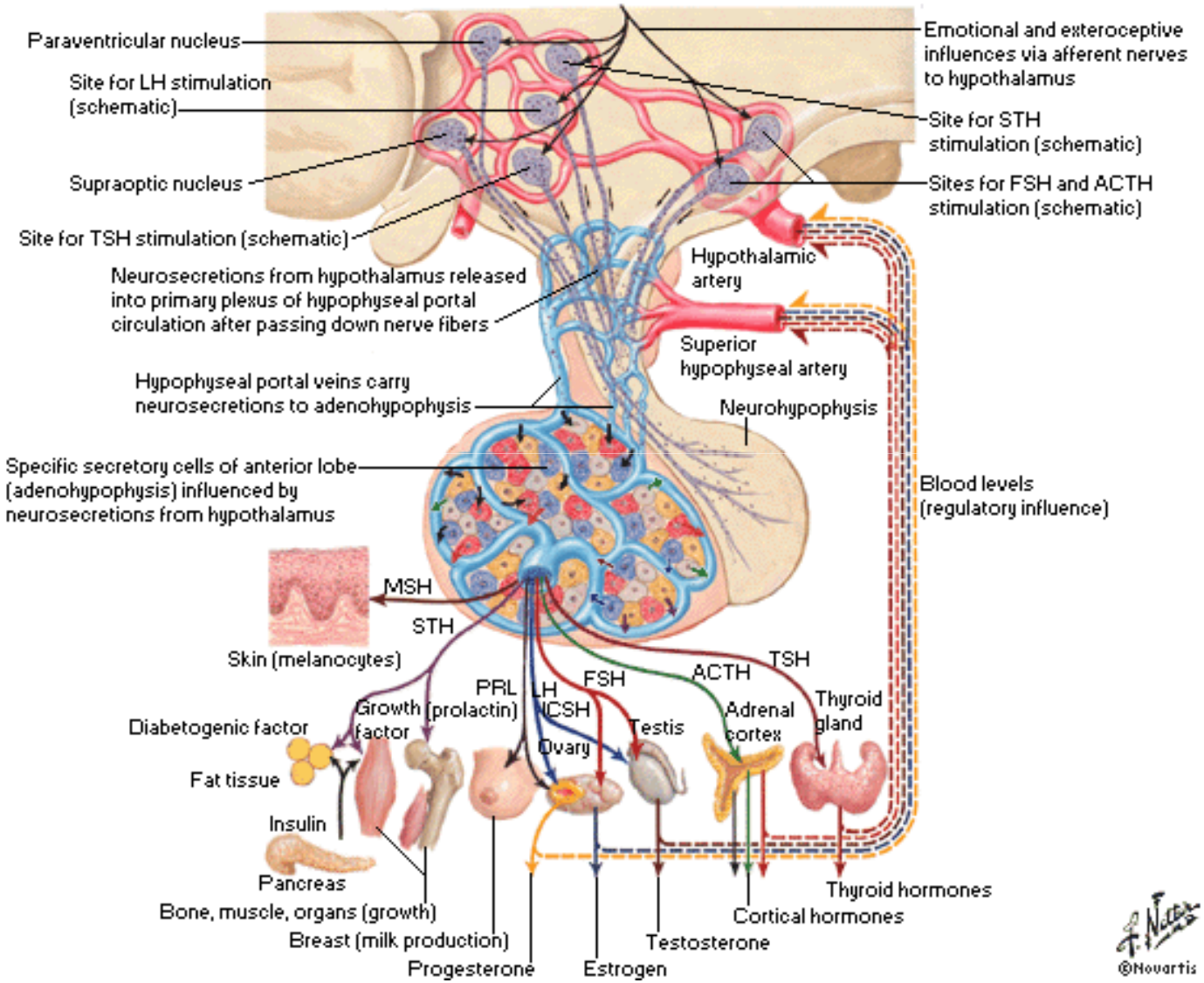
Overview of hypothalamic hormones

Term	Alternative name	Site of production	Struc	Effect
Thyreoliberin (TL)	**TRH (thyrotropin-releasing hormone)**	nucl. paraventricularis, suprachismaticus, ventromedialis, dorsomedialis	3 AA	Thyreotrophs -TSH production
Corticoliberin (CL)	**CRH (corticotropin-releasing hormone)**	nucl. paraventricularis	41 AA	Corticotrophs - ACTH
Gonadoliberin (GL)	**GnRH (gonadotropin-releasing hormone)**	nucl. praeopticus, arcuatus	10 AA	Gonadotrophs -FSH a LH
Somatoliberin (SL)	**GRH (growth hormone releasing hormone)**	nucl. arcuatus, ventromedialis	44 AA	Somatotrophs -Somatotrophin (GH) production
Somatostatin (SS)	**GIH (growth hormone releasing hormone)**	Nucl. arcuatus, ventromedialis, paraventriculais	14 AA	Somatotrophs Somatotrophin (GH) Production
Dopamine	**PIH (prolactin inhibiting hormone)**	nucl.ventromediais	Amin	Lactotrophs Prolactin production

Overview of trophic hormons

Name / altern, name	Alternative names	Production	Structure	Target tiisue
GH (Growth hornone)	Somatotrophin	Somatotrophs, Acidophilic c.	Polypeptide 191 AA	Bones Connective tissue
PRL (Prolactin)	Lactotrophin	Lactotrophs Acidophilic c.	Polypeptide 198 AA	Mammary gland
ACTH Adreno-corticotropin hormone	Corticotrophin	Corticotrophic c.	Polypeptide 39 AA	Supraren cortex
TSH (Thyreostimulating hormone)	Thyreotrophin	Thyreotrophs Basophilic c.	Glycopeptide 89+112 AA	Thyroid gland
LH (Luteinizing hormone)	Gonadotrophin	Gonadotrophs Basophilic c.	Glycopeptide heterodimer α 89+ β115 AA	Testis Ovaries
FSH (Follicle-stimulating hormone)	Gonadotrophin	Gonadotrophs Basophilic c.	Glycopeptide heterodimer α 96 + β111 AA;	Testis Overies

Overview of trophic hormons



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Relationship Among Hypothalamic, Pituitary, Target Glands, and Feedback Hormones

Hypothalamic Regulatory Hormone	Pituitary Hormone	Target Gland	Feedback Hormone
TRH	TSH	Thyroid gland	T_4, T_3
LH-RH	LH	Gonad	E_2, T
LH-RH	FSH	Gonad	Inhibin, E_2, T
GH-RH, SMS	GH	Multi-organs	IGF-1
PIF	Prolactin	Breast	?
CRH, ADH	ACTH	Adrenal	Cortisol

ADH = Antidiuretic hormone; CRH = Corticotropin-releasing hormone; E2 = Estradiol; FSH GH = Growth hormone; GH-RH = Growth hormone-releasing hormone; IGF = Insulin-like growth factor; LH = Luteinizing hormone; LH-RH = Luteinizing hormone-releasing hormone; PIF = Prolactin release-inhibitory factor; SMS = Somatostatin; T = Testosterone; T_4 = Thyroxine; TRH = Thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone

Hypopituitarism

- Partial hypopituitarism (selected hormones)
- Panhypopituitarism (all adenopituitary hormones)
- Mixed syndrome (combined with excess syndrome)

Hypopituitarism – Definition; Epidemiology

- Def: Group of syndromes characterized by deficiency of few or near all anterior pituitary hormones; or deficiency combined with abundance of one of the pituitary hormones.; the first description made in 1914 by the german physician Dr Morris Simmonds.
- Occ: relatively rare; prevalence 45/100.000; incidence ~ 4 new cases per year; may be 31 per 100,000 annually;
- Etio: traumatic brain injury, spontaneous subarachnoid hemorrhage (SAH) or radiation therapy involving the head have a higher risk of hypopituitarism; Traumatic brain injury → ¼ have persistent pituitary hormone deficiencies (incl. subtle or non-specific symptoms); Many cases of hypopituitarism remain undiagnosed.
- Types:
  - **Panhypopituitarism** = deficiency of the all or almost all adenohypophyseal (trophic) hormones
  - **Partial hypopituitarism** = selective deficiency of one of trophic hormone produced by adenohypophysis
  - **Mixed pituitary syndrome** = combination of the abundance (e.g. adenama) of one hormone (or) and deficiency of other hormones

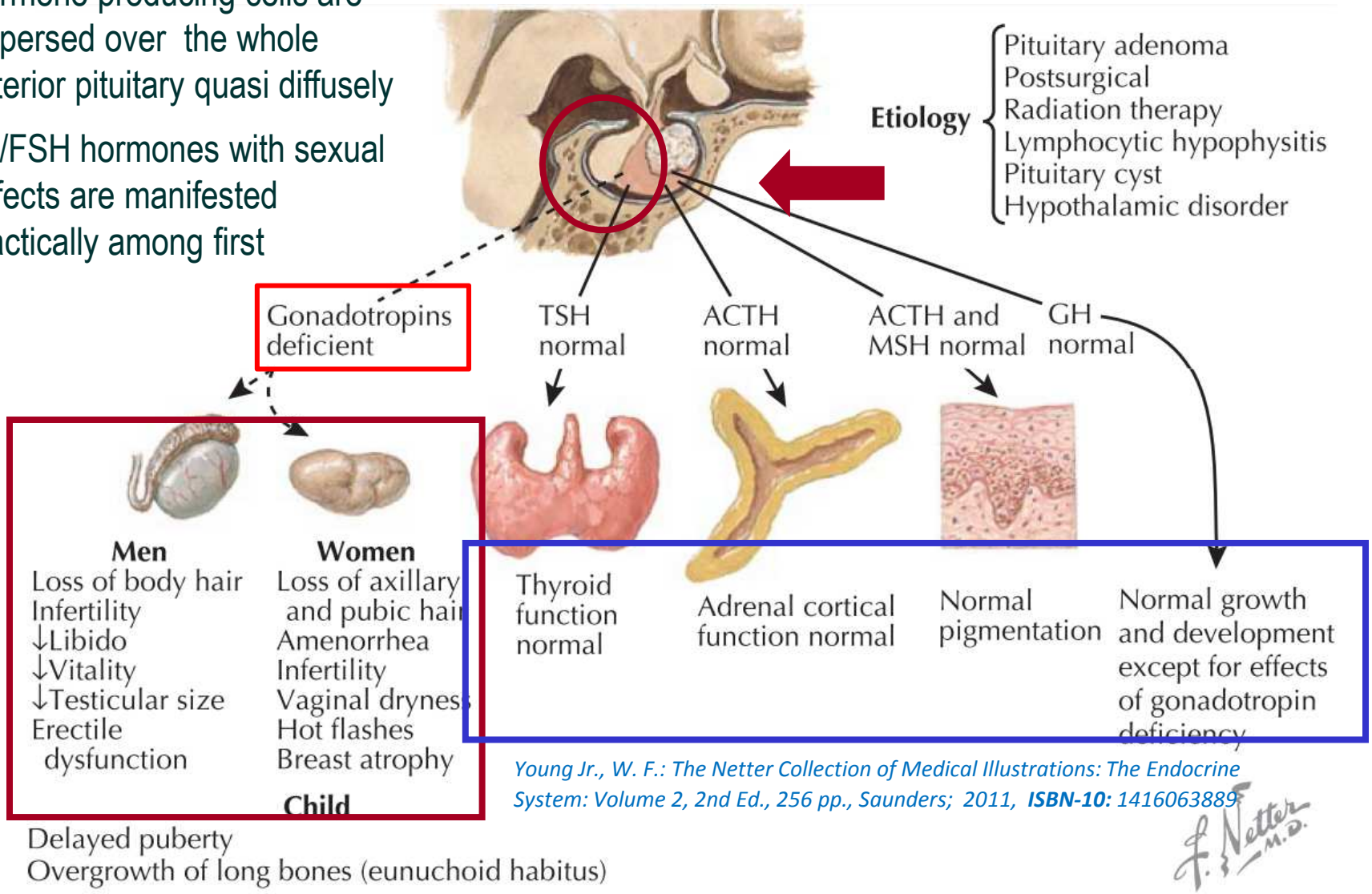
Hypopituitarism – Causes

- ~ 60% tumors of the pituitary gland, ~ 10% other lesions in pituitary, 20% due to other causes; 11% no identified cause
- **Tumors:** pituitary adenomas (the most common case); rarely other tumors (craniopharyn-gioma, meningioma, chordoma, ependymoma, glioma), metastasis
- **Iatrogenic:** radiation damage; neurosurgical procedures,
- **Inflammations, infiltrations:** a) bacterial/viral brain infections (abscess, encephalitis, meningitis,) b) or the gland (autoimmune or lymphocytic hypophysitis);
- **Infiltrations:** a) abnormal cell infiltration (neurosarcoidosis, Langerhans' cell histiocytosis); b) hemochromatosis (iron deposition)
- **Empty sella syndrome** (unexplained disappearance of pituitary tissue)
- **Vascular**: hemorrhage; infarction (loss of blood supply) of the pituitary.
- **Genetic abnormalities** - isolated deficiencies (GH, PRL) or combined anterior and posterior pituitary hormone deficiencies.

- In the most of cases: **3 or more hormones** are deficient; the most common is FSH and LH insufficiency leading to sex hormone abnormalities; **Growth hormone deficiency** is more common in people with an underlying tumor than those with other causes.

Mild anterior pituitary deficiency

- Hormone producing cells are dispersed over the whole anterior pituitary quasi diffusely
- LH/FSH hormones with sexual defects are manifested practically among first



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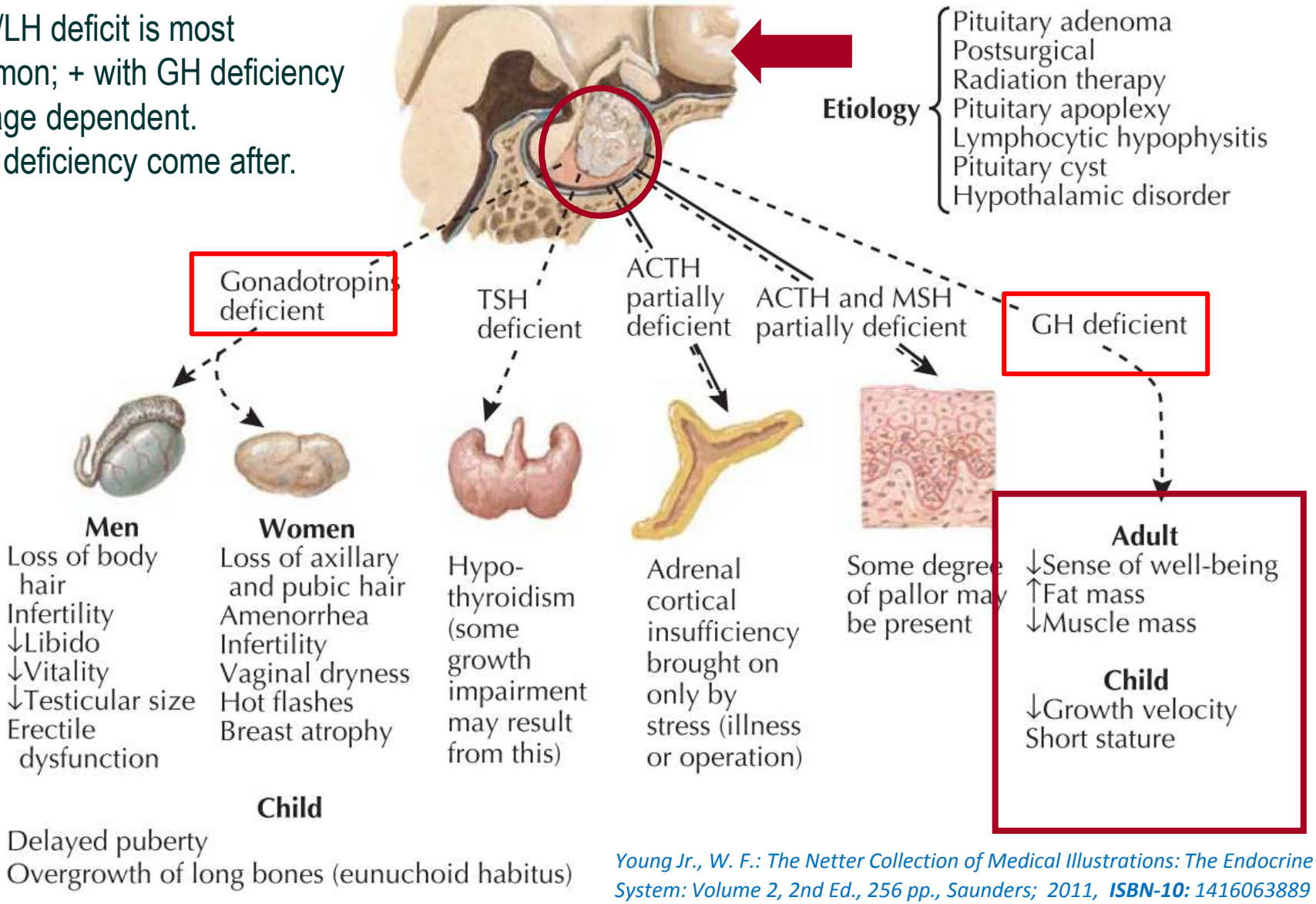
Moderate anterior pituitary deficiency

- FSH/LH deficit is most common; + with GH deficiency are age dependent.
- TSH deficiency come after.



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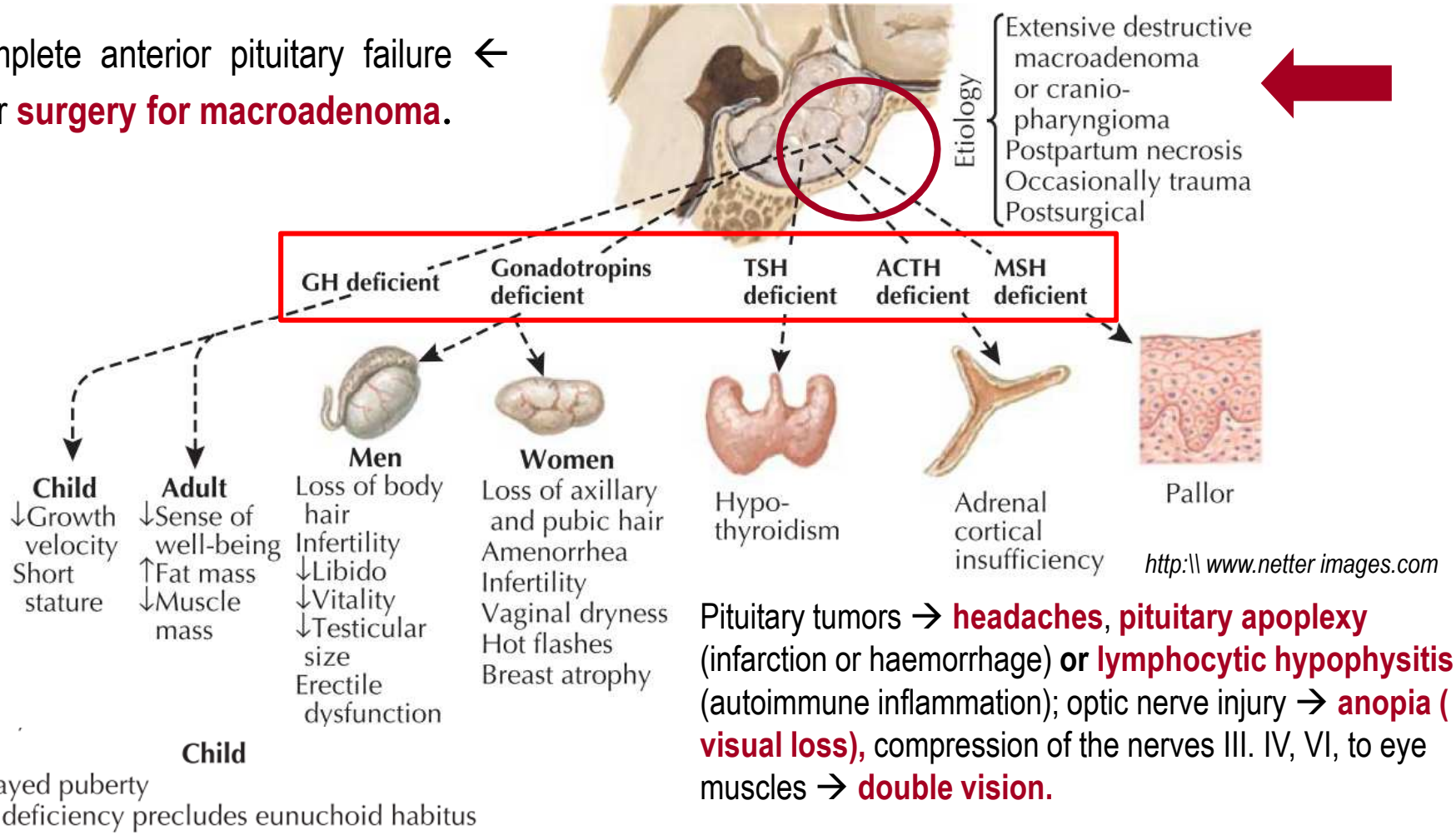
Severe anterior pituitary deficiency

Progressive destruction (>75%), mild hypogonadism becomes more severe, general symptoms of thyroid and adrenal cortical hypofunction, progress.

Complete anterior pituitary failure ← after **surgery for macroadenoma**.



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Pituitary tumors → **headaches**, **pituitary apoplexy** (infarction or haemorrhage) **or** **lymphocytic hypophysitis** (autoimmune inflammation); optic nerve injury → **anopia (visual loss),** compression of the nerves III. IV, VI, to eye muscles → **double vision.**

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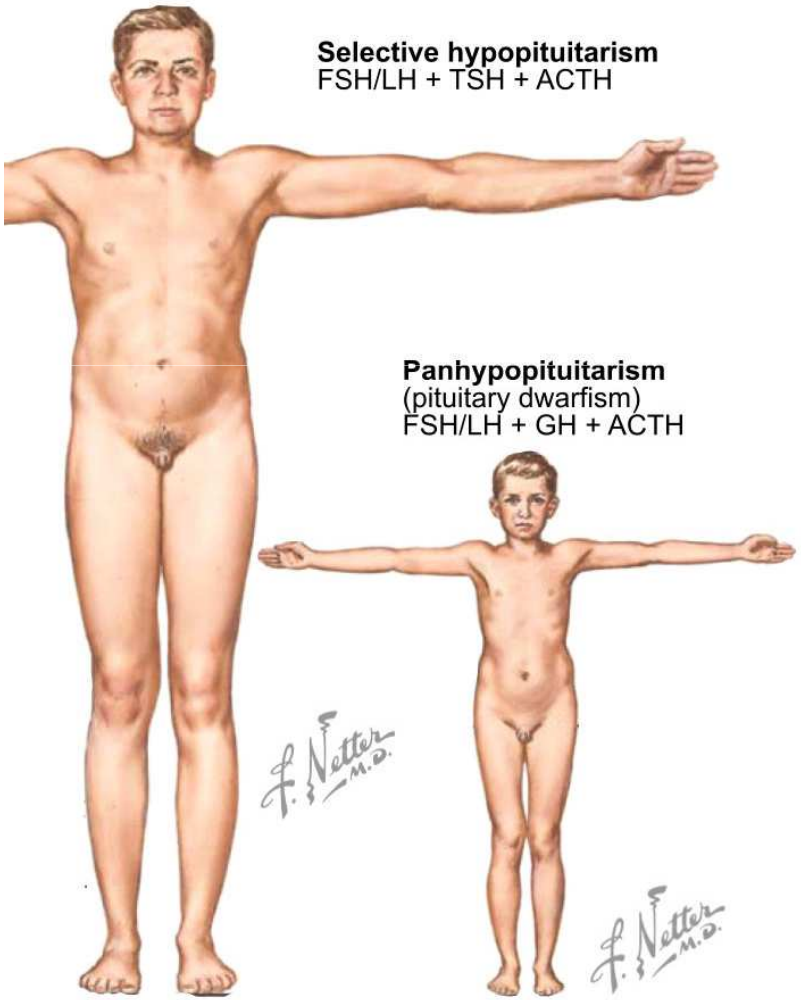
A. Prepubertal hypopituitarism - Clinics

- **Partial hypopituitarism** – LH/FSH deficient; growth normal;
- **Panhypopituitarism** – visible growth deficit; dwarfism ; congltive functions are preserved

- **GH:** delayed & slow outgrowth, delayed closure of epiphyses growing up to 40y (retardation); lack of muscle mass; central obesity,.; attention, memory dis.
- **FSH/LH:** Men: lack of hairness (scrotal, trunck), high voice; small genitals, penis,; Females: oligo-/ ameno-rrhea (menstruation); infertility, osteoporosis (bone fragi-lity), delayed puberty
- **ACTH:** low performance, pale skin (ACTH + MSH); failure to thrive, hypoglycemia, anemia, hyponatremia.
- **TSH:** tiredness, intolerance to cold, constipation, weight gain, hair loss, slowed thinking, slowed heart rate, low blood pressure (congenital, childhood); extreme inborn forms → **cretinism (mental retardation)**



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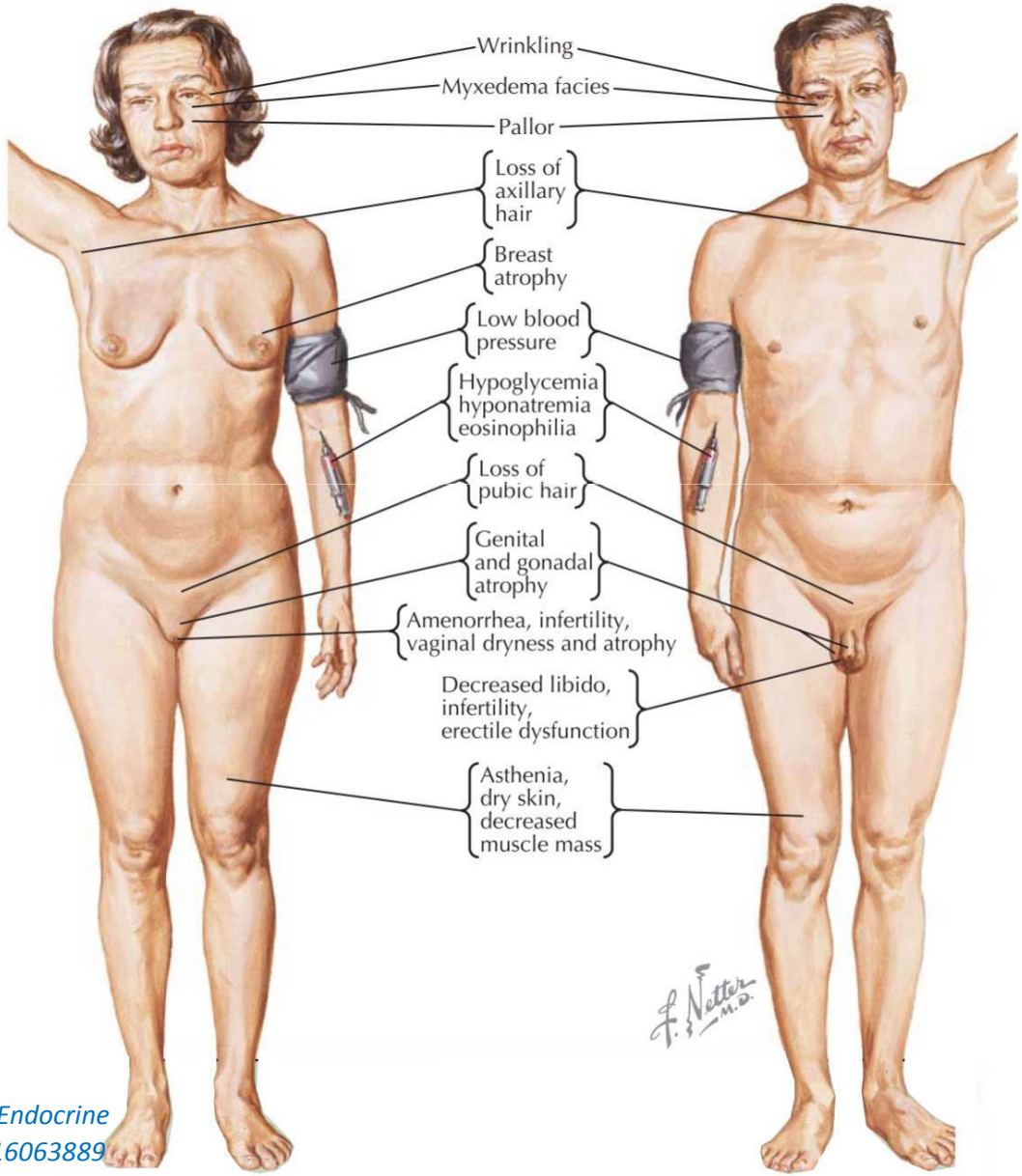
B. Panhypopituitarism (postpubertal) adult - Clinics

Simmonds disease

chronic deficit (LH/FSH + GH+PRL+ ACTH)

- **TSH:** myxedematous face, pergamon-like dry pallor - yellowish skin; wrinkles on face cold intolerance, bradycardia, hypotension drowsiness
- **ACTH**: Hypotension, tirednes, fatigue, loss of appetite; hypoglycemia, hyponatremia,
- **LH/FSH:** Female: breast atrophy, wrinkles around eyes & mouth; amenorhea, Man: erectile dysfunction, loss of pubic hair; Both: gonadal atrophy, decreased libido, infertility.
- **GH** + testosterone, estogens: muscle atrophy, osteoporosis



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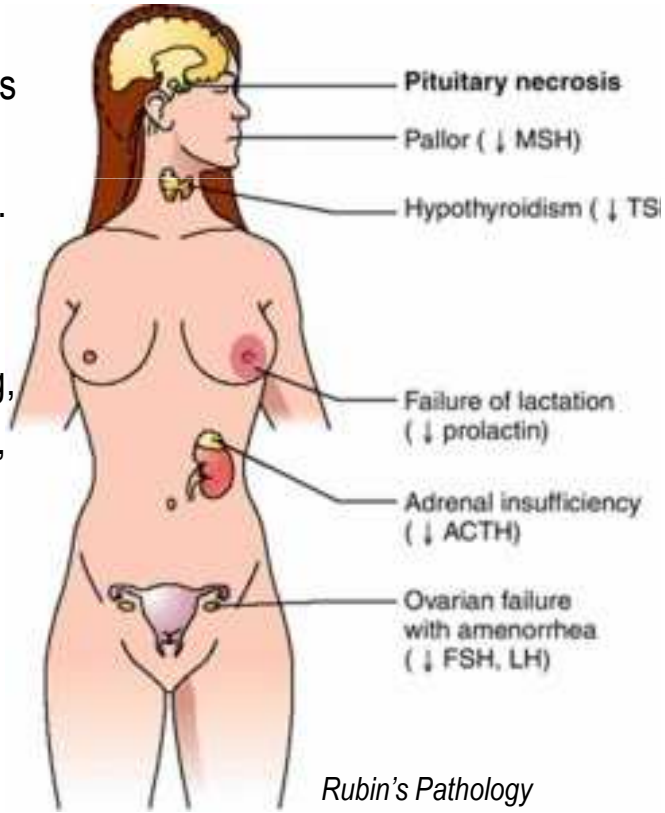
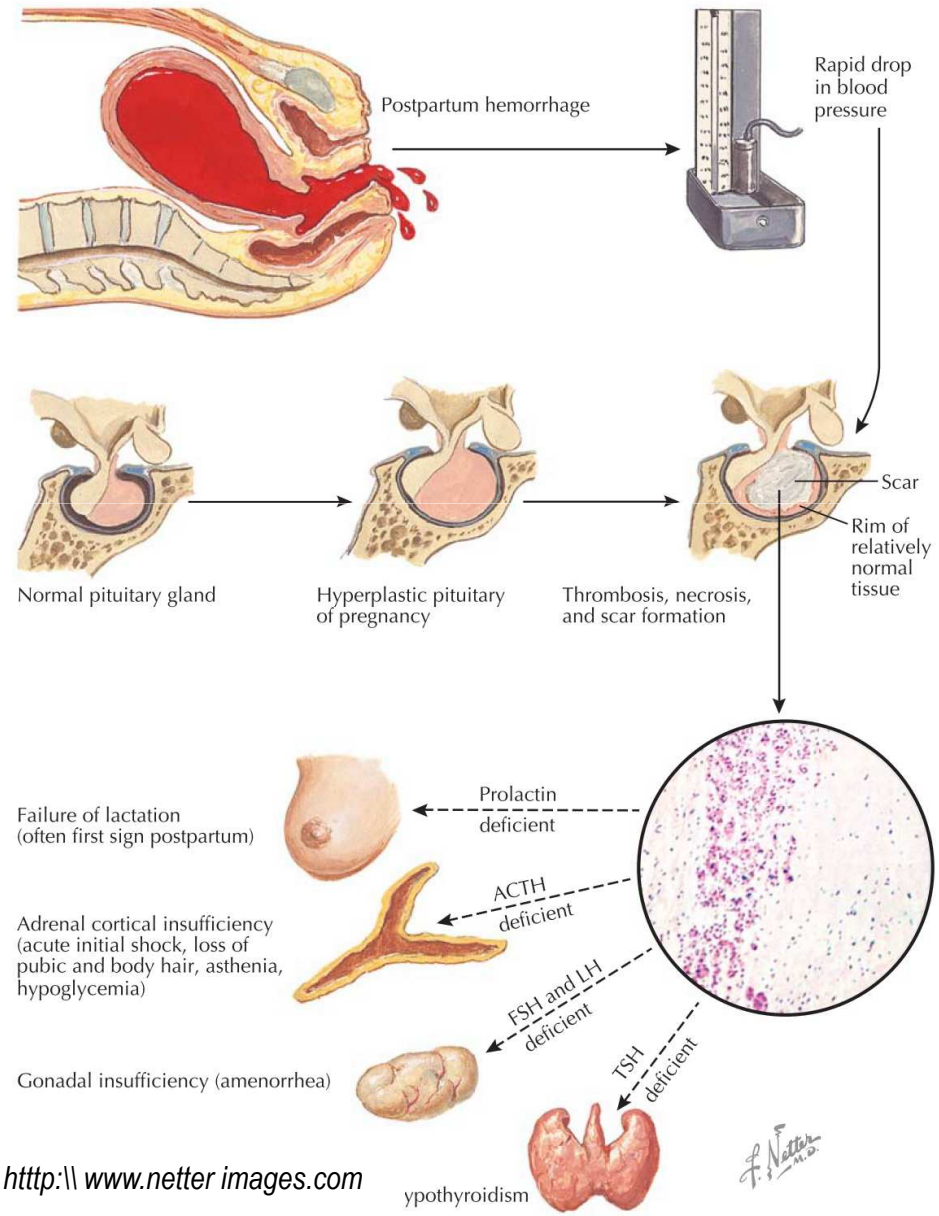
C. Acute hypopituitarism (Sheehan sy.)

- Late in pregnancy well perfused pituitary is swollen and vulnerable to blood pressure.
- Pressure during the labor (?) → blood cummulation in head → pituitary hemorrhage
- Postpartum bleeding → pituitary infarction (ischemia)

Lactation stops first; other functions later. ACTH/cortisol lack → weak stress copying, hypoglycemia, asthenia, tendency to **collapse, shock, vomiting**



Rubin's Pathology



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Pituitary crisis

- Def.: Acute worsening of clinical picture upon various kinds of stress in persons with hypopituitarism
- Triggering events: infection incl. sepsis; diarrhea, vomiting, dehydration, lack of food, hypoglycemia cold, acute myocardial infarction, cerebrovascular accident, surgery, trauma, anesthesia, use of sedatives, sleeping pills,
- Sy: A. Digestive sy.: nausea, vomiting; B. Circulatory sy.: high fever, circulatory failure, shock; C. Neuropsychiatric sy.: headache, confusion, convulsions, convulsions, coma

Examples of mutations related to the embryogenesis of pituitary gland

Advanced topic

- **Gene Pit-1 (**POU1F1 gene, 3p11) : POU homeodomain TF important for the development of somatotrophs, lactotrophs, and thyrotrophs → **combined pituitary hormone deficiency (CPHD) + absence of GH, prolactin (PRL), and TSH.**
- **Gene PROP1** (5q): pituitary specific **paired-like homeo-domain transcription factor** -> inactivate LH, FSH, GH, PRL, and TSH.
- **Gene HESX1** (3p21): member of the paired-like class of homeobox genes important for development of the optic nerve and the pituitary. Mutations of HESX1 → septo-optic dysplasia, a rare congenital anomaly (forebrain, optic nerve hypoplasia, hypopituitarism). Endocrinopathies are characterized by **growth hormone deficiency followed by TSH and ACTH deficiency.**
- **Gene PITX2:** expressed in the fetal and adult pituitary → Rieger syndrome, an AD condition with variable phenotypic expression including pituitary abnormalities.
- **Genes LX3/LX4:** belong to the LIM family of homeo-box genes that are expressed early in Rathke's pouch.
  - LHX3 mutations → **GH, TSH, LH, FSH, and PRL deficiencies**.
  - LX4 gene mutations → **GH, TSH, and ACTH deficiency**

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Advanced topic

Selective central hormonal defects

Isolated gonadotropin (GnRH) deficiency (Kallmann sy.)

- 1944 by Franz Josef Kallmann (German-American genetist)
- Occ: 3-5 x more common in males than females (1:8,000); most cases are sporadic, familial forms have been described (X-linked; AD or AR).
- Etio: X-linked (mutations of the KAL1 (Xp23.3) (extracellular matrix component with putative antiprotease activity and cell adhesion function). neurons destined to secrete GnRH fail to migrate from their origin in the olfactory anlage to their normal location in the hypothalamus.
  - AD – linked KAL2 - gene encoding the fibroblast growth factor receptor 1 (8p11).
  - AR- trasmitted KAL3 (not yet identified)
- Clin: **hypogonadotropic hypogonadism** (HH) in either sex (due to GnRH deficiency) may resemble **dalayed puperty** - failure to strat or complete puberty, lack of testicles, micropenis (5-10%), Cryptorchidism (undescended testicles) at birth, Infertility
- + non-reproductive features; **anosmia (**absent sense of smell); **50% of HH cases**
  - Cleft, lips / palate and other anomalies (may also be present)
  - Diagnosed at puberty ← delay in secondary sex characteristics

Clinical Manifestations of Pituitary Tumors Secondary to Mass

- Headache
- Chiasmal syndrome
- Hypothalamic syndrome
- Disturbances of thirst, appetite, satiety, sleep, and temperature
- Diabetes insipidus
- Syndrome of inappropriate ADH secretion (SIADH)
- Obstructive hydrocephalus
- Cranial nerves III, IV, V_1, V_2, and VI dysfunction
- Frontal and temporal lobe syndromes
- Cerebrospinal fluid rhinorrhea

Prevalence of Pituitary Adenoma

Adenoma Type	Prevalence (%)
GH cell adenoma	15
PRL cell adenoma	30
GH and PRL cell adenoma	7
ACTH cell adenoma	10
Gonadotroph cell adenoma	10
Nonfunctioning adenoma	25
TSH cell adenoma	1
Unclassified adenoma	2

ACTH=Adrenocorticotropic hormone; GH=Growth hormone; PRL=Prolactin; TSH=Thyroid-stimulating hormone

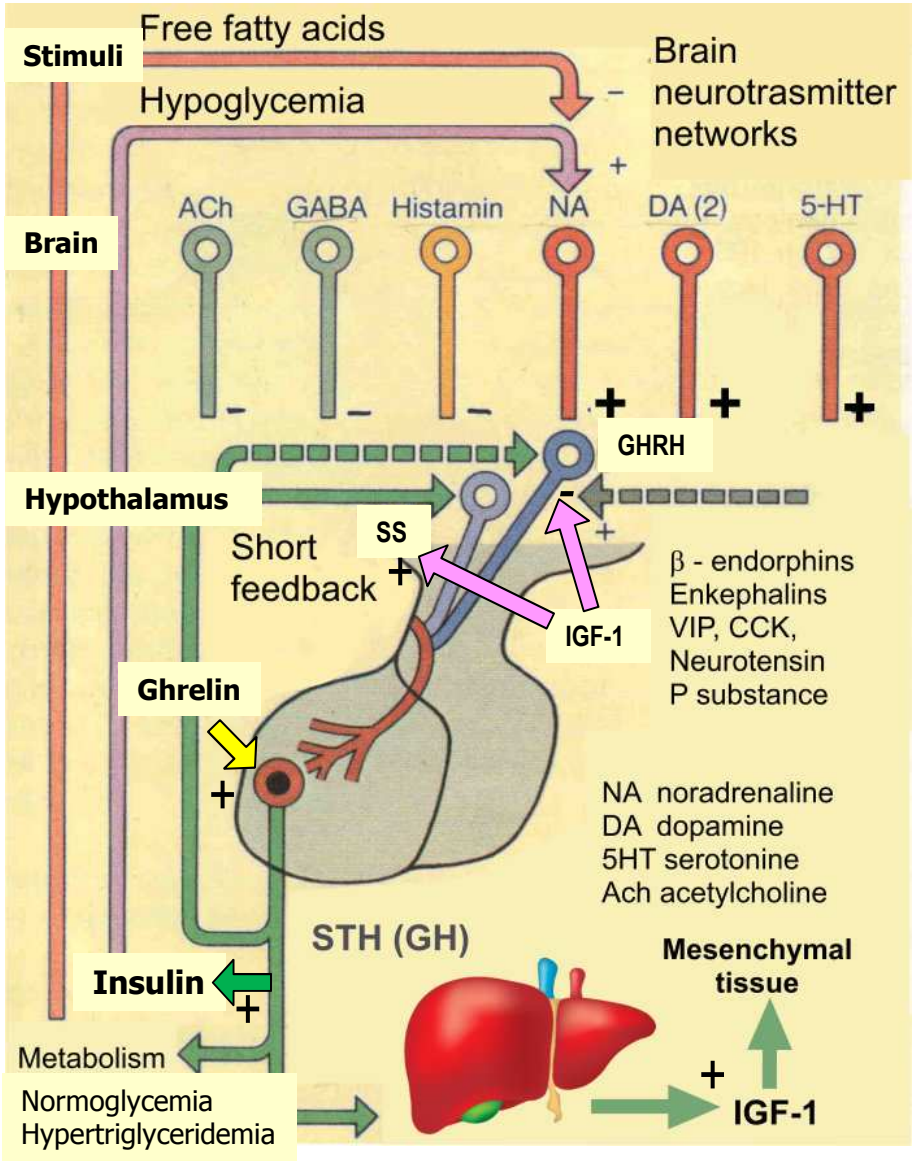
Anterior pituitary hormones
Growth hormone

- Physiological overview
- Overactivity prepubertal – Giantism
- Overactivity postpubertal – Acromegaly
- Underproduction - Dwarfism

GH function and regulation

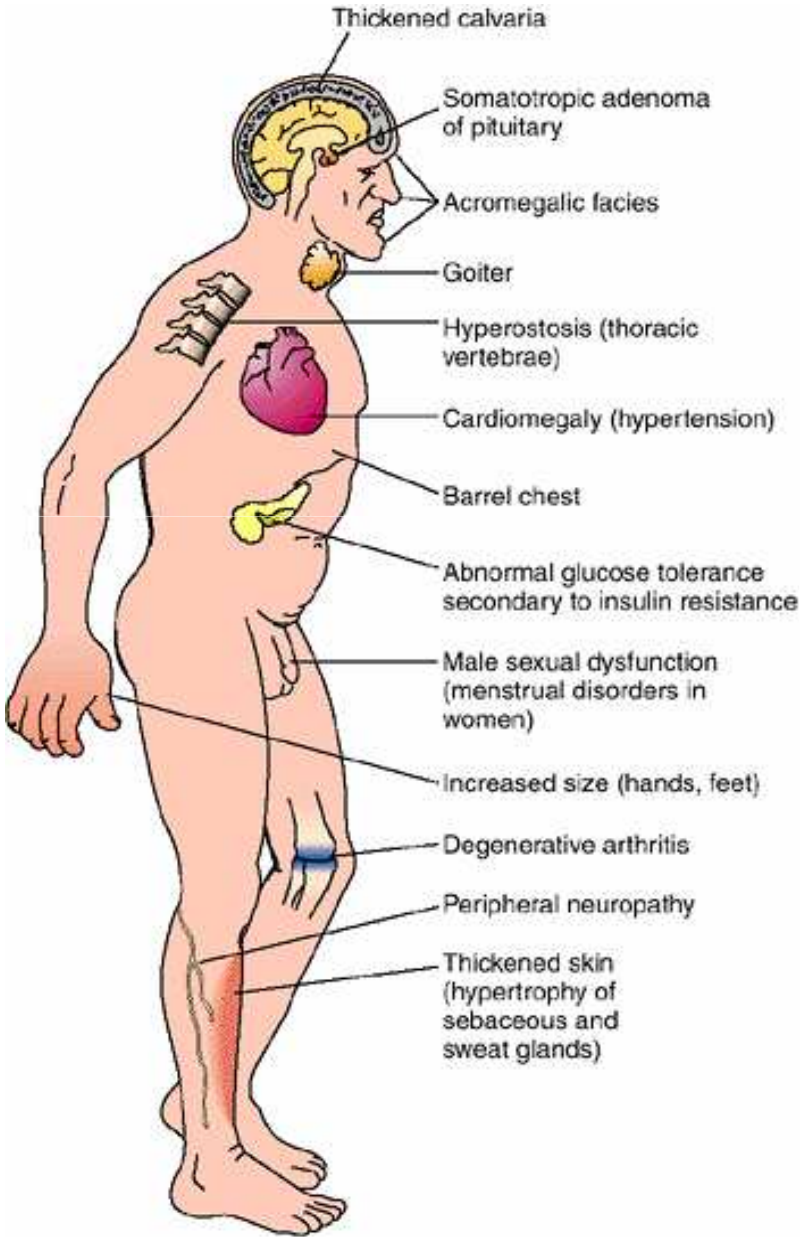
Physiological role:

- Direct effects : GH → GH-R (receptor from cytokine superfamily IL-2, 4 - like) in adipocytes),
  - Fat catabolism: a) blockade of lipid, TAG uptake; b) TAG hydrolysis → ↑ glucose uptake from blood to cells → hyperglycemia)
  - Electrolyte changes:e.g. ↓Na+, ↓K+, ↓PO_4^- (plasma; ↓Cl^- renal excretion
- Indirect effects: GH → (+) synthesis of IGF-1 in the liver → growth effects, proliferation of mesenchymal cells
- Combined GH+IGF1:
  - Protein anabolism (incl. AA uptake from plasma to cells; mRNA and protein synthesis)
  - Carbohydrate: normoglycemic effector (GH → (-) Ins – uptake of glucose + glycogen synth. in fat, liver, muscles; feedback GH → (+) Ins secretion (hyperinsulinemia).



Acromegaly - Clinics

- **Trophic & vegetative changes**
  - **Acral enlargement** - coarsening of facial features, calvaria, hands, feet, macroglossia
  - Sensory and motor peripheral **neuropathy**
  - **Arthralgias (75%),** neuropathic joints, Carpal tunnel syndrome, muscular atrophy, neuropathic joints
  - **Thick and course skin**, skin tags, malocclusion and tooth gaps
  - **Hypertrophy of glands** - excessive sweating
- **Cardiovascular**
  - Cardiomegaly, hypertension, congestive heart failure
- **Endocrine**
  - Impaired glucose tolerance → Diabetes mellitus
  - Pituitary mass effect including headache and visual field defects Pituitary insufficiency (partial or complete)
  - Sy. of hyperprolactinemia
- **Other:** Snoring, sleep apnea

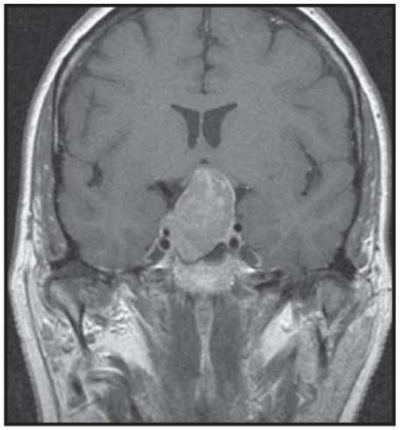


Stryer, D.S., Rubin, E: Rubin's Pathology; Cliniciphysiological foundation of medicine. Lippincot, LWW, 1616 pp.

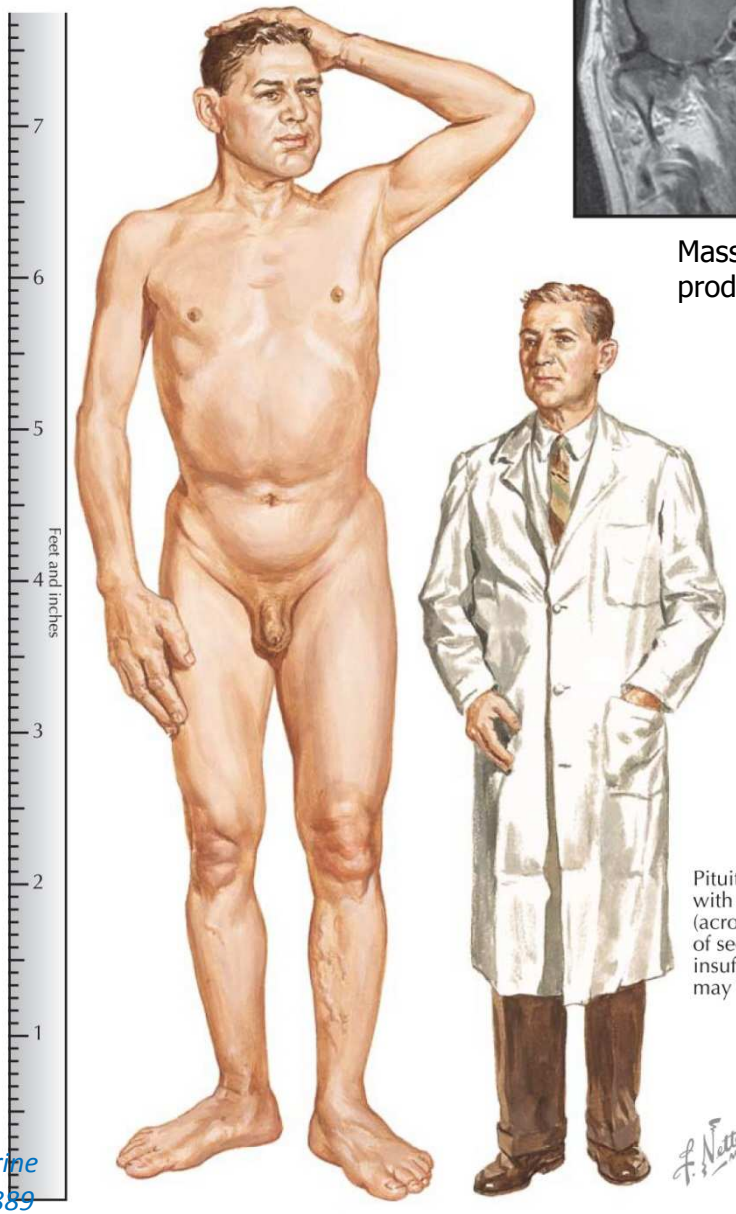
Giantism - Clinics

- Etio: a) eosinophilic adenoma, b) autononic hypersecretion of somatomedins, (prior to epiphyseal closure).
- Pediatric gigantism (< 5 years) - duplications of genes in locus **Xq26**; gene **GPR101** (1,000 x stronger activity in gigantism)
- Sy:
  - **Giant body** – growth of bones continuous
  - **Hypertension**
  - **Skin changes**, incl. thickening, oiliness, acne; hirsutism in woman,
  - Coarsening of facial features, (forehead, nose, lips, jaw);
- Characteristics are more similar to those seen in **acromegaly** closer to the adolescen-ce.

MRI (coronal view) shows a large GH-secreting pituitary tumor in a 16-year-old adolescent boy with gigantism.



Massive adenoma producing GH



Pituitary giant contrasted with average-size man (acromegaly and signs of secondary pituitary insufficiency may or may not be present)

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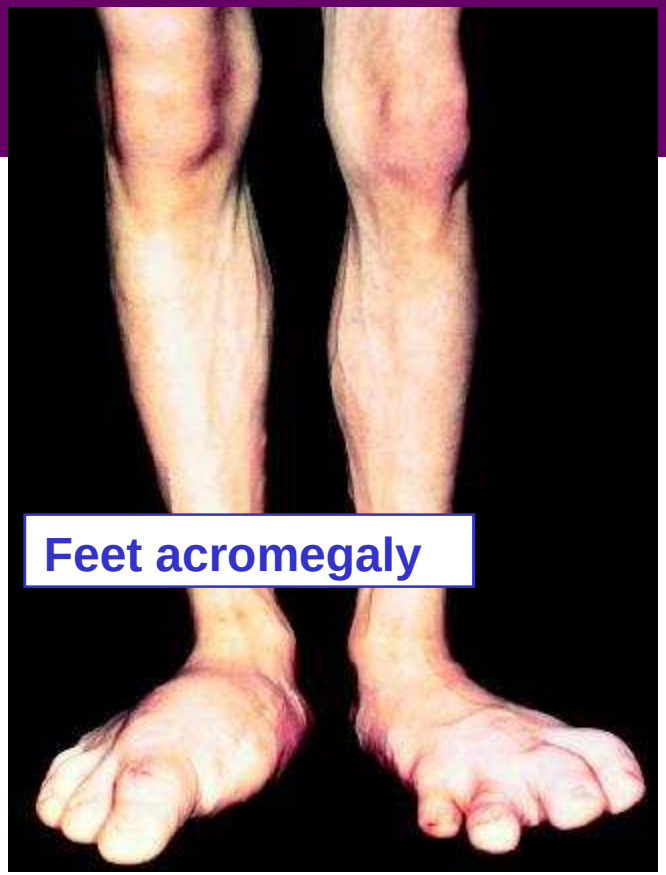
Pathophysiology of growth hormone

R.W., tallest person in history (2.720 m; 199 kg), with his father (1918 – 1940) died at age 22.
http://www.anatomybox.com/gigantism

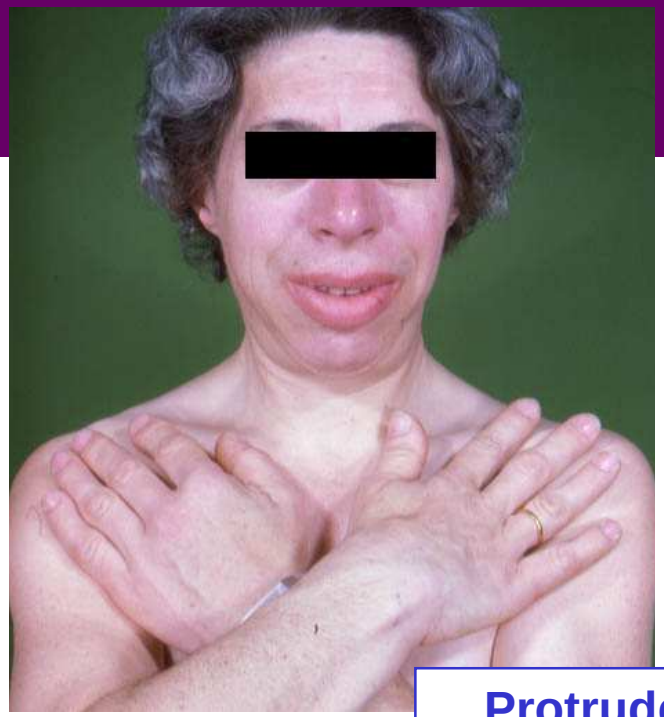
http://jcem.endojournals.org/content/vol84/issue12/images/large/eg1296222001.jpeg

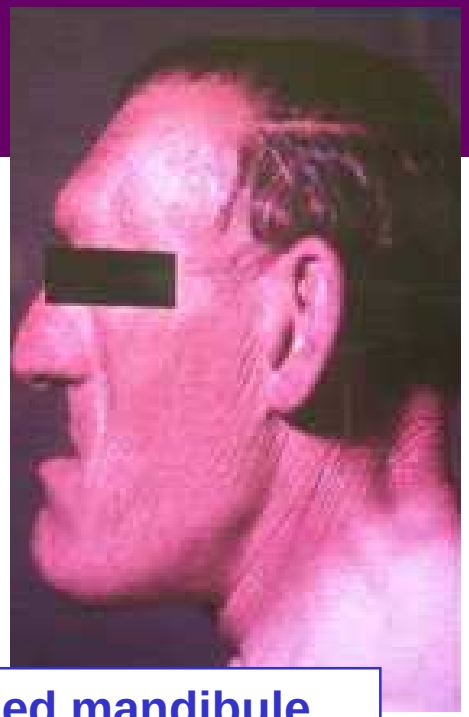
Symptoms by frequency

- Arthralgia (75%)
- Amenorrhea in women (72%)
- Hyperhidrosis (64%)
- Sleep apnea (60%)
- Headaches (55%)
- Paresthesia or carpal tunnel syndrome (40%)
- Loss of libido or impotence (36%)
- Hypertension (28%)
- Goiter (21%)
- Visual field defects (19%)



Feet acromegaly





Protruded mandibule

Macroglossia

Sausage –shaped fingers

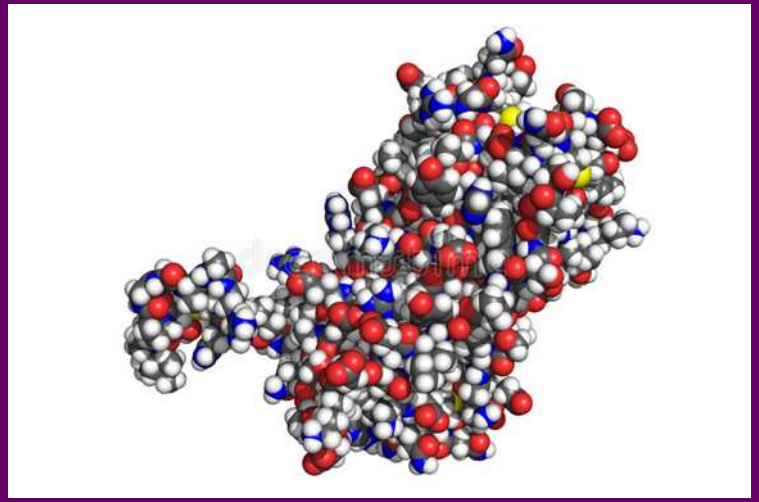
Growth hormone deficiency

- **Isolated growth hormone deficiency (IGHD)**
  - Etio: AR, AD or X-linked recessive. types of familial and sporadic disorders.
  - Mutations (deletions, substitutions, splice site mutations) in genes for human growth hormone (GH) or the growth hormone-releasing hormone (GHRH) receptor.

- **Laron syndrome (LS)**
  - Clin.: heterogeneous gr. of dwarfing disorders unique to each particular family; obesity + high GH + low insulin-like growth factor-I (IGF-I); fertility, inteligency, other hormonal effects are normal
  - LS community shows lower than average cancer occ. (?)
  - Occ: Mediterranean origin (esp. Sephardic Jews); America, African pygmies.
  - Etio: 30 GH-receptor mutations

Endocrinologists Jaime Guevara-Aguirre and Arlan Rosenbloom with a population of Ecuadorians dwarves immune to cancer.

Ecuadorian man with Laron syndrome; Family



Anterior pituitary hormones
Prolactine

- Physiological overview
- Prolactine deficiency
- Prolactin overactivity

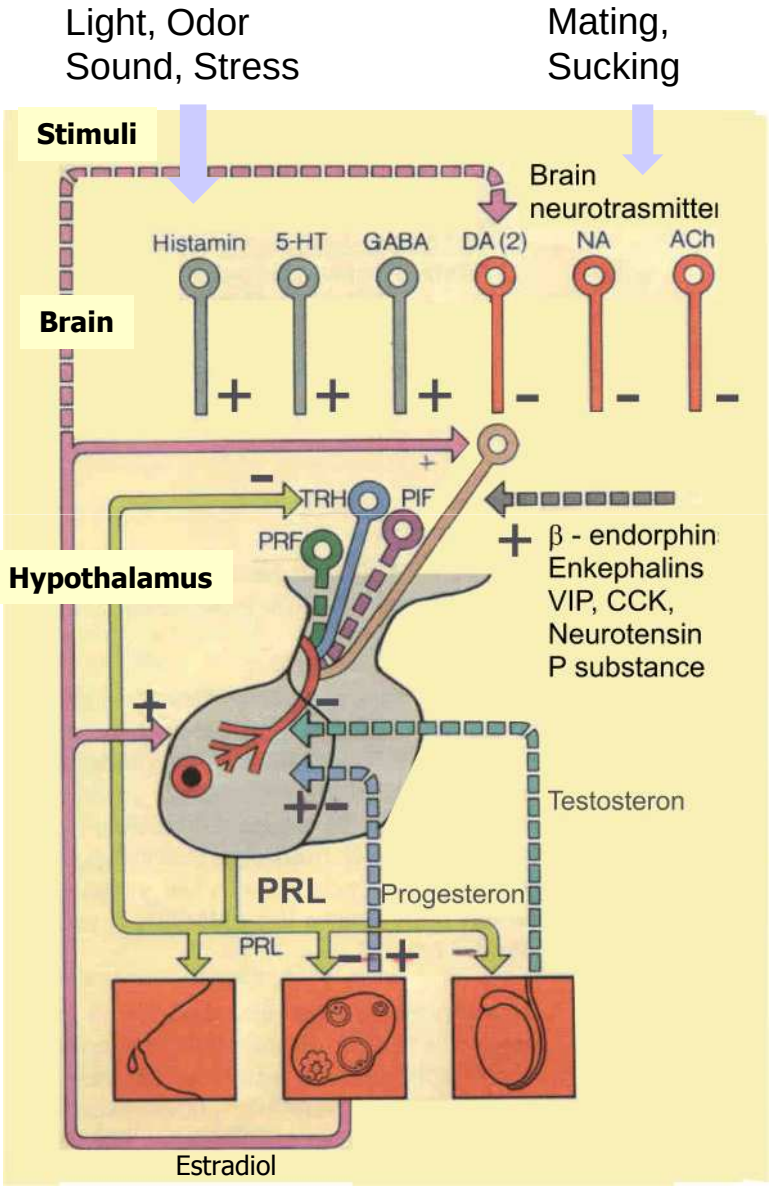
Prolactin (PRL)

- Prolactin (PRL) ← Stricher and Giveter (1928); 23 kDa polypeptide; Blood: < 20-25 ng/ml;, PRL - receptor is of cytokine type
- Secreted by mammotrophic cells in anterior pituitary.
- Ectopic: endometrium, myometrium, brain, mammary gland, lymphocytes, spleen, thymus,
- Inhibitors: PIF; Dopamine (DA) via cAMP and it is possible that there is a special gene regulation for each site production.
- Stimulants: PRF, TRH, VIP (vasointestinal peptide)
- In breastfeeding: suckling of the nipples - blocks DA

Physiological role:

Women

- Maintenance of corpus luteum after conception (luteotropin, mammotropin)
- Stimulation/ maintenance of lactation – suckling → mechanoreceptors
- Milk production – PRL stimulate milk protein genes (casein), (+) AA uptake, glucose, galactose, phospholipids, spermidine



Prolactin (PRL)

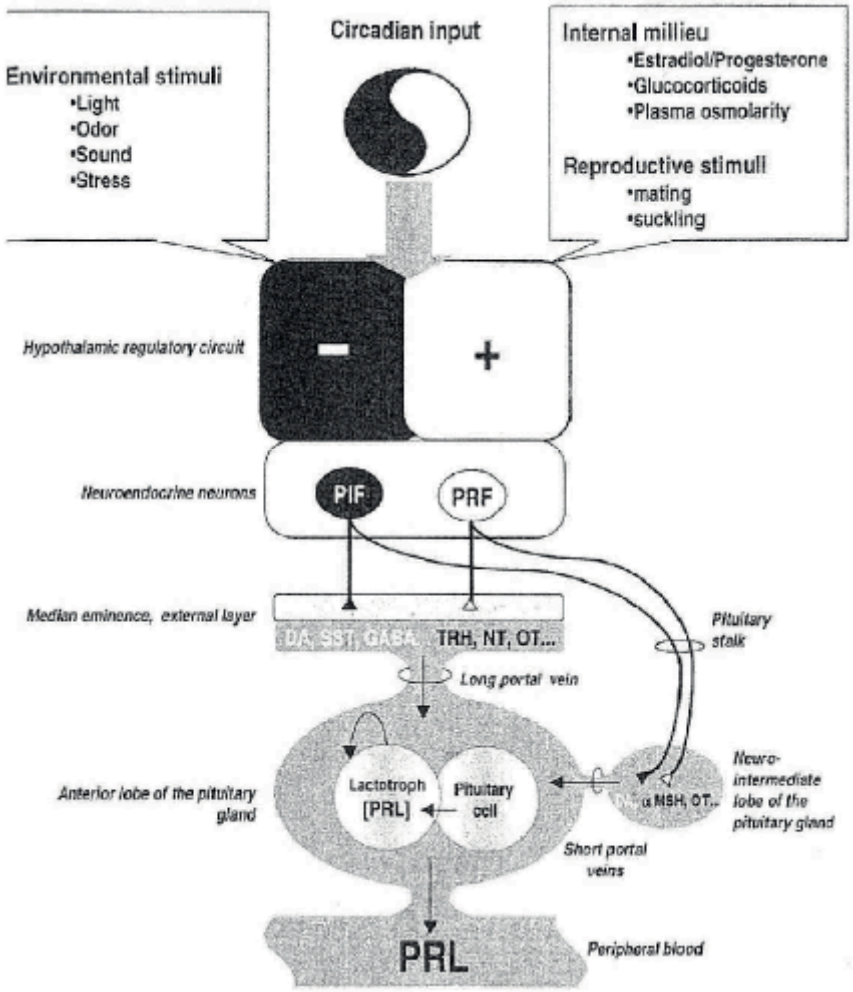
- Hyperprolactinemia → bone loss }export Ca2+ to breast milk
- Ovarian progesteron secretion
- Mucification of vagina, Maternal drive

Men - prostate.

- Testes - proliferation of male seminal vesicles - there is negative correlation between sperm, men's fertility and prolactin levels
- Prostate - protective factor for the prostate epithelium; sexual dimorphism
- Paternal care (?) fish, birds; mammals

Either sex:

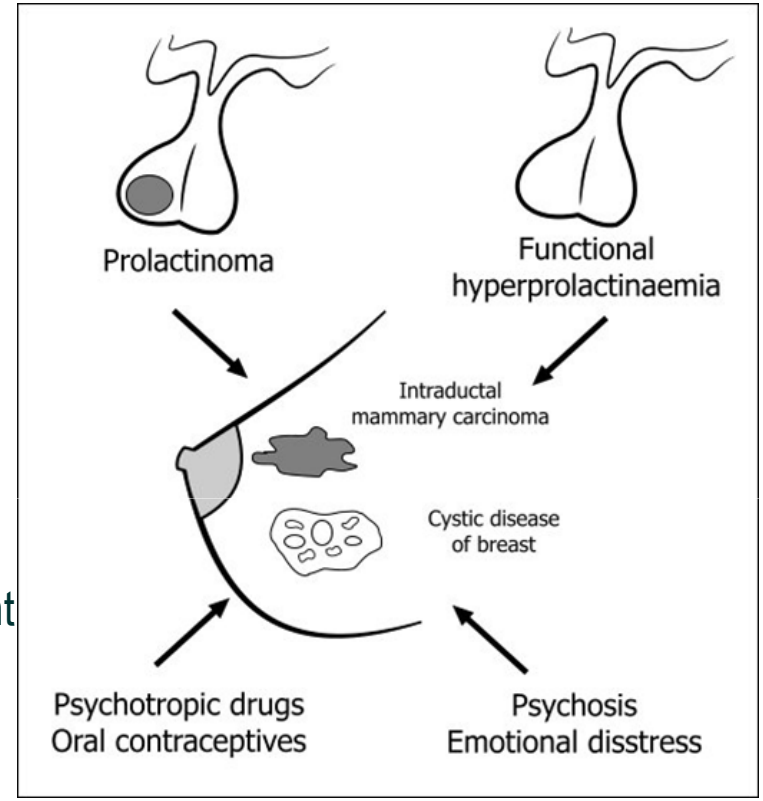
- Immune system, osmotic balance, angiogenesis, hormonal mediator of nervous, endocrine and immune systems.
- Transport of liquid and electrolytes in intestinal mucosa
- Vascular growth inhibitor - endothel has high-affinity receptor for prolactin 16-kDa.



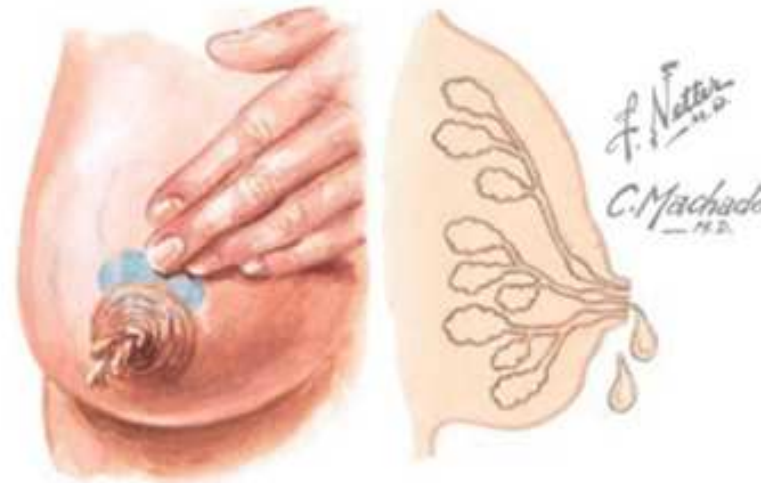
Regulatiory factors of prolactin release

Prolactin excess (Hyperprolactinemia)

- Etio: adenoma, ectorpic overproduction, drugs, psychogenic
- Sy:
- Both sex: infertility, decreased sex drive, libido, osteopenia (bone loss, trabecular bones) - restoration of gonadal function halts bone loss and increases bone mineralisation`
  - Mass effect (tumor – prolactinoma) → headaches, visual field defects;
- Women: **Galactorea –amenorhea sy.**
  - **Dysmenorhea** – oligomenorrhea, amenorrhea (no periods or irregular periods)
  - **Galactorrhea** - production of breast milk when not pregnant or nursing
  - Other: vaginal dryness (pain during an intercourse)
- Men:
  - **Erectile dysfunction** - trouble getting or keeping an erection
  - **Gynecomastia** - breast enlargement, rarely galactorrhea
  - **Decreased muscle mass and body hair** ← reduced testosterone by PRL

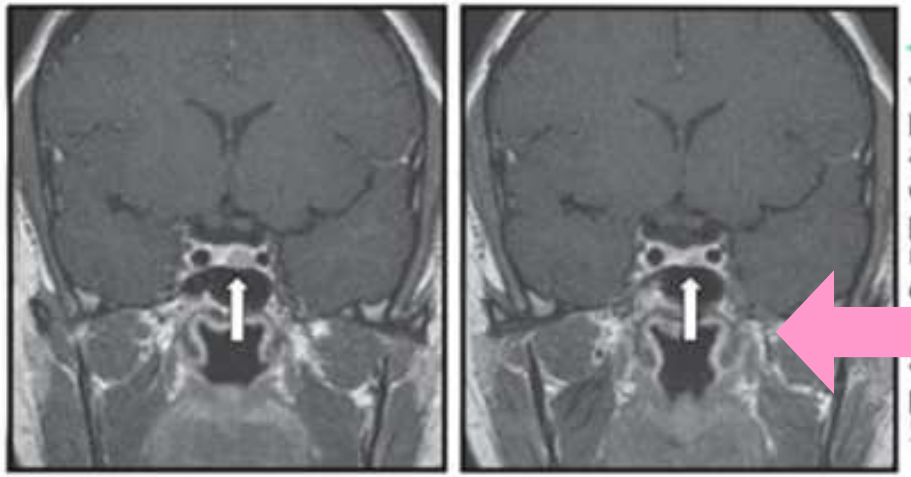


Hyperprolactinemia



▲ In premenopausal women, hyperprolactinemia causes bilateral spontaneous galactorrhea

Mass- effects of overgrowing prolactinoma
Scotoma, Anopia (defects in visual field) due to damage of n.II (chiasma opticum); Headache, Diplopia (double vision), Ptosis (drop of eyelid) Opthalmoplegias (palsy of oculomotor muscles) n.III, n.IV, n.VI



Serial MRI (coronal sections) in patient with 9 mm prolactin- secreting microadenoma (left). After tumor size decreased by 50% (right)

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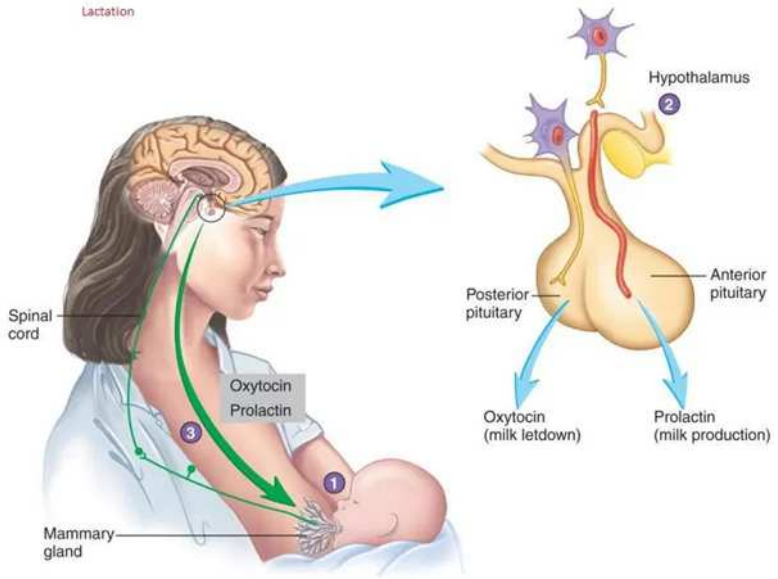
Prolactin deficiency

- **Production (Pre-receptor) deficiency** → hypoprolactinaemia
- **Post-receptor deficiency**: reduction of PRL receptors in testes to 20% in sterile men
- In men: a) infertility, b) erectile dysfunction, c) hypofunction of the seminal vesicles, oligospermia, asthenospermia.
- 1 or 2 years after the bariatric surgery levels of the hormone prolactin reduced.
- Decreased paternal care (?) Men parents have higher PRL than men who aren't parents. } increased prolactin 2 weeks before the birth)
- waning of immunity (cellular and lymphatic), after suppression of prolactin secretion by bromocriptine or in hypophysectomized animals

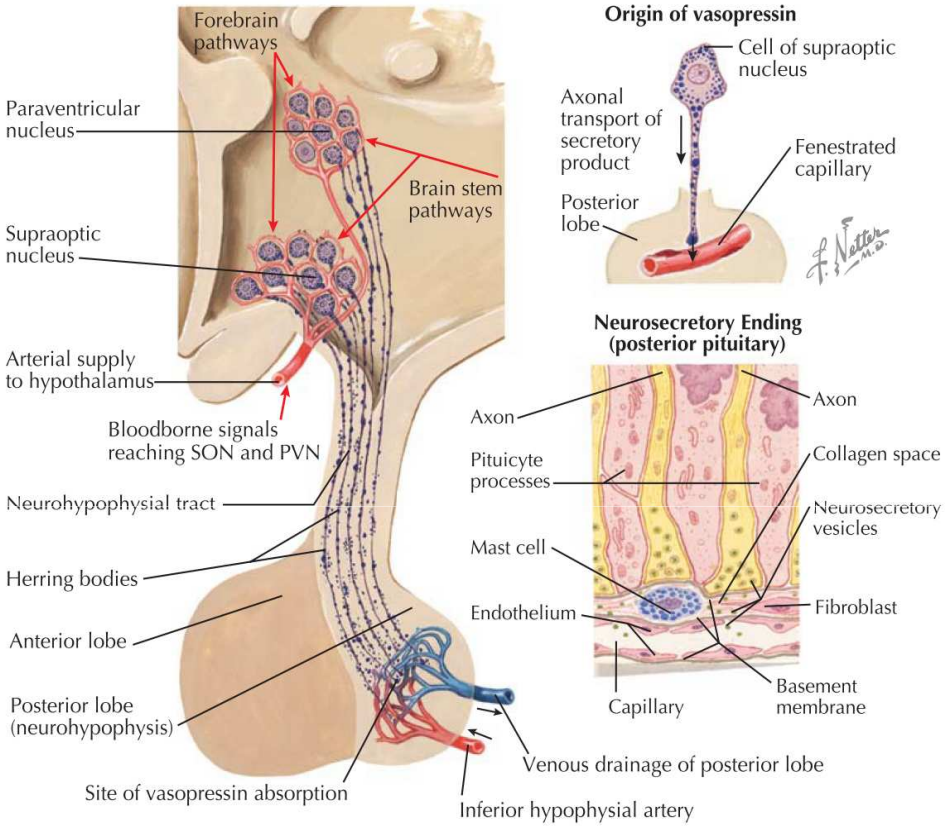


Disorders of neurohypophyseal hormones

Vasopressin (Antidiuretic hormone)

- Vasopressin (antidiuretic hormone (ADH), arginine vasopressin (AVP), argipressin) = synthesized as provasopressin
- **Production:** nucl. supraopticus → axonal transport to neurohypophysis; quanta released based on local hyperosmolality; half-time in blood 16–24 minutes
- **Stimulation:** volumoreceptors/osmoreceptors (hypothalamus, liver ??)

- **Effects:** receptors V1 and V2 (cAMP- depend.)
- a) Kidney: reabsorption of solute-free water in collecting ducts→ **hyperosmolar oliguria + hypoosmolar hypervolemia** ;
- b) Body: constriction of small muscular arteries and arterioles → vascular resistance and raises arterial blood pressure.
- c) Brain: social & sexual behavior, pair bond formation, maternal care (rodents)



Vasopressin → V2 receptor → cAMP- dep. expression of aquaporin-2 (AQP2) → building water channels in outer and inner medullary collecting duct (OMCD & IMCD) in the kidney → water absorption down the osmotic gradient from the tubules to blood

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Vasopresin deficiency – Diabetes insipidus

- **Causes:** 30% (1/3) undiscovered (idiopatic)
  - ***Neurogenic form (central, hypothalamic DI)*** the most common causes
  - Primary – genetic: DIDMOAD (Wolframov sy.), AD, AR
  - Organic destruction of neurohypophysis (trauma of skull base + tumor (32%), meningitis, aneurysms, trombosis, hypophysectomy (20%)
  - ***Nefrogenic form*** – damage of renal tubuli (pyelonephritis, amyloidosis, polycystic kidney, interstitial nephritis)
  - genetic disorders poruchy caused by mutation of genes for **aquaeporins** –(proteins of water channels)
  - ***Psychogenic form*** *(dipsogenic DI, DDI)* – secondary decrrease of ADH: compulsive water drinking (*primary hyperdipsia*); often combination DDI + affective disorders; in 20% of schisophrenias

Hypovasopresinism (Diabetes insipidus) - Clinics

Sy:

- **Polyuria –** mostly 4-8 l/d, even 20 l/d); night awakeings + urination **(nycturia)** → **dehydration** → thirst → drinking more water (polydipsia) **(polydipsia)**
- Urine is thin - having a low concentration of ions - **hyposmolar**
- The extracellular **hyperosmolarity** → **encefalopathy**
- Severe **hypovolemia and hypotension** → **circulatory failure**
- Skin is dry, termoregulation disorders **(hyperthermia a hypothermia)**
- hypovolemia, hypotension and circulatory failure .
  The skin is dry, affects thermoregulation (hyperthermia and hypothermia).

Hypervasopresinism (SIADH)
Schwartz - Barterr sy. inadequate ADH secretion

- Causes:
  - *1. Damage to CNS* - meningitis, SAH, surgery
  - *2. Ectopic ADH* – Ca lung, Ca duodenum, pancreas, leukemia
  - *3. Exogenic reasons – drugs :* chlorpropamid, morphin, barbiturates
- Symptoms:
  - **oliguria** ← increased reabsorption of water in kidney → **hypervolemia**
  - **hyponatremia** ← dilutional + reflex aldosterone decrease
  - **hypoosmolarity** ← decreased Na^+, Cl-, plasma proteins
  - **Water poisoning sy.**
    - <140 mmol/l feelings of thirst, anorexia,
    - 120-130 mmol / l - vomiting, muscle weakness, fatigue and cramps.
    - <120 mmol / l - hyposmolar encephalopathy – low consciousness, ethargy, confusion
    - <110 mmol / l - hypoosmolar coma