ENDOCRINOLOGY

PITUITARY

Kenneth Alonso, MD, FACP

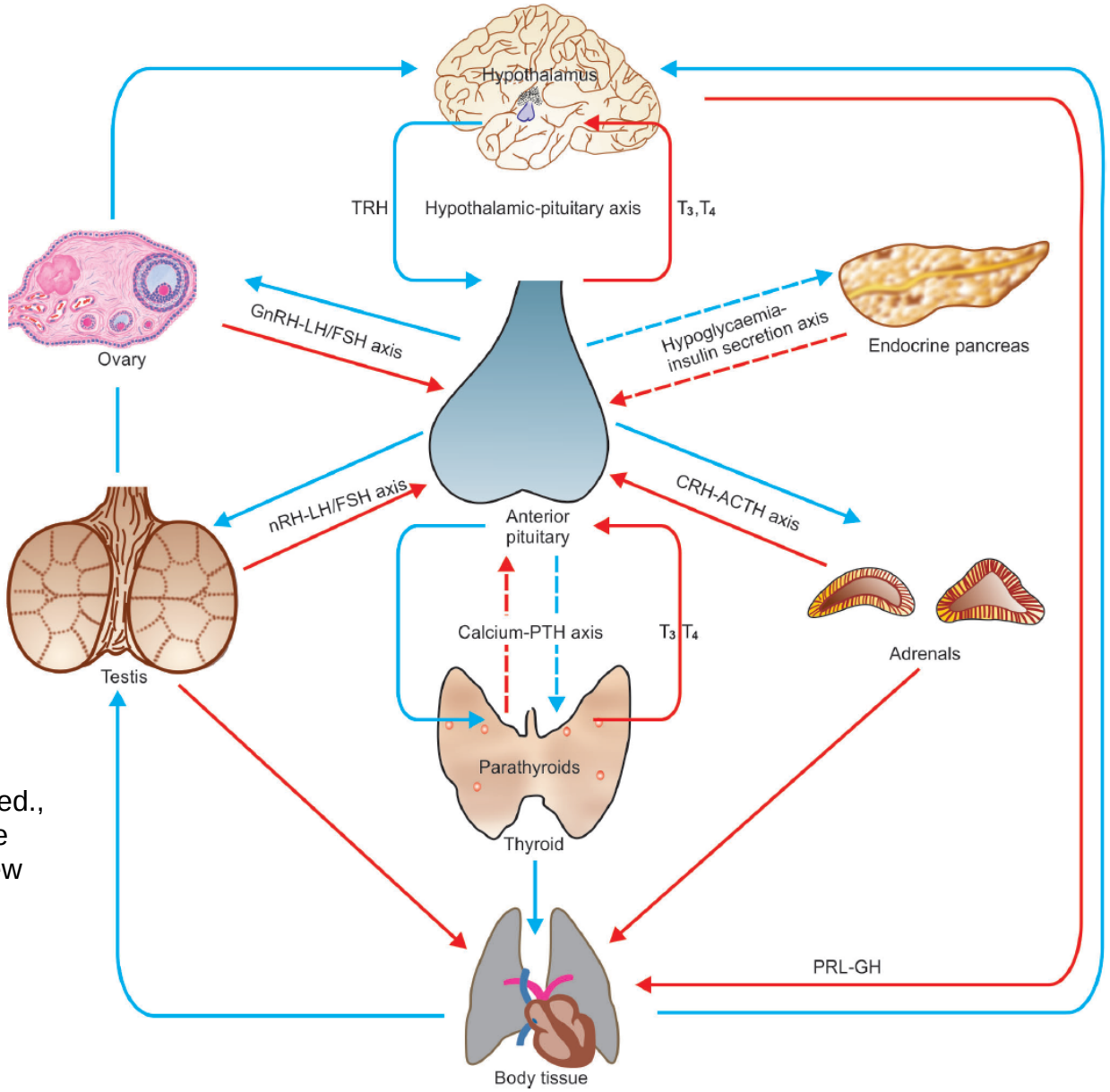


Figure 25.1 Endocrine organs and the presence of feedback controls. Both positive and negative feedback controls exist for each endocrine gland having a regulating (R) and stimulating (S) hormone. Those acting through hypothalamic-pituitary axis include: thyroid hormones on TRH-TSH axis, cortisol on CRH-ACTH axis, gonadal steroids on GnRH-LH/FSH axis and insulin-like GH on GHRH-GH axis. Those independent of pituitary control (shown by interrupted arrows) have also feedback controls by calcium on PTH, and hypoglycaemia on insulin release by pancreatic islets.

Mohan, H, Textbook of Pathology, 7th ed., Health Science Publishers. New Delhi. 2015.

Pituitary

- The pituitary gland is composed of two morphologically and functionally distinct components:
- (1) The anterior lobe(adenohypophysis)
- Constitutes about 80% of the gland.
- The production of most pituitary hormones is controlled in large part by positively and negatively acting factors from the hypothalamus
- Carried to the anterior pituitary by a portal vascular system

Anterior pituitary

- There are six terminally differentiated cell types in the anterior pituitary:
- Somatotrophs, producing growth hormone (GH)
- Mammosomatotrophs, producing GH and prolactin (PRL)
- Lactotrophs, producing PRL
- Corticotrophs,
- Producing adrenocorticotropic hormone (ACTH) and pro-opiomelanocortin (POMC), melanocyte stimulating hormone (MSH)

Anterior pituitary

- Thyrotrophs
- Producing thyroid stimulating hormone (TSH)
- Gonadotrophs
- Producing follicle-stimulating hormone (FSH) and luteinizing hormone (LH).
- FSH stimulates the formation of graafian follicles in the ovary
- LH induces ovulation and the formation of corpora lutea in the ovary and also regulate testosterone production and spermatogenesis in males

Anterior pituitary

- Somatotrophs, mammosomatotrophs, and lactotrophs are derived from stem cells in Rathke's pouch that express the pituitary transcription factor, PIT-1.
- Steroidogenic factor -1 (SF-1) and GATA-2 are factors that are required for gonadotroph differentiation.
- Maximal secretion of pituitary hormones is at midnight.

Pituitary

- (2) The posterior lobe (neurohypophysis).
- Consists of modified glial cells (pituicytes) and axonal processes extending from the hypothalamus through the pituitary stalk to the posterior lobe.
- Synthesized in the hypothalamus and stored within the axon terminals residing in the posterior pituitary are oxytocin and antidiuretic hormone (ADH, also called vasopressin).
- In response to appropriate stimuli, the preformed hormones are released directly into the systemic circulation through the venous channels of the pituitary.

Hypothalamic control of pituitary hormones

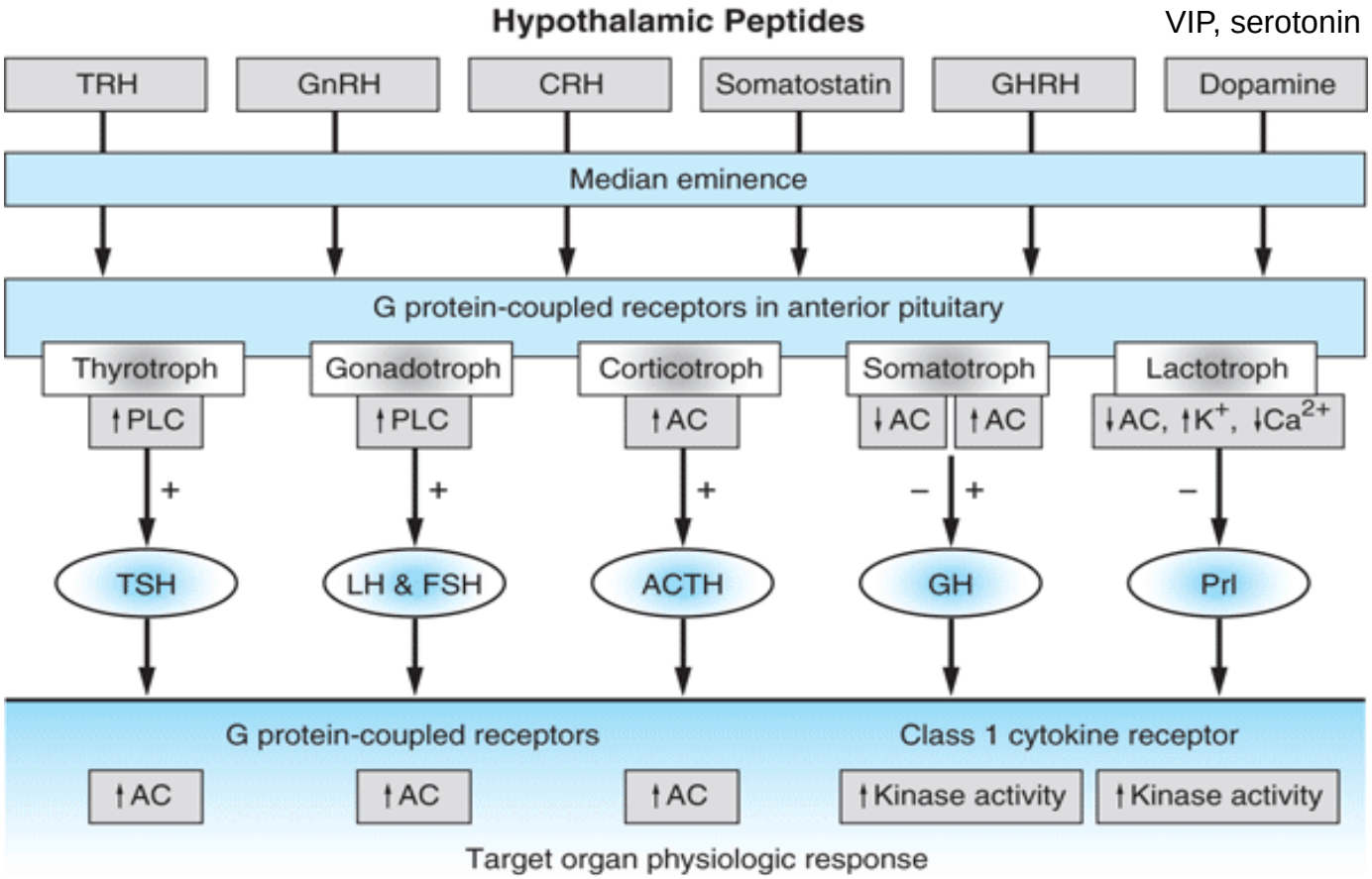


Fig. 3-3 Accessed 02/01/2010

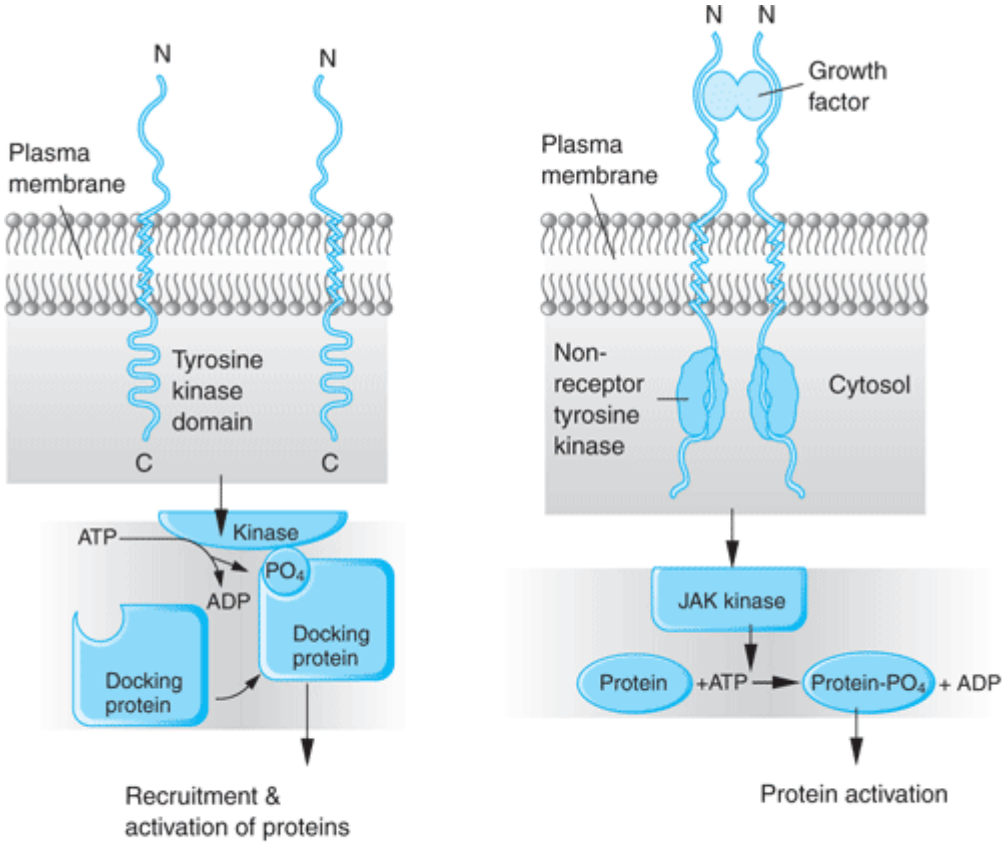
Peptide hormone receptors

- Peptide hormone receptors span the plasma membrane and bind ligand outside the cell.
- Pituitary releasing hormones as well as TSH, LH, FSH, and ACTH bind to the amino terminal of the particular receptor.
- Their signal is then transduced to the cell interior by binding to a series of G-proteins with intrinsic tyrosine or serine kinase activity.
- The activated kinase recruits and phosphorylates downstream proteins, producing a cellular response.

Peptide hormone receptors

- G-proteins are heterotrimers, composed of a specific α-subunit that binds guanine nucleotide and interacts with the receptor and, released, intracellular effectors.
- β,γ subunits are covalently bound to the α-subunit.
- GH and prolactin binding differs in that their receptors do not have intrinsic tyrosine kinase activity in their intracellular domain.
- They are closely associated with kinases that are activated with binding of the hormone.

Peptide hormone receptors (G-protein)



(Modified, with permission, from Cooper GM. *The Cell: A Molecular Approach,* 2nd ed. Sinauer, 2000.)

Fig. 1-6 Accessed 02/01/2010

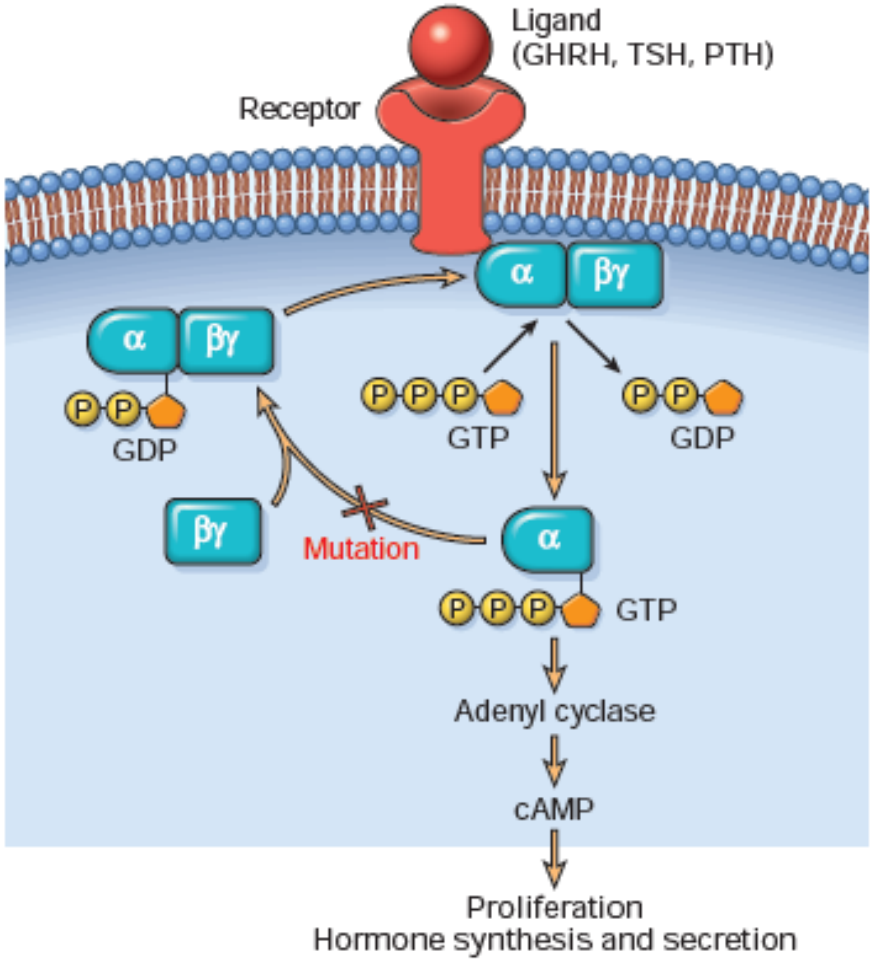


Figure 24-3 G-protein signaling in endocrine neoplasia. Mutations that lead to G-protein hyperactivity are seen in a variety of endocrine neoplasms, including pituitary, thyroid, and parathyroid adenomas. G proteins (composed of α and βγ subunits) play a critical role in signal transduction, transmitting signals from cell surface receptors (GHRH, TSH, or PTH receptor) to intracellular effectors (e.g., adenyl cyclase), which then generate second messengers (cAMP, cyclic adenosine monophosphate) that stimulate cellular responses. GDP, guanosine diphosphate; GTP, guanosine triphosphate; P_i, inorganic phosphate. See Figure 24-1 for other abbreviations.

Peptide hormone receptors (linked)

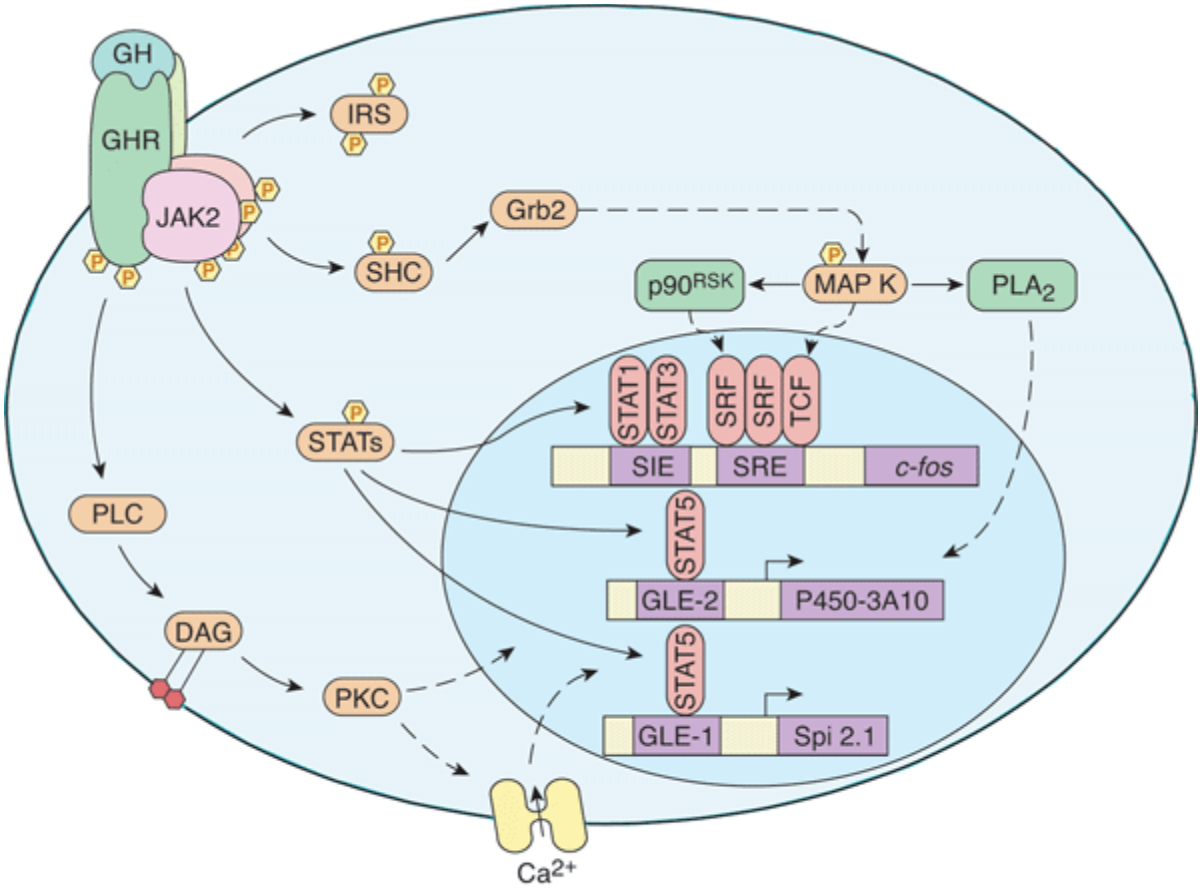


Fig. 24-4 Accessed 02/01/2010

Anterior pituitary

- Acidophilic staining glycoproteins
- GH
- Prolactin
- Basophilic staining glycoproteins
- TSH
- FSH and LH
- Chromophobe (poorly staining)
- POMC

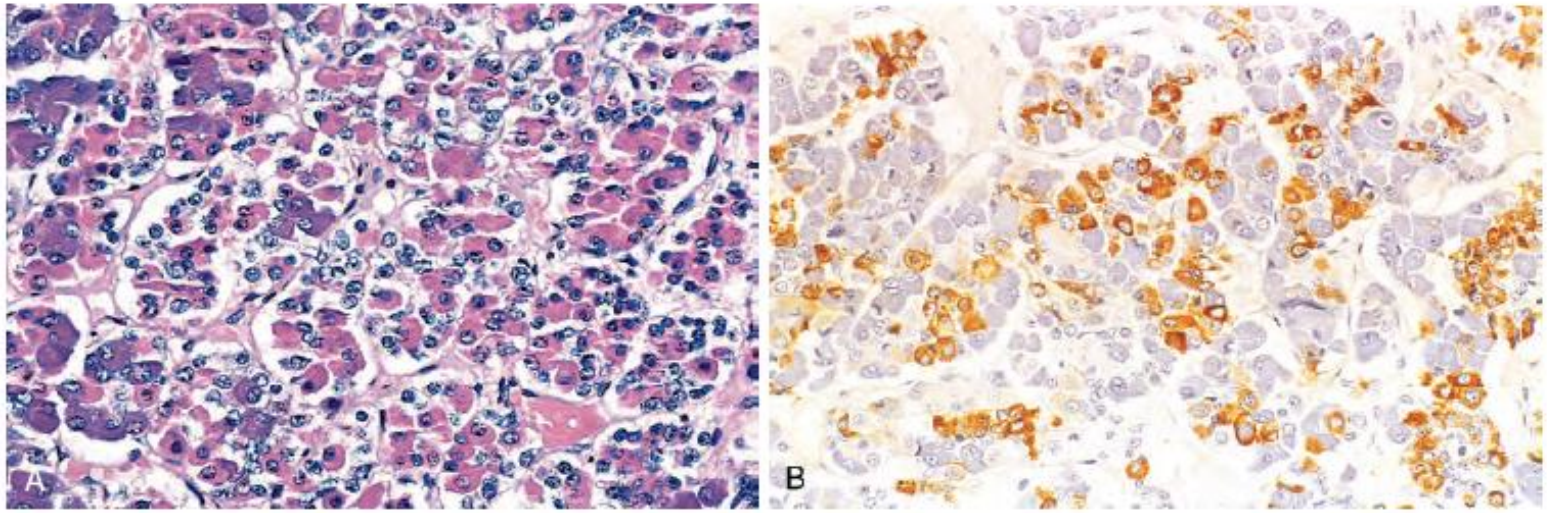


Figure 24-2 **A,** Photomicrograph of normal pituitary. The gland is populated by several distinct cell populations containing a variety of stimulating (tropic) hormones. Each of the hormones has different staining characteristics, resulting in a mixture of cell types in routine histologic preparations. **B,** Immunostain for human growth hormone.

Growth hormone

- Somatotrophs are the source of GH production.
- They constitute half the hormone producing cells in the pituitary.
- GH is secreted in a pulsatile fashion.
- GH stimulates production of insulin growth factor (IGF-1) in liver.
- GH is a counter-regulatory hormone (decreases glucose uptake).
- GH stimulates protein synthesis in muscles (and, via IGF-1, at the organ level as well as in chondrocytes where it promotes linear growth).
- GH mobilizes fatty acids as well.

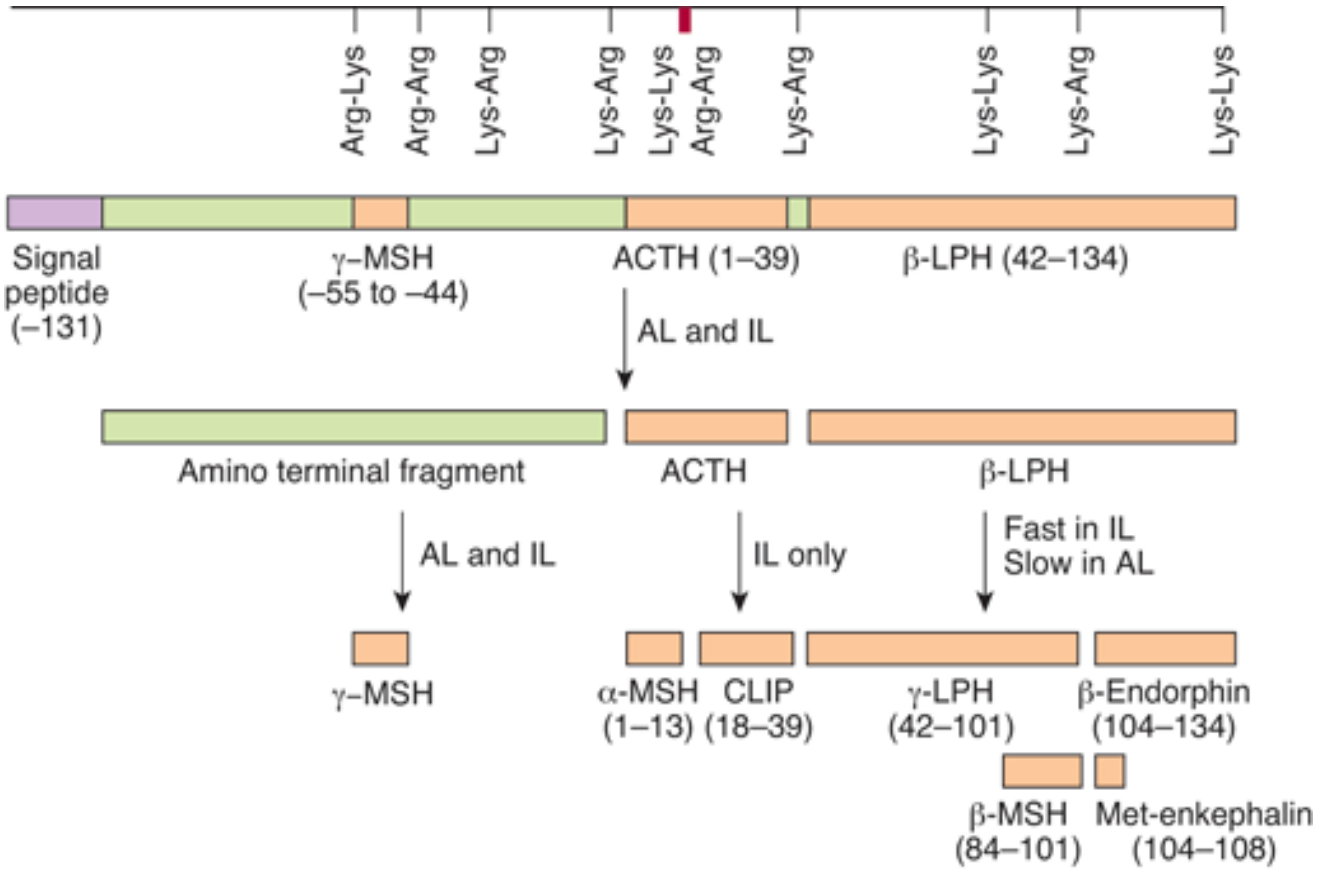
The other pituitary hormones

- Lactotrophs are the source of Prolactin production.
- Prolactin and GH are structurally related. They belong to same cytokine-hematopoietin family.
- Prolactin inhibits GH production.
- Thyrotrophs are the source of TSH production.
- Gonadotrophs are the source of LH and FSH production.
- TSH, FSH, and LH share an identical α-unit and differ in β-subunit.
- Thyrotroph, lactotroph, and gonadotrophs do not act via cAMP-dependent pathways.

The other pituitary hormones

- Chromophobes are the source of POMC (pro-opiomelanocortin),
- ACTH is synthesized from POMC.
- α-MSH is present on the N-terminal end of ACTH.
- β-endorphin and β-lipotropin are also derived from POMC.

POMC



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

Fig. 24-2 Accessed 02/01/2010

Pituitary mass

- As the mass expands, it may give rise to elevated intracranial pressure
- Among the earliest changes referable to mass effect are radiographic abnormalities of the sella turcica, including sellar expansion, bony erosion, and disruption of the diaphragma sella.

Pituitary mass

- Because of the close proximity of the optic nerves and chiasm to the sella, expanding pituitary lesions often compress decussating fibers in the optic chiasm.
- This gives rise to visual field abnormalities, classically in the form of defects in both lateral (temporal) visual fields, so-called bitemporal hemianopsia.

Pituitary mass

- Medical emergencies:
- On rare occasions, hemorrhage into the mass is associated with expansion of the lesion and gland infarction (pituitary apoplexy)
- The gland doubles in size during pregnancy (without corresponding increase in blood supply from portal system, resulting in relative anoxia).
- Sheehan's post-partum necrosis presents shortly following childbirth
- More than one pituitary hormone is not produced because of gland infarction.

Hyperpituitarism

- Arising from excess secretion of trophic hormones.
- Causes include:
- Pituitary adenoma, hyperplasia, and carcinomas of the anterior pituitary
- Secretion of hormones by non-pituitary tumors
- ACTH by small cell carcinoma of the lung (50%)
- Rarely, carcinoids of the lung, islet cell tumors, medullary carcinoma of the thyroid
- Hypothalamic disorders

Table 24-1 Classification of Pituitary Adenomas

Pituitary Cell Type	Hormone	Adenoma Subtypes	Associated Syndrome*
Lactotroph	Prolactin	Lactotroph adenoma Silent lactotroph adenoma	Galactorrhea and amenorrhea (in females) Sexual dysfunction, infertility
Somatotroph	GH	Densely granulated somatotroph adenoma Sparsely granulated somatotroph adenoma Silent somatotroph adenoma	Gigantism (children) Acromegaly (adults)
Mammosomatotroph	Prolactin, GH	Mammosomatotroph adenomas	Combined features of GH and prolactin excess
Corticotroph	ACTH and other POMC-derived peptides	Densely granulated corticotroph adenoma Sparsely granulated corticotroph adenoma Silent corticotroph adenoma	Cushing syndrome Nelson syndrome
Thyrotroph	TSH	Thyrotroph adenomas Silent thyrotroph adenomas	Hyperthyroidism
Gonadotroph	FSH, LH	Gonadotroph adenomas Silent gonadotroph adenomas ("null cell," oncocytic adenomas)	Hypogonadism, mass effects, and hypopituitarism

ACTH, Adrenocorticotrophic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; POMC, pro-opiomelanocortin; TSH, thyroid-stimulating hormone.

*Note that nonfunctional (silent) adenomas in each category express the corresponding hormone(s) within the neoplastic cells, as determined by special immunohistochemical staining on tissues. However, these adenomas do not produce the associated clinical syndrome, and typically present with *mass effects* accompanied by *hypopituitarism* due to destruction of normal pituitary parenchyma. These features are particularly common with gonadotroph adenomas.

Partially adapted from Asa SL, Essat S: The pathogenesis of pituitary tumors. Annu Rev Pathol Medch Dis 4:97; 2009.

Pituitary adenoma

- 10% of intracranial neoplasms
- Peak incidence, age 30-50 years
- Monoclonal origin
- Macroadenoma if >1cm diameter
- The majority of pituitary adenomas are non-functional.
- 20% of normal adults may harbor silent adenoma
- Growth hormone and prolactin are the usual combination if more than one hormone is produced by the adenoma

Molecular abnormalities

- Receptors may be up-regulated or down-regulated with exposure to hormone or deprivation of hormone.
- Approximately 40% of somatotroph cell adenomas bear mutations of the GNAS gene at 20q13.
- Lead to constitutive activation of Gsα, persistent generation of cAMP, and unchecked cellular proliferation.
- GNAS mutations have also been described in a minority of corticotroph adenomas

Molecular abnormalities

- 3% of adenomas are associated with germline MEN1 mutation (11q13).
- Patients with p27/KIP1 as a result of CDKN1B mutation (12p13) may present with MEN-1 like syndrome.
- Other germline mutations include PRKAR1A (protein kinase A regulatory subunit, at 17q24) in Carney syndrome as well as AIP (aryl hydrocarbon receptor interacting protein) in growth hormone secreting lesions.

Molecular abnormalities

- Molecular abnormalities associated with aggressive behavior are overexpression of cyclin D1, mutations of TP53, and epigenetic silencing of the retinoblastoma gene (RB).

Table 24-2 Genetic Alterations in Pituitary Tumors

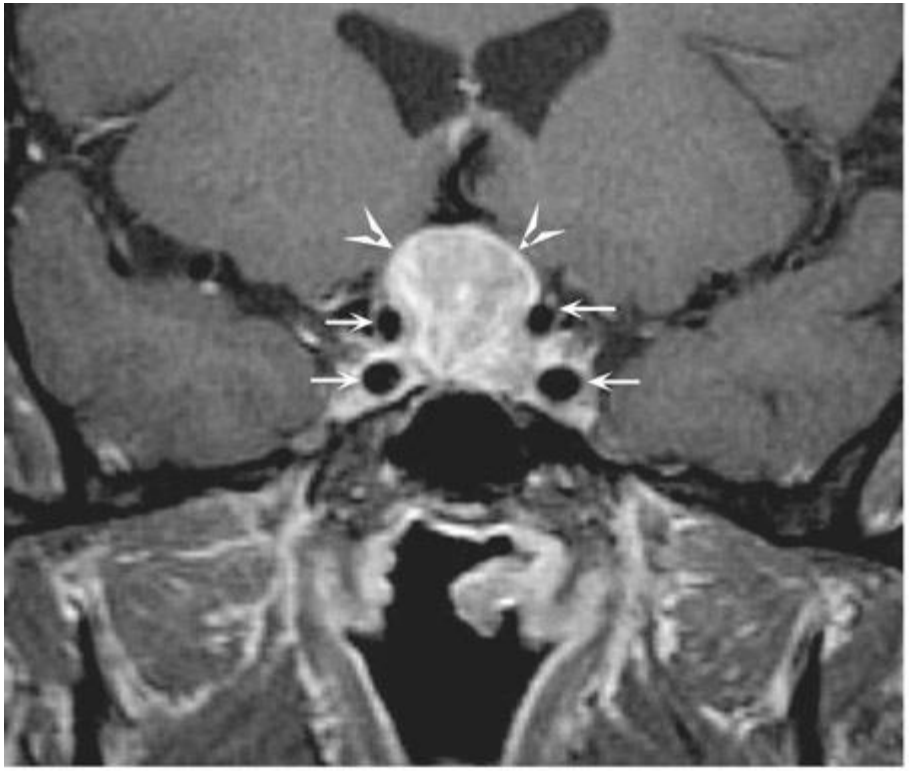
Gene	Protein Function	Mechanism of Alteration	Most Commonly Associated Pituitary Tumor
Gain of Function			
GNAS	GNAS encodes for alpha subunit of stimulatory G-protein, Gsα. Oncogenic mutation of GNAS constitutively activates Gsα, leading to upregulation of intracellular cyclic AMP (cAMP) activity	Activating mutation	GH adenomas
Protein kinase A, regulatory subunit 1 (PRKAR1A)*	*PRKAR1A* encodes for a negative regulator of protein kinase A (PKA), a downstream mediator of cAMP signaling. Loss of PKA regulation leads to inappropriate cAMP activity	Germline inactivating mutations of *PRKARIA* are present in autosomal dominant Carney complex	GH and prolactin adenomas
Cyclin D1	Cell cycle regulatory protein; promotes G1-S transition	Overexpression	Aggressive adenomas
HRAS	Ras regulates multiple oncogenic pathways including proliferation, cell survival and metabolism	Activating mutation	Pituitary carcinomas
Loss of Function			
MEN1*	MEN1 encodes for menin, a protein with protean roles in tumor suppression, including repression of oncogenic transcription factor JunD, and in histone modification.	Germline inactivating mutations of *MEN1* (multiple endocrine neoplasia, type 1)	GH, prolactin, and ACTH adenomas
CDKN1B (p27/KIP1)*	The p27 protein is a negative regulator of the cell cycle	Germline inactivating mutations of CDKN1B ("MEN-1-like" syndrome)	ACTH adenomas
Aryl hydrocarbon receptor interacting protein (AIP)*	Receptor for aryl hydrocarbons and a ligand-activated transcription factor	Germline mutations of *AIP* cause pituitary adenoma predisposition [PAP] syndrome	GH adenomas (especially in patients younger than 35 years of age)
Retinoblastoma (RB)	Retinoblastoma protein is a negative regulator of the cell cycle (Chapter 7)	Methylation of *RB* gene promoter	Aggressive adenomas

ACTH, Adrenocorticotrophic hormone; GH, growth hormone.
*Genetic alterations associated with *familial* predisposition to pituitary adenomas.
Partially adapted from Boikos SA, Stratakis CA: Molecular genetics of the cAMP-dependent protein kinase pathway and of sporadic pituitary tumorigenesis. Hum Mol Genet 16:R80-R87, 2007.

Gross features

- The typical pituitary adenoma is soft and well-circumscribed.
- Small adenomas may be confined to the sella turcica, but with expansion they frequently erode the sella turcica and anterior clinoid processes.
- Larger lesions usually extend superiorly through the diaphragm sella into the suprasellar region, where they often compress the optic chiasm and adjacent structures,such as some of the cranial nerves.

Pituitary microadenoma



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J:
Harrison's Principles of Internal Medicine, 17th Edition: http://www.accessmedicine.com

Fig. 333-4 Accessed 03/01/2010

Coronal T1-weighted postcontrast MR image shows a homogeneously enhancing mass (arrowheads) in the sella turcica and suprasellar region compatible with a pituitary adenoma; the small arrows outline the carotid arteries.

Gross features

- In as many as 30% of cases, the adenomas are not grossly encapsulated and infiltrate neighboring tissues such as the cavernous and sphenoid sinuses, dura, and on occasion, the brain itself. (invasive adenoma)

Histopathology

- Typical pituitary adenomas are composed of uniform, polygonal cells arrayed in sheets or cords.
- Supporting connective tissue, or reticulin, is sparse
- Accounts for the soft, gelatinous consistency of many of these tumors.
- Mitotic activity is usually sparse.
- This cellular monomorphism and the absence of a significant reticulin network distinguish pituitary adenomas from non-neoplastic anterior pituitary parenchyma
- Atypical adenomas have a high mitotic rate and nuclear p53 expression.

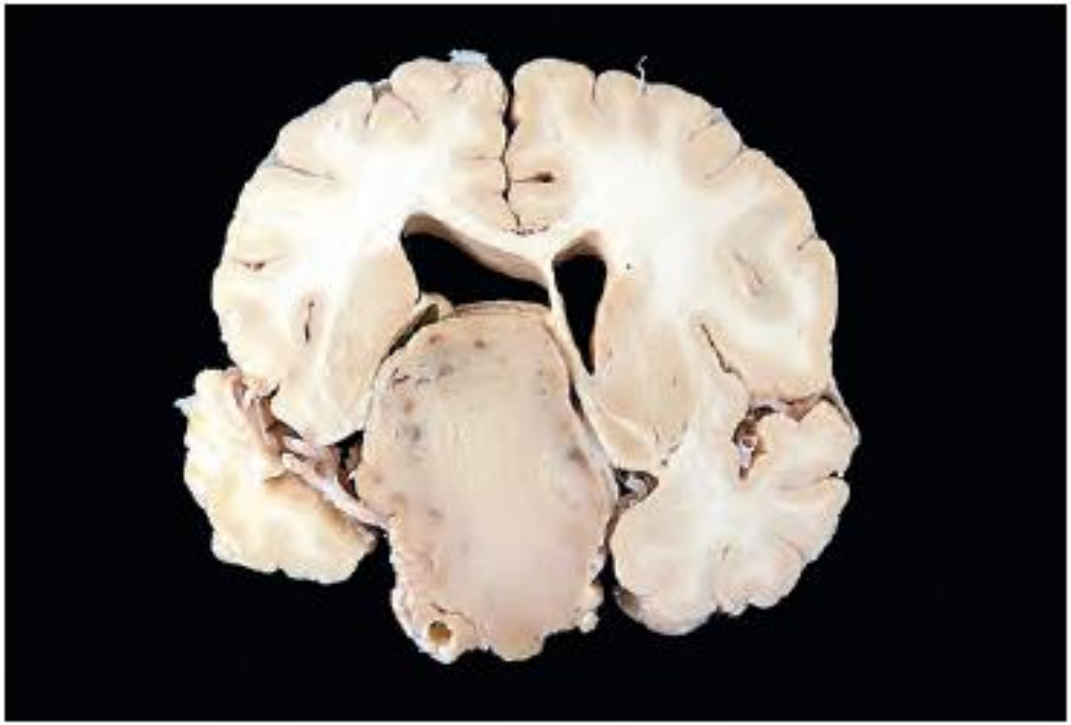


Figure 24-4 Pituitary adenoma. This massive, nonfunctional adenoma has grown far beyond the confines of the sella turcica and has distorted the overlying brain. Nonfunctional adenomas tend to be larger at the time of diagnosis than those that secrete a hormone.

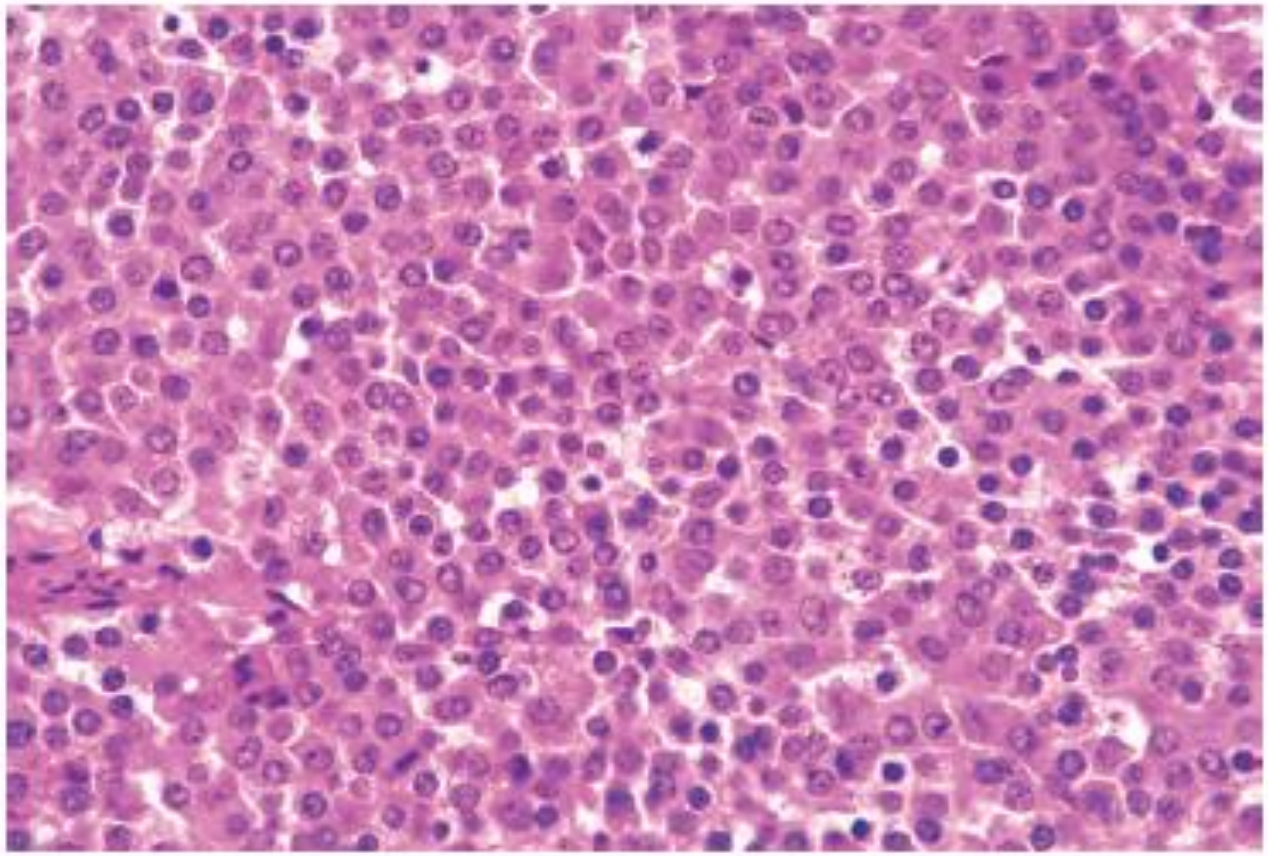


Figure 24-5 Pituitary adenoma. The monomorphism of these cells contrasts markedly with the mixture of cells seen in the normal anterior pituitary. Note also the absence of reticulin network.

Medical treatment

- Prolactinoma treated generally with a dopamine agonist, if microadenoma.
- Octreotide is a somatostin analogue that inhibits the release of growth hormone, TSH, glucagon, insulin, gastrin, and vasoactive intestinal peptide.
- It is used in treatment of acromegaly, carcinoid syndrome, variceal bleeding.
- Diarrhea (decreases splanchnic blood flow), diminished gallbladder contractility (stone formation) are noted with use.

Medical treatment

- Leuprolide is a gonadotropin releasing hormone analogue that can be used to modulate LH/FSH release.
- It is administered in a pulsatile fashion to stimulate ovulatory cycle
- It is administered continuously to suppress LH/FSH production (prostate cancer, endometriosis).
- Surgical removal is the usual approach for large tumors.

Lactotroph adenomas

- 30% of all pituitary adenomas
- The overwhelming majority of lactotroph adenomas are comprised of chromophobic cells with juxtanuclear localization of the transcription factor PIT-1 (sparsely granulated lactotroph adenomas)
- Much rarer are the acidophilic densely granulated lactotroph adenomas, characterized by diffuse cytoplasmic PIT-1 expression.
- May have dystrophic calcification (“pituitary stone”)
- Prolactin levels elevated

Prolactin excess

- Prolactin excess associated with amenorrhea, galactorrhea, loss of libido, and infertility.
- 20-40 year old women present with menstrual irregularities
- More difficult to diagnose in men or older women
- Physiologic hyperprolactinemia occurs in pregnancy.
- Prolactin levels are also elevated by nipple stimulation, as occurs during suckling,and as a response to stress.

Prolactin excess

- Pathologic hyperprolactinemia can also result from lactotroph hyperplasia caused by loss of dopamine-mediated inhibition of prolactin secretion.
- Head trauma with damage to the pituitary stalk.
- Loss of hypothalamic inhibition
- Dopamine antagonists
- Hyperthyroidism
- Renal failure

Somatotroph adenomas

- 10-25% of pituitary tumors
- Densely granulated adenomas are composed of monomorphic, acidophilic cells that stain for GH
- Bi-hormonal adenomas resemble the densely granulated pure somatotroph adenomas and stain for both GH and prolactin.
- Sparsely granulated adenomas are composed of chromophobe cells with considerable nuclear and cytologic pleomorphism and focal, weak staining for GH.

Growth hormone excess

- Hormone excess is a result of a pituitary adenoma or hyperplasia.
- GH stimulates the hepatic secretion of insulin-like growth factor 1 (IGF-1)
- If hormone excess occurs before epiphyseal closure, the clinical syndrome of gigantism is seen.
- This is characterized by a generalized increase in body size with disproportionately long arms and legs.
- All organs are enlarged.

Gigantism

Fig. 333-8
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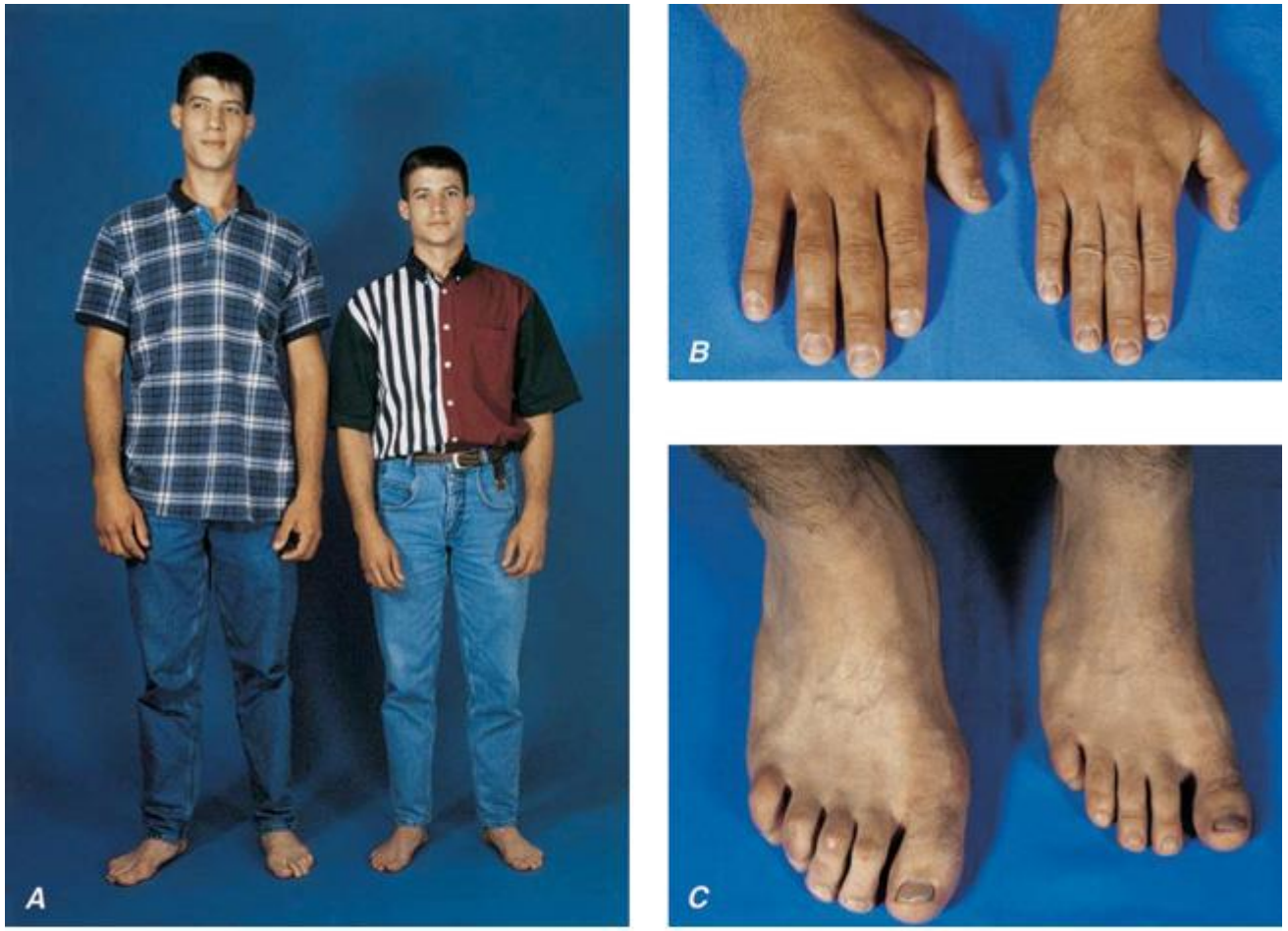
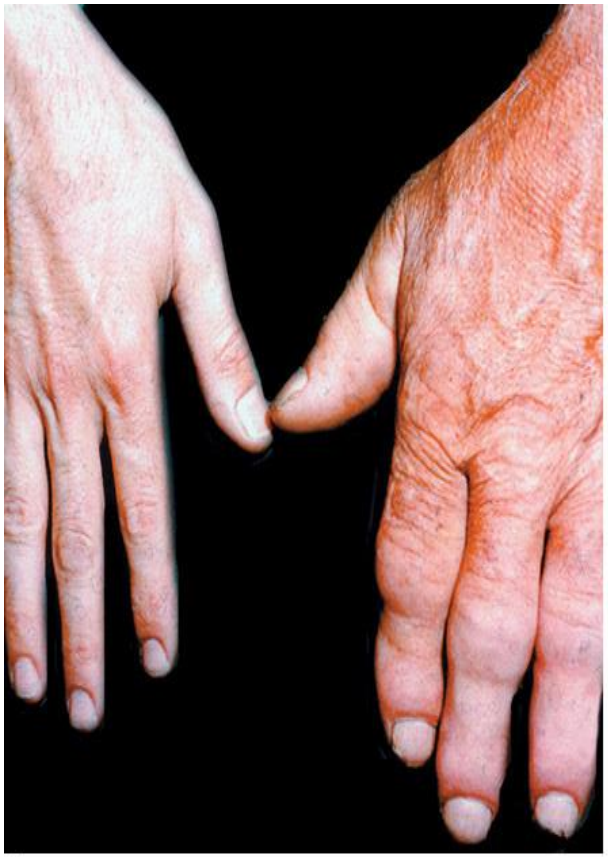


Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Growth hormone excess

- If hormone excess occurs after epiphyseal closure, the clinical syndrome of acromegaly is seen:
- Leonine facies. The bones of the face broaden and the jaw is enlarged and protruces (prognathism)
- Bone density may increase (hyperostosis) in both the spine and the hips.
- Spade-like hands. The hands are enlarged, and the fingers become thickened and sausage-like.
- The feet are enlarged as well.
- The tongue is enlarged as are other organs and viscera (thyroid, heart, liver, and adrenals),

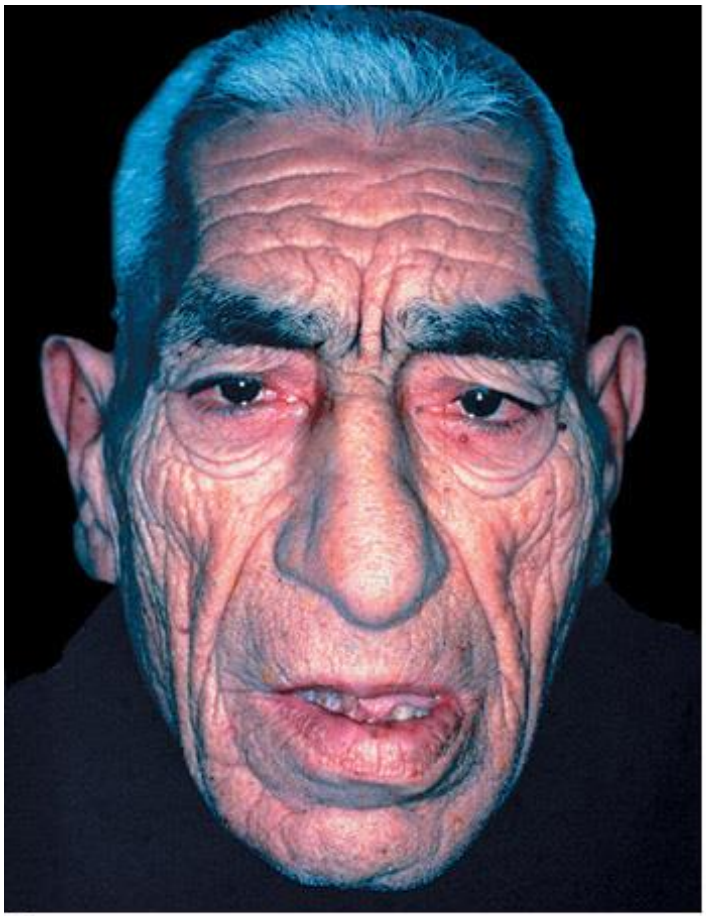
Acromegaly



A

Source: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ: *Fitzpatrick's Dermatology in General Medicine*, 7th Edition: http://www.accessmedicine.com

Fig. 157-20 Accessed 02/01/2010



B

Source: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ: *Fitzpatrick's Dermatology in General Medicine*, 7th Edition: http://www.accessmedicine.com

Growth hormone excess

- Diabetes mellitus is common as is hypertension.
- Increased risk of gastrointestinal cancer.
- Production not suppressed with glucose load.
- Somatomedin-C level is measured.
- GH secretion is maximal at midnight
- Somatomedin-C is integrated response to GH and IGF-1 production and may be measured at any time

Corticotroph adenomas

- 15% of pituitary adenomas
- 70% of all cases of Cushing's syndrome
- Women 3-10:1
- 30-50 years of age
- 20% clinically silent
- In the pediatric age group, primary adrenal tumors are more common cause of Cushing's syndrome
- 30% are pituitary adenoma
- Males

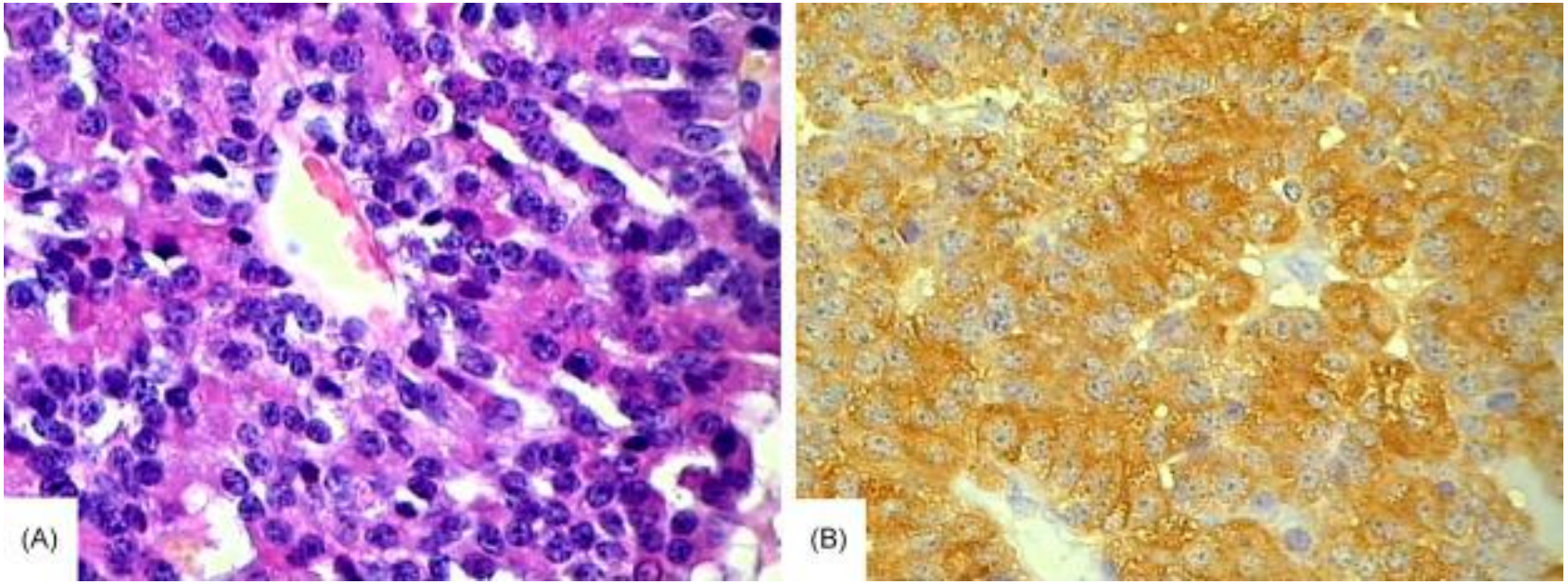
Corticotroph adenomas

- Densely granulated
- Most common
- Basophilic cells
- Sinusoidal architecture
- Stain positively with periodic acid-Schiff (PAS) because of the presence of carbohydrate in proopiomelanocortin (POMC), the ACTH precursor molecule
- Sparsely granulated
- Usually present as macroadenoma
- Chromophobic or weakly staining with variable immunoreactivity to POMC or β-endorphin.

Corticotroph adenomas

- Crooke cell adenomas
- Tumor cells show a homogeneous hyaline material composed of filaments occupying large areas of the cytoplasm and displacing organelles and secretory granules to the cell periphery (Crooke hyaline changes).
- Tumor cells are large and have a homogeneous glassy, slightly acidophilic cytoplasm with granular basophilia limited to the cell periphery and juxtanuclear region. Nuclei may be atypical.
- Aggressive
- All arise from TPIT lineage (gene at 1q24.2)

Corticotroph adenoma



A. Corticotroph adenoma showing a sinusoidal growth of basophilic cells
B. Intense immunostaining for ACTH (B)

Stefano La Rosa, Silvia Uccella, **Pituitary Tumors: Pathology and Genetics** *in Encyclopedia of Cancer (Third Edition), 2019.* Fig. 5.

Corticotroph adenomas

- Nelson syndrome.
- Large destructive pituitary adenomas can develop in patients after surgical removal of the adrenal glands for treatment of Cushing syndrome.
- There is a loss of the inhibitory effect of adrenal corticosteroids on a pre-existing corticotroph microadenoma.
- Because the adrenals are absent in persons with this disorder, hypercortisolism does not develop, and patients present with mass effects due to the pituitary tumor.
- Hyperpigmentation my be present.

Cortisol excess

Symptoms, signs and morbidities*	Prevalence %
Weight gain or obesity/abdominal obesity	95
Facial plethora	90
Facial fullness	90
Decreased libido/erectile dysfunction	90
Thin skin	85
Menstrual abnormalities/amenorrhea	80
Decreasing growth velocity**	70-80
Arterial hypertension	75
Hirsutism	75
Depression/emotional lability	70
Dyslipidemia	70
Striae (especially if red or purple and more than 10 mm wide)	70-90

https://doi.org/10.1590/2359-3997000000174

Cushing's syndrome

- Discriminatory features
- Easy bruising
- Facial plethora
- Proximal muscle weakness or myopathy
- Striae
- Particularly if red-purple and >1cm wide
- In children:
- Weight gain with decreasing growth velocity
- If onset at a young age:
- Hypertension, vertebral osteoporosis, thin skin

Etiology

Cushing's syndrome etiology*	Prevalence**
ACTH-dependent Cushing's syndrome	**80%**
Cushing's disease	70%
Ectopic ACTH syndrome	10%
ACTH-independent Cushing's syndrome	**20%**
Adrenal adenoma	10%
Adrenal carcinoma	5%

https://doi.org/10.1590/2359-3997000000174

Cortisol excess

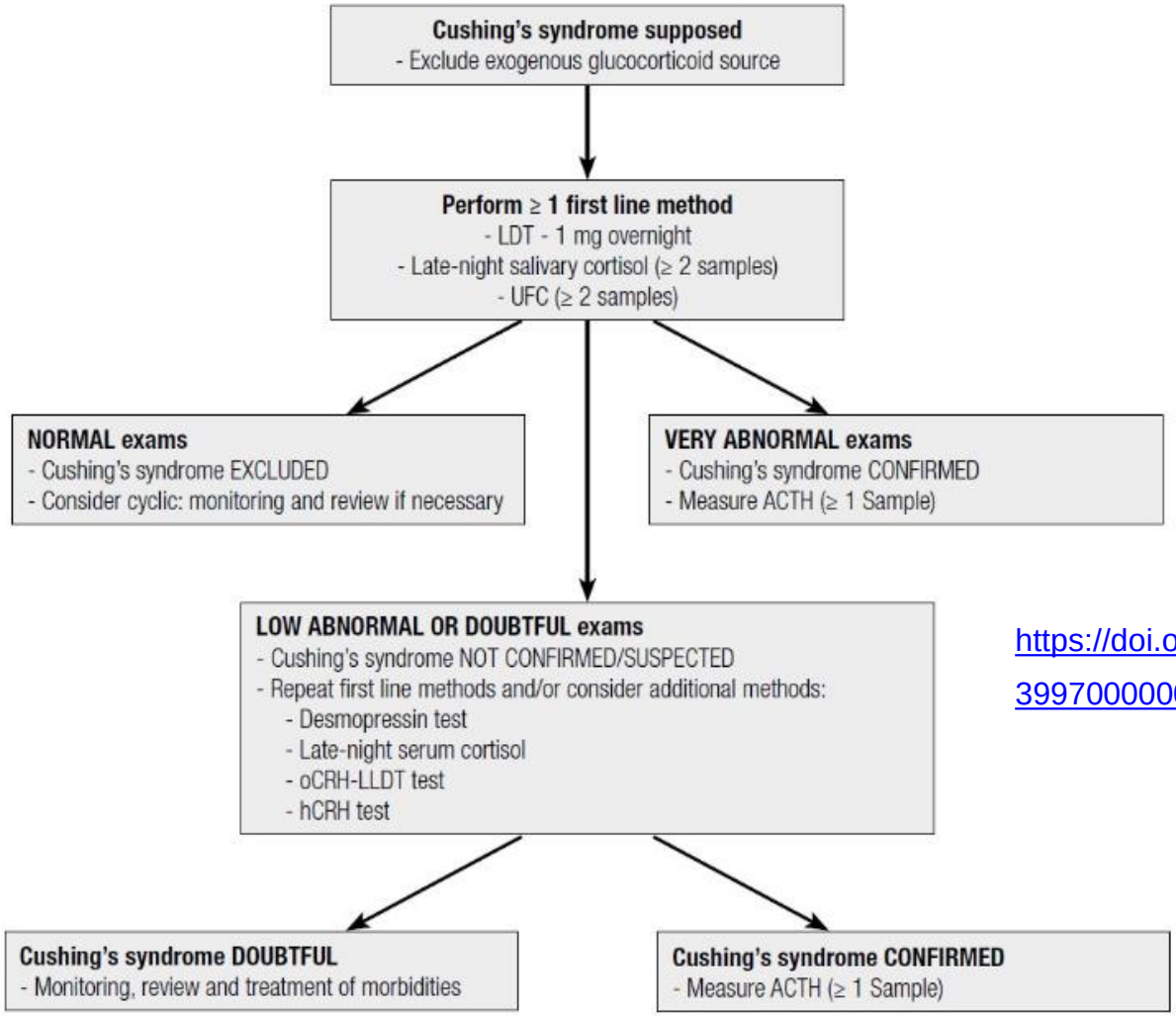
- Hyperpigmentation usually seen with ectopic production of ACTH
- At least two screening tests must be performed to establish a working diagnosis.
- Must exclude those taking medications metabolized by CYP3A4, those on oral contraceptives (cease at least 1 month before testing), those with depression or PTSD, those with heavy alcohol use.
- MRI imaging of the sella turcica with the use of contrast

Table 4 Laboratory methods for Cushing's syndrome diagnosis

Method	Reference value	Sensitivity %	Specificity %
First-line methods			
Low-dose dexamethasone suppression test - 1 mg overnight (serum cortisol) (27)	> 1.8 µg/dL	> 95	80
Longer low-dose dexamethasone suppression test - 2 mg/day for 48 h – 0.5 mg 6/6 h (serum cortisol) (68)*	> 1.8 µg/dL	92-100	92-100
Late night salivary cortisol (µg/dL or ng/dL or mmol/L) (56)	> 2X ULNR	88-100	82-100
Urinary free cortisol 24 h (µg/24 h) (68)	> 3-4X ULNR	90-98	45-95
Other methods (second-line)			
Late-night serum cortisol (patient awake) (78)	> 7.5 µg/dL	96	100
Ovine CRH after longer low-dose dexamethasone suppression test (serum cortisol) (81-84)	> 1.4 µg/dL (15')	< 100	< 100
Human CRH test (plasma ACTH, pg/mL; serum cortisol, µg/dL) (86)	Peak > 54 pg/mL and > 12 µg/dL (baseline)	91.3	98.2
Desmopressin test (plasma ACTH, pg/mL; serum cortisol, µg/dL) (90)	Δ > 18 pg/mL and > 12 µg/dL (baseline)	86.6-100	92.8

Δ: delta: peak less baseline value; ULNR: upper limit of normal range; * Meta-analysis showed a similar or lower accuracy than that of the low-dose dexamethasone suppression test (1 mg overnight) (54); serum cortisol: µg/dL; to nmol/L, multiply by 27.59; ACTH: pg/mL; to pmol/L, multiply by 0.2202; urinary cortisol: µg/24 h; to nmol/24 h, multiply by 2.759.

https://doi.org/10.1590/2359-3997000000174



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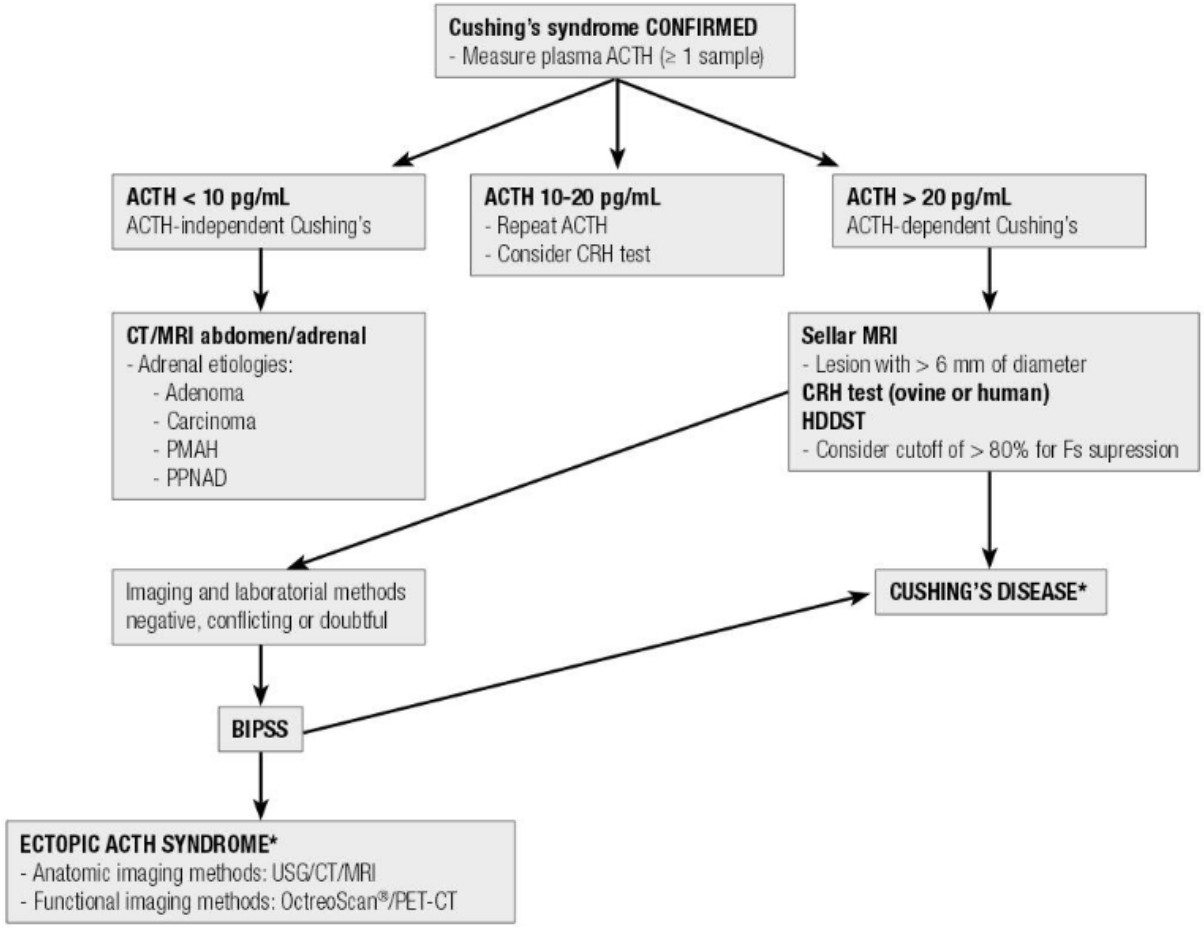
LDT: low-dose dexamethasone suppression test with 1 mg overnight; UFC: urinary free cortisol; oCRH: ovine; hCRH: human CRH; LLDT: longer low-dose dexamethasone suppression test (2 mg/day for 48 h).

Figure 1 Flowchart of Cushing's syndrome diagnosis.



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HDDST: high-dose dexamethasone suppression test (8 mg overnight); CT: computed tomography; MRI: magnetic resonance imaging; PMAH: primary macronodular adrenal hyperplasia; PPNAD: primary pigmented nodular adenocortical disease; BIPSS: bilateral and simultaneous petrosal sinus sampling; USG: ultrasound; PET-CT: positron emission tomography-computed tomography; * Even before the definition of Cushing's disease or EAS, anatomical images of the neck/chest/abdomen/pelvis are commonly obtained to contribute to the identification of the ACTH-producing source.

Figure 2 Flowchart for differential diagnosis of ACTH-dependent Cushing's syndrome

Thyrotroph adenoma

- 1% of pituitary adenomas
- 40-50 years of age
- Measurable serum TSH levels in the presence of elevated FT4 and FT3 concentrations
- Hypersecretion of GH and/or PRL, resulting in acromegaly and/or an amenorrhea/galactorrhea syndrome, are the most frequent associations
- The occurrence of invasive macroadenomas is particularly high among patients with previous thyroid ablation by surgery or radioiodine
- Chromophobes

Thyrotroph adenoma

- The presence of a goiter is the rule, even in the patients with previous partial thyroidectomy
- Thyroid residue may regrow as a consequence of TSH hyperstimulation.
- The occurrence of uni- or multinodular goiter is frequent (about 72% of reported cases), but progression towards functional autonomy seems to be rare.
- 5% of regrown thyroid nodule may be malignant

Gonadotroph adenoma

- Can be difficult to recognize because they: (1) secrete hormones inefficiently (as opposed to prolactinomas) and variably
- (2) the secretory products (LH, FSH) usually do not cause a recognizable clinical syndrome
- Present in middle age a space occupying lesions
- Impaired LH secretion leads to decreased energy and libido in men (due to reduced testosterone)
- and amenorrhea in premenopausal women.

Hypopituitarism

- Arising from deficiency of trophic hormones.
- 75% of parenchyma lost
- Isolated pituitary hormone deficiencies are rare.
- Subarachnoid hemorrhage and traumatic brain are most common causes
- Other causes:
- Ischemic injury (Sheehan syndrome, shock, sickle crisis), surgery or radiation, inflammatory reactions (sarcoid, tuberculosis, basilar meningitis)
- Compression of pituitary by tumor mass
- Non-functional pituitary adenomas.

Hypopituitarism

- Rathke cleft cyst
- Lined by ciliated cuboidal epithelium with occasional goblet cells and anterior pituitary cells can accumulate proteinaceous fluid and expand, compromising the normal gland.
- Craniopharyngioma
- Arise from Rathke's pouch during embryogenesis
- 5-10 years of age and >65 years of age
- 1-5% of all intracranial tumors
- Mass effect in pituitary as well as hypothalamus
- Pituitary hormones and ADH secretion affected

Craniopharyngioma

- Patients usually come to attention because of headaches and visual disturbances
- Children sometimes present with growth retardation due to pituitary hypofunction and GH deficiency.
- Abnormalities of the WNT signaling pathway, including activating mutations of the gene encoding β-catenin, have been reported

Craniopharyngioma

- Two distinct histologic variants are recognized:
- Adamantinomatous
- Most often observed in children
- Consists of nests or cords of stratified squamous epithelium embedded in a spongy “reticulum” that becomes more prominent in the internal layers.
- “Palisading” of the squamous epithelium is frequently observed at the periphery.
- Compact, lamellar keratin formation (“wet keratin”) is a diagnostic feature of this tumor
- Dystrophic calcification is a frequent
- Additional features include cyst formation, fibrosis, and chronic inflammation.

Craniopharyngioma

- Papillary craniopharyngioma
- Contain both solid sheets and papillae lined by well-differentiated squamous epithelium. These tumors usually lack keratin, calcification, and cysts.
- The squamous cells of the solid sections of the tumor lack the peripheral palisading and do not typically generate a spongy reticulum in the internal layers.
- Rare calcifications.

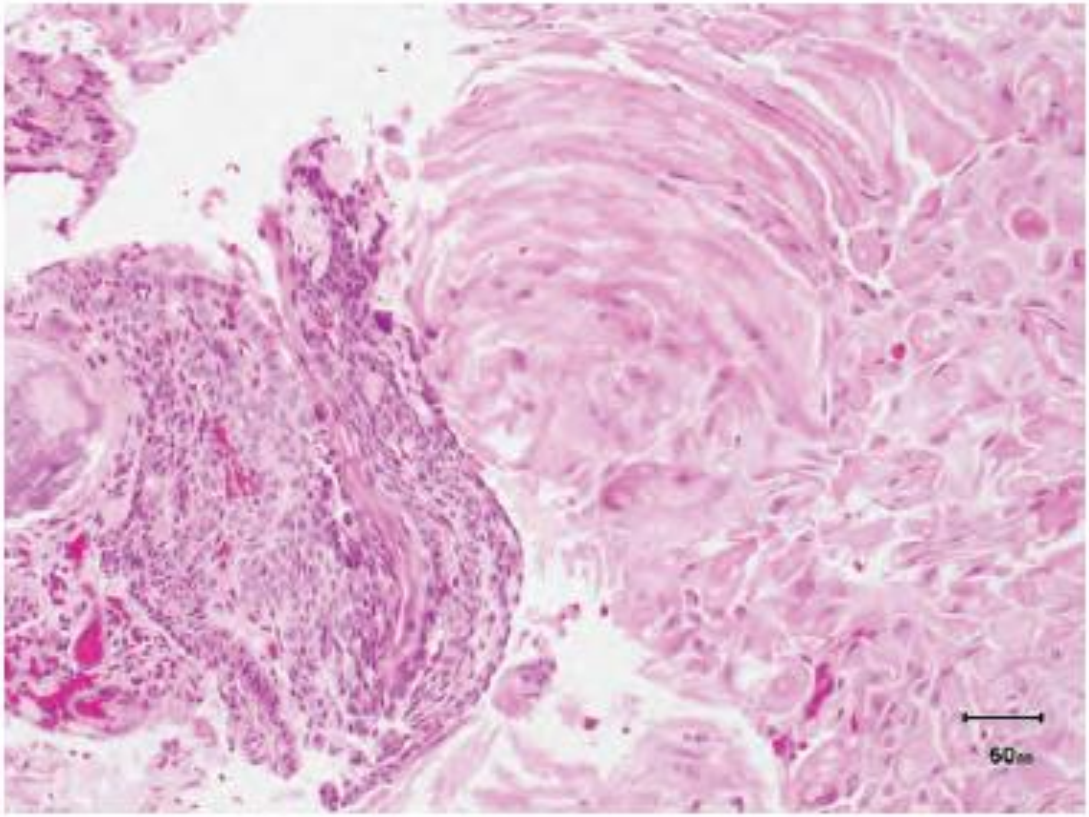


Figure 24-7 Adamantinomatous craniopharyngioma, demonstrating characteristic compact, lamellar "wet" keratin (right half of photomicrograph) and cords of squamous epithelium with peripheral palisading on the left. (Courtesy Dr. Charles Eberhart, Department of Pathology, Johns Hopkins University, Baltimore, Md.)

Hypopituitarism

- Empty sella syndrome
- Multiparous women
- A defect in the diaphragma sella allows the arachnoid mater and cerebrospinal fluid to herniate into the sella, expanding the sella and compressing the pituitary.
- Visual defects and prolactin excess common
- As a secondary cause, surgical removal of the pituitary
- Mutation of PIT-1 gene at 3p11.2
- Childhood
- GH, prolactin, TSH deficiency

Growth hormone deficiency

- Growth rate retarded in infants if deficient in growth hormone [0.25% incidence].
- No electrolyte abnormalities as adrenal secretion of mineralocorticoids not dependent on pituitary hormone.
- Hypothyroidism rare.
- May see delayed puberty.
- Somatomedin-C levels are low.
- First check growth charts to determine whether growth rate is slowing.
- Short is not an illness.

Height gain as related to age

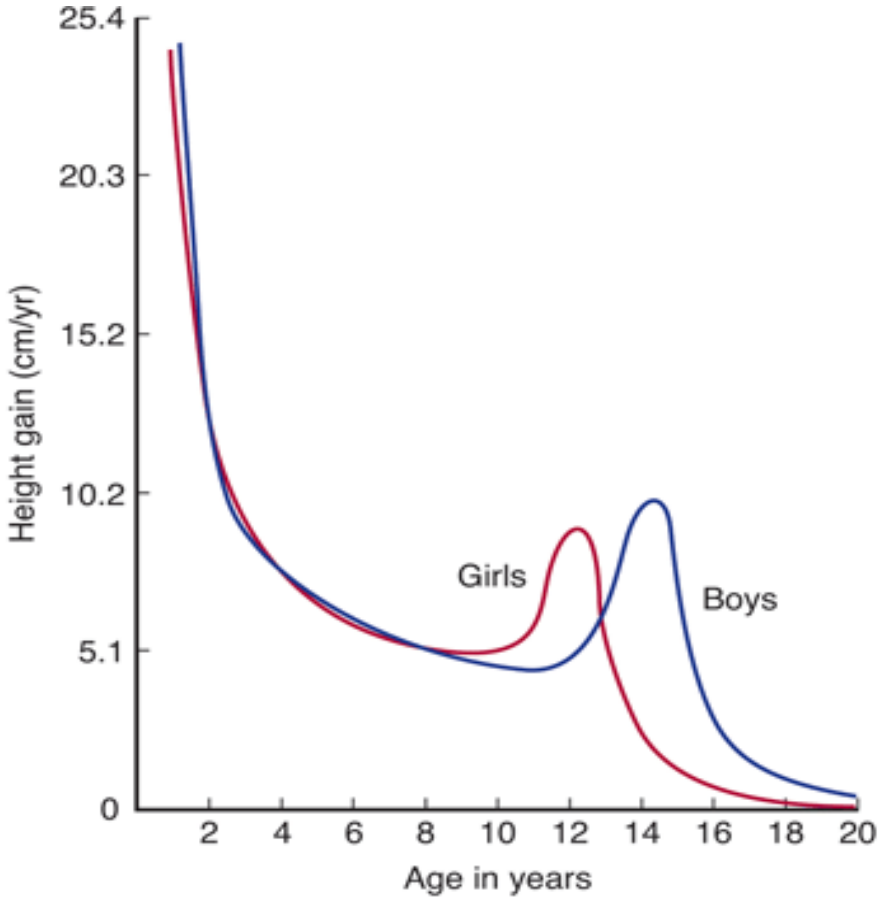
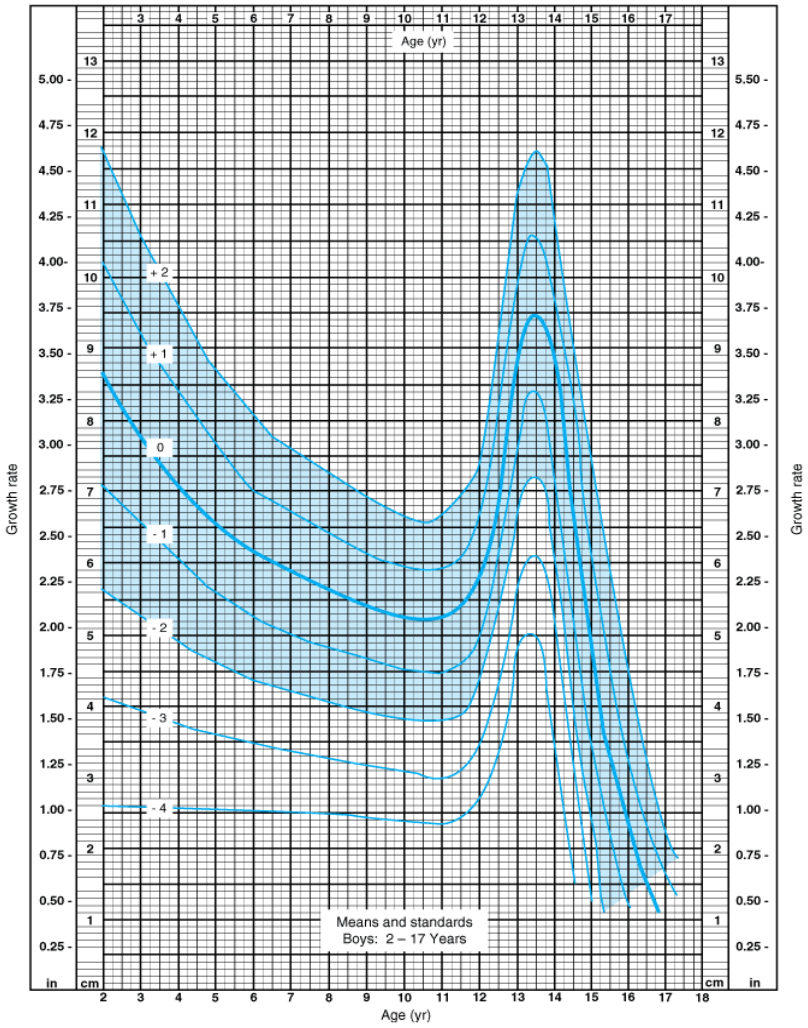
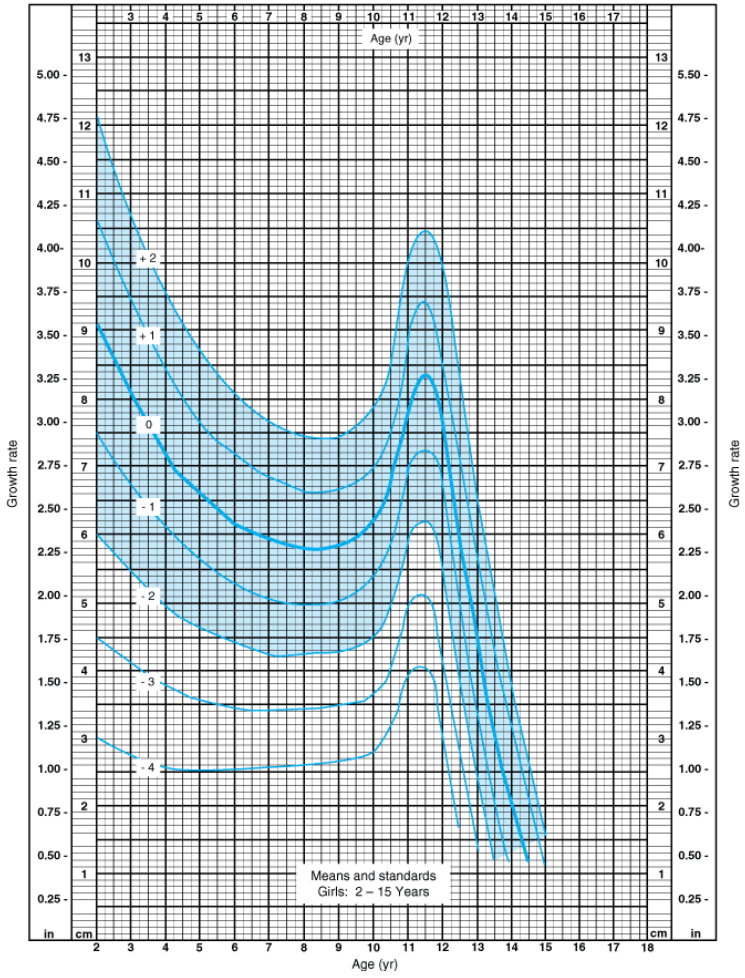


Fig. 24-8 Accessed 02/01/2010

Velocity of growth





(Redrawn, with permission, from Genentech, Inc.) Figs. 7-3, 4 Accessed 02/01/2010

Hazards of growth hormone administration

- In normal patients, growth hormone administration is associated with the evolution of carpal tunnel syndrome and may precipitate diabetes mellitus.
- Growth hormone is not an anti-aging agent.

Antidiuretic hormone

- The most important function of ADH is to conserve water by restricting diuresis during periods of dehydration and hypovolemia.
- Decreased blood pressure, sensed by pressure sensing receptors (baroreceptors) in the cardiac atria and carotids, stimulates ADH release.
- An increase in plasma osmotic pressure detected by osmoreceptors also triggers ADH secretion.
- States of hypervolemia and increased atrial distention result in inhibition of ADH secretion.

Antidiuretic hormone

- Diabetes insipidus.
- ADH deficiency
- Characterized by excessive urination (polyuria) due to an inability of the kidney to resorb water properly from the urine.
- Serum sodium and osmolality are increased by the excessive renal loss of free water, resulting in thirst and polydipsia.
- Hyponatremia is common.
- Central (CNS) or Nephrogenic (renal tubules resistant to ADH)
- Small cell carcinoma of the lung a frequent cause

Oxytocin

- Dilation of the cervix in pregnancy results in massive oxytocin release, leading to contraction of the uterine smooth muscle, facilitating parturition (uterine labor).
- Similarly, oxytocin released upon nipple stimulation in the postnatal period acts on the smooth muscles surrounding the lactiferous ducts of the mammary glands and facilitates lactation.