

Anterior Pituitary Gland

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 - Adrenocorticotrophic Hormone(ACTH)
 - Gonadotropins: FSH, LH
 - THYROID-STIMULATING HORMONE (TSH)
- Hypopituitarism
- Pituitary Tumor
 - Prolactinoma
 - Acromegaly
 - Cushing's disease

Anatomy

Anatomy

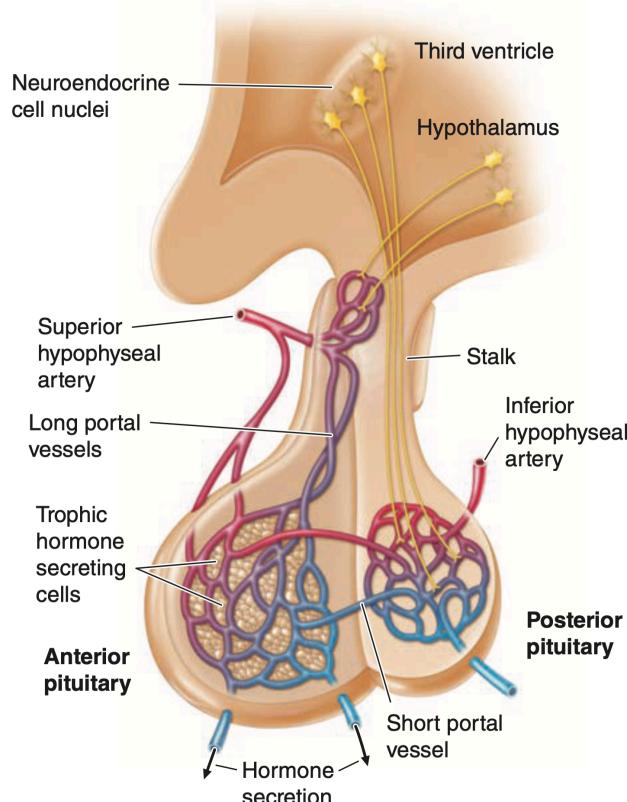


FIGURE 378-2 Diagram of hypothalamic-pituitary vasculature. The hypothalamic nuclei produce hormones that traverse the portal system and impinge on anterior pituitary cells to regulate pituitary hormone secretion. Posterior pituitary hormones are derived from direct neural extensions.

- The pituitary gland weighs ~600 mg and is located within the sella turcica ventral to the diaphragma sella; it consists of anatomically and functionally distinct anterior and posterior lobes.
- Blood supply of the pituitary gland comes from the superior and inferior hypophyseal arteries.
- The hypothalamic-pituitary portal plexus provides the major blood source for the anterior pituitary.

Anterior Pituitary Hormone Expression and Regulation

TABLE 378-1 Anterior Pituitary Hormone Expression and Regulation

CELL	CORTICOTROPE	SOMATOTROPE	LACTOTROPE	THYROTROPE	GONADOTROPE
Tissue-specific transcription factor	T-Pit	Prop-1, Pit-1	Prop-1, Pit-1	Prop-1, Pit-1, TEF	SF-1, DAX-1
Fetal appearance	6 weeks	8 weeks	12 weeks	12 weeks	12 weeks
Hormone	POMC	GH	PRL	TSH	FSH, LH
Protein	Polypeptide	Polypeptide	Polypeptide	Glycoprotein α , β subunits	Glycoprotein α , β subunits
Amino acids	266 (ACTH 1–39)	191	198	211	210, 204
Stimulators	CRH, AVP, gp-130 cytokines	GHRH, ghrelin	Estrogen, TRH, VIP	TRH	GnRH, activins, estrogen
Inhibitors	Glucocorticoids	Somatostatin, IGF-1	Dopamine	T_3 , T_4 , dopamine, somatostatin, glucocorticoids	Sex steroids, inhibin
Target gland	Adrenal	Liver, bone, other tissues	Breast, other tissues	Thyroid	Ovary, testis
Trophic effect	Steroid production	IGF-1 production, growth induction, insulin antagonism	Milk production	T_4 synthesis and secretion	Sex steroid production, follicle growth, germ cell maturation
Normal range	ACTH, 4–22 pg/L	<0.5 μ g/L ^a	M <15 μ g/L; F <20 μ g/L	0.1–5 mU/L	M, 5–20 IU/L; F (basal), 5–20 IU/L

^aHormone secretion integrated over 24 h.

Abbreviations: F, female; M, male. For other abbreviations, see text.

Source: Adapted with permission from Melmed S: Hypothalamic-pituitary regulation, in P Conn (ed): *Conn's Translational Neuroscience*. San Diego, CA: Elsevier; 2017.

Anterior pituitary hormones

- Growth Hormone(GH)
- Adrenocorticotropic Hormone(ACTH)
- Prolactin(PRL)
- Gonadotropins: FSH, LH
- THYROID-STIMULATING HORMONE (TSH)

Hormone	Stimulators	Inhibitors	Target
GH	GHRH, ghrelin	Somatostatin, IGF-1	Liver, bone, other tissues
ACTH	CRH, AVP, gp-130 cytokines	Glucocorticoids	Adrenal
PRL	Estrogen, TRH, VIP	Dopamine	Breast, other tissues
FSH, LH	GnRH, activins, estrogen	Sex steroids, inhibin	Ovary, testis
TSH	TRH	T3, T4, dopamine, somatostatin, glucocorticoids	Thyroid

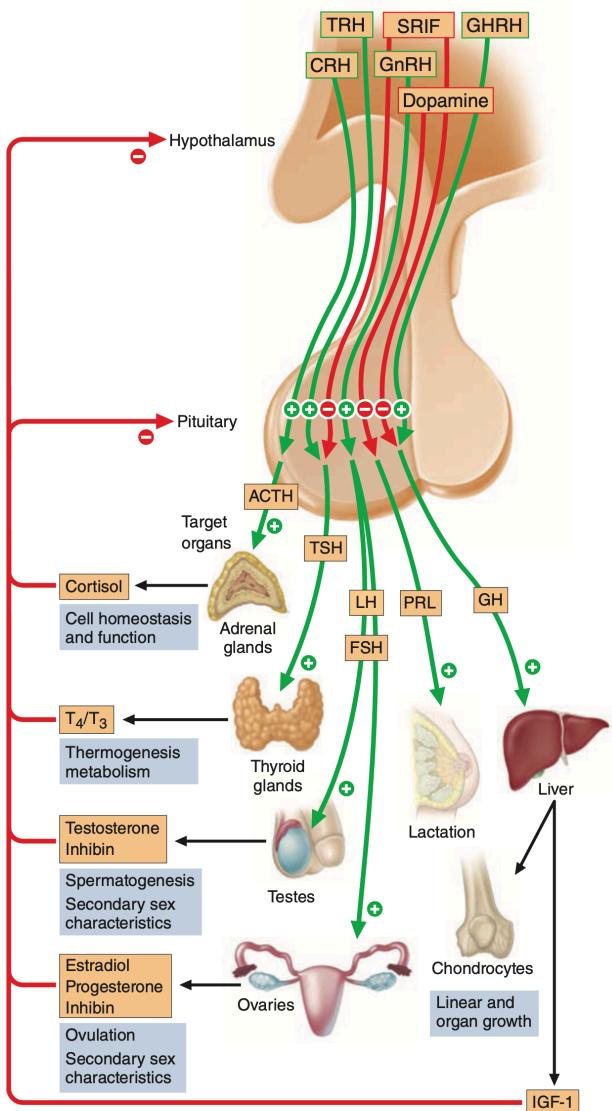
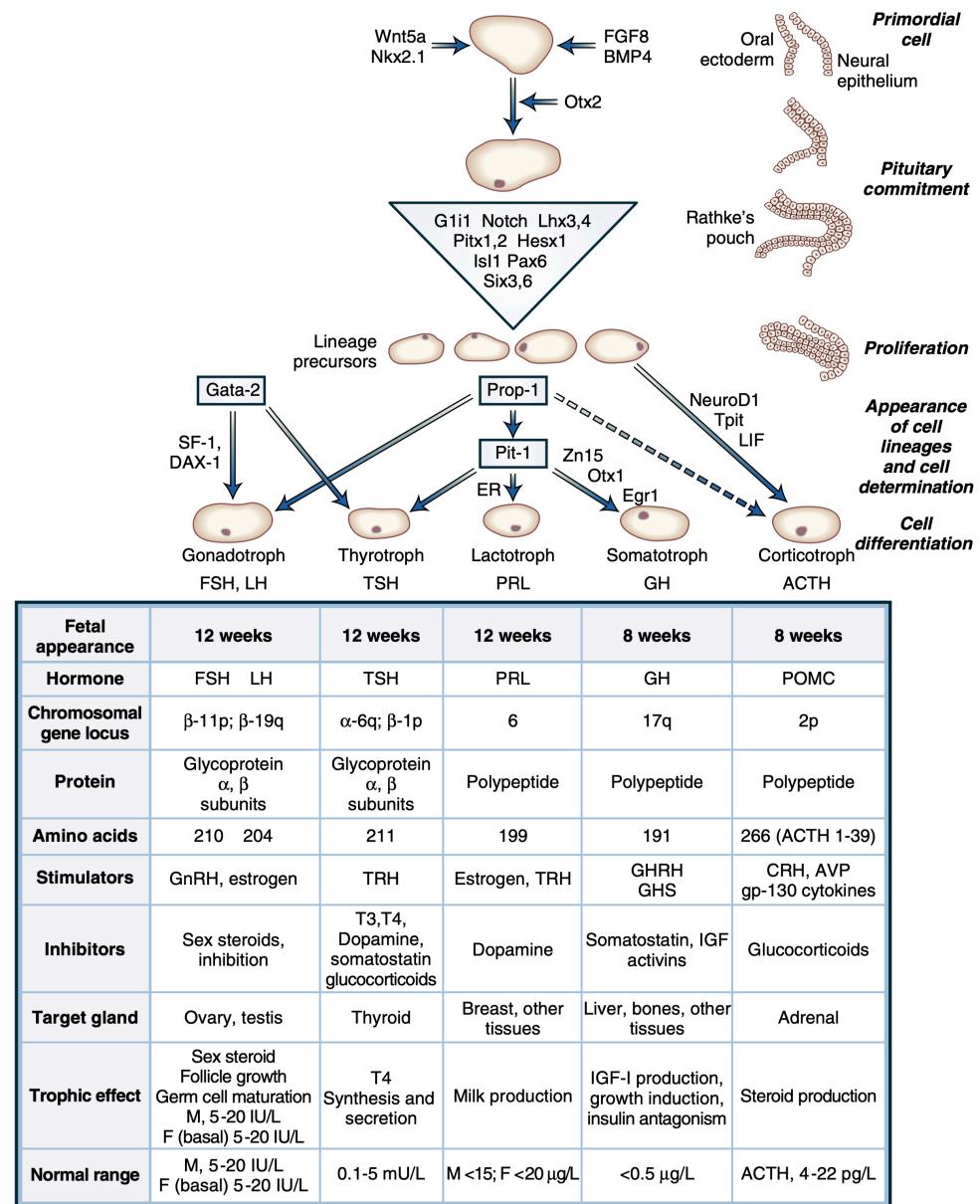
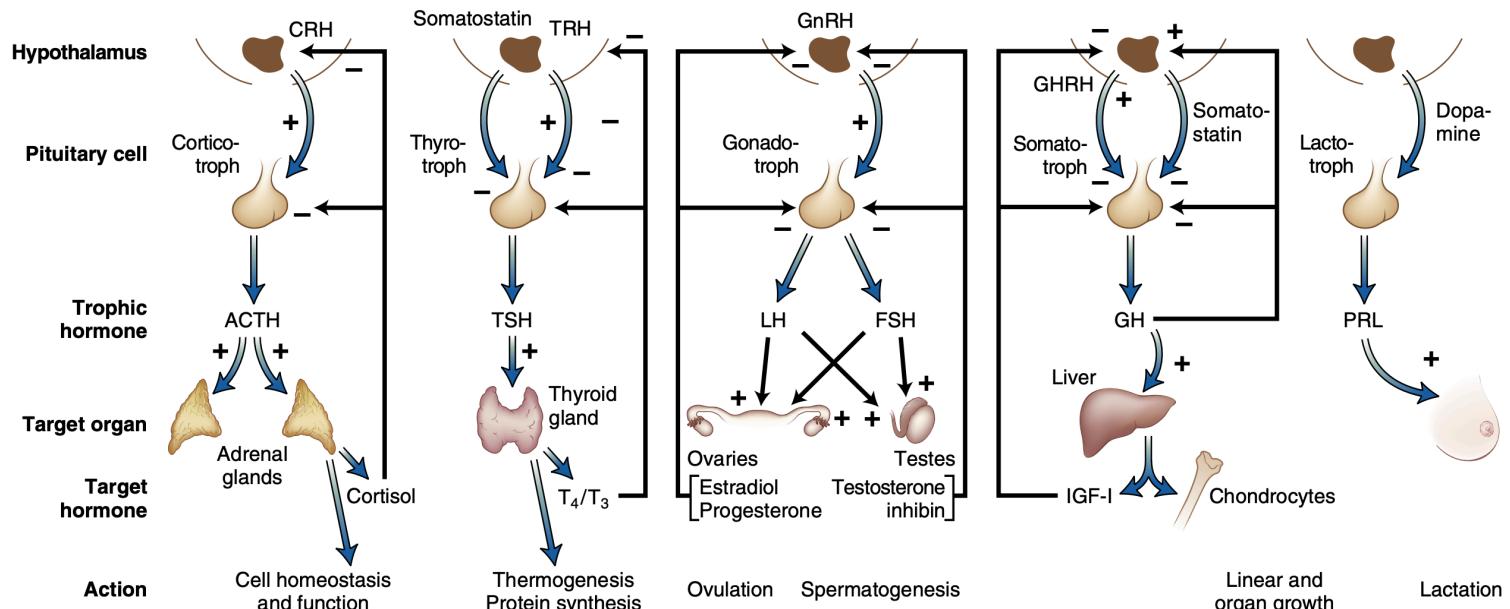
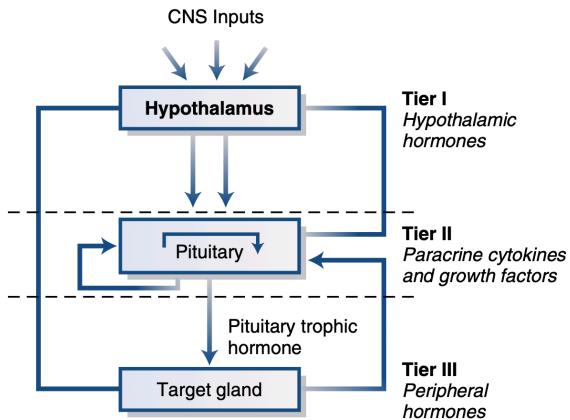


FIGURE 378-1 Diagram of pituitary axes. Hypothalamic hormones regulate anterior pituitary trophic hormones that in turn determine target gland secretion. Peripheral hormones feed back to regulate hypothalamic and pituitary hormones. For abbreviations, see text.



Fetal appearance	12 weeks	12 weeks	12 weeks	8 weeks	8 weeks
Hormone	FSH LH	TSH	PRL	GH	POMC
Chromosomal gene locus	β -11p; β -19q	α -6q; β -1p	6	17q	2p
Protein	Glycoprotein α , β subunits	Glycoprotein α , β subunits	Polypeptide	Polypeptide	Polypeptide
Amino acids	210 204	211	199	191	266 (ACTH 1-39)
Stimulators	GnRH, estrogen	TRH	Estrogen, TRH	GHRH GHS	CRH, AVP gp-130 cytokines
Inhibitors	Sex steroids, inhibition	T_3, T_4 , Dopamine, somatostatin glucocorticoids	Dopamine	Somatostatin, IGF activins	Glucocorticoids
Target gland	Ovary, testis	Thyroid	Breast, other tissues	Liver, bones, other tissues	Adrenal
Trophic effect	Sex steroid Follicle growth Germ cell maturation M, 5-20 IU/L F (basal) 5-20 IU/L	T4 Synthesis and secretion	Milk production	IGF-I production, growth induction, insulin antagonism	Steroid production
Normal range	M, 5-20 IU/L F (basal) 5-20 IU/L	0.1-5 mU/L	M <15; F <20 μ g/L	<0.5 μ g/L	ACTH, 4-22 pg/L

Pituitary Hormone Axes



- **Fig. 8.4** Control of hypothalamic-pituitary target organ axes. *ACTH*, adrenocorticotrophic hormone; *CRH*, corticotropin-releasing hormone; *FSH*, follicle-stimulating hormone; *GH*, growth hormone; *GHRH*, growth hormone-releasing hormone; *GnRH*, gonadotropin-releasing hormone; *IGF*, insulin-like growth factor; *LH*, luteinizing hormone; *PRL*, prolactin; T_3 , triiodothyronine; T_4 , thyroxine; *TRH*, thyrotropin-releasing hormone; *TSH*, thyroid-stimulating hormone. (Adapted from Melmed S. Mechanisms for pituitary tumorigenesis: the plastic pituitary. *J Clin Invest*. 2003;112:1603–1618.)

Pituitary Disorders

- The most frequent cause of pituitary disorders is pituitary gland tumors.
- Two types of tumors exist (secretory and non-secretory).
- The problems fall into three categories:
 - Hypersecretion
 - It is usually caused by a secretory pituitary gland tumor.
 - Hyposecretion
 - It is usually caused by a non-secretory tumor, interfering the ability of the normal pituitary gland to create hormones.
 - It can also be caused by a large secretory tumor. It can also happen after surgery or the radiation therapy.

Pituitary Disorders

- Tumor mass effects
 - As a pituitary gland tumor grows and presses against other areas in the brain, it may cause headaches, vision problems, or other health effects related to hyposecretion.
 - It can be seen in any type of pituitary tumor that grows large enough.
- Injuries, certain medications, and other conditions can also affect the pituitary gland. Loss of normal pituitary function also has been reported after major head trauma.

Hypopituitarism

TABLE 379-1 Etiology of Hypopituitarism^a

Development/structural

- Midline cerebral defect syndromes
- Pituitary dysplasia/aplasia
- Primary empty sella
- Congenital hypothalamic disorders (septo-optic dysplasia, Prader-Willi syndrome, Bardet-Biedl syndrome, Kallmann syndrome)
- Congenital central nervous system mass, encephalocele

Genetic

- Combined pituitary hormone deficiencies
- Isolated primary hormone deficiencies

Traumatic

- Surgical resection
- Radiotherapy damage
- Head injuries

Neoplastic

- Pituitary adenoma
- Parasellar mass (germinoma, ependymoma, glioma)
- Rathke's cyst
- Craniopharyngioma
- Hypothalamic hamartoma, gangliocytoma
- Pituitary metastases (breast, lung, colon carcinoma)
- Lymphoma and leukemia
- Meningioma

Infiltrative/inflammatory

- Lymphocytic hypophysitis
- Hemochromatosis
- Sarcoidosis
- Histiocytosis X
- Granulomatous hypophysitis
- Transcription factor antibodies
- Immunotherapy

Vascular

- Pituitary apoplexy
- Pregnancy-related (infarction with diabetes; postpartum necrosis)
- Subarachnoid hemorrhage
- Sickle cell disease
- Arteritis

Infections

- Fungal (histoplasmosis)
- Parasitic (toxoplasmosis)
- Tuberculosis
- Pneumocystis jirovecii*

Acquired Hypopituitarism

- Hypothalamic infiltration disorder
- Inflammatory lesions
- Cranial irradiation
 - doses as low as 18 Gy with higher doses (30–50 Gy) that can reach 50% to 100% within 3 to 5 years.
- Lymphocytic hypophysitis
- Pituitary apoplexy
 - Trauma, hemorrhage(Sheehan Syndrome)
- Empty sella

TABLE 8.14 Pituitary Dysfunction After Cranial Irradiation in Various Conditions

Condition Treated	Schedule	Dose (Gy)	Pituitary Dysfunction
Leukemia and lymphoma	Fractionated TBI	7–16	Isolated GHD, mostly pubertal children
	Fractionated cranial	18–24	Isolated GHD, mostly pubertal children Precocious puberty girls only
Nonpituitary brain tumors	Conventional fractionated cranial	30–50	GHD (30–100%) Gonadotrophin, TSH, ACTH, Prl (3–20%) Precocious puberty both sexes
Nasopharyngeal carcinoma and skull-base tumors	Conventional fractionated cranial	50–70	GHD (100% within 5 yr) Gonadotrophin, TSH, ACTH, Prl (20–50%)
Pituitary tumors	Conventional fractionated cranial	30–50	GHD (100% within 5 yr) Gonadotrophin, TSH, ACTH, Prl (20–60%)

Prl, Prolactin; *TBI*, Total body irradiation.

Modified from Darzy KH. Radiation-induced hypopituitarism after cancer therapy: who, how and when to test. *Nat Clin Pract Endocrinol Metab*. 2009;5:88–99.

TABLE 8.15 Assessment of Anterior Pituitary Function

Test	Dose	Normal Response	Side Effects
ACTH			
Insulin tolerance	0.1–0.15 U/kg IV	Peak cortisol response $>18 \mu\text{g}/\text{dL}$, or increase by $7 \mu\text{g}/\text{dL}$	Sweating, palpitation, tremor
Metyrapone	Oral administration of 30 mg/kg at 11 PM	Peak 11-DOC $\geq 7 \mu\text{g}/\text{dL}$ Peak cortisol $\leq 7 \mu\text{g}/\text{dL}$ Peak ACTH $>75 \text{ pg/mL}$	Nausea, insomnia, adrenal crisis
CRH stimulation	100 μg IV	Peak ACTH \geq twofold to fourfold Peak cortisol $\geq 20 \mu\text{g}/\text{dL}$ or $\uparrow \geq 7 \mu\text{g}/\text{dL}$	Flushing
ACTH stimulation	250 μg IV or IM or 1 μg IV	Peak cortisol $\geq 20 \mu\text{g}/\text{dL}$	Rare
TSH			
Serum T ₄ (free T ₄)			
Total T ₃			
TSI—third generation			
TRH stimulation	200–500 μg IV	Peak TSH \geq 2.5-fold or $\uparrow \geq 5$ –6 mU/L (females), $\uparrow \geq 2$ –3 mU/L (males)	Flushing, nausea, urge to micturate
PRL			
Serum PRL			
TRH stimulation	200–500 μg IV	PRL \geq 2.5-fold	Flushing, nausea, urge to micturate
LH/FSH			
Serum LH and FSH		Elevated in menopause and in men with primary testicular failure	
Serum testosterone		300–900 ng/mL (age-adjusted normal ranges)	
GnRH stimulation	100 μg IV	LH \geq twofold to threefold, or by 10 IU/L FSH 1.5–2-fold, or by 2 IU/L	Rare
GH			
Insulin tolerance	0.1–0.15 U/kg	GH peak $>5 \mu\text{g}/\text{L}$	Sweating, palpitation, tremor
Glucagon	1–1.5 mg IM	GH peak $>3 \mu\text{g}/\text{L}$	Nausea, headaches
L-Arginine plus GHRH		Peak GH $>9 \mu\text{g}/\text{L}$	
L-Arginine	0.5 g/kg (max 30 g) IV over 30 min		Nausea
GHRH	1 $\mu\text{g}/\text{kg}$		Flushing

ACTH, Adrenocorticotrophic hormone; CRH, corticotropin-releasing hormone; 11-DOC, 11-deoxycorticosterone; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, growth hormone-releasing hormone; GnRH, gonadotropin-releasing hormone; IM, intramuscular; IV, intravenous; LH, luteinizing hormone; PRL, prolactin; T₃, triiodothyronine; T₄, thyroxine; TSH, thyroid-stimulating hormone; TRH, thyrotropin-releasing hormone.

Treatment of hypopituitarism

TABLE 379-3 Hormone Replacement Therapy for Adult Hypopituitarism^a

HORMONE DEFICIT	HORMONE REPLACEMENT
ACTH	Hydrocortisone (10–20 mg/d in divided doses)
	Cortisone acetate (15–25 mg/d in divided doses)
	Prednisone (5 mg A.M.)
TSH	L-Thyroxine (0.075–0.15 mg daily)
FSH/LH	Males
	Testosterone gel (5–10 g/d)
	Testosterone skin patch (5 mg/d)
	Testosterone enanthate (200 mg IM every 2 weeks)
	Females
	Conjugated estrogen (0.65–1.25 mg qd for 25 days)
	Progesterone (5–10 mg qd) on days 16–25
	Estradiol skin patch (0.025–0.1 mg every week), adding progesterone on days 16–25 if uterus intact
GH	For fertility: menopausal gonadotropins, human chorionic gonadotropins
	Adults: Somatotropin (0.1–1.25 mg SC qd) Children: Somatotropin (0.02–0.05 mg/kg per day)
Vasopressin	Intranasal desmopressin (5–20 g twice daily) Oral 300–600 µg qd

Pituitary tumors

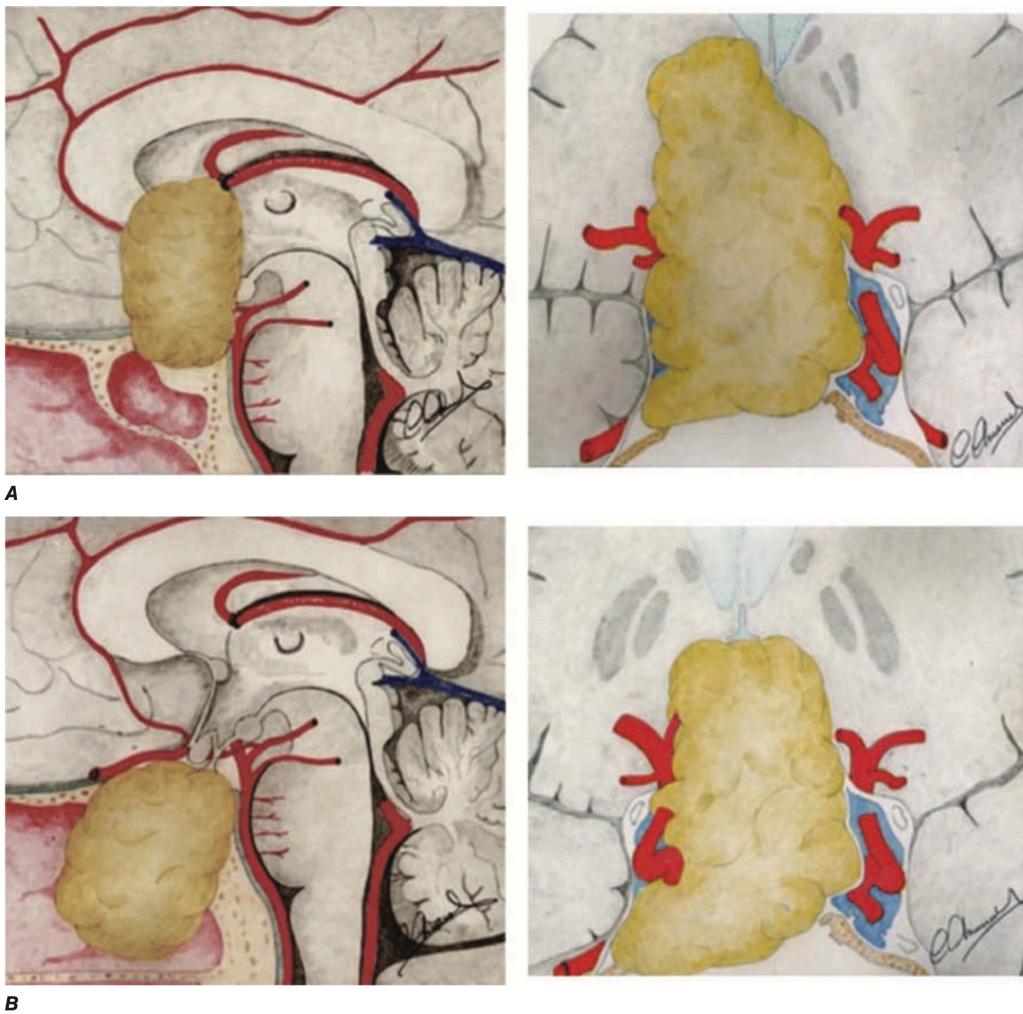
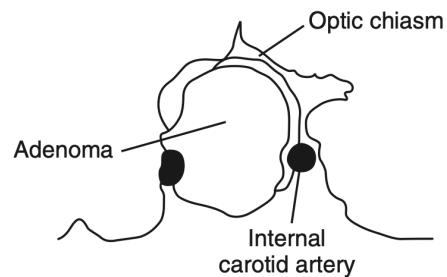
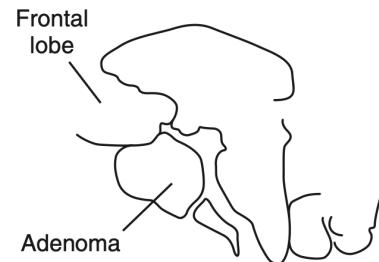
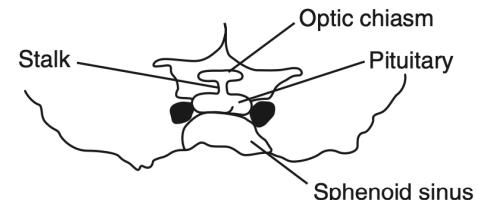
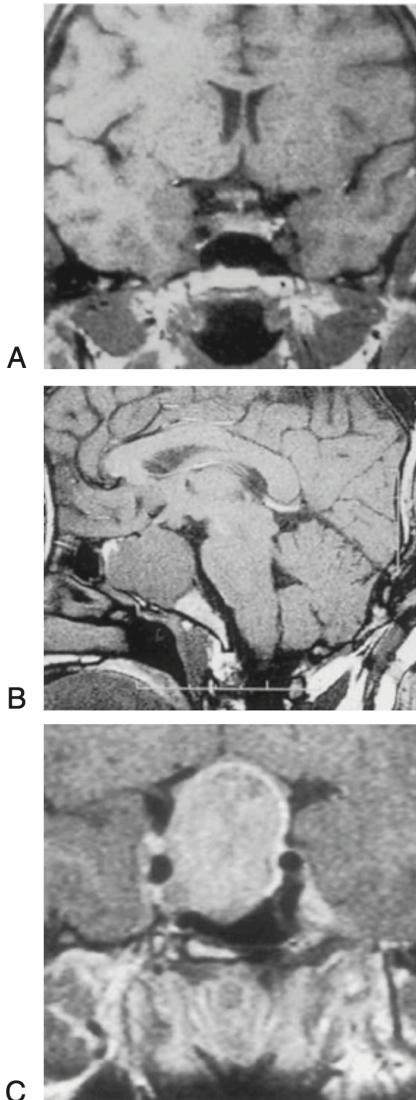


FIGURE 380-1 Expanding pituitary mass. Pituitary mass expansion may (A) impinge vital soft tissue structures and (B) invade the sphenoid sinus. (Reproduced with permission from P Cappabianca et al: Size does not matter. The intrigue of giant adenomas: a true surgical challenge. *Acta Neurochir (Wien)* 156:2217, 2014.)

Pituitary 附近



• **Fig. 9.1** Magnetic resonance images of the pituitary. (A) Coronal section of a normal pituitary gland. (B) Sagittal view of a large pituitary adenoma lifting and distorting the optic chiasm and invading the sphenoid sinus and impinging the frontal lobe. (C) Coronal view of a large macroadenoma elevating the optic chiasm and invading the right cavernous sinus.

Mass effect

TABLE 9.1 Local Effects of an Expanding Pituitary, Parasellar, or Hypothalamic Mass

Impacted Structure	Clinical Effect
Pituitary	Growth failure, adult hyposomatotropism, hypogonadism, hypothyroidism, hypoadrenalinism
Optic tract	Loss of red perception, bitemporal hemianopia, superior or bitemporal field defect, scotoma, blindness
Hypothalamus	Temperature dysregulation, obesity, diabetes insipidus; thirst, sleep; appetite, behavioral, and autonomic nervous system dysfunctions
Cavernous sinus	Ptosis, diplopia, ophthalmoplegia, facial numbness
Temporal lobe	Uncinate seizures
Frontal lobe	Personality disorder, anosmia
Central	Headache, hydrocephalus, psychosis, dementia, laughing seizures

Neuro-ophthalmologic tract	<i>Field defects:</i> Bitemporal hemianopia (50%), amaurosis with hemianopia (12%), contralateral or monocular hemianopia (7%)
	Scotomas—junctional; monocular central, arcuate, altitudinal; hemianopic
	Homonymous hemianopia
	<i>Acuity loss:</i>
	Snellen
	Contrast sensitivity
	Color vision
	Visual evoked potential
	<i>Pupillary abnormality:</i>
	Impaired light reactivity
	Afferent defect
	<i>Optic atrophy:</i>
	Papilledema
	Cranial nerve palsy—oculomotor, trochlear, abducens, sensory trigeminal
	Nystagmus
	Visual hallucinations
	Postfixation blindness

TABLE 380-2 Screening Tests for Functional Pituitary Adenomas

	TEST	COMMENTS
Acromegaly	Serum IGF-1 Oral glucose tolerance test with GH obtained at 0, 30, and 60 min	Interpret IGF-1 relative to age- and sex-matched controls Normal subjects should suppress growth hormone to <1 µg/L
Prolactinoma	Serum PRL	Exclude medications MRI of the sella should be ordered if PRL is elevated
Cushing's disease	24-h urinary free cortisol Dexamethasone (1 mg) at 11 P.M. and fasting plasma cortisol measured at 8 A.M. Late night salivary cortisol ACTH assay	Ensure urine collection is total and accurate Normal subjects suppress to <5 µg/dL Distinguishes adrenal adenoma (ACTH suppressed) from ectopic ACTH or Cushing's disease (ACTH normal or elevated)
Gonadotropinoma	Baseline FSH, LH, free α subunit, ovarian hyperstimulation, estrogen (females), testosterone (males) TRH stimulation test with assays for LH, FSH, free α subunit, free LHβ, free FSHβ subunits	Rare; more commonly nonfunctioning adenomas Consider screening for hypopituitarism Some gonadotropinomas exhibit an inappropriate gonadotropin response to TRH
TSH-producing adenoma	Free T ₄ , free T ₃ , TSH, free α subunit	Key feature is an inappropriately normal or high TSH in the setting of elevated free T ₄ and T ₃

Abbreviations: ACTH, adrenocorticotropin hormone; FSH, follicle-stimulating hormone; GH, growth hormone; IGF-I, insulin-like growth factor I; LH, luteinizing hormone; MRI, magnetic resonance imaging; PRL, prolactin; TSH, thyroid-stimulating hormone.

TABLE 380-3 Classification of Pituitary Adenomas^a

ADENOMA CELL ORIGIN	HORMONE PRODUCT	CLINICAL SYNDROME
Lactotrope	PRL	Hypogonadism, galactorrhea
Gonadotrope	FSH, LH, subunits	Silent, ovarian hyperstimulation, hypogonadism
Somatotrope	GH	Acromegaly/gigantism
Corticotrope	ACTH/none	Cushing's disease or silent
Mixed growth hormone and prolactin cell	GH, PRL	Acromegaly, hypogonadism, galactorrhea
Other plurihormonal cell	Any	Mixed
Acidophil stem cell	PRL, GH	Hypogonadism, galactorrhea, acromegaly
Mammosomatotrope	PRL, GH	Hypogonadism, galactorrhea, acromegaly
Thyrotrope	TSH	Thyrotoxicosis
Null cell	None	Hypopituitarism/none
Oncocytoma	None	Hypopituitarism/none

^aHormone-secreting tumors are listed in decreasing order of frequency. All tumors may cause local pressure effects, including visual disturbances, cranial nerve palsy, and headache.

Note: For abbreviations, see text.

Source: Adapted with permission from S Melmed: Pathogenesis of pituitary tumors. Nat Rev Endocrinol 7:257, 2011.

Other Sellar masses

- Craniopharyngiomas
- Rathke's cysts
- Sella chordomas
- Meningiomas
- Histiocytosis
- Pituitary metastases
- Hypothalamic hamartomas and gangliocytomas
- Hypothalamic gliomas and optic gliomas
- Brain germ cell tumor

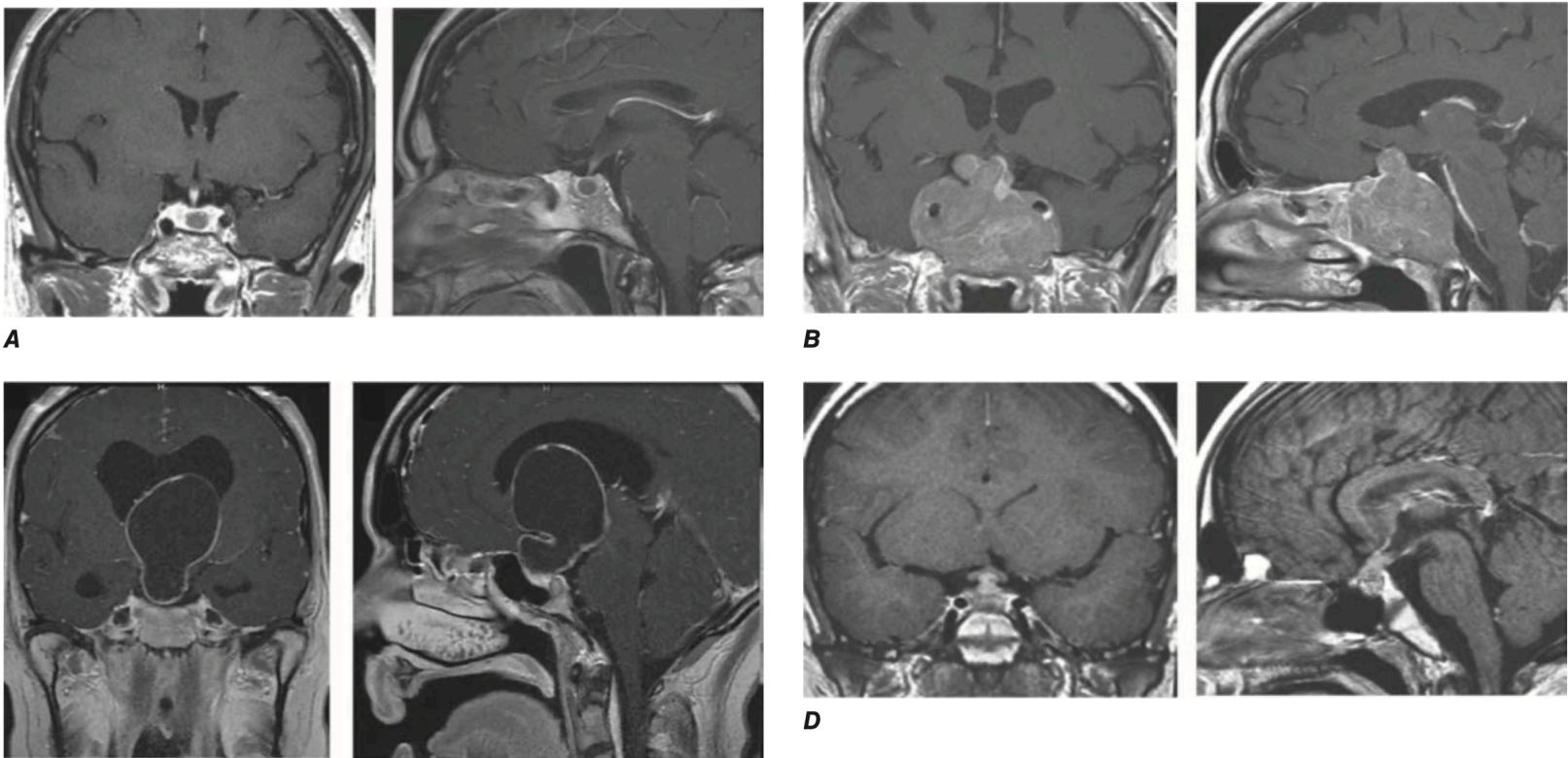
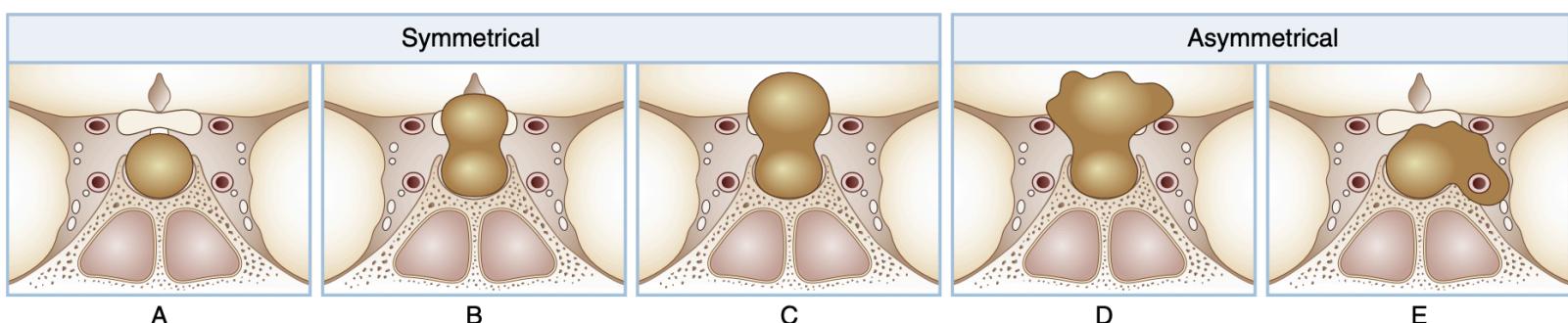
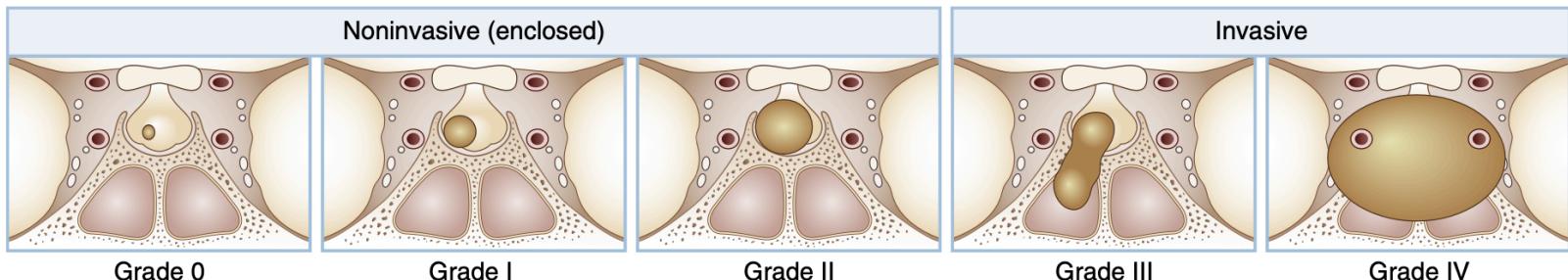
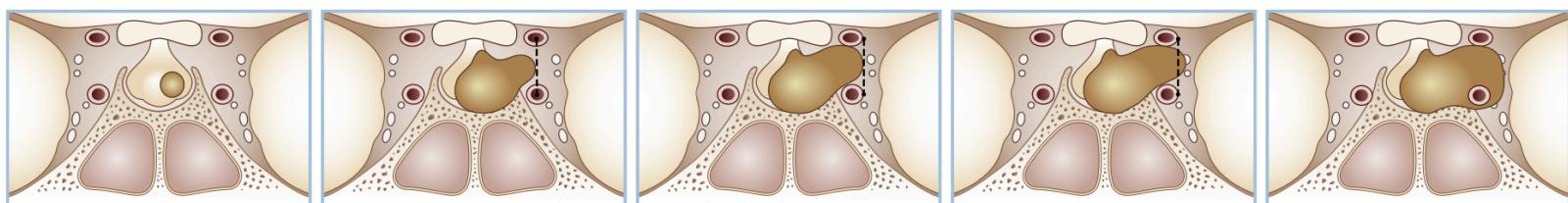


FIGURE 380-4 Imaging differential diagnosis of sellar masses. **A.** Microadenoma. **B.** Macroadenoma. **C.** Craniopharyngioma. **D.** Hypophysitis with stalk thickening. (C: Reproduced with permission from Muller HL: Childhood craniopharyngioma. Recent advances in diagnosis, treatment and follow-up. *Horm Res* 69:193, 2008. A, B, D: Used with permission from Vivien Bonert, MD.)



HARDY CLASSIFICATION SYSTEM



KNOSP CLASSIFICATION SYSTEM

B

Prolactinoma

Etiology and Prevalence

- Prolactin: Normal range: M<15, F<20 µg/L
- Prolactinomas are the most frequently encountered secretory pituitary tumors
- incidence of approximately 30 per 100,000 population
- The female:male ratio for microprolactinomas is 20:1; macroprolactinomas is 1:1
- Macroprolactinomas have a greater propensity to grow and tumor size correlates with serum PRL levels
- PRL level higher than 200 ng/mL is strongly indicative of a PRL- secreting pituitary tumor
 - < 100 µg/L → microadenomas
 - > 200 µg/L → macroadenomas
- MRI should be performed in all patients with hyperprolactinemia

TABLE 380-5 Etiology of Hyperprolactinemia**I. Physiologic hypersecretion**

- Pregnancy
- Lactation
- Chest wall stimulation
- Sleep
- Stress

II. Hypothalamic-pituitary stalk damage

- Tumors
 - Craniopharyngioma
 - Suprasellar pituitary mass
 - Meningioma
 - Dysgerminoma
 - Metastases
- Empty sella
- Lymphocytic hypophysitis
- Adenoma with stalk compression
- Granulomas
- Rathke's cyst
- Irradiation

Trauma

- Pituitary stalk section
- Suprasellar surgery

III. Pituitary hypersecretion

- Prolactinoma
- Acromegaly

IV. Systemic disorders

- Chronic renal failure
- Hypothyroidism
- Cirrhosis
- Pseudocyesis
- Epileptic seizures

V. Drug-induced hypersecretion

- Dopamine receptor blockers
 - Atypical antipsychotics: risperidone
 - Phenothiazines: chlorpromazine, perphenazine
 - Butyrophenones: haloperidol
 - Thioxanthenes
 - Metoclopramide
- Dopamine synthesis inhibitors
 - α -Methyldopa
- Catecholamine depletors
 - Reserpine
 - Opiates
 - H₂ antagonists
 - Cimetidine, ranitidine
 - Imipramines
 - Amitriptyline, amoxapine
 - Serotonin reuptake inhibitors
 - Fluoxetine
- Calcium channel blockers
 - Verapamil
 - Estrogens
 - Thyrotropin-releasing hormone

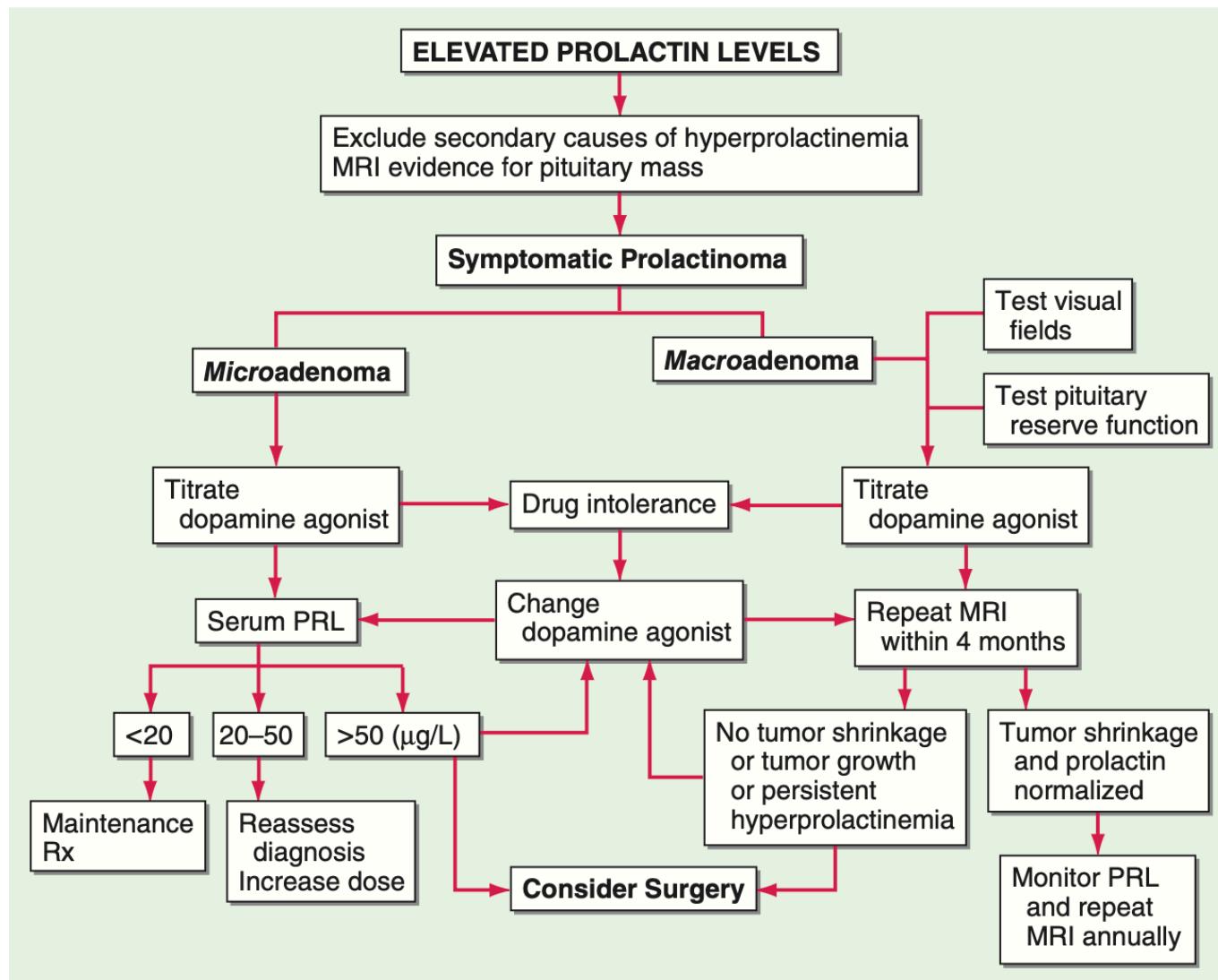
Presentation and Diagnosis

- Women:
 - amenorrhea, infertility, galactorrhea, visual field defects, mass effects
 - Galactorrhea is present in up to 80% of hyperprolactinemic women.
 - Decreased libido, weight gain, and mild hirsutism
 - If hyperprolactinemia is sustained, vertebral bone mineral density can be reduced.
- Men:
 - impotence, loss of libido, infertility, headache, visual field defects, mass effects
 - Long-standing, secondary effects of hypogonadism including osteopenia, osteoporosis, reduced muscle mass, and decreased beard growth

TABLE 9.16 Signs and Symptoms of Prolactinomas

Associated With Tumor Mass	Associated With Hyperprolactinemia
Visual field abnormalities	Amenorrhea, oligomenorrhea, infertility
Blurred vision or decreased visual acuity	Decreased libido, impotence, pre-mature ejaculation, oligospermia
Symptoms of hypopituitarism	Galactorrhea
Headaches	Osteoporosis
Cranial nerve palsies	
Pituitary apoplexy	
Seizures (temporal lobe)	
Hydrocephalus (rare)	
Unilateral exophthalmos (rare)	

Management of prolactinoma



Medical treatment

- Medical management of prolactinomas with dopamine agonist drugs has been widely recommended as the treatment of choice
- Oral dopamine agonists (cabergoline and bromocriptine) are the mainstay of therapy for patients with micro- or macroprolactinomas.
- About 20% of patients (especially males) are resistant to dopaminergic treatment
- Side Effects of dopamine agonists:
 - Nausea , nasal stuffiness, depression, digital vasospasm Postural hypotension ,symptoms of psychosis CSF rhinorrhea, hepatic dysfunction and cardiac arrhythmias (rare)

Cabergoline

1. A long-acting dopamine agonist (0.5 to 1.0 mg twice weekly).
2. Normalizes PRL and resumption of normal gonadal function in 80% of microadenomas; normalizes PRL and shrinks 70% of macroadenomas.
3. Mass effect symptoms usually improve within days after cabergoline initiation; improvement of sexual function requires several weeks of treatment .

Bromocriptine mesylate

1. A short-acting dopamine agonist, preferred when pregnancy is desired.
2. Initiated by administering a low bromocriptine dose (0.625–1.25 mg) at bedtime with a snack, followed by gradually increasing the dose. Most patients are controlled with a daily dose of 7.5 mg (2.5 mg tid)

Surgery

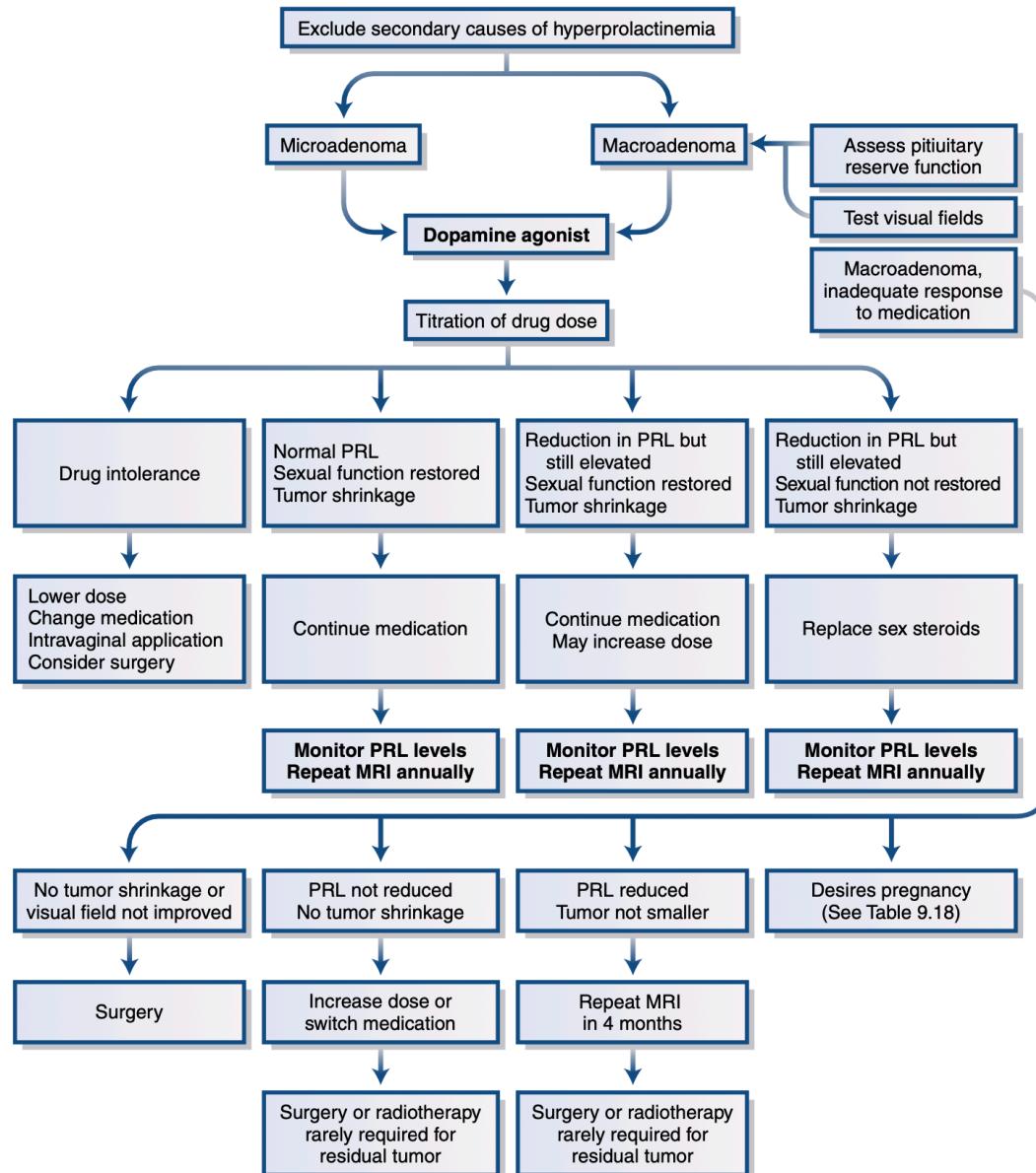
- Indications include dopamine resistance or intolerance and the presence of an invasive macroadenoma with compromised vision that fails to improve after drug treatment.
- Initial PRL normalization is achieved in about 70% of microprolactinomas on, but only 30% of macroadenomas can be resected successfully.
- Follow-up studies have shown that hyperprolactinemia recurs in up to 20% of patients within the first year after surgery; long-term recurrence rates exceed 50% for macroadenomas.

Radiation Therapy

- Radiotherapy is reserved for aggressive tumors that do not respond to maximally tolerated dopamine agonists and/or surgery.
- Linear accelerator radiotherapy is effective in controlling or reducing the tumor size.
- It takes years to achieve maximal effect.
- Higher doses are associated with complication

Chemotherapy

- For aggressive PRL-secreting tumors unresponsive to other therapies, temozolomide, an alkylating compound that readily crosses the blood-brain barrier, may control tumor growth.



• **Fig. 9.26** Prolactinoma management. After secondary causes of hyperprolactinemia have been excluded, subsequent management decisions are based on clinical imaging and biochemical criteria. *MRI*, magnetic resonance imaging; *PRL*, prolactin.

Management of patients planning pregnancies

Microadenoma	Macroadenoma
Discontinue dopamine agonist when pregnancy test is positive	Consider surgery before pregnancy Ensure bromocriptine sensitivity before pregnancy
Periodic visual field examinations during pregnancy	Monitor visual fields expectantly and frequently
Postpartum magnetic resonance imaging (MRI) after 6 weeks ^a	Administer bromocriptine if vision becomes compromised Or continue bromocriptine throughout pregnancy if tumor previously affected vision Consider high-dose steroids or surgery during pregnancy if vision is threatened or adenoma hemorrhage occurs Postpartum MRI after 6 weeks

^aPituitary MRI may be performed during pregnancy if deemed necessary.

Acromegaly

Incidence

The prevalence of acromegaly is estimated to range from 28 to 137 cases per million. Recent surveys indicate an increase in the annual incidence to about 10 cases per million

Pathogenesis

GH and IGF1 act both independently and dependently to induce features of hypersomatotropism.
Acromegaly is caused by pituitary tumors secreting GH or very rarely by extrapituitary disorders

Etiology

TABLE 380-6 Causes of Acromegaly

	PREVALENCE, %
Excess Growth Hormone Secretion	
Pituitary	98
Densely or sparsely granulated GH cell adenoma	60
Mixed GH cell and PRL cell adenoma	25
Mammosomatotrope cell adenoma	10
Plurihormonal adenoma	
GH cell carcinoma or metastases	
Multiple endocrine neoplasia 1 (GH cell adenoma)	
McCune-Albright syndrome	
Ectopic sphenoid or parapharyngeal sinus pituitary adenoma	
Extrapituitary tumor	<1
Pancreatic islet cell tumor	
Lymphoma	
Excess Growth Hormone-Releasing Hormone Secretion	
Central	<1
Hypothalamic hamartoma, choristoma, ganglioneuroma	
Peripheral	<1
Bronchial carcinoid, pancreatic islet cell tumor, small-cell lung cancer, adrenal adenoma, medullary thyroid carcinoma, pheochromocytoma	

Abbreviations: GH, growth hormone; PRL, prolactin.

Source: Data from S Melmed: Medical progress: Acromegaly. N Engl J Med 355:2558, 2006.

Cause	Prevalence (%)	Hormonal Products	Clinical Features	Pathologic Characteristics
Excess GH Secretion				
Pituitary	98			
Densely granulated GH cell adenoma	30	GH	Slow growing, clinically insidious	Resemble normal somatotrophs, numerous large secretory granules
Sparingly granulated adenoma	30	GH	Rapidly growing, often invasive	Cellular pleomorphism, characteristic ultrastructure
Mixed GH cell and PRL cell adenoma	25	GH and PRL	Variable	Densely granulated somatotrophs, sparsely granulated lactotrophs
Mammosomatotroph cell adenoma	10	GH and PRL	Common in children; gigantism, mild hyperprolactinemia	Both GH and PRL in same cell, often same secretory granule
Acidophil stem cell adenoma		PRL and GH	Rapidly growing, invasive, hyperprolactinemia dominant	Distinctive ultrastructure, giant mitochondria
Plurihormonal adenoma		GH (PRL with α GSU, FSH/LH, TSH, or ACTH)	Often secondary hormonal products are clinically silent	Variable; either monomorphic or plurimorphous
GH cell carcinoma or metastases		GH	Usually aggressive	Documented metastasis
MEN1 (adenoma)		GH or PRL	Pancreatic, parathyroid, or pituitary tumors	Adenoma
McCune-Albright syndrome		GH, PRL	Classic triad	Hyperplasia
Ectopic sphenoid or parapharyngeal sinus pituitary adenoma		GH	Ectopic mass	Adenoma
Familial acromegaly		GH	Young patients	Large adenomas
Carney syndrome		GH	Classic syndrome	Adenoma
Extrapatuitary Tumor				
Pancreatic islet cell tumor	<1			Small pituitary
Excess GHRH Secretion				
Central—hypothalamic hamartoma, choristoma, ganglion-neuroma	<1		Hypothalamic mass	Somatotroph hyperplasia
Peripheral—bronchial carcinoid, pancreatic islet cell tumor, small cell lung cancer, adrenal adenoma, medullary thyroid carcinoma, pheochromocytoma	1	GH, PRL	Systemic features	Somatotroph hyperplasia, rarely adenoma
ACTH, Adrenocorticotrophic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, growth hormone-releasing hormone; α GSU, glycoprotein α -subunit; LH, luteinizing hormone; MEN1, multiple endocrine neoplasia type 1; PRL, prolactin; TSH, thyroid-stimulating hormone.				
Adapted from Melmed S. Medical progress: Acromegaly. <i>N Engl J Med</i> . 2006;355:2558–2573; Melmed S, Braunstein GD, Horvath E, et al. Pathophysiology of acromegaly. <i>Endocr Rev</i> . 1983;4:271–290.				

Physical changes

- Enlarged nose and prognathism
- Overgrowth of extremities
- Prominence of the brow
- Jaw malocclusion
- Acral overgrowth
- Soft-tissue hypertrophy
- Hyperhidrosis
- Thickened skin

Respiratory complications

- Upper airway obstruction
- Ventilatory dysfunction
- Sleep apnea
- Excessive snoring

Metabolism and endocrine complications

- Impaired glucose tolerance
- Insulin resistance and hyperinsulinemia
- Diabetes mellitus
- Other endocrinologic derangements

Gastrointestinal complications

- Colonic polyps
- Colonic cancer

Local tumor effects

- Headache
- Visual impairments
- Increased intracranial pressure
- Hypopituitarism
- Apoplexy

Cardiovascular complications

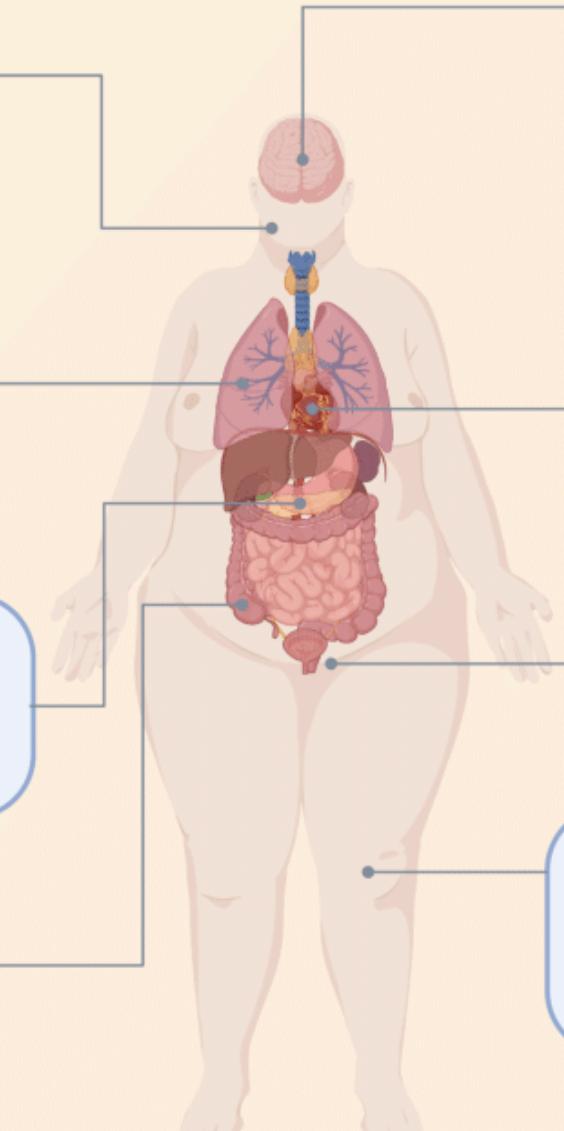
- Hypertension
- Cardiomyopathy
- Arrhythmias
- Congestive heart failure
- Coronary heart disease
- Valve disease
- Atherosclerosis
- Stroke

Reproductive disorders

- Menstrual disturbance
- Galactorrhea
- Decreased libido

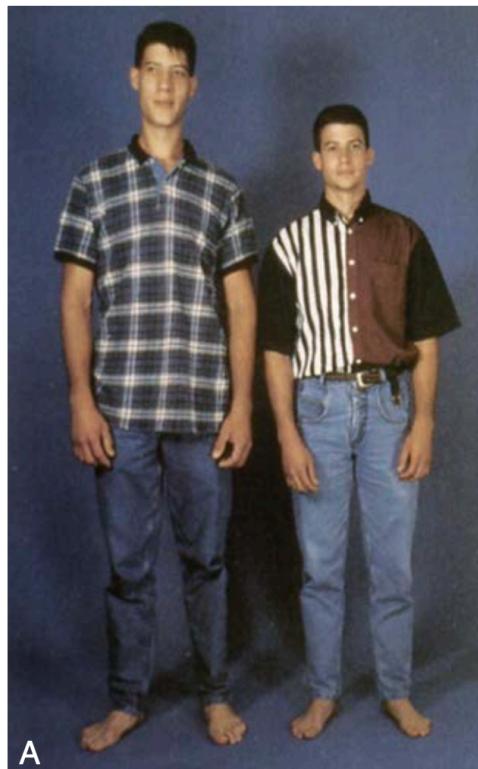
Skeletal system complications

- Carpal tunnel syndrome
- Arthropathy
- Osteoporosis
- Vertebral fractures
- Thickened articular cartilage



Local Tumor Effects		
Cranial nerve palsy, Headache, Pituitary enlargement, Visual field defects		
Somatic Effects		Visceromegaly
Acral Enlargement <ul style="list-style-type: none"> Thickness of hand and feet soft tissue Cardiovascular <ul style="list-style-type: none"> Asymmetric septal hypertrophy Cardiomyopathy Congestive heart failure Hypertension Left-ventricular hypertrophy Colon <ul style="list-style-type: none"> Polyps Pulmonary <ul style="list-style-type: none"> Narcolepsy Sleep apnea—central and obstructive Sleep disturbances 	Musculoskeletal <ul style="list-style-type: none"> Acroparesthesia Arthralgias and arthritis Carpal tunnel syndrome Gigantism Hypertrophy of frontal bones Jaw malocclusion Prognathism Proximal myopathy Skin <ul style="list-style-type: none"> Hyperhidrosis Oiliness Skin tags 	<ul style="list-style-type: none"> Kidney Liver Prostate Salivary gland Spleen Thyroid Tongue

Endocrine And Metabolic Effects	
Carbohydrate	Multiple endocrine neoplasia type 1
<ul style="list-style-type: none"> • Diabetes mellitus • Impaired glucose tolerance • Insulin resistance and hyperinsulinemia 	<ul style="list-style-type: none"> • Hyperparathyroidism • Pancreatic islet cell tumors
Electrolytes	Reproduction
<ul style="list-style-type: none"> • Increased aldosterone • Low renin 	<ul style="list-style-type: none"> • Decreased libido, impotence, low sex hormone-binding globulin • Galactorrhea • Menstrual abnormalities
Lipids	Thyroid
<ul style="list-style-type: none"> • Hypertriglyceridemia 	<ul style="list-style-type: none"> • Goiter • Low thyroxine-binding globulin
Minerals	
<ul style="list-style-type: none"> • Hypercalciuria, increased 1,25(OH)2D3 • Urinary hydroxyproline 	



Acromegaly

- More than 95% acromegaly harbor a GH-secreting pituitary adenoma
- Mixed GH-cell and PRL-cell adenomas are composed of distinct somatotrophs expressing GH and lactotrophs expressing PRL.
- Screening colonoscopy for colon cancer should be performed at diagnosis
- The most significant mortality determinants are GH levels and the presence of coexisting cardiac disease.
- Control of GH levels to less than 2.5 µg/L significantly reduces morbidity and mortality

Diagnosis

Measurement of Growth Hormone and IGF1 Levels

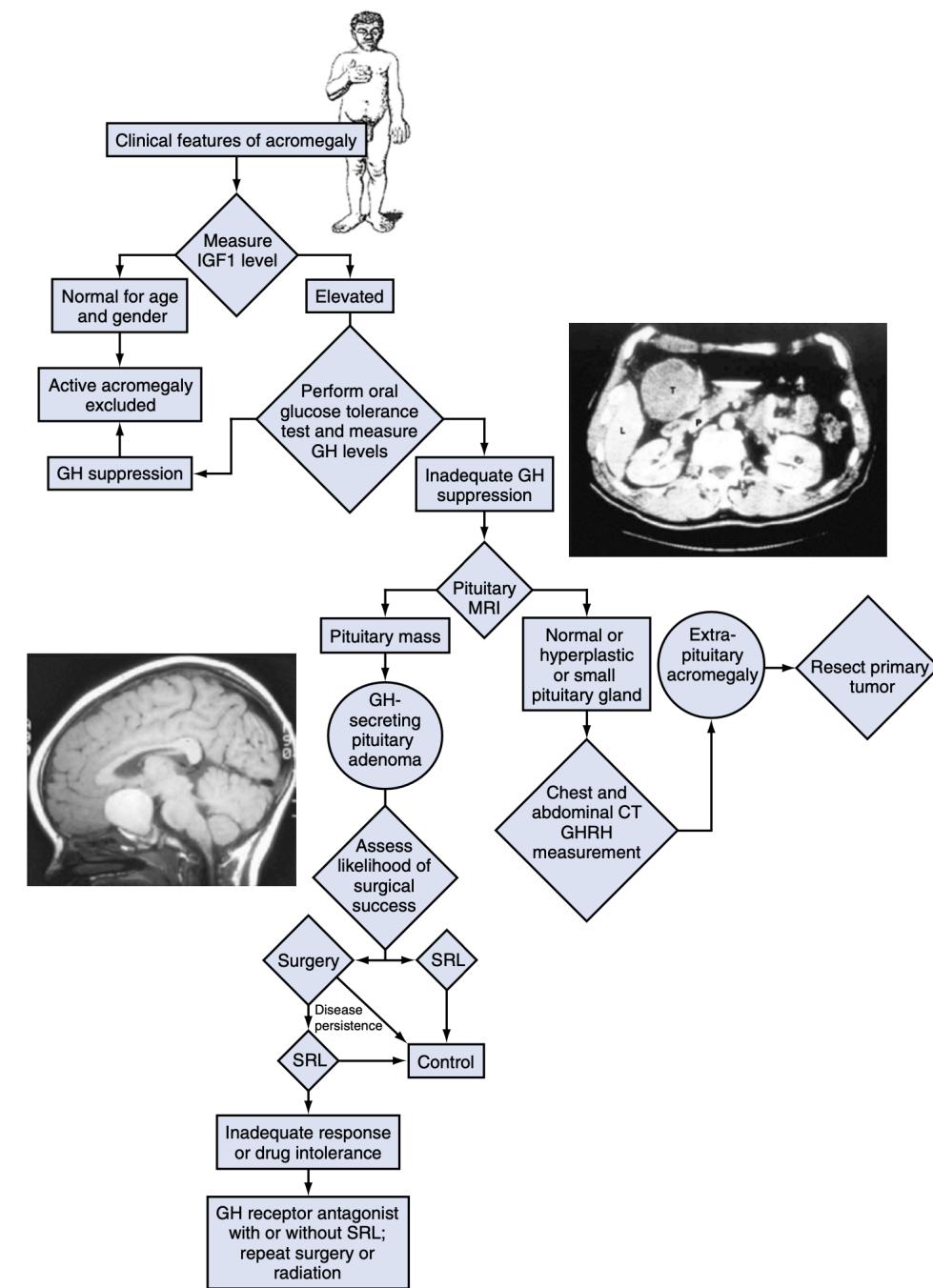
- Age- and sex-matched serum IGF-I level provides a useful laboratory **screening measure**.
- The diagnosis is confirmed by demonstrating the failure of GH suppression to $< 1\mu\text{g/L}$ within 1 h of an oral glucose load (75 g).
- Differential Diagnosis.
 - GHRH
 - Ectopic

Oral Glucose Tolerance Test (OGTT)

For the diagnosis of acromegaly

Blood sampling: GH at 0 min, 30 min, 60 min, 90 min, 120min

- Normal response: GH nadir < 1 ng/mL, usually at 60 min
- Acromegaly:
 - GH nadir > 1 ng/mL (lower cut-off in newer more sensitive assays); 1/3 increase, 1/3 remain unchanged, 1/3 fall modestly (but not < 1 ng/mL)
- False positive: starvation, protein-caloric malnutrition, anorexia nervosa



Management goals

- Control tumor growth.
- Relieve central compressive effects.
- Preserve or restore pituitary trophic hormone function.
- Treat comorbidities (hypertension, cardiac failure, hyperglycemia, sleep apnea, arthritis).
- Normalize mortality rates.
- Prevent biochemical recurrence

Surgery

- Transsphenoidal surgical resection by an experienced surgeon is the preferred primary treatment for both microadenomas (cure rate 70%) and macroadenomas (<50% cured).
- Soft tissue swelling improves immediately after tumor resection. GH levels return to normal within an hour, and IGF-I levels are normalized within 3–4 days.
- In 10% of patients, acromegaly may recur several years after apparently successful surgery; hypopituitarism develops in up to 15% of patients after surgery.

Radiation therapy

- External radiation therapy or high-energy stereotactic techniques are used as adjuvant therapy for acromegaly.
- Patients may require interim medical therapy for several years before attaining maximal radiation benefits.
- Most patients also experience hypothalamic-pituitary damage, leading to gonadotropin, ACTH, and/or TSH deficiency within 10 years of therapy.

Medical treatment

Somatostatin Analogues(somatostatin receptor ligands)

- Somatostatin analogues exert their therapeutic effects through SSTR2 and SSTR5 receptors, both express in GH-secreting tumors.
- Octreotide is administered by subcutaneous injection, beginning with 50 g tid; the dose can be increased gradually up to 1500 g/d.
- Sandostatin-LAR is a sustained-release, long-acting octreotide sustaining for several weeks. GH suppression occurs for as long as 6 weeks after a 30-mg intramuscular injection; long-term monthly treatment sustains GH and IGF-I suppression and also reduces pituitary tumor size in 50% of patients
- Anreotide autogel, a slow-releasing somatostatin analogue, suppresses GH and IGF-I hypersecretion after a 60-mg subcutaneous injection. Long-term monthly administration controls GH hypersecretion in two-thirds of treated patients.

Side Effects

- drug-induced suppression of gastrointestinal motility and secretion
- suppresses postprandial gallbladder contractility and delays gallbladder emptying

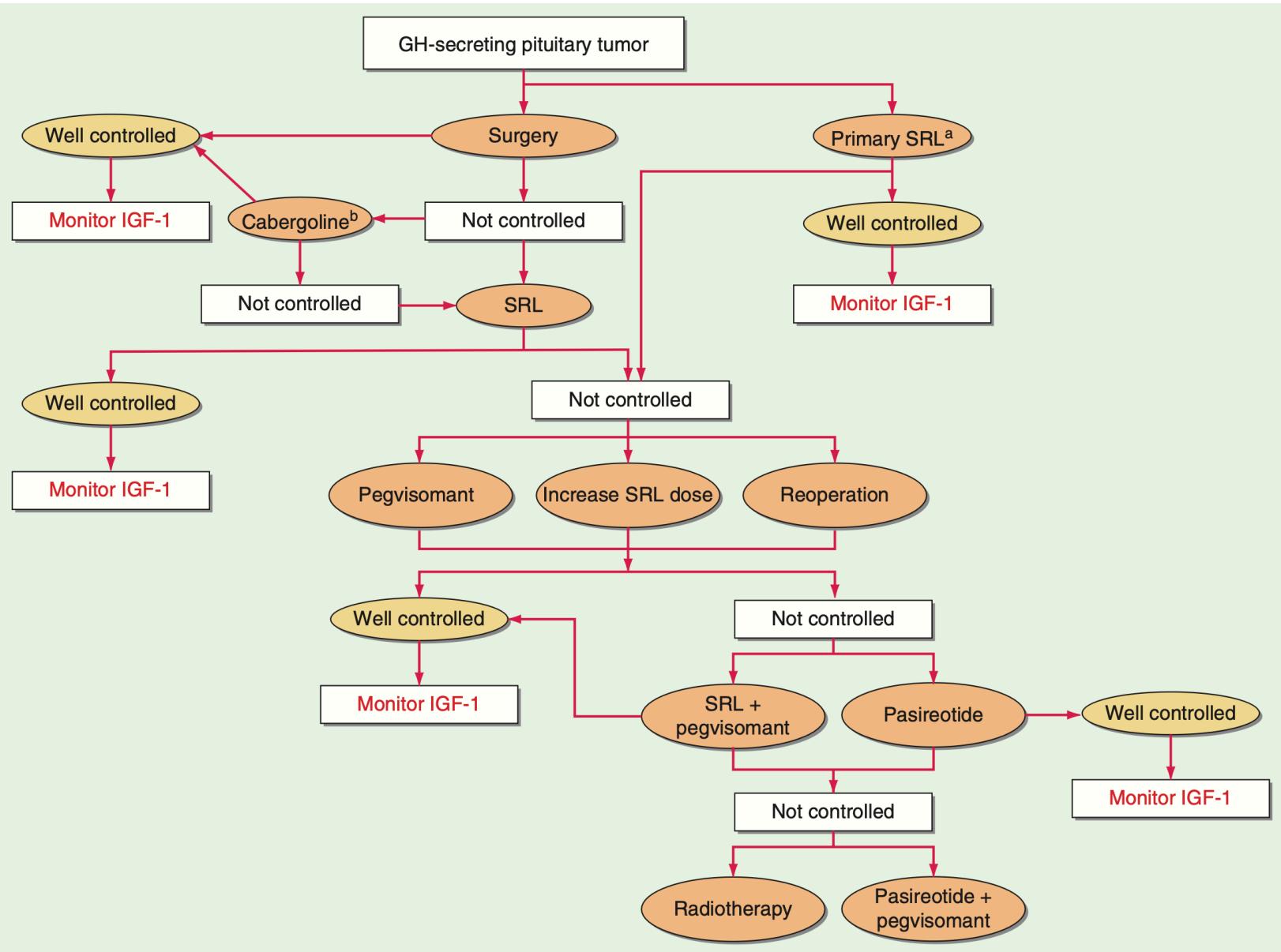
Medical treatment

GH Receptor Antagonist

- Blocking peripheral GH binding to its receptor. Consequently, serum IGF-I levels are suppressed.
- Pegvisomant(daily subcutaneous injection 10–20mg) normalizes IGF-I in >90%.
- GH levels remain elevated as the drug does not have antitumor actions.
- Side effects include reversible liver enzyme elevation, and lipodystrophy.
- Combined with somatostatin has been used effectively inresistant patients.

Dopamine Agonists

- Bromocriptine and cabergoline may modestly suppress GH secretion in some patients.
- High doses of bromocriptine(20mg/d) or cabergoline(0.5mg/d) are usually required to achieve modest GH therapeutic efficacy.
- Combined treatment with octreotide and cabergoline may induce additive biochemical control compared with either drug alone.



Goals

- Control GH and IGF1 secretion
- Control tumor growth
- Relieve central compressive effects, if present
- Preserve or restore pituitary trophic hormone function
- Treat comorbidities (hypertension, cardiac failure, hyperglycemia, sleep apnea, arthritis)
- Normalize mortality rates
- Prevent biochemical recurrence

TREATMENTS					
Characteristic	Surgery	Radiotherapy	SRL	GHR Antagonist	Dopamine Agonist
Advantages					
mode	Transsphenoidal resection	Noninvasive	Monthly injection	Daily injection	Oral
Biochemical control					
GH <2.5 µg/L	Macroadenomas, <50% Microadenomas, >80%	~35% in 10 years	~55–65%	Increases	<15%
IGF1 normalized		<30%	~55–65%	>65%	<15%
Onset	Rapid	Slow (years)	Rapid	Rapid	Slow (weeks)
Patient compliance	One-time consent	Good	Must be sustained	Must be sustained	Good
Tumor mass	Debulked or resected	Ablated	Growth constrained or shrinks ~50%	Unknown	Unchanged
Disadvantages					
Cost	One time	One time	Ongoing	Ongoing	Ongoing
Hypopituitarism	~10%	>50%	None	Very low IGF1 if overtreated	None
Other	Tumor persistence or recurrence, 6% Diabetes insipidus, 3% Local complications, 5%	Local nerve damage Second brain tumor Visual and CNS disorders, ~2% Cerebrovascular risk	Gallstones, 20% Nausea, diarrhea	Elevated liver enzymes (rare)	Nausea, ~30% Sinusitis High dose required

OUTCOMES		
Feature	Evaluation	Treatment
Safe Biochemical Activity		
Nadir GH <0.4 µg/L	Assess GH/IGF1 axis Evaluate adrenal, thyroid, and gonadal axes Periodic but less frequent MRI	None or no change in current treatment
Age-matched normal IGF1 Asymptomatic No comorbidities		
Unsafe Biochemical Activity		
Nadir GH >0.4 µg/L	Assess GH/IGF1 axis Evaluate pituitary function Periodic MRI	Weigh treatment benefit vs. risks Consider new treatment if being treated
Elevated IGF1 Discordant GH and IGF1 Asymptomatic No comorbidities		
Unsafe Biochemical and Clinical Activity		
Nadir GH >1 µg/L	Assess GH/IGF1 axis Evaluate pituitary function Assess cardiovascular, metabolic, and tumoral comorbidity Periodic MRI	Actively treat or change treatment
Elevated IGF1 Clinically active tumor growing		

CNS, Central nervous system; GH, growth hormone; GHR, growth hormone receptor; IGF1, insulin-like growth factor type 1; MRI, magnetic resonance imaging; SRL, somatostatin receptor ligand.

Modified from Melmed S. Medical progress: acromegaly. *N Engl J Med*. 2006;355:2558–2573.

TABLE 9.31 Medical Therapy of Acromegaly

Therapy	Receptor Target	Route of Administration	Dose	Frequency	Side Effects	Efficacy (GH/IGF1 Normalization)
Cabergoline	D2 receptor	Oral	1–4 mg	Biweekly up to daily	Nausea, dizziness, orthostatic hypotension	30–40%
Octreotide	SST2, SST5	SC	50–400 µg/day	One to three times daily	Nausea, vomiting, diarrhea, constipation, abdominal pain, cholelithiasis/biliary sludge, bloating, bradycardia, fatigue, headache, alopecia, dysglycemia	50–60%
Octreotide LAR	SST2, SST5	IM	20–40 mg	Monthly		
Lanreotide Autogel	SST2, SST5	Deep SC	6–120 mg	Every 4–6 weeks		
Pasireotide LAR	SST1, SST2, SST3, SST5	IM	40–60 mg	Monthly	Same as above, with more hyperglycemia	Up to 80%
Oral octreotide ^a	SST2, SST5	Oral	40–80 mg	Twice daily	Nausea, vomiting, diarrhea, dyspepsia, cholelithiasis, headache, dizziness, dysglycemia	65%
Pegvisomant	GH receptor	SC	10–40 mg	Daily to once weekly (less frequent when used in combination)	Transaminase elevation, lipodystrophy, arthralgias	60–90%

^aInvestigational

D2, Dopamine type 2; GH, growth hormone; IGF1, insulin-like growth factor type 1; IM, intramuscular; LAR, long-acting release; SC, subcutaneous; SSTR, somatostatin receptor.

Modified from Langlois F, McCartney S, Fleseriu M. Recent progress in the medical therapy of pituitary tumors. *Endocrinol Metab (Seoul)*. 2017;32:162–170; Melmed S. New therapeutic agents for acromegaly. *Nat Rev Endocrinol*. 2016;12:90–98.

Summary

- Surgery is the preferred primary treatment for GH-secreting microadenomas.
- The high frequency of residual GH hypersecretion after macroadenoma resection usually necessitates adjuvant or primary medical therapy for these larger tumors.
- Patients unable to receive or respond to unimodal medical treatment may benefit from combined treatments, or they can be offered radiation.
- Very rarely, repeat surgery may be required.

ACTH-Secreting Tumors (Cushing Disease)

Etiologies of hypercortisolism

- Most commonly iatrogenic caused by exogenous glucocorticoids (though underreported)
- Cushing's disease (60–70% of non-iatrogenic CS): ACTH- secreting pituitary adenoma (usually microadenoma) or hyperplasia
- Adrenal tumor (10–15%): adenoma or (rarely) carcinoma
- Ectopic ACTH (10–15%): small cell lung carcinoma, carcinoid, islet cell tumors, medullary thyroid cancer, pheochromocytoma
- Cushing's disease is 5–10 times more common in women than in men.

Clinical presentation

TABLE 380-7 Clinical Features of Cushing's Syndrome (All Ages)

SYMPTOMS/SIGNS	FREQUENCY, %
Obesity or weight gain (>115% ideal body weight)	80
Thin skin	80
Moon facies	75
Hypertension	75
Purple skin striae	65
Hirsutism	65
Menstrual disorders (usually amenorrhea)	60
Plethora	60
Abnormal glucose tolerance	55
Impotence	55
Proximal muscle weakness	50
Truncal obesity	50
Acne	45
Bruising	45
Mental changes	45
Osteoporosis	40
Edema of lower extremities	30
Hyperpigmentation	20
Hypokalemic alkalosis	15
Diabetes mellitus	15

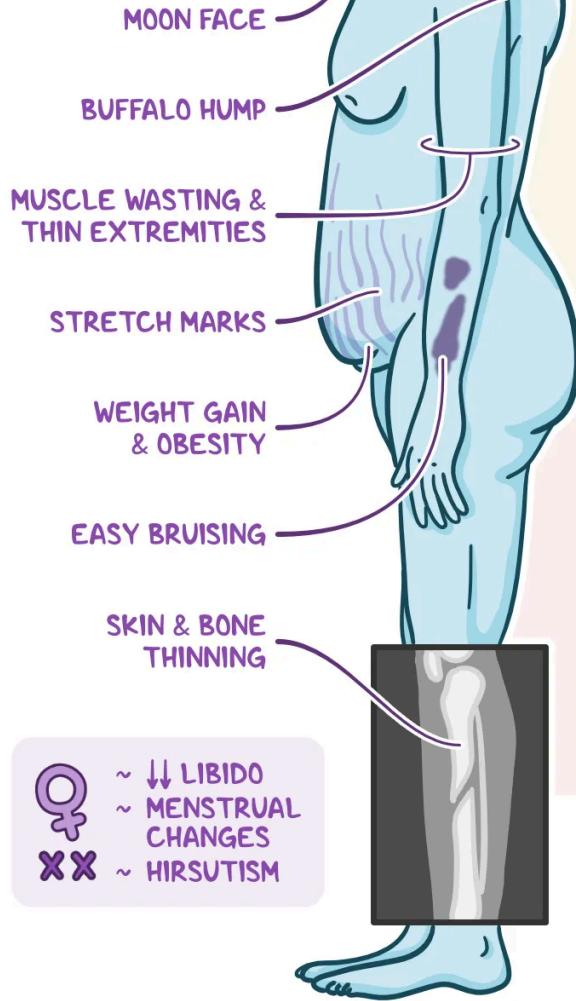
Source: Adapted with permission from MA Magiokou et al, in Wierman ME: Diseases of the Pituitary. Totowa, NJ: Humana; 1997.

TABLE 15.9 Symptoms and Signs for the Diagnosis of Cushing Syndrome

Discriminatory	Less Discriminatory
<p>Signs</p> <ul style="list-style-type: none"> • Facial plethora • Proximal myopathy • Cutaneous striae (red-purple, >1 cm wide) • Bruising • In children—weight gain with reduced height percentile 	<p>Signs</p> <ul style="list-style-type: none"> • Central obesity • Buffalo hump, supraclavicular fullness • Facial fullness • Acne and hirsutism • Skin thinning • Poor wound healing • Peripheral edema
<p>Symptoms and complications (especially at a young age)</p> <ul style="list-style-type: none"> • Hypertension • Diabetes mellitus • Osteoporosis and vertebral fractures 	<p>Symptoms and complications</p> <ul style="list-style-type: none"> • Fatigue • Weight gain • Depression, mood and appetite change, impairment of concentration and memory • Back pain • Oligomenorrhea, polycystic ovary syndrome • Recurrent infections • Kidney stones

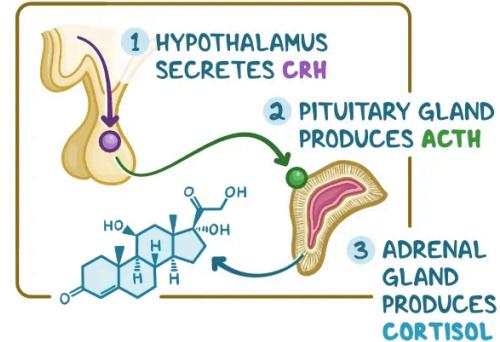
Data from Nieman LK, Biller BM, Findling JW, et al. Diagnosis of Cushing's syndrome, an Endocrine Society Clinical Guideline. *J Clin Endocrinol Metab.* 2008;93:1526–1540.

SYMPTOMS of CUSHING SYNDROME



BACKGROUND

- * SET of SYMPTOMS RESULTING from EXPOSURE to ↑↑ LEVELS of CORTISOL
~ aka HYPERCORTISOLISM
- * ENDOGENOUS or EXOGENOUS SOURCES of EXCESS CORTISOL



CAUSES

- * LONG-TERM USE of GLUCOCORTICOID MEDICATIONS
- * PITUITARY TUMOR
~ CUSHING DISEASE
- * ECTOPIC ACTH-PRODUCING TUMOR
- * ADRENAL TUMOR



DIAGNOSIS

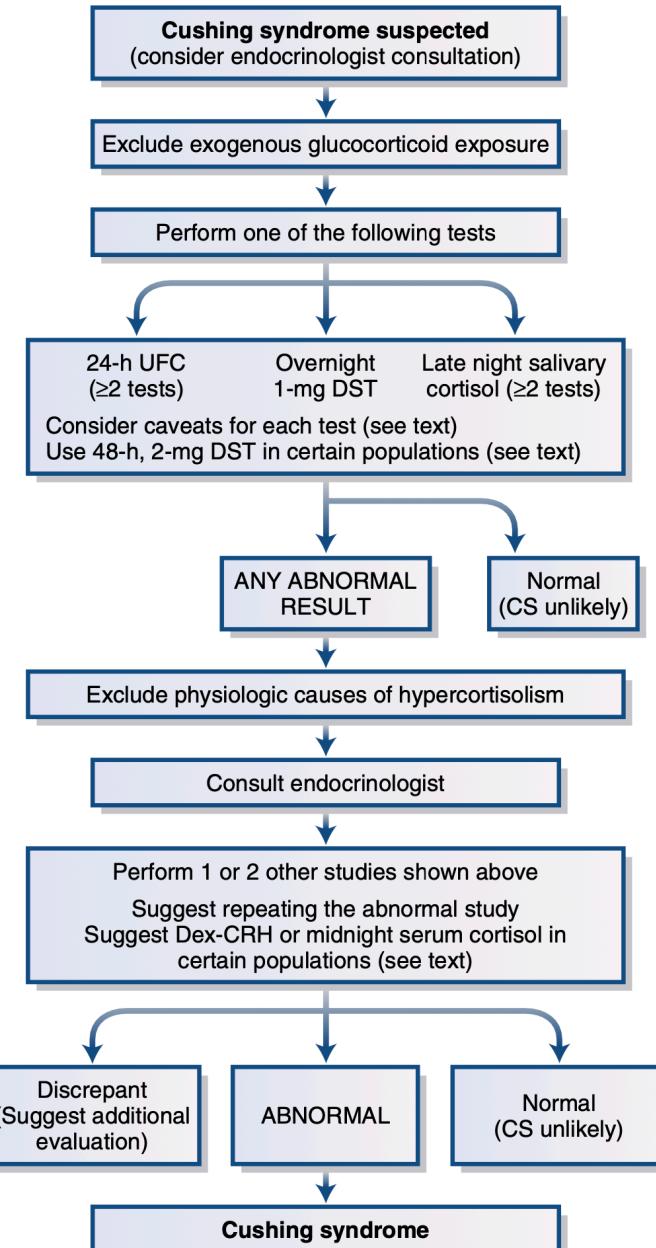
- * MEDICAL HISTORY
- * PHYSICAL EXAM
- * LAB TESTS
 - ~ 24-HOUR URINARY FREE CORTISOL TEST
 - ~ LATE-NIGHT SALIVARY CORTISOL
 - ~ LOW- or HIGH-DOSE DEXAMETHASONE TEST
- * IMAGING

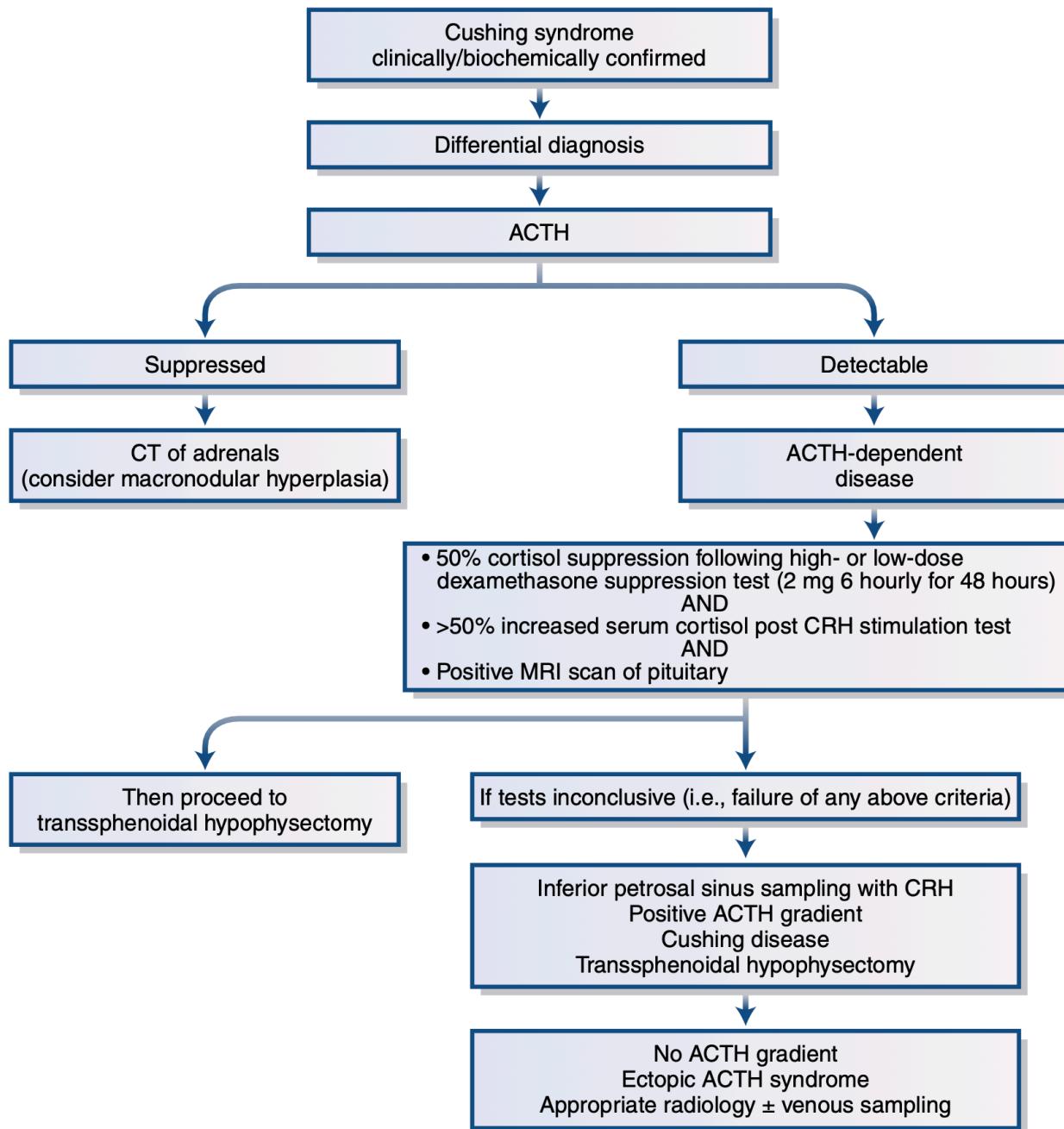




Laboratory Investigation

- Diagnosis—Does the Patient Have Cushing Syndrome?
 - 24 hours urine free cortisol
 - Low-dose dexamethasone suppression test
 - Late night salivary cortisol/circadian rhythm of plasma cortisol
- Differential Diagnosis—What Is the Cause of the Cushing Syndrome?
 - Plasma ACTH
 - High dose dexamethasone suppression test
 - Corticotropin-releasing hormone
 - Inferior petrosal sinus sampling
 - CT, MRI scanning of pituitary, adrenals
 - Scintigraphy
 - Tumor markers





Diagnostic Tests

- 24 hour Urine Free Cortisol
 - A. Purpose: Screening for Cushing's syndrome
 - B. Procedure: 24 hour urine free cortisol level.
(Normal range: 4.3~176.0 µg/24hr)

- Overnight Dexamethasone Suppression Test
 - A. Purpose: Screening for Cushing's syndrome
 - B. Procedure
 - Give 1 mg dexamethasone orally at 11 pm
 - Check cortisol at 8 am of the following day prior to food intake
 - C. Interpretation
 - Normally serum cortisol are suppressed to < 1.8 (2.0) $\mu\text{g/dL}$
 - Depression, restless sleep, emotional or physical stress, recent heavy alcohol consumption, obesity, thyrotoxicosis, acromegaly, pregnancy, oral contraceptives, phenytoin, rifampin and barbiturates → false positive

- Low Dose Dexamethasone Suppression Test (LDDST)
 - A. Purpose: Confirmation of Cushing's syndrome
 - B. Procedure
 - Day 1: Obtain baseline serum cortisol, ACTH at 8 am
 - Day 1-2: Give dexamethasone 0.5 mg q6h po x 2 days
 - Day 3: Check serum cortisol level at 8 am
 - C. Interpretation: normal response → serum cortisol < 2 µg/dL at 8 am on D3

- High Dose Dexamethasone Suppression Test (HDDST)
 - A. Purpose: D/D of Cushing's disease or ectopic ACTH secretion
 - B. Procedure
 - Day 1: Obtain baseline serum cortisol, ACTH at 8 am
 - Day 1-2: Give dexamethasone 2 mg q6h po x 2 days
 - Day 3: Check serum cortisol level at 8 am
 - C. Interpretation
 - Cushing's disease: D3 cortisol level is < 50% of D1 baseline cortisol level;
 - Ectopic ACTH: non-suppressible

Management of Cushing's Disease

- Selective transsphenoidal resection is the treatment of choice for Cushing's disease
- Remission rate is 80% for microadenomas , but <50% for macroadenomas.
- After tumor resection, a postoperative period of symptomatic ACTH deficiency that may last up to 12 months. This usually requires low-dose cortisol replacement.
- Biochemical recurrence occurs in approximately 5% initially successful surgery was

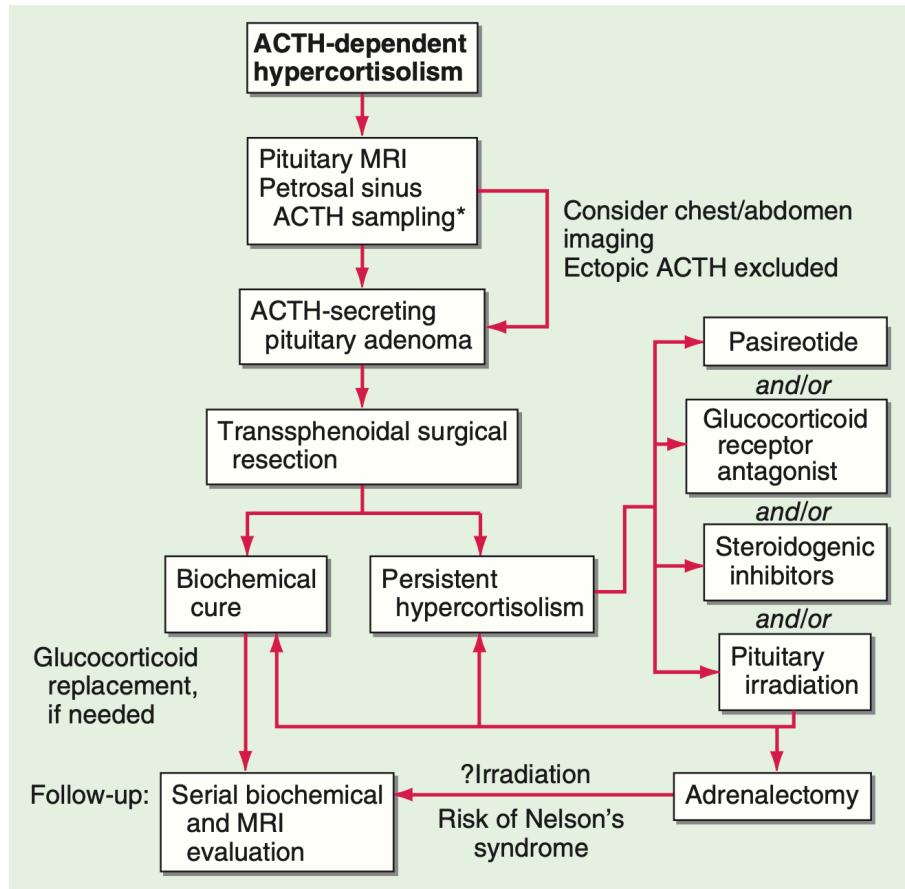
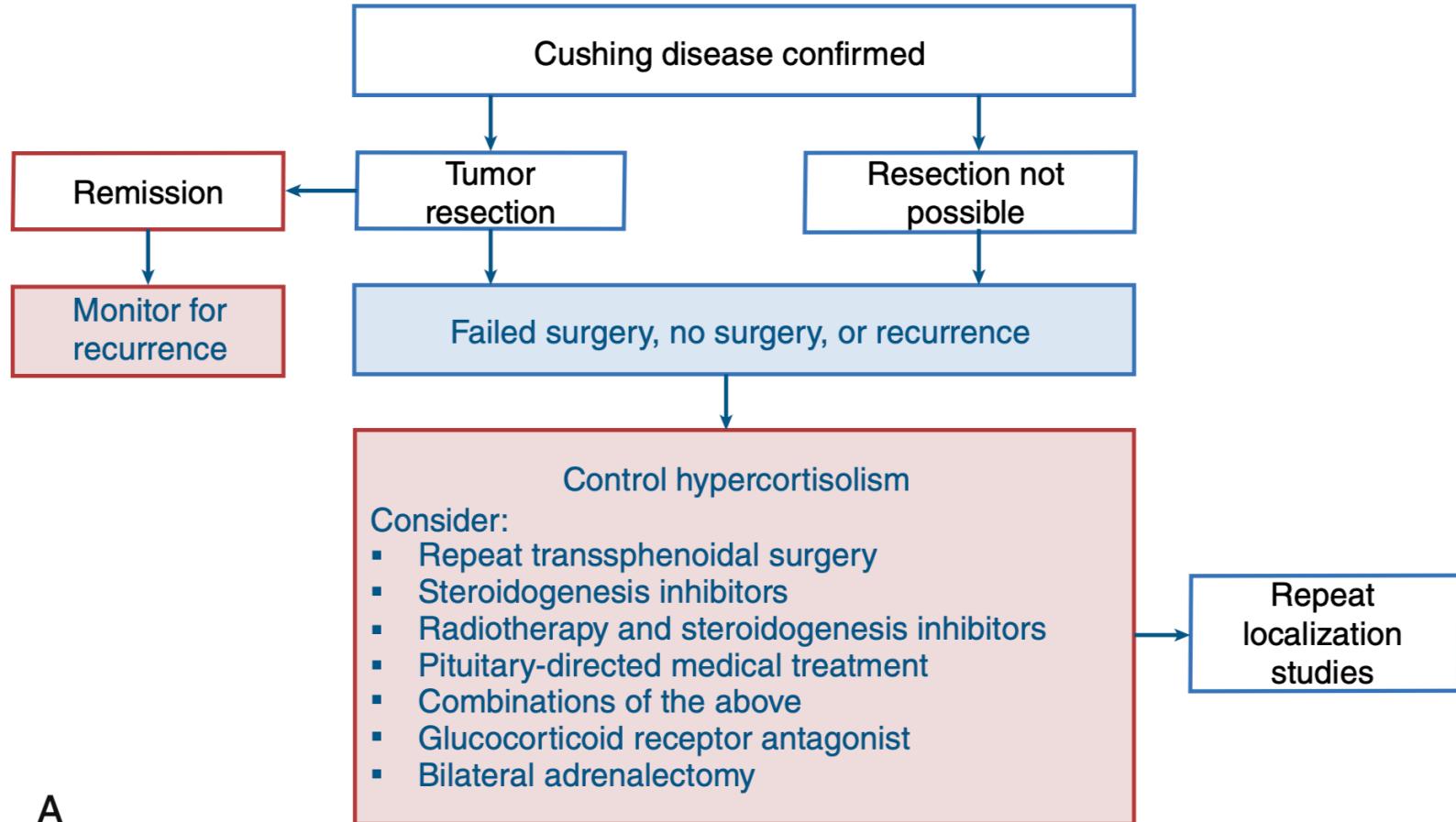


FIGURE 380-9 Management of Cushing's disease. ACTH, adrenocorticotropin hormone; MRI, magnetic resonance imaging; *, Not usually required.



A

Medical treatment for Cushing's disease

- *Pasireotide LAR* 10–40 mg intramuscularly, an SRL with high affinity for SST5 > SST2 receptor subtypes, may control hypercortisolism in a subset of patients with ACTH-secreting pituitary tumors.
- *Osilodrostat* (2 mg twice daily titrated up to 30 mg twice daily), an oral 11 β -hydroxylase inhibitor that blocks adrenal gland cortisol biosynthesis, normalized 24-h UFC in 86% of patients.
- *Ketoconazole* (600–1200 mg/d), an imidazole derivative antimycotic agent, inhibits several P450 enzymes and effectively lowers cortisol.
- *Mifepristone* (300–1200 mg/d), a glucocorticoid receptor antagonist, blocks peripheral cortisol action
- *Metyrapone* (2–4 g/d) inhibits 11 β -hydroxylase activity and normalizes plasma cortisol in up to 75% of patients.
- *Mitotane* (3–6 g/d orally in four divided doses) suppresses cortisol hypersecretion by inhibiting 11 β -hydroxylase and cholesterol side-chain cleavage enzymes and by destroying adrenocortical cells.
- Other agents include *aminoglutethimide* (250 mg tid), *trilostane* (200–1000 mg/d), *cypionate* (24 mg/d), and IV *etomidate* (0.3 mg/kg per h)

Take Home Message

- Hormone
 - TSH/ACTH/GH/PRL/FSH,LH
- Pituitary tumors
 - Prolactinoma ()
 - Acromegaly (72 hours OGTT tests)
 - Cushing's disease (overnight/low dose/high dose Dexamethasone Suppression Test)

References

- Harrison's Principles of Internal Medicine, 21e
- William's Endocrinology, 14e
- Pocket Medicine, 8e
- 臺大醫院代謝內分泌檢查工作手冊

Thanks for your attention!

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