Pituitary disorders

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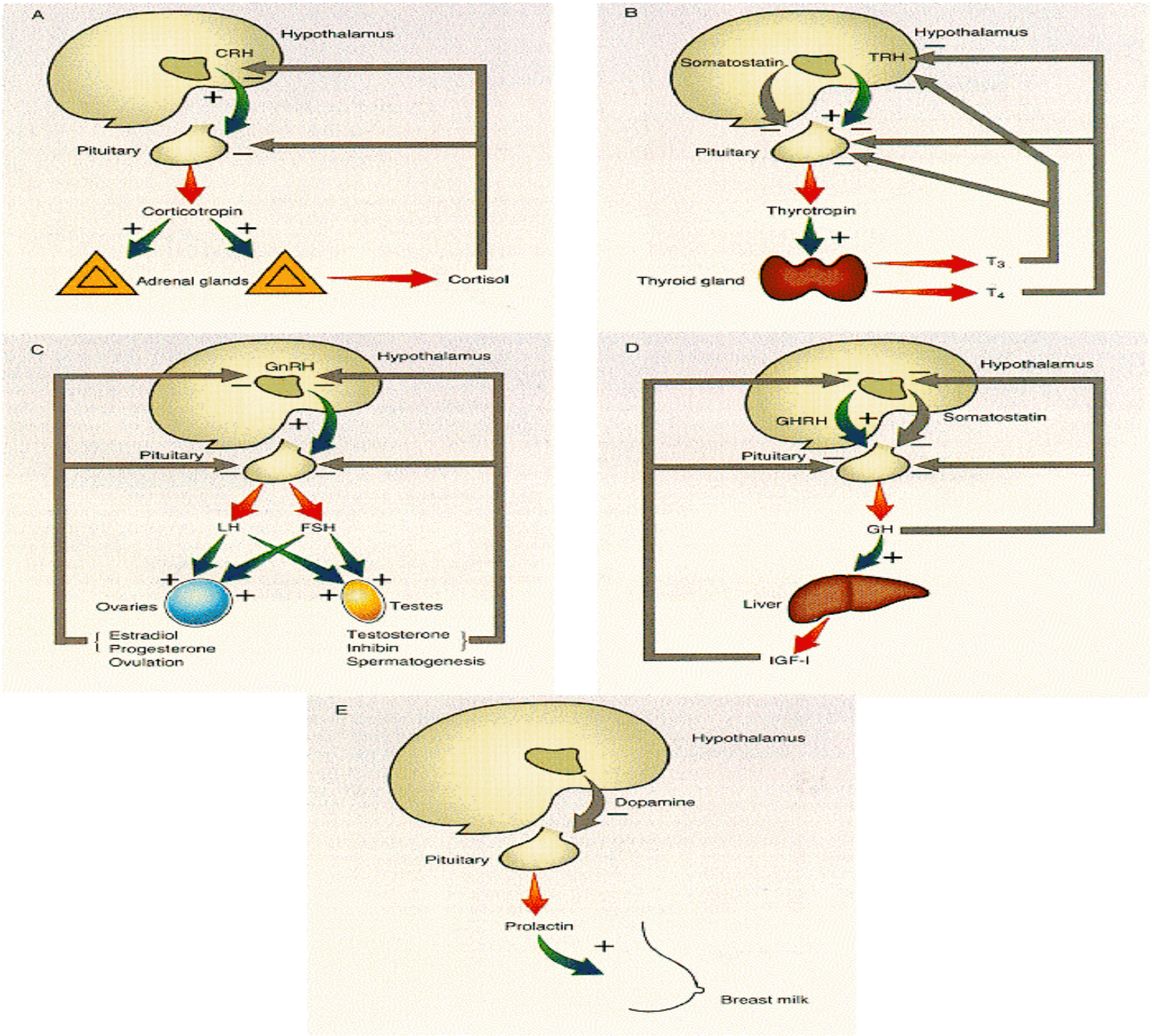
Pituitary disorders

- Anterior pituitary disorders
  - Pituitary Hypersecretion
    - Hipersecretion of PRL: Hyperprolactinemia
    - Hipersecretion of GH : Acromegaly
    - Hypersecretion of ACTH :Cushing's disease
  - Pitutary Insufficiency
    - Hypopituitarism : Gonadotropin, GH, TSH, ACTH,or Prolactin deficiency
- Posterior pituitary disorders
  - Posterior pituitary insufficiency : Central diabetes insipidus

Anterior pituitary disorders


A
Hypothalamus
CRH
Pituitary
Corticotropin
Adrenal glands
Cortisol
B
Hypothalamus
Somatostatin
TRH
Pituitary
Thyrotropin
Thyroid gland
T_3
T_4
C
Hypothalamus
GnRH
Pituitary
LH
FSH
Ovaries
Testes
Estradiol
Progesterone
Ovulation
Testosterone
Inhibin
Spermatogenesis
D
Hypothalamus
GHRH
Somatostatin
Pituitary
GH
Liver
IGF-I
E
Hypothalamus
Dopamine
Pituitary
Prolactin
Breast milk

Major Hypothalamic Hormones and their Effect on Anterior Pituitary Hormones

Hypothalamic stimlatory hormones	Pituitary hormones
Corticotropin-releasing hormone — 41 amino acids; released from paraventricular neurons as well as supraoptic and arcuate nuclei and limbic system	Adrenocorticotropic hormone — basophilic corticotrophs represent 20 percent of cells in anterior pituitary; ACTH is product of proopiomelanocortin (POMC) gene
	Melanocyte-stimulating hormone — alternate product of POMC gene
	Endorphins — also products of POMC gene
Growth hormone-releasing hormone — two forms, 40 and 44 amino acids	Growth hormone — acidophilic somatotrophs represent 50 percent of cells in anterior pituitary
Gonadotropin-releasing hormone — 10 amino acids; mostly released from preoptic neurons	Luteinizing hormone and follicle-stimulating hormone — gonadotrophs represent about 15 percent of anterior pituitary cells
Thyrotropin-releasing hormone — three amino acids; released from anterior hypothalamic area	Thyroid-stimulating hormone — thyrotropes represent about five percent of anterior pituitary cells
Prolactin-releasing factors — include serotonin, acetylcholine, opiates, and estrogens	Prolactin — lactotrophs represent 10 to 30 percent of anterior pituitary cells
Hypothalamic inhibitory hormones	
Somatostatin — 14 amino acids	Inhibits the release of growth hormone
Prolactin-inhibiting factors — includes dopamine	Major prolactin control is inhibitory

Acromegaly

- Acromegaly is the clinical syndrome that results from excessive secretion of growth hormone (GH)
- Its annual incidence is three to four per million people
- The mean age at diagnosis is 40 to 45 years.
- Growth hormone excess that occurs before fusion of the epiphyseal growth plates in a child or adolescent is called pituitary gigantism

Acromegaly

- Clinical Manifestations
  - The onset of acromegaly is insidious, and its progression is usually very slow.
  - The interval from the onset of symptoms until diagnosis is about 12 years
  - At diagnosis, about 75 percent of patients have macroadenomas (tumor diameter 10 mm or greater)
  - The clinical features : high serum concentrations of both GH and insulin-like growth factor-I (IGF-I), which is GH-dependent.
    - Excess GH and IGF-I have both somatic and metabolic effects (show table).

Risks of Long-term Exposure to Elevated Serum Growth Hormone (GH) Concentrations[†]

Arthropathy
- Unrelated to age of onset or to GH secretion
- Usually occurs with long duration
- Reversibility
  - Rapid symptomatic improvement
  - Irreversibility of bone and cartilage lesions

Neuropathy
- Peripheral nerves
  - Intermittent anesthesias, paresthesias
  - Sensorimotor polyneuropathy
- Reversibility
  - Onion bulbs (whorls) do not regress

Cardiovascular disease
- Cardiomyopathy
  - LV diastolic function decreased
  - LV mass increased; arrhythmias
  - Fibrous connective tissue hyperplasia

Hypertension
- Exacerbates cardiomyopathy
- Reversibility
  - May progress even if GH secretion reduced

Respiratory disease
- Upper airway obstruction
  - Soft tissue overgrowth
- Reversibility
  - Improves with reduction in GH secretion

Malignancy
- Increased risk
- Increased colonic polyps
- Reversibility
  - Effect of therapy on risk unknown

Carbohydrate intolerance
- Diabetes mellitus
- Reversibility
  - Improves with reduced GH secretion

[†]Adapted from Melmed, S, Dowling, RH, Frohman, L, et al. Am J Med 1994; 97:468.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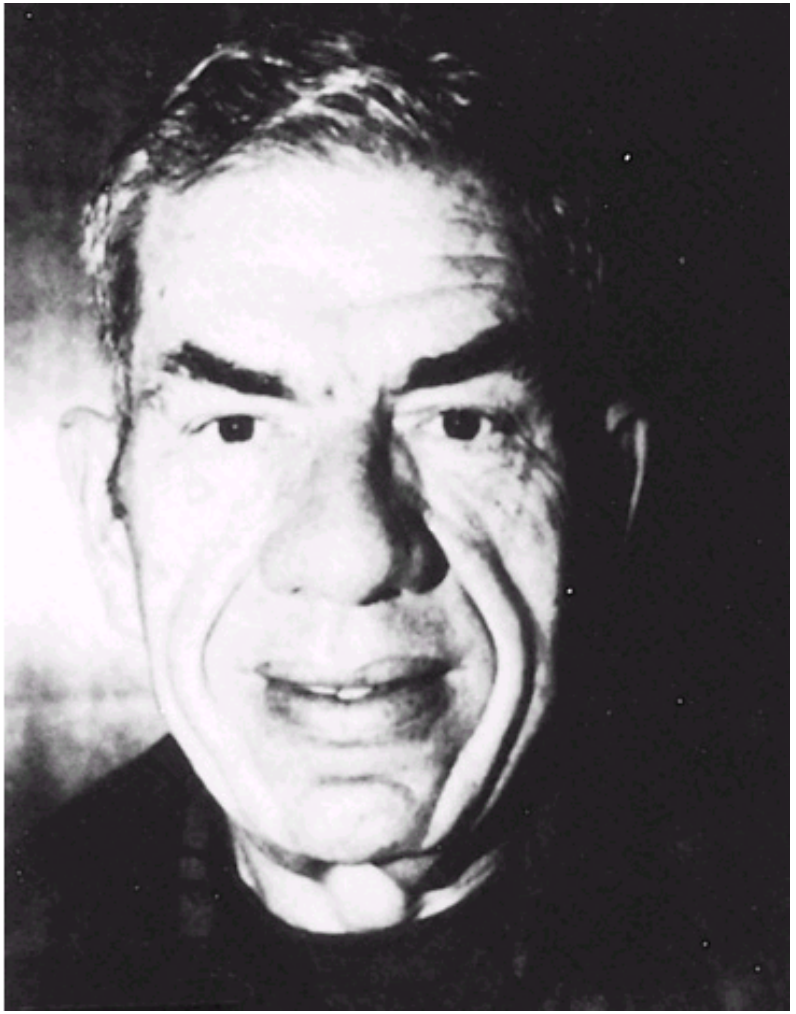
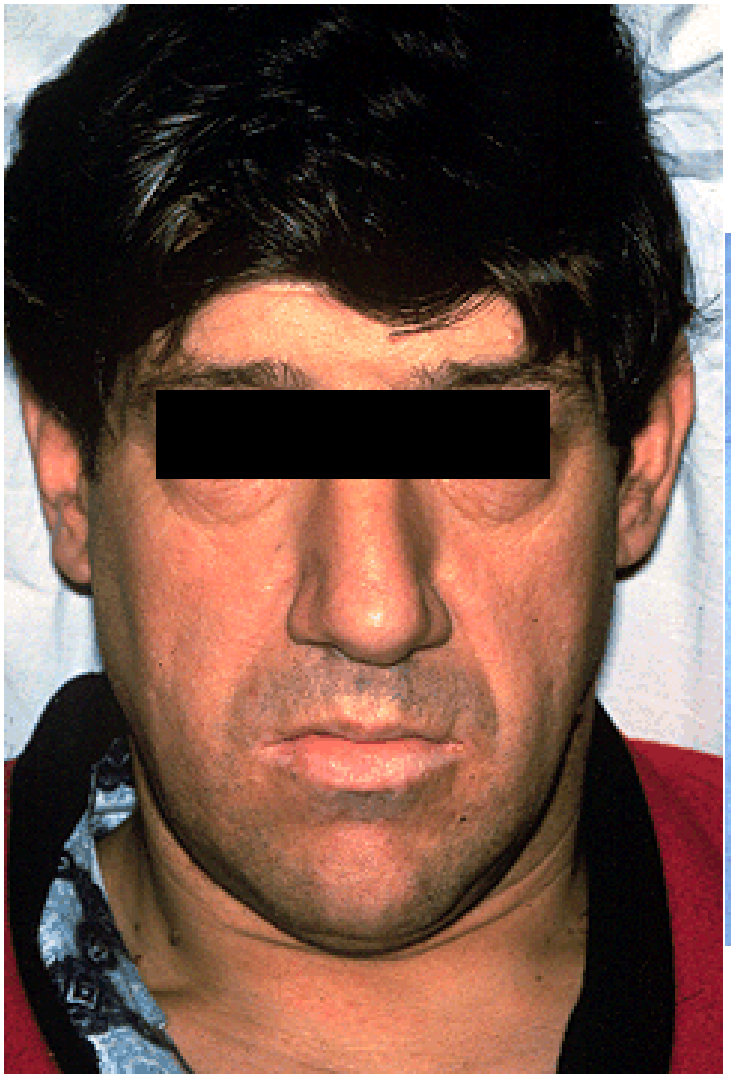
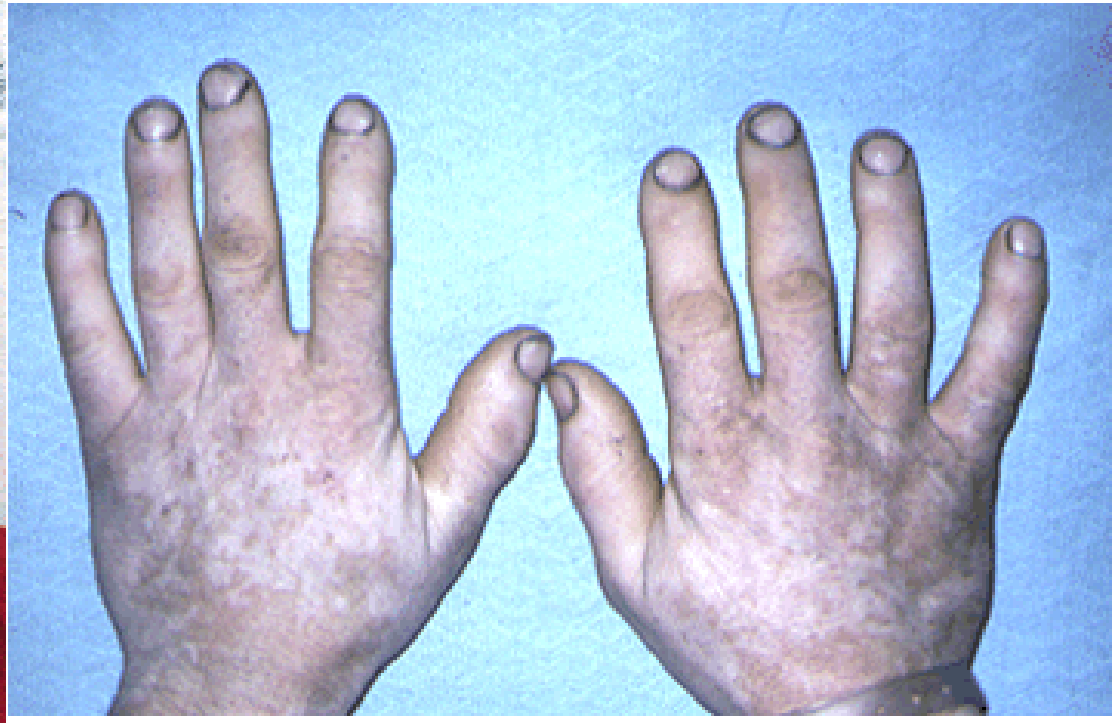






Causes of Acromegaly†

Excess growth hormone secretion

Pituitary (98 percent)
- GH-cell adenoma (60 percent)
- Mixed GH-cell and PRL-cell adenoma (25 percent)
- Mammosomatotroph-cell adenoma (10 percent)
- Plurihormonal adenoma
- GH-cell carcinoma
- Multiple endocrine neoplasia-I (GH-cell adenoma)
- McCune-Albright syndrome (rarely-adenoma)
- Ectopic sphenoid or parapharyngeal sinus pituitary adenoma

Extrapituitary tumor
- Pancreatic islet-cell tumor (very rare)

Excess growth hormone-releasing hormone secretion

Central ectopic (<1 percent)
- Hypothalamic hamartoma, choristoma, ganglioneuroma

Peripheral ectopic (1 percent)
- Bronchial carcinoid, pancreatic islet-cell tumor, small cell lung cancer, adrenal adenoma, medullary thyroid carcinoma, pheochromocytoma

Excess growth factor activity

Acromegaloidism (very rare)

†Adapted from Melmed, S, N Engl J Med 1990; 322:966.

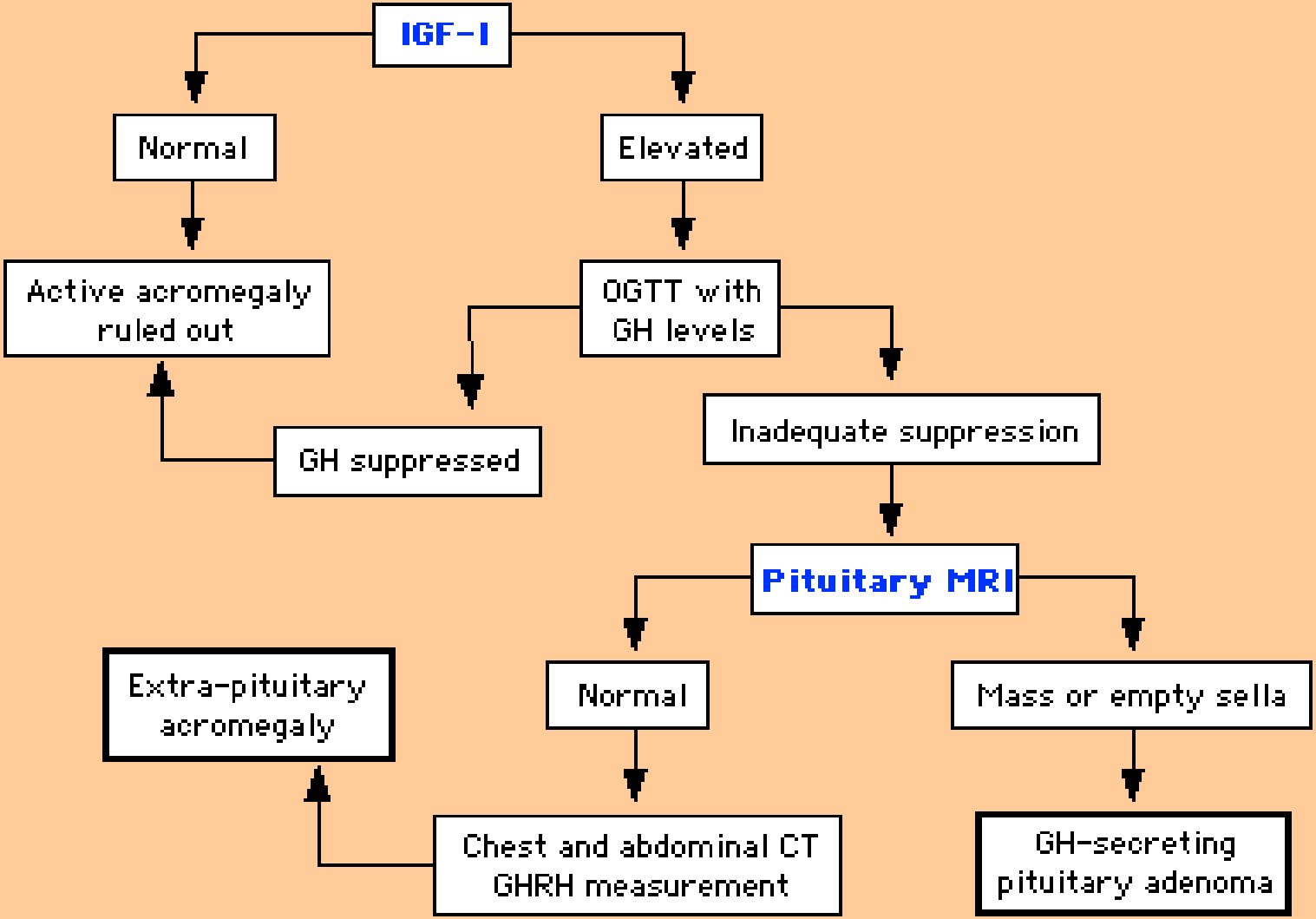
Diagnosis of acromegaly

- Documenting Excess GH Secretion
  - Serum IGF-I concentration
    - The best single test for the diagnosis of acromegaly
    - Serum IGF-I concentrationsdo not vary from hour to hour according to food intake, exercise or sleep
  - Serum GH concentration
    - GH secretion in normal subjects is pulsatile, diurnal, and stimulated by a variety of factors, including short-term fasting, exercise, stress, and sleep
    - The most specific dynamic test for establishing the diagnosis of acromegaly is an oral glucose tolerance test.
    - In normal subjects, serum GH concentrations fall to 1 ng/mL or less within two hours after ingestion of 75 g glucose.
    - In contrast, the post-glucose values are greater than 2 ng/mL in over 85 percent of patients with acromegaly

Diagnosis of acromegaly

- Determining The Source Of Excess GH
  - MRI
    - Once GH hypersecretion has been confirmed, the next step is magnetic resonance imaging (MRI) of the pituitary
    - 75 % of patients with somatotroph adenomas (macroadenoma = tumor diameter 10 mm or more)
    - It is important to remember that MRI does not distinguish between functioning and nonfunctioning tumors
    - Ectopic GHRH secretion accounts for only 0.5 percent of cases of acromegaly

Algorithm for the Diagnosis of Acromegaly†



†Adapted from Melmed, S, Anterior pituitary. In: Current Practice of Medicine, Korenman, S (Ed), 1996.

Treatment of acromegaly

- The goals of therapy in acromegaly are to lower the serum IGF-I concentration
- To achieve these goals, the adenoma secreting GH must be identified.
- When effective control of GH hypersecretion is achieved, serum GH and IGF-I concentrations decline to normal
- The characteristic tissue overgrowth and related symptoms gradually recede, and the metabolic abnormalities improve.

Treatment of acromegaly

- Transsphenoidal Surgery
  - the treatment of choice for patients with somatotroph adenomas
  - after transsphenoidal surgery, serum GH⇓ (1 to 2 hr), and serum IGF-I (7 to 10 days)
  - Side effect :
    - Deficiency of one or more pituitary hormones, central diabetes insipidus, cerebrospinal fluid rhinorrhea, meningitis.

Treatment of acromegaly

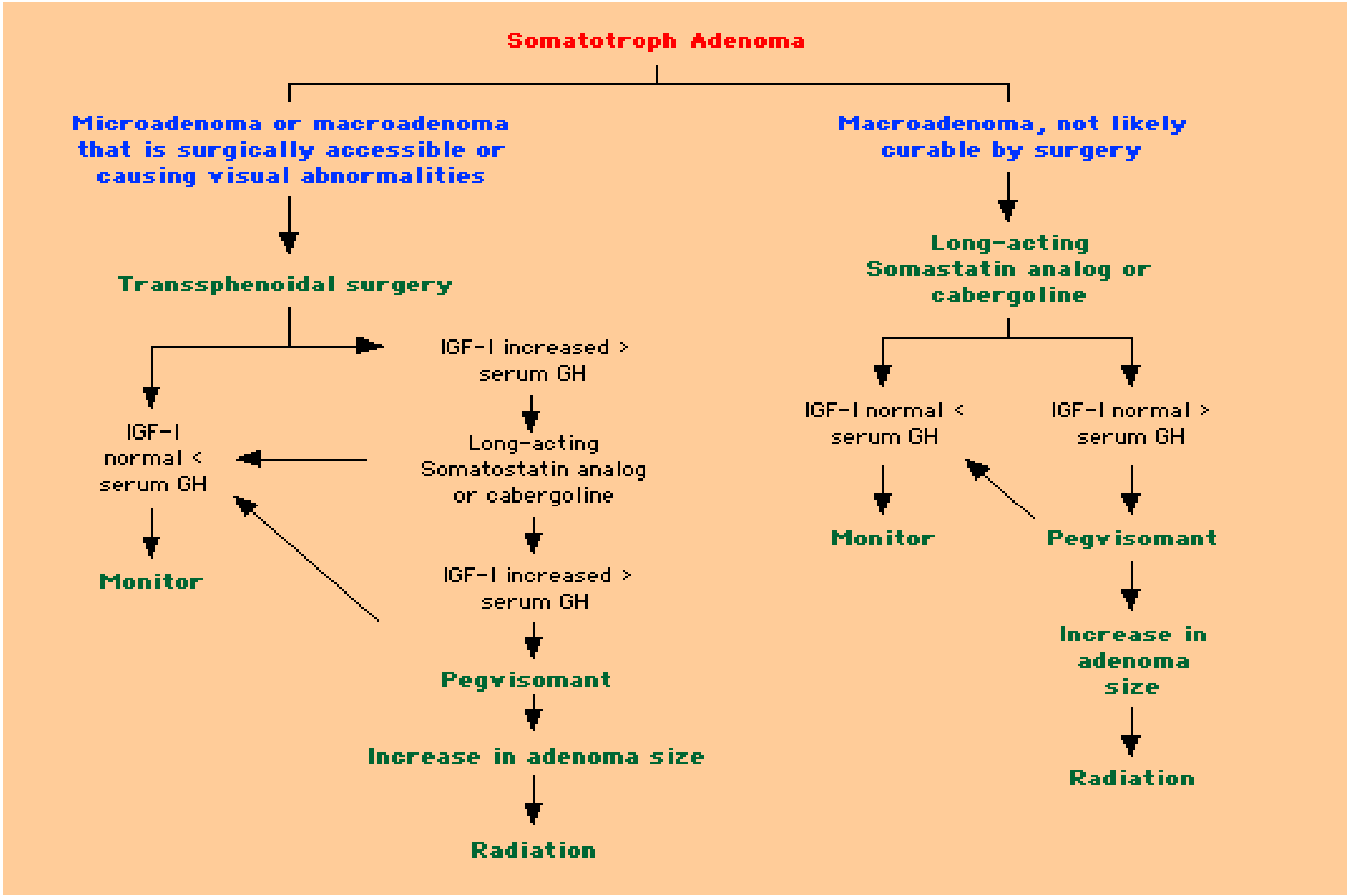
- Medical therapy
  - Somatostatin Analogs:
    - Octreotide (analog of somatostatin) inhibits GH secretion by binding to specific receptors for somatostatin and its analogs
    - The initial dose of the short-acting form of octreotide is 100 µg subcutaneously every 8 hours
    - The short-acting form of octreotide : ⇓ IGF-1 to normal in 53 percent of 115 patients, who received 100 µg every eight hours for six months and in 68 percent of those who received 300 µg each dose[1]

1. Ezzat, S, Snyder, PJ, Young, WF, et al. Octreotide treatment of acromegaly: A randomized, multicenter study Ann Intern Med 1992; 117:711.

Treatment of acromegaly

- Dopamine agonists :
  - Dopamine agonists, bromocriptine and cabergoline, may inhibit GH secretion
  - In a study of 64 patients, cabergoline decreased serum GH concentrations to <2.0 ng/mL in 46 percent and serum IGF-I concentrations to <300 ng/mL in 39 percent [2]
  - Bromocriptine is less effective than cabergoline. In 549 patients treated with bromocriptine reported in 31 different studies, serum IGF-I concentrations decreased to normal in only 10 percent.

2. Abs, R, Verhelst, J, Maiter, D, et al. Cabergoline in the treatment of acromegaly: A study in 64 patients. J Clin Endocrinol Metab 1998; 83:37.



Treatment of acromegaly Algorithm for the management of acromegaly caused by a pituitary adenoma. The goal is a normal serum IGF-I concentration for age and gender and a serum GH concentration <1 ng/mL after a glucose load.

Mortality in acromegaly

- Several retrospective studies : mortality in patients acromegaly of between 2-3 times that of an age and sex matched
- Causes of death :
  - Death from cardiovascular and cerebrovascular diasease appear to be predominate in most major epidemiologic surveys.
- Mortality and morbidity → prognostic factors : tumour size, suprasella extension, preoperative GH levels, duration onset to diagnosis, and overall duration of the disorders.

Hypopituitarism

- Hypopituitarism is a clinical syndrome of deficiency in pituitary hormone production.
- Panhypopituitarism refers to involvement of all pituitary hormones; however, only one or more pituitary hormones are often involved, resulting in partial hypopituitarism.
- The clinical manifestations : depend upon the cause as well as the type and degree of hormonal insufficiency.
- Patients may be asymptomatic or present with symptoms related to hormone deficiency, or a mass lesion, or nonspecific symptoms such as fatigue.

Major Causes of Hypopituitarism

Pituitary diseases

Mass lesions – pituitary adenomas, other benign tumors, cysts
Pituitary surgery
Pituitary radiation
Infiltrative lesions – lymphocytic hypophysitis, hemochromatosis
Infarction – Sheehan syndrome
Apoplexy
Genetic diseases – pit-1 mutation
Empty sella syndrome

Hypothalamic diseases

Mass lesions – benign (craniopharyngiomas) and malignant tumors (metastatic from lung, breast, etc.)
Radiation – for CNS and nasopharyngeal malignancies
Infiltrative lesions – sarcoidosis, Langerhans cell histiocytosis
Trauma – fracture of skull base
Infections – tuberculous meningitis

Clinical manifestations

- Damage to the anterior pituitary :
  - suddenly or slowly, can be mild or severe, and can affect the secretion of one, several, or all of its hormones.
  - ACTH deficiency : secondary adrenal insufficiency
  - TSH deficiency : thyroxine deficiency
  - Gonadotropin deficiency: FSH ⇓ and LH⇓ → causes hypogonadism
  - Growth hormone deficiency : short stature (children), in adult :
    - Diminished muscle mass and increased fat mass .
    - Increased risk of cardiovascular disease
    - Decreased bone mineral density
    - Diminished sense of well being
  - Prolactin deficiency: The only known presentation of prolactin deficiency is the inability to lactate after delivery.

Diagnosis of hypopituitarism

- Hormonal studies should be performed in pairs of target gland and their respective stimulatory pituitary hormone for proper interpretation.
  - ACTH and Cortrosyn stimulation test
  - TSH and thyroxine
  - FSH, LH, and either estradiol or testosterone (as appropriate for sex)
  - Prolactin
  - GH provocative testing
- **Imaging Studies:**
  MRI or computed axial tomography of the pituitary

Treatment of hypopituitarism

- Glucocorticoids are required if the ACTH-adrenal axis is impaired.
  - This is particularly important in sudden collapse due to pituitary apoplexy or acute obstetric hemorrhage with pituitary insufficiency.
  - Do not delay initiation of a possibly life-saving treatment pending a definitive diagnosis.
- Treat secondary hypothyroidism with thyroid hormone replacement.
- Treat gonadotropin deficiency with sex-appropriate hormones.
  - In men, testosterone replacement is used and modified if the patient desires fertility.
  - In women, estrogen replacement is used with or without progesterone as appropriate.
- GH is replaced in children as appropriate.
  - GH is not routinely replaced in adults unless the patient is symptomatic.

Posterior pituitary disorders

Diabetes Insipidus

- Central diabetes insipidus — Central DI is associated with deficient secretion of antidiuretic hormone (ADH)
- Nephrogenic diabetes insipidus — Nephrogenic DI is characterized by normal ADH secretion but varying degrees of renal resistance to its water-retaining effect.

Antidiuretic Hormone (ADH; Vasopressin)

- The major renal effect of ADH is to increase the water permeability of the luminal membrane of the collecting duct epithelium via the ADH-sensitive water channels
- When ADH is present, epithelial permeability increases markedly, and water is reabsorbed
- In the absence of ADH, permeability of the epithelium is very low and reabsorption of water decreases, leading to polyuria.

Central Diabetes Insipidus

- Central diabetes insipidus (DI) is characterized by decreased release of antidiuretic hormone (ADH), resulting in a variable degree of polyuria
- Polyuria can be arbitrarily defined as a urine output exceeding 3 L/day in adults
- Lack of ADH can be caused by disorders that act at one or more of the sites involved in ADH secretion: the hypothalamic osmoreceptors; the supraoptic or paraventricular nuclei; or the superior portion of the supraopticohypophyseal tract

Diagnosis and Differential Diagnosis of Polyuria

- Onset of polyuria
  - The onset is usually abrupt in central DI and almost always gradual in nephrogenic DI or primary polydipsia.
  - The new onset of nocturia in absence of other causes of nocturia is often a first clue to DI.
- Family history
  - There are familial forms of both central and nephrogenic DI.
- Plasma sodium concentration
  - Low plasma sodium concentration at presentation (less than 137 meq/L due to water overload) is usually indicative of primary polydipsia,
  - High-normal plasma sodium concentration (greater than 142 meq/L due to water loss) points toward DI

Diagnosis and Differential Diagnosis of Polyuria

- Water restriction test
  - We generally recommend that the patient stop drinking two to three hours (administration of hypertonic saline 0.05 mL/kg per min for no more than two hours) before coming to the office or clinic
    - The measurement of the urine volume and osmolality every hour and plasma sodium concentration and osmolality every two hours.
    - The healthy individual will soon reduce urine flow to 0.5 mL/min at a concentration greater than that of plasma,
    - The patient with complete diabetes insipidus will maintain a high urine flow at a specific gravity less than 1.005 (200 mosm/kg of water).
    - The test should be terminated if the body weight falls by more than 3%, since serious consequences of dehydration may ensue.

Diagnosis and Differential Diagnosis of Polyuria

- Vasopressin Test
  - The ADH-insensitive (nephrogenic) disease must be distinguished from the ADH-sensitive (central) form
  - This is done following water deprivation by injection of aqueous vasopressin or desmopressin acetate.
  - Give 5 units of aqueous vasopressin subcutaneously and measure urine osmolality after 1 hour; patients with complete central diabetes insipidus will show an increase of > 50% in urine osmolality, while patients with nephrogenic diabetes insipidus do not respond.

Etiology

- Idiopathic DI: 30 to 50 % (autoimmune)
- Familial disease : mutation in the gene controlling the synthesis of the ADH precursor
- Neurosurgery or trauma (usually transsphenoidal)
- Cancer: Primary or secondary (most often due to lung cancer, leukemia, or lymphoma)
- Hypoxic encephalopathy: Hypoxic encephalopathy or severe ischemia (as with cardiopulmonary arrest or shock)
- Infiltrative disorders
- Post-supraventricular tachycardia
- Acute fatty liver of pregnancy
- Anorexia nervosa

Treatment of central diabetes insipidus

- Treatment of this disorder is primarily aimed at decreasing the urine output, usually by increasing ADH (eg, arginine vasopressin or AVP) activity.
- Replacement of previous and ongoing fluid losses is also important.
  - Most patients with central DI have a normal or only mildly elevated plasma sodium concentration
  - Correction of the hypernatremia requires repair of water deficit.

Treatment of central diabetes insipidus

- Desmopressin :
  - a two-amino acid substitute of ADH that has potent antidiuretic but no vasopressor activity
  - It is usually administered intranasally and in an oral tablet form
  - The intranasal preparation ; initial dose of 5 µg at bedtime can be titrated upward in 5 µg increments depending upon the response of the nocturia and then additional daytime doses added.
  - The daily maintenance dose is about 5 to 20 µg once or twice a day.
- Other drugs
  - Chlorpropamide
  - Carbamazepine or clofibrate
  - Thiazide diuretic or NSAID

Thank you