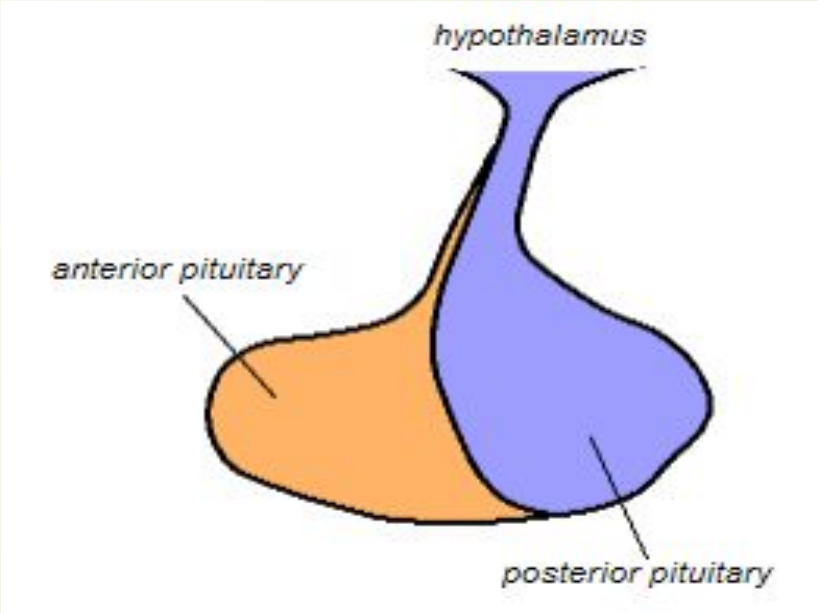
THE ENDOCRINE SYSTEM



By Dr. Esraah Alharris
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Department of Pathology
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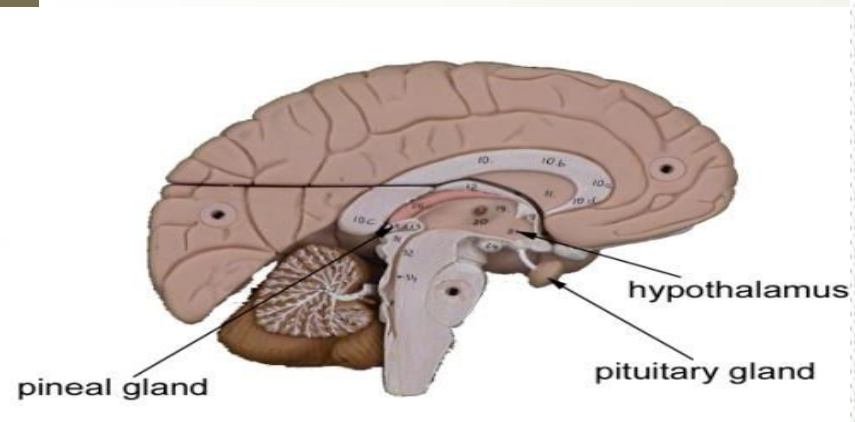
- A 42-year-old man presents with increasing fatigue and occasional headaches. He states that recently he has had to change his shoe size from 9 to 10, and he also thinks that his hands and jaw are now slightly larger. Physical examination reveals a prominent forehead and lower jaw, enlarged tongue, and large hands and feet. Initial laboratory examination reveals increased serum glucose. Which of the following is the most likely explanation for this constellation of clinical findings?
- a. Acromegaly
- b. Apoplexy
- c. Cretinism
- d. Diabetes
- e. Gigantism

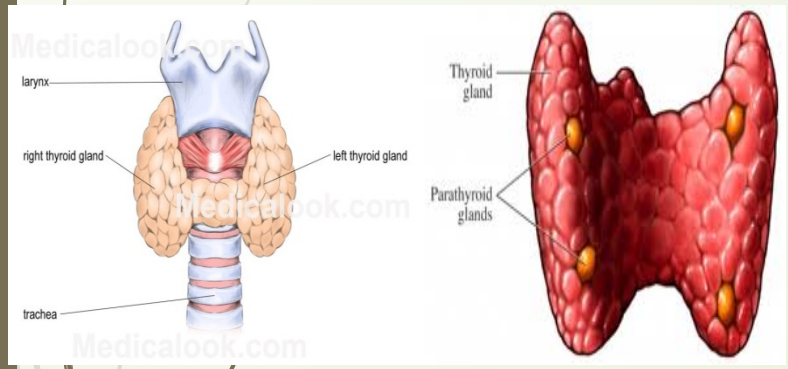
Endocrine System

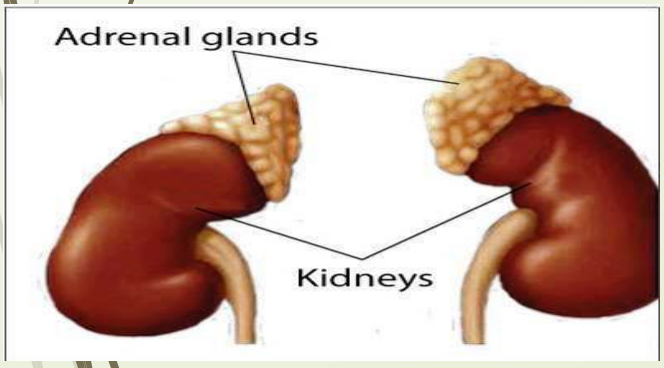
- Endocrine signaling occurs through secreted hormones acting on target cells distant from the site of synthesis; target tissue responses also typically include feedback regulation of the original hormone production. Hormones are broadly classified as:
- Peptide or amino acid–derived hormones that interact with cell surface receptors
- Steroid hormones that diffuse across plasma membranes and interact with intracellular receptors

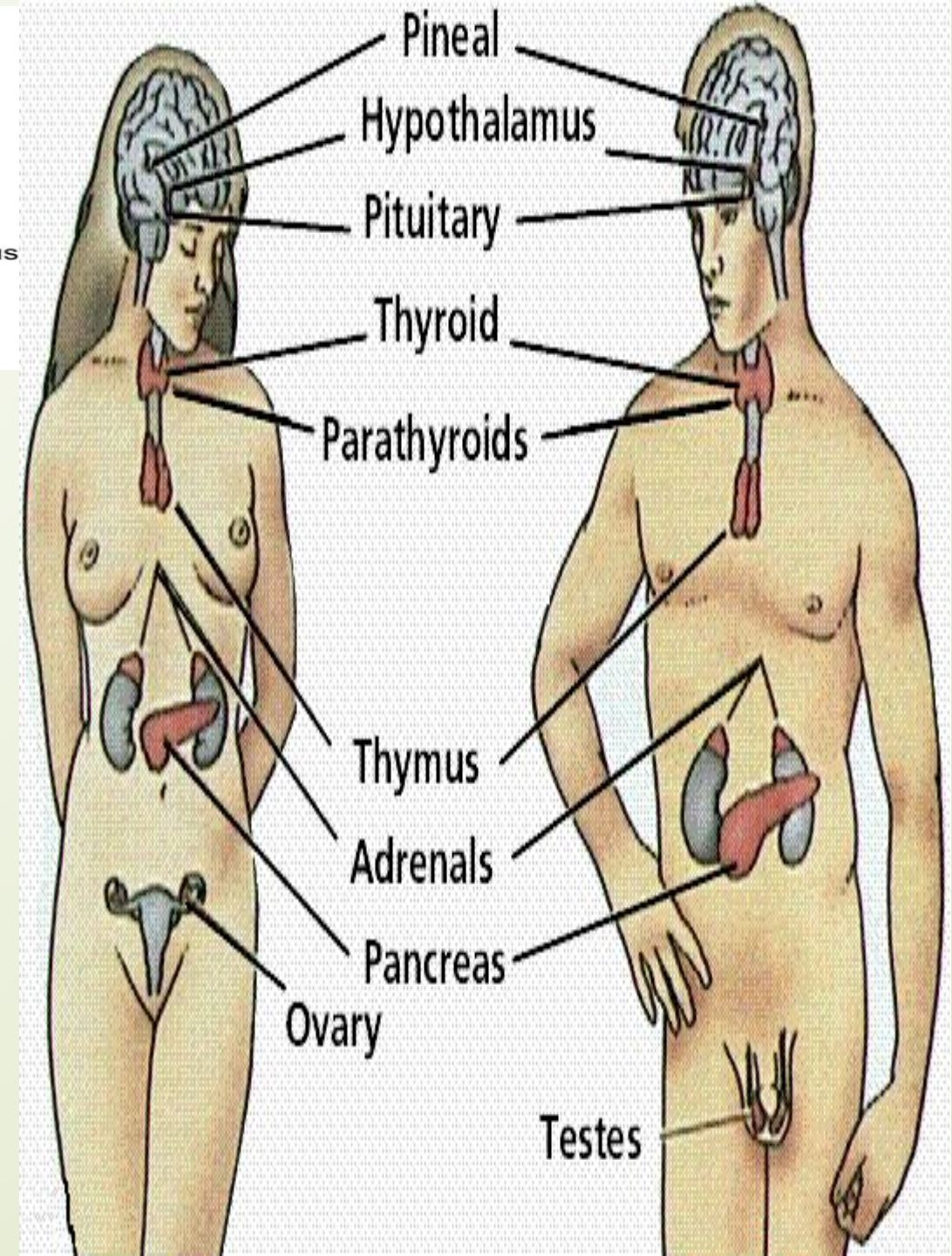
Endocrine disorders result from either:

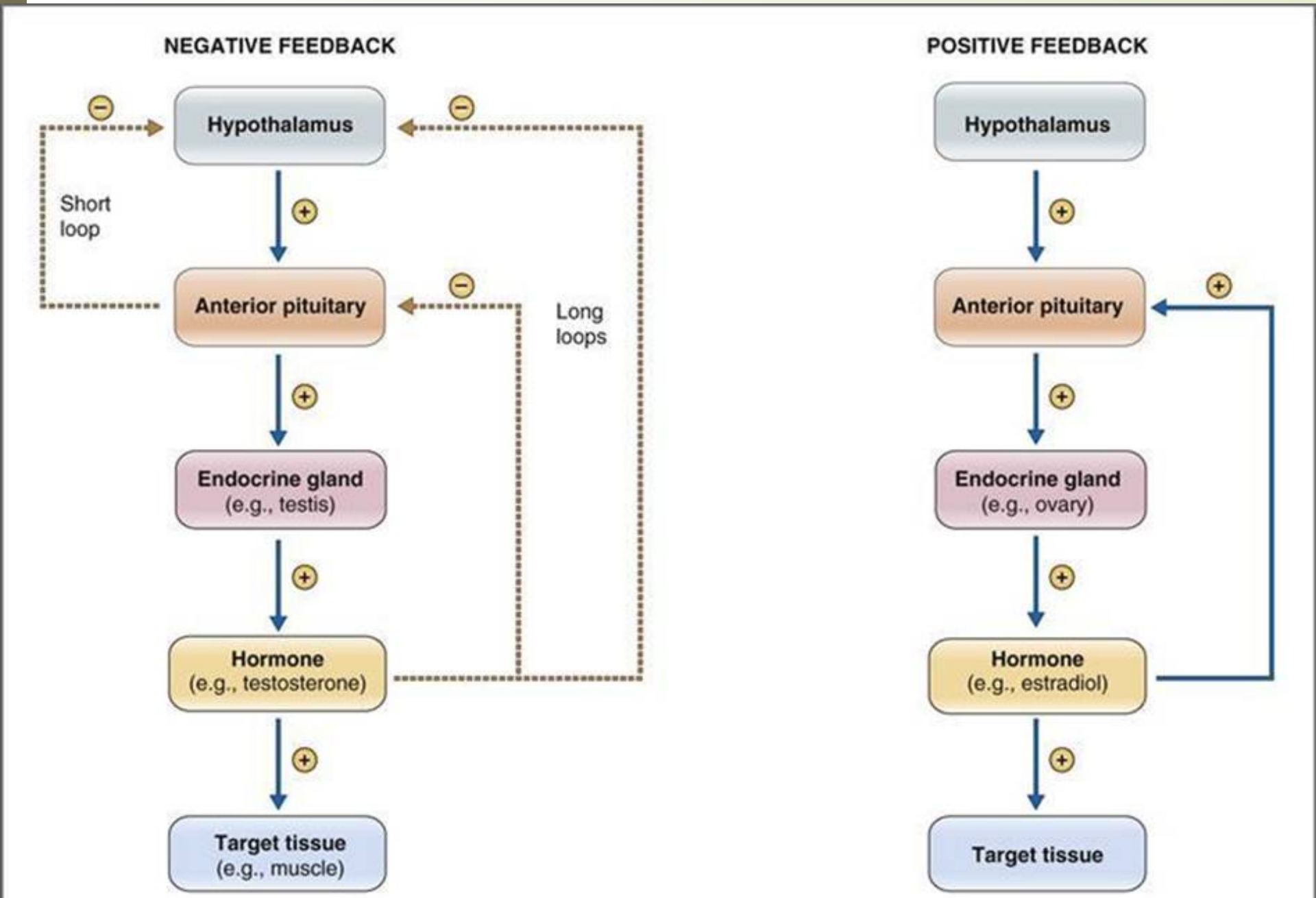
- Hormone underproduction or overproduction
- Mass lesions that can be nonfunctional or can be associated with abnormal hormone levels


hypothalamus
pineal gland
pituitary gland


larynx
right thyroid gland
left thyroid gland
trachea
Thyroid gland
Parathyroid glands

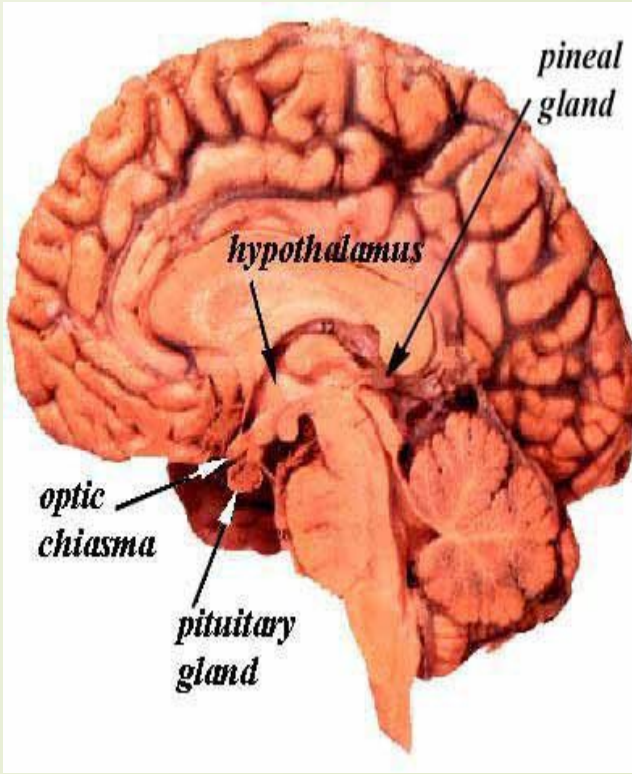

Adrenal glands
Kidneys


Pineal
Hypothalamus
Pituitary
Thyroid
Parathyroids
Thymus
Adrenals
Pancreas
Ovary
Testes


NEGATIVE FEEDBACK
Hypothalamus
Short loop
Anterior pituitary
Long loops
Endocrine gland (e.g., testis)
Hormone (e.g., testosterone)
Target tissue (e.g., muscle)
POSITIVE FEEDBACK
Hypothalamus
Anterior pituitary
Endocrine gland (e.g., ovary)
Hormone (e.g., estradiol)
Target tissue

HYPOTHALAMUS

- The hypothalamus is the portion of the brain that maintains the body's internal balance (Homeostasis).
- link the nervous system to the endocrine system via the pituitary gland.
- Hypothalamus is located below the thalamus.
- regulation of certain metabolic processes and other activities of the autonomic nervous system.
- synthesizes and secretes certain neurohormones release hormones (RH) ,which stimulate or inhibit the Function of pituitary gland.



Functions of the Hypothalamus

- Autonomic nervous system regulation
- Hormone production
- Endocrine regulation
- Circadian rhythm regulation
- Limbic system interaction
- Various
  - Temperature regulation
  - Feeding

Primary hormones secreted by the hypothalamus include:

- **Anti-diuretic hormone (ADH):** This hormone increases water absorption into the blood by the kidneys.
- **Corticotropin-releasing hormone (CRH):** CRH sends a message to the anterior pituitary gland to stimulate the adrenal glands to release corticosteroids, which help regulate metabolism and immune response.
- **Gonadotropin-releasing hormone (GnRH)**: GnRH stimulates the anterior pituitary to release follicle stimulating hormone (FSH) and luteinizing hormone (LH), which work together to ensure normal functioning of the ovaries and testes.
- **Growth hormone-releasing hormone (GHRH)** or **growth hormone-inhibiting hormone (GHIH)** (also known as somatostain): GHRH prompts the anterior pituitary to release growth hormone (GH); GHIH has the opposite effect. In children, GH is essential to maintaining a healthy body composition. In adults, it aids healthy bone and muscle mass and affects fat distribution.

Hormones secreted by the hypothalamus cont`d

- **Oxytocin**: Oxytocin is involved in a variety of processes, such as orgasm, the ability to trust, body temperature, sleep cycles, and the release of breast milk.
- **Prolactin-releasing hormone (PRH)** or **prolactin-inhibiting hormone (PIH)** (also known as dopamine): PRH prompts the anterior pituitary to stimulate breast milk production through the production of prolactin. Conversely, PIH inhibits prolactin, and thereby, milk production.
- **Thyrotropin releasing hormone (TRH):** TRH triggers the release of thyroid stimulating hormone (TSH), which stimulates release of thyroid hormones, which regulate metabolism, energy, and growth and development.

HYPOTHALAMUS

Neuronal Neoplasms	Gangliocytomas
	Neurocytomas
Glial Neoplasms	Gliomas
	Pituicytomas (including oncocytic, ependymal and granular cell variants) Hypothalamic and optic gliomas
Neural Stromal Neoplasms	Schwannomas
	Meningiomas
	Chordomas
Other stromal neoplasms	Vascular & mesenchymal tumors
	Lymphomas
	Germ cell tumors
Infiltrating Neoplasms	PitNETs (Pituitary neuroendocrine tumors)
	Craniopharyngiomas
	Germ cell tumors including teratomas
Metastatic Neoplasms	

HYPOTHALAMUS LESION

- **Neoplasms imay induce hypofunction or hyperfunction of the anterior pituitary, or combinations of these manifestations.**

  - **Gliomas**
  - **Craniopharyngiomas**

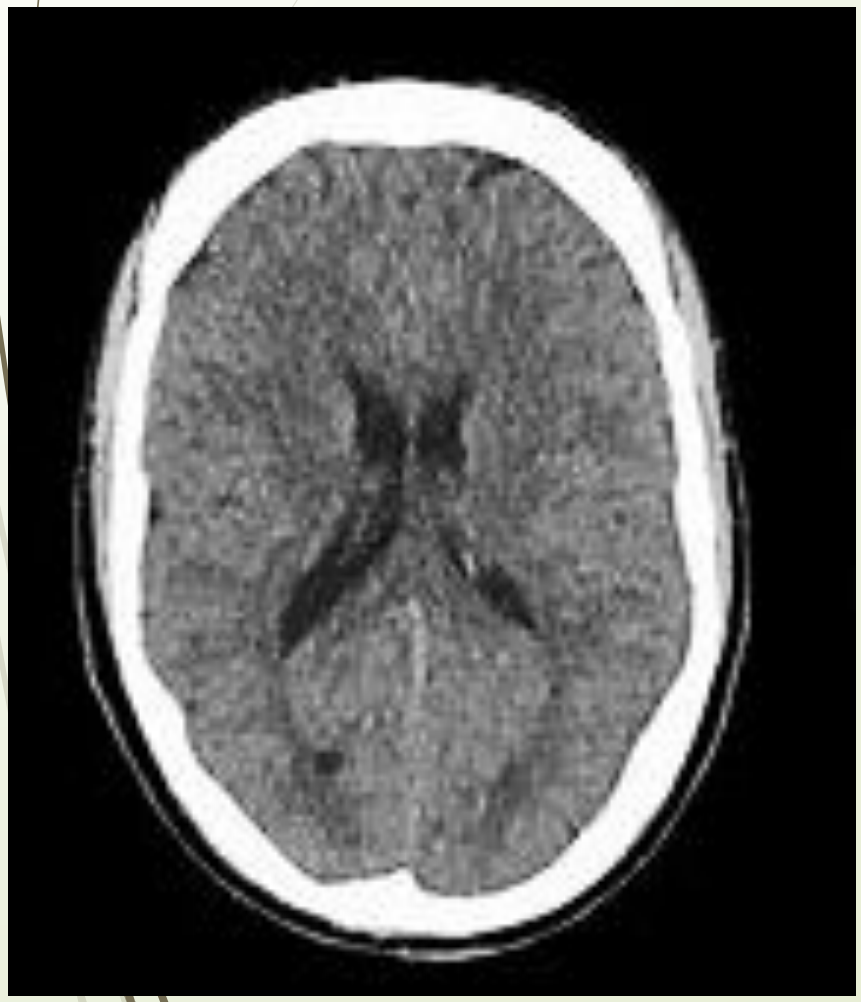
- **1% to 5% of intracranial tumors**
- **A bimodal age distribution**

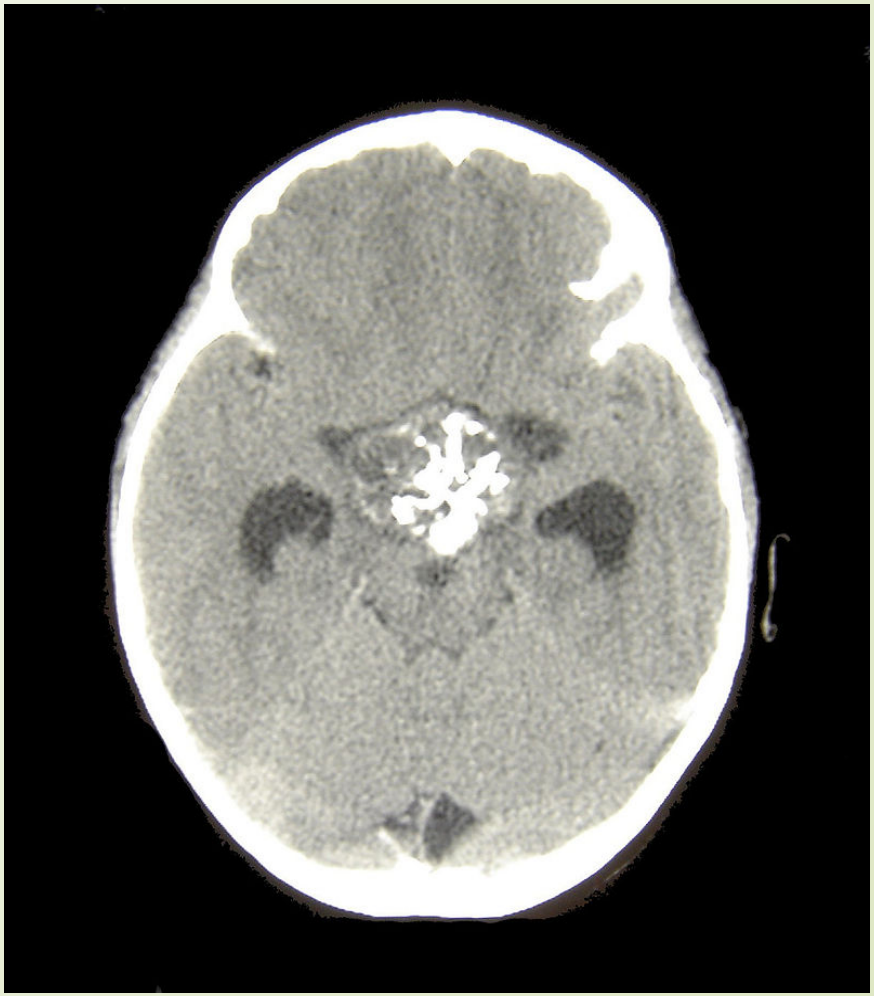
(5 to 15 years) Adults 65

- **Headaches and visual disturbances**
- **Vomting with out nousea**
- **Altered level of consciousness**

Children might present with growth retardation due to pituitary hypofunction and GH deficiency

Morphology. In CT scan Craniopharyngiomas average 3 to 4 cm in diameter; they may be encapsulated and solid, but more commonly they are cystic and sometimes multiloculated

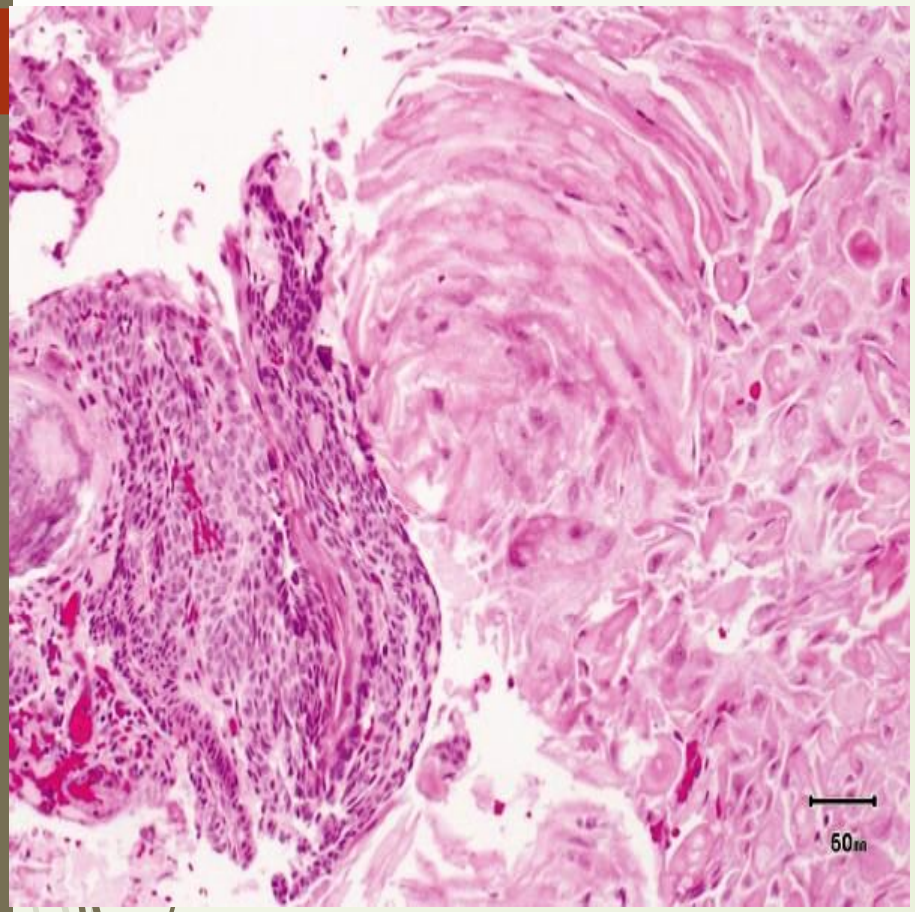


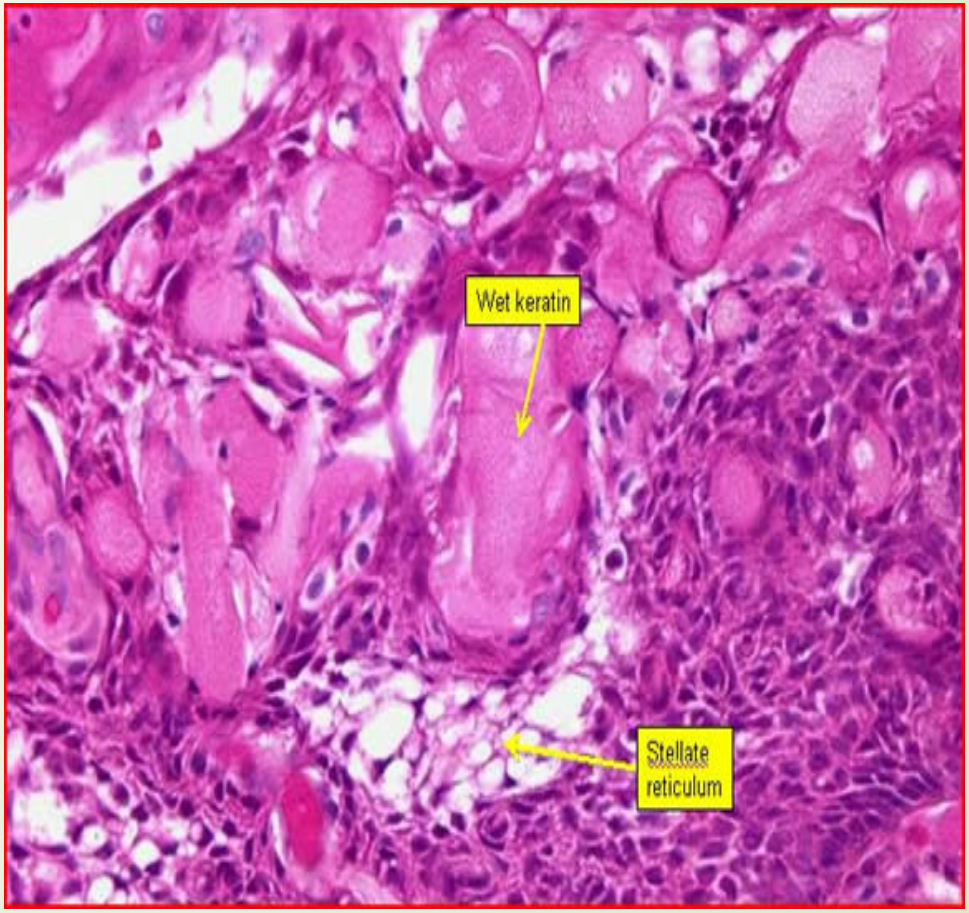


Two distinct histologic variants are recognized:

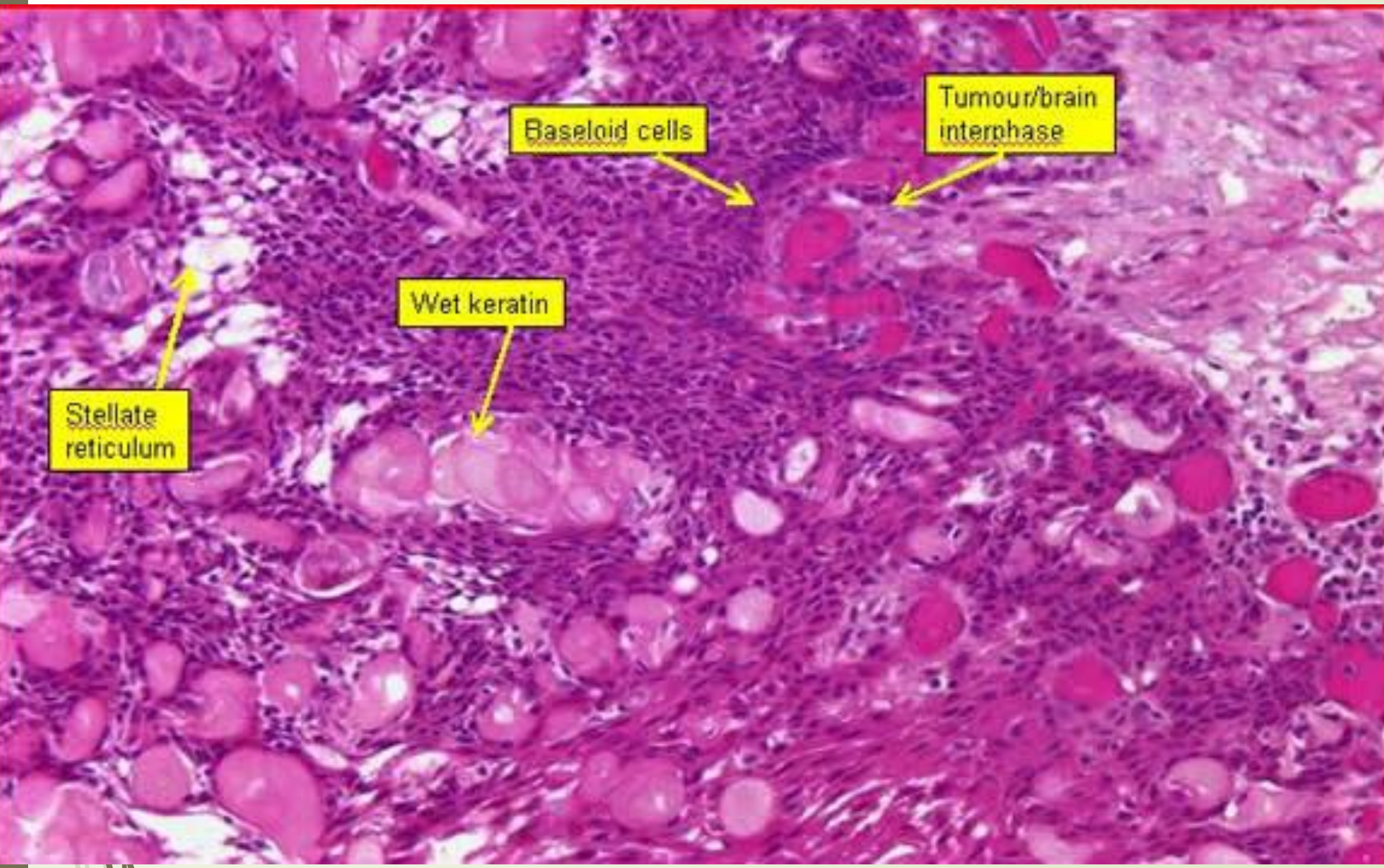
- **Adamantinomatous craniopharyngioma** (most often observed in children)
- **Papillary craniopharyngioma** (most often observed in adults).

Hypothalamic Suprasellar Tumors

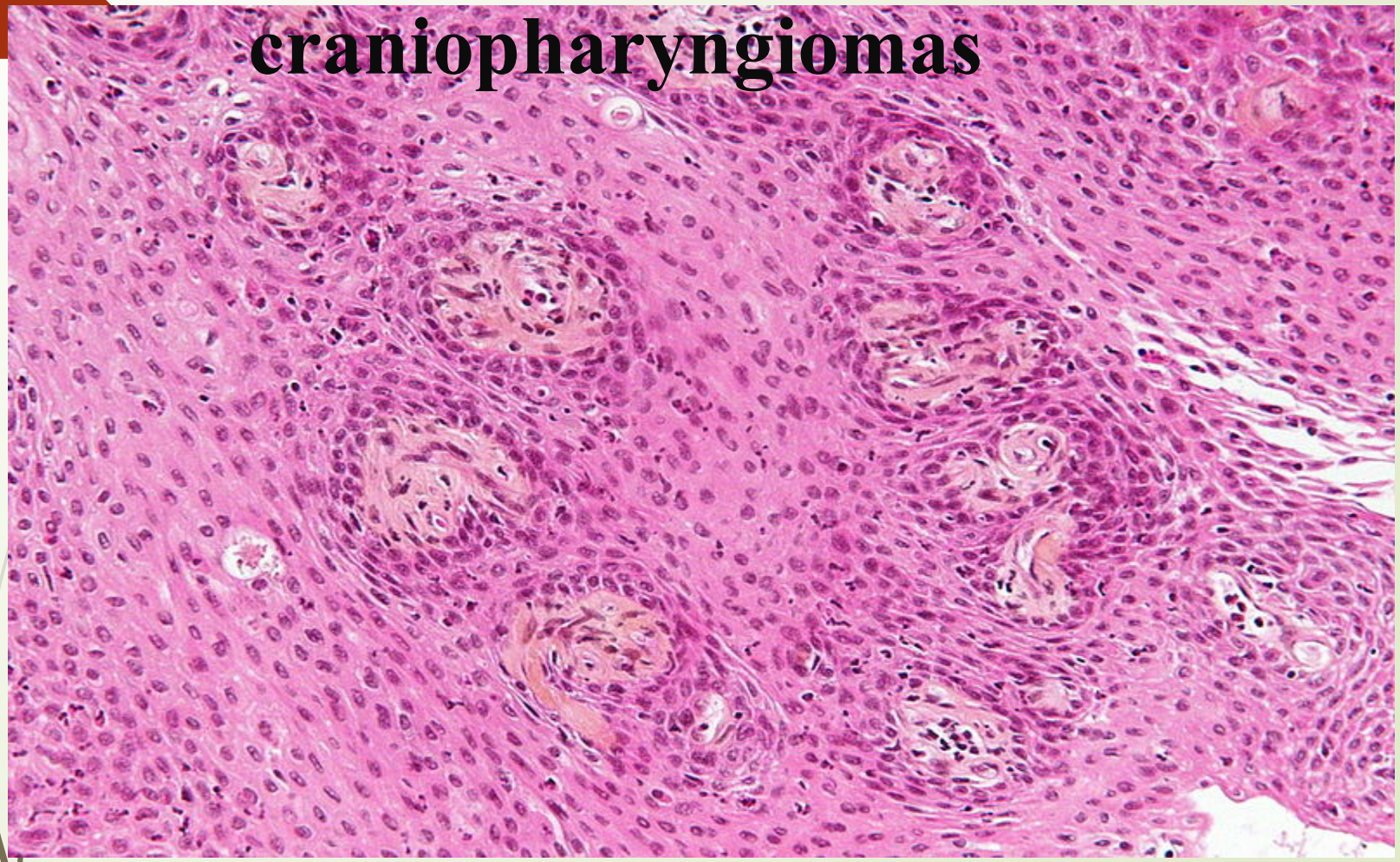




consists of nests or cords of stratified squamous epithelium embedded in a spongy "reticulum" that becomes more prominent in the internal layers. "Palisading" of the squamous epithelium is frequently observed at the periphery. Compact, lamellar keratin formation ("wet keratin") is a diagnostic feature of this tumor


Baseloid cells
Tumour/brain interphase
Wet keratin
Stellate reticulum

Papillary craniopharyngiomas



contain both solid sheets and papillae lined by well-differentiated squamous epithelium. These tumors usually lack keratin, calcification, and cysts.

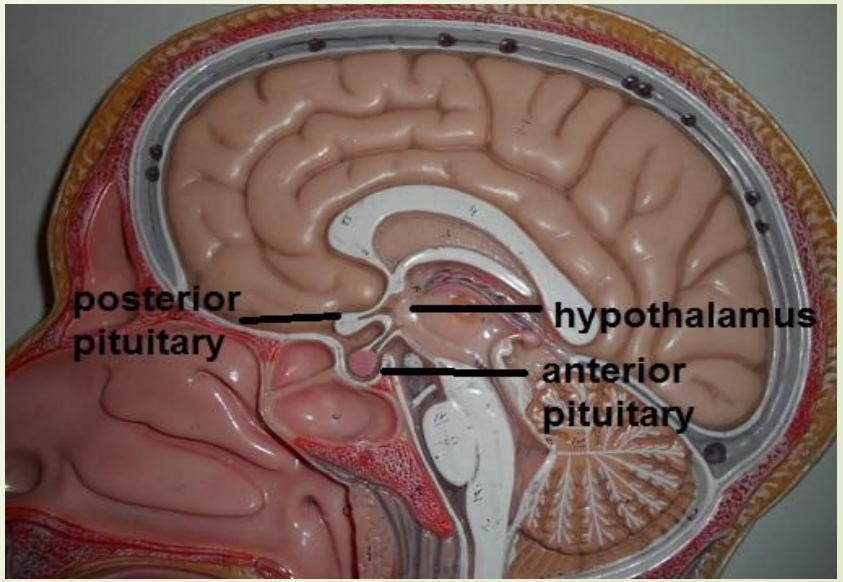
Prognosis:-

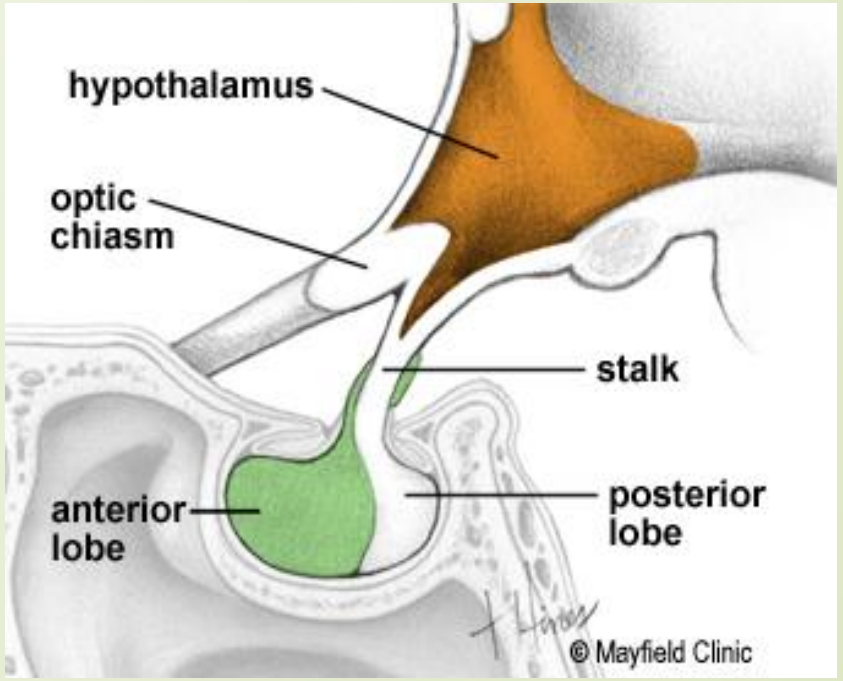
- Craniopharyngiomas are generally benign but are known to recur after resection.
- Recent research[has demonstrated a malignant tendency of craniopharyngiomas (but rare).
- Malignant craniopharyngiomas are very rare, but are associated with poor prognosis

Pituitary gland

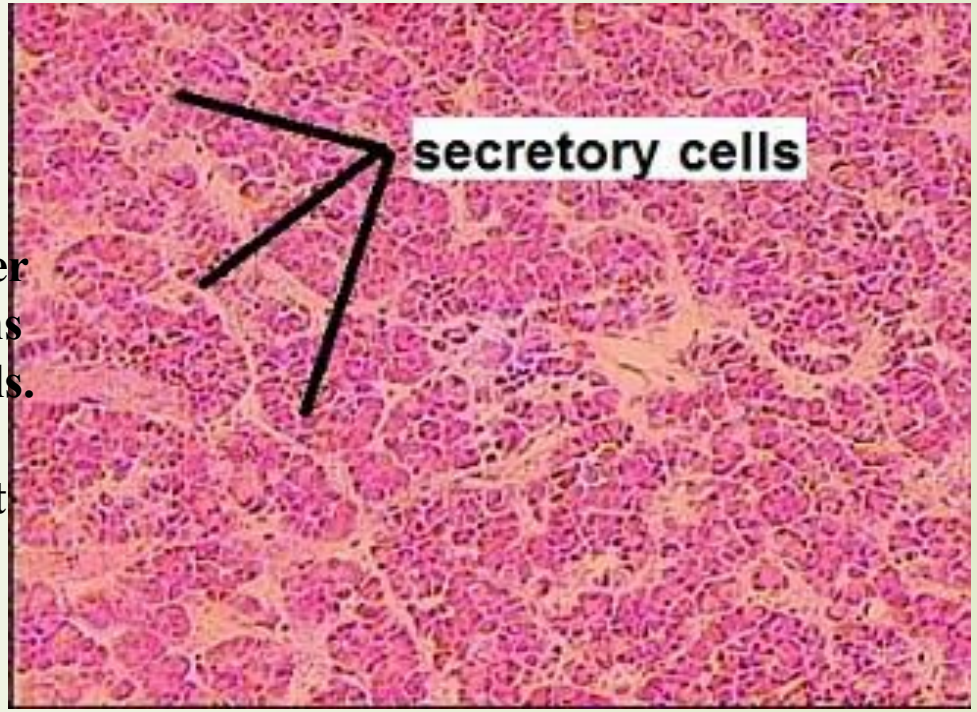
Pituitary Gland

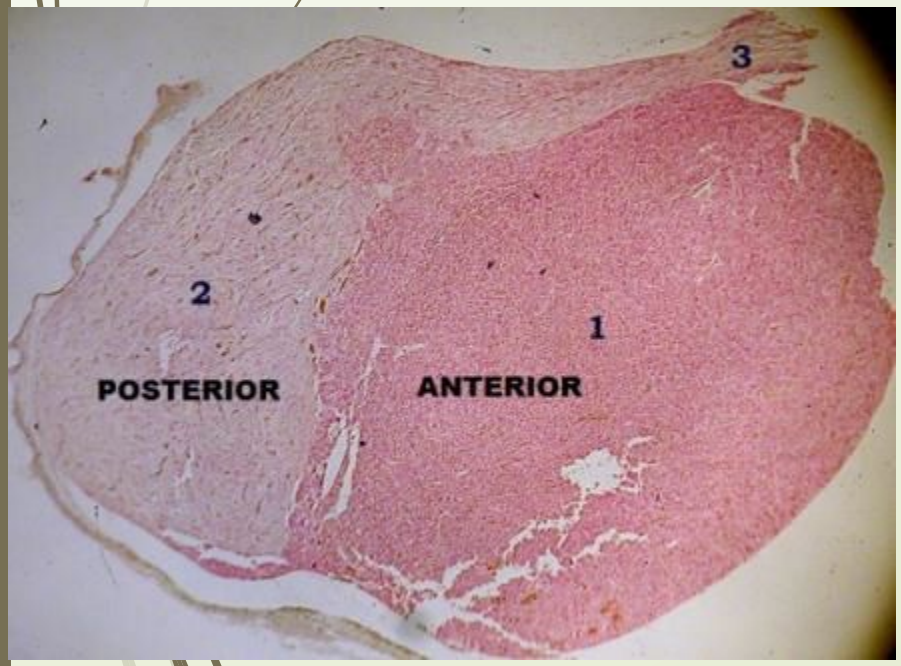
- Is a small Pea sized mass of glandular tissue that lies at the base of the brain within the confines of the sella turcica. It is connected to the hypothalamus by a "stalk," composed of axons extending from the hypothalamus.
- There are two separate components:
  - Anterior
  - Posterior

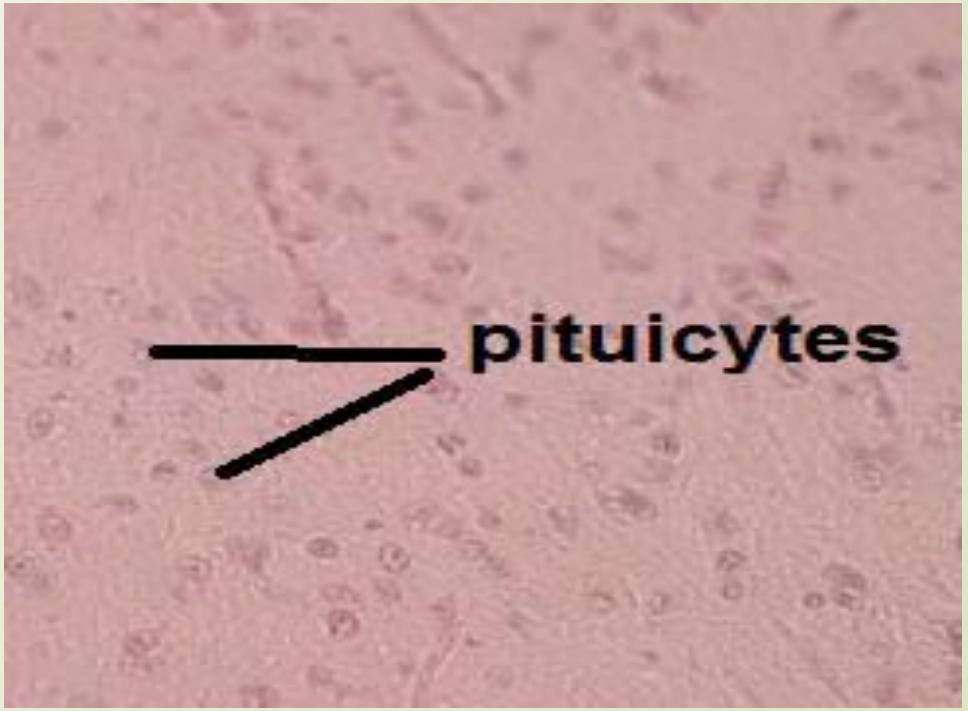


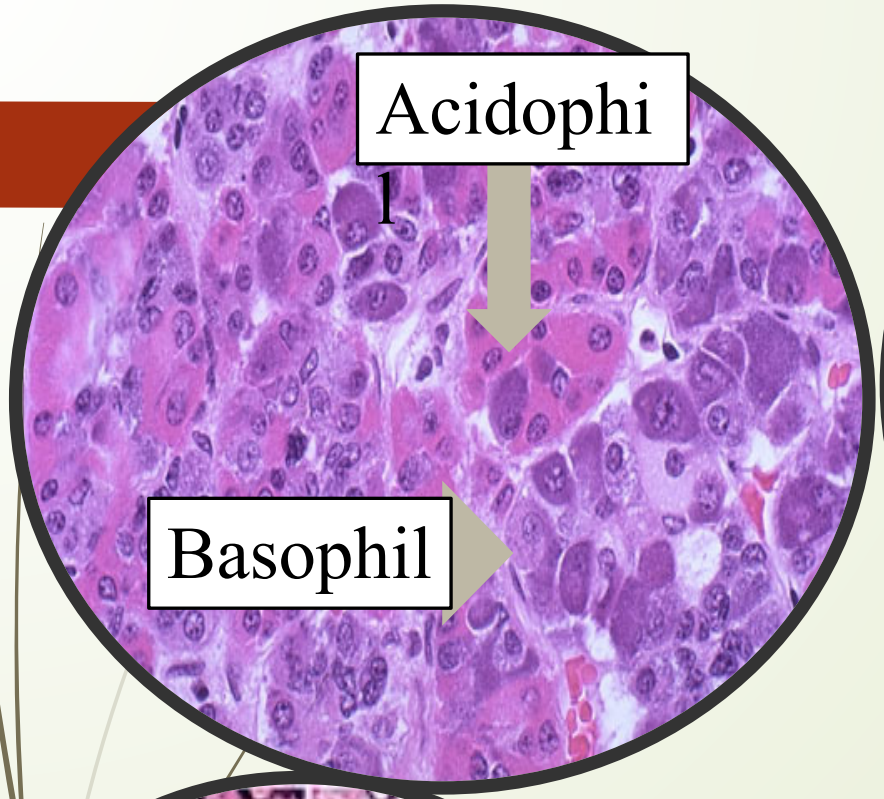


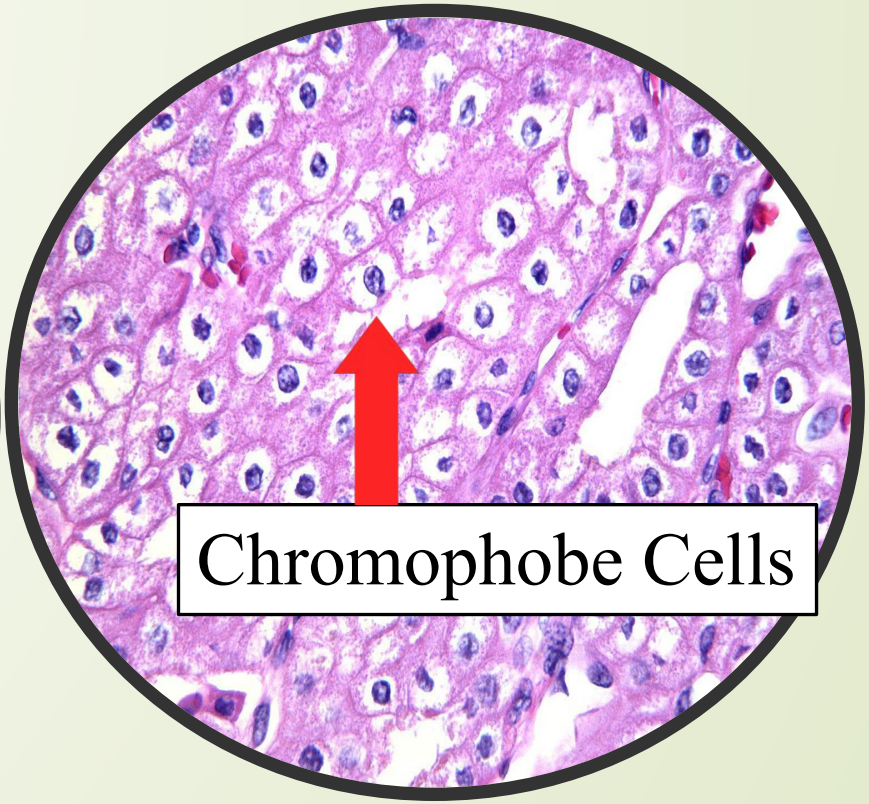
Anterior Pituitary (adenohypophysis) under a microscope and it looks 'busy.' It contains a large number of cells called secretory cells.
Posterior Pituitary (neurohypophysis). When compared to the anterior pituitary it looks empty. It contains neural cells called pituicytes.

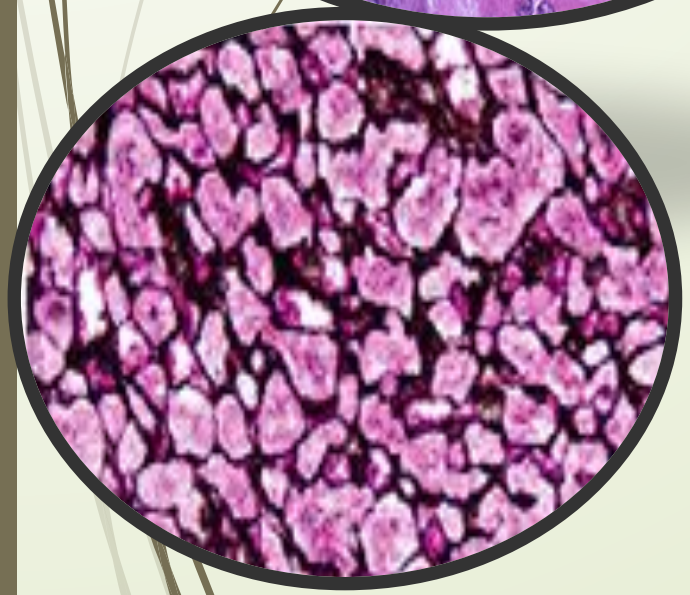






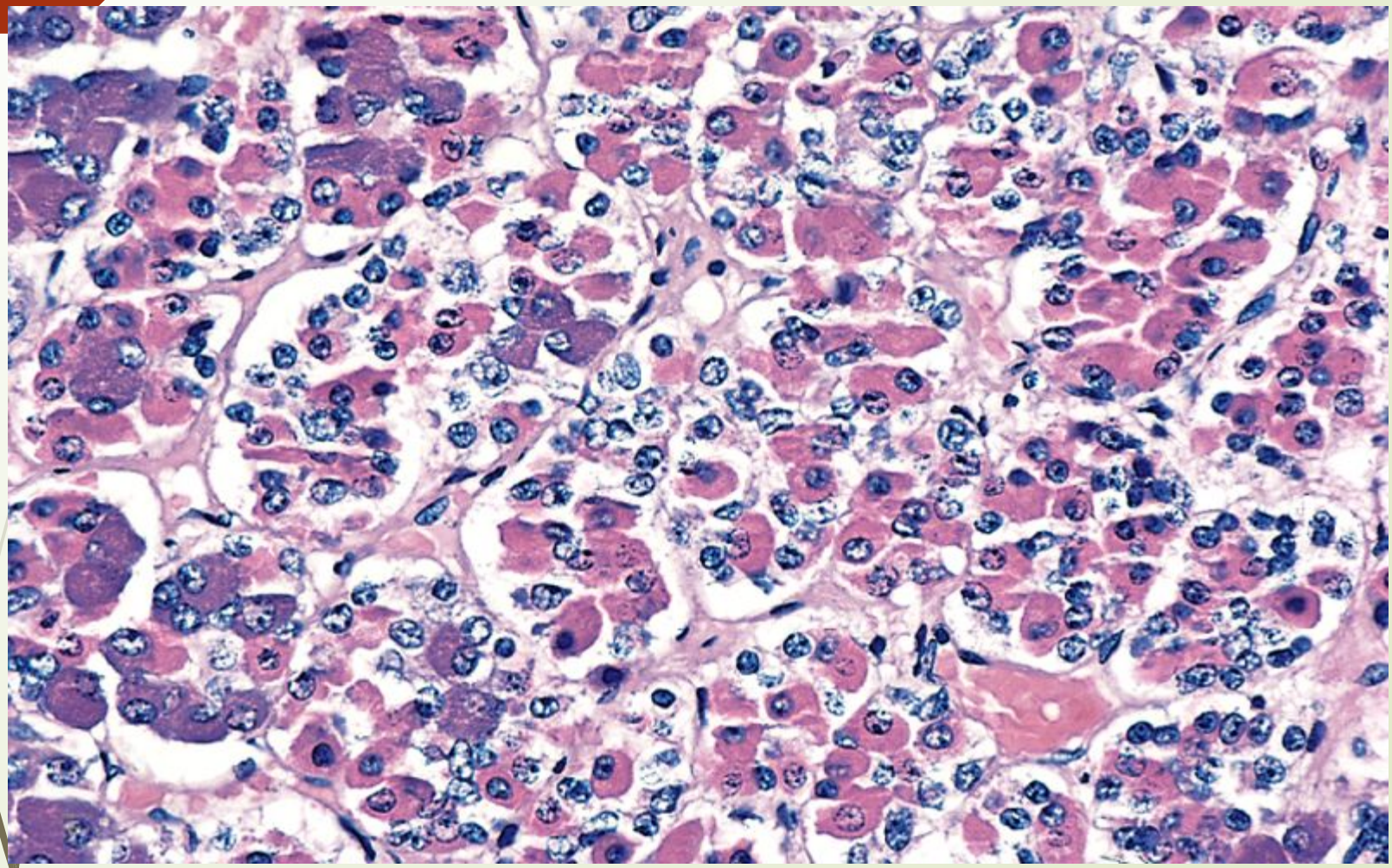




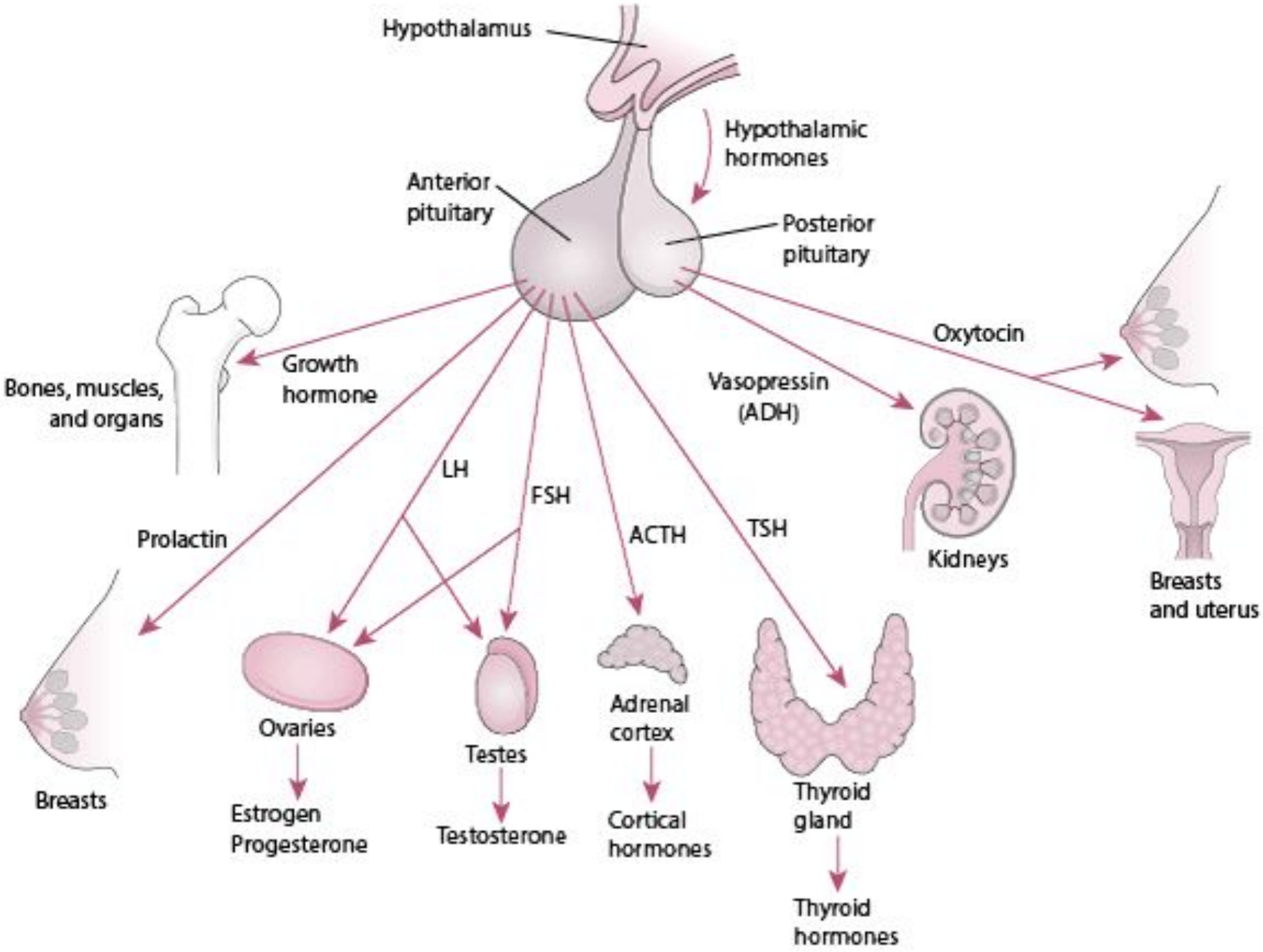


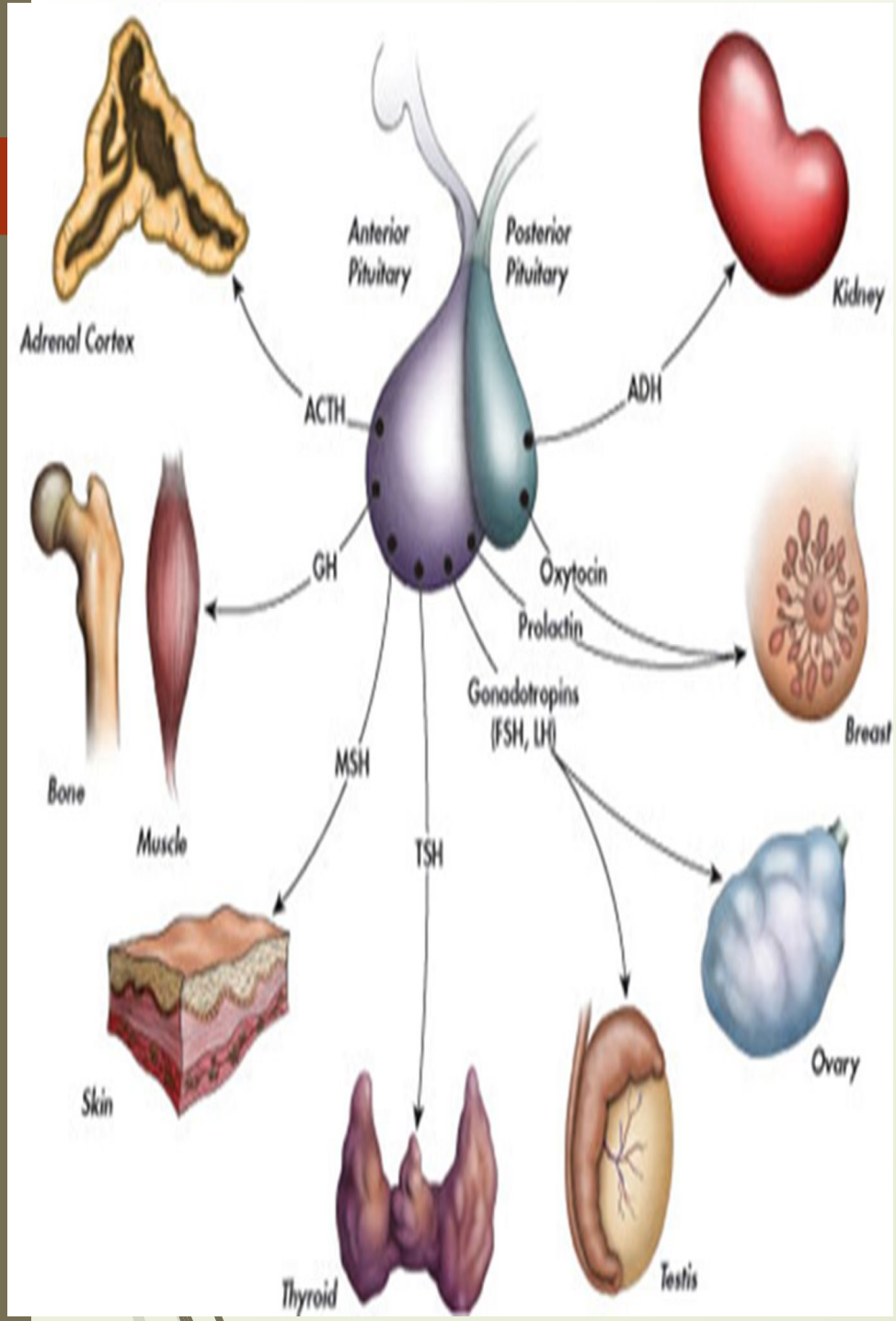
In routine histologic sections of the anterior pituitary, a colorful array of cells is present that contain eosinophilic cytoplasm (acidophil), basophilic cytoplasm (basophil), or poorly staining cytoplasm (chromophobe) cells

Normal anterior pituitary



The gland is populated by several distinct cell populations containing a variety of stimulating (trophic) hormones. Each of the hormones has different staining characteristics, resulting in a mixture of cell types in routine histologic preparations.


Hypothalamus
Hypothalamic hormones
Anterior pituitary
Posterior pituitary
Bones, muscles, and organs
Growth hormone
Oxytocin
Vasopressin (ADH)
Kidneys
Breasts and uterus
Prolactin
LH
FSH
ACTH
TSH
Breasts
Ovaries
Estrogen
Progesterone
Testes
Testosterone
Adrenal cortex
Cortical hormones
Thyroid gland
Thyroid hormones



- **Somatotrophs**
  - **Production growth hormone (GH)----acidophilic**
- **Mammotrophs**
  - **Producing prolactin (Prl)-------- acidophilic**
- **Corticotrophs**
  - **Producing ACTH, MSH, and endorphins are derived-basophilic------- basophilic**
- **Thyrotrophs**
  - **Producing thyroid stimulating hormone-TSH-------- pale basophilic**
- **Gonadotrophs**
  - **Producing Follicle-stimulating hormome (FSH) and Luteinizing hormone (LH) basophilic-------basophilic**

The **melanocyte-stimulating hormones**, **MSH**, or **melanotropins** or **intermedins :-** release of melanin (a process referred to as melanogenesis) by melanocytes in skin and hair

posterior pituitary stores and secretes *(but does not synthesize)* the following important endocrine hormones:

- **Antidiuretic hormone (ADH, also known as vasopressin and arginine vasopressin AVP), the majority of which is released from the supraoptic nucleus in the hypothalamus.**
- **Oxytocin, most of which is released from the paraventricular nucleus in the hypothalamus.**

Oxytocin is one of the few hormones to create a positive feedback loop. For example, uterine contractions stimulate the release of oxytocin from the posterior pituitary, which, in turn, increases uterine contractions. This positive feedback loop continues throughout labour

Pituitary Gland Disorders

Clinical Manifestations of Pituitary Disease

- ***Hyperpituitarism:***
- ***Hypopituitarism:***
- ***Local mass effects:***

Hyperpituitarism

- Until proven otherwise , hyperfunction of the anterior pituitary means an **Pituitary Adenoma:**
- **OTHER causes of hyperpituitarism include pituitary hyperplasia.**
- **Carcinomas of the anterior pituitary**
- **Secretion of hormones by non-pituitary tumors, and certain hypothalamic disorders**

Tumors of pituitary gland:

A- Adenoma:

Most common cause of hyperpituitism, usually in anterior lobe

- **Microadenoma (< 1cm) or macroadenoma (> 1cm)**
- **Benign**
- **Functioning or non-functioning (macroadenoma)**
- **Acidophil, basophil, or chromophobe.**
- **Prevelance 14%**
- **Peak age incidence 35-60 years old**
- **Majoirity sporadic.**
- **5% heretible.**

Pathogenesis

Guanine nucleotide-binding protein (*G-protein*) mutations are the best characterized molecular abnormalities.

MENI mutation (tumor suppressor protein) .

Symptoms:-

- Not all pituitary tumors cause symptoms.
- Functioning can cause a variety of signs and symptoms depending on the hormone they produce.
- Nonfunctioning are related to their growth and the pressure they put on other structures.

A- Functioning Adenoma

1-Prolactinomas

Lactotroph cells :- Most common functional pituitary tumor
(30%)

In women, prolactinoma might cause:

Milky discharge from the breasts

Irregular menstrual periods or amenorrhea

Unovulatory infertility

In men

hypogonadism

Erectile dysfunction

Lowered sperm count

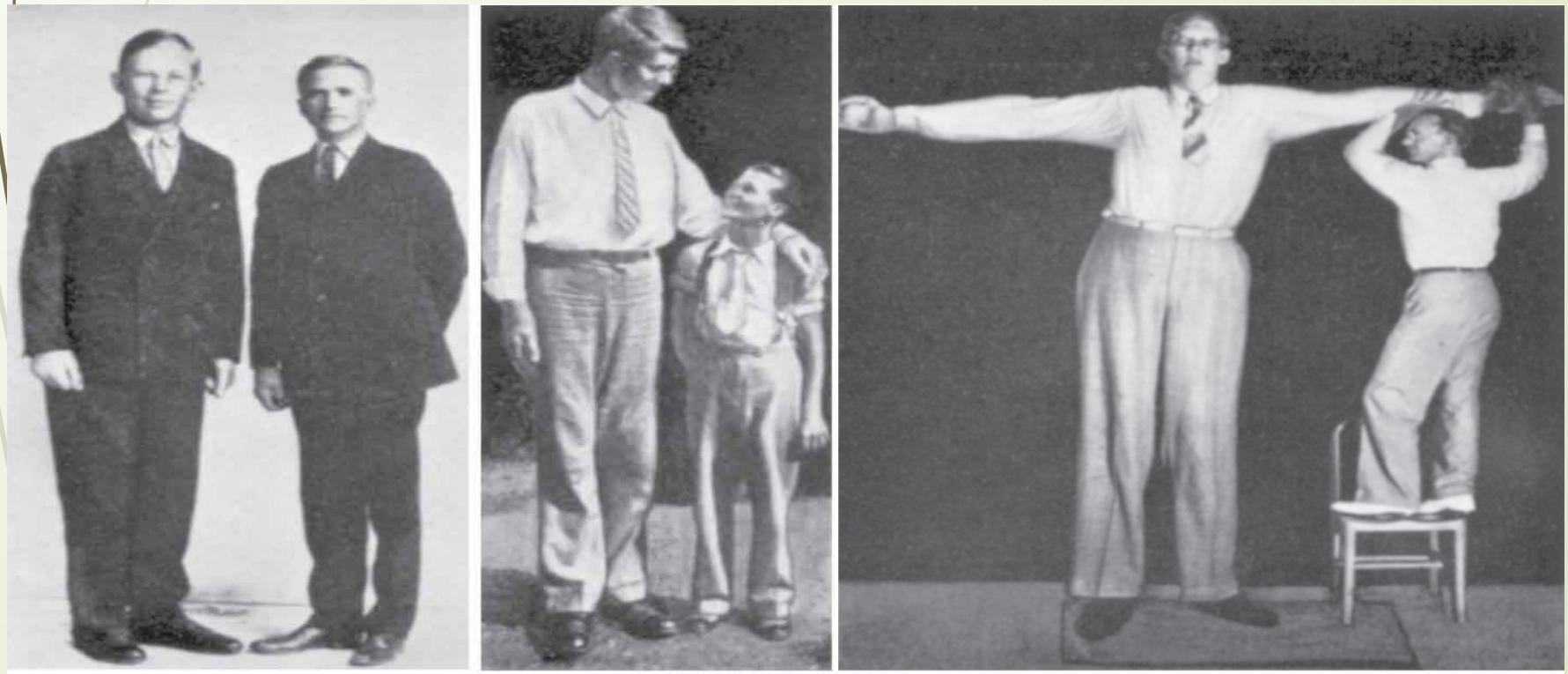
Loss of sex drive

Breast growth

2-Somatotrophic Adenomas second most common functioning adenoma

A. GIGANTISM

Hypersecretion of Growth Hormone (GH) occurs before puberty…before closure of growth plates, growth in the length of all bones occurs.



Courtesy C.M. Charles and C.M. MacBryde.

Fig. 65-1. The clinical features of growth hormone (GH) excess. Robert Wadlow, the "Alton giant," weighed 9 pounds at birth but grew to 30 pounds by the time he was 6 months old. By his first birthday, he had reached 62 pounds. At the time of his death at age 22 from cellulitis of the feet, he was 8 feet, 11 inches tall and weighed 475 pounds.

B. ACROMEGALY

After epiphyseal closure, fat accumulation around midsection and upper back
Exaggerated facial roundness
Thinning of the arms and legs

GH excess is also associated with:-

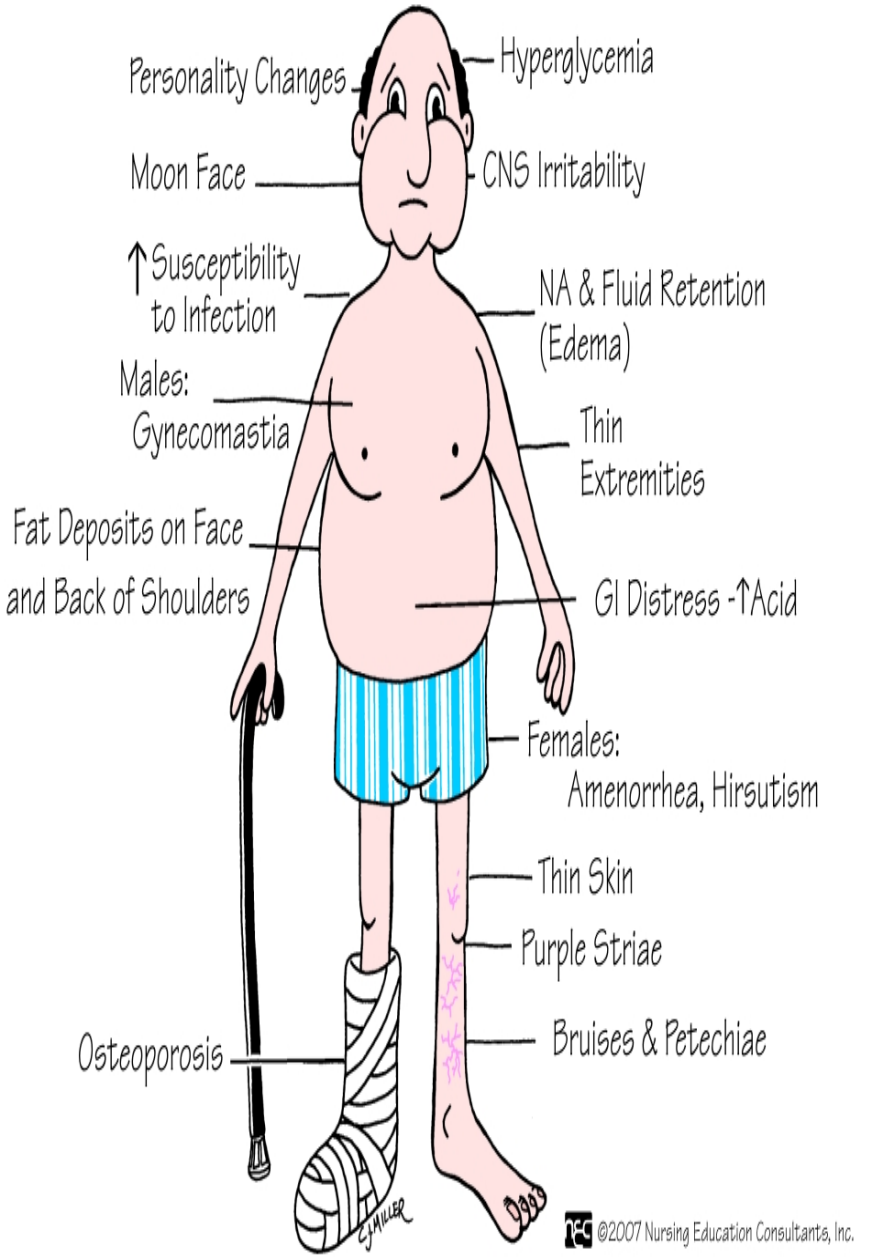
- High blood pressure
- High blood sugar
- CHF
- Muscle weakness
- Bone weakening , arthritis (joints pain)
- Bruising , Stretch marks, Increased body hair
- Increase risk of intestinal cancers

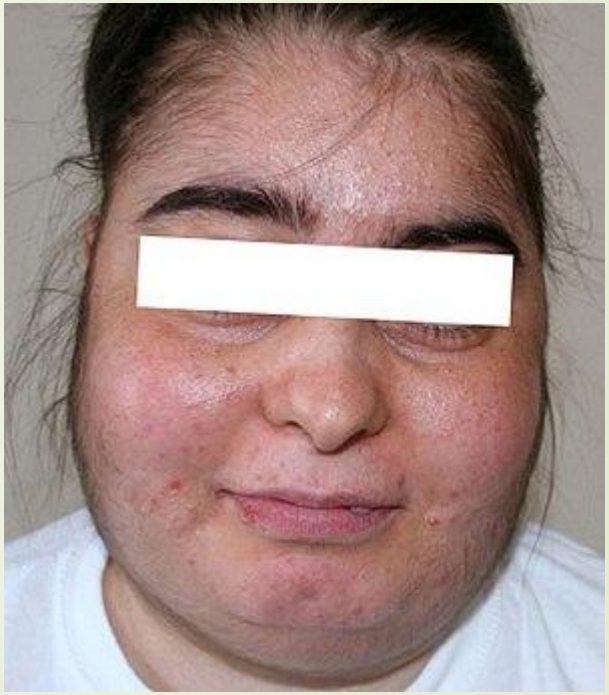
3-ACTH (corticotroph cells)

Mostly microadenoma
May be clinically silent
Increased release of both cortisol and androgenic hormones
Large aggresive adenoma may develop after surgical removal of adrenal gland in tx. Of Cushing syndrome (Nelson syndrome)

- Serum glucose levels increased ….(gluconeogenesis) eventually the islet cells of the pancreas cannot produce enough insulin and DM results.
- Loss of protein stores occurs, muscle wasting
- Humoral immunity is reduced, decreasing the threshold to infection
- Skin tissues lose collagen, and become very thin: tearing and bruising easily
- Excess body and facial hair growth in women (from excess androgen secretion)
- Mood swings and psychosis may occur as the effect of excess cortisol on cognitive function.
- Truncal obesity: results from the mobilization of fat in the lower parts of the body, to the trunk causing the abdomen to become protuberant as the extremities become thin and wasted.

CUSHING'S SYNDROME





4- Gonadotroph adenomas (10% to 15% of pituitary adenomas).

5- Thyrotroph adenomas (1% of pituitary adenomas) are rare causes of hyperthyroidism.

B-Nonfunctioning pituitary adenomas

(25% to 30% of pituitary adenomas) include non-secretory (“silent”) typically present with mass effects.

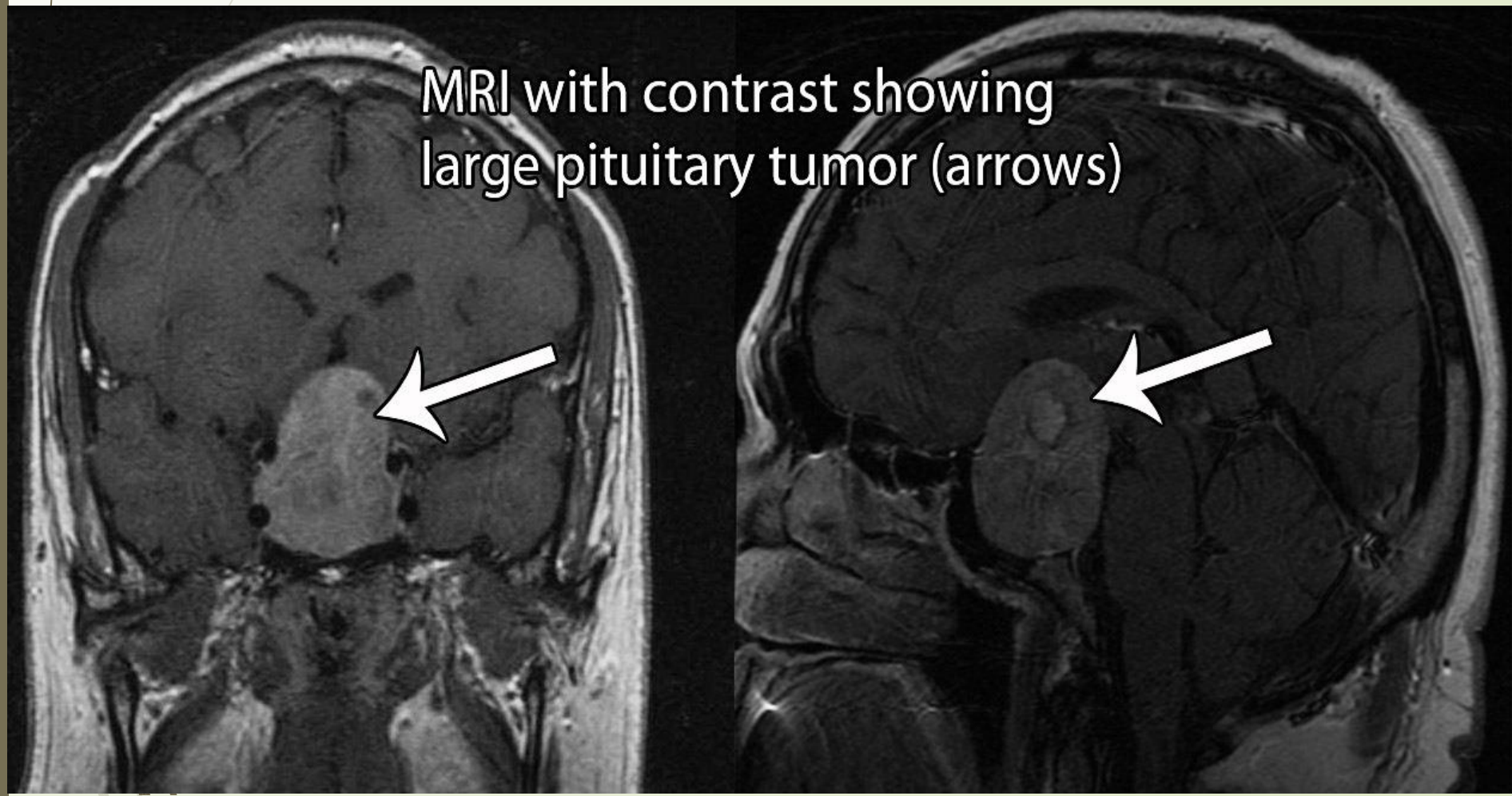
Pituitary carcinomas

They are quite rare (less than 1%); most are functional (secreting Prl or ACTH most commonly). **Diagnosis of carcinoma requires the demonstration of metastases**.

Diagnosis

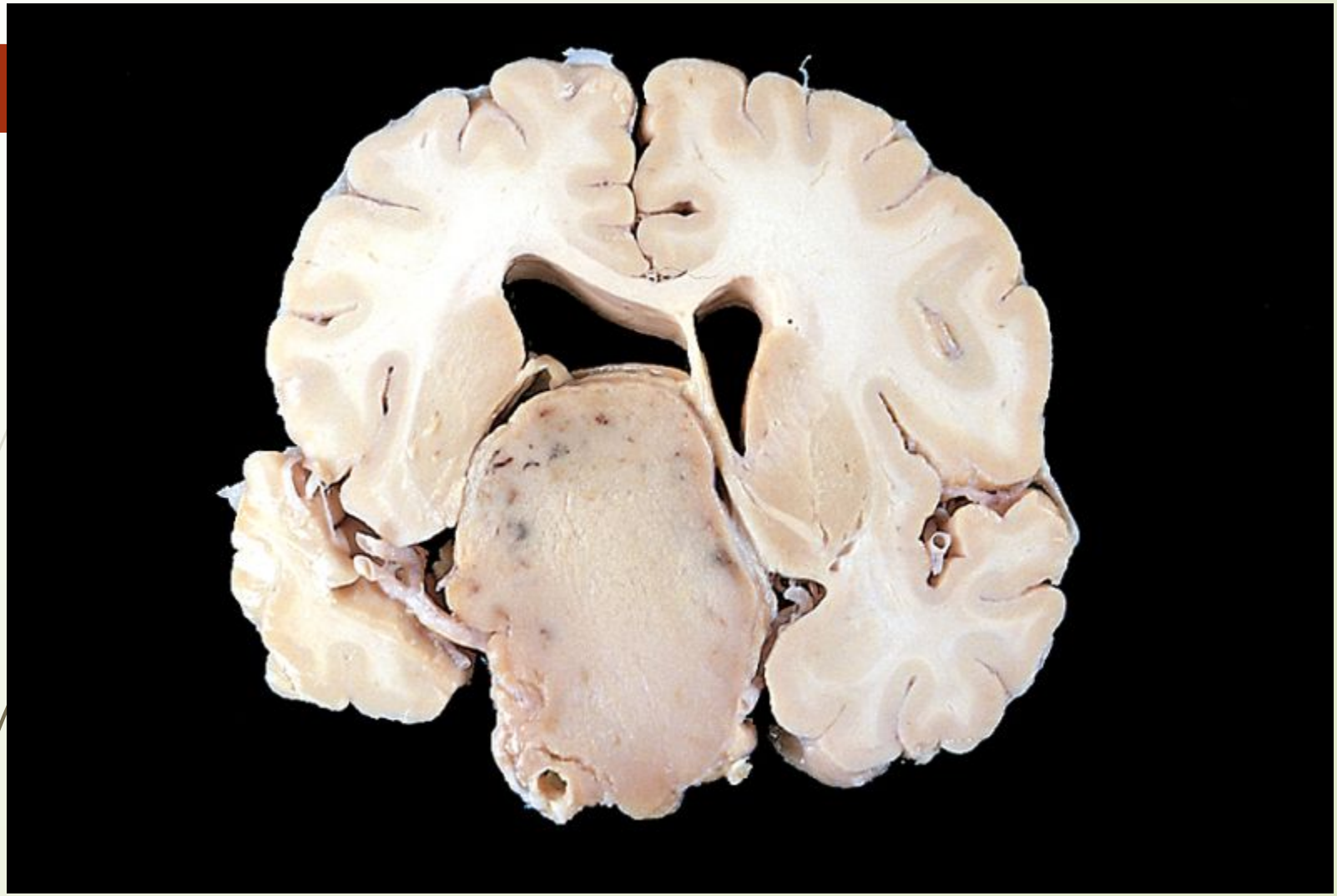
- A detailed history and perform a physical exam. He or she might order:
- Vision testing. This can determine if a pituitary tumor has impaired pt. sight or peripheral vision.
- Blood and urine tests. These can determine whether you have an overproduction or deficiency of hormones.
- Abdominal ultrasound to exclude extra pituitary source of hormones excess.

- **Brain imaging. A CT scan or MRI scan of your brain can help your doctor judge the location and size of a pituitary tumor.**

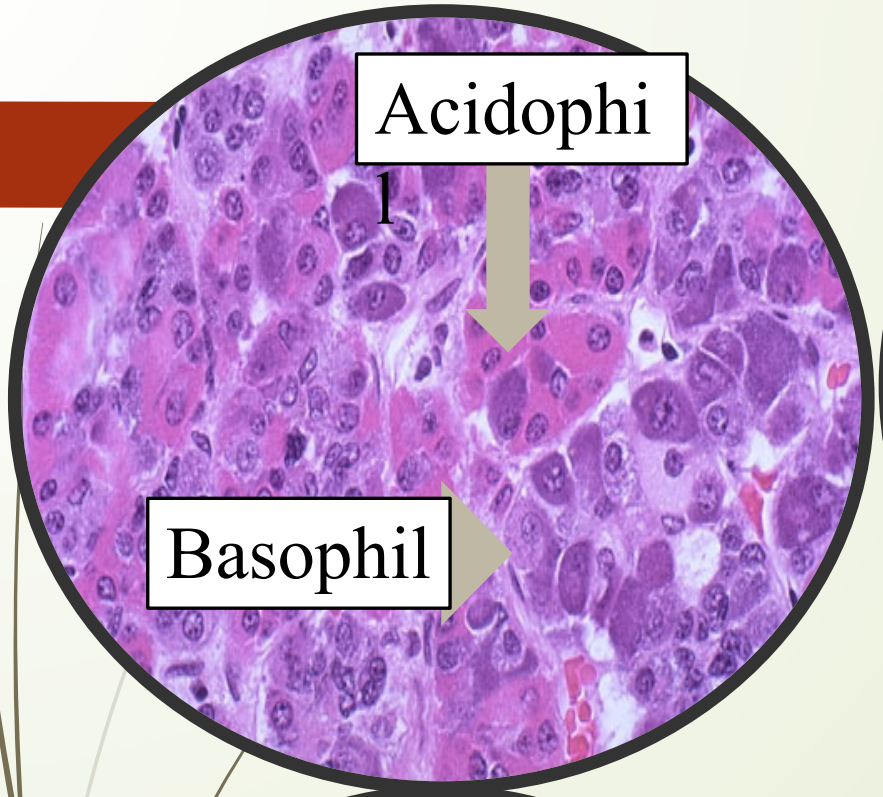


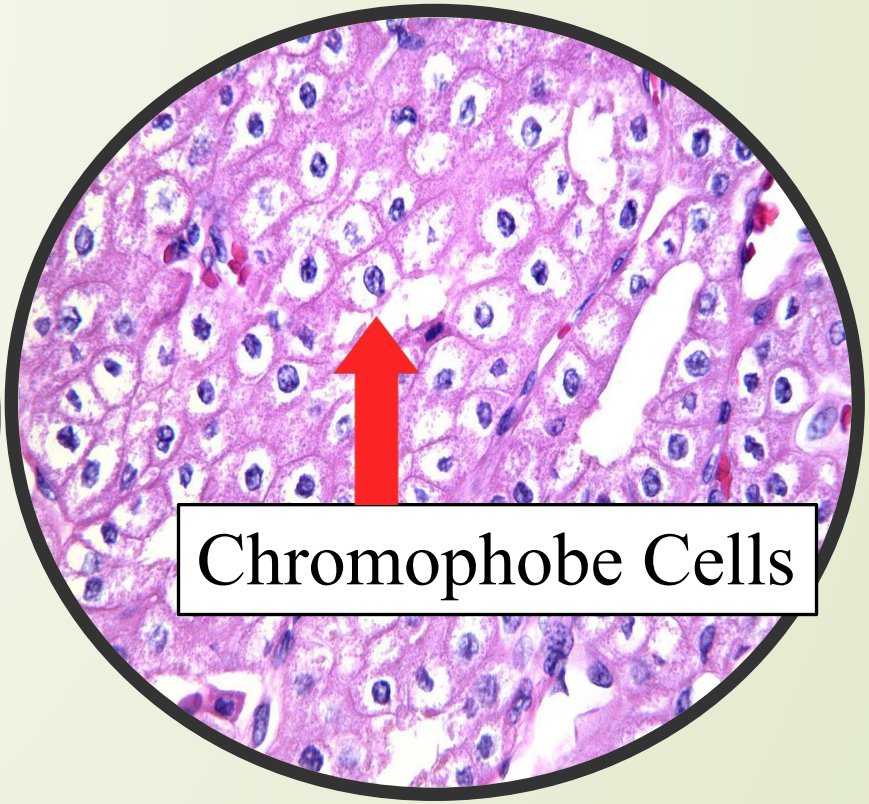
- **Gold standard is histopathological study after excision.**

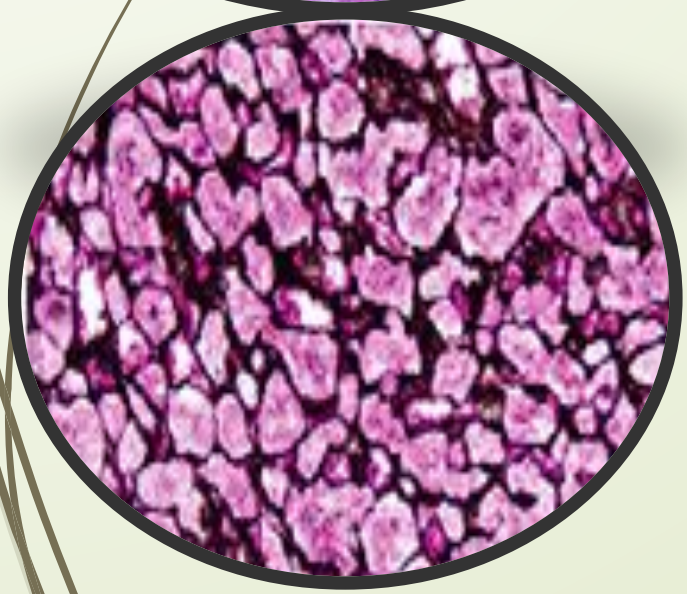
Pituitary adenoma gross



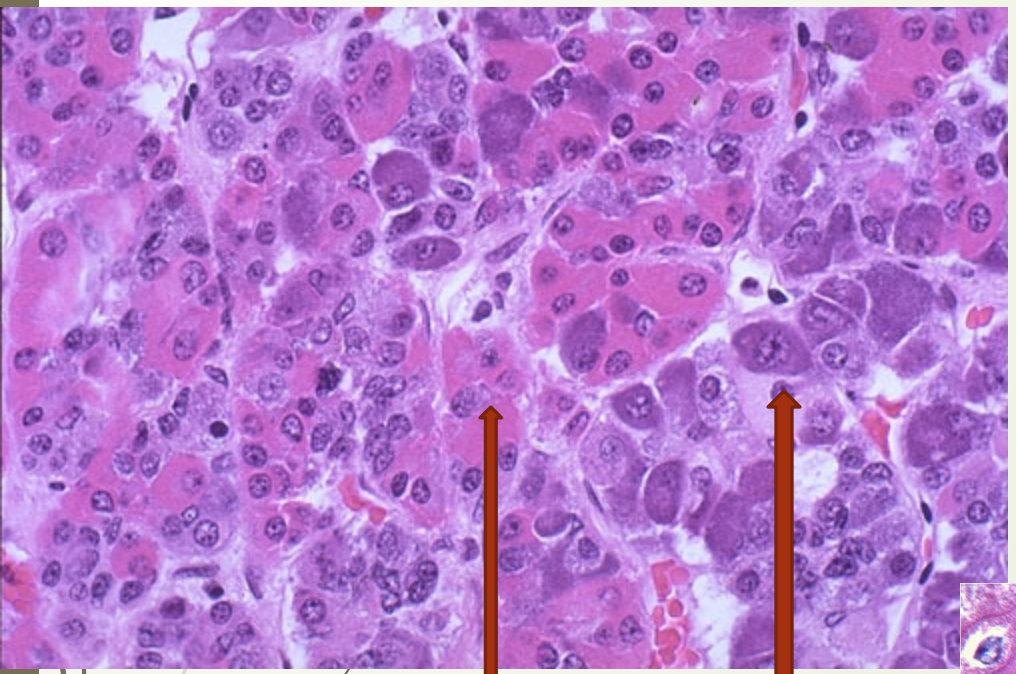
This massive, adenoma has grown far beyond the confines of the sella turcica and has distorted the overlying brain. Nonfunctional adenomas tend to be larger at the time of diagnosis than those that secrete a hormone.







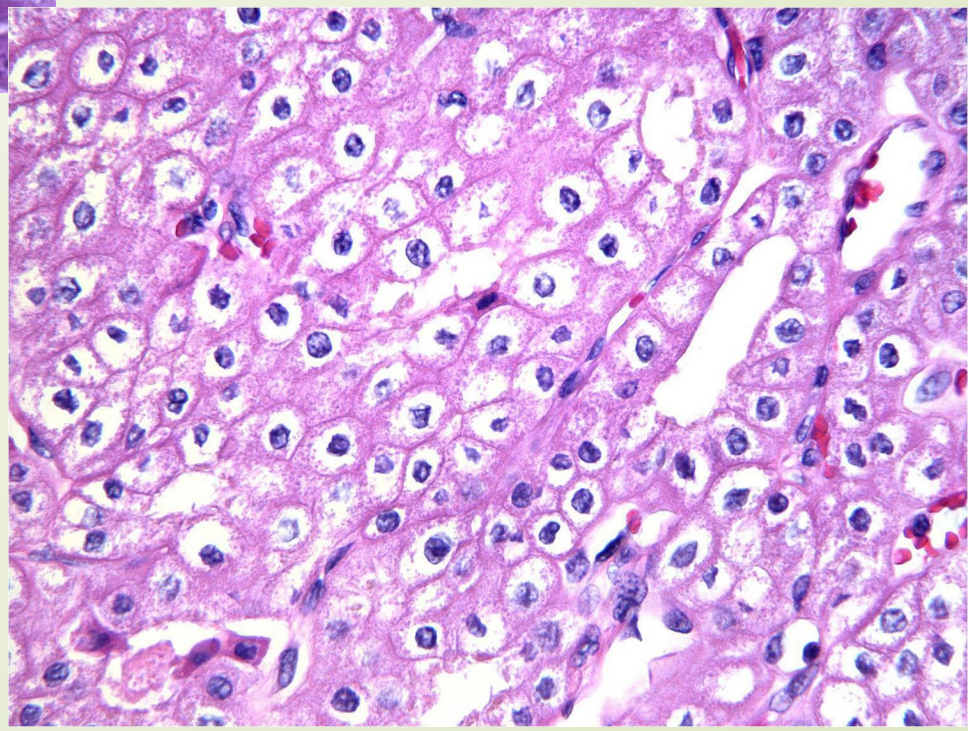
In routine histologic sections of the an
pituitary, a colorful array of cells is pr
that contain eosinophilic cytoplasm
(acidophil), basophilic cytoplasm
(basophil), or poorly staining cytoplas
(chromophobe) cells



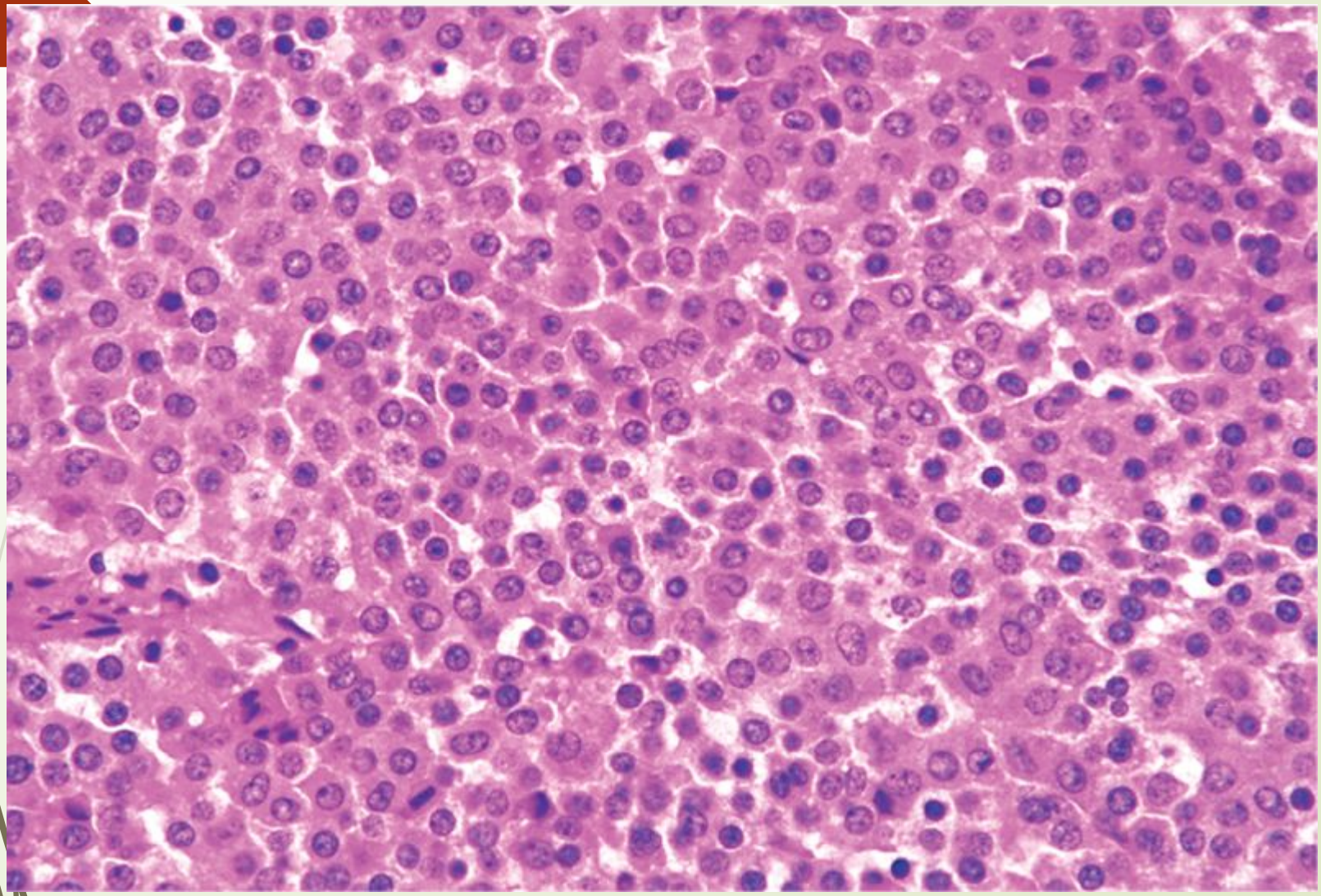
acidophil

Basophil

Chromophobe



Pituitary adenoma



The monomorphism of these cells contrasts markedly to the mixture of cells seen in the normal anterior pituitary. Note also the absence of connective tissues.

Hypopituitarism

- ***Tumors and other mass lesions in sella.***
- ***Traumatic brain injury and subarachnoid hemorrhage .***
- ***Pituitary surgery or radiation:***
- ***Pituitary apoplexy***
- ***Ischemic necrosis of the pituitary (sheehan syndrome) .***
- ***Rathke cleft cyst.***
- **Empty sella syndrome.**

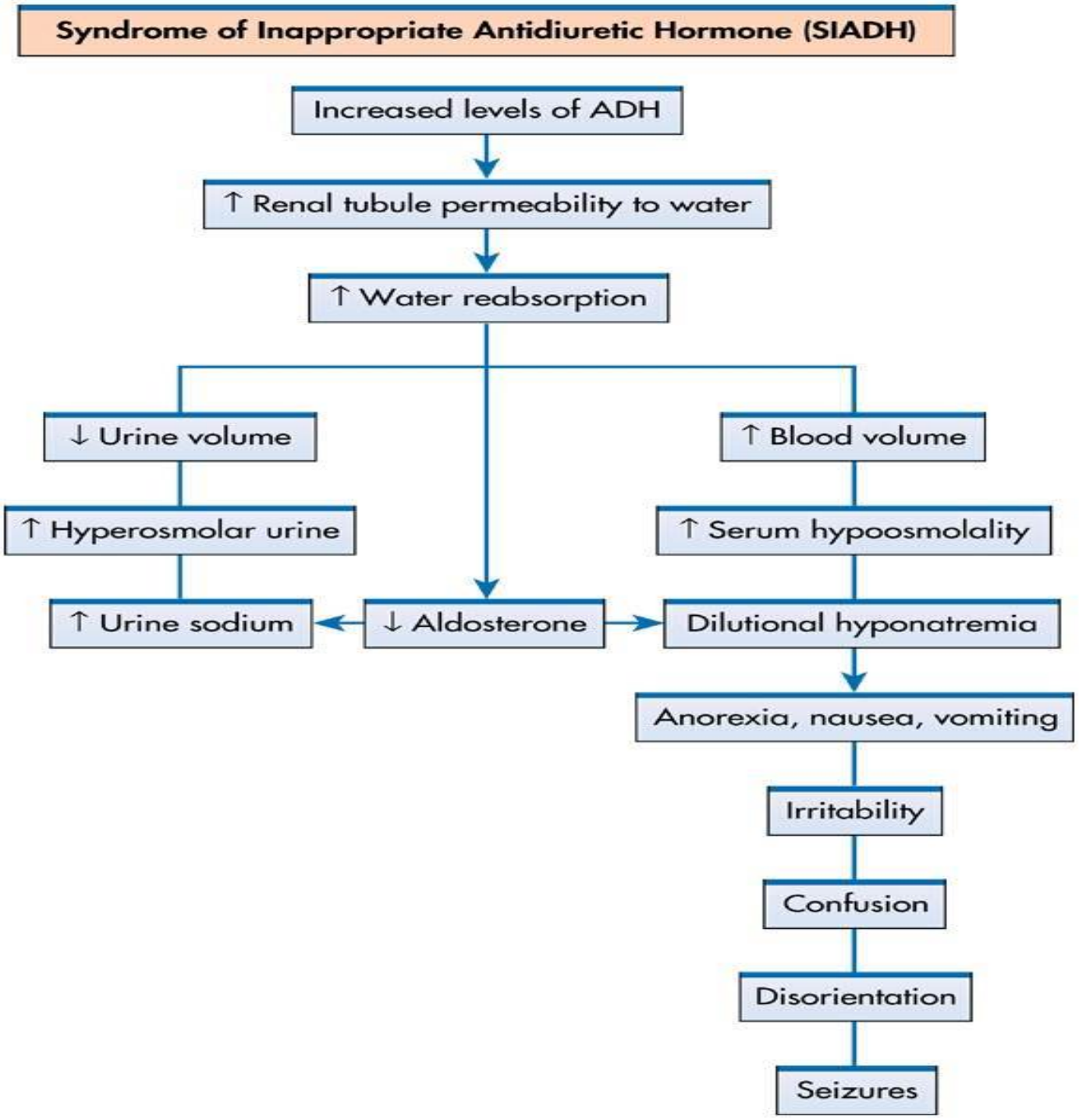
- ***Genetic defects:*** **Congenital deficiency of transcription factors required for normal pituitary function.**
- ***Hypothalamic lesions***
- ***Inflammatory disorders and infections***

Sheehan's Syndrome

- post-partum pituitary necrosis results from a sudden infarct of the anterior lobe precipitated by obstectric hemorrhage or shock.
- Such a syndrome can be precipitated by DIC, sickle cell anemia, Cavernous thrombosis, temporal arteritis, or traumatic injury.
- The posterior pituitary, because it receives its blood directly from arterial branches, is much less susceptible to ischemic injury and is therefore usually not
- Subsequently, the deficiency of TSH & ACTH may induce hypo-thyroidism and adrenociortical insufficiency

Posterior Pituitary syndrome

- *Diabetes insipidus*. ADH deficiency causes diabetes insipidus, a condition characterized by excessive urination (polyuria) due to an inability of the kidney to resorb water properly from the urine.
- *central* must be differentiated from *nephrogenic* diabetes insipidus.
- Serum sodium and osmolality are increased.
- thirst and polydipsia.
- develop life-threatening dehydration.


Syndrome of Inappropriate Antidiuretic Hormone (SIADH)
Increased levels of ADH
↑ Renal tubule permeability to water
↑ Water reabsorption
↓ Urine volume
↑ Blood volume
↑ Hyperosmolar urine
↑ Serum hypoosmolality
↑ Urine sodium
↓ Aldosterone
Dilutional hyponatremia
Anorexia, nausea, vomiting
Irritability
Confusion
Disorientation
Seizures

Clinical manifestations

Posterior pituitary hypofunction can be protean, and depend on the specific hormone(s) that are lacking.

Diagnosis:-

Biochemical diagnosis of pituitary insufficiency

- **Demonstrating low levels of trophic hormones in the setting of low target hormone levels**
- **Provocative tests may be required to assess pituitary reserve**