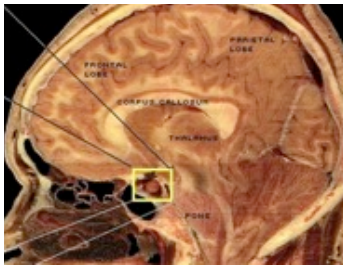
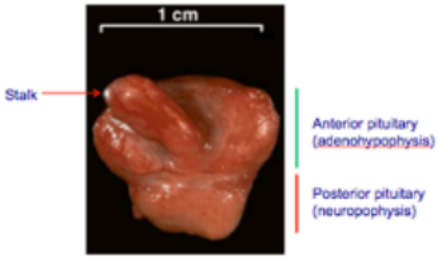
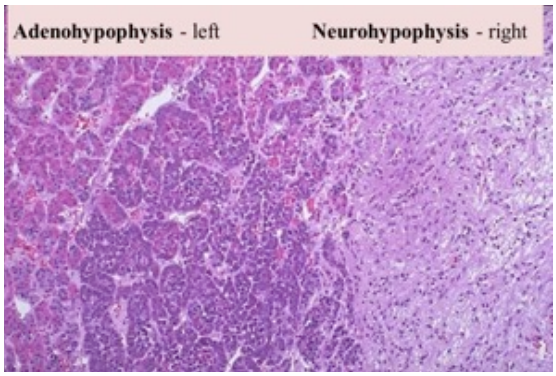
PATHOLOGY II - Endocrine Path

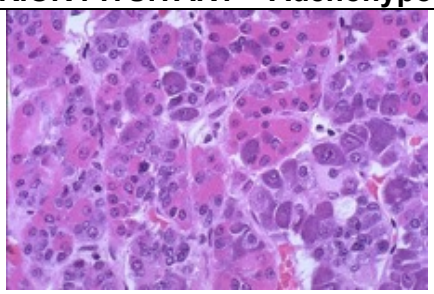
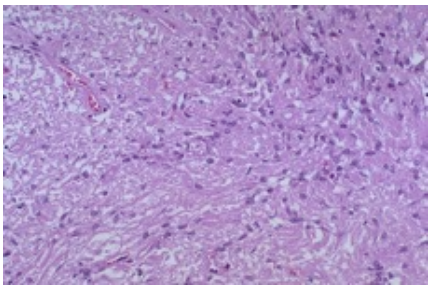
PITUITARY GLAND

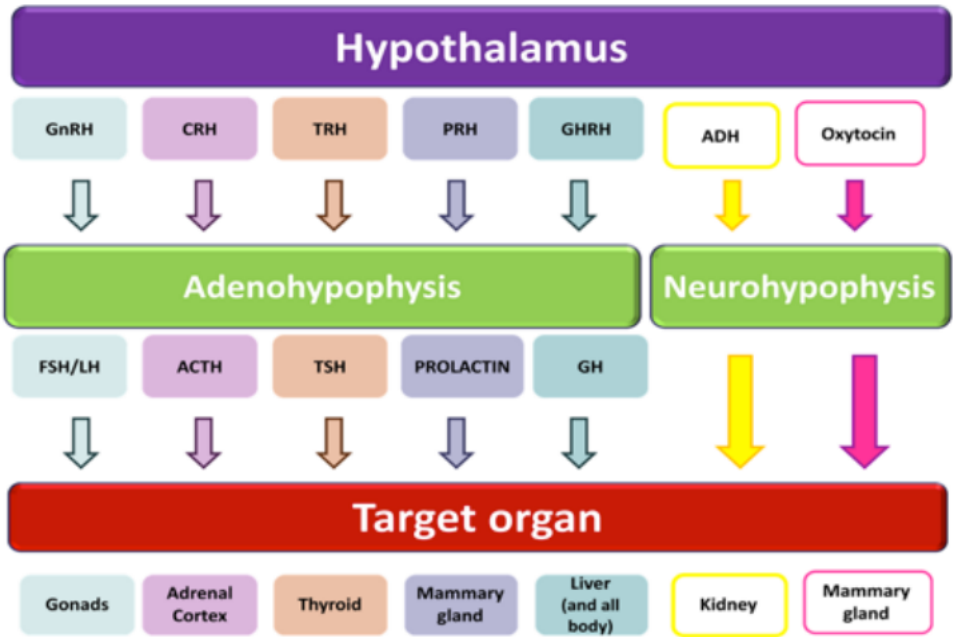




- Pituitary gland is connected to the hypothalamus by the ***pituitary stalk***
- ***Rathke's pouch*** **–** Ectodermal invagination of the roof of primitive mouth, which gives origin to the anterior pituitary gland (adenohypophysis)



ANTERIOR PITUITARY – Adenohypophysis	POSTERIOR PITUITARY – Neurohypophysis
 **ACIDOPHILS** secrete GH & PRL **BASOPHILS** secrete ACTH, TSH, & gonadotrophins (FSH & LH) **CHROMOPHOBES** have few cytoplasmic granules, without significant secretory activity	 Histology similar to neuroglial tissue, with glial cells (***pituicytes***), nerve fibers (from the hypothalamus), nerve endings, & intra-axonal neurosecretory granules **ADH** & **Oxytocin** produced in the hypothalamus are transported via intra-axonal neurosecretory granules where they are stored Given appropriate stimuli, hormones are released into venous channels into system



POSTERIOR PITUITARY – HYPOTHALAMUS

- Hypothalamic neurons synthesize **Oxytocin & ADH**
- Oxytocin & ADH are transported from the axons of the hypothalamic-hypophyseal tract to the posterior pituitary
- Oxytocin & ADH are stored in axon terminals in the posterior pituitary
- Hypothalamic neurons fire; APs arriving at the axon terminals cause oxytocin & ADH to be released into the blood

POSTERIOR PITUITARY HORMONES: Summary of Regulation & Effects			
HORMONE *Chemical structure & type*	**REGULATION OF RELEASE**	**TARGET ORGAN & EFFECTS**	**EFFECTS OF HYPOSECRETION ↓ & HYPERSECRETION ↑**
OXYTOCIN *Peptide, mostly from neurons in PVN nucleus of hypothalamus*	**Stimulated** by impulses from hypothalamic neurons in response to cervical/uterine stretching & suckling by infant **Inhibited** by lack of appropriate neural stimuli	**Uterus** – stimulates uterine contractions; initiates labor **Breast** – initiates milk ejection	Unknown
ANTIDIURETIC HORMONE (ADH) *Peptide, mostly from neurons in SON nucleus of hypothalamus*	**Stimulated** by impulses from hypothalamic neurons in response to ↑ [blood solute] or ↓ blood volume; also stimulated by pain, some drugs, low BP **Inhibited** by adequate hydration of the body & by alcohol	**Kidneys** – stimulate kidney tubule cells to reabsorb water	↓ Diabetes insipidus ↑ Syndrome of inappropriate ADH secretion (SIADH)

ANTERIOR PITUITARY – HYPOTHALAMUS

- When appropriately stimulated, hypothalamic neurons secrete *releasing or inhibiting hormones* into the primary capillary plexus
- Hypothalamic hormones travel through the portal veins to the anterior pituitary where they stimulate or inhibit release of hormones made in the anterior pituitary
- In response to releasing hormones, the anterior pituitary secretes hormones into the secondary capillary plexus. This in turn empties into the general circulation

ANTERIOR PITUITARY HORMONES: Summary of Regulation & Effects

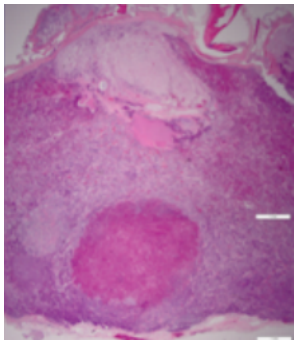
HORMONE *Chemical structure & type*	REGULATION OF RELEASE	TARGET ORGAN & EFFECTS	EFFECTS OF HYPOSECRETION ↓ & HYPERSECRETION ↑
GROWTH HORMONE *Protein, Somatotropic cells* **[ACIDOPHILS]**	**Stimulated** by GHRH release, which is triggered by low blood levels of GH, as well as by many secondary triggers including *hypoglycemia, ↑free AAs, ↓FAs, exercise, other types of stressors*. **Inhibited** by feedback inhibition by GH & IGFs & by *hyperglycemia, hyperlipidemia, obesity, & emotional deprivation via either ↑GHIH (somatostatin) or ↓GHRH.*	**Liver, Muscle, Bone, Cartilage, & Other Tissues –** anabolic hormone; stimulates somatic growth; mobilizes fat; spares glucose *Growth promoting effects mediated indirectly by IGFs*	↓ Pituitary Dwarfism (children) ↑ Gigantism (children); Acromegaly (adults)
THYROID-STIMULATING HORMONE *Glycoprotein, Thyrotropic cells* **[BASOPHILS]**	**Stimulated** by TRH & in infants indirectly by cold temperature. **Inhibited** by feedback inhibition by THs on anterior pituitary & hypothalamus & by GHIH.	**Thyroid gland** – stimulates thyroid gland to release thyroid hormones (T_3, T_4)	↓ Cretinism (children), ↑ Hyperthyroidism; effects similar to Graves' Disease (Ab mimic TSH)
ACTH *Peptide, Corticotropic cells* **[BASOPHILS]**	**Stimulated** by CRH; stimuli that ↑CRH release, including *fever, hypoglycemia, & other stressors.* **Inhibited** by feedback inhibition by glucocorticoids.	**Adrenal cortex** – promotes release of glucocorticoids & androgens (mineralocorticoids to a lesser extent)	↓ Rare ↑ Cushing's Disease
FOLLICLE-STIMULATING HORMONE *Glycoprotein, Gonadotropic cell* **[BASOPHILS]**	**Stimulated** by GnRH. **Inhibited** by feedback inhibition by inhibin, estrogen in females, & testosterone in males.	**Ovaries** – triggers ovulation & stimulates ovarian production of estrogen & progesterone **Testes** – promotes testosterone production	↓ Failure of sexual maturation ↑ No important effects
LUTEINIZING HORMONE *Glycoprotein, Gonadotropic cell* **[BASOPHILS]**	**Stimulated** by GnRH. **Inhibited** by feedback inhibition by estrogen & progesterone in females & testosterone in med.	**Ovaries** – stimulates ovarian follicle maturation & estrogen production **Testes** – stimulates sperm production	↓ Failure of sexual maturation ↑ No important effects
PROLACTIN *Protein, Prolactin cells* **[ACIDOPHILS]**	**Stimulated** by ↓PIH; release enhanced by estrogen, birth control pills, breast-feeding, dopamine-blocking drugs. **Inhibited** by PIH (dopamine).	**Breast secretory tissue** – promotes lactation	↓ Poor milk production in nursing women ↑ Inappropriate milk production (galactorrhea); Cessation of menses in females; Impotence in males

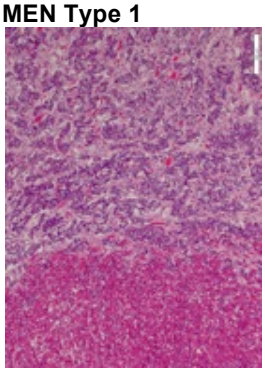
PATHOLOGY OF PITUITARY GLAND

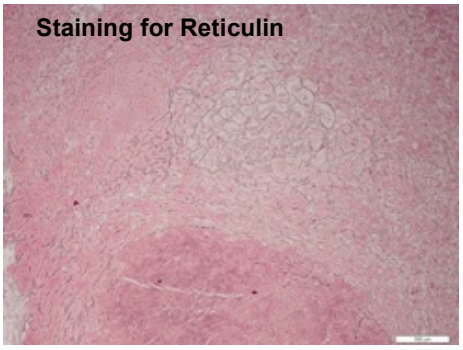
Pituitary Adenomas, Hypopituitarism (Sheehan Syndrome, Empty Sella Syndrome), SIADH, Sellar/Suprasellar tumors

I. PITUITARY ADENOMAS

- **BENIGN**
- 10% of intracranial tumors
- Prevalence rate in general population 15%, but most are *detected incidentally at autopsy*
- ***Functioning*:** Actively secrete hormones; endocrinologically apparent
- ***Non-Functioning*:** Do not secrete hormones; primarily mass effect – anatomically apparent
- **MOLECULAR PATHOGENESIS:**
  - Mutations that lead to ***G-protein hyperactivity*** are seen in a variety of endocrine neoplasms
  - G proteins play a critical role in signal transduction, transmitting signals from cell surface receptors (GHRH, TSH, or PTH) to GTP
- *Biologic behavior cannot be predicted on morphology*
- **Pituitary adenomas develop in MEN Type 1**





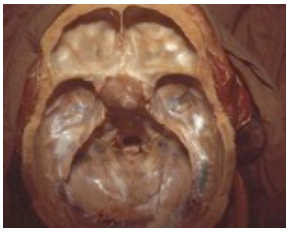


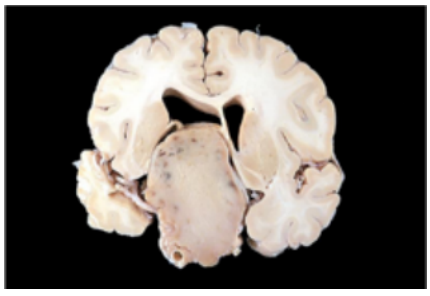
PITUITARY MICROADENOMAS – 70% of Pituitary Adenomas

- Measure < 1 cm in diameter
- Usually ***functioning*** (secretes hormones)
- Manifest w/ endocrine abnormalities, depending on hormone produced
- **3 Most Common:** *Prolactinoma, GH-producing adenoma, ACTH-producing adenoma*

PITUITARY MACROADENOMAS

- Measure > 1 cm in diameter
- Usually ***non-functioning*** (do not secrete hormones)
- Manifest by compression of adjacent structures
- **Most Common Manifestations (Mass Effect):** *Headache, Hypopituitarism, Visual loss*
  - **"Tunnel Vision" – *bitemporal hemianopia***





INVASIVE PITUITARY ADENOMA – This massive, ***non-functional*** 'invasive adenoma' has grown far beyond the confines of the sella turcica & has distorted the overlying brain.

Adenomas with high mitotic rate, >3% labeling index w/ immunostaining for the proliferation marker **Ki-67** & increased **p53** staining (p53 mutations) are classified as ***atypical adenomas***.

PROLACTIN (Lactotroph) **Stimulated by TRH** **Inhibited by Dopamine**	Promotes hyperplasia of mammary glands during pregnancy & **lactation** Accounts for sexual gratification after intercourse, resulting in ***sexual refractory*** period. *Abnormally high levels account for loss of libido/impotence.* At high levels, PRL inhibits production of sexual hormones (estrogen, testosterone)

1. PROLACTINOMA – Lactotroph Adenoma

- **Most Common pituitary adenoma**, accounts for 30% of all pituitary adenomas
- May occur as part of MEN Type 1
- *More common in **Women** (5:1) **before the age of 40***
  - **Classical Presentation:** *amenorrhea, galactorrhea, infertility +/- decreased libido*
    - Hyperplasia of mammary glands & lactation → **Galactorrhea (breast discharge)**
    - At high levels, it inhibits production of sexual hormones → **Amenorrhea**
    - Accounts for sexual gratification after intercourse, resulting in sexual refractory period → **↓Libido**
  - Manifestations in men are milder & may go unnoticed: ↓Libido, Impotence, Gynecomastia, Vision changes (bitemporal hemianopia)
- **DIAGNOSIS**
  - **Serum prolactin levels** – *tend to correlate with the size of the adenoma*
    - No absolute level of prolactin is diagnostic of a pituitary tumor, but < 200 ng/mL is not likely a prolactinoma
    - Prolactin levels > 1000 ng/mL occur with MACROadenoma
  - **MRI of the head**
  - **Non-neoplastic causes of hyperprolactinemia must be excluded** – drugs (H_2 blockers, metoclopramide, estrogen), trauma, hypothalamic damage or malfunction, physiologic (late stages of pregnancy cause ↑PRL), nipple stimulation, stress, renal failure & **hypothyroidism**
    - *We run tests for suspected hypothyroidism because hypothyroidism leads to ↑TRH, which stimulates TSH & prolactin*
- **TREATMENT**
  - Surgery – endoscopic endonasal transsphenoidal resection of pituitary tumors
  - Dopamine agonist – inhibit growth of lactotrophs → shrinkage of the adenoma
    - Bromocriptine
    - Cabergoline: New, no significant side effects, now treatment of choice
- **Clinical Vignette:** *32 y/o F c/o recent visual problems & slight breast discharge. She has not had her period for the past 6 months & is upset that she has been unable to become pregnant, despite trying for the past year with her husband. Laboratory workup reveals a negative pregnancy test, normal TSH, & significantly elevated levels of prolactin. MRI of the head shows enlargement of the structure located in the sella turcica.*

GROWTH HORMONE	**Direct Effects** on Liver production of IGF, ↑ Lipolysis, & ↑Carbohydrate metabolism (↑ blood sugar) **Indirect Effects** (via IGF) on Skeletal muscle to ↑ cartilage formation & skeletal growth and Extra-skeletal effects to ↑ protein synthesis, cell growth & proliferation

2. GH-PRODUCING ADENOMA

- 2nd most common ***functioning*** pituitary adenoma
- Children → **GIGANTISM**
- Adult → **ACROMEGALY**
- **DIAGNOSIS**
  - **Neuroimaging to detect pituitary adenoma**
  - **Elevated serum GH & its intermediary IGF-1** *(aka somatomedin-C)*
  - Suppression test by oral glucose (Oral Glucose Tolerance Test)
    - *Level of GH & IGF-1 is **NOT** suppressed by glucose*
    - **Diagnosis is confirmed** when there is elevation of IGF-1 +
      - Obvious clinical manifestations + tumor identified on MRI
      - *or* GH > 0.4 after OGTT
    - **Diagnosis is excluded** when there is no elevation of IGF-1 & GH < 0.4 ng/mL after OGTT *(even if there are obvious clinical manifestations)*
- **TREATMENT**
  - Surgical removal of pituitary adenoma
  - Pharmacological treatment
    - Somatostatin inhibits GH production – tx w/ ***somatostatin analogs*** *(i.e. **octreotide**)*
    - Tx w/ ***GH-receptor antagonists*** *(i.e. pegnisomant)* to block GH action on target organs

ACROMEGALY – Caused by GH-Secreting Tumor in the Anterior Pituitary

- Excess GH production *after closure of epiphyseal growth plate* (**Adults**)
- Causes growth of: bones of face/feet/fingers & viscera—heart/liver/adrenals/soft tissues
- Develops over many years/decades
- 5% of cases due to ectopic production or exogenous administration
- **Equal prevalence in males & females**
- **COMPLICATIONS**
  - Cardiomyopathy & heart failure
  - Arthritis
  - *Diabetes mellitus*
    - *Patients can have hyperglycemia because GH increases glucose levels & is normally one of the body's mechanisms to prevent serious hypoglycemia. Elevated blood glucose levels can be significant enough in acromegaly to cause diabetes. For normal individuals, a glucose load will cause almost complete suppression of GH secretion, but it will not suppress GH secretion in patients with a GH-secreting pituitary adenoma.*
  - Gonadal dysfunction
  - Risk of GI cancer

- **Clinical Vignette:** *38 y/o M c/o gradually enlarging hands & feet over the past several years. Looking at his driver's license picture from 15 years ago for comparison, his facial features have become obviously coarsened. Laboratory evaluation shows mildly elevated plasma glucose levels, & MRI of the brain reveals an enlarged mass in the sella turcica. Given the suspected diagnosis, specialized testing is performed in which GH levels are measured after administration of an oral glucose load. No measurable decrease is seen.*

GIGANTISM – Caused by GH-Secreting Tumor in the Anterior Pituitary

- Excess GH production *before closure of epiphyseal growth plate* (**Children**)
- Increase in body size, very long arms & legs, exceptionally tall stature
- Other Manifestations: delayed puberty, frontal bossing & prominent jaw, gaps between teeth, ↑sweating, irregular menstruation, large hands & feet w/ thick fingers & toes, release of breast milk, sleep problems, thickening of facial features, weakness

3. ACTH-PRODUCING ADENOMA

- 3rd most common ***functioning*** pituitary adenoma
- Manifests with signs & symptoms due to ***hypercortisolism*** (excess cortisol)
- **CUSHING DISEASE:** Hypercortisolism due to ACTH-producing adenoma
- **CUSHING SYNDROME:** Hypercortisolism due to any other condition (i.e. paraneoplastic syndrome, exogenous administration, etc.)
- **NELSON SYNDROME:** Rapid enlargement of an ACTH-producing microadenoma after bilateral adrenalectomy for Cushing syndrome
    - *Removal of both adrenal glands eliminates production of cortisol. The lack of cortisol's negative feedback can allow any pre-existing pituitary adenoma to grow unchecked.*

4. TSH-PRODUCING ADENOMA

- Rare
- Causes hyperthyroidism
- *Clinical manifestations in Thyroid Disorders section*

5. FSH/LH-PRODUCING ADENOMA

- Rare
- Overproduction of FSH or LH rarely causes endocrinological disturbances: Amenorrhea in premenopausal women, decreased libido in men
- Usually manifests by **mass effect**: Headache, Vision deficits, Hypopituitarism

II. HYPOPITUITARISM: *Sheehan Syn, Empty Sella Syn, Lymphocytic Hypophysitis*

- Condition due to ***damage to the anterior pituitary*** gland with resultant deficiency of one or more hormones
- Manifestations vary because of the damage – *symptoms don't arise until >75% loss of pituitary parenchyma*
  - Can occur suddenly or gradually, be mild or severe, affect the secretion of one/several/all of its hormones
- **CAUSES**: Diseases of the pituitary gland or the hypothalamus
  - **PITUITARY DISEASES**
    - Pituitary tumors/cysts, or treatment of such tumors – 75%!
    - Infiltrative lesions – ***Lymphocytic hypophysitis***, hemochromatosis, sarcoidosis
    - Infarction – ***Sheehan syndrome***
    - Apoplexy – *bleeding into pituitary adenoma*
    - Genetic diseases – Pit-1 mutation
    - ***Empty sella syndrome***
  - **HYPOTHALAMIC DISEASES**
    - Tumors – benign (craniopharyngiomas) & malignant (metastatic from lung, breast, etc.) – 15%
    - Radiation for CNS & nasopharyngeal malignancies
    - Infiltrative lesions – sarcoidosis, Langerhans cell histiocytosis
    - Trauma – fracture of skull base
    - Infections – tuberculous meningitis
- **CLINICAL MANIFESTATIONS**
  - Presentation is the sum of the consequences of each hormone deficiency
  - **ACTH DEFICIENCY** → Cortisol deficiency *(not aldosterone!)*
    - Most severe form: Death due to acute adrenal crisis
    - Mild chronic form: Lassitude, fatigue, anorexia, weight loss, ↓ libido, hypoglycemia, eosinophilia
    - ***Secondary hypocortisolism*** (due to ACTH deficiency) is **NOT** associated with other features of Addison disease, such as: *salt wasting, volume contraction, hyperkalemia, hyperpigmentation*
  - **TSH DEFICIENCY** → Fatigue, cold intolerance, decreased appetite, constipation, facial puffiness, dry skin, bradycardia, delayed relaxation phase of the deep tendon reflexes, & anemia
  - **GONADOTROPIN DEFICIENCY** → ***secondary hypogonadism*** in both men & women
    - **WOMEN** – ovarian hypofunction & ↓estradiol
      - Premenopausal women: Irregular periods or amenorrhea, anovulatory infertility, vaginal atrophy, & hot flashes. No physical findings initially, but after several years, breast tissue decreases, & bone mineral density declines.
    - **MEN** – testicular hypofunction & ↓testosterone
      - ↓ Energy & libido, hot flashes if sufficiently severe, ↓ bone mineral density
      - Wasting of skeletal muscle does not occur for several years
  - **GROWTH HORMONE DEFICIENCY**
    - **CHILDREN** – short stature
    - **ADULT WOMEN** (not yet confirmed) -- ↓ bone mineral density, dyslipidemia, cardiovascular disease, impaired psychological function
    - **ADULT MEN** -- ↑ fat mass w/ ↓ lean body mass, ↓ bone mineral density
  - **PROLACTIN DEFICIENCY** → inability to lactate after delivery
    - *Isolated prolactin deficiency is rare*

DEFICIENT HORMONE	CLINICAL FEATURES
ACTH	**Adrenal insufficiency:** Hypotension, tachy, fatigue, vomiting
TSH	**Hypothyroidism:** cold intolerance, constipation, bradycardia Thyroid Function Studies – Low TSH, Low T_3, T_4
FSH/LH	Women: Infertility, amenorrhea Men: ↓ Libido/infertility
GH	↓ Lean body mass & strength
PROLACTIN	Inability to lactate after delivery

1. SHEEHAN SYNDROME

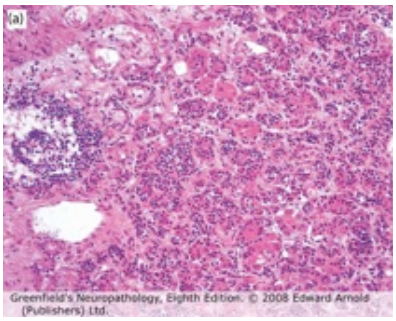
- **HYPOPITUITARISM caused by *post-partum infarction* of the anterior pituitary gland**
- Complication of ***past-partum hemorrhage*** causing severe **HYPOTENSION**
- *In developed countries, post-partum hemorrhage rarely leads to Sheehan Syndrome thanks to improved OB care*
- *In developing countries, post-partum pituitary infarction is still a common cause of hypopituitarism*
- Other causes of pituitary infarction: DIC, ↑ intracranial pressure, shock
- **CLINICAL PRESENTATIONS (3)**
  - **SEVERE –** Lethargy, anorexia, weight loss, inability to lactate during 1st days or weeks after delivery
  - **LESS SEVERE** – *Failure of post-partum lactation* & failure to resume menses in the weeks & months after delivery, *loss of pubic hair*, milder degrees of fatigue, anorexia, & weight loss
  - **MILD** – delay in recognition for many years after the initiating event
- **MECHANISM**
  - During pregnancy, hyperplasia of the lactotrophs in the anterior pituitary occurs – the pituitary almost doubles in size, but the blood supply does not increase! In post-partum hemorrhage, the blood supply to the anterior pituitary can become sufficiently inadequate to meet its needs & cause infarction
- **PATHOPHYSIOLOGY**
  - Deficiency of GH, prolactin, gonadotropin, TSH, & ACTH
    - *There will be elevated levels of hypothalamic releasing hormones due to the loss of negative feedback. All hypothalamic releasing hormones may be elevated except dopamine because prolactin stimulates dopamine secretion – Hypoprolactinemia leads to decreased levels of dopamine*
  - *Rare development of overt Diabetes Insipidus*
  - **Development of a small pituitary within a sella of normal size → "EMPTY SELLA" on MRI**
- **TREATMENT**
  - Same as for other causes of hypopituitarism
- **Clinical Vignette:** *38 y/o F developed a massive post-partum hemorrhage, which eventually stabilizes with use of multiple blood transfusions. A few weeks later she complains that she has been unable to lactate since delivering her baby. She feels lethargic & weak. She often gets dizzy when she stands up. Physical examination is unremarkable, except that her axillary & pubic hair seem a little sparser than before & her pulse rate increases by 20 beats/min upon standing from a supine position. Injection of CRH causes only a blunted elevation of serum ACTH. Similarly, injection of GnRH analog causes only a blunted elevation of FSH & LH levels. Serum prolactin in abnormally low.*

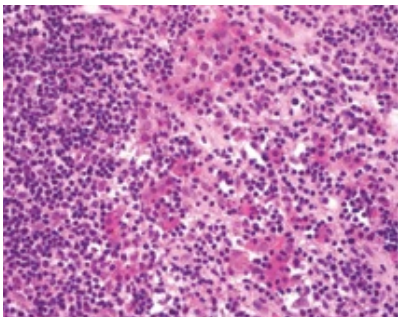
2. EMPTY SELLA SYNDROME

- Sella turcica appears ***empty*** on MRI due to shrinkage & flattening of the pituitary gland
- **PRIMARY FORM**: due to small defect in arachnoid allowing leakage of CSF into the sella (compresses pituitary)
  - **Most Common in Obese Women w/ HTN**
  - Also found in rare ***idiopathic intracranial HTN***
  - Usually *asymptomatic* & compatible w/ normal life
- **SECONDARY FORM:** due to any pathology that causes destruction of the pituitary gland (Sheehan, surgery, etc.)
  - Variable manifestations of hypopituitarism

3. LYMPHOCYTIC HYPOPHYSITIS

- *An autoimmune disease in which the pituitary gland is infiltrated by lymphocytes, plasma cells & macrophages, & its function is usually impaired. It has to be suspected in pregnant women & in women with recent delivery presenting with hyperprolactinemia, headache, visual field alterations and changes of one or more pituitary hormone secretions with secondary impairment of related peripheral target glands, especially when associated with other autoimmune endocrine or non-endocrine disorders.*





Inflammatory infiltrate may obscure the pituitary parenchyma.
Residual parenchymal cells may acquire oncocytic change.

POSTERIOR PITUITARY DEFICIENCY DISORDERS

Diabetes Insipidus, Syndrome of Inappropriate ADH Secretion (SIADH)

ADH: **ANTIDIURETIC HORMONE** Aka Vasopressin	**Major Function –** maintain ***osmotic homeostasis*** by regulating water balance ADH also helps maintain plasma volume & BP in hypovolemia ↑ Plasma osmolarity → ↑ ADH secretion → ↑ aquaporin channels in collecting duct

1. DIABETES INSIPIDUS

- *Condition caused by the inability of the kidney to reabsorb water resulting in inappropriately dilute urine*
- **NEUROGENIC/CENTRAL DIABETES INSIPIDUS**: deficient production of ADH caused by damage to hypothalamus or pituitary gland – *head injury, surgery, tumor, infection*
- **NEPHROGENIC DIABETES INSIPIDUS:** unresponsiveness of kidney to ADH – *drugs (**lithium**, amphotericin B, methoxyflurance, **demeclocycline** – tetracycline type antibiotic), hypercalcemia, polycystic kidney disease*
- **CLINICAL MANIFESTATIONS:** *polyuria, polydipsia, hypernatremia & hyperosmolarity, enuresis, life-threatening dehydration if unable to obtain water*

2. SYNDROME OF INAPPROPRIATE ADH SECRETION (SIADH)

- ***Excessive secretion of ADH*** from the neurohypophysis or **other** sources
- **Characterized by 3 Major Signs:** Water retention, hyponatremia (serum Na^+ < 135 mEq/L), urine osmolarity > serum osmolarity
- **Most Important Manifestations are Neurologic due to Hyponatremia:** *Lethargy, confusion, seizures, coma*
- **CAUSES**
  - ECTOPIC ADH production, usually from ***small cell carcinoma of the lung***
  - CNS DISEASE: Meningitis, head trauma, subarachnoid hemorrhage
  - LUNG DISEASE: Pneumonia, abscess, COPD
  - DRUGS: Cyclophosphamide & many others
- **TREATMENT**
  - Water restriction, hypertonic saline, urea
  - ADH-receptor antagonists: ***Demeclocycline***, **vaptans**
- **CAUTION:** Rapid correction of hyponatremia may cause *Central Pontine Myelinolysis (& Locked-in Syndrome)*
  - ***Central Pontine Myelinolysis*** *(AKA Osmotic Demyelination Syndrome) - demyelination may affect the pons & other areas of the brain. Lesion may extend dorsally to involve sensory tracts & leave patients with a locked in syndrome. When Na^+ is replaced too rapidly (> 14 mEq/L per 8 hours) & neurologic symptoms start to develop, it is critical to prevent further Na^+ increases by stopping hypertonic fluids.*
  - ***Locked-in Syndrome*** *– a state of wakefulness & awareness with quadriplegia & paralysis of the lower cranial nerves, results in the inability to show facial expression, move, speak, or communicate, except possibly by coded eye movements. Typically results from a pontine hemorrhage or infarct*

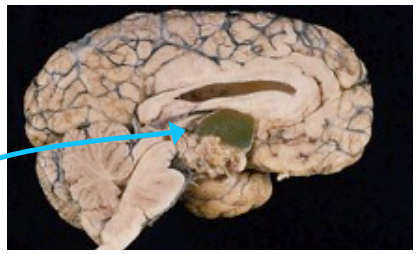
BRAIN TUMORS: PRIMARY < METASTATIC

Primary Brain Tumors: ***Gliomas (45-50%)***, *Meningioma, Pituitary adenoma, Primitive neuroectodermal tumor,* ***Craniopharyngioma (3%)***, *Schwannoma, Lymphoma, Hemangioblastoma, Germ cell tumors*

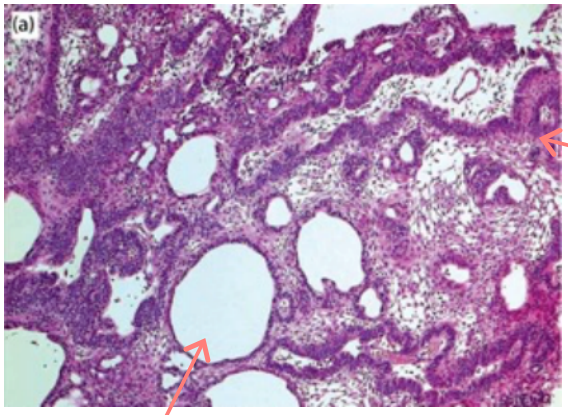
WHO GRADING: MALIGNANCY SCALE

- GRADE I: Slow growing, well demarcated; cure achieved by total resection
- GRADE II: Slow growing but diffusely infiltrative; long survival (>5 years), but not definitive cure w/ resection; eventually transform into higher grade tumors
- GRADE III: Histological evidence of malignancy (atypia & mitotic activity); patients receive adjuvant radiation/chemoRx; survival short than Grade II (~2-3 years)
- GRADE IV: Most malignant, mitotically active, & necrosis-prone; shortest survival (<1 years), but this depends on availability of effective treatment

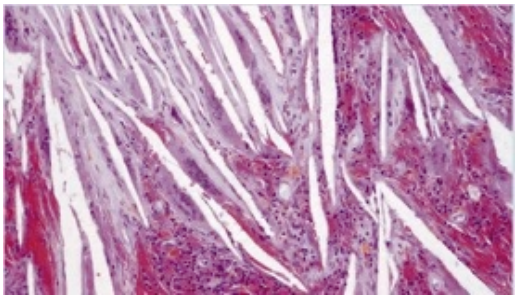
1. CRANIOPHARYNGIOMA, GRADE 1

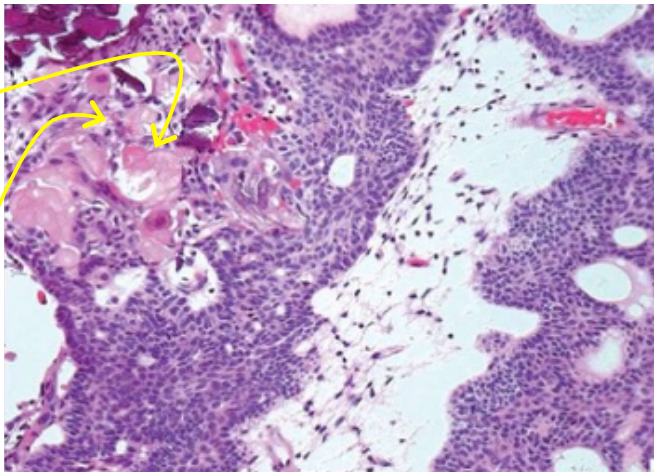


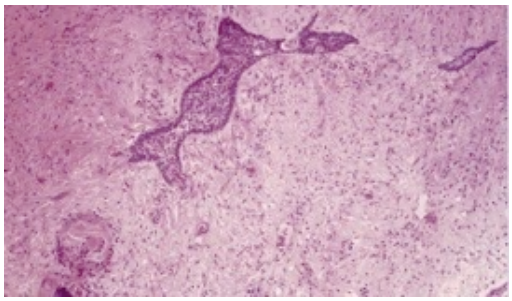
- Most Common Non-neuroepithelial tumor in **Children**
- Bimodal incidence:
  - CHILDREN, 5-15: Adamantinomatous variant
  - Adults, 40-50: Papillary variant
- **HISTOGENESIS:** epithelial cell rests of Rathke's pouch
- **TYPICAL GROSS APPEARANCE**
  - **SUPRASELLAR** location
  - Often cystic
  - **Calcium Deposits**
  - Contains a thick, oil-like fluid described as "**black sludge**" or "machinery oil"
- **PRESENTATION**: *Headache, growth retardation, visual deficits, Diabetes Insipidus*
- **PROGNOSIS:** recurrence rate dependent on extent of surgical resection; overall survival 64-96%
- **Clinical Vignette:** *A 14 y/o boy presents with 3 months of lethargy, headaches, & muscle weakness. His parents note that he drinks water excessively. His vital signs are normal. A 24-hour urine collection shows polyuria. The fasting blood sugar is normal. An X-ray film of the brain reveals suprasellar calcification.*



Cholesterol Clefts

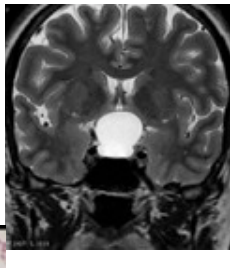


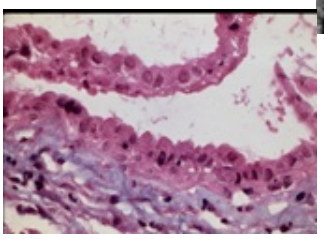




Marked Gliotic Reaction w/
ROSENTHAL FIBERS

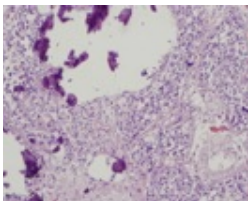
2. RATHKE CLEFT CYST





- Cyst developing in the plane of separation between Adenohypophysis & Neurohypophysis
- The "cleft" is created by the Rathke's pouch originating from the palate
- Lined by **respiratory epithelium**
- *Asymptomatic* in the great majority of cases – ***often incidental autopsy finding***
- Rarely, it manifests w/ headache, vision deficits, & hypopituitarism (mass effect)

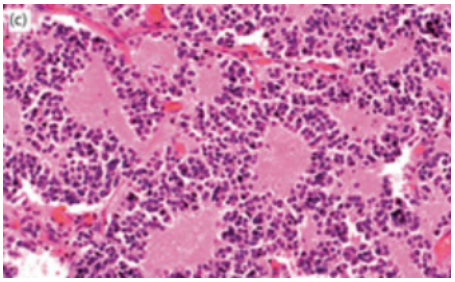
PINEAL GLAND



- Small gland composed of loose, neuroglial stroma, & nests of "epithelial-appearing" pineocytes
- The gland contains ***corpora arenacea*** **(brain sand)**
  - Useful marker for mid-line on plain film skull radiographs
- Pineocytes have photo sensory & neuroendocrine functions
  - Melatonin, which plays a role in circadian rhythm & the sleep-wake cycle
- All pineal tumors are RARE
  - *Germinomas,* ***Pinealomas***, ***Pineoblastomas***, ***Pineocytomas***

1. PINEOCYTOMA

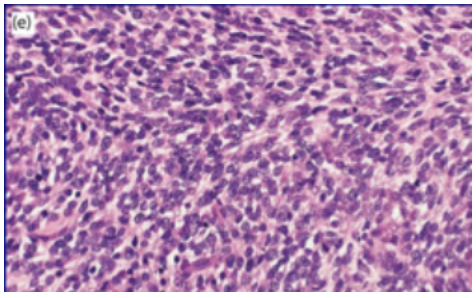
- GRADE I
- **Adults** (Mean age: **38 y/o**)
- Neuro-ophthalmologic signs: **Parinaud Syndrome** – *Paresis of upward gaze, ptosis, & loss of pupillary light & accommodation reflexes by compression by the pineal tumor*
- Long interval between onset of symptoms & surgery
- ***Excellent prognosis***



PINEOCYTOMA – Large, irregular ***rosettes*** & strong immunoreactivity for **neuronal markers**

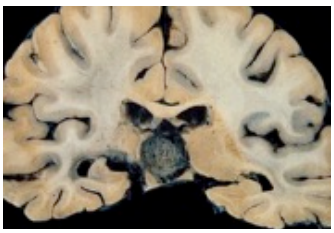
2. PINEOBLASTOMA

- GRADE IV: most malignant
- **Children & Young Adults** (Mean age: **18 y/o**)
- Neuro-ophthalmologic signs: **Parinaud Syndrome** – *Paresis of upward gaze, ptosis, & loss of pupillary light & accommodation reflexes by compression by the pineal tumor*
  - Same clinical manifestations as Pineocytoma
- Short interval between onset of symptoms & surgery
- ***Poor prognosis: survival < 1 year!***

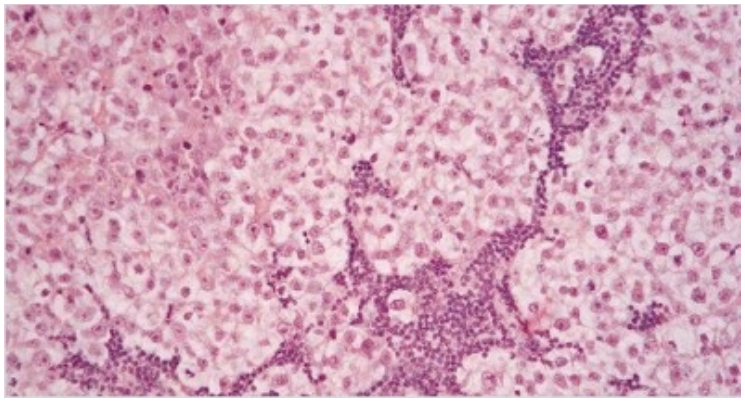


PINEOBLASTOMA – Composed of primitive, ***small round cells*** similar to medulloblastoma

3. GERMINOMA

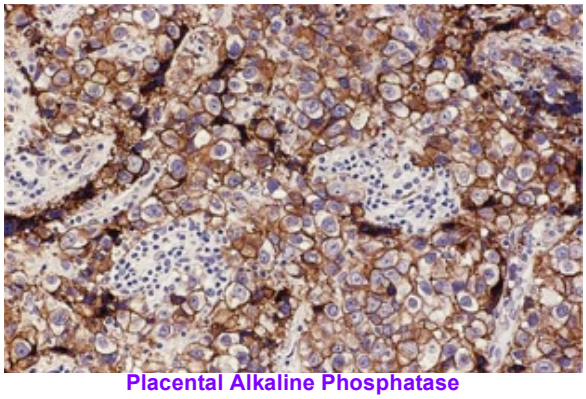


- **Most Common CNS germ cell tumor**
- Like all other extra-gonadal germ cell tumors, it preferentially **affects the MIDLINE**
- **PINEAL GLAND** is the most frequent site, then Suprasellar Region
- **Multifocal lesions** are common, either simultaneously or sequentially
- **Extremely radiosensitive w/ 85% survival rate**



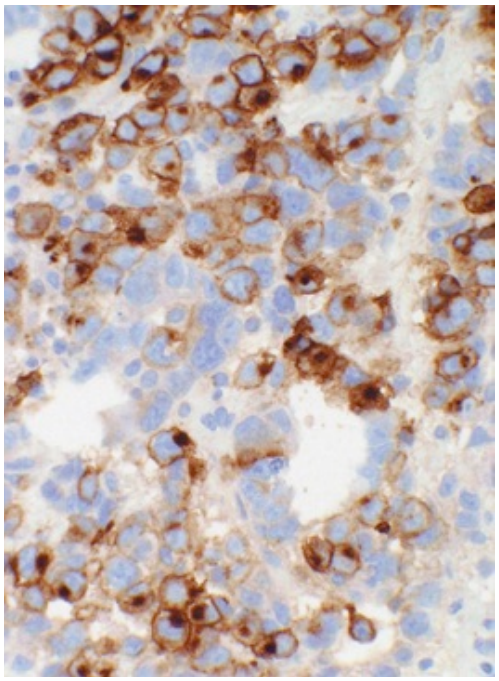
DUAL CELL POPULATION

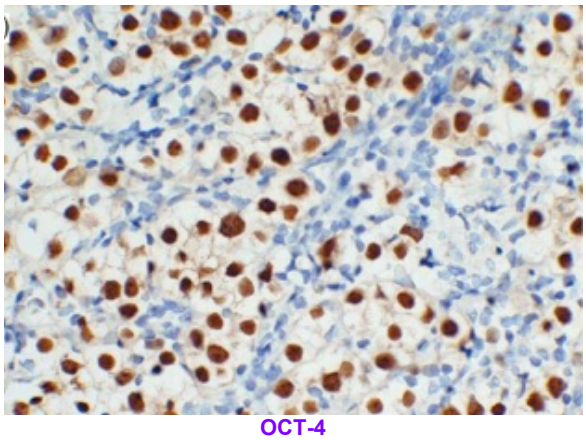
1. **Tumor cells w/ prominent nucleoli**
2. **Lymphocytes**



Placental Alkaline Phosphatase

CD-17





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