# ENDOCRINOLOGY

## PITUITARY GLAND

ANATOMY / EMBRYOLOGY:

- ADENOHYPOPHYSIS: Anterior lobe.
  - DEVELOPMENT: It develops from **Rathke's Pouch**, an outpocketing of ectoderm that grows upward from the *oral cavity*.
    - **Craniopharyngioma** is a neoplasm of Rathke's Pouch, anywhere along the migration path of Rathke's Pouch toward the adenohypophysis.
  - CELL-TYPES / HORMONES:
    - **Corticotropes**: basophilic, ACTH.
    - **Lactotropes**: eosinophilic, Prolactin
    - **Somatotropes**: eosinophilic, GH. Constitutes half of all cells of the adenohypophysis.
    - **Thyrotropes**: pale basophilic cells, TSH. Only 5% of cells.
    - **Gonadotropes**: basophilic, FSH and LH
- NEUROHYPOPHYSIS: Posterior lobe.
  - DEVELOPMENT: It develops as a direct extension of the hypothalamus.
  - CELL-TYPES / HORMONES: **Pituicytes** are glial-like cells of the posterior pituitary, containing hormones produced in the hypothalamus.
    - **Oxytocin:** Produced in the **Paraventricular Nucleus** of Hypothalamus, which surrounds third ventricle, and carried in Magnocellular neurons to the posterior pituitary.
    - **Vasopressin (ADH):** Produced in **Supraoptic Nucleus** of Hypothalamus and carried in Magnocellular neurons to the posterior pituitary.
      - **Diabetes Insipidus:** Inability to secrete ADH in the posterior pituitary, resulting in profuse non-sweet diuresis.
      - ECTOPIC ADH PRODUCTION: Inappropriately high secretion of ADH can result from lung tumors. Clinically this result in retention of excess water without retention of sodium, which leads to **hyponatremia**.
- INTERMEDIATE LOBE: Between anterior and posterior lobes.

LACTATION: Four hormones participate in lactation.

- **Estrogen**: It stimulates ductal proliferation and breast development during growth.
- **Progesterone**: Causes proliferation of acini in the breasts.
- **Prolactin**: It stimulates the synthesis of milk.
- **Oxytocin**: It stimulates the contraction of the acini and the ejection of milk.

PORTAL SYSTEM: **Portal Vein** of Hypothalamus is unique in that it carries venous blood *to an organ* (the adenohypophysis), hence the name "portal."

**HYPOPITUITARISM**:

- PATHOGENESIS: Many, diverse causes
  - **SHEEHAN SYNDROME**: Ischemic necrosis or infarct of pituitary gland, secondary to hypotension occurring in the late stage of pregnancy or post-partum in women.

        - PATHOGENESIS: Common cause of Sheehan Syndrome is **post-partum hemorrhage**.
            - The enlargement of the pituitary during late-stage pregnancy renders it susceptible to ischemia with any reduced blood flow.
        - SYMPTOMS: Amenorrhea, hypothyroidism, possible adrenal atrophy.
    - **EMPTY SELLA SYNDROME**: Radiologic term for an enlarged sella turcica, with an atrophied or compressed pituitary gland.
        - **Secondary Empty Sella Syndrome:** Secondary to surgical removal of the pituitary.
        - **Primary Empty Sella Syndrome:** Downward bulge of arachnoid membrane into the sella, compressing the pituitary onto the sella floor.
            - Condition is often associated with **Pituitary Adenomas**. However, you still see hypopituitarism.
    - **LYMPHOCYTIC HYPOPHYSITIS**: Autoimmune disease. Lymphocytic inflammation of the adenohypophysis, occurring in middle-aged women.
    - PITUITARY TUMORS: Pituitary tumors usually result in **hypofunction** of the other parts of the pituitary, due to compression by the tumor.
        - **CRANIOPHARYNGIOMA:** Tumor of Rathke's Pouch can compress the pituitary and result in hypofunction and atrophy.
        - PITUITARY ADENOMAS
    - ISOLATED GONADOTROPIN DEFICIENCY (**KALLMAN SYNDROME**): Failure to proceed through puberty, congenital absence of smell, clef palate, other anomalies.
        - PATHOGENESIS: X-linked defect coding for Neural Cell-Adhesion Molecule (**N-CAM**) ------> failure of migration of GnRH-secreting neurons ------> primary deficiency in GnRH.
    - PITUITARY APOPLEXY: Hemorrhagic infarction of a pituitary adenoma, usually without functional consequences, because enough of the normal pituitary remains.
    - IATROGENIC HYPOPITUITARISM: Radiation therapy, neurosurgery.
    - INFILTRATIVE DISEASES: Hand-Schuller-Christian Disease, Hemochromatosis.
    - ISOLATED GROWTH HORMONE DEFICIENCY: **Pituitary dwarfism** (rarer than Achondroplasia), caused by defective GH genes, or GH resistance (African Pygmies, Laron-type dwarfism).
- CLINICAL:
    - SYMPTOMS: Atrophy of thyroid, adrenal, or gonads, depending on which hormones are deficient. Deficient growth in children.
    - **Adiposal Genital Dystrophy:** Young boys with abnormal obesity and underdeveloped gonads. It can result from hypopituitarism.

PITUITARY ADENOMAS:

- CLINICAL:
    - **Reticulin Stain** of the pituitary can distinguish an adenoma from normal tissue. If it is an adenoma, then the *connective-tissue partitions disappear*, and it is a solid mass. Normal pituitary tissue has reticulin-positive partitions.
    - **Ballooning Sella:** Surgical term for a sella turcica that is full of pituitary tissue, a pituitary adenoma. Contrast to an empty sella, as in Empty Sella Syndrome.
    - **Bitemporal Hemianopsia:** Tunnel vision is a common symptom that can result from any pituitary tumor, due to compression of the optic chiasm. Continued growth of the tumor can result in total blindness.
- PATHOLOGY:
    - **Microadenoma:** Less than 10 mm in size. They are usually asymptomatic unless they secrete hormones.
    - **Macroadenoma:** Tumors greater than 10 mm in size. They cause symptoms resulting from local compression of neighboring structures: tunnel-vision, headache, oculomotor palsies, hypothalamic dysfunctions.
- **LACTOTROPE ADENOMA**: *The most common pituitary adenoma.*
    - **Hyperprolactinemia** results in amenorrhea, galactorrhea, and infertility in women. It results in impotence and decreased libido in men.
        - Functional hyperprolactinemia can also be caused by a defect in the pituitary stalk ------> lost dopamine inhibition in tuberoinfundibular system.
    - SYMPTOMS:
        - Women: amenorrhea, galactorrhea.
        - Men: Impotence, testicular atrophy.
    - TREATMENT: **Bromocriptine** (Dopamine-agonist) can be used to inhibit further release of prolactin.
- **SOMATOTROPE ADENOMA**:
    - PATHOLOGY: Can be acidophilic (slow-growing) or chromophobic (fast-growing)

    - **GIGANTISM:** Hypersecretion of GH before the growth-plates have closed. Now it is rare, because gonadotrope adenomas are usually diagnosed and removed in childhood.
    - **ACROMEGALY**: Hypersecretion of GH after the growth plates have closed.
        - SYMPTOMS:
            - Overgrowth of mandible and maxilla, thickened nose, space between incisor teeth, enlarged hands and feet, larger hat-size.
            - Hyperglycemia and Diabetes, one fifth of patients.
            - Hypercalcuria and renal stones, one fifth of patients.
            - Variety of CV, cerebrovascular, and neurological problems, including HTN, CHF, paresthesias, arthralgias.
- **CORTICOTROPE ADENOMA**: *Has a higher chance of becoming malignant than the other adenomas.*
    - CLINICAL: Associated syndromes
        - **Cushing's Disease** (see adrenal gland later) is defined as hypercorticism caused by an overproduction of ACTH. This can be caused by (1) Pituitary Corticotrope Adenoma, or (2) Ectopic production of ACTH by another tumor, such as carcinoid tumor or small-cell carcinoma of the lung.
        - **NELSON'S SYNDROME:** Corticotrope adenoma due to disinhibition of ACTH, resulting from bilateral adrenalectomy.
            - The adrenals are removed (due to a primary adrenal tumor) ------> disinhibition of ACTH release in pituitary ------> hyperplasia and adenoma of pituitary.
    - PATHOLOGY:
        - **Crooke Hyalinization:** Bundles of fine, keratin-positive intermediate filaments. *They are an indication of functional suppression of ACTH by excess cortisol*. They occur in non-tumorous corticotrope cells, but they may also occur in the corticotrope adenoma itself.
- **GONADOTROPE ADENOMA**:
    - SYMPTOMS: Most often occurs in middle-aged men.
        - Results in *paradoxic hypogonadism*. This could be due to insufficient functional release of LH, or loss of the normal *pulsatile pattern of LH secretion* needed for gonadal development.
    - PATHOLOGY: Chromophobic or acidophilic.
- THYROTROPE ADENOMA: Rarest of all pituitary adenomas.
- NONFUNCTIONAL PITUITARY ADENOMA:
    - NULL CELL ADENOMA: Chromophobic cells containing secretory granules, but still do not secrete active hormones.
        - ONCOCYTOMA: Variant of null cell adenoma. Enlarged, eosinophilic, granular cells.
    - SILENT ADENOMA: Well-differentiated tumors that, for some reason, still do not secrete hormone.

**CRANIOPHARYNGIOMA**: Benign tumor of squamous epithelial cells of Rathke's Pouch, the embryologic anlage of the pituitary.

- PATHOLOGY: Paradoxically, the tumor is usually *on top of* the pituitary, and it is often attached to the hypothalamus, which makes it difficult to remove surgically.
    - **Cystic**: It can be cystic, and it can resemble the enamel of teeth (which isn't surprising because it originates from oral cavity embryologically).
    - **Papillary:** Papillary form can have mucus-secreting cells, similar to salivary glands found in the mouth.
- CLINICAL: **Panhypopituitarism** can occur if the tumor compresses the pituitary causing pressure atrophy.
    - **Diabetes Insipidus** is often associated with the tumor, for unknown reasons.
    - **Fröhlich Disease (Adipo-Genital Dystrophy):** Disease can occur secondary to pan-hypopituitarism, from a craniopharyngioma in childhood.
- RELATED TUMORS:
    - **Rathke's Pouch Cysts:** Non-neoplastic cyst surrounded by Rathke's Pouch epithelial cells.
    - **Germinoma:** Germ-cell tumors can happen in a variety of locales, due to their embryological origin and migration.
        - **Pineal Germinoma:** The most common tumor of the pineal gland is a germinoma.
        - **Suprasellar Germinoma:** Germ-cell tumors also occur right above the pituitary, beneath the hypothalamus.
        - TREATMENT: They are successfully treated with radiation therapy.

**THYROID and PARATHYROID GLANDS**

THYROID ANATOMY and PHYSIOLOGY:

- EMBRYOLOGY: Medial and lateral thyroid tissue derive from different sources.
  - **Foramen Cecum:** Forms the medial portions of the thyroid gland. It is an invagination of the tongue.
    - **Thyroglossal Duct:** The thyroid tissue descends from its original location in the tongue, creating this cord as it goes. The duct eventually atrophies.
  - **Ultimobranchial Body:** Forms the lateral portions of the thyroid. It derives from the fifth branchial pouch.
    - **C-Cells** (Calcitonin-secreting) are derived from the ultimobranchial bodies.
- CONGENITAL ANOMALIES:
  - LINGUAL THYROID: Failure of thyroid to descend during embryogenesis.
  - HETEROTROPHIC THYROID TISSUE: Nests of thyroid tissue found anywhere along the pathway of thyroid descent down the thyroglossal duct.
  - LATERAL ABERRANT THYROID: Thyroid tissue found in lymph nodes surrounding the normal thyroid. Some think it has embryological origin and others think it may actually be metastases from an occult thyroid carcinoma.
  - **THYROGLOSSAL DUCT CYST**: Persistent thyroglossal duct.
    - **Pyramidal Lobe:** Another name for the persistent duct.
    - CLINICAL: It presents as a *midline, firm, cystic structure.* This helps to distinguish it from other structures.
- HISTOLOGY:
  - **Thyroglobulin** is synthesized in the Thyroid follicular cells and secreted into the lumen of the thyroid follicles.
  - **ORGANIFICATION**: The process of iodinating the thyroxines, forming MIT and DIT, and then forming $T_3$ and $T_4$.
    - On the outside of the membrane, in the lumen, **peroxidase** catalyzes the oxidation of iodide and its attachment to Thyroglobulin, forming **Mono-iodothyronine (MIT)** and **di-iodothyronine (DIT)**.
    - MIT and DIT then join to form $T_3$ and $T_4$
  - REABSORPTION / MOBILIZATION: ***TSH promotes the endocytosis and breakdown of the colloid.*** *That is its primary mode of stimulating thyroid secretion.*
    - TSH works by a G-Protein / cAMP second messenger system.
    - TSH promotes the reorganization of the cytoskeleton and the reaching out of the membrane, to begin endocytosis of the Thyroglobulin.
    - Thyroglobulin is then endocytosed into the follicular cell, and those endosomes merge with internal lysosomes to form **Phagolysosomes**.
    - Phagolysosomes then degrade the big thyroglobulin molecules into individual amino acids, and $T_3$ and $T_4$ are released.
    - The globulin components are resecreted back into the colloid lumen.
    - $T_3$ and $T_4$ are lipophilic and thus are through to go out into the blood by simple diffusion.
  - SECRETION:
    - **Thyroxine ($T_4$)**: The most common form of Thyroid released. It is less potent than $T_3$, more prevalent than $T_3$, and binds to TBG far more readily than $T_3$.
    - **Triiodothyronine ($T_3$):** $T_4$ is converted to $T_3$ in the bloodstream. $T_3$ is far more potent and has a lower binding affinity for TBG.
  - ABNORMAL HISTOLOGY:
    - **Excessive Stimulation of Thyroid** (Goiterous Hypothyroidism, Grave's Disease) ------> excessive breakdown of follicular thyroglobulin ------> thyroid enlarges but *follicles becomes smaller*.
      - Colloid is lost and follicular cells become hypertrophied.
    - **Deficient Stimulation of Thyroid** (TSH Deficiency, Thyroid Adenoma) ------> deficient breakdown of follicular thyroglobulin ------> *follicles are enlarged*.
      - There is excessive storage of colloid and follicular cells become atrophied.
- THYROID HORMONE: Thyroid hormone increases the metabolic rate, especially catabolic but also anabolic.
  - Catabolic Functions:
    - Stimulates basal metabolic rate and metabolism of carbohydrates, lipids, and proteins. It stimulates mitochondrial oxidative phosphorylation.
    - Stimulates **thermogenesis** by uncoupling oxidative phosphorylation from ATP production (thus wasting energy).
    - Raises blood sugar by enhancing gluconeogenesis and glycogenolysis.
    - Promotes lipolysis in adipose tissue.

- Anabolic Functions:
  - Promotes the synthesis of many proteins: structural proteins (growth), hormones, enzymes (which leads to increased metabolism).
  - Promotes glucose utilization and fatty acid synthesis in the liver.
- Physiologic Effects: Increased GI motility, thermogenesis, increased cardiac output.

**NONTOXIC (COLLOID) GOITER**: **Euthyroid** goiter, either diffuse or multinodular.

- PATHOGENESIS: A deficiency of thyroid production leads to increased secretion of TSH, which causes the thyroid to become goiterous. The increased TSH is sufficient to correct the problem yield **euthyroid** secretion thyroid hormone, thus the goiter is described as "non-toxic."
  - In addition to iodine deficiency, certain foods can cause it: turnips, rutabaga, cabbage, rape seeds, rale.
- SUBTYPES:
  - **Diffuse Non-Toxic Goiter**: Early stages of disease, gland is diffusely enlarged. Amount of colloid is decreased.
  - **Multinodular Non-Toxic Goiter**: Chronic disease. Soft, glistening, reddish nodules containing large amounts of colloid.
- PATHOLOGY: **Colloid cysts** may be formed by the coalescence of multiple nodules of excess colloid.
  - The nodules themselves are usually **cold**, meaning they do not take up iodide in a $^{131}$I-Uptake Test. Functional thyroid-secreting is found in the non-nodular parts of the thyroid.
- CLINICAL: Related to anatomical enlargement of thyroid gland.
  - Dysphagia, inspiratory stridor, hoarseness of voice, venous congestion of head and neck.
  - If hyperthyroidism develops, then the term **toxic multinodular goiter** is applied (see later).
  - TREATMENT: Exogenous thyroid hormone to suppress excess TSH secretion. Use radioactive iodine if the TSH secretion is refractory to the thyroid treatment.

**HYPOTHYROIDISM**:

- **CRETINISM**: Congenital hypothyroidism, leading to retardation and deficient growth.
  - CLINICAL:
    - Baby born with puffy eyelids, narrow palpebral fissures (similar to Down's Syndrome), protruded tongue. Infants are apathetic and sluggish, poor growth and failure to thrive. Often see refractory anemia and dilated heart.
    - TREATMENT: Give supplemental $T_4$. It is treatable if you catch it immediately and give thyroid hormone supplements.
  - SUBTYPES:
    - **Sporadic Cretinism:** Congenital malformation of thyroid. There is no goiter and the thyroid is small.
    - **Endemic Cretinism:** Thyroid due to maternal dietary deficiency of iodine. The thyroid is goiterous at birth.
- **MYXEDEMA**: Adult hypothyroidism
  - SYMPTOMS:
    - **Cold Intolerance**. Patients always feel cold due to lack of thermogenesis.
    - SKIN:
      - **Non-pitting edema** of extremities (known as myxedema). It results from accumulation of proteoglycans.
      - Puffy eyelids, characteristic apathetic facies, enlarged tongue (due to proteoglycans).
      - Coarse, frowsy hair.
      - Pale, cool skin, and scaly dermatitis.
    - CV: Decreased cardiac output
      - **Myxedema Heart:** A dilated heart with pericardial effusion.
    - CNS: Lethargy, somnolence, memory loss, depression, cerebellar ataxia, dulled reflexes.
      - Deafness and/or night-blindness may be seen.
    - GI: Constipation, fecal impaction.
- **GOITEROUS HYPOTHYROIDISM**:
  - ENDEMIC GOITER: Iodine deficiency. Endemic to Great Lake region of USA (rare), central Africa, Himalayas.
  - ENDEMIC CRETINISM:
  - DRUG-INDUCED GOITER (ANTI-THYROID AGENTS): **Lithium** can induce goiterous hypothyroidism.
  - IODIDE-INDUCED GOITER: Usually iatrogenic, as in the treatment of thyroiditis.
  - **HASHIMOTO'S THYROIDITIS**: See Thyroiditis below.

**HYPERTHYROIDISM (THYROTOXICOSIS)**:

- SYMPTOMS: Symptoms common to all forms of hyperthyroidism.
  - Palpitations, tachycardia, high cardiac output.
    - You see **high systolic pressure** (indicative of high cardiac output) but **normal to low diastolic pressure** (indicative of low peripheral resistance). Thus you see a high pulse pressure.
    - Increased Cardiac Output can lead to high-output cardiac failure.
  - **Heat Intolerance**. Patients always feel hot, due to the excessive thermogenesis.
  - Nervousness, fatigue (low exercise tolerance), excessive perspiration, difficulty sleeping.
  - Very fine-amplitude tremor of the hands.
  - Systolic bruit heard over thyroid, due to excessive vascularity of thyroid.
  - **Thyroid Storm:** Acute attack of severe hyperthyroidism. Hyperpyrexia, dehydration (due to hyperperistalsis), hypertension, tachycardia, arrhythmias.
- **GRAVE'S DISEASE**:
  - PATHOGENESIS: **Long-Acting Thyroid Stimulatory (LATS)** are IgG auto-antibodies formed against TSH receptors in the thyroid gland. They activate the thyroid gland and have a longer-lasting activity than TSH itself.
    - Genetic predisposition (HLA-B8, HLA-DR3), plus sensitization to antigens of *Yersinia Enterocolitica* are thought to play roles.
  - PATHOLOGY:
    - **Diffuse, non-nodular enlargement** of thyroid.
    - Follicles become smaller and lose colloid. The follicular cells become hypertrophied (taller). Thyroid has a scalloped or "moth-eaten" appearance.
  - SYMPTOMS: All of the symptoms of hyperthyroidism above, plus exophthalmos.
    - **EXOPHTHALMOS:** Ophthalmopathy is *not* caused by hyperthyroidism itself. It is caused by inflammation and swelling in the retro orbital space, probably due to a local auto-immune reaction of different antibodies.
      - Ocular muscles are infiltrated by lymphocytes and plasma cells and become edematous.
      - Fibroblasts proliferate in retro-orbital space causing the proptosis.
    - Long-standing Grave's Disease can actually lead to **hypothyroidism** and destruction of the gland.
  - DIAGNOSIS: Established by a **$^{131}$I-Uptake Test**. Rapid, diffuse uptake of $^{131}$I into the Thyroid gland, plus elevated levels of $T_3$ and $T_4$, is diagnostic of Grave's Disease.
- **TOXIC MULTINODULAR GOITER**: Toxic progression of non-toxic multinodular goiter. The thyroid nodules become functional and autonomous.
  - PATHOLOGY: Two histological patterns recognized
    - **Diffuse micronodules**: Characterized by multiple groups of small hyperplastic follicles, intermixed with nodules of varying size that are evidently non-functional.
    - **Discrete macro-nodules**: One or two macro-nodules dominate the gland. All of the $^{131}$I is taken up into these discrete areas, and the rest of the Thyroid gland is atrophied.
  - CLINICAL: Patients tend to be older.
    - Hyperthyroid symptoms are usually less severe than in Grave's Disease. **No exophthalmos** at all.
- **TOXIC ADENOMA**: Primary hyperthyroidism caused by a benign, functional, thyroid-secreting tumor.
  - DIAGNOSIS:
    - TSH levels are low, naturally.
    - $^{131}$I-Uptake Test shows a **hot nodule** of excessive iodide uptake, in a background of minimal uptake.
    - A **cold nodule** (non-functional) may result from hemorrhage of the tumor. Normally, however, cold nodules are indicative of malignant tumors.
- OTHER CAUSES of HYPERTHYROIDISM:
  - HYPERSECRETION of TSH:
  - IODINE-INDUCED HYPERTHYROIDISM:

**THYROIDITIS**:

- **HASHIMOTO THYROIDITIS**: *The most common cause of Goiterous Hypothyroidism.*
  - PATHOGENESIS: Primarily cell-mediated (Type IV), but also some antibody-dependent (Type II) auto-immunity against the thyroid gland.
    - Antibodies are found against the colloid and against follicular microsomes.
  - PATHOLOGY:

        - Symmetrical, diffuse (non-nodular) enlargement of thyroid. Cut-surface is pale to creamy, due to heavy infiltration of leukocytes.
        - Most of the follicles are completely gone, due to inflammatory destruction.
        - **Hürthle cells:** Large, eosinophilic cells, indicative of oxyphilic metaplasia of thyroid follicular cells; the cells have lost their function.
    - CLINICAL: Found in middle-aged women, and often associated with other auto-immune diseases (RA, SLE, Sjögren's, MG, IDDM)
        - Thyroid enlargement is painless.
        - Patients remain euthyroid until late in course of disease, after which they become hypothyroid.
- **SUBACUTE (DEQUERVAIN) THYROIDITIS**:
    - PATHOGENESIS: Occurs subsequent to a **viral infection**: Influenza, adenovirus, echovirus, coxsackie virus.
    - PATHOLOGY: Destruction of follicles allows the release of colloid ------> granulomatous inflammation against the colloid itself and formation of **foreign-body giant cells**.
    - CLINICAL: Self-limited (resolves in a few months) febrile illness, pharyngitis-like, with no lymphadenopathy.
        - $^{131}$I-uptake test shows *decreased* uptake of iodide diffusely.
        - Thyroid is moderately enlarged and exquisitely tender. Hoarseness, dysphagia.
- **RIEDEL'S (WOODY) THYROIDITIS**: Rare disease. Idiopathic localized fibrosis of the thyroid.
    - CLINICAL: Occurs in old people. Gradual onset of painless goiter, with only anatomical symptoms (hoarseness, dysphagia, stridor).
        - Thyroid may become bound to underlying tissue, making it extremely difficult to remove surgically.
        - It must be differentiated from a thyroid cancer.
- SILENT THYROIDITIS: Painless, self-limited subacute thyroiditis.

**FOLLICULAR ADENOMA of the THYROID**: Solitary **cold nodules** (don't take up iodide).

- PATHOGENESIS: They often arise as the dominant nodule in a non-toxic multinodular goiter.
- PATHOLOGY: Encapsulated tumor. The capsule is *not* penetrated (in carcinoma, the capsule is penetrated by tissue). Multiple subtypes. A single tumor can only be of a single subtype:
    - **Embryonal Adenoma**
    - **Fetal Adenoma**: Has a microfollicular pattern.
    - **Simple Adenoma**: Mature follicles with normal amount of colloid.
    - **Colloid Adenoma**
    - **Hürthle Cell Adenoma**
    - **Atypical Adenoma**: Most likely to become cancerous.

**THYROID CARCINOMA**:

- PATHOGENESIS: Two things have been shown to generally cause thyroid cancer.
    - **Goiter**: Thyroid carcinoma has higher incidence in regions of endemic goiter.
    - **Radiation Treatment:** Any radiation treatment of thyroid (such as Hiroshima) has been shown to cause cancer.
- **PAPILLARY CARCINOMA**:
    - CLINICAL: Occurs in younger population, slight predilection for females.
        - Good prognosis -- even if there is metastases to regional nodes.
        - Can present as **cold nodule** on a thyroid scintiscan.
        - Typically metastasizes via **lymphatics** to regional nodes.
    - PATHOLOGY: Papillae with central fibrovascular core. **No capsule** -- the capsule has been penetrated.
        - **Psammoma Bodies** can be found.
- **FOLLICULAR CARCINOMA**:
    - PATHOLOGY: Whitish, indistinct borders, and **no capsule**.
        - Diagnosis of carcinoma is made (rather than adenoma) when the capsule is penetrated.
        - Two subtypes: Minimally Invasive and Widely Invasive Carcinomas.
    - CLINICAL: Tends to metastasize **hematogenously**, **to bones** of shoulder, pelvis, sternum, skull.
        - Also has a good prognosis.
- **MEDULLARY CARCINOMA**:
    - PATHOGENESIS:
        - **C-Cell Hyperplasia** is the precursor lesion to medullary carcinoma. At-risk patients (MEN Types 2A and 2B) are monitored for levels of calcitonin, CEA, and/or chromogranin.

        - **MEN Type-II:** *Familial* Medullary Carcinoma is associated with MEN Type-II, while sporadic carcinoma is not.
    - PATHOLOGY: Tumor of **Parafollicular** or **C-Cells**. Firm thyroid nodule with cervical lymphadenopathy.
        - **Endocrine-Type Amyloid**: Deposition of amyloid in the stroma of the thyroid represents deposits of calcitonin and pro-calcitonin.
        - Will see bands of epithelial cells, with histologically variably appearance: trabecular, tubular, carcinoid-like, pseudo-papillary patterns.
    - DIAGNOSIS:
        - Familial form associated with Multiple Endocrine Neoplasia (**MEN Type II**)
        - **Calcitonin is markedly elevated**, up to tenfold.
        - **Carcino-Embryonic Antigen (CEA) Positive**: This tumor marker is useful for diagnosis and tracking of the tumor.
            - **Chromogranin** is another tumor marker that is sometimes monitored.
            - Can also be positive for other markers: ACTH, Substance-P, hCG, glucagon, insulin.
    - SYMPTOMS: Related to endocrine secretion.
        - Carcinoid Syndrome: Watery diarrhea, due to release of VIP, serotonin.
        - Cushing Syndrome
    - TREATMENT: Total thyroidectomy. Local recurrences are common.
- **ANAPLASTIC CARCINOMA**: Highly aggressive, rapidly fatal tumor. Can compress the trachea and cause suffocation.
    - CLINICAL: Dysphagia, dyspnea, from physical compression. Also highly metastatic.
- THYROID LYMPHOMA:

PARATHYROID ANATOMY and PHYSIOLOGY:

- EMBRYOLOGY: They derive from branchial clefts III and IV.
    - **3rd Branchial Cleft**: Gives rise to the lower 2 parathyroid glands.
    - **4th Branchial Cleft**: Gives rise to the upper 2 parathyroid glands.
- ANATOMY: They are about the size and shape as a piece of rice, brown to presence of glycogen. Anatomical location is on the posterior of thyroid, at a variable height.
    - **Chief Cells:** Secrete PTH. Most numerous cell.
        - Plasma membrane thrown into folds. The more active the cell, the more folds there are.
    - **Water Clear (Wasserhelle) Cells:** Inactive Chief cells whose cytoplasm is packed with glycogen.
    - **Oxyphil Cells:** Large eosinophilic cells appearing after puberty. Function unknown.
    - **Fat Cells:** Fat is normally present in parathyroids, increasing with age. The absence of fat suggests hyperplasia or an adenoma.
- PARATHYROID HORMONE:
    - SYNTHESIS: It is synthesized as a pre-pro-hormone, **preproparathyroid hormone**.
        - **Proparathyroid:** Signal sequence is removed in the ER.
        - **Parathyroid:** The pro-sequence is removed in the Golgi before active PTH is packaged into vesicles.
    - STRUCTURE: 84 amino acids in length, only internal 24 of which are functional.
    - FUNCTION:
        - BONE: It stimulates osteoclastic resorption of bone ------> higher blood $Ca^{+2}$. It does so *indirectly*, by stimulating **osteoblasts** to release osteoclastic tropic factors.
        - KIDNEY:
            - It stimulates the resorption of calcium.
            - It stimulates the excretion of phosphate (distal tubule, inhibit $Na^{+}$/phosphate resorption).
            - It stimulates synthesis of Vitamin-D by up-regulating **1-hydroxylase** in the kidney.
        - INTESTINE: It stimulates the dietary absorption of calcium indirectly, by up-regulating levels of Vitamin-D.
    - REGULATION:
        - High blood $Ca^{+2}$ levels suppress PTH synthesis secretion.
        - High blood $Mg^{+2}$ levels *stimulate* PTH release, but not synthesis. Hypomagnesemia impairs the release of PTH.

**HYPOPARATHYROIDISM**:

- PATHOGENESIS:
  - SECONDARY HYPOPARATHYROIDISM: Surgical resection of parathyroids during thyroidectomy is the most common cause of hypoparathyroidism.
  - IDIOPATHIC HYPOPARATHYROIDISM: Rare. Thought to have an autoimmune basis. Autoantibodies against parathyroid gland.
    - Can be seen as part of **Polyglandular Autoimmune Syndrome Type I**: hypoparathyroidism, adrenal insufficiency, and chronic mucocutaneous candidiasis.
  - **DIGEORGE SYNDROME:** Congenital agenesis of the 3rd and 4th Pharyngeal Pouches, resulting in aplasia of Thymus and Parathyroids.
- CLINICAL:
  - SYMPTOMS: All are related to hypocalcemia, and range in severity.
    - **Tetany:** Decreased $Ca^{+2}$ leads to increased excitability at neuromuscular junction.
    - **Stridor:** Laryngeal spasm
    - Psyc: Can see depression, paranoia, psychosis.
  - SIGNS:
    - **Chvostek's Sign:** Spasm of facial muscles following a tap on one side of the face over the area of the Facial Nerve.
    - **Opisthotonos:** Spastic contraction of all muscles, especially flexors ------> arching of back and neck in characteristic fashion.
    - **Trousseau Sign:** Compress the upper arm with a tourniquet, and see carpal spasm. Seen in latent tetany.
    - **Erb's Sign:**
- LABS:
  - **Hypocalcemia** (low $Ca^{+2}$) is responsible for most symptoms.
  - **Low Alkaline Phosphatase**, indicative of low rate of bone-remodeling.
  - **Hyperphosphatemia**, due to impaired renal excretion of phosphate.
- TREATMENT: PTH and Vitamin-D supplements.
- **PSEUDOHYPOPARATHYROIDISM**: End-organ insensitivity to PTH.
  - PATHOGENESIS: In the kidney, it is caused by decreased $G_s$ activity at the PTH-receptor ------> decreased cAMP ------> deficient tubular resorption of $Ca^{+2}$.
    - Levels of PTH will actually be increased.
  - CLINICAL:
    - **Albright Hereditary Osteodystrophy:** Patients with familial pseudohypoparathyroidism characteristically have short stature, short fingers, short neck.
      - Associated resistance to other hormones (TSH, FSH and LH, Glucagon) is frequently also seen.

**HYPERPARATHYROIDISM**:

- PATHOGENESIS:
  - PRIMARY HYPERPARATHYROIDISM:
    - **PARATHYROID ADENOMA**: 80% of cases of hyperparathyroidism.
      - PATHOLOGY:
        - A **pseudo-capsule**, or rim of normal parathyroid tissue, is around the outside of the adenoma.
          - This is an essential finding -- it distinguishes it from Primary Parathyroid Hyperplasia which is diffuse.
        - **No Fat Cells** in the adenoma.
        - Cellular pleomorphism is present, although the tumor is benign.
        - The other three glands will tend to be atrophic when one gland is hyperactive.
    - **PRIMARY PARATHYROID HYPERPLASIA**: 15% of cases. Diffuse hypersecretion of PTH.
      - CLINICAL: One third of cases is associated with MEN Types 1 and 2A
      - PATHOLOGY: Usually is Chief Cell hyperplasia, but can also be Clear Cell hyperplasia.
        - All four glands are enlarged. There is no capsule, and no pleomorphism is present.
    - **PARATHYROID CARCINOMA**: 1% of cases.
      - PATHOLOGY: It cannot be distinguished from a Thyroid Carcinoma histologically, only symptomatically.

        - It is usually a functional tumor, and complications of hyperparathyroidism are usually the cause of death.
    - SECONDARY HYPERPARATHYROIDISM:
        - **RENAL OSTEODYSTROPHY**:
            - PATHOGENESIS: **Renal Failure** causes hyperparathyroidism by two mechanisms:
                - **1-Hydroxylase** activity is deficient in the failing kidney ------> inadequate production of 1,25-$(OH)_2$-Vit-D ------> inadequate intestinal $Ca^{+2}$ absorption ------> higher PTH.
                - **Hyperphosphatemia** results from a failing kidney, because $PO_4^{-3}$ excretion is insufficient ------> higher PTH.
            - LABS:
                - Despite the high PTH, calcium tends to be *low* due to the renal failure.
                - Phosphate levels are variable, depending on the functionality of the kidney.
            - PATHOLOGY: Parathyroid Glands will become diffusely hyperplastic, in response to the low calcium levels.
                - **TERTIARY HYPERPARATHYROIDISM:** If the parathyroid glands become hyperplastic enough from secondary hyperparathyroidism (as in renal failure), eventually they will become autonomous (unresponsive to calcium levels). This is called tertiary hyperparathyroidism.
        - Other Causes:
            - **Sprue**: Intestinal Malabsorption of Vitamin-D and/or $Ca^{+2}$
            - **Vitamin-D Deficiency** ------> hypocalcemia ------> hyperparathyroidism.
            - Fanconi Syndromes, renal tubular acidosis.
- PATHOLOGY:
    - **Howship Lacuna:** Microscopic focus of bone resorption.
- CLINICAL:
    - LABORATORY FINDINGS of HYPERPARATHYROIDISM:
        - **Hypercalcemia**: High blood $Ca^{+2}$
        - **Hypophosphatemia**: Low blood $PO_4^{-3}$
        - **Increased Alkaline Phosphatase**: Alkaline Phosphatase is indicative of high rates of bone turnover. It is a product of *osteoblastic* activity (PTH stimulates osteoblasts which in turn stimulate osteoclasts).
    - SYMPTOMS / COMPLICATIONS:
        - **Osteitis Fibrosis Cystica (Von-Recklinghausen Disease):** Lytic bone lesions caused by hyperparathyroidism. See Bone section.
            - Resorption of the distal phalanges characteristically occurs.
        - **Metastatic Calcification:** Calcification of soft tissues resulting from hypercalcemia or hyperphosphatemia.
        - **Kidney Stones:** Calcium kidney stones, metastatic calcification of glomerulus.
- **HYPERCALCEMIA**: Hypercalcemia is caused by many things other than hyperparathyroidism.
    - **PARANEOPLASTIC HYPERCALCEMIA**: *The most common cause of hypercalcemia is as a paraneoplastic syndrome of another tumor.* 34.4% of cases.
        - **Parathyroid Hormone Related Peptide (PTHRP):** Peptide secreted by many malignant tumors that acts similarly to PTH.
        - Tumors that commonly secrete PTHRP:
            - Lung
            - Breast
            - Squamous Cell Carcinoma of the Head and Neck
            - Renal Cell Carcinomas
            - Multiple Myeloma
        - LABS: Hypercalcemia is the most consistent finding. *Both phosphate and alkaline phosphatase levels are variable.*
            - Contrast to Primary Hyperparathyroidism, in which you consistently find low phosphate and high alkaline phosphatase.
    - **Primary Hyperparathyroidism**: 34.2% of cases.
    - **Vitamin D Excess:** 12.1% of cases. Usually dietary excess, taking vitamin-D supplements.
    - **Hyperthyroidism**: 3.9%
    - **Milk Alkali Syndrome**: 2.3%
    - **Sarcoidosis / Dysproteinemia**: 1.5%
    - **Laboratory Error**: 13.4%

## ADRENAL GLANDS

NORMAL STRUCTURE and FUNCTION:

- EMBRYOLOGY:
  - **Adrenal Cortex**: It arises from mesenchymal cells near the urogenital ridge.
  - **Adrenal Medulla**: Originates from neuroectodermal cells, and is related to sympathetic ganglia embryologically.
  - *The Adrenal glands are larger than the kidneys during fetal life.* The **Fetal Zone** of adrenal tissue atrophies shortly after birth.
- HISTOLOGY:
  - **Zona Glomerulosa:** Semi-acinar, smaller cells around outside.
    - SECRETE: It secretes **Aldosterone**.
      - Stimulated by: Angiotensin, Potassium.
      - Inhibited by: Atrial Natriuretic Peptide (ANP), Somatostatin.
  - **Zona Fasciculata:** Arranged in cords, covering the majority of the cortex.
    - **Lipid Droplets** of steroid product are common in these cells, giving the cells a "frothy" appearance.
    - SECRETE: They secrete **Cortisol**
    - An ACTH-Secreting Pituitary tumor will cause enormous hypertrophy of this layer.
  - **Zona Reticularis:** Nearest the cortex.
    - SECRETE: They secrete Cortisol and weak androgens, such as **dehydroepiandrosterone (DHEA)**

**CONGENITAL ADRENAL HYPERPLASIA (CAH)**: Any deficiency in Cortisol synthesis results in increased ACTH ------> continual stimulation of and diffuse hyperplasia of adrenal glands.

- **21-HYDROXYLASE ($P450_{C21}$) DEFICIENCY**: Most common cause of CAH. 90% of cases.
  - PATHOGENESIS: 21-Hydroxylase converts **17-hydroxyprogesterone ------> 11-deoxycortisol**. Synthesis is shunted down the androgen pathway.
  - EPIDEMIOLOGY: 1/10,000 among white. 1/500 among Eskimos.
  - SYMPTOMS:
    - Virilization of females: pseudohermaphroditism, baby girl may be mislabeled as boy.
    - Chronically high androgens lead to stunted growth.
  - SUBTYPES:
    - **Virilizing CAH**: Congenital virilization.
    - **Salt-Wasting CAH**: Variant in which aldosterone synthesis is deficient.
    - **Late-Onset CAH:** Presents as a syndrome similar to Polycystic Ovary, in young women.
  - TREATMENT: Give synthetic cortisol to suppress excess ACTH secretion.
- **11beta-HYDROXYLASE ($P450_{C11}$) DEFICIENCY**: 5% of cases.
  - PATHOGENESIS: 11beta-Hydroxylase converts **11-deoxycortisol ------> Cortisol**. With deficiency, androgens build up again.
    - **11-deoxycortisol** also builds up, and it is a weak mineralocorticoid ------> hypertension, salt retention.
- RARE DEFICIENCIES:
  - 17alpha-HYDROXYLASE DEFICIENCY: Hypokalemic alkalosis and hypertension.
  - 3beta-HYDROXYLASE DEFICIENCY: Impaired synthesis of all steroid hormone classes.
  - CHOLESTEROL SIDE-CHAIN CLEAVAGE ENZYME ($P450_{SCC}$) DEFICIENCY: Virtually no secretion of cortisol or aldosterone.

ADRENAL INSUFFICIENCY:

- **CHRONIC ADRENAL INSUFFICIENCY (ADDISON DISEASE)**:
  - PATHOGENESIS: Most cases are idiopathic.
    - **Autoimmune Adrenalitis**: 75% of cases. Granulomatous, lymphocytic inflammation of adrenal glands, of auto-immune origin.
      - Genetic Predisposition: HLA-B8, HLA-DR3, HLA-DR4
      - Evidence has been shown for both humoral autoimmunity (anti-adrenal antibodies), and cellular immunity (decreased suppressor T-Cells).
    - Other Causes: Metastatic carcinoma, amyloidosis, sarcoidosis, fungal infections.
  - POLYGLANDULAR ENDOCRINOPATHIES: 50% of cases are associated with these rare, familial diseases:

        - **POLYGLANDULAR AUTOIMMUNE SYNDROME TYPE I:** Triad of adrenal insufficiency, hypoparathyroidism, and chronic mucocutaneous candidiasis.
            - Cause unknown, but it is not linked to any HLA haplotypes, unlike the other causes of adrenal insufficiency.
        - **POLYGLANDULAR AUTOIMMUNE SYNDROME TYPE II (SCHMIDT SYNDROME):** More common than Type-I. Includes Adrenal Insufficiency (always), Hashimoto's Thyroiditis, Grave's Disease, IDDM, and premature ovarian failure.
    - PATHOLOGY: Atrophic, shrunken adrenal cortex, overlying a normal medulla.
    - SYMPTOMS: Progressive weakness, cachexia
        - **Hyperpigmentation**: Results from increased secretion **Melanocyte-Stimulating Hormone (MSH)**, another metabolite of **Pro-Opiomelanocortin (POMC)**, the same precursor from which ACTH comes.
        - Hyponatremia, Hyperkalemia: result from deficient mineralocorticoids.
        - Hypotension, Hypoglycemia.
        - **Acute Apoplexy:** Acute, fulminant progression of the deficiency can occur, with results similar to Waterhouse-Friderichsen Syndrome.
- **ACUTE ADRENAL INSUFFICIENCY (WATERHOUSE-FRIDERICHSEN SYNDROME)**: Acute, bilateral, hemorrhagic infarction of the adrenals.
    - PATHOGENESIS: Occurs secondary to shock and DIC, in a septicemic infection. The adrenals bleed out.
        - **Generalized Shwartzman Reaction**: Endotoxic hemorrhaging.
        - Tiny fibrin thrombi occlude the vessels going to the adrenal glands ------> infarction.
        - BUGS:
            - ***Neisseria Meningitidis*** is the most common agent causing the infection.
            - Also Pneumococci, Staph, Strep, Haemophilus, Diphtheria.
            - Herpes Virus can cause it.
    - PATHOLOGY: Complete and sudden collapse of cortical function requires immediate treatment.
    - SYMPTOMS: Would see symptoms of shock (tachypnea, tachycardia), infection (fever, leukocytosis), and DIC (petechia, thrombocytopenia, increased PT and PTT).
- **SECONDARY ADRENAL INSUFFICIENCY**:
    - **CORTICOSTEROID WITHDRAWAL**: Abrupt withdrawal of corticosteroids is a very common cause of acute adrenal insufficiency.
    - **NELSON SYNDROME:** Surgical removal of the adrenals leads to chronically high levels of ACTH and MSH.
        - SYMPTOMS: Patient's face will be round and hyperpigmented.
    - Pan-Hypopituitarism
    - ACTH deficiency: rare. MSH would also be deficient, hence the characteristic hyperpigmentation would be absent.

**CUSHING SYNDROME**: Hypersecretion of Cortisol from any cause.

- PATHOGENESIS:
    - **CUSHING DISEASE**: Hypersecretion of Cortisol resulting from hypersecretion of ACTH. *With the exception of corticosteroid administration, Cushing Disease accounts for the majority of cases of Cushing Syndrome.* The excessive ACTH can result from several different places:
        - **Pituitary Hypersecretion of ACTH**. This can result from a corticotrope microadenoma, or diffuse corticotrope hyperplasia.
        - **Ectopic ACTH production** from some other tumor.
            - **Small-Cell Carcinoma** of Lung is responsible for majority.
            - Carcinoids, neural-crest tumors, thymoma
        - **Ectopic CRH production** from some other tumor.
            - Medullary carcinoma of the thyroid, prostate adenocarcinoma, bronchial carcinoid.
            - Tumors can secrete both ACTH and CRH.
    - **ADRENAL ADENOMA**: Rare.
        - PATHOLOGY: Thin rim of normal tissue surrounds the tumor.
            - **Lipofuscin** is found in the tumor.
            - The rest of the adrenal cortical tissue, and the contralateral gland, is usually atrophic.
    - **ADRENAL CORTICAL CARCINOMA**: Most adrenal carcinomas are functional tumors.
        - SYMPTOMS: Grim prognosis, survival only 2-3 years, even with surgical resection. The tumor is very difficult to resect completely, and it comes back.
            - Non-functional carcinomas (minority) are especially malignant.

- **CHRONIC CORTICOSTEROID ADMINISTRATION**: *By far the most common cause of Cushing Syndrome.*
- BILATERAL MICRONODULAR DYSPLASIA:

- PATHOLOGY:
  - **Diffuse Adrenal Hyperplasia**: 75% of cases
  - **Nodular Adrenal Hyperplasia**: 25% of cases, grossly visible nodules.
- SYMPTOMS / CLINICAL:
  - OBESITY:
    - **Moon Facies:** Fat accumulation in face, characteristic appearance.
    - **Flush Face:** Hyperemia and excess accumulation of RBC's in the face give it a flush appearance.
    - **Truncal Obesity:** Obesity in the thorax and abdomen, with relatively thin extremities.
    - **Buffalo Hump:** Characteristic fat-collection over the skin covering thoracic spinal column.
  - SKIN / MUSCLE:
    - **Muscle Atrophy**
    - **Thin Skin:** Purple striae result from the stretching of thin skin.
    - **Acanthosis Nigricans:** Darkening of skin around neck, as occurs with Insulin resistance.
  - METABOLIC:
    - **Cortisol Diabetes**: Hyperglycemia and Glucose Intolerance.
    - Hypokalemia and hypertension (due to Aldosterone-induced renal excretion of potassium)
  - BONE: Osteoporosis due to negative $Ca^{+2}$-balance. Back pain, and wasting of proximal muscles.
    - Glucocorticoids inhibit $Ca^{+2}$ absorption in gut ------> negative $Ca^{+2}$-Balance ------> PTH is stimulated to restore $Ca^{+2}$ in the blood ------> $Ca^{+2}$ is taken from bone.
    - Glucocorticoids inhibit the gonadotropins ------> inhibit estrogen ------> more $Ca^{+2}$ resorption.
      - This effect also holds for men. Testosterone levels are down-regulated, and $Ca^{+2}$ resorption increases as a result.
    - Glucocorticoids inhibit collagen synthesis in osteoblasts.
  - BLOOD:
    - Immune suppression, lymphopenia, eosinopenia.
    - **Hyperglobulia:** Elevated RBC count.
  - ENDOCRINE: Acne. Virilization, amenorrhea in females, impotence in males.
  - LABS:
    - Increased levels of **17-hydroxysteroids** found in the urine.
    - **Dexamethasone Suppression Test:** It is used to distinguish ACTH-dependent Cushing Disease from ACTH-Independent Cushing Syndrome.
      - Cushing Disease: High dose dexamethasone will suppress pituitary secretion of ACTH, but it will not suppress primary hypersecretion of Cortisol (as in an adrenal tumor).

**CONN SYNDROME**: Primary hypersecretion of Aldosterone from any cause.

- PATHOGENESIS:
  - **Cortical Adenoma:** Most common. Well-demarcated and benign. Can easily be removed by surgical resection.
  - **Nodular Cortical Hyperplasia**
  - **Adrenocortical Carcinoma:** It is very rare for an adrenal carcinoma to secrete aldosterone.
- PATHOLOGY: Yellow tumor, with clear, lipid-rich cells arranged in cords or alveoli.
  - In contrast to Cushing syndrome, the non-neoplastic adrenal cortical tissue is *not atrophic*, because excess aldosterone does not suppress ACTH secretion.
- SYMPTOMS:
  - **Severe Hypertension**
  - **Hypernatremia**
  - **Hypokalemia**:
    - Polyuria and polydipsia is thought to result from hypokalemia.
    - **Metabolic Alkalosis** also occurs secondary to hypokalemia. Excess aldosterone ------> excess $H^+$ ions are lost to the urine ------> metabolic alkalosis. Excess $NH_3$ and $HCO_3^-$ are secreted into the urine, creating an alkaline urine as well.
- TREATMENT: *Conn Syndrome is a treatable form of essential HTN.*
  - Surgical resection or ablation of tumor.
  - Dietary sodium restriction.
  - **Spironolactone**: Aldosterone antagonist.

MISCELLANEOUS ADRENAL TUMORS:

- ADRENAL MYELOLIPOMA:
- ADRENAL CYSTS:
- METASTATIC CANCER: Commonly originates from lung or breast carcinoma, or from malignant melanoma.

**MULTIPLE ENDOCRINE NEOPLASIA (MEN)**:

- **MEN TYPE 1 (WERNER SYNDROME)**:
  - PATHOGENESIS: Genetic defect on chromosome 11.
  - TRIAD: **Pituitary adenoma, parathyroid hyperplasia or adenoma, islet-cell tumor of pancreas**.
- **MEN TYPE 2A (SIPPLE SYNDROME)**:
  - PATHOGENESIS: Genetic defect on chromosome 10.
  - TRIAD: **Pheochromocytoma, Medullary Carcinoma of Thyroid, parathyroid hyperplasia.**
    - Occasionally find gliomas, glioblastomas, meningiomas.
- **MEN TYPE 2B**:
  - TRIAD: **Pheochromocytoma, Medullary Carcinoma of Thyroid, Mucosal Neuroma Syndrome**.
    - **Mucosal Neuroma Syndrome**: Neuromas of conjunctiva, oral cavity, larynx, GI tract. They are always found in this syndrome.

**PHEOCHROMOCYTOMA**: Primary, benign, functional tumor of chromaffin cells in adrenal medulla.

- PATHOGENESIS: The majority are sporadic. The minority are associated with MEN Types 2A and 2B.
- PATHOLOGY: Tumors can get very large and are usually unilateral, but can be bilateral.
  - **Zellballen:** Characteristic large balls of neoplastic chromaffin cells.
- SYMPTOMS: Tumor is benign 90% of the time.
  - **Hypertension**:
    - **Essential HTN** of varying degrees, from asymptomatic to malignant, is found.
      - The HTN will usually be refractory to treatment by traditional anti-hypertensives.
    - **Paroxysmal HTN**, episodic attacks of hypertension, overlies the essential HTN and adds even more to the blood pressure.
      - It is often experienced as nervous spells, bringing the tumor to clinical attention.
      - The paroxysm is often triggered by events that put pressure on the abdominal cavity, such as exercise, lifting, defecating, abdominal palpation.
  - Paradoxic orthostatic hypotension.
  - Sweating, palpitations, increased metabolism, and other symptoms mimicking hyperthyroidism.
- LABS:
  - Neuron-specific enolase, chromogranin, and synaptophysin all stain positive in the tumor.
  - **Vanillyl Mandelic Acid (VMA)**, breakdown product of both Epi and NE, is found in excess in the urine.

PARAGANGLIONIC TUMORS: Tumors arising in or around the sympathetic ganglia, outside the adrenal medulla.

- **PARAGANGLIOMA (CHEMODECTOMA)**: Essentially, it is an extramedullary pheochromocytoma.
  - PATHOLOGY: The tumor is identical histologically to a pheochromocytoma, but it arises in non-adrenal locations. May arise anywhere there are sympathetic ganglia:
    - **Organs of Zuckerkandl**: Retroperitoneal cluster of sympathetic paraganglia, next to abdominal aorta.
    - Posterior mediastinum and urinary bladder are other locales.
    - **Carotid Body Tumor**
- **NEUROBLASTOMA**: *Neuroblastoma is one of the most important malignant tumors of childhood.* It and the Wilms Tumor are the two most common childhood malignant tumors.
  - EPIDEMIOLOGY: 10% of all childhood cancers, and 15% of cancer deaths among children.
  - PATHOGENESIS: It is a tumor of **primitive neural crest cells**, the embryonic precursor cells to the sympathetic ganglia.
    - Cause is unknown but is related to faulty, unregulated, or continued embryogenesis of the sympathetic nervous system after birth.
  - PATHOLOGY:

        - Location: Can arise in any location where neural crest cells originate. Adrenal Medulla is location 30% of time.
        - **Rosettes:** Little neuroblasts with their cytoplasmic tails (like vestigial dendrites) all pointing inward, creating characteristic spherical cluster of cells.
        - Pseudorosettes: Neoplastic cells surrounding a blood vessel.
        - **Small-Blue-Cell Tumor:** A neuroblastoma is a small-blue-cell tumor. Crowded cells with little cytoplasm.
    - CLINICAL: Tumor is highly malignant, but it has a good prognosis because of high remission rate.
        - PROGNOSIS:
            - **Remission**: Tumor has a high spontaneous remission rate, due to its maturing into a benign **ganglioneuroma**. All of the neoplastic cells differentiate into ganglion cells, and you are left with a benign tumor.
                - *The younger the child, the greater the chance of spontaneous remission, and the better the prognosis.* Children younger than 1 has a better than 50/50 chance of spontaneous remission.
            - **N-*myc*** oncogene has been found in 30% of tumors, translocated from chromosome 2 to chromosome 1. Its presence indicates a worse prognosis.
        - SYMPTOMS: Hypercoagulability of blood, from hemorrhage of tumor and invasion of blood marrow.
        - LABS: **Vanillylmandelic Acid (VMA)** is found in excess in the urine, as in pheochromocytoma.
- **GANGLIONEUROMA**: The benign counterpart to neuroblastoma. Found in older children and young adults.
    - PATHOLOGY: Typically arises in posterior mediastinum, or adrenal medulla.

## THYMUS and PINEAL GLAND

ANATOMY and PHYSIOLOGY:

- EMBRYOLOGY: Thymus derives from the **3rd and 4th Pharyngeal Pouches**
- CONGENITAL ANOMALIES:
    - **Severe Combined Immunodeficiency (SCID)**: Both B and T cell deficiencies, associated with severe thymic dysplasia.
    - **DiGeorge Syndrome**: Agenesis of the 3rd and 4th pharyngeal pouches, resulting in aplasia of thymus of parathyroids.
        - Associated congenital heart defects, dysmorphic facies.
        - Susceptibility to infections, especially *Candida*.
    - **Nezelof Syndrome**: Similar to DiGeorge Syndrome, without parathyroid and cardiac involvement.
    - **Wiskott-Aldrich Syndrome**: Hypoplastic thymus, eczema, thrombocytopenia. Sex-linked recessive.
    - **Reticular Dysgenesis**: Severe immunodeficiency with death *in utero* or right after birth.
    - **Swiss-Type Hypogammaglobulinemia**: Failure of thymus to descend from neck into mediastinum. Autosomal recessive thymic hypoplasia or dysplasia.
        - Infants die within a few years.
    - **Ataxia** Telangiectasia: Diffuse telangiectasia and cerebellar ataxia. Frequent lymphoma. Thymic is involuted.

THYMIC HYPERPLASIA: *Thymic Hyperplasia is associated with Myasthenia Gravis.* Two third of MG patients show thymic hyperplasia.

THYMIC TUMORS:

- **BENIGN THYMOMA**: Benign thymomas are more common than malignant thymomas.
    - CLINICAL: *Thymoma is associated with Myasthenia Gravis.* 10% of MG patients have a benign thymoma.
    - PATHOLOGY: Cystic degeneration occurs, and the entire thymus may undergo cystic degeneration.
- **MALIGNANT THYMOMA**: About one fourth of thymomas have malignant features.
    - **TYPE-I MALIGNANT THYMOMA**: Identical to benign thymoma histologically, except it penetrates its capsule, and it may metastasize to regional nodes, lung, liver, bone.

    - **TYPE-II MALIGNANT THYMOMA (THYMIC CARCINOMA)**: Very uncommon malignant tumor with variable appearance. Histologically, it resembles one or another carcinomas (such as squamous cell), and it is unique in that it contains malignant epithelial cells.
- OTHER TUMORS OF THE THYMUS:
    - CARCINOID TUMOR:
    - SMALL CELL CARCINOMA:
    - GERM CELL TUMORS:

**PINEAL GLAND**: Epithalamus, which secretes **melatonin**, which helps us sleep.

- **Germ Cell Tumors** are the most frequent tumors to be found in the pineal gland.

---

# THE SKIN

NORMAL STRUCTURE and FUNCTION:

- LAYERS OF EPIDERMIS:
  - **Stratus Basale:** Contains *Stem Cells*. Some minimal cell division occurs in this layer.
  - **Stratum Spinosum:** This is the main proliferative layer. Some synthesis begins in this level too.
    - Membrane-Coating Granules (MCG) begin formation in this layer, near the top.
  - **Stratum Granulosum:** This is the mature *synthetic layer*, where **keratinocytes** are synthesizing the granular components (Keratin, MCG) of skin.
  - **(Stratum Lucidum):** *Only thick skin*, a thin layer of flat cells marking the uppermost border of the Stratum Granulosum. They aren't apparent in thin skin.
  - **Stratum Corneum:** 15-20 layers of dehydrated, non-nucleated keratinocytes, packed with tonofilaments containing filaggrin.
- EPIDERMAL MIGRANT CELLS:
  - MELANOCYTES:
  - LANGERHANS CELLS:
  - MERKEL CELLS:
- DERMAL-EPIDERMAL BASEMENT MEMBRANE ZONE:
  - LAMINA LUCIDA
  - LAMINA DENSA
- THE DERMIS
- HAIR FOLLICLES

DERMATOLOGY VOCABULARY: Definitions adapted from Steadman's Dictionary

- Types of Lesions:
  - **Macule**: A small, discolored patch or spot on the skin, neither elevated above nor depressed below the skin's surface.
  - **Papule**: A small, circumscribed, solid elevation on the skin, less than 0.5 cm.
  - **Plaque**: Slightly larger circumscribed elevation, greater than 0.5 cm.
  - **Vesicle**: A small (less than 0.5 cm) circumscribed elevation of the skin containing fluid.
  - **Bulla**: A large blister appearing as a circumscribed area of separation of the epidermis from the subepidermal structure (subepidermal bulla) or as a circumscribed area of separation of epidermal cells (intraepidermal bulla) caused by the presence of serum, or occasionally by an injected substance.
  - **Pustule**: A small circumscribed elevation of the skin, containing purulent material.
  - **Eczema**: Generic term for inflammatory conditions of the skin, particularly with vesiculation in the acute stage, typically erythematous, edematous, papular, and crusting. Sometimes referred to colloquially as tetter, dry tetter, scaly tetter.
    - Followed often by lichenification and scaling and occasionally by duskiness of the erythema and, infrequently, hyperpigmentation
    - Often accompanied by sensations of itching and burning
    - The vesicles form by intraepidermal spongiosis.
  - **Nevus:** It literally means a hamartoma. In common use, a benign melanocytic neoplasm of the skin, or mole.
- Dermatological Structures:
  - **Keratinocyte**: A keratin-secreting stratified squamous epithelial cell.
  - **Panniculus:** The superficial fascia which contains an abundance of fat deposit in its areolar substance.
  - **Rete Ridges:** Downward thickening of the epidermis between the dermal papillae; peg is a misnomer because the dermal papillae are cylindrical but the epidermal thickening between papillae is not.
- Dermatopathology:
  - **Acanthosis**: An increase in the thickness of the stratum spinosum of the epidermis.
  - **Acantholysis**: Separation of individual epidermal keratinocytes from their neighbor, as in conditions such as Pemphigus Vulgaris and Darier's disease.
  - **Parakeratosis**: Retention of nuclei in the cells of the stratum corneum of the epidermis, observed in many scaling dermatoses such as psoriasis and subacute or chronic dermatitis.
  - **Hyperkeratosis**: Thickening of the horny layer of the epidermis or mucous membrane.

SELECTED INFECTIONS with CUTANEOUS MANIFESTATIONS:

- BACTERIAL INFECTIONS:
  - **IMPETIGO**: *Staphylococcus Aureus.* Weeping, oozing lesions; red patches developing into pustules.
  - **SCALDED-SKIN SYNDROME**: *Staphylococcus Aureus.* Bullous lesions leading to desquamation in infants.
    - It is a result of the toxin -- not the bugs themselves. No bugs are found in the lesion.
    - It will heal without scarring, if treated carefully and not spread.
- **TINEA (RINGWORM):** Fungal infection caused by the dermatophytes, *Epidermophyton*, *Microsporum*, and *Trichophyton*.
  - PATHOLOGY: The fungi infect the **stratum corneum** layer of the epidermis. They don't go any deeper.
  - SPECIFIC INFECTIONS:
    - TINEA CRURIS: Jock itch does *not* occur over mucous membranes, hence the scrotum is not involved.
    - TINEA CAPITIS: Head
    - TINEA CORPORIS: Trunk
    - TINEA PEDIS: Feet
- VIRAL INFECTIONS:
  - **HERPES SIMPLEX**:
    - **Group Lesions:** Characteristic lesion is groups of vesicles, that may become confluent, but that heal without scarring.
  - VARICELLA-ZOSTER (CHICKEN-POX): Herpetic lesions over dermatomal distribution.
  - HUMAN PAPILLOMAVIRUS (HPV): Causes benign keratinocytic neoplasms.
    - **VERRUCA VULGARIS**: Common warts, HPV-2,4. Most frequent on dorsum of hands or on face.
    - **PLANTAR WARTS**: HPV-1, frequently painful and difficult to get rid of.
    - **VERRUCA PLANA**: HPV-3. Small flat papules on the face.
    - **CONDYLOMA ACUMINATUM**: Venereal warts
      - HPV-1,6 are the most common causes.
      - HPV-16,18 will lead to squamous carcinoma of cervix.
    - BOWENOID PAPULOSIS
    - EPIDERMODYSPLASIA VERRUCIFORMIS
  - ERYTHEMA INFECTIOSUM (FIFTH DISEASE): Caused by Human Parvovirus B19.
  - MOLLUSCUM CONTAGIOSUM: Caused by the Molluscum Contagiosum poxvirus.
- ARTHROPOD INFESTATIONS:
  - **SCABIES**: very itchy lesions, typically between fingers.
    - PATHOLOGY: Little red papules.
  - PEDICULOSIS:
  - ARTHROPOD BITES:

EPIDERMAL DISEASES of EXCESSIVE CORNIFICATION:

- ICHTHYOSIS:
- DARIER DISEASE (KERATOSIS FOLLICULARIS)

**PSORIASIS**: Persistent, abnormal epidermal squamous-cell hyperplasia.

- PATHOGENESIS:
  - GENETIC: Psoriasis has a genetic component. The more severe the disease, the more likely it is to be familial.
    - HLA-B13, B17, Bw6 are found commonly and indicate worse prognosis.
  - ENVIRONMENT: Psoriasis is like a hypersensitive response to normal injury (physical, sunlight, chemical), except that it doesn't go away after the injury.
    - Inflammatory neutrophils probably release Epidermal Growth Factor (EGF), which stimulates excessive growth.
  - CELL-PROLIFERATION: Abnormal or unregulated cell-proliferation occurs. There is a decrease in the number of beta-receptors, and decreased levels of cAMP, but the mechanism is unclear.
  - MICROCIRCULATORY CHANGES: Capillary loops in the dermal papillae become venular. Neutrophils are thus attracted to the (venous) vessels, and they accumulate in places where they are not normally found.
    - You see neutrophilic infiltrates in the epidermal layers; normally they remain in dermis.
- PATHOLOGY:
  - **Hypergranulosis:** Increased thickness of the granular layer of the epidermis.

    - **Parakeratosis:** Cell-nuclei of keratinocytes grow all the way up into the cornified layer, where they are not supposed to be.
    - **Elongation of Rete Ridges**: Excessive proliferation of the basal layer cause it to get thrown into folds. Looks like a "picket fence."
    - **Munro Microabscesses:** Dense collections of neutrophils in the stratum corneum.
- SYMPTOMS: Large, erythematous, scaly plaques, commonly on dorsal extensor surfaces.
    - Severity of disease varies.
    - **Psoriatic Arthritis** (Rheumatoid negative) is often also found.
- TREATMENTS: Anthralin, topical corticosteroids, systemic methotrexate in severe cases.

DYSHESIVE DISORDERS and RELATED DISEASES:

- **PEMPHIGUS VULGARIS**:
    - PATHOGENESIS: Type-II (antibody-dependent cellular cytotoxicity) hypersensitivity response against squamous epithelial cells.
    - PATHOLOGY:
        - **Desmosomal Dissolution:** Antibodies to keratinocytes causes dissolution of desmosomes ------> epidermis falls apart (acantholysis)
        - **Acantholysis**: Separation of the stratum spinosum and outer epidermis from the underlying basal epidermis.
        - **Acantholytic Cells:** Rounded, detached keratinocytes found in the fluid of the bullae. In contrast to erythema multiforme, these are vital epithelial cells.
    - SYMPTOMS / CLINICAL:
        - **Bullae**: Progressive flaccid bullae resembling a second-degree burn, which can be fatal.
        - **Nikolsky's Sign:** Sliding thumb across the skin separates the outer layer from the underlying basal cells.
    - TREATMENT: Corticosteroids.
- **EPIDERMOLYSIS BULLOSA**: Hereditary group of disorders, in which blisters are formed in response to minor trauma. Underlying defect involves easy separation between the dermis and epidermis.
    - EPIDERMOLYTIC EPIDERMOLYSIS BULLOSA (EB-SIMPLEX)
    - JUNCTIONAL EPIDERMOLYSIS BULLOSA
    - DERMOLYTIC EPIDERMOLYSIS BULLOSA
- **BULLOUS PEMPHIGOID**: Autoimmune disease similar to pemphigus, but acantholysis is absent.
    - PATHOGENESIS: Circulating IgG antibodies bind to the **BP antigen** in the lamina lucida. The antigen is on basal cells that are attached to hemidesmosomes, and binding causes separation of the hemidesmosomes.
    - PATHOLOGY: Complement is activated as a result of Ab-binding.
        - **Dermal-epidermal separation** in the lamina lucida occurs as a result. This differs from acantholysis (separation within the epidermis), as seen in Pemphigus.
- DERMATITIS HERPETIFORMS: Intensely pruritic urticaria-like plaques over the extensor surfaces of the body.
    - PATHOGENESIS: Related to **gluten-sensitivity** in patients with HLA-B8 and HLA-DRw3 haplotypes. The disease can be controlled with gluten-free diet.

DISEASES of BASAL KERATINOCYTIC INJURY:

- **ERYTHEMA MULTIFORME**: Hypersensitivity reaction to drugs or infectious agents.
    - PATHOGENESIS: Evidence of both Type-III and Type-IV hypersensitivity reactions.
        - Drugs: Sulfonamides, other drugs.
        - Infectious agents: Herpes Simplex, *Mycoplasma*.
    - PATHOLOGY:
        - Sparse lymphocytic infiltrate into epidermis.
        - Necrosis and pyknosis of individual epidermal cells.
    - SYMPTOMS: Characteristically, both skin and mucous membranes are involved.
        - Peak incidence 20's-30's.
        - **Target Lesions**: Maculopapular rash with characteristic target-lesions on gross-inspection. The target-lesions may coalesce to form large areas of necrosis.
    - **STEVENS-JOHNSON SYNDROME:** Dreaded complication, severe form of Erythema Multiforme.
        - TRIAD:
            - Erythema Multiforme
            - Mucous membrane inflammation (conjunctivitis, stomatitis, urethritis, bronchitis)

        - Systemic involvement: fever, headache, malaise
    - May also see (rare): glomerulonephritis, myocarditis, arthritis, encephalitis.
- **LUPUS ERYTHEMATOSUS (SLE)**:
    - PATHOGENESIS: Involves both Type-III and Type-IV autoimmune reactions.
        - Type-III: Deposition of anti-dsDNA immune complexes at the dermal-epidermal junction.
        - Type-IV: T-Cell reactivity to basal cells.
    - PATHOLOGY / SYMPTOMS: Inflammatory response ------> erythematous plaques ------> atrophy and scarring of epidermis.
        - Lesions start out hot, edematous, and swollen and end up scarred, shrunken, and contracted.
        - Plaques are typically **piecemeal**, rather than confluent as we see in Erythema Multiforme.
    - SUBTYPES:
        - **CHRONIC CUTANEOUS LUPUS ERYTHEMATOSUS (DISCOID LUPUS)**: A non-systemic disease only of the skin.
            - PATHOLOGY: **Discoid papules** with hyperkeratotic margins and a depigmented center.
            - SYMPTOMS: Lesions usually limited to face, scalp, and ears.
        - **SUBACUTE CUTANEOUS LUPUS ERYTHEMATOSUS**: May see musculoskeletal involvement, but further systemic involvement is rare.
            - SYMPTOMS: Lesions occur in classic photosensitive areas: (1) malar rash, and (2) V-neck area of upper chest.
        - **ACUTE CUTANEOUS LUPUS ERYTHEMATOSUS**: Full blown disease with systemic involvement.
- LICHEN PLANUS: Chronic eruption of flat-topped, shiny, violaceous papules on flexor surfaces, male genitalia, and buccal mucosa of unknown cause.
    - PATHOLOGY: It may form linear groups of lesions.
        - Microscopically characterized by a bead-like subepidermal lymphocytic infiltrate.
    - CLINICAL: Spontaneous resolution is common after months to years.

INFLAMMATORY DISEASES of VASCULAR BEDS: The most common diseases of the skin occur by allergic reactions.

- **URTICARIA and ANGIOEDEMA**:
    - **URTICARIA (HIVES)**:
        - PATHOGENESIS: **Type-I** immediate-type, IgE-mediated hypersensitivity against a variety of antigens.
            - IgE sticks to Mast Cells and basophils.
            - Subsequent interaction with antigen causes degranulation ------> local and systemic inflammatory responses.
        - PATHOLOGY: Raised, pale, pruritic papules and plaques that appear and disappear within a few hours.
            - *The epidermis remains untouched* in a pure urticarial reaction. The reaction is a vasodilation and inflammatory infiltrate (lymphocytes, eosinophils) of the underlying dermis.
    - **ANGIOEDEMA**: Edema involves the deeper dermis and subcutaneous tissues.
        - **DERMATOGRAPHISM**: Linear-hives with a rick-pink flare, in which you can write on the lesion and the impression sticks.
- **LEUKOCYTOCLASTIC VASCULITIS**: Also known as **Cutaneous Necrotizing Venulitis**, **Hypersensitivity Angiitis**
    - PATHOGENESIS: Type-III immune-complex reaction results in elaboration of complement ------> endothelial damage and fibrin deposition.
        - May be associated with HBV.
        - May occur in conjunction with SLE, RA, ulcerative colitis.
    - PATHOLOGY / CLINICAL: Small-vessel vasculitis showing fibrinoid necrosis of small vessels.
        - **Petechial hemorrhages**.
- **ALLERGIC CONTACT DERMATITIS (POISON IVY)**:
    - PATHOGENESIS: Type-IV delayed, cell-mediated hypersensitivity reaction against poison ivy in the epidermis. Antigens are taken up Langerhans cells and presented to T-Cells.
    - PATHOLOGY:
        - **Eczematous dermatitis**, inflammatory reaction with vesiculation.
        - Epidermal edema is seen, with T-Cell infiltrates.

DERMAL CONNECTIVE TISSUE DISEASES:

- SCLERODERMA (PROGRESSIVE SYSTEMIC SCLEROSIS):
- EOSINOPHILIA-MYALGIA SYNDROME:

- PSEUDOXANTHOMA ELASTICUM:
- SARCOIDOSIS:

INFLAMMATORY DISORDERS of PANNICULUS:

- **ERYTHEMA NODOSUM**: Septal Panniculitis Without Vasculitis.
    - SYMPTOMS: Self-limited, tender nodules over the extensor surfaces of the lower extremities.
    - PATHOLOGY: Inflammation of subcutaneous tissues around the cutaneous septa.
    - PATHOGENESIS: Triggered by a variety of drugs and bugs, and associated with various diseases.
- WEBER-CHRISTIAN DISEASE: Lobular Panniculitis Without Vasculitis.
- ERYTHEMA INDURATUM: Lobular Panniculitis With Vasculitis.

ACNE VULGARIS:

**MELANOCYTIC NEOPLASIA**:

- BENIGN / PRE-MALIGNANT LESIONS:
    - **MELANOCYTIC NEVUS (MOLE)**: Benign, melanocytic neoplasm with symmetric, well-circumscribed margins, with diameter **less than 6 mm**
        - **Lentigo**: A freckle. Melanocytes are limited to the basal-cell layer.
        - **Junctional Nevus**: Melanocytes cluster at the tips of the rete ridges.
        - **Compound Nevus**: Nests of melanocytes seen in the epidermis and dermis.
        - **Dermal Nevus**: Intraepidermal melanocytic growth ceases, and melanocytes are confined entirely to the dermis.
        - **Skin Tag**: Dermal component is terminally differentiated into neuro-mesenchyme, and all that is left is a skin tag.
    - **ATYPICAL NEVUS**: Nevus with abnormal growth patterns. Cytologic atypia are not found.
    - **DYSPLASTIC NEVUS**: Malignant nevus with abnormal growth pattern and cytologic atypia.
- TUMOR PROGRESSION:
    - **RADIAL GROWTH-PHASE MELANOMA**: Intermediate lesion. A dysplastic nevus, in the dermal epidermal junction, that spreads outward. At this point the lesion is curable by wide excision.
    - **VERTICAL GROWTH-PHASE MELANOMA**: By definition, *a melanoma that has extended into the lower half of the reticular dermis.* High-grade lesion with very high chance of metastasis.
        - Cells may appear white or contain no pigment.
        - Dominant site of growth is shifted from the epidermis to the dermis.
    - **METASTATIC MELANOMA**: Both lymphatic and hematogenous. Every organ may be involved, and widespread, multiple metastases are common.
- TYPES of MELANOMA:
    - **NODULAR MALIGNANT MELANOMA**: Very rare, deadly tumor that *skips the radial growth phases* and arises as an already-anchored malignant tumor in the vertical growth phase.
    - **LENTIGO MALIGNANT MELANOMA**: Also called a **senile freckle**. Large, pigmented macule that occurs on sun-damaged skin. Invasion is not as prominent as in superficial spreading melanomas.
    - **ACRAL LENTIGINOUS MELANOMA**: Most common form of melanoma in dark-skinned persons.
        - SYMPTOMS: Arises in palms, soles, or sub-uncal region. Often presents as a pigmented streak on the nail-bed.
            - They are often picked up late and can metastasize. Hence somewhat worse prognosis.
- CLINICAL:
    - NUMBER: *The greatest single predictor of whether a nevus will be malignant is the* ***number of nevi*** *the patient has.* Patients with over 50 nevi on the body tend to develop a melanoma.
    - **CLARKE'S STAGING**: Growth-Phase of Tumor
        - **Stage I**: Melanoma *in situ*, limited to epidermis.
        - **Stage II**: Radial-Growth-Phase melanoma that has invaded the papillary dermis.
        - **Stage III**: Vertical-Growth-Phase melanoma that has invaded the reticular dermis.
        - **Stage IV**: Vertical-Growth-Phase melanoma that has invaded the collagen bundles beneath the reticular dermis.
        - **Stage V**: Subcutaneous invasion, metastases.
    - **ABCD CRITERIA**: Things that indicate malignancy.
        - **Asymmetry** of lesion

        - **B**orders are irregular
        - **C**olor variation. Can see black, blue, red in the lesion. White can be seen too and is an ominous sign, as it generally means the lesion has already entered vertical growth phase.
        - **D**iameter is larger than 6 mm.
    - PROGNOSTIC FEATURES:
        - **Mitotic Rate:** Aside from the growth-phase, it is the most powerful indicator of prognosis. Patients with no mitosis have a greater chance for survival.
        - **Lymphocytic Response:** An infiltrating, lymphocytic response to the tumor is a good sign.
    - TREATMENT: Melanomas are resistant to chemotherapy and radiation therapy. Once it has metastasized, the prognosis is dismal.
- OTHER BENIGN LESIONS:
    - CONGENITAL MELANOCYTIC NEVUS:
    - EPITHELIOID-CELL NEVUS (SPITZ TUMOR):

**BENIGN KERATOSES**: Precursor lesions to basal cell and squamous cell carcinomas.

- **SEBORRHEIC KERATOSIS**: *The benign counterpart to Basal Cell Carcinoma.*
    - CLINICAL: Benign, stuck on, sharply demarcated papule or plaque. Lesion looks like it was **stuck on** the skin and cut out with a cookie cutter.
    - PATHOLOGY: Sheets of squamous cells that resemble basal cells (basal keratinocytes).
        - **Horn Cysts:** Microscopic structures, indicating a benign lesion.
        - The cells are thought to be derived from hair-follicle germ-cells.
        - The cells resemble Basal Cell Carcinoma, except they do not grow inward (invade), and never metastasize.
- **ACTINIC KERATOSIS**: *The benign counterpart to Squamous Cell Carcinoma*.
    - CLINICAL: Circumscribed, erythematous, scaly patch or plaque, usually on the back of the hand or the face.
        - **Sand-paper lesions**: They have characteristic sand-paper quality when touched.
    - PATHOLOGY: Abnormal squamous cells begin at the basal layer. As the lesion progresses, atypia progress from the basal layer to the surface. When the abnormal cells stretch from the basal layer to the surface, then you have a carcinoma *in situ*.
        - **Parakeratosis**: Keratinization in the lesion is not normal. The keratin layer does not slough off normally and thus accumulates, similar to psoriasis. Thus a plaque forms.
    - TREATMENT: Actinic Keratosis can be reversed by withdrawing UV radiation and sometimes applying cytotoxic treatment. But, it often progresses to squamous cell carcinoma.
- KERATOACANTHOMA

**BASAL CELL CARCINOMA**: *Basal cell carcinoma is the single most common malignant neoplasm in human beings.*

- PATHOGENESIS: Caused by UV-light damage. Very rare or unheard of in black skin, but very common in white skin.
- CLINICAL:
    - LOCATION: Basal cell tumors very commonly occur in the head and neck region. Less often, they occur on upper body, but almost never on lower body.
    - **Pearly white papules** are typical lesion, 2-3 mm in diameter. The lesions almost look translucent on the naked skin.
        - The tumors can erode (superficial, central depression) or ulcerate (deeper hole in center).
    - INVASIVE: In the gray-zone between benign and malignant. They almost never metastasize, but they can be very invasive and destructive, so they're called malignant.
        - They can grow downward, right through the dermis, then muscle, and then bone.
- PATHOLOGY: Multiple nests and elongated fingers of small, very basophilic epithelial cells.
    - **Morphea-like Basal Cell Carcinoma**: A particularly nasty variant. Pale, tough, scar-like tumor.
        - Tiny nests of basal cells in a very fibrotic stroma.
- TREATMENT: Electrodesiccation and curettage.

**SQUAMOUS CELL CARCINOMA**:

- PATHOGENESIS: UV-light induced chromosomal damage. Very rare in black skin.

- **Squamous Cell Carcinoma *in situ***: Essentially, an actinic keratosis that spans the entire thickness of the epidermis, but does not invade the dermis. There is no clear cut line you can draw between actinic keratosis and squamous cell carcinoma *in situ*.
- PATHOLOGY: Raised, hyperkeratotic lesions that may ulcerate if large. The squamous cells **regress** in maturity. In an advanced SCC, 99% of the squamous cells, throughout the thickness of the skin, show no maturity.
- SYMPTOMS: Tend to occur on backs of hands or on the face, lips, or ears.

SKIN-APPENDAGE TUMORS:

- CYLINDROMA
- SYRINGOMA
- ECCRINE POROMA
- TRICHOEPITHELIOMA

FIBROHISTIOCYTIC NEOPLASMS:

- DERMATOFIBROMA:
- ATYPICAL FIBROXANTHOMA:

KAPOSI SARCOMA:

MYCOSIS FUNGOIDES (PRIMARY CUTANEOUS T-CELL LYMPHOMA):

---

# THE EYE

NORMAL STRUCTURE and FUNCTION:

EYELIDS and ORBIT:

- BLEPHARITIS:
- CHALAZION:
- XANTHELASMA:

EXOPHTHALMOS:

CONJUNCTIVA: Lined by stratified columnar epithelium.

- HYPEREMIA
- HEMORRHAGE:
- CONJUNCTIVITIS:
- INFECTIONS:
    - **TRACHOMA**: ***Chlamydia Trachomatis*** **Types A, B, and C**.
        - EPIDEMIOLOGY: It is the *leading cause of blindness worldwide.* Prevalent in Asia, Middle East, parts of Africa.
        - PATHOLOGY: Slow, indolent infection of conjunctiva and cornea.
            - Binocular involvement.
            - Primarily lymphocytic infiltrates, involving especially upper conjunctiva.
            - Inflammation leads to scar formation ------> **corneal opacities**.
            - Histology: **chlamydial inclusions** will be visible in the cytoplasm of conjunctival epithelium.
    - OTHER CHLAMYDIAL INFECTIONS
        - **Inclusion Blennorrhea:** Newborn infected through the birth canal. Purulent conjunctivitis caused by *Chlamydia Trachomatis* Types D-K.
        - **Inclusion Conjunctivitis**: Chronic follicular conjunctivitis in adults and older children.
    - OPHTHALMIA NEONATORIUM: *N. Gonorrhea* or *C. Trachomatis* infection of the newborn. Silver nitrate drops given prophylactically at birth.
- DRY EYE SYNDROME:
- PINGUECULA and PTERYGIUM:
    - PINGUECULA: Conjunctival lump, located nasal to the corneoscleral limbus.
    - PTERYGIUM: Triangular fold of vascularized conjunctiva. It grows horizontally onto the cornea, forming the shape of an insect wing.

CORNEA:

- INJURY: Corneal laceration. Since the cornea is avascular and does not heal, the only cure is a **corneal transplant**.
- **HERPES SIMPLEX KERATITIS**: Inflammation of cornea, primarily **HSV-1** but also HSV-2. *HSV is the most common cause of corneal ulcers in the U.S.*
    - SYMPTOMS: Usually an asymptomatic plaque that heals without ulceration, but ulcerations can occur.
        - **Superficial Punctate Keratopathy:** Multiple miniature corneal ulcers forming linear, branching fissures. The ulcers heal by scar formation, and corneal opacities result.
            - **Fluorescein stain** illuminates the ulcers.
    - PATHOLOGY:
        - HSV inclusion bodies are visible microscopically.
- ONCHOCERCIASIS: *Onchocerca Volvulus.* Parasite that is the cause of River Blindness. Microfilaria infiltrate many ocular tissues.
- ARCUS SENILIS: White ring of lipid deposition in the peripheral cornea, occurring with aging.
- BLAND KERATOPATHY: In hypercalcemia, calcium deposits across the central portion of the cornea.
- CORNEAL DYSTROPHIES: Hereditary, non-inflammatory disorders of the cornea.
    - EPITHELIAL DYSTROPHIES

- STROMAL DYSTROPHIES
- ENDOTHELIAL DYSTROPHIES

LENS:

- **CATARACTS**: Opacities of the lens.
  - **Senile Cataracts:** With age, clefts form between adjacent lens fibers, and material accumulates between the clefts.
    - The opacities start at the periphery of the lens and work their way inward.
- **PRESBYOPIA**: Age-associated loss of the capacity for accommodation for near vision.
  - PATHOGENESIS: Lens fibers lose their elasticity. They persist indefinitely, with new lens forming on the outside of the old lens fibers, causing the lens to enlarge.

UVEA: The choroid, ciliary body, and iris.

- NORMAL FUNCTION: The uvea provides nutritive support for the retina. It is heavily pigmented, allowing it to absorb light that passes through the retina.
- **UVEITIS**:
  - PATHOGENESIS:
    - AIDS: Disseminated fungal infection of the eye.
  - SYMPTOMS: Red eye, photophobia, blurred vision, ciliary flush, constricted pupils (miosis).
  - PATHOLOGY:
    - **Keratitic Precipitates:** Leukocytes collected on the posterior surface of the cornea.
    - Severe inflammation will disrupt the blood supply to the retina ------> retinal ischemia.
  - COMPLICATIONS:
    - **Posterior Synechiae**: Adhesions developing between the iris and the lens.
    - **Peripheral Anterior Synechiae:** Adhesions between the peripheral iris and anterior chamber angle, which can lead to **secondary narrow-angle glaucoma**.
- **SYMPATHETIC OPHTHALMITIS**: *Bilateral* granulomatous uveitis secondary to an eye injury.
  - PATHOGENESIS: Believed to be an autoimmune reaction in both eyes, after sensitization to uveal antigens in either eye.
  - CLINICAL: Latency period of 4-6 weeks.
    - **Sympathetic Eye:** The eye that was not injured. It also gets inflamed at the same time as or shortly after the originally injured (Exciting) eye.
  - PATHOLOGY:
    - **Dalen-Fuchs Nodules**: Nodules containing reactive RPE, epithelioid cells, macrophages. They appear between Bruch's membrane and the RPE.
- SARCOIDOSIS:

RETINA:

- HEMORRHAGE:
- OCCLUSIVE VASCULAR DISEASE:
  - **CENTRAL RETINAL ARTERY OCCLUSION**: Leads to retinal ischemia, which results in blindness, if the problem isn't corrected very quickly.
    - **Cherry Red Spot:** Macula remains red while the rest of the retina becomes ischemic. The macula retains blood supply because it gets blood from the choroid underneath.
    - **Amaurosis Fugax:** Unilateral blurred vision occurring with pinpoint retinal emboli.
  - **CENTRAL RETINAL VEIN OCCLUSION**:
    - SYMPTOMS: Flame-shaped hemorrhages and edema. Vision may recover surprisingly well.
      - Closed-angle glaucoma is a late sequel to venous occlusion.
- **HYPERTENSIVE RETINOPATHY**:
  - PATHOLOGY / CLINICAL: Arteriolar narrowing and focal spasm.
    - **Waxy Spots**: Due to protein and lipid transudates. In HTN they have a "soft" appearance on funduscope.
    - **Cotton Wool Spots:** Edematous axonal fibers, due to ischemic injury to nerve fibers.
    - **Arteriovenous (AV)-Nicking**: Due to sclerosis of the venous walls -- not due to compression by the overlying arteries.
    - **Flame-shaped hemorrhages**: Hemorrhages in the retinal nerve fiber layer.

        - **Copper Wiring:** Arteriolar narrowing can decrease visibility of the blood column, making the vessel appear orange rather than red, so-called "copper wiring."
    - STAGES of HYPERTENSIVE RETINOPATHY:
        - **Stage I**: Mild narrowing
        - **Stage II**: Focal spasm
        - **Stage III**: Hemorrhages and exudates
        - **Stage IV**: **Optic disc edema** (due to ischemia) and hemorrhage, which can lead to retinal detachment.
    - **Malignant Hypertension**: In the eye, characterized by necrotizing arteriolitis, with fibrinoid necrosis and thrombosis of the retinal arterioles.
- **RETINAL DETACHMENT**: Opening up of the *potential space* between the retina and the underlying Retinal Pigment Epithelium. This deprives the retina of its only source of nutrient, and permanent blindness results.
    - **Rhegmatogenous Retinal Detachment:** Associated with retinal tear and with degenerative changes in vitreous.
    - **Tractional Retinal Detachment:** Retina is pulled toward the center of the eye, as a result of *adhesions* between the retina and vitreous.
        - CAUSES: Diabetic Retinopathy, Retinopathy of Prematurity, Intraocular Infections
    - **Exudative Retinal Detachment:** Accumulation of fluid between retina and RPE.
        - CAUSES: Choroiditis, Choroidal Hemangioma, Choroidal Melanoma.
        - TREATMENT: *Early* retinal detachment can be treated by punching holes in the retina and allowing the fluid to drain. Punctate scars will result, but overall vision will be saved.
- **RETINITIS PIGMENTOSA**:
    - PATHOGENESIS: Multiple genetic abnormalities. Accelerated destruction of photoreceptors by the Retinal Pigment Epithelium (RPE) leads to permanent loss of photoreceptors.
    - CLINICAL: Night-blindness and loss of peripheral visual fields.
    - PATHOLOGY: Loss of retinal photoreceptors (rods and cones), and pigment accumulation within the retina.
- **MACULAR DEGENERATION**: *The most common cause of reduced vision in the U.S.*
    - PATHOGENESIS: Age-related. The macula is not vascularized, and nutrients must diffuse through the choroid plexus to supply it. Any loss of diffusion in the choroid will lead to macular ischemia.
        - **Drusen:** Drusen is metabolic debris that builds up in the macula, underneath the photoreceptor cells. That leads to edema ------> ischemia ------> macular angiogenesis in response ------> partial retinal detachment (only at macula) and loss of macular vision.
- **CHERRY RED-SPOT of MACULA**: Characteristically seen with **Tay-Sachs Disease**, in which the cherry red spot is the only *normal* part of the retina. Ganglioside deposits in the ganglion-cells create a pallor around the outside of the red-spot, leaving the red-spot visible.
- RETINOPATHY of PREMATURITY (RETROLENTAL FIBROPLASIA): Bilateral iatrogenic retinopathy, resulting from hyper-oxygenation in premature infants who suffered from IRDS.

DIABETES:

- **DIABETIC RETINOPATHY**:
    - PATHOLOGY / PROGRESSION:
        - **BACKGROUND RETINOPATHY:** Asymptomatic damage to retina
            - Vascular basement membrane thickening
            - Degeneration of **pericytes** (cells that surrounds vessels) ------> capillary microaneurysms.
                - Microvascular obstruction ------> focal retinal infarcts.
            - **Waxy Exudates:** Capillary microaneurysms increase permeability, leading to waxy exudates. The exudates are yellow and lipid-laden, and have a "hard" appearance in funduscope.
        - **PROLIFERATIVE RETINOPATHY:**
            - **Neovascularization** occurs in response to retinal hypoxia.
                - **Hemorrhage** of newly formed, friable, vessels.
                - Gliosis forms around the neovascularization.
            - **Scar formation** ------> retina becomes anchored to the vitreous ------> scar contracts ------> **<u>retinal detachment</u>.**
    - TREATMENT: **Laser treatment**
- DIABETIC IRIDOPATHY: Leads to Glaucoma in Diabetes.
- DIABETIC CATARACTS: In IDDM, it results from an osmotic effect caused by the accumulation of sorbitol.

OPTIC NERVE:

- PAPILLEDEMA:
- OPTIC ATROPHY:

**GLAUCOMA**: Optic nerve atrophy, usually resulting from elevated intraocular pressure (IOP), secondary to obstruction of aqueous humor.

- PATHOGENESIS: **Aqueous humor obstruction** anywhere along the path of aqueous humor draining ------> increased intraocular pressure.
    - **Lamina Cribrosa:** The portion of the sclerae that the optic nerve fibers pass through. In intraocular hypertension, it bows backwards, impinging on the optic nerve fibers and ultimately destroying them. This results in **optic nerve atrophy**, the ultimate result of prolonged glaucoma.
- SUBTYPES:
    - CONGENITAL GLAUCOMA (BUPHTHALMOS): Aqueous obstruction caused by congenital anomaly.
        - **Buphthalmos:** Congenital enlarged eyes.
    - **PRIMARY OPEN-ANGLE GLAUCOMA**: The most common type of glaucoma in the United States.
        - PATHOGENESIS. Caused by aqueous humor obstruction.
            - Aqueous humor is able to reach the trabecular meshwork unimpeded. Anterior chamber angle of the eye remains normal.
            - IOP is usually increased, but not always.
            - **Diabetes** and myopia are both risk factors for open-angle glaucoma.
    - **PRIMARY CLOSED-ANGLE GLAUCOMA**: The iris is displaced anteriorly far enough that it impinges on the trabecular meshwork. The anterior chamber-angle becomes narrow. IOP is always increased.
        - PATHOGENESIS: **Chronic uveitis** can lead to closed angle Glaucoma, as well as idiopathic.
        - MECHANISM:
            - *Pupils Constricted:* The iris is relaxed enough that it doesn't obstruct the flow of aqueous humor.
            - ***Pupils Dilated:*** *The iris is contracted and aqueous humor flow is acutely obstructed, resulting in paroxysmal increased intraocular pressure.*
        - **ACUTE CLOSED ANGLE GLAUCOMA:** *If the pupils remain contracted for a prolonged period of time, this leads to an **acute emergency**. Hypotensive treatment must start immediately or else sight will be lost.*
            - Patient experiences severe pain.
    - **SECONDARY GLAUCOMA**: Secondary to inflammation, hemorrhage, adhesions.
    - **LOW-TENSION GLAUCOMA**: Glaucoma without increased intraocular pressure.
        - **Lamina Cribrosa Defect:** In some people, there is a primary defect in the lamina cribrosa such that it bulges under normal pressure ------> impinge on optic nerve fibers ------> optic atrophy without any increased IOP.
- PATHOLOGY:
    - **Optic Nerve Cupping** seen on funduscopic exam.
    - **Optic Nerve Atrophy** results from prolonged intraocular hypertension.
        - Increased IOP leads to bowing of the lamina cribrosa ------> impinges on optic nerve fibers ------> optic nerve atrophy
    - **Ganglion-cell layer degeneration:** Ganglion cells of the retina degenerate, impairing vision.
- CLINICAL:
    - *Peripheral vision is lost first, followed by central vision.* Patient therefore may not notice visual loss in early glaucoma.
    - In severe cases of glaucoma, you may see central retinal artery occlusion.

MYOPIA: Nearsightedness. The focal point of light occurs in front of the retina. Correct with diverging lens.

PHTHISIS BULBI: Non-specific, end-stage eye, characterized by atrophy of the eyeball.

NEOPLASMS:

- **UVEAL MELANOMA**: *The most common primary tumor of the eye.*
    - PATHOLOGY: The tumor arises from uveal melanocytes.
        - They tend to arise in the posterior part of the eye, behind the RPE. Hence they are not easily visible. As they grow they can cause retinal detachment.

- SYMPTOMS: They can cause hemorrhage, cataracts, glaucoma, retinal detachment, inflammation.
  - **Heterochromia:** Variegation in color of the eye, with involvement of the iris.
  - **Metastases** is hematogenous -- not lymphatic. *It often metastasizes to the liver*.
- TREATMENT: Enucleation of the eye.

- **RETINOBLASTOMA**: Tumor of retinal cells occurring in children.
  - PATHOGENESIS: Defects in the **Retinoblastoma (Rb) tumor suppressor gene** cause the tumor.
    - **Familial Retinoblastoma:** Binocular retinoblastoma, caused by a defect on chromosome 13. Only one more mutation is then required ("two-hit hypothesis") to cause the tumor in each eye.
    - **Sporadic Retinoblastoma:** More common, uniocular. Mutations in both Rb genes are required to cause a sporadic tumor to develop.
  - PATHOLOGY: It's a **little-blue-cell tumor**.
    - **Rosettes:** Blue cells form rosettes, as they do with other little-blue-cell tumors.
  - SYMPTOMS: Fatal if untreated. Survival is high with enucleation of eye.
    - **No red reflex** will be seen on fundoscopic exam. This can help in early detection.
    - Prognosis: The prognosis correlates with how far the tumor has traveled along the optic nerve. The further it has traversed along the optic nerve, the worse prognosis.
    - Metastasis: Exophytic tumors can metastasize to the brain: Retina ------> vitreous ------> trabecular meshwork ------> brain.

---

# BONE

BONE STRUCTURE and FUNCTION:

- TYPES of BONE:
  - **LAMELLAR BONE**: All normal bone in the adult skeleton.
    - General Properties:
      - Parallel arrangement of **Type-I Collagen** fibers.
      - Few osteocytes in the matrix.
      - Uniform osteocytes in lacunae parallel to the long axis of the bone.
    - Subtypes:
      - **Circumferential Bone**: Outer periosteal and inner endosteal portions of the cortex.
      - **Concentric Lamellar Bone**: Bone forming parts of the haversian system, with haversian canals in the center.
      - **Interstitial Lamellar Bone**: Bone not forming part of the haversian system, interspersed in-between the haversian canals.
      - **Trabecular Lamellar Bone**: Cancellous bone surrounding the medullary cavity.
  - **WOVEN BONE**: (1) The bone of the embryonic skeleton, and (2) Bone that forms in response to injury, to heal a fracture.
- TYPES of CARTILAGE
  - **Hyaline Cartilage:**
  - **Fibrocartilage:** Symphysis pubic, menisci, insertions of joint capsules.
  - **Elastic Cartilage:** Pinna of ear, epiglottis, arytenoid cartilages.

BONE GROWTH:

- ZONE of GROWTH:
  - RESERVE ZONE
  - PROLIFERATIVE ZONE: Most if not all chondrocyte division occurs here.
  - HYPERTROPHIC ZONE : Chondrocytes mature and release **matrix vesicles** into the longitudinal septal matrix.
  - CALCIFICATION ZONE: Mineralization, within matrix vesicles, begins to occur.
    - Most chondrocytes undergo apoptosis in this zone.
    - Capillaries invade from the metaphysis and resorb dead chondrocytes, leaving **transverse spicules**, on which ossification can occur.
  - OSSIFICATION ZONE
- **Mineralization (Matrix Vesicles)**: The primary seeds of calcification within the growth plate. They are aligned along the longitudinal septae of the cartilage matrix of the calcification zone in the growth plate.
  - **Phase 1**: Calcification begins as a hydroxyapatite crystal *inside* of the matrix vesicle. It later progresses to outside.
    - **Calcium-binding lipids** and **Alkaline Phosphatase** are both located in the matrix vesicle (on the membrane) and help raise local levels of calcium and phosphate (respectively) to facilitate mineralization.
    - As $Ca^{+2}$ and $PO_4^{-3}$ accumulates, their **ion product** gets large enough that they precipitate inside the vesicle.
  - **Phase 2**: Intravesicular matrix crystals get bigger and rigid. They penetrate the vesicle membrane and seed the outside. At that point, further crystallization can occur without the help of more matrix vesicles.
- **Osteoid**: Uncalcified, newly laid-down collagenous matrix. Osteoblasts lay down osteoid before it is calcified.
  - Decalcified osteoid stains **red** on special non-decalcified stains.
  - Osteoid also contains matrix vesicles.

**GROWTH DISORDERS**:

- **CRETINISM**: Bone abnormalities are related to a defect in bone maturation.
  - PATHOLOGY: The hypertrophied and proliferative zones are deficient.
  - SYMPTOMS:
    - Limbs disproportionately short in relation to trunk.
    - Unusually large head.
- **ACHONDROPLASIA**:

    - PATHOGENESIS: Failure of endochondral bone formation.
        - Mutation is in the **Fibroblast Growth Factor (FGF) Receptor**. Mechanism unknown.
        - Autosomal dominant mutation, but the large majority of cases are new mutations.
    - PATHOLOGY:
        - Primarily the long bones are affected.
    - SYMPTOMS: Short extremities with normal sized head, which appears large in comparison.
        - The cranium arises from membranous ossification (direct formation of bone) and does not depend on growth plates.
        - Spine is normal length.
- MORQUIO SYNDROME: Mucopolysaccharidosis Type-IV, deposition of mucopolysaccharides (keratan sulfate) in developing bones.
    - SYMPTOMS: Severe dwarfism, dental defects, mental retardation, corneal opacities, increased urinary excretion of keratan sulfate.
- **SCURVY**: Ascorbic Acid Deficiency, leading to deficient production of **hydroxyproline** and **hydroxylysine**, essential constituents of collagen.
    - PATHOGENESIS: Ascorbic acid is required for:
        - Hydroxylation of proline and lysine.
        - Glycosylation of hydroxyproline and hydroxylysine.
    - PATHOLOGY: All connective tissues are affected.
        - **Type-I Collagen** is the one primarily affected.
        - **Trümmerfeld:** "Field of Ruin," referring to the disorganized appearance of the metaphysis.
    - SYMPTOMS:
        - Poor wound-healing, poor bone growth.
        - Widespread capillary bleeding (petechiae): vascular walls are poorly formed.
- Asymmetric Cartilage Growth:
    - **SCOLIOSIS**: Lateral curvature of spine.
    - **KYPHOSIS**: Anterior curvature of spine.

MODELING ABNORMALITIES:

- **OSTEOPETROSIS (MARBLE BONE DISEASE)**: Rare disorder of abnormally dense bone with little or no marrow cavity.
    - PATHOGENESIS: Hypofunction of osteoclasts leads to short, block-like, radiodense bones.
        - Failure of osteoclasts in the metaphysis area forces extra bone (that is not resorbed) to grow downward into the medullar space, hence the medullary space is filled.
        - Bones are heavy but they still fracture easily.
    - PATHOLOGY:
        - **Erlenmeyer Flask Deformity:** Characteristic widening of the metaphysis and diaphysis of the bone, giving it the appearance of a flask.
        - "Bone within a bone." Failure of resorption gives that characteristic appearance.
        - **No Ruffled Border**: The normal ruffled border of osteoclastic activity is absent.
    - SYMPTOMS: There are severe (recessive) and milder (dominant) subtypes.
        - **Severe Osteopetrosis (Autosomal Recessive):** Patient often dies of sepsis secondary to leukopenia.
            - **Anemia:** Results because the marrow cavity is largely filled collagen so there isn't much room for growth.
                - In compensation, you will see extramedullary hematopoiesis in liver, spleen.
            - Hydrocephalus, infections, death in infancy.
        - **Mild Osteopetrosis (Autosomal Dominant):** Mild anemia or no symptoms at all.
    - TREATMENT: Bone marrow transplantation may give rise to new functional osteoclasts.
- PROGRESSIVE DIAPHYSEAL DYSPLASIA (CAMURATI-ENGELMANN DISEASE): Autosomal dominant disorder of children in which cylindrization of bones does not proceed appropriately. Patients experience pain, fatigue, gait abnormalities.
- **OSTEOGENESIS IMPERFECTA**: Defective synthesis of Type-I Collagen. Bones are thin and weak, and prone to thousands of fractures.
    - GENERAL SYMPTOMS:
        - Multiple fractures after birth.
        - Thin skin.
        - **Blue sclerae** due to poor collagen formation. It is blue because the underlying choroid is visible.

        - Hearing abnormalities leading to total deafness eventually, due to abnormal ossicles.
        - Kyphoscoliosis and flat feet.
        - **Dentinogenesis Imperfecta:** Loss of teeth, teeth abnormalities.
        - Type-II (cartilage) formation is normal. Patient may even have excessive cartilage growth, which can be mistaken for cancer.
    - SUBTYPES:
        - **OI Type I**: Severe disease and total deafness.
        - **OI Type II**: Autosomal recessive, lethal perinatal disease.
        - **OI Type III**: Progressive and less severe.
            - Kyphoscoliosis, teeth abnormalities as long-term complications.
            - Sclerae are blue at birth but may become white later.
        - **OI Type IV**: Mildest form, with dominant pattern of inheritance.
            - The sclerae are normal.
            - Number of fractures decreases over time. Patients can be vigorously treated with orthopedic devices.

**FRACTURE**:

- FRACTURE TYPES:
    - Transverse fracture
    - Compression fracture
    - Spiral fracture: Combined tension and compression results in angulation and displacement of the fracture ends.
- FRACTURE HEALING:
    - **INFLAMMATORY PHASE**: 1st Week Post-fracture
        - Hemorrhage of the fracture occurs, followed by clot formation. Standard inflammatory response ensues, to clean up the mess.
        - By first week, the clot is organized (invasion of clot by blood vessels), and fibrosis has started.
        - Early bone formation after a fracture is **woven bone** (disorganized, embryonic bone).
    - **REPARATIVE PHASE**: Lasting for months after the fracture. It proceeds from the periphery toward the center of the fracture.
        - **CALLUS:** Callus consists of granulation tissue containing cartilage. It is the initial bone formed after a fracture.
            - **External Callus** forms from the periosteum, growing inward toward the cortical fracture.
            - **Internal Callus** forms from the endosteum, growing outward toward the cortical fracture.
        - **Cutting Cones** are formed by osteoclasts from the haversian canals, going toward the fracture-site.
        - **Neovascularization** occurs throughout, providing vascularization to the forming callus.
    - **REMODELING PHASE**: Starting several weeks after the fracture, and may occur for years.
    - SPECIAL CASES:
        - **PRIMARY HEALING**: Bone fractures resulting from surgical cuts, with no surround tissue damage. No callus need be formed. Rather, cortical bone is formed directly and fills the gap; haversian system is maintained.
        - **NON-UNION**: A fracture site that does not heal. Causes:
            - The ends are too far apart or misaligned.
            - Poor blood supply, poor circulation.
            - Infection
- STRESS FRACTURES:

**AVASCULAR NECROSIS (ASEPTIC NECROSIS, OSTEONECROSIS)**: Death of bone or bone marrow in the absence of infection.

- PATHOGENESIS:
    - **Caisson's Disease** (the Bends) can cause nitrogen **gas-emboli** to lodge in bone.
    - **Steroids** over a long time can also cause bone infarcts, due to **fat emboli**
    - Trauma
    - Systemic diseases: Polycythemia, SLE, Gaucher Disease, Sickle Cell
    - Radiation
- PATHOLOGY: They tend to occur in the subarticular part of the epiphysis.
- ASSOCIATED DISEASES:

- **Legg-Calvé-Perthe Disease**: Idiopathic necrosis of the femoral head in children.
- **Köhler Disease**: Necrosis of the Navicular bone.
- **Osteochondritis Dessicans:** Subarticular infarcts in a variety of weight-bearing joints.

REACTIVE BONE FORMATION:

- **HETEROTROPHIC CALCIFICATION**:
  - **METASTATIC CALCIFICATION**: Calcification of soft tissues, secondary to hypercalcemia.
  - **DYSTROPHIC CALCIFICATION**: Calcification of soft tissues, secondary to injury or necrosis.
- **MYOSITIS OSSIFICANS**: Also known as **Fibrodysplasia Ossificans Progressiva**. Formation of reactive bone in muscle subsequent to an injury.
  - PATHOGENESIS: **Hereditary Form** of the disease can occur with no obvious stimulus, or in response to injury.
  - PATHOLOGY: It resembles a *bone tumor* and must be distinguished from it radiographically.
    - **Woven bone** is formed in granulation tissue.
      - Woven Bone is the same thing as embryonic bone, in which collagen fibers are disorganized and form interlacing networks.
    - **Zonation Effect:** *Myositis Ossificans is well-formed (radiodense) around the periphery of the lesion, and poorly formed in the center, whereas a bone tumor is the exact opposite.*
  - SYMPTOMS: "Petrified Man" appearance.
    - Patient usually presents with rock-hard mass in shoulder or neck.
    - **Hallux Valgus:** Enlarged, inwardly turning great toe is characteristic of the inherited disease.
    - Often die from being unable to chew ------> malnutrition. Or they develop respiratory infections.
- **HYPERTROPHIC OSTEOARTHROPATHY:** Clubbing of the fingers.
  - PATHOGENESIS: May be related to **hypoxia** of distal phalanges. Or may be a bone-growth factor that makes the distal phalanges overgrow.
    - **Thoracic Neoplasms** are characteristically associated with clubbing: small-cell carcinoma of lung, mesothelioma, thymoma.
    - **Chronic Hypoxia** or cyanosis (as in longstanding congenital heart defects) is also associated with clubbing.
  - PATHOLOGY: Terminal phalanges are markedly enlarged, and nails grow over them, giving them the clubbed appearance.

INFECTIONS:

- **OSTEOMYELITIS**:
  - PATHOGENESIS:
    - ROUTE: **Direct penetration** (wounds, fractures, surgery) is the most common cause. Hematogenous spread (septicemia) can also lead to osteomyelitis.
    - BUGS:
      - ***Staph. Aureus*** is most common culprit, particularly by direct penetration.
      - ***Strep. Epidermidis***
      - *E. Coli*
      - *Pseudomonas*
      - *Klebsiella*
      - ***Salmonella***: Associated with blood-borne osteomyelitis, in case of **Sickle Cell Disease** or IV drug users.
  - PATHOLOGY:
    - Progression of Infection:
      - Infection usually starts in metaphysis, due to the nature of the vasculature there.
      - CYCLE: Infection leads to pus in marrow cavity ------> increased medullary pressure ------> **pressure necrosis** of bone ------> that allows for more infection.
      - Infection ultimately spreads from metaphysis to periosteum, where it may infect the joint or form a draining sinus.
      - Most common sites of infection: the ends of long bones -- knee, ankle, hip.
    - **Sequestrum:** Bone-abscess. Bone spicules undergo necrosis and fall into the abscess.
    - **Involucrum:** Overgrowth of cortical bone just outside a bone-abscess, forming a sheath around the sequestrum.
    - **Cloaca:** Hole formed in the bone leading to the outside, formation of a draining sinus.

        - **Brodie Abscess:** Reactive bone formation, surrounding and containing the infection.
    - SYMPTOMS:
        - **Vertebral Osteomyelitis:** *Staph Aureus* can spread right through intervertebral disks and infect the entire spine. *E. Coli, Salmonella, Brucella* can also cause vertebral osteomyelitis.
            - Complications: vertebral collapse, spinal abscesses, compression fractures.
        - COMPLICATIONS:
            - Septicemia: septicemia may occur secondary to osteomyelitis.
            - Acute Bacterial Arthritis
            - Pathologic Fractures
            - Squamous Cell Carcinoma: Arising from the epithelial cells lining a draining sinus tract.
            - Fusion of the joint space.
            - Shortening of the limbs in children.
        - **CHRONIC OSTEOARTHRITIS**: Chronic infection of entire bone is incurable. Bone must be amputated, or patient treated for life.
    - TREATMENT: *Very difficult to treat* because the bone-abscesses are not readily accessible. Catch it early, and give IV antibiotics for about 6 weeks.
- **TUBERCULOSIS**:
    - **TUBERCULOUS SPONDYLITIS (POTT DISEASE)**: Tuberculosis of the spine.
        - PATHOLOGY: Affects vertebral bodies, but the lamina and spines are spared.
            - **Granulomas** form as always, leading to caseous necrosis of bone marrow, and cystic spaces in bone.
            - **Cold Abscess** occurs when the necrosis erupts into the spinal ligaments anteriorly. It is not associated with inflammation (hence cold)
            - **Psoas Abscess:** Abscess of psoas muscle.
        - SYMPTOMS:
            - **Kyphoscoliosis** results from collapse of vertebral bodies.
    - TUBERCULOUS ARTHRITIS
    - TUBERCULOUS OSTEOMYELITIS of LONG BONES
- SYPHILIS:

LANGERHANS CELL HISTIOCYTOSIS (HISTIOCYTOSIS X): All three diseases show punched out, lytic bone lesions, with virtually no reactive bone formation.

- EOSINOPHILIC GRANULOMA: One or two lesions are typical.
- HAND-SCHÜLLER-CHRISTIAN DISEASE: *Bony lesions are prominent* in calvarium, ribs, pelvis, scapula.
- LETTERER-SIWE DISEASE: Severe multisystemic disease, but bone lesions are not prominent.

**OSTEOPOROSIS**: Reduction in bone mass per unit volume.

- PATHOGENESIS: Primary osteoporosis cause is unknown, but some factors are known.
    - **PRIMARY OSTEOPOROSIS**: Osteoporosis of post-menopausal women. Cause unknown, but proposed factors:
        - Genetic Factors: Peak bone mass occurs during young adulthood, and the extent of peak bone mass is largely genetic.
        - **ESTROGEN**: Estrogen decline leads to accelerated bone loss.
            - *Estrogen normally inhibits the production of IL-1 and IL-6 by monocytes*, *which prevents them from differentiating into osteoclasts.*
            - Estrogen loss leads to a higher number of osteoclasts, and a possible imbalance between osteoblastic and osteoclastic activity.
        - Aging:
            - Decreased 1alpha-hydroxylase activity in kidney ------> decreased Vitamin-D
            - Decreased $Ca^{+2}$ absorption with age.
        - Calcium Intake tends to decrease in the diet of the elderly.
        - Exercise is decreased in the elderly.
        - Environmental factors: cigarette smoking in women.
    - **SECONDARY OSTEOPOROSIS**: Osteoporosis with a known cause.
        - Corticosteroid Administration.
        - Hyperthyroidism (*not* hyperparathyroidism, which causes Osteitis Cystica).
        - Hypogonadism ------> decreased estrogen *or* androgen production ------> osteoporosis.

        - Multiple Myeloma and other hematologic malignancies can cause decreased bone mass, irrespective of other bone abnormalities.
        - Malabsorption: Anything causing calcium malabsorption.
        - Alcoholism
        - **Weightlessness:** If the bones don't bear weight against gravity, then they atrophy.
- PATHOLOGY / LABS:
    - **Osteopenia =** Decreased bone mass in long bones and hip, seen on X-Ray.
    - **PTH, Calcium, Phosphate, and Alkaline Phosphate levels are all normal**. *This distinguishes Osteoporosis from Osteomalacia clinically.*
    - There is no deficiency of mineralization. This distinguishes it from osteomalacia.
- SYMPTOMS:
    - Compression fractures of spine.
    - Hip fractures.
    - **Dowager Hump:** Patient becomes shorter and may develop kyphosis.
- TREATMENT: **Estrogen Replacement Therapy (ERT)** must be initiated at the start of menopause. ERT does not increase bone density but only prevents bone loss.

**OSTEOMALACIA and RICKETS**: Primary failure of calcification of bone.

- VITAMIN-D METABOLISM:
    - *De Novo* synthesis starts in the skin. UV-light is required for synthesis.
    - Vitamin-D is absorbed from gut as **Vitamin-D3**
    - LIVER: **25-hydroxylase** converts Vitamin-D3 into **25-OH-Vit-D**
        - This form of Vitamin-D is already 10-100X more active than Vitamin-D3
    - KIDNEY: **1-hydroxylase** converts 25-OH-Vit-D into **1,25-$(OH)_2$-Vit-D**
        - This form of Vitamin-D is 1000X more active than Vitamin-D3
- PATHOGENESIS:
    - **Vitamin-D Deficiency** can result from:
        - Congenital defect (Rickets, see below)
        - Inadequate exposure to sunlight.
        - Deficient dietary intake.
        - **Defective intestinal absorption** (fat malabsorption) leads to calcium deficiency: cholestatic diseases, pancreatic insufficiency, celiac disease, Crohn disease. *This is the most common cause of Osteomalacia*.
    - **Hypophosphatemia** also leads to Osteomalacia / Rickets. Anything that causes low blood phosphate will do it.
        - **X-Linked Hypophosphatemia**: Impaired tubular resorption of phosphates, leading to Rickets.
        - **Fanconi Syndromes**: Renal tubular acidosis leading to urinary wastage of phosphate.
        - **Tumors (Oncogenic Osteomalacia)**: Hemangiomas, prostate cancer, neurofibromatosis.
        - Aluminum toxicity.
- **OSTEOMALACIA**: Vitamin-D Deficiency in adults.
    - PATHOLOGY: Looks virtually identical to osteoporosis on X-Ray. You tell the difference by labs.
        - **Pseudofractures of Milkman-Looser Syndrome**: Radiolucent transverse defects seen only in osteomalacia. They are painful.
        - **Osteoid Seams**: Due to defective mineralization, the border of osteoid (uncalcified bone) is thicker than usual.
    - LABS:
        - **Low calcium, low phosphate.** *This distinguishes it from Osteoporosis.*
        - **High alkaline phosphatase**. *This distinguishes it from Osteoporosis.*
    - SYMPTOMS: Clinical picture resembles osteoporosis. Arthritic pain, non-specific complaints, fractures.
- **RICKETS**:
    - SUBTYPES:
        - **Type-1 Vitamin-D Dependent Rickets:** Deficiency of renal **1-hydroxylase** activity ------> deficient Vitamin-D. Treat with administration of 1,25-$(OH)_2$-D
        - **Type-2 Vitamin-D Dependent Rickets**: Defect in Vit-D receptor ------> inherited **end-organ resistance** to Vitamin-D. 1,25-$(OH)_2$-D levels are very high but ineffective. It helps to give them repeated calcium.
        - **X-Linked Hypophosphatemia (Vit-D Resistant Rickets).** This is the most common cause of Rickets.
            - The disease is caused by impaired tubular resorption of Rickets.
            - Treat with Phosphate and 1,25-$(OH)_2$-D

- PATHOLOGY: Epiphyseal plate is 5-15X wider than normal, irregular, and lobulated. Hypertrophic zone and growth plate is enlarged and decalcified, due to failed calcification.
  - **Non-decalcified stain** will show lots of osteoid (red) and very little calcium (green).
    - Green = calcified bone.
    - Red = non-calcified osteoid.
  - **Rachitic Rosary:** Rows of beads at the costochondral junction, seen in kids with Rickets.
    - 'Thought to be due to inadequate resorption of unmineralized cartilage at the base of the growth plate. Fusiform enlargement of cartilage at costochondral joints results.
- LABS:
  - **Hypocalcemia (low $Ca^{+2}$)** is the primary defect, due to impaired intestinal $Ca^{+2}$ absorption.
  - **Hyperparathyroidism (high PTH)** occurs in compensation for hypocalcemia
  - **Hypophosphatemia (low $PO_4^{-3}$)**
- SYMPTOMS:
  - Kids are apathetic, irritable, short attention span.
  - **Pigeon Chest (Pectus Carinatum):** Wide curvature of ribs is characteristic of Rickets.
  - Potbelly, resulting from abdominal weakness.
  - Curved long bones in the extremities.

**PRIMARY HYPERPARATHYROIDISM**:

- **VON RECKLINGHAUSEN DISEASE (OSTEITIS CYSTICA)**:
  - PATHOLOGY: Resorptive lesions visible microscopically and radiographically.
    - Bone spicules around the outside of a cystic space, with osteoclasts on the inside of the space.
    - **Anchovy Paste:** Chronic disease shows bone cysts that look like anchovy paste (brown gelatinous material) grossly.
    - THREE STAGES of DISEASE:
      - **Dissecting Osteitis:** Osteoclasts bore their way into the cortex as **cutting cones**.
      - **Osteitis Fibrosa:** Marrow is replaced by hemosiderin-laden macrophages, lose fibrosis, and reactive woven bone.
      - **Osteitis Fibrosa Cystica:** Hemorrhage and cystic degeneration.
        - **Brown Tumor** is the characteristic appearance of this late stage disease.
  - LABS:
    - **High Alkaline Phosphatase**, indicative of high osteoblastic activity.
  - SYMPTOMS: "Stones, bones, moans, groans."
    - **Stones:** Kidney stones.
    - **Bones:** Cystic changes in bone.
    - **Moans:** Psychiatric depression associated with hypercalcemia.
    - **Groans:** GI disturbances associated with hypercalcemia.
- **RENAL OSTEODYSTROPHY**: Bone lesions caused by hyperparathyroidism secondary to **renal failure**. Renal failure causes hyperparathyroidism by two mechanisms:
  - **1-Hydroxylase** activity is deficient in the failing kidney ------> inadequate production of 1,25-$(OH)_2$-Vit-D ------> inadequate intestinal $Ca^{+2}$ absorption ------> higher PTH.
  - **Hyperphosphatemia** results from a failing kidney, because $PO_4^{-3}$ excretion is insufficient ------> higher PTH.

**PAGET DISEASE of BONE**: Disordered bone-remodeling. Extensive resorption is followed by excessive bone formation.

- EPIDEMIOLOGY: Common disorder, especially in persons of English decent.
- PATHOGENESIS: Unknown.
  - **Viral inclusions** were recently discovered in the osteoclasts of Paget Disease.
- PATHOLOGY: There is an uncoupling of osteoclastic and osteoblastic activities.
  - STAGES:
    - **"Hot" Osteoclastic Stage**: Flame-shaped or wedge-shaped lytic lesions of the cortex. Osteoclasts are initially hyperactive.
    - **"Mixed" Osteoclastic / Osteoblastic Stage (Reactive Hyperostosis)**: Formation of **larger-than-normal bones** in response to osteoclastic hyperactivity above.
    - **"Cold" Burnt-Out Stage**: Thickened and disordered bones with little additional activity.
  - **Large Multinucleated Osteoclasts**: Visible microscopically. Each osteoclast possesses more than 12 nuclei.

    - **Mosaic Cement-Lines** constitute characteristic microscopic appearance. They result from the increased osteoblastic and osteoclastic activity. They represent layers where osteoclastic resorption stops and osteoblastic activity fills in the gaps.
    - Virus-like inclusions are seen on EM.
- LABS: **Enormous increase in alkaline phosphatase** is characteristic of Paget Disease.
    - Calcium and phosphate remain normal.
    - X-RAY: Irregular, patchy increased bone density, especially in the skull.
- SYMPTOMS: Patients with mild disease are asymptomatic and require no treatment.
    - **Larger hat size**, hearing loss, platybasia (flattening of base of skull).
        - **Hyperostosis Frontalis Interna:** Enlargement of frontal bone of skull.
    - **Leontiasis Ossea:** Lion-like face, resulting from increase in facial-bone size.
    - **Pagetic Steal:** Patients can feel light-headed, because increased skull-size diverts blood to the skull away from the cerebrum.
    - COMPLICATIONS:
        - **Fractures:** Complete transverse fractures, or incomplete fractures (infractions).
        - **High output cardiac failure**. Increased blood-flow to bone requires higher CO.
        - **Osteosarcoma:** Increased risk for formation of osteosarcoma. 1% of Paget's Disease patients form the tumor.

GAUCHER DISEASE:

BENIGN NEOPLASMS:

- **FIBROUS DYSPLASIA**:
    - SYMPTOMS: Presents in children as pain in thigh. Lesion involves only one bone, typically the femur.
        - **Antalgic Gait:** Limping due to pain.
        - Patient may appear bow-legged due to Shepherd's Crook Deformity.
    - VARIANTS:
        - **Polyostotic Fibrous Dysplasia:** More rare form of disease in which multiple bones are involved.
        - **McCune-Albright Syndrome:** 1% of cases, Polyostotic Fibrous Dysplasia associated with café-au-lait spots and precocious puberty.
    - PATHOLOGY / DIAGNOSIS: Lesion is slow-growing, well-demarcated, and strictly benign. It does not grow into neighboring bone.
        - **Shepherd's Crook Deformity:** Bowing of the bone. Altered angle between the body and the neck of the femur. Characteristic finding is only found in the proximal femur.
            - Results from multiple small pathologic fractures.
        - **Ground-Glass Appearance:** Inside the lesion. Neither dark (as in a cyst) nor radiodense (as in solid bone). It is in-between.
        - Metadiaphyseal Lesion: Lesion involves both the metaphysis and diaphysis
        - **Bone Scan:**
            - **Technetium Pyrophosphate** is a tracer injected into blood. It is then scanned to see if the bone lesion takes it up. A positive scan indicates that **uptake of phosphate** (active bone formation) is occurring.
                - Tracer is taken up wherever there is increased blood flow in bone.
                - Tracer is taken up wherever there is increased osteoblastic activity.
            - Bone-scan will show all growth-plates still active (in a kid), and the lesion is metabolically active.
        - Histology:
            - Fibrosis in the marrow space.
            - No lamellar bone surrounding medullary cavity, but instead very thin and irregular spicules of woven bone.
    - TREATMENT: **Curettage** (cut out with curved blade) and pack with new bone from a bone graft. Treatment must be done to correct Shepherd's Crook Deformity. Lesion may recur but is not malignant.
- **OSTEOID OSTEOMA**:
    - SYMPTOMS: Fairly common tumor.
        - Pain, worsened at night and made better by aspirin.
        - Common location is **posterior spine**.

        - May present as **painful scoliosis**. Scoliosis by itself is not painful, so you must look for a causative lesion, which is usually osteoid osteoma.
    - DIAGNOSIS:
        - X-RAY: **Radiolucent central nidus** is surrounded by a dense sclerosis, all occurring within a bone, typically the tibia.
        - Bone Scan: Positive for increased uptake of bone in the lesion.
    - PATHOLOGY:
        - **Nidus** is the actual lesion, containing osteoid (uncalcified bone). It is surrounded by intense reactive bone formation, forming the radiodense perimeter.
        - The nidus is well innervated which explains the pain.
    - TREATMENT: Lesions usually "burn out" and heal on their own within 3 years.
        - **NSAID's** specifically relieve pain, as the lesion secretes prostaglandins.
        - Surgery: If need be, you only need remove the central nidus. The reactive sclerosis will eventually go away by itself.
- **GIANT CELL TUMOR of BONE**: Benign yet aggressive, solitary lesion.
    - PATHOLOGY: Benign lesion, but it is locally aggressive. It doesn't penetrate neighboring bone, but it can push the bone out considerably in expansile fashion.
        - Location: Starts at the **metaphysis** and can grow in both locations, pushing outward toward the epiphysis, and downward toward the diaphysis. They are always in the epiphysis.
            - *It does not penetrate the periosteum*, hence it is classified as benign, yet still aggressive.
        - Histology: **Multinucleated Giant Cells** are found, interspersed among fibrous histiocytic cells. The Giant Cells are *not* thought to be neoplastic. Only the stromal cells are known to be neoplastic.
            - **TRAP Positive**: Tartrate Acid Phosphatase is found in the giant cells. TRAP is characteristic of osteoclasts, thus the giant cells are thought to derive from osteoclasts.
    - SYMPTOMS: Young adults, 30-40.
        - Metastasis are rare, but there is a high rate of recurrence. Tumors occurring at **distal radius** have the highest likelihood of recurrence.
    - TREATMENT: Curettage and refill with bone.
        - **Phenol** can be used to kill the bone.
        - **Bone Cement:** Filling in with bone cement increases the margins around the excision, and greatly decreases the likelihood of recurrence.
- **OSTEOCHONDROMA**: *The most common benign primary bone tumor*, it is also known as **exostosis.**
    - PATHOGENESIS: Development defect at the **Ring of Ranvier** of the epiphyseal plate. The Ring is defective, which makes the bone grow laterally rather than longitudinally toward the metaphysis. Result is formation of osteochondroma.
    - SYMPTOMS: Occurs in childhood, often those who have just undergone growth spurts. Lesions should stop progressing when growth stops.
    - DIAGNOSIS:
        - X-RAY: They are Single or multiple bony projections around joints.
            - The lesion appears *directly contiguous with the marrow space*, giving it a characteristic appearance.
        - LABS: Slightly elevated bone scan. Other labs normal.
    - SUBTYPES:
        - **SOLITARY OSTEOCHONDROMA**: More common.
        - **HEREDITARY MULTIPLE OSTEOCHONDROMATOSIS**: Autosomal dominant disorder that is not uncommon.
            - **Dwarfism** may result from continued lateral growth of bone, instead of longitudinal growth.
            - Long-term increased risk of **chondrosarcoma**. It only occurs in about 1% of lesions, but an individual can have several bony lesions, increasing the chances.
    - PATHOLOGY: **Cartilage Cap** is the lesion. Bone forms underneath the cap, analogous to bone formation at a growth plate.
- **ENCHONDROMA:**
    - PATHOGENESIS: It is *not* thought to be hereditary. Cases are sporadic, with no family history noted.
        - Failure of endochondral ossification ------> cartilage builds up and forms enchondromas. Cartilage remains in the bone beneath growth plates.
    - SUBTYPES:
        - **SOLITARY ENCHONDROMA**: Solitary lesions
        - **OLLIER ENCHONDROMATOSIS**: Multiple enchondromas. *Not hereditary, but there is a significant chance for malignant transformation to **chondrosarcoma**.*

- PATHOLOGY:
  - **Enchondromas:**
    - Pre-malignant cartilaginous tumor, resulting from the buildup of cartilage in the bone.
    - They can occur as solitary lesions or multiply (as in Ollier Disease)
    - They lie in the cancellous region of bone, and they can grow up against the periosteum -- but they don't penetrate it, hence they are benign.
- DIAGNOSIS:
  - **Punctate Calcification:** Characteristic X-Ray appearance, indicating the presence of cartilage.
  - **Lobular Appearance** on X-ray is also characteristic of presence of cartilage.
- SYMPTOMS: Patients are 20-50. Not-too-painful, multiple cartilaginous lesions in bone, can be located almost anywhere.
  - COMPLICATION: **Chondrosarcoma**. 20% risk. Virtually *all* chondrosarcomas are thought to originate as enchondromas.
- **MAFFUCI SYNDROME:** Rare related syndrome. Multiple enchondromas plus cavernous hemangiomas of the skin.
  - 50% of patients develop chondrosarcomas. Other cancers are also seen.

- **NONOSSIFYING FIBROMA**: Benign solitary lesion of childhood, usually asymptomatic. It arises in the metaphysis of long bones, usually femur or tibia.
- SOLITARY BONE CYST: Benign fluid-filled lesion in childhood and adolescence. It is not neoplastic, but a disturbance in bone growth with superimposed trauma.
- ANEURYSMAL BONE CYST: Uncommon, expansive hyperemic lesion arising from the surface of bone. Cyst contains granulation tissue and giant cells.
- OSTEOBLASTOMA: Uncommon benign tumor resembling an osteoid osteoma, but it larger and it is not painful.
- CHONDROBLASTOMA: Uncommon benign tumor found in the epiphysis of long bones.
- CHONDROMYXOID FIBROMA: Uncommon tumor, with characteristic eccentric, lucent defect surrounded by sclerotic bone, on X-Ray. Childhood and adolescence.

MALIGNANT NEOPLASMS:

- **OSTEOSARCOMA**: *Most common primary malignant bone tumor, one fifth of all bone cancers.*
  - PATHOGENESIS:
    - **Paget Disease** is a risk-factor for osteosarcoma, in which case the tumor would occur in old people rather than young people as it usually does.
      - This tumor is associated with a defect in the **Rb Tumor Suppressor gene**.
  - DIAGNOSIS / PATHOLOGY:
    - X-RAY: Destructive lesion on X-Ray.
      - Bone scan will show increased uptake of phosphate.
      - The lesion is not well-demarcated on X-Ray, indicative of a malignant lesion.
      - **Codman's Triangle:** Radiologic finding of elevation of the periosteum, caused by the tumor pushing out on the periosteum.
    - Confirm diagnosis with **open biopsy** of lesion.
    - Histology: Malignant osteoblast cells secreting an osteoid matrix.
  - SYMPTOMS: Tumor usually occurs in adolescents, slight predilection for males.
    - Tumor is highly metastatic, and metastases are often present when the tumor is discovered.
    - Location: Tumor usually arises in the metaphysis around the knee, on either side.
    - Metastases: **Hematogenous spread to lungs** is very common. Death is usually by lung metastases.
  - TREATMENT: 5-yr survival rate of 50-70% as long as the tumor doesn't recur. If it recurs (due to incomplete excision), then the survival is 10-15%.
    - **Pre-operative chemotherapy** is administered to eradicate the **micro-metastases** that we assume are there, and to help shrink the primary tumor to aid in excision.
    - **Wide Excision** must be performed on all sarcomas -- take out the tumor plus a margin of normal tissue.
- **CHONDROSARCOMA**: The second most common primary malignant tumor of bone.
  - SYMPTOMS: Presents in *older age group*, 40's-70's.
    - Tumor is slow growing and is more likely to recur than to metastasize. 70% 5-yr survival.
  - DIAGNOSIS:
    - X-RAY: **Punctate Calcifications** again indicate a cartilaginous lesion.
    - Bone scan is intensely positive.

- PATHOLOGY: Indolent, slower-growing malignant tumor. Radio-translucent, bluish-gray tumor with smooth, shiny cut surface.
    - Location: **axial skeleton**. Shoulder, pelvis, and ribs.
    - Histology: Mass of cartilage resembling an enchondroma, except it shows pleomorphism and nuclear atypia. Nevertheless, the cells are well-differentiated.
        - It is impossible to distinguish low grade chondrosarcoma from an enchondroma.
- TREATMENT: Because it is slow-growing, *enchondromas are unresponsive to chemotherapy or radiation therapy.* Surgical excision is only viable option, and that isn't always possible either.
    - There appears to be something in the cartilage that actually blocks the radiation from accessing the tumor.

- **EWING SARCOMA**:
    - PATHOGENESIS:
        - Tumor cells are thought to originate as **neuroectodermal** cells from the marrow.
        - Translocation **t(11:22)** is found in the tumor cells.
    - DIAGNOSIS:
        - LABS: WBC, sed-rate, LDH, alkaline phosphatase are all elevated.
            - Bone scan and gallium scan are both positive.
        - **Infection** should be in the differential diagnosis, because labs indicate infection, and the radiographic lesions look like they could be infection.
    - X-RAY: Destructive lesion, diffuse lytic lesions.
        - **Railroad Track Sign:** Characteristic thin-line within the cortex, seen on X-ray.
    - PATHOLOGY:
        - Location: Lesion is located in the **diaphysis** of long bones. It starts off in the marrow but then sends finger-like (lytic) projections into the cortex. It actually eats through the cortical bone.
        - Histology: It's a **small blue-cell tumor**. The tumor cells contain lots of glycogen and are PAS positive.
    - SYMPTOMS: Young kids. Tumor is extremely aggressive and metastases are common.
    - TREATMENT: **Chemotherapy** has dramatically improved prognosis. Pre-operative chemotherapy is used to shrink the primary tumor before resection.
- **MULTIPLE MYELOMA**:
    - PATHOGENESIS: Several causative factors
        - Genetic predisposition
        - Chronic antigenic stimulation: chronic stimulation of B-Cells can cause plasma cell malignancy.
        - Chromosomal abnormalities
    - PATHOLOGY: **Monoclonal spikes** in the Protein Electrophoresis are found, indicating an abundance of a single type of antibody.
    - SYMPTOMS: Middle-aged person with multiple lytic lesions.
        - **Lytic Bone "Punch" Lesions:** Characteristic lesions, especially in the calvarium, due to cancer cells secreting an **osteoclast-activating factor**.
        - Dismal prognosis, even with treatment. 50% 5-yr survival.
        - COMPLICATIONS:
            - **Amyloidosis** is characteristic of Multiple Myeloma. Amyloidosis of Multiple Myeloma is considered to be a primary amyloidosis, since the origin of the amyloid is directly related to the increase in immunoglobulins.
            - **Light-Chain Cast Nephropathy**: Severe renal involvement, causing mesangioproliferative glomerulonephritis and tubulointerstitial inflammation.
    - DIAGNOSIS:
        - Sheets of plasma cells found in the bone marrow.
        - Significant Monoclonal M-Component found in serum or urine.
            - **Monoclonal Gammopathy of Unknown Significance (MGUS)** is part of the differential diagnosis. It is diagnosed when a monoclonal spike is found in the absence of the other diagnostic features. MGUS later advances to full-blown Multiple Myeloma in many cases.
        - Radiologic demonstration of lytic bone lesions, or diffuse demineralization of bone.
        - Bone scan is often negative, because tumors do not incite osteoblastic activity to try and heal.
- **METASTATIC TUMORS**: *The most common malignant tumor of bone is metastasis.*
    - **Breast cancer**
    - **Prostate cancer**
    - Other carcinomas.

# JOINTS

NORMAL STRUCTURE and FUNCTION:

- TYPES of JOINTS:
  - DIARTHROSIS (SYNOVIAL JOINT):
    - UNIAXIAL JOINT:
      - Hinge Joint: elbow
      - Pivot Joint: radioulnar joint.
    - BIAXIAL JOINT: Movement through two axes, as in the wrist.
    - POLYAXIAL JOINT: Ball-and-socket joints. Shoulder and hip.
    - PLANE JOINT: Patella, allowing articular surfaces to glide over one another.
  - SYNARTHROSIS: Joint that has little or no movement.
    - SYMPHYSIS: Contains fibrocartilage, as in pubic symphysis.
    - SYNCHONDROSIS: Contains articular cartilage but no synovium, as in sternomanubrial joint.
    - SYNDESMOSIS: Fibrous tissue with no cartilage, as in cranial sutures and the distal tibiofibular articulation.
    - SYNOSTOSIS: Pathologic bony bridge between two bones, as in ankylosis.
- UNIT LOAD: The unit force per volume of articular cartilage. Normal unit pressure of weight-bearing joints i 20-26 $kg/cm^3$. Chronic excessive unit pressure leads to osteoarthritis.
- DEVELOPMENT of JOINTS:
  - **Apical Ectodermal Ridge (AER):** The structure which directs limb development and always lies at the outskirts of the developing limb. It stimulates the underlying mesoderm to form limbs.
- JOINT STRUCTURE:
  - **SYNOVIUM**:
    - **Type-A Cells**: Macrophages containing lysosomes and dense bodies.
    - **Type-B Cells**: Secrete hyaluronic acid.
    - **Synovial Membrane** is expressed by both cell-types. Extensive protective membrane thrown into folds.
    - **Synovial Fluid:** *The articular cartilages get all of their nutrients through the synovial fluid.* Loss of the fluid leads to necrosis of the articular cartilages.
  - ARTICULAR CARTILAGE:
    - HISTOLOGICAL CHARACTERISTICS:
      - Gliding Zone
      - Transitional Zone
      - Radial Zone
      - Calcified Zone
      - **Tide Mark:** It separates the articular cartilage from the underlying bone.
        - Below the tide mark, cartilage receives its nutrients from the synovial fluid.
        - Above the tide mark, calcified cartilage receives nutrients from the epiphyseal nutrient arteries.
    - CHEMICAL CHARACTERISTICS:
      - **Proteoglycans:** They hold a lot of water (synovial fluid) and keep the joint lubricated.
      - **Hyaluronic Acid:** Its negative charge prevents the entry of fibrinogen, $alpha_2$-macroglobulin, and other clotting factors.
        - Hemarthroses (presence of blood and hence iron in joint) and Ochronosis (homogentisic acid in joint) both cancel this negative charge, and clotting factors enter joint space as a result.

**OSTEOARTHRITIS**: Non-inflammatory degeneration of the articular cartilages of synovial joints.

- PATHOGENESIS:
  - **PRIMARY OSTEOARTHRITIS:** Idiopathic wear-and-tear arthritis occurring with old-age.
    - **Loss of Proteoglycans** ------> loss of capacity to hold water.
      - **Keratin Sulfate** is decreased.
    - **Collagenase, Cathepsin** are released, which degrade the proteoglycans and articular cartilages.
  - **SECONDARY OSTEOARTHRITIS:** Osteoarthritis secondary to trauma, crystal deposits, infection, osteonecrosis, hemarthroses.

- PATHOLOGY: Process of destruction.
    - Loss of proteoglycans ------> dehydration of joint ------> loss of mechanical strength of cartilage, and death of chondrocytes.
    - **Fibrillation:** Cracks form in the articular cartilage surface.
        - Fluid can flow into the cracks. Pieces of cartilage can break off and incite foreign-body granulomatous reactions in the joints space.
    - **Eburnation:** Complete wearing away of articular cartilage. Resulting bone is hyper-osseus on the surface, due to reactive bone formation.
- CLINICAL FINDINGS:
    - **Heberden's Nodes:** Characteristic enlargements of **distal interphalangeal (DIP) joints**, seen in osteoarthritis of elderly women.
    - **Osteophytes (Bone Spurs):** Buildup of reactive bone formation into the joint space.
    - **Joint Mouse:** A bone spur that has broken loose into the joint space. It is moveable, but with time it becomes coated with a layer of regenerative cartilage.
- **Chondromalacia**: Type of osteoarthritis in young people, affecting the patellar surface of the femoral condyles, and producing pain in the knee.

**RHEUMATOID ARTHRITIS**:

- PATHOGENESIS: Autoimmune disease, with evidence of both humoral (Type-III) and cellular (Type-IV) mechanisms.
    - HEREDITY: Definite hereditary predisposition to disease.
    - **EBV** infection may be the predisposing infection that induces immune-sensitivity.
        - It contains the **Rheumatoid Arthritis Associated Nuclear Antigen (RANA)**.
- PATHOLOGY:
    - **Rheumatoid Factor:** IgM **anti-idiotype antibodies**, against the Fc portion of IgG. These immune-complexes deposit in joints and other soft tissues.
        - Complement also collects in the joint space, as C3 is a part of the complex deposits in joints. However, complement is not found in circulating rheumatoid factor.
        - Rheumatoid Factor is associated with RA, but it is not specific for RA.
    - **Pannus:** Finger-like projections of synovial membrane, representing proliferation of synovial membrane in response to chronic (lymphocytic) inflammation.
        - **Allison-Ghormley Bodies:** Follicular centers of lymphocytes found within the pannus.
        - The Pannus contributes to erosion of the joint. It causes breakdown of articular cartilage.
            - $PGE_2$ and IL-1 are both released and contribute to joint erosion.
- CLINICAL FINDINGS:
    - Hand-involvement characteristically involves the **proximal interphalangeal (PIP) joints,** and **knuckles (MCP joints)**, as opposed to the DIP joints.
    - **Rheumatoid Nodules:** They consist of a center of **fibrinoid necrosis** (fibrin, degraded collagen), surrounded by granulomatous inflammatory cells (first macrophages, and further out, lymphocytes and plasma cells).
        - Can be found in any soft tissue, but they are usually located in pressure-points, such as elbow, knee.
    - **Subluxation:** Due to degeneration of joint-space, one articular end overrides the other.
    - **Boutonniere Deformity:** Protrusion of knuckles that results from subluxation of joints.
    - **Ulnar Deviation:** Contraction of ulnar muscles leads to ulnar deviation.
    - **Bony Ankylosis:** Complete fusion of the articulating surfaces, leading to loss of function of the joint. A late-stage complication of RA.
- SYMPTOMS: A systemic joints in which all joints may be involved. The **TMJ joint** and hip is often involved, as well as the PIP, MCP joints, and the wrist.
- TREATMENT:
    - Anti-Inflammatory Agents: NSAID's steroids.
    - Remission-Inducing Drugs: gold salts, penicillamine, anti-malarial drugs.
    - Immunosuppressive Agents: Methotrexate.
- **FELTY SYNDROME**: Rheumatoid arthritis, plus splenomegaly and leukopenia.

**SPONDYLARTHROPATHIES**: All of them are inflammations of the spine that have autoimmune etiologies, particularly associated with **HLA-B27** haplotype.

- **ANKYLOSING SPONDYLITIS**: Inflammatory arthropathy of the sacroiliac joint, associated with HLA-B27 haplotype.
- **REITER SYNDROME**: Probably the most common cause of arthritis in young males.

    - PATHOGENESIS: Unknown. Usually occurs as a sequel to a veneral disease, where the veneral disease is the immune-sensitizing agent (presumably).
    - SYMPTOMS:
        - CLASSIC TRIAD:
            - **Polyarticular Arthritis**: Seronegative for Rheumatoid Factor, but positive for HLA-B27
            - **Urethritis**
            - **Conjunctivitis**
        - **Kerato-Blennorrhagicum:** Mucocutaneous lesions over palms, soles, and trunk, often found in Reiter's Syndrome.
- **PSORIATIC ARTHRITIS**: Seronegative arthritis associated with Psoriasis.
- **ENTEROPATHIC ARTHRITIS**: Seronegative arthritis associated with Ulcerative Colitis and Crohn's Disease.

**SEPTIC ARTHRITIS**: Arthritis caused by infection or as a direct sequel to infection.

- PATHOGENESIS:
    - **Gonorrhea (*Neisseria Gonorrhea*)** is most frequent cause in young adults. It is caused by a gonococcal septicemia.
    - Staph and Strep
    - **Tuberculous Arthritis**: Potts disease of the spine. See bone section above.
- SYMPTOMS: It is usually **monoarticular**, which is hint to look for an infectious cause.
    - There is purulent inflammation. You can aspirate the joint fluid and culture for bugs.

**LYME DISEASE:** Infection of *Borrelia Burgdorferi*

- SYMPTOMS:
    - **Erythema Chronica Migrans:** Characteristic rash indicating initial infection. Enlarging, red, annular plaque.
    - **Aseptic (Autoimmune) Arthritis:** A late sequel to the original infection.
    - Other sequelae: Encephalitis, myocarditis and fatal arrhythmias, which can be fatal.

**JUVENILE ARTHRITIS (STILL DISEASE)**: Any chronic inflammatory arthritis in children. Rheumatoid Factor is often absent.

- Seropositive: Less than 10% of cases are positive from Rheumatoid Factor.
- Polyarticular Disease Without Systemic Symptoms: About 25% of cases. Polyarticular arthritis with no systemic symptoms.
- Polyarticular Disease With Systemic Symptoms: About 20% of cases have arthritis fever, rash, hepatosplenomegaly, lymphadenopathy, pericarditis, anemia.
- Pauciarticular: Involvement of only a few large joint.

JOINT-DEPOSITION DISEASES:

- **GOUT**: Deposition of uric acid crystals in joints.
    - EPIDEMIOLOGY: Occurs in adult men, with peak incidence in 50's. Incidence is related to alcohol intake, diet, intelligence, socioeconomic status.
    - PATHOGENESIS:
        - Gout results from **hyperuricemia.** Uric acid is the product of purine metabolism and is created as a byproduct of the **xanthine oxidase** enzyme.
            - Normal amount of urate in blood = 7 mg/dL
            - For unknown reasons, *not all patients with hyperuricemia develop gout.*
        - **Primary Gout:** Idiopathic gout is nearly always caused by *impaired excretion (secretion) uric acid in the kidneys* ------> hyperuricemia.
            - **Lesch-Nyhan Syndrome:** A rare cause of Gout due to an inborn error of metabolism.
                - **Hypoxanthine-Guanine Phosphoribosyl Transferase (HGPRT)** is deficient, leading to a deficiency of the Salvage Pathway ------> buildup of purine metabolites ------> gout.
        - **Secondary Gout:** Hyperuricemia can occur secondary to lots of things.
            - **Leukemias, Lymphomas:** Chemotherapy causes lots of cell death, a high rate of cell-turnover, and lots of purine metabolites ------> hyperuricemia.

        - Drugs: Thiazide diuretics, other drugs. Acidic drugs compete with urate for urinary secretion.
        - **Alcohol:** Ethanol increases turnover of ATP, and it leads to increased amounts of organic acids, which compete with urate for urinary secretion.
        - Renal failure.
    - PATHOLOGY: Neutrophilic inflammation occurs in response to the urate crystals. Neutrophils ingest the crystals and in response they release proteolytic enzymes, which destroys articular cartilage.
        - **Tophus:** Collection of long needles of **monosodium urate** crystals.
            - The crystals are **non-birefringent** under polarized light, which distinguishes them from Calcium Pyrophosphate Deposition Disease.
            - Tophi can accumulate in soft tissues in chronic, untreated gout.
        - **Urate Nephropathy:** Chronic hyperuricemia can lead to urate kidney stones.
    - SYMPTOMS: Bouts of acute arthritis, usually involving only one joint (monoarticular).
        - **Podagra:** Classic gout of the big toe.
    - TREATMENT:
        - *Do not use aspirin.* In low doses, it competes with urate for urinary excretion and thus is counterproductive.
        - **Indomethacin** is a good choice for an NSAID for pain.
        - Avoid alcohol.
        - **Allopurinol** for prevention and maintenance. It inhibits xanthine oxidase.
- **CHONDROCALCINOSIS (PSEUDOGOUT)**: Also known as **Calcium Pyrophosphate Deposition Disease (CPPD).**
    - EPIDEMIOLOGY: *Pseudogout is slightly more common than gout.*
    - PATHOGENESIS: Accumulation of inorganic pyrophosphate in the synovial fluid (from breakdown of ATP), precipitated with calcium, leads to deposits of calcium pyrophosphate.
        - Associated with diseases: hyperthyroidism, hyperparathyroidism, ochronosis.
    - PATHOLOGY:
        - SUBTYPES:
            - **CHONDROCALCINOSIS**: Accumulation of calcium pyrophosphate in cartilage. *When the crystals are in the cartilage, there is no inflammatory reaction.* The disease in the cartilage is **non-inflammatory.**
            - **PSEUDOGOUT**: Accumulation of calcium pyrophosphate in synovial joints. When the disease gets into the joints, it becomes **inflammatory**.
        - The calcium pyrophosphate crystals are **birefringent** under polarized light, which distinguishes them from monosodium urate crystals.
    - SYMPTOMS: Occurs in older population, no gender predilection.
        - Pseudogout is a self-limited acute arthritis. Unlike gout, the big toe is usually spared.
- **CALCIUM HYDROXYAPATITE DEPOSITION DISEASE**: Hydroxyapatite deposited into joint tissues.
    - PATHOLOGY: Most often it is peri-articular -- the calcium hydroxyapatite is deposited into the patellar tendon abnormally.
        - Hydroxyapatite is calcium phosphate dihydrate: $Ca_{10}(PO_4)_6(OH)_2$
        - The crystals are normally non-inflammatory, but if they reach the joint space they become inflammatory.
    - **MILWAUKEE SHOULDER:** Calcium hydroxyapatite deposited into the **rotator cuff**, after a chronically injured shoulder.

OTHER CAUSES of ARTHRITIS:

- HEMOPHILIA: **Hemarthrosis**, bleeding into joints,
- HEMACHROMATOSIS
- **OCHRONOSIS**: Defect in **homogentisic acid oxidase**, leading to deposition of ochronotic pigment in joints.
    - Osteoarthritis: Eventually the joints degenerate; the arthritis is non-inflammatory.
    - Locations: Disease occurs in intervertebral disks, among other places.

TUMORS of JOINTS:

- **GANGLION CYST**: Non-neoplastic cyst occurring in joint capsules. Occurs over the dorsum of the wrist. Bang it over the top with a bible to get rid of it (Preacher's Cyst).
- SYNOVIAL CHONDROMATOSIS:
- **GIANT-CELL TUMOR of TENDON SHEATH**: They are small, benign lesions in the tendon sheath.
    - PATHOLOGY: Giant cells, with interspersed fibroblasts and histiocytes.

- **Localized Nodular Tenosynovitis (Giant Cell Tumor of Hand)** is the *most common soft tissue tumor of the hand.*
- **PIGMENTED VILLONODULAR SYNOVITIS**: Closely related disease
  - PATHOLOGY: Exuberant, heavily pigmented villous synovial overgrowth containing pigmented cells, lipid-laden histiocytes, and multinucleated giant cells.

SOFT TISSUE TUMORS:

- **SYNOVIAL SARCOMA**:
  - **PATHOLOGY: Biphasic** fibrous plus epithelial components.
    - Fibrous: atypical spindle cells.
    - Epithelial: malignant synovial epithelial cells.
  - CLINICAL: Rare; it's a nasty tumor. It is small and not usually detected until metastases are already present. 5-yr survival is about 50%.
- FIBROUS TUMORS
  - **MALIGNANT FIBROUS HISTIOCYTOMA (MFH)**:*The most common of soft-tissue sarcomas,* but they are still rare. About 10% of the time it can arise in bone.
    - PATHOGENESIS: It is usually a **secondary sarcoma**, occurring secondary to radiation or some other disease, such as **Paget's Disease**.
    - SYMPTOMS: Extremely aggressive tumor. It is more aggressive in bone than in soft tissue.
      - High rate of metastasis, with free access to the bone marrow ------> hematogenous spread to lungs.
    - PATHOLOGY: Soft hemorrhagic lesion. When it occurs in bone, it can grow right through the cortex.
      - Fibroblastic Cells in **storiform (cartwheel)** pattern, as in radiating bundles. They infiltrate the marrow space.
      - Foam-filled histiocytes are interspersed.
      - Tumor Giant-cells may be seen.
  - NODULAR FASCITIS:
  - FIBROMATOSIS:
    - **Dupuytren Contracture:** It is a palmar fibromatosis, most common form of fibromatosis. Characteristic flexion of the fourth and fifth digits.
    - **Peyronie Disease:** Penile fibromatosis. Induration, mass in shaft of penis.
    - Plantar fibromatosis.
  - FIBROSARCOMA: ADIPOSE TUMORS
  - LIPOMA: The most common soft-tissue mass.
  - ANGIOLIPOMA:
  - LIPOSARCOMA: The second most common sarcoma in adults.
- RHABDOMYOSARCOMA
  - EMBRYONAL RHABDOMYOSARCOMA
  - BOTRYOID RHABDOMYOSARCOMA (SARCOMA BOTRYOIDES)
  - ALVEOLAR RHABDOMYOSARCOMA
  - PLEOMORPHIC RHABDOMYOSARCOMA
- SMOOTH MUSCLE TUMORS
  - LEIOMYOMA
  - LEIOMYOSARCOMA
- VASCULAR TUMORS

---

# THE CENTRAL NERVOUS SYSTEM

NORMAL STRUCTURE and FUNCTION:

- HISTOLOGY
  - **NEURONS**:
    - **Nissl Bodies:** Basophilic Rough ER
    - **Chromatolysis:** Injury to a neuron, causing it to swell. The basophilic Nissl substance gets displaced to the periphery and partially lost.
  - **ASTROCYTES**: Neuroectodermal cells that play a role in healing CNS injuries.
    - Two types of astrocytes:
      - **Fibrillary Astrocytes:** Located in the white matter, with long, thin, processes. Most gliomas originate from fibrillary astrocytes.
      - **Protoplasmic Astrocytes:** Located in the grey matter, with flat, branching processes.
    - **Gliosis:** Proliferation of astrocytes in response to injury, to form a **glial scar**. Unlike a fibroblast scar, the glial scar is made of *intracellular* components -- not extracellular.
  - **OLIGODENDROGLIA**: Neural-crest origin. They are the myelin-producing cells of the CNS.
    - The myelin is *intracellular* contained inside the cells themselves. They extend cytoplasmic processes around neurons to myelinate them.
    - CO poisoning and PML can both target oligodendroglia and cause demyelination as a result.
  - **EPENDYMA**: Cuboidal to flat epithelial cells that line the ventricular chambers. They are not very good regenerating themselves.
  - **MICROGLIA**: CNS phagocytic resembling macrophages. They only account for 5% of glial cells.
    - In a real CNS infection, macrophages and other phagocytic cells are recruited from the peripheral circulation, and microglial cells play a very minor role if any role in fighting infection.
    - **Microglial nodules** are formed in response to viral, Rickettsial, and protozoal infections of the CNS.

CONGENITAL MALFORMATIONS:

- DYSRAPHIC STATES:
  - **SPINA BIFIDA**
    - **SPINA BIFIDA OCCULTA**: Neural tube defect restricted to the vertebral arches. Usually asymptomatic.
    - **MENINGOCELE**: Usually in lumbar back, herniation of meninges as a fluid-filled sac.
    - **MENINGOMYELOCELE**: Herniation of meninges plus spinal canal, causing entrapment of nerve roots.
    - **RACHISCHISIS**: Very severe failure of neural tube closure. The spinal column is converted to a gaping canal and is often unrecognizable.
  - **ANENCEPHALY**:
    - PATHOGENESIS: Results from the injury to the fetus that occurs at a crucial *time*: the **8th-9th day** of gestation. The eyes are still present, but the cranium and brain is absent.
      - Developmental event is thought to be failure of closure of the **anterior neuropore**.
    - PATHOLOGY: **Cerebrovasculosa** is a discoid mass of highly vascularized, poorly differentiated neural tissue, which takes place of the normal brain in anencephalic fetuses.
- MALFORMATIONS of SPINAL CORD:
  - DIMYELIA: Complete duplication of spinal cord.
  - DIASTEMATOMYELIA: Bifurcation leading to partial duplication of spinal cord.
  - HYDROMYELIA: Dilatation of the central canal of spinal cord.
  - SYRINGOMYELIA: The presence in the spinal cord of longitudinal cavities lined by dense, gliogenous tissue. Formation of an extra tube within the spinal cord.
    - SYRINGOBULBIA: Variant of syringomyelia, in which slit-like cavities are also located in the medulla.
- **ARNOLD-CHIARI MALFORMATION**: Malformed posterior fossa structures resulting from caudad traction and displacement of the rhombencephalon caused by tethering of the spinal cord; may or may not be accompanied by spina bifida and associated anomalies such as meningomyelocele; weak evidence of autosomal recessive inheritance.
- **CONGENITAL HYDROCEPHALUS**: Usually caused by congenital atresia of the Sylvian Aqueduct.

- DISORDERS of CEREBRAL GYRI:
  - POLYMICROGYRIA: Presence of small and excessive gyri.
  - PACHYGYRIA: Presence of too few gyri that are broader than normal.
  - LISSENCEPHALY: Cortical surface is smooth, with only slight furrows.
  - HETEROTOPIA: Focal displacements of grey matter into the white matter. Often accompanied by seizures and mental retardation.
- CHROMOSOMAL DEFECTS:
  - **DOWN SYNDROME**: They have a propensity to develop the histologic features of Alzheimer's disease at a very early age.
  - **TRISOMY 13-15**
    - **Holoprosencephaly:** Microcephalic brain with absence of the interhemispheric fissure.
    - **Arrhinencephaly:** Absence of the rhinencephalon -- the olfactory tracts and bulbs.
    - Absence of the Corpus Callosum
- EPILEPSY

TRAUMA:

- **EPIDURAL HEMATOMA**: Accumulation of blood between the skull and the dura.
  - PATHOGENESIS: Blow to the **side of the head** ------> rupture of **middle meningeal artery** within the dural skull table ------> epidural hematoma.
    - The middle meningeal artery occupies the potential space between the skull and the dura.
    - The temporal bone (side of head) is the weakest bone in the skull and is particularly subject to damage.
  - PATHOLOGY / CLINICAL: *An epidural hematoma is an acute medical emergency that must be treated within 24-48 hrs of injury, or the patient will die.* Since the blood is arterial, the hematoma slowly and relentlessly gets larger.
    - **Cerebral Hypoxia:** Hematoma gets larger ------> compression of the venous sinuses in brain ------> vascular stagnation and hypoxia.
      - **Cushing Reflex:** Physiologic response to cerebral hypoxia, aimed to increase blood flow to the brain.
        - Heart rate slows, to increase ventricular filling.
        - Systolic pressure (cardiac output) goes up.
    - **Uncal (Transtentorial) Herniation:** As the hematoma continues to grow, uncal herniation will ultimately result (see below).
    - **No concussion:** Concussion is the transient loss of consciousness due to trauma, which occurs when the brain is jarred within the cranial vault.
      - *Epidural hematomas are **not** usually preceded by concussion.* A blow to the side of the head doesn't cause significant jarring of the brain, because the falx-cerebri prevents the brain from moving in that direction.
  - TREATMENT: It is **100% curable** if caught in time. Simply stop the bleeding and relieve the intracranial pressure by evacuating the blood.
- **SUBDURAL HEMATOMA**: Bleeding into the subdural space, between the dura and the arachnoid.
  - PATHOGENESIS: Caused by rupture of the parasagittal **bridging veins.**
    - This usually results from forceful **anteroposterior displacement** of the cranium, as occurs from Motor Vehicle Accidents (MVA's), falls, sporting mishaps, victims of child abuse.
    - The free-floating brain (and arachnoid) moves in one direction, while the skull (and dura) are moving in the opposite direction. This produces a shearing force that tends to localize to the bridging veins.
    - The shearing force causes the bridging veins to tear right at the **Sagittal Sinus**, where they are passing through the theoretical **subdural space**.
  - PATHOLOGY: Initially, the bleeding usually *stops spontaneously*, as the blood is venous and will thrombose.
    - STRUCTURE: Tissue responses to the hematoma encapsulate it.
      - **Outer Membrane:** Formed by granulation tissue, between the hematoma and the dura.
      - **Inner Membrane:** Forms 2 weeks later along the inner aspect of the hematoma.
    - THREE FATES of the hematoma:
      - Asymptomatic: Hematoma may be reabsorbed and cleaned up.
      - Hematoma may remains static and calcify.
      - **Re-bleeding / Expansion**: The hematoma may re-bleed by injury to the outer membrane. This creates a **new hematoma** immediately subjacent to the original hematoma. This process can continue, until you're left with a large hematoma that is compartmentalized.

        - Re-bleeding usually occurs within 6 months of original injury, if its going to occur.
    - CLINICAL:
        - **Elderly People:** Subdural hematomas tend to be found in the elderly. In the elderly you see a somewhat atrophied brain, which widens the subdural space and puts strain on the bridge veins, making them break easier.
        - *Blood may or may not be found in the CSF*. The hematoma may be so confined as to stay out of the CSF.
        - SYMPTOMS: Headaches, focal motor weaknesses, possible seizures.
            - **Dementia:** Diffuse, bilateral subdural hematoma (not uncommon) will lead to dementia. This is one of the rare *curable* forms of dementia.
- **SUBARACHNOID HEMORRHAGE**: Bleeding into the subarachnoid space, of any etiology.
    - PATHOGENESIS:
        - **Rupture of arterial aneurysms** is responsible for two thirds of cases.
        - Ascending dissecting aneurysms in Marfan's Syndrome.
        - May occur with cerebral contusion or laceration, but other hemorrhages are usually also found.
        - May occur secondary to blood dyscrasias, infections, vasculitis, tumors.
- **CEREBRAL CONTUSION**: Bruise of the cortical surface of the brain.
    - PATHOGENESIS: Results from forceful anteroposterior displacement of brain, as in a moving hitting a struck object.
        - **Coup:** Injury of the part of the head that was struck (usually frontal area).
        - **Contrecoup:** Injury of the opposite part of the head (usually occipital), that can be bruised as a result of the jiggling of the brain in response to injury.
    - PATHOLOGY / CLINICAL:
        - Contusions are permanent. A glial scar is formed and the tissue is lost forever.
- PENETRATING WOUNDS: If the medulla is not immediately involved, then the immediate threat to life is hemorrhage.
    - Seizures can often be found 6 to 12 months after a gunshot wound
- SPINAL CORD INJURIES
    - HYPEREXTENSION INJURY: Sharp posterior angulation of the spinal cord, as in a diving accident.
    - HYPERFLEXION INJURY: Sharp anterior angulation of spinal cord.
    - CONSEQUENCES:
        - Concussion of spinal cord: transient, reversible loss of function.
        - Contusion of spinal cord: Results from more severe trauma. Complications:
            - **Myelomalacia:** Edema and softening of the spinal cord secondary to contusion.
            - **Hematomyelia:** Blood within the spinal cord.

CIRCULATORY DISORDERS:

- VASCULAR MALFORMATIONS:
    - **ARTERIOVENOUS MALFORMATION**: *Common, congenital malformation.*
        - PATHOLOGY: Focal absences of capillary beds. Veins will contain oxygenated blood, and cerebral tissue will be hypoxic in places.
        - COMPLICATIONS:
            - Aneurysm of veins.
            - High pressure veins can rupture, leading to cerebral hemorrhage.
            - High output cardiac failure, due to increased CO to compensate for the hypoxia.
    - CAVERNOUS ANGIOMA: Less common. Large vascular spaces compartmentalized by fibrous walls. May be asymptomatic, or may find bleeding or focal neurological disturbances.
    - TELANGIECTASIA: Focal aggregates of uniformly small vessels.
    - VENOUS ANGIOMA: Randomly distributed enlarged veins. Usually asymptomatic.
- ANEURYSMS:
    - **BERRY ANEURYSM**:
        - PATHOGENESIS: Development defect leads to congenital muscular weakness of arterial walls.
        - PATHOLOGY: **Saccular** aneurysm forms, like a berry with a stalk.
            - LOCATION: Characteristically located at arterial junctions in the Circle of Willis, primarily in the branch points of the Carotid (anterior) system.
                - Junction of Anterior Cerebral and Anterior Communicating Arteries
                - Anywhere along the Internal Carotid Complex, where the Internal Carotid joins with the Circle of Willis.
                - At the trifurcation of the Middle Cerebral Artery

        - CLINICAL:
            - **Rupture** ------> subarachnoid hemorrhage and death if not treated. 35% mortality during initial hemorrhage. "Worst headache of my life," with sudden onset, followed by coma.
            - **CN palsies:** The aneurysm can get so large as to compress CN III, IV, and/or VI.
            - Seizures: It can get large enough to compress the medial temporal lobe and provoke seizures.
        - TREATMENT: It is easily treated surgically when detected.
    - **ATHEROSCLEROTIC ANEURYSM**: **Fusiform** aneurysms, can occur anywhere. Often occur in Internal Carotid artery.
        - CLINICAL: They rarely rupture. The major complication is thrombosis which leads to occlusive stroke.
    - **MYCOTIC ANEURYSM**: Aneurysms caused by septic emboli, usually thrown from infected heart valves.
        - PATHOGENESIS: Vast majority of the time, it occurs secondary to **subacute bacterial endocarditis** (*Staph Aureus, Strep*), but other infections could cause it, too.
        - PATHOLOGY: The septic emboli usually lodge in a branch of the Middle Cerebral Artery, where they cause focal inflammation, weakness, and thus enlargement (aneurysm).
        - COMPLICATIONS:
            - The aneurysm may rupture ------> cerebral hemorrhage.
            - The septic emboli may seed suppurative meningitis or a cerebral abscess.
    - **CHARCOT-BOUCHARD ANEURYSM:** Aneurysms resulting from hypertension. See cerebral hemorrhage below.
- **CEREBRAL HEMORRHAGE (HEMORRHAGIC STROKE)**: **Longstanding hypertension** is the most important cause of hemorrhagic stroke.
    - **HYPERTENSIVE HEMORRHAGE**:
        - CHARACTERISTIC LOCATIONS of hemorrhage:
            - **Basal Ganglia:** 65% of cases.
                - The **lenticulostriate arteries** come off the Middle Cerebral Artery and supply the basal ganglia. They are very small arteries coming off a very big, high-pressure artery, thus they are susceptible to rupture under the stress of prolonged HTN.
                - Infarct of neighboring **internal capsule** also often occurs, resulting in hemiplegia and hemiparesis.
            - **Pons:** 15% of cases. Hemorrhage is a catastrophic event leading to damage to the reticular formation and instant death.
            - **Cerebellum**: 8% of cases. Abrupt ataxia, accompanied by occipital headache and vomiting. Life-threatening, but it can be treated if caught in time.
        - PATHOLOGY:
            - **Lipohyalinosis:** Deposition of lipid and hyaline material in cerebral arterioles, making them weak and susceptible to rupture.
            - **CHARCOT-BOUCHARD ANEURYSMS:** Small fusiform aneurysms forming in cerebral arterioles as a result of hypertension.
                - They are located on the trunk of an artery rather than at the bifurcation.
                - They form in longstanding hypertension, and their rupture is responsible for some cases of cerebral hemorrhage.
        - CLINICAL: Onset of symptoms is abrupt, and weakness usually dominates. Death occurs in hours or days, either by uncal herniation or intraventricular hemorrhage.
    - **INTRAVENTRICULAR HEMORRHAGE**: Occurs in premature, hypoxic babies, and is due to anoxia of the endothelial cells of vessel walls, leading to massive leakage into CSF.
    - OTHER CAUSES of Hemorrhage: Arteriovenous malformation, thrombocytopenia, Rickettsial infections, embolic infarction.
- **GLOBAL ISCHEMIA and INFARCTION (SHOCK)**: Ischemia to the brain resulting from reduced blood flow.
    - **WATERSHED INFARCTS**: Wedge-shaped infarcts that occur where there is low blood flow -- on the outlying regions, between the regions of the Anterior and Middle Cerebral Arteries, for example.
    - **LAMINAR NECROSIS**: The **4th-6th cell layers** (deeper layers of gray-matter) get lower blood flow than the other cell layers and thus are the first to infarct in case of stroke.
        - Higher up grey matter receives its blood supply by small penetrating arteries. Thus the 1st thru 3rd layers actually have a richer blood supply.
    - **Selective Neuronal Sensitivity:** Certain regions require more oxygen and are especially susceptible to hypoxic necrosis.
        - **Ammon's Horn of the Hippocampus**
        - **Purkinje Cells of Cerebellum**.
            - **Red Neurons:** Dead Purkinje cells form "red neurons" on histology.

        - **Bergmann's Glia**: Astrocytes proliferate in response to the ischemia and replace the Purkinje cells.
    - Cortical neurons of 3rd thru 5th layer.
- **REGIONAL ISCHEMIA and INFARCTION (STROKE)**: Ischemia to the brain resulting from occlusion or hemorrhage of regional vessels.
    - PATHOLOGY:
        - SUBTYPES:
            - **Hemorrhagic Infarcts**: See Cerebral Hemorrhage above.
            - **Bland (Occlusive) Infarcts**: Infarcts caused by a blood clot.
        - Initial damage occurs by **coagulative necrosis**, and it is repaired by gliosis. The resulting **glial scar** actually contains intracellular material -- not extracellular.
    - CLINICAL MANIFESTATIONS:
        - **Transient Ischemic Attacks (TIA's):** Focal neurological disturbances, often only lasting for minutes. They often are the premonition for a larger stroke to come.
            - Believed to be caused by **microemboli** (fibrin emboli) that dissolve on their own, causing transient microinfarcts.
        - **Stroke in Evolution:** Uncommon, usually reflecting propagation of a thrombus in carotid or basilar arteries.
        - **Completed Stroke:** Stable neurologic deficit.
    - LOCATIONS: Strokes can occur in five general regions
        - LARGE ARTERIES OF THE NECK: Thrombus usually leads to infarction of the Middle Cerebral Artery. Usually secondary to **atherosclerosis**.
        - CIRCLE OF WILLIS: Trifurcation of the Middle Cerebral Artery is the usual location where a **mural thrombus** from the heart will lodge.
        - PARENCHYMAL ARTERIES AND ARTERIOLES: These vessels get damaged by **hypertension** and become stenotic due to **arteriosclerosis.** Can also be damaged by **cerebral vasculitis** or other vasculitides.
            - **Lacunar Infarcts:** Focal ischemic lesions secondary to arteriolar sclerosis.
            - **Multiple Infarct Dementia:** Dementia resulting from ischemia in small vessels. It can be confused with Alzheimer's.
            - **Hypertensive Encephalopathy:** The cerebral complications of hypertension.
                - Fibrinoid necrosis and arteriosclerosis can lead to small arterial bleeds (petechiae), especially in malignant hypertension.
                - **Vasogenic Cerebral Edema**, papilledema can occur secondary to the vascular damage.
                - Patient will show headache, vomiting, and can progress to coma, death.
        - CAPILLARY BEDS: Can get infarcted secondary to emboli.
            - **Fat Emboli**: From corticosteroids.
            - **Air Emboli**: As in the bends
        - **CEREBRAL VEINS**: Venous thrombosis or blockage leads to vascular stasis, ischemia, and cerebral edema. CAUSES:
            - **Dehydration:** As in an infant with GI fluid loss. This leads to **inspissation** (increased viscosity) of blood.
            - Birth Control Pills
            - Polycythemia Vera, Sickle Cell Disease
            - **Septic Thrombosis**: Thrombophlebitis leading to hydrocephalus, usually secondary to Mastoiditis or complicated Otitis Media.
            - **Meningioma**: Obstruction by neoplasm blocking a dural sinus.

**CEREBRAL EDEMA**: Swelling in the brain leads to hypoxia and can lead to herniation if not controlled.

- **Vasogenic**: Edema from leakage from blood vessels.
    - Can occur from getting knocked on the head, or from a tumor.
    - It is self-perpetuating: some edema can compress veins, leading to vascular stagnation and further edema.
- **Cytogenic: Uremia** from renal failure.
    - **Dry edema**: When you cut the brain, no fluid leaks out, *because all the retained fluid is intracellular*.
- **Interstitial Edema**: Edema from hydrocephalus.
    - Blocked absorption of CSF ------> ventricular system backs up ------> cerebral edema.
- TREATMENT: Edema usually reaches its peak after 48 hours, after which the danger of herniation subsides.

- Give them **oxygen**. Hypoxia will perpetuate the edema.
- Give **mannitol** to diurese them to get off the fluid.

**CEREBRAL HERNIATION**:

- **UNCAL HERNIATION**: As the hematoma continues to grow, ultimately the medical aspect of the temporal lobes will herniate through the tentorial fissures ------> compression of midbrain ------> coma followed by rapid death.
  - **3rd Nerve Palsy**: Due to location of CN III surrounding the midbrain, patient will likely show 3rd nerve palsies before death. Patient will therefore have **fixed, dilated pupils**.
  - **Mesencephalic Veins (Great Veins of Rosenthal)**: The paired midbrain veins get compressed by the herniation, leading to further vascular stagnation and ischemia of the midbrain.
    - Bilateral herniation will therefore cut off circulation to the midbrain ------> **hemorrhagic necrosis of midbrain** ------> death by necrosis of Reticular Activating System.
- **TONSILLAR HERNIATION**: Herniation of the cerebellar tonsils through the foramen magnum ------> compression of the medulla ------> death by infarct of the respiratory center, **central respiratory arrest**.
  - As opposed to uncal herniation, *no hemorrhagic necrosis* will be seen.
- **CINGULATE HERNIATION**: Unilateral herniation of the cingulate gyrus across the Falx Cerebri, to the other side. It is not in itself fatal, but it usually occurs with other problems.

CEREBROSPINAL FLUID (CSF):

- HYDROCEPHALUS:
  - **NON-COMMUNICATING HYDROCEPHALUS**: Hydrocephalus due to a ventricular obstruction, usually from a congenital malformation (Congenital Hydrocephalus), or from neoplasm.
  - **COMMUNICATING HYDROCEPHALUS**: Hydrocephalus due to impaired resorption of CSF by the Arachnoid Villi, which leads to **interstitial edema**.

**MENINGITIS**:

- **BACTERIAL (SUPPURATIVE) MENINGITIS**:
  - CLINICAL:
    - CSF will show:
      - **PMN's**, due to purulent inflammation.
      - **Decreased glucose**, because the bugs like to eat the glucose.
      - **Increased protein**, due to higher rate of cell turnover and killed PMN's.
    - **Kernig's Sign:** When the hip is flexed, patient shows pain in the knee, and complete leg extension is impossible.
    - **Brudzinski's Sign:** Flex the neck, and the patient's legs passively flex too.
  - ***ESCHERICHIA COLI***: Especially in newborns.
  - ***HAEMOPHILUS INFLUENZAE***: If not vaccinated, incidence occurs between 3 months to 3 years. Before 3 months, maternal antibodies are protective.
    - Elicits a **fibrinous exudate.**
  - ***STREPTOCOCCUS PNEUMONIAE***: Common in adult meningitis.
  - ***NEISSERIA MENINGITIDIS***:
    - Initial Phase: **Meningococcemia**, which can lead to **Waterhouse-Friderichsen Syndrome**. Also see fever, malaise, petechial rash.
    - The meningitis tends to occur at the base of the brain.
- **TUBERCULOUS MENINGITIS (*MYCOBACTERIUM TUBERCULOSIS*)**: Infection classically occurs at the *base of the brain*, particularly at the Sylvian Fissure, and consists of a fibrinous exudate.
  - **Tuberculoma:** Giant granuloma can form.
- **VIRAL MENINGITIS**: Milder, usually self-limited infection.
  - LABS: CSF will have normal glucose and will have lymphocytes.

**NEUROSYPHILIS**: *T. Pallidum*. Three manifestations:

- **MENINGOVASCULAR SYPHILIS**: Secondary Syphilis.
  - Slight meningeal infection with the spirochetes. Will see lymphocytes and elevated protein in CSF.

    - Will see thickened meninges and obliterative endarteritis.
- **TABES DORSALIS**: Tertiary Syphilis.
    - Degeneration and demyelination of the posterior columns of the spinal column, as a direct extension (*Wallerian Degeneration*) of damage in the dorsal roots. Spirochetes usually are not found, and it is thought to be an immune reaction.
    - SYMPTOMS: Loss of position-sense, proprioception.
    - **Charcot Joint:** Arthritis of neuropathic origin, usually seen in the knees and hips in patients with syringomyelia or tabetic syphilis who have lost pain sensation and position sense in these joints due to posterior column spinal cord degeneration.
- **DEMENTIA PARALYTICA**: Subacute syphilitic meningeo-encephalitis.
    - PATHOLOGY: In this case, the *T. Pallidum* bugs actually cause the disease. They are present in the frontal lobes, where they have been dormant for decades.
        - **Frontal Atrophy**: They cause focal loss of cortical neurons in the frontal lobe, with meningeal thickening. Will also see lymphocytic infiltrates.
        - **Rod Cells**: Microglia cells that proliferate around the spirchoetes (gliosis). Characteristic appearance, like "raindrops."
    - SYMPTOMS: Occurs in late-stage Tertiary Syphilis
        - **Marked dementia**: from frontal atrophy.
        - **Paralysis:** from frontal atrophy, atrophy of the motor strip.
        - **Blindness:** Atropy of the optic nerve, secondary to fibrosis of the meninges surrounding the optic chiasm.

**MYCOTIC INFECTIONS**:

- **ACTINMYCOSIS, NOCARDIA**: Can cause infection even in immunocompetent people.
- **CRYPTOCOCCAL MENINGITIS**: Ocassionally causes infection in immunocompetent people, but mostly immunocompromised.
    - PATHOLOGY: *C. Neoformans* yeast has an enormous polysaccharide capsule, which renders helpless when immunocompromised.
- **ASPERGILLUS:** They invade the microvasculature, and in immunocompromised hosts, they can lead to multiple hemorrhagic infarcts.
- **MUCOR MYCOSIS:**
    - PATHOGENESIS: *Rhizopus* molds infect the nasal cavity and paranasal sinuses by being inhaled.
        - Occurs in immunocompromised and poorly controlled Diabetics.
    - PATHOLOGY: They invade blood vessels in CNS ------> inflammation and infarction. Deadly.
- **HISTOPLASMOSIS**: Can form non-caseating granulomas in the brain (immunocompromised), which resembles Sarcoidosis histologically.

**PARASITIC INFECTIONS**:

- **TOXOPLASMOSIS**: *Toxoplasma Gondii*
    - PATHOLOGY: **Ring-enhanced lesion** is frequently seen on CT with AIDS patients.
        - Center of lesion is often necrotic and devoid of bugs. Bugs are around the perimeter of the lesion, which is where biopsy should be taken.
        - Cysts are formed in the brain, which eventually rupture. Immunocompetent folks then kill all the bugs.
            - **Bradyzoites** remain within the cyst: slowly-reproducing toxoplasma.
            - **Tachyzoites** is the name of the bugs that rupture from the cyst. Rapidly proliferating if not checked by immunity.
- **CYSTICERCOSIS**: *Taenia Solium*, pork tapeworm. It is the leading cause of Epilepsy in Mexico, where they eat undercooked pork.
    - PATHOLOGY: Cysticerci (the eggs) go to brain where they occupy space (cystic, non-inflammatory). Once they die, inflammation ensues.
- **AMEBIASIS**: Rarely, it infiltrates the brain through the lamina cribrosa into the frontal meninges.
- **MALARIA:** *Only P. Falciparum* can cause problems in the brain via **microinfarcts** and hemorrhages in the blood. The other Plasmodium species don't do it.

**CEREBRAL ABSCESS**: Can be caused by mastoiditis, chronic sinusitis, otitis media.

- Actually see fibroblasts infiltrating the infection and walling it off to form an abscess.
- Daughter abscesses may form beneath the original abscess, spreading the infection.

**ENCEPHALITIS**:

- GENERAL FEATURES: The entire brain will show massive active **hyperemia** -- red and bloody.
    - **Cuffing**: Perivascular lymphocytic infiltrates, lymphocytes marginating on the side of venules. This can lead to **hemorrhage** secondarily.
    - **Microglial nodules**: glial scars left by the virus. Microglial nodules are characteristic of viral infections.
- **POLIOMYELITIS**:
    - PATHOLOGY: Inflammation of the anterior horn (grey matter) of the spinal cord. Polio normally infects and destroys neurons in the *anterior horn* and *brain-stem nuclei*.
        - **Bulbar Poliomyelitis** is infection brain-stem nuclei, which is deadly, as polio destroys the respiratory centers of the brain.
    - SYMPTOMS: Initially fever, malaise, headache, followed shortly by meningeal signs, motor deficits, and paralysis.
        - Residual Symptoms: Asymmetric and patchy paralysis, most prominently in lower limbs.
- **RABIES**:
    - PATHOGENESIS:
        - Virus replicates in striated muscle at site of bite. Then it travels up nerve endings to spinal cord and brain.
        - Virus hooks to Acetylcholine receptors at neuromuscular junction.
    - PATHOLOGY: The virus localizes to the **hypothalamus** and **CN nuclei** of brain stem (particularly CN IX and X)
        - **Negri Bodies:** Characteristic cytoplasmic inclusions.
    - SYMPTOMS: Fatal encephalitis. hypertonic muscle contraction, convulsions, coma, death.
        - **Madness:** Results from infection of hypothalamus.
        - **Hydrophobia**: Results form excruciating pain on swallowing, as it would precipitate spasmodic contraction of throat muscles.
- HERPES ENCEPHALITIDES:
    - **HSV ENCEPHALITIS**: *The most important viral infection of the human nervous system.* Primarily HSV-1 infection.
        - PATHOGENESIS: In Herpes Labialis, HSV-1 probably resides dormant in the Gasserian (Trigeminal) Ganglion. The proximity of this ganglion to the temporal lobes explains the virus' affinity for the temporal lobes.
        - CLINICAL:
            - HSV-1 infection is localized to one or both **temporal lobes**. Usually it is unilateral.
            - **Infantile HSV Encephalitis:** Infants infected through the birth canal (with HSV-2) get a **viremia** and get Encephalitis *all over the brain*, rather than in just the temporal lobes.
        - PATHOLOGY: Fulminant infection, temporal lobes become swollen, hemorrhagic, necrotic.
            - **Nuclear inclusions**: Viral inclusions are in the nucleus and not the cytoplasm, although viral particles may be found in the cytoplasm as well.
    - **CYTOMEGALOVIRUS (CMV)**: Causes encephalitis in immunocompromised hosts.
        - PATHOLOGY: Will see periventricular calcifications grossly in the brain.
            - **CMV inclusions** are characteristic gigantic inclusions, which are both cytoplasmic and nuclear.
        - CLINICAL:
            - In fetuses, CMV infection leads to the TORCH complex.
            - In babies, CMV encephalitis is fatal.
- ARTHROPOD-BORN ENCEPHALITIDES: Family of encephalitides caused by **Arboviruses**. The viruses natural host is **birds**, and many of them infect horses as well as people.
    - ST. LOUIS ENCEPHALITIS:
    - WESTERN EQUINE ENCEPHALITIS: More benign disease.
    - VENEZUELAN ENCEPHALITIS:
    - EASTERN EQUINE ENCEPHALITIS: Deadly. 50% mortality.
    - CALIFORNIA ENCEPHALITIS:
- **ENCEPHALITIS LETHARGICA (VON ECONOMO ENCEPHALITIS)**: Preferentially infects the midbrain, and the encephalitis that in 1917 caused an epidemic that subsequently led to a lot of cases of **Parkinson's Disease**.

- **SUBACUTE SCLEROSING PANENCEPHALITIS (SSPE)**: Sequel to Measles infection. Protracted, insidious disease causing personality changes, cognitive deficits, ultimately stupor and death.
- **PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)**: Caused by the **JC Papovavirus**, which normally inhabitates the kidney in healthy hosts.
    - PATHOLOGY: The JC virus characteristically infects **oligodendrocytes**, leading to oligodendrocyte death and **demyelination**.
        - **Ground-glass inclusions**: Oligodendrocytes contain characteristic inclusions.

**AIDS ENCEPHALOPATHY**: Manifested clinically as a progressive dementia, accompanied by motor abnormalities.

- PATHOGENESIS: Caused by HIV-1 infection of macrophages and microglial cells in the CNS.
- PATHOLOGY:
    - Multinucleated giant cells and microglial nodules will be found.
    - Vacuolar degeneration of the white matter.

SPONGIFORM (PRION) ENCEPHALOPATHIES:

- KURU:
- CREUTZFELDT-JACOB DISEASE (CJD):
- GERSTMANN-STRAUSSLER-SHEINKER SYNDROME (GSS):
- ANIMAL DISEASES: Mad Cow Disease and Scrapie.

DEMYELINATING DISEASES:

- **MULTIPLE SCLEROSIS (MS)**: *The most common chronic CNS disease of young adults*, with prevalence approaching 1:1000.
    - PATHOGENESIS:
        - Immune Factors: Probably a Type-II hypersensitivity immune response against **myelin basic protein**, resulting in demyelination. This has not been proven, though.
            - Perivascular lymphocytes and macrophages are found in chronic MS lesions.
            - **Experimental Autoimmune Encephalitis (EAE):** Experimental model in primates, showing pathological findings similar to MS when the primates were injected with myelin basic protein.
        - Genetic Factors: HLA-DR2, 25% MZ concordance.
        - Environmental Factors: The disease is predominantly found in temperate climates.
    - PATHOLOGY: Patchy demyelination throughout the white matter.
        - **MS Plaque**: The hallmark lesion of MS. Visible grossly in the white matter of the cortex.
            - Plaque Locations: It is often found along the optic nerve and chiasm. Later it localizes to the paraventricular white matter of the corona radiata.
            - Plaque Contents:
                - Total loss of myelin is found in the plaque.
                - Perivascular lymphocytic infiltrates are found in the region.
                - Also see macrophages and lots of edema.
    - DIAGNOSIS: Demonstrate 2 or more separate CNS lesions, with positive focal neurological signs.
    - CLINICAL: Onset in 30's-40's, with exacerbations and remissions occurring over many years. Life expectancy can be 20-30 yrs, and death is often by complications of respiratory failure, or coma.
        - Female:male ration of 1.5:1
        - Lateral Gaze Paralysis, blurred vision, are common early findings, because the earliest plaques tend to be found at Medial Longitudinal Fasciculus (MLF), the area that controls conjugate gaze.
- METACHROMATIC LEUKODYSTROPHY (MLD): A metabolic disorder, usually of infancy, characterized by myelin loss, accumulation of metachromatic lipids (**galactosyl sulfatidates**) in the white matter of the central and peripheral nervous systems, progressive paralysis, and mental retardation; psychosis and dementia are seen in adults
    - autosomal recessive inheritance
    - A deficiency of **arylsulfatase**
- KRABBE DISEASE: A metabolic disorder of infancy with rapidly progressive cerebral degeneration, massive loss of myelin, severe astrocytic gliosis, and infiltration of the white matter with characteristic multinucleate globoid cells; metabolically there is gross deficiency of lysosomal cerebrosidase (**galactosylceramide beta-galactosidase**); autosomal recessive inheritance

- ADRENOLEUKODYSTROPHY (ALD): An X-linked recessive disorder affecting young males, characterized by chronic adrenocortical insufficiency, skin hyperpigmentation, progressive dementia, spastic paralysis, and other intellectual and neurological disturbances, due to myelin degeneration in the white matter of the brain.
- ALEXANDER DISEASE: A rare, fatal central nervous system degenerative disease of infants, characterized by psychomotor retardation, seizures, and paralysis; megaloencephaly is associated with widespread leukodystrophic changes, especially in the frontal lobes.
- POSTINFECTIOUS ENCEPHALOMYELITIS:
- CENTRAL PONTINE MYELINOLYSIS (PONTINE DEGENERATION):

NEURONAL STORAGE DISEASES:

- TAY-SACHS DISEASE:
- HURLER SYNDROME:
- GAUCHER DISEASE:
- NIEMANN-PICK LIPIDOSIS:

METABOLIC NEURONAL DISEASES:

- PHENYLKETONURIA (PKU):
- CRETINISM:
- WILSON DISEASE:

VITAMIN DEFICIENCIES:

- WERNICKE SYNDROME: Caused by Thiamine deficiency, usually secondary to malnutrition and alcoholism.
- HEPATIC ENCEPHALOPATHY: Caused by excessive $NH_3$, secondary to hepatic failure.
- SUBACUTE COMBINED DEGENERATION of SPINAL CORD: Caused by Vitamin-B12 deficiency.

DEGENERATIVE DISEASES:

- **PARKINSON DISEASE**:
  - PATHOGENESIS: Loss of dopamine in Nigrostriatum leads to over-activation and dysregulation of the Basal Ganglia.
    - **Idiopathic Parkinsonism**: Most common, occurs with elderly.
    - **Von-Economo Encephalitis**: Encephalitis Epidemic of 1917, as portrayed in Awakenings, led to Parkinsonian symptoms.
    - Averse Effects of Anti-Psychotics.
    - **MPTP** is a by-product of some street-drug opioids, which can cause Parkinsonian symptoms. Creutzfeldt-Jacob Disease has Parkinsonian symptoms.
  - PATHOLOGY:
    - **Depigmentation:** Substantia Nigra normally appears black on cross-section, whereas in Parkinson's disease it is not pigmented.
    - **Lewy Bodies:** Spherical eosinophilic cytoplasmic inclusions found within some neurons of the Substantia Nigra.
  - SYMPTOMS:
    - Lead Pipe Rigidity: Resistance to movement.
    - **Resting Tremor**: To be distinguished from an intention tremor (as in Cerebellar Syndrome). This is a tremor when there is no movement.
      - This tremor is of a lower frequency than corresponding Intention Tremor (tremor with voluntary cerebellar movements)
      - The tremor is better when in motion, so it is less debilitating than a moving tremor.
    - **Akinesia / Bradykinesia**: Inability to initiate movement, or slow initiation of movement.
      - This symptom responds well to treatment.
    - Postural Instability
    - Cognitive Problems
- **HUNTINGTON DISEASE**:
  - PATHOGENESIS:

        - **Autosomal Dominant**: **Chrom 4** defect is one of the few truly autosomal dominant disorders, where one bad gene leads to full expression of the disease.
            - **Genomic Imprinting:** When the gene is inherited from the father rather than the mother (paternal allele), clinical disease manifests earlier and tends to be more severe.
    - PATHOLOGY: Bilateral atrophy of the **putamen** and **head of the caudate** nucleus.
    - SYMPTOMS: Involuntary movements of all parts of the body, cognitive and emotional disturbances.
        - Disease onset can occur anywhere from childhood to adulthood. Onset is usually at about 40 years of age.
        - The cognitive and emotional disturbances precede the motor disturbances, sometimes by several years.
        - **Chorea:** Irregular, spasmodic, involuntary movements of the limbs or facial muscles, often accompanied by hypotonia.
        - **Athetosis**: Constant succession of slow, writhing, involuntary movements of flexion, extension, pronation, and supination of the fingers and hands, and sometimes of the toes and feet.
- **AMYOTROPHIC LATERAL SCLEROSIS (ALS, LOU GEHRIG DISEASE)**:
    - PATHOGENESIS / EPIDEMIOLOGY: Patients are in 50's. Most cases are sporadic, but some familial cases (Chrom 21q) have been identified.
    - PATHOLOGY: **Loss of motor neurons** accompanied by gliosis.
        - THREE LOCATIONS: Neurons are damaged and/or lost in three characteristic areas
            - Anterior horn of spinal cord
            - **Hypoglossal Nucleus (CN XII)** is brain stem.
            - Upper motor neurons of cerebral cortex: many of the giant **pyramidal cells of Betz** are lost.
    - SYMPTOMS: Usually fatal within 2-4 years of onset.
        - Progressive muscular atrophy: affected muscles are pale and shrunken.
        - Increased reflexes, due to upper motor neuron lesion. Positive Babinski. Spastic irritability of muscles.
        - **Fasciculations** (fibrillary twitching) is an early sign of disease.
        - Unintelligible speech due to lost control of tongue.
        - *Intellectual function remains intact* to the end.
- **ALZHEIMER DISEASE**:
    - PATHOGENESIS:
        - **Amyloid beta-Protein**: Amyloid fibrils accumulate in the neuritic plaques of Alzheimer's.
            - The gene for the Amyloid Precursor Protein is located on Chrom 21, and **Down's Syndrome** (Trisomy 21) is characterized by early-onset Alzheimer's.
        - **Neurofibrillary Tangles**: Paired helical fragments consisting of an abnormal form of microtubule-associated protein (MAP). Normally, this protein is thought to stabilize microtubules in neurons, but in Alzheimer's it is dysfunctional.
    - PATHOLOGY: Dementia is accompanied by cerebral atrophy and widened cerebral fissures.
        - The morphological findings constitute a TRIAD:
            - **Neuritic Plaques:** Spherical lesions containing a dense core of amyloid.
            - **Neurofibrillary Tangles:** Occupy the cytoplasm of pyramidal cells. Under EM, they appear as paired helical filaments. They are often found but are not pathognomonic.
            - **Granulovacuolar Degeneration**: Refers to circular clear zones in the cytoplasm of pyramidal cells of the hippocampus. Often accompanied by the neurofibrillary tangles.
                - **Hirano Bodies:** Eosinophilic rods found within the neurons of the hippocampus.
        - Generalized cerebral atrophy, with narrow gyri and widened cerebral fissures.
    - CLINICAL: Irreversible, relentlessly progressive dementia.
- **PICK DISEASE**:
    - PATHOLOGY: *Frontal* or *temporal* **lobar atrophy.** Unlike Alzheimer's, the atrophy is restricted to the frontal and temporal lobes.
        - **Pick Bodies:** Both eosinophilic, and stain heavily with silver stain (**argentophilic**), characteristic inclusions of densely aggregated neurofilaments.
        - Balloon Neurons: Neurons are swollen and contain no Nissl substance.
    - CLINICAL: The dementia is indistinguishable from Alzheimer's dementia.
- SPINOCEREBELLAR DEGENERATION:
    - CEREBELLO-OLIVARY DEGENERATION of HOLMES
    - FRIEDRICH ATAXIA:

BRAIN CANCER GENERAL FEATURES:

- BENIGN -vs- MALIGNANT:

- "Benign" tumors are still invasive, but they are called benign because their growth is indolent, and survival may be 5-10 years.
- Benign tumors can be deadly due to the physical presence of the tumor and mass action (infarct, herniation).

- GENERAL SYMPTOMS:
  - Headache
  - Cognitive loss
  - **Seizures**: Either motor or sensory, depending on location. Especially associated with meningiomas and benign neuroectodermal tumors (astrocytoma, oligodendroglioma, ganglioneuroma).\

NEUROECTODERMAL TUMORS:

- **ASTROCYTE TUMORS**:
  - CLINICAL: *The older the patient, the more likely it is that an astrocyte tumor will be malignant.* The location of astrocytic tumors also correlate with AGE:
    - **Adulthood / Old Age**: Tumors occur in cerebral hemispheres and are usually malignant (Glioblastoma Multiforme)
    - **Young Adults / Adolescence**: Tumor occurs in spinal cord.
    - **Childhood**: Tumors occur in cerebellum, midbrain, pons, optic nerve, and are usually benign (Astrocytoma).
  - **ASTROCYTOMA**: About 20% of primary brain tumors.
    - LOCATIONS:
      - **Brain-stem Glioma**: Childhood astrocytoma of the pons, which is inoperable and therefore **fatal**.
        - The tumor is diffuse and grossly resembles "hypertrophy" of the pons.
      - **Cerebellar Astrocytoma:** Tumor has cystic structure and is **curable** because it can be operated on.
    - PATHOLOGY: Tumor generally has poorly defined borders and a fish-flesh appearance.
    - CLINICAL: Average life-expectancy of about 5 years.
  - **ANAPLASTIC ASTROCYTOMA**: Intermediate-grade tumor, with greater cellularity, higher pleomorphism, and more anaplasia than the Astrocytoma. Life expectancy = 3 years.
  - **GLIOBLASTOMA MULTIFORME**: *Glioblastoma Multiforme is more common and more deadly than benign Astrocytoma.* 40% of all primary brain tumors, and the most common brain tumor of old people.
    - PATHOLOGY: Hemorrhage and necrosis is common. Red = recent hemorrhages; yellow = remote hemorrhages.
      - Endothelial-Cell Proliferation: The tumor secretes a vasogenic factor, causing endothelial proliferation. This can lead to further hemorrhage.
    - CLINICAL: Life expectancy 18 months.
      - **Butterfly Glioblastoma:** Rapidly fatal, bilateral tumor of the cerebral hemispheres, that crosses the Corpus Callosum.
- **OLIGODENDROGLIOMA**: Tumor of oligodendrocytes occurring in white matter.
  - PATHOLOGY:
    - **Fried-Egg Cells:** Eosinophilic cells with a halo. Characteristic fried-egg appearance.
  - CLINICAL: Life expectancy is decent, 12-15 yrs.
    - **Seizures:** Due to proliferation of myelin, seizures are very common.
- **EPENDYMOMA**:
  - LOCATION: They usually arise in the **fourth ventricle** or **filum terminale**. Paradoxically, they rarely arise in the Lateral Ventricles, where there is the most ependymal tissue.
  - PATHOLOGY:
    - **Perivascular Rosettes**
  - SYMPTOMS: Occurs in children and young adults.
    - Hydrocephalus secondary to obstruction. Complications may include herniation.
- **MEDULLOBLASTOMA**: Common neuronal tumor of childhood, that *always occurs in the cerebellum*.
  - PATHOGENESIS: Tumor cells originate from the **external granular layer** of the cerebellar cortex. These cells normally only exist for about the first year of life.
  - PATHOLOGY: It's a **small-blue-cell tumor.**
    - **Rosettes:** The little blue cells arrange themselves into rosettes, often with blood vessel in the middle.
  - LOCATION: The tumors almost exclusively arise in the **cerebellar vermis**.
  - CLINICAL: 65% cure rate.

        - **Metastases** can occur all the way down the spine to the sacrum. It can be treated with radiation therapy, but you must radiate all the way the spine to prevent recurrence of the tumor.
    - SYMPTOMS: Child will have cerebellar dysfunction, maybe hydrocephalus.
    - TREATMENT: Ionizing radiation is effective, but the tumor often disseminates through subarachnoid space before it can be treated.
- **PAPILLOMA of CHOROID PLEXUS:** Occurs in babies.
    - **Hypersecretory Hydrocephalus:** The tumors can be functional, leading to hypersecretion of CSF by the choroid plexus and hence hydrocephalus.
- GANGLIOGLIOMA: A rare tumor comprised of a glioma component and an atypical neuronal (ganglion) cell component; in younger patients often associated with seizures.

MESENCHYMAL TUMORS:

- **MENINGIOMA**: Common benign tumor of adults, peak incidence in 4$^{th}$ decade, but young adults get it too. It can occur almost anywhere along calvarium.
    - PATHOGENESIS: The tumor cells originate from the **arachnoid membrane**.
    - PATHOLOGY: They are well-encapsulated, and they displace the brain tissue but do not infiltrate it.
        - **Psammoma Bodies:** Whorled structures with calcifications on the inside of the whorl.
        - **Hyperostosis:** Reactive bone formation in the overlying skull table can occur in response to the tumor. This can complicate surgery.
    - SYMPTOMS: Wide variety of locations depending on location and size of tumor.
        - **Seizures** are more common the neurological deficits, since neuronal tissue is compressed rather than destroyed.
        - Headaches are common.
    - TREATMENT: Surgery is curative -- when the meningioma can be reached.
- SCHWANNOMA: See Schwannoma below.

ECTOPIC TUMORS:

- CRANIOPHARYNGIOMA: See Endocrine.
- DERMOID and EPIDERMOID CYSTS:
- LIPOMA:
- GERM-CELL TUMORS: See Endocrine.
- **HEMANGIOBLASTOMA**: Usually occurs in cerebellum, but can occur elsewhere.
    - PATHOLOGY: Composed of capillaries and stromal cells.
    - CLINICAL:
        - In 20% of cases, the endothelial cells secrete erythropoietin and induce polycythemia.
        - Associated with Lindau Syndrome and von-Hippel Lindau Syndrome.
- LYMPHOMA:
- **METASTASES**: Metastases to brain are common.
    - **Bronchogenic Carcinoma**
    - **Malignant Melanoma**
    - Also breast, kidney, colon.
- **COLLOID CYST (PARAPHYSEAL CYST)**: Benign cyst made of respitratory epithelium. It can obstruct the foramen of Munro, and it contain mucus concretions. Complete obstruction can lead to instant death.

HEREDITARY INTRACRANIAL NEOPLASMS:

- **NEUROFIBROMATOSIS**: Autosomal dominant disorder featuring neurofibromas, cafe-au-lait spots, and ocular abnormalities.
    - **Neurofibromatosis Type-I (Von Recklinghausen Disease):** Relatively common. Mostly skin and nerve lesions. Optic nerve gliomas.
    - **Neurofibromatosis Type-II:** Bilateral acoustic neuromas, multiple meningiomas. Actually a separate genetic origin and a different disease.
- **TUBEROUS SCLEROSIS (BOURNEVILLE DISEASE)**:
    - PATHOGENESIS: Autosomal dominant with varied penetrance.
    - PATHOLOGY:

        - **Tubers:** Hamartomas, bizarre conglomerates of nerve cells and glial cells, occurring throughout the CNS.
        - **Candle Guttering:** Tubers, with giant astrocytes, studding the ventricular walls. They are at risk of forming **subependymal giant cell astrocytoma**.
    - SYMPTOMS: Seizures, mental retardation.
- **LINDAU SYNDROME**: Hereditary cerebellar hemangioblastoma.
    - **VON-HIPPEL LINDAU SYNDROME:** Hereditary hemangioblastomas occurring in the retina and the CNS.
        - Other Symptoms: Pheochromocytoma, renal cysts and tumors, pancreatic cysts and tumors.
- **STURGE-WEBER SYNDROME (ENCEPHALOFACIAL ANGIOMATOSIS)**: *Not familial or inherited*. Rare, angiomas of the brain and face.
    - PATHOLOGY:
        - **Port Wine Stain:** Characteristic angioma of the face.
        - Will see venous distensions in the meninges, particularly in Parieto-Occipital area.
    - SYMPTOMS: Mental deficiency.

**PERIPHERAL NERVES and MUSCLES**

REACTIONS to INJURY:

- AXONAL DEGENERATION:
  - **DISTAL AXONOPATHY**: Selective degeneration of the distal parts of axons, sparing the central part nearer the cell body.
    - **Dying-Back Neuropathy:** Neuropathies that are restricted to the distal portions of the axons.
  - NEURONOPATHY: Neuropathy focused on the central part of the neuron, much less common. Occurs with poliomyelitis.
  - **WALLERIAN DEGENERATION**: After an injury to an axon, the subsequent degeneration of all axonal fibers distal to the injury.
    - All fibers proximal to the injury are unaffected, because they can still get nutrition from the neuronal cell body.
- SEGMENTAL DEMYELINATION: Preferential loss of myelin, without actually destroying the axonal fibers.

PERIPHERAL NEUROPATHIES:

- INFLAMMATORY DEMYELINATING NEUROPATHY
- DIABETIC NEUROPATHY
- UREMIC NEUROPATHY
- ALCOHOLIC NEUROPATHY
- VASCULITIC NEUROPATHY
- TOXIC NEUROPATHY
- PARANEOPLASTIC NEUROPATHY
- AMYLOID NEUROPATHY
- PARAPROTEINEMIC NEUROPATHY
- HEREDITARY NEUROPATHY:
  - **CHARCOT-MARIE-TOOTH DISEASE**: Hereditary Peroneal Muscular Atrophy. It is the most common form of *inherited* peripheral neuropathy.
- AIDS NEUROPATHY
- CRYPTOGENIC NEUROPATHY

NERVE TRAUMA:

- TRAUMATIC NEUROMA:
- PLANTAR NEUROMA (MORTON NEUROMA):

NERVE TUMORS:

- SCHWANNOMA:
  - **ACOUSTIC SCHWANNOMA (ACOUSTIC NEUROMA)**: Intracranial schwannoma that always occurs on the eighth nerve.
    - LOCATION: Always occurs at the transition where oligodendroglial cells become peripheral Schwann cells. This corresponds to the **internal auditor meatus.**
    - SYMPTOMS: Tinnitus, deafness, eight nerve palsies, Bell's Palsy (compression of Facial Nerve in Internal Auditory Meatus).
  - INTRASPINAL SCHWANNOMA: Occurs along the **dorsal roots** of the spinal cord, but not the ventral roots.
- NEUROFIBROMA:
- MALIGNANT SCHWANNOMA (NEUROFIBROSARCOMA):

MYOFIBRIL TYPES:

| **Type-I Muscle Fibers** | **Type-II Muscle Fibers** |
|---|---|
| **Red, Slow-Twitch** | **White Muscle, Fast-Twitch** |

| | |
|---|---|
| Aerobic, mitochondrial metabolism. Contains lots of myoglobin. | Embden-Meyerhof Pathway, Glycolysis. |
| Muscles don't change size much with exercise. | Muscles can hypertrophy with androgenic steroids, or atrophy with disuse. |
| Postural muscles undergoing tonic contraction. | Clonic, fast contractions. |
| Do not stain for ATPase | Stains darkly for ATPase. |

- The myofibril type is determined by the lower motor neurons.
- In humans, no muscle is composed of a single myofibril type.

**DUCHENNE/BECKER MUSCULAR DYSTROPHY:** Severe muscle-wasting disease.

- PATHOGENESIS: Deficiency of enzyme **Dystrophin**, a membrane cytoskeletal protein, like spectrin, found in muscle. Located on X-Chromosome.
    - Dystrophin molecules form an intracellular network (anchored to cytoplasm), important in forming mechanical properties of muscle.
    - Muscles lacking dystrophin increased osmotic fragility, less flexibility, and don't have normal interactions between the sarcolemma and extracellular calcium.
- PATHOLOGY: Relentless degeneration of muscle fibers with progressive fibrosis.
    - Regenerative Process: Some muscle regeneration occurs in response to the destruction, but regenerative efforts are eventually overcome by fibrosis.
    - End-Stage: Muscles have been replaced with fibrofatty tissue. Skeletal muscle is almost completely gone, while muscle spindles are relatively spared.
- LABS:
    - **Alkaline-Phosphatase Reaction**: Unlike the inflammatory myopathies, it does not excessively stain endomysial connective tissue.
    - **Creatinine Kinase** is markedly elevated.
- SYMPTOMS: Death by 17 years
    - Failure to walk by 18 months
    - **Pseudohypertrophy** of calf muscles.
    - Progressive retardation.
    - Cardiac problems (frequent cause of death)

**DERMATOMYOSITIS**:

- PATHOGENESIS: Thought to be autoimmune etiology.
- PATHOLOGY: Autoantibodies and **complement-mediated** attack against the microvasculature of skeletal muscle tissues, leading to skeletal muscle ischemia.
    - **Perifascicular Atrophy:** Atrophy of muscle fibers around the periphery of a fascicle, near the perimysium. It is due to chronic and repeated ischemia of muscle fascicles. Central fibers are spared, because they have a better blood supply.
    - Involvement of the skin in dermatomyositis is presumably related to the same autoantibodies against microvasculature.

**MYASTHENIA GRAVIS (MG)**:

- PATHOGENESIS: Caused by autoantibodies directed against the acetylcholine receptor at the neuromuscular junction.
    - Thymus plays a role in pathogenesis, and disease is associated with thymomas.
- CLINICAL: **Fatigable weakness** results from inflammation at the motor end-plate and decreased number of receptors.
    - **Cholinesterase Inhibitors** will make MG patients stronger, while it will make normal patients ultimately weaker.