Neuro - Tissue Reactions

- Anoxia
  - Neurons most sensitive to anoxia reside in the hippocampus, Purkinje cells, and larger neocortical neurons
  - Affect watershed areas first
  - "red" shrunken neurons
- Decreased consciousness can result from diffuse axonal injury in absence of localizing findings with trauma
  - Due to stretching and tearing of axons
- Primary reaction to injury – edema
  - Return of function related to resolution of edema
- Liquefactive necrosis

Bacterial Meningitis

- Suppurative involvement of the meninges
  - Located in subarachnoid space; communicates with CSF
- Hematogenous dissemination
  - No complement in CSF
- CSF
  - Increased protein, decreased glucose
  - PMNs
  - Gram stain – bacteria
  - Positive culture
- Clinical features
  - Headache, fever
  - Nuchal rigidity, Kernig’s sign
  - Focal neurological deficits
  - Increased intracranial pressure

Other Infections

- Viral meningitis
  - “aseptic meningitis”
  - Slight increase protein, no decrease in glucose
  - Lymphocytes
  - Echovirus, mosquito-borne viruses (west nile virus, eastern equine virus)
- Brain Abscess
  - “ring” enhancement of abscess
    - central area of low density, & surrounding area of low density due to edema
  - Fibrosis around abscess
  - CSF – increased protein, few cells

Bacterial Meningitis

<table>
<thead>
<tr>
<th>Group</th>
<th>Gram pos cocci</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal</td>
<td>Group B strep E coli</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-18 years</td>
<td>Neisseria meningitidis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5 and &gt;25 years</td>
<td>Streptococcus pneumoniae</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV Drug user</td>
<td>Staphylococcus aureus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonate or immunosuppressed child</td>
<td>Listeria monocytogenes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Syphilis

- Meningovasculitis
  - Infiltration of meninges and vessels by lymphocytes and plasma cells; may cause symptoms of meningitis or vascular occlusion.
- General Paresis
  - Atrophy, loss of cortical neurons especially in frontal lobes, gliosis, proliferation of microglial cells (rod cells), perivascular lymphocytes and plasma cells.
- Tabes Dorsalis
  - Inflammatory lesions involving dorsal nerve roots. Loss of axons and myelin in dorsal roots with Wallerian degeneration of dorsal columns. (T. pallidum is absent in cord parenchyma.)
### Encephalitis

- **Viruses**
  - Headache, fever, seizure, altered consciousness
  - Increased intracranial pressures, no other CSF findings
  - Neonates and immunosuppressed – herpes, cytomegalovirus, HIV
  - Adults – vector-borne infections (West Nile, eastern equine, etc.); polio
  - Most hematogenous
  - Spread along nerves: rabies, herpes simplex

- **Pathology**
  - Perivascular cuffing by lymphocytes and plasma cells;
  - Neuronal necrosis;
  - Inclusion bodies;
  - Microglial proliferation and glial nodules;
  - Hemorrhagic necrosis
  - Rod cells: reactive microglial cells

### Specific Pathologic Findings

- **Herpes**
  - Necrosis and hemorrhages in temporal lobe
- **Cytomegalovirus**
  - Owl’s eye nuclear inclusions; cytoplasmic inclusions
  - Periventricular necrosis, focal calcifications
- **Rabies**
  - Negri bodies in Purkinje cells of cerebellum

### HIV

- **Immunosuppression**
  - Cryptococcus (India ink preparation) – mononuclear, normal protein, normal glucose
  - Herpes, cytomegalovirus, toxoplasmosis, PML
- **AIDS-Dementia Complex**
  - Cognitive, motor, and behavioral dysfunction. The symptoms are due to subcortical lesions, with microscopic changes mainly in basal ganglia, thalamus, and subcortical white matter
  - HIV antigen is found in microglia, macrophages and multinucleated giant cells (formed by fusion of macrophages)
  - Microscopic changes include: foci of necrosis, gliosis, and/or demyelination, microglial nodules, multinucleated cells

### Progressive multifocal leukoencephalopathy

- More common in immunosuppressed
- Intellectual deterioration and dementia over months
- JC papovavirus
- Multiple (multifocal) areas of demyelination in the white matter
- Little, if any, inflammatory reaction
- Inclusion bodies found in oligodendrocyte nuclei, large astrocytes with bizarre nuclei

### Subacute Sclerosing Panencephalitis

- Rare disease of children and adolescents
- Associated with a defective measles virus (myxovirus)
- Personality changes, intellectual decline progressing to dementia. The course is progressive deterioration, with a duration of 1 month to several years.
- Changes involve both white matter and gray matter with cortical atrophy and demyelination.
- Oligodendrocytes and neurons contain inclusion bodies

### Spongiform Encephalopathy

- **Creutzfeldt-Jakob Disease**
  - 40 and 80 years of age
  - Sporadic; transmission has occurred by corneal transplant or administration of contaminated growth hormone
  - Dementia and myoclonus
  - Deterioration, with death occurring usually in 3-12 months
  - Routine CSF findings are usually normal
  - Spongiform encephalopathy in gray matter throughout brain and spinal cord
- **Kuru** - Cannibalism
- **"Mad Cow" Disease** – new variant CJD
Toxicities

- Alcholol
  - Associated with petechial hemorrhages and gliosis of the mamillary bodies, discoloration of structures (hemosiderosis) surrounding the third ventricle, aqueduct, and fourth ventricle
  - toxic vs. nutritional; DEFICIENCY OF THIAMINE
  - peripheral neuropathy
    - bilateral limb numbness, tingling, and paresthesia
  - alcoholic cerebellar degeneration; ataxia, wide-based gait; cerebellar vermic atrophy
  - cognitive problems and dementia
  - psychiatric: anxiety, hallucinations, paranoid delusions

Toxicities

- Systemic Diseases
  - Liver failure (alcoholic cirrhosis): hyperammonemia – asterixis
  - Uremia: symmetric, peripheral neuropathy
  - Diabetes
    - Bilateral symmetrical neuropathy
    - Autonomic instability
    - Neurogenic bladder
  - Nutritional
    - subacute combined degeneration – Vitamin B12
      - generalized weakness and paresthesias; loss of vibration and position sense; motor defects limited to legs; mental symptoms include irritability, apathy, somnolence, suspiciousness, confusional psychosis, and intellectual deterioration
      - folic acid deficiency: developmental abnormalities, especially closure of neural tube

Trauma – Intracranial Hemorrhages

- Epidural hematoma
  - Middle meningeal artery
    - “lucid” interval between an initial loss of consciousness and later accumulation of blood
    - Worse prognosis (comatose, herniation)
- Subdural hematoma
  - Delayed onset of symptoms – headache and confusion
  - Localized hematoma in association with skull fracture
  - Tearing of bridging veins beneath the dura
- Duret hemorrhages
  - Medial temporal lobe herniation

Berry Aneurysm

- Congenital weakness of intracerebral artery wall (1 in 100)
- Saccular aneurysm near Circle of Willis
- If ruptures, results in subarachnoid hemorrhage (headache, blood in CSF)
- Rupture when reach 4-7 mm
- Often asymptomatic until rupture
- Associated with other malformations, familial syndromes
  - Autosomal dominant polycystic disease
  - Ehler’s-Danlos syndrome
- Does not result in herniation
Other Hemorrhages

- germinal matrix hemorrhage
  - Premature infants
    - Hypoxemia, hypercarbia, acidosis, changes in blood pressure
  - Hemorrhage into germinal matrix
  - Extend into cerebral ventricles (intraventricular hemorrhage)
  - Organization of blood can lead to obstruction of aqueduct of Sylvius and hydrocephalus
- "coup" injury
  - Injury to stable head adjacent to site of blow
- contrecoup injury
  - Moving head strikes a stable object
  - Force is transmitted to opposite side of the head
    - Backward fall – contusions to inferior frontal lobes, temporal tips, and inferior temporal lobes

Alzheimer’s Disease

- Progressive dementia with memory loss
- Neurofibrillary tangles
  - Hippocampus, amygdala, neocortex
  - "congophilic angiopathy" – deposition of amyloid in arteriolar media
- Multiple associations
  - Formation and aggregation of the Aβ peptide derived from abnormal processing of amyloid precursor protein; cleavage by β-secretase
  - Inheritance of ApoE4 gene
  - Mutations in presenilin genes
- Cerebral atrophy (hydrocephalus ex vacuo)

Degenerative Diseases

- Parkinson’s
  - Clinical findings
    - Difficulty initiating movement
    - Muscular rigidity
    - Expressionless facies
    - "pill-rolling" tremor
  - Loss of pigmented neurons in substantia nigra
- Pick’s disease
  - Similar to Alzheimer’s, but more frontal features and less memory loss
  - "knife-like" gyral atrophy of frontal and temporal lobes; sparing of parietal and occipital lobes
  - Pick bodies – intracytoplasmic, faintly eosinophilic rounded inclusions
  - Stain for tau protein

Degenerative Diseases

- Huntington’s Chorea
  - Midlife
  - Autosomal dominant
  - Worsening choreiform movements
  - Behavioral change without memory loss
  - Expansion of CAG repeats on chromosome 4 (huntingtin gene)
  - Atrophy, neuronal loss with gliosis in caudate, putamen, and globus pallidus
- Dementia with Lewy bodies
  - Clinical features of Alzheimer’s and idiopathic Parkinson’s
  - Spheroidal, intraneuronal, cytoplasmic, eosinophilic inclusions – stain for α-synuclein

Inherited Degenerative – Children

- Tay-Sachs
  - Disease of infancy and childhood
  - Deficiency of hexosaminidase A
- Metachromatic leukodystrophy
  - Affect white matter extensively
  - Cause myelin loss and abnormal accumulation of myelin
  - Lysosomal enzyme defects

Multiple Sclerosis

- Lesions separated in time and space
- Central demyelination (oligodendrocytes)
- Progressive with relapses and remissions
- Optic nerve most common presentation
- Oligoclonal immunoglobulins in CSF
- Both motor and sensory
### Ischemic Stroke
- Involves thrombotic obstruction of arterial flow
  - Most common: thrombosis of atherosclerotic plaque and downstream ischemia
  - Less common: embolic disease
- Most common: middle cerebral artery
- Primary pathophysiology: advanced atherosclerosis, atherosclerosis of carotids, hypercholesterolemia
  - May be preceded by transient ischemic attacks

### Hemorrhagic stroke
- Hemorrhage in area of internal capsule, putamen,
- Primary pathophysiology: hypertension
- Progression depends on rate and size of bleed
- May result in increased intracranial pressures and herniation
- Contralateral weakness, sensory loss
- Both limbs, distal>proximal
- No aphasia (except motor dysarthria)

### Lacunar infarcts
- Hypertension of straight penetrating end arteries of middle cerebral artery
- Hypertension leads to arteriolosclerosis and narrowing of lumen
- Chronic ischemia leads to development of cysts (remember necrosis of brain results in liquefactive necrosis) – lacunae
- Area of internal capsule
- May precede hemorrhagic stroke
- Usually incidental finding

### Arteriovenous malformation
- Young to middle aged adults (Senator Tim Johnson)
- Mimic tumor, stroke
- Mass lesion consisting of tortuous vessels
- Frontal lobe – behavior changes, seizures
- May bleed slowly or suddenly
- Gliosis (reaction to slow blood leakage)

### Neoplasms
- Neoplasias of glial cells and epithelial linings, not axons or nerves
- Differential
  - Adult vs. children
  - Rate of development (years to weeks)
  - Location (cerebral vs. extracerebral vs. spinal cord)
  - Morphology on CT (diffuse vs. well demarcated)
### Tumor vs. Other

- **Length of development** – subacute
- **Localizing signs and symptoms**
  - Unilateral
  - Specific location – visual, symptoms
  - Seizure activity
- **Primary (solitary) vs. Metastases (multiple)**
  - Intracerebral
  - Tumor emboli settle in vessels in gray-white junction
  - Don’t metastasize outside of cranium; within cranium, spread through arachnoid space

### Adults

- **Meningioma**
  - Most common benign brain tumors
  - 30% of adult brain and CNS tumors
  - Dural (extracerebral) location, growth over months, well-circumscribed, often asymptomatic until large
  - Tumor of arachnoid - elongated cells with pale, oblong nuclei, pink cytoplasm, psammoma bodies

- **Glioblastoma multiforme**
  - 25% of adult tumors (half of glial tumors)
  - Most common intracranial malignant tumor
  - Middle age
  - Rapidly progressive intracerebral growth (weeks to months)
  - Invasive, not circumscribed
  - Necrosis, nuclear pseudopalisading, hyperchromatic cells
  - Perinecrotic palisading
  - Glomeruloid vascular proliferation

- **Astrocytomas**
  - 25% of adult tumors (half of glial tumors)
  - Most common intracranial malignant tumor
  - Middle age
  - Rapidly progressive intracerebral growth (weeks to months)
  - Invasive, not circumscribed
  - Necrosis, nuclear pseudopalisading, hyperchromatic cells
  - Perinecrotic palisading
  - Glomeruloid vascular proliferation

- **Oligodendromas**
  - Intracerebral glial tumors
  - Solitary, well-circumscribed masses
  - Homogeneous cells with dark nuclei, stain with GFAP

- **Oligodendromas vs. astrocytomas**
  - Astrocytomas less well circumscribed
  - Astrocytomas more common

- **Cerebral lymphoma**
  - HIV patients
  - B-cell large cell lymphoma (CD19, CD20)

- **Ependymomas**
  - Arise in ventricles or spinal canal
  - Rare in adults
  - Myxopapillary variant – more common in adults than children
    - Cuboidal cells around papillary cores in a myxoid background
    - Arise in ventricles

- **Schwannomas**
  - Cerebellopontine angle, eighth nerve

### Other Adult

- **Cerebral lymphoma**
  - HIV patients
  - B-cell large cell lymphoma (CD19, CD20)

- **Ependymomas**
  - Arise in ventricles or spinal canal
  - Rare in adults
  - Myxopapillary variant – more common in adults than children
    - Cuboidal cells around papillary cores in a myxoid background
    - Arise in ventricles

- **Schwannomas**
  - Cerebellopontine angle, eighth nerve

### Children

- **Most commonly occur in posterior fossa**
  - Involve cerebellum – ataxia, gait disturbances
  - Block CSF flow, cause hydrocephalus

- **Astrocytoma – best prognosis**
  - Pilocytic astrocytoma – cystic cerebellar astrocytoma
  - Older children
  - Stain with GFAP, long cellular processes

- **Astrocytoma**
  - Pilocytic astrocytoma – cystic cerebellar astrocytoma
  - Older children
  - Stain with GFAP, long cellular processes

- **Ependymomas**
  - Arise in ventricles or spinal canal
  - Rare in adults
  - Myxopapillary variant – more common in adults than children
    - Cuboidal cells around papillary cores in a myxoid background
    - Arise in ventricles

- **Schwannomas**
  - Cerebellopontine angle, eighth nerve

### Other Adult

- **Cerebral lymphoma**
  - HIV patients
  - B-cell large cell lymphoma (CD19, CD20)

- **Ependymomas**
  - Arise in ventricles or spinal canal
  - Rare in adults
  - Myxopapillary variant – more common in adults than children
    - Cuboidal cells around papillary cores in a myxoid background
    - Arise in ventricles

- **Schwannomas**
  - Cerebellopontine angle, eighth nerve

### Children

- **Most commonly occur in posterior fossa**
  - Involve cerebellum – ataxia, gait disturbances
  - Block CSF flow, cause hydrocephalus

- **Astrocytoma – best prognosis**
  - Pilocytic astrocytoma – cystic cerebellar astrocytoma
  - Older children
  - Stain with GFAP, long cellular processes

- **Astrocytoma**
  - Pilocytic astrocytoma – cystic cerebellar astrocytoma
  - Older children
  - Stain with GFAP, long cellular processes

- **Ependymomas**
  - Arise in ventricles or spinal canal
  - Rare in adults
  - Myxopapillary variant – more common in adults than children
    - Cuboidal cells around papillary cores in a myxoid background
    - Arise in ventricles

- **Schwannomas**
  - Cerebellopontine angle, eighth nerve
Children

- Medulloblastoma
  - Peak age 5 years
  - Midline, small blue round cells
  - Homer Wright pseudo-rosettes
  - Poor prognosis
- Ependymoma
  - Older children and adolescents
  - Floor of fourth ventricle
  - Tumor rosettes
  - Poor prognosis

Spinal Cord Tumors

- Intramedullary (10%)
  - Ependymomas
  - Astrocytomas
  - Glioblastomas
- Extramedullary (90%)
  - Schwannomas
  - Neurofibromas
  - Meningiomas

Neurofibromatosis

- Familial syndromes – neurocutaneous syndromes
  - Type I (peripheral)
    - Autosomal dominant
    - Café au lait spots
    - Schwannomas (cranial nerves, peripheral nerves, neurofibromas (intracranial)); may be multiple
    - Plexiform neurofibromas
  - Type II (Central)
    - Autosomal dominant (chromosome 22)
    - Bilateral schwannomas of the eighth nerves or multiple meningiomas

Tuberous Sclerosis

- “phakomatoses” – hamartomas and neoplasms develop throughout the body
- Cutaneous abnormalities
- Cortical tubers – hamartomas of neuronal and glial tissues
- Other features
  - Renal angiomyolipomas, renal cysts
  - Subungual fibromas
  - Cardiac rhabdomyomas

Increased intracranial pressure

- Symptoms
  - Papilledema
  - Cranial nerve dysfunction (bilateral)
  - Increased opening pressure on spinal tap (check for papilledema first!)
  - Progressive evolution of loss of consciousness, herniation
- Hydrocephalus
  - Communicating
  - Non-communicating
  - Hydrocephalus ex-vacuo

Forms of Herniation

- Cingulate gyrus herniation
- Midline shift
- Uncal herniation
- Cerebellar tonsil herniation
- Downward displacement (central herniation)
### Developmental Defects

- **Anencephaly**
  - absence of the brain or of all parts except the basal ganglia, brainstem and cerebellum.
  - failure of closure of the anterior neuropore
  - Elevated maternal serum α-fetoprotein

- **Holoprosencephaly**
  - cerebral hemispheres fail to divide properly.
  - associated with trisomy 13-15 and other chromosomal defects
  - total or partial lack of division of telencephalic vesicles, optic vesicles, and/or olfactory vesicles

- **Meningomyelocele**
  - meninges and spinal cord protrude through overlying defect in the vertebral column
  - lumbosacral location.
  - also have hydrocephalus and Arnold-Chiari malformation

- **Encephalocele**
  - meninges and brain tissue protrude through a skull defect.

### Spinal Column

- **Spina bifida** - general term for a midline skeletal defect in the spine of any type.
  - Spina bifida occulta - closure defect of posterior vertebral arch; may be associated with overlying dimple, hair
  - Congenital dermal sinus - least serious and most common mid-line defect. Defects range from dimpling of skin over lumbosacral area to sinus tracts in this region.
  - Meningocele - sac containing meninges & CSF protrudes through skeletal defect (rare)

- **Syringomyelia** – cervical vertebrae

### Dandy-Walker

- malformation of vermis (anterior vermis displaced rostrally, inferior vermis reduced to abnormal white matter on medial surfaces of hemispheres)

- cystic dilatation of fourth ventricle, with wall of cyst composed of ependyma and leptomeninges
  - lateral displacement of cerebellar hemispheres by 4th ventricle

- increased volume of posterior fossa, with upward displacement of lateral venous sinuses.

- obstruction of foramina of Luschka and Magendie, with production of hydrocephalus

### Arnold-Chiari

- **Type I (adult type)** has variable herniation of cerebellar tonsils and is frequently accompanied by syringomelia

- **Type II (infantile type)**, called the Arnold-Chiari malformation here,
  - polymicrogyria
  - meningomyelocele
  - hydrocephalus

- beak-shaped colliculi, displacement of the medulla and fourth ventricle down into the cervical segments

### Other

- **Central pontine myelinolysis**
  - Too rapid correction or normalization of hyponatremia
  - Osmotic demyelination
  - Results from chronic adaptation to hyponatremia with formation of intracellular osmoles

- Most often a result of alcoholism
  - Can also occur with rapid normalization of sodium from SIADH

- Prognosis is poor
Response to Injury - Axons

- **segmental demyelination**
  - dysfunction of Schwann cell or damage to myelin sheath (no 1st abnormality of axon)
  - disintegrating myelin engulfed by Schwann cells, later macrophages
  - denuded axon undergoes remyelination
    - newly formed internodes are shorter than normal
    - several new internodes are required to bridge gap
    - new myelin thinner than original
  - sequential episodes of demyelination and remyelination leads to concentric skeins and formation of "onion bulbs"

- **newly formed internodes are shorter than normal**
  - several new internodes are required to bridge gap
  - new myelin thinner than original
  - sequential episodes of demyelination and remyelination leads to concentric skeins and formation of "onion bulbs"

Response to Injury - Axons

- **axonal degeneration**
  - implies primary destruction of axon with secondary disintegration of myelin sheath
  - may be due to trauma, ischemia, underlying abnormality of neuron or axon
  - response to transection: *Wallerian degeneration*
    - axon breaks down within one day
    - Schwann cells catabolize myelin and engulf axon fragments
    - macrophage phagocytosis of axonal and myelin debris
    - stump (proximal portion) shows degenerative changes in most distal 2 or three internodes
    - if neuron remains viable, undergoes regenerative activity

Response to Injury - Axons

- **symptoms associated with neuronal degeneration**
  - lower motor neurons - muscular atrophy, fasciculations, weakness
  - upper motor neurons - hyperreflexia, spasticity, and a Babinski reflex
- **nerve regeneration**
  - involves growth cone at end of remaining stump
  - multiple, closely aggregated thinly myelinated small-caliber axons (regenerating cluster)
  - haphazard growth and mass of tangled fibers - pseudoneuroma
  - slow rate of axonal transport - growth only 2 mm/day
  - denervated muscle usually re-innervated by adjacent fibers before original fiber regenerates

Amyotrophic Lateral Sclerosis (Lou Gehrig's Disease)

- **Clinical Characteristics**
  - Middle-aged
  - 10% familial; genetic locus Cu/Zn binding superoxide dismutase gene
  - Loss of upper and lower motor neurons
  - Progressive, symmetric muscular weakness
  - May present with bulbar symptoms, with sparing of the extra-ocular muscles
  - Intact mental function; death from respiratory complications
  - Pathology
    - Gliosis and loss of motor neurons
    - Pallor of lateral corticospinal tracts
    - Neuronal loss in anterior horns of spinal cord
    - Denervation atrophy of muscle fibers

Werdnig-Hoffman disease (infantile progressive spinal muscular atrophy)

- "floppy infant syndrome": severe form of lower motor neuron disease which presents in neonatal period
- Death within a few months from respiratory failure or aspiration pneumonia
- Autosomal recessive condition, pathogenesis unknown
- Morphology
  - severe loss of lower motor neurons with profound neurogenic atrophy of muscle
  - degeneration of motor axons of the anterior roots

Guillain-Barre Syndrome

- **Clinical Characteristics**
  - Life-threatening diseases of peripheral nervous system
  - Death (2-5%) from respiratory paralysis; recovery over several weeks if respiratory function maintained
  - Acute illness, symmetric, *ascending paralysis* (distal to proximal)
  - Motor>sensory with loss of deep tendon reflexes
  - Elevation of CSF protein (no white cells)
  - Pathology
    - 2/3 cases preceded by influenza-like illness
    - Most intense inflammation in spinal and cranial motor roots (anterior roots)
    - Autoimmune *segmental demyelination*: nerve conduction slowed
    - Thought to be T-cell mediated, but treatable with plasmapheresis
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

- Clinical Characteristics
  - radiculopathy
  - chronic relapsing, remitting course
  - symmetric, mixed sensorimotor polyneuropathy

- Morphology - Similar to GB, because of chronic nature, well-developed onion-bulb structures are seen

- Biopsy of sural nerves shows recurrent demyelination and remyelination with onion bulb structures

- Clinical remissions with steroid treatment and plasmapheresis

Infectious Neuropathies

- Varicella-Zoster (post Chicken Pox)/Shingles
  - latent infection of the sensory ganglia of the spinal cord and brain stem
  - virus transported along sensory nerves to infect epidermal cells; reactivation vesicles appear distributed along dermatome (very painful!!!)
  - reactivation may be related to decreased cell mediated immunity
  - affected ganglia show neuronal destruction with abundant mononuclear infiltrates; regional necrosis with hemorrhage

Hereditary Neuropathies

- HMSN I (Charcot-Marie-Tooth disease)
  - autosomal dominant/most common
  - presents in childhood or early adulthood; normal life span; limited disability
  - progressive, symmetric muscular atrophy, particularly in the calf muscles (peroneal muscular atrophy)
  - suggests Schwann cell abnormality
    - palpable nerve enlargement/hypertrophy - demyelination and remyelination of peroneal nerve

- HMSN II - similar to HMSN I, presents at later age and nerve enlargement is not seen; autosomal dominant

- HMSN III (Dejerine-Sottas disease)
  - AR; present in infancy; delay in acquisition of motor skills
  - slow progression of distal weakness plus truncal weakness
  - enlarged, palpable peripheral nerves, onion bulb formation

Acquired Metabolic and Toxic Neuropathies

- Hand/foot (distal) symmetric distribution
- Numbness tingling (primarily sensory)

- diabetes mellitus, alcoholism, uremic neuropathy

- industrial or environmental chemicals - axonal degeneration
  - acrylamide, heavy metals (arsenic, lead), vinca alkyloids (plants, drugs), organophosphates (pesticides)

- tumor-associated syndromes

Tumor-associated syndromes

- direct infiltration or compression of peripheral nerves (Pancoast’s; cauda equina involvement)

- Plasma cell dyscrasias (Two types)
  - Amyloid (light chain deposition) vs. monoclonal IgM gammopathy
  - compression syndromes - similar to carpal tunnel syndrome

- Paraneoplastic syndromes - solid tumors
  - most often associated with small cell carcinoma of the lung
  - degeneration of dorsal root ganglion cells with proliferative responses by satellite cells and inflammatory infiltrates
    - plasma cells and lymphocytes, predominantly CD8
  - sensorimotor lesion - weakness and sensory deficits more pronounced in the lower extremities that progress over months to years
  - Eaton-Lambert syndrome

Schwannomas

- Benign
  - neural crest derived Schwann cells
  - within cranial vault, most common location is the cerebellopontine angle, attached to eighth nerve
  - extradural tumors most commonly found in association with large nerve trunks

- Malignant schwannoma (malignant peripheral nerve sheath tumor, MPNST)
  - highly malignant, locally invasive
  - multiple recurrences with eventual metastatic spread
  - never arise from malignant degeneration of benign schwannoma; arise from plexiform neurofibromas (NF-1)
### Neurofibroma
- **Cutaneous/peripheral nerve form**
  - markers of diverse lineages, including Schwann cells, perineurial cells, and fibroblasts
  - Unencapsulated, highly collagenized masses of spindle cells
- **Plexiform neurofibroma**
  - defining lesion of neurofibromatosis type 1
  - difficult to remove surgically
  - high potential for malignant transformation; frequently multiple

### Myasthenia gravis
- **Clinical features**
  - if before age 40, F>M
  - motor weakness which fluctuates – increases with muscle use
    - exacerbations by intercurrent illness
    - sensory and autonomic functions not affected
  - characteristic temporal and anatomical distribution
    - extracranial muscles commonly involved (ptosis and diplopia)
- **Diagnostic features**
  - decrement in motor responses with repeated stimulation
  - Tensilon test: transient improvement when administered anticholinesterase agents

### Myasthenia gravis
- decrease in number of muscle acetylcholine receptors secondary to anti-receptor antibodies
  - can be passively transferred to animals
  - circulating anti-AChR causes decrease in receptor number (increased receptor internalization and destruction) and damage to post-synaptic membrane secondary to complement fixation
- **often associated with thymic hyperplasia or thymomas**: patients respond to thymectomy
- **Morphology**
  - muscle biopsies unrevealing; may have diffuse changes with Type 2 atrophy
  - immune complexes present in synaptic cleft
  - thymic hyperplasia with germinal centers

### Eaton-Lambert syndrome
- paraneoplastic syndrome (most commonly small cell carcinoma of the lung)
- proximal muscle weakness with autonomic dysfunction
- does not respond to Tensilon test or show increased weakness with repetitive stimulation
- ACh receptors OK, but fewer vesicles are released on synaptic transmission
- passive transfer of syndrome with IgG

### Botulism (Clostridium botulinum)
- secondary to toxin production in improperly prepared foods or an anaerobic infection
  - No infection with organism; absobption of ingested toxin
  - Neonates: necrotizing intestinal infection by *C. botulinum* from honey
- paralysis due to disruption of presynaptic neurotransmitter release

### Types of muscle fibers

<table>
<thead>
<tr>
<th></th>
<th>Terms</th>
<th>Characteristics</th>
<th>Function</th>
<th>pH 4.2</th>
<th>pH 9.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Slow type, red type</td>
<td>have many mitochondria, myoglobin, and oxidative enzymes</td>
<td>wt. bearing and sustained force</td>
<td>dark</td>
<td>light</td>
</tr>
<tr>
<td>Type II</td>
<td>Fast type, white type</td>
<td>rich in glycolytic enzymes</td>
<td>rapid, purposeful movement</td>
<td>light</td>
<td>dark</td>
</tr>
</tbody>
</table>

- Determinant of muscle fiber type - determined by the motor neuron that innervates it (i.e., if the neuron type changes, the muscle type will change along with it); staining for ATPase
Response to Injury - Muscle

- **Denervation atrophy** - secondary to axonal loss
  - **group atrophy** - type group becomes denervated
  - down regulation of myosin and actin synthesis
  - decreased cell size with resorption of myofibrils
  - **cytoskeletal reorganization** - rounded zone of disorganized fibers (target fiber)
  - type 2 fiber atrophy - inactivity or disuse; also pyramidal tract disorders, neurodegenerative diseases

- **Reinnervation**
  - muscle fibers re-innervated by sprouts from adjacent nerves incorporated into muscle fiber group for that nerve
  - orphaned fibers assumes fiber type of neighbors; leads to type grouping

---

**Duchenne’s muscular dystrophy**

- **Epidemiology**
  - X-LINKED (1/3500 males)
  - female carriers show increased plasma levels of creatine kinase and mild muscle damage
  - mutations in gene for dystrophin; 1/3 new mutations

- **Clinical Characteristics**
  - most severe of the dystrophies
  - early motor milestones met on time; develop inability to keep up with peers
  - clinically manifest by age of five; wheelchair by 10 or 12
  - weakness begins in pelvic girdle muscles and extends to shoulder; use of arms to get up called “Gower’s maneuver”
  - cognitive impairment to mental retardation

- **Morphology**
  - degeneration, necrosis, and phagocytosis of muscle fibers
  - variation in muscle fiber size with both small and giant fibers; fiber splitting
  - increased numbers of internalized nuclei (muscle regeneration)
  - replacement of muscle fibers by fatty infiltrate

- **Clinical Findings**
  - serum creatine kinase elevated in first decade; may return to normal as muscle is destroyed
  - enlargement of calf muscles: pseudohypertrophy
  - progressive; death by early 20’s from respiratory insufficiency, lung infection, or cardiac decompensation
  - changes in heart result in heart failure or arrhythmias

---

**Becker’s Muscular Dystrophy**

- **X-LINKED RECESSIVE**
  - similar to Duchenne’s, but less common and less severe
  - onset later in childhood and into adolescence
  - slower, variable rate of progression
  - involves changes to, not loss of dystrophin gene locus
  - normal life span with rare cardiac involvement

---

**Other**

- **Facioscapulohumeral muscular dystrophy**
  - AUTOSOMAL DOMINANT
  - disease of adolescents-young adults
  - weakness of muscles of face, neck, and shoulder girdle
  - dystrophic myopathy with inflammatory infiltrate

- **Limb-girdle dystrophy**
  - AUTOSOMAL RECESSIVE/SPORADIC CASES
  - onset as adolescent or young adults
  - weakness of proximal muscles of upper and lower extremities
  - progression variable; variable dystrophic myopathy
Myotonic dystrophy

- Myotonia = sustained involuntary contractions
  - patients c/o stiffness, unable to release grip
  - percussion of thenar eminence elicits myotonia
- Epidemiology/inheritance
  - AUTOSOMAL DOMINANT
  - increasingly severe and at younger age in succeeding generations: ANTICIPATION
- Etiology/Pathogenesis
  - gene for myotonin-protein kinase, unstable mutation
  - damage collects with each generation

Myotonic dystrophy

- Clinical Characteristics
  - late childhood with gait difficulties, foot weakness
  - progresses to involve hand and wrist extensors
  - atrophy of muscles of face (ptosis)
  - cataracts present in nearly every patient
  - also: frontal balding, gonadal atrophy, cardiomyopathy, smooth muscle involvement, decreased plasma IgG, and abnormal glucose tolerance test
- Morphology
  - muscle dystrophy similar to DMD
  - increase in the number of internal nuclei in chains
  - ring fibers
  - relative atrophy of Type I fibers
  - dystrophic changes in muscle spindle fibers (unique)

Congenital Myopathies

- onset in early life, nonprogressive or slowly progressive course, proximal or generalized muscle weakness, hypotonia; "floppy babies" or may have severe joint contractures
- Syndromes
  - Nemaline myopathy
  - Lipid myopathies
  - Mitochondrial myopathies
  - Cradle’s syndrome
  - Pompe’s disease
- Also: ion channel myopathies (periodic paralysis and myotonia associated with hyper-, hypo-, or normokalemia
  - malignant hyperthermia – dramatic hypermetabolic state associated with induction of anesthesia; familial susceptibility

Toxic Myopathies

- thyrotoxic myopathy - proximal muscle weakness, fiber necrosis with regeneration, interstitial lymphocytes; focal myofibril degeneration with fatty infiltrate
- hypothyroidism - cramping and aching of muscles with slowed reflexes and movements; fiber atrophy, internal nuclei, glycogen aggregation, accumulation of mucopolysaccharides (myxedema)
- thyrotoxic periodic paralysis - episodic weakness often accompanied by hypokalemia; M>F, Japanese descent; dilatation of sarcoplasmic reticulum and intermyofibril vacuoles
- alcohol-induced - drinking with RHABDOMYOLYSIS/ myoglobinuria; pain generalized or confined to single muscle group; swelling of myocytes with fiber necrosis, myophagocytosis, and regeneration

Loss of Pigment

- Vitiligo
  - Irregular, well-demarcated macules devoid of pigment
  - Loss of melanocytes
    - autoimmunity
    - neurohumoral factors
    - toxic melanin synthesis metabolites
- Albinism
  - Congenital absence of pigmentation
    - Multiple abnormalities

Increased Pigmentation

- Freckles (ephilis)
  - Tan-red to brown macules
  - ↑ with sun exposure
- Melasma
  - Darkening of skin
  - Under hormonal control (menopause, pregnancy)
- Lentigo
  - Macular (flat), delimited pigmented area
Nevi

- **Progression**
  - begins as small tan dot; grows as uniformly colored tan-brown area with well-defined, rounded borders
  - after 1-2 decades gradually flattens and returns to normal

- **Maturation of Nevi**
  - migration of cells into dermis accompanied by process termed “maturation”
  - less mature, more superficial cells are larger, produce more melanin pigment, grow in nests
  - more mature, deeper nevi cells are smaller, produce little or no pigment, grow in cords
  - the lack of maturation in melanomas is a key feature distinguishing melanomas from nevi

Dysplastic Nevi (BK moles)

- **Pathogenesis**
  - autosomal dominant, familial syndromes associated with hundreds of lesions on body surfaces (both sun exposed and non-exposed areas)
  - may be associated with chromosomal instability
  - most are clinically stable, but may undergo stepwise progression to malignant melanoma

- **Pathology**
  - larger than usual nevi; flat macules with variegation of pigmentation
  - characterized by abnormal pattern of growth and aberrant differentiation; cytologic atypia
  - focal areas of eccentric melanocytic growth
  - associated with subjacent lymphocytic infiltrate

Seborrheic keratosis

- **Clinical features**
  - middle aged or older individuals; commonly affect trunk
  - multiple small lesions on face of blacks: dermatosis papulosa nigra
  - sign of Leser-Trelat: paraneoplastic syndrome

- **Pathologic features**
  - well-demarcated, flat, coin like plaques mm-cm
  - uniformly tan to dark brown
  - velvety to granular surface
  - trabecular arrangement of sheets of basilar cells with keratin pearls
  - pores impacted with keratin with keratin-filled cysts
  - variable melanin pigmentation in basilar cells***

Melanoma

- **Color or size change of pre-existing mole or new lesions**
- Asymmetrical, irregular borders, variegated colors
- Large, irregular nuclei w/clumped chromatin and red nucleoli
- Radial growth first, then vertical growth
  - Degree of vertical growth is predictive of prognosis
- Lymphocytic infiltrate
  - Immune reaction important in controlling progression of tumor
- Assoc. w/p16INK4a

Acanthosis Nigricans

- **Clinical features**
  - cutaneous marker for associated benign and malignant conditions
  - benign: 80% heritable trait/obesity/endocrine disease/rare congenital syndromes
  - malignant type: underlying adenocarcinoma
  - hyperpigmented zones of skin involving flexoral areas – axilla, skin folds of neck, groin, and anogenital areas

- **Pathogenesis**
  - may be associate with abnormal production of epidermal growth factors
Keratoacanthoma
• Clinical features
  – rapidly developing benign neoplasm; 1–several cm.
  – resembles squamous cell carcinoma but may heal spontaneously
  – flesh-colored, dome-shaped nodules with central, keratin-filled plug
• Pathologic features
  – keratin-filled crater surrounded by lip of proliferating epithelial cells
  – atypical, eosinophilic, "glassy" cytoplasm; stromal response with inflammatory cells
  – host response may determine regression or progression

Adnexal Tumors
<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Cell Type</th>
<th>Location</th>
<th>Histological Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cylindroma</td>
<td>Apocrine gland</td>
<td>Forehead, scalp</td>
<td>Islands of basoid cells that fit together like jigsaw puzzle; fibrous, dermal matrix</td>
</tr>
<tr>
<td>Hyaladroneoma papilliferum</td>
<td>Apocrine gland</td>
<td>Ducts lined by apocrine type cells</td>
<td></td>
</tr>
<tr>
<td>Syringoma</td>
<td>Eccrine gland</td>
<td>Multiple, small, tan papules on lower eyelids</td>
<td>Eccrine ducts lined by membranous eosinophilic cubules</td>
</tr>
<tr>
<td>Trichoepithelioma</td>
<td>Hair follicle</td>
<td>Multiple, semitransparent, dome-shaped papules on face, scalp, and upper trunk</td>
<td>Pale, pink glassy cells; resembles uppermost portion of hair follicle</td>
</tr>
<tr>
<td>Sebaceous adenoma</td>
<td>Sebaceous gland</td>
<td>Cytoplasmic lipid vacuoles</td>
<td></td>
</tr>
</tbody>
</table>

Skin Cancer
• Squamous cell carcinoma
  – Sharply defined, red scaly lesions
  – Sheets w/keratin pearls and intracellular bridging
  – Can involve oral mucosa
  – Assoc w/p53, immunosuppression, HPV, UVB, dysfxn of Langerhans cells
• Basal cell carcinoma
  – Pearly papules, telangiectasia
  – Local destruction and invasion of bone and sinuses
  – Palisading cells in tumor nests and tongues
  – Lymphocytic infiltrate
  – Familial: two hit hypothesis
  – Sporadic: PTCH, p53

Acute Dermatoses
<table>
<thead>
<tr>
<th>Type I Hypersensitivity</th>
<th>Type IV Hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria and angioedema</td>
<td>Injected or systemically distributed antigen</td>
</tr>
<tr>
<td>Eczema</td>
<td>Contact or systemically distributed antigen</td>
</tr>
<tr>
<td>Erythema multifforme</td>
<td>Systemically distributed antigen</td>
</tr>
</tbody>
</table>

Urticaria and Angiodema
• **hives**: raised, pale, well-delimited pruritic areas; appear/disappear within hours
  – represent edema of the superficial portions of the dermis
• **angioedema**: egglike swelling with prominent involvement of deeper dermis and subcutaneous fat
• Worse in areas of rubbing and warmth, skin folds due to increased vascular flow (waistband, neckline, under breasts, etc.)
• Vascular reaction mediated by vasoactive substances
  – degranulation of mast cells: IgE-mediated allergic responses or complement-mediated responses
  – direct release of histamine by physical stimuli (cold)
  – non-specific release of mediators by mast cells by drugs or neurological response

Acute Eczematous Dermatitis
• Type IV cell-mediated hypersensitivity; prototype: poison ivy
• immunologically specific, mononuclear, inflammatory response that reaches its peak 24 to 48 hour after antigenic challenge
• intensely pruritic, fiery red, with numerous vesicles
  – “eczema” means to boil-over – redness, oozing plaques, vesicle formation
• requires previous sensitization: develops 7-10 days after 1st challenge; 2-3 days on subsequent challenge
• evolution of lesions from acute inflammation to chronic hyperplastic lesions
  – initial edematous inflammation
  – epidermal spongiosis and microvesicular formation
  – chronic: hyperplasia and hyperkeratosis (acanthosis)
  – prone to bacterial superinfection
### Erythema multiforme
- Self-limited hypersensitivity to certain infections and drugs
- Multiform lesions: macules, papules, vesicles, or bullae
- Associated infections, drug hypersensitivities, tumors, collagen vascular diseases.
  - Penicillin, sulfonamides, barbiturates, salicylates, hydantoins, antimalarials
  - Lupus, dermatomyositis, periarteritis nodosa
- Bilateral involvement of extremities (especially shins)
- Lymphocyte-mediated epidermal necrosis
  - Accumulation of lymphocytes at dermal-epidermal border with dermal edema
  - Epidermal necrosis, blister formation; sloughing with shallow erosions
- Variants
  - Febrile disease in children: Stevens-Johnson Syndrome
  - Toxic epidermal necrolysis

### Pemphigus vulgaris
- Separation of stratum spinosum from basal layer
- Vesicle contains lymphocytes, macrophages, eosinophils, neutrophils and rounded keratinocytes (“acantholytic cells”)
- IgG autoantibodies to intercellular substance of the epidermis (desmoglein)
- May be associated with other autoimmune diseases such as myasthenia gravis, SLE

### Bullous pemphigoid
- Subepidermal, large tense blisters with erythematous base
- Subepidermal, non-acantholytic blisters
- Roof of vesicle is lamina densa
- Eosinophils predominate cell along with fibrin, lymphocytes, neutrophils
- Mast cell migration from venule toward epidermis
- Autoimmune disease characterized by circulating IgG antibodies to glycoprotein of lamina lucida
- Linear deposition of complement, recruitment of neutrophils, and release of major basic protein

### Epidermolysis bullosa
- Hereditary
- Formation of blisters at sites of minor trauma
- Subepidermal vesicle with few inflammatory cells in dermis
- Classification
  - Epidermolytic epidermolysis bullosa:
    - Within basal keratinocytic layer, with intact epidermis
  - Junctional epidermolysis bullosa:
    - Within lamina lucida
  - Dermolytic epidermolysis bullosa:
    - Roof of vesicle is lamina densa
- Involve extensive flaws in the dermal component of the basement membrane zone and structural proteins of anchoring filaments, lamina densa

### Psoriasis
- Common, familial (1-2% of population in US)
- Large, erythematous, scaly plaques with silvery scales
  - Commonly observed on extensor-dorsal surfaces, nail changes occur in 30%
- Severe disease may be associated with arthritis, myopathy, enteropathy, etc.
- Pathogenesis (T-cell mediated):
  - Deregulation of epidermal proliferation & an abnormality in the dermal microcirculation
  - Increased TNF associated with lesions; TNF-antagonists provide significant improvements

### Psoriasis
- Pathology (Entire skin is abnormal)
  - Thickened epidermis (hyperkeratosis and parakeratosis) w/ a thinned/absent stratum corneum. Dilated and Tortuous Capillaries
  - Elongated papillae with Munro’s abscesses
  - Collections of neutrophils at top of elongated papillae
  - Collections of acute inflammatory cells in epidermal spinous layer & mononuclear inflammatory cells in dermis
  - Auspitz’ sign – multiple, minute bleeding points when a scale is removed
### Lichen Planus
- **Multiple, symmetrically distributed “pruritic, purple, polygonal papules”**
  - usually appear on the flexor surface of the wrists
  - Resolve in 1-2 years
- **Pathologic features**
  - prominent band like lymphocytic infiltrate along dermoepidermal junction which replaces papillary/rete ridge
  - degeneration of basal keratinocytes; Saw-toothing of dermal interface
  - fibrillary, eosinophilic bodies represent dead keratinocytes: colloid, Civatte, or Sabouraud bodies
  - hypergranulosis and hyperkeratosis
- Wickham striae = white dots or lines
- Pathogenesis = likely T-cell mediated immune reaction to antigens in basal layer

### Dermatitis herpetiformis
- **urticaria-like plaques with eroded erythematous blisters**
  - Occur on the elbows, knees, buttocks: Intensely Pruritic
  - adult males (3rd-4th decade)
  - related to HLA-B8/DRW3 haplotype and gluten sensitivity
- **Pathologic features**
  - deposits of **granular IgA to gliadin** at dermal-epidermal interface, mainly at the tips of the dermal papillae
  - receptor for gluten found in dermal papillae
  - collection of neutrophils at tips of papillae (microabscesses)

### Osteogenesis Imperfecta
- “Brittle bone disease”
- Autosomal dominant
- Deficiencies in type I collagen
- Affects bones, joints, eyes, ears, skin, and teeth
- Extreme skeletal fragility, confused with child abuse
- Major subtypes
  - type I is most common; autosomal dominant; increased fractures, blue sclerae, hearing loss
  - basic abnormality is "too little bone"; marked cortical thinning and attenuation of trabeculae

### Ostopenrosis
- “Stone bones” or “Marble bone” disease – too much bone formation (too little resorption)
  - bones lack medullary canal, decreased bone marrow
- Pathologic fractures, anemia, hydrocephaly, cranial nerve dysfunction
  - neural foramina small; cranial nerves compressed
  - abnormally brittle bones; short stature
- deficient osteoclast activity
  - diffuse symmetric skeletal sclerosis
- two forms - "malignant" (autosomal recessive; die shortly after birth); "benign" (autosomal dominant; live to adulthood)

### Dwarfism
- **Achondroplastic Dwarfism**
  - Autosomal dominant; 80% of cases new mutations
  - Most common disease of the growth plate
  - defect in proliferation of chondrocytes
  - mutation in FGF receptor; inhibition of cartilage formation
  - Normal trunk length, shortened limbs, enlarged head
  - Prominent forehead – “frontal bossing”
  - NO changes in longevity, intelligence, or reproductive status
  - Premature closure of growth plate; Normal growth hormone levels
- **Thanatophoric dwarfism/dysplasia**
  - most common form of lethal dwarfism
  - mutation in FGF receptor
  - respiratory insufficiency due to underdeveloped thoracic cavity

### Paget’s Disease
- **Osteitis Deformans - “matrix metabolic madness”**
- **Presentation**
  - Elderly male
  - Bone pain, axial skeleton – pelvis/skull/femur
  - Cranial nerve compression of nerves, thickened skull (↑’d hat size)
- **Mechanism (?pararmyxovirus)**
  - Early phase – inflammatory, Increased osteoclastic resorption with disordered osteoid synthesis
  - Late phase – burned out sclerosis
- **most serious consequence – development of osteosarcoma (1 - 10%) - jaw, pelvis, or femur**
- **Increased alkaline phosphatase, Tile-like mosaic of osteoid formation pathognomonic**
- **Urinary excretion of hydroxyproline**
Osteomyelitis

- Clinical course
  - fever, systemic illness
  - 60% positive blood cultures, radionuclide scans may be helpful if X-rays negative
- Associations
  - Developed countries, dental/sinus infection → bone
  - Compound fractures
  - Toes and feet of diabetics with chronic ulcers; bone surgery
  - Intravenous drug use
  - Underdeveloped countries, hematogenous spread
  - Ends of long bones most common (esp. children); also vertebrae in adults

Osteomyelitis

- Pathogenesis
  - 80-90% (penicillin-resistant) ***Staph. aureus***.
  - complication of sickle cell – Salmonella
  - drug addicts – Pseudomonas
  - infants/neonates – Group B streptococcus
  - TB – vertebrae (Pott’s disease and Psoas abscess)
- Morphology
  - sub-periosteal chronic nidus of infection = Brodie’s abscess
  - smoldering infection → osteoblastic activity → Garre’s sclerosing osteomyelitis
  - devitalized bone (sequestra) surrounded by reactive bone formation (invulcrum)
  - draining sinus tracts to surface
    - Squamous cell carcinoma at orifice of sinus tract

Fibrous dysplasia

- benign disorder; risk of pathologic fracture
  - localized bone defects found incidentally
- replacement of bone and marrow with abnormal proliferation of haphazardly arranged woven bone
- monostatic (single site) – 70%
  - 70% childhood, arrests at puberty
  - involves ribs, femur, tibia
- polystatic form (multi-site) – 25%
  - begins earlier, may extend into middle age
  - craniofacial in 50%
  - polystatic with endocrinopathy: 3-5%, skin pigmentation (café au lait spots), precocious sexual development = Albright’s

Aseptic Necrosis

- Causes
  - mechanical vascular disruption; thrombosis and embolism; vessel injury
  - corticosteroids; radiation therapy; sickle cell anemia; alcohol abuse
- Morphology
  - cancellous bone, marrow most affected; cortex not affected
  - subchondral wedge-shaped infarcts extending into epiphysis
  - empty lacunae (death of osteocytes)
  - increased bone density (sclerosis)
- Bone pain
- Pieces of dead bone that becomes separated is called a sequestrum

Other

- Aneurysmal bone cyst
  - Solitary, expansile, erosive lesion of bone
  - Adolescent females (2:1)
  - Metaphysis of lower extremity long bones
  - Secondary to localized hemorrhage due to trauma, vascular disturbance, or increased venous pressure
  - Sometimes secondary to tumors or fibrous dysplasia
  - Tenderness and pain with limited range of motion
  - Appears as cyst on x-ray

Osteoporosis

- Reduced bone mass with increased porosity & thinning of trabeculae & cortex
- Involves entire skeleton, but some areas more affected than others
- Increased risk of fractures: femoral neck, vertebral compression fractures, Colles fracture of wrist
- Not detected by x-ray until 30-40% loss; serum calcium, phosphorus, alkaline phosphatase normal
- Rx: estrogen replacement therapy, bisphosphonates, PTH, adequate Vit D & calcium, exercise

www.bonetumor.org
### Osteoporosis
- **Primary:**
  - *senile:* normal age-related, steady decline in bone mass after 4th decade
  - Reduced replicative potential of osteoblasts relative to osteoclastic break-down
  - Loss accentuated by reduced physical activity with age
  - Women/whites more severely affected due to lower peak bone mass
- **Secondary:** hyperparathyroidism, hypogonadism, pituitary tumors, corticosteroids, multiple myeloma

### Primary Bone Tumors -- benign
- **Osteoid Osteoma**
  - Interlacing trabeculae of woven bone surrounded by osteoblasts
  - <2 cm in proximal tibia and femur, pain controlled by NSAIDs
- **Osteoblastoma**
  - Same morphology as osteoid osteoma but found in vertebrae
- **Giant cell tumor (20-40)**
  - Epiphysis of long bones
  - Locally aggressive (necrosis, hemorrhage, reactive bone formation), *soap bubble* appearance on XR, spindle shaped cells with *giant cells* (fused osteoclasts)

### Primary Bone Tumors -- malignant
- **Osteosarcoma (men 10-20)**
  - Metaphysis of long bones
  - Associated with Paget's of bone, LiFraumeni, bone infarcts, radiation, retinoblastoma, multiple enchondromas
  - Codman's triangle = elevated periosteum
- **Ewing's Sarcoma (boys <15)**
  - Anaplastic small blue cells (look like lymphocytes: lymphoma, rhabdomyosarcoma, neuroblastoma, oat cell carcinoma)
  - “Onion-skin” of bone and Homer-Wright Rosettes, diaphysis, t(11:22)
  - Medullary cavity; anemia, systemic symptoms (fever)
- **Chondrosarcoma (Men 30-60)**
  - Can arise from osteochondroma
  - Axial skeleton

### Palmar, Plantar, Penile Fibromatoses
- Dupuytren's contracture (palmar)
  - Irregular or nodular subcutaneous thickening of the palmar fascia with fibrosis, deposition of collagen
  - Either unilaterally or bilaterally (50%)
  - Slowly progressive flexion contracture, mainly of fourth and fifth fingers
- Plantar involvement occurs without flexion contracture
- Penile fibromatosis ( Peyronie's disease) occurs as a palpable induration or mass on the dorsolateral aspect of the penis
- May be genetic; males>females; 20-25% may stabilize; others may resolve or recur following resection

### Desmoid – Aggressive Fibromatosis
- Extra-abdominal: musculature of the shoulder, chest wall, back and thigh
- Abdominal desmoids
  - Women
  - Musculoaponeurotic structures of the anterior abdominal
  - During or following pregnancy
- Intra-abdominal desmoids: mesentery or pelvic walls, often in patients having Gardner's syndrome
- Reaction to injury, genetic factors; may recur if incompletely excised
- Unicentric, unencapsulated, infiltrate surrounding structures
- May recur after excision
Other Non-Neoplastic Conditions

• Nodular (Pseudosarcomatous) Fasciitis
  – Reactive fibroblastic proliferation – may occur after trauma
  – several weeks history of a solitary, rapidly growing, painful mass
  in extremities
  – young and middle-aged adults of either sex
  – attachment to fascia with apparent invasive characteristics

• Traumatic Myositis Ossificans
  – characterized by presence of metaplastic bone; not restricted
to skeletal muscle; not inflammatory; not always ossified
  – preceded by trauma; most often extremities in young, athleticism active males

• Lipoma/Liposarcoma
  • Lipomas
    – lipomas are the most frequent soft tissue tumor
    – peak incidence 5th and 6th decades
    – arise in subcutaneous tissues, 5% multiple, usually small
    with delicate capsule
  • Liposarcomas - uncommon
    – arise from primitive mesenchymal cells; no assoc. with
    adipose tissue
    – retroperitoneum and deep tissues of the thigh (less
    frequently in the mediastinum, omentum, breast, and axilla)
    – peak in 5th to 7th decades
    – Large, multilobulated with projections into surrounding
    tissues; cystic softening, hemorrhage, and necrosis are
    common
    – large, bulky tumors of deep tissues or cavities often recur
    after resection; well-differentiated forms metastasize late or
    not at all

Leiomyoma/Leiomyosarcoma

• Leiomyoma
  – >95% of leiomyomas in female genital tract
  – in addition to female genital tract, leiomyosarcomas
  occur in the retroperitoneum, wall of the
  gastrointestinal tract, and subcutaneous tissue
  – benign - small, multiple, adolescence and early
  adulthood
• Leiomyosarcoma
  – malignant – uncommon
  – superficial - good prognosis; deep - poor prognosis
  – Histologically, leiomyosarcoma is differentiated from
  leiomyoma by the number of mitoses per high
  power field

Rhabdomyosarcoma

• Rhadobomyosarcoma
  – Children; one of more common soft tissue tumors in
  head/neck/urogenital areas; highly malignant
  – rapidly enlarging masses located near surface of body
  – deep neoplasms grow to large masses; 20-40% have
  metastases at diagnosis
  – SARCOMA BOTRYOIDES - variant of embryonal form;
grapelike clusters, occurs in children under 10; nasopharynx,
bladder, vagina
  – Stain with vimentin
  • Synovial Sarcoma
    – Multipotential mesenchymal cells, not synovial cells
    – develop in vicinity of large joints (knee); deep seated mass that
    has been noted for several years;
    – morphologically resembles synovium
    – t(X;18) translocation

Vulva

• Bartholin cyst - acute infection of Bartholin gland
  may lead to blocked duct with abscess; excise or
  permanently open duct
• Vulvar vestibulitis - glands at posterior introitus can
  be inflamed; chronic, recurrent condition is very
  painful and can lead to small ulcerations; surgical
  removal of inflamed mucosa may help
• Lichen simplex chronicus—aka hyperplastic
dystrophy
  – Results from chronic rubbing/scratching secondary
to pruritus
  • Can occur in eczema, psoriasis, nervousness, etc.
  – thickening of vulvar squamous epith. and
  hyperkeratosis
  – Not precancerous

Vulva – Miscellaneous Disorders

• Lichen sclerosus—aka chronic atrophic vulvitis
  – Thinning of epidermis, degeneration of basal
  cells, replacement of dermis with fibrous tissue
  and lymphocytic infiltrate
    • Lymphocytic cell infiltrate --- underlying dermal
    fibrosis
    – Epidermis becomes thinned, scarred, and
    hyperkeratotic
      • Skin is pale gray and “parchment-like”
  – Labia is atrophied
  – Most common after menopause
  – not precancerous, but risk of subsequent
  carcinoma is 1-4%
Vulva – Neoplasms of the Vulva

• Papillary hidradenoma
  – Most common benign tumor of the vulva
  – Presents as a nodule at labia majora or interlabial folds
  – Consists of tubular ducts with myoepithelial layer
  – Characteristic of sweat glands and sweat gland tumors
  – Cure is via simple excision

• Condyloma acuminatum – benign sq. cell papilloma
  – Caused by HPV (usually types 6 and 11)
  – A proliferation of stratified squamous epithelium
  – Wartlike lesions, usually multiple and coalescing
    • Koilocytic atypia (nuclear atypia and perinuclear vacuolization)
    • In healthy individuals, it will regress

Vulva - Cancer

• Vulvar carcinoma—rare; 3% of all female genital ca; 85% squamous cell
  – Peak occurrence in older women
  – Preceded by pre-malignant changes
    • Vulvar intraepithelial neoplasia (VIN) 1-3, and/or vulvar dystrophy
    • Associated with high risk HPV (types 16, 18, 31, 33)
      • Same ones that cause sq. cell CA of the cervix and vagina
      • Other HPV types cause papillomatous lesions elsewhere
    • Associated with squamous cell hyperplasia and Lichen sclerosus

Extramammary Paget Disease

– Large tumor cells in epidermis of labia majora demarcated from normal epithelial cells
– Present with pruritic, red, crusting, sharply demarcated area
– Cells show apocrine, eccrine and keratinocyte differentiation
– Clear cells containing glycogen
– Sometimes associated with underlying adenocarcinoma of the apocrine sweat glands

Vagina

• Atresia/total absence (extremely rare)
  – Deformed/non-functioning vagina, or total lack of vagina (vaginal agenesis)
  – Usually manifests at puberty due to amenorrhea
  – Disruption of uterovaginal flow requires emergent surgery

• Septate/double vagina
  – Rare; failure of total fusion of mullerian ducts (longitudinal septum), or the failure of mullerian ducts to fuse with the urogenital sinus (transverse septum)
  – Septum that runs either longitudinally or transverse
  – May be asymptomatic
  – A transverse septum is more likely to block uteran outflow and result in amenorrhea

Gartner duct cyst

– Retention cyst arising from Gartner’s ducts occurring along the remnants of Wolffian ducts
– Usually asymptomatic and small

Vaginal intraepithelial neoplasia (VAIN) – CIN of the vagina

– Precancerous lesion; high risk papilloma viruses (types 16, 18), may be multicentric
  • Analogous to high-grade CIN
  • 10-30% associated with squamous neoplasms in vulva or cervix
– Graded as mild, moderate, or severe
– White or pigmented plaques on the vagina
– Risk of progression to invasive cancer ↑ with age/immunosuppression

Squamous cell carcinoma

– Rare; (0.6/100,000 yearly)
– 95% squamous cell, upper posterior vagina
– Usually due to extension of sq. cell CA of the cervix or vulva
  #1 Risk factor – sq. cell CA in cervix or vulva
  Vagina usually not the primary site
**Vagina**

- **Adenocarcinoma (clear cell variant)**
  - Clear cell variant found in daughters of mothers who took diethylstilbestrol (DES), an anti-abortifacient (only 0.14% develop it)
  - Presents age 15-20
  - Vaginal adenosis = precursor to clear cell adenocarcinoma
- **Embryonal rhabdomyosarcoma**
  - <5 yo; tumor of malignant embryonal rhabdomyoblasts; bulky mass
  - may fill and project out of vagina (sarcoma botryoides)
  - Projection resembles a “bunch of grapes”

**Cervix**

- **Endocervical polyps**
  - Soft, mucoid polyps w/loose, fibromyomatous stroma
  - inflammatory proliferation of cervical mucosa – NOT TRUE NEOPLASMS
  - found in 2-5% of adult women
    - Most in endocervical canal; may protrude thru os
    - Protrusion can lead to irregular spotting and post-coital bleeding
  - associated with dilated mucous-secreting endocervical glands
  - inflammation, squamous metaplasia
  - Tx - simple curettage or surgical excision

- **Cervical Intraepithelial Neoplasm (CIN)**
  - HPV most important agent (95% of cervical ca), but NOT only factor in development of
  - Viral gene product E6—interrupts cell death cycle by binding p53
  - E7—bind RB and disrupts cell cycle
  - CIN stages
    - CIN I – mild dysplasia involving lower 1/3 – raised or flat lesion, indistinguishable from condylomata acuminata
    - CIN II – moderate dysplasia – atypical cells in lower 2/3
    - CIN III – severe dysplasia/carcinoma in situ (if it’s full thickness)
    - **Koilocytes may be present at all stages**
  - Takes 10 years to go CIN I → CIN II
  - Takes another 10 to go CIN II → CIN III

- **Squamous cell carcinoma – 95% of cervical cancer**
  - Peak occurrence in middle aged women
  - Usually from pre-existing CIN at squamocolumnar junction
  - PAP decreases mortality via early detection of CIN and CA
  - Intraepithelial and invasive neoplasm
  - 3 forms - fungating (exophytic), ulcerating, infiltrative
  - extends by direct continuity
  - metastasizes to lymph nodes; liver, lungs, bone marrow
  - PAP decreases mortality via early detection of CIN and CA
  - Histology - 95% large cells, keratinizing or non-keratinizing

**Cervix**

- **Cinical Course/Management**
  - Symptoms - irregular vaginal bleeding, leukorrhea, bleeding or pain on coitus; dysuria
  - PAP smear is insufficient for prevention/diagnosis
  - All abnormalities visualized by colposcopy
  - Acetic acid application will reveal CIN
    - White patches of cervix; follow up with punch biopsy
  - CIN I - Pap smear follow-up
  - CIN II, III – cryotherapy, laser, loop electrosurgical excision procedure (LEEP), or cone biopsy
  - Invasive CA - hysterectomy and/or radiation (depends on stage)
  - Survival: 80-90% stage I; 75% stage II; 35% stage III; 10-15% stage IV

**Uterus**

- **Endometrial Hyperplasia**
  - Abnormal proliferation of endometrial glands, usually caused by excess estrogen stimulation
  - Excess estrogen may be due to...
    - Anovulatory cycles, polycystic ovary dz, estrogen-secreting ovarian tumors (ex. granulosa cell tumors), and estrogen replacement therapy
  - Manifest clinically with postmenopausal bleeding
  - Can be a precursor lesion of endometrial carcinoma
    - Risk of CA directly correlated with degree of cellular atypia
  - Simple hyperplasia (aka cystic or mild) rarely leads to carcinoma
    - high grade (atypical or adenomatous + atypia) - cellular atypia, irregular epithelium; 25% lead to carcinoma
Female Genital Uterus

• **Endometrial Carcinoma:**
  - Most common invasive cancer of female genital tract and has best prognosis
  - Associated with prolonged estrogen stimulation, nulliparity, diabetes, obesity, hypertension, infertility
  - 55-65 year old women; present with bleeding
  - Most are well differentiated with a glandular pattern (85% adenocarcinoma), can be polyploid or diffuse
  • Less common variants: papillary serous - older women, more aggressive; tumors with squamous elements
  - Most forms spread by direct extension, metastasize late

• **Endometrial Polyps:**
  - benign sessile masses of any size
  - Asymptomatic or irregular bleeding
  - Most common cause of menorrhagia 20-40 age group
  - Two types - functional endometrium or cystic hyperplastic
  - association with endometrial hyperplasia and tamoxifen

• **Hyperestrinism**
  - Anovulatory cycles: excessive estrogen stimulation relative to progesterone
    - associated with polycystic ovarian syndrome, obesity, malnutrition, systemic disease
    - Common at menarche and perimenopausal
  - Inadequate luteal phase: deficient progesterone production by corpus luteum
    • Manifests as infertility, menorrhagia or amenorrhea
  - Iatrogenic: oral contraceptives, estrogen replacement

• **Leiomyoma (fibroids)**
  - Most common tumors in women
  - Reproductive age; blacks>whites
  - Estrogen sensitive
  - characteristic whorled pattern of smooth muscle bundles
  - Often asymptomatic; may cause bleeding, infertility

• **Leiomyosarcoma:**
  - 40-60 year olds; not preceded by leiomyoma; rare
  - characterized by cellular atypia and high mitotic index: >10 mitoses per high power field (400X)
  - metastasis to lungs, bone, brain, and abdomen

Menstrual Cycle

• **Proliferative Phase:** estrogen mediated
  - proliferation of glands and stroma

• **Ovulation:** stimulated by LH surge
  - Confirmed by: basal vacuolization of epithelium, secretory or predecidual changes

• **Secretory Phase:** progesterone mediated
  - Most prominent during 3rd week, tortuous glands and spiral arteries; 4th week shows exhaustion and gland atrophy

• **Menstrual Phase:** prostaglandin mediated
  - Prostaglandins → vasospasm and necrosis → spasm of the myometrium
  - basal layer remains, upper 2/3 of endometrium shed

Fallopian Tubes

• **Inflammation:** PID causes suppurative salpingitis, may result in hydrosalpinx; *N. gonorrhoeae* – 60% of cases, *C. trachomatis* also common
  - Complications: infertility, adhesions

• **Neoplasia:**
  - paratubal cysts – Mullerian duct remnants form hydatid(s) of Morgagni found in fimbria and ligaments; translucent and filled with serous fluid
  - Uncommon: adenomatoid, papillary adenocarcinoma
Testicular Cancer

- **Sex Cord-Stromal Tumors (5%)**:
  - Leydig (Interstitial) cell tumor - 20-60 years old, most benign, androgen producing
  - Presents as testicular swelling, gynecomastia or precocious puberty
  - Brown, homogenous, circumscribed nodules; Reinke crystals
  - Sertoli cell tumor (Androblastoma) - Gray-white, homogenous, trabeculae resemble seminiferous tubules
  - Secrete androgens, but not clinically significant; benign

Endometriosis

- Presence of endometrial glands/stroma outside of the uterus
- Found in ovaries, uterine ligaments, rectovaginal septum, pelvic peritoneum
- Common cause of INFERTILITY
- Dysmenorrhea, dyspareunia, dyschezia
- Tissue under hormonal control = cyclic changes w/blooding during normal menstrual cycle
- “chocolate cysts” in ovaries (blood, lipid debris); scarring of fallopian
- Likely causes: Retrograde menstruation, Differentiation of dispersed coelemic epithelium, Lymphohematogeneous spread

Ectopic Pregnancy

- Implantation of fetus in any site other than uterus
  - Tubes (90%), ovary, abdominal cavity, cornual end
- 1/150 pregnancies
- Predisposing factors – PID w/ chronic salpingitis (35-50%), peritubal adhesions from appendicitis or endometriosis, leiomyomas, previous surgery, IUD
- Embryo undergoes usual development, but placenta is poorly attached, may separate and cause hematosalpinx or rupture
- Presents most commonly with pain, pelvic hemorrhage, shock, sx of acute abdomen – MEDICAL EMERGENCY!

Polycystic Ovary Disease

- previously known as Stein-Leventhal syndrome
- “Numerous cystic follicles”
- persistent anovulation, obesity, hirsutism, and rarely virilism
- Ovaries(bilateral) 2x normal size and studded w/subcortical cysts; theca interna hyperplasia; Corpora Lutea ABSENT
- LH stimulation of theca lutein cells → excessive production of androgens which is converted to estrogens
- Caused by unbalanced or asynchronous release of LH by pituitary: ↑ LH, ↓ FSH, ↑ testosterone
- Associated w/ Insulin resistance; ↑ risk of endometrial cancer; prolactinoma may be involved in 25%

Ovarian Epithelial Tumors

- 65-70% overall frequency, 90% of malignant ovarian tumors
- histology: cystadenomas, cystadenofibromas, adenofibromas
- risk of malignancy increases with amount of solid epithelial growth
- Clinical signs: low abdominal pain/enlargement, GI complaints, urinary complaints, ascites with peritoneal extension (exfoliated cells in fluid)
- Metastasis to liver, lungs, GI, regional nodes, opposite ovary common
- 80% of serous and endometrioid tumors positive for CA-125
- BRCA is a marker for increased risk
- fallopian tubal ligation and OCT reduce relative risk

Ovarian Epithelial Tumors

- **Serous tumors**
  - Tall, ciliated columnar epithelial lined serous fluid filled cysts, on surface of ovary
  - Can be benign or boarderline (age 20-50) or malignant (>50)
  - Serous cystadenocarcinomas are most common malignant ovarian tumor (40%)
  - Often bilateral and contain psammoma bodies
  - Benign: smooth cyst wall, no epithelial thickening
  - Boarderline: increasing papillary projections into cyst, some nuclear atypia, no destruction of stroma
  - Peritoneal spread with desmoplasia causing intestinal obstruction
Ovarian Epithelial Tumors

- **Mucinous tumors**
  - Rare before puberty or after menopause
  - Large number of big cysts filled with glycoproteins, not on surface, **not bilateral**, tall columnar epithelium **without cilia**
  - Associated with **pseudomxoma peritonei**: extensive mucinous ascites

- **Endometrioid tumors**
  - Unlike mucinous and serous, most are endometrioid tumors are malignant
  - Contain tubular glands that resemble endometrium
  - Combination of cystic and solid areas, 50% bilateral

- **Clear Cell Adenocarcinoma**
  - Large cells with clear cytoplasm

- **Cystadenofibroma**
  - Pronounced desmoplasia underlying columnar epithelial neoplasia
  - Metastatic spread is uncommon

- **Brenner tumors**
  - Uncommon transitional cell tumors, sometimes found with mucinous cystadenomas
  - Usually unilateral, can become quite massive
  - Sometimes surrounded by plump fibroblasts with hormonal activity
  - Can secrete estrogens

Stromal Ovarian Tumors

- **Ganulosa-Thecal (mixed: gran=malignant, thecal=benign)**
  - Sheet/cords of cuboidal to polygonal cells
  - **Call-Exner** bodies: small follicles w/eosinophilic secretions
  - Estrogen secreting: precocious puberty
  - Assoc. w/endometrial hyperplasia/carcinoma (adult women)

- **Thecoma-Fibroma (benign)**
  - Solid, bundles of spindle shaped fibroblasts w/lipid droplets
  - **Meig’s Syndrome**: R-sided hydrothorax, ovarian tumor, ascites
  - Hormonally inactive
  - Assoc. w/ basal cell nevus syndrome

Teratomas

- Germ cell tumor with all three germ layers
- From totipotent cells → usually found in gonads
- 3 categories:
  - Mature (benign) – most are cystic (dermoid cysts), tissue resembles adult tissue, unilateral, karyotype 46,XX, reproductive females
  - Immature (malignant) – rare, tissue resembles fetal or embryonic tissue, adolescent women
    - Frequently metastasize through capsule
  - Monodermal (specialized) – rare, unilateral, may be functional
    - struma ovari – thyroid tissue, can cause hyperthyroid
    - ovarian carcinoid – from intestinal epithelium, produces 5-HT

Non-Neoplastic Breast Disease

**FIBROCYSTIC CHANGE**:
- Most common breast condition
  - Bilateral/multiple formation of blue-domed cysts that result in pain/tenderness that varies cyclically
  - Causes microcalcification (confused with cancer)

**GYNECOMASTIA**:
- Most commonly caused by cirrhosis; usually unilateral

**PROLIFERATIVE DISEASE**:
- Proliferation of epithelial/glandular tissue; increased risk for carcinoma if >4 epithelial layers or atypia
- **Sclerosing Adenosis**
  - Increased numbers of acini compressed by fibrous tissue (silt-like); **slight increase in cancer**
Inflammatory Breast Disease

- Fat necrosis: trauma-related; chalky, white, hard lesions from saponification
- Lactation Mastitis: staph infection from nursing; may → abscess
- Galactocele: cystic dilation with viscous “milk” after lactation cessation
- Mammary Duct Ectasia: interstitial granulomatous inflammation leading to duct dilation; thick/sticky nipple discharge, lump/retracted nipple; post-menopause
- Granulomatous Mastitis: epithelial granulomas in multiparous women; may be a hypersensitivity reaction secondary to lactation
- Silicone Breast Implants: → chronic inflammation/fibrosis

Ductal Breast Carcinoma

- Typically divided into Ductal Carcinoma in Situ (DCIS) and Invasive Ductal Carcinoma
- DCIS: periductal concentric fibrosis with chronic inflammation
  - Linear or branching microcalcifications seen on mammography; associated with intraductal necrosis
- Invasive: streaks of white elastic stroma with foci of calcification, irregular borders signifying escape from the ductal basement membrane; highly scirrhous, desmoplastic tumor
- If mass is palpable, half of patients will have lymph node metastasis
- Fixation to chest wall, lymphedema → peau d’orange, cooper ligament tethering to skin, retraction of nipple

Non-ductal breast carcinoma

- **Lobular carcinoma in-situ**
  - Proliferation in one or more terminal ducts – distended lobules
  - Incidental finding on biopsy for another reason – nonpalpable
  - Often multifocal and bilateral, can progress to carcinoma
  - No cell adhesion – lack e-cadherin
- **Invasive lobular carcinoma**
  - Tends to be bilateral and multicentric
  - Single file cells, can be concentric and have bull’s eye appearance
  - Present as palpable mass or density on mammogram
  - Well differentiated tumors express hormone receptors

Non-ductal breast carcinoma

- **Medullary carcinoma**
  - Associated with BRCA-1 mutation
  - Bulky, soft tumor with large cells and lymphocytic infiltrate
- **Colloid carcinoma**
  - Occurs in older women, grows very slowly
  - Cells surrounded by extracellular pale gray-blue mucin
- **Tubular Carcinoma**
  - Women in late 40’s
  - Well-formed tubules in terminal ductules
  - Absence of myoepithelial layer
  - Multifocal or bilateral tumors

Spontaneous abortions

- 10-15% of recognized pregnancies; probably close to 22% of all conceptions; chromosomal studies are recommended with habitual or recurrent abortion or with malformed fetus
- **fetal influences**
  - defective implantation
  - genetic or acquired developmental abnormality
  - chromosomal abnormalities in >50%
- **maternal influences**
  - inflammatory diseases (local and systemic),
  - uterine abnormalities
  - infection
- **Placental abnormalities**
  - placenta acreta - partial or complete absence of the decidua with adherence of placenta directly to myometrium; failure of placental separation may cause postpartum bleeding (life threatening); up to 60% association with placenta previa; uterine rupture (placenta percreta)
  - placenta previa - implantation in the lower uterine segment or cervix associated with serous antepartum bleeding and premature labor
  - placenta abruptio - separation of the placenta prior to delivery
- **Twin placenta**
  - monochorionic implies monozygotic twins; may have one or two amnions
  - dizygotic twins usually have dichorionic, diamniotic placenta
- **Placenta**
  - Placental abnormalities
  - placenta acreta - partial or complete absence of the decidua with adherence of placenta directly to myometrium; failure of placental separation may cause postpartum bleeding (life threatening); up to 60% association with placenta previa; uterine rupture (placenta percreta)
  - placenta previa - implantation in the lower uterine segment or cervix associated with serous antepartum bleeding and premature labor
  - placenta abruptio - separation of the placenta prior to delivery
- **Twin placenta**
  - monochorionic implies monozygotic twins; may have one or two amnions
  - dizygotic twins usually have dichorionic, diamniotic placenta
Pre-eclampsia/eclampsia

- **Pre-Eclampsia**: hypertension, proteinuria, and edema
- **Eclampsia**: add convulsions, CNS disturbances, and DIC
- 6% of pregnant women; last trimester; primiparas
- DIC in eclampsia results in lesions in liver, kidneys, heart, placenta, and brain
- The primary pathology appears to involve inadequate placental blood flow and ischemia: trophoblast-dependent
- HELLP syndrome - hemolysis/elevated liver enzymes/low platelets associated with microangiopathic hemolysis with DIC and fibrin deposition
- Eclampsia is heralded by convulsions. It usually represents vascular damage to the CNS with the development of DIC.
  - Microscopic lesions include arteriolar thrombosis, arteriolar fibrinoid necrosis, petechial hemorrhages, and diffuse microinfarcts.

Other Moles

- **Incomplete (Partial) Mole**
  - Villi INCOMPLETELY involved; usually focal
  - karyotype is triploid (69,XXY) or tetraploid (92,XXXY)
  - *EMBRYO IS VIABLE for weeks, so fetal parts may be found*
  - Presentation with nonviable fetus and irregular vaginal spotting, but uterine size NOT increased and NO increased risk of choriocarcinoma
- **Invasive mole**
  - mole that penetrates and may even perforate uterine wall; tumor is locally destructive
  - vaginal bleeding and irregular uterine enlargement; persistent elevated HCG; may present several weeks after a mole has been evacuated
  - hydropic villi may embolize to lungs and brain, but do not grow as true metastases; responsive to chemotherapy

Complete (Classic) Mole

- characterized by growth and cystic swelling of COMPLETE chorionic villi with trophoblastic proliferation
- NO EMBRYO IS PRESENT; uterus is filled with grape-like clusters; volume is MUCH GREATER than in normal pregnancy
- more than 90% have 46,XX diploid pattern, all derived from the sperm (duplication of uniploid sperm; 46YY not viable)
- proliferation of both cytotrophoblasts and syncytiotrophoblasts
  - grape-like clusters of swollen, watery chorionic villi
  - villi are not atypical in structure
- presents about 14th week (8-24 wk) with vaginal bleeding, uterus larger than normal pregnancy, high HCG levels
- about 10% develop persistent trophoblastic disease and 3-5% WILL DEVELOP CHORIOCARCINOMA

Choriocarcinoma

- epithelial malignancy of trophoblastic cells from *previously normal or abnormal pregnancy*
- rapidly invasive, widely metastasizing; but responds well to chemotherapy
- 50% arise in hydatidiform (classic) moles (1 in 40 moles), 30% in previous abortions, 22% in normal pregnancies
- *no chorionic villi*; proliferation of both cytotrophoblasts surrounded by rim of syncytiotrophoblasts
- does not produce large, bulky mass
- produces high levels of HCG in absence of pregnancy
- metastases to lungs, vagina, brain, liver, kidney