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GOLF BALLS, PEBBLES, SAND, AND BEER

Remember the Mayonnaise Jar

A professor stood before his philosophy class with some items in front of him. When the class began, wordlessly, he picked up a very large and empty mayonnaise jar and proceeded to fill it with golf balls. He then asked the students if the jar was full. They agreed that it was.

The professor then picked up a box of pebbles and poured them into the jar. He shook the jar lightly and the pebbles rolled into the open areas between the golf balls. He asked the students again if the jar was full. They agreed that it was.

Next, the professor picked up a box of sand and poured it into the jar. Of course, the sand filled up everything else. He asked once more if the jar was full. The students responded with a unanimous “Yes!”

The professor then produced two cans of beer from under the table and poured the entire contents into the jar, effectively filling the empty space between the sand. The students laughed. “Now,” said the professor as the laughter subsided, “I want you to recognize that this jar represents your life. The golf balls are the important things: your family, your children, your health, your friends, and your favorite passions – things that if everything else was lost and only they remained, your life would still be full.

“The pebbles are the other things that matter: your job, your house, your car. The sand is everything else – the small stuff. If you put the sand into the jar first,” he continued, “there is no room for the pebbles or the golf balls. The same goes for life. If you spend all your time and energy on the small stuff, you will never have room for the things that are important to you. Pay attention to the things that are critical to your happiness. Play with your children. Take time to get medical checkups. Take your partner out to dinner. Play another 18. There will always be time to clean the house and fix the disposal. Take care of the golf balls first, the things that really matter. Set your priorities. The rest is just sand.”

One of the students raised her hand and inquired what the beer represented. The professor smiled and said, “I’m glad you asked. It just goes to show you that no matter how full your life may seem, there’s always room for a couple of beers.”

CLP, October, 2006

Dear M2s,

The 2.5 hour NBME subject exam on Mon. March 28, 2016 will cover the entire Pathology course/lectures/labs. There will be 125 multiple choice questions including 15-17 images.
JOINT DISEASES
This session is covered in Dec. 2015

Steve Nandkumar, M.D.
JOINT DISEASES

NORMAL JOINT

Joints (articulations) are structures that unite two or more bones. They provide both movement and mechanical support.

Joints are of two types

- Synovial (Diarthroses or cavitated)
- Non-synovial (Synarthroses or solid)

SYNOVIAN

A smooth membrane lining the joint capsule and attached to the bone (osseous insertion). It is one to four cell layers in thickness. The synovial cells (synoviocytes) produce various proteins, Ig, lysozymes, and hyaluronic acid and also have phagocytic functions.

SYNOVIAL FLUID

It is a filtrate of plasma + hyaluronic acid. It serves as a lubricant and provides nutrition to the articular cartilage.

ARTICULAR CARTILAGE

A hyaline cartilage, 2–4 mms thick, serves as a shock absorber and provides wear resistant surface.

Hyaline cartilage = Type 2 collagen, water, proteoglycans (chondroitin sulfate, Keratan sulfate), chondrocytes

Type 2 collagen → tensile strength, transmits weight (load). Force per cubic cm of articular cartilage is unit load.
Water and proteoglycans → turgor and elasticity

NOTE: The articular cartilage has no vascular, lymphatic, or nerve supply
CHONDROCYTES produce

Type 2 collagen
+ Proteoglycans
+ Enzyme inhibitors (TIMP)

matrix synthesis

In balance

degradation enzymes (MMP)

matrix degradation

CYTOKINES such as IL-1 and TNF produced by chondrocytes, synoviocytes, fibroblasts and inflammatory cells cause matrix degradation.

NOTE: MMP – Matrix metalloproteinases
TIMP – Tissue inhibitor of metalloproteinases

OSTEOARTHRITIS

Also known as Degenerative Joint Disease (DJD).

DEFINITION
– An intrinsic disease of the articular cartilage characterized by biochemical and metabolic changes causing erosion and degeneration.
– This is NOT a primary inflammation of the joint. Any inflammation that occurs is secondary.

OSTEOARTHRITIS

PRIMARY OR IDIOPATHIC

AGE RELATED
– May affect single or multiple joints
– Stress-related wear and tear of articular cartilage

SECONDARY (5% OF CASES)

1. Macro or microtrauma to joint
2. Congenital deformity
3. Diabetes mellitus
4. Ochronosis
5. Hemochromatosis
6. Marked obesity

NOTE: Ochronosis is alkaptonuria – An inborn error of metabolism associated with deficiency of homogentisic acid oxidase leading to deposition of homogentisic acid in tissues → OA
**RISK FACTORS**

**Age**
Increasing incidence of OA with increasing age, 80 – 90% incidence > 65 years.

**Gender**
Male – Hips
Female – Fingers and knees

**Race**
Whites > Non-whites

**Occupation**
RSI repetitive stress injury, e.g., ballet dancers → ankles, basketball players → knees, shoulders, elbows, baseball players → shoulders, elbows

**Genetics**
Susceptible genes on chromosomes 2 and 11; genes for PG (prostaglandins) and WNT (Wingless Integration 1) pathways

**Hormones**
Increased risk with elevated estrogens and increased bone density

**PATHOGENESIS**

Normal articular cartilage performs two functions:
- Ensure friction-free movement with the help of synovial fluid
- Act as a shock absorber in weight bearing joints (load is spread across the joint surface so that bones can handle it)

**For the above functions the cartilage must be:**
- ELASTIC
- RESILIENT WITH HIGH TENSILE STRENGTH

Cartilage is formed by Type II collagen, proteoglycans, and water. CHONDROCYTES produce Type II collagen and proteoglycans (the cartilaginous matrix) but are also responsible for matrix degradation by secreting degrading enzymes (along with enzyme inhibitors).

Normally matrix synthesis = matrix degradation. If chondrocytes do not function well, the integrity of the matrix is affected and disease (DJD) develops (more degeneration than regeneration).

In DJD, for reasons that are not clear, chondrocytes produce IL-1, TNF-α, and NO etc. These stimulate production of catabolic metalloproteinases; inhibit the synthesis of Type II collagen and proteoglycans. **THERE IS INCREASED WATER ACCUMULATION AND DECREASED PROTEOGLYCANS IN THE CARTILAGE ALONG WITH APOPTOSIS OF CHONDROCYTES.**

IL-6 and prostaglandins also ↑ matrix degradation. Thus, the net result is CARTILAGE DESTRUCTION.

Cytokines are pro inflammatory and so inflammatory cells are seen in DJD.

**MORPHOLOGY**

Chondrocyte damage causes initial focal proliferation but they are lost with time

- Superficial areas of the articular cartilage are eroded/degraded and **SHOW SPLITTING (FRICTION) AND FRAYING → CHONDROMALACIA**
- Fissures formed extend through the thickness of the cartilage and into the subchondral bone
- Subadjacent bone is thickened and ivory-like in consistency (EBURNATION) due to pressure.
- Fragments of cartilage/bone dislodge and float freely in the joint cavity (joint mice!)
- Subchondral bone cysts develop due to synovial fluid accumulation (driven through cracks in the cartilage/bone).
- **OSTEOPHYTES** (bony outgrowths or spurs) capped by hyaline and fibrous cartilage are seen at the margins.
- Mild chronic synovitis (non-specific) noted; synovial pannus forms
CLINICAL FEATURES

Insidious disease: occurs in 50’s age group.
– Deep achy joint pain and stiffness in the morning; limitation of movement
– Crepitus (crackling sound due to exposed bones rubbing against each other)
– Joint swelling and effusion
– Heberden nodes (osteoophytes in the DIP joint of fingers) in women (not in men)
  Bouchard’s nodes (osteoophytes in PIP joint of fingers)
– Osteophytes may compress nerve roots (radicular pain, muscle spasm, atrophy, neuro deficits etc.)
– Commonly knee, hip, hands, feet, cervical and lumbar areas involved.

Course
– Slow progressive course with long–term disability. Surgery (joint replacement) can help.

CRYSTAL ASSOCIATED ARTHRITIS

Crystals may deposit in the joints and lead to cytokine mediated cartilage destruction and arthritis.

These crystals may be:

<table>
<thead>
<tr>
<th>ENDOGENOUS</th>
<th>EXOGENOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Monosodium urate (MSU)</td>
<td>Steroid esters</td>
</tr>
<tr>
<td>2. Calcium pyrophosphate dihydrate (CPPD)</td>
<td>Talcum (magnesium/aluminum silicate)</td>
</tr>
<tr>
<td>3. Calcium phosphate (hydroxyapatite)</td>
<td>* Polyethylene</td>
</tr>
<tr>
<td>4. Calcium oxalate</td>
<td>* Methyl methacrylate</td>
</tr>
<tr>
<td></td>
<td>* Silicone</td>
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</tbody>
</table>

*These materials are used in “prosthetic joints.” Wear and tear over time can lead to failure of prosthesis and arthritis due to debris formation.

I. GOUT (LATIN GUTTA = DROP)
Arthritis caused by the deposition of monosodium urate crystals.

HYPERURICEMIA IS THE SINE QUA NON (LATIN = WITHOUT WHICH NOT) FOR THE DEVELOPMENT OF GOUT.

Serum or plasma urate > 6.8 - 7 mg/dl is Hyperuricemia
Normal values: Males: 4–7.0 mg/dl
               Females: 2.7–6.0 mg/dl

NOTE: Hyperuricemia is present in about 10% of the Western population but only < 0.5% will develop gout.

PATHOGENESIS

In gout there is:
1. Overproduction of uric acid (occasionally “normal” levels are seen) and/or
2. Increased or decreased excretion of uric acid; normal excretion in most cases
Increased levels of uric acid $> 7$ mg/dl exceed the saturation value of urate at normal body temperature and blood pH, leading to crystal formation and deposition in articular and extra articular tissues.

- **Primary (90%) cause unknown**
- **Secondary (10%) cause known**

**GOUT**

**Lesch-Nyhan Syndrome**
X-linked disease; occurs only in males; associated with HGPRT deficiency
- Hyperuricemia
- Gouty arthritis
- Mental retardation; neurologic deficits
- Self-mutilation

The total-body urate pool is the net result between urate production and excretion. Urate production is influenced by dietary intake of purines and the rates of de novo biosynthesis of purines from nonpurine precursors, nucleic acid turnover, and salvage by phosphoribosyltransferase activities. The formed urate is normally excreted by urinary and intestinal routes. Hyperuricemia can result from increased production, decreased excretion, or a combination of both mechanisms. When hyperuricemia exists, urate can precipitate and deposit in tissues as tophi.

Urate is filtered, reabsorbed, secreted and again reabsorbed by the kidneys. URAT1 (urate transporter 1) gene is involved in reabsorption process. GLUT 9 (glucose transporter 9) is also involved.

**Table 33–4. Causes of Hyperuricemia**

<table>
<thead>
<tr>
<th>Cause</th>
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<tbody>
<tr>
<td><strong>“Essential” hyperuricemia</strong></td>
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<tr>
<td>Overproduction (associated with hyperuricaciduria)</td>
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<tr>
<td>Underexcretion (associated with normal or decreased renal excretion of uric acid)</td>
</tr>
<tr>
<td><strong>Renal retention</strong></td>
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<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>Drug therapy: diuretics, salicylates, pyrazinamide, ethambostol</td>
</tr>
<tr>
<td>Poisons: lead, alcohol</td>
</tr>
<tr>
<td>Organic aciduria: acetacetate, lactate</td>
</tr>
<tr>
<td>Endocrinopathies: hypothyroidism, hyperparathyroidism</td>
</tr>
<tr>
<td>Increased turnover of nucleic acids</td>
</tr>
<tr>
<td>Myeloproliferative syndromes</td>
</tr>
<tr>
<td>Chemotherapy of malignant tumors, especially leukemias and lymphomas</td>
</tr>
<tr>
<td><strong>Specific enzyme defects</strong></td>
</tr>
<tr>
<td>Deficiency of hypoxanthine-guanine phosphoribosyltransferase</td>
</tr>
<tr>
<td>Complete (Lesch-Nyhan syndrome)</td>
</tr>
<tr>
<td>Partial</td>
</tr>
<tr>
<td>Abnormal phosphoribosyl pyrophosphate synthetase</td>
</tr>
</tbody>
</table>
OTHER FACTORS CONTRIBUTING TO GOUT ARE
- Age
- Genetic predisposition, e.g., familial, HGPRT x-linked abnormalities
- Alcohol
- Obesity
- Drugs, e.g., Thiazides
- Lead (Saturnine gout)

PATHOGENESIS

Crystal deposition depends on:
1. uric acid levels
2. Temperature
3. pH
4. other cations

Crystallization needs a nucleating agent such as collagen, proteoglycans cartilage fragments and other crystals.

MSU crystals in cells activate NALP3 (NACHT LRR (lysine rich residue) Pyrin domain protein 3), inflammasome caspase 1 is formed leading to cytokine release
MORPHOLOGY  The changes seen are:

A. **Acute Arthritis**  
   Long, slender needle-shaped, negatively birefringent MSU crystals 5-25 μ in length. Many PMNs engulfing crystals in synovium and synovial fluid  
   – Congested, edematous, inflamed synovium with lymphocytes, plasma cells, and macrophages  
   – Acute attack remits with crystal resolubilization  

B. **Chronic Arthritis**  
   With repeated attacks of inflammation  
   – Urate deposits seen as chalky white encrustations in the synovium and articular surfaces  
   – Synovium is hyperplastic, thick, fibrotic → pannus  
   – Cartilage/bone eroded and destroyed  
   – Fibrous or bony ankylosis of joints with loss of joint function  

C. **Tophi – Pathognomonic Hallmark of Gout!**  
   – Aggregates of urate crystals surrounded by inflamed tissue with monos/macros/giant cells and fibroblasts  
   – Occurs in joint, periarticular tissues, tendon, ligaments, soft tissues, bursa, fingertip, nose, ear lobes, and kidneys.  

D. **Gouty Nephropathy**  
   Deposition of urate crystals in the tubules and interstitium (Tophus formation)  
   – Uric acid renal stones (25% cases)  
   – Pyelonephritis (secondary to obstruction)  
   – Renal failure (10% of deaths in gout)  

CLINICAL FEATURES  
– Age > 30  
– More common in males than females  

There are four stages:  
– **Asymptomatic hyperuricemia**  
   Occurs around puberty in males, postmenopause in females  
– **Acute arthritis**  
   Sudden onset of severe joint pain with features of swelling, inflammation, fever  
   – 50% involve first MPJ (monoarticular) of great toe (called PODAGRA)  
   – 90% experience acute attacks in lower and upper extremities  
   – Recovery with or without Rx  
– **Asymptomatic intercritical period (intervals between acute attacks) - cause unknown**  
   Repeat acute attacks occur within months or years  
   – Without Rx recurrent attacks become polyarticular and frequent (at shorter intervals)  
   – Patients may then develop chronic gouty tophus after years  
– **Chronic tophaceous gout**  
   Usually develops several years after the first acute attack (mean about 12 years)  
   – Articular erosions, (punched out lytic rat-bite lesions), ankylosis, “crippling disease”  
   – Osteoclastic activity is increased; (x-ray of joints are helpful).  
   – Skin ulcers if tophus is in subcutaneous areas
**Other features are:**

- HTN/AS
- Nephropathy

**Laboratory Findings**

↑ serum uric acid (hyperuricemia) (occasionally normal levels seen)

↑ urine uric acid (hyperuricosuria) (over 600 mg/24 hours urine)

**Synovial Fluid Analysis**

MSU (mono sodium urate) crystals, on polarized light microscopy, are seen as needle-shaped crystals. With a red plate compensator, crystals are yellow and blue (those at right angles). When the stage is rotated through 90°, the colors will reverse (blue→yellow; yellow→blue).

**Treatment**

Treat hyperuricemia

- < 600 mg uric acid daily excretion in urine → uricosuric drugs
  - Probenecid: Block uric acid carriers in the tubules
  - Sulfinpyrazone

- For > 600 mg uric acid daily excretion in urine → Allopurinol (↓ xanthine oxidase so less uric acid production).

**II. Pseudo Gout (Calcium Pyrophosphate Dihydrate Disease)**

CPPD or chondrocalcinosis or Pseudogout is characterized by deposition of CPPD crystals. This may be:

<table>
<thead>
<tr>
<th>IDIOPATHIC</th>
<th>HEREDITARY</th>
<th>SECONDARY</th>
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<tbody>
<tr>
<td>(Sporadic)</td>
<td>Occurs in early life</td>
<td>Hyperparathyroidism</td>
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<td></td>
<td>Severe DJD</td>
<td>Hemochromatosis</td>
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<tr>
<td></td>
<td>Association with chromosome 8q</td>
<td>Hypomagnesemia (↓ Mg)</td>
</tr>
<tr>
<td></td>
<td>Mutations of ANK H gene on chromosome 5</td>
<td>Ochronosis</td>
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<tr>
<td></td>
<td></td>
<td>Hypothyroidism</td>
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<tr>
<td></td>
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<td>Hypophosphatasia</td>
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</table>

**Note:** ANK H gene (Homologue for ankylosis gene) codes for a transmembrane protein (transport channel protein) that regulates transport of inorganic pyrophosphate.

**Pathogenesis**

Matrix enzymes responsible for producing and degrading pyrophosphate ARE ALTERED! So CPP deposition occurs!
**MORPHOLOGY**
- Seen as chalky white friable crystals, do not dissolve in water (unlike MSU)
- 0.5 to 5µ weakly birefringent rod-shaped or rhomboid crystals
- Seen as oval blue, purple aggregates on H and E (hematoxylin and Eosin stain)
- Rarely simulate “tophus”

Crystal deposition in articular matrix, meniscus, synovium and intervertebral discs → involves joint spaces; followed by acute/chronic inflammation due to IL-8 release; neutrophils also cause damage.

**CLINICAL FEATURES**
- Usually > 50 years of age
- Over 85 years, prevalence is 30-60%
- Usually asymptomatic
- May mimic RA/OA

**Rx:** Supportive

**INFECTIOUS ARTHRITIS**

Microorganisms can infect joints

**A. Suppurative Arthritis**
(Pyogenic or bacterial arthritis)

- Gono
- Staph
- Strep
- *H. influenza*

<table>
<thead>
<tr>
<th>Gram-negative bacilli, (E. coli, Pseudomonas, Salmonella)</th>
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<tbody>
<tr>
<td>Late adolescence</td>
</tr>
<tr>
<td>Young adults</td>
</tr>
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</table>

**RISK FACTORS**
- I.V. drug abuse
- Immuno deficient/suppressed state
- Trauma
- Previous joint diseases

**CLINICAL FEATURES**
Acute onset of pain, swelling, limitation of motion, usually monoarticular
- Fever, leucocytosis, ↑ ESR

**TREATMENT:** Antibiotics following culture studies
B. **TB Arthritis**  Develops as a complication of tuberculous osteomyelitis or spread from another site (hematogenous from lung!)
   - Caseation necrosis with granuloma formation
   - Synovitis, pannus formation, bone erosion, ankylosis
   - Chronic disease can cause severe destruction

C. **Lyme Arthritis**
   Caused by B. Burgdorferi (spirochete) following deer tick (Ixodes ricinus complex) bite
   The disease progresses through 3 stages:
   **Stage 1**: The bite site becomes red with indurated or pale centre. This is called erythema chronicum migrans; fever and lymphadenopathy occur; lesions disappear in a few weeks’ time.
   **Stage 2** (early disseminated stage): Hematogenous spread leads to annular skin lesions, lymphadenopathy, muscle and joint pain, cardiac arrhythmias, meningitis, and cranial nerve involvement. IgM and IgG antibodies against Borrelia antigen are formed. Spirochetes survive in CNS and endothelial cells.
   **Stage 3** (late disseminated stage): After 2 to 3 years, chronic arthritis and joint damage occur.
   Remitting migratory arthritis involving knees, shoulders, elbows and ankles is noted. There is Chronic papillary synovitis, synovial hyperplasia, fibrin deposition, onion skin thickening of arterial walls occur; silver stains show organisms near blood vessels in 25% of cases.
   **Pathogenesis**: T cells to Borrelia outer surface protein A cross-react with unknown self-antigen.

D. **Viral Arthritis**  HCV, HBV, EBV, HIV, Rubella, Parvovirus B19 etc. can cause direct infection or autoimmune mediated damage.

**RHEUMATOID ARTHRITIS**

   - It is a chronic systemic inflammatory disorder affecting many tissues and organs.
   - In the joints, there is a non-suppurative proliferative synovitis often progressing to destruction of articular cartilage and ankylosis of the joints.

**MORPHOLOGY**

1. **Joints**
   - A symmetric arthritis affecting the small joints of the hands and feet (PIP and MP joints), ankles, knees, wrist, elbows, and shoulders.
   - Acute and chronic papillary lymphocytic synovitis. Lymphoid follicles, B-cells, CD4 + T cells, macrophages, plasma cells are seen.
   - Increased vascularity
   - Neutrophil accumulation in the synovium
   - Organizing fibrin on the synovium or floating in the joint space (rice bodies)
   - Increased osteoclastic activity in the bone with synovial penetration, erosions, subchondral cyst formations and osteoporosis
   - **PANNUS FORMATION** (pannus = cloak)
     It is an inflamed fibrovascular, synovial tissue with inflammatory cells, fibroblasts and granulation tissue causing erosion of the underlying cartilage/bone.
     - Cartilage destruction with fibrous ankylosis and bony ankylosis
     - Periarticular inflammation and edema with joint swelling and effusions.
     - Destruction of surrounding “support” tissues causes deformities of joints (swan neck or boutonniere deformity)

2. **Skin**
   - **RHEUMATOID NODULES** (25% OF CASES)
     - Firm, nontender, ovoid, nodules in skin and subcutaneous tissue (also in other organs, such as heart, aorta, lungs, spleen, etc.)
     - Microscopically there is a central zone of fibrinoid necrosis surrounded by a prominent palisade or rim of macrophages, lymphocytes, plasma cells, and granulation tissue.
3. **Rheumatoid Vasculitis**
   - Acute necrotizing vasculitis involving small or large arteries. Vital organs can be affected.
   - Obliterating endarteritis can cause ulcers and gangrene (digital vessels) and peripheral neuropathy (vasa nervorum).
   - Leukocytoclastic vasculitis can cause purpura and ulcers, nail bed infarctions.

4. **Others**
   - Pleuritis, pericarditis
   - Lung – interstitial fibrosis
   - Eye – keratoconjunctivitis, uveitis

**PATHOGENESIS**

- RA is an “autoimmune disease” occurring in an immunogenetically susceptible host exposed to an “arthritogenic” antigen.

**FACTORS INVOLVED IN PATHOGENESIS**

1. Genetic susceptibility – HLA DR1, HLA DR4, HLA DRB1, PTPN 22 polymorphism
2. Microbial agents - ? virus
3. Autoimmunity – role of T and B cells
4. Mediators of joint damage – cytokines (IL-1, IL-6, IL-8, TNF), RANK ligand etc.

**CLINICAL FEATURES**

- 1% prevalence
- Female: male = 3 to 5:1
- 35–50 years of age
- Associated with cigarette smoking
1. Constitutional features e.g., malaise, fatigue, and fever
2. Joint manifestations

- Slow insidious onset (50%)  
  - SYMMETRIC ARTHRITIS with pain, swelling, morning stiffness, and limitation of movements affecting the small joints of hands and feet, wrists, ankle, elbow, knees  
  - Slow progressive course with partial or complete remission in 20% of cases.

Radiologic Findings
- Narrowing of joint space  
- Erosion/loss of articular cartilage  
- Joint effusion and osteopenia  
- Deformity of joints (swan neck, boutonniere’s) due to inflammation/damage of supporting structures  
- Synovial cysts (Baker’s cyst in posterior knee)

3. Raynaud phenomenon, chronic leg ulcers

LABORATORY TESTS

1. RA Factor (RF)
   - IgG or IgM or IgA antibodies directed against Fc portion of IgG are present in serum and synovial fluid. Cause – unknown.  
   - RF present in 80% of cases of RA (absent in 20% of cases); also occurs in 10-20% healthy people and other diseases (e.g., SLE, SBE, sarcoidosis, TB, leprosy, hepatitis B, syphilis, malaria, etc.).  
   - RF forms immune complexes with IgG and causes a Type III hypersensitivity reaction leading to inflammatory damage.  
   - High titres indicate increased severity, poor prognosis, and systemic complications

2. Anti CCP Antibodies
   Anticyclic citrullinated peptide antibodies are more specific, but less sensitive for the diagnosis of RA than serum RF. These autoantibodies may be present as long as 10 years before the clinical diagnosis of RA.

<table>
<thead>
<tr>
<th>Specificity</th>
<th>Sensitivity</th>
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<tbody>
<tr>
<td>RF</td>
<td>60–65%</td>
</tr>
<tr>
<td>Anti CCP</td>
<td>98–99%</td>
</tr>
</tbody>
</table>

NOTE: Post-translational modifications of arginine containing peptides by PAD (peptidyl arginine deiminase) yields citrulline. It is present in Fibrillin, histone peptides and basic myelin protein. Please do not confuse this with amino acid citrulline in Kreb’s cycle.

3. Joint Fluid Analysis
   A sterile, turbid synovial fluid with increased protein, low mucin, low viscosity inclusion bearing PMNs.
4. ESR ↑
5. Normochromic, normocytic, anemia (due to ineffective erythropoiesis)
6. Thrombocytosis
**COURSE**
1. 25% cases – mild with remission
2. 25% cases → slow progression with relapses/remission
3. 50% cases → progressive disease with serious joint damage

**COMPLICATIONS** noted in RA:
1. Amyloidosis (5–10% of cases)
2. Vasculitis
3. Rx effects (GI bleeding and perforation; infections)

**JUVENILE IDIOPATHIC ARTHRITIS** (Formerly known as Juvenile Rheumatoid Arthritis)

- JIA occurs **before 16 years** of age. The cause is unknown and is perhaps due to genetic, infectious, and environmental factors. Arthritis must be **present for at least 6 weeks** to make a diagnosis.

JIA is categorized into 7 main types based on the number of joints involved during the first 6 months of disease and the involvement of other organs.

- **Oligoarthritis** accounts for approximately 50% of JIA and is defined as involvement of fewer than 5 joints. This type often includes **uveitis** (inflammation in the eyes).
- **Polyarthritis** requires arthritis in 5 or more joints.
- **Systemic arthritis** accounts for approximately 10% to 20% of JIA and is characterized by high fever, rash, and inflammation of other organs, in addition to arthritis.
- **Enthesitis-related arthritis** often affects the spine, hips, and **entheses** (attachment points of tendons to bones) and occurs mainly in boys older than 8 years.
- **Psoriatic arthritis** includes children who have arthritis with the rash of psoriasis.
- **JIA RF negative type**
- **Undifferentiated arthritis**

**NOTE:**
1. Rheumatoid factor and rheumatoid nodule are **ABSENT**
2. **ANA is positive**
   Other features are similar to rheumatoid arthritis.

**STILL DISEASE**
- J.R.A. with acute febrile onset, systemic manifestations, skin rash, hepatosplenomegaly, lymphadenopathy, serositis, and leucocytosis (15,000–25,000 cells/µL)

**SERONEGATIVE SPONDYLOARTHROPATHIES**
These are characterized by the following features:
1. Pathologic changes begin in the ligaments (attached to the bones) rather than in the synovium
2. Involvement of **Sacroiliac joints**; plus/minus arthritis in other peripheral joints
3. R.F. is **ABSENT**. Hence seronegative
4. Usually HLA-B27 association (90% cases)

**Examples:** Ankylosing Spondylitis, reactive arthropathies and psoriatic arthritis (please read Robbins)

**NOTE:** **Reactive Arthritis** – A disease caused by autoimmune reaction initiated by prior infection.

Causative organisms:
1. involving GU system → *Chlamydia*
2. involving GI system → *Salmonella, Shigella, Yersinia, Campylobacter*
3. HIV

Arthritis occurs within one month of a primary infection; e.g., **REITER SYNDROME** (arthritis, uveitis, conjunctivitis, cervicitis, non-gonococcal urethritis).
### Table 10-4. Synovial Fluid Findings in Various Diseases of Joints

<table>
<thead>
<tr>
<th>Property</th>
<th>Normal</th>
<th>Noninflammatory</th>
<th>Hemorrhagic</th>
<th>Acute Gouty Arthritis</th>
<th>Septic Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>3.5 mL</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Appearance</td>
<td>Clear, colorless</td>
<td>Clear, straw</td>
<td>Bloody or xanthochromic</td>
<td>Turbid yellow</td>
<td>Turbid yellow</td>
</tr>
<tr>
<td>Viscosity</td>
<td>High</td>
<td>High</td>
<td>V</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Fibrin clot</td>
<td>0</td>
<td>Usually 0</td>
<td>Usually 0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mucin clot</td>
<td>Good</td>
<td>Good</td>
<td>V</td>
<td>Poor to poor</td>
<td>Poor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WBC (no./cu. mm³)</th>
<th>&lt;200</th>
<th>&lt;5000</th>
<th>&lt;10,000</th>
<th>Range</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>750-4,500</td>
<td>300-98,000</td>
<td>300-75,000</td>
<td>13,500</td>
<td>17,800</td>
</tr>
<tr>
<td>Gonorrhea Arthritis</td>
<td>2500-105,600</td>
<td>138,000</td>
<td>215,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic Arthritis</td>
<td>15,600</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neutrophils (%)</th>
<th>&lt;25</th>
<th>&lt;25</th>
<th>&lt;50</th>
<th>Range</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>48-64</td>
<td>8-98</td>
<td>5-96</td>
<td>63</td>
<td>45</td>
</tr>
<tr>
<td>Gonorrhea Arthritis</td>
<td>20-96</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic Arthritis</td>
<td>75-100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood-glucose difference (mg/dL)</th>
<th>&lt;10</th>
<th>&lt;10</th>
<th>&lt;25</th>
<th>Range</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>0-41</td>
<td>6</td>
<td>0-88</td>
<td>12</td>
<td>31</td>
</tr>
<tr>
<td>Gonorrhea Arthritis</td>
<td>0-108</td>
<td>97</td>
<td>40-122</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic Arthritis</td>
<td>57</td>
<td>96</td>
<td>71</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 10-4. (continued)

<table>
<thead>
<tr>
<th>Property</th>
<th>Normal</th>
<th>Noninflammatory</th>
<th>Hemorrhagic</th>
<th>Acute Gouty Arthritis</th>
<th>Septic Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
</tr>
</tbody>
</table>

I = increased; D = decreased; Neg = negative; V = variable; WBC = white blood count; + = positive.
1For example, degenerative joint disease, traumatic arthritis, some cases of pigmented villonodular synovitis.
2For example, tumor, hemophilia, neuroarthropathy, trauma, some cases of pigmented villonodular synovitis.
3For example, RA, Reiter's syndrome, acute gouty arthritis, acute pseudogout, SLE.
4Mucus clot test adds little additional information to WBC count.
5For example, pseudomonic.
6In purulent arthrophy of undetermined cause, very high synovial fluid lactate (>200 mg/dL) indicates a nongonococal septic arthritis (gram-negative bacilli, gram-positive cocci, fungi). Lactate is < 200 mg/dL in gonococcal infection, gonit, RA, osteoarthritis, trauma.
7Use saline instead of acetic acid, which changes the joint fluid.
8Glucose concentration may give spurious results unless obtained after prolonged fasting; and differences between joint and blood samples may not be significant unless >50 mg/dL.
9Joint tap should be performed, preferably after the patient has been fasting for >4 hrs, and a blood glucose determination should be performed simultaneously.
10Mucous should be cultured anaerobically and aerobically. Culture for tubercle bacilli should be performed.
11Synovial fluid analysis is primarily useful to diagnose or rule out infectious arthritis, gout, or pseudogout.

To distinguish inflammatory from noninflammatory conditions, synovial fluid WBC > 10000/cu mm and >75% PMNs have sensitivities of 94% and 73% and specificities of 84% and 98%, respectively.

### Table 10-6. Synovial Fluid Findings in Acute Inflammatory Arthritis of Various Etologies

<table>
<thead>
<tr>
<th>Disease</th>
<th>WBC</th>
<th>Complement Activity</th>
<th>Rheumatoid Factor</th>
<th>Crystals</th>
<th>Other Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute gouty arthritis</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Monosodium urate; within PMNs during acute stage</td>
<td></td>
</tr>
<tr>
<td>Acute chondrocalcinosis</td>
<td>1</td>
<td>I</td>
<td>0</td>
<td>Calcium pyrophosphate</td>
<td></td>
</tr>
<tr>
<td>Reiter's syndrome</td>
<td>Markedly I</td>
<td>I</td>
<td>0</td>
<td>Macrophages with ingested leukocytes</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>1</td>
<td>Low</td>
<td>Usually +</td>
<td>Abundant lymphocytes (sometimes &gt; 50%); immature lymphocytes and monocytes present</td>
<td></td>
</tr>
<tr>
<td>Juvenile rheumatoid arthritis</td>
<td>1</td>
<td>Low</td>
<td>0</td>
<td>I.E. cells may be present</td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Usually very low</td>
<td>Low or 0</td>
<td>V</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Arthritis associated with psoriasis, ulcerative colitis, ankylosing spondylitis</td>
<td>1</td>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0 = absent; + = positive; I = increased; LE = lupus erythematosus; V = variable.
1Measurement of rheumatoid factor and complement in synovial fluid is rarely helpful; antimicrobial antibody determination is not useful.
2Crystals of gout and pseudogout should be identified within polymorphonuclear neutrophils using polarized light microscopy. Finding of characteristic crystals is diagnostic of gout and of chondrocalcinosis. Must be differentiated from crystals of corticosteroid crystals and cholesterol or tule (after recent joint infections). Crystals are engulfed by WBCs during acute attack but between acute episodes may lie free in fluid.
DISEASES OF THE BONE

(Brent Beenders, PhD)
(based on previous notes – self-study)

Dr. Brett Bartlett’s ppt. will be on the web
BONE PATHOLOGY

TERMINOLOGY
- Epiphysis
- Metaphysis
- Diaphysis
- Physis (growth plate)
- Cortical bone = compact bone
- Trabecular bone = cancellous bone = spongy bone

CELL TYPES & NORMAL PHYSIOLOGY

Osteoprogenitor cells: pluripotent cells stimulated by TGF-β differentiate into osteoblasts or chondroblasts

Osteoblasts (bone forming cells) express receptors for PTH, vitamin D, estrogen among others
- when stimulated synthesize and secrete osteoid (uncalcified bone matrix proteins, especially type I collagen)
- Mineralize bone by depositing hydroxyapatite crystals on matrix in concentric circles to form lamellar bone; process involves secretion of alkaline phosphatase
- Osteocalcin binds to hydroxyapatite. It is unique to bone and is a sensitive and specific marker for osteoblast activity
- Osteoblasts are active ~3 months, then undergo apoptosis, become surrounded by calcified matrix and transform into osteocytes, or become flattened, bone surface lining cells

Osteocytes are mature osteoblasts housed in lacunae; they communicate via gap junctions in cytoplasmic processes extending through canaliculi in calcified matrix
- Function to regulate second-to-second concentrations of calcium and phosphorus and translate mechanical force into biologic activity for bone remodeling

Osteoclasts are multinucleated giant cells derived from same cell line as macrophages; responsible for bone resorption
- Maturation stimulated by IL-1, IL-3, IL-6, IL-11, TNF, GM-CSF and M-CSF
- Osteoclasts are activated to resorb bone when RANK interacts with RANK-ligand from osteoblasts
- Osteoprotegerin (OPG) acts as decoy for RANK-ligand, blocking activation of osteoclasts
- Have receptors for calcitonin which inhibits bone resorption
- Ruffled border acts as giant lysosome to resorb bone creating Howship lacunae (26.2, see 17.11 Lange)
BONE MODELING AND REMODELING

- Osteoblasts and osteoclasts act in coordination as “basic multicellular unit”
- Peak bone mass achieved in 20s after cessation of modeling
- Bone mass influenced by vitamin D receptor type, nutrition, physical activity, hormonal status, age

![Bone Marrow Diagram]

BONE GROWTH AND DEVELOPMENT

Embryogenesis:
- cranial neural crest => cranial and facial skeleton
- araxial mesoderm => axial skeleton
- lateral plate mesoderm => appendicular skeleton
- Cartilage model begins ossification at ~ 8th week
  Primary ossification begins in midshaft as cartilage model is replaced by mineralized bone
  Secondary ossification begins in epiphyses forming physes or growth plates
- Homeobox genes control basic blueprint and orderly formation
- Indian hedgehog gene and parathyroid hormone related protein (PTHRP) regulate sequence of chondrocyte growth and maturation

Woven bone (primary):
- seen in fetal bone and at growth plates, gradually remodeled and replaced by lamellar bone
- presence in adults indicates pathology
- Lamellar bone (secondary): replaces primary bone

PATHOLOGY

CONGENITAL BONE DEFECTS

Definitions:
- **Dysostoses**: developmental anomalies resulting from localized problems in migration of mesenchymal cells and their formation of condensations
- **Dysplasias**: Mutations in the regulators of skeletal organogenesis such as cellular signaling mechanisms (growth factors and receptors), and matrix components (types 1 and 2 collagen) – affect cartilage and bone tissues globally
- Aplasia (failure of a bone(s) to develop)

**Fanconi anemia** - congenital absence of radius and thumb

**Thrombocytopenia Absent Radius (TAR) syndrome** – absent radius, but thumb present
- Simple congenital absence of phalanx, rib, clavicle
- Polydactyly, extra ribs; Syndactyly; Long spider, like digits
- Ex. Homeobox HOXD-13 transcription factor mutation leading to extra digit between 3rd and 4th fingers and syndactyly

**Craniorachisis** – failure of closure of spinal column and skull causing meningomyelocele or meningoencephalocele

**Achondroplasia** – most common disease of the growth plate
- Point mutation (arg for gly375) in FGFR3 gene on chromosome 4 leads to defect in paracrine signaling causing a reduction and disorganization in the proliferation of chondrocytes in the growth plate
- Autosomal Dominant, but 80% due to new mutations

**Clinical features:** shortened proximal extremities (rhizomelia), bowed legs (genu varum, lumbar lordosis, frontal bossing and midface hypoplasia, foramen magnum stenosis is common

**Thanotropic dwarfism** – lethal form of dwarfism

**Osteogenesis Imperfecta** (Brittle Bone Disease)
- Defect in type 1 collagen leads to brittle bones, as well as defects in other tissues with type 1 collagen (joints, eyes, ears, skin, teeth)
- Often autosomal dominant, but variable in genetic cause and phenotypic severity
- Type I – usually acquired genetic defect; normal life span; increased number of fractures in childhood that decrease after puberty; **blue sclera** because of decreased collagen content revealing underlying choroid; **hearing loss** due to sensorineural deficits and abnormalities of middle and inner ear; **small, misshapen, blue-yellow teeth** secondary to dentin deficiency
- Type II – always fatal in utero or in the perinatal period
- Types 2, 10, and 11 Collagen Diseases – important components of hyaline cartilage
- Pathology is rarer than type 1 collagen defects
- Mucopolysaccharidoses – deficiencies in acid hydrolase enzymes that degrade dermatan sulfate, heparan sulfate, and keratan sulfate
- Ex. Hurler syndrome - gargoylism
- Hunter syndrome – X-linked, only MPS that is not autosomal recessive; relatively milder
- Clinical features often include short in stature with chest wall abnormalities and malformed bones as well as coarse facial features, clouding of the cornea (except Hunter), joint stiffness, and mental retardation.  Pathology is generally progressive

**Osteopetrosis** (Marble Bone Disease) – reduced osteoclast bone resorption resulting in diffuse, symmetric skeletal sclerosis

**Infantile malignant osteopetrosis** (AR) – Evident in utero or shortly after delivery.  Characterized by multiple fractures, anemia, and hydrocephaly.  Postpartum mortality common.  Survivors have cranial nerve problems (optic atrophy, deafness, facial paralysis); repeated infections because of decreased hematopoiesis; extramedullary hematopoiesis; and hepatosplenomegaly.
- AD benign forms (types I & II) may not be detected until adolescence or adulthood.  Characterized by repeated fractures. Mild cranial nerve deficits and anemia are also common
- Also Carbonic Anhydrase type II type
  
  **Mechanisms:**
  - Carbonic anhydrase II deficiency – carbonic anhydrase II is required by osteoclasts and renal tubular cells to excrete H+ ions
– Mutation in ClC-7 chloride channel gene leading to dysfunctional H+ ATPase on ruffled border of osteoclasts

**Morphology:** bones lack medullary canal; ends of long bones are bulbous (Erlenmeyer flask deformity); neural foramina are small and compress nerves; primary spongiosa persists and fills medullary cavity leaving no room for hematopoietic marrow and preventing formation of mature trabeculae; bone tends to be primarily woven architecture

*Although bones are large they are brittle*
– Tx: bone marrow transplant

### METABOLIC & ACQUIRED BONE DISORDERS

**Osteoporosis** – characterized by osteopenia (decrease in bone mass)
– Localized in disuse osteoporosis
– Generalized in metabolic bone disease
– Most common causes are senile and post-menopausal
– Peak bone mass determined by vitamin D receptor, genes for collagen 1A1, estrogen receptor, insulin-like growth factor 1 and its binding protein, physical activity, diet, muscle strength, hormonal state
– Bone loss begins in 20s or 30s
– Whites more susceptible than blacks, women more than men
– Age related changes: osteoblasts lose replicative and synthetic capacity over time; growth factors lose potency over time => low turnover osteoporosis (primary)
– Reduced physical activity: Mechanical forces are important stimuli for bone remodeling; load magnitude influences bone density more than load cycles
– Genetic factors: vitamin D receptor is major determinant for peak bone mass
– Nutritional status: calcium deficiency, increased PTH, reduced vitamin D influence senile osteoporosis
– Hormonal influences: Post-menopausal osteoporosis characterized by estrogen deficiency dependent acceleration of bone loss that may be as much as 2% of cortical bone and 9% of cancellous bone per year, reaching 35% loss of cortical bone and 50% trabecular bone 30-40 years after menopause
– 1 in 2 women will experience an osteoporotic fracture
– Tx: estrogen replacement strategies
– Decreased estrogen leads to increased IL-1, IL-6 and TNF which stimulate osteoclast activity; also increased RANK-RANKL activity and decreased amount of OPG => high turnover osteoporosis (secondary)

**Secondary causes of osteoporosis**
– Prolonged glucocorticoid therapy – increase bone resorption and reduce bone formation
– Tx individuals on long-term steroid therapy with bisphosphonates prophylactically
– Clinical course: microfractures in vertebrae eventually lead to compression and collapse leading to loss of height, lumbar lordosis and kyphoscoliosis; asymptomatic until advanced

**Diseases Caused by Osteoclast Dysfunction**

**Paget Disease** (Osteitis Deformans)
– 3 stages: 1) Initial osteolytic stage with excessive bone resorption followed by 2) mixed osteoclastic-osteoblastic stage ending with predominant osteoblastic activity followed by 3) diminished cell activity and osteosclerotic stage. Net gain in bone mass, but bone is disorganized and weak.
– Usually begins in adulthood; affects 5-11% of whites in England, France, Germany, Austria, and New Zealand. Rare in Scandinavia, China, Japan, Africa
– Osteitis deformans – slow inflammatory process caused by a **paramyxovirus** (RSV, measles)
– IL-6 and M-CSF produced in excess leading to increased osteoclast activity; hyperresponsive to vitamin D and RANKL
Clinical Picture:
- mosaic pattern of lamellar bone (jigsaw puzzle)
- Often asymptomatic discovered incidentally
- Elevated alkaline phosphatase, increased urinary excretion of hydroxyproline
- May be monostotic or polyostotic (85% cases); axial skeleton or proximal femur most commonly involved
- Pain is most common presenting problem caused by microfractures and bone overgrowth compressing cranial and spinal nerve roots
- Leontiasis ossea when bones of head and face involved (bones of head and face become very heavy and deformed)
- Secondary osteoarthritis and chalk stick-type fractures of lower extremities common; compression fractures of spine and kyphosis may occur
- Overlying skin may be warm and arteriovenous shunts may occur contributing to high-output heart failure
- Increased incidence of bone tumors
- giant cell tumor, giant cell reparative granuloma, extraosseous masses of hematopoiesis; increased incidence of osteosarcoma, malignant fibrous histiocytoma, chondrosarcoma

Tx: unless there is a tumor, symptoms are suppressed with calcitonin and bisphosphonates

DISEASES ASSOCIATED WITH ABNORMAL MINERAL HOMEOSTASIS

Rickets and Osteomalacia (see ch. 9)
- Defects in matrix mineralization usually due to a deficiency of vitamin D or vitamin D resistance
- Rickets in children; osteomalacia in adults

Hyperparathyroidism (von Recklinghausen disease of bone/osteitis fibrosa cystica)
- Primary hyperparathyroidism – primary dysfunction of parathyroid gland
- Secondary hyperparathyroidism usually caused by prolonged hypocalcemia resulting in compensatory hypersecretion of PTH – milder skeletal abnormalities
- Increased PTH detected by osteoblasts which then stimulate osteoclasts leading to increased bone resorption affecting entire skeleton
- Advanced hyperparathyroid-related skeletal changes – osteitis fibrosa cystica
- Affects cortical bone more than cancellous bone
- Diagnosis: x-ray of hand reveals characteristic changes to radial aspect of middle phalanges of index and middle fingers
- Cortical cutting cones
- Dissecting osteitis in cancellous bone along length of trabeculae
- Decrease in bone density (osteopenia)
- Microfractures and secondary hemorrhage lead to mass of reactive tissue (brown tumor)
  => Generalized osteitis fibrosa cystica (von Recklinghausen disease of bone) = increased bone cell activity, peritrabecular fibrosis, cystic brown tumors in severe hyperparathyroidism
- Bony changes resolve with treatment of hyperparathyroidism

Renal Osteodystrophy
Skeletal changes that occur with chronic renal disease
1) increased osteoclastic resorption mimicking osteitis fibrosa cystica
2) osteomalacia (reduced matrix mineralization)
3) Osteosclerosis
4) Growth retardation
   a) Osteoporosis
- Changes are related to pathological vitamin D metabolism and hyperparathyroidism
Pathogenesis: Chronic renal failure results in **phosphate retention and hyperphosphatemia**

- Hyperphosphatemia induces **secondary hyperparathyroidism** because phosphate regulates PTH secretion
- Hypocalcemia results from decreased levels of vitamin D because of impaired renal hydroxylase activity and reduced intestinal absorption because of low levels of 1,25-dihydroxy vitamin D
- Vitamin D normally suppresses PTH gene expression and secretion but compromised renal function leads to increased levels of PTH at all levels of calcium
- Secondary hyperparathyroidism increases osteoclast activity
- Renal failure also causes metabolic acidosis leading to more bone resorption/demineralization
- Iatrogenic aluminum deposition from dialysis interferes with deposition of calcium hydroxyapatite promoting osteomalacia (aluminum also contributes to dialysis encephalopathy and microcytic anemia)
- Dialysis associated deposition of B2-microglobulin amyloid in bone and periarticular structures.

### BLOOD CHEMISTRY IN METABOLIC BONE DISEASES

<table>
<thead>
<tr>
<th>Bone Disease</th>
<th>Calcium</th>
<th>Phosphate</th>
<th>Alkaline Phosphatase</th>
<th>PTH</th>
<th>Vitamin D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Osteomalacia &amp; Rickets</td>
<td>Low/Normal</td>
<td>Variable</td>
<td>High/Normal</td>
<td>Normal</td>
<td>Low/Normal</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>High</td>
<td>Low</td>
<td>Normal/High</td>
<td>High</td>
<td>Normal</td>
</tr>
<tr>
<td>Paget Disease of Bone</td>
<td>Normal</td>
<td>Normal</td>
<td>Very High</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Renal Osteodystrophy</td>
<td>Normal/Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Normal</td>
</tr>
</tbody>
</table>

### FRACTURES

- Complete vs. incomplete
- Closed = overlying tissue intact)  
- Compound = fracture communicates with skin surface
- Comminuted = bone is splintered
- Displaced = bone ends do not align
- Pathologic fracture = fracture in bone with preexisting disease process
- Stress fracture = slowly developing fracture that occurs with increased physical activity
- Fracture leads to formation of a hematoma => osteoprogenitor cells activated and hematoma and fractured bone ends form soft procallus that links ends of fractured bone but provides no structural strength (occurs within 1 week)
- Woven bone is formed and repair tissue reaches maximal size by 2-3 weeks; endochondral ossification occurs to form a bony callus
- If fracture is incompletely mobilized then constant movement at fracture site prevents proper callus formation, central portion of callus may undergo cystic degeneration and create a false joint, pseudoarthrosis
- Fracture through an open growth plate can impair future growth

### OSTEONECROSIS (AVASCULAR NECROSIS)

- Ischemia of bone marrow due to 1) mechanical vascular interruption (fracture); 2) corticosteroids; 3) thrombosis and embolism (nitrogen bubbles in dysbarism); 4) vessel injury (vasculitis, radiation therapy); 5) increased intrasosseous pressure with vascular compression; 6) venous hypertension
- Medullary infarcts – cancellous bone and bone marrow; cortex not affected because of collateral blood flow
Clinically silent unless large such as in Gaucher disease, dysbarism, hemoglobinopathies
- Subchondral infarcts – wedge shaped with bone plate as base and epiphysis at apex; overlying cartilage unaffected unless collapse occurs
  Cause chronic progressive pain, often collapse and cause secondary osteoarthritis
- Healing is by creeping substitution

Notable Fractures and Infarct-Associated Lesions:
  Legg-Calve-Perthes Disease
  Osgood-Schlatter disease
  Köhler Bone disease
  Slipped Capital Femoral Epiphysis

INFECTIONS – OSTEOMYELITIS

Pyogenic Osteomyelitis – bacteria infect bone via hematogenous spread, extension from contiguous site, or direct implantation
- Staph. aureus causes 80-90% cases in which an organism is recovered
- E. coli, Pseudomonas, Klebsiella also common, esp. with GU infections
- H. Influenzae and group B strep common during neonatal period
- Salmonella in sickle cell disease
  - In neonates and children metaphysis or epiphysis commonly affected; subperiosteal spread lifting periostium is also common in children; epiphyseal infection may spread through articular surface leading to a septic joint
  - In adults epiphysis and subchondral region commonly affected
  - Sequestrum (piece of dead bone) may occur as a result of ischemic and suppurative necrosis
  - During healing a sleeve of living tissue may form around dead bone forming an involucrum
  - Brodie abscess – small intraosseous abscess that involves cortex and is walled off by reactive bone
  - Sclerosing osteomyelitis of Garré occurs in the jaw and involves extensive new bone formation

Clinical Presentation: fever, chills, leukocytosis, intense localized pain, but may present with only unexplained fever or localized pain with out fever in milder cases; x-ray may show area of lytic bone surrounded by zone of sclerosis; blood cultures are usually positive
- Tx with antibiotics and surgical drainage
- May also be complicated by pathologic fracture, secondary amyloidosis, endocarditis, sepsis, squamous cell carcinoma in sinus tract or sarcoma

Tuberculous Osteomyelitis
- Most common in immigrants and immunocompromised; 1-3% of TB cases will result in osseus infection; occasionally only site of infection
- Spread is via direct extension, hematogenous spread, or via lymphatics
- Vertebrae are most commonly affected (Pott disease), followed by knees and hips

Skeletal Syphilis
- May be caused by either Treponema pallidum or Treponema pertenue
- Congenital syphilis – bone lesions appear by 5th month of gestation, spirochetes localize in areas of endochondral ossification and periostium
- Acquired tertiary syphilis – affects nose, palate, and skull, long tubular bones (saber shins)
- Morphology: edematous granulation tissue with numerous plasma cells and necrotic bone; gummata;
- Use silver stain to detect
BONE TUMORS AND TUMOR-LIKE LESIONS

General Info:
- Matrix producing and fibrous tumors most common; osteochondroma and fibrous cortical defect most common benign tumors
- Myeloma, lymphoma and leukemia most common malignant neoplasms
- Osteosarcoma, then chondrosarcoma followed by Ewing sarcoma most common primary tumors of bone
- Benign tumors most common occur before age 30; malignant tumors most likely in elderly
- Osteosarcoma most commonly occurs in adolescence, usually around knee
- Chondrosarcomas mid to late adulthood and more commonly involve trunk, limb girdles, and proximal long bones
- Chondroblastomas and giant cell tumors more likely to occur in epiphysis of long bones
- Ewing sarcoma, osteofibrous dysplasia, adamantinoma occur in diaphysis
- Li Fraumeni syndrome (p53 mutation) and hereditary retinoblastoma (RB) frequently associated with bone sarcomas
- Bone infarcts, chronic osteomyelitis, radiation, Paget disease, metal prostheses also associated with higher incidence of bone tumors (secondary causes much less common than primary)
- Benign tumors often asymptomatic but pain is not uncommon; sudden pathologic fracture should raise suspicion
- Histologic grade most important prognostic feature of sarcoma

Bone-Forming Tumors
Osteoma – subperiosteal osteomas commonly arise on inside of face or skull bones
- Usually solitary
- Middle aged adults
- Gardner syndrome presents with multiple osteomas
- Differential includes reactive bone of infection, trauma, and hemangioma
- Slow growing and clinically insignificant unless they obstruct or impinge on other structures; do not transform into osteosarcoma

Osteoid Osteoma and Osteoblastoma - Benign

Osteoid osteoma occur in teens or 20s, more commonly in men than women
- Most commonly in femur or tibia; less than 2 cm. in size
- Painful due to excess prostaglandin E2 produced by osteoblasts; pain is more severe at night and is relieved by aspirin

Osteoblastoma more frequently involves spine; causes dull achy pain that is not responsive to salicylates
Tx by surgical excision

Osteosarcoma
- Malignant mesenchymal tumor of bone in which cancerous cells produce bone matrix
- Most common primary malignant tumor of bone (excluding myeloma and lymphoma) accounting for 20% of all primary bone cancers
- 75% occur in patients younger than 20, smaller peak in elderly (usually associated with Paget disease, bone infarcts, or irradiation)
- Metaphyseal region of long bones most common site affected, (60% around knee)

Pathogenesis:
- Genetic mutations primary factor: hereditary retinoblastoma (RB gene) has 1000x risk of osteosarcoma, and RB gene mutations present in 60-70% tumors
- Morphology: Tumor cells vary in size and shape
- Tumor cells are bone producing creating coarse lacelike structure
– Clinical course: Painful progressively enlarging mass; sudden fracture common; tumor lifts periosteum creating a triangular shadow on radiographs called **Codman triangle**
– Metastasize early, very aggressive
– Tx: limb salvage therapy

**Cartilage-Forming Tumors**

**Osteochondroma** (exostosis) – benign cartilage capped outgrowth of bone, usually mushroom shaped
– Arise from metaphysis near growth plate of long bones
– Males affected 3-5x more than females
  – Hyaline cartilage appears like disorganized growth plate, undergoes endochondral ossification
  – Stop growing when growth plates close
– Multiple hereditary exostosis (AD) caused by inactivation of EXT gene in growth plate chondrocytes
  – Solitary osteochondromas usually appear in late adolescence or early adulthood, but multiple osteochondromas occur in children

**Chondroma**
– Tend to arise from metaphyseal region of tubular bones of **hands and feet**
– Ollier disease = multiple enchondromatosis
– Maffucci syndrome = multiple enchondromatosis with soft tissue hemangiomas; risk developing sarcomatous transformation as well as ovarian carcinomas and brain gliomas
– Thought to develop from growth plate rests
– Small blue-gray, translucent nodules of cartilage
– Generally asymptomatic, but occasionally painful and cause pathologic fracture
  Radiologically appear as oval translucency surrounded by thin ring of radiodense bone (O-ring)

**Chondroblastoma**
– Rare benign tumor more common in adolescent males near the knee, but also pelvis and ribs in older patients
– Targets epiphyses and apophyses; very cellular with little cartilage; calcification produces chicken wire pattern
– Generally painful, often cause joint effusions and joint pathology
– May metastasize with surgical excision or fracture

**Chondromyxoid Fibroma**
– Very rare, difficult to distinguish from sarcoma
– Mostly affects males in teens and 20s, especially metaphysis of long bones
– Cells show varying degrees of cytologic atypia, small areas of calcification, occasional osteoclast-type giant cells
– Clinical Presentation: localized dull, achy pain; x-ray shows area of radiolucency
– Tx: surgical excision
– No threat of malignant transformation or metastasis

**Chondrosarcoma**
– Produce neoplastic cartilage
– Half as common as osteosarcoma, second most common malignant matrix producing tumor of bone
– Usually presents in patients older than 40 although some varieties present earlier
– Large bulky tumors composed of hyaline and myxoid cartilage
– Variants include conventional (hyaline and/or myxoid); clear cell (sheets of large malignant chondrocytes with abundant clear cytoplasm and numerous osteoclast-type giant cells); dedifferentiated; mesenchymal (islands of well-differentiated hyaline cartilage surrounded by sheets of small round cells that may look like Ewing Sarcoma)
– Generally arises in pelvis, shoulders, or ribs, but clear cell variant arises in epiphyses of long tubular bones; vary rarely involves distal extremities (different from enchondroma)
Clinical presentation: painful, progressively enlarging mass; the more radiolucent the mass the greater likelihood the tumor is high grade
- Low grade tumors grow slowly and cause reactive thickening of bone cortex
- High grade tumors destroy cortex and form soft tissue mass
- Tx: surgical excision +/- chemotherapy

Fibrous and Fibro-Osseous Tumors (among the more common skeletal lesions)

Fibrous Cortical Defect and Nonossifying Fibroma
- Fibrous cortical defect is found in 30-50% of all children older than 2
- Considered developmental defect, not neoplastic
- Most commonly arise in distal femur or proximal tibia
- May grow in size and progress to nonossifying fibroma
- Clinical presentation: generally asymptomatic detected incidentally on x-ray; lesion is sharply demarcated radiolucency surrounded by zone of sclerosis.
- The lesion consists of gray to yellow-brown tissue composed of fibroblasts and histiocytes often arranged in pinwheel (storiform) pattern.
- Usually resolve spontaneously, but nonossifying fibroma may present with pathologic fracture and may require surgical excision.

Fibrous Dysplasia
- Cells fail to differentiate into mature structures

Monostotic fibrous dysplasia (70% cases) – equal prevalence in boys and girls, most common in early adolescence, usually ceases with growth plate closure
- Generally asymptomatic discovered incidentally
- Does not evolve into polyostotic form

Polyostotic fibrous dysplasia (without endocrine dysfunction)
27% cases, continues to cause problems into adulthood; craniofacial involvement in 50% of moderate cases and 100% of severe cases; polyostotic disease is often progressive
- Pelvic and shoulder girdles commonly involved
- Spontaneous and recurrent fractures common

McCune Albright syndrome (polyostotic fibrous dysplasia with café au lait spots and endocrinopathies)
- Endocrine involvement may include precocious sexual development, hyperthyroidism, GH secreting pituitary adenomas, primary and adrenal hyperplasia

Mechanism is due to a somatic mutation during embryogenesis of the G-protein that couples receptor activation to adenyl cyclase leading to constitutive activation and hyperfunction of involved cells.
- Bone and skin lesions are often unilateral

Morphology: trabeculae are curvilinear and lack rim of osteoblasts
- X-ray generally shows ground glass appearance with well-defined margins
- Lesions may lead to pathologic fractures

Fibrosarcoma and Malignant Fibrous Histiocytoma
- Fibroblastic collagen producing tumors of bone
- Occur at any age, but more common in elderly
- Large, hemorrhagic, tan-white masses generally arise in metaphyses of long bones and pelvic flat bones; often destroy underlying bone and invade soft tissues
MISCELLANEOUS TUMORS

**Ewing Sarcoma and Primitive Neuroectodermal Tumor (PNET)**
- Malignant small round cell tumors of bone and soft tissue; cells resemble lymphoma, rhabdomyosarcoma, neuroblastoma, oat cell carcinoma
- 6-10% of primary malignant tumors of bone, second most common bone sarcoma in children; Ewing sarcoma usually presents between 10 and 15 years of age and 80% of cases younger than 20; most prevalent in whites, blacks rarely get this tumor
- T(11;22)(q24;q12) translocation in 85% of tumors; fusion of EWS gene on 22q12 acts as oncogene creating constitutively active transcription factor stimulating cell proliferation
- Morphology: arises in medullary cavity, invades cortex and periosteum; tumor is composed of sheets of uniform small, round cells slightly larger than lymphocytes
- Tumors arise in diaphysis of long tubular bones (femur) and flat bones of the pelvis
- Present as painful, enlarging mass with signs of inflammation at tumor site; constitutional systemic findings of inflammation common
- X-ray shows lytic tumor with permeative margins extending into soft tissues
- Periosteal reaction shows layers of reactive bone deposited in onion skin fashion
- Tx involves surgical excision and chemotherapy +/- radiation therapy
- Prognosis with treatment is 75% 5 year survival, 50% long-term cure

**Giant Cell Tumor**
- Multinucleated osteoclast-type giant cells of mononuclear lineage, sometimes called osteoclastoma
- Uncommon, benign, locally aggressive
- Most common between 20s and 40s
- Morphology: tumors are large, red-brown, cystic degeneration is common
  - Necrosis, hemorrhage, hemosiderin deposition, reactive bone formation common
- Differential diagnosis includes: brown tumor of hyperparathyroidism, giant cell reparative granuloma, chondroblastoma, pigmented villonodular synovitis
- Clinical course: in adults involves epiphyses and metaphyses; in adolescents involve only metaphysis and doesn’t cross growth plate; most commonly arise around knee but any bone can be involved; pathologic fractures common

**Metastatic Disease**
- **MOST COMMON TUMOURS OF BONE**
  - prostate, breast, kidney, lung cancer most commonly responsible in adults
  - neuroblastoma, Wilms tumor, osteosarcoma, Ewing sarcoma, and rhabdomyosarcoma are most common in children
- Lesions are usually multifocal, but carcinoma of kidney and thyroid often produce solitary metastases
- Axial skeleton most commonly affected
- Lesions are lytic, blastic or mixed
SKIN DISEASES Parts I and II

Allan Campbell, M.D.
(ppts. will be on the web)
MALE G.U. AND RENAL TUMOURS

(The following notes are from Dr. Tangella and may be useful)

Dr. N. Howell’s ppt. will be on the web
Male Urogenital System

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DISORDERS OF PENIS

MALFORMATIONS
- Hypospadias: More common, abnormal opening of urethra along ventral aspect of penis, urethral orifice anywhere along the shaft, increased risk of urinary tract infection, associated with inguinal hernia and undescended testes.
- Epispadias: Urethral orifice on dorsal aspect of penis, associated with urinary tract infection.

DISORDERS OF PENIS

- Inflammatory lesions: Most are caused by sexually transmitted diseases.
- Balanitis: Inflammation of glans penis, due to poor hygiene in uncircumcised males.
- Balanoposthitis: Inflammation of overlying prepuce of gland.
- Paraphimosis: Stenotic prepuce with forcibly retracted over glans penis, causes congestion, swelling and pain.

DISORDERS OF PENIS

- Genital candidiasis: Occurs due to poor local hygiene, common in diabetes mellitus; lesions present at erosive, painful, intensely pruritic lesions involving glans penis, scrotum and adjacent areas.
- Diagnosis by scrapings or biopsy specimens.

Neoplasms

- Squamous cell carcinoma, relatively uncommon, most occur in uncircumcised patients over 40 years of age associated with HPV type 16 and type 18.
- Carcinoma of scrotum occurs in exposure to environmental irritants such as coal tar and soot.
- Three major variants of squamous cell carcinoma in situ, all are associated with HPV.

Neoplasms

- Bowen's disease: Solitary plaque-like lesion on shaft of penis, can occur on vulva and oral mucosa, progresses to invasive component in 10% of cases.
- The other variants of carcinoma in situ include erythroplasia of Queyrat (erythematous patch/plaque of the glans penis) and Bowenoid papulosis involves penile shaft.
Neoplasms

- Squamous cell carcinoma may cause indurated ulcer.
- Variant of squamous cell carcinoma known as verrucous carcinoma characterized by less striking cytologic atypia and bulbous rounded deep margins.
- Most cases of squamous cell carcinoma of penis are indolent and locally infiltrative lesions.
- Metastasis in 25% of patients (inguinal lymph nodes).
- Overall five-year survival: 75%.

Condyloma acuminatum of the penis.

Condyloma acuminatum of the penis: Low magnification reveals the papillary (villose) architecture.

Condyloma acuminatum of the penis. The epithelium shows vacuolization (koliocytosis), characteristic of human papillomavirus (HPV) infection.

Bowen disease (carcinoma in situ) of the penis. The epithelium above the intact basement membrane (not seen in this picture) shows hyperchromatic, dysplastic atypical epithelial cells with scattered mitoses above the basal layer.

* Here is a squamous cell carcinoma of the head of the penis. Note the encrusted, raised, growth, which increases the risk for such carcinomas. The neoplasia is red to bluish with an ulcerated surface.
* This is a squamous cell carcinoma of the penis (penectomy specimen) that is a larger reddish brown fungating mass.

Carcinoma of the penis. The glans penis is deformed by a firm, ulcerated, infiltrative mass.

LESIONS OF SCROTUM, TESTES, AND EPIDIDYMIS

Here is a normal testis and adjacent structures. Identify the body of the testis, epididymis, and spermatic cord. Note the presence of two vestigial structures, the appendix testis and the appendix epididymis.

CRYPTORCHIDISM AND TESTICULAR ATROPHY

CRYPTORCHIDISM
* Failure of testicular descent into scrotum
* Testis descent from coelomic cavity into pelvic by third month of gestation and through inguinal canal into scrotum during last two months of intrauterine life
* Diagnosis of cryptorchidism difficult to establish before one year of age, especially in premature infants.

This is the microscopic appearance of normal testis. The seminiferous tubules have numerous germ cells. Sertoli cells are inconspicuous. Small dark oblong spermatogonia are seen in the center of the tubules.
CRYPTORCHIDISM AND TESTICULAR ATROPHY

- Cryptorchidism associated with congenital syndrome such as Prader-Willi syndrome.
- Vast majority cause of cryptorchidism cause is unknown.
- Involves right testis more than left.
- 25% bilateral.

CRYPTORCHIDISM AND TESTICULAR ATROPHY

- Microscopically tubular atrophy by 5 to 6 years of age, hyalinization present at time of puberty.
- Loss of tubules is associated with hyperplasia of intestinal Leydig cells.
- Foci of intratubular germ cell neoplasia may be present.
- Intratubular germ cell neoplasia is not seen in atrophic changes due to trauma, ischemia, radiation, or chemotherapy.

CRYPTORCHIDISM AND TESTICULAR ATROPHY

- Cryptorchidism associated with 4-fold increase in testicular malignancy.
- Orchiopexy does not alter the risk of malignancy.

INFLAMMATORY LESIONS

- Inflammatory lesions of testes more common than epididymis.
- Nonspecific epididymitis and orchitis, usually result secondary to ascending infection of testis through the vas deferens or lymphatics of spermatic cord.

On the left is a normal testis. On the right is a testis that has undergone atrophy. Bilateral atrophy may occur with a variety of conditions including chronic alcoholism, hypopituitarism, atherosclerosis, chemotherapy or radiation, and severe prolonged illness. A cryptorchid testis will also be atrophic. Inflammation may lead to atrophy. Mumps, the most common cause for orchitis, usually has a patchy pattern of involvement that does not lead to sterility.

A. Normal testis shows tubules with active spermatogenesis. B. Testicular atrophy. The tubules show Sertoli cells but no spermatogenesis. There is thickening of basement membranes and an apparent increase in interstitial Leydig cells.
INFLAMMATORY LESIONS

ORCHITIS
- Complicates mumps infection in roughly 20% of adults but rarely in children.
- Granulomatous inflammation of testis can occur in tuberculosis.

TESTICULAR NEOPLASMS

OTHER FACTORS
- Increasing frequency of testicular cancers are testicular dysgenesis including testicular feminization and Klinefelter's syndrome.
- MOST COMMON CYTOGENETIC ABNORMALITIES IN TESTICULAR TUMORS is Isochromosome of short arm of chromosome 12.

TESTICULAR NEOPLASMS

TESTICULAR NEOPLASMS SEMINOMA
- Seminoma identical to ovarian dysgerminoma and germinomas occurring in central nervous system and other extragonadal sites.
- Grossly, large, soft, well demarcated, homogeneous grey-white tumors.
- Intact tunica albuginea.
- Large tumor may contain focal areas of coagulation necrosis but no hemorrhage.
- If hemorrhage present, look for non-seminomatous germ cell component.
TESTICULAR NEOPLASMS

- Microscopically, large cells with distinct clear borders, clear glycogen-rich cytoplasm and nuclei with conspicuous nucleoli.
- These cells are divided into lobules by intervening fibrous septae.
- Lymphocytic infiltrate is present.
- Granulomatous inflammation may be present with syncytiotrophoblast-like giant cells that stain positive for human chorionic gonadotropin.

Seminoma of the testis appears as a fairly well circumscribed, pale, fleshy, homogeneous mass.

TESTICULAR NEOPLASMS

SPERMATOCYTIC SEMINOMA

- Older patients.
- Mixture of medium-sized, large, uninucleate or multinucleate tumor cells.
- No ITGCN
- Metastasis rare.

TESTICULAR NEOPLASMS

EMBRYONAL CARCINOMA

- Ill-defined invasive masses with foci of hemorrhage and necrosis.
- Microscopically primitive-looking cells with basophilic cytoplasm, indistinct cell borders, large nuclei with prominent nucleoli.
- May occur in sheets and contain glandular structures and papillae.
- Usually mixed with other germ cell components.

Embryonal carcinoma. In contrast to the seminoma the embryonal carcinoma is a hemorrhagic mass.
Embryonal carcinoma shows sheets of undifferentiated cells as well as primitive glandular differentiation. The nuclei are large and hyperchromatic.

This is the histologic pattern of embryonal carcinoma. Sheets of blue cells are trying to form primitive tubules.

YOLK SAC TUMOR (ENDODERMAL SINUS TUMORS)
- Children less than 3 years of age.
- Tumors represent endodermal sinus differentiation
- Grossly large well demarcated.
- Microscopically cuboidal to columnar epithelial cells in sheaths, glands and papillae.
- Occasional microcyt contain eosinophilic hyaline globules.
- Structures resembling primitive glomeruli, so-called Schiller-DuVall bodies.
- Alpha fetoprotein is present in cytoplasm.

An endodermal sinus tumor (yolk sac tumor) of the testis is shown composed of primitive germ cells that form glomeruloid or embryonal-like structures. These tumors are most frequent in children, but overall they are rare.

CHORIOCARCINOMA
- Differentiation of germ cells towards trophoblastic lines.
- Grossly small nonpalpable lesions.
- Microscopically sheets of small cuboidal cells intermingled with large eosinophilic syncytiotrophoblastic cells (cytotrophoblasts and syncytiotrophoblasts).
- Placental villous formation not seen.
- Human chorionic gonadotropin seen in syncytiotrophoblastic elements.

Choriocarcinoma shows clear cytotrophoblastic cells with central nuclei and syncytiotrophoblastic cells with multiple dark nuclei embedded in eosinophilic cytoplasm. Hemorrhage and necrosis are prominent.
TERATOMA

- Differentiation along somatic lines.
- Can be mature or immature.
- Mature forms contain fully differentiated tissues.
- Immature forms contain immature somatic elements.
- **Teratomas with malignant transformation.**
  Malignant transformation of pre-existing teratomatous elements, usually squamous cell carcinoma or adenocarcinoma.
- Most cases occur adults.
- Teratomas in prepubertal males usually benign.

TERATOMA

- All testicular teratomas in adults should be regarded as malignant neoplasms.

MIXED GERM CELL TUMORS

- Account for 60% of testicular germ cell neoplasms
- Most common combination is teratoma, embryonal cell carcinoma and yolk sac tumors.
- Clinical features: Painless enlargement of testis.
- Seminomas remain confined to testis for long periods of time.

MIXED GERM CELL TUMORS

- Metastasis commonly seen in iliac and para-aortic lymph nodes (note-not inguinal).
- Non-seminomatous germ cell neoplasm metastasize earlier.
- Most common sites are liver and lung.
Staging of testicular neoplasm

- Stage 1: Tumor confined to testis.
- Stage 2: Metastasis confined to retroperitoneal lymph nodes below the level of diaphragm.
- Stage 3: Metastasis beyond retroperitoneal lymph nodes.

Testicular Neoplasms

**ASSAY FOR TUMOR MARKERS**

- Seminoma: 10% have elevated HCG.
- Embryonal carcinoma: 90% of elevated HCG or AFP or both.
- Yolk sac tumor: 100% of elevated AFP.
- Choriocarcinomas: 100% of elevated HCG.
- Teratoma: 50% have elevated HCG or AFP or both.
- Mixed tumors: 90% have elevated HCG and AFP.
TREATMENT OF TESTICULAR GERM CELL NEOPLASM

- Chemotherapy
- 7,000 to 8,000 new cases diagnosed each year but only 400 die.
- Seminomas are radiosensitive as well as chemosensitive.

PROSTATE Prostatitis

- Prostatitis- Acute and Chronic
- Acute bacterial prostatitis- E. coli and gram negative rods
- Usually concomitant with urethral and bladder infection.

PROSTATITIS

- Chronic prostatitis: may follow episodes of acute prostatitis or may develop insidiously without previous history of acute prostatitis.
- If cultures are positive, then chronic bacterial prostatitis.
- If cultures are negative, then chronic abacterial prostatitis, also called prostatodynia (majority of cases).

ACUTE PROSTATITIS

- Other causes of abacterial prostatitis include Chlamydia trachomatis and ureaplasma urealyticum.
- Microscopically, neutrophil inflammatory infiltrate, congestion and stromal edema, should see neutrophils within prostatic glands
- Occasional glandular destruction.
- Abscess formation may occur in diabetic patients.

CHRONIC PROSTATITIS

- Microscopic features of chronic prostatitis includes lymphoid infiltrate, evidence of glandular injury and frequent concomitant acute inflammation.
- You must have tissue destruction with other inflammatory cells such as neutrophils for a diagnosis of chronic prostatitis.

GRANULOMATOUS PROSTATITIS

- Variety of different insults such as disseminated tuberculosis, sarcoidosis, fungal infection, and Wegener's granulomatosis.
- Caseous necrosis is specific to tuberculous prostatitis and not seen in other types of granulomatous prostatitis.
- Clinically, dysuria, urinary frequency, lower back pain and suprapubic pain.
NODULAR HYPERPLASIA OF PROSTATE

- Grossly, prostate gland is enlarged with multiple fairly well circumscribed nodules.
- Nodules are more pronounced in inner (central) and transitional regions.
- The cut surface is solid but may contain occasional cystic areas.

NODULAR HYPERPLASIA OF PROSTATE

- Anatomy—MUST KNOW DIFFERENT ZONES OF PROSTATE
- Androgens and estrogens play a synergistic role in development.
- Dihydrotestosterone (DHT) is a major factor in development of benign prostatic hyperplasia.
- Hence, use of 5 alpha-reductase inhibitors in treatment of nodular hyperplasia (testosterone is converted to dihydrotestosterone by 5 alpha-reductase).
NODULAR HYPERPLASIA OF PROSTATE

- Clinically, only 10% of patients with BPH manifest with symptoms, most common is lower urinary tract obstruction with hesitancy.
- Severe obstruction to the urinary tract may result in hydrenephrosis.

Carcinoma of Prostate

- Most common visceral cancer in males.
- Second cause of cancer-related deaths in men over 50 years of age after carcinoma of lung.
- Overall frequency is greater than 50% in men older than 80 years.
- Androgens play a significant role in development.
- Hence administration of estrogens suggests diethylstilbestrol which is used for treatment.

CARCINOMA OF PROSTATE

- Genetic factor: Susceptibility locus on chromosome 1 as well as chromosome 10.
- CAG repeats in androgen receptor gene linked with higher incidence of prostate cancer in African-Americans.
- Environmental factors: Linked to certain industrial settings, more cancer in Scandinavia, less common in Japan, diet high in animal fat has been suggested as risk factor.
CARCINOMA OF PROSTATE

- Grossly, 70-80% occur in outer (peripheral) glands.
- Hence digital exam is useful.
- Because of peripheral nature of involvement obstruction symptoms are not common.
- Grossly show ill-defined nodules.
- Metastasis to pelvic regional lymph nodes.
- Denonvilliers fascia helps preventing the spread from prostate to rectum.

CARCINOMA OF PROSTATE

- Microscopically, proliferation of small glands in a back-to-back configuration.
- The nucleus has prominent nucleoli. Basal cell layer is absent.
- Areas of prostatic intraepithelial neoplasia may be noted in adjacent areas.
- Gleason grading system is the most common grading system.

*Anteascendence of the prostate. Carcinomatous tissue is seen on the posterior aspect (lower left). Note the solid whitish tissue of cancer in contrast to the stongy appearance of the benign peripheral zone on the contralateral side.*

*Carcoma of the prostate showing perineural invasion by malignant glands. Compare to a benign gland (left).*
A. Low grade (Gleason score 1 + 1 = 2) prostate cancer consisting of back to back, uniformly sized malignant glands. Glands contain eosinophilic, rhomboidal prostatic crystals, a feature that is more commonly seen in cancer than in benign glands and more frequently seen in lower grade than in higher grade prostate cancer.

B. Needle biopsy of the prostate with variably sized, more evenly dispersed glands of moderately differentiated (Gleason score 3 + 3 = 6) adenocarcinoma. C. Poorly differentiated Gleason score (5 + 5 = 10) adenocarcinoma, composed of sheets of malignant cells.

These sections through a prostate removed via radical prostatectomy reveal irregular yellowish nodules, mostly in the posterior portion seen here superimposed. This proved to be prostatic adenocarcinoma. Prostate glands containing adenocarcinoma are not necessarily enlarged. Adenocarcinoma may also coexist with hyperplasia. However, prostatic hyperplasia is not a premalignant lesion. Staging of prostatic adenocarcinoma is based upon how extensive the tumor is.

By immunoperoxidase staining with antibody to prostate-specific antigen (PSA), this adenocarcinoma of prostate shows positivity. PSA is better known as a serum test to detect nodules that may have prostate cancer.
Renal Tumors

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Benign Tumors

- Renal Papillary Adenoma
  - Small, discrete adenomas arising from the renal tubular epithelium
  - Found commonly (7% to 22%) at autopsy
  - Frequently papillary – papillary adenomas in the most recent international classifications

Morphology – Renal Papillary Adenoma

- Small tumors, usually less than 5 mm in diameter
- Present within the cortex
- Appear grossly as pale yellow-gray, discrete, well-circumscribed nodules
- On microscopic examination, they are composed of complex, branching, papillomatous structures with numerous complex fiords. Cells may also grow as tubules, glands, nests, and sheets of cells. The cells are cuboidal to polygonal in shape and have regular, small, central nuclei, scanty cytoplasm, and no atypia.
- By histologic criteria, these tumors do not differ from low-grade papillary renal cell adenocarcinoma
- Share some immunohistochemical and cytogenetic features (trisomies 7 and 17) with papillary cancers
- The size of the tumor was once used as a prognostic feature, with a cutoff of 3 cm separating those that metastasize from those that rarely do.

Renal Papillary Adenoma

- Tumors of relatively small size, 1 to 3 cm in diameter, are increasingly being detected during x-ray procedures performed for nonrenal symptoms
- Occasional reports of small tumors that have metastasized
- The current view is to consider and treat all adenomas, regardless of size, as early cancers until an unequivocal marker of benignity is discovered

Renal Fibroma of Hamartoma
(Renomedullary Interstitial Cell Tumor)

- On occasion, at autopsy, small foci of gray-white firm tissue, usually less than 1 cm in diameter, are found within the pyramids of the kidneys
- Microscopic examination of these nodules discloses fibrolast-like cells and connective tissue
- Ultrastructurally, the cells have features of renal interstitial cells.
- The tumors have no malignant propensities

Angiomyolipoma

- This is a benign tumor consisting of vessels, smooth muscle, and fat
- Angiomyolipomas are present in 25% to 50% of patients with tuberous sclerosis, a disease characterized by lesions of the cerebral cortex that produce epilepsy and mental retardation as well as a variety of skin abnormalities.
Both germline and somatic mutations in the tyrosine kinase domain of the MET gene have been identified.

A second gene, called PRCC (for papillary renal cell carcinoma), on chromosome 1, has also been implicated in sporadic tumors, largely in children exhibiting characteristic (X;1) translocations.

This causes PRCC to fuse with a gene called TFE-3 on the X-chromosome, and the fusion protein dysregulates mitotic checkpoints, allowing abnormal segregation of chromosomes.

Unlike clear cell carcinomas, papillary carcinomas are frequently multifocal in origin.

Chromophobe Renal Carcinoma

- Represents 5% of renal cell cancers.
- Composed of cells with prominent cell membranes and pale eosinophilic cytoplasm, usually with a halo around the nucleus.
- On cytogenetic examination, these tumors exhibit multiple chromosome losses and extreme hypodiploidy.
- They are, like the benign oncocytoma thought to grow from intercalated cells of collecting ducts and have an excellent prognosis compared with that of the clear cell and papillary cancers.
- Histologic distinction from oncocytoma can be difficult.

Collecting Duct (Bellini Duct) Carcinoma

- Represents approximately 1% or less of renal epithelial neoplasms.
- They arise from collecting duct cells in the medulla.
- A number of chromosomal losses and deletions have been described for this tumor, but a distinct pattern has not been identified.
- Histologically, these tumors are characterized by nests of malignant cells enmeshed within a prominent fibrotic stroma, typically in a medullary location.

Morphology – Renal Cell Carcinomas

- Characteristic macroscopic appearance.
- The tumor may arise in any portion of the kidney, but more commonly, it affects the poles, particularly the upper one.
- Clear cell neoplasms arise most likely from proximal tubular epithelium, and occur as solitary unilateral lesions.
- They are spherical masses, which can vary in size, composed of bright yellow-gray-white tissue that distorts the renal outline.
- The yellow color is a consequence of the prominent lipid accumulations in tumor cells.

- There are commonly large areas of ischemic opaque, gray-white necrosis, foci of hemorrhagic discoloration, and areas of softening.
- The margins are usually sharply defined and confined within the renal capsules.
- Papillary tumors, though to arise from distal convoluted tubules, can be multifocal and bilateral.
- They are typically hemorrhagic and cystic, especially when large.
- Papillary carcinomas are the most common type of renal cancer in patients who develop dialysis-associated cystic diseases.

- As tumors enlarge, they may bulge into the calyces and pelvis and eventually may fungate through the walls of the collecting system to extend even into the ureter.
- One of the striking characteristics of this tumor is its tendency to invade the renal vein and grow as a solid column of cells within this vessel.
- Further extension produces a continuous cord of tumor in the inferior vena cava and even in the right side of the heart.
Clear cell carcinoma, the growth pattern varies from solid to trabecular (cordlike) or tubular (resembling tubules).

- The tumor cells have a rounded or polygonal shape and abundant clear or granular cytoplasm;
- The latter on special stains contains glycogen and lipids;
- The tumors have delicate branching vasculature and may exhibit cystic as well as solid areas;
- Most tumors are well-differentiated, but some show marked nuclear atypia with formation of bizarre nuclei and giant cells.

Papillary carcinoma is composed of cuboidal or low columnar cells arranged in papillary formations. Interstitial foam cells are common in the papillary cores.

- Psammoma bodies may be present. The stroma is usually scanty, but highly vascularized.

Chromophobe renal carcinoma is made up of pale eosinophilic cells, often with a perinuclear halo, arranged in solid sheets with a concentration of the largest cells around blood vessels.

Collecting duct carcinoma is a rare variant showing:

- Irregular channels lined by highly atypical epithelium with a hobnail pattern;
- Sarcomatoid changes arise infrequently in all types of renal cell carcinoma and are a distinctly ominous feature of these tumors.

Clinical Course

- The three classic diagnostic features of renal cell carcinoma are costovertebral pain, palpable mass, and hematuria, but these are seen in only 10% of cases.
- The most reliable of the three is hematuria, but it is usually intermittent and may be microscopic; thus, the tumor may remain silent until it attains a large size.

Clinical Course

- Generalized constitutional symptoms, such as fever, malaise, weakness, and weight loss.

- This pattern of asymptomatic growth occurs in many patients, so the tumor may have reached a diameter of more than 10 cm when it is discovered.

- In current times, however, many of these tumors are being discovered in the asymptomatic state by incidental radiologic studies (e.g., computed tomographic scan or magnetic resonance imaging) usually performed for nontestinal indications.

- Renal cell carcinoma is classified as one of the great mimics in medicine because it tends to produce a diversity of systemic symptoms not related to the kidney.

Clinical Course

- In addition to the fever and constitutional symptoms mentioned earlier, renal cell carcinoma produce a number of paraneoplastic syndromes including polycythemia, hypercalcemia, hyperviscosity, hepatic dysfunction, tachycardia, arrhythmia, Cushing syndrome, cardiomyopathy, hyperplasia, and amyloidosis.

- One of the common characteristic of this tumor is its tendency to metastasize widely before giving rise to any local symptoms or signs.

- In 35% of new patients with renal cell carcinoma, there is radiologic evidence of metastases at the time of presentation.

- The most common locations of metastasis are the lung (more than 50%) and bones (35%), followed in order by the regional lymph nodes, liver and adrenals, and brain.
Clinical Course

- The average 5-year survival rate of patients with renal cell carcinoma is about 45% and up to 70% in the absence of distant metastases.
- With renal vein invasion or extension into the perinephric fat, the figure is reduced to approximately 15% to 20%.
- Nephrectomy has been the treatment of choice, but partial nephrectomy to preserve renal function is being done with increasing frequency and similar outcome.

Urothelial Carcinomas of the Renal Pelvis

- Approximately 5% to 10% of primary renal tumors originate from the urothelium of the renal pelvis.
- These tumors span the range from apparently benign papillomas to invasive urothelial (transitional cell) carcinomas.
- Renal pelvic tumors usually become clinically apparent within a relatively short time because they lie within the pelvis and by fragmentation, produce noticeable hematuria.
- They are almost invariably small when discovered.
- These tumors are almost never palpable clinically; however, they may block the urinary outflow and lead to palpable hydronephrosis and flank pain.

Urothelial Carcinomas of the Renal Pelvis

- On histologic examination, pelvic tumors are the exact counterpart of those found in the urinary bladder.
- Urothelial tumors may occasionally be multiple, involving the pelvis, ureters, and bladder.
- In 50% of renal pelvic tumors, there is a preexisting or concomitant bladder urothelial tumor.

- On histologic examination, there are also foc of atypia or carcinoma in situ in grossly normal urothelium remote from the pelvic tumor.
- There is an increased incidence of urothelial carcinomas of the renal pelvis and bladder in patients with analgesic nephropathy.
- Infiltration of the wall of the pelvis and calyces is common.
- For this reason, despite their apparently small deceptive benign appearance, the prognosis for these tumors is not good.
- Five-year survival rates vary from 50% to 70% for low grade superficial lesions to 10% with high-grade infiltrating tumors.
URINARY BLADDER

ANATOMY: A hollow muscular organ with the shape of a four-sided inverted pyramid.

HISTOLOGY:

Consists of mucosa:

- Urothelium (normal has 5-7 layers of cells)
- Lamina propria
- Muscularis mucosae
- Muscularis
- Adventitia/perivesical fat

FUNCTION:

- Stores urine
- Aids micturition

CONGENITAL ANOMALIES

A. **Diverticulum** — A pouch-like eversion or evagination of bladder wall due to focal failure of development of normal muscle or obstruction during fetal development.
   - May be associated with urine stasis, infection, stone formation, and rarely cancer.
B. **Exstrophy** — A developmental failure in the anterior wall of bladder and abdomen. Bladder thus is like an open sac exposed to the outside.
   - Mucosa undergoes ulceration, inflammation and metaplastic changes, (columnar or squamous metaplasia).
   - Associated with infection, increased incidence of adenocarcinoma of bladder and occasionally epispadias
C. **Persistent Urachus** — Urachus is a vestigial remnant connecting the allantois to the dome of the bladder. Persistence of urachus may give rise to urachal cysts, infections, and adenocarcinomas.

CYSTITIS

INFLAMMATION OF THE BLADDER IS CYSTITIS.

CAUSATIVE AGENTS:

1. Bacteria/TB, fungus, virus, chlamydia, parasite, etc.
2. Drugs – cyclophosphamide
3. Radiation
4. Indwelling catheters

ACUTE CYSTITIS

- Edema, congestion, ulceration
- acute inflammatory cells

CHRONIC CYSTITIS

- Chronic inflammatory cells, granulation tissue, fibrosis; thick, inelastic wall

HEMORRHAGIC CYSTITIS IS DUE TO RADIATION, CHEMO DRUGS AND ADENOVIRUS.

CLINICAL FEATURES

1. Frequency
2. Pain – lower abdominal, pelvic
3. Dysuria (difficult or painful urination)

CYSTITIS CAN PREDISPOSE TO RENAL INFECTIONS (PLEASE REVIEW UTI)
**SCHISTOSOMA HAEMATOBIUM INFECTIONS ARE COMMON CAUSE OF CYSTITIS IN EGYPT/MIDDLE EAST.**

**INTERSTITIAL CYSTITIS (HUNNER ULCER)**
- A chronic cystitis with inflammation and fibrosis of bladder wall.
- Mucosal ulceration (Hunner ulcer) occurs
- **MAST CELLS** are usually present.
- Most frequently seen in women; cause unknown (? Autoimmune)

**NOTE:** Disease mimics flat CIS and hence biopsies are done.

**MALAKOPLAKIA**
- A type of chronic cystitis associated with *E. coli/Proteus.*

**GROSS FEATURES**
- Soft, yellow, raised, 3-4 cm mucosal plaques.

**MICROSCOPIC:**
- **LARGE FOAMY MACROPHAGES WITH ABUNDANT GRANULAR CYTOPLASM, PAS STAIN POSITIVE (VON HANSSMANN CELLS)**
- **EM SHOWS PHAGOLYSOSOMES WITH BACTERIAL DEBRIS.**
- **MICHAELIS-GUTMANN BODIES PRESENT** (laminated calcium concretions in lysosomes) IN MACROPHAGES OR OUTSIDE
  - Lymphocytes/Giant cells noted.

Similar lesions can occur in lungs, colon, kidneys, prostate, bone, etc.

**NOTE: ETIOLOGY IS DUE TO DEFECTIVE PHAGOCYTOSIS OR DEGRADATION OF BACTERIA BY MACROPHAGES.**

**NEPHROGENIC ADENOMA**

Injury can cause urothelium to become metaplastic and resemble renal tubular epithelium. Such cells/tubules form a papillary exophytic nodule and mimic a cancer. Simple excision is curative.

**UROTHELIAL NEOPLASMS**

![Image](image.png)

**EPIDEMIOLOGY:**
♂:♀ = 3:1
50-80 years
Whites > Blacks
Squamous cell CA more common in African countries (Egypt) due to Schistosomiasis.

**RISK FACTORS:**
- Cigarette smoking
- Analgesic abuse
- Azo dyes, Arylamines
- Cyclophosphamide
- Schistosomiasis
- Radiation

**GENETICS:**
- Deletions of 9p and 9q; 17p, 11p, 13q, 14q
- P53 mutations

95% OF BLADDER TUMORS ARE OF UROTHELIAL (TRANSITIONAL CELL) ORIGIN

Lesions may be:

- **Papillary** or **Flat**
  - Invasive
  - Non-invasive
  - Invasive
  - Non-invasive

I. **BENIGN UROTHELIAL TUMOURS**

**PAPILLOMA**

More common in men than women
- Above age 50
- Asymptomatic or painless hematuria

**Sub-Types**

- **Exophytic Papilloma**
  - Finger-like papillae with loose fibrovascular connective tissue core
  - Surface urothelium resembles normal “urothelium”

- **Inverted Papilloma**
  - Interanastomosing cords of bland urothelium extending into lamina propria

**TREATMENT** - Excision is helpful, but recurrences are common.

II. **MALIGNANT UROTHELIAL TUMORS**

A. **Papillary Neoplasm of Low Malignant Potential**

B. **Low-Grade Papillary Carcinoma**

C. **High-Grade Papillary Carcinoma**
  - These lesions can be differentiated by cytoarchitectural details (nuclear size, shape, nucleoli, mitoses, chromasia, cell cohesiveness etc.), i.e., more abnormal changes → high grade carcinoma.

**NOTE:**
- 10% of low grade cancers are invasive
- 80% of high grade cancers are invasive
- 40% of invasive tumors spread to lymph nodes, liver, lung, and bone marrow

D. **Carcinoma-In-Situ (CIS)**
  - Usually multifocal, FLAT lesions
  - Dyscohesive, atypical cells confined to full-thickness of urothelium
E. **Invasive Urothelial CA**

**MICRO:** DEPTH OF INVASION IS OF GREATEST PROGNOSTIC SIGNIFICANCE (i.e., tumor invasion of lamina propria, muscle).

**GRADING AND STAGING (TNM) ARE VERY IMPORTANT.**

F. **Squamous Cell Carcinoma, Small cell Ca, Adenocarcinoma, Mixed Carcinomas are uncommon**

**CLINICAL FEATURES**

- **PAINLESS HEMATURIA**
  - Frequency, urgency
- **DYSURIA**
  - Ureretic obstruction → Pyelonephritis, Hydronephrosis

**DIAGNOSIS**

- Urine cytology, biopsy
  - Newer tests to detect tumour are available eg. BTA, NMP-22 (see notes on urinalysis)

**COURSE:**

- Recurrence (true recurrence vs. new tumors). Lesions are usually MULTIFOCAL.
- Invasion/spread to lymph nodes (40%), lungs, liver, bone-marrow

**TREATMENT:** Transurethral resection with periodic cystoscopic exam./ urine cytology
  - BCG injections
  - Radical cystectomy, Chemotherapy for invasive lesions

**PROGNOSIS: DEPEND ON TYPE AND STAGE OF TUMOUR**

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>10 Year Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary urothelial neoplasm of low malignant potential</td>
<td>98%</td>
</tr>
<tr>
<td>Papillary urothelial carcinoma low grade</td>
<td></td>
</tr>
<tr>
<td>Papillary urothelial carcinoma high grade</td>
<td>40%</td>
</tr>
<tr>
<td>Squamous cell carcinoma – 70% die in one year</td>
<td></td>
</tr>
</tbody>
</table>

Invasive carcinomas have a poor prognosis (45% death rate).
INDEX OF TERMS

Menopause (From Greek month) – relates to menses

Menopause Cessation of menses (usually occurs at about 49 years of age)

Menolipsis Temporary cessation of menses

Menorrhagia Excessive uterine bleeding at the time of menses

Metrorrhagia uterine bleeding, usually of normal amount, occurring at irregular intervals

Menometrorrhagia Excessive bleeding occurring both during menses and at irregular intervals

Menorrhea Normal discharge of menses

Dysmenorrhea Painful menstruation

Polymenorrhea Abnormally frequent menstruation

Dyspareunia Difficult or painful coitus

Menarche (Men + arche – Greek for beginning) Beginning of the menstrual function

Oligomenorrhea (Greek oligos – scanty) Scanty menstruation

Leukorrhea White discharge

Amenorrhea Absence or suppression of menstruation

D and C Dilatation and curettage (dilate cervix, curette endometrium)

ECC Endocervical curettage

EMB Endometrial biopsy

Fractional curettage is ECC and EMB
**CYTOLOGY**

**Cells of the Vagina and Cervix**

**Squamous cells**

- Superficial
- Intermediate
- Parabasal
- Basal (not seen usually)

**Columnar Cells**

I. **CYTOPLASM DENOTES CELL TYPE**

1. Orangophilia (orange staining cytoplasm) → keratin
   This signifies “squamous” cells.
2. Vacuoles/secretions → suggest “adeno” (i.e., column) cells

II. **CELL PATTERN**

- Squamous cells seen arranged in “sheets” or isolated forms
- “Adeno” cells arranged in aggregates or nests (cell-balls)
III. **NUCLEUS DECIDES “MALIGNANCY”**

The cytomorphologic features are:

1. **Abnormal nuclear cytoplasmic ratio** (N:C ratio) in favour of nucleus.
   - Normal cells N:C = 1:4
   - Abnormal cell N:C = 1:1 or 1:2

2. Pleomorphism
3. Hyperchromasia
4. **Coarse chromatin**
   - Uniform, fine chromatin → usually normal
   - Coarse, irregular “lumpy” chromatin → malignancy

5. **Mitoses**
   Atypical mitoses – bipolar form
   indicate malignancy
   - ring form
   - quadripolar form

6. Nucleoli (generally indicate “adeno”/glandular lesions)

**Non-nuclear feature of malignancy**

7. Diathesis (cell background)
   “Benign cells” usually have a clean background.*
   “Malignant cells” usually show a background of inflammatory cells, debris, fibrin, red blood cells, etc.

* Clean background usually indicates “benign” cells.
What are the exceptions? 1.______________________________________________________________
2. _______________________________________________________________________________
3. _______________________________________________________________________________

A Benign/normal cytology
B CIN I (LSIL)
C CIN II (HSIL)
D. CIN III (HSIL)

NOTE: HPV (Human Papilloma Virus) testing by immuno histochemical methods is useful in detecting CIN lesions. ASCUS – Atypical cells of unknown significance also occur.

<table>
<thead>
<tr>
<th></th>
<th>Pap Smear</th>
<th>HPV Testing</th>
<th>Both Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>55.4%</td>
<td>94.6%</td>
<td>100%</td>
</tr>
<tr>
<td>Specificity</td>
<td>96.8%</td>
<td>94.1%</td>
<td>92.5%</td>
</tr>
</tbody>
</table>

NOTE: False negative rate is about 10 – 20% (due to sampling error).
### Classification of Cytologic Reports

<table>
<thead>
<tr>
<th>Papanicolaou</th>
<th>Normal</th>
<th>Benign Atypia</th>
<th>Mild Dysplasia</th>
<th>Moderate Dysplasia</th>
<th>Severe Dysplasia</th>
<th>In Situ Cancer</th>
<th>Invasive Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN*</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>II</td>
<td>III</td>
<td>IV and V</td>
<td>Invasive Cancer</td>
</tr>
<tr>
<td>Other</td>
<td>Negative</td>
<td>Suspicious or inconclusive</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Cervical intraepithelial neoplasia

### Recommended Nomenclature

#### For Cervical Cytology Smears

- Unsatisfactory (Reason and Recommendations)
- No Abnormal Cells
- Abnormal Cells Consistent with Benign Atypia (Nondysplastic)
  - Metaplasia
  - Inflammatory
  - Trichomonas Effect
  - Yeast Effect
  - Viral Effect
  - Radiation Effect
  - Others (Specify)
- Abnormal Cells consistent with Dysplasia
  - Mild Dysplasia
  - Moderate Dysplasia
  - Severe Dysplasia
- Abnormal Cells Consistent with Malignant Disease
  - Type Unspecified
  - Consistent with In Situ Squamous Carcinoma
  - Consistent with Invasive Squamous Carcinoma
  - Consistent with Adenocarcinoma
- Abnormal Cells Not Specifically Categorized
  - (See Comments)

#### Comments and Recommendations

**NOTE:** THE ABOVE CLASSIFICATIONS ARE OBSOLETE BUT ARE OF HISTORICAL INTEREST.
THE 2001 BETHESDA SYSTEM

Box 2. The 2001 Bethesda System (Abridged)

SPECIMEN ADEQUACY
Satisfactory for evaluation (note presence/absence of endocervical/transformation zone component)
Unsatisfactory for evaluation . . . (specify reason)
Specimen rejected/not processed (specify reason)
Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of (specify reason)

GENERAL CATEGORIZATION (Optional)
Negative for intraepithelial lesion or malignancy
Epithelial cell abnormality
Other

INTERPRETATION/RESULT
Negative for intraepithelial lesion or malignancy
Organisms
Trichomonas vaginalis
Fungal organisms morphologically consistent with Candida species
Shift in flora suggestive of bacterial vaginosis
Bacteria morphologically consistent with Actinomyces species
Cellular changes consistent with herpes simplex virus
Other non-neoplastic findings (Optional to report; list not comprehensive)
Reactive cellular changes associated with inflammation (includes typical repair)
radiation
intrauterine contraceptive device
Glandular cells status posthysterectomy
Atrophy

Epithelial Cell Abnormalities
Squamous cell
Atypical squamous cells (ASC) of undetermined significance (ASC-US) cannot: exclude HSIL (ASC-H)
Low-grade squamous intraepithelial lesion (LSIL) encompassing: human papillomavirus/mild dysplasia/cervical intraepithelial neoplasia (CIN) 1
High-grade squamous intraepithelial lesion (HSIL) embracing: moderate and severe dysplasia, carcinoma in situ; CIN 2 and CIN 3
Squamous cell carcinoma

Glandular cell
Atypical glandular cells (AGC) (specify endocervical, endometrial, or not otherwise specified)
Atypical glandular cells, favor neoplastic (specify endocervical or not otherwise specified)
Endocervical adenocarcinoma in situ (AIS)
Adenocarcinoma

Other (List not comprehensive)
Endometrial cells in a woman ≥40 years of age

Automated review and ancillary testing (Include as appropriate)

Educational notes and suggestions (Optional)

Comments on quality indicators such as partially obscuring inflammation or blood may also be added to the "satisfactory" designation. A specimen is considered "partially obscured" when 50% to 75% of the epithelial cells cannot be visualized. Specimens with more than 75% of epithelial cells obscured are "unsatisfactory.”
Specimens that cannot be accessioned by the laboratory, if unlabelled for example, are also designated as “unsatisfactory”; these are distinguished from specimens that have been processed by the laboratory and determined to be unsatisfactory following microscopic evaluation.

General Categorization
The "general categorization" is an optional component of the Bethesda System, designed to allow clinicians and/or their staff to triage reports readily. The previous category headings of "within normal limits" and "benign cellular changes" have been combined into a single category “negative for intraepithelial lesion or malignancy.” In this way, reactive changes are more clearly designated as “negative.” "Other” has been added as a category for cases in which there are no morphological abnormalities in the cells per se; however, the findings may indicate some increased risk: for example, benign-appearing "endometrial cells in a woman ≥40 years of age” (see below).
These categories are mutually exclusive; therefore, if several findings are present, the general categorization is based on the most clinically significant result (eg, epithelial cell abnormality).

Interpretation/Result
The workshop participants unanimously supported the view that cervical cytology is primarily a screening test, which in some instances may serve as a medical consultation by providing an interpretation that contributes to a diagnosis. However, a patient’s final diagnosis, and therefore management, must integrate clinical and laboratory results. Therefore, in the 2001 Bethesda
Pathology M-2 – Female Genital Notes

SEMC Pathology

GYNECOLOGIC CYTOLOGY REQUEST/REPORT FORM

PATIENT NAME

STREET

ADDRESS

CITY

STATE/ZIP

DATE OF BIRTH

BILL TO:

☐ Self Pay

☐ Physician Bill

☐ Medicare No.

☐ IPA Case No.

☐ Insurance (pay of care must be included)

INSURANCE/SECOND TO MEDICARE

NAME

POLICY NO.

ADDRESS

ATTENTION MEDICARE PATIENTS: SEMC PATHOLOGY AGREES TO ACCEPT THE MEDICARE ALLOWED AMOUNT AS PAYMENT IN FULL. IT IS IMPORTANT TO UNDERSTAND THAT IF THIS SERVICE IS DENIED BY MEDICARE THE PATIENT WILL BE BILLABLE AND IS RESPONSIBLE FOR PAYMENT OF THE FULL AMOUNT.

DOCTOR'S NAME

DIAGNOSIS:

DIAGNOSTIC RUSH:

☐ YES

☐ NO

DATE SPECIMEN OBTAINED

PREVIOUS CYTOLOGY:

DATE

OTHER:

YES

NO

SPECIMEN TYPE:

☐ CERVICAL

☐ VAGINAL

☐ ENDOMETRIAL

PATIENT HISTORY:

☐ PRENATAL

☐ PREMENOPAUSAL

☐ POSTMENOPAUSAL

LMP

☐ POSTPARTUM

PATIENT PHYSICAL FINDINGS:

☐ CERVICAL LESION

YES

NO

☐ OTHER SPECIFIC

☐ YES

☐ NO

* Risk factors for cervical cancer include early age at first sexual intercourse; multiple sexual partners; history of sexually transmitted diseases, including human papilloma virus; cigarette smoking; and possible use of birth control pills.

** Risk factors for endometrial cancer include: obesity, diabetes mellitus; and infertility.

TESTING PERFORMED BY SEMC PATHOLOGY 1270 MERCANTILE DR., HIGHLAND, IL CLI#:14D0982965

BELLOW INFORMATION FOR LABORATORY USE ONLY

SPECIMEN ADEQUACY

☐ Satisfactory

☐ Unsatisfactory

T-Zone Sampling

☐ Present

☐ Absent

☐ Scant cellularity

☐ Poor fixation/preservation

☐ Presence of foreign material

☐ Partially/Completely obscuring inflammation

☐ Partially/Completely obscuring blood

☐ Excessive cytolytic or autolyzing

☐ No endocervical component

☐ Not representative of site

GENERAL CATEGORIZATION

☐ Negative for Intraepithelial Lesion or Malignancy

☐ Epithelial Cell Abnormality: See Interpretation/Result (specify "squamous" or "glandular" as appropriate)

☐ Other: See Interpretation/Result (e.g. endometrial cells in a woman ≥ 60 years of age)

☐ ORGANISMS

☐ Trichomonas vaginalis

☐ Fungi organisms morphologically consistent with candida spp

☐ GIH in favor of endocervical villogiosis

☐ Bacteria morphologically consistent with actinomyces spp

☐ Cellular changes consistent with herpes simplex virus

GENERAL MALIGNANCY

☐ Squamous cell

☐ Adenocarcinoma

☐ Other

OTHER NON-NEOPLASTIC FINDINGS

☐ Atrophy with inflammation (atrophy, vaginitis)

☐ Radiation

☐ Intracrine contraceptive device (IUD)

☐ Other

EPITHELIAL CELL ABNORMALITIES

☐ Squamous cell

☐ Low grade squamous intraepithelial lesion (LSIL) encompassing: HPV + mild dysplasia/CIN 1

☐ High grade squamous intraepithelial lesion (HSIL) encompassing: moderate and severe dysplasia, CIN 2 and CIN 3

☐ Squamous cell carcinoma

☐ Adenocarcinoma

☐ Extravaginal adenocarcinoma

☐ Atypical endometrial cells: consistent with underlying endometrial hyperplasia

☐ Other malignant neoplasms: Specify

HISTORICAL INFORMATION

☐ This case selected for a QA review

☐ Previous specimen reviewed and diagnosis confirmed

☐ Previous specimen reviewed

☐ This specimen reviewed because of patient history

COMMENTS

☐ Repeat pap smear in 3 months

☐ Repeat pap smear after clearing inflammation

☐ Suggested biopsy
CERVIX

(Collare from Latin = neck)

The distal 3.5 cm or so of the uterus is the cervix. The vaginal portion of the cervix is covered by stratified squamous epithelium surrounding a central opening called EXTERNAL OS. Cephalic to the external OS is the ENDOCERVIX lined by mucus producing columnar epithelium that dips down into the underlying stroma as invaginations (endocervical glands). The endocervix opens into the lower uterine segment at the INTERNAL OS.

CERVICITIS

In healthy women, the vagina contains aerobic and anaerobic organisms along with staph, strep, E coli, and enterococci and lactobacilli. They utilize glycogen in shed epithelial cells causing an acidic pH. Lactobacilli produce lactic acid and H2O2 and protect the vagina. Infections, trauma and pH changes cause squamous metaplasia of the reserve (epithelial) cells. The epithelium covers endocervical gland openings, causing blockage, mucus accumulation and formation of “NABOTHIAN Cysts.”

ACUTE AND CHRONIC CERVICITIS

Organisms such as Gonococcus, Chlamydia, Herpes, T. Vaginalis, etc., cause STD (sexually transmitted diseases) and cervicitis.

The cervix shows acute inflammation (neutrophils) and chronic inflammation (lymphocytes, plasma cells, macrophages) along with stromal congestion and edema.

- Erosions, ulcers may form with subsequent repair.
- Patients may be asymptomatic or may have discharge per vaginum

NOTE: Severe reparative changes can cause shedding of ATYPICAL SQUAMOUS CELLS (OF UNDETERMINED SIGNIFICANCE - ASCUS). They mimic precancerous lesion.

TREATMENT – ID the organism; use antibiotics or other agents.

ENDOCERVICAL POLYP

- 2–5% of adult woman
- asymptomatic; vaginal bleeding or “spotting” occurs
- small, sessile, mass seen at the cervical OS
- shows edematous, inflamed stroma with mucous glands

TREATMENT – Excision

NOTE: Microglandular hyperplasia of cervix (benign proliferating glands) with acute inflammation is associated with oral contraceptive pill use, pregnancy and post partum state.
CERVICAL INTRAEPITHELIAL NEOPLASIA AND CARCINOMA

Preneoplastic and neoplastic lesions of the cervix can cause abnormal cellular changes (such as loss of polarity and maturation, atypical nuclei with hyperchromasia, abnormal mitoses, etc.) in the squamous and columnar epithelium. Pap smears can help in early detection/screening and management of such lesions.

PATHOGENESIS

Risk factors

- HPV infection (IMPORTANT); HPV 16 is associated with 60% of cancer cases; HPV 18 about 10%.
- Early age at first intercourse
- Multiple sexual partners
- Male partner with multiple previous sexual partners
- Cigarette smoking
- Multiparity
- Genital infections (Chlamydia)
- Oral contraceptives
- “Occupation” sex workers ↑ nuns ↓
- Immune status (HIV)

![Diagram of cervical neoplasia pathogenesis](image)

**FIGURE 22–18** A, Postulated steps in the pathogenesis of cervical neoplasia. Conditions influencing progression are listed at the lower center of the diagram. B, Approximate lifetime risks of acquiring HPV infection (left) and dying of cervical cancer (right). The intermediate steps include risks of infection with high-risk HPV types, development of advanced cervical intraepithelial neoplasia (CIN), and progression to invasive carcinoma.

- Occurs in free (episomal) form, e.g., condyloma or a genomic form, e.g., carcinoma
- HPV DNA can be detected by hybridization techniques in 95% of cancers
- Low-risk HPV (6, 11, etc.) can be differentiated from high-risk HPV (16, 18, etc.)
- E6 and E7 oncogenes inhibit p53 and RB genes respectively, thus promoting cell growth and DNA synthesis while inhibiting apoptosis. Centrosome duplication, genomic instability and up-regulation of telomerase occur.
- Biomarkers, such as cyclin E, p16 and ki-67, are increased (correlate with HPV infections).
- Other chromosomal changes include deletions at 3p and amplification of 3q (involves HPV 16)
ABNORMAL EPITHELIAL CHANGES

**Table:**

<table>
<thead>
<tr>
<th>Time</th>
<th>Epi Involvement (thickness)</th>
</tr>
</thead>
<tbody>
<tr>
<td>About 1–7 Years</td>
<td>1/3 Mild dysplasia = CIN I = LSIL (low grade squamous intraepithelial lesions)</td>
</tr>
<tr>
<td>Months to 20 years</td>
<td>2/3 Moderate dysplasia = CIN II</td>
</tr>
<tr>
<td></td>
<td>Almost full Severe dysplasia = CIN III = HSIL (High grade squamous intraepithelial lesion)</td>
</tr>
<tr>
<td></td>
<td>Full Carcinoma-in-situ</td>
</tr>
<tr>
<td></td>
<td>Microinvasive cancer</td>
</tr>
</tbody>
</table>

**Note:**

- CIN cases Regress Persist Progress Invasive CA
  - LSIL 60 30 10 2 % of cases
  - HSIL 30 60 10 % of cases

- Carcinoma in-situ involves full thickness of epithelium basement membrane is intact; no invasion
- Microinvasive Carcinoma Lesion breaks through basement membrane into stroma Tumors depth within 5 mm from base of epithelium 7 mm maximum lateral extension

**Clinical Features**

Women are mostly asymptomatic. These lesions are picked up on routine pap smears – ASCUS, LSIL, HSIL etc.
MANAGEMENT

ASCUS

HPV-ve  HPV+ve

Yearly follow-up

LSIL/HSIL

NOTE: LSIL cases can be followed conservatively (wait, HPV-ve HPV+ve

repeat pap smear etc.)

Yearly follow-up

COLPOSCOPY

1. Abnormal areas seen as white patches after acetic acid application
2. Abnormal vascular patterns (mosaic, punctation) seen.

“ALL SUCH ABNORMAL AREAS MUST BE BIOPSIED”

SCHILLER’S TEST

Used in detecting abnormal sites for bx. Normal epithelial cells contain glycogen

+ Lugols’ iodine (painted on the epithelium)

Brown color (BENIGN)

CIN/cancer cells utilize glycogen. Since they lack glycogen, they do not react with iodine → NO COLOR CHANGE. They appear pale or white. BIOPSY SUCH AREAS!

TREATMENT

1. Excision
2. Cryotherapy
3. LEEP (Loop Electrical excision Procedure) NOTE: Annual follow-up PAP smear is recommended
4. Laser
5. Conization

CARCINOMA OF CERVIX

12,000 new cases a year (about 12,340 predicted for 2013)
3,500 deaths a year (about 4030 predicted for 2013).

Significant reduction in morbidity and mortality due to PAP SMEARS (screening). Most lesions are detected early, treated and hence such dramatic gains.
1. CIN lesions occur at about age 30
2. Invasive cancers → about 45
MORPHOLOGY

A. Gross
   1. Exophytic
   2. Ulcerative
   3. Infiltrative
   Friable, grey, red mass

B. Microscopic

- Squamous Cell Carcinoma (80%)
- Adenocarcinoma (15%)
- Adenosquamous Carcinoma (both 5%)
- Non-Keratinizing
- Keratinizing
- Small Cell *

1. Regular type
2. Clear cell type
   (associated with DES)

NOTE: Non-keratinizing carcinoma → most common, best prognosis
Small cell carcinoma → least common, worst prognosis
Neuroendocrine small cell ca is associated with high risk HPVs.
*Some books consider small cell type under squamous ca; others under neuroendocrine type.

TUMOR SPREAD
1. Local (vagina, urinary bladder, ureter, rectum)
2. Distant (lymph nodes, liver, lung, bone marrow)

CLINICAL FEATURES
- Asymptomatic
- Bleeding/discharge
- Pain
- Dysuria
- Others

STAGING

<table>
<thead>
<tr>
<th>STAGE</th>
<th>Description</th>
<th>5-year Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAGE 0</td>
<td>C.I.S.</td>
<td>100%</td>
</tr>
<tr>
<td>STAGE I</td>
<td>Cancer confined to cervix; microinvasive cancer</td>
<td>80 - 95%</td>
</tr>
<tr>
<td>STAGE II</td>
<td>Cancer extends beyond cervix, but not onto pelvic wall</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>or vagina lower third</td>
<td></td>
</tr>
<tr>
<td>STAGE III</td>
<td>Cancer extends onto pelvic wall and involves lower</td>
<td>&lt; 50%</td>
</tr>
<tr>
<td></td>
<td>third of vagina</td>
<td></td>
</tr>
<tr>
<td>STAGE IV</td>
<td>Cancer extends beyond pelvis; rectum/bladder involved;</td>
<td>10–15%</td>
</tr>
<tr>
<td></td>
<td>metastases present</td>
<td></td>
</tr>
</tbody>
</table>

MANAGEMENT

- C.I.S.:
  1. Conization
- Microinvasion:
  2. Simple hysterectomy
- Invasive Carcinoma:
  1. Hysterectomy with node dissection
  2. Radiation, Chemotherapy
NOTE: HPV vaccine (against types 6, 11, 16 and 18) prevents infection (100% of HSIL cases due to types 16 and 18) and by inference cervical cancer. Protection lasts up to 5 years.

CAUSE OF DEATH IN CERVICAL CANCER IS UREMIA.

Ureter/urinary bladder invasion causes obstructive uropathy, pyelonephritis and renal failure.

FALLOPIAN TUBES

Inflammation of fallopian tubes is salpingitis. It is considered as a part of PID.

PELVIC INFLAMMATORY DISEASE (P.I.D.)

- Inflammation of tubes and tubo-ovarian tissue (also lower and upper genital tract)
- Causative organisms: gonococcus (most common 60%), chlamydia, staph, strep, coliform bacteria, clostridia; also, T.B. (2%)
- Occur as part of STD (sexually transmitted disease) or following abortion/deliveries, etc., (puerperal sepsis, etc.)
- 2–7 days after gonococcal infection, organisms spread upward to tubes/ovaries, causing acute suppurative inflammation (mucosal and submucosal)
  - Acute salpingitis → pus → pyosalpinx
    - enzymes lyse pus
to ovary (salpingo-oophoritis) → hydrosalpinx
  - Tubo-ovarian abscess
- Staph, strep, etc. usually affect the muscle and serosa via lymphatic/vascular spread (mucosal involvement is less likely). Bacteremia occurs → infect meninges, joints, and cardiac valves

Chronic salpingitis may resolve resulting in a “fibrous nodule” → called salpingitis isthmica nodosa.

NOTE: In gonococcal PID
- Cervix → cervicitis → usually asymptomatic
- Endometrium → usually spared
- Adult vagina → resistant to infection
- In children → vulvo-vaginitis (vaginal mucosa is delicate and more vulnerable).

CLINICAL FEATURES
- Fever, pelvic pain, vaginal discharge
- Adnexal mass, tenderness

DIAGNOSIS
- Gram stain and culture, DNA/ RNA testing, ultrasound, CT scan etc.

COMPLICATIONS
- Peritonitis
- Intestinal obstruction due to adhesions
- Bacteremia → meningitis, arthritis, endocarditis
- Infertility/sterility → due to tubal blockage. If pregnancy occurs, it may lead to ectopic gestation (see page 20)

TREATMENT
- Antibiotics
- Surgery
FEMALE GENITAL II NOTES

UTERUS/PLACENTA

Steve Nandkumar, M.D.
ENDOMETRIUM

### Common Types of Endometrium

<table>
<thead>
<tr>
<th><strong>Proliferative</strong></th>
<th><strong>Secretory</strong></th>
<th><strong>Menstrual</strong></th>
<th><strong>Gestational</strong></th>
<th><strong>Atrophic</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 4–14</td>
<td>Day 15–28</td>
<td>Day 0–3</td>
<td>Occurs foll. Gestation</td>
<td>Post menopause</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Progesterone</td>
<td></td>
<td>Hormones from placenta</td>
<td>Lack of hormones due to ovarian inadequacy</td>
</tr>
<tr>
<td>Straight, tubular uniform glands evenly spaced 2–3 layers of cells mitoses seen (both in glands and stroma)</td>
<td>Sub nuclear vacuole (sign of ovulation) irregular tortuous glands with serrated margins and luminal secretions</td>
<td>Crumbling glands with blood and neutrophils</td>
<td>Hypersecretory glands; cells jut into the lumen nuclei large and atypical <em>(Arias-Stella phenomenon)</em></td>
<td>Dilated cystic glands with atrophic lining cells; may contain secretions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stromal edema pre-decidual changes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### ENDOMETRITIS

Inflammation of the endometrium is uncommon.

- **Acute Endometritis**
  - Caused by staph, strep. group A, chlamydia
  - Occurs following delivery or due to retained products of conception

- **Chronic Endometritis**
  - Occurs in association with → 1. P.I.D.
  - I.U.D. (intrauterine device)
  - TB
  - Post partum, missed abortion states
  - 15% cases, cause unknown

**Micro.** PLASMA CELLS, lymphocytes, mononuclear cells seen

- **Clinical features:** Discharge, bleeding, pain, infertility are noted

- **Treatment:** Evacuate uterus (D and C – dilatation and curettage)
  Antibiotics

**NOTE:** PLASMA CELLS ARE DIAGNOSTIC OF CHRONIC ENDOMETRITIS:

Lymphocytes and occasional macrophages can occur in normal endometrium. Neutrophils → during menstruation and in acute endometritis
DYSFUNCTIONAL UTERINE BLEEDING

- Abnormal uterine bleeding due to a functional cause OUTSIDE THE UTERUS. THERE IS A DYSFUNCTION OF THE HYPOTHALAMIC PITUITARY OVARIAN AXIS.

- Organic causes, i.e., fibroid, polyp, cancer, etc. are ABSENT. There is NO COAGULOPATHY.

- There are two types of D.U.B. based on the presence or absence of ovulation.

  I Anovulatory Cycles – common at menarche and perimenopause due to hormonal changes.

    Other causes are:
    - Pit/hypothalamic
    - Thyroid disease
    - Adrenal disorders
    - Ovarian tumors (estrogen producing), polycystic ovaries
    - Obesity, malnutrition, stress, etc.
    - Unknown

  NOTE: There is failure of ovulation, excessive endometrial stimulation by estrogen, failure of progestational secretory phase. Hence, endometrium shows proliferating “cystic dilated” glands disordered architecture, stromal breakdown and necrosis → bleeding.

  II. Ovulatory cycles
      A. Inadequate luteal phase   LAZY CORPUS LUTEUM
      Corpus luteum fails to mature or regresses prematurely → so progesterone ↓, hence secretory changes are slow to develop. Thus, secretory changes as seen on biopsy will lag behind changes expected for the chronological date of the cycle by more than 2 days e.g., “25th day” secretory endometrium will look like a 20-day endometrium on biopsy. The cycle is short and menstruation occurs early.

      B. Irregular shedding defect   Patients have regular recurring menorrhagia i.e. menstruation lasts for 7 days or more. Secretory phase extends into the menstrual cycle due to increased progesterone. A biopsy done on the 5th day shows persistent secretory endometrium along with menstrual/early proliferative endometrium. This is hyperactive corpus luteum.

CHRONIC ESTROUS STATE/ENDOMETRIAL HYPERPLASIA

- Absolute high or relatively high levels of estrogen NOT BALANCED by progesterone (called a CHRONIC ESTROUS STATE - HYPERESTROGENISM) lead to endometrial hyperplasia.

- Commonly seen at perimenopause, young women with anovulatory cycles, ovarian tumors producing estrogen, ovarian stromal hyperplasia

- Stein-Leventhal syndrome, estrogen replacement therapy, DES (Diethylstilboestrol), Tamoxifen use, etc.

PTEN – Phosphatase and tensin homologue gene, on chromosome 10, is a tumor suppressor gene. It encodes for a lipid phosphatase that dephosphorylates PIP3 (phosphotidyl inositol triphosphate) to form PIP2 (a biphosphate). This compound blocks or negatively regulates AKT (Activated serine / threonine kinase or protein kinase B) phosphorylation in the PI3k pathway. So there is cell-cycle arrest, apoptosis, and inhibition of cell motility.

INACTIVATION/LOSS OF PTEN, ACTIVATES AKT PATHWAY leading to cell proliferation and tumourigenesis. Somehow, there is activation of estrogen receptors even without a ligand.

PTEN loss occurs in endometrial hyperplasia (20% cases) and in endometrial carcinoma (30-80%) cases.
ENDOMETRIAL HYPERPLASIA – There is increased number of glands and so increased gland:stromal ratio. There are 3 types:

<table>
<thead>
<tr>
<th>Cystic or Simple (with or without atypism)</th>
<th>Adenomatous (Complex Hyperplasia Without Atypism)</th>
<th>Atypical (Complex Hyperplasia With Atypism)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irregular, cystic glands increase in number, lining cells 3–4 layers thick</td>
<td>More crowded glands; less stroma in between</td>
<td>Back to back arrangement of glands, usually no stroma; mitoses seen; atypical nuclei, nucleoli</td>
</tr>
<tr>
<td>1% - 8% progresses to cancer</td>
<td>– more stratified cells</td>
<td>About 30% risk for cancer</td>
</tr>
</tbody>
</table>

NOTE: Squamous, tubal or mucinous metaplasias may occur in any of the 3 types.

(Increased estrogen) Hyperestrogenism causes → cystic hyperplasia → adenomatous → atypical polyps C.I.S. ↓ endometrial cancer

TREATMENT
– Hormonal (progesterone) → usually low rate of regression
– Surgery (hysterectomy)

ENDOMETRIAL POLYP
– Pedunculated or sessile mass, 0.5 to 3 cm. size
– Single or multiple
– There are two types: Functional type where endometrium resembles adjacent normal endometrium
  Hyperplastic type (cystic and adenomatous type) or atrophic type
- Associated with hyperestrogenism, Tamoxifen use, etc. Tamoxifen is pro-estrogenic in uterus but anti-estrogenic in breast.
– Associated with alterations of 6p21 chromosome (clonal stromal cells) involving HMGIY (High mobility Group) gene
– Clinical features - asymptomatic or vaginal bleeding

Rx – Surgery, if indicated

ENDOMETRIAL CARCINOMA
– Most common invasive cancer of genital tract
– Occurs in peri/post menopausal women, 55–65 years of age.
– Risk factors
  1. Obesity
  2. Nulliparity
  3. D.M.
  4. H.T.N.
  5. Infertility
  6. Breast diseases/ovarian Ca e.g. HNPCC (Hereditary non-polyposis colon carcinoma)
  7. Endometriosis
  8. Cowden syndrome (PTEN mutation present)

IMP. Any CHRONIC ESTROUS (HIGH ESTROGEN) state can cause cancer
GROSS
– Tumors are soft, necrotic, hemorrhagic
– May be exophytic or infiltrative

MICROSCOPIC
– **Adenocarcinoma** (most common –60%) (also called endometrioid carcinoma)
– **Adenoacanthoma** (adenocarcinoma with benign squamous epithelium), 20%
– **Adenosquamous carcinoma** (squamous component is malignant), 7% – poor prognosis
– **Papillary carcinoma** (resembles serous papillary carcinoma of ovary) – poor prognosis
– **Clear cell carcinoma** – poor prognosis. The last 2 types constitute 5 – 15 % of cases.

NOTE: – Adenocarcinoma and adenoacanthoma have the same 5-year survival rate.

**ENDOMETRIAL CANCER**
There are two types

<table>
<thead>
<tr>
<th>TYPE 1 85%</th>
<th>TYPE II 15%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Associated with increased estrogens</strong></td>
<td><strong>Not associated with increased estrogens</strong></td>
</tr>
<tr>
<td>Endometrial hyperplasia</td>
<td>Endometrial atrophy</td>
</tr>
<tr>
<td>– Age 55-65; obese women</td>
<td>– Age 65-75; thin women</td>
</tr>
<tr>
<td>– Endometrioid carcinoma</td>
<td>– Papillary serous Ca, clear cell carcinoma</td>
</tr>
<tr>
<td>– Well-differentiated</td>
<td>– Poorly differentiated</td>
</tr>
<tr>
<td>– Peritoneal, transtubal, lymphatic spread minimal</td>
<td>– Peritoneal, transtubal, lymphatic spread +++</td>
</tr>
<tr>
<td>– Good prognosis</td>
<td>– Poor prognosis</td>
</tr>
<tr>
<td>– PTEN inhibition, <strong>PTEN protein absent</strong></td>
<td>– P53 mutation</td>
</tr>
<tr>
<td>Beta Catenin, K- RAS, PI3K, p53 mutations noted</td>
<td>– <strong>P53 protein present</strong> ( overexpressed)</td>
</tr>
<tr>
<td>Micro satellite instability noted</td>
<td></td>
</tr>
</tbody>
</table>

**GRADING OF TUMOR**
FIGO grade I – well differentiated, glandular pattern; solid areas < 5% of tumour
grade II – moderately differentiated; glandular tumor + partly solid areas < 50%
grade III – poorly differentiated; totally solid, minimal to no glands; solid areas > 50%

**TUMOR SPREAD**
– Invades muscle and periuterine tissue, peritoneum
– Spreads to lymph nodes, lungs, liver, bone

**STAGING**

<table>
<thead>
<tr>
<th>5-year Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Cancer confined to corpus</td>
</tr>
<tr>
<td>II. Cancer involves corpus and cervix</td>
</tr>
<tr>
<td>III. Cancer extends outside uterus but not beyond true pelvis</td>
</tr>
<tr>
<td>IV. Cancer extends outside true pelvis; bladder, rectum involved</td>
</tr>
</tbody>
</table>

For **TYPE II CARCINOMAS** - 3 year survival rate is < 50%
5 year rate is < 35%
CLINICAL FEATURES
- Asymptomatic
- Bleeding per vaginum; discharge (leukorrhea)
- Pap smears/jet lavage technique may yield adequate cells for dx
- CT or ultra sound of endometrium; > 5 mm thickness in post-menopausal women is SUSPICIOUS.
- Endometrial bx, D and C will help in diagnosis

TREATMENT
- Surgery
- Radiation therapy

NOTE: ALL PERI/POST MENOPAUSAL BLEEDING MUST BE EVALUATED FOR PRE NEOPLASTIC/NEOPLASTIC UTERINE LESIONS (ENDOMETRIAL CANCER)

ADENOMYOSIS
- Occurs in 15–20% of women
- NESTS OF ENDOMETRIUM (GLANDS AND STROMA) are seen in the muscle at least 2–3 mm away from the base of the endometrium (zona basalis)
- Cause unknown (? extension of glands into muscle; ? müllerian remnants)
- Blood extending into these foci may cause reactive muscle hypertrophy
- Clinical features similar to those of endometriosis

ENDOMETRIOSIS
- OCCURS IN 10% WOMEN BETWEEN 20–40 YEARS OF AGE.
- ENDOMETRIAL GLANDS AND STROMA PRESENT OUTSIDE THE UTERUS.
- Ectopic tissue may involve ovary (CHOCOLATE CYST), tubes, pelvic ligaments, peritoneum, bladder, rectum, lung, skin, nodes, etc.
- Increased susceptibility of some women to endometriosis may be due to genetic, hormonal, and immune factors.
- Gene abnormalities (involving Steroidogenesis factor 1 and estrogen receptors) lead to increased production of estrogens and prostaglandins along with increased resistance to progesterone.
- Theories of endometriosis
  1. Sampson’s retrograde implantation theory – backflow of menstrual tissue via tubes leads to implantation of tissue in the pelvic areas
  2. Meyer’s coelomic metaplasia theory – coelomic epithelium normally lines tube, ovary, endometrium, so such ectopic sites → endometriosis (may develop from metaplasia)
  3. Halban’s lymphatic/vascular spread (theory)
- MICRO. Ectopic foci reveal (two out of three features needed for dx of endometriosis)
  - Endometrial glands
  - Stroma
  - Hemosiderinophages
- Ectopic tissues respond cyclically to hormones and bleed, leading to inflammation, repair, scars, adhesions, etc.
- Such tissues contain enzyme “aromatase” cytochrome P450 and hence can produce their own “estrogen” due to pro-inflammatory cytokines eg. IL 1, IL 6, TNF, PGE2. Progesterone resistance is noted.
- Steroidogenesis factor 1 gene and estrogen receptor gene abnormalities are also noted. They activate pathways leading to increased estrogen and PG synthesis with resistance to progesterone.
CLINICAL FEATURES

- Triad of
  - Pelvic pain
  - Dysmenorrhea → painful menstruation
  - Dyspareunia → painful coitus
  - Dysuria, painful defecation, infertility, sterility (30-40% of cases) also present

TREATMENT

- Medical (suppress menstruation)
- Oral contraceptive pills
- Androgens
- Lupron
  Recovery follows cessation of Rx, as ectopic sites become fibrotic
- Surgery – TAH, BSO (total abdominal hysterectomy with bilateral salpingo-oopherectomy) as indicated (advanced cases presenting as adnexal masses)

LEIOMYOMA (FIBROID)

- Most common benign smooth muscle tumor
- More common in blacks than whites; between 20–40 years of age.
- Cytogenetic abnormalities occur in 40% of tumors, 60% show normal karyotype.
- Estrogen dependent tumor (↑ in pregnancy, ↓ in post menopause)
- May be single or multiple
- Occurs submucosally, intramurally, subserosally, well circumscribed, firm bulging masses
- Composed of smooth muscle bundles with whorled appearance
- Mitoses very rare
- Hyalinization, fibrosis, calcification, cystic changes occur (red degeneration → soft red leiomyoma)

Benign leiomyomas may be of the following subtypes: 1. Bizarre (symplastic) type with nuclear atypism and giant cells
2. Benign metastasizing type, e.g., lung “metastasis”
3. Peritoneal leiomyomatosis.

CLINICAL FEATURES

- Asymptomatic, mass effects on surrounding structures, pain, bleeding, frequent urination, infertility, etc. are noted
- In pregnant women these maybe spontaneous abortion, fetal malposition, uterine inertia, post partum hemorrhage (PPH)

NOTE: LEIOMYOMA VERY RARELY BECOMES A LEIOMYOSARCOMA

TREATMENT

- Removal of fibroid (simple excision for single tumour)
- Surgery
- Hysterectomy
- Embolization of uterine artery
LEIOMYOSARCOMA

- Uncommon tumors, originate de novo in uterus
- Very rarely originate from a leiomyoma
- Chromosomal deletions seen are DIFFERENT than those of a leiomyoma
- Occur in women between 40–60 years of age.
- Tumors present as infiltrative or polypoid masses;
- Microscopic features:
  - Hypercellularity
  - Nuclear atypism
  - Necrosis
  - Mitoses (very important for dx)

<table>
<thead>
<tr>
<th>Malignant tumors</th>
<th>Mitoses 10 or more /10 h.p. field with or without atypism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5–10/10 h.p. field with atypism</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Uncertain Malignant Potential</th>
<th>0–5/10 h.p. field</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NOTE: &lt; 5cm. size unlikely to be a sarcoma.</td>
</tr>
</tbody>
</table>

- Tumors spread to liver, lung, brain, bones, abdomen
- High recurrence after removal
- 5-year survival 40% (anaplastic tumors 10–15%)

ENDOMETRIAL STROMAL TUMORS

- Originate from endometrial stroma; ER PR and CD 10 positive.
  1. Stromal nodule → benign
  2. Low grade stromal sarcoma (endolymphatic stromal myosis); invades lymphatics/ muscle
  3. Stromal sarcoma – high grade, mitoses +++, high recurrence 5-year survival rate is 50%
  - t(7;17) translocation seen; involves JAZF1 and JJAZ1 genes (fusion protein is anti-apoptotic)
    (JAZF is Juxtaposed with another zinc finger; a transcription repressor).

CARCINOSARCOMA (Mixed Malignant Müllerian Tumor – MMMT)

- Tumors occur in older women > 60 years of age with history of radiation Rx
- Bulky fleshy masses protrude through cervical os, may bleed

  Endometrial adenocarcinoma + stromal sarcoma

  Bone
  Fat
  Cartilage

  Mesenchymal derivation

- Tumor cells (epithelial and stromal) are positive for epithelial cell markers
- 5-year survival rate 25–30%

ADENOSARCOMA

- Tumours with benign endometrial glands and **malignant stroma**
- Present as polypoid masses with discharge/ bleeding; occur in women during 4 and 5 decades
- Estrogen sensitive tumors; oophorectomy necessary.
- Recurrent rate is 25%
PLACENTA

A disc shaped organ, it weighs about 1/7 of the weight of the fetus (i.e., about 600 gm). It has two surfaces:
- Maternal composed of spongy tissue (lobes) called cotyledons
- Fetal with dilated blood vessels and covering membranes

The attached membranes are:
- Chorion
- Amnion

The umbilical cord attached to the fetal surface has two arteries and one vein.

Placenta consists of chorionic villi

ABORTION
- 10% of all pregnancies; with sensitive hCG testing additional 22% cases are detected
- Cause:
  - Implantation defect
  - Maternal (infection, inflammation; trauma, systemic diseases)
  - Fetal (genetic or acquired abnormality)
  - Chromosomal abnormalities seen in 50% cases of abortion

MICROSCOPIC
- Gestational endometrium
- Edematous villi (hydropic change) with ↓ stromal vessels
- Decidual necrosis, hemorrhage, and inflammation
- Fetal products usually not seen; if present, send for chromosome analysis (in cases of habitual abortion and malformed fetus)

ECTOPIC PREGNANCY
- Occurrence 1:150 gestations
- Implantation of zygote in a site other than the uterus
- These sites are:
  - Tubal 90%
  - Ovary
  - Abdominal cavity
- Causes of ectopic pregnancy:
  - P.I.D. 35–50%
  - Peritubal adhesions
  - ‘Normal’ tube (cause unknown) 50%
  - I.U.D.
  - Leiomyomas/endometriosis/previous surgery
**COURSE OF ECTOPIC TUBAL PREGNANCY**

- Death of Embryo, Proteolysis and Absorption of Tissue (Spontaneous regression)
- Tubal Hemorrhage (Hematosalpinx)
- Tubal Abortion
- Tubal Rupture
- Products of conception fall into abdominal cavity (abdominal pregnancy)
- Rarely lithopedion (mummy)

**CLINICAL FEATURES**
- Symptoms/signs of pregnancy (usually seen 4–6 weeks after the first “missed” period)
- Acute abdomen (pain) due to tubal rupture, bleeding, falling Hb/Hct, shock
- Serum hCG, ultrasound exam of uterus/tube are helpful. D and C of uterus shows “**no villi**”

**TREATMENT**
- Surgery
- Methotrexate (drug) if necessary

**GESTATIONAL TROPHOBLASTIC DISEASE**
A disease characterized by proliferation of trophoblasts with progressive malignant potential. Three types are noted:

**I. HYDATIDIFORM MOLE (VESICULAR MOLE)**
- Hydatid = bunch of grapes (grape-like); Hydatisia (Gr) = a drop of water; Mola (L) = millstone/ false
- Molar pregnancy incidence 1:1,000 pregnancies in U.S. conception
  1:100 in Far East, India, Indonesia
- Occurs in teenage mothers or between 40–50 years of age.
- There are two types of vesicular moles:

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>COMPLETE (CLASSIC)</th>
<th>PARTIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>46XX(46XY)</td>
<td>69XXX or 69XXY triploid or 92XXXX tetraploid</td>
</tr>
<tr>
<td>Fetal parts</td>
<td>Absent unless there is a twin pregnancy!</td>
<td>Present</td>
</tr>
<tr>
<td>Villous edema</td>
<td>All villi</td>
<td>Some villi</td>
</tr>
<tr>
<td>Trophoblast proliferation</td>
<td>Diffuse, circumferential</td>
<td>Focal, slight</td>
</tr>
<tr>
<td>Atypism</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Serum hCG</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>hCG in tissue</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Behavior</td>
<td>2% choriocarcinoma</td>
<td>Rare</td>
</tr>
<tr>
<td>p57 protein</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

**NOTE:** p57kip2 gene (cyclin dependent kinase inhibitor) inhibits cell cycle. This is a paternally imprinted gene (absent in paternal X chromosomes). Hence, androgenetic moles do not have p57 protein in nuclei of stromal cells and trophoblasts. REMEMBER P P P – PARTIAL p57 POSITIVE!
COMPLETE MOLE

90% cases

23X sperm + sperm DNA X2

egg no maternal chromosomes (cause unknown)

46XX or 46XY

10% cases

23X or Y

23X or Y

Two sperms

egg as above

PATERNAL DNA ONLY

(androgenetic mole)

PARTIAL MOLE

haploid

23X

23Y

one or two sperms

69XXY

diploid

46XY

MATERNAL AND PATERNAL DNA

NOTE: Maternal and paternal chromosomes present. How cytogenetic changes lead to molar “appearance” is not known.

GROSS

– Products of conception (POC) delicate, friable, with grape-like vesicles seen; hemorrhage noted.

MICROSCOPIC

– Edematous (hydropic) villi; central cavitations (scalloped cisterns) in complete moles

– Atypical trophoblastic proliferation

– Paucity/absence of vessels in chorionic villi

CLINICAL FEATURES

– Bleeding late first or early second trimester; by US the dx is usually made around 8 weeks

– Anemia

– Passing of vesicles per vaginum

– Mother unable to feel fetal movements

– Uterus much larger than expected

– Absent fetal heart tones

ULTRASOUND EXAM IS DIAGNOSTIC (no fetus)

SERIAL SERUM hCG TITRES. hCG is very high and continues to increase or plateaus out at high level.
COURSE
Molar pregnancy  →  85–90% benign
  About 10% invasive mole
  About 2.5% choriocarcinoma

MANAGEMENT
– Recommend baseline chest x-ray to rule out metastases
– Serial hCG titers are very important
– Evacuate uterus (D and C) → tissue exam → flow cytometry, genetic studies, etc.
– Treatment:
  1. Chemotherapy (methotrexate, actinomycin D) offers excellent response (continue until hCG
titer becomes low → disappears)
  2. Surgery (hysterectomy if needed)
– FOLLOW-UP CAREFULLY FOR A YEAR. RECOMMEND PATIENT NOT GETTING PREGNANT FOR AT LEAST ONE YEAR.

II. INVASIVE MOLE
– About 10% of vesicular moles become invasive, penetrate uterine muscle with severe hemorrhage
  and rupture. There is local destruction, invasion of parametrial tissue and vessels.
– Trophoblasts may embolize to distant sites but do not grow as true metastases. These respond very
  well to chemotherapy, regress and disappear.

CLINICAL FEATURES
– Vaginal bleeding/discharge
– Features of vesicular mole
– Severe hemorrhage
– Persistent hCG elevation (even after uterine evacuation)

MANAGEMENT
– Chemotherapy (methotrexate)
– Hysterectomy only with uterine rupture and bleeding

III. CHORIOCARCINOMA
– A malignant gestational trophoblastic disease originating from:
  – Hydatidiform mole  50%
  – Abortion  25%
  – Ectopic gestation  2.5%
  – Normal pregnancy  22.5%
  – Occurrence 1 in 20,000 to 30,000 pregnancies in the United States; 1 in 2,500 pregnancies in
  Nigeria
  – Teratomas may give rise to choriocarcinoma. Gonadal non-gestational choriocarcinoma
  exists.

GROSS
– Fleshy, yellow mass with hemorrhage, cystic softening and necrosis; tumor invades surrounding
  tissue such as myometrium, serosa, etc.

MICROSCOPIC
– Atypical trophoblasts with mitoses and proliferation.
– CHORIONIC VILLI ARE ABSENT (IMPORTANT)
– Necrosis, hemorrhage, inflammation noted
– Vascular, lymphatic invasion seen
**CLINICAL FEATURES**

Usually vaginal bleeding, spotting, or foul-smelling discharge following ectopic gestation, abortion, molar pregnancy, or even normal pregnancy.
- D and C/Tissue Dx/hCG titers are helpful (titers may fluctuate owing to tumor necrosis).
- Tumors metastasize to lungs 50%, vagina 30%, brain, liver, kidney, etc.
- Metastatic chorio carcinoma may be discovered without a detectable primary because the latter has undergone total necrosis.

**MANAGEMENT**

- As for vesicular mole.

**PROGNOSIS**

- With chemotherapy there is a 100% survival rate for patients whose tumor is confined to the uterus and 83% when there is metastases.

**Poor prognostic factors are:**
- Brain involvement
- Number of mets. noted is > 8
- hCG > 10^5 IU/L
- Time between end of antecedent pregnancy and start of chemotherapy is > 12 months

Gestational choriocarcinoma has a much better prognosis than non-gestational choriocarcinoma, as the former responds very well to chemotherapy unlike the nongestational type. WHY?

**NOTE:** Most women with GTD, following successful therapy, have normal subsequent pregnancies/deliveries.

**TOXEMIA OF PREGNANCY (PRE-ECLAMPSIA/AND ECLAMPSIA) – A STUDENT PRESENTATION IN CLASS**
FEMALE GENITAL III NOTES

OVARY/VULVA/VAGINA

Steve Nandkumar, M.D.
OVARIES

There are two ovaries, R and L. Each measures about 4 x 2.5 x 1.5 cm and weighs 3-4 gm.

Most common benign nonneoplastic cysts are follicular and luteal cysts. Granulosa cells and theca cells (hyperthecosis) produce estrogen.

STEIN-LEVENTHAL SYNDROME (or polycystic ovarian disease)
– Occurs in 3–6% of teenagers and young women

Features are:
– Obesity 40%
– Hirsutism 50% ; male pattern alopecia
– Oligomenorrhea/amenorrhea – anovulation
– Infertility 75%
– Virilism
– Bilateral, enlarged cystic, ovaries (2 x size)

MICROSCOPIC
– Many subcortical follicular cysts with hyperthecosis
– Thickened tunica albuginea
– Corpus luteum usually absent

PATHOGENESIS
1. Hormonal theory
   – Abnormal pulsatile release of pituitary gonadotropins (cause not known) leads to LH ↑
     FSH ↓
   – Hence androgens ↑ estrogens ↑
2. Enzymatic theory
   – Poor regulation of enzymes involved in androgen biosynthesis leading to androgen ↑
3. Insulin resistance theory
   – Exact cause unknown
4. Mechanical barrier theory (old theory – now discarded)
   – Thick tunica albuginea prevents release of ovum into the fallopian tube. Hence, causes infertility.

**MANAGEMENT**

- Wedge resection of ovary
- Oral pills/Clomid, etc.

**NOTE:** This syndrome constitutes a chronic estrus state, hence endometrial hyperplasia, cancers etc. can be a complication.

**OVARIAN TUMORS**

- 6% of all cancers in woman
- 50% of all cancer deaths involving female genital tract
- 80% are benign and occur between 20–45 years of age
- Malignant tumors occur between 40–65 years of age

**RISK FACTORS**

- Nulliparity, women with low parity
- Familial syndromes 3–4% of ovarian cancers, e.g., Li-Fraumeni syndrome – breast and ovary cancer
- Lynch syndrome II → ovary, colon, endometrial cancer
- (Breast cancer) BRCA-1/BRCA-2 mutations → ovarian cancer / HNPCC
- Mutations in p53 gene occurs in 50% of cancers
- K – RAS mutation in 30% of cases
- HER2/neu oncogene expression → 30% of tumors
- ↓ poor prognosis
– Oral contraceptive pills/multiparity/tubal ligation decrease risk for ovarian cancer (40-50%)
– Gonadal dysgenesis in children ↑ risk

**TYPES OF OVARIAN TUMORS**

<table>
<thead>
<tr>
<th>Incidence</th>
<th>% Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Surface epithelial tumors</td>
<td>65–70%</td>
</tr>
<tr>
<td>II. Germ cell tumors</td>
<td>15–20%</td>
</tr>
<tr>
<td>III. Sex cord stromal tumors</td>
<td>5–10%</td>
</tr>
<tr>
<td>IV. Metastatic tumors</td>
<td>5%</td>
</tr>
</tbody>
</table>

Ovarian tumors are classified as:
– Benign
– Borderline (low grade malignant potential)
– Malignant

I. **TUMORS OF SURFACE EPITHELIUM**

A. **Serous Tumors** (Tumor marker Ca125).

These cystic neoplasms are:
1. lined by ciliated columnar cells resembling those of fallopian tube.
2. filled with clear, serous (watery) fluid.

There are 3 subtypes of serous tumors

<table>
<thead>
<tr>
<th>Benign</th>
<th>Borderline</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lined by one layer of benign cells</td>
<td>Two to three layers of lining cells forming papillae; occasional mitoses seen</td>
<td>atypical/anaplastic glands/papillae; many mitoses (papillary Ca) Psammoma bodies seen</td>
</tr>
</tbody>
</table>

CURE FOLLOWING REMOVAL

Krás, BRAF, ERBB2

Tumors (borderline and malignant) may distort the ovarian architecture or may OCCUR ON THE SURFACE ALONE (MICRO PAPILLARY SEROUS CARCINOMA).

PERITONEAL SPREAD OCCURS AS

Non-invasive implants, e.g., borderline tumors; no tissue destruction

Invasive implants with tissue destruction, e.g., malignant tumors

<table>
<thead>
<tr>
<th>Prognosis</th>
<th>Borderline</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confined to ovary</td>
<td>100%</td>
<td>70%</td>
</tr>
<tr>
<td>Peritoneal involvement</td>
<td>90%</td>
<td>25%</td>
</tr>
</tbody>
</table>

**NOTE:** Primary serous papillary tumors of peritoneum can occur.
B. Mucinous Tumors associated with smoking, KRAS mutation
- Tumor epithelium resembles that of endocervix/endometrium (müllerian type) or intestine
- Tumors may arise from endometriotic sites
  - May be benign – single layer of cells
  - Borderline – four layers of cells (nuclei)
  - Malignant – atypical nuclei/crowding of glands, back to back arrangement/mitoses/necrosis
- Tumors with lining epithelium resembling cervix/endometrium are “müllerian” mucinous type.
- More common are tumors with epithelium resembling “intestine” look like villous adenomas.
- Good prognosis, (better than serous tumors)
- 10-year survival 95% (borderline) and 90% (invasive malignant)

**NOTE** Tumors produce sticky, gelatinous mucin and can reach large size and weight. Rupture can cause spillage into abdomen causing PSEUDOMYXOMA PERITONEI (JELLY BELLY) with mucinous ascites. Death occurs as a result of adhesions and obstruction. Similar tumours of appendix, gall bladder, ascending colon, and cecum can also cause pseudo myxoma peritonei. APPENDICEAL MUCINOUS TUMORS ARE THE MOST COMMON CAUSE OF JELLY BELLY (usually with secondary spread to ovary and peritoneum).

C. Endometrioid Tumors
Resemble endometrial adenocarcinoma
- 80% percent are malignant; benign, borderline also exist
- 15–30% have a co-existent endometrial cancer (two independent cancers rather than metastases)
- 15–20% coexist with endometriosis (occurs in women who are a decade younger)
- 5-year survival 40–50%

**NOTE:** PTEN, P53, KRAS, Beta catenin mutations seen; microsatellite instability present.

D. Clear Cell Tumor
- Tumor cells have CLEAR, EMPTY cytoplasm; hob-nail nuclei jutting into lumen
- a variant of clear cell cancer of endometrium
- May be associated with endometriosis or endometrioid carcinoma of ovary
- 5-year survival 65% (tumors confined to ovary); tumours are however aggressive spread and have a poor prognosis

E. Brenner Tumor – mostly benign
- Tumor contains nests of urothelium within stroma; may produce hormones
- Mucin producing columnar cells also seen; asso. with serous or mucinous tumours

F. Cystadenofibroma
- Cysts with glands and stroma (benign)

G. Undifferentiated
- Anaplastic
- Poor prognosis
II. **GERM CELL TUMORS** – Similar to testicular tumors

<table>
<thead>
<tr>
<th>TERATOMA</th>
<th>CHORIO CARCINOMA</th>
<th>DYSGERMINOMA</th>
<th>ENDODERMAL SINUS TUMOR (Yolk sac tumour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>May be mature, immature, or special type</td>
<td>Similar to placental tumor (please see notes)</td>
<td>Similar to seminoma of testis</td>
<td>Tumors differentiate towards yolk sac</td>
</tr>
<tr>
<td>Mature teratoma (dermoid cyst) with hair/tooth/cheesy material/bone seen</td>
<td>Poor prognosis</td>
<td>Associated with gonadal dysgenesis, teratoma</td>
<td>Schiller-Duvall bodies present*</td>
</tr>
<tr>
<td>Lining epithelium is ectoderm- skin, glia endoderm- lung tissue mesoderm- smooth muscle, cartilage etc.</td>
<td>Does not respond to treatment; usually fatal</td>
<td>Malignant</td>
<td>Hyaline droplets present within and without cells (this is alpha fetoprotein)</td>
</tr>
<tr>
<td>Struma ovarii → thyroid tissue seen</td>
<td></td>
<td>Malignant – Radiosensitive – Good prognosis and survival (over 80%)</td>
<td>Prognosis not good as tumors are aggressive. Chemotherapy helps</td>
</tr>
<tr>
<td>1% become malignant</td>
<td></td>
<td>Express receptor Tyrosine kinase c KIT Oct3, oct4, Nanog Markers Oct = octamer binding transcription factor</td>
<td></td>
</tr>
</tbody>
</table>

* (A central vessel surrounded by tumor cells within a space lined by tumor cells (glomerulus-like structure))

**NOTE** All benign teratomas arise from an ovum after the first meiotic division with a 46-XX karyotype (parthinogenesis – haploid germ cell duplication).
- Strumal carcinoids can occur.
- Immature teratomas → tissue resembles that of fetus/embryo. **IMMATURE NEUROEPITHELIUM** seen decides grade of tumor.

Malignant teratomas (1% cases) are squamous or basal cell Ca, Melanomas, thyroid Ca, etc.

**CLINICAL FEATURES:** Young women, teenagers with abdominal pain, infertility, ovarian torsion (15% cases). Limbic encephalitis may occur rarely.
- *Sometimes asymptomatic*

**Treatment:** Surgery, chemotherapy (if necessary)

III. **SEX CORD STROMAL TUMORS**
These are derived from the sex cords of primitive gonads or from the mesenchymal stroma.

**A. Thecoma-Fibroma**
Tumors contain fibroblasts (fibroma)
- Spindle cells and fat (thecoma) → fat stains are positive
- Thecomas may produce hormones (estrogen, androgens)
- Tumors associated with:
1. **Meig’s syndrome** → tumor with ascites + right side hydrothorax (cause unknown). 40% of cases
2. **Basal cell nevus syndrome**

**B. Granulosa-Theca Cell Tumors**
- Occur in post menopausal age; also in children
- Solid yellow-white mass with cystic changes
- Cords, sheets, nests of granulosa cells with **CALL EXNER** bodies (resemble immature Graffian follicle); spindle shaped cells with cleaved, elongated (coffee bean) nuclei
- Theca cells are polygonal or cuboidal
- Produce estrogens → endometrial hyperplasia, carcinoma, breast disease
- Granulosa cell component → 5–25% malignant
- 10-year survival overall 85%

**NOTE:** Inhibin (suppresses FSH) and Calretinin are positive (tumour markers).

**C. Sertoli-Levydig Cell Tumor (Arrhenoblastoma) (androblastoma)**
- Composed of cells resembling Sertoli cells/tubules
- Occur between 20–30 years of age.
- Tumors produce androgens → virilism or defeminization
- Pure Sertoli cell tumors produce estrogen
- Pure Leydig cell (hilus) tumor contains **REINKE CRYSTALLOID**

**D. Pregnancy Luteoma**
- Nodules of theca cells in ovary due to circulating gonadotropins
- May produce androgens → virilism (can affect fetus)

**NOTE:** **GONADOBLASTOMA** – Germ cells plus sex cord stromal tumor – Dysgerminoma/gonadal dysgenesis seen. Abnormal sexual development; phenotypic females 80%, phenotypic males 20% (undescended testes and female secondary organs)

**IV. METASTATIC TUMORS** (Krukenberg’s)
- Occur in older women
- Usually bilateral
- Primary site maybe lung, breast, GI tract, stomach (75% cases) (mucus → **signet ring cells**) etc.
- Clinical history, immunostains can help detect the primary site.

**CLINICAL FEATURES OF OVARIAN TUMORS**
Most ovarian neoplasms present with
- no symptoms (unexpected finding during pelvic exam. in 30% cases or during surgery).
- abdominal pain and distension (ascites).
- pressure effects on GI/GU systems.
- hormonal effects, etc.
- abdominal or vaginal bleeding.
- weakness, weight loss, cachexia.

**SPREAD**
- Peritoneum (implants → ascites), omentum, diaphragm etc.
- Nodes, liver, lung, GI tract, etc.
- Opposite ovary (50% cases → poor prognosis)
MANAGEMENT
- Pelvic exam
- Tumor markers Ca^{125} (for serous and endometrioid tumours)/osteopontin, etc. ultrasound/CT scan helpful.

NOTE: Most tumors are extraovarian (Stage III) at the time of diagnosis.

TREATMENT
- Surgery (second look operation → to assess effect of treatment; r/o recurrence).
- Chemotherapy
- Radiation therapy

NOTE: Currently, there is NO good screening test for detecting ovarian tumors. Hence, by the time a diagnosis is made, the disease has spread and this leads to a poor prognosis and death. Prophylactic oophorectomy (in BRCA mutations) may help.

VULVA

Infections of the vulva cause VULVITIS with resultant itching (pruritus) and discharge. These are considered as part of STD (sexually transmitted diseases).

I. GENITAL HERPES (HSV)
- Caused by HSV (Herpes Simplex Virus) types 1 and 2 (more by type 2 than type 1)
- Occurs commonly in teenagers and young women
- Spread by sexual intercourse → contact transmission
- Infection affects vulva, vagina, cervix, oropharynx, anal canal, etc.

CLINICAL FEATURES
- Occurs in 30% of infected women; 3–7 days after exposure, painful red papules → vesicles and ulcers are formed PRIMARY HERPES
- Discharge, dysuria, fever, malaise, tender enlarged lymph nodes seen
- Diagnosis by cytologic examination of smears → cells with intranuclear inclusions (Cowdry inclusions). Nuclei are purple, homogeneous with dark INTRANUCLEAR inclusion surrounded by a halo; cells fuse → multinucleated giant cells. Immunostains are helpful.

COURSE
Lesions heal spontaneously or recur. Virus persists (latent phase) in nerve ganglia with shedding of virus during active infection RECURRENT HERPES. Virus may infect newborns → neonatal herpes seen in 50% of cases with normal vaginal delivery. C-section delivery preferred.

II. HUMAN PAPILLOMA VIRUS (HPV) – VENEREAL WARTS
A DNA virus of papova family with many types spread by sexual contact
- Affects vulva, vagina, cervix, penis, perineum, oropharynx and tonsils etc.
- HPV types 6 and 11 → condyloma acuminatum (genital warts)
- Warts reveal koilocytes – virus affected cells with atypical dark angulated nuclei with surrounding halo.
- HPV types 16, 18, 31, 33, etc., → cervical intraepithelial neoplasia (CIN), VIN, carcinomas, etc.
- HPV may infect newborns delivered vaginally, leading to juvenile laryngeal papillomatosis in children 4–5 years of age.
**Treatment**
- Surgical excision
- Podophyllin (anti viral drug)
- HPV vaccine

### III. GRANULOMA INGUINALE
- Caused by an encapsulated, gram-negative rod called *Calymmatobacterium donovani* (klebsiella granulomatis).
- Smears from lesions on Giemsa stain or silver stain show macrophages with coccobacilli in vacuoles (*DONOVAN BODIES – closed safety pin appearance*).
- Following exposure, a papule forms (genital, inguinal, perianal areas), leads to ulcer → painless indurated mass with discharge.
- MICRO. Non-specific inflammation, pseudoepitheliomatous hyperplasia, granulation tissue seen.
- Healing with scars causes strictures of vulva, urethra, or anal canal.
- Lymphatic obstruction/lymphedema occurs (elephantiasis).
- Treatment: antibiotics

### IV. LYMPHOGRAHANULOMA VENEREUM (LGV)
- Common in Asia, Africa, and South America.
- Caused by Chlamydia trachomatis, a small, gram-negative encapsulated bacterium (L1 – L3 serotypes); often co-exist with gonorrhea.
- Papules or ulcerative lesions of vulva, followed by lymphadenopathy/adenitis and rupture.
- Lesions show neutrophilic and granulomatous changes. Chlamydial inclusions seen in epithelial cell cytoplasm.
- Tissues (on biopsy) show stellate microabscesses.
- Reparative fibrosis causes obstruction, lymphedema, and strictures. Rectal strictures are common.
- Antibodies to organism can be detected serologically; Nucleic acid amplification testing helpful.
- Treatment: Antibiotics

**NOTE:** Diseases III and IV are common in tropical and sub-tropical countries and not in USA

### V. CHANCROID (SOFT CHANCRE)
- Caused by a gram-negative coccobacillus, Haemophilus ducreyi.
- Commonly seen in Asia and Africa. Serves as an important cofactor for HIV transmission.
- 3 – 5 days after sexual contact, painful papules, ulcers form on penis, vagina or periurethral areas.
- Ulcers are NOT INDURATED.
- After 1 – 2 weeks, lymph nodes involved in 50% of cases → lymphadenopathy (called *buboes*) which may ulcerate → sinus formation.
- MICRO. Serpentine necrosis, granulation tissue, lymphocytes, plasma cells seen.
- Coccobacilli seen on gram or silver stains; cultures and PCR testing help.

**TREATMENT** - Antibiotics

### VI. CANDIDIASIS (MONILIASIS)
- A fungal infection occurs in 10% of women, 2% are symptomatic.
- D.M., pregnancy, oral contraceptives are risk factors.
- Pruritus; thick, white, curd-like discharge present; wet mounts (smears) show organisms (candida).

**TREATMENT** - Antibiotics/antifungals
VII. TRICHOMONIASIS
- A protozoan organism, occurs in 15% of women in STD clinics
- Trichomonas vaginalis trophozoites cause infection (cervico vaginitis), urethritis
- Pruritus, dysuria, dyspareunia, vaginal discharge present (profuse, frothy, watery, yellow)
- Mucosa of cervix fiery red “strawberry” appearance on colposcopy exam.
- Organisms seen on wet mounts (smears) → flagellated, motile trichomonads are seen
- Look like “lymphocytes” on cytology

TREATMENT
- Antibiotics

VIII. NONGONOCOCCAL URETHRITIS AND CERVICITIS
- Caused by chlamydia trachomatis, mycoplasma, trichomonas, ureaplasma, etc.
- Clinical features similar to that of gonorrhea
- Disease diagnosed after gonorrhea is ruled out

REITER’S SYNDROME
- Urethritis + conjunctivitis + arthritis + mucocutaneous lesions following non-gonococcal infection (Post-infectious disease that is immune mediated): associated with HLA B-27.

IX. GONORRHEA
- Caused by gram-negative diplococci (N. Gonorrhea)
- Following sexual intercourse, bacteria attaches to mucosal receptors by pili and adhesion molecules (OPA for opaque, a cell membrane protein) enters cells and spreads causing infection
- Two to seven days after exposure, dysuria, urinary frequency, urethral discharge (men) and vaginal discharge and Bartholin gland inflammation (women) occur.
- Infection can spread and cause P.I.D. (pelvic inflammatory disease) and sterility.
- Epididymitis, orchitis, prostatitis, proctitis, oropharyngitis, urethritis/stricture occur in men.
- Abdominal infections, perihepatitis, disseminated infections can occur (in complement deficiency)
- In newborn causes eye infection (ophthalmia neonatorum); not common nowadays
- Diagnosis by ID, culture, and nucleic acid testing
- Treatment: Antibiotics

X. SYPHILIS – (LUES)
- Caused by spirochete T. pallidum, a gram –ve, slender cork screw organism; spread by sexual intercourse; also transplacentally
- Following exposure (mucocutaneous entry) organisms spread by lymphatics/blood vessels

There are 3 stages:

A. Primary Syphilis

- Hard chancre (red, non-tender, indurated lesion)

  → Painless ulcer

  → Enlarged painless lymph nodes

- Lesions show:
  1. Proliferative endarteritis (immune mediated)
  2. Lymphoplasmacytic inflammation, granuloma

- Spirochetes seen (from lesions) by dark field microscopy or immunofluorescence
  Specific for treponema
Antibodies formed e.g., tests are FTA-ABS, MHATP NonTreponemal antigens e.g. tests are RPR, VDRL are diagnostic

Primary syphilis resolves in 4–6 weeks, spontaneously or with treatment

B. **Secondary Syphilis**

Two months after primary syphilis, patients develop generalized lymphadenopathy and mucocutaneous lesions/superficial erosions, etc.

- Lesions are usually maculo-papular, symmetrical (palms and soles)
- Condyloma LATUM can occur anywhere (axilla, ano-genital area common)
- Hepatitis, iritis, renal, and GI involvement occur
- “Lesions” then **RESOLVE → early latent phase syphilis (lasts for 1 year)**
  
  Late latent phase syphilis (asymptomatic) then follows (in untreated patients)

- Spirochetes/serologic tests for syphilis (STS – antibody detection) are positive

C. **Tertiary Syphilis** (Latent syphilis)

- Occurs after 10–20 years of initial disease.
- About 33% of untreated cases develop tertiary syphilis (rare nowadays).

**CVS Syphilis**

- Syphilitic aortitis (80%)
- Aortic valve incompetence and aneurysms

**Neurosyphilis (5-10%)**

- Tabes dorsalis
- Meningovascular syphilis
- General paresis
- Asymptomatic neurosyphilis (33%)
  
  diagnosed by CSF abnormalities

**Benign Tertiary Syphilis**

- Delayed hypersensitivity

  GUMMAS (rare) rubbery mass;

  a granuloma with central coagulation

  necrosis and surrounding

  lymph/plasma cells/giant cells/macrophages

  Rim of fibrous tissue

**NOTE:** In Neurosyphilis, CSF glucose is decreased, proteins and cells are increased; Abs are +++

- Gummas occur in bone, skin, mouth, upper airway, liver (hepar lobatum)
- Spirochetes are RARE
- Antitreponemal Ab tests are positive. CSF antibodies indicate neurosyphilis. NonTreponemal Ab tests are negative.

**TREATMENT:** Antibiotics (penicillin, etc.)

**CONGENITAL SYPHILIS:** It occurs when spirochetes cross the placenta and infect the fetus.

Intrauterine, perinatal deaths, abortions etc. can occur. Infantile and childhood features affecting skin, liver, lung, bones, eye, teeth, and 8th nerve (deafness) occur.
SEROLOGIC TESTS FOR SYPHILIS (STS)

There are 2 types:

I. NON-TREPOLEMAL ANTIBODY TESTS

Such tests detect antibodies against cardiolipin present in both host tissues and the treponemal cell walls.
- RPR (Rapid Plasma Reagin) and VDRL (Veneral Disease Research Lab) are widely used as screening tests and to monitor results of therapy.
- Tests are often negative in early stages of disease; positive in about 4 – 6 weeks after infection.
- Tests are negative in late latent or tertiary syphilis; titres usually fall after successful therapy.
- 15% of VDRL tests are false positive, e.g., old age, acute infections, SLE, drug addiction, pregnancy, leprosy, hypergammaglobulinemia.

II. TREPONEMAL ANTIBODY TESTS

A. FTA-ABS (Fluorescent Treponemal Antibody Absorption) test
B. MHA (Microhemagglutination assay) test

These tests become positive within 4-6 weeks after infection, remain positive indefinitely, even after successful treatment. False-positive results occur in 2% of cases.

NOTE: STS may be false positive or negative in HIV cases

BARTHOLIN’S ABSCESS/CYST

- Common at any age
- Bartholin’s glands in vulva may be infected causing an abscess/adenitis etc.
- Cysts occur and are 3–5 cm in size, lined by transitional epithelium/squamous metaplastic epithelium

Treatment:
- Excision
- Marsupialization (cyst left open permanently, drainage complete, scar tissue forms and destroys lining epithelium)

NONNEOPLASTIC EPITHELIAL DISORDERS (VULVAR DYSTROPHY)

LEUKOPLAKIA

- Present as a white patch or scaly, plaque-like mucosal thickening = leukoplakia
- Leukoplakia may be benign or malignant. Hence all leukoplakic lesions MUST BE BIOPSIED FOR Dx and Rx.

THERE ARE 2 TYPES OF NNED

A. Lichen Sclerosus (chronic atrophic vulvitis)
- Can occur at any age; most common in postmenopausal, elderly women.
- Cause unknown (perhaps autoimmune); associated with vitiligo, thyroiditis, PA etc.
- Lesions seen as white, gray, parchment-like changes, labia atrophies, and introitus becomes narrow.
- Microscopic exam shows atrophic epidermis, hydropic degeneration of basal layer, loss of rete pegs, prominent subepithelial dermal fibrosis, and non-specific dermal inflammation
- Pruritus (itching) occurs
- Insidious, slowly progressive disease
- 1 to 5% may develop cancer
B. **Lichen Simplex Chronicus (Squamous Hyperplasia)**
- A non-specific condition resulting from scratching the skin to relieve pruritus of known/unknown cause
- Presents as a white plaque
- Microscopically, there is hyperkeratosis, hypergranulosis, acanthosis (hyperplasia) with mitoses; dermal inflammation seen.
- May be a risk factor for cancer when there is ATYPISM of cells (VIN-vulvar intraepithelial neoplasia usually associated with HPV)

**VULVAR CANCER**
- Three percent of all genital cancers
- Two-thirds of cases occur in women > 60 years of age

**VIN - vulvar intraepithelial neoplasia:**
Intraepithelial lesions may be associated with smoking and HPV (types 16, 18, etc.), leading to VIN (vulvar intraepithelial neoplasia) (CIS or Bowen’s disease are other terms used). These lesions occur in women < 40 years of age. Lesions may be the BASALOID TYPE OR WARTY TYPE.

**VULVAR CARCINOMA**

**GROSS**
- VIN lesions are discrete, fleshy, or pigmented macular
- Exophytic, erosive or ulcerating mass also seen

**THERE ARE 2 TYPES**

<table>
<thead>
<tr>
<th>MICROSCOPIC</th>
<th>TYPE I</th>
<th>TYPE II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>Women &lt; 40</td>
<td>&gt; 60 years</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>30% cases</td>
<td>70% cases</td>
</tr>
<tr>
<td>Melanoma</td>
<td>asso. with HPV</td>
<td>no</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>no</td>
<td>asso. with NNED</td>
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<tr>
<td>Verrucous squamous cell carcinoma</td>
<td>basaloid type</td>
<td>keratinizing type</td>
</tr>
<tr>
<td></td>
<td>multifocal</td>
<td>unifocal</td>
</tr>
<tr>
<td></td>
<td>no</td>
<td>p53 mutation</td>
</tr>
</tbody>
</table>

**CLINICAL FEATURES**
- Asymptomatic
- Pruritus discharge, bleeding

**SPREAD**
- Lymphatics → lymph nodes positive in 65% cases (inguinal, pelvic, iliac, periaortic)
- Vascular → liver, lung, etc.

**PROGNOSIS** Depends on the stage of tumor:
1. Lymph node involvement (good prognosis without node involvement)
2. Depth of tumor invasion (< 5 mm → good prognosis)
3. Tumor size (< 2.0 cm, good prognosis)

* If prognostic factors are poor, 5-year survival is < 10%.

**TREATMENT**
- Vulvectomy plus lymphadenectomy; Verrucous carcinoma seldom metastasizes; good prognosis
- 5-year survival, 60–80%
EXTRAMAMMARY PAGET'S DISEASE
- Occurs in older women
- Cells originate from primitive progenitor cells; may display apocrine, eccrine, keratinocyte differentiation
- Presents as a red, crusted, pruritic, well-demarcated skin lesion on the labia majora/perianal area
- Biopsy shows tumor cells in the epidermis
- Tumor cells (Paget’s cells) are ovoid with central nucleus and a surrounding halo; cytoplasmic mucopolysaccharide stains positive with PAS, Alcian blue, mucicarmine; CEA positive
- Lesions may be confined to skin (intraepidermal), adjacent hair follicles and sweat gland, or in 30% of cases may be associated with underlying carcinoma (as opposed to Paget’s disease of the breast, which has 100% underlying carcinoma).
- Intraepidermal Paget’s → slow growing with good prognosis following excision. Paget’s associated with underlying tumor → metastases within 2-5 years; poor prognosis.

VAGINA

Vagina = Sheath

Gartner’s duct cyst → derived from Wolffian (mesonephric) duct
- Occur as submucosal cysts in lateral vaginal wall

Mucous cysts – derived from Müllerian (para mesonephric) duct remnants
- Occur in proximal vagina

VAGINITIS
- Inflammation of vagina associated with STDs.

CARCINOMA OF VAGINA

A. Squamous Cell Carcinoma
- 1% of all female genital cancers; occur in females > 60 years of age
- Most are associated with HPV and previous cancer of the cervix and vulva
- Occur in upper post wall as a plaque → mass and extend into the cervix and other perivaginal tissues leading to fistulae

MICROSCOPIC
- 95% are squamous cell carcinomas

CLINICAL FEATURES
- Asymptomatic
- Vaginal discharge, bleeding, or spotting
- Present as urinary or rectal fistula

SPREAD
- Iliac nodes (upper vaginal cancer)
- Inguinal nodes (carcinoma from lower 2/3)
B. **Vaginal Adenocarcinoma**
   - D.E.S. (Diethylstilbestrol) used in 1960’s for treating threatened abortion caused
     1. vaginal/cervical structural abnormalities;
     2. vaginal adenosis – glands of Müllerian origin, benign, incidence 35–90%; and
     3. vaginal **CLEAR CELL** adenocarcinoma (0.14% incidence).
   - These occurred in young women/teenagers whose mothers were treated with D.E.S. during the first 18 weeks of gestation.
   - Squamous epithelium normally replaces mullerian epithelium at about 10 weeks of gestation, DES interferes with this process in the first 18 weeks; so Mullerian epithelium persists → adenosis/ ca.
   - Tumors located in the upper third, anterior wall of vagina

**PROGNOSIS**
- Depends on the stage of tumor
- Good for D.E.S. related adenocarcinoma (survival > 80%) following surgery and radiation therapy.
- Squamous cell cancer, prognosis is poor

**NOTE (IMPORTANT):** Metastatic Vaginal Carcinomas (from cervix, vulva) are MORE COMMON than primary carcinomas.

**BOTRYOID SARCOMA** (Sarcoma Botryoides) Greek ‘botrys’ = grapes
- Occurs in young girls under age five
- Tumors present as a polypoid vaginal mass with grape-like clusters of tissue (botryoid = grape like)
- **ORIGINATES FROM EMBRYONAL Rhabdomyoblasts AND IS HENCE A RHABDOMYOSARCOMA.**
- Tumor cells resemble a tennis racket (small nuclei with cytoplasmic extension at one end); rarely - striations are seen; myofibrils with **Actin and Myosin** are noted.
- Tumor cells crowded in a subepithelial layer called **CAMBIUM** layer; deeper tissue is fibromyxomatous, edematous, and contains inflammatory cells plus tumor (hence, diagnosis may be mistaken for an inflammatory polyp).
- Similar tumors occur in biliary tract and urinary bladder

- Spread Peritoneal cavity Urinary tract (causes obstruction) may cause death
  
  **Also to lymph nodes and other organs by blood.**

**TREATMENT** Vaginectomy plus chemotherapy/radiation therapy

**NOTE:** Please see “Rhabdomyosarcoma” in soft tissue tumours for additional details.

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DISEASES OF THE BREAST

Frank Bellafiore, M.D.
A Tour of Breast Pathology

Frank J. Bellafiore, MD
Director of Breast, Hematologic, and Endocrine Pathology
Saline Pathology

Normal Breast Histology

- Lactiferous duct
- Extra-lobular duct
- Terminal duct-lobular unit (TDLU)
  - Duct epithelial lining cells
  - Myoepithelial cells
  - Intraductal abnormal
- Hormonal state determines lobular histology

Growth and Developmental Abnormalities

- Hypoplasia and amastia
- Macromastia - adolescent, gravid, & penicillamine-induced
- Ectopic breast tissue
- Aberrant breast tissue
Inflammatory and Reactive Tumefactions

- Fat necrosis
- Pregnancy and lactation associated changes
- Mammary duct ectasia
- Diabetic mastopathy
- Miscellaneous

Fat Necrosis

- Most often secondary to trauma, surgery, or radiation
- Painless superficial mass, firm and well circumscribed, often with overlying skin retraction
- Most often sub- or peri-areolar
- Mammography - usually a spiculated, poorly defined mass that may contain punctate or large irregular Ca^2+
- Sonography - almost always a discrete mass

Pregnancy and Lactation Associated Lesions

- Lactating adenoma
- Others - puerperal mastitis, mammary infarct, galactocele

Lactating Adenoma

- Occurs only in pregnancy
- May represent hyperplastic lobules rather than a true adenoma
Mammary Duct Ectasia

- Probably related to stasis of breast duct secretions with subsequent leakage and periductal inflammation
- 2/3 present in women between ages 40-70
- Usually presents with nipple discharge, bloody, pain, palpable
- Mammography - may be helpful, but often looks like comedocarcinoma
Diabetic Mastopathy

- Patients usually insulin-dependent diabetes
- Usually women, average age 34–47
- Firm to hard, ill-defined, non-tender mass, possibly bilateral, that may spontaneously regress
- Mammography - localized increased density, often non-specific, but may resemble carcinoma or fibroadenoma

Miscellaneous

- Granulomatous lobular mastitis
- Sarcoidosis
- Inflammatory pseudotumor
- Vasculitis/Collagen-Vascular Diseases
- Silicone mastitis
- Amyloid tumor
- Infectious

Granulomatous Lobular Mastitis

- Breast mass in women of childbearing age that mimics carcinoma
- Women usually parous and/or on oral contraceptives
- Cause unknown with a strong tendency to recur
- Rx- Antibiotics, +/- steroids, surgery
Benign Neoplasms and Proliferations
- Papilloma, complex sclerosing lesions, and florid papillomatosis of the nipple
- Myoepithelial neoplasms
- Adenosis and microglandular adenosis
- Fibroepithelial neoplasms
- Miscellaneous mesenchymal neoplasms

Papillomas
- Solid or cystic; solitary or multiple; central or peripheral
- Majority central: bloody nipple discharge most common symptom, and more often seen in central/cystic lesions rather than peripheral/solid lesions: multiple lesions more often peripheral and typically present with a palpable lesion
- Solitary lesions - avg. age 6th decade
- Multiple lesions - avg. age 4th-5th decade
- Mammography - Ca++, mass, opacities

Papillomas (cont’d.)
- Treatment - excisional biopsy recommended, especially if atypical component is present, since ADH, DCTS, or carcinoma may also be present.
- RR of carcinoma 1.5-2 compared to normal, with a substantially greater risk if there are multiple papillomas.
Radial (Complex) Sclerosing Lesion

- Often multiple, may be bilateral, occur with equal frequency in benign and carcinomatous breasts
- Most often women 40-60
- Usually nonpalpable and detected by mammogram: mammo shows spiculated stellate with central dense or lucent core, usually without Ca++, mammo doesn’t reliably distinguish RSL from CA

RSL (cont’d.)

- Treatment - excisional biopsy for full evaluation to rule out focal carcinoma
- Prognosis - Relative risk (RR) for CA is 1.8, and increases to 5.8 when ADH is present
- LCIS is most frequent CA arising in a RSL, followed by DCIS and tubular CA

Florid Papillomatosis of the Nipple

- Usually women between 40-50, bilaterality very uncommon; fewer than 5% in men
- Usually only present for a short time before symptoms - bloody discharge, pain, itching, thickening or mass lesion of nipple; nipple may be red, ulcerated, warty, granular in appearance and be mistaken for Paget’s

Florid Papillomatosis of the Nipple (Cont’d.)

- Treatment - careful bilateral breast exam to exclude concurrent carcinoma and complete excision of the lesion usually requiring removal of the nipple but not mastectomy; if completely excised and no CA or Paget’s found, subsequent risk for CA is relatively low
- Coexisting CA - 50% of men, 16.5% of women
Adenomyoepithelioma

- Women 20-80, avg. age 50-60
- Solitary, unilateral, painless mass in peripheral portion of breast, occas. central
- Most patients describe recent onset
- Mammogram - usually well-circumscribed, non-Ca++ mass, but Ca++ may be present
- Treatment - complete local excision
- Prognosis - malignancy rare, local recurrence common if not completely excised
Myoepithelioma
- Very rare
- Similar to adenomyoepithelioma, but composed only of myoepithelial cells with no glandular component

Adenosis
- A proliferative lesion largely derived from the TDLU
- Epithelial and myoepithelial components
- May present with Ca+++s or as a distinct palpable or radiographically detectable mass (adenosis tumor)
- Avg age 30, usually ≤ 2cm, mammmo usually shows a nonspecific oval/lobular mass.

Adenosis (cont’d.)
- Florid adenosis - hyperplasia of epithelial and myoepithelial cells in a lobulocentric pattern; the most cellular type of adenosis
- Sclerosing adenosis - preferential preservation of myoepithelial cells with variable atrophy of epithelial cells and accompanying lobular fibrosis; may not be limited to a lobulocentric pattern; confers a RR of subsequent CA of about 2.2 compared to normal women

Adenosis (cont’d.)
- Tubular adenosis - formation of ductules arranged mostly longitudinally
- Treatment - excisional biopsy
Fibroepithelial neoplasms
- Fibroadenomatoid change (sclerosing lobular hyperplasia)
- Fibroadenoma
- Phyllodes tumor

Fibroadenomatoid Change
- Younger women; avg. 32 years
- Presents as localized mass up to 8 cm.
  usually in UOQ. +/- pain
- Mammo - nonspecific well-defined mass.
  +/- Ca++;
- Treatment - excisional biopsy

Fibroadenoma
- Most common breast tumor in adolescent and young women: < 5% older than 50 yrs
- Most present as painless, firm, well-defined solitary mass, but may be nonpalpable; 15% have multiple; usually less than 4 cm.
- Juvenile fibroadenoma - usually < 20 yrs.
  may grow rapidly, differ from usual type by high stromal cellularity and epithelial hyperplasia, but no stromal overgrowth

Fibroadenoma (cont’d.)
- Treatment - local excision with inclusion of a small rim of normal breast tissue
Phyllodes Tumor

- Avg age is 45: present with firm/hard, discrete, palpable tumor; usually unilateral; can’t clinically distinguish between FA and PT
- >4 cm or rapid growth favors PT
- May evolve from a FA that was previously stable for years
- Mammo - rounded or lobulated, sharply defined, opaque mass; U/S may or may not show cysts

Phyllodes Tumor (cont’d.)

- 3 categories: benign, borderline, & malignant
- Distinguished from FA by stromal overgrowth (40x field with stroma only), variable stromal cellularity, often highly cellular in periductal regions, variably myxoid stroma, mitotically active stroma, & presence of elongated epithelial-lined clefts
Phyllodes Tumor (cont’d.)

- Benign - few if any mitoses, border usually well-defined, slight-mod pleomorphism
- Malignant - marked hypercellular stromal overgrowth, usually ~5 mitoses/10hpf, usually invasive tumor border, stromal cellular pleomorphism common, may contain heterologous stromal sarcomatous elements

Benign Phyllodes Tumor

- Do not metastasize
- 20% chance of local recurrence after excision

Malignant Phyllodes Tumor

- 25% metastasis rate
- 60-70% local recurrence rate

Phyllodes Tumor (cont’d.)

- Borderline - usually microscopically invasive border, 2-5 mitoses/10hpf, moderate stromal cellularity heterogeneously distributed, with stroma often resembling fibromatosis or a low-grade fibrosarcoma
- All - may exhibit epithelial hyperplasia

Borderline Phyllodes Tumor

- <5% chance of metastases
- >25% local recurrence rate (25-45%)
Phyllodes Tumor Survival Rates
- Overall 95%
- Local recurrences (30%) & mets (10%) usually occur within 3 years of primary treatment
- Most deaths occur within 5 years of dx, with virtually all occurring in patients with high grade primaries or recurrences
- Most tumors not responsive to chemo or radiation therapy

Benign Mesenchymal Neoplasms
- Pseudangiomatous stromal hyperplasia
- Lipoma
- Hemangioma
- Granular cell tumor
- Hamartoma
- Fibromatosis
- Fibrous tumor
- Myofibroblastoma
- Mxoma
- Nerve sheath tumors
- Leiomyoma
- Others

Treatment of Phyllodes Tumors
- Fundamental principle is complete excision to prevent local recurrence
- Local recurrences tend to be higher grade and have a higher risk of chest wall invasion
- Features that predispose to local recurrence: incomplete excision, invasive tumor border, and secondary tumor nodules
Fibrocystic Change

- Single most common disorder of breast, postmortem studies have shown 60% incidence.
- Peak incidence at or just before menopause; but frequently diagnosed between 20-40, and rarely develop after menopause.
- Excessive estrogen is thought to play a role, but oral contraceptives decrease the risk.
- No increased risk of CA in absence of proliferative change.
- Clinical presentation - lumps, breast nipple discharge, and or mammary densities Ca+/-.
Morphologic Features of Fibrocystic Change

- Cyst formation, apocrine metaplasia, and stromal fibrosis
- Sclerosing adenosis
- Proliferative breast disease (epithelial hyperplasia - ductal or lobular)

Apocrine Metaplasia

- May be cystic and or papillary
- Most common in women over 30
- May or may not be palpable
- No significant increased risk for developing Ca
- No specific treatment is indicated unless there is bloody discharge or cytologic atypia

Proliferative Breast Disease

- Confers increased risk of developing CA
- Entities that fall within this category include: moderate/florid ductal epithelial hyperplasia, sclerosing adenosis, and papillomas (latter 2 already discussed)

Ductal Epithelial Hyperplasia

- Usual type: confers a RR of 1.1-2.5
- Atypical ductal hyperplasia: RR depends on age and family history
Breast Carcinoma

- 1 in 9 women will develop the disease; 1/3 of these will die of the disease
- Rare before age 25, but incidence increases after that
- Most commonly arise in UOQ

Breast Carcinoma Risk Factors

- Genetic predisposition
- Increasing age
- Proliferative breast disease
- Cystic lesions or endometrial CA
- Radiation exposure
- Geographic (US, Europe, Asia)
- Length of reproductive life: higher if longer
- Parity: multiparous, nulliparous
- Age of first child: higher if older than 30
- Obesity
- 5 Exogenous estrogen

Relative Risk Categories for Invasive Breast Ca

- No increased risk
  - Mild ductal hyperplasia (RR 1)
- Slightly increased risk
  - Moderate ductal hyperplasia (RR 1.4 to 2.5)
- Mildly increased risk
  - Atypical hyperplasia, ductal or lobular
  - Neoplastic (RR 2.1 to 4.1)
  - Presence of ductal (RR 1.6 to 5.5)
- High risk
  - Atypical hyperplasia, ductal or lobular
  - With family history (RR 6 to 22)
  - Previous breast biopsies (RR 3 to 12)
  - Ductal carcinoma in situ (RR 5 to 10)
  - Lobular carcinoma in situ (RR 1.1 to 10)

Main Histologic Types of Breast Carcinoma

- In Situ Carcinoma: 15-30%
- Invasive Carcinoma: 70-85%
In Situ Carcinoma

- Ductal carcinoma in situ (DCIS): 80%
- Lobular carcinoma in situ (LCIS): 20%

Ductal Carcinoma In Situ

- Mamm - most sensitive detection method: densities and/or granular linear cyst type CA - 3 are most frequent findings
- Most common lesions are non-palpable
- Age range - same as invasive ductal CA
- RR of bilateral disease: 1.9 (1 yr), 2.4 (4 yrs)
- Grading schemes are used to assess risk of recurrence after breast conserving therapy, based upon nuclear grade, necrosis, and architectural patterns
- Architectural patterns: cribriform, micropapillary, solid, comedo, and papillary
- High grade lesions usually are ER/PR, aneuploid, high proliferative rate & periductal angiogenesis. HER2 neu
  - p53, abnormal bid-2, low grade lesions are opposite

DCIS (cont’d.)

- Treatment - based upon several factors
- Mastectomy - large sized DCIS that cannot be removed by adequate excision, large multifocal areas of DCIS, patients who can’t undergo radiation, or "VNP 8-9, 0-2" = local recurrence rate and 100% cure rate
- Breast conservatory with or without radiation - "VNP 3-4" no rad, "VNP 5-7" with rad, recurrence for biopsy alone 10%, rad for biopsy with rad 2-11%
- RR for subsequent invasive CA is 8-10
Atypical Ductal Hyperplasia (ADH)

- Proliferative lesion of ductal cells with some, but not all, of the features of DCIS, whether qualitative or quantitative.
- Quantitative criteria - histologic features of DCIS but either less than 2 ducts involved (Page criteria) or less than 2 mm of involvement (Pavassoli criteria).
- RR for subsequent invasive CA is around 5, but depends on age and family history.
- Treatment - excision followed by close follow-up.

Lobular Carcinoma In Situ (LCIS)

- A microscopic lesion that does not form a palpable mass and infrequently has Ca++.
- Mammography is not an effective method for detecting LCIS.
- Avg. age 44-54; bilateral LCIS very common (avg. of 40%).
- IDC & LCIS together give much higher risk of contralateral disease compared to LCIS or IDC alone (57% vs 22-28%).

LCIS (cont’d.)

- RR for subsequent invasive carcinoma is 8-10.
- Diagnostic criteria - At least 50% of the ductules within one lobule must be filled and expanded by LCIS cells.
Atypical Lobular Hyperplasia (ALH)

- A lobular proliferation with some features of LCIS, but insufficient to qualify for the diagnosis
- RR for subsequent invasive CA around 5, but depends on age and family history
- Quantitative criteria - LCIS cells involve less than 50% of ductules within a lobule
- Qualitative criteria - LCIS cells fill and expand less than 50% of ductules within a lobule

Invasive Carcinoma

- Ductal carcinoma: 79%
- Lobular carcinoma: 10%
- Tubular carcinoma: 6%
- Colloid carcinoma: 2%
- Medullary carcinoma: 3%
- Other: metaplastic, endocrine, secreatory, adenoid cystic, and others

Invasive Ductal Carcinoma

- Largest single category of invasive Ca
- Most common in women mid-late 50’s who present with a palpable or mammographically detected mass with or without skin fixation, edema, “peau d’orange”, nipple retraction, Paget’s, ulceration
- This category of invasive breast Ca has the worst overall prognosis compared to others
IDC (cont’d)

- Treatment
  - MRM for some patients (e.g., diffuse local disease, multicentric disease, etc.) with or without radiotherapy for locoregional control
  - NIH Consensus Conference (1990) - breast conservation for majority of Stage I and II, usually limited to tumors not 4cm, provides survival rates equivalent to MRM and ND

IDC (cont’d)

- Conservative therapy = excision of tumor and 1cm of surrounding breast tissue followed by radiotherapy and axillary node dissection
- Risk of local and distant recurrence in node negative patients can be reduced from 30% to 20% by adjuvant tamoxifen and combination chemotherapy

Sentinel Node Biopsy

- Sentinel node biopsy may be potentially useful for assessing status of axillary nodes as patients with clinically negative nodes may be spared an axillary dissection
- Some studies have shown that sentinel node biopsy accurately predicts axillary node status 97.5% of the time
Invasive Lobular Carcinoma

- Second most common invasive breast Ca
- Median age 50-57
- Majority present with palpable mass, but 10% are not palpable due to diffuse growth pattern
- Mammogram fails to detect the lesion due to few Ca - ill-defined margins and multicentric
- Treatment should parallel that of invasive ductal carcinoma
- Depends on size and capsular involvement of lesion
- Stage for stage prognosis is similar to invasive ductal carcinoma

Tubular Carcinoma

- Predominantly women, median age 60
- Most present with a palpable mass, usually 1cm (20%)
- Mammography shows speculated mass without Ca x-rays
- In order to qualify 75% of tumor must show appropriate histology
- Metastases and death from disease are rare in pure tubular carcinoma, thus, conservative therapy is ideal

Colloid (Mucinous) Carcinoma

- More common in older women, accounts for 7% of tumors in women 70 years old
- Presenting symptom is usually a mass with avg duration prior to presentation 3 months or less
- Mammography - circumscribed mass only rarely containing Ca x-rays
- Tumor should be 75% mucinous to make the diagnosis
- Prognosis is better than IDC, with post-mastectomy survivals of almost 100% 5 yr, 80% 10 yr, and 60% 25 yr
- Role of breast conservation and radiation is uncertain
Medullary Carcinoma

- Women tend to be a little younger than typical invasive ductal
- Usually present as a well-defined, firm mass, typically firm
- Can be mistaken clinically and radiographically for a fibroadenoma
- Very strict pathology criteria must be used for diagnosis
- Often a high proportion of normal breast tissue after treatment
- Median disease-specific survival is around 5 years, even in stage II patients
- Patients tend to have a lower overall frequency of axillary node metastasis
- Some breast cancers may involve more than 1 breast
- Patients with node-negative disease and 1 or more involved nodes have worse outcomes, similar to typical invasive ductal carcinomas
Metaplastic Carcinoma

- An admixture of adenocarcinoma with areas of spindle, squamous, or osteoclast-like differentiation
- Metaplastic component may appear benign or malignant
- Age range and clinical features similar to invasive ductal; although a history of more rapid growth is usually given
- Avg. size is 3-4 cm
- Mammography shows circumscribed contours
- Hormonal response and metastases to the lungs and bones; cell type may influence prognosis

Carcinomas with Endocrine Differentiation

- Clinical features identical to typical IDC, but more likely to be well-circumscribed
- Very rarely any systemic evidence of ectopic hormone production
- No controlled studies comparing patients with age- and stage-matched controls; no current evidence to suggest prognosis or recommended treatment is different from typical IDC
Secretory Carcinoma

- Has been termed “infantile carcinoma” due to several reports in children, including boys, but adults are also affected
- A rare neoplasm that usually presents as a circumscribed mass; 5 cm
- Majority follow a low-grade clinical course with a favorable prognosis. If nodes positive, stage involves 3 nodes
- Local excision is preferred treatment in children with node dissection only if involvement is clinically suspected

Adenoid Cystic Carcinoma

- Age similar to typical IDC, avg. 50 yrs
- Typically women, but may occur in men
- Typically presents as a discrete, firm, palpable mass, most 1–3 cm
- Mammography: very few reported cases detected by mammogram
- Diagnosis: Microscopic examination of almost all reported cases, all reported cases of metastatic disease have involved the lung with or without involvement of brain, bone, and liver
LIVER AND BILIARY TRACT DISEASES

Gregory G. Freund, M.D.
Liver and Biliary Tract Disease

University of Illinois
College of Medicine at Urbana-Champaign

Gregory G. Freund, MD

2008

Normal Liver

- Normal adult liver weight 1400-1600g
- Blood arrives via portal vein (60-70%) and by the hepatic artery (30-40%)
- Hepatocellular organization
  - Hepatic acinus is divided into three zones
    - Zone 1: closest to the vascular supply
    - Zone 2: intermediate between zones 1 and 3
    - Zone 3: closest to the hepatic venule
  - Hepatic parenchyma
    - Cribiform anastomosing sheets, cords or "plates"
    - Limiting plate hepatocytes abut the portal tracts
    - Hepatocytes are generally mononuclear but binucleation is not uncommon

Gross

Normal Liver

Low Power

Portal Triad
Normal Liver

Central Vein

Normal Liver (cont.)

Blood Flow

Normal hepatic blood flow is about 1500 mL/min in adults, of which 25-30% is derived from the hepatic artery and 70-75% from the portal vein.

Hepatic artery supplies 45-50% of the liver’s oxygen requirements and the portal vein supplies the remaining 50-55%.

Normal hepatic blood volume is about 450 mL (almost 10% of total blood volume).

time it takes for red blood cells to traverse from the portal vein to the central vein is approximately 8-9 s.

Blood Flow
**Metabolic Functions**

Only the liver and (to a lesser extent) muscle are able to store significant amounts of glycogen.

The liver and kidney are unique in their capacity to form glucose from lactate, pyruvate, amino acids (mainly alanine), and glycerol (derived from fat metabolism).

When carbohydrate stores are saturated, the liver converts excess ingested carbohydrates (and proteins) into fat. The fatty acids thus formed can be used immediately for fuel or stored in adipose tissue or the liver for later consumption.

The liver performs a critical role in protein metabolism. Without this function, death usually occurs within several days. The steps involved include (1) deamination of amino acids, (2) formation of urea (to eliminate the ammonia produced from deamination), (3) interconversions between nonessential amino acids, and (4) formation of plasma proteins.

---

**The Biliary System**

The biliary system consists of the liver, common bile duct, gallbladder, and small intestine. The liver produces bile, which is stored in the gallbladder and released into the small intestine to aid in fat digestion.

---

**Bilirubin Metabolism**

Bilirubin, a byproduct of heme catabolism, is transported to the liver and conjugated with glucuronic acid to form bilirubin glucuronide. It is then excreted in the bile.

---

**Bilirubin Metabolism Diagram**

- Bilirubin (B) is converted to bilirubin glucuronide (B-()((G)+U)2)
- Bilirubin glucuronide is excreted in the bile.

---

**Pathology M-2 – Liver Notes**

Pathology M-2 – Liver Notes
**Serum Tests in Liver Disease**

**Parenchymal (hepatocytes):** AST, ALT

**Canalicular (biliary):** ALP, 5′NT, GGT, bilirubin

**Synthetic function and metabolism:** INR, factors V, VII, bilirubin, albumin

---

**Bilirubin**

† Reaction with diazonium salt (diazotized sulfanillic)
* Direct (fast) - CONJUGATED - water soluble
* Indirect: UNCONJUGATED - lipid soluble

† Hyperbilirubinemia
  † Elevated direct (>0.3 mg/dl) and indirect (>1.0 mg/dl) reacting bilirubin indicates impairment of bile secretion
  † Elevated indirect reflects impaired conjugation (hemolytic anemia, ineffective erythropoiesis, Gilbert’s and Crigler-Najjar syndromes)

---

**Aminotransferases**

† Aspartate aminotransferase – AST.
† Catalyzes the transfer of the γ-amino acid group of aspartate to the γ-keto group of ketoglutarate to form oxaloacetic acid. Half-life 18 h
  † Tissue distribution: liver, heart, skeletal muscle, kidney and brain
† Alanine aminotransferase – ALT, <35.45 U/L
  † Catalyzes the transfer of the γ-amino acid group of alanine to the γ-keto group of ketoglutarate to form pyruvic acid. Half-life 36 h
  † Tissue distribution: liver

---

**Aminotransferases (cont.)**

† AST and ALT are elevated in nearly all liver disorders < 35.45 U/L
† Highest levels associated with conditions causing hepatic necrosis (viral hepatitis, toxin induced liver damage, circulatory collapse)
† Absolute levels correlate poorly with severity of liver injury and prognosis
† AST and ALT levels parallel each other except:
  † Alcoholic hepatitis - AST/ALT > 2
  † Fatty liver of pregnancy AST/ALT > 1

---

**Alkaline Phosphatase**

† Hydrolyzes synthetic phosphate esters at pH 9
† Tissue distribution: bone, intestines, liver, placenta, 25-85 IU/L, half-life 7 days
† Elevated levels of ALP (in absence of bone disease [Paget's, bone met] or pregnancy) Usually reflects impaired biliary tract function
  † Increase is due to increased synthesis of ALP by hepatocytes and biliary tract epithelium
† Elevations in ALP
  † 1-2X: parenchymal liver disorders (hepatitis and cirrhosis)
  † 3-10X: biliary tract obstruction (extra- or intrahepatic)

---

**γ-Glutamyl transpeptidase**

† Catalyzes the transfer of γ-glutamyl groups from peptides to other amino acids
† Tissue distribution: primarily hepatobiliary system
† GGT correlates with ALKPHOS and is the most sensitive indicator of biliary tract disease (>40 U/L)
† GGT elevations are nonspecific and are associated with pancreatic, cardiac, renal and pulmonary disorders as well as diabetes and alcoholism
**Albumin**

- Albumin: most important serum protein produced by the liver (3.5-5.5 g/dl)
  - Half-life: 14 days, therefore not a good indicator of acute liver injury
  - Excellent indicator of severity of chronic liver disease

**Prothrombin Time**

- PT, which is normally 11-14 s (depending on the control), measures the activity of fibrinogen, prothrombin, and factors V, VII, and X.
- Relatively short half-life of factor VII (4-6 h) makes the PT useful in evaluating hepatic synthetic function of patients with acute or chronic liver disease.
- Because only 20-30% of normal factor activity is required for normal coagulation, prolongation of the PT usually reflects severe liver disease unless vitamin K deficiency is present. Failure of the PT to correct following parenteral administration of vitamin K implies severe liver disease; correction normally requires 24 h.

**Blood Ammonia**

- Ammonia end product of amino acid and nucleic acid metabolism
- Liver is the only tissue that can detoxify ammonia, converting it to urea in the ura cycle
- Marked elevation in ammonia reflects severe hepatocellular necrosis (80%) normal 47-65 mmol/L
- Only rough correlation between ammonia level and hepatic encephalopathy
  - Ammonia, conversion of glutamic acid to glutamine lowering γ-aminobutyric acid (GABA)

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<th>ALT</th>
<th>LD</th>
<th>ALP</th>
<th>TP</th>
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**Overview of Hyperbilirubinemia**

**Disorders Causing Predominantly Unconjugated Hyperbilirubinemia**

- Overproduction of bilirubin (increased turnover)
  - Increased destruction of circulating erythrocytes (hemolytic anemia)
  - Ineffective erythropoiesis (thalassemia and pernicious anemia)
- Impaired bilirubin conjugation
- Neonatal jaundice
  - Hereditary glucuronyl transferase deficiency
    - Gilbert’s syndrome
    - Crigler-Najjar syndrome
Jaundice

Neonatal Jaundice

- Effects almost every infant between the 2nd and 5th day of life
- During gestation, the placenta clears fetal bilirubin, in the newborn, the liver serves this function
- Enzymatic “immaturity” accounts for unconjugated bilirubinemia
- Breast fed due beta-glucuronidases in milk
- Unconjugated bilirubinemia >20 mg/dl may lead to kernicterus (bilirubin encephalopathy)
  unconjugated bilirubin deposited in the lipid-rich basal ganglia]

Gilbert’s Syndrome

- Mild persistent hyperbilirubinemia
- Most common cause of mild persistent hyperbilirubinemia aside from hemolytic anemias
- Manifested in the second decade of life with a total bilirubin of <3 mg/dl
- Partial deficiency of UDP-glucuronyl transferase

Crigler-Najjar

- Type 1: absence of UDP-glucuronyl transferase
  - Rare (recessive inheritance)
- Infants present with unconjugated bilirubinemia of 15-50 mg/dl, usually die from kernicterus in first year of life
- Type 2: partial deficiency of UDP-glucuronyl transferase
  - May not be evident until adolescence with unconjugated bilirubinemia of 6-25 mg/dl
  - Neurological complications are uncommon

Disorders Causing Combined Conjugated and Unconjugated Hyperbilirubinemia

- Familial defects
  - Dubin-Johnson syndrome
  -Rotor syndrome
  - Benign familial recurrent cholestasis
  - Recurrent jaundice of pregnancy
- Acquired defects
  - Drug induced cholestasis
  - Postoperative jaundice
  - Hepatitis and cirrhosis
- Extrahepatic biliary obstruction

Dubin-Johnson Syndrome

- Autosomal recessive inheritance
- Defect in biliary excretion of bilirubin, cholephilic dyes and porphyrins
- Bilirubin ranges from 2.5 mg/dl and is predominantly conjugated
- Patients usually are asymptomatic but may have enlarged livers
- Intra-hepatocellular brown/black pigment in the centrolobular region of the liver is a characteristic finding
- “Unique pigment” melanin-related
**Dubin-Johnson Syndrome**

- Lipofuscin
- Brown pigment in liver cells

**Rotor Syndrome**

- Rare (recessive inheritance)
- Impairment of hepatic storage capacity
- Similar to D-J clinically, but
  - There is no pigment in the liver
  - Diconjugated/monoconjugated bilirubin ratio is < 1.0

**Recurrent Jaundice of Pregnancy**

- Characterized by intrahepatic cholestasis in the third trimester
- Pruritus and jaundice (bilirubin <103 μmol/l)
- Histologically:
  - Varying degrees of bile stasis
  - Few parenchymal changes
- Clinical and laboratory abnormalities subside promptly after delivery and are normal in 1-2 wks

**Scratch Marks on Legs**

**Cholestasis with Bile Plugs**

**Acute Hepatitis**

- Viral Hepatitis
  - Hepatitis A
  - Hepatitis B
  - Hepatitis C
  - Hepatitis D
  - Hepatitis E
  - Hepatitis G
- Toxins induced hepatitis
- Drug induced hepatitis
Viruses which Cause Hepatitis

- Acute Hepatitis (cont.)
  - Signs and Symptoms
    - Prodromal symptoms: fatigue, malaise, anorexia, vomiting, arthralgia, myalgia, headache, photophobia, pharyngitis, cough followed in about 2 weeks by jaundice
    - Icteric phase: enlarged tender liver
    - Recovery phase: some liver enlargement
  - Laboratory Findings
    - Prodromal phase: variable elevation in AST and ALT
    - Icteric phase: moderate to marked elevation in bilirubin, peak in transaminase levels (usually marked increase)
    - Specific viral markers are elevated

Hepatitis A
- 27-nm RNA hepatovirus
- 150,000 cases/year USA
- Transmitted almost exclusively by fecal-oral route
- Incubation: 2-6 wks, Averg 30 d
- Virus is found in liver, bile, feces and blood during late incubation period and pre-icteric phase of illness
- Does not lead to chronic hepatitis/ICC/carry state
- Rarely fatal

Hepatitis B
- 42-nm hepatadnavirus, DNA virus, 8 different genotypes that may alter disease
- 300,000 cases/year USA
- Percutaneous transmission - oral transmission is possible
- Incubation: 6-42 weeks, Averg 12-14 wk
- 42 nm Dane particle contains three proteins detected serologically
  - Hepatitis B surface antigen (HBsAg)
  - Inner Hepatitis B core antigen (HBeAg)
  - E antigen (HBeAg) secretory form of HBeAg
**Clinical Outcomes After Acute Infection**

- **Subclinical Disease**
  - 60-65%
  - Recovery 100%

- **Acute Hepatitis**
  - 20-25%
  - Fulminant Hepatitis 1%
  - Recovery 99%

- **Persistent Infection**
  - 4%
  - Cirrhosis 20-60%
  - Chronic Hepatitis 10-33%

- **“Healthy” Carrier**
  - Window 5-10%
  - Recovered
  - Vaccinated, recovered

**Hepatitis D**

- Enveloped dsRNA virus which requires encapsulation by HBsAg (or other hepatitis virus) for its replication and function
- HDV can infect a person simultaneously with HBV, co-infection or after a person is already infected with HBV - super-infection
- Dx made by detection of anti-HDV or HDV RNA in serum
- HDV infection can lead to:
  - Fulminant hepatitis in a mild case of HBV (4%)
  - Acute hepatitis in asymptomatic chronic carrier
  - Chronic progressive hepatitis (80%)
- Prevalence rate of 1-10%, USA

**Hepatitis C**

- Hepatitis virus, RNA, at least 6 genotypes
- One of the causative agents of transfusion-associated hepatitis (90-95%)
- Only 4% of Hep C attributed to blood transfusion, 50% to drug use
- Seroprevalence 0.2%, USA
- Incubation: 2-26 wks
- HCV has a high rate of progression to chronic disease (exceeding 50.85%)
- EtOH synergistic role in exacerbating HBC
**Clinical Outcomes**

Acute Infection

- 10% Recovery
- >60% Fulminant Hepatitis
- 20% Cirrhosis
- 80% Chronic Hepatitis
- 80% Stable Disease
- 10% Stable Cirrhosis
- 50% Death

**Pathway**

- Incubation
- Acute Disease
- Chronic Disease
- Recovery

- Jaundice
- Symptoms
- HCV-RNA
- Transaminases
- IgG anti-HCV

**Table: Diagnostic Tests for Hepatitis**

<table>
<thead>
<tr>
<th>RNA</th>
<th>anti-HCV (ELA)</th>
<th>S-1-1 (SBA)</th>
<th>C100-3 (SBA)</th>
<th>C33c (SBA)</th>
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</tr>
</tbody>
</table>

**Hepatitis E**

- RNA enterovirus virus
- Enteric mode of spread (water born)
- Incubation: 2-8 wks
- No chronic hepatitis/hepatocellular carcinoma
- Can result in fulminant hepatitis (high mortality rate in pregnant women approaching 20%)

**Hepatitis G**

- ssRNA
- Percutaneously transmitted
- Incubation period unknown
- 1-2% of US blood donors
- Does not appear to cause important liver disease or affect the response of patients with chronic hepatitis B or C to antiviral therapy. HGV co-infection may improve survival in patients with HIV infection
Pathogenesis

- None of the hepatitis viruses appears to be directly cytopathic to hepatocytes.
- Clinical manifestation of disease are determined by the immunologic response of the host (T cell mediated).

Pathology: Acute Viral Hepatitis

- Gross: liver slightly enlarged and green (depending on degree of jaundice).
- Histology:
  - Random necrosis of isolated liver cells and liver cell clusters
  - Confluent bodies (fragmented eosinophilic hepatocytes)
  - Confluent necrosis leading to bridging necrosis (F-F, C-E and/or C-P)
  - Lobular disarray from cellular swelling, regeneration and necrosis
  - Reactive changes in Kupffer and sinusoidal cells (including: hypertrophy, hyperplasia)
  - Portal tract inflammation (predominantly mononuclear)

Pathology: Acute Viral Hepatitis

- Apoptotic/Connexin Body
- Ballooning Degeneration
- Activated Kupffer Cells (PAS+)

Pathology: Acute Viral Hepatitis

- Acute Viral Hepatitis
- Lobular Collapse

Pathology: Acute Viral Hepatitis

- Bridging Necrosis-portal tract linkage

Pathology: Acute Viral Hepatitis

- Portal Tract Inflammation with sinusoidal spread

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Pathology: Fulminant Viral Hepatitis

- Gross: Liver is small and soft in consistency with wrinkled capsule
- Histology
  - Massive necrosis involving entire liver or random areas
  - Complete destruction of contiguous lobules with liquefaction of hepatocytes
  - Portal tracts are preserved

Fulminant Viral Hepatitis

- Acute Submassive Viral Hepatitis

Toxic and Drug Induced Acute Hepatitis

- Common agents (some)
  - Acetaminophen (toxic 25g) - fulminant hepatitis
  - Alcohol (toxic and idiosyncratic reaction) - chronic active hepatitis
  - Isoniazid (toxic and idiosyncratic reaction) - acute viral hepatitis
  - Sulfuric acid (toxic and idiosyncratic reaction) - acute viral hepatitis
  - Phenacetin (toxic and idiosyncratic reaction) - acute viral hepatitis
  - Chlorpromazine (cholestatic idiosyncratic reaction) - cholestasis can progress to PBC-like disorder
  - Antituberculosis (toxic and idiosyncratic reaction) - pseudohydatidic liver disease

Natural History of Acute Hepatitis

Chronic Hepatitis

- Chronic persistent hepatitis
- Chronic active hepatitis
  - Disorders associated with chronic hepatitis
    - Chronic hepatitis B
    - Chronic hepatitis D
    - Chronic hepatitis C
    - Autoimmune chronic hepatitis

Chronic Hepatitis (cont.)

- Signs and symptoms: broad ranging from asymptomatic to debilitating disease. Common features include:
  - Fatigue
  - Persistent or intermittent jaundice
- Laboratory findings
  - Moderate elevation in transaminases with
    - ALT>AST
  - Elevations of viral markers
Pathology: Chronic Persistent Hepatitis

- Histology
  - Mononuclear inflammatory infiltrate confined to the portal tracts
  - Limiting plate hepatocytes are intact
  - "cobblestone" arrangement of liver cells (indicative of hepatocellular regeneration)
  - Minimal periportal fibrosis

Pathology: Chronic Active Hepatitis

- Histology
  - Piecemeal necrosis
    - chronic inflammatory infiltrate extending from portal tracts to adjacent parenchyma
    - Necrosis of limiting plate hepatocytes
  - Bridging necrosis
  - Fibrosis (may result in cirrhosis)

Chronic Active Hepatitis

- Marked Interface Hepatitis
- Incipient Cirrhosis

Postnecrotic Cirrhosis

- Postnecrotic cirrhosis represents the final pathway of many advanced liver injuries
- Hepatitis B and C are the antecedent factor in 25-33% of cases
- Signs and symptoms
  - Portal hypertension >60% of patients with
  - Laboratory findings
  - Slightly elevated bilirubin
  - Slightly elevated AST
Major Sequelae of Cirrhosis

- Portal hypertension
- Variceal bleeding
- Portal hypertensive gastropathy (indolent GI bleeding)
- Splenomegaly (thrombocytopenia, jaundice)
- Ascites (clinical detectable at 500 ml)
- Spontaneous bacterial peritonitis
- Hepatorenal syndrome (azotemia, sodium retention and oliguria)
- Hepatic encephalopathy (ammonia)

Ascites

The accumulation of ascitic fluid represents a state of total-body sodium and water excess, but the event that initiates this imbalance is unclear.

Ascites is the accumulation of excess fluid within the peritoneal cavity. It is most frequently encountered in patients with cirrhosis and other forms of severe liver disease.

Pathology: Postnecrotic Cirrhosis

- Gross: shrunk, distorted liver composed of large nodules of liver cells separated by broad dense bands of fibrous tissue
- Histology: nearly complete loss of lobular architecture with connective tissue separating regenerating islands of hepatocytes

Cirrhosis (gross)

Cirrhosis (H&E)
**Postnecrotic Cirrhosis**

- Macronodular Cirrhosis

**Autoimmune Hepatitis**

- Chronic hepatitis of unknown etiology
- Female predominance (70%)
- Elevated serum IgG levels
- High titers of autoantibodies (ANA, SMA, AMA, and LKM)
- Increased frequency of HLA-B8 and DRw3
- Signs and symptoms: fatigue, malaise, anorexia, amenorrhea, acne, arthralgias, and jaundice
- Laboratory findings: mild to moderate elevations in AST, hypogammaglobulinemia, presence of rheumatoid factor

**Alcohol Related Liver Disease**

- Alcoholic fatty liver
- Alcoholic hepatitis
- Alcoholic cirrhosis

**Alcohol Related Liver Disease (cont.)**

- Alcoholism is the most common cause of cirrhosis
  - Quantity and duration of drinking define steatosis
    - Only 10-15% of persons exceeding 50 g/d ETOH (4 oz/100 proof whiskey, 15 oz wine, 48 oz beer) develop cirrhosis
  - Incidence lower (5%) in those without cofactors like chronic viral hepatitis

- Alcoholic fatty liver: minimal or absent
- Alcoholic hepatitis: anorexia, vomiting, nausea, minimal jaundice, pruritus, and lower hepatoegstes
- Alcoholic cirrhosis: anorexia and malnutrition with cirrhosis, portal hypertension, severe jaundice
- Laboratory findings:
  - Slight elevation of AST
  - AMA (+), marker with antihepatitis, moderate elevation of AST, with 

- Alcoholic fatty liver
- Alcoholic hepatitis
- Alcoholic cirrhosis

- Alcoholic fatty liver: minimal or absent
- Alcoholic hepatitis: anorexia, vomiting, nausea, minimal jaundice, pruritus, and lower hepatoegstes
- Alcoholic cirrhosis: anorexia and malnutrition with cirrhosis, portal hypertension, severe jaundice
- Laboratory findings:
Pathology: Alcoholic Fatty Liver

- Gross: liver is enlarged, yellow, greasy and firm
- Histology
  - Hepatocytes are distended by large macrovesicular (predated by microvesicular fat) cytoplasmic fat vacuoles
- Pathogenesis of fat accumulation
  - Impaired fatty acid oxidation
  - Increased uptake and esterification of FAs
  - Diminished lipoprotein biosynthesis

Pathology: Alcoholic Hepatitis

- Gross: appearance between fatty liver and cirrhotic liver
- Histology
  - Single cell and scattered focal liver cell necrosis
    - Often with balloononing degeneration
    - Concentrated in the centrilobular regions
  - Mallory bodies
    - Hepatocytes with eosinophilic cytoplasmic inclusions
  - Inflammatory infiltrate
    - Neutrophilic
    - Pericellular mononuclear
  - Sinusoidal and perisinusoidal fibrosis

Alcoholic Fatty Liver

Alcoholic Hepatitis

Fatty infiltration
Focal Liver Necrosis

Alcoholic Hepatitis

Mallory’s Hyaline
Pathology: Alcoholic Cirrhosis

- Gross: Brown, shrunk and nonfatty
- Histology
  - Web-like septa of connective tissue in periportal and pericentral zones that eventually connect portal tracts and central veins
  - A fine connective tissue network surrounds small nodules of remaining liver cells which regenerate and form larger nodules

Alcoholic Cirrhosis

- Micronodular Cirrhosis

- Early Fibrosis

- Late Fibrosis

- Sclerosed Vein

Etiology of Cirrhosis

- Primary biliary cirrhosis
- Secondary biliary cirrhosis

Biliary Cirrhosis
Primary Biliary Cirrhosis

- The cause of PBC is unknown, but it is often associated with autoimmune disorders such as:
  - CREST (calcinosis, Raynaud's, esophageal dysmotility, and telangiectasia)
  - Sjögren syndrome (dry eyes, dry mouth)
  - Autoimmune hepatitis
  - Renal tubular acidosis

- 90% of patients have a circulating IgG AMA (90% to the 70-kDa component of peroxisomal), and 40-50% have anti-LKM1 antibody

- Symptoms and presentations:
  - Pruritus, jaundice, anorexia, dark urine, light stools, and hypergammaglobulinemia

- Laboratory findings:
  - Conjugated hyperbilirubinemia
  - Increased ALP, CPK, 5'-NT

Histology

- 4 stages

- Earliest recognizable lesion - chronic non-suppurative destructive cholangitis
  - Destruction of small and medium bile ducts
  - Dense infiltrate of acute and chronic inflammatory cells
  - Mild fibrosis
  - Occasionally - steats, periductal granulomas and lymphoid follicles

Pathology (con)

- Stage II inflammatory infiltrate becomes less prominent, the number of bile ducts is reduced, and smaller bile ductules proliferate

- Stage III progression over a period of months to years leads to a decrease in interlobular ducts, loss of liver cells, and expansion of periporal fibrosis into a network of connective tissue scars

- Stage IV cirrhosis

Portal Tract Inflammation Around Bile Duct

- Cytokeratin 7

Primary Biliary Cirrhosis

- Portal Tract Granuloma

- Lymphoid Follicle Formation at Site of Destroyed Bile Duct

- Piecemeal Necrosis
Secondary Biliary Cirrhosis

- Secondary biliary cirrhosis results from prolonged partial or total obstruction of the common bile duct or its major branches
- Adults (most common cause)
  - Posthepatic obstruction
  - Gallstones usually with superimposed infections
  - Cholangitis
- Children (rare; common causes)
  - Congenital biliary atresia
  - Cystic fibrosis
- Signs and symptoms
  - Fever, jaundice, pruritus, dark urine, light stools and hepatosplenomegaly
- Laboratory findings
  - Conjunctival hyperbilirubinemia
  - Increased ALP/PHOS/GGT, 5’NT

Pathology: Secondary Biliary Cirrhosis

- Gross: liver is yellow-green in color, hard with a finely granular cut surface
- Histology
  - Cholestasis
    - Dilated large and small bile ducts with thickened bile
    - Canalicular bile
    - Hepatocellular cytoplasmic bile
    - Bile lakes
  - Centrilobular and subsequent periportal necrosis
  - Portal bile duct and ductule proliferation
  - Portal tract edema and fibrosis with subsequent finely nodular cirrhosis

Secondary Biliary Cirrhosis

- Bile Stained Cirrhotic Liver

Cholestasis

Secondary Biliary Cirrhosis

- Bile Duct Proliferation

Cardiac Cirrhosis

- Cardiac cirrhosis results from prolonged severe right-sided heart failure
- Retrograde transmission of elevated venous pressure via the IV and hepatic veins leads to congestion of liver
- Prolonged congestion leads to poor liver perfusion and ischemia
- Signs and symptoms
  - Enlarged tender liver in a patient with valvular heart disease, constrictive pericarditis or long standing cor pulmonale
- Laboratory findings
  - Mild conjugated or unconjugated hyperbilirubinemia
  - Slightly increased AST
**Pathology: Cardiac Cirrhosis**

- Gross: swollen firm liver with cut surface showing alternating red (congested) and pale (fibrotic) areas - "nutmeg liver"
- Histology:
  - Dilated hepatic sinuoids
  - Centrilobular fibrosis with stellate pattern extending out from the central vein

**Cardiac Cirrhosis**

- Nutmeg Liver

**Cardiac Cirrhosis**

- Centrilobular Fibrosis

- Chronic passive congestion

**Tumors of the Liver**

- Hepatocellular adenoma
- Focal nodular hyperplasia
- Hemangiomata
- Hepatocellular carcinoma
- Metastatic tumors

**Hepatocellular Adenoma**

- Benign tumors of the liver found predominantly in women in their 3rd-4th decades
- These tumors are prone to rupture
- Associated with oral contraceptive use
- Pathology:
  - Gross: pale yellow-tan nodules frequently bile stained and well demarcated
  - Histology: sheets and cords of nearly normal looking hepatocytes, absence of portal tracts and delicate to pronounced capsule

**Hepatocellular Adenoma**

- Single Adenoma
**Hemangioma**

- Microscopic

**Hepatocellular Carcinoma**

- One of the most common tumors worldwide, especially prevalent in regions of Asia and sub-Saharan Africa, in the USA and western Europe much less common
- Hepatocellular carcinoma is more common in men and usually arises in a cirrhotic liver in the 5th-7th decade of life
- Chronic liver disease of any type is a risk factor for HCC
- Most common associations include chronic HBV and HCV, non-alcoholic liver disease, and common disorders include elevated AFP levels, hemochromatosis, Mimacan and aflatoxin B1
- Signs and symptoms: abdominal pain with detection of an abdominal mass
- Laboratory findings: elevated alpha-fetoprotein, 500-1000 mg/L found in 70-80% of patients, jaundice is rare

**Pathology: Hepatocellular Carcinoma**

- Gross
  - Focal or diffuse liver enlargement in three patterns
  - Unifocal
  - Multifocal
  - Diffuse infiltrative
- Discrete tumor masses appear yellow-white punctuated by areas of hemorrhage and necrosis
- Histology
  - Well differentiated (trabecular or acinar pattern) is anaplastic
  - Bile may be seen in well differentiated tumors

**Hepatocellular Carcinoma**

- Microscopic

**Hepatocellular Carcinoma**

- Microscopic
**Hepatocellular Carcinoma**

- Microscopic

**Fibrolamellar Carcinoma**

- Fibrolamellar carcinoma occurs in young men and women is unassociated with HBV and cirrhosis and has a better prognosis than HCC
- Gross: well circumscribed non-encapsulated single large hard tumor
- Histology: characterized by collagenous bands coursing through nests and cords of well differentiated liver cells in a lamellar pattern

**Metastatic Tumors**

- Metastatic tumors of the liver rank second to cirrhosis as a cause of liver failure
- Incidence of metastatic liver carcinoma is 20 times greater than that of primary liver cancer
- The liver is the most common site of metastasis outside the lymph nodes due to its size, high rate of blood flow, diffuse perfusion and Kupffer cell filtration function
- Signs and symptoms: usually silent with nonspecific features such as weakness, weight loss, fever, sweating, and loss of appetite
Metastatic Tumors

- Metastatic Adenocarcinoma

Infiltrative and Metabolic Diseases Affecting the Liver

- Fatty Liver
- Wilson's disease
- Hemochromatosis
- Hürthle's syndrome
- Alpha-1-antitrypsin deficiency
- Granulomatous infiltrations
- Amyloidosis

Diseases of the Gallbladder

- Diseases of the Gallbladder
  - Gallstones
  - Acute cholecystitis
  - Chronic cholecystitis
  - Cancer of the gallbladder

Gallstones

- At autopsy 20% of women and 8% of men over 40 years have gallstones
- Three major types of gallstones
  - Cholesterol stones
  - Pigment stones (20%)
  - Mixed stones
- Stone composition
  - Cholesterol and mixed stones: 70% cholesterol monohydrate and an admixture of calcium salts, bile acids, bile pigments, proteins, fatty acids and phospholipids
  - Pigment stones: >90% calcium bilirubinate and <10% cholesterol

Gallstones

- Cholesterol Stones (top)
- Mixed Stones (middle, 5)
- Pigment Stones (bottom)
Pigment Stones

- Pigment stones form in the presence of increased amounts of unconjugated, insoluble bilirubin in bile
- Chronic hemolytic states (sickle cell anemia)
- Acute hepatic disease
- Infections in the biliary tree (Asians)

Gallstone Disease

- Signs and symptoms: bilious colic characterized by severe, steady ache or pressure in the epigastrium or RUQ with frequent radiation to the right scapula
- Laboratory findings: slight elevation in serum bilirubin not exceeding 85.5 mmol/l
- Stone morphology
  - Cholesterol stones are pale yellow in color and round to oval in shape
  - Pigmented stones
    - Black stones (usually found in sterile bile)
    - Green stones (usually found in infected bile)

Normal Gallbladder

<table>
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<tr>
<td>Positive Courvoisier sign</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Negative Courvoisier sign</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Gallbladder

- Epithelium

Acute Cholecystitis

- Acute inflammation of the gallbladder usually follows obstruction of the cystic duct by a stone
- Mechanical inflammation - increased luminal pressure and distention resulting in ischemia
- Chemical inflammation - release of lysosomal enzymes and other local tissue factors
- Bacterial inflammation - may play a role in 50-80% of patients
- Signs and symptoms: progressively worsening attack of biliary colic, fever and vomiting
- Laboratory findings: leucocytosis (10-15 K cell/l), mild elevation in bilirubin
**Pathology: Acute Cholecystitis**

- **Gross**
  - Gallbladder is enlarged, tense often bright red or bluish, viscerous to green-black with thin layer of fibrin or a definite suppurative covering
  - On cut section, the lumen is filled with cloudy or turbid bile, gallstones are identified and the gallbladder wall is thickened and edematous

- **Histology**
  - Acute inflammation - edema, leukocytic infiltration, vascular congestion, abscess formation and/or gangrenous necrosis

**Acute Cholecystitis**

- Acute Pyalulent Cholecystitis (gross)

**Acute Cholecystitis**

- With Peritonitis

**Acute Cholecystitis**

- Microscopic

**Chronic Cholecystitis**

- Almost always associated with gallstones and thought to result from repeated episodes of acute cholecystitis

- **Pathology**
  - **Gross**
    - Extremes variable, serosa is usually smooth but dotted by subserosal fibrosis
    - On cut section, the gallbladder wall is variably thickened and the lumen contains freely free greenish concrement bile and stones
  - **Histology**
    - subepithelial and subserosal fibrosis with mononuclear cell infiltrate and Rossiter-Neubauer sinuses (outgrowths of the mucosal epithelium)
Chronic Cholecystitis

- Microscopic
  - RA Sinuses

Complications of Cholecystitis

- Gallbladder empymema and abscess
  - Superinfection of stagnant bile with pre-forming bacteria (high risk of gram negative sepsis)
- Gallbladder gangrene and perforation
  - Free perforation is associated with 50% mortality
- Fistula formation and gallstone fistulas
  - Gallstone ileus - mechanical obstruction of intestine by large galling pebble, at time of surgery
- Liver bile duct and pseudocyst gallbladder
  - Calcium salt deposition within wall of gallbladder predisposing to gallbladder carcinoma

Cancer of the Gallbladder

- Most cancers of the gallbladder develop in conjunction with gallstones but the risk is low
- Female:male ratio is 4:1 and mean age is 70
- Over 75% of tumors are resectable at surgery and 1-year mortality rate of resectable tumors is 95%
- Signs and symptoms: unremitting RUQ pain associated with weight loss and jaundice
- Pathology
  - Most carcinomas of the gallbladder are adenocarcinomas but 5% are squamous carcinomas
  - Most have invaded the liver at time of resection

Cancer of Gallbladder

- Gross

Diseases Bile Ducts

- Diseases of the Bile Ducts
  - Cholelithiasis cyst
  - Cholelithiasis
  - Sclerosing Cholangitis
  - Cholangiocarcinoma
**Choledochal Cyst**

- Cystic dilatation of the common bile duct presenting in children before age 10 with a 4:1 female:male ratio.
- Signs and symptoms: cholangitis and/or biliary obstruction.

**Choledocholithiasis**

- Caused by presence of stones into the common bile duct
- Majority of common bile duct stones are cholesterol or mixed stones
- Complications:
  - Cholangitis
  - Obstructive jaundice
  - Common bile duct stones should be suspected in any patient with cholangitis and serum bilirubin > 8 mg/dL
- Pneumatosis
- Secondary biliary cirrhosis

**Sclerosing Cholangitis**

- Primary sclerosing cholangitis may appear as an isolated entity or in association with inflammatory bowel disease (especially ulcerative colitis) or multifocal fibrocystic syndrome.
- Signs and symptoms: chronic or intermittent biliary obstruction, jaundice, pruritus, RUQ pain or acute cholangitis
- Pathology: Fibrosing cholangitis of bile ducts ("onion skin fibrosis") with lymphocytic infiltrate and progressive atrophy and obliteration of lumen.
- Disease culminates in biliary cirrhosis
- Patients with sclerosing cholangitis are at risk for developing cholangiocarcinoma. Eventually 10 to 20% of the patients will develop cancer.
Sclerosing Cholangitis

Levin, PSC, Chronic Cholangitis and Secondary Biliary Cirrhosis.

Cholangiocarcinoma

- Predisposing factors: some chronic hepatobiliary parasitic infections, congenital anomalies with ectatic ducts, sclerosing cholangitis and ulcerative colitis.
- Slight male predominance (60%) with peak age in 5-7th decades.
- Signs and symptoms: biliary obstruction, painless jaundice, pruritis, weight loss and acholic stools.
- Pathology: adenocarcinoma, often well differentiated and desmoplastic.

Painless jaundice is the most common presentation. Pruritis, mild right upper quadrant pain, anorexia, fatigue, and weight loss also may be present. Cholangitis is the presenting symptom in about 10% of patients, but occurs more commonly after biliary manipulation in these patients. Except for jaundice, physical examination is usually normal in patients with cholangiocarcinoma. Occasionally, asymptomatic patients are found to have cholangiocarcinoma while being evaluated for elevated alkaline phosphatase and gamma-glutamyltransferase levels.

Cholangiocarcinoma

Microscopic (well differentiated)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Liver cell carcinoma</th>
<th>Bile duct carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell of origin</td>
<td>Hepatocytes</td>
<td>Bile duct cell</td>
</tr>
<tr>
<td>Geographic distribution</td>
<td>Marked variability</td>
<td>Worldwide</td>
</tr>
<tr>
<td>Age distribution</td>
<td>Young persons</td>
<td>Older persons</td>
</tr>
<tr>
<td>Sex predilection</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Presence of cirrhosis</td>
<td>Common</td>
<td>None</td>
</tr>
<tr>
<td>Liver cell proliferation</td>
<td>May be present</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Nucleoli</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Binucleoli</td>
<td>May be present</td>
<td>Absent</td>
</tr>
<tr>
<td>Membrane reactivity</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Mitochondria</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Glycogen content</td>
<td>Soft and hemoglobin</td>
<td>Hard and wisps</td>
</tr>
<tr>
<td>Preferential spread</td>
<td>Through sinus</td>
<td>Through pseudobulb</td>
</tr>
</tbody>
</table>

Cholangiocarcinoma

Microscopic (desmoplastic)

Classification of Liver Disease

- Parenchymal
- Hepatobiliary
- Vascular
Classification of Liver Disease - Parenchymal

1. Functional disorders associated with jaundice
   - Gilbert’s syndrome
   - Crigler-Najjar syndrome
   - Dubin-Johnson syndrome
   -Rotor syndrome
   - Cholestasis of pregnancy
   - Familial intrahepatic cholestasis
2. Hepatitis (viral, drug-induced, toxic, ischemic)
   - Acute
   - Chronic (persistent or active)

Classification of Liver Disease - Parenchymal (cont.)

1. Cirrhosis
   - Alcohol
   - Nutritive (tropical, nutritional, Laurence-Adams’)
   - Parasites
   - Injuries
   - Hemochromatosis
   - Three types: Wilson’s disease, paraneoplastic, cystic fibrosis of pancreas, alpha-1 antitrypsin deficiency
2. Space occupying lesions
   - Hematoma, metastatic tumor
   - Abscess (pyogenic, amebic)
   - Cysts (polycystic disease, hepatic cystosis)
   - Granulomas

Classification of Liver Disease - Hepatobiliary

1. Extrahepatic biliary obstruction (stone, tumor, stricture)
2. Cholangitis (septic, PVB, PSC, drug, toxic)

Classification of Liver Disease - Vascular

1. Chronic passive congestion
2. Cardiac cirrhosis
3. Hepatic vein thrombosis (Budd-Chiari syndrome)
4. Pyphlebitis
5. Arteriovenous malformations
6. Veno-occlusive disease
PANCREAS
DIABETES MELLITUS

G. Freund  M.D.

(ppts. on the web)
The Exocrine Pancreas

2007
Gregory G. Freund, MD
University of Illinois

Pancreas
- 60-140 grams
- 15 cm
- Head, body and tail
- Duct of Wirsung
- Duct of Santorini
- 80%-85% exocrine
- 2-2.5L/day bicarb-rich fluid + enzymes
- Acid → Secretin → water/bicarb
- Fatty acids, peptides, AAs → cholecystokinin → enzymes

Normal Pancreas

Acini

Digestive Enzymes
- Trypsin, Chymotrypsin, Aminopeptidases, Elastase, Amylases, Lipase, Phospholipases and Nucleases.
  - Proenzymes (excp. Amylase and lipase)
  - Zymogen granules
  - Trypsinogen to trypsin by duodenal enteropeptidase
  - Acinar cells resistant + inhibitors/trypsins

Islets
Islets of Langerhans
- 1 million clusters
- 1-1.5 grams
- beta (68%), alpha (20%), delta (10%), Pancreatic Polypeptide (2%)

Pancreatitis
- Acute Pancreatitis
  - Characterized by the acute onset of abdominal pain resulting from enzymatic necrosis and inflammation of the pancreas.
- Chronic Pancreatitis
  - Characterized by repeated bouts of mild to moderate pancreatic inflammation with continued loss of pancreatic parenchyma and replacement by fibrous tissue.

Acute Pancreatitis
- 10–20 cases/100,000
- 80% associated with biliary tract disease (m:f, 1:3) and alcoholism (m:f, 6:1)
- 35–60% gallstones present
- 5% of persons with gallstones develop pancreatitis
- Less common causes: infection, vasculitis, hypercalcemic states, pancreatic duct occlusion by parasites
Pathophysiology
- Duct obstruction
  - Interstitial edema → impaired blood flow ischemia → acinar cell injury
- Direct acinar cell injury
  - Release of intracellular enzymes/lysosomal hydrolases → intracellular enzyme activation → acinar cell injury
- Defective intracellular transport
  - Delivery of proenzymes to lysosomes → intracellular enzyme activation → acinar cell injury

Clinical Features
- Abdominal pain
- Systemic organ failure (5% fatal)
  - Shock, ARDS, Acute renal failure
- DIC
- Infection
- Pancreatic abscess
- Pancreatic pseudocyst
- Duodenal obstruction

Lab Features
- Serum amylase increased
  - 2-12 hrs, peak 24 hrs, duration 48-72 hrs
- Serum lipase increased
  - 2-6 hrs, peak 24 hrs, duration 7-10 days
- Amylase/creatinine clearance increased
  - 1-2 days, duration 7-10 days

Morphology
- Microvascular leakage causing edema
- Necrosis of fat by lipolytic enzymes
- Acute inflammation
- Proteolytic destruction of parenchyma
- Destruction of blood vessels causing interstitial hemorrhage

Acute Pancreatitis (Gross)

Hemorrhagic Necrosis
Acute Pancreatitis

Fat Necrosis

Acute Pancreatitis

Ischemic Necrosis

chronic pancreatitis

- Alcoholism, middle-aged men
- Pathophysiology
  - Ductal obstruction
  - Secreted proteins (lipolysin/cystatin c)
  - Oxidative stress
  - Interstitial fibrosis
  - Protein-calorie malnutrition

The sentinel acute pancreatitis event (SAPE) hypothesis for development of chronic pancreatitis. A critical episode of acute pancreatitis activates cytokine-induced transformation of pancreatic stellate cells (PSC), which results in collagen production and fibrosis. (from Whitcomb.97)
**Clinical Features**
- Recurrent abdominal pain
- Pancreatic insufficiency
- Pseudocyst
- Duct obstruction
- Malabsorption, steatorrhea
- Diabetes

**Lab Features**
- Serum amylase, up/down/nml
- Serum lipase, up/down/nml
- Benitiromide test
  - Hydrolysis by chymotrypsin of the tripeptide BTP

**Morphology**
- Fibrosis
- Islet sparing
- Duct obstruction

**Chronic Pancreatitis (Gross)**
- Fibrosis

**Chronic Pancreatitis**
Endocrine Cell Proliferation

Pancreatic Psuedocyst
- Almost all arise after acute or chronic pancreatitis
- Usual single (5-10 cm)
- Formed by drainage of secretions from damaged walled off areas

Extensive pseudocyst disease. A CT scan in a patient with alcoholic chronic pancreatitis demonstrates multiloculated pseudocyst disease.

Pancreatic Psuedocyst

Pseudocyst Wall

Cystic Tumors
- Less than 5% pancreatic neoplasms
- Elderly women
- Body and tail

Microcystic Adenoma (Gross)
Carcinoma of Pancreas

- 5th cause of death USA
- Low 5 year survival
- Smoking (2-5X risk)
- ? Chronic pancreatitis, alcohol, fatty diets, diabetes
- 90% pt mutation codon 12 K-ras
- 60-80% mutation p53

Clinical Features

- Abdominal pain
- Obstructive jaundice 50% (head of pancreas)
- Weight loss, anorexia, malaise and weakness
- Migratory thrombophlebitis (Trousseau sign) 10%
- Elevated CA19-9

Morphology

- 60% head, 15% body, 5% tail, 20% diffuse
- AdenoCA of duct epithelial origin
  - Adenosquamous pattern
  - Sarcomatoid
  - Acinar cell CA

Pancreatic Adenocarcinoma (Gross)

Pancreatic Adenocarcinoma
Islet Cell Tumor

- Adults
- Benign or malignant
- Head, body and tail (smaller than 2 cm)
- Hormones
  - Insulinoma (most common, 10% malignant)
  - Attacks of hyperglycemia (blood glucose >50 mg/dl)
  - Gastrinomas (up to 50% malignant)
  - Hypersecretion of gastric acid and severe peptic ulcers (Zollinger-Ellison Syndrome)
Diabetes Mellitus

Clinical diabetes mellitus is a syndrome of disordered metabolism with inappropriate hyperglycemia due either to an absolute deficiency of insulin secretion or a reduction in the biologic effectiveness of insulin (or both).

Classification of Diabetes

I. Type 1 diabetes (-cell destruction, usually leading to absolute insulin deficiency)
   A. Immune-mediated
   B. Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)

III. Other specific types of diabetes
   A. Genetic defects of -cell function characterized by mutations in:
      1. Hepatocyte nuclear transcription factor (HNF) 4 (MODY 1)
      2. Glucokinase (MODY 2)
      3. HNF-1 (MODY 3)
      4. Insulin promoter factor (IPF) 1 (MODY 4)
      5. HNF-1 (MODY 5)
      6. Neurul (MODY 6)
      7. Mitochondrial DNA
      8. Proinsulin or insulin conversion
      9. Genetic defects in insulin action
         1. Type A insulin resistance
         2. Leptachauism
         3. Rabson-Mendenhall syndrome
         4. Lipodystrophy syndromes

IV. Gestational diabetes mellitus (GDM)

V. Diseases of the exocrine pancreas—pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemorrhorhages, fibrocystic pancreatitis

VI. Endocrinopathies—acromegaly, Cushing’s syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma

VII. Drug- or chemical-induced—Vasopressin, genticin, nitric acid

VIII. Other genetic syndromes sometimes associated with diabetes—Down’s syndrome, Klinefelter’s syndrome, Turner’s syndrome, Wilm’s syndrome, Friedreich’s ataxia, Huntington’s chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, parathyria, Prader-Willi syndrome
Hyperglycemia

Table 17-8. Clinical Features of Diabetes at Diagnosis

<table>
<thead>
<tr>
<th>Type of Diabetes</th>
<th>Normal glucose tolerance</th>
<th>Impaired fasting glucose or impaired glucose tolerance</th>
<th>Insulin required for</th>
<th>Diabetes Mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Normal glucose tolerance</td>
<td>Impaired fasting glucose or impaired glucose tolerance</td>
<td>Insulin required for</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>Type 2</td>
<td>Normal glucose tolerance</td>
<td>Impaired fasting glucose or impaired glucose tolerance</td>
<td>Insulin required for</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>Other</td>
<td>Normal glucose tolerance</td>
<td>Impaired fasting glucose or impaired glucose tolerance</td>
<td>Insulin required for</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>Gestational</td>
<td>Normal glucose tolerance</td>
<td>Impaired fasting glucose or impaired glucose tolerance</td>
<td>Insulin required for</td>
<td>Diabetes Mellitus</td>
</tr>
</tbody>
</table>

Acute Complications

Chronic Complications

Table 522-3. Manifestations of Diabetic Embolization

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Black stools</td>
</tr>
<tr>
<td>Black stools</td>
<td>Faintness</td>
</tr>
<tr>
<td>Faintness</td>
<td>Confusion</td>
</tr>
<tr>
<td>Confusion</td>
<td>Diaphoresis</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>Shock</td>
</tr>
<tr>
<td>Shock</td>
<td>Death</td>
</tr>
</tbody>
</table>

NAD: Nicotinic acid
6PGD = glyceraldehyde-3-phosphate dehydrogenase
PARP = poly(ADP-ribose) polymerase
ADPR = polymerized ADP-ribose
HEAD AND NECK PATHOLOGY

Steve Nandkumar, M.D.
HEAD AND NECK PATHOLOGY

ORAL CAVITY

The oral mucosa is usually well protected by the following defenses:
– Competitive suppression of potential pathogens by organisms
– Secretory IgA and other IgGs produced by lymphocytes/plasma cells
– Antibacterial effects of saliva
– Diluting and irrigating effects of water (drinks) and food. Failure of these defenses can cause infections

INFLAMMATIONS

I. HERPES SIMPLEX VIRUS INFECTIONS
– caused by HSV-1 (herpes simplex virus type 1) and sometimes by HSV-2 (genital herpes)

Primary Infections
– usually occur in children 2 to 4 years old (following droplet infection).

They are mostly asymptomatic
– in 10% to 20% of cases, there is acute gingivostomatitis with fever and lymphadenopathy.
– morphology consists of vesicles, bullae, which rupture to form painful, shallow ulcers
– microscopically there is acantholysis with epidermal cells containing eosinophilic INTRANUCLEAR INCLUSIONS mononuclear cells or multinuclear giant cells are seen on TZANCK TEST (cell scrapings of lesions examined by cytologic stains)
– lesions heal spontaneously within 3-4 weeks; virus may however travel via nerves and reside in the local ganglia (trigeminal) in a dormant state
– virus may be reactivated by exposure to cold, wind, sunlight, allergic reactions, URTI, pregnancy, immunosuppression, etc.
– in adults, reactivation causes COLD SORES

Recurrent infections
– herpetic labialis, stomatitis, etc. with features of vesicles and ulcers occur. They are milder and usually heal within 7 days.

II. APHTHOUS ULCERS (CANKER SORES)
– common in first two decades of life; affects 40% of U.S. population
– cause is obscure; may be prevalent in some families
– single or multiple, painful, recurrent, superficial ulcerations of oral mucosa
– inflammation seen is nonspecific
– lesions heal spontaneously within 7-10 days or may persist for weeks
– Recurrent lesions are associated with celiac disease, inflammatory bowel disease etc.

III. ORAL CANDIDIASIS (THRUSH OR MONILIASIS)
Candida organisms (yeast) are components of the normal flora of the oral cavity in 50% of cases
– Candidiasis (oral lesions) occurs in immune incompetent patients, HIV, diabetes mellitus, neutropenia, xerostomia, general debility, and antibiotic therapy

Figure 31-24. The oral cavity, soft palate, and palatine tonsils. The palatoglossal arch partly hides the tonsil; the palatopharyngeal arch, visible above, is hidden by the tonsil below.
Candidiasis consists of 3 types:
- pseudomembranous
- erythematous
- hyperplastic

**Pseudomembranous type:** lesions consist of an inflammatory membrane containing many matted candida, fibrinopurulent exudates covering a red, inflamed base (appears as a plaque-like white, curd-like adherent membrane)

IV. **GLOSSITIS**
Inflammation of the tongue
- occurs in deficiencies of vitamin B₁₂, riboflavin, niacin, pyridoxine, iron; sometimes seen in sprue, syphilis, and trauma due to dentures, chemicals, etc.
- tongue is beefy red with atrophy of papillae and mucosa exposing underlying vasculature; ulcers may occur.

V. **XEROSTOMIA**
- means dry mouth
- occurs in Sjögren’s syndrome, following radiation, or drug use
- oral mucosa is **D R Y** with fissuring and ulcerations

VI. **HAIRY LEUKOPLAKIA - CAUSED BY EBV**
- occurs in immune suppressed or immuno compromised states, e.g., following cancer therapy, post transplantation, etc. (20% of cases) and HIV (80% of cases)
- an uncommon white, confluent patch of thick, hairy (fluffy) lesion on the oral mucosa/lateral border of tongue
- microscopically, there are keratotic squames arranged in layers over an acanthotic mucosa; koilocytosis (koilos = hollow, cytos = cell) may be noted
- lesions associated with HPV, HIV (80% of cases), also candida organisms
- **HAIRY LEUKOPLAKIA (80% of cases) IS VIRTUALLY RESTRICTED TO HIV INFECTIONS** and may antedate HIV, which usually appears in two to three years

**SOFT TISSUE LESIONS**

These present as masses, are **R E A C T I V E** in nature, and represent inflammations and benign hyperplasias caused by irritation or any unknown mechanisms.

I. **IRRITATION FIBROMA (61% of cases)**
- occurs at the gingivodental margin (bite line) in the buccal mucosa
- consists of a nodular, fibrous tissue mass with a few inflammatory cells covered by squamous mucosa

II. **PYOGENIC GRANULOMA (PREGNANCY TUMOR) (12% of cases)**
- occurs in young children, adults, and pregnant women
- presents as a highly vascular, pedunculated, gingival mass
- resembles a capillary hemangioma
- microscopically, reveals fibrous stroma with many endothelium lined vascular spaces; (looks like granulation tissue); inflammation noted
- lesion can bleed, ulcerate, grow rapidly
- may regress or become fibrous (peripheral ossifying fibroma)
- treatment is surgical excision
NOTE: Peripheral ossifying fibroma (22% of cases) may or may not arise from a previous pyogenic granuloma. Rx is surgical. Recurrence rate is 15% to 20%

III. PERIPHERAL GIANT CELL GRANULOMA (GIANT CELL EPULIS) (5% of cases)
- an inflammatory mass in the gingiva; occurs following chronic inflammation
- covered by intact gingival mucosa, or may be ulcerated
- microscopically, there are many foreign body-like giant cells scattered in a fibrous, vascular stroma; chronic inflammatory cells and hemosiderinophages are seen.
- treatment by surgical excision

IV. MUCOCELE (MUCOUS RETENTION CYST)
- occurs in the lower lip as a raised, circumscribed bluish mass
- involves trauma to a salivary duct with obstruction and/or spillage of secretion into surrounding tissue
- Treatment: Excision of cyst with removal of involved salivary gland

V. RANULA
- a form of mucocele, occurs in the floor of the mouth
- there is duct blockage with cyst-like dilatation of sublingual glands
- presents as a mass, usually on one side
- microscopically, the cyst has a lining of fibroconnective tissue or granulation tissue with the lumen containing mucin and inflammatory cells.
- treatment is by unroofing the cyst or by simple excision (including part of sublingual gland)

WHITE LESIONS

I. LEUKOPLAKIA
Leukos = white
Plax = plaque like

It is defined simply as a white plaque or patch on the oral mucous membranes. It cannot be removed by scraping and is used as a loose “clinical term” without any histologic connotation.
- 85% to 90% of white plaques are caused by epidermal proliferation
- These plaques may range from benign to atypical/dysplastic to carcinoma in situ to malignant lesions
- All leukoplakic lesions must be considered precancerous or malignant unless proved otherwise; hence, a definite diagnosis is made by BIOPSY ALONE!

ETIOLOGY
The cause is multifactorial. Tobacco use is the MOST COMMON followed by alcohol, local irritation, ill-fitting dentures, etc. HPV has been identified in tobacco-related lesions.

CLINICAL FEATURES
- Usually between 40 to 70 years of age
- M:F = 2:1
- Can occur as solitary or multiple white plaques indistinct or sharply demarcated, thick, smooth, wrinkled, or indurated
- Common sites involved are buccal mucosa, floor of mouth, tongue, lower lip, hard palate, gingiva
- Microscopically, the lesions may vary from hyperkeratosis and acanthosis without atypia in 80% of cases to dysplasia and carcinoma in situ/overt carcinoma in 5% to 25% of cases
- Nonspecific lymphocytic and macrophage infiltration is seen under the lesion
TREATMENT
- Identify and eliminate risk factors such as tobacco use or alcohol consumption
- If lesions persist, despite removal of risk factors, AN INCISIONAL OR EXCISIONAL BIOPSY IS WARRANTED followed by definitive treatment as needed

Erythroplakia
Also called dysplastic leukoplakia, it presents as a red, velvety, eroded lesion with poorly defined irregular borders. The clinical features are similar to those of leukoplakia. However, this lesion is much more atypical than leukoplakias and has a much higher risk of malignant transformation (more than 90%). “Speckled leukoerythroplakia” combines features of both erythroplakia and leukoplakia. Treatment is the same as for leukoplakia.

II. CARCINOMA OF ORAL CAVITY
Squamous cell carcinoma (95% of cases) is the MOST COMMON malignant neoplasm of the oral cavity.
- 3% of all cancers in the U.S.
- Though readily accessible to discovery and biopsy, many cancers are detected late and hence the survival rate is low
- Also such patients develop MULTIPLE OTHER TUMORS (at the rate of 3% to 7% per year) elsewhere (field cancerization effect). These second primary tumors are the most common cause of death.

ETIOLOGY
- The most common cause is use of tobacco (smoking, chewing, and buccal pouches) – two to four times the risk for carcinoma.
- Other causes are:
  - Alcohol (smoking and drinking) – six to fifteen times the risk
  - Use of betel nuts and paan (India), marijuana, etc., also chronic irritation and infection
  - HPV (16, 18, and 33 subtypes) – HPV positive tumours have a better prognosis
  - Sunlight (actinic radiation) and pipe smoking predispose to cancer of lower lip
  - Genetic changes (chromosomal deletions, mutations, etc. involving p16, p53, p63; cyclin D1, EGFR overexpression; Notch 1).
  - Family history of head and neck cancer

MORPHOLOGY
Cancers usually occur in the vermilion border of lower lip, floor of the mouth, tongue lateral border, hard palate, soft palate, gingiva and base of tongue (descending order of frequency).
- Present as raised, firm, pearly white plaques or verrucous areas of thickening (leukoplakia, erythroplakia) or as a painless, non-healing ulcerating mass with indurated margins
- Microscopically, the squamous cell carcinomas may be well differentiated keratinizing to poorly differentiated anaplastic types with INVASION
- Metastases to regional lymph nodes, liver, lungs, and bones occur (more so with cancers in the floor of mouth 60%, and base of tongue 50%, lower lip cancers rarely metastasize)

CLINICAL FEATURES
Occurs between 40 to 80 years of age
- Males greater than females
- Asymptomatic lesions, painless or painful masses/ulcers

PROGNOSIS
- Depends on the size of tumor (≤ 2 cm better prognosis)
- Nodal involvements and metastases (TNM staging)
- With treatment, lip lesions → five-year survival rate is 90%
  Floor of mouth, tongue lesions → five-year survival rate is 20% to 30%
Other white lesions of the oral cavity include keratoacanthoma, Lichen planus, aspirin burn, oral candidiasis, and nicotinic stomatitis.

**NOSE**

![Diagram of the interior of the pharynx and nose](image)

Figure 34-4. Interior of the pharynx

The common inflammatory disorders are infectious rhinitis (common cold), allergic rhinitis (hayfever), nasal polyps, chronic rhinitis and sinusitis.

**LETHAL MIDLINE GRANULOMA (POLYMORPHIC RETICULOSIS)**

- It is an angiocentric non-Hodgkin’s lymphoma; common in China
- The tumor cells are T cells/NK (natural killer) cells; CD16, CD56, CD2, and CD3 are expressed; highly associated with EBV
- Presents as ulcerating, destructive masses involving the nose and paranasal cavities with erosion of cartilage, bone and soft tissues; secondary infections, rhinitis, sinusitis occur
- Tumor cells are angiocentric (surround blood vessels) and angioinvasive causing luminal growth and occlusion with downstream ischemia; tumor related granulomatous inflammation noted.
- Lymphomas may be present concurrently elsewhere
- Hemophagocytic syndrome occurs (histiocytes phagocytose blood and blood cells)
- Treatment for lymphoma is effective

5
NASOPHARYNX

TUMORS OF NASOPHARYNX

Inverted Papilloma (Sinonasal or Schneiderian papilloma)
- A benign, but locally aggressive tumor, occurring in nose and paranasal sinuses; may be associated with HPV, types 6 and 11
- Papillomatous squamous epithelial proliferation that is inward growing into the mucosa (hence, INVERTED). Other forms such as exophytic and cylindrical exist.
- Can RECUR and invade orbit or skull if inadequately excised; rarely a frank carcinoma may arise

Olfactory Neuroblastoma (Esthesioneuroblastoma)
- Tumor originates from neuroendocrine cells in the olfactory mucosa
- Located in the superior and lateral part of nose
- Composed of lobular nests of small round cells surrounded by vascular stroma
- Cells stain for S-100 protein, chromogranin, synaptophysin, NSE (neuron specific enolase) and CD56 (on immunohistochemical stain)
- E.M. shows membrane-bound secretory granules
- Tumors look like lymphoma, Ewing’s sarcoma, embryonal rhabdomyosarcoma, neuroblastoma, and primitive neuroectodermal tumor (PNET)
- Highly malignant, tends to metastasize widely
- Five-year survival rate is 40 to 90%

Nasopharyngeal Carcinoma
- Most common cancer in African children, most common in South China adults, uncommon in U.S.
- Environmental role: migrating from a high incidence to a low incidence area decreases incidence
- E.B.V. genome identified in tumor epithelial cells; E.B.V. IgA present in serum (85% of cases)
- Morphologically, tumors are present as masses; also occur in the tonsil, posterior tongue, or upper airways
- Microscopic patterns
  - Keratinizing squamous cell carcinoma
  - Non-keratinizing squamous cell carcinoma
  - Undifferentiated carcinoma
  The undifferentiated tumor is composed of large epithelial cells arranged in syncytium-like nests. The nuclei are round, vesicular, and reveal prominent nucleoli. Many admixed mature T lymphocytes are seen (hence tumor is called LYMPHOEPITHELIOMA)
- The tumor grows silently and often spreads to lymph nodes (70%) and other sites (orbit, cranial cavity and base of skull)
- Radiation therapy (choice of Rx): undifferentiated carcinoma is more sensitive than the other types (keratinizing SCC is the least)
- Three-year survival rate is 50% to 70%
LARYNX

Vocal Cord Nodules (Polyps)
- These reactive BENIGN nodules are more common in men than women
- Associated with heavy smokers/singers (SINGER’S NODULES)
- Smooth, round sessile or pedunculated masses located on the true vocal cords; may ulcerate
- Microscopically, reveal a loose myxoid, fibrovascular connective tissue core covered by a keratotic/hyperplastic/dysplastic squamous epithelium; inflammation present
- Clinically causes hoarseness of voice
- Nodules are bilateral whereas polyps are unilateral

Treatment
- Remove irritant, stop smoking, voice rest
- Simple excision

TUMORS OF LARYNX

I. LARYNGEAL SQUAMOUS PAPILLOMA/PAPILLOMATOSIS
- These are benign tumors: small, soft, single (in adults), or multiple (in children) masses, less than 1 cm in size occurring on true vocal cords
- May ulcerate and cause hemoptysis; hoarseness noted
- Associated with HPV types 6 and 11
- Lesions show finger-like projections of benign squamous epithelium surrounding a central fibrovascular core
- Lesions may regress spontaneously at puberty or may be surgically excised
- They may recur leading to several surgeries

II. CARCINOMA OF LARYNX
- 2% of all cancers
- M:F = 7:1
- Occurs usually after 40 years of age
- Risk factors include: smoking (tobacco), alcohol, asbestos, nutrition deficiency; irradiation, and HPV (5% of cases)
MORPHOLOGY

95% of cancers are squamous cell carcinomas.
- Tumors appear as smooth, white or red thickenings, or irregular verrucous, or ulcerated lesions, or fungating masses
- Tumors may be:  
  - GLOTTIC  60% to 75%
  - SUPRAGLOTTIC  25% to 40%
  - SUBGLOTTIC  < 5%
- Besides the vocal cords, tumors may originate on the epiglottis, aryepiglottic folds, or pyriform sinuses
- Microscopically, lesions may occur as a spectrum:

Epithelial Hyperplasia → Mild Dysplasia → Moderate Dysplasia

```
                 Keratinizing S.C.C.
                        ↓
              Severe Dysplasia or C.I.S.
                 Non-Keratinizing S.C.C. ← Invasive Carcinoma
```

- THE RISK OF DEVELOPING AN OVERT CANCER IS DIRECTLY PROPORTIONAL TO THE LEVEL OF ATYPIA WHEN THE LESION IS FIRST SEEN. BIOPSY IS A MUST FOR DIAGNOSIS

CLINICAL FEATURES
- Hoarseness (most common), pain, dysphonia, hemoptysis, or even dysphagia

Course and Prognosis
The prognostic factors are:

A. Location of Tumor
- Supraglottic → rich lymphatic supply; so there is more spread (30% to lymph nodes)
- Glottic → sparse lymphatics; so spread is uncommon
- Subglottic → presents as clinically quiet lesions; hence, diagnosed late (presents in an advanced state)

B. Staging
INTRINSIC TUMORS → (confined to larynx, 60% of cases) have a better prognosis than EXTRINSIC TUMORS (spread beyond the larynx). TNM STAGE IS IMPORTANT

TREATMENT

Surgery, radiation, or combined therapy:
- Five-year survival rates are: 80% (glottic), 65% (supraglottic), 40% (subglottic)
- One-third of patients die of cancer due to secondary infections, metastases and cachexia
EAR

Infections and inflammations such as otitis media occur in infants and children. Viruses and bacteria such as S. pneumoniae, H. influenza, B. hemolytic strep (ACUTE INFECTIONS) and Pseudomonas aeruginosa, Staph aureus, fungi (CHRONIC INFECTIONS) are causative

I. CHOLESTEATOMA
   - Associated with chronic otitis media
   - A cyst, 1 to 4 cm in size, lined by keratinizing squamous epithelium or metaplastic mucus secreting epithelium; lumen filled with amorphous debris and squames/cholesterol
   - Cysts may rupture with secondary inflammation and reactive giant cells
   - Cysts may enlarge to form soft tissue masses and may even ERODE the ossicles, labyrinth, bone, etc.
   - Treatment is by surgical excision

II. OTOSCLEROSIS
   - There is ABNORMAL BONE DEPOSITION IN THE MIDDLE EAR involving the rim of oval window where the footplate of stapes rests
   - Uncoupling of bone resorption and bone formation leads to a slowly progressive fibrosis, ankylosis and bone overgrowth immobilizing middle ear bone (stapes) leading to HEARING LOSS
   - Occurs in young to middle-aged adults; may be familial, autosomal dominant

SALIVARY GLANDS

There are major (parotid, submandibular, and sublingual) and minor salivary glands.

Figure 31-19. Superficial relations of the parotid gland and the branches of the facial nerve on the face and in the neck.
INFLAMMATION (SIALADENITIS)

INFLAMMATION (SIALADENITIS)

Sialadenitis may be due to: Virus, Bacteria, and Autoimmune Disease (e.g., Sjogren syndrome).

Nonspecific Sialadenitis
- Associated with ductal obstruction due to stones (sialolithiasis) affecting the submandibular gland
- Staph. aureus and Strep viridans are the common organisms causing inflammation
- Dehydration, medicines, etc., can cause decreased salivary function aggravating sialadenitis
- Gland is usually UNILATERALLY, painfully enlarged with purulent discharge
- Nonspecific interstitial inflammation or suppurative necrosis and abscess formation are noted
- Treatment is medical or surgical

TUMORS OF THE SALIVARY GLANDS
Tumors of the salivary glands constitute a heterogeneous group of lesions of great morphologic variations and originate in both the major and minor salivary glands.

Classification

The common tumors are:
- Pleomorphic adenoma (mixed tumor) 50% BENIGN
- Warthin’s tumor 10% BENIGN
- Mucoepidermoid carcinoma 15% MALIGNANT
- Adenocarcinoma (NOS) * 10% MALIGNANT
- Adenoid cystic carcinoma 5% MALIGNANT
- Malignant mixed tumor 3 to 5% MALIGNANT

* NOS – not otherwise specified

NOTE:
- 80% of the tumors arise in the PAROTID GLAND
- 15% to 30% of tumors in the PAROTID are MALIGNANT
- 70% to 90% of tumors in the sublingual glands are MALIGNANT, i.e., (malignancy is inversely proportional to size of the gland)
- TUMORS are common between 50 to 70 years of age
- M:F = 1:1 usually

A. Pleomorphic Adenoma
- Most common tumor of both the major and minor salivary glands; 60% of tumors in the parotid gland, radiation exposure increases risk.
- PLAG1 (pleomorphic adenoma gene) overexpression causes cell proliferation → tumor
- Morphologically, a round, well-circumscribed demarcated “encapsulated” slow growing mass
- Microscopically, composed of EPITHELIAL/MYOEPITHELIAL elements arranged as ducts, nests, or acini scattered in a MESENCHYMAL MATRIX of myxoid, chondroid, hyaline, and osseous tissue (presents a varied pattern and hence called a “mixed” tumor)
- ALL CHANGES SEEN ARE BENIGN
- HISTOGENESIS of tumor is MYOEPITHELIAL OR DUCTAL RESERVE CELL
- Clinically, tumor presents as a painless, mobile, discrete mass; there is usually tumor infiltration beyond “capsule”; hence, ENUCLEATION ALONE will not suffice (recurrence rate is 25%)
- TREATMENT is excision of the gland (with free margins). Sometimes facial nerve may have to be sacrificed!
- MALIGNANT TRANSFORMATION can occur in a benign mixed tumor called CARCINOMA EX PLEOMORPHIC ADENOMA. The incidence is about 10% for tumors of more than 15 years duration. This malignant mixed tumor is very aggressive with a 30% to 50% mortality rate in five years.
B. **Warthin’s Tumor (Papillary Cystadenoma Lymphomatosum)**
   - Arises almost always in the parotid gland
   - More common in males than females
   - More common in smokers (eight times the risk) than non-smokers
   - Morphologically, the tumor (also called an **ADENOLYMPHOMA**) is a round, encapsulated mass occurring in the superficial parotid gland; cysts or clefts with secretions are seen
   - Microscopically, the cystic spaces are lined by papillary projections of double layered epithelium [surface columnar cells with eosinophilic cytoplasm (oncocyes) resting on cuboidal cells] with a surrounding lymphoid stroma with germinal centers. Secretory cells are also seen in the columnar cell layer
   - **HISTOGENESIS** is unsure. It is thought to represent a heterotopic salivary tissue trapped in a regional lymph node which is then incorporated in the salivary gland, during embryogenesis. Presence in “node” not to be considered a metastasis
   - Treatment is surgical excision. Recurrence rate is 2%

C. **Mucoepidermoid Carcinoma**
   - Most common **MALIGNANT** salivary gland tumor
   - 60% to 70% of tumors occur in the parotid
   - Most common radiation induced neoplasm
   - Morphologically consists of a circumscribed tan to gray mass with poor encapsulation and **INfiltrATION** of the margins
   - Microscopically, tumors are composed of cords, sheets, or cysts of squamous, mucous or hybrid (squamous plus mucous) cells; **mucin stain is positive**. There are three grades as follows:
     - Low grade tumor – composed largely of mucous cells (gland pattern)
     - Intermediate grade – hybrid cells
     - High grade – composed largely of squamous cells with **focal** mucin production (can be mistaken for squamous cell carcinoma alone)
   - **Treatment:** Surgical excision and radiation in high-grade cancer
   - **Prognosis**
     - Low grade tumor → low recurrence rate 15%, rare metastases; five-year survival rate is 90%
     - Intermediate and high grade tumors → recur and metastasize in 30% of cases; five-year survival rate is 50%

D. **Adenoid Cystic Carcinoma**
   - Most common in the minor salivary glands (palate); also in nose, sinuses, upper airways
   - Presents as a small, poorly encapsulated, infiltrative, gray-pink mass
   - Microscopically, tumor cells present a cribriform, glandular pattern with cystic spaces (lumen) containing “secretions” (actually **hyaline material** representing excess basement membrane); individual tumor cells are small with dark nuclei and scanty cytoplasm
   - Clinically, a slow growing, painful tumor with tendency to **invade nerves**; stubbornly recurrent
   - Tumors may metastasize (50% of cases) to liver, bone, and brain
   - Treatment is surgical excision with radiation when necessary
   - Five year survival rate is 60% to 70%; drops to 15% at 15 years.

**MINOR SALIVARY GLAND TUMORS HAVE A POORER PROGNOSIS THAN THOSE OF MAJOR GLANDS**

**NOTE:** MECT 1 (Mucoepidermoid carcinoma translocated) and MAML 2 (Master molecule like) genes’ fusion t (11;19) results in an abnormal protein that affects Notch and c-AMP signaling pathways leading to tumourigenesis in Warthin’s and Mucoepidermoid Ca.
THE PITUITARY GLAND

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Objectives: See college objectives
THE PITUITARY GLAND

I. THE PITUITARY GLAND

– Often called the “Master Gland”
– Significant impact on various organ and endocrine systems
– Located at the base of the brain in the sella turcica, just posterior to the optic chiasm
– Approximately 1 cm in greatest dimension normally

A. Divided into:
   – anterior pituitary (adenohypophysis).
   – posterior pituitary (neurohypophysis).
   (See attached diagrams on pages 6 and 7)

II. THE ANTERIOR PITUITARY

A. Portal vascular system from the hypothalamus that allows for direct blood flow for the hypothalamic releasing hormones into the anterior portion of the gland

B. Constitutes approximately 80% of the gland, by volume

C. Derived from Rathke’s pouch

D. Composed of various cells based on morphologic staining characteristics
   1. Acidophils (eosinophilic or pink)
   2. Basophils basophilic or blue)
   3. Chromophobes (poorly staining)

E. Cell types based on hormone production
   1. Somatotrophs: produce growth hormone; constitute approximately half of all the hormone producing cells in the anterior pituitary.
   2. Lactotrophs: produce prolactin; essential for lactation
   3. Corticotrophs:
      a. Adrenocorticotropic hormone (ACTH)
      b. Pro-opiomelanocortin
      c. Melanocyte-stimulating hormone (MSH)
      d. Endorphins
      e. Lipotropin
   4. Thyrotrophs: thyroid stimulating hormone (TSH)
   5. Gonadotrophs:
      a. Follicle stimulating hormone (FSH)
      b. Luteinizing hormone (LH)

III. THE POSTERIOR PITUITARY

A. Consists of modified glial cells called pituicytes

B. Derived from the downward migration of the floor of the 3rd ventricle of the brain
C. Axonal processes extending from nerves located in the supraoptic and paraventricular nuclei of the hypothalamus through the pituitary stalk.

D. Releases two hormones:
   1. **Oxytocin**: stimulates milk let down during lactation and induces uterine contractions during labor.
   2. **Antidiuretic Hormone (ADH)**, also known as vasopressin: stimulates the kidney to resorb water in the process of making urine.

IV. HYPERPITUITARISM

   A. **Hyperpituitarism**: defined as abnormally increased secretion of pituitary hormones.
   
   B. Most often hyperpituitarism is caused by a functional adenoma (benign) within the anterior lobe.
   
   C. Less often due to hyperplasia (benign) or carcinoma (malignant) of the anterior lobe.
   
   D. Mass effect will also cause signs and symptoms
      1. Enlargement of the sella turcica
      2. Visual field abnormalities (e.g., bitemporal hemianopsia)
      3. Increased intracranial pressure, which can lead to papilledema and headaches

V. PITUITARY ADENOMAS

   A. Usually composed of a single cell type and produce excess of a single dominant hormone; some single cell types may produce more than one hormone
   
   B. Comprise about 10% of intracranial neoplasms
   
   C. Found incidentally in up to 25% of routine autopsies
   
   D. Peak incidence from 30–50 years old
   
   E. Most cases of adenomas occur as isolated neoplasms, but about 3% are associated with Multiple Endocrine Neoplasia (MEN) Type I
   
   F. **Microadenoma**: less than 1 cm in diameter
   
   G. **Macroadenoma**: 1 cm or greater
   
   H. Non-functioning adenomas are more likely to be diagnosed at a later stage, hence they tend to be larger than functioning adenomas at the time of diagnosis.
   
   I. The majority of adenomas are monoclonal in origin, indicating they arise from a single abnormal somatic cell.
Pathology M-2 –The Pituitary Gland

<table>
<thead>
<tr>
<th>Prolactin Adenoma</th>
<th>20–30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth Hormone (GH)</td>
<td>15%</td>
</tr>
<tr>
<td>GH + Prolactin</td>
<td>5%</td>
</tr>
<tr>
<td>ACTH</td>
<td>10–15%</td>
</tr>
<tr>
<td>Gonadotrophin producing</td>
<td>10–15%</td>
</tr>
<tr>
<td>Null cell adenoma</td>
<td>20%</td>
</tr>
<tr>
<td>TSH producing</td>
<td>1%</td>
</tr>
<tr>
<td>Other pleurihormonal</td>
<td>15%</td>
</tr>
</tbody>
</table>

J. Types

1. **Prolactinomas**
   a. Variable in size
   b. Prolactin levels correlate with size of the adenoma
   c. Cause amenorrhea, galactorrhea, loss of libido, infertility
   d. Diagnosis more readily made in younger women (20–40 y/o) because of the sensitivity of menses to effect of prolactin
   e. Symptoms are more subtle in men and older females
   f. Can be treated with bromocriptine, a dopamine receptor agonist, causing reduction in size of neoplasm.
   g. Hyperprolactinemia – causes include:
      (1) Pituitary adenomas
      (2) Pregnancy
      (3) Significant stress
      (4) Lack of dopamine inhibition on the lactotrophs
         (i) Head trauma
         (ii) “Stalk effect” of suprasellar region (mild hyperprolactinemia)
         (iii) Drugs: reserpine, anti-psychotic meds
      (5) Estrogens, renal failure, hypothyroidism

2. **Growth Hormone (Somatotroph Cell) Adenomas**
   a. Second most common functioning pituitary adenoma
   b. ↑ hepatic insulin-like growth factor I (IGF-I)
   c. In children, results in *gigantism* before epiphyseal plate closure
   d. In adults, results in *acromegaly*
      (1) Acromegaly associated with:
         (i) Enlargement of the jaw and protrusion (prognathism)
         (ii) Enlarged hands and feet
         (iii) Gonadal dysfunction, diabetes mellitus, generalized muscle weakness, hypertension, arthritis, congestive heart failure and increased risk of GI cancers

3. **Corticotroph Adenoma**
   a. Excess production of ACTH which leads to ↑ cortisol

**NOTE:** Hypercortisolism = **Cushing’s Syndrome**  

Hypercortisolism due to ↑ ACTH from the pituitary is known as **Cushing’s Disease**

b. Large pituitary adenomas can result if adrenals are removed for **Cushing’s Syndrome** (results in loss of inhibitory feedback by cortisol); this is known as **Nelson’s Syndrome**
c. Usually pre-existing microadenoma grows dramatically
d. Can present with hyperpigmentation secondary to ↑ ACTH effect

4. **Gonadotrophin producing adenoma (LH & FSH)**
   a. 10–15% of pituitary adenomas
   b. Often difficult to recognize because the hormone is secreted inefficiently or irregularly.
   c. Most often found in middle-aged men and women when they are large enough to produce neurologic/mass effects such as:
      1. Impaired vision, headaches, diplopia
      2. Sometimes hormone deficiencies can be found, commonly it will be ↓ LH, which leads to ↓ energy and libido in men secondary to ↓ in testosterone; will cause amenorrhea in women.

5. Thyrotrophin producing adenomas
   a. Rare: only 1% of all pituitary adenomas, hence a rare cause of hyperthyroidism

6. Some adenomas may release more than one hormone: mixed cell types or one cell type secreting more than one hormone.

7. Up to 20% of adenomas are “null cell adenomas”; they generate no detectable hormones.
   a. Typically present with mass effect
   b. May also produce hypopituitarism secondary to compression of residual normal pituitary

8. Pituitary carcinomas
   a. Very rare and most are non-functional
   b. Variable histology (from well-differentiated to poorly-differentiated or pleomorphic growth pattern)
   c. Requires demonstration of metastases to qualify as malignant (e.g., lymph nodes, bone, liver).

9. Pituitary adenomas and carcinoma
   a. Treatment involves surgical excision and radiation

**VI. HYPOPITUITARISM**

A. Defined as decreased secretion of pituitary hormones, which result from diseases of the pituitary or hypothalamus.

B. Occurs when 75% or more of the pituitary parenchyma is destroyed or absent (i.e., very rarely can be congenital).

C. Most cases arise from a destructive process of the pituitary gland.

D. Causes: tumors, surgery, radiation, Rathke cleft cyst, pituitary apoplexy, ischemic necrosis of pituitary and Sheehan’s Syndrome (post-partum necrosis of the anterior pituitary), Empty Sella Syndrome, genetic defects in the hormone production, tumors or conditions of the hypothalamus (e.g., sarcoidosis).

E. Pituitary apoplexy
   1. Rare complication of adenoma
   2. Acute, spontaneous hemorrhage into the pituitary
   3. Most often seen with null cell adenomas and ACTH producing adenomas.
   4. Neurosurgical emergency to relieve compression effects to pituitary and possibly hypothalamus.
F. Sheehan’s syndrome
   1. Most common form of clinically significant ischemic necrosis of the anterior pituitary
   2. During pregnancy, the anterior pituitary enlarges to almost twice-normal size, but the venous
      blood flow doesn’t really increase proportionally; a relative hypoxia develops
   3. Sudden infarction occurs with ↓ BP and/or hemorrhage into the pituitary
   4. Posterior pituitary is much less susceptible to ischemic injury and not usually effected.

G. Empty Sella Syndrome
   1. Any condition that destroys part or all of the pituitary
      a. **Primary empty sella**: defect in the diaphragma sellae allowing herniation of arachnoid
         and CSF into the sella with compression of pituitary (classic patient: obese, multiparous
         females)
      b. **Secondary empty sella**: gland or adenoma is removed or destroyed in treatment.

VII. POSTERIOR PITUITARY SYNDROMES

A. Diabetes insipidus: ADH deficiency
   1. Head trauma, tumors, and inflammatory conditions of the posterior pituitary
   2. Large amount of fluid loss—diuresis!

B. Syndrome of inappropriate ADH (SIADH)
   1. Excessive retention (resorption) of free water, which results in hyponatremia (↓ serum Na+)
   2. Most common cause is secretion of ADH or ADH-like substances by malignant neoplasms
      (small cell carcinoma), non-neoplastic conditions of the lung, or local injury of the
      hypothalamus, post, pit., or both
   3. Signs/symptoms: hyponatremia, cerebral edema and resultant neurologic dysfunction
   4. Blood volume remains normal and peripheral edema does not develop
   5. Treatment: water restriction, loop diuretics and salt tablets

VIII. HYPOTHALAMIC SUPRASELLAR TUMORS

A. Neoplasms in this location may induce hypo- or hyperfunction of the anterior pituitary, diabetes
   insipidus, or combination of conditions.

B. Most common neoplasms are gliomas and craniopharyngiomas.
1. BEGINNING FORMATION OF RATHKE'S POUCH AND INFUNDIBULAR PROCESS

2. NECK OF RATHKE'S POUCH CONSTRIC TED BY GROWTH OF MESODERM

3. RATHKE'S POUCH "PINCHED OFF"

4. "PINCHED OFF" SEGMENT CONFORMS TO NEURAL PROCESS, FORMING PARS DISTALIS, PARS INTERMEDIA AND PARS TUBERALIS

5. PARS TUBERALIS ENCIRCLES INFUNDIBULAR STALK (LATERAL SURFACE VIEW)

6. MATURE FORM
THE PARATHYROID GLAND

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Objectives: See college guidelines
THE PARATHYROID GLAND

I. THE PARATHYROID GLANDS

A. Derived from the developing pharyngeal pouches; the glands can be found anywhere along the descent of the pharyngeal pouches from the carotid sheath to the anterior mediastinum; normal human will have a total of four glands located just posterior to the thyroid lobes (two on each side).

B. ~10% of humans will have only two or three glands

C. Each gland will weigh ~35–40 mg.

D. Most of the gland is composed of chief cells, which contain secretory granules of parathyroid hormone (PTH).

E. Second type of cell present: oxyphil and transitional oxyphil are found throughout the gland.

F. Stromal fat increases in the gland through early life; by age 25 the maximum amount of stromal fat has developed; in a normal gland, ~30% of the gland is adipose.

II. PARATHYROID HORMONE (PTH) PHYSIOLOGY

A. Activity of the gland is influenced by the level of free (ionized) calcium in the blood.

B. PTH is synthesized and secreted in response to low calcium levels.

C. PTH
   1. activate osteoclasts.
   2. increase tubular resorption of calcium in the kidney.
   3. increase urinary phosphate excretion.
   4. stimulate GI calcium absorption.
   5. activate metabolic changes of vitamin D compounds in kidney.

III. HYPERCALCEMIA: ABNORMALLY HIGH SERUM CALCIUM

A. Certain malignancies can have associated elevated calcium (breast, lung, multiple myeloma) which is due to bone resorption and release of excessive calcium.

B. Bone resorption occurs secondary to:
   1. Osteolytic metastases and local cytokines
      a. tumor cells and inflammatory cells release cytokines which induce local osteolysis, e.g., TNF-α and IL-1, which both effect osteoclasts and their precursors
   2. Release of PTH-related protein (PTHrP)
      a. most frequent cause of non-metastatic solid tumors is release of PTHrP
      b. it is similar to PTH and appears to stimulate PTH receptors
      c. patients with PTHrP induced hypercalcemia are thought to have a poorer prognosis
IV. HYPERPARATHYROIDISM: PRIMARY, SECONDARY, TERTIARY (RARE)

A. **Primary hyperparathyroidism:** spontaneous, autonomous overproduction of PTH; very common endocrine disorder
   1. Adenoma 75% of cases (see below)
   2. Primary hyperplasia (diffuse or nodular) 10–15% of cases (see below)
   3. Parathyroid carcinoma < 5% of cases
   4. Disease generally of adults; more common in women than men
   5. Annual incidence is 25/100,000 in U.S. and Europe
   6. Effects mostly people 50 y/o and older
   7. ? associated with irradiation to head and neck 30–40 year prior
   8. Can be symptomatic or asymptomatic
      a. Symptoms classically stated as “Painful bones, renal stones, abdominal groans and psychic moans”
      b. Bone pain from fractured weakened bones (osteoporosis) or osteitis fibrosa cystica (cysts formation within the bones from osteoclast stimulation)
      c. Increased urinary calcium can lead to nephrocalcinosis and nephrolithiasis (found in 20% of newly diagnosed patients)
         i. **GI disturbances:** constipation, nausea, peptic ulcers pancreatitis and gall stones
         ii. **CNS disturbances:** depression, lethargy and eventually seizures
         iii. **Neuromuscular problems:** weakness and fatigue
         iv. **Cardiac abnormalities:** aortic and/or mitral valve calcifications

B. **Secondary hyperparathyroidism:** secondary response of elevated PTH in patients with chronic renal failure; caused by any condition which results in chronically low serum calcium levels which leads to compensatory overactivity of the parathyroid glands, which become hyperplastic
   1. Renal failure is by far the most common cause of secondary hyperparathyroidism.
   2. **Mechanism:** poor phosphate excretion which leads to elevated serum phosphate; elevated phosphate levels depress serum calcium; low calcium stimulates the parathyroid glands; in secondary hyperparathyroidism, the parathyroid glands are hyperplastic
   3. The symptoms of secondary hyperparathyroidism are generally less severe than with primary hyperparathyroidism.
   4. Vascular calcification associated with secondary hyperparathyroidism may result in significant ischemic damage to the skin and other organs; this is referred to as **calciphylaxis.**
   5. Other causes include inadequate calcium intake, steatorrhea (increased fat within the feces) and vitamin D deficiency.

C. **Tertiary hyperparathyroidism:** rare condition seen in patients with secondary hyperparathyroidism; parathyroids become autonomous in secretory activity; surgical excision seems to be the only way to control PTH levels

V. PARATHYROID ADENOMAS

A. Almost always solitary; usually demarcated margin from other normal parathyroid tissue.

B. Associated with hyperparathyroidism (elevated calcium)

C. Range from 0.5–5 grams

D. The other uninvolved glands are usually normal or smaller than normal.

E. ~10–20% will have the Parathyroid Adenoma 1 (PRAD 1) genetic defect.
F. Multiple Endocrine Neoplasia 1 (MEN I): homozygous loss of a putative suppressor gene on 11q13; has been found in sporadic parathyroid tumors without MEN I.

G. Tests for adenomas can include ultrasound, nuclear medicine, and MRI scans.

H. Rx: surgical removal of the adenoma(s)

VI. PRIMARY HYPERPLASIA
A. Can occur with MEN I or MEN IIa
B. Classically all four glands are involved, but there is frequently asymmetry of enlargement
C. Combined weight of the glands rarely exceeds 1.0 gram

VII. PARATHYROID CARCINOMA
A. Difficult to distinguish from adenomas microscopically
B. One gland is enlarged
C. Local invasion and metastases are the only reliable criteria for malignancy

VIII. HYPOPARATHYROIDISM: MUCH LESS COMMON THAN HYPERPARATHYROIDISM
A. Can be surgically induced: often associated with thyroidectomy or too much parathyroid tissue taken in parathyroid surgery
B. Congenital absence of all glands (e.g., DiGeorge Syndrome = thymic aplasia)
C. Primary (idiopathic) Atrophy of the Glands; most likely an autoimmune process; 60% of the patients have autoantibodies directed against calcium-sensing receptors on the parathyroid gland cells; binding of this autoantibody may prevent PTH release.
D. Familial Hypoparathyroidism: often associated with mucocutaneous candidiasis and primary adrenal insufficiency
E. Clinical manifestations of hypoparathyroidism:
   1. tetany: neuromuscular irritability from low ionized calcium levels (circumoral numbness, parathesias of extremities, carpopedal spasm, laryngospasm, seizures)
   2. mental status changes: confusion, depression, psychosis, hallucinations
   3. intracranial changes: Parkinson-like movements, papilledema
   4. ocular changes to include calcification of the lens
   5. cardiovascular changes: conduction defects (prolonged QT interval)
   6. dental abnormalities: if low calcium occurs during early development can have hypoplasia of teeth, failure of eruption, defective enamel and root formation

IX. PSEUDOHYPOPARATHYROIDISM: Resistance of organs to normal or elevated levels of PTH
A. Hypocalcemia results with ensuing secondary hyperparathyroidism
B. Type 1 and Type 2 pseudohypoparathyroidism described and documented
C. Patient is short, thickset and obese; 4th and 5th metacarpals and metatarsals are shortened; mental retardation is common.

D. Most are hypocalcemic, but a minority can be eucalcemic

X. PSEUDOPSEUDOHYPOPARATHYROIDISM

A. Very rare condition

B. Same physical changes as pseudohypoparathyroidism

C. Normal calcium and phosphorus in serum; respond normally to PTH stimulation; ? incomplete form of pseudoparathyroidism

XI. PARATHYROID TOXICOSIS

A. If calcium increases rapidly into abnormal range, all symptoms of hypercalcemia can worsen suddenly leading to vomiting, dehydration, azotemia, stupor and even death. Most cases appear to result from hemorrhage or infarction of an adenoma of the parathyroid with release of PTH into the blood stream.

B. Treatment:
   1. Hydration
   2. Diuresis
   3. Administer phosphate
   4. Monitor electrolytes (especially potassium and magnesium)
THYROID

Steve Nandkumar, M.D.
THYROID

GLOSSARY

Hyperthyroidism – A hypermetabolic state caused by elevated levels of T₃ and T₄ due to a hyperfunctioning thyroid

Thyrotoxicosis – A hypermetabolic state caused by elevated levels of T₃ and T₄ due to excessive leakage of hormones out of a “nonhyperactive” thyroid

Graves’ disease – Enlargement of the thyroid associated with hyperthyroidism, ophthalmopathy, and dermopathy

Pretibial myxedema – Thickening and induration of skin (orange peel texture) over the shins; there is deposition of hydrophilic, mucopolysaccharides in the dermis

Jod-Basedow’s disease or phenomenon – Secondary hyperthyroidism due to iodine treatment (in nodular goiter, euthyroid patient)

Hypothyroidism – A hypometabolic state associated with decreased levels of T₃ and T₄

Myxedema – Hypothyroidism in older children or adults

Cretinism – Hypothyroidism developing in infancy or early childhood

Hashimoto’s disease – Thyroiditis of autoimmune origin

Hashitoxicosis – Thyrotoxicosis occurring in Hashimoto’s disease

Pendred’s syndrome – Deafness and goiter due to metabolic block in the iodide organification step of hormone synthesis

Hurthle cells (Askanazy cells) – Metaplastic follicular cells with acidophilic, granular cytoplasm seen in Hashimoto’s disease

Goiter – Non-neoplastic, non-inflammatory enlargement of the thyroid gland

Plummer’s disease or syndrome – Hyperthyroidism due to a hyperfunctioning nodule in a multinodular goiter

Reidel’s struma (Ligneous Thyroiditis) – “Thyroiditis” with extensive fibrosis of unknown cause

Euthyroidism – “Normal” thyroid status

LATS – Long-Acting Thyroid Stimulator

LATS-P – Long-Acting Thyroid Stimulator Protector

TSI – Thyroid Stimulating Immunoglobulin (IgG)

TBI – Thyroid Binding Immunoglobulin

TBG – Thyroid Binding Globulin (transport protein)

PBI – Protein Bound Iodine

TG – Thyroglobulin (colloid material present in follicles)
Thyroid Testing Protocols

Thyroid Profile

<table>
<thead>
<tr>
<th>Reflexive Thyroid Profile—TSH</th>
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<tr>
<td>&lt;0.10</td>
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<tr>
<td>0.10-0.39</td>
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<tr>
<td>0.4-6.0</td>
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<tr>
<td>&gt;6.0</td>
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</tbody>
</table>

- Hyperthyroid Suspect
- Borderline Thyroid Status
- No Thyroid Dysfunction
- Hypothyroid Suspect

A Strategy for Investigation of Thyroid Function

- Raised → Hyperthyroid
- Raised → Hyperthyroid
- <0.1 → FT<sub>4</sub> or T<sub>3</sub> → Normal → FT<sub>4</sub> or T<sub>3</sub>

Request for Thyroid Function Test

- Normal → Subclinical Hyperthyroid
- Normal → Subclinical Hypothyroid
- Low → Hypothyroid

Note: About 1/3 of patients tested are being treated, and of this about 15% will give discordant TSH-T<sub>4</sub> values.

Adapted from: Caldwell ET al. The Lancet, May 12, 1983.
Table/Courtesy David Plant
INTRODUCTION
The medical investigation of the thyroid gland falls into two broad categories: the evaluation of function and the investigation of masses. While there are areas of overlap, it is easier to look at these two problems serially.

EMBRYOLOGY, ANATOMY, AND HISTOLOGY
Day 24: Development of thyroid gland begins with a medial endodermal downgrowth from the floor of the primitive pharynx in the region of the primitive tongue. The thyroid diverticulum enlarges and descends into the anterior neck, maintaining its attachment to the tongue by a thin tube—the thyroglossal duct.

Week 7: Thyroid reaches final location anterior to the trachea. The thyroglossal duct usually disappears at this time. A vestigial pit in the tongue—foramen cecum—marks the place of primitive thyroid attachment.

Week 10: Epithelial cells form.

Week 11: Follicles form and colloid synthesis begins.

Pyramidal lobe is found arising from the isthmus in about 50% of cases.

Parafollicular Cells (Calcitonin Secreting) – arise from neural crest derivatives from the ultimobranchial body and fuse with the thyroid gland. The C-cells are usually confined to the middle and upper thirds of the lateral lobes. They have been located by immunoperoxidase staining for calcitonin within the follicles as well as within the parafollicular spaces.

Weight – varies with many factors including age, diet, pregnancy, etc. (about 15 to 25 gm in the adult).

The Follicle – is the functional unit in the thyroid – consists of spheroids of epithelial cells within which is located the colloid (a concentrated solution of thyroglobulin). Thyroid hormone synthesis and storage occur within the follicular epithelial cells and the colloid.

Anatomic Notes – The relationship of the thyroid gland to the following structures is essential to an understanding of the pathology, treatment, and complications of thyroid disease: parathyroid glands, crico-thyroid cartilage, carotid arteries, trachea and recurrent laryngeal nerve.

Congenital Anomalies
– Abnormalities of thyroid descent are the most common.
– Removal of abnormally located thyroid tissue must be done with caution; the ectopic thyroid tissue MAY represent the only functioning thyroid tissue in the patient.
– Thyroglossal duct cysts are the single most common anomaly.
  1. Occur anteriorly in the midline
  2. Sinus tracts occur in 1/3 of cases
  3. Usually 1 to 3 cm in diameter
  4. Cyst is lined by respiratory or squamous epithelium
  5. Surrounded by lymphoid tissue (often with germinal centers)
  6. Presence of adjacent thyroid follicles (often scanty) distinguishes from branchial cleft cyst
  7. Less than 100 tumors have been reported arising from these cysts

– Other anomalies include: mediastinal thyroid tissue, intrathyroidal thymic, and intrathyroidal parathyroid tissue.
Heterotopic Thyroid Tissue—CONTROVERSY

- “Although frequently referred to as lateral aberrant thyroid, the vast majority of instances represent metastasis from occult papillary carcinoma.” Geoffrey Mendelsohn, *Diagnosis and Pathology of Endocrine Diseases*, 1988.

NEONATAL CONSIDERATIONS

The thyroid gland is functional by the end of the first trimester, following which the fetus is dependent on its own resources – with thyroid hormone necessary to further development.

**Neonatal Hypothyroidism**

1. **Incidence** – 1 in 4,000 births (10–15% by enzyme defects, 80–85% by thyroid dysgenesis and 5% by TSH receptor abnormalities)
2. **Cretinism** – large tongue, defective nervous system development, mental retardation, neuromuscular abnormalities, and short stature
3. **Mandatory screening of T4 or TSH in all newborns**
4. **Neonatal TSH and T4 elevated normally immediately after birth**
5. **If replacement of thyroid hormone is not started quickly, by six months irreversible mental deficiency will develop.**

Low T₃ and rT₃ in fetus due to poor peripheral conversion from T₄ (lack of 5’MDI – monodeiodinase)

**THYROID HORMONE SYNTHESIS**

There are four sequential steps:

1. **UPTAKE OR TRAPPING**  
   Iodine, present as iodide and iodate in diet, is absorbed, bound to albumin and transported to thyroid. Transfer into the cells is mediated by a plasma membrane protein called Na/I symporter. This is an energy dependent process and depends on oxidative metabolism in the gland. Lack of iodine increases expression of Na/I symporter; sufficient iodine inhibits Na/I symporter.

   **NOTE:**  
   Thiocyanates and perchlorates block this uptake by inhibiting iodide transport.

2. **OXIDATION (ORGANIFICATION, IODINATION)**  
   
   \[ \text{Iodide} \rightarrow_{\text{Peroxidase}} \text{oxidized form} + \text{tyrosyl residues in thyroglobulin} \]
   \[ \downarrow \text{MIT – moniodotyrosine} \]
   \[ \text{DIT – diiodotyrosine} \]

   **NOTE:**  
   Pendrin (present in the apex of the cell) is an anion transporter and mediates iodine influx into the lumen of the follicle. It is produced by SLC26A4 (solute carrier family 26 member 4) gene. Lack of Pendrin causes Pendred syndrome (Goitre + deafness). Pentrin, related to Pendrin, is present in the Organs of Cortii in the inner ear.
3. **OXIDATIVE COUPLING**

MIT + DIT \[\rightarrow\] T₃ (thyronine)  
peroxidase  
DIT + DIT \[\rightarrow\] T₄ (thyroxine)

These are incorporated in thyroglobulin (storage).

**NOTE:** Steps 2 and 3 are inhibited by thiouracil and mercaptozole (anti thyroid drugs). Excess iodide can also inhibit organification (Wolff-Chaikoff effect).

4. **RELEASE**

Thyroglobulin (containing T₃ and T₄) \[\rightarrow\] T₃/T₄  
proteases  
peptidases  

This reaction occurs in phagolysosomes.  
[Pinocytosis of thyroglobulin \[\rightarrow\] colloid droplets \[\rightarrow\] lysosomes (phagolysosomes)]  
T₃ and T₄ are released into capillaries (circulation).

MIT \[\rightarrow\] Iodotyrosine  
Inactive (not utilized in release)  
DIT \[\rightarrow\] Iodide + tyrosyl residues  
Dehalogenase

Iodide \[\rightarrow\] small leak into circulation; reused in hormone synthesis.

**NOTE:** Iodide/ lithium can inhibit proteolysis (step 4) and hormone release.

All T₄ production occurs in thyroid

T₃ – 20% production in thyroid  
80% by peripheral conversion of T₄ \[\rightarrow\] T₃  
facilitated by 5'MDI (monodeiodinase)  
in liver and kidney  

**HORMONE TRANSPORT**

Hormones exist in Bound Form or Free Form  
Bound Form  Free Form

<table>
<thead>
<tr>
<th></th>
<th>Bound Form</th>
<th>Free Form</th>
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</thead>
<tbody>
<tr>
<td>T₄</td>
<td>99.97%</td>
<td>0.03%</td>
</tr>
<tr>
<td>T₃</td>
<td>99.70%</td>
<td>0.3%</td>
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</table>

Free hormones are active and correlate with the metabolic state.

Bound forms are transported by  
TBG 70%  
TTR (Transthyretin) 20%  
Alb 10%  
HDL  

T₃ (active)  
transported by TBG  
T₄  
rT₃ reverse (inactive)
**METABOLISM**

1. **T₄** → 5’MDI → sequential monodeiodination → **T₃** → excretion

2. Hepatic conjugation with glucuronate and sulfate → deiodination → bile secretion → fecal excretion

Usual American adult diet contains 300 μg of iodine/day.

Most is reduced to iodide ion in the gut, rapidly absorbed and distributed to the extracellular fluid – from there, iodide is removed by the thyroid gland (which can concentrate up to 30 times the plasma amount), kidney (for clearance), salivary glands and gastric mucosa (which excrete it to be reabsorbed) – small amounts are lost in sweat, milk and urine.

Iodide in the thyroid is rapidly organified and bound to tyrosyl residues on thyroglobulin (which is secreted by the thyroid epithelial cell into the follicular lumen and contains 90–95% of total body iodine) – mono and diiodotyrosine residues combine to form T₄ and T₃.

**T₄** – 90 μg secreted daily, half-life 5–7 days, portion converted peripherally (by 5’MDI) to **T₃** (about 1/4), only 0.03% circulates as free hormone.

**T₃** – 6 μg secreted daily, half-life 1 day, total **T₃** available (with peripheral conversion of **T₄**) 26 μg/day, only 0.3% circulates as free hormone.

**THYROID HORMONE METABOLISM AND REGULATION**

Control of thyroid hormone secretion and action occurs at three levels:

1. Hypothalamic-pituitary-thyroid axis
2. Autoregulatory mechanisms within the thyroid
3. Peripheral hormone conversion

Hypothalamic TRH (thyrotropin-releasing hormone, thyroliberin), released by supraoptic and paraventricular nuclei, is necessary for the increased synthesis and release of TSH by the thyrotropes and TRH regulates the sensitivity of these cells to feedback control.

Negative feedback by thyroid hormones occurs at the pituitary level – correlates well with circulating free **T₄** levels. **T₃** also acts on the hypothalamus.

Autoregulation within the gland – low content of glandular iodide is associated with enhanced sensitivity to TSH with the production of a higher proportion of **T₃** to **T₄**.

At target cell level – 5’MDI (monodeiodinase) activity is inhibited with decreasing production of **T₃** and decreasing metabolic activity in such states as: malnutrition, liver disease, generalized debility, pregnancy, stress, and steroid therapy.
**ACTIONS**
- T₄ and T₃ bind to nuclear chromatin receptors TR (T₃ with more affinity than T₄) leading to transcription of specific portions of the genome and production of new proteins.
- Thyroid hormones stimulate calorigenesis, are needed for temperature maintenance, are needed for normal growth (excess will switch protein anabolism to catabolism with muscle wasting and weakness), affect carbohydrate, lipid, and vitamin metabolism, and increase the number and function of alpha and beta adrenergic receptors with increased SNS activity in hyperthyroidism (tachycardia, sweating, tremors) and depressed SNS activity in hypothyroidism. They also increase LDL receptor expression in tissues so LDL degradation occurs.

**THYROID TESTING**

**EVALUATING THYROID FUNCTION**
A wide array of tests are available for determining thyroid function. A handful of tests, properly utilized will suffice in almost all circumstances.

Total serum T₄ – in the absence of abnormalities in serum thyroxine-binding proteins, TT₄ correlates well with thyroid function.

TT₄ can be improved by measuring the binding proteins (T₃RU–T₃ resin uptake). **NOTE:** this is NOT a test to measure T₃. Free T₄ is approximated by Free Thyroxine Index (FTI) (TT₄ × T₃RU) and can be determined directly (by dialysis—the “gold standard”). Direct measurements are seldom done outside a research setting. T₃ and rT₃ (reverse T₃) levels can be obtained by RIA or EIA – seldom needed in routine practice.

**Thyroglobulin**
- Detectable in most euthyroid patients
- Cannot be accurately interpreted in the presence of antithyroglobulin antibodies
- Serum levels transiently increased following needle biopsy
- Used in the diagnosis of thyrotoxicosis factitia: because all causes of excessive thyroid hormone secretion are accompanied by increased levels of thyroglobulin; low or undetectable levels of thyroglobulin (in the absence of anti-TG antibodies) in a thyrotoxic patient is diagnostic of exogenous thyroid hormone administration
- Serum TG levels are helpful in following patients with differentiated thyroid carcinomas – less helpful in screening for the same

**TSH, Thyroid-Stimulating Hormone**
- The single most sensitive test to detect hypothyroidism – increases in TSH connote low functional thyroid hormone status
- Elevations can occur in non-thyroidal illness (usually mild and transient), with pregnancy and Human Chorionic Gonadotropin (HCG) secreting tumors (cross reactivity in assay)
- Low values are seldom helpful in determining hyperthyroidism

**TRH Stimulation Test**
- Used primarily to assess hypothalamic-pituitary axis

**Thyroid Autoantibodies**
- Formed against thyroglobulin and a microsomal antigen
- Weakly positive titers are found in 5–10% of normal individuals
- Hashimoto’s thyroiditis: microsomal + 95%, thyroglobulin + 60%
- Graves’ disease: microsomal + 85%, thyroglobulin + 30%
- Frequency of positive antibodies NOT INCREASED in patients with thyroid nodules, multinodular goiter, or thyroid carcinoma
**Thyroid-Stimulating Immunoglobulins (TSI)**
- Formerly known as LATS (long acting thyroid stimulator), binds to TSH receptor and stimulates thyroid follicular cells
- Thought to be the cause of thyrotoxicosis in Graves’ disease (not all are positive)
- Congenital hyperthyroidism secondary to transplacental passage of TSI usually occurs with high maternal titers; the majority of women with high titers have unaffected children

**Thyroid-Binding Immunoglobulins (TBI)**
- Binds to TSH receptor but does not stimulate follicular cells
- Implicated in some cases of neonatal hypothyroidism

**HYPERTHYROIDISM**

A hypermetabolic state caused by elevated levels of T₃ and T₄ due to a hyperfunctioning thyroid gland. The term hyperthyroidism and thyrotoxicosis are used interchangeably.

**Causes**

- **Common**
  - Diffuse toxic hyperplasia (Graves’ Disease) 85%
  - Toxic multinodular Goiter
  - Toxic adenoma

- **Uncommon**
  - Acute or subacute thyroiditis
  - Iodide-induced hyperthyroidism
  - Iatrogenic hyperthyroidism
  - Thyroid carcinoma
  - Choriocarcinoma
  - TSH secreting pituitary adenoma
  - Struma ovarii (ovarian tumor)
  - Neonatal thyrotoxicosis from mother with Graves’ disease

**CLINICAL FEATURES**

These relate to:

- Hypermetabolism (BMR ↑)
- Overactivity of sympathetic nervous system

A. **Cardiac Manifestations**
- Increased cardiac output, HTN, cardiac hypertrophy
- Tachycardia, palpitations, and cardiomegaly
- Arrhythmias (atrial fibrillation) – cause not known
- CHF (congestive heart failure – high output type)
- Dilated cardiomyopathy (low output failure)

B. **Eye Changes**
- Staring gaze due to SNS overstimulation of eyelid muscle
- Lid lag and lid retraction

C. **Neuromuscular Changes**
- Tremor and hyperactivity
- Nervousness, anxiety, inability to concentrate, emotional lability, and insomnia
- Muscle weakness, fatigue, and atrophy with decreased muscle mass (myopathy)

D. **Skin Changes**
- Warm, moist, and flushed
- Sweating and heat intolerance
E. **Gastrointestinal Changes**  
   – Increased appetite and hyperphagia with weight loss  
   – Gut motility is increased → diarrhea  

   **Liver** - Mild fatty change  

F. **Skeletal Changes**  
   Bone resorption due to thyroid hormones is increased  
   – Osteoporosis and fractures  
   – Calcium levels in serum and urine elevated (20% of cases)  

G. **Lymphoid Changes**  
   – Generalized lymphoid hyperplasia with lymphadenopathy  

H. **Effects on Sex**  
   – Oligomenorrhea  
   – Loss of libido  

I. **Thyroid Storm**  
   – Abrupt onset of severe hyperthyroidism is due to acute elevation of catecholamines as might occur in shock, sepsis, surgery, stress, infections, etc.  
   – This is a medical emergency and needs prompt treatment. The cause of death in untreated cases is cardiac arrhythmias/cardiac failure.  

J. **Apathetic Hyperthyroidism**  
   – Elderly patients with various other co-morbid conditions may show a “blunted response” to thyroid hormone excess. Lab tests help in diagnosis of this condition.  

**NOTE:**  
Elderly patients with cardiac problems must have thyroid function studies.  

**DIAGNOSIS:**  
Elevated serum T₄ and T₃ (bound and free forms)  

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<tr>
<th></th>
<th><strong>Primary Hyperthyroidism</strong></th>
<th><strong>Secondary Hyperthyroidism</strong></th>
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<tbody>
<tr>
<td>T₄</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>TSH</td>
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R.A.I.U.: Radioactive iodine uptake increase indicates a hyperfunctioning gland.  

**GRAVES’ DISEASE**  

**It is usually a triad of**  

1. Hyperthyroidism due to hyperfunctioning diffuse enlargement of the thyroid.  
2. Infiltrative ophthalmopathy → exophthalmos  
3. Infiltrative dermopathy → pretibial myxedema  

**Any one of these may be absent!**  

– Most common cause of hyperthyroidism  
– F:M = 7:1  
– Usually occurs between 20–40 years  
– Familial predisposition associated with HLA-B8 and DR3  
– Association with polymorphism of CTLA-4 gene. (Cytotoxic T-lymphocyte associated-4 gene).  
   CTLA-4 functions as a receptor and prevents T cell response to self-antigens; PTPN22 gene (protein tyrosine phosphatase) produces a lymphoid phosphatase that inhibits T cell function.  
– Associated with susceptibility loci on chromosome 6p and 20q
– Association with other autoimmune diseases such as SLE, PA, type I DM, and Addison’s
disease, etc.
– Other risk factors include smoking, stress, post-partum state and increased iodine intake.

PATHOGENESIS

A. An AUTOIMMUNE DISEASE with the Following Antibodies

a. TSI – Thyroid stimulating immunoglobulin – QUITE SPECIFIC FOR GRAVES’.
Autoantibodies to TSH receptor. An IgG combines with receptors and stimulates adenylate cyclase
→ T₃, T₄ are increased.
b. Thyroid growth stimulating, Ig. (TGI) stimulates TSH receptor.
c. TSH – binding inhibitor Ig. (TBII) – These are anti-TSH receptor antibodies.

There are two subtypes

1. Prevent TSH binding to receptors so ↓ function
2. Some mimic TSH function upon binding to receptors, so ↑ function

d. Antibodies to TG and peroxidase enzyme. Thyroid peroxidase antibodies (TPO Ab) occur in 80%
of cases.

B. Mechanism of Autoimmune Reaction
The exact mechanism is unknown. T-cells normally recognize self-antigens on thyroid. A breakdown in
this immune tolerance causes thyroid Ags to be presented by HLA molecules to autoreactive T cells.
These stimulate B lymphocytes through co-stimulatory molecules to produce auto Ab to TSH receptors
causing stimulation of T₄, T₃ synthesis.

GROSS CHANGES
– Symmetric enlargement of gland with diffuse hypertrophy and hyperplasia – weight is 80.0 gm →
parenchyma is soft, meaty, and red

MICRO CHANGES

Hyperplasia – TOO MANY CELLS
– Crowding with papillae jutting into lumen; NO FIBROVASCULAR CONNECTIVE TISSUE
CORE IN PAPILLA (in contrast to those of papillary carcinoma)
– Pale colloid with scalloped margins
– Increased lymphoid tissue with aggregates of T and B cells with plasma cells; prominent germinal
centers are seen.

Pre-op Rx with iodine → involution of epithelium with colloid accumulation
Rx with antithyroid drug → decreases T₃ and T₄ synthesis so TSH ↑→ epithelial hyperplasia and
hypertrophy is exaggerated
CLINICAL FEATURES
Similar to those mentioned under hyperthyroidism

Eye Changes Seen
in 10% of Cases
Autoimmune inflammation (CD₄ and CD₈ cells) of retro-orbital fat and extraocular muscles due to Abs binding to TSH receptors expressed in these sites; cytokines TNF, IL-1, IFN-γ are released

↓
Proteoglycans/hyaluronic acid deposition
↓
Edema of tissues with subsequent fibrosis

Proptosis, diplopia → malignant exophthalmos (pushing forward of eye balls)

Skin Changes
seen in < 5%
of cases
Pretibial myxedema due to glycosaminoglycans deposition and lymphocyte infiltration.

– Skin over shins is pigmented, papular or nodular and resembles an orange peel (texture-wise)
– Thyroid acropachy (clubbing of nails) in < 1% of cases

TREATMENT  25% of cases undergo spontaneous remission
– Surgery
– Drugs
– Radiation therapy

HYPOTHYROIDISM

– A hypometabolic state with low serum levels of T₃ and T₄.

Causes

These are

Thyroid (Primary)          Extrathyroid (Secondary)

Insufficient Thyroid Parenchyma
Defective Hormone Synthesis
Pituitary lesions – TSH deficiency
Developmental-dysgenesis
TSH receptor mutations
Biosynthetic defects - congenital
Iodine lack
Hypothalamic lesion – TRH deficiency
Radiation
Surgery
Hashimoto’s disease
Drugs (lithium, etc.)
Thyroid hormone resistance
(receptor mutation – T₃, T₄ cannot bind to receptors)

NOTE: The most common cause is Hashimoto’s disease (auto immune thyroiditis) in Iodine sufficient areas of the world.

Iodine deficiency is the most common cause of hypothyroidism in the world.
CRETINISM

Hypothyroidism in infants or early childhood
- Endemic cretinism associated with iodine lack as seen in China, Africa, Himalayas less common.
- Sporadic cretinism occurs due to enzyme deficiencies affecting hormone synthesis.
- Features include impaired development of CNS and skeletal system
- Short stature, MR, coarse facial features, protruding tongue, and umbilical hernia
- Maternal T<sub>3</sub>/T<sub>4</sub> cross placenta and help fetal brain growth till fetal thyroid takes over T<sub>3</sub>, T<sub>4</sub> synthesis (about week 11 of fetal life)
- Neonatal test for hypothyroidism → TSH as a screening test. If high, consider hypothyroidism and treat after proper investigation.

MYXEDEMA (GULL DISEASE)

- Hypothyroidism in older children or adults
- Slowness of physical and/or mental activity
- Clinical features relate to a low BMR and low SN system activity (features are usually the opposite of those presented for hyperthyroidism)
- Deposition of glycosaminoglycans and hyaluronic acid in subcutaneous tissue, skin and viscera
- Fatigue, apathy, obesity and cold intolerance are common
- Diminished cardiac output → dyspnea, decreased exercise capacity. T3, T4 regulate transcription of sarcolemmal genes producing Ca ATPase needed for myocardial contraction.

LAB TESTS

Anti thyroid Ab are increased
1. Ab to TSH-receptor 20% of cases
2. Ab to TPO (peroxidase) 90–95% of cases
3. TBII 10–20% of cases
4. Anti- microsomal Abs occur
   - Ck (creatine kinase) ↑
   - Cholesterol, Triglycerides ↑
   - Anemia present

NOTE: TSH level in serum is the most sensitive screening test for hypothyroidism.

LAB DIAGNOSIS

<table>
<thead>
<tr>
<th>Primary Hypothyroidism (Thyroid)</th>
<th>Secondary Hypothyroidism (Pituitary)</th>
<th>Tertiary Hypothyroidism (Hypothalamic)</th>
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<td>T&lt;sub&gt;3&lt;/sub&gt;/T&lt;sub&gt;4&lt;/sub&gt;</td>
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<td></td>
</tr>
<tr>
<td>TSH</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>TSH response to TRH</td>
<td>exaggerated</td>
<td>absent</td>
</tr>
</tbody>
</table>

TREATMENT

1. Treat cause if possible
2. Thyroid hormone administration (replacement therapy)

QUESTIONS: What is myxedema coma?

Can there be clinical hypothyroidism with elevated T3, T4, and TSH?
**THYROID HORMONE RESISTANCE**
Thyroid hormone receptors (TR) α and β types may undergo mutation
- Hence, there is poor response to T₃, T₄
- So T₃, T₄ may be elevated, TSH is normal or elevated as pituitary is resistant to T₃/T₄ hormones. TSH response to TRH is normal

**TREATMENT**
Supplemental thyroid hormone (dose depends on alleviating symptoms and signs)

**HASHIMOTO’S THYROIDITIS** (Struma lymphomatosa)
- An autoimmune disease characterized by a chronic lymphocytic thyroiditis with associated “antithyroid antibodies.”
  - More common in woman (F:M = 10:1)
  - Prevalent between 45 and 65 years; also occurs as a major cause of nonendemic goiter in children
  - A familial disease associated with HLA-DR5 and HLA-DR3 (minority of cases with thyroid atrophy)
  - Concordance rate in monozygotic twins is 40%; asymptomatic siblings have Abs in 50% cases
  - Associated with other autoimmune diseases such as SLE, PA, RA, DM, Addison’s disease, Myasthenia gravis, Sjögren’s syndrome, Turner’s syndrome, Down’s syndrome

**PATHOGENESIS**
Involves cellular and humoral immunity

Thyroid cell damage/death occurs due to
1. CD8+ cytotoxic T cell-mediated cell death.
2. CD4+ cytokine mediated cell death.
3. Ab mediated ADCC → death.

**NOTE:**
Graves’ and Hashimoto’s disease occupy two ends of the same spectrum of autoimmune disease.
- Autobodies against thyroid antigens are common to both, but their specific EPITOPES are different and hence their functional consequences DIFFER.
MORPHOLOGY

Classic (enlarged)

GROSS Two forms are seen

Fibrous (atrophic)

1. Diffusely enlarged gland (symmetric or asymmetric)
   Capsule is intact; parenchyma is pale, gray tan, and looks “lymphoid” (non-atrophic type).
2. Atrophic gland → DR3 associated

MICROSCOPIC

1. Extensive parenchymal infiltration by mononuclear inflammatory infiltrate (lymphocytes, monocytes, and plasma cells)
2. Well-developed germinal centers
3. Follicular destruction with pink epithelial cells (Hürthle cells) – a metaplastic change
4. Atrophy with fibrosis – broad bands of collagen (scars) surround small thyroid acini.

NOTE: FNA shows Hurthle cells and many lymphocytes/mononuclear cells → think Hashimoto disease.

CLINICAL FEATURES

Usually painless, enlarged gland causes
1. Disfiguration – neck mass
2. Dysphonia – pressure on voice box
3. Dysphagia – esophagus
4. Dyspnea - trachea

There is usually HYPOTHYROIDISM.

LAB TESTS

Auto Abs frequently seen against
1. TSH receptor
2. TG
3. TPO
4. Na-I symporter

NOTE: ANTIBODIES TO TSH-RECEPTOR ARE SPECIFIC

QUESTION: What is Hashitoxicosis?

COMPLICATION

INCREASED RISK OF B-CELL LYMPHOMA OF THYROID (MARGINAL ZONE TYPE)

Possible increased risk of PAPILLARY CA (controversial).

TREATMENT: Medical

Surgical

Occasional cases in children are self-limiting!

ACUTE THYROIDITIS

- Inflammation of the thyroid usually associated with infections (acute or chronic), caused by bacteria, TB, fungi, and Pneumocystis, etc.
- Infection may be hematogenous or by direct seeding
- Treat with antibiotics
SUBACUTE THYROIDITIS (de Quervain’s thyroiditis) (granulomatous thyroiditis)
- Occurs between 30–50 years
- F:M = 3 to 5:1
- Association with HLA–B35
- Caused by viral infection or post viral inflammation; usually in summer, history of URTI.
  - Viral antigen or virus induced-tissue damage antigen → HLA B35
  - T-cells → cytotoxicity → thyroiditis
  - Macrophages
- Self-limiting disorder (6–8 weeks for recovery)

MICRO
- Damaged follicles due to acute inflammation and microabscesses. Granulomatous changes due to spilled colloid.
- Chronic inflammation and fibrosis

CLINICAL FEATURES
- Fever, malaise, myalgia, neck swelling and pain
  - Transient hyperthyroidism followed by asymptomatic hypothyroidism may be seen. Full recovery occurs in 6–8 weeks

REIDEI’S THYROIDITIS (Ligneous thyroiditis)
- Rare disease of unknown cause
- Antithyroid Abs are seen (autoimmune disease)
- Extensive fibrosis involving the thyroid and contiguous neck structures
- Thyroid is fixed, painless, woody hard and mimics a malignancy
- May be associated with idiopathic fibrosis elsewhere such as mediastinum, retroperitoneum etc.
- May cause pressure symptoms along with hypothyroidism

GOITER
From gutter (L) = Throat

A nonneoplastic, non inflammatory enlargement of the thyroid gland

CAUSE
- Impaired synthesis of hormones
  - Compensatory rise in TSH levels
    - Hypertrophy and hyperplasia of follicle cells
      - Enlarged thyroid → reaches euthyroid state. If not, goitrous hypothyroidism

Goiters’ may be:

<table>
<thead>
<tr>
<th>1. Diffuse or Nodular</th>
<th>Based on Size</th>
<th>2. Toxic or Non-toxic (simple)</th>
<th>Based on Function</th>
</tr>
</thead>
</table>
DIFFUSE NONTOXIC (SIMPLE) GOITER (Colloid goiter)
There are two subtypes

A. Endemic Goiter
   – Occurs in more than 10% of the population in a given region, e.g., Alps, Andes, and Himalayas

   **Cause**
   1. Lack of iodine (in soil, water, and food)
   2. Goitrogens (dietary substances causing decreased hormone synthesis)
      a. Excess calcium
      b. Vegetables such as cabbage, cauliflower, brussel sprouts, and turnips
      c. Cassava root (contains thiocyanate)

B. Sporadic Goiter (less common)
   – Occurs mainly in females (puberty and young adults)

   **Usually due to**
   1. Substances interfering with hormonogenesis
   2. Biosynthesis – enzyme defects (autosomal recessive conditions)
   3. Unknown cause (most cases)

MORPHOLOGY

Gross

A. **Stage of Hyperplasia**
   diffusely enlarged gland (weight: 100–150 gm) – no nodularity.
   – Crowded follicles with papillae
   – Colloid filled follicles vary in size and shape

B. **Stage of Colloid Involution**
   – Follicular epithelium involutes, flat
   – Follicles now rich in colloid due to less demand or treatment (colloid goiter)

CLINICAL COURSE:
Enlarged gland may present as a neck mass with pressure effects on neighboring structures, neck pain.
   – Hypothyroidism (children), euthyroidism (adults), rarely hyperthyroidism
   – TSH is elevated or at upper limit of normal.
   – T₃/T₄ low or normal in euthyroid state

MULTINODULAR GOITER (Adenomatous goiter)
A simple goiter, over time (several months) becomes multinodular due to repeated episodes of hyperplasia and involution.

Thus diffuse (simple) goiter → Hyperplasia → Multinodular goiter → Involution

PATHOGENESIS
   – Normal thyroid cells have different sensitivity to TSH and thus differing proliferative potential
   – Cell proliferation may be Monoclonal
       Polyclonal
   – With time monoclonal nodules emerge (by themselves or from a polyclonal population owing to growth advantage). Mutations in proteins of the TSH signaling pathway are noted.
Differential development leads to multi-nodularity, uneven tensions, and stresses resulting in rupture of follicles and vessels causing hemorrhage, fibrosis, scarring and calcification; nodularity occurs.

**MORPHOLOGY**

**A. Gross**
- Multinodular, asymmetric, enlarged gland (weight about 1000–2000 gm)
- Areas of hemorrhage, fibrosis, scarring, cyst formation, and calcification are seen.
- Capsule incomplete or indistinct

**B. Microscopic**
- Areas of follicular epithelial hyperplasia and hypertrophy admixed with foci of flat inactive epithelium and degenerative changes

**CLINICAL COURSE:**
Presents as a neck mass with resultant pain, disfiguration, dysphonia, dysphagia, and dyspnea.
- Possible effects on large vessels in the neck and thorax. With arms raised pressure on external jugular vein causes facial plethora congestion and dyspnea (Pemberton’s sign) seen in plunging goiter or substernal goiter; SVC syndrome seen
- Euthyroidism, occasionally hypothyroidism, rarely hyperthyroidism (*Plummer’s syndrome* 10% cases)

**NOTE:** Goiters mask or mimic neoplastic diseases of thyroid
- Goiters are NOT risk factors for malignancy. (However, some believe that they MAY BE associated with a LOW RISK for malignant tumors – less than 5%).

**TREATMENT**
- Hormonal replacement (T₃/T₄ suppresses TSH)
- Surgery

**THYROID NEOPLASMS**

**GENERAL CONSIDERATIONS**
Thyroid nodules evoke concern as such masses may be “neoplastic.”
- Occurrence of solitary palpable nodules in adult – 3–7%. With ultrasound → about 25%.
- Single nodules are more common in women (F:M = 4:1)
- Solitary nodules are more likely to be neoplastic than are multiple nodules
- Nodules in younger patients are more likely to be neoplastic
- Nodules in males are more likely to be neoplastic
- Nodules that take up RAI (radioactive iodine) are more likely to be benign
- Most nodules are benign (cysts, abscesses, thyroiditis and goiter)
- Most neoplastic nodules are adenomas
- Less than 1% of solitary nodules is malignant

**EVALUATION OF THYROID NODULES**
The reason for evaluation is to decide which patients must undergo surgical intervention, either for treatment or definitive diagnosis.

“Fine needle aspiration biopsy cytology has been shown to have greater accuracy in diagnosing thyroid nodules than other screening methods. Its use has been shown to decrease the rate of surgical excision of thyroid nodules (benign) and increased the rate of malignant disease discovered in excised nodules. Studies have indicated that thyroid FNA is also the most cost-effective method available of screening for thyroid malignancy.” W. Howard Hoffman, M.D., Pathologist, Feb. 1986.
SCANS
- Use I-131, I-125, I-123, or Tc-99, all of which are preferentially taken up in the thyroid gland
- “Cold” nodules have little or no uptake, most nodules are cold, 15–20% of cold nodules are malignant,
  differential diagnosis includes: adenoma, abscess, cyst, hematoma, teratoma, parathyroid adenoma/cyst,
  thyroiditis, radioactive iodine therapy, previous surgery, papillary carcinoma, follicular CA, anaplastic
  CA, medullary CA, parathyroid CA, lymphoma, metastatic tumor
- “Hot” nodules show hyperfunction and are rarely malignant

ADENOMAS
- These are benign tumors and originate from follicular epithelium → hence follicular adenomas.

PATHOGENESIS
Normally TSH binds to TSH receptor on follicular cells. This causes activation of stimulating G protein and
through the GTP → GDP conversion results in increased cyclic AMP and protein kinases leading to increased
cell growth and hormone synthesis. Mutations of TSH receptor (gain of function) or the α subunit of G protein
( GNAS) involve signaling pathway and lead to overproduction of cyclic AMP and “clonal proliferation” of
cells → TOXIC ADENOMA (10–75% of cases).

IN NON-FUNCTIONING ADENOMAS
1. PAX-8/PPARγ fusion gene occurs due to translocation t(2;3) in 10% of cases (see notes on follicular
carcinoma).
2. Point mutation in RAS oncogene or PI3K( phosphotidyl inositol 3- kinase) sub unit occurs in 20% of cases.

MORPHOLOGY (Criteria for diagnosis)
- Singleness
- Complete fibrous encapsulation
- Clear distinction between architecture inside and outside the capsule
- Uniform histologic architecture within the capsule
- Compression of surrounding “normal” thyroid tissue
- Areas of hemorrhage, fibrosis, calcification and cystic change are noted

MICROSCOPIC
All adenomas exhibit a follicular pattern
Subtypes are:
- Normofollicular (simple)
- Macrofollicular (colloid)
- Microfollicular (fetal)
- Trabecular (embryonal)
- Hürthle cell (oxyphilic, oncocytes

Adenomas revealing necrosis, mitoses and hypercellularity are of concern. Many such lesions usually represent
a well-differentiated follicular carcinoma.

IMPORTANT: LOOK FOR CAPSULAR AND/OR VASCULAR INVASION FOR CONFIRMATION.

THE DEFINITIVE DIAGNOSIS OF ADENOMAS CAN BE MADE ONLY AFTER CAREFUL
HISTOLOGIC EXAMINATION OF THE RESECTED SPECIMEN.

NOTE: CHECK THE CAPSULE OF THE ADENOMA FOR INVASION, NOT THE THYROID
CAPSULE.
CLINICAL FEATURES
- Painless mass; may cause pressure effects
- Nonfunctioning adenomas are the most common. They are “cold” nodules.
  Hyperfunctioning adenomas cause hyperthyroidism → hot nodules.

RAIU
Ten percent cold nodules may prove to be malignant
Hot nodules are also seen

TREATMENT
- Medical – T₄ treatment. Why?
- Surgical (FNA, Scan RAI, then surgery)

THYROID CANCER
- 1–5% of all non skin cancers; about 5-6/100,000 population
- 0.2% of all cancer deaths
- F:M = about 3:1 (perhaps due to expression of estrogen receptors on thyroid cells).

PATHOGENESIS

Environmental Factors
1. Ionizing radiation (during first two decades of life), e.g., treatment for enlarged tonsils and adenoids, acne, and tinea capitis as done in the past. Nine percent of children developed cancer over decades. Nuclear disasters, e.g., Chernobyl in 1986.
2. Goiter and autoimmune diseases (Hashimoto’s disease → malignant lymphoma)
3. Prolonged TSH stimulation, (some tumors express TSH receptors).

Genetic Factors
Mutations activate 2 oncogenic pathways: 1. MAP kinase pathway
2. PI3K/AKT pathway

A. Papillary Carcinoma
1. Rearrangements of RET (rearranged during transfection) or NTRK1 (neurotrophic tyrosine kinase receptor 1) receptors.
   RET (on chromosome 10 q 11) and NTRK1 (on chromosome 1 q 21) are NOT EXPRESSED on thyroid epithelial cells. In papillary carcinoma, owing to reciprocal translocations of chromosomes 10 and 17, a fusion gene RET/PTC is formed. This leads to unregulated growth signal and tumor formation, (seen in 20 - 40% of cancers). Translocation of NTRK1 leads to constitutive activation of tyrosine receptor domain, (seen in 5–10% of cancers).
2. Mutations of BRAF gene occur in 33–50% of cancer.
3. RAS mutations occur in 10–20% of cancer.

B. Follicular Carcinoma
1. RAS gain of function mutation in 50% of cases; PTEN loss of function mutation noted.
2. PAX-8/ PPARγ, fusion gene, a t(2;3) translocation, occurs in 33 – 50% of cases.
3. Mutations in PI-3K/ AKT signaling pathways (33-50 % cases).
   Note: AKT = AK, a strain of mouse T = thymoma; it is a protein kinase B (increases protein synthesis, and inhibits apoptosis).

NOTE: (PAX-8 paired homeobox gene → needed for thyroid development)
(PPARγ - peroxisome proliferator-activated receptor γ) - a nuclear hormone receptor useful in terminal cell differentiation.

C. Medullary Carcinoma
Germ line RET mutations occur in MEN-II associated carcinomas, (95% of cases); in sporadic Ca 50%.
D. **Anaplastic Carcinoma**

These arise *de novo* or from dedifferentiation of a well-differentiated (papillary or follicular carcinoma). Inactivating point mutations in p53 gene, Beta catenin gene etc. are common in anaplastic carcinoma.

**TYPES OF THYROID MALIGNANCY**

I. **PAPILLARY CARCINOMA ( >85%)**

- Most common form of cancer, associated with previous exposure to radiation
- Occurs usually between the ages of 20–40.
- Associated with Gardner syndrome and Cowden’s disease (familial goiter and skin hamartomas)

**GROSS**

Tumors present as small scars, may be encapsulated with cystic degeneration and hemorrhage.
- May be solitary or multifocal

**MICROSCOPIC**

1. Papillary pattern – branching papillae with fibrovascular cores, lining cells
- Nuclear changes – vesicular nuclei (ORPHAN ANNIE EYE NUCLEI); intranuclear eosinophilic inclusions or grooves are invaginations of cytoplasm!
3. Psammoma bodies – concentric calcific structures formed within core of papillae, not seen in other types.

**NOTE:** #2 IS THE MOST IMPORTANT DIAGNOSTIC FEATURE!

**Encapsulated Papillary Carcinomas** — (Seen in 10% of cases)
- Tumor is small, encapsulated, rarely spreads, and so has a GOOD PROGNOSIS. Formerly called “papillary adenomas”!

**Follicular variant** — Follicular patterns noted – NUCLEI LOOK LIKE THOSE OF PAPILLARY CA — (Orphan Annie type) – Prognosis is that of a papillary carcinoma.

**Tall Cell Variant Ca** (Occurs in older people)
- Tall columnar type tumor cells with pink cytoplasm. Invades vessels and metastasizes and hence has POOR PROGNOSIS.

**NOTE:** Fifty percent of papillary carcinomas metastasize to the adjacent lymph nodes. Spread is hence mostly lymphatic and less vascular

**CLINICAL FEATURES**

1. Presents as a neck mass; pressure effects may be seen.
2. May present as an enlarged “cervical lymph node”

**TREATMENT**

- Thyroidectomy (no need to remove cervical lymph nodes)

**PROGNOSIS**

- Ten-year survival rate is 98%. Local or regional recurrence is 5–20%; distant metastases 10–20% (lung/bones). Tumor spread into extra thyroidal tissue, metastases, and old age are less favorable factors.
II. **FOLLICULAR CARCINOMA** (5 - 15%)
- Occurs more in women between the ages of 40–50 years
- Increased in cases of iodine deficiency (hence, association with goiter!)
- Follicular adenoma and follicular carcinoma show RAS mutations and hence may be related tumors.

**GROSS**
- Well encapsulated or circumscribed mass. Hence, difficult to differentiate from follicular adenoma. 
  Look for capsular, vascular, or perithyroidal infiltration to confirm the diagnosis of **minimally invasive follicular carcinoma**. **IMPORTANT!**

**MICRO**
Tumors present a “follicular” pattern resembling normal thyroid
- Sometimes tumor cells with abundant, pink cytoplasm (Hurthle cells) are seen.
- Psammoma bodies, nuclear features of papillary carcinoma ARE ABSENT! (When present the tumor is a follicular variant of papillary carcinoma).
- Other variants such as polygonal cell type, spindle cell type, etc., may be present.

**CLINICAL FEATURES**
- Presents as a mass/mass effects
- Usually a painless nodule
- Rarely hyperfunctional, may present as a “warm” nodule on RAI scan.

**PROGNOSIS**
Depends on
- Size and stage of the tumor
- Degree of anaplasia of cells
- Capsular/vascular invasions (50% distant metastases). Extrathyroid invasion (about 75% metastases)
- Spread usually vascular → to lungs, liver, and bones
- Minimally invasive follicular carcinoma 10-year survival rate is > 90%.
- Invasive follicular carcinoma 10-year survival rate is about 50%

**TREATMENT**
Medical, surgical, and radiation therapy

III. **MEDULLARY CARCINOMA** (5%)
- F:M = 1:1
- Tumors originate in parafollicular ‘C’ cells (neuroendocrine origin)
- Tumors produce **calcitonin** (important tumor marker) also CEA (carcino embryonic antigen), somatostatin, ACTH, serotonin, VIP (vasoactive intestinal polypeptide), insulin, glucagon, etc.
- May be associated with amyloid production (50–80)
- The tumors are of the following types:
### Sporadic (70%)
1. Somatic mutation in RET protooncogene (some cases) in codon 918
2. Tumors occur in the 40–50 age group.
3. C-cell hyperplasia absent
4. Usually solitary
5. Neck mass with pressure effects; occasionally paraneoplastic features
6. Aggressive tumors with spread by vascular system
7. Five-year survival about 50%

### Familial Associated with MEN-II A or B Syndrome
1. Germ line mutation in RET protooncogene (codon 634 in IIA and codon 918 in IIB)
2. Children and young adults
3. Present
4. Bilateral and multicentric
5. Usually asymptomatic
6. Aggressive with vascular spread Type II B has worse prognosis
7. About 50%

### Familial (Not Associated with MEN)
1. Mutations occur at codons 768 and 804, not 634
2. Occurs in the 40–50 age group
3. Present
4. Bilateral and multicentric
5. Usually asymptomatic
6. Fairly indolent
7. Good prognosis

**NOTE:** Hypocalcemia is **NOT** a prominent feature despite calcitonin ↑

### GROSS
- Pale, gray-tan tumor with foci of hemorrhage, necrosis, and infiltration

### MICRO
- Nests and trabeculae of polygonal to spindle-shaped cells, small cell anaplastic cells also seen
- Amyloid present (document by congo red and polarization) → derived from calcitonin
- Tumor stains for calcitonin, CEA and other neuroendocrine markers (immunohistochemical stains)
- E.M. (electron microscopic) studies reveal membrane bound dense core granules (150–300 microns size)

### TREATMENT
1. Surgery, radiation, chemotherapy
2. Screen family members for
   a. ↑ calcitonin levels
   b. RET mutation
      - If positive, offer prophylactic thyroidectomy
3. Overall 10-year survival rate 50–80%

### IV. ANAPLASTIC CARCINOMA
- About 1–2% of thyroid cancers
- Occurs in older people, age about 65–70 years
- Fifty percent of patients have a history of multinodular goiter, 20% have a history of differentiated thyroid carcinoma (usually papillary type), 20–30% have a concurrent papillary Ca.
- Tumors may be composed of bizarre giant cells, spindle cells (sarcomatoid pattern) or small cells (small cell Ca – may mimic a malignant lymphoma!); cytokeratin positive cells seen
- Aggressive tumors with invasion of surrounding structures of the neck
- Loss of P53 gene
- Mortality rate is about 100%, death occurs within six months due to pressure effects on vital structures of the neck.
V. **MALIGNANT LYMPHOMA**
   1–3% of all thyroid malignancies
   - More common in woman between 55–75 years; F:M = 3:1
   - Risk factors are autoimmune thyroiditis (Hashimoto’s)
   - Systemic malignant lymphoma can secondarily involve the thyroid
   - Histologically usually a large cell B cell lymphoma
   - Five-year survival about 30–50%

VI. **METASTATIC TUMORS**
   - One percent of all thyroid malignancy
   - Common sites are lung, breast, GI tract, kidney and skin (melanoma). Tumors metastasize to the thyroid owing to a rich blood supply

**NOTE:** If a tumor in the thyroid is NOT obviously of thyroidal origin, THINK METASTASIS!

**IMPORTANT**

**THYROGLOBULIN (TG) IS A RELATIVELY SPECIFIC TUMOR MARKER FOR PAPILLARY AND FOLLICULAR CARCINOMAS.**
### MEN OR MEA SYNDROMES

| Multiple endocrine neoplasms – MEN | Multiple endocrine adenomatosis – MEA |

<table>
<thead>
<tr>
<th><strong>MEN-I</strong> (Wermer’s syndrome)</th>
<th><strong>MEN-II or IIa</strong> (Sipple’s syndrome)</th>
<th><strong>MEN-IIb or III</strong> (William syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PITUITARY</strong></td>
<td><strong>PARATHYROID</strong></td>
<td>Adenomas</td>
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<tr>
<td><strong>PANCREATIC</strong></td>
<td><strong>ISLETS</strong></td>
<td>Adenomas +</td>
</tr>
<tr>
<td><strong>ADRENAL</strong></td>
<td>Hyperplasia ++</td>
<td>Carcinoma +++</td>
</tr>
<tr>
<td><strong>THYROID</strong></td>
<td>Cortical hyperplasia +</td>
<td>Pheochromocytoma ++</td>
</tr>
<tr>
<td><strong>EXTRAENDOCRINE CHANGES</strong></td>
<td>Medullary carcinoma +++</td>
<td>Medullary Ca +++</td>
</tr>
<tr>
<td><strong>PEPTIC ULCER</strong></td>
<td>C-cell hyperplasia +++</td>
<td>C-cell hyperplasia +++</td>
</tr>
<tr>
<td><strong>MUTANT GENE LOCUS</strong></td>
<td>Brain tumors (Glioma, meningiomas)</td>
<td>Mucocutaneous neuromas</td>
</tr>
<tr>
<td></td>
<td>11 q 13 (MEN I)*</td>
<td>10 q 11.2 (RET)*</td>
</tr>
</tbody>
</table>

**NOTE:** Frequency
- Uncommon +
- Common +++

* Tumor suppressor gene encodes for “Menin”-function unknown (perhaps cell cycle regulation and transcription). Menin can activate or inactivate other proteins.

RET (rearranged during transfection) gene codes for a transmembrane receptor of tyrosine kinase family. This transduces signals for cell growth and differentiation through downstream activation of MAP (mitogen activated protein kinase) signaling pathway. Germline mutation leads to gain of function due to constitutive activation.

Loss of function mutation is associated with Intestinal aganglionosis and Hirschsprung disease.

### MEN-I
- Primary hyperparathyroidism occurs in 80–90% of cases
- Pancreatic tumors are the leading cause of mortality and morbidity, e.g., gastrinomas → Zollinger-Ellison syndrome; Insulinoma → hypoglycemia; duodenal gastrinomas are MOST COMMON.
- Pituitary tumor (prolactinoma) is frequently seen. Acromegaly can occur.
- Carcinoid tumor, lipomas, adenomas of thyroid and adrenal cortex also occur
- Genetic screening not of benefit

### MEN-II
- C cell hyperplasia and medullary Ca occur in 100% of cases
- Pheochromocytomas occur in 40–50% of cases
- Parathyroid hyperplasia occurs in 10–20% of cases.
- Neuromas in MEN IIB occur in skin, mucosa, eyes, GI and Respiratory tract
- Genetic screening, for germ-line RET mutations, is recommended. If positive, prophylactic thyroidectomy is done to prevent development of medullary Ca of thyroid.
ADRENAL NOTES

ANATOMY AND HISTOLOGY

The adrenal glands, relatively larger during fetal life, are found atop the kidneys. In adult life the adrenal glands are surrounded by fat. Both adrenal arteries arise from the aorta, with the left adrenal vein draining into the left renal vein, while the right adrenal vein drains into the inferior vena cava.

The gland itself is organized in layers, with two distinct zones recognizable grossly: the cortex and the medulla.

The zona glomerulosa is variable in thickness (10%) beneath the capsule. The zona fasciculata (75-80%) and zona reticularis (15%) work together in the production of both cortisol and androgens.

<table>
<thead>
<tr>
<th>C</th>
<th>Capsule</th>
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<tbody>
<tr>
<td>O</td>
<td>Glomerulosa (aldosterone)</td>
</tr>
<tr>
<td>R</td>
<td>Fasciculata (cortisol androgen)</td>
</tr>
<tr>
<td>T</td>
<td>Reticularis</td>
</tr>
<tr>
<td>E</td>
<td>Portal Circulation</td>
</tr>
<tr>
<td>X</td>
<td>Medulla (catecholamines)</td>
</tr>
</tbody>
</table>

ADRENAL CORTEX 80 – 90% of gland; mesenchymal origin

ADRENAL MEDULLA 10% of gland; neural crest origin
BIOSYNTHETIC PATHWAY: STEROIDOGENESIS

ACETATE ↓
CHOLESTEROL ↓ SCC
Δ5 – PREGNENOLONE

PROGESTERONE 17α
↓
17-OH PREGNENOLONE L → DEHYDRO
EPIANDROSTERONE

DEOXYCORTICOSTERONE 17α
↓
17-OH PROGESTERONE 3 L ↓ 3
ANDROSTENEDIONE

CORTICOSTERONE 17β
↓
11-DEOXYCORTISOL 21 ↓ 3
ESTRONE

ALDOSTERONE 11-DEOXYCORTISOL 17β
↓
CORTISOL α 11
TESTOSTERONE
ESTRIOL

NOTE:
SCC – Side chain cleavage enzyme
17α – 17α hydroxylase
17β – 17β hydroxylase
21 – 21 hydroxylase
11 – 11 hydroxylase
3 – 3β-hydroxysteroid dehydrogenase
18 – Oxidase (aldosterone synthase)
L – Lyase (Desmolase)
L → Lyase (Desmolase)
A – Aromatase

MINERALOCORTICOID PATHWAY
GLUCOCORTICOID PATHWAY
SEX HORMONE PATHWAY

STEROID TRANSPORT

Cortisol (15-30 mg/day) → Free form (metabolically active) < 5%

a. Transcortin or cortisol binding globulin (CBG) – high affinity
b. Albumin (low affinity, high capacity)
c. Cortisol metabolites are inactive and poorly bound to protein.

Aldosterone (50-250 µg/day) → Bound to proteins
STEROID METABOLISM

A. Cortisol → conjugation with glucuronic acid in liver and hence becomes inactive
   Also cortisol → cortisone (inactive)
   Measured as urinary 17-OHC (hydroxy corticoids) or kGC (ketogenic corticoids) or urinary free cortisol

B. Aldosterone → conjugation with glucuronic acid in liver → inactive
   Measured as aldosterone

C. Dehydroepiandrosterone (15-30 mg/day) → urinary 17 ketosteroids

NOTE: urinary 17 ks → 2/3 from adrenal
     (ketosteroids) → 1/3 from testis
     → all from adrenal

METABOLIC AND ANTI-INFLAMMATORY ACTIONS OF GLUCOCORTICOIDS

Carbohydrate Metabolism: increase in blood glucose level, decreased glucose uptake by tissues, increase in gluconeogenesis and glycogenolysis. ANTI-INSULIN EFFECT

Protein Metabolism: increase catabolism, decrease synthesis, negative N₂ balance

Fat metabolism: regulation of fatty acid mobilization, redistribution of fat (more trunk obesity), lipolysis increases

Inhibition of Allergic and Inflammatory Reactions: decrease antibody formation, decreased lymphatic tissue, inhibits granulocytes/monos, decreases cell mediated immunity and cytokine production; lymphopenia, eosinopenia occur, decreased membrane permeability to water

RELATIVE GLUCOCORTICOID AND MINERALOCORTICOID ACTIVITY

<table>
<thead>
<tr>
<th></th>
<th>Glucocorticoid</th>
<th>Mineralocorticoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Corticosterone</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Deoxycorticosterone</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>0.3</td>
<td>300</td>
</tr>
</tbody>
</table>
ACTH and adrenal cortical hormones, in addition to the well-documented circadian rhythm (which necessitates correct timing, normals and protocols for testing), are secreted in an episodic manner – DHEA-S has a more “blunted” release, making it less difficult to interpret.

**Structure of Pro-opiomelanocortin (POMC) – present in brain, pituitary, lymphocytes**

<table>
<thead>
<tr>
<th>N-terminal Fragment</th>
<th>ACTH</th>
<th>b-lipotropin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>g-lipotropin</td>
<td>b-endorphin</td>
</tr>
</tbody>
</table>

ACTH works by attaching to a membrane receptor, which activates adenylate cyclase, which in turn forms cyclic AMP, which activates protein kinase within the cell.

The circadian rhythm and pulsatile secretion of renin matches aldosterone and often parallels cortisol.

**NOTE:** ACTH is cleaved into α-MSH and CLIP (corticotrophin-like intermediate lobe peptide).
<table>
<thead>
<tr>
<th>Clinical Disorder</th>
<th>Hormone Abnormality</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing’s Syndrome</td>
<td>Cortisol up, ?androgen and aldosterone up</td>
<td>Obesity, hypertension, muscle wasting, hirsutism, weakness, amenorrhea, acne, hyperglycemia</td>
</tr>
<tr>
<td>W 1:10,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M 1:30,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conn’s Syndrome</td>
<td>Aldosterone up, renin down</td>
<td>Hypertension, headache, hypokalemia, weakness</td>
</tr>
<tr>
<td>1:2,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Androgen Excess</td>
<td>17-KS and DHEA and KGC and testosterone and 17-OH-progesterone all up, cortisol and 17-OHC down</td>
<td>Hirsutism, short stature, amenorrhea, abnormal genitalia</td>
</tr>
<tr>
<td>(Congenital adrenal hyperplasia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:15,000 homozygous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:75 heterozygous</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Disorder</th>
<th>Hormone Abnormality</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenocortical deficiency</td>
<td>ACTH up, cortisol and aldosterone down</td>
<td>Abdominal distress, dehydration, weakness, hyponatremia, hyperkalemia, postural hypotension, pigmentation, weight loss, BUN up</td>
</tr>
<tr>
<td>Addison’s Disease (primary adrenal destruction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:50,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary adrenal atrophy</td>
<td>Cortisol and ACTH down</td>
<td>Weakness, weight loss, anorexia</td>
</tr>
<tr>
<td>(ACTH deficiency)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:10,000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CUSHING’S SYNDROME (HYPERCORTISOLISM)

Major Clinical Findings: weight gain, central obesity, moon face and plethora, muscular weakness, malaise, depression or psychosis, oligomenorrhea/amenorrhea, hirsutism, striae, acne, skin thinning, bruising, polyuria, nocturia, decreased libido/impotence in men, hypertension, diabetes/impaired glucose tolerance, osteoporosis, increased risk of infections

**Cause**

**Exogenous** (most common)
Use of steroids e.g., autoimmune diseases, post- organ transplantation.

**Endogenous**

1. Pituitary Hypothalamic Disease (CUSHING’S DISEASE) 70%
2. Ectopic ACTH production (e.g., small cell Ca of lung) 10%
3. Adrenal causes
   - Adenoma 10%
   - Carcinoma 5%
   - Hyperplasia 5%

CUSHING’S SYNDROME: INVESTIGATION

**TABLE 321-4 Diagnostic Tests to Determine the Type of Cushing’s Syndrome**

<table>
<thead>
<tr>
<th>Test</th>
<th>Pituitary Macro-adenoma</th>
<th>Pituitary Micro-adenoma</th>
<th>Ectopic ACTH or CRH Production</th>
<th>Adrenal Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma ACTH level</td>
<td>↑ io ↑↑</td>
<td>N to ↑</td>
<td>↑ io ↑↑↑</td>
<td>↓ &lt;10</td>
</tr>
<tr>
<td>Percent who</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>respond to high-dose</td>
<td>&lt;90</td>
<td>&gt;95</td>
<td>&lt;10 &lt;90</td>
<td>&lt;10</td>
</tr>
<tr>
<td>dexamethasone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent who</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>respond to CRH</td>
<td>&gt;90</td>
<td>&gt;90</td>
<td>&lt;10 &lt;90</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

Note: ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; N, normal; ↑, elevated; ↓, decreased. See text for definition of a response.

**FIGURE 321-7** Diagnostic flowchart for evaluating patients suspected of having Cushing’s syndrome. *This group probably includes some patients with pituitary-hypothalamic dysfunction and some with pituitary microadenomas. In some instances, a microadenoma may be visualized by pituitary magnetic resonance scanning. 17-KS, 17-ketosteroids; DHEA, dehydroepiandrosterone; ACTH, adrenocorticotropic hormone; CT, computed tomography.
TESTS

1. **PLASMA CORTISOL**
   
   **Normal Values**
   
   - 8 a.m. = 5 to 25 µg/dl
   - 8 p.m. = 2 to 12 µg/dl

   **In C.S.**
   
   1. Plasma cortisol is elevated
   2. There is **LOSS OF DIURNAL VARIATION**

2. **LOSS OF DIURNAL VARIATION**
   
   a. In normal persons with “normal” sleep-wake schedule, plasma cortisol is high at 7-8 a.m.; low at 8 p.m. (or midnight)

   **In C.S.**
   
   This **VARIATION IS LOST**

   A midnight cortisol level \[ > 7.5 \text{ µg/dl} \] is diagnostic

   b. **Salivary Cortisol**

   Salivary cortisol levels correspond to plasma cortisols. Measuring **MIDNIGHT SALIVARY CORTISOL** level (salivette test kits) is helpful.

   **In C.S.**
   
   The midnight salivary cortisol value is \[ > 0.35 \text{ µg/dl} \]

3. **24 HOUR URINE FREE CORTISOL (UFC)**

   Cortisol is excreted in urine
   
   - free form
   - conjugated form (with glucuronides)

   **NORMAL VALUES** = 20-140 µg/day

   **In C.S.**
   
   The UFC is 3 to 4 times high.

   **NOTE:** Three UFC tests must be done for high sensitivity and specificities.

4. **OVERNIGHT DEXAMETHASONE SUPPRESSION TEST (DST)**

   **Principle:** Dexamethasone suppresses pituitary ACTH in normal persons, but not in most patients with endogenous C.S.

   1 mg. dexamethasone is taken orally at 11 p.m. (or midnight). Fasting plasma cortisol is measured at 8 a.m. the next day.

   **IN NORMAL PERSONS**

   Dexamethasone suppresses ACTH and hence cortisol, so plasma cortisol values are:

   - \(< 5.0 \text{ µg/dl (old assay)}\)
   - \(< 1.8 \text{ µg/dl (new immuno assay)}\)

   **In C.S.** **THERE IS USUALLY NO SUCH SUPPRESSION**

   i.e., plasma cortisol values are still high. **FALSE POSITIVE TESTS** (lack of suppression) occur in obesity, stress, D.M., estrogen use, etc.
5. **LOW DOSE DST**  
Same principle as above, but test is less sensitive, specific and more inconvenient  
– Baseline values are obtained (plasma cortisol or UFC)  
– 0.5 mg dexamethasone is given orally every 6 hours for 2 days  
– 24 hour urine is collected on 2nd day  
– Assay for UFC and 17-OHCS  

<table>
<thead>
<tr>
<th>In C.S.</th>
<th>UFC is &gt; 10 µg/day</th>
<th>17-OHCS is &gt; 2.5 mg/day</th>
<th>NO Suppression</th>
</tr>
</thead>
</table>

**IN NORMAL PERSONS**  
UFC < 10 µg/day  
17-OHCS < 2.5 mg/day  
Suppression

6. **HIGH DOSE D.S.T.**  
High dose dexamethasone tends to suppress ACTH produced by pituitary adenomas*. Ectopic tumors producing ACTH are not suppressed by dexamethasone.  

– Obtain baseline 24 hour UFC  
– 2 mg dexamethasone given orally every 6 hours for 2 days  
– Measure 24 hour UFC on day 2  

<table>
<thead>
<tr>
<th>In C.S.</th>
<th>Due to pituitary MICROADENOMA UFC values are suppressed to 90% of baseline value, (some indicate 50% reduction).</th>
</tr>
</thead>
</table>

*NOTE: 1. Pituitary MACROADENOMAS are suppressed minimally  
2. ECTOPIC TUMORS, e.g., lung carcinoids may express glucocorticoid receptors and may show ACTH suppression by dexamethasone.

7. **PLASMA ACTH**  

| In C.S. | Adrenal lesions < 5-10 pg/ml  
Pit/Hypo. lesions 30-150 pg/ml (50% cases may be within normal range)  
Ectopic tumors 200 pg/ml |
|---------|--------------------------|

8. **METARYPONE TEST**  
Metarypone (drug) blocks 11-beta hydroxylase enzyme. So cortisol production decreases. In Cushing’s disease (pituitary adenomas), ACTH levels increase due to loss of feed back inhibition. Ectopic ACTH producing tumors are not affected.

9. **PETROSAL SINUS SAMPLING**  
Blood samples (collected from petrosal sinus and peripheral vein) are assayed for ACTH. PSS: Peripheral sample ratio > 2 is suggestive of Cushing’s disease.
MORPHOLOGY

A. Pituitary Lesions – Microadenoma of basophils  F:M = 4:1  Age 20 – 30 years
– Macroadenoma (size > 1.0 cm) of basophils
– Corticotroph cell hyperplasia

B. Hypothalamic Lesion – CRH producing tumor

NOTE: Regardless of cause, the basophilic cells display homogenous light basophilic at times condensed cytoplasm due to accumulation of intermediate keratin filaments (CROOKE’S HYALINE CHANGE)

C. Adrenal Lesions
1. Adrenal atrophy
   a. E.g., exogenous steroid use causes ACTH suppression and hence cortical atrophy.
2. Adrenal hyperplasia
   a. Primary (cause unknown)
   b. Secondary (more common)
      Primary hyperplasia
      a. Pigmented nodular type ( lipofuscin pigment )
         – Nodules, black or brown, < 0.3 cm
         – Familial, occurs in children
      b. Massive macronodular type ( sporadic)
         – Nodules > 0.3  to 3 cm.  occurs in adults
         Genetic mutations: 1. McCune –Albright syndrome – a GNAS mutation
         2. cyclic AMP genes  PRK1RA( protein kinase 1 receptor alpha)
            and PDE11A ( phosphodiesterase 11 alpha)
         3. Non- ACTH hormones( GIP, LH,ADH, Serotonin) stimulate  their
            receptors ectopically expressed in cortex; cortisol production
            increases ( cause ?).
      Secondary hyperplasia
      a. Diffuse type
         Bilateral diffuse, gland enlargement
         wt. usually 25-40 gm (both glands); lipid-rich clear cells/ lipid poor cells
      b. Nodular type
         Bilateral nodular gland enlargement
         wt. = 30-50 gm.
         Lipid-rich clear cells/lipid-poor compact cells
3. Adrenal adenoma  10%
4. Adrenal carcinoma  5%
   a. Uncommon
   b. Occurs in children
   c. Produces more hypercortisolism than other lesions

D. ECTOPIC LESIONS producing ACTH, Cortisol, CRF
PRODUCTION AND SECRETION OF ALDOSTERONE (RAA SYSTEM)

Hypothalamus → Pituitary → ACTH → adrenal cortex

Angiotensinogen → Renin → Angiotensin I → Angiotensin II → Angiotensin III

Lungs: converting enzyme (ACE) → Angiotensin III

Kidney (juxtaglomerular cells): sympathetic input → Blood pressure → Na+

Aldosterone → K+

NOTE: Renin is inhibited by AT, ANP and ↑ K levels. AT acts through AT receptors. (AT1 and AT2). AT is destroyed by angiotensinase enzyme. Many tissues (heart, lung, brain, placenta, uterus, adrenals, kidneys) have local RAA systems.

HYPERALDOSTERONISM

- Excess aldosterone levels in blood
- Hypertension with hypernatremia Na↑ and hypokalemia K↓(or normoekalemia)
- H ions ↓ HCO3 ↑ metabolic alkalosis +
- Increased urinary loss of bicarbonate and ammonium ions
- Hypokalemic tetany, HTN induced cardiac failure and renal damage may occur
- Edema usually absent (due to escape phenomenon; what is this?)

PRIMARY HYPERALDOSTERONISM

Causes:
1. Adrenal adenoma (unilateral) Conn’s syndrome 80%
2. Idiopathic bilateral hyperplasia of adrenals
3. Glucocorticoid supressible type (rare)
4. Adrenal carcinoma (rare)

NOTE Per Robbins, # 2 is 60% and # 1 is 35%
Adrenal adenoma

- F:M = 2:1
- Age: 30-50 years
- Unilateral, well-circumscribed mass < 2.0 cm
- Lipid laden cells similar to “zona fasciculata” cells
- Spironolactone bodies seen (eosinophilic, laminated, round, cytoplasmic inclusion following diuretic Rx)

Idiopathic bilateral hyperplasia

- Occurs in children/young adults
- Diffuse, nodular hyperplasia
- Cells resemble normal glomerulosa cells
- Overactivity of aldosterone-synthase gene CYP11B2. (CYP – Cytochrome P_{450})

Glucocorticoid suppressible or remediable type

- Familial, uncommon
- Due to a chimera gene [fusion between aldosterone synthase gene CYP11B2 and 11β-hydroxylase gene CYP11B1]
- Hybrid cells with features of zona glomerulosa and fasciculata cells
- Cells are under ACTH control; hence glucocorticoids that suppress ACTH, minimize hyperaldosteronism.

SECONDARY HYPERALDOSTERONISM

Caused by increased renin production leading to increased aldosterone synthesis

**Causes:**
1. Hypertension
2. Renal vascular stenosis
3. Nephroarteriosclerosis
4. J. G. cell tumor (Juxta glomerular apparatus tumor)
5. Edema states (cirrhosis, nephrotic syndrome, CHF)
6. Pregnancy (estrogens increase renin levels, progesterones have antialdosterone action)

**NOTE:** Rarely, aldosterone producing tumors, e.g., ovarian tumors may cause hyperaldosteronism

**What is Bartter’s Syndrome?**

<table>
<thead>
<tr>
<th></th>
<th>aldosterone</th>
<th>plasma renin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IMPORTANT:</strong> 1° hyperaldosteronism*</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>2° hyperaldosteronism</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

**NOTE:** *Aldosterone not suppressed by saline loading. Aldosterone: PR activity > 30 is suggestive of hyperaldosteronism.*
CONGENITAL ADRENAL HYPERPLASIA
(adrenogenital syndrome)

Autosomal recessive disorder

Partial or complete lack of biosynthetic enzymes usually leads to decreased or absent production of aldosterone and/or cortisol, and increased production of androgens. This leads to increased ACTH secretion (why?), adrenal cortical stimulation, and hyperplasia (adrenal glands are bilaterally enlarged to about 10–15 times normal).

21-HYDROXYLASE DEFICIENCY: Most common (95% of cases). CYP21B gene abnormality.

Clinical features: Three forms occur; classic(salt wasting), simple virilizing, and non-classic (mild).

1. Salt wasting
   (complete) K ↑ H ↑ acidosis
   21-Hydroxylase lack
   in utero → mother’s kidneys
   handle electrolyte imbalances
   Post delivery → salt losing crisis,
   CVS collapse, death.

   Virilism owing to shunting of substrates into the androgen pathway also occurs.
   male infants → enlarged genitalia, precocious puberty, muscles +++
   female infants → clitoral enlargement, labial fusion (pseudohermaphroditism)
   adult women → acne, amenorrhea, hirsutism
   adult men → oligospermia, infantile testes, short stature

NOTE: Adrenal medullary dysplasia with decreased catecholamine production occurs in this condition. Lack of glucocorticoids affects catecholamine production.

2. Simple virilizing form (without salt wasting)
   This occurs in partial 21-hydroxylase deficiency. There is less mineralocorticoid synthesis but enough for salt reabsorption. Testosterone levels are increased.

3. Non-classic (late-onset, mild) form - partial 21- hydroxylase deficiency
   more common than the classic form; occurs in childhood and puberty
   patients may be asymptomatic/mild hirsutism, acne and menstrual problems

Diagnosis:
1. Demonstrating biosynthetic enzyme deficiencies
2. Genetic studies
3. Routine neonatal metabolic screening
4. Molecular testing for antenatal detection of CYP21B mutation

NOTE: Per new Big Robbin’s CYP 21B = CYP21A2 and CYP21A = CYP21A1.
COMMON FORMS OF CONGENITAL ADRENAL HYPERPLASIA

Autosomal recessive disorders

<table>
<thead>
<tr>
<th>Deficient Enzyme</th>
<th>Clinical Findings</th>
<th>Lab Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-Hydroxylase (95%)</td>
<td>Hirsutism, K+ up, Na+ down, amenorrhea, precocious puberty, masculinization</td>
<td>Cortisol ↓, aldosterone ↓, ACTH, renin, androgens ↑</td>
</tr>
<tr>
<td>Due to gene CYP21B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>inactivation by</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pseudogene CYP21A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11b-Hydroxylase (2%)</td>
<td>Masculinization, precocious puberty, hypertension, K+ down</td>
<td>aldosterone and cortisol down, androgens, 17-KS, ACTH, prog and DOC all up</td>
</tr>
<tr>
<td>17a-Hydroxylase (rare)</td>
<td>Hypertension, K+ down, female immaturity</td>
<td>androgens, estrogens, corticosteroids down; progesterone and ACTH up</td>
</tr>
</tbody>
</table>

**NOTE:** In 11-hydroxylase and 17-hydroxylase deficiencies, DOCA (deoxycorticosterone) functions as a potent mineralocorticoid and causes HTN.

ADRENOCORTICAL INSUFFICIENCY (HYPOADRENALISM)

Primary Hypoadrenalism: Acute type (adrenal crisis)

**Causes**

- A patient with chronic hypoadrenalism facing stress (requiring steroids but adrenals do not respond)
- Exogenous steroid use where drugs are stopped abruptly. **NOTE:** ALWAYS TAPER DRUGS SLOWLY BEFORE STOPPING. WHY?
- Massive adrenal hemorrhage as seen in:
  - Newborns following difficult, prolonged delivery
  - Anticoagulant therapy
  - D.I.C.
  - Bacterial sepsis (W.F. syndrome)
WATERHOUSE-FRIDERICHSEN SYNDROME (ACUTE PRIMARY HYPOADRENALISM)

Usually occurs in children

Associated with:
- Overwhelming sepsis caused by *n. meningitidis, pseudomonas, pneumococcus, H. influenzae,* or *staphylococcus* infection.
- Severe hypotension and shock.
- D.I.C. with purpura
- Bilateral adrenal hemorrhage (caused by vasculitis, D.I.C.).

Fever, sepsis, D.I.C., positive blood cultures help in diagnosis.

Prompt diagnosis and Rx with antibiotics are helpful. Adrenal glands can recover and resume function. Occasionally, the course is abrupt and death occurs quickly.

PRIMARY CHRONIC HYPOADRENALISM (ADDISON’S DISEASE)

90% of the cortex must be affected/destroyed before symptoms and signs appear in a patient.

Causes:
- Idiopathic (autoimmune adrenalitis) 60–70% (MOST COMMON)
- T.B. fungi (20%)
- H.I.V., opportunistic infections, viruses, etc.
- Metastatic carcinoma, e.g., from lungs, breast, etc.
- Sarcoidosis, hemochromatosis, amyloidosis
- Drugs
- Genetic disorders

Autoimmune Adrenalitis (More common in white women)

There are 3 types:
I. **Autoimmune Polyendocrine Syndrome (APS1)**
   Autoimmune adrenalitis, chronic mucocutaneous candidiasis, ectodermal dystrophy (affecting skin, nails, teeth), hypoparathyroidism, PA, hypogonadism
   **Cause:**
   - AIRE (autoimmune regulator) gene mutation on chromosome 21 (this gene normally occurs in thymus and helps promote death of self reactive T cells during central tolerance)

II. **APS 2**
   - Gene mutation on chromosome 6
   - Adrenalitis, thyroiditis, D.M.

III. **Isolated Autoimmune Type**
   - Immune destruction restricted to the adrenal glands. Disease overlaps with APS2.
CLINICAL FEATURES IN ADDISON’S DISEASE

- G.I. → anorexia, nausea, vomiting, diarrhea
- ASTHENIA (weakness), fatigue, weight loss
- Hyperpigmentation due to ↑ ACTH (MSH)
- Hypotension, hypoglycemia, hypovolemia
- Serum Na ↓, K ↑ HCO₃ ↓ Cl ↓
- Antiadrenal antibodies present (50% of cases)
- Associated with HLA-B8 and DR-3
- Glands are small, atrophic, shrunken with a few cortical cells, medulla is preserved, lymphocytic infiltration prominent
- Death due to vascular collapse and coma. In Addisonian crisis, prompt Rx is a must

SECONDARY HYPOADRENALISM

Causes:
1. Hypothalamic/pituitary disease, such as infarcts, infection, tumor, irradiation
2. Hypothalamic/pituitary suppression due to drugs (steroids)

<table>
<thead>
<tr>
<th></th>
<th>Primary Hypoadrenalism</th>
<th>Secondary Hypoadrenalism</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>*Adrenal response to ACTH</td>
<td>No</td>
<td>yes</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>Present</td>
<td>absent</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>↓</td>
<td>normal or near normal</td>
</tr>
</tbody>
</table>

* ACTH stimulation test. “Plasma cortisol increase is the expected response,’’ following ACTH injection. 250 µg of co-syntrophin given 1M. Measure plasma cortisol after 60 minutes. > 18 µg/dl is normal response.
ADRENOCORTICAL NEOPLASMS

Adenomas
- Well circumscribed, nodular, about 2.5 cm size
- Yellowish brown with necrosis, hemorrhage, cystic changes and calcification
- May be nonfunctional (discovered incidentally) or functional (adjacent cortex is ATROPHIC)
- Cells resemble normal cortical cells, nuclei may be pleomorphic, mitoses not usually seen

Adrenal Carcinomas
- Rare cortical neoplasms; associated with Li Fraumeni syndrome and Beckwith’s syndrome.
- Occur at any age
- Usually functional (hyperadrenalism)
- Highly malignant and large with necrosis, hemorrhage and cystic changes
- Tumor cells may mimic those of an adenoma or may show atypical giant cells, mitoses, capsular or sinusoidal invasion, etc.
- Metastases to nodes, lungs, liver (vascular spread is common)
- 50–90% mortality, usually within 2 years

Myelolipoma
- A benign tumor composed of mature fat and myeloid (hematopoietic) cells
- F:M = 1:1, usually between fifth and seventh decades
- 50% cases – usually incidental discovery, but some may be massive and cause abdominal pain, hematuria, palpable mass, hemorrhage, and hypertension

NOTE: Adrenal incidentaloma – any adrenal mass discovered incidentally (usually by imaging studies done for some other condition).
ADRENAL MEDULLA

The adrenal medulla is a part of the neural crest system and contains chromaffin cells (neuroendocrine cells) and their supporting (sustentacular) cells.

**Biosynthesis of catecholamines**

- Phenylalanine
- ↓
- Tyrosine
- ↓ Hydroxylase
- Dihydroxyphenylalanine (DOPA)
- Decarboxylase ↓
- Dihydroxyphenylethylamine (Dopamine)
- Hydroxylase ↓
- Norepinephrine (NE)
- N-methyl transferase ↓
- Epinephrine

**NOTE:** Chromaffin cells also produce histamine, serotonin, renin, neuropeptide hormones, chromogranin A, ACTH, somatostatin, synaptophysin etc.

**Metabolism**

- Urine Metabolites
  - VMA – 80%
  - Metanephrines – 10–15%
  - Free catecholamines – < 1%

- Norepinephrine
  - Epinephrine
  - MAO
  - 3,4 Dihydroxy Mandelic Acid
  - COMT
  - Normetanephrine
  - Metanephrine
  - MAO
  - Vanillylmandelic Acid (VMA)
  - Homovanillic Acid (HVA)

**NOTE:** MAO – Monoamino oxidase
COMT – Catechol-o-methyltransferase
**PHEOCHROMOCY TOMAS**

- Tumors of the adrenal medulla (90%) or paraganglia (10%)
- 0.005% to 0.1% of unselected autopsies
- 0.4% to 0.6% of patients with severe and sustained hypertension
- Most common between third and fifth decades
- M:F ratio 1:1 in adults/2:1 in children
- 29% secrete only norepinephrine; 15% secrete only epinephrine; the rest secrete both; ACTH, serotonin, histamine, renin, etc. are also produced
- 24-hr urinary VMA and metanephrines (detects 80–90% of cases) are helpful
- Plasma catecholamines have disadvantages: intermittent secretors difficult to diagnose, large overlap of normal/abnormal values, many conditions may elevate plasma catecholamine levels (coffee, alcohol, drugs)
- Associated with a number of familial syndromes: MEN IIA and IIB, Lindau-von Hippel disease, von Recklinghausen’s disease, Sturge-Weber syndrome

**Gross Features:**
- Small, well circumscribed tumors to large, hemorrhagic ones weighing 4 kilograms
- Vascularized lobules with cystic and necrotic changes seen
- Fresh tissue + potassium dichromate $\rightarrow$ dark brown color of chromaffin cells (oxidation of stored catecholamines)

**Micro:**
- Polygonal or spindle cells arranged in nests or aggregates
- Cytoplasmic globules seen; granules stain positive with silver stains
- Round nuclei with “a salt and pepper” chromatin
- Immuno stains S-100, chromogranin, synaptophysin are positive
- E.M. studies show membrane-bound, electron dense granules
- Cellular atypia, mitoses, capsular, or vascular invasion may be present
- **DIAGNOSIS OF MALIGNANCY IS BY PRESENCE OF METS, ONLY!** (Seen in nodes, liver, lungs, bone, etc.)

**Clinical Features:**
- Paroxysmal HTN 2/3 cases Headache, sweating, palpitations, tachycardia, tremors
- Sustained chronic HTN 1/3 cases chest pain, nausea, vomiting
- Other endocrinopathies/paraneoplastic syndromes, such as Cushing’s syndrome (ACTH production)
- Paroxysmal episodes with sudden catecholamine release can cause acute CHF, MI, cardiac arrhythmias, pulmonary edema, CVA $\rightarrow$ death
- Catecholamine cardiomyopathy occurs due to
  1. Direct cytotoxicity
  2. Vasoconstrictive ischemia

**Treatment:**
- Medical – drugs causing adrenergic blockade
- Surgical

What is the “rule of 10’s” in pheochromocytoma?
PARAGANGLIOMA

- Paraganglia are neuroendocrine cell clusters associated with sympathetic and parasympathetic nervous system occurring in an extra-adrenal and adrenal location
- Paraganglioma are tumours of paraganglia. Based on location, there are 2 types:
  1. Paravertebral type (sympathetic) produce catecholamines, e.g., bladder, organs of Zuckerkandl
  2. Associated with head and neck vessels (parasympathetic) e.g., carotid body tumors arise in carotid body
     Chemodectomas arise in jugulotympanic body. These normally sense $O_2$ and $CO_2$ levels in blood.
- MICRO.
  Nests (Zellballens) of ovoid tumour cells with pink, granular cytoplasm and vesicular nuclei supported by spindle stromal sustentacular cells
  Neuroendocrine markers, CD 56 CD 57 and S-100 (sustentacular cells) are positive

- All such paragangliomas are uncommon.
- Occur between 50–60 years; present as neck masses
- Multicentric (15–25% cases), malignant (10–40%), metastasize (10%), fatal (50%)

GENETICS

Succinate dehydrogenase enzyme is involved in mitochondrial electron transport and $O_2$ sensing. SDH controls HIF1 alpha (hypoxia inducible factor 1 alpha).

Mutations of SDH genes (SDHB, SDHC, and SDHD) cause loss of function and hence increased HIF1-alpha activity and tumour formation (Paraganglioma).

<table>
<thead>
<tr>
<th>Familial paraganglioma</th>
<th>Type 1</th>
<th>Type 3</th>
<th>Type 4</th>
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</thead>
<tbody>
<tr>
<td>Gene involved</td>
<td>SDH D</td>
<td>SDH C</td>
<td>SDH B</td>
</tr>
<tr>
<td>Associated lesion</td>
<td>Pheochromocytoma</td>
<td>Pheo.</td>
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<tr>
<td></td>
<td>Paraganglioma</td>
<td>paraganglioma</td>
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Revised Feb. 29, 2012
CNS LECTURES

Dr. Brett Bartlett

NOTE: Dr. Bartlett’s ppts. will be available on the path. web site
NEURODEGENERATIVE DISORDERS

J.A. Weyhenmeyer, Ph.D.

(notes may be helpful)

Reading Assignment: Robbins and Curriculum
Objectives: College Objectives
NEURODEGENERATIVE DISORDERS

- Common features – diseases of neurons that selectively affect one or more functional systems; usually characterized by progressive and symmetric involvement; degenerative diseases that affect similar brain regions produce similar clinical syndromes.

Diseases of the cerebral cortex
- Primary or secondary degeneration of the cortex (bilateral) results in dementia (global impairment of cognitive function that usually is progressive and interferes with normal social and work activities) – deficits in intellectual performance, judgment, abstract thinking, and memory.
- Alzheimer’s disease (AD)
  - One of the most common degenerative diseases of the brain; 4% over age 65 are incapacitated by organic dementias, 10% have mental deterioration but can still function; 50-60% of patients with organic dementia have AD; occurring mainly in individuals over 45, with the highest incidence in the ninth decade.
  - Clinical:
    - Progressive dementia with increasing loss of memory, intellectual function and disturbances in speech.
    - Initial – slight dulling of intellect (thought processes slowed, social and economic activities impaired, memory impaired, speech disorder (anomia), echolalia, difficulty in comprehending written and oral speech).
    - Depression is common (25% of patients); agitation restlessness common.
    - Motor signs more apparent as the disease progresses; may include slow, shuffling gait and myoclonus; in late stages – generalized weakness and muscle contractions, bladder and bowel difficulties.
  - Etiology??
    - Evidence for genetic or familial predisposition – risk of developing AD increased 4–5 fold among first generation relatives of AD patients; concordance in identical twins >60% (non-genetic factors are also important).
    - Familial (10% of all cases).
      - Amyloid precursor protein (APP) gene (chromosome 21, close to centromere (AD1 locus)).
• Amyloid precursor protein (APP) gene encodes protein precursor for β-amyloid peptide (A4), accumulates in senile plaques and (brain) blood vessel walls of AD (and Down’s).
• APP gene mutation may account for 2% to 3% of cases.
• Presenilin 1 (chromosome 14) and 2 (chromosome 1) – presenilin proteins involved with segregation of chromosomes; may account for remaining cases of familial AD.
• Late onset AD – individuals with multiple (2+) copies of the ApoE4 gene (chromosome 19) are 8x more likely to develop AD than individuals who carry a single copy.
• Hypothesis – ApoE functions as a “pathological chaperone,” binding to β-amyloid and making it insoluble.
• Current studies of amyloidogenesis exploring possibility that abnormal APP processing in AD alters control of cell growth, eventually leading to neuronal loss.
• Pathology:
  • Gross – diffuse cerebral atrophy; may be more severe in frontal and temporal lobes (hippocampus); degree of atrophy variable (brain weight between 850-1150g at autopsy, normal is 950 to 1350g).
  • Histology – loss of both neurons and neuropil in cortex, with secondary demyelination in subcortical white matter; greatest loss of large cortical neurons; most characteristic findings are senile plaques and neurofibrillary tangles.
    • Neurofibrillary tangle – accumulation of filaments within body of swollen neuron; paired helical filaments (10 nm in dia with twist every 80 nm) first appear in the hippocampus (especially CA1 region and subiculum), and subsequently throughout the cortex.
    • Presence in cortex not necessary for diagnosis if sufficient numbers of neuritic plaques are present.
  • Senile plaques – found throughout cortex and hippocampus (number of plaques/field correlated with degree of intellectual loss); consist of a core of amyloid material and a corona of abnormally enlarged neurites – terminal axons.
    • Tangles and plaques occur with advancing age in the absence of dementia, but in AD their numbers are significantly increased.
  • Granulovacuolar degeneration – clear neuronal cytoplasmic vacuoles containing basophilic inclusions; found only in cell bodies.
  • Hirano bodies – rod-shaped eosinophilic inclusions containing actin in a paracrystalline array; found in cell bodies and processes.
• Lab:
  • CSF – normal.
  • Generalized slowing of EEG.
  • Cerebral blood flow reduced as neurons die and oxygen demand is reduced.
• Neurochemistry:
  • 50-90% decrease in choline acetyltransferase activity in cerebral cortex and hippocampus – selective loss of ACh neurons (from deep nuclei in septum to hippocampus and basal nucleus of Meynert to the cerebral cortex).
  • CRF and somatostatin decreased, both found in degenerating neurites of senile plaques.
  • Glutamate may be involved in loss of large neurons in both cortex and hippocampus.
• Diagnosis – established by clinical exam and confirmed by mental status and neuropsychologic tests (genetic – ApoE4, tau protein, physical (pupillary response)); confirmed by histopathology at autopsy.
• Treatable dementias – general paresis, normal-pressure hydrocephalus, chronic subdural hematoma, nutritional deficiencies (Wernicke-Korsakoff syndrome, Marchiafava-Bignami disease, pellagra, vitamin B12 deficiency with subacute degeneration of spinal cord and brain).
• Course – progressive, ending in complete incapacity and death (4-10 yrs).
• Rx – dependent on increasing the function of cholinergics.

• Pick’s disease (lobar atrophy)
  • Relatively rare form of dementia (<5% of organic dementias).
  • Onset between 40 and 60 yrs.
  • Etiology – unknown, although familial cases have been reported.
  • Clinical – similar to AD; frontal lobe disturbances (e.g., lapses in social behavior, lack of restraint).
• Pathology:
  • Gross – circumscribed involvement of temporal and frontal lobes, mild involvement of parietal lobe, pre- and postcentral gyri largely spared.
  • Histology – most characteristic feature is presence of Pick bodies (argentophilic intracytoplasmic inclusion bodies) in neurons of hippocampus and neighboring structures (roughly the size of the affected neuron’s nucleus with tightly compressed filaments that leave small empty holes).
  • Affected cortex shows less specific but severe neuronal loss and spongy gliosis; scattered surviving neurons appear swollen, with pale, eosinophilic cytoplasm and eccentric nucleus.
Diseases of basal ganglia and brainstem

- **Huntington’s disease**
  - A progressive hereditary disorder (appearing between ages of 20 and 50); characterized by a movement disorder with an insidious onset of random inadvertent fidgeting or purposeless movements that progress to chorea over a period of years, dementia and personality disorder.
  - **Etiology – genetic:**
    - Prevalence is 8/100,000; transmitted as autosomal dominant with full penetrance (each child has a 50% chance of being affected).
    - Abnormal gene located on the short arm of chromosome 4; predictive testing with the G-8 probe.
  - **Clinical – triad of movement disorder (choreiform), personality disorder and dementia.**
    - Onset – insidious, beginning with clumsiness, dropping objects, fidgetiness, irritability and neglect, progressing to choreic movements and dementia.
    - Choreiform movements – involuntary movements that appear purposeless and abrupt; muscles affected in random manner (movements flow from one part of the body to another).
    - Early movements may be difficult to distinguish since they are often incorporated into intentional movements (e.g., may tap fingers incessantly or constantly make grooming maneuvers).
    - Changes in facial expression can be incorporated into normal facial movements with seductive winking or pursing of lips.
    - Dysarthria may be early feature, unintelligible speech common in fully advanced cases.
    - Dysphagia common at all stages – contributes to ultimate cause of death in many patients (aspiration pneumonia).
    - Difficulty with eye movements is common (impaired initiation of saccades, inability to make saccade without head movement or blink, impaired fixation, smooth pursuit is interrupted).
    - Mental – organic dementia with progressive impairment of memory and intellect, apathy and lack of personal hygiene.

- **Pathology:**
  - Gross – brain shrunken with mild to moderate atrophy visible in frontal and parietal lobes (in more severe cases brain weight may be reduced by as much as 30%).
  - Striatal loss responsible for movement disorder; dementia results from damage in cortex and deep nuclei.
• Histology:
  • Loss of medium sized spiny type-1 striatal neurons and their GABAergic projections (to globus pallidus and substantia nigra) – supports view that restricted neuronal population is involved.
  • Corresponding fibrillary astrocytosis (particularly in striatum); in advanced stages, striatum may be completely devoid of cells (choreic movement replaced by dystonia and akinesia).
  • Neurochemistry – no specific neurotransmitter loss.
  • Loss of striatal neurons responsible for decrease in striatal/nigral GABA and its synthesizing enzyme (glutamic acid decarboxylase), choline acetyltransferase, DA and ACh receptors.
  • Lab – blood, urine and CSF normal.
• Diagnosis – clinical triad of chorea, dementia and personality disorder, genetic screen.

• Course and Rx:
  • Disorder is progressive, resulting in total disability and death within 15 yrs; even when chorea is controlled, personality disorder and mental changes result in complete disability.
  • Motor disorders aggravated by Rx for chorea (e.g., akinesia, apraxia and gait disorder) may result in motor disability remaining unchanged.
  • Dopamine antagonists (neuroleptics e.g., haloperidol) attenuate the chorea and effect behavior (irritability, paranoia, emotional outbursts and bizarre behavior are decreased); no effect on the progressive dementia.

• Parkinson’s disease
  • Tremor, muscular rigidity and loss of postural reflexes; most frequent basal ganglia disorder; leading cause of neurologic disability in individuals >60.
  • Multiple forms:
    • Primary (idiopathic, shaking palsy) parkinsonism – no definable cause, most common extrapyramidal syndrome in the aged; more common in males than females; relatively common with a prevalence of 2:1000.
    • Typical patient is between 50 and 70; unilateral tremor is most common initial symptom that results in medical consultation.
    • Secondary (symptomatic) and parkinsonism-plus syndromes – definable cause:
      • Postencephalitic parkinsonism – a prominent sequelae of encephalitis epidemic between 1919 and 1926; typically reveal hemiplegia, bulbar or ocular palsies, dystonia, tics and behavioral disorder in addition to parkinsonian symptoms.
- Arteriosclerotic parkinsonism – multiple small lacunar infarcts throughout brain; nerve cell loss is diffuse - may be greater in globus pallidus than in substantia nigra.
- Drug induced parkinsonism.
  - Environmental toxins – injection of the pyridine derivative MPTP (n-methyl 4-phenyl-1,2,3,6 tetrahydropyridine); industrial pollutants of an allied chemical structure may be important.

- Clinical:
  - Classic signs – tremor, rigidity, akinesia and postural instability (TRAP); disorders of posture, equilibrium and autonomic function are common.
  - Early signs (usually present for years before more obvious symptoms).
    - Immobile face, infrequent blinking.
    - Poverty of movement – tendency to maintain a single position for long periods, progresses to difficulty with fine motor tasks (buttoning shirt, performing finger movements that require dexterity), dragging the involved leg, feeling loss of power in affected limb, changes in handwriting (micrographia), change in posture (simian - bent over), change in voice quality (monotone).
  - Advanced disease – resting tremor, cogwheel rigidity, bradykinesia/akinesia, postural instability, masked face, reptilian stare, drooling and inarticulate speech.

- Pathology:
  - Gross – loss of pigmented neurons in substantia nigra (zona compacta) and locus coeruleus.
  - Histology – Lewy bodies (eosinophilic core surrounded by a clear halo) in neuronal cytoplasm - not pathognomonic for PD but highly characteristic; cell loss in basal nucleus of Meynert (basis for PD dementia??).

- Neurochemistry:
  - Physiologic role of DA system – inhibits striatum (counterbalances excitatory cholinergic activity).
    - Release of inhibitory DA input on striatal ACh activity – accounts for efficacy of anti-cholinergics.
  - Selective depletion of DA in striatum – correlated with extent of degeneration in substantia nigra; motor symptoms do not manifest until 70-90% of nigral neurons are destroyed.
  - Endogenous toxic factor – H2O2 byproduct of DA metabolism that is normally catabolized by catalase or peroxidase (reduced in the nigral region of PD patients); failure of these enzymes to detoxify H2O2 exerts a cytotoxic effect on
amine producing neurons by generating free hydroxy radicals, superoxide radicals or lipid peroxide.

- **Course and Rx:**
  - All forms are progressive leading to variable periods of motor disability.
    - Primary parkinsonism – 25% are severely disabled or die within 5 years, 65% within 10 years, 80% within 15 years.
  - Rate of progression is defined by degree of DA deficiency – determines drug Rx.
    - Compensated phase – decision to use drugs is determined by patient’s symptoms (mild with no functional impairment - no drug therapy; some degree of akinesia and rigidity - drug therapy may be warranted).
    - Anti-cholinergics – muscarinic antagonists - moderate improvement of all symptoms; usefulness restricted by side effects (dryness of mouth, blurred vision, urinary retention, obstipation, behavioral abnormalities, psychotic episodes).
    - Antihistamines – anti-parkinsonian action due to their anti-cholinergic properties.
    - Tricyclics – block DA reuptake and storage, and have an anti-cholinergic action (may improve akinesias, rigidity and depressive symptoms).
  - Decompensated phase (established signs of Parkinson’s disease; difficulty with daily routines).
    - Levodopa/carbidopa – therapeutic limitation is appearance of involuntary movements (mild, choreiform to severe, dystonic).
    - Ergoline derivatives (bromocriptine) – activate DA receptors, less potent than levodopa/carbidopa; side effects include nausea, vomiting and hypotension.
    - Monoamine oxidase inhibitors (L-deprenyl) – MAO-B inhibitor (form present in striatum; DA is major substrate for MAO-B), accumulation of DA prolonging its action.

- **Surgery:**
  - VL -relieves contralateral resting tremor (action tremor not affected) and rigidity (disturbances in gait, posture and speech not improved) - best candidate is patient with unilateral tremor and rigidity of arm, with slowly progressing disease.
  - Globus pallidus (pallidotomy).
  - Transplant – experimental trials with adrenal medullary autografts and neonatal nigral cells.

- **Progressive supranuclear palsy**
• Pseudobulbar palsy, supranuclear ocular palsy affecting primarily vertical gaze, extrapyramidal rigidity, gait ataxia and dementia; usually begins in sixth decade; death within 10 yrs.
• Clinical:
  • Gait – impaired gait an early sign (unsteadiness, patient suddenly falls for no apparent reason); motor disturbances progress to slowness and stiffness of movement.
• Visual:
  • Diplopia also common initial symptom.
  • Characteristic feature – preservation of ocular movements with oculocephalic maneuvers (indicates ocular palsy is supranuclear); vertical gaze more affected than lateral gaze, and downward gaze more affected than upward gaze (results in tripping over low objects, difficulty going down stairs and eating).
  • Saccades slow, prolonged and finally restricted; eventually all voluntary saccadic and pursuit eye movements lost.
  • Sustained contraction of frontalis muscle, lid retraction and infrequent eye blink give patient a surprised facial expression.
• Dysphagia may predispose to aspiration pneumonia.
• Dementia is common.
• Pathology:
  • Gross – atrophy is especially prominent in brainstem (midbrain and cerebellum).
  • Histology – neuronal degeneration in substantia nigra, pontine tegmentum, periaqueductal gray and globus pallidus, while cortex is spared; neurofibrillary tangles (15 nm straight filaments) are prominent and distinct from usual paired helical filaments seen in Alzheimer’s and Parkinson’s.
• Lab:
  • EEG slow and disorganized.
  • CT scan and MRI show atrophy of pons and midbrain.
• Course – progressive; death in 6–10 yrs (intercurrent infection).
• Diagnosis – triad of mental disorder, supranuclear ophthalmoplegia and abnormal gait.
• Treatment – anti-parkinsonian drugs (e.g., anti-cholinergics, amantadine, L-DOPA) are effective early in the disorder.

Spinocerebellar degenerations
• Friedreich’s ataxia
• Familial and hereditary disease with degeneration of dorsal spinal cord and cerebellum; characterized by trunk and limb ataxia, absence of tendon reflexes, loss of limb proprioception and extensor plantar responses; clubfoot and scoliosis are common; cardiomyopathy is frequent.
• One of the most common hereditary diseases of the nervous system (autosomal recessive disorder involving chromosomes 9 and 11); usually begins between ages 7 and 13.
• Clinical:
  • Motor – ataxia of gait (most common symptom and first to appear); results from a combination of cerebellar asynergia and ataxia due to proprioceptive loss; movements are jerky, awkward and poorly controlled; intention tremor in arms, dysarthria may become so severe that speech is unintelligible; weakness of muscles common.
  • Sensory – loss of vibratory and position sense are early signs (posterior columns); loss of 2 pt. discrimination, stereognosis, pain appreciation, temperature and tactile sensation are occasionally seen.
  • Reflexes – tendon reflexes in legs almost always absent.
  • Nystagmus (fixation type); optic atrophy.
  • Clubfoot (75%) and scoliosis are characteristic.
• Pathology:
  • Gross – spinal cord and cerebellum may be normal or slightly shrunken (4.38).
  • Histology:
    • Spinal cord – degeneration of posterior funiculi, lateral corticospinal tracts and dorsal/ventral spino-cerebellar tracts; compact fibrillary gliosis is extensive; degeneration also involves dorsal roots, ganglia and peripheral nerves; loss of cells in Clarke’s column (substantia gelatinosa to a lesser extent).
    • Cerebellum – atrophy of Purkinje and dentate neurons.
    • Brainstem – degeneration of corticospinal tracts in medulla.
  • Neurochemistry – decreased activity of lipoamide dehydrogenase and mitochondrial malic enzyme.
  • Lab – normal.
• Course – onset early and progresses to complete incapacity by age 20; death results from intercurrent infection.

**Olivopontocerebellar atrophy**
• Ataxia (first legs, then arms, hands and bulbar musculature).
• Pathology:
- Pontine and cerebellar (Purkinje) neurons affected.
- Microscopic – cerebellar cortex shows extensive loss of Purkinje neurons, reactive hypertrophy and proliferation of Bergmann’s astrocytes.

**Motor neuron disease**

- **Amyotrophic lateral sclerosis (ALS)** – progressive degeneration of corticospinal tracts and α-motor neurons, resulting in both upper (primary lateral sclerosis) and lower (progressive muscular atrophy) motor neuron disease; important features include absence of neurologic or organ system involvement and sparing of voluntary eye muscles and urinary sphincters
  - Subgroups:
    - Familial ALS – 10%; usually autosomal dominant; pathological changes in lateral columns, anterior horn cells, spinocerebellar tracts and posterior columns.
    - Secondary ALS – may occur in association with plasma cell hycrasias (multiple myeloma, macroglobulinemia), lead poisoning.
    - Sporadic ALS – most common form; pathologic changes are limited to lateral columns and anterior horn cells.
  - Clinical – disease of middle to late life.
    - Initial signs vary depending on extent of upper and lower motor neuron involvement - gait disturbance, limb weakness, dysarthria and dysphagia are common; deficits are usually symmetric; reflexes increased or depressed (depending on balance of upper and lower motor neuron damage); dysarthria and dysphagia caused by a combination of upper and lower motor neuron disease; respiratory impairment present in all at some point.
  - Pathology – familial:
    - Gross appearance of spinal cord – decrease in size of ventral roots of lumbar and cervical segments.
  - Histology:
    - Pallor (loss of myelin) in lateral and anterior columns affecting both lateral and anterior corticospinal tracts (most pronounced in lateral CST).
    - Ventral horn – MN population reduced; those that remain are degenerating with evidence of karyolysis and chromatolysis.
  - Pathology – sporadic:
    - Anterior horn cells are reduced in number, remaining cells are shrunken and contain lipofuscin; notable is lack of cellular reaction around degenerating cell.
    - Degeneration of corticospinal tracts is nonspecific (demyelination may be secondary).
• Lab – EMG changes vary with stage of disease and amount of lower motor neuron damage (in advanced disease - fibrillations).
• Course – progressive disease with death in 5 yrs when upper and lower motor neuron signs are both present.
• Treatment – no medical therapy effectively changes the rate of deterioration.
CNS TRAUMA AND VASCULAR DISORDERS

J.A. Weyhenmeyer, Ph.D.

Reading Assignment: Robbins and Curriculum
Objectives: College Objectives
Vascular Disease and Trauma

I. Vascular diseases.

A. General.

1. Adult brain -- 1500 g of neurons and glia that require uninterrupted supply of 150 g glucose and 72 L of O₂ every 24 hr. Can function for only a few minutes if O₂ or glucose content reduced below critical levels.

2. Anatomy -- internal carotid arteries give rise to ophthalmic and anterior choroidal arteries before dividing into anterior and middle cerebals -- they supply the optic nerves and retina, and anterior portion of the hemisphere (frontal, parietal, anterior temporal). Vertebral arteries give rise to posterior inferior cerebellar, anterior, and posterior spinals, then join to form the basilar artery. Basilar gives rise to paramedian, short and long circumferentials and the posterior cerebals at the midbrain. Vertebrobasilar system supplies cervical cord, brain stem, cerebellum, thalamus, auditory and vestibular functions of the inner ear, medial temporal and occipital lobes.

   a. Vascular anastomoses.

      1. External carotid with vertebrals.
      2. External carotid with the internal carotid (through the orbit).
      3. Circle of Willis -- connects vertebrobasilar and carotid systems (through the posterior communicating arteries).
      4. Obstruction of internal carotid in the neck may be bypassed by a collateral path from the external carotid to the ophthalmic to the internal carotid.
      5. Segmental obstruction of vertebral artery can be bypassed by interconnections between the external carotid and distal vertebral anastomoses.
      6. Middle cerebral occlusion may be symptomless if there are interconnections between the posterior and anterior cerebral arteries.

3. Cerebral arteries constrict in response to increased blood pressure and dilate with hypotension to assure constant perfusion pressure and blood flow through capillary networks.

4. Only arterioles, which are highly sensitive to changes in PaCO₂ and PaO₂, respond to drugs.

   a. Increase PaCO₂ -- arterioles dilate and blood flow increases. CO₂ tension reduced -- arterioles constrict and blood flow is reduced. Changes in PaO₂ have the opposite effect.
   b. Focal cerebral activity -- accelerated metabolism in appropriate region with an increase in blood flow.

5. Clinical.

   a. Frequency of symptomatic CVA disease -- depends on age, gender, and geographic location.
   b. Except for embolic causes, stroke is uncommon before age 40. Incidence of cerebral infarction is greatest between ages of 60 and 80; cerebral hemorrhage between ages of 40
and 60; cerebral embolism and primary subarachnoid hemorrhage between ages of 50 and 70.

c. Stroke-prone profile.

1. Age -- incidence of stroke is increased 2-fold in each successive decade after age 55.
2. Gender -- 30% more frequent in men than women.
3. Race -- more common in blacks than whites.
4. Other predisposing factors.

a. Transient ischemic attacks (TIAs) -- precede stroke in <50% of cases. After a single TIA -- 10 to 20% have a stroke within the year, most within the month.

b. Hypertension -- elevated systolic or diastolic or both -- accelerate progression of atherosclerosis, predisposing to atherothrombotic stroke. Compromised cerebral arterioles -- predisposing to parenchymatous hemorrhage.

c. Cardiovascular disease -- includes congenital anomalies.

d. Cardiac dysrhythmia -- atrial fibrillation is associated with an increased risk of cerebral embolism.

d. Signs and symptoms of stroke.

1. Usually asymptomatic until the disorder reaches an advanced stage. Premonitory symptoms are infrequent -- when they occur, they may be non-specific (headache, dizziness, drowsiness, and confusion -- may be present for minutes to hours).
2. TIAs -- probably due to microemboli from an atherothrombotic plaque.
3. Onset and course-- cardinal feature sudden onset of neurologic symptoms. A stroke may rarely occur without apparent manifestations (silent area of the brain affected). Classic evidence of a stroke -- rapid onset of loss of normal function with a maximum severity within 1 hr.

a. Carotid artery disease -- contralateral weakness or numbness; dysphasia, dyspraxia, and confusion (dominant hemisphere); transient blurring of vision or blindness (ipsilateral eye); homonymous visual field loss; and ipsilateral headache.

b. Vertebralbasilar disease -- upper spinal/lower brainstem - weakness or paralysis of the legs or all 4 extremities while consciousness is intact; vertigo; ataxia (unsteady gait, clumsy limb movements); dysarthria, dysphagia; uni- or bilateral loss of sensation; and occipital headache; labyrinth and cochlea - vertigo, nausea, vomiting, tinnitus; and acute unilateral deafness; pons and midbrain - occipital headache; light headedness (syncope); mental confusion or coma; diplopia; and uni- or bilateral numbness or weakness; cerebral hemisphere, occipital lobes, temporoparietal areas - homonymous visual field loss; blindness - cortical type; temporal lobe seizures; and transient global amnesia.

e. Resolution.

1. If symptoms subside within 24 hr -- considered a TIA.
2. If symptoms exceed 24 hr -- reversible ischemic neurologic deficit (RIND) accounts for protracted symptoms that eventually resolve completely.
3. If symptoms persist indefinitely and when non-hemorrhagic lesion is shown by MRI or CT scan -- cerebral infarction.
4. If death occurs in the first 72 hr -- most likely due to cerebral hemorrhage.

f. Transient ischemic attacks -- thought to result from ischemia that is too brief to cause infarction.

1. Defined as syndromes that last <24 hr, usually last only min.
2. Show a high frequency of severe stenosis or occlusion of major arteries.
3. Two types of TIA syndromes -- transient monocular blindness (TMB) - develops within seconds as a sudden, painless darkness or blurring that affects vision uniformly, or from above downward; transient hemispheric attack (THA) - affects the middle cerebral artery -- combined focal motor and sensory deficits.
4. Clinical continuum from TIA to infarction.

B. Hypoxia, ischemia, and infarction.

1. Brain receives 15% of resting cardiac output and accounts for 20% of O₂ consumption.
   a. Brain may be deprived of O₂ in several ways.

   1. Anoxic anoxia -- low inspired pO₂.
   2. Anemic anoxia -- oxygen carrier hemoglobin reduced.
   3. Histotoxic anoxia -- exemplified by cyanide poisoning.
   4. Stagnant (ischemic) anoxia -- cessation of blood flow.

   b. If blood supply is interrupted for 30 sec -- brain metabolism is altered; 1 min -- neuronal function may cease; 5 min -- anoxia initiates a chain of events that may end in cerebral infarction.

   c. Exposure to any form of severe hypoxia is rapidly followed by severe hypotension and cardiac arrest. Ischemia is last common path of all forms of hypoxia.

   d. Difference between hypoxia and ischemic (stagnant) anoxia -- blood flow stops in ischemia allowing both local accumulation of metabolic products and pH changes.

2. Ischemic (hypoxic) encephalopathy.

   a. Ischemia may be caused by -- arterial occlusion due to atherosclerosis, thrombus or embolus, systemic hypotension, or blood constituents that are to viscous to move through the system (i.e., polycythemia, dysproteinemia, or thrombocytosis). Other potential causes -- meningitis or arteritis due to tuberculosis, syphilis, fibromuscular dysplasia, polyarteritis nodosa, occlusion of veins that drain the brain, dissection hematoma.

   b. If perfusion pressure falls below critical levels -- increasing tissue ischemia secondary to progressive reduction in flow is manifested as ischemic encephalopathy.

   c. Some neurons are particularly susceptible to ischemia (hippocampal).

   d. Selective vulnerability -- excitotoxins (glutamate and aspartate) appear to play a role in cell death.
e. Pathology.

1. First visible changes occur between 12 and 24 hr after insult.
2. Affected neurons -- eosinophilic cytoplasm, small pyknotic nucleus (ischemic cell damage -- red neurons).
3. Process can be widespread but not uniform. Nerve cells die, disappear, and are replaced by fibrillary gliosis.
4. Hippocampal pyramidal cell layer more severely affected than granular layers.
5. Most severe ischemia in tissue supplied by most distal branches of cerebral arteries -- produces wedge-shaped areas of coagulation necrosis called border zone or watershed infarcts.

f. Ischemic encephalopathy occurs after episodes of profound systemic hypotension (cardiac arrest with delayed/slowed resuscitation).

g. Clinical expression reflects pathologic severity -- mild - transient post-ischemic confusional state with complete recovery; severe - loss of almost all cortical function and remaining comatose or in a persistent vegetative state.

3. Cerebral infarction (dry and wet).

a. Evolution of an infarct -- 1) local vasodilatation, 2) stasis of blood with segmentation of red cells, 3) edema, and 4) necrosis of brain tissue.

b. Almost all infarctions are caused by local vascular occlusion.

c. Although most infarcts are pale, a "red infarct" is occasionally seen following a local hemorrhage into necrotic tissue. Gray matter - petechial hemorrhages; white matter - pale (ischemic) infarcts.

d. Signs and symptoms produced by infarction are called stroke -- a pathologically imprecise term. Stroke implies acute onset of focal neurologic syndrome, such as hemiparesis, secondary to vascular event. Stroke may result from either a vascular occlusion (producing an infarction) or hemorrhage.

e. With occlusion, the size and shape of infarct is determined by both the vessel occluded and its anastomotic connections. Internal carotid -- circle of Willis often provides complete collateral flow. Middle and anterior cerebri have partial anastomoses between distal branches. Although severe stenosis can be tolerated, occlusion always results in an infarct. Small vessels have little or no anastomosis, so occlusion always results in infarct. This ensures that small to medium vessel occlusion, which would go unnoticed in other tissues, may result in significant symptoms in the brain.

f. If interruption is prolonged and infarction results, brain tissue first softens, then liquefies. A cavity forms when debris is removed by microglia. Astroglia surround and invade the softened area and new capillaries are formed. The cavity may collapse or become the site for the formation of a small cyst that fills with fluid.


g. Small cystic infarcts, or lacunae, are the most common type of infarction. Usually found in the basal ganglia, internal capsule, and at the base of the pons. Lacunae result from the occlusion of perforating arteries.

h. Most vascular occlusions are either thrombotic or embolic.

1. Thrombotic occlusions -- majority caused by atherosclerosis, occur at bifurcations of carotid or vertebrobasilar system.
a. Circle of Willis patent -- asymptomatic with carotid occlusion. If Circle's capacity is reduced by atherosclerosis or an abnormal pattern of circulation -- infarction may range from small distal lesion to the whole hemisphere.

b. Posterior circulation does not have the same anastomotic protection. Atherosclerosis of the basilar is seriously incapacitating and often fatal.

c. Prior to total occlusion -- ephemeral focal neurological signs and symptoms (transient ischemic attacks) suggest significant atherosclerotic disease.

d. Although atherosclerosis is the most common cause of thrombotic occlusion, it may also be caused by arteritides (cranial arteritis and granulomatous arteritis of the N.S.).

2. Emboli -- usually result in occlusion of intracerebral arteries (by clotted blood, neoplasm, fat, air, or other foreign substances), often producing an infarct in only part of a major cerebral artery territory.

a. Cardiac and carotid emboli usually affect middle cerebral artery territory. Small emboli tend to affect most distal branches in the border zone between middle and anterior cerebral arteries.

b. Course -- similar to that of infarction except that vasospasms may be superimposed.

c. Most emboli are sterile but some may contain bacteria (secondary to acute or subacute endocarditis, lung infection).

d. Air embolism -- usually follows injuries or surgical procedures involving the lungs, dural sinuses, or jugular veins. May also result from a release of nitrogen bubbles into the general circulation following a rapid reduction in barometric pressure.

e. Fat embolism -- rare. Always arise from a bone fracture.

f. In children -- cerebral emboli are commonly associated with valvular heart disease (rheumatic or congenital).

g. Most common symptom of cerebral embolism is a TIA (results from microemboli from atherosclerotic plaques on aortocranial arteries -- discharge cholesterol and calcium into the bloodstream).

h. Pathology -- arterial bed that contains lodged embolus may go into spasm. Tissue becomes ischemic -- infarction. If embolus lyses, blood flow is restored and hemorrhagic infarction may follow. Hemorrhagic infarcts -- bleeding is perpetual and restricted to infarcted cortex. Infarcted white matter does not become hemorrhagic -- reflects different caliber and density of vessels supplying white matter.

i. Anemic infarction.

1. Not detectable until 6-12 hr after occurrence. Earliest sign -- slight discoloration and softening of affected area, gray matter architecture blurred and white matter losses fine grained appearance.

2. After 48-72 hr, softening and disintegration of affected area with pronounced edema of the infarct and adjacent tissue -- may be sufficient to produce herniation.

3. Resolution -- progressive tissue liquefaction and cyst formation. Leptomeninges may form outer wall of cyst.
4. Histopathology -- similar to other necrotic tissue. Influx of PMN's followed by prolonged macrophage invasion with progressive tissue digestion. Major difference -- no collagen scar (astrocytes don't produce collagen). Fibroblasts are found around blood vessels and have a role in resolution of infarct -- resulting in a cyst rather than a scar. Astrocytosis is prominent about the 2nd week of resolution -- results in fibrillar gliosis that surrounds and replaces necrotic region. Time for infarct to resolve ranges from weeks to months.

j. Signs and symptoms of cerebral infarct depend on the region affected.

4. Intracranial hemorrhage -- results from the rupture of a vessel anywhere in the cranial cavity. Classified according to location (extradural, subdural, subarachnoid, parenchymatous, intraventricular), the nature of the ruptured vessel (arterial, capillary, venous), or cause (traumatic, coagulation defect, degeneration, hypertension, infection). Although intracerebral hemorrhage are most often associated with prior history of hypertension, they may also be caused by blood dyscrasias (acute leukemia, aplastic anemia, polycythemia, thrombocytopenic purpura, seury), bleeding into tumors, amyloid angiopathy, and silent angiomas.

a. Spontaneous (non-traumatic) -- 3 general categories.

1. Hypertensive hemorrhages resulting from microaneurysms (Charcot-Buchard aneurysms) that form at bifurcations of small intraparenchymal arteries. Bursting destroys aneurysm and surrounding brain tissue.

a. Major sites of hemorrhages are putamen (35%), lobar white matter (15%), thalamus (10%), pons (10%), cerebellar cortex (10%).

b. Pathology -- i.e., basal ganglia hemorrhage -- expansion of affected cortex and flattening of gyri. There is possible uncinate herniation as well as displacement of the midbrain to the opposite side. If the vessel ruptures into the ventricles, blood clots can become lodged in the foramina of the 4th ventricle (Luschka and Magendie) -- resulting in hydrocephalus. The mass effect of the clot causes distortion of ventricles, with the ipsilateral ventricle being compressed. Resolution begins with appearance of macrophages. Over a period of months, the macrophages digest the clot, leaving a slit-like cavity surrounded by fibrillary astrocytosis.

c. Clinical course -- initial mortality rate of ~ 40%, and in majority of cases hemorrhage has ruptured into ventricles. Most common site for a single hemorrhage is the basal ganglia. Relative good prognosis for initial survivors -- resolution of hematoma may be accompanied by a return of function. Recurrence is rare. Supratentorial hemorrhages -- result in progressive hemiplegias. Cerebellar hematomas -- result in ataxia, eye movement abnormalities, and intractable vomiting. Wherever its location -- raised intracranial pressure, coma, and hemiation rapidly become the dominant picture.

d. CT has revolutionized the diagnosis and management of cerebral hemorrhage.

2. Subarachnoid hemorrhage -- usually results from an aneurysm (developmental -- berry, congenital, arteriosclerotic, inflammatory, or traumatic) or more rarely, an
arteriovenous malformation. It is considered primary when the ruptured vessel traverses the subarachnoid space (arterial aneurysm of the Circle of Willis); secondary when hemorrhage of the brain parenchyma ruptures through the subarachnoid space.

a. Berry aneurysm -- most common form of aneurysm (95% of all aneurysms). The most common sites (85%) are at the junction of carotid and posterior communicating arteries, anterior communicating artery, major bifurcation of middle cerebral in the Sylvian fissure. 95% of single aneurysms are on the anterior circulation. Most common site on the internal carotid is the junction with the posterior communicating artery. Posterior aneurysms most frequently occur at the apical bifurcation of the basilar artery.

b. Pathogenesis -- berry aneurysms develop because the arterial elastic lamina, and perhaps the media, are defective. The wall bulges to form saccular fundus composed of fibrous tissue. A laminated blood clot and fibrin may be deposited on wall. Activities associated with acute rises in ICP (straining at stool, lifting heavy weights, sexual intercourse) are all associated with rupture. The likelihood of rupture is increased when diameter of the aneurysm increases above 10 mm.

c. Lab data -- CSF is usually grossly bloody with xanthochronic supernatant. CSF pressure almost always high, protein is elevated, and glucose may be abnormally low. Reactive pleocytosis may occur late. CT scan may show intra- or extraparenchymal hematoma (in severe hemorrhage blood may appear in basal cisterns, Sylvian or interhemispheric fissures, or cerebral convexities). Arteriography is the definitive diagnostic procedure.

d. Clinical -- signs and symptoms result from compression of the cranial nerves of the brain, thrombosis in the aneurysm, and dispersing of emboli to distal branches, or bleeding. Patient usually complains of sudden severe headache ("the worst headache I've ever had"). Some patients remain alert and lucid; others become confused, delirious, amnestic, lethargic, or comatose. Loss of consciousness implies a grave prognosis. Neck stiffness and Kernig sign are hallmarks of subarachnoid hemorrhage. Lower back pain sometimes more prominent than headache. Fever is common. Neurologic signs may point to the site of bleeding. Hemiparesis or aphasia suggests middle cerebral artery, paraparesis, or abulia suggests proximal anterior cerebral artery. 25-50% of patients die with their first rupture. Most who survive improve and recover consciousness in min. Rebleeding is common -- prognosis significantly more grave.

e. Treatment -- definitive treatment is surgical. A major issue is how to forestall rebleeding before surgery -- bed rest, sedatives, analgesics, laxatives.

3. Mixed CNS and subarachnoid hemorrhage -- primarily result from vascular malformations.

a. Arteriovenous malformation -- tangles of abnormal vessels with characteristics between arteries and veins. 90% of AVM's are found in the cerebral hemispheres. Bleeding is most frequent in males between 10 and 30 yr. In 2/3's of the cases -- bleeding into the parenchyma and the
subarachnoid space. In 1/4 of cases — bleeding is into the subarachnoid space alone. Bleeding and seizures are the most common clinical presentation.

b. Cavernous hemangiomas -- large, cavernous vascular channels.

c. Capillary hemangiomas -- composed of blood vessels that resemble capillaries (narrow, thin-walled, and lined with thin endothelium). Almost never bleed.

5. Hypertensive vascular disease -- associated with intracerebral hemorrhage (see above), occlusive atherosclerotic vascular disease, atheroembolic infarcts, lacunae, subcortical leukoencephalopathy, hypertensive encephalopathy.

a. Lacunae (little lakes) -- are small necrotic foci, most common in deep areas of brain (basal ganglia, thalamus, internal capsule, hemispheric white matter, pons). Most result from occlusion of deep penetrating arterioles (due to emboli or atherosclerosis) that follows long-term hypertension. If pigmented macrophages are present it suggests a hemorrhagic component. Often asymptomatic, but there are a vulnerable sites (i.e., internal capsule) that produce symptoms.

b. Subcortical leukoencephalopathy (Binswanger's disease) -- diffuse loss of deep hemispheric white matter in some hypertensive patients with progressive dementia. Irregular loss of axons and myelin, areas of widespread gliosis with arteriolar sclerosis of long penetrating arteries (white matter). Frequently co-exists with atherosclerotic cerebrovascular disease.

c. Hypertensive encephalopathy -- associated with malignant hypertension and with the acute hypertension seen in eclampsia and acute nephritis.

1. Clinical -- headache, drowsiness, vomiting, convulsions, progressing to stupor and coma. Symptoms may be reversed when blood pressure is reduced. Treat with hypotensive agents (nitroprusside).

2. Pathology -- cerebral edema, petechial hemorrhages, fibrinoid necrosis of small artery walls.

3. Associated with failure of autoregulation (generalized arteriolar dilatation), high cerebral blood flow, and breakdown of blood-brain barrier with development of cerebral edema.

6. Spinal cord -- arterial blood supply by anterior (1) and posterior (2) spinal arteries.

a. Most common vascular injury is a low flow state due to interruption of feeding tributaries (particularly associated with dissecting aortic aneurysms). Damage is concentrated in anterior horns (gray) of mid- and lower thoracic cord. Occlusion of anterior spinal artery rare.

b. Spinal cord hemorrhage is most commonly associated with trauma.

II. Trauma.

A. General - cerebral trauma is a major cause of persisting neurologic handicap. Affects mostly young (between the ages of 15 and 24), particularly males (male:female, 3:1).
1. Most important anatomic feature is the skull.
2. Effect of trauma on the skull and brain depend on shape of object, force of impact, and whether head is in motion at the time of impact.
3. The major structures affected by head trauma are the skull, dura, leptomeninges, and brain.
   a. Nature of skull injury divided into closed head injuries, depressed fractures or compound fractures.
      1. In closed head injuries -- no injury to the skull or a linear fracture. These cases can be subdivided into those with no significant structural damage to the brain (concussion) and those with destruction of brain tissue (related to edema, contusion, laceration, or hemorrhage).
      2. In depressed fractures -- pericranium is intact but a fragment of fractured bone is depressed inward, compressing or injuring brain tissue.
      3. Compound fracture -- indicates direct communication between scalp and brain through depressed or comminuted fragments of bone and lacerated dura. Less likelihood of simple concussion and more likelihood of severe brain damage.
4. Complications -- vascular lesions (hemorrhage, thrombosis, aneurysm); infection (osteomyelitis, meningitis, abscess), rhinorrhea, otorrhea, pneumocele, leptomeningeal cysts, injury to cranial nerves and focal cerebral lesions.
   a. Post-traumatic brain edema may occur with herniation, brainstem compression, direct hemorrhage may follow
   b. Skull fractures -- conduit for infection.
   c. Hydrocephalus may develop secondary to blood or infection in the ventricle, aqueduct, or subarachnoid space.
   d. Death may occur even though there is no apparent physical disruption of tissue.
   e. Delayed sequelae -- post-traumatic epilepsy (usually with cortical contusion or laceration); delayed intracerebral hemorrhage (so-called split apoplexy).
5. Sequelae -- convulsive seizures, psychosis (and other psychiatric disorders), "post-traumatic syndrome."
6. Pathology
   a. Concussion -- brief loss of consciousness with no immediate or delayed evidence of structural damage. Consciousness may be lost for a few seconds to several hours.
   b. If coma is >6 hr -- presumed to be brain injury - there appears to be a continuum of diffuse brain injury resulting from acceleration/deceleration of the head -- diffuse axonal injury (DAI). Coma for 6-24 hr -- mild DAI. More prolonged coma associated with focal signs, cerebral edema, and grave prognosis.
   c. Brain swelling -- may be caused in part by cerebral edema. There is also an increase in the intravascular blood volume in brain. Swelling may be diffuse or focal.
   d. Contusion and laceration -- pia-arachnoid intact with contusion; membranes are torn with laceration. These lesions are typically found in frontal and temporal poles and their basal surface (contact with bony protuberances). Contusions may occur with or without skull fracture. They may be found at a site opposite the injury (contrecoup contusion).
1. Degree of damage to the meninges and brain is related to the force of the blow: minor injury -- mild meningeal hemorrhage and petechial hemorrhages on the surface of the brain; severe injury -- meninges and brain may be torn, and may be extensive hemorrhagic necrosis.

e. Evolution of pathologic changes -- related to the nature of the injury.

1. Superficial lacerations of the meninges and brain -- heal by gliosis with the formation of small punched out areas (no meningeal covering).

2. Larger areas of necrosis extending deep into brain -- heal by scar formation (composed of glia, fibroblasts, and meninges).

7. Signs and symptoms -- changes in consciousness is the most common symptom of head injury. Coma may be brief or more prolonged, lasting for hours, days, or weeks when there is swelling, hemorrhage, DAI, or contusion or laceration of brain. Prolonged coma is not uncommon when the brain or brainstem has been severely contused or lacerated. Period of mental confusion following recovery of consciousness is roughly proportional to the degree of brain injury. Presence of focal signs is dependent on the extent and site of damage.

8. Diagnosis and management.

a. Glasgow coma scale -- semi-quantitative measure of severity of brain injury (measure verbal response, eye opening, and motor response) -- not valid in children, patients in shock, intoxicated, hypoxic, or postectal.

b. Patients are admitted to the hospital for any of the following -- loss of consciousness for 10 min. or more, focal signs on neurologic examination, post-traumatic seizure, depressed skull fracture or penetrating wounds, persistent alteration of consciousness, basilar skull fracture, or CSF leak.

9. Course and prognosis.

a. Prognosis related to site and severity of injury. Mortality rate -- 0% with simple concussion, 2% with mild degree of cerebral edema and congestion, 5% with cerebral contusion, 41% with cerebral laceration. Death may result from direct effect of injury or complications.

b. Post-traumatic amnesia -- may occur in the period immediately after recovery of consciousness in patients with concussion or minor contusion. Degree is related to severity of brain damage.

c. Headaches, dizziness, or vertigo may be found in the immediate post-traumatic period.

10. Treatment -- can be either operative or non-operative care of patient, and control of increased ICP (can be combated by the administration of steroids (dexamethasone) or i.v. hypertonic solutions (sucrose)).

B. Hematoma.

1. Epidural hematoma -- localized collections of blood between the skull and dura.

a. Hemorrhage into the extradural space usually caused by a tear in the wall of a meningeal artery, usually the middle meningeal. Skull fracture is usually necessary to produce
arterial rupture. The hematoma is usually large and located over the convexity of the hemisphere (middle fossa).

b. Signs and symptoms.

1. Typical sequence of events -- loss of consciousness at the time of injury, lucid interval for several hours, subsequent relapse into coma and the development of a contralateral hemiplegia.
2. In 50% of cases, lucid interval is not observed because the damage to the brain was so severe -- immediate and long-lasting coma.
3. Signs of brain compression, coma, and hemiplegia usually develop in a few hr after the injury.
4. Finding that is valuable in the diagnosis and location of the hematoma -- dilated, fixed pupil accompanied by paralysis of C.N. III on the ipsilateral side (due to compression of the nerve by the hippocampal gyrus when herniated over the free edge of the tentorium).

c. Diagnosis -- made by CT.
d. Course and prognosis -- mortality 100% in untreated patients, over 30% in treated patients. In fatal cases, gradual increase in the depth of the coma -- death results from failure of cardiac and respiratory centers following herniation.
e. Treatment -- removal of the clot.

Subdural hematoma -- results from rupture of bridging veins that connect the venous system to the large dural venous sinuses, bleeding into the subdural space between the dura and arachnoid. Almost always secondary to head injury, may be mild or unnoticed; found in newborns and infants as a complication of delivery and postnatal trauma.

a. Subdurals are the result of inertial (movement) rather than impact forces.

1. They occur most frequently where freedom of movement is greatest (convexity of the hemisphere). They are relatively uncommon where little movement is possible (posterior fossa).

b. Pathology -- bleeding into the subdural space is almost always venous (except when branches of the middle meningeal are lacerated by skull fragments -- in older patients, dura does not strip and acute hemorrhage occurs in the subdural space with clinical manifestations of an epidural).

1. Blood in the subdural space is not absorbed but organized or encapsulated by the dura. New capillaries enter the clot and gradually absorb the liquefied blood.
2. In survivors -- result of a small subdural is thickening of the dura by addition of organized membrane. If the clot is large, a subdural cyst is formed.
3. Cerebral cortex is compressed by the clot -- may result in herniation of the brain through the tentorium -- damaging remote areas of the brain -- producing false localizing signs.

c. Subdurals are classified as either acute or chronic. In both types, patients are more likely to be men than women, and generally older with other types of head injuries. Falls or assaults are more likely causes than vehicle accidents.
1. Acute subdural -- usually associated with obvious trauma, often with other brain injuries. Requires surgery within the first 24 hrs.
   a. Because bleeding is venous and at a lower pressure, onset of symptoms is usually delayed, manifesting as a gradual decline in the level of consciousness with possible focal signs.
   b. Symptoms -- headache, state of consciousness is variable (depends on degree of cerebral damage). After recovery from the coma -- irritability, mental confusion or varying degrees of coma, contralateral hemiplegia, or central facial weakness in 50% of the patients.
   c. Signs -- common signs are fluctuations in the level of consciousness and hemiplegia (usually spastic, increased tendon reflexes, and Babinski sign).

2. Subacute subdural hematomas -- symptoms appear in 3 to 20 days post-injury.
3. Chronic subdural -- much less obvious in terms of symptoms.
   a. Older people and alcoholics are common victims (usually atrophy of brain resulting in increased range of brain movement -- translating into a higher risk of tearing the bridging veins). Subdural are often bilateral in these patients.
      1. Because of slow progression, brain can accommodate to the mass effect -- chronic subdural can produce greater cerebral distortion and herniation than acute subdural before symptoms and signs develop.
   b. Symptoms -- intermittent headache, confusion, inattention, obtundation, and hemiparesis. Often vague and insidious in onset. Symptoms may be mimicked or masked by concomitant disease (i.e., cerebrovascular disease, dementia).
   c. Signs -- same as acute subdural except that convulsive seizures and papilledema are more frequently seen. Manifestations are diverse -- some patients are thought to be demented, others are suspected of an intracranial tumor because of the slow progression.
4. There are no characteristic symptoms that distinguish an acute subdural from a cerebral contusion or laceration, or a chronic subdural from an intracranial tumor.
5. Rx -- evacuation of the clot and the neomembrane.

C. Parenchymal injuries -- trauma to the brain itself. Four categories: concussion, contusions and lacerations, traumatic intracerebral hemorrhage, and diffuse axonal injury.
1. Concussion -- transient loss of consciousness following head trauma. Duration is usually short. There is almost always complete recovery.
   a. Angular (rotational) acceleration of head is more potent than translational (anteroposterior) movement in producing concussion (effectiveness of the left hook).
2. Contusions and lacerations.
a. Contusions -- occur when blunt trauma crushes or bruises brain tissue without rupturing the pia.

1. Contusions are either directly related to injury at the site of impact (coup) or opposite the impact (contre coup), or indirectly as brain moves and strikes irregularities on the inner surface of the skull.
2. Contusions usually affect only the crowns of gyri, leaving the depths of sulci intact. There is often substantial attenuation of underlying white matter under the adjacent intact cortex. This is opposite what happens in ischemic lesions where the gray matter is more extensively damaged to the white matter.
3. Pathology -- foci of hemorrhagic gray matter and subsequent removal of gray matter leaving an irregular yellow-brown crater with a reactive glial tissue floor (called "plaques jaunes").

b. Lacerations -- tears in brain tissue resulting from a more severe blunt trauma, often accompanied by other damage (fractures, local hemorrhage, necrosis). Resolution results in a yellow-brown gliotic scar that involves cortex and deeper structures.

3. Traumatic intracerebral hemorrhages -- contained within the brain. They are often multiple, involving frontal and temporal lobes as well as deep structures. They may result from rupture of intracerebral vessels at time of trauma.

4. Diffuse axonal injury -- severe neurologic impairment after trauma without massive, grossly visible brain damage.

a. Clinical -- deeply comatose, may recover only to point of persistent vegetative state.

b. Pathology -- widespread white matter damage in the form of ruptured axons and spheroids (circular or elongated granular bodies containing cell organelles), local dilations of axons seen around edges of infarcts, axonal dystrophies, and situations of axonal damage.

c. Pathogenesis -- shearing forces that occur during acceleration and deceleration of brain cause rupture of axons.

D. Spinal cord trauma -- may occur following penetration or compression injury. Majority of acute spinal injuries are in individuals under age 35, greatest incidence between the ages of 20 and 24. Male:female ratio, 3:1.

1. Penetrating wounds (stabbing, shooting) -- lacerations are sometimes combined with hemorrhage (hematomyelia).

2. Compression injuries -- most often caused by subluxation, dislocation, or fracture of vertebrae. They are most common in cervical and lumbar regions.

a. Vertebral dislocation without permanent bone displacement -- concussion inducing transient loss of function -- usually complete recovery.

b. Displacements and fractures -- may produce contusions, lacerations, or transection -- usually severe permanent damage if not complete paralysis.

1. Cervical spondylosis -- with the narrowed canal even a small displacement may result in severe damage.
3. Vascular damage -- may be a contributing factor, adding to local ischemia, infarction, edema, and hemorrhage to the direct physical disruption.

4. Most frequent mechanism of spinal cord injury -- indirect severe force applied to the vertebral column (sudden flexion, hyperextension, vertebral compression, or rotation of the vertebral column). Spinal cord may be contused, stretched, lacerated, or crushed.

5. Pathology -- type of injury determines the extent and nature of cord damage.
   a. Early stages after acute injury -- cord is swollen, reddish, soft, and mushy. Subarachnoid and subdural spaces are obliterated. Cross-sectional examination -- centrally located hemorrhages and softening. Microscopic examination -- fragmented myelin sheaths, splayed myelin, lamellae, broken axons, and eosinophilic neurons. Changes extend for several segments above and below the site of injury.
   b. Edema subsides within several weeks, hemorrhages are absorbed, acute exudate (red cells, polys, lymphocytes, and plasma cells) is replaced by macrophages.
   c. Resolution stage may last for up to 2 yr. -- often resulting in cavitation, gliosis, and fibrosis.
   d. Late stage (5+ yr.) -- tissue becomes shrunken and cord is replaced by fibrous tissue. Proliferation of connective tissue results in a dense adhesive arachnoiditis.

6. Signs and symptoms -- are related to the level, type, and severity of injury.
   a. Cauda equina lesion -- flaccid, areflexic paralysis, sensory loss, and paralysis of bladder and rectum. If the conus is damaged -- urinary/fecal incontinence, failure of erection and ejaculation, paralysis of pelvic floor muscles, sensory impairment (saddle region).
   b. Spinal cord concussion -- transient neurologic symptoms with recovery in minutes to hours.
   c. Spinal shock -- following abrupt, complete, or incomplete lesion. Immediate complex paralysis and anesthesia below the lesion with hypotonia and areflexia. Areflexic hypotonic state is gradually replaced by pyramidal signs. Tender reflexes return and frequently become brisk with reflex spasms of paralyzed limbs. The classic reflex spasm is a withdrawal reflex or mass reflex.
   d. Chronic and complete transection -- permanent motor, sensory, and autonomic paralysis below the level of the lesion.
   e. Chronic and incomplete transverse section -- depends on pathways involved. Brown-Séquard syndrome -- ipsilateral paresis, ipsilateral hemiplegia, contralateral loss of pain and temperature, ipsilateral impairment of vibration and joint position, little loss of tactile sensation.
   f. Central cervical cord syndrome -- results in weakness (more marked in arms than legs), urinary retention, patchy sensory loss below the level of the lesion, hands may be paralyzed or moderately weak.
   g. Anterior cervical cord syndrome -- immediate complete paralysis, mild to moderate impairment of pinprick response and light touch below the level of the lesion, position and vibration sense are spared. May be caused by acutely ruptured disc.
   h. Posterior cord syndrome -- pain and paresthesias (symmetric and burning) in neck, upper arms, and trunk.

7. Diagnosis -- complete radiographs at the time of injury.
8. Course and prognosis -- estimated that 40% of all spinal cord injury patients die within the first 24 hrs. Long-term survival depends on level and extent of the lesion, age of the patient, and availability of special treatment units.

9. Treatment -- 5 phases.

a. Emergency treatment with attention to circulation, breathing, patient airway, appropriate immobilization of the spine, and transfer to specialized center.

b. Treatment of general medical problems (hypotension, poikilothermy, ileus).

c. Spinal alignment.

d. Surgical decompression of the cord.

e. Structured rehab program.
CNS INFECTIONS

J.A. Weyhenmeyer, PhD
CNS Infection

I. General.

A. Convenient to divide CNS infections into those affecting the meninges and CSF (meningitis) and those affecting the brain parenchyma (encephalitis).

B. Routes of infection.

1. Bloodstream -- most common portal of entry.
2. Direct implantation -- invariably traumatic, sometimes iatrogenic.
3. Local extension -- established infection in ears, paranasal sinus, osteomyelitic foci in the skull, congenital sinus tracts may extend to meninges or brain.
4. Peripheral nervous system -- conduit for some viruses.

C. Some bacteria may produce exotoxins that can seriously affect nervous system without the pathogen actually invading it.

II. Meninges.

A. Most important features of nervous system that affect the pathophysiology of infection are that the brain is surrounded by meninges and bathed in CSF.

B. Meningitis -- inflammation of the leptomeninges and subarachnoid space. Usually results from infection, but chemical and carcinomatous meningitis are possible.

C. Acute purulent meningitis -- essentially an infection of the pia, arachnoid and the CSF. Infections may reach the ventricles directly from the choroid plexus or by reflux through the foramina of Magendie and Luschka.

1. Most commonly encountered causal organisms -- E. coli in the neonate; Haemophilus influenzae in infants and children; Neisseria meningitidis in adolescents and young adults; Pneumococcus in the very young or old, and following trauma. All 3 pathogens are inhabitants of the nasopharynx in the majority of people

2. Pathology -- similar regardless of causative organism. Inflammatory reaction in the pia, subarachnoid, CSF, ventricles and adjacent structures. Initially, hyperemia of the meningeal vessels, followed by a migration of neutrophils into the subarachnoid space. Subarachnoid exudate increases (particularly over the base of the brain) and extends into the sheaths of the cranial and spinal nerves, and the perivascular spaces of the cortex. Within days, lymphocytes and histiocytes increase, and there is an exudation of fibrinogen and other blood proteins.

Within two weeks, plasma cells appear and the cellular exudate becomes organized into two layers (outer, next to arachnoid, of neutrophils and fibrin, and inner, next to pia, of lymphocytes and plasma cells). Later, fibroblasts participate in the organization of the exudate, resulting in fibrosis of the arachnoid and loculation of pockets of exudate. Adhesions at the base of the brain may interfere with CSF flow -- hydrocephalus. The inflammatory reaction and fibrosis of meninges around cranial nerves may cause cranial nerve palsy. Diagnosis and therapy depend on isolation and identification of the organism.

a. CSF is cloudy and sometimes purulent, increased pressure (above 180 mm H2O), pleocytosis (up to 100,000 PMN's/mm³, usual number is 1000 to 10,000), increased
protein (most cases fall in the range of 100 to 500 mg/dL) and markedly reduced sugar (40 mg/dL or 40% of blood glucose concentration). Gram negative diplococci can be found in intra- and extracellularly stained smears. Measurement of CSF lactic dehydrogenase (LDH) is of prognostic and diagnostic value - fractions 1 and 2 (presumably derived from brain tissue) rise sharply in patients who die or develop neurologic sequelae.

b. PMN's (polymorphonuclear leukocytes) fill entire subarachnoid space in severely affected areas and are found around the leptomeningeal blood vessels in less severe cases.

3. Signs and symptoms -- general signs of infection (fever) with added signs and symptoms of meningeal irritation -- headache, photophobia, irritability, clouding of consciousness (drowsiness, confusion, stupor and coma), and neck stiffness (resistance to passive movement on forward bending). Brudzinski sign - flexion at the hip and knee in response to forward flexion of the neck; Kernig sign - inability to completely extend the legs.

4. Special features of meningococcal meningitis (acute cerebrospinal fever) - should be suspected during epidemics of meningitis

a. Causative organism -- *Neisseria meningitidis*. Organism may gain access to meninges from nasopharynx through the cribriform plate or via blood. CSF may be teeming with organisms before infection of meninges is evident.

b. Pathology -- death may occur before significant pathological changes in N.S. In the usual case (death does not occur for several days after onset of disease), there is an intense inflammatory reaction in meninges. The inflammatory reaction is most intense over convexity of brain and around cisterns at base of brain, it rarely breaks into the parenchyma.

c. Symptoms.

1. Onset -- chills and fever, headache, nausea and vomiting, pain in the back, stiff neck, and prostration.
2. Patient is irritable. In children -- sharp shrill cry (meningeal cry) is a frequent characteristic.
3. With progression -- sensorium becomes clouded and stupor or coma may develop. Convulsive seizures are often seen as an early symptom, especially in children.

d. Signs.

1. Patient appears acutely ill, may be confused, stuporous or semicomatose.
2. Pulse rapid, respiratory rate increased, blood pressure normal.
3. Petechial rash may be found in skin, mucous membranes, or conjunctiva, never in the nail beds.
4. Rigidity of neck with positive Kernig and Brudzinski signs.
5. Reflexes are usually depressed.

e. Diagnosis -- with certainty only by examination of the CSF and isolation of the organism.

f. Prognosis -- mortality rate untreated - 50 to 90%; with therapy - about 10%.

h. Treatment.

1. Penicillin G or ampicillin administered i.v.
2. Dehydration is common, and may require i.v. fluid replacement.
3. Seizures can be controlled with phenytoin, diazepam, or phenobarbital.
4. Cerebral edema may require osmotic diuretics (if there is evidence of impending herniation - pressure over 400 mm H2O).

i. Prophylaxis -- rifampin

D. Acute chemical meningitis can be caused by release or injection of irritative substance (e.g., procaine, methotrexate) into the CSF -- increased PMNs and protein, normal sugar content in CSF.

E. Acute lymphocytic meningitis -- viral.

1. Similar to bacterial meningitis with meningeal irritation, but less fulminating. CSF findings are markedly different -- lymphocyte rather than PMN pleocytosis. Protein elevation is moderate, sugar is normal. Self-limiting disease, only symptomatic treatment is necessary, there are no life threatening complications.
2. Viruses isolated from CSF -- RNA viruses -- mumps, echovirus, coxsackie virus; DNA viruses -- Epstein-Barr, herpes simplex II. Most common etiology -- coxsackie virus B, echovirus, mumps.
3. Signs of meningeal irritation -- headache, photophobia, and neck stiffness.
4. Special features of coxsackie virus induced aseptic meningitis.

a. Groups A and B are the most frequent cause of aseptic meningitis.
b. Symptoms and signs -- similar to those that follow infection with other viruses that cause aseptic meningitis. Onset -- acute or subacute with fever, headache, malaise, nausea, and abdominal pain. Neck stiffness and vomiting usually begin 24-40 hr after initial symptoms.
c. CSF -- pressure normal or slightly increased. Mild to moderate pleocytosis. Protein is normal or slightly increased, and sugar is normal.
d. Diagnosis -- only established after recovering virus from feces, throat washings or CSF, or by demonstrating viral Abs in serum.
e. Can be differentiated from meningitis caused by bacteria and yeast due to the relatively low cell count and normal sugar content in CSF.

F. Chronic (tuberculous) meningitis.

1. Archetype produced by Mycobacterium tuberculosis. Tuberculous meningitis differs from that caused by most common bacteria -- course is more prolonged, mortality rate is higher, CSF changes less severe, treatment is less effective in preventing sequelae. Dramatic increase in incidence of both systemic and meningitis tuberculosis over the last 10 years related mainly (although not exclusively) to the HIV epidemic.
2. Pathogenesis -- always secondary to TB elsewhere in the body. Onset may coincide with acute miliary dissemination or clinical evidence of activity in primary focus.
3. Pathology.

a. Small white tubercles are found over the convexities and base of the brain. Meninges are thickened, most apparent at the base of brain, with a thick gelatinous exudate that obliterates the pontine and interpeduncular cisterns and extending to the meninges around
the medulla, floor of the third ventricle, subthalamic region, optic chiasm and basal surface of the temporal lobes.

b. Ventricles are moderately dilated, ependymal lining is covered with exudate or appears roughened (granular ependymitis).

c. Histopathology -- subarachnoid space contains a gelatinous or fibrous exudate that is composed of inflammatory cells (lymphocytes, plasma cells, macrophages, and fibroblasts). Focal densities are tubercles, sometimes with caseous necrosis and giant cells. Arteries may show obliterative endarteritis with inflammatory infiltrates in their walls and intimal thickening. Dense fibrous adhesive arachnoiditis is common around the base of the brain.

4. Symptoms.

a. Onset -- usually subacute, with headache, vomiting, fever, bursts of irritability, and nocturnal wakefulness. Headache becomes progressively more severe. Bulging fontanelles can be seen in infants. Pain often causes the infant to produce a shrill cry (meningeal cry).

b. Prodromal stage lasts 2 weeks to 3 months.

c. Stiff neck and vomiting evident within a few days.

d. Convulsive seizures are common in children.

e. With progression, patient becomes stuporous or comatose.

5. Signs.

a. Early -- fever, irritability, stiff neck, Kernig and Brudzinski signs. Tendon reflexes may be exaggerated.

b. Initial irritability is replaced by apathy, confusion, lethargy, and stupor. Papilledema, cranial nerve palsies, focal neurologic signs are common in late stages. There may be an external ophthalmoplegia, usually incomplete, unilateral, and involving the oculomotor nerve.

c. Convulsions, coma, hemiplegia occur as the disease advances.

d. Temp is only moderately elevated in the early stages, and rises to high levels before death. Terminal stages -- respiration becomes irregular -- Cheyne-Stokes type.

6. Diagnosis -- established by recovery of organism from CSF.

a. CSF -- increased ICP, slightly cloudy or ground glass appearance with the formation of a clot on standing. Moderate pleocytosis (25-500 cells/mm³), lymphocytes predominate. Increased protein, decreased sugar (20-40 mg/dl). Absence of growth when CSF is inoculated on routine culture media.

b. Smears of CSF -- acid-fast bacilli.

c. Diagnostic aids -- thorough search for primary focus (chest X-ray) and TB skin test.

7. Course and prognosis.

a. Natural course of disease 6-8 months.
b. Recovery rate is 90% with early diagnosis and appropriate treatment. Presence of cranial nerve involvement, confusion, lethargy, elevated CSF protein on admission -- poor prognosis.

8. Treatment -- should be started immediately without waiting for bacteriologic confirmation. Isoniazid supplemented with rifampin and ethambutol are used and continued for 18-24 months.

G. Meningitic neurosyphilis-- chronic meningitis with all the complications; perivascular inflammatory reaction that is rich in plasma cells.

1. Clinical picture of acute or subacute meningitis, often with cranial nerve palsies.
2. Interval between primary infection and meningeal symptoms may be months to years, usually within 1 year.
   a. Increased ICP and hydrocephalus.
   b. Cranial nerve palsies due to nerve damage by infection.
   c. Focal neurologic signs are due to thrombosis of small vessels adjacent to the inflamed meninges.

4. Signs may disappear without treatment, but nerve palsies are permanent.

H. Subdural empyema (suppuration in a preformed space)-- pus between the inner surface of the dura and the outer surface of the arachnoid.

1. Bacterial (occasionally fungal) infection of skull or air sinuses that can spread to the subdural space. Subdural pus may form layers thick enough to compress the brain and produce a mass effect.
2. Pathogenesis.
   a. Infection may result from the direct extension of an infection in the middle ear, nasal sinuses, or meninges; or may develop as a complication of a compound fracture or in the course of septicemia. Acute attack of sinusitis preceding subdural empyema is common.
   b. Chronic infection of mastoid or paranasal sinuses with thrombophlebitis of venous sinuses (resulting in venous occlusion and brain infarction) and necrosis of cranial vault commonly precedes the development of subdural infection.
   c. Infection is most often due to streptococcus.

3. Pathology -- depends on the mode of entry.
   a. In trauma cases -- there may be osteomyelitis of overlying skull.
   b. When the abscess is secondary to infection of nasal sinuses or middle ear -- thrombophlebitis of venous sinuses or osteomyelitis of frontal or temporal bone are common findings. After a paranasal infection -- subdural pus is found at the frontal poles and extends to convexity of frontal lobe. After ear infection -- pus passes over the falx to the tentorium and occipital poles.
   c. Thrombosis or thrombophlebitis of cortical veins is common -- results in hemorrhagic softening of gray and white matter.
d. Subarachnoid space beneath subdural empyema is filled with purulent exudate.

4. Symptoms and signs.
   a. Local pain and tenderness is present in region of the infected nasal sinus or ear. Orbital swelling is secondary to frontal sinus disease.
   b. Chills, fever, and severe headache are common initial symptoms. Neck stiffness and Kernig sign are present. With progression of the infection -- patient lapses into confused, somnolent, or comatose state.
   c. Thrombophlebitis of cortical veins -- results in seizure and focal neurologic signs (unilateral motor seizures, hemiplegia, hemianesthesia, aphasia, and paralysis of lateral conjugate gaze).
   d. Late stages -- increased ICP, papilledema.

5. Lab data.
   a. Marked peripheral leukocytosis.
   b. CSF -- increased pressure, clean and colorless, moderate pleocytosis (50 to 1000 cells/mm³ with 10-80% PMNs). Protein increased (75-300 mg/dl), and sugar is normal.
   c. CT scan reveals a crescent-shaped hypodensity at the periphery of brain, mass displacement of ventricles and midline structures.

6. Diagnosis.
   a. Subdural empyema should be considered when meningeal symptoms or focal neurologic signs are found in patients with a suppurative process in nasal sinuses, mastoid process, or other cranial structures.
      a. Mortality rate is 25-40% with failure to make early diagnosis. If untreated, death is within 6 days following the onset of focal neurological signs.
      b. Gradual recovery from focal neurologic signs after recovery from infection.

7. Treatment -- prompt surgical evacuation of pus (drainage through enlarged multiple burr holes or osteoplastic flap) and systemic antibacterial therapy (penicillin and chloromphenical).

I. Fungal -- mycosis of CNS results in one or more tissue reactions -- meningitis, meningoencephalitis, abscess or granuloma formation, and arterial thrombosis. Subacute or chronic meningitis or meningoencephalitis are most common.

1. Most frequent organisms -- *Candida albicans*, *Mucor*, *Aspergillus fumigatus*, and *Cryptococcus neoformans*. With opportunistic fungi -- CNS is only infected after major changes in the host -- lower resistance (extensive use of antimicrobial therapy that destroys normal nonpathogenic bacterial flora and treatment with immunosuppressive or corticosteroids), systemic illness (Hodgkin's disease, leukemia, diabetes mellitus, AIDS), or interference with host's immune responsiveness.

2. Patterns of fungal infections.
   a. Chronic meningitis.
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b. Vaculitis – most frequent with *Mucor* or *Aspergillus*; invasion of blood vessel wall with resulting thrombosis and cerebral infarction. Often hemorrhagic and subsequently septic.

c. Parenchymal invasion – usually in form of granulomas or abscesses; most common agents are *Candida* and *Cryptococcus*.

3. Cryptococcosis – most common CNS mycotic infection.

a. Pathogenesis -- infection by small yeast-like spherules. Respiratory tract is the usual site of entry. Cryptococcosis is usually associated with debilitating disease (lymphosarcoma, reticulum - cell sarcoma, leukemia, Hodgkin's disease, multiple myeloma, sarcoidosis, tuberculosis, diabetes mellitus, renal disease, lupus erythematosus).

b. Pathology -- infiltration of the meninges with mononuclear cells and cryptocoecus.

c. Symptoms and signs.

1. Onset is subacute. Meningeal symptoms predominate.
2. Large granulomas can be found in the brain, cerebellum, or brainstem and cause some of the clinical symptoms as lesions expand.
3. Definitive diagnosis -- meningeal involvement and recovery of organism from CSF.

d. Lab data.

1. CSF -- increased pressure, slight to moderate pleocytosis (10 to 500 cells/mm³), protein increased, and sugar decreased (15 to 35 mg/dl).
2. Organism can be cultured from urine, blood, stool, sputum, and bone marrow.

e. Course -- untreated -- fatal within a few months, but may last for several years with recurrent remissions and exacerbations.

f. Treatment -- some success with amphotericin B and 5-fluorocytosine.

III. Brain, spinal cord and peripheral nervous system

A. Bacterial encephalitis -- parenchymal infection of the brain (majority of bacterial CNS infections manifest as meningitis). Bacterial infections that are commonly complicated by encephalitis or meningoencephalitis - Legionnaires' disease, *M. pneumoniae* infections, and *L. monocytogenes* meningoencephalitis (most likely to occur in immunosuppressed and debilitated individuals, well known and occasionally fatal cause of meningitis in newborns).

B. Tuberculosis -- may occur as a tuberculoma (intraparenchymal mass that may be several cm's in diameter causing a mass effect).

1. Histopathology -- central core of caseous necrosis surrounded by granulomatous reaction. Organisms visualized with acid-fast stains. Calcification may occur in inactive lesions.

C. Neurosyphilis -- comprises several different syndromes resulting from infection of brain or spinal cord by the spirochete treponema pallidum. Tertiary stage -- occurs in only about 10% of those at risk.
1. Paretic -- results from diffuse parenchymal invasion by treponema leading to widespread cell death and brain atrophy.
   a. Histopathology -- loss of cortical neurons with proliferation of microglia and gliosis (produces a wind-swept appearance of the cortex).
   b. Pathology -- cortical gyri are atrophic, sulci are widened and filled with CSF. Ventricles are enlarged and walls are covered with sand-like granulations (granular ependymitis).
   c. Clinical -- manifests as an insidious but progressive loss of mental and physical functions with mood alterations (delusions of grandeur). End stage -- dementia of a bizarre nature (general paresis of the insane). Presenting symptom is uncomplicated dementia with progressive loss of memory, impaired judgment, and emotional liability.
   d. Treatment -- can arrest but not reverse decline in neurologic function. Penicillin is effective, but the results depend on the extent and nature of the neuropathology when the treatment is started.

2. Tabes dorsalis (locomotor ataxia).
   a. Clinical -- manifests as lightening-like pains, progressive ataxia, loss of tendon reflexes, variable loss of proprioception, dysfunction of the bowel, bladder, and genital organs.
   b. Histopathology -- loss of axons and myelin, pallor and atrophy in dorsal columns. Initial -- lymphocytes and plasma cells infiltrate spinal leptomeninges and intraspinal portion of dorsal roots. Late -- shrinkage of the lumbar and sacral dorsal roots as well as the dorsal funiculus. Optic and other cranial nerves may be infiltrated and shrunked.
   c. Damage to dorsal roots leads to: a) impaired joint position and ataxia; b) loss of superficial and deep sensation, loss of pain sensation results in skin and joint damage (Charcot joints); c) lightening pains; d) weakness; e) wasting and hypotonia of muscles, absence of deep tendon reflexes; f) irregular or unequal pupils or show impaired response to light (94%), Argyll Robertson pupils (react to accommodation but not to light) (48%). Tabes dorsalis is seldom fatal.

D. Brain abscess -- encapsulated or free pus in the brain following acute purulent infection.

1. Etiology -- most common organisms causing brain abscess are streptococci. May follow direct injection of organism (usually traumatic), local extension from adjacent foci (especially mastoiditis), hematogenous spread (usually from primary site in heart, lung, or bone - one-third of all brain abscesses) In children, > 60% of brain abscesses are associated with congenital heart disease (tetralogy of Fallot the most common anomaly associated with cerebral abscess).

2. Pathology.
   a. Initial -- suppurative inflammation of brain tissue (purulent cerebritis), septic thrombosis and aggregates of degenerating leukocytes; proceeds to necrosis.
   b. When host defense contains the spread of infection, macroglia and fibroblasts proliferate to surround infected necrotic tissue. A fibrous capsule surrounds necrotizing cerebritis (one of few instances where there is fibrosis with collagen production in brain -- fibroblasts (derived from blood vessels) produce the collagen); outside fibrous capsule is a zone of gliosis.

3. Symptoms and signs -- those of any expanding lesion in the brain.
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4. Lab data.
   a. Availability of CT scans and the hazards of lumbar puncture contradict the use of the latter for diagnostic purposes.
   b. CSF -- findings are consistent with those seen in acute purulent meningitis. Raised ICP (> 200 mm H2O in 70% and > 300 mm H2O in 60% of patients). CSF clear and colorless (may be cloudy or tinted in early stages). Cell count (mostly PMNs) directly related to stage of encapsulation and its proximity to the meningeal or ventricular surface. Rupture of the abscess into ventricle results in a sudden rise in pressure, free pus in the CSF with a cell count of 20,000-50,000/mm³. Protein is moderately increased (with unruptured abscess), sugar is normal. A decrease in sugar below 40 mg/dl indicates that bacteria have invaded meninges.

5. Diagnosis -- straightforward when convulsions, focal neurologic signs, increased ICP develop in patient with congenital heart disease, acute or chronic infection of middle ear, mastoid process, nasal sinuses, heart or lungs. In the absence of an obvious focus of infection the diagnosis may require CT scan or cerebral angiography.

6. Treatment -- if the abscess is due to bacteria and the sensitivity is not known, penicillin and chloramphenicol are recommended. If the thick-walled lesion does not resolve, surgical intervention may be necessary.

7. Prognosis -- untreated -- death with rare exception; in patients managed with CT, mortality < 10%. Sequelae -- development of new abscess if the primary focus still exists, residual neurologic deficits and recurrent convulsive seizures (prophylactic phenytoin or phenobarbital).

E. Viral encephalitis.

1. Viral infection of the CNS is almost always preceded by primary infection elsewhere; rabies and herpes simplex are exceptions.
2. Pathology -- most characteristic features are perivascular and parenchymal mononuclear cell infiltrate (lymphocytes, plasma cells, macrophages), glial nodules and neuronophagia; a more direct expression of viral involvement is the appearance of intranuclear inclusion bodies.
3. Latency - herpes simplex and varicella zoster can remain latent in host cells for months or years after initial infection.
4. Other viral effects on CNS.
a. Reyes syndrome -- toxic etiology? It most frequently follows a viral infection (usually influenza or chicken pox) and is associated with severe and sometimes fatal brain edema.

5. Identification of viral encephalitis -- brain biopsy with direct identification using labeled antibodies -- most important in diagnosis of herpes simplex encephalitis.

6. Acute viral encephalitis.

a. Arthropod-borne (arbovirus) encephalitides. Small, spherical ether-sensitive viruses that contain RNA. Most are now officially classified as togaviruses. Viruses develop within the cytoplasm of infected cells, often in vacuoles.

1. Togaviruses multiply in blood sucking arthropods. Humans are incidental hosts (infection in humans breaks the chain of infection).
2. Approximately 80 arboviruses are known to cause human disease ranging from hemorrhagic fever (yellow fever) to arthralgias, rashes, and encephalitis. Most important types -- eastern and western equine encephalitis, Venezuelan equine encephalitis, St. Louis encephalitis, and California encephalitis.
3. Difficult to isolate. The diagnosis is based on a 4-fold rise in Ab titer.

b. Equine encephalitis (arbovirus).

1. Three distinct types occur in U.S. -- eastern equine encephalitis (EEE), western equine encephalitis (WEE), and Venezuelan equine encephalitis (VEE). WEE occurs in all parts of U.S., but is most frequent in western 2/3's of the country. EEE is usually localized to Atlantic and Gulf coasts and the Great Lakes area.
2. Pathology.

a. In EEE -- the brain is congested with widespread degeneration in neurons. Meninges and perivascular spaces are infiltrated with PMN's and round cells. In some areas, accumulation of inflammatory cells are so great that it gives the appearance of an abscess. Lesions are found in both white and gray matter, most intensive in cerebrum and brainstem.

b. In WEE -- lesser degree of inflammation, primarily mononuclear. More extensive demyelination and a greater frequency of petechial hemorrhage.


a. In EEE -- sudden onset of drowsiness, stupor, or coma with convulsive seizures, headache, vomiting, stiff neck, and high fever. Cranial nerve palsies, hemiplegia, and reflex asymmetry are common.

b. In WEE -- less severe. Onset is acute with general malaise and headache occasionally followed by convulsions, nausea, and vomiting. Moderate fever and neck stiffness. Headaches increase in intensity with progression. Drowsiness, lethargy, or coma may occur.

4. Lab data.

a. Leukocytosis (especially with EEE) in blood.
b. CSF (greatest changes in EEE) -- moderate to large increase in ICP. CSF is cloudy or purulent and contains 500-3000 cells/mm³ (PMN's predominate). Protein is increased, sugar is normal. Following the acute stage, the cell count drops and lymphocytes predominate.

5. Diagnosis -- serologic methods.
6. Course and prognosis.
   a. In EEE -- mortality rate 50%. Duration of the disease -- 1 day to 4 weeks. Sequelae -- mental deficiency, cranial nerve palsies, hemiplegia, aphasia, and convulsions are common.
   b. In WEE -- fatality rate < 10%.
   c. In VEE -- mortality rate < 0.5%.

c. St. Louis encephalitis (38 cases in Paris, IL in 1932).

1. Virus -- a mosquito-transmitted flavivirus.
2. Epidemics follow two patterns -- rural epidemics tend to occur in the western U.S. (cycle involves birds as the intermediate host); urban epidemics occur primarily in the Midwest, Mississippi River Valley, and eastern U.S. (humans are the intermediate host).
3. Pathology -- mild degree of vascular congestion, occasional petechial hemorrhage. Slight infiltration of meninges and blood vessels with mononuclear cells. Focal accumulation of inflammatory and glial cells in the brain parenchyma. Degeneration of neurons. Both gray and white matter are affected. Thalamus and midbrain are more affected than cortex.
4. Symptoms and signs.
   a. Infection usually results in "inapparent infection".
   b. In patients that do manifest clinical signs -- onset may be abrupt or preceded by a prodromal illness. Characterized by headache, myalgia, fever, sore throat, and/or GI symptoms. Headache increases in severity and neck stiffness develops. Other common signs -- change (increase or decrease) in tendon reflexes, coarse intention tremor in fingers, lips, and tongue, ataxia, and absence of abdominal reflexes. In severe cases -- delirium, coma or stupor, disturbances of vesical and rectal sphincters, and focal neurologic signs.
5. Lab data.
   a. Leukocytosis in blood.
   b. CSF -- usually abnormal with mild pleocytosis (100 cells/mm³), lymphocytes predominate. Sugar is normal.
6. Diagnosis -- only by isolation of virus from blood, CSF, or brain, or detection of Abs in serum.
7. Course and prognosis -- runs acute course, with death or recovery within 2-3 weeks.
8. Treatment -- none.

d. California encephalitis.

1. LaCrosse virus -- most frequent in midwestern states and along the eastern seaboard.
2. California serogroup classified among the bunyaviruses.
3. Transmitted by woodland mosquitoes.
4. Symptoms -- headache, nausea and vomiting, changes in sensorium, meningeal irritation, and UMN signs.
5. Lab data -- peripheral blood count is elevated. CSF contains increased lymphocytes and other findings of viral encephalitis.
6. Course and prognosis -- fatality low (< 1%). Recovery usually in 7-10 days.
7. Diagnosis -- serology.

e. Herpes simplex encephalitis -- single most important cause of fatal sporadic encephalitis in the U.S. Early diagnosis is crucial because there is an effective antiviral treatment.

1. Etiology -- type 1 (HSV-1, oral herpes) -- responsible for almost all H.S. encephalitis in adults. Neonates -- HSV-2 (genital herpes) encephalitis occurs as part of disseminated infection or localized disease, and is acquired during delivery.
2. Pathogenesis.

a. HSV-1 is transmitted by respiratory or salivary contact. Primary infection usually occurs in childhood or adolescence, and is usually subclinical. 50% of population has Abs to HSV-1 by age 15.

   1. HSV-1 encephalitis -- more than half the cases are in patients > 20 years, suggesting that the disease occurs from endogenous reactivation rather than primary infection.
   2. During primary infection -- HSV-1 becomes latent in trigeminal ganglia. Non-specific stimuli can reactivate the virus which manifests as herpes labialis (cold sores). The virus reaches the brain by coursing through branches of trigeminal nerve to the basal meninges.

b. HSV-2 -- spread by sexual contact, causes aseptic meningitis in adults.

3. Pathology -- in fatal cases -- there is an intense meningitis with widespread destruction in brain parenchyma. Necrotic inflammatory or hemorrhagic lesions are most common in frontal and temporal lobes. Unusual degree of cerebral edema accompanying neurotic lesions. Cowdry type A inclusions (eosinophilic intranuclear inclusions) are common in neurons.
4. Symptoms and signs.

a. Most common early symptoms are headache and fever. Onset is usually abrupt, may have major motor or focal seizures. Encephalitis may also evolve slowly with expressive aphasia, paresthesias, or mental changes.

b. Stiff neck or other signs of meningeal irritation.
c. Mental deficits -- confusion, personality changes from withdrawal to agitation and hallucinations. It runs a progressive course with increasing impairment of consciousness or development of focal neurologic signs.

5. Lab data.
   a. Moderate leukocytosis.
   b. CSF pressure is elevated. Pleocytosis (10-1000 cells/mm³), lymphocytes or occasionally PMN's predominate. Sugar is usually normal, may be low.
   c. EEG is abnormal with diffuse slowing or focal changes over the temporal lobes.

6. Diagnosis -- early diagnosis is established by recovery of virus or demonstration viral antigen in brain.

   a. Fatal in approximately 70% of cases. Recovery may be complete in mild cases, but those who survive acute disease may be left with severe neurologic residuals.
   b. Corticosteroids are used to decrease life-threatening edema.
   c. Acyclovir -- reduces mortality from 70 to 30%.

F. Herpes zoster (varicella, shingles) -- produces inflammatory lesions in the dorsal root ganglia, pain, and skin eruptions in the distribution of the ganglia. Overt CNS involvement is rare, but correspondingly more severe.

1. Herpes zoster virus is identical to the varicella virus (causative agent of chicken pox). It is a large DNA-containing virus that has the same structure as the herpes virus. The virus recovered from patients with chicken pox is serologically identical to the virus recovered from patients with shingles.

2. Pathology.
   a. Infected ganglia of spinal or cranial nerve roots are swollen and inflamed.
   b. Inflammatory reaction -- chiefly lymphocytic, few PMN's. Inflammatory process commonly extends to meninges and into root entry zone (posterior poliomyelitis). Some inflammation frequently occurs in the ventral horn. Damage may be severe enough to produce cavitation. It is typical to see gliosis in the ventral horns, atrophy of the spinal roots, and neurogenic atrophy of denervated muscle.

3. Symptoms and signs.
   a. Most common initial symptom is neuralgic pain or dysesthesia in the distribution of affected root, followed in 3-4 days by reddening of skin and appearance of vesicles. Vesicles contain clear fluid, and are covered with a scab in 10 days to 2 weeks.
   b. Involvement is almost always unilateral.
   c. Common symptoms -- initial meningeal irritation (may be only effect), reduced cutaneous sensation, muscle weakness, headache, stiff neck, and confusion.

a. Involvement of spinal tracts -- may resemble a Brown-Sequard syndrome or a transverse or ascending myelitis.
b. Brain involvement -- mental confusion, ataxia, and focal neurologic symptoms.
c. Polyneuritis.
d. Injury to eyes, scarring of skin, facial or other palsies, and post-therapeutic neuralgia (pains are sharp and shooting in nature, may persist for months or years, often refractory to all forms of treatment).
e. Death can occur from paralysis of respiratory muscles. In survivors, respiratory compromise is an important cause of long-term morbidity.

5. Lab data.

a. CSF -- may be normal in many cases when only 1 thoracic segment involved, but abnormal when cranial ganglia are involved, or when paralysis is evident, or when other neurologic signs are present. Cell count is elevated, and lymphocytes predominate. Protein and suger content are normal.

6. Diagnosis -- characteristic rash.

7. Treatment -- no effective means of preventing herpes.

a. Systemic antivirals (acyclovir) decrease pain, virus shedding, and healing time. They do not prevent postherpetic neuralgia.
b. Treatment for postherpetic neuralgia -- it is refractory to the usual analgesics. Amitriptyline, carbamazepine, and phenytoin are effective therapies.

G. Rabies -- (hydrophobia, lyssa, rage) acute viral disease transmitted by the bite of a rabid animal. Characterized by variable incubation period, restlessness, hyperesthesia, convulsions, laryngeal spasms, and widespread paralysis. Severe encephalitis is almost always fatal.

1. Etiology -- an enveloped bullet-shaped virus containing single stranded RNA. Classified as a rhabdovirus (rod-shaped virus). Present in saliva of the infected animal, transmitted to humans by bites or abrasions on the skin. Once inoculated, the virus replicates in muscle cells, travels to CNS via sensory and motor nerves (axonal transport). Dissemination in CNS is rapid (early selective involvement of the limbic system). Incubation period -- 1 to 3 months (10 days to 1 year are the extremes). Incubation period directly related to severity of the bite and its location

2. Pathology -- generalized encephalitis and myelitis.

a. Perivascular infiltration of entire CNS with lymphocytes and some PMN's.
b. Intense edema and vascular congestion. Widespread neuronal degeneration and inflammation, (most severe in basal nuclei, midbrain, medulla).
c. Negri bodies (eosinophilic inclusions that are aggregates of viral particles) are pathognomonic and found only in neurons (most frequently in pyramidal neurons of hippocampus and Purkinje cells of the cerebellum).


a. Onset -- initial -- pain or numbness in region of the bite, fever, apathy, drowsiness, headache, and anorexia. Lethargy passes rapidly into a state of excitability. There may
be delirium with hallucinations and bizarre behavior (thrashing, biting, severe anxiety), and profuse flow of saliva. Spasmodic contractions of pharynx and larynx are precipitated by an attempt to consume liquid or solid food (patient refuses to accept any liquids -- hence the hydrophobia).

b. In the advanced stage -- extraordinary CNS excitability (slight touch is painful, minute movements may progress to convulsions); disease progresses to flaccid paralysis; periods of alternating mania and stupor, then coma and death due to respiratory failure.

H Cytomegalovirus (cytomegalic inclusion body disease) -- occurs in utero by transplacental transmission, may also occur in immunosuppressed patients. CMV-infected cells appear as large, swollen cells that often contain large eosinophilic intranuclear and cytoplasmic inclusions.

1. In utero infection -- a necrotizing periventricular infection that leads to brain destruction with characteristic periventricular calcifications. Hydrocephalus, hydranencephaly, microencephaly, cerebellar hypoplasia, or other developmental defects may be found. Convulsive seizures, focal neurologic signs, and mental retardation are common in survivors.

2. In immunosuppressed patients -- infection starts as ependymitis that extends to subependymal brain. Outlying focal necrotizing lesions with characteristic large CMV-infected cells (intranuclear and cytoplasmic inclusion bodies) are found. In AIDS -- multiple microglial nodules are present. The encephalitis has a subacute or chronic course.

3. Antivirals (acyclovir) are not effective in infants. They are reported to be beneficial in some adult infections.

I. HIV-1.

1. AIDS -- invariably fatal. It is characterized by a severe deficiency of cell-mediated immunity that predisposes the individual to opportunistic infection and unusual malignant tumors. Underlying immune deficiency -- infection of T-helper (T4) lymphocytes and possibly other immune cells by the retrovirus.

a. Pathogenesis.

1. Primary abnormality -- severe cellular immunodeficiency attributed to infection of T4 helper cells, results in reversal of T-helper to T-suppressor cell ratio, cell-mediated immune anergy, depressed lymphoproliferative response to mitogens, and reduced natural killer cell activity.

2. Macrophages and B cells are also infected -- may contribute to hypergammaglobulinemia, impaired Ab response to new antigens, and increased blood levels of immune complexes.

3. HIV genome is both integrated into cellular genome and free within the cell. Infection is probably permanent. Asymptomatic carrier state may last for years.

4. Normal antigenic activation of infected lymphocyte is suggested to trigger expression of viral genes and viral replication -- leads to cytopathic effects on lymphocytes and then illness.

5. Loss of cell-mediated immunity increases the susceptibility to opportunistic infection. Pneumocystis carinii (PCP) is the most common (60% of cases) opportunistic infection.
b. CNS pathogenesis -- in addition to the opportunistic infection and lymphoma, HIV is probably an important cause of neurologic disease (HIV may be present in basal ganglia).

c. Symptoms and signs -- depend on the particular opportunistic infection or neoplasm. Acute infection may be asymptomatic or a transient non-specific mononucleosis-like illness with fever, malaise, GI symptoms, myalgia, sore throat, diarrhea, and generalized adenopathy. Neurologic complications are common -- occur in 60% of HIV-infected patients with clinical illness.

1. Meningitis in AIDS -- may be caused by viruses, fungi, mycobacteria, or tumor cells. Cryptococcal meningitis is the most common. Asceptic meningitis (rarely encephalitis) resembles viral meningitis.

2. Subacute encephalitis -- most common cerebral syndrome of viral etiology, also known as "AIDS dementia." Characterized by insidious onset of cognitive, behavioral, and motor impairment. Early -- impaired memory, diminished concentration, mental slowness, confusion, apathy, social withdrawal, loss of libido, poor balance, and leg weakness. Behavioral changes may include organic psychosis that mimics schizophrenia or depression. Most patients progress for weeks or months to state of severe dementia, mutism, incontinence, paraplegia, and occasionally myoclonus.

a. Histopathology -- microscopic foci of multinucleated giant cells, macrophages, and lymphocytes with adjacent microglial cells, reactive astrocytes, and some vacuolation and pallor of surrounding myelin (pathognomonic for HIV). Lesions are found in cerebral and cerebellar white matter.

b. CSF -- normal or shows mild pleocytosis with protein elevation. Gamma globulin level may be increased (Ab production against HIV).

c. CT -- cortical atrophy, loss of white matter, and enlarged ventricles. MRI -- widespread white matter disease.

d. Subacute encephalopathy is attributed to secondary pathogens (CMV, atypical mycobacteria, Toxoplasma) and/or primary lymphoma.

e. Focal or multifocal neurologic syndrome may be caused by infection, neoplasm, or vascular complications.

3. Cranial neuropathies have been associated with recurrent HIV meningitis.

4. Vacuolar myelopathy -- found in 20 to 30% of patients at autopsy; 50% have signs and symptoms of spinal cord dysfunction.

a. Pathology -- vacuolation and accumulation of lipid-laden macrophages in the white matter of the cord (similar to B12 deficiency). Myelopathy is most severe in middle and lower thoracic regions of the cord.

b. Clinical -- progression to spastic paraparesis with hyporeflexia and Babinski sign, ataxia, incontinence. May also result in burning paresthesias, areflexia, and loss of the extensor plantar response.

5. Peripheral neuropathy -- demyelinating neuropathy with focal inflammatory demyelination; there is a variable degree of axon loss.
a. Disorders in AIDS include -- distal symmetric sensorimotor neuropathy with either a mononeuropathy multiplex or a distal symmetric disorder, acute Guillain-Barre syndrome or polyradiculopathy.

b. Clinical -- burning paresthesias, distal weakness, and atrophy, paraparesis, sensory changes, and areflexia. Sphincter functions may be affected.

c. CSF -- mild to moderate mixed pleocytosis, mild protein elevation, oligoclonal bands, and elevated gamma globulin.

d. Lab data -- virtually all patients with clinically apparent AIDS have Abs to HIV.

e. Diagnostic -- HIV serology and T-cell findings, cutaneous anergy and lymphopenia are consistent findings. Serum gamma globulins are elevated, and circulating immune complexes are detected.

f. Neurologic.

1. EEG -- focal or diffuse slowing.
2. CSF -- culture may be diagnostic in fungal, mycobacterial, or lymphomatous meningitis.
3. CT -- distinguishes focal from diffuse brain lesions. MRI is especially useful in HIV encephalopathy -- showing extensive white matter abnormalities when CT scan may be normal.

g. Course, prognosis and treatment.

1. AIDS is progressive and eventually fatal. Life can be prolonged by treatment of secondary infections and neoplasms. Relapse, new infection, or malignant tumors are inevitable.
2. AZT (3' azido-3-deoxythymidine) -- blocks viral replication by incorporation into DNA copy of the viral RNA genome and termination of DNA replication. AZT penetrates blood brain barrier and may be effective against HIV in CNS.

J. Slow virus diseases (conventional) -- cause chronic inflammatory or demyelinating diseases (subacute sclerosing panencephalitis, progressive rubella panencephalitis, and progressive multifocal leukoencephalopathy).

1. Subacute sclerosing panencephalitis (SSPE, Dawson's disease) -- caused by a defect in the production of the measles virus. Generally occurs in children; is always preceded by an attack of measles in distant past, often early in life or occasionally by previous immunization against measles. Characterized by progressive dementia, incoordination, ataxia, myoclonic jerks, and other focal neurologic signs.

a. Pathology -- brain normal or unusually firm (in long standing, severe cases), regions of granularity or focal destruction. Perivascular and parenchymal lymphoplasmacytic infiltrate in the cortex and white matter. Inclusion bodies frequently found in oligos, some neurons, and astocytes. Patchy areas of demyelination and dense fibrillary gliosis are observed.

b. Symptoms -- gradual onset without fever. Personality changes, forgetfulness, inability to keep up with school work, restlessness are common. Followed in the course of weeks to
months by incoordination, ataxia, myoclonic jerks of trunk and limb muscles, apraxia and loss of speech; seizures and dystonic posturing may occur. Vision and hearing can be affected. In the terminal stage -- rigid quadriplegia simulating complete decortication.

c. Lab data.

1. CSF -- elevated levels of measles Ab (in serum also). Cell count and pressure are normal. Protein is normal with a striking increase in immunoglobulin content.
2. EEG -- widespread abnormality of cortical activity with a "burst suppression" pattern of high-amplitude slow wave complexes.
3. CT -- cortical atrophy and focal or multifocal low-density lesions in the white matter.

d. Pathogenesis -- M protein (associated with surface of viral coat) is required for assembly and budding of the virus. Brain cells of affected patients do not produce the M protein, and therefore manufacture defective virus incapable of extracellular spreading. Accumulation of measles virus nucleocapsids within cells (cell-associated infection) or virus spread occurs by cell fusion.

e. Course, prognosis, and treatment.

1. Course is prolonged, usually lasting for several years.
2. Spontaneous long-term improvement or stabilization is seen in 10% of patients.
3. No specific therapy.

2. Progressive multifocal leukoencephalopathy (PML) -- a non-inflammatory demyelinating disease that occurs in immunocompromised hosts. Viral infection of oligodendrocytes (cell death) -- demyelination is the principal pathologic effect. Two closely related papoviruses have been implicated -- JC virus (accounts for majority of cases) and SV40 (reported in only a few cases).

a. Pathology -- white matter has irregular margins with sunken gray translucent appearance and soft texture. Numerous areas of demyelination (there may be large damaged regions, affecting whole lobes in the cerebrum, brainstem, and cerebellum; occasionally the spinal cord is involved). The appearance of the oligos is diagnostic -- nuclei are spherical but grossly enlarged and contain inclusion bodies that range from a violet smudge to homogeneous eosinophilic masses. They are most frequent at margin of the lesion. Within the lesion there are bizarre giant astrocytes with irregular, hyperchromatic, and sometimes multiple nuclei. There are many foamy macrophages containing myelin debris, but little inflammation. Axons coursing through the lesion are spared.

b. Clinical -- develop provent but focal and relentlessly progressive neurologic signs and symptoms. Onset is subacute to chronic with hemiplegia, sensory abnormalities, and other focal signs. Dementia usually follows. CT scans and MRI's show extensive, often multifocal lesions in white matter (gray matter is spared).

c. Diagnosis -- detection of viral antigen in brain tissue.

d. Lab data -- CSF -- normal. EEG -- non-specific diffuse or focal slowing.

e. Prognosis and treatment -- symptoms -- progressive and death usually follows in a few months. Treatment -- use of DNA inhibitors has been attempted (results are not encouraging).
K. Slow virus diseases (unconventional) -- lack features of ordinary viruses. All show the characteristic spongiform encephalopathy with non-inflammatory degenerative disease. The agents are composed of a 27 kD heavily glycosylated protein (prion -- proteinaceous infective particle) that represents a modification of 30 kD protein found in normal tissue and coded for by the host genome.

1. Subacute spongiform encephalopathy (Creutzfeldt-Jakob disease, transmissible agent dementia) -- manifests clinically as rapidly progressive dementia. Mode of transmission of obscure, but a few cases of iatrogenic transmission (corneal transplant, deep implantation electrodes, contaminated human growth hormone) have been reported.

   a. Pathology -- disease is so rapid that despite neuronal loss, there is little if any gross atrophy. The spongiform change is pathognomonic and can be seen in cortex, and sometimes other regions of gray matter (consists of variable vacuolation in the neuropil).
   
   b. Clinical -- gradual onset of dementia in mid- or late life. Vague prodromal symptoms -- anxiety, fatigue, dizziness, headache, impaired judgment, and unusual behavior. Once memory loss has occurred, it progresses rapidly. Most frequent signs (besides dementia) are pyramidal tract disease, extrapyramidal signs, and myoclonus.
   
   c. Lab data -- CSF is normal. CT scans show cerebral atrophy, enlarged ventricles, and widened sulci.
   
   d. Course and prognosis -- rapid course and death within 1 year.
   
   e. Treatment -- none.
   
   f. Transmissibility -- mode of transmission unknown. Transmissible spongiform encephalopathy agents are highly resistant to physical or chemical treatment (autoclaving or formalin). Sodium hydrochlorite (household bleach) is effective.

2. Kuru -- progressive and fatal neurologic disorder that occurs exclusively among natives of the Fore tribe (New Guinea). It is transmitted by cannibalism (eating infected brain).

   a. Pathology -- morphologic changes are similar to Creutzfeldt-Jakob but most prominent in cerebellum and striatum. Widespread neuronal loss, neuronal and astrocytic vacuolization, astrocytic proliferation of Kuru plaques (amyloid deposits consisting of 27 kD prion protein) are seen in about 60% of cases.
   
   b. Clinical -- cerebellar ataxia and "shivering tremor" that progresses to complete motor incapacity and death in < 1 year.

L. Protozoal -- malaria, toxoplasmosis, amebiasis, trypanosomiasis, rickettsial infections (typhus, Rocky Mountain spotted fever), and metazoal diseases (cysticercosis, echinococcosis).

1. Cerebral toxoplasmosis -- occurs in fetuses and immunosuppressed adults. In the fetus -- maternal infection may be followed by cerebritis in fetus, production of multifocal necrotizing lesions. In the adult (particularly common in AIDS) -- progressive, multifocal, necrotizing and often hemorrhagic encephalitis; organisms may be present in pseudocysts and/or free in tissue.

   a. Etiology and pathology.

   1. Toxoplasma -- minute, oval, pyriform, rounded, or elongated protoplasmic masses with a central nucleus.
2. Inflammatory reaction is in the wall of CNS blood vessel, producing miliary granulomas. Granulomatous lesions are found throughout CNS, meninges, and ependyma. Complication -- hydrocephalus from occlusion of cerebral aqueduct.

3. Lesions in retina are common.

b. Symptoms.

1. Congenital form -- common manifestations are inanition, microcephaly, seizures, mental retardation, spasticity, opisthotonos, chorioretinitis, microthalamus, and defects in eye development. There may be internal hydrocephalus. Calcified nodules in the brain can be found on CT scans or radiographs.

2. Acquired toxoplasmosis -- often asymptomatic in normal host. May present like an infectious mononucleosis with lymphadenopathy. Severe infection is most likely in the immunocompromised host. Manifestations may include -- pneumonitis, myocarditis, myositis, chorioretinitis. Neurologic involvement: 1) encephalopathy with confusion, delirium, obtundation, and coma, with occasional seizures; 2) meningoencephalitis with headache, stiff neck, focal or generalized seizures leading to status epilepticus or coma; 3) most common presentation -- focal signs due to single or multiple mass lesions.

c. Lab data.

1. Moderate to severe anemia with mild leukocytosis or leukopenia.

2. CSF -- increased pressure, protein increased. Inconsistent pleocytosis, mostly lymphocytes.

3. CT -- calcification in congenital infection. Low density focal lesions.

d. Diagnosis.

1. Congenital toxoplasmosis -- should be considered in the newborn with chorioretinitis, microcephaly, seizures, mental retardation, cerebral calcifications, and evidence of systemic infection.

2. Acquired -- definitive diagnosis can only be made following isolation of organism from biopsy of brain or other tissue.

e. Course, progress, treatment.

1. Congenital -- prognosis is poor, 50% die within a few weeks. In survivors, mental retardation and neurologic defects are common.

2. Acquired infection in immunocompetent patient -- self limited, no treatment required.

3. Acquired infection in immunocompromised patient -- frequently results in death. Can be treated successfully with pyrimethamine and sulfadiazine.
DISEASES OF THE PERIPHERAL NERVOUS SYSTEM AND SKELETAL MUSCLE

J.A. Weyhenmeyer, PhD

Reading Assignment: Robbins and Curriculum
Objectives: College Objectives
PERIPHERAL NERVOUS SYSTEM

Peripheral nerves have a very restricted range of pathological reactions and usually become symptomatic because 1) a type of degeneration occurs which gives rise to a peripheral neuropathy or 2) a tumor forms.

It is important to note that, unlike the CNS, degeneration and regeneration can occur in the PNS.

INJURY

Slight injury affects the myelin only, more severe injury affects the axon as well and the most severe disrupts the connective tissue. Three classes of injury are also described: Class 1 in which a conduction block is produced by, for example, transient ischemia which is rapidly reversible or paranodal demyelination in which recovery occurs in a few weeks (a mild structural damage in which there is loss of small areas of myelin around the nodes of Ranvier); Class 2 follows severe crush injuries in which there is axonal interruption but the endoneurium is undamaged. The prognosis is good because regeneration occurs through the original Schwann cell tubes. There may be muscle atrophy (denervation atrophy) and recovery may take months; Class 3 follows severe injury to axons, Schwann cells and endoneurium. Denervation atrophy of the skeletal muscle follows. In this class the formation of neuromas and aberrant regeneration are common.

DEGENERATION – 3 basic degenerative processes are described.


1. **Wallerian**

This follows peripheral transection of an axon.

Proximally there is degeneration to the nearest node of Ranvier. If close enough to the cell body, chromatolysis occurs.

Distally there is degeneration of the axon and myelin, both of which are digested by Schwann cells which proliferate in order to do this.

2. **Axonal**

This follows neuronal dysfunction (i.e., damage to or some underlying abnormality of the cell body or axon).

Degeneration extends back towards and as far as the cell body, and chromatolysis often develops (Wallerian degeneration). Schwann cell proliferation occurs.

If the dysfunction can be halted, regeneration and some recovery may occur.

3. **Segmental demyelination**

This is analogous to demyelination in the brain.

There is selective loss of individual myelin internodes with preservation of the axon. Remaining Schwann cells proliferate with resultant remyelination. The new myelin sheaths are thinner than normal and the internodal lengths are shorter.

There are repeated episodes of demyelination and remyelination with resultant concentric arrangements of alternating Schwann cell processes and collagen = “onion bulbs” (hypertrophic neuropathies).

**N.B.** The difference between “segmental demyelination” and “paranodal demyelination” is that paranodal is much less severe and the etiology is different.

**REGENERATION**

Outgrowths of multiple sprouts from the distal ends of the axons appear, and in the absence of obstruction grow down the nerve trunk at 2 mm/day in association with Schwann cells which remain after digesting the degenerated axon.

Often in Wallerian degeneration, secondary to traumatic injury, a hematoma or scar may form which causes obstruction to the distal stump of the nerve which produces a tangled, often painful, mass of nerve fibers = amputation or traumatic neuroma.
PERIPHERAL NEUROPATHY

Neuropathy is a general term denoting functional disturbances and/or pathological changes in the P.N.S.

Neuropathies may be mild or severe; acute, subacute, or chronic; and may have relapses and remissions. The peripheral neuropathies most commonly encountered are diabetic and alcoholic - both predominantly axonal. The major categories are inflammatory, infectious (e.g., leprosy, diphtheria, varicellar-Zoster), hereditary, acquired metabolic, toxic (industrial or environmental chemicals), associated with malignancy (invasion or paraneoplastic), and traumatic (lacerations, avulsions, compressions, e.g., Carpal Tunnel Syndrome and ‘Saturday night palsy’).

Polyneuropathy is caused by both diffuse demyelination and axonal degeneration. The longest axons are affected first, and the condition is typically symmetric. The patient presents with distal signs and symptoms in the limbs, e.g., motor weakness and loss of deep tendon reflexes or “glove and stocking” sensory loss. If the ANS is involved, there may be postural hypotension, constipation, and impotence.

The classification of peripheral neuropathies is based mainly on the type of clinical syndrome that develops and are classified as 1) axonopathies and 2) demyelinating. These two entities may occur separately or together.

With axonal degeneration muscle weakness is accompanied by fasciculations and wasting of the muscles. Demyelination causes conduction failure, but not denervation, and fasciculations and wasting do not occur. Different etiological agents preferentially affect axons of different diameters or affect sensory, motor or autonomic axons to different degrees.

Focal and multifocal neuropathy (N.B. these are the new recommended terms)
Many etiologic agents produce generalized damage, but some result in focal damage (e.g., vasculitis) and affect only individual nerves, hence the term focal neuropathy (mononeuropathy). If more than one nerve is involved, then the condition is called multifocal neuropathy (mononeuropathy multiplex). Focal neuropathies may become widespread and may, therefore, present as a polyneuropathy. Focal neuropathies are usually asymmetrical, but polyneuropathies are usually symmetric.
### TABLE 22-2. PRINCIPAL NEUROPATHIC SYNDROMES*

<table>
<thead>
<tr>
<th>Acute ascending motor paralysis with variable sensory disturbance—Acute demyelinating neuropathies</th>
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<tbody>
<tr>
<td>Acute idiopathic polyneuropathy (Landry-Guillain-Barré syndrome)</td>
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<tr>
<td>Infectious mononucleosis with polyneuropathy</td>
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<tr>
<td>Hepatitis and polyneuropathy</td>
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<tr>
<td>Diphtheritic polyneuropathy</td>
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<td>Toxic polyneuropathies (e.g., triorthocresyl phosphate)</td>
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<th>Subacute sensorimotor polyneuropathy</th>
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<tr>
<td>(1) Symmetric—Mostly axonal neuropathies</td>
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<tr>
<td>Alcoholic polyneuropathy and beriberi</td>
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<tr>
<td>Arsenic polyneuropathy</td>
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<td>Lead polyneuropathy</td>
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<tr>
<td>Vinca alkaloids and other intoxications</td>
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<tr>
<td>(2) Asymmetric—Axonal neuropathies with focal and/or diffuse pathology</td>
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<tr>
<td>Polyarteritis nodosa and other arteritides</td>
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<td>Sarcoidosis</td>
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<tr>
<th>Chronic sensorimotor polyneuropathy</th>
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<tr>
<td>(1) Acquired—Axonal neuropathies with focal and/or diffuse pathology</td>
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<tr>
<td>Carcinomatous</td>
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<td>Paraproteinemias (demyelinating)</td>
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<td>Uremia</td>
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<td>Diabetes</td>
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<td>Connective tissue diseases</td>
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<td>Amyloidosis</td>
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<td>Leprosy</td>
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<tr>
<td>(2) Inherited—Mostly chronic demyelination with hypertrophic changes</td>
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<tr>
<td>Peroneal muscular atrophy (Charcot-Marie-Tooth disease)</td>
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<tr>
<td>Hypertrophic polyneuropathy (Déjérine-Sottas disease)</td>
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<td>Refsum’s disease</td>
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<th>Chronic relapsing polyneuropathy—Mixed pathology</th>
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<tr>
<td>Idiopathic polyneuropathy</td>
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<td>Porphyria</td>
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<td>Beriberi and intoxications</td>
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<tr>
<th>Mono or multiple neuropathy—Focal axonal or demyelinating pathology</th>
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<tr>
<td>(The new terms would be “focal” and “mutifocal”</td>
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<tr>
<td>Pressure palsies</td>
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<tr>
<td>Traumatic palsies</td>
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<tr>
<td>Serum neuritis</td>
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<tr>
<td>Zoster</td>
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<tr>
<td>Tumor invasion with neuropathy</td>
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<td>Leprosy</td>
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For 25–70% of peripheral neuropathies the etiology is not found. Of these at least 45% are probably hereditary, and 20% inflammatory or demyelinating, but a significant number are still undiagnosed as to etiology. *(N.B. The term neuropathy replaces the term “peripheral neuritis.”)*

**The current clinical terminology** is as follows:

1. **Acute inflammatory demyelinating polyradiculoneuropathy** (i.e., spinal roots involved). (AIDP) (synonymous with Guillain-Barré syndrome). Etiology: 1) Nutritional deficiencies, 2) toxins, 3) therapeutic agents (e.g., vincristine, isoniazid), 4) systemic diseases (arteritis, diabetes, amyloidosis), 5) inflammatory or demyelinating (e.g., Guillain-Barré), and 6) hereditary.

2. **Demyelinating neuropathy (myelinopathy)**. The initial pathological changes are in the Schwann cells or myelin.

3. **Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)**. This condition is common worldwide, and occurs at all ages (peak 5th and 6th decades). It starts with an illness similar to AIDP and becomes either chronic relapsing or chronic progressive.

4. **Neuronopathy**. The initial pathology is in the cell body (e.g., Herpes zoster and polio).

5. **Large-fiber neuropathy** which gives rise to loss of position, vibration and touch and pressure senses, decreased tendon reflexes, and LMN involvement.

6. **Small-fiber neuropathy** in which there is decreased pain and temperature sensation, spontaneous pain, ANS involvement, but preservation of joint position, vibration and touch and pressure sensations.

**Definitions**

**Paresthesia and dysesthesia (interchangeable)** - unpleasant or unusual sensations that are with or herald a PNS disorder. May be provoked or spontaneous.

**Hyperesthesia** - exaggerated response to normally painful stimuli.

**Alloodynia** - pain produced by normally nonpainful stimuli.

**Negative symptoms** - loss of function or sensibility.

**Plexopathy** - disease confined to lumbar or brachial plexus

**Positive symptoms** - abnormal spontaneous sensations or movements (e.g., tingling, fasciculation)

**Radiculopathy** - disease confined to one or more spinal roots.

**A few major examples of the various types of neuropathies follow.**

A. **Inflammatory**

    **AIDP - acute inflammatory demyelinating polyradiculoneuropathy** (Landry’s-Guillain-Barré Syndrome)

    This is an acute demyelinating neuropathy for which there is a wide variety of antecedent events: 40% - “viral prodrome”; 5% - Mycoplasma; 10% - allergy; 25% - other (including surgery); 20% - no known antecedent event. It is the most common cause of acute paralytic illness in developed countries and occurs mostly in
young adults with a second lesser peak in the 45-64 years age group. In the U.S. the incidence is 1 to 2 cases/100,000/annum.

This is a rapidly progressive motor neuropathy with variable sensory features. In the severe form there is pronounced muscle weakness and paralysis leading to respiratory paralysis and facial diplegia (bilateral paralysis). The CSF often contains protein > 0.55 g/liter after the first week with a normal or minimally increased cell count.

With the elimination of poliomyelitis, Guillain-Barré syndrome has become the commonest cause of acute generalized paralysis with an annual incidence of 0.75 to 2 cases/100,000 worldwide.

Landry et al. first described the condition in 1866, and in 1916 Guillain and Barré, French army neurologists, and A. Strohl carried out the electrophysiologic recordings. They also described the CSF findings of increased protein with a normal or slightly increased cell count which enabled the condition to be distinguished from poliomyelitis and other neuropathies.

The diagnosis is difficult because of the variable initial presentation and extensive differential diagnosis and often depends upon the clinical acumen and experience of the physician.

Clinical

In acute Guillain-Barré, typically there is fine paresthesia in the toes or finger tips and, in several days, leg weakness. Difficulty in walking is a common early complaint accompanied by bilateral footdrop and a waddling wide-based unsteady gait. Fifty percent start in the lower limbs and spread up. This is followed by variable arm, facial (common and helps to differentiate from most other neuropathies), and esophageal weakness. The weakness usually ascends from the thighs to the arms in days. Pain is a common complaint presenting as bilateral sciatica, or aching in the large muscles of the upper legs, flanks, or back (“Charley horse”). There is symmetrical limb weakness, and bilateral weakness of the facial muscles (in 1/3 of patients). Tendon reflexes are absent or greatly reduced, and there is minimal loss of sensation. In severe cases respiration (vital capacity < 50%), eye movements, swallowing, and autonomic functions are also affected, and the patient may require mechanical ventilation for up to one year. Several recurrences may occur at intervals of 10-15 years.

In the mildest cases there is minimal muscle weakness.

(Variants of Guillain-Barré syndrome are described, e.g., Fisher’s syndrome.)

Laboratory Findings

The most sensitive and specific are abnormalities of nerve conduction (occur before the increased CSF protein), i.e., conduction block (caused by the demyelination) which in the motor nervous system produces weakness. In the sensory nervous system, spontaneous discharges arise (caused by the demyelination) and are probably responsible for the paresthesias and pain.

In the serum activated - protein - synthesizing lymphocytes are found and C dependent antimyelin antibodies. Biopsy of a nerve is rarely indicated and the diagnosis is made on the less invasive techniques and clinical presentation.

Differential diagnosis - in order of importance - spinal cord compression; transverse myelitis; myasthenia gravis; basilar artery occlusion; neoplastic meningitis; vasculitic neuropathy; polymyositis; metabolic myopathies; paraneoplastic neuropathy; hypophosphatemia; heavy-metal intoxication; neurotoxic fish poisoning; botulism; poliomyelitis; tick paralysis.

(Please do not attempt to memorize this list - I included it in order to emphasize the complexity of diagnosing the condition).
About 2/3 of the cases follow an infection - usually mundane and viral but includes HIV, CMV, EBV with hepatitis or mononucleosis, asymptomatic hepatitis. *Campylobacter jejuni enteritis* has recently been recognized as an important early disease, often associated with severe or variant forms of the neuropathy. However, there has not been any consistent demonstration of any infectious agent and an immunologically mediated disorder of obscure origin is generally favored.

A small group of Guillain-Barré cases occurs in the presence of some underlying disease, e.g., lupus, Hodgkin’s, sarcoidosis, or HIV infection. The condition can occur with pregnancy (in the third trimester) or postpartum, but does not affect the fetus.

**Current evidence** indicates a 1º T cell mechanism which results in inflammation, and during the acute phase there are circulating activated T cells and increased IL-2 in the serum. It is hypothesized that, at least in some cases, there is an early Ab attack on myelin and that in others it is mainly an inflammatory process. Circulating antineural Abs have been demonstrated. It may not be a single entity and there may be multiple triggering events.

**Outcome and Rehabilitation**

Recovery occurs over weeks or months, often the weakness ceases to advance after 1-3 weeks, after which there is a plateau for several weeks followed by slow improvement. Only about 15% have no residual deficit; 3-8% die from complications (largely avoidable), e.g., ARDS, sepsis, pulmonary embolism; 65% are left with persistent minor problems (footdrop, distal numbness); 5-10% have permanent weakness, imbalance, and decreased sensation. Patients who only experience mild symptoms and show early improvement have the best prognosis.

The illness may be less severe in children than in adults.

**Pathology**

Microscopically, there is focal inflammation of the peripheral nerve with demyelination and accumulations of lymphocytes and macrophages. These inflammatory lesions are scattered throughout the peripheral NS with some predilection for proximal nerve trunks.

Electron microscopy reveals, as the earliest sign, splitting of myelin lamellae by macrophages which later strip the myelin off the axon and digest it. Schwann cells are left intact. Apparently lymphocytes do not participate directly. The axons are usually spared. This EM picture is unique among the demyelinating neuropathies.

**Therapy**

Hospitalization for at least a few days. Recovery, in all but the mildest cases is due to special care units with experience in the various complications which may occur. Plasma exchange is the current therapy, but this may be replaced by daily infusions of γ globulin.

**B. Acquired Metabolic**

**Diabetic Neuropathy**

There are two types: 1) symmetric polyneuropathies, 2) mononeuropathies, and mixtures of the two are common.

This is often one of the most troublesome complications of diabetes mellitus. Its occurrence is capricious and most occur late in the disease. The signs and symptoms are distal, symmetric, and predominantly sensory. The polyneuropathy is principally an axonopathy but there are also suggestions of a
demyelinating component. The etiology is not clear, but a metabolic dysfunction is prominent in rapidly reversible neuropathies of the newly diagnosed diabetics.

C. **Hereditary**

Most affect strength and sensation—hereditary motor and sensory neuropathies (HMSN). Others affect sensation and the autonomic N.S.—hereditary sensory and autonomic neuropathies (HSAN).

**Peroneal Muscular Atrophy** (Charcot-Marie-Tooth Disease HMSN I and II)

This relatively common neuropathy is dominantly inherited and is a slowly progressive sensorimotor disease. There is weakness and wasting in the lower leg and foot producing the characteristic “inverted champagne bottle limb.” “Onion bulb” formation is a prominent feature. The disease is compatible with the normal life span.

**PERIPHERAL NERVE SHEATH TUMORS**

**Schwannomas** (neurilemmomas) and **Neurofibromas**

**Schwannomas** arise from Schwann cells and show a predominance for sensory nerves, e.g., VIII cranial nerve. The tumor is white/grey and firm, solitary, circumscribed, encapsulated, and in an eccentric position on proximal nerves or spinal nerve roots. Characteristically they have areas of high cellularity (Antoni A) (possibly with palisaded nuclei and fibers called Verocay bodies) and areas of low cellularity called Antoni B. Nerve fibers are not present in the body of the tumor, but are compressed to one side, therefore it might be possible to remove the tumor without cutting the nerve.

**Schwannomas** on cranial and spinal nerve roots produce the most serious symptoms. Patients with acoustic Schwannomas c/o tinnitus (ringing in the ears) deafness, and if the tumors are large pressure on V and VII cranial nerves producing palsies, or brain stem compression and hydrocephalus. Spinal root Schwannomas may present with slowly progressive cord compression or cauda equina syndrome. More distal tumors produce local complaints. There is evidence that benign Schwannomas may transform to malignant ones.

**Neurofibromas** arise from Schwann cells, perineural cells or fibroblasts. The commonest forms are the cutaneous neurofibroma, which may become quite large and pedunculated and very rarely become malignant, and peripheral nerve neurofibromas (solitary neurofibromas). Both occur sporadically as well as in association with neurofibromatosis Type I (NFI). Microscopically neurofibromas are composed of loose interlacing bands of delicate spindle cells with elongated, slender, wavy nuclei. Often there is a loose myxoid stroma. Those associated with peripheral nerves have nerve fibers scattered throughout the mass and the tumor cannot be removed without cutting the nerve.

Both Schwannomas and neurofibromas contain S100 protein which is a very useful marker in distinguishing from fibrous tissue tumors.

The **neurofibromatoses** are cancer-prone hamartomatoses that involve a variety of tissues and cell types. They comprise at least two autosomal dominant disorders of which there are 100,000 cases in the United States.

Neurofibromatosis-1 (NF1, von Recklinghausen, peripheral NF) and Neurofibromatosis-2 (NF2, bilateral acoustic neurofibromatosis, central NF) are clinically and genetically distinct.

**Neurofibromatosis-1** (> 90% of the cases) is one of the most common autosomal dominant diseases (1 per 2,500-3,300 births) worldwide and is the most common hereditary tumor syndrome caused by a single gene.
1. **Multiple neurofibromas** appear during puberty or in adulthood. They are associated with nerve trunks anywhere in the skin or any internal site (especially the acoustic nerve). The nodules consist of tangled arrays of all the elements in the peripheral NS (Schwann cells, axons, fibroblasts) and microscopic to massive nodules (plexiform neurofibromas) may be seen anywhere. There is often subcutaneous or fusiform enlargement of distal nerves.

2. **Schwannomas** may also occur in this condition.

3. **Café au lait spots** develop in childhood and 6 or more > 5 mm in diameter in a child or > 1.5 cm in diameter in an adult means that von Recklinghausen’s disease is most likely present. Giant melanosomes are found in the epidermal cells. The spots often overlie neurofibromas.

4. **Lisch nodules** are pigmented iris hamartomas which do not produce problems and help in the diagnosis as they only occur in von Recklinghausen’s disease.

Patients with neurofibromatosis-1, or with a family history of such, are more susceptible to the oncogenic effect of radiation than patients without this genetic defect and patients offered radiation therapy, in place of surgery for some malignant process, should be informed of the increased risk of the development of malignant peripheral nerve sheath tumors and other sarcomas.

The condition is disfiguring (elephant man) and may be very serious, a) because there is a greater risk of developing tumors, e.g., optic gliomas, meningiomas, pheochromocytomas, b) because of the location of the nodules, and c) malignancies arise in 3% of the cases (especially those attached to large nerve trunks of the neck and extremities). Also scoliosis or erosive bone defects may develop.

The affected gene is on chromosome 17 which seems to encode a protein that acts as a negative regulator of a growth stimulating pathway (tumor suppressor gene).

**Neurofibromatosis-2**

This is much rarer than type 1 (1:150,000) and most patients have peripheral neurofibromas and Café au lait spots and bilateral acoustic **Schwannomas** are present but Lisch nodules are absent. **Chromosome 22** (functions unknown) is implicated.

The genes for NF-1 & 2 both act as tumor suppressor genes.

Both Schwannomas and neurofibromas may develop marked nuclear pleomorphism, giant cells, and myxoid or xanthomatous degeneration.

**Malignant transformation** may occur in both types but much less so in Schwannomas. The malignant tumors resemble a fibrosarcoma and they occur mostly in von Recklinghausen’s neurofibromatosis. **Except** in von Recklinghausen’s disease, Schwannomas and neurofibromas occur in the fifth and sixth decades of life.

\[ \text{V cranial nerve} = \text{trigeminal} \]
\[ \quad \text{sensory - face, teeth, mouth, and nasal cavity} \]
\[ \quad \text{motor - muscles of mastication} \]

\[ \text{VII cranial nerve} = \text{facial} \]
\[ \quad \text{large motor root - muscles of facial expression} \]
\[ \quad \text{smaller root - parasympathetic and special sensory} \]
SKELETAL MUSCLE

Please review the normal structure of skeletal muscle.

Most often muscles are secondarily affected and are not often the site of a primary disease. For example, they become affected in both upper and lower motor neuron diseases and certain systemic diseases (e.g., sarcoidosis and various forms of arteritis). Snake venoms, alcohol, some drugs, and viral infections also affect muscles. Muscle can also be infected by bacteria from surrounding tissues and specifically infected by e.g., *Trichinella spiralis*.

The more specific diseases of muscle fall into two general categories, **myopathic and neurogenic**.

**Myasthenia** = muscular disability: any constitutional anomaly of muscle.

**TABLE 28-5. Major Categories of Neurogenic and Myopathic Disease of Muscle**

<table>
<thead>
<tr>
<th>Neurogenic Disease</th>
<th>Myopathic Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myasthenic syndromes</td>
<td>Inflammatory myopathies</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Polymyositis-dermatomyositis (p. 207)</td>
</tr>
<tr>
<td>Lambert-Eaton syndrome</td>
<td>Myositis associated with collagen vascular disease</td>
</tr>
<tr>
<td>Congenital myasthenia</td>
<td>Muscular dystrophies</td>
</tr>
<tr>
<td>Denervation atrophy</td>
<td>Duchenne or Becker</td>
</tr>
<tr>
<td></td>
<td>Limb girdle</td>
</tr>
<tr>
<td></td>
<td>Facioscapulohumeral</td>
</tr>
<tr>
<td></td>
<td>Myotonic dystrophy</td>
</tr>
<tr>
<td></td>
<td>Inherited metabolic and congenital</td>
</tr>
<tr>
<td></td>
<td>McArdle’s syndrome (p. 153)</td>
</tr>
<tr>
<td></td>
<td>Mitochondrial myopathies</td>
</tr>
<tr>
<td></td>
<td>Nemaline myopathy</td>
</tr>
<tr>
<td></td>
<td>Hyper- or hypokalemic periodic paralysis</td>
</tr>
<tr>
<td></td>
<td>Central core disease</td>
</tr>
<tr>
<td></td>
<td>Centronuclear or myotubular myopathy</td>
</tr>
<tr>
<td></td>
<td>Congenital fiber - type disproportion</td>
</tr>
<tr>
<td></td>
<td>Acquired metabolic and toxic</td>
</tr>
<tr>
<td></td>
<td>Steroid-induced</td>
</tr>
<tr>
<td></td>
<td>Hypothyroid and thyrotoxic</td>
</tr>
<tr>
<td></td>
<td>Alcohol</td>
</tr>
<tr>
<td></td>
<td>Chloroquine</td>
</tr>
<tr>
<td></td>
<td>Epsilon-aminocaproic acid</td>
</tr>
<tr>
<td></td>
<td>D-Penicillamine</td>
</tr>
<tr>
<td></td>
<td>Procainamide</td>
</tr>
</tbody>
</table>

10
**BASIC PATHOLOGIC REACTIONS**

These are atrophy, degeneration, regeneration and various other myopathic changes.

1. **Atrophy** - this occurs in the following instances: lack of use, general malnutrition, ischemia, and denervation. The fibers become smaller and angulated on cross-sectional appearance (especially with denervation, when denervated fibers are compressed by adjacent innervated fibers). The myofibrils and other organelles are lost, but the marginal nuclei persist and appear to be increased in number as the fiber shrinks. Eventually there is interstitial fibrosis and decreased muscle volume.

2. **Degeneration** - occurs in a number of diseases. Usually only a part of the fiber is affected and the fiber can reconstitute from the remaining undamaged segments. The fibers or parts of the fibers become necrotic and are removed by macrophages.

3. **Regeneration** - is accomplished by the activation and proliferation of myoblasts. These are small, spindle shaped satellite cells and the mechanism is similar to that during muscle development in the fetus.

4. **Increased variation in fiber diameter** - is seen in both neurogenic and myopathic diseases.

5. **Increased number of central nuclei** - is nonspecific and just indicates a disturbance. (This is also seen in about 5% of normal muscle fibers).

6. **Hypercontraction** - of localized segments are often seen at edges of biopsy specimens and in Duchenne’s dystrophy.

7. **Ring fibers** - are produced when the peripheral myofibrils are reoriented to run circumferentially. They are characteristic of myotonic dystrophy.

8. **Fiber splitting** - appears as clefts in a myofiber and is probably due to defective regeneration.

In LMN lesions (e.g., poliomyelitis), both Types I (“slow-twitch”) and II (“fast-twitch”) myofibers are affected. In UMN lesions (e.g., strokes), Type II fibers are mainly affected. In H and E stained sections, Type I and Type II fibers cannot be distinguished. However, with ATPase at different pH’s the two types can be differentiated.

In humans, Type I and II fibers are in random array. Motor units contain muscle fibers dispersed amongst those of other motor units and ATPase gives a checkerboard appearance.

The fiber type is determined by the innervation and if a muscle is denervated and then reinnervated by another nerve the muscle fiber will change its biochemical characteristics to match those of the fibers innervated by that nerve.

Slow twitch fibers (Type I) contain abundant myoglobin, oxidative enzymes and mitochondria. ATPase at pH 4.2 produces a dark stain. These fibers are responsible for tonic contraction and maintenance of posture.

Fast twitch fibers (Type II) are richer in glycolytic enzymes and stain darkly with ATPase at a pH 9.4. They are responsible for rapid phase contractions.

**MYOPATHIC DISEASE** (subdivided into four groups)

1. **Myositis** - (Inflammatory myopathies)

The most important forms are seen in the collagen vascular diseases (polymyositis and polyarteritis nodosa). Direct invasion by blood-borne microbes is rare, but when present, bacterial toxins may proteolyze large areas of muscle.
Polymyositis is a chronic inflammatory myopathy of uncertain cause. When a skin rash is also present, particularly about the eyes, face, and extensor surfaces of the limbs, the condition is called dermatomyositis (the classic presentation of this rash is a lilac or heliotrope discoloration of the upper eyelids). Dermatomyositis affects all age groups, about 1 in every 100,000, and females more often than males. A recent clinical trial of patients with dermatomyositis has shown encouraging results with IVIG (intravenous immunoglobulin). In polymyositis there is symmetric proximal muscle weakness with varying degrees of pain and often with the rash. The muscle weakness usually begins proximally in the shoulders and pelvic girdle and spreads to the neck and distal extremities. Pharyngeal muscle weakness is common. The condition occurs at any age with bimodal peaks at 5–15 years and 50–60 years. The muscle weakness and disability are the most important clinical findings.

The clinical presentation is very variable and in 20% of patients is accompanied by a connective tissue disorder, e.g., SLE (systemic lupus erythematosus), systemic sclerosis, or Sjögren’s syndrome. An associated malignancy occurs in 15% of males and slightly less in females over the age of 50 years.

In juvenile dermatomyositis there is widespread vasculitis of the skin and GI tract, and therefore, myositis, bowel infarction with perforation and skin ulcers are prominent features. The differential diagnosis includes SLE, systemic sclerosis, rheumatoid arthritis, and myasthenia gravis and muscular dystrophies. Ocular muscles are almost always spared and therefore myositis can be distinguished from myasthenia gravis. EMG (EMG = electromyography and is used to study the intrinsic properties of skeletal muscle) distinguishes between inflammatory muscle disease and neuron and receptor diseases. Muscle injury produces increased levels of enzymes, e.g., creatine kinase (the most sensitive) and aldolases. Polymyositis is believed to be of immune origin, and auto antibodies and ANAs (antinuclear antibodies) (e.g., rheumatoid factor) are found in some cases. In juvenile dermatomyositis, immune complexes are found in the affected blood vessels. Also in polymyositis/dermatomyositis, cell-mediated immunity has been implicated and helper and cytotoxic T lymphocytes have been found in the inflammatory infiltrate, and the muscle fibers may be damaged by cell-mediated cytotoxicity. The laboratory tests, however, are helpful but nonspecific except for the Jo-1 antigen antibody (against histidyl tRNA synthetase) which is present in 25% of adults with myositis and is considered to be specific (Jo = the name of the patient in which the antigen was first described).

Histologically there is necrosis of groups or single muscle cells, phagocytosis of muscle cell fragments (more characteristic of myositis than dystrophies), and prominent perivascular, endomysial, and perimysial inflammatory infiltrates. Central vacuolization of the muscle fibers is virtually pathognomonic for polymyositis. Most of the cells are T cells with markers, e.g., IL-2 receptors. CD4+ and CD8+ cells are also present. Sixty percent of peripheral T cells and some monocytes are CD4+ and it is a marker for T helper inducer cells. Thirty percent of peripheral T cells are CD8+ and it is a marker for cytotoxic cells. In dermatomyositis the greater percentage of B cells causes activation of humoral immunity. In chronic cases, foci of fibrosis and/or fat replacing muscle is seen.

Histologically, the skin rash, which is present in about 40% of cases, presents as edema with mononuclear cells around blood vessels.

In children and some adults with acute involvement, widespread necrotizing vasculitis develops involving the lungs, kidneys, heart, and other organs. In adults diffuse pulmonary fibrosis with anti-Jo-1 antibodies is frequent.

Diagnosis of polymyositis is made on biopsy tissue. The condition is characterized by remissions and exacerbations. Most cases respond to immunosuppressive therapy, and there is a 75% 5-year survival rate in adults and more than 75% in children. There is believed to be a 13–20% risk of malignancy of lungs, ovaries, and stomach in patients with dermatomyositis.
**Polyarteritis nodosa (PAN)**

Medium to small sized arteries are involved with a transmural acute necrotizing inflammation. The lesions are focal, random, and episodic in nature and frequently produce irregular aneurysmal dilatations, nodularity and vascular obstruction, and sometimes infarctions. Any organ may be involved, except the lungs and aorta and its primary branches. In some cases however, the lesions are entirely microscopic. The clinical presentation is unpredictable because of the variety of organs involved.

PAN occurs most often in middle age with a male–female ratio of 2 or 3:1. The cause and pathogenesis are unknown, but immune complexes are suggested. Recently, antineutrophil cytoplasmic antibodies (ANCA) have been identified in the circulation of patients with PAN, but their role is still speculative. The organs involved in descending order of frequency are: kidney, heart, liver, GIT, pancreas, testes, skeletal muscle, NS, and skin. The lesions are sharply segmental and occur at branch points and bifurcations. There is initially an acute transmural vasculitis often with fibrinoid necrosis of the inner half of the wall. Later there is fibrous thickening of the wall and a mononuclear infiltrate which eventually disappears. All stages may coexist in different vessels or even the same vessel. The clinical presentation is very varied and includes muscle weakness. Diagnosis is by biopsy (kidney and skeletal muscle).

2. **Muscular Dystrophy**

There is a family of genetically determined myopathies ranging from mild motor weakness with relatively normal life (Becker type) to a very severe type with early death (Duchenne’s dystrophy). Becker is about 1/10th as common as Duchenne. They constitute a subgroup of inherited metabolic diseases. Cardiac muscle is also commonly affected. Both Duchenne and Becker types are due to mutations in the same gene.

a. **Duchenne’s dystrophy** is the most common and devastating of the dystrophies (1 per 10,000 males). It is caused by a mutation of a gene located on the short arm of the X chromosome. Most patients are sons of carrier mothers (because males do not live long enough to be fathers!), but some acquire the mutation de novo, while rarely females with Lyonization of the normal X chromosome are affected. (Lyonization = inactivation of an X chromosome in a cell - according to Lyon hypothesis, i.e., Barr Body.)

The normal gene produces dystrophin, a protein present in small quantities in muscle. Dystrophin has considerable homology with a cytoskeletal α-actinin and spectrin, is membrane associated, and is localized to the T-tubule system. The mutation produces decreased dystrophin with resultant abnormal cell contraction and progressive muscle weakness (possibly by interfering with calcium release or the weakening of myocytes). The changes are most marked in the muscles around the shoulder girdles and pelvis, and then those of the extremities.

Microscopically vacuoles, fragmentation, and coagulation necrosis of individual myofibers is seen followed by invasion of macrophages. Some of the damaged myofibers regenerate (from myoblasts and if only small parts of a fiber are destroyed there can be some reconstitution). Nuclei become central, contraction bands (marked shortening of some sarcomeres and increased variation in the diameter of the fibers) appear, fiber splitting takes places and there is variation in the diameter of the fibers. Other damaged fibers are removed and replaced by fibrofatty tissue whilst the unaffected fibers undergo hypertrophy. The fibrofatty tissue and the hypertrophy result in pseudo-hypertrophy, especially in calf muscles. Later, as more myofibers degenerate, the muscles shrink and become pale and flabby as they are replaced by fibrofatty tissue.

Duchenne’s dystrophy starts in early childhood and is characterized by difficulty in standing, walking, and getting out of a chair. The muscle weakness is progressive and most evident in the lower extremities, and eventually the upper extremities may also be affected. However, pseudohypertrophy of the calf muscles often exists (this starts out as hypertrophy of the muscle fibers, but as the disease progresses and the muscles atrophy there is an increase in fat and
connective tissue). Involvement of the trunk muscles leads to spinal curvature and sometimes to respiratory encroachment. By 12 years of age most of the patients are in wheelchairs, and by age 20, death occurs, mostly from pulmonary infections (weak muscles and aspirated foods). Cardiac failure may also occur (degeneration of cardiac cells). Decreased dystrophin may affect the neuronal membrane skeleton leading to intellectual impairment.

**Diagnosis** is made from the distinctive clinical features, the increased serum muscle enzymes (especially creatine kinase), and electromyography. The diagnosis can be confirmed by biopsy.

Researchers at Guy’s Hospital, London, have reported excellent results from a test using peripheral blood lymphocytes to detect carriers of Duchenne or Becker type muscular dystrophy. (More and more tests are becoming available that allow the detection of carriers of certain diseases - I quote from Hospital Practice, March 15, 1991 - “It’s becoming clear, however, that choosing a mate may soon include, among other things, how you like the cut of the genes!”)

b. **Myotonic dystrophy** - This is an autosomal dominant disease with a mutation on chromosome 19 of a gene that normally codes for a protein kinase termed myotonin-protein kinase. Many other systems, as well as muscles, are affected. The chief symptom is that of myotonia (sustained, involuntary contraction of a group of muscles). Atrophy of facial muscles occurs with ptosis. The disease appears at a younger age in each succeeding generation = anticipation.

Histologically, there are central nuclei, ring fibers (peripheral myofibrils form a ring around central ones which run longitudinally), sarcoplasmic masses devoid of striations, chains of nuclei, and type 1 fiber atrophy.

3. **Inherited Metabolic and Congenital Myopathies**

These include myophosphorylase deficiency (McCardle’s syndrome), acid maltase deficiency, phosphofructokinase deficiency, and mitochondrial myopathies. In congenital myopathies, most present as a “floppy infant” with symmetric weakness, most severe proximally. Nemaline (rod body) myopathy is an autosomal dominant disease which causes hypotonia and weakness. The nemaline rod on electron microscopy is shown to be masses of round Z body material.

**N.B.** Phosphofructokinase deficiency = Type VII glycogen storage disease

McCardle’s syndrome = Type V glycogenosis and is compatible with a normal life span.

These two disorders are associated with impaired energy production, muscle weakness, and muscle cramps after exercise and failure to detect increased serum lactate after exercise. Acid maltase deficiency produces glycogen storage in many organs and early deaths. Acid maltase is a lysosomal enzyme. A deficiency causes Type II glycogenosis (Pompe’s disease). Cardiomegaly is the most prominent feature.

Mitochondrial myopathies are a group of disorders with a defect in: a) substrate transport (carnitine metabolism and the pyruvate dehydrogenase complex), b) energy conservation (ATPase deficiency) and c) respiratory chain (cytochrome deficiency). Widespread effects are produced and may be mixtures of a, b, or c).

4. **Acquired Metabolic and Toxic Myopathies**

The major disorders occur in hypo- and hyperthyroidism and steroid-induced myopathy. There is diffuse muscle weakness and sometimes wasting. There is not any pathognomonic morphology. The diagnosis is by exclusion and history of hormonal deficiency.

The toxins involved are alcohol (= ethanol myopathy which occurs after “binge” drinking and results in muscle breakdown and myoglobinuria), an antifibrinolytic agent (epsilon-aminocaproic acid), chloroquine, steroids, D-penicillamine, and procainamide.
NEUROGENIC DISEASE

1. **Myasthenia Gravis (MG)** is the most frequent of the myasthenic syndromes which are characterized by muscle weakness and fatigability.

   This is an autoimmune disease with antibodies to acetylcholine receptors (AChR) at the muscle end plate. This leads to muscle weakness and marked fatigability. During the past two decades remarkable progress has been made in the understanding of this disease and it is the most thoroughly understood of all human autoimmune diseases.

   There are about 25,000 affected persons in the U.S. The age of onset peaks at about 20 years. There is a female-male ratio of 3:1, but a second smaller peak (males) occurs later. Children born to mother’s with MG often develop transient myasthenic syndromes. Two-thirds of the cases are associated with thymic hyperplasia and 15-20% with thymomas. Some patients have other associated autoimmune diseases, e.g., SLE, Sjögren’s syndrome (dry eyes and mouth due to immunologically mediated destruction of lacrimal and salivary glands; there is often an association with rheumatoid arthritis and with other autoimmune disorders), rheumatoid arthritis, and hyperthyroidism.

   **Pathogenesis** - 90% of cases have circulating antibodies to AChR, but these may be absent in mild cases. Muscular weakness occurs because the antibodies cause increased degradation of receptors, possibly by complement-mediated lysis of receptors, and inhibition of ACh binding. Thymic hyperplasia is often associated with the appearance of AChR on the surface of some thymic epithelial cells and myoid cells, and some neoplastic epithelial cells in thymomas express AChR. It is assumed that these antigens sensitize B cells to produce auto antibodies. (Thymomas are rare neoplasms of the thymus which involve the epithelial elements and 90% are benign.)

   Very few histologic changes are noted, but by immunocytochemistry and immunofluorescent stains, complement and IgG can be detected in the neuromuscular junctions. By EM simplification and a marked reduction in number of AChRs (the simplification takes the form of reduced or abolished junctional folds).

   **Clinically,** there is considerable variation in the course of the disease. The presence of thymoma and high titers of circulating AChR antibodies indicate a poor prognosis. Weakness and fatigue start in the most active muscles (extraocular, facial, tongue, extremities), and in severe cases other muscles become progressively involved. Eventually, trunk and limb muscles and speech and swallowing are also affected. Respiration becomes compromised, which leads to pulmonary infections and death. In milder cases there might only be a mildly increased fatigability of extraocular muscles and muscles of the face.

   **Therapy** includes thymectomy for hyperplasia, removal of a tumor, anticholine esterases, and immunosuppressive agents. For patients with severe generalized disease, there is about a 10% death rate in 10 years.

   Overall more than 90% of patients respond to treatment with long-term reduction in disability and improvement in quality of life.

   There are other myasthenic syndromes, e.g., Lambert-Eaton syndrome, 2/3 of which are associated with a malignancy (usually small cell carcinoma of the lung).
FIGURE 1. Compared with the normal mammalian neuromuscular junction (top), that in myasthenia gravis (bottom) is characterized by a widened synaptic space, a flattened postsynaptic membrane, and a reduced number of acetylcholine receptors. Note that each acetylcholine molecule normally interacts with only one receptor before it is degraded into choline by acetylcholinesterase. In myasthenia gravis, the use of antiacetylcholine esterase medication allows acetylcholine to interact with more than one receptor.
FIGURE 3. Antibodies against acetylcholine receptors can induce postsynaptic dysfunction through a number of mechanisms. One mechanism is to block binding sites on acetylcholine receptors (A). Another is to modulate the number of receptors by cross-linking, leading to endocytosis followed by lysosomal sequestration and proteolytic degradation of the receptors (B). Antibody-induced activation of the complement system (c) may contribute to dysfunction in two ways: by accelerating receptor loss (through C3 binding, for example), or by destroying the postsynaptic membrane via complement component-derived membrane attack complexes.
FIGURE 4. The initiation and maintenance of autoimmune myasthenia gravis may involve the following events: Acetylcholine receptors are phagocytosed by macrophages or other antigen-presenting cells (A). The receptors are then processed (B) and transported to the cell surface, where they are displayed in association with class II MHC molecules. Specific helper T cells recognize the acetylcholine receptor-class II complex; recognition involves the CD3 complex and the CD4 molecule on the helper T cells and cytokines (such as IL-1) secreted by the antigen-presenting cell (C). Activated helper T cells secrete B-cell growth and differentiation factors, which stimulate B cells that have bound acetylcholine receptor antigenic fragment (D) to differentiate into plasma cells (E) that then secrete anti-acetylcholine receptor antibodies (F). Subsequent binding of specific antibody to acetylcholine receptors causes synaptic dysfunction.
2. **Denervation Atrophy**
   This occurs in peripheral neuropathies in which there is axonal degeneration leading to denervation and muscle atrophies, e.g., amyotrophic lateral sclerosis (ALS) which is a motor neurone disease affecting both the upper and lower motor neurons. The muscle may become reinnervated by collateral sprouting from an adjacent nerve fiber. This leads to “type grouping” as the reinnervated fiber will be the same type as the one providing the “sprout”. Thus, on staining with ATPase, that distinguishes Type I from Type II fibers; the types are grouped rather than scattered (checkerboard) as is seen normally. With further denervation, muscle fibers atrophy in groups (“group atrophy”). Type grouping and group atrophy are the hallmarks of denervation.

   Clinically, there is muscle weakness and loss of muscle mass and fasciculations may be seen (fine, repetitive, multifocal contractions). These latter are a manifestation of hypersensitivity, which results from an increased number of AChRs, scattered over the whole surface rather than concentrated at the neuromuscular junctions.

**TRICHINOSIS**

This is a worldwide condition which is contracted by eating inadequately cooked meat or even smoked meat with viable cysts of *Trichinella spiralis*. The major vector is pork. The condition is uncommon in the United States because of the restrictions.

Animals ingest adult worms in contaminated food

\[
\text{Humans} \quad \downarrow \quad \text{Larvae} \quad \downarrow \quad \text{striated muscle and encyst within a myofiber} \quad \downarrow \quad \text{Human}
\]

cyst wall digested and parasites attach to small intestinal wall, mature and copulate, and the females release larvae which enter the lacteals and then the circulation. Some enter the lungs and cause interstitial pneumonitis, others reach the CNS and cause meningitis and gliosis about small arteries. Most importantly some of the larvae invade skeletal muscles (especially the most active muscles, e.g., diaphragm, extraocular, intercostals and extremities). In the skeletal muscles, the larvae may encyst and remain dormant for years. Some larvae may also enter cardiac muscle and cause interstitial myocarditis, which may lead to heart failure. In the heart muscle, the larvae undergo necrosis and do not become encysted. In the intestinal “phase,” vomiting and diarrhea may occur. In the CNS, the meningitis gives rise to headaches, disorientation, and symptoms of encephalitis, and in the muscles, widespread aches and pains and periorbital and facial edema.
SOFT TISSUE TUMORS

TABLE 21-2. Common Soft Tissue Tumors and Tumor-Like Lesions

<table>
<thead>
<tr>
<th>Designation</th>
<th>Common Locations</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipoma</td>
<td>Subcutaneously on back, shoulders, abdomen, or proximal extremities; intestinal tract</td>
<td>Mostly in adults</td>
</tr>
<tr>
<td>Fibroma</td>
<td>Ovary, along nerve trunks (neurofibroma)</td>
<td>Fibromatoses more common (see below)</td>
</tr>
<tr>
<td>Fibrous histiocytoma</td>
<td>Skin (dermatofibroma, fibroxanthoma, sclerosing hemangioma)</td>
<td>Less frequent than rhabdomyosarcomas; hamartomatous</td>
</tr>
<tr>
<td>Rhabdomyoma</td>
<td>Head and neck region; heart; vagina; vulva</td>
<td>Uterine are most common tumor in females</td>
</tr>
<tr>
<td>Leiomysarcoma</td>
<td>Uterus, gastrointestinal tract, subcutaneously from blood vessel walls</td>
<td></td>
</tr>
<tr>
<td>Granular cell tumor</td>
<td>Tongue, subcutaneously in trunk and upper extremities</td>
<td></td>
</tr>
<tr>
<td><strong>Malignant</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>Retroperitoneum, lower extremities; less often inguinal canal, mediastinum, omentum, chest wall</td>
<td>Less common than lipomas</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>Thigh, knee, trunk, forearms, wherever fibrous tissue is found</td>
<td>Tend to involve deeper structures rather than subcutaneous fibrous tissue</td>
</tr>
<tr>
<td>Malignant fibrous histiocytoma</td>
<td>Skeletal muscle of extremities, retroperitoneum, subcutaneous tissue, elsewhere</td>
<td>Most common soft tissue sarcoma in adults</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>Head and neck region, genitourinary tract, retroperitoneum, extremities</td>
<td>Most common soft tissue sarcoma of children and adolescents; rare after age 45</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>Uterus, gastrointestinal tract, abdomen, retroperitoneum, blood vessel walls</td>
<td>Principally in adults; rare in children; even extruterine more common in women</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>About but not within joint cavities, parapharyngeal region, mediastinum, abdominal wall</td>
<td>No benign counterpart</td>
</tr>
<tr>
<td><strong>Tumor-like lesions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial fibromatoses</td>
<td>Palms (Dupuytren’s contracture), soles of feet, penis (Peyronie’s disease)</td>
<td>Collagenous strictures</td>
</tr>
<tr>
<td>Deep fibromatoses (desmoids)</td>
<td>Anterior abdominal wall in women; musculature of shoulder, chest wall, back, and thigh; abdomen in both sexes</td>
<td>Lie in the interface between nonneoplastic proliferation and fibrosarcoma</td>
</tr>
<tr>
<td>Nodular (pseudosarcomatous)</td>
<td>Subcutaneously in upper extremities of adults, trunk, back, elsewhere; in infants, head and neck</td>
<td>Commonly mistaken clinically for a neoplasm</td>
</tr>
</tbody>
</table>

Forty percent involve the lower extremities, 20% the upper extremities, 10% the head and neck, and 35% the trunk and retroperitoneum. Benign tumors are more common than malignant, and in fact, malignant soft tissue tumors comprise less than 2% of all cancers. Sarcomas may occur in children, but 75% are in adults.

Rhabdomyomas and Rhabdomyosarcoma

Rhabdomyomas in an extracardiac location are extremely rare, and within the heart are probably hamartomas.

Rhabdomyosarcomas (RMS) are much more common than their benign counterpart. They are the most common soft tissue sarcoma in children. RMS may occur anywhere, but less than 25% arise in muscles. Forty percent arise in the head and neck, 30% are genitourinary, and 20–25% in the muscles of the extremities. The majority are nondescript, grey, sometimes myxoid, infiltrative masses that cannot be distinguished from other sarcomas. There is one variant which resembles a bunch of grapes, hence, its name “botryoid”. This variant can be seen projecting into the vagina, bladder, or other space.

Histologically the sarcomas are very variable, and four subtypes are described: 1) embryonal, 2) botryoid, 3) alveolar, and 4) pleomorphic. The cells are highly pleomorphic, and in the more differentiated tumors ribbon-like cells with cross striations and several nuclei may be seen.

Electron microscopy may be very helpful in the diagnosis, and monoclonal antibodies to desmin and muscle actins, as well as molecular probes, are proving to be increasingly useful.
BRAIN TUMORS

Steve Nandkumar, M.D.
PATIENT HISTORIES

Case 1a. A 62-year-old, Fortune 500 company Chief Executive Officer (CEO) complains of headache, nausea, and occasional vomiting. Investigations reveal a mass in the CNS. A biopsy is done. Patient expires despite Rx (treatment).

Case 1b. A 10-year-old boy is found to lack coordination and has abnormal gait. Investigations reveal a “cerebellar mass” which is then excised.

Case 2. A Big Ten University volleyball coach is noted to have occasional memory loss, headache, and altered mentation. Symptoms progress gradually over a few weeks. One day he collapses during practice and dies.

Case 3. A 16-year-old girl is admitted with severe headache, nausea, and vomiting. CT-scan reveals a large mass involving the fourth ventricle. A biopsy is done and radiation therapy is subsequently helpful.

Case 4. A 12-year-old boy is admitted with complaints of headache, vomiting, and shortness of breath. He develops respiratory distress and dies suddenly. An autopsy reveals a cerebellar mass.

Case 5. A 46-year-old woman is admitted with a history of seizures mainly involving the left lower limb. A cerebral convexity mass is discovered and excised.

Case 6. A 65-year-old former chief of CIA while testifying before congress develops seizures and becomes unconscious. Investigations reveal a deep-seated “mass” in the white matter. Patient expires (despite treatment) within six months.

Case 7. A 42-year-old male complains of headache, tinnitus (ringing in the ears), and partial deafness. CT reveals a “cerebello-pontine angle” mass on the right side. It is surgically removed.

Case 8. A 28-year-old man has a dark irregular mole excised from his neck. One year later the patient is admitted with vomiting, becomes comatose, and expires.
BRAIN TUMORS

GLOSSARY

Neuroglial cells — gliomas
1. Astrocytes — astrocytoma
   — glioblastoma multiforme
2. Oligodendroglia — oligodendroglioma
3. Ependyma — ependymoma
4. Microglia — primary brain lymphoma

Neurons (ganglion cells) — gangliocytoma
Neurons + neuroglial cells — ganglioglioma

Embryonal (primitive undifferentiated) — medulloblastoma
— primitive neuroectodermal tumor
— neuroblastoma

Meninges — meningioma
Schwann cells — Schwannoma (neurilemmoma)
— neurofibroma

NOTE: Neuroglia are:

A) Macrogia (derived from neuroectoderm) — astrocytes (supporting stromal cells)
   — oligodendroglia (produce myelin)
   — ependyma (lining cells of ventricles and central canal of spinal cord)

*B) Microglia (derived from mesoderm) — originates from bone marrow (mononuclear phagocyte system)

TUMORS ORIGINATING FROM MACROGLIA ARE CALLED GLIOMAS

![Diagram of common intracranial tumors](image)

FIGURE 28-130
The distribution of common intracranial tumors.
CNS TUMORS

Any intracranial mass or space-occupying lesion (SOL) may be a tumor. Following history, physical examination, and investigations (CT scan – more specific, MRI – more sensitive), the lesion can be localized and a biopsy obtained (if the tumor is accessible) to confirm and obtain a diagnosis.

GENERAL FACTS ABOUT BRAIN TUMORS

1. Incidence: 3/100,000 between 0–4 years
   17–18/100,000 between 65–80 years
   average about 8–9/100,000 overall
   Mortality rate is 5/100,000

2. More common in men than women
   – Mortality M > F
   – More common in whites than blacks

3. Etiology
   Genetics – p53 mutation, loss of chromosome 10
   Virus – e.g., Epstein-Barr virus, papova virus, (JC virus, BK virus)*
   Chemical – BCNU, CCNU (bis-chloroethyl nitrosourea and chloroethyl-chlorohexyl nitrosourea)
   Radiation –
   Phakomatoses – malformations/tumors (see end of handout)

4. Most common brain tumors are GLIOMAS.

5. 70% of tumors in adults are SUPRATENTORIAL.

6. 70% of tumors in children are INFRATENTORIAL.

7. Most brain tumors are potentially biologically malignant. Tumors may be histologically benign, but can kill if located in a vital area, e.g., brainstem, fourth ventricle.

8. Most tumors tend to have an infiltrating margin (tumor cells extend beyond the visible edge) and hence cannot be resected without sacrificing normal brain tissue around. The resulting quality of life must be kept in mind when attempting brain surgery!

9. Brain tumors may spread (seed) via the CSF to involve the CNS spinal axis, e.g., medulloblastoma, astrocytoma, metastatic cancers (lung, breast cancer).

10. EXTRANEURO METASTASIS IS UNCOMMON. Occasionally medulloblastoma, glioblastoma multiforme may however do so. Operations such as V-P (ventriculoperitoneal) shunting can enhance metastases.

11. Clinical features may be local or general.
   **Local effects** depend on the exact site of tumor and cause pressure, dysfunction, or even destruction. Seizures, mental and emotional changes, etc. can occur.
   **General effects** – increased intracranial pressure manifesting as
   a. Headache
   b. Vomiting
   c. Papilledema (25%) – **IMPORTANT SIGN OF ↑ ICP**.

*NOTE: J.C., BK are initials of patients in whom the viruses were first discovered.
Herniation of the brain can occur when a tumor expands and forces the adjacent normal brain tissue through orifices or areas of low resistance.

Thus

a. Subfalcial herniation (cingulate gyrus is pushed underneath the falx cerebri) – causes compression of anterior cerebral vessels, leg weakness, sensory loss occur.

b. Tentorial herniation (uncus, the medial part of temporal lobe is pushed through the tentorial notch). Midbrain is forced through also causing:
   - pressure on contralateral cerebral peduncle → ipsilateral hemiparesis on side of mass (changes called Kernohan’s notch)
   - Compression of oculomotor nerve with pupil dilatation.
   - Compression of posterior cerebral artery leading to ischemia of occipital visual cortex.
   - Rupture of vessels near pons/midbrain causing DURET’S hemorrhage (usual fatal).

c. Cerebellar tonsil herniation (through foramen magnum → medulla forced through → death). Seen usually in infratentorial tumors.

12. Paraneoplastic syndromes: Immune response against tumor antigens lead to cross-reaction with antigens in CNS and PNS. Autoantibodies are formed. Eg. Limbic encephalitis, Lambert-Eaton myasthenia syndrome (Abs against voltage-gated calcium channel), NMDA (N-methyl-D-aspartate) receptor Ab syndrome (syndrome of psychosis, catatonia, epilepsy, coma).

13. Tumor markers – Immunohistochemical methods are used to diagnose tumors. GFAP (glial fibrillary acid protein) → gliomas (astrocytomas, oligodendroglialomas, ependymomas). It is not present in meningiomas or metastatic tumors. S-100 protein occurs in Schwannoma.

CLASSIFICATION OF BRAIN TUMORS

<table>
<thead>
<tr>
<th></th>
<th>Primary (30%)</th>
<th>Metastatic (70%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLIOBLASTOMA MULTIFORME</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>High grade astrocytoma</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>Low grade astrocytoma</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Oligodendroglia</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Ependymoma</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Meningiomas</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Schwannomas</td>
<td>5–10%</td>
<td></td>
</tr>
<tr>
<td>Primary brain lymphoma</td>
<td>1–2%</td>
<td></td>
</tr>
<tr>
<td>Pituitary tumors</td>
<td>9%</td>
<td></td>
</tr>
</tbody>
</table>

SPINAL CORD TUMORS

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwannomas</td>
<td>29%</td>
</tr>
<tr>
<td>Meningiomas</td>
<td>25%</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>13%</td>
</tr>
</tbody>
</table>

NOTE: Metastatic tumors (80,000–150,000 cases/year) are more common than primary brain tumors (about 30,000 cases/year). (Per Robbins primary tumors are 50-75% and metastatic tumors are 25-50%).
ASTROCYTOMAS

– Occur between 40–60 years; M > F
– Present in cerebral hemisphere, brainstem, cerebellum, spinal cord

GROSS
– Poorly defined, gray, infiltrative masses with soft cystic and gelatinous areas

MICRO
– Three types are seen

<table>
<thead>
<tr>
<th>(Low grade) well-differentiated astrocytoma</th>
<th>High grade anaplastic astrocytoma</th>
<th>Glioblastoma Multiforme (G.M.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade II</td>
<td>Grade III</td>
<td>Grade IV</td>
</tr>
</tbody>
</table>

GRADING SYSTEM FOR BRAIN TUMORS (WHO - World Health Organization SCHEME)

<table>
<thead>
<tr>
<th>Cellularity</th>
<th>Nuclear atypism</th>
<th>Mitoses</th>
<th>Vascular endothelial Proliferation</th>
<th>Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>GR I</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GR II</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GR III</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>GR IV</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

NOTE: Gr IV tumors have increased cellularity, nuclear atypism, mitoses, vascular endothelial proliferation, and/or necrosis.

NOTE:
– Tumors tend to become more anaplastic with time.
– Histology is extremely variable from one area to another and hence a small biopsy may not be representative of the entire lesion.
– Tumor marker Ki-67 (proliferative marker) may be helpful. (ki = karnofsky index)

GLIOBLASTOMA MULTIFORME

– A highly malignant astrocytoma with multiple areas of hemorrhage, necrosis, and color changes.

MICRO
– SERPENTINE NECROSIS WITH PSEUDO PALISADING PATTERN
– Vascular endothelial proliferation due to VEGF (vascular endothelial growth factor) forms prominent vascular tufts (glomeruloid bodies)
– In GLIOMATOSIS CEREBRI multiple areas/entire brain involved by tumor.

GENETIC CHANGES

In Low Grade Astrocytomas
– p53 inactivation; also IDH1 and IDH2 (Isocitrate dehydrogenase) mutations noted on immunostains
– PDGF-A/receptor overexpression
In High Grade Astrocytoma

- Disruption of RB gene, P16/CDKN2A gene, another “gene” on chromosome 19q.

In Glioblastoma

<table>
<thead>
<tr>
<th>Primary GM</th>
<th>Secondary GM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Older patients</td>
<td>Younger patients</td>
</tr>
<tr>
<td>2. Tumor arises de novo (no association with a</td>
<td>Arises from a previous low grade astrocytoma</td>
</tr>
<tr>
<td>previous tumor)</td>
<td></td>
</tr>
<tr>
<td>MDM2 overexpression</td>
<td>PDGF-A amplification</td>
</tr>
<tr>
<td>P16 deletion</td>
<td></td>
</tr>
<tr>
<td>PTEN mutation</td>
<td></td>
</tr>
<tr>
<td>Activation of RAS, PI-3K</td>
<td></td>
</tr>
<tr>
<td>Inactivation of p53 and RB gene</td>
<td></td>
</tr>
</tbody>
</table>

TREATMENT

- Surgery, radiation Rx chemotherapy

NOTE: MDM2 = murine double minute 2
Its protein inhibits p53.

- Low grade astrocytoma  → 5-year mean survival
- G.M.  → 15 month survival;  2 year survival is 25 %.

BRAIN STEM GLIOMAS

- Occur in first two decades of life
- 20% of all primary tumors in this age group
- 1/2 progress to G.M.
- 20–40% (5-year survival). Depends on location.
  - Pontine – most common, aggressive, poor prognosis
  - Cervico medullary – less aggressive
  - Tectal – “benign” course

JUVENILE PILOCYTIC ASTROCYTOMA

- Occur in children/young adults
- Located in cerebellum, optic nerves, floor and lateral wall of 3rd ventricle, cerebrum and spinal cord
- Abnormal genetic changes are rare; associated with NF1 shows loss of neurofibromin.
  Activating mutation in serine threonine kinase BRAF noted.

GROSS  A well-circumscribed solid/cystic tumor with a mural nodule in the wall

MICRO  Usually a grade 1 tumour

- Composed of pilocytes → bipolar cells with G.F.A.P. positive, long, thin, processes
- Rosenthal fibers (sausage-shaped pink cells) and eosinophilic granular bodies are seen
- Microcysts present

COURSE/PROGNOSIS

- SLOW GROWING “BENIGN TUMOR” – VERY GOOD PROGNOSIS
- SURVIVAL: FOLLOWING RESECTION IS ABOUT 40 YEARS (CEREBELLAR MASS)
- OPTIC NERVE TUMOURS GROWING INTO HYPOTHALAMUS  →  BAD PROGNOSIS
OLIGODENDROGLIOMA

- M = F (in incidence)
- Occurs between 30–50 years
- Usually occurs in cerebral hemisphere (white matter) of frontal and temporal lobe
- Tumor has
  - Aggregates of clear cells (fried egg appearance) with round nuclei and surrounding inter anastomosing capillary network.
  - Calcifications (90%).
  - Tumor cells surround neurons forming perineuronal satellitosis.
  - Associated astrocytoma occurs in 50% of cases (mixed gliomas – not sure)
- Average survival is about 5–10 years following treatment (i.e., surgery, radiation therapy, chemotherapy). May be 10 – 20 years in grade II tumours.

MOLECULAR GENETICS

- Loss of heterozygosity for 1p and 19q chromosomes (80 % cases); EGFR protein overexpression is noted.
  - LONGER lasting response to Rx
  - Loss of 9p, 10q; CDKN2A mutation
  - SHORT lasting response to Rx

NOTE: Those tumors with NO loss of 1p and 19q are refractory to Rx.

Oligoastrocytoma has both oligo and astrocytomas. This tumour is monoclonal!

EPENDYMOMA

- Originates from ependymal lining cells of ventricles
- Occurs between 10–20 years; in adults occurs in spinal cord
- Usually in the 4th ventricle; mass is solid or papillary (close to pons and medulla)
- Tumor cells are dark, hyperchromatic, and carrot-shaped, attempting to form “ependymal canals”

Structures seen are:

a. True rosette: tumor cells with long, hairlike processes surrounding a well-defined lumen.

b. Pseudorosette: tumor cells with long, hairlike processes ending in a anucleate tangle in the center.

c. Glial vascular rosette: hairlike processes of tumor cells surround a blood vessel and extend to its walls.

CLINICAL FEATURES

- Tumor causes obstructive hydrocephalus
- CSF spread is common
- Average survival following surgery/radiation therapy is 4 years
  5 year survival is 50 % for posterior fossa tumours

NOTE: Proximity to pons/medulla makes complete resection “impossible”. 
FILUM TERMINALE TUMOR (Myxopapillary Ependymoma)

- Occurs in adults in the central canal of spinal cord; associated with NF type 2 (gene on chromosome 22)
- Supratentorial tumours show chromosome 9 abnormalities
- Tumor presents as a well-circumscribed mass
- Composed of papillary structures with fibrovascular connective tissue core surrounded by clear cuboidal tumor cells
- A myxoid background with mucopolysaccharides is seen
- **EXCELLENT PROGNOSIS FOLLOWING SURGERY**
- Tumor may **RECUR**, if it extends into subarachnoid space and involves cauda equina (nerve roots)

CHOROID PLEXUS PAPILLOMA

- Originates from c. plexus (? papova virus association)
- In adults occurs in 4th ventricle
- In children → lat. ventricles
- Tumor resembles normal choroid plexus
- Transthyretin is a reliable tumor marker
- Causes secretory or obstructive hydrocephalus
- Choroid plexus carcinoma is rare.

TUMORS OF NEURONS / NEUROGLIA

GANGLIOCYTOMA

- Occurs in floor of 3rd ventricle, temporal lobe, hypothalamus
- Composed of neoplastic neurons (ganglion cells)

GANGLIOGLIOMA

- Occurs in the temporal lobe
- Composed of neoplastic neurons (ganglion cells) and neuroglia
- Immunohistochemical studies for neuronal proteins, synaptophysin, neurofilaments help

DYSEMBRYOPLASTIC NEOEPITHELIAL TUMOR (DNT)

- Occurs in childhood; presents as a **SEIZURE** disorder
- Seen in **superficial temporal lobe**; a nodular cystic mass

MICRO

- Tumour cells arranged as multiple discrete intracortical nodules with myxoid background
- Small, round neuron-like cells arranged in columns around central cores of processes (SPECIFIC GLIO NEURONAL ELEMENTS) with a myxoid background
- Large neurons appear as “neurons floating in pools of mucopolysaccharides.”
- There is focal cerebral cortical dysplasia (maloriented neurons)
- Neoplastic “glial tissue” (a low grade astrocytoma) may be seen.
- **COMPLEX** lesions show both specific element and glial component

COURSE

A slow growing tumor with good prognosis following surgery
NEUROBLASTOMA
- Rare tumors occurring in children
- Involves the deep cerebral hemisphere
- Composed of small undifferentiated cells with pseudorosettes
- Neuronal proteins, neurofilaments, synaptophysin present
- Clinically, a highly aggressive neoplasm

NOTE: Neurocytoma is a low-grade tumor occurring near the 3rd ventricle/ lateral ventricle.

MEDULLOBLASTOMA
- Tumor originates from primitive, undifferentiated cells (embryonal cells)
  - Loss of chromosome (17p-); duplication of long arm of 17 (i17q); MYC amplification seen
  - Abnormalities involving WNT, NOTCH and Sonic hedgehog patched pathways seen
- Occurs in children, exclusively in the midline of cerebellum
- In adults, tumors occur in a lateral location
- A well-circumscribed, gray, friable tumor may extend onto the surface and involve leptomeninges

MICRO
- Sheets of small cells with little cytoplasm and dark hyperchromatic nuclei (resembling small cell carcinoma of the lung); mitoses ++; ki-67 +++
  - They can DIFFERENTIATE INTO
    1. NEURONS → rosettes seen
    2. NEUROGLIA → GFAP +ve
- TUMOR CAN SPREAD INTO MENINGES AND SEED VIA CSF TO INVOLVE THE ENTIRE NEURAXIS!
  - Involvement of cauda equina → DROP METASTASES

CLINICAL FEATURES
- Causes obstructive hydrocephalus, cerebellar dysfunction

TREATMENT
- Highly malignant; however, quite radiosensitive!
- Surgery; radiation therapy of entire neuraxis (IMPORTANT!)
- 5-year survival rate about 75% - (10 years = 50%)

NOTE: Genetic changes/gene expression patterns may be useful predictors of clinical outcome

PNET (PRIMITIVE NEUROECTODERMAL TUMOR)
- Tumor of embryonal cells; may be central (CNS) or peripheral (similar to Ewing’s tumour).
- Tumors similar to medulloblastoma but genetically different; occur in cerebral hemisphere (locations other than cerebellum) in children; in adults > 50% occur in the posterior cranial fossa.
- with treatment, 5-year survival rate is > 70%
- Disease relapses in 50% of adults

ATYPICAL TERATOID/RHABDOID TUMOR (AT/RT)
- A highly malignant childhood tumor, seen before age 5
- Occurs in both supratentorial and infratentorial location
- TUMOR RESEMBLES RHABDOMYOSARCOMA
- Rhabdoid cells contain eosinophilic cytoplasm and eccentric nuclei; mitosis ++
  - Small cells, mesenchymal and epithelial cells are also seen
- EMA (epithelial membrane antigen), Vimentin, Actin, Keratin are positive
- Desmin, Myoglobin are ABSENT
IMP: Gene hSNF5/ INI 1 ON CHROMOSOME 22 IS LOST (> 90 % cases). This gene is involved in chromatin remodeling. INI 1 protein is lost. SNF = sucrose non-fermenting; INI = Integrase interactor

POOR PROGNOSIS, survival less than one year.

MENINGIOMAS

– Tumors arise from meningotheial cells of arachnoid or from stromal arachnoid cells of choroid plexus; occurs in many different locations
– 15% of primary brain tumors
– F:M = 3:2 (tumors exhibit sex hormone receptors in women with size increment during pregnancy)
– (10:1 in spinal meningiomas)
– Uncommon in children; occurs usually in mid and late life
– Tumor reveals loss of long arm of chromosome 22 (22q-) NF 2 locus; Non-NF2 locus in 50 -60% cases
– Tumors may be:
  1. Sporadic (most common)
  2. Iatrogenic - associated with irradiation – occurs 5-35 years later.
  3. Associated with neurofibromatosis type 2 (mutations seen in NF2 gene) and Gorlins syndrome.

GROSS

– Well-circumscribed, yellow-gray firm mass attached to the dura; encapsulated with a polypoid appearance
– Tumor may spread like a sheet on the dura (en plaque variant), causing HYPEROSTOSIS in the overlying bone
– Tumors close to/extend into dural sinuses – hemorrhage during operation is a major problem

MICRO

– Several types
  a Meningothelial – whorled clusters of cells (syncytial)
  b Fibroblastic – abundant collagen present
  c Transitional = a + b
  d Psammomatous – psammoma bodies (psammos – Greek – “sand”)
  e Papillary – aggressive; tendency to recur
– CEA, keratin, EMA (epithelial membrane antigen) are noted on immunochemical studies

CRITERIA FOR MALIGNANCY (ANAPLASTIC TYPE)

– MITOSES with atypism (> 20 mitoses per 10 high power field)
– NECROSIS
– CEREBRAL INVASION
– METASTASES

ATYPICAL MENINGIOMAS

exist with features of mitoses, necrosis, hypercellularity

INVASION OF BONE OR DURAL SINUSES IS NOT A FEATURE OF MALIGNANCY

COURSE

– Slow growing tumor with pressure effects, headache, seizures, brain dysfunction, anosmia, vision problems, etc.

PROGNOSIS

– EXCELLENT WITH “RESECTABLE” TUMORS
– 15% RECURRENCE RATE
– INTRAVENTRICULAR TUMORS HAVE A POOR PROGNOSIS
MALFORMATIVE TUMORS

1. Craniopharyngioma
2. Epidermoid cyst
3. Dermoid cyst
4. Colloid cyst (3rd ventricle)

CRANIOPHARYNGIOMA
– Benign intra or suprasellar tumors
– Derived from Rathke’s pouch remnants
– Seen in children/young adults (5-15 years) or in adults (50-60 years)
– Cystic, multiloculated, encapsulated with squamous/columnar epithelium/structures resembling enamel organ of the tooth
– Bone formation, calcification – seen (on x-rays)

Clinical features include headache, endocrine dysfunction (diabetes insipidus) and visual disturbances
Treatment – Surgical removal effects cure

PRIMARY BRAIN LYMPHOMA (PBL)
– 1–2% of intracranial tumors; 2% of extranodal lymphomas
– Usually occurs in:
  – Immunosuppressed cases, AIDS, etc.; post-transplant cases
  – Immunocompetent people > 60 years
  – Autoimmune diseases

GROSS
– Occurs in periventricular areas (gray and white matter are involved)
– Present as:
  – Solitary mass 40–50%
  – Multiple masses 30%
  – Meningeal disease 10%
  – (Bone marrow, lymph nodes, and other sites are usually NORMAL)

MICRO
– Malignant cells are/look like malignant lymphoma cells
– Arranged as concentric rings around blood vessels with reticulin separating infiltrating tumor cells (seen on reticulin special stain). This is called HOOPING EFFECT (see image above).
– Associated benign T cells, B cells and plasma cells are seen in the adjacent areas
– Angiotropic lymphoma (intravascular lymphoma) can cause brain infarcts
– NECROSIS IS PROMINENT
– Immunostains confirm B cell origin (high grade lymphoma, large cell type) with BCL 6 positivity
– In immunosuppressed cases, Epstein-Barr virus genome is present in B cells

PROGNOSIS
– Poor; most patients expire
  – ≤ 3 months – immune compromised patients
  – 18 months – immune competent patient

NOTE: Brain does not have any lymphatics – systemic lymphomas can secondarily affect the brain/spinal cord/ and/or meninges (secondary lymphoma of brain).
METASTATIC TUMORS

- 70% of intracranial tumors are metastatic
- They originate from
  - Lung – 40%
  - Breast – 19%
  - Melanoma – 10%
  - Kidney – 7%
  - GI tract – 7%
  - Choriocarcinoma
  - Systemic leukemias/lymphomas (involve meninges, nerve roots, and epidural space)

**Metastatic tumors may involve**
- **Brain parenchyma** – well circumscribed masses, usually at gray-white matter junction; edema, necrosis seen
- **Meninges** – diffuse or nodular meningeal carcinomatosis, e.g., small cell carcinoma of the lung, adenocarcinoma of breast, lung, etc.

**NOTE:** In 30% of patients with brain metastases, no primary tumor can be found (unknown primary).

**CLINICAL MANIFESTATIONS**

- Mass lesions; may be the first sign of a cancer (elsewhere)
- Prognosis: not good

**GERM CELL TUMORS**

- Primary brain G.C.T. occur in the pineal gland (male predominance), CP (cerebello-pontine) angle, and the supra sellar areas
- Originate from

  - Normal resident germ cells
  - Ectopic Germ cells
  - Migratory germ cells

- Occur in adolescents and young adults, 90% of cases in the first two decades of life.
- Tumors are similar to gonadal G.C.T.

  - Germinoma (= Seminoma or Dysgerminoma)
  - Embryonal Ca
  - Chorio Ca
  - Teratoma

- A NON-CNS PRIMARY MUST BE EXCLUDED BEFORE A DIAGNOSIS OF PRIMARY CNS GCT IS MADE!
- Clinical features include precocious puberty in boys, ocular dysfunction and hydrocephalus.
- Treatment similar to gonadal G.C.T. surgery
- Chemotherapy, radiation therapy
- 5 year survival rate is > 85%
- Complication → dissemination into CSF/brain surface
PINEAL GLAND TUMORS

There are 2 primary tumors originating in pineocytes

<table>
<thead>
<tr>
<th>Pinealocytoma</th>
<th>Pinealoblastoma</th>
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<tbody>
<tr>
<td>Well differentiated</td>
<td>Poorly differentiated</td>
</tr>
<tr>
<td>Seen in adults</td>
<td>seen in children</td>
</tr>
<tr>
<td>Good prognosis</td>
<td>– Spreads via CSF</td>
</tr>
<tr>
<td></td>
<td>– Associated with germline mutations in RB gene/retinoblastomas</td>
</tr>
<tr>
<td></td>
<td>– Poor prognosis</td>
</tr>
</tbody>
</table>

The MOST COMMON pineal gland tumor is a GERMS CELL TUMOR.

NERVE SHEATH TUMORS

– These tumors are derived from Schwann cells (produce myelin), perineurial cells, and fibroblasts. They may involve the cranial (vestibular branch of 8th nerve; also 3, 5, and 9th nerves), spinal nerves, or peripheral nerves. There are two tumors:

Neurilemmoma
(Schwannoma)

nerve        tumor

Neurofibroma
(plexiform type)

nerve

– Solitary, well circumscribed
– Eccentric location
– Encapsulated
– NO NERVE fibers (NO AXONS) in the body of tumor
– Antoni A (highly cellular areas)
  Antoni B (low cellular areas)
  Verocay bodies present
– S-100 protein present
– Easy to resect surgically
– Malignant change is rare
– Associated with NF2 mutation
  (NF2 protein absent)

– Usually multiple
– Fusiform diffuse involvement of nerve trunks
– Not usually encapsulated
– NERVE FIBERS in the body of tumor
– Delicate spindle cells with wavy, slender nuclei; loose myxoid background; increased collagen bundles with “shredded carrot” appearance
– Fibroblasts, mast cells, infl. cells seen
– S-100 protein present
– Difficult – entire ‘nerve’ is removed
– Malignant change +++
– Associated with NF1

MICRO
– Antoni A areas = highly cellular areas with nuclear palisading
– Antoni B areas = less cellular with microcysts and myxoid areas
– Verocay bodies = “nuclear free zones” lying between regions of nuclear palisading
SCHWANNOMA
– These tumors occur between 40–60 years; F:M = 2:1; involve the cerebellopontine angle and internal auditory meatus. They cause tinnitus, deafness, nerve palsies, etc. Once a diagnosis is made, surgical excision is helpful.
– Overall prognosis is quite good, with < 5% recurrence rate.

NOTE: These tumors are also called ACOUSTIC NEUROMAS when they involve the vestibular branch of the 8th nerve (usually sensory branch). Extradural tumors involve both sensory and motor branches of spinal nerve roots. They may be within spinal canal or span bony foramina (dumb-bell tumor).

NEUROFIBROMA

Cutaneous neurofibroma
– Polypoid/nodular cutaneous masses
  – Skin hyperpigmentation seen
  – Low risk for malignancy
  – Removed for cosmetic reason
MICRO: Spindle shaped cells with wavy appearance; collagen ++

Solitary neurofibroma
– Involves peripheral nerves

Plexiform neurofibromas
– Associated with NF type 1
– Difficult to remove as nerve trunks are involved with intraneural spread
– Increased risk of malignancy

MALIGNANT NERVE SHEATH TUMOR
– Highly aggressive with frequent recurrence and metastases
– Arise de novo (sporadic) or from a plexiform neurofibroma (NF1) in 50% cases
– p53, RB, p16 mutations seen
– Radiation therapy is a risk factor

MICRO
– Anaplastic tumor cells with necrosis and mitoses
– Tumor may show epithelial, bone, cartilage, and skeletal muscle (Triton tumor) differentiation
– S-100 protein positive in some cases

PROGNOSIS
Not good

NOTE: NF 1 gene protein Neurofibromin activates GTPase which inhibits RAS activity. No Neurofibromin (loss of heterozygosity) leads to tumour formation. NF 2 gene product Merlin together with Actin (cytoskeletal protein) controls cell surface expression of growth factor receptors (EGFR) No Merlin = loss of control and cell proliferation.
NEUROCUTANEOUS DISORDERS (PHAKOMATOSES)

Phakos = patch
Phakomata = tumor-like

Also known as **FAMILIAL TUMOUR SYNDROMES**, these are inherited, familial, slowly progressive disorders that occupy the borderland between malformations and neoplasms of the brain, spinal cord, nerves, skin and other tissues. Most are autosomal dominant and linked to mutations of tumor suppressor genes.

**TUBEROUS SCLEROSIS**
*(EPILOIA, BOURNEVILLE’S DISEASE)*

**CLINICAL FEATURES**  
1 in 6000 births

- Adenoma sebaceum [hamartoma of skin (face)]
- Peri/subungual fibromas
- Cardiac rhabdomyoma, pulmonary myoma
- Renal angiomyolipoma
- Pancreatic, renal, hepatic cysts
- Gliarial nodules of retina
- Tubers (white nodules 1–2 cm in size likened to potatoes) in the cortex and ventricles (candle guttering)
- Gliarial nodules (subependymal) may form astrocytomas
- Mental retardation/seizures
- Skin lesions – localized leathery shagreen patches, hypopigmented (ash-leaf) patches, angiofibromas
- Gene mutations involve:
  - TSC1 → chromosome 9q 34 (protein hamartin)
  - TSC2 → chromosome 16p 13.3 (protein tuberin)

These proteins control cell cycle and have tumor suppressor activity. They inhibit Mtor. Loss of function mutations allow increase in Mtor and consequent cell proliferation (tumor).

NOTE: Mtor = mammalian target of Rapamycin (a type of kinase); it promotes protein synthesis and cell growth.

**VON HIPPEL-LINDAU SYNDROME**

**CLINICAL FEATURES** – 1 in 30,000 to 40,000

- Hemangioblastoma of cerebellum (Lindau)
- Hemangioblastoma of retina (Von Hippel)
- Angioblastoma of brainstem/spinal cord

**Gross** – A fluid-filled cyst with mural nodules is seen

**Micro** – Thin walled blood vessels/capillaries with surrounding lipid-containing vacuolated, PAS positive stromal cells.

- 10% of cases have polycythemia (erythropoietin production by angioblastomas)
- Syringomyelia
- Pancreatic, renal, hepatic cysts
- Pheochromocytomas of adrenals
- Renal cell carcinoma

**GENE MUTATION** involves 3p 25–26

- VHL protein normally modulates or suppresses mRNA elongation by RNA polymerase II and regulates cell cycle proteins
- Hypoxia induced factor 1 (HIF1) acts as a transcription factor for regulation of VEGF expression. VHL protein normally degrades HIF1 – a mutated VHL protein (loss of function) increases HIF1 and so VEGF.
NEUROFIBROMATOSIS (VON RECKLINGHAUSEN’S DISEASE)

There are two types:

TYPE 1 (NF1) (1 in 3,000 incidence)

**CLINICAL FEATURES** – Neurofibromas

- Solitary

- Plexiform type involving nerve trunks (3% risk for malignancy)

- Astrocytomas, optic gliomas
- Ependymomas
- Meningiomas
- Pheochromocytoma
- Pigmented skin lesions (café au lait spots)
- Spinal cord compression/spinal deformities
- Pigmented iris hamartomas (Lisch nodules)
- Gene mutation on 17q 11.2 (protein neurofibromin regulates signal transduction; see page 13)
- Genotype changes may not correlate with clinical phenotype

TYPE 2 (NF2) (1 in 40,000 to 50,000)

- Bilateral acoustic neuromas, multiple meningiomas
- Ependymomas of spinal cord
- Schwannosis (Schwann cell ingrowth into spinal cord)
- Meningioangiomatosis (proliferation of meningeal cells and blood vessels into brain)
- Glial hamartia (nodular glial cell aggregates in abnormal locations of cortex)
- Cataracts
- **GENE LOCUS** – 22q 12 mutation seen (protein merlin – function see page 13)

STURGE WEBER SYNDROME

**CLINICAL FEATURES**

- Hemangiomas of the face (in the area supplied by 5th cranial nerve), trunk, extremities **(PORT WINE STAIN)**
- Meningeal angiomatoses
- Mental retardation/seizures
- Hemiplegia/hemiparesis
- Radiopacities in the skull due to intracranial calcification (TRAM TRACK appearance)
- Gene defect unknown

**NOTE:** OTHER HEREDITARY SYNDROMES associated with brain tumors:

- **WERMER’S (MEN-1)** → pituitary adenomas, malignant Schwannoma
- **TURCOT’S** → astrocytoma, medulloblastoma, colon polyps
- **LI FRAUMENI** → glial tumors, medulloblastoma, breast cancer, ovarian cancer

- **GORLIN SYNDROME** → Medulloblastoma; PTCH gene mutation
- **COWDEN SYNDROME** → Dysplastic gangliogliocytoma of cerebellum
  **PTEN mutation seen**
AUTOPSY

Steve Nandkumar, M.D.
AUTOPSY

Definition

Autopsia (Greek) = seeing for oneself. Consists of both external and internal examination of the body to determine the cause of death (COD).

Macroscopic and microscopic exam of the viscera along with analysis of body fluids (blood, urine, etc.) and tissues by special methods is useful in establishing the cause of death.

Autopsy vs. Necropsy

Types of Autopsy

1. Regular (conventional) autopsy (called post or post-mortem)
2. Forensic or medicolegal autopsy

Partial vs. complete autopsy

History of Autopsy

Development of medicine, anatomy, and autopsy from ancient times.

King Athotis circa 4000 B.C. Haruspicy – predicting future by studying entrails (liver) of animals
Babylon

Egypt → India → Greece → Rome → Middle East (Arabia) → Italy (Europe) → Germany/Austria → United Kingdom → United States

Medical education/reform/Flexner report → 1920 and 1950’s.
Autopsy as a teaching tool.

Decline of autopsy between 1960 and now.

Causes:
1.
2.
3.
4.
5.

STATUS OF AUTOPSY TODAY → R.I.P.
AUTOPSY PATHOLOGY

Much of the material in this section is taken from CAP Practice Guidelines for Autopsy Pathology: 1. Autopsy performance prepared by the Autopsy Committee in 1992 and published in the January 1994 issue of Archives of Pathology and Laboratory Medicine. These comprehensive guidelines are only summarized in this manual and pathologists may wish to make use of the complete guidelines in developing autopsy quality improvement programs.

INDICATIONS FOR PERFORMING AUTOPSIES

The accreditation manual of the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) states that the medical staff, with other appropriate hospital staff, should develop and use criteria that identify deaths in which an autopsy should be performed. Further, the medical staff should attempt to secure autopsies in all deaths that meet the criteria; the mechanism for documenting permission to perform an autopsy should be defined; the medical staff and the attending practitioner, in particular, should be informed when an autopsy is being performed; and the findings from autopsies are to be used as a source of clinical information in quality assessment and improvement activities. To comply with these JCAHO guidelines, every institution should establish its own specific recommendations by means of consultation between the pathology staff and the rest of the medical staff.

The College of American Pathologists’ Board of Governors approved in 1990 a list of conditions in which it may be desirable to perform an autopsy, and this may serve as a basis for developing criteria in individual institutions:

1. Deaths in which autopsy may help to explain unknown and unanticipated medical complications to the attending physician;
2. All deaths in which the cause of death or a major diagnosis is not known with reasonable certainty on clinical grounds;
3. Cases in which autopsy may help to allay concerns of, and provide reassurance to, the family and/or the public regarding the death;
4. Unexpected or unexplained deaths occurring during or following any dental, medical, or surgical diagnostic procedures and/or therapies;
5. Deaths of patients who have participated in clinical trials (protocols) approved by institutional review boards;
6. Unexpected or unexplained deaths that are apparently natural and not subject to forensic medical jurisdiction;
7. Natural deaths that are subject to, but waived by a forensic medical jurisdiction, such as persons dead on arrival at hospitals; deaths occurring in hospitals within 24 hours of admission; and deaths in which the patient sustained or apparently sustained an injury while hospitalized;
8. Deaths resulting from high-risk infections and contagious diseases;
9. All obstetric deaths;
10. All perinatal and pediatric deaths;
11. Deaths in which it is believed that an autopsy would disclose a known or suspected illness that may have a bearing on survivors or recipients of transplant organs; and
12. Deaths known or suspected to have resulted from environmental or occupational hazards.

In a medical examiner’s or coroner’s case, these criteria for autopsies should be coordinated with local jurisdictional guidelines and should follow the statutes of the jurisdiction.
**AUTOPSY “PROCESS”**

1. Request for autopsy by physician/family.
2. Autopsy permit signed by next of kin (verbal authorization acceptable with two witnesses; prefer written authorization).
3. Pathology/laboratory notified.
5. Body sent to morgue. Patient I.D. confirmed by wrist band. Confirms absence of vital signs in deceased!
6. Autopsy partial/complete performed by pathologist.
7. Gross exam.
8. Micro exam. Other tests as needed.
9. Written provisional diagnosis given within 2 working days (better to contact physician with verbal report first).
10. Final diagnosis made within 4 weeks (unless there are extenuating circumstances). Clinicopathologic correlation noted.
11. Q.A. measures; e.g. mortality/morbidity conference; confirm diagnosis/unexpected findings, etc.
12. Educational/research needs.

**NOTE:**

Q-Probe Study (by C.A.P. – College of American Pathologists)

Out of 2,459 autopsies examined,

1. 40% of autopsies had one major unexpected finding contributing to death.
2. 17% had a minor finding contributing to death.
3. 32% had a minor finding not contributing to death.

**REF:** Quality Improvement Manual in Anatomic Pathology, 2nd edition, CAP Publication.

**REF:** Autopsy Pathology – “A Manual and Atlas” by Drs. Finkbeiner, Ursell, Davis.
EYE DISEASES

Dr. Amy Lin, UIC

Notes and PPT on the web

(SELF - STUDY)