OUTLINES IN PATHOLOGY

John H. Sinard, MD, PhD

SHAREWARE VERSION 1.0

May 2006

USAGE AGREEMENT

This work was originally published in 1996 by Saunders Publishing Company. Saunders was subsequently bought out by Mosby, who was later bought out by Elsevier. In 2005, when all of the printed copies of the work in stock had been sold, Elsevier made the decision not to reprint the book or request a second edition.

In the interests of continuing to keep this available to Pathologists and Pathology Residents who might find it useful, I re-acquired the copyright, and have prepared this shareware version. The content is as originally published in 1996, although the format is slightly different. It is distributed under standard shareware terms:

- you may use this for your own personal use, but may not publish it or any portion of it, in any form without the author's permission
- you may not attempt to de-compile, scan, or otherwise covert the work into a different format which could serve as a basis for a derivative work
- you may share copies of the entire work with anyone who wishes to use it or evaluate it for their own personal use. Any such copies must include this agreement.
- if you decide to use it, please send $15 US Dollars (check or money order) to the author, John Sinard, to help cover the costs of production/distribution of this and subsequent editions. Please send to: 4421 Ridge Rd., North Haven, CT 06473. Please include an email address and I will attempt to contact you should a new edition become available.

Please honor these terms. I think they are quite reasonable.

PREFACE and ACKNOWLEDGEMENTS

There are a lot of excellent pathology texts available. When I began my formal training in pathology, I was at first glad to discover this was the case, and then later somewhat overwhelmed by the large volume of material which needed to be digested. To help me in assimilating this large amount of information, I began early in my residency (and later with much greater fervor as my boards approached), to assemble a set of comprehensive outlines which discussed all of the major and at least mentioned most of the minor non-neoplastic and neoplastic disease processes. In assembling these outlines, I drew on material from multiple general and specialty textbooks of pathology. Into this framework, I inserted notes from numerous lectures, seminars, journal articles, and many informal discussions with attendings, often over the sign-out microscope. Where they contributed to an understanding of disease processes, I added discussions of anatomy, embryology, cell biology, and physiology. The result of this effort is in the pages which follow.

When I first started to make these outlines, it was certainly not with any plans towards having them published. However, colleagues of mine who have seen them (and used them) have found them very helpful, and it was consistently suggested that I look into getting them published. Obviously, since you are reading this, the W.B. Saunders Company also thought others might find this helpful. Because of the outline format used, this work is not intended to replace any existing pathology text. Rather, it is intended as a study guide for pathologists in training, especially those preparing for the anatomic pathology boards, as a quick reference guide for pathologists in practice, and as a concise yet comprehensive summary for medical students interested in pathology. Only time will tell how successfully this work fulfills these goals. Every effort has been extended to assure both the accuracy and completeness of this material. However, as our understanding of disease processes evolves, the framework in which we view these processes must shift to accommodate. I would certainly welcome any comments from readers, especially as pertains to errors or omissions which may have made their way into this text, or any other suggestions as to how these outlines might be improved.

Although the task of assimilating the information from various sources into a consistent outline format was largely my effort, I would like to extend special thanks to a few of the individuals who have indirectly made this text possible. I particularly acknowledge the influence of Juan Rosai, the director of the pathology residency training program during my first year at the Yale-New Haven Hospital. The framework of my approach to pathology was developed largely in line with his instruction, and his dedication to resident teaching has in a large way shaped my philosophy of pathology training. I would also like to thank Jon Morrow and Stuart Flynn, each of whom also served a year as program director during my training and contributed to my approach to this subject. I also acknowledge the much appreciated mentorship of Stuart Flynn and the instruction of many of the other senior faculty in the Department of Pathology at Yale during my early "formative" years as a pathologist, including Maria Luisa Carcangiu, Darryl Carter, Richard Eisen, Walker Smith, Brian West, Raymond Yesner, and others. I can only hope that some of their wisdom has made its way into my head and thus into these outlines. Equally important has been the contributions of my colleagues in training, both in a direct way to the text of this work and in an indirect way to my understanding of pathology. I thank, in particular, Vinita Parkash, David Rimm, and Harold Sánchez. Finally, I thank Chris Gilligan for convincing me to have these outlines published.

OUTLINES IN PATHOLOGY

John H. Sinard, MD, PhD

General Topics

Organ Systems

INFLAMMATION

Cell Injury

Reversible
- Cell swelling (depletion of ATP, Na leak, water enters)
- Cytoplasmic Fatty Change (altered lipid metabolism)
- Blebs on cell surface with loss of microvilli
- Nuclear chromatin clumping
- ER swelling / detachment of ribosomes
- Small densities in mitochondria

Irreversible
- Cytoplasmic eosinophilia (loss of ribonucleoproteins)
- Nuclear shrinkage / pyknosis / karyolysis / karyorrhexis
- Cell membrane defects and myelin figures
- Large mitochondrial deposits / swelling of mitochondria
- Swelling of lysosomes, lysis of ER
- Loss of coenzymes and RNA
- If reperfused, influx of calcium; calcification

Apoptosis
- AKA: "Programmed cell death"
- A physiologic process which occurs in the ABSENCE of inflammation
- Affects single cells (unlike necrosis or inflammatory injury, which usually affects regions)
- Pyknosis, chromatin clumping
- DNA digestion is internucleosomal, resulting in a ladder pattern on gel electrophoresis (unlike the diffuse smear seen in non-physiologic necrosis)

Acute Inflammation

Overview:
- Reaction of tissue (not simply cells) to injury; involves soluble factors, inflammatory cells, fibroblasts, vessels
- Can be initiated by physical injury, bacteria, immune complexes, neurotoxins, endotoxin, etc.
- Occurs in viable tissue - if tissue is dead, inflammation will occur at periphery
- Inflammation is a process, not an event

History
- Cornelius Celsus (1st century): tumor, rubor, calor, dolor; (swelling, redness, heat, pain). Loss of function was later added as another sign of inflammation
- John Hunter (1793) - noted that inflammation is nonspecific host response with 'salutary' effect
- Julius Cohnheim (1888) - detailed microscopic descriptions of inflammation in frog mesentery - stressed the importance of the vasculature
- Elie Metchnikoff (1882) - phagocytosis and the cellular component of inflammation

Vascular Changes
- Transient vasoconstriction (seconds to minutes)
- VASODILATION of arterioles; increased blood flow produces redness and heat
- Increased permeability (transudate initially (low protein content, specific gravity <1.012), then exudate); produces swelling and pain
- Local decreased blood of circulation (partial stasis)
- Margination, emigration, and chemotaxis of leukocytes

Soluble Inflammatory Mediators (by Action)
- Increased Vascular Permeability:
  Histamine *PAF* *Leukotrienes C,D,E*
  Serotonin C3a Bradykinin
- Vasodilatation:
  Prostaglandins E,D,I Serotonin Bradykinin
- Vasoconstriction:
  Thromboxane A_2 Leukotrienes C,D,E
- Chemotaxis:
  C5a Interleukin-1 (indirectly)
  C3a *Leukotriene B_4* Endotoxin
- Opsinization:
  Fc fragment of IgG C3b
- Smooth Muscle Contraction:
  Bradykinin Leukotrienes
- Platelet Aggregation:
  Thromboxane A_2 promotes Prostacyclin inhibits
- Pain:
  Bradykinin PGE_2
- Fever:
  Interleukin-1 TNF Prostaglandins

Soluble Inflammatory Mediators (by Agent)
- Histamine (mast cells, basophils): β- imadazolylethylamine (decarboxylated histidine); vasodilation and increased vascular permeability, mucous production
- Serotonin (mast cells): 5-hydroxytryptamine; vasodilation and increased vascular permeability
- Platelet Activating Factor (basophils): acetylated glycerol ether phosphocholine; platelet aggregation, vasodilation and increased permeability (100-10000 x more potent than histamine)
- Interleukin-1 (all cells types): stimulated by immune complexes, promote chemotaxis by endothelial effects, systemically: causes fever, sleepiness, leukocytosis
- Tumor Necrosis Factor (stimulated macrophages): AKA cachectin; effects similar to IL-1
- Anaphylatoxins: C3a and C5a - see below
- Complement System (plasma factors)
  - C5a: chemotaxis, some increase in vascular permeability
  - C3a: increase vascular permeability, chemotaxis
  - C3b: opsinization - activation of leukocyte needed
  - C5b-9: membrane attack complex
  - Fc: opsinization - no activation needed
- Kinin System (plasma factors)
  - Bradykinin: nonapeptide; increased vascular permeability, dilated blood vessels, pain, smooth muscle contraction
  - Kallikrein: enzyme which cleaves kininogens to form Bradykinin; chemotactic, causes platelet aggregation
  - Hageman factor (Factor XIIA): initiates clotting, fibrinolytic, kinin, and complement systems
- Arachidonic Acid Metabolism (leukocytes)
  - Inhibited by corticosteroids
  - Two arms: Lipoxygenase and Cyclooxygenase
  - Lipoxygenase: production of leukotrienes: B: chemotaxis; C,D,E: vasoconstriction, bronchoconstriction, vascular permeability
  - Cyclooxygenase: production of thromboxane A_2 (vasoconstriction, platelet aggregation), prostacyclin PGI_2 (vasodilation, decreased platelet aggregation), and prostaglandins (PGD_2: vasodilatation and edema, PGE_2: pain, fever). This pathway is inhibited by aspirin and by Indomethacin

Adhesion of Leukocytes to Vascular Endothelium (Margination)
- On Leukocytes:
  - LFA-1, MAC-1, CD11/CD18 : heterodimers with different alpha subunits (150-180kD) but the same beta subunit(95kD); belong to integrin family (see below)
  - When stimulated by chemotactic factors (C5a, TNF), receptors in the intracellular vesicles move to the surface
- On Endothelial Cells:
  - ICAM-1: intercellular adhesion molecule (polys, lymphocytes)
  - ELAM-1: endothelial leukocyte adhesion molecule (polys)

VCAM-1: vascular cell adhesion molecule (lymphocytes, monocytes)
Expression increased by interleukin-1 and TNF

Cellular Components
Initially, neutrophils predominate (24-48 hrs). Life expectancy in tissue of 4 days
Later, monocytes and lymphocytes predominate (chemotactic signals for monocytes persist longer)
When monocytes enter tissue, undergo conversion to tissue macrophages - long half life

Modulators of the Inflammatory Response
Persistence of initiating/complicating agent (microorganisms, either initial agent or secondary infection; devitalized tissue, foreign bodies)
Immunologic function/access (leukocyte function, immunosuppression (steroids), vascularity of tissue)
Systemic Factors (nutritional states, diseases (eg diabetes))
Extent/degree of tissue injury

Organization
Process by which coagulated blood is converted to granulation tissue, a loose collection of numerous inflammatory cells and debris in a matrix of fibrin, newly formed blood vessels, and fibroblasts/myofibroblasts
Myofibroblasts mediate wound contraction
With increasing "organization" , debris is removed, cellularity decreases. Fibrosis and scarring can occur.

Chronic Inflammation

In contrast to acute inflammation (which is predominantly exudative), chronic inflammation is proliferative
Chronic inflammation develops when stimulus persists
Macrophages and Giant Cells: central actors
Plasma cells, lymphocytes
Eosinophils: granules contain major basic protein (highly cationic, MW 14kD, toxic to parasites)
Fibroblasts and myofibroblasts

PATTERNS OF CHRONIC INFLAMMATION

Serous
Exudate of predominantly serum; (e.g. burn blister)

Fibrinous
Fibrin and inflammatory cells; (e.g. pericarditis)

Suppurative
Neutrophils, often walled off; (e.g. abscess)

Granulomatous
Induced by the presence of indigestible foreign bodies or by large excess of antibody over antigen
Epithelioid histiocytes: less phagocytic than macrophages, highly active protein synthesis machinery
Central caseous necrosis may be present
Giant Cells:
• Langhans': nuclei arranged around periphery; more common with infectious causes
• Touton: nuclei aggregate in center of cell; more common in foreign body reactions
Causes: infectious (tuberculosis, leprosy, syphilis, Actinomycosis, cat-scratch, fungi, parasites), foreign bodies (sutures, splinters, silicosis, berylliosis), antibody mediated (rheumatic fever, rheumatoid disease), idiopathic (sarcoidosis)

Ulcer
Necrosis, granulation tissue, loss of epithelium (e.g. peptic ulcer)

Outcomes of Inflammation

Depends on degree of tissue injury and persistence of initiating agent(s)
Resolution: restoration of the site to normal
Regeneration: replacement of lost specialized cells by similarly differentiated cells, with or without restoration of normal tissue architecture
Repair / scarring: replacement of lost tissue by granulation tissue and fibrosis
Metaplasia: replacement of one type of tissue (usually epithelium) with another type of tissue

Repair

Wound Healing
1° Intention (small wounds): ends of wound sutured together
2° Intention (larger wounds): tissue must grow in from edges

Growth Factors
Epidermal Growth Factor (EGF): 6 kD peptide, binds to tyrosine kinase receptors, mitogenic
Platelet Derived Growth Factor (PDGF): 30 kD highly cationic heterodimer; produced by macrophages, endothelium, and smooth muscle cells as well as platelets; competence factor, but requires a progression factor for mitogenesis
Fibroblast Growth Factor (FGF): potent angiogenic agent
Transforming Growth Factor (TGF): α: similar to EGF; β: growth inhibitor (ceases liver regeneration following partial hepatectomy), fibroblast chemotaxis
Alpha Interferon: growth inhibitor
Prostaglandin E2: growth inhibitor

Collagen
10 types: I in skin and bone, II in cartilage, III in blood vessels and uterus, IV in basement membranes. I-III are fibrillar, rest are amorphous
Synthesis: 3 tropocollagen alpha chains form left handed helix (Gly every third position), alpha hydroxylation of proline, secreted as procollagen, ends cleaved, forms filaments, cross linked via lysine oxidation
As wound heals, type III collagen replaced by type I; maximum strength at 3 months

Cell-Cell Interactions
Integrins: families of heterodimeric cell surface receptors; many bind matrix proteins by recognizing the tripeptide Arg-Gly-Asp (RGD); include fibronectin receptor
All members of an integrin family share the same beta subunit

Cell Matrix Components
Elastin: 70kD, covalently crosslinked chains, long half life
Laminin: most abundant glycoprotein in basement membrane, 850kD cross-shaped tripeptide; spans basement membrane binding to cell surface and other matrix components; center of cross contains binding site for cell surface laminin receptors; ends of short arms bind collagen IV; end of long arm binds heparin
Proteoglycans: glycosaminoglycans (long, non-branching polysaccharide chains of repeating disaccharide units, 4-50kD: e.g. heparan sulfate, heparin, hyaluronic acid, chondroitin sulfate, etc.) linked to protein core (protein usually ~5% total mass of 3-5 Megadaltons)
Fibronectin: major adhesion molecule of the interstitial tissue; 440kD disulfide linked dimer; binds to cell surface, fibrin, collagen, and heparin; cells bind to fibronectin by a receptor which recognizes RGD sequence (Arg-Gly-Asp) on fibronectin; in addition to cell adhesion, also directs cell migration during embryogenesis

IMMUNOLOGY

Antibodies

Constant region determines antibody class; variable region determines antigen specificity

Composed of heavy and light chains: each heterotetramer of 2 heavy and 2 light chains results in 2 antigen binding sites

- IgM: pentameric (10 heavy and 10 light chains plus joining J-chain); initially membrane bound; first antibody released into circulation in response to a new antigen
- IgD: bound to B-Cell surface; rarely released into circulation
- IgG: Major antibody of immune response; 4 subclasses (1, 2a, 2b, 3); MW=140kD (2x50kD + 2x20kD)
- IgA: monomeric in serum, dimeric (contains joining J-chain and secretory fragment) in secretions: milk, saliva, tears
- IgE: most commonly found on surface of mast cells; mediate hypersensitivity reactions

Antibody diversity is generated by genetic rearrangement of the DNA during B-Cell maturation. At each splicing, random bases are added by terminal deoxy-transferase (TdT) to generate "non-template directed diversity"

First, heavy chain undergoes D-J joining, then V-DJ joining. VDJ-C splicing (class switching) occurs later at mRNA level. Then, κ rearranges. If non-productive, the other κ gene rearranges. If still non-productive, λ rearranges.

	Chromosome	V	D	J	C
Heavy Chain:	8	100-200	>10	6 + 3ψ	5 classes
κ-Light Chain:	2	40-80	-	5	1
λ-Light Chain:	22	>40	-	[6 J-C Units]	

On chromosome 8, the heavy chain constant regions are arranged as: μ, δ, $\gamma 3$, $\gamma 1$, $\gamma 2b$, $\gamma 2a$, ε, α

B-Cells

10-20% circulating lymphocytes

Found in superficial cortex of LN's and white pulp of spleen

- CD10: pre-B cells: CALLA (common acute lymphoblastic leukemia antigen)
- CD19 (Leu12): pre-B to mature B cells; not on plasma cells
- CD20 (Leu16, L26): pre-B (after CD19) to mature B; not on plasma cells
- IgM: surface receptor

T-Cells

Arise in bone marrow, mature in thymus; 80-90% circulating lymphocytes

Paracortical areas of LN's; periarteriolar sheaths of spleen

- CD1 (Leu 6): expressed on immature thymocytes
- CD2 (Leu 5): sheep RBC receptors; all T-Cells, NK Cells
- CD3 (Leu 4): all T-Cells; associated with the T-Cell Receptor
- CD4 (Leu 3a): (60% T-Cells): helper & delayed-type hypersensitivity reactions; binds MHC class II
- CD8 (Leu 2): (30% T-Cells): cytotoxic and 'suppressor' ; binds MHC I
- CD5 (Leu 1): all T-Cells (peripheral and thymic)
- CD7 (Leu 9): all T-Cells
- CD25: IL-2 receptor (activated T, B, and monocytes)
- α/β Receptor: 95% T-Cells; associated with CD3
- γ/δ Receptor: 5% T-Cells; CD4– and CD8–; associated with CD3

T-Cell receptor (chromosome 7) undergoes VDJ rearrangement:

	V		D	J	C
α Chain:	50-100		-	50-100	1
β Chain:	75-100	$\beta 1$ unit	1	6	1
		$\beta 2$ unit	1	7	1
γ Chain:	8 + 7ψ	$\gamma 1$ unit	-	1 + 2ψ	1
		$\gamma 2$ unit	-	1 + 2ψ	1
δ Chain:	4		2	3	1

The δ chain sequences are located between the V and J sequences of the α chain; therefore, when α rearranges, the δ chain gene is deleted

CD3, associated with the TCR, transduces activating signals

NK Cells (Large granular lymphocytes)

Can lyse tumor cells or virus infected cells without prior sensitization; insert pore forming proteins (perforins) into victim, making them leaky

- CD16: all NK cells and granulocytes; low affinity Fc receptor
- CD56 (Leu19) and CD2 positive
- CD3 NEGATIVE

K Cells, which mediate antibody dependent cell-mediated cytotoxicity, are probably a subset of NK cells

Macrophages

Arise from circulating monocytes

Antigen presenting cells - lots of MHC Class II on surface

- CD11b: receptor for C3b; monocytes, granulocytes, NK
- CD13: blood monocytes and granulocytes
- CD33: myeloid stem cells and mature monocytes

Cytokines: (Interleukins)

IL1: made by monocytes, macrophages, endothelium, etc.; activates resting T-cells, chemotactic (via endothelial effects), fever

IL2: made by activated T-Cells; autocrine stimulation of T-Cells; stimulates B-cells, NK Cells, activates monocytes

IL3: made by activated T-Cells; stimulates stem cells

IL4: growth and differentiation of B and T Cells

IL5: differentiation of activated B-Cells to plasma cells

IL6: maturation of T and B Cells, inhibits fibroblast growth

Gamma-Interferon: made by sensitized T-Cells; activates macrophages, induces expression of HLA-Class II molecules on macrophages and endothelial cells, direct anti-viral effects

Major Histocompatibility Complex

AKA: MHC (Chromosome 6)

HLA = Human Leukocyte Antigen

Part of immunoglobulin supergene family

Class I

HLA-A, HLA-B, HLA-C

Heterodimer of 44 kD protein (3 Ig domains) with 11.6 kD beta-2-microglobulin (chromosome 15; 1 Ig domain)

Present on all nucleated cells and platelets

Involved in restricting the action of CD8+ cytotoxic T-Cells

Disease Associations:

- B27: ankylosing spondylitis, postgonnococcal arthritis, acute anterior uveitis, Reiter's syndrome
- A3: hemochromatosis
- BW47: 21-hydroxylase deficiency
- A1, B8: Addison's disease

Class II (immune response genes)

HLA-D region: subregions DP, DQ, DR

Heterodimer of alpha and beta (34kD and 29kD) chains, each with two Ig domains

Found on monocytes, macrophages, dendritic cells, B-cells, some activated T-cells; can be induced on endothelial cells, fibroblasts, and renal tubule cells with γ-interferon

Mixed Lymphocyte Reaction: T-Cells proliferate in response to foreign Class II

Involved in restricting the action of CD4+ helper T-Cells

Disease Associations:
- DR2: Lupus; Multiple Sclerosis
- DR3: chronic active hepatitis, Sjögren's syndrome, insulin dependent diabetes, Grave's disease, Lupus
- DR4: rheumatoid arthritis, drug-induced lupus, giant-cell arteritis, Takayasu's arteritis
- DR5: Hashimoto's thyroiditis
- DR8: Primary biliary cirrhosis

Class III

Components of complement system within the MHC gene region: include C2, C4, and Bf

May also include TNF-alpha and TNF-beta

Hypersensitivity Reactions

Type I (Anaphylactic Type)

Reaction within minutes - may be systemic or localized

Systemic form can be fatal within an hour from massive laryngeal edema, pulmonary edema and hemorrhage

Local form (atopy) often hereditary

Bee sting, cutaneous swelling (hives), hay fever, bronchial asthma, allergic gastroenteritis (food allergy)

Antigen binds to IgE on surface of sensitized mast cells and basophils, crosslinking IgE receptors resulting in degranulation with release of rapidly acting factors (via rapid increase in cAMP) and subsequent production and release of slow acting factors

Some factors can directly induce degranulation independent of IgE: C3a, C5a, codeine, morphine, mellitin (in bee venom), trauma, heat, cold, sunlight

Primary (rapidly acting) factors:
- histamine: bronchial smooth muscle contraction, increased vascular permeability
- eosinophil and neutrophil chemotactic factors
- granule matrix derived factors: heparin, proteases

Secondary (slow reacting substances of anaphylaxis):
- Leukotrienes C4, D4: most potent vasodilators known
- Prostaglandin D2: bronchospasm and vasodilation
- Leukotriene B4: chemotactic for neutrophils
- Platelet activating factor

Type II (Antibody Mediated Type)

AKA: Cytotoxic Type (although not always cytotoxic)

Antibodies directed against normal or modified cell surface or tissue components induce cell lysis

Complement Dependent

Two mechanisms:
- Direct lysis by complement activation
- Lysis by opsonization (C3b) - often involves RBCs

Eg: Transfusion reactions, erythroblastosis fetalis, autoimmune hemolytic anemia or thrombocytopenia, certain drug reactions

Antibody Dependent Cell Mediated Cytotoxicity

Monocytes, neutrophils, eosinophils, or NK cells recognize cells by Fc portion of IgG bound to cell and kills cell without phagocytosis

Eg, Goodpasture's syndrome

Anti-Receptor Antibodies

Non-cytotoxic

Eg, myasthenia gravis from antibody to ACh receptor

Type III (Immune Complex Mediated)

Antigen-antibody complexes produce tissue damage by activation of serum mediators (primarily complement)

Systemic Form

Acute serum sickness is the prototype (described in 1905)

Antibodies are produced to a large dose of administered antigen (~5 days after administration). Ag-Ab complexes are deposited in the tissues, often inducing localized type I hypersensitivity reactions in glomeruli, joints, skin, heart, serosal surfaces, and small blood vessels where they can activate complement. An inflammatory reaction ensues (~10 days) with resulting fever, urticaria, arthralgias, lymphadenopathy, proteinuria

Inflammation in and around vessels causes an acute necrotizing vasculitis with fibrinoid deposition and acute inflammation (innocent bystander destruction)

Localized Form (Arthus Reaction)

Introduction of antigen to which patient has been sensitized

Localized tissue necrosis resulting from acute immune complex vasculitis, usually in the skin

Lesion develops over 4-10 hrs; may ulcerate

Histology shows fibrinoid necrosis of vessels, platelet thromboses, edema, hemorrhage, and numerous neutrophils

Type IV (Cell Mediated)

Mediated by sensitized T-Cells

Delayed-Type Hypersensitivity

Eg tuberculin reaction: reddening and induration begins 8-12 hrs after injection; peaks 24-72 hrs.

Histology: perivascular cuffing of mononuclear cells in deep and superficial dermis

Induration is caused by fibrin deposition in interstitium

Reaction mediated by CD4+ T-Cells: memory T-Cells release lymphokines to amplify response, specifically macrophage chemotactic and activating factors

T-Cell Mediated Cytotoxicity

CD8+ cytotoxic T-Cells kill cells via pore formation; recognize modified self- MHC Class I antigens

Organ Transplant and Rejection

Transplants can be autologous (self), syngeneic (monozygotic twins), allogeneic (same species), or xenogeneic (different species)

Donor lymphocytes etc. in graft have both class I and class II MHC antigens - responsible for increasing rejection

Immunosuppression: cyclosporin suppresses activation of CD4+ T-Cells; anti-CD3 is new agent

Hyperacute Rejection

Minutes to hours

Mediated by preformed antibodies

Produces Arthus type reaction with antigen-antibody mediated fibrinoid vasculitis

Acute Rejection

Weeks to months
- Interstitial: Cell mediated, CD4+ and CD8+ T-Cells
- Vascular: humorally mediated: antibody binds to vessel walls - activation induces vasculitis

Subacute Rejection

Months

Vasculitides with marked thickening of intima of vessels, proliferation of fibroblasts and myocytes, luminal narrowing

Chronic Rejection

Months to years

Intimal fibrosis, interstitial scarring, tissue atrophy

Graft vs Host Disease

Occurs when immunologically competent cells are transferred into a recipient with an impaired immune system. Transferred cells "outreact" the endogenous lymphoid tissue

Most commonly occurs following non-autologous bone marrow transplant

Greatest damage occurs to skin, intestine, spleen, and liver

Immunologic Deficiency Syndromes

Agammaglobulinemia of Bruton

X-linked; restricted to males
Virtual absence of B-Cells and Ig's from serum (small amounts of IgG may be seen), despite normal number of pre-B cells in marrow; abnormal maturation
Severe recurrent infections seen beginning at about 8 months age, especially pyogenic organisms (staph, H Influenza); conjunctivitis, pharyngitis, otitis media, bronchitis, pneumonia, skin infections
Normal handling of most viral and fungal infections (normal cell-mediated immunity) except poliovirus, echovirus, hepatitis, enterovirus
High incidence of autoimmune type diseases

Isolated IgA Deficiency

Very common; 1/600 individuals
Familial or acquired in association with toxoplasmosis, measles, or some other viral infection
Respiratory, GI, and urogenital tract infections
Autoimmune diseases more common, esp. SLE and RA
Defect in differentiation of IgA B-Cells; 40% have anti-IgA antibodies

DiGeorge's Syndrome (Thymic Hypoplasia)

Selective T-Cell deficiency resulting from failure of development of the third and fourth pharyngeal pouches (thymus, parathyroids, C-cells of thyroid)
No cell mediated response, tetany (from hypocalcemia), congenital defects involving the heart, great vessels; may have abnormal appearing mouth, ears, facies
Not genetic; intrauterine damage before 8th week
Partial DiGeorge's syndrome exists
Nezelof's Syndrome: absent thymus but with normal parathyroids

Severe Combined Immunodeficiency Disease (SCID)

Heterogeneous disorder: autosomal recessive and X-linked recessive forms
Both T-Cell and B-Cell immunity impaired; generally greater loss of T-Cell immunity
Abnormal differentiation of stem cells due either to intrinsic defect or abnormal thymic signals for differentiation
Usually succumb to opportunistic infections in first year of life: Pseudomonas, Candida, Pneumocystis, CMV, HSV
50% of patients with the autosomal recessive form lack adenosine deaminase, accumulating deoxy ATP which is toxic to lymphocytes

Wiskott-Aldrich Syndrome

AKA: Immunodeficiency with Thrombocytopenia and Eczema
X-linked recessive; vulnerable to recurrent infections
Always progressive T-Cell deficit, sometimes also B-Cell deficit
Spleen shows near complete absence of white pulp
Poor antibody response to polysaccharide antigens
IgM levels in the serum are low; IgA and IgE are elevated
Patients prone to develop malignant lymphoma

Ataxia-Telangiectasia Syndrome

Autosomal recessive disorder resulting in predominantly a defect of T-Cell maturation
Associated clinically with cerebellar ataxia, telangiectasia, decreased serum alpha-fetoprotein levels, ovarian dysgenesis
IgA, IgE, and IgG levels often low; IgM often high
Defect is abnormal repair of X-ray damage, resulting in chromosomal instability
Patients prone to develop Lymphoma, leukemia, gastric carcinoma

Common Variable Immunodeficiency

Heterogeneous group of disorders characterized by hypo–gammaglobulinemia (usually all Ig's, sometimes just IgG)
Term refers to disorders for which no primary defect or secondary cause can be identified
Three types:
• Predominant Intrinsic B-Cell Defect
• Predominant T-Cell Disorder with
T-helper cell defect OR T-suppressor cell surplus
• Autoantibodies to T or B Cells
Hyperplastic B-Cell areas
Patients suffer recurrent bacterial infections and parasitic infections (Giardia common); also have a high frequency of autoimmune disorders, sometimes progressing to lymphoid malignancy; also sprue-like illness and non-caseating granulomas in the liver

Leukocyte Adhesion Deficiency

Autosomal recessive - chromosome 21
Deficiency in synthesis of the common β-chain of adhesion molecules LFA-1, Mac-1 and CD11/CD18 (binding of leukocytes to ICAM-1 on endothelial cells)

Chronic Granulomatous Disease of Childhood

Most commonly X-linked; affects males
Neutrophils lack the "respiratory burst" upon phagocytosis
Deficient production of hydrogen peroxide due to deficiency in the H_2O_2-myeloperoxidase system
Patients particularly susceptible to infections by coagulase positive organisms (like Staph aureus)

Complement Deficiencies

C2: connective tissue diseases (lupus-like syndromes)
C3: Bacterial infections
C5-8: Recurrent Neisseria infections (gonococcal, meningococcal)

Chediak-Higashi Syndrome

Autosomal recessive - appears to be a microtubule defect
Neutropenia, impaired chemotaxis, impaired lysosomal fusion, impaired degranulation
Also, oculocutaneous albinism
Prone to infections; giant lysosomes by EM

Acquired Immunodeficiency Syndrome

AKA: AIDS
June 1981: 5 young male homosexuals in LA reported to CDC as having contracted Pneumocystis pneumonia. 2 died.
Etiologic agent identified 1983-4

Epidemiology

Risk Factors:
• Homosexuality
• IV Drug Abuse
• Blood or blood product recipients

- Heterosexual contact with infected individuals

Transmission:

- Venereal - in US, homosexual transmission most common, but heterosexual transmission is increasing at a greater rate; in Africa, heterosexual transmission most common
- Parenteral: 90% efficiency for blood products, more common for hemophiliacs since factor VIII is concentrated from multiple donors; also IV drug users
- Perinatal: transplacentally in utero, birth canal, or via breast milk

Human Immunodeficiency Virus (HIV)

Formerly HTLV-III, but unlike HTLV-I and II which are transforming, HIV is cytopathic

Spherical retrovirus (related to lentivirus), with two strands of genomic RNA (10kb genome, at least 8 genes)

Core proteins (gag) , reverse transcriptase (pol), envelope glycoproteins (env) are gp120 and gp41, plus vif (budding), tat III, rev, nef, and vpr (infectivity)

gp120 shows a high degree of variability and polymorphisms

Related to SIV (simian immunodeficiency virus) and HIV-2, a virus causing an AIDS like illness in West Africa. HIV-2 and HIV-I are 40% homologous, HIV-2 and SIV are 70%

Infects cells by high affinity interaction between gp120 and CD4 on T-helper cells and macrophages. Virus is then internalized and integrated, but not activated until the cell is stimulated

Virus isolated from white cells can only infect white cells. Virus isolated from brain can infect both brain and white cells. May be different strains.

Activation results in the death of T-Cells by unclear mechanism; prior to death, cell appears to lose its ability to respond to antigens

Monocytes and macrophages (also express low levels of CD4) can be infected, are usually not killed, and may serve as the reservoir for 'latent' infection. Infected monocytes are likely to be the mode of transmission into the CNS.

Neuroleukin: neuron growth factor with 30% sequence homology with gp120 - receptors on neurons may therefore bind HIV.

Immune Dysfunction

Loss of CD4+ T-Cells results in inversion of the CD4:CD8 ratio (normally 2; can go down to 0.5)

CD4+ cells are source of IL-2, IFN-γ, chemotactic factors

AIDS patients typically have hypergammaglobulinemia (polyclonal B-Cell activation - may be 2° to CMV, EBV, of gp120 itself)

In spite of increased Ig production, AIDS patients cannot mount proper response to new antigens

Natural History

Anti-HIV antibodies detectable 3-17 wks after exposure

2-8yr incubation or 'latency' period

CD4 counts <200 usually seen in clinical AIDS (normal >700)

When CD4 count drops below 50, increased risk of lymphoma

30-50% develop an acute mononucleosis-like illness

Persistent generalized lymphadenopathy

AIDS related complex (ARC): long lasting fever (>3 months), weight loss, diarrhea

Secondary Infections/Neoplasms: Pneumocystis, cryptosporidium (GI), toxoplasmosis, cryptococcus (CNS), candidiasis, MAI, CMV, HSV, PML; Burkitt's lymphoma, Kaposi's sarcoma, Immunoblastic B-Cell Lymphoma, Primary CNS lymphomas, Hodgkin's disease

Autoimmune Diseases

Immunologic Tolerance

Failure of immune system to respond to an antigen

Tolerance can be natural (develops during fetal life) or acquired (develops under immune suppression)

Desensitization: temporary "tolerance" produced by administering large doses of antigen which use up the remote antibodies and cells

Since cooperation between B and T-Cells is necessary, only need to tolerize one of them

In general, T-Cells tolerize at a lower antigen dose, and this tolerance lasts longer than B-Cell tolerance; high doses of antigen can tolerize both T and B Cells

Postulated mechanisms:

Clonal Deletion

Self-reacting clones are deleted

Since normal individuals have lymphocytes with receptors for self antigens (DNA, myelin, collagen), it is also postulated that some self reacting immature B-Cells are inactivated but not actually deleted (clonal anergy).

Suppression of Auto-reactive Lymphocytes

Suppressor Cells: T-Cells actively limit immune response

Idiotype-Anti-Idiotype

Antibodies to self-reacting antibodies limit response

Antibody Blocking

Potentially responding cells are blocked by presence of circulating antibody

Mechanisms for Overcoming Tolerance

Emergence of a Sequestered Antigen

Bypass T-Helper Cell Tolerance

Modification of the antigen by complexing to drugs or microorganisms - recognized by non-tolerant T-Cells

Cross reaction between non-tolerant T-Cells to infecting organisms and other 'self' antigens

Polyclonal B-Cell Activation: direct, non-specific activation of B-Cells: e.g., bacterial lipopolysaccharide can induce mice to make antibodies to DNA, RBC antigens, etc.

Idiotype Bypass Mechanisms

Anti-idiotype antibodies will look like the antigen - these can stimulate the response

Microbial antigens (or other portions of antibodies directed against them) can cross react with self-reactive lymphocytes

Imbalance of Suppressor-Helper Function

E.g., T-suppressor activity decreases with age in some mice

Increased Expression of Class II MHC on Tissues

Summary of Autoantibodies

Disease	Antigen
Lupus	dsDNA, Smith Antigen
Sjögren's	SS-B (La), SS-A (Ro)
Scleroderma: Diffuse	Scl-70 (DNA topoisomerase I)
Scleroderma: CREST	Centromere
Polymyositis	tRNA synthetase (esp. histidinyl)
Hashimoto's	[T-Cell defect]; later: thyroglobulin, TSH receptor
Grave's	TSH receptor
Myasthenia Gravis	Acetylcholine receptor
Primary Biliary Cirrhosis	Mitochondria
Chronic Active Hepatitis	Smooth Muscle
Pemphigus Vulgaris	Adherens-Junction (suprabasal)
Pemphigus Foliacious	Desmoglian (more superficial)
Bullous Pemphigoid	Anti-skin basement membrane
Dermatitis Herpetiformis	IgA at dermal-epidermal junction
Goodpasture's Synd.	Anti-GBM
Pernicious Anemia	Parietal Cells; Intrinsic factor

Systemic Lupus Erythematosus

- Multi-system disease of autoimmune origin, acute or insidious in onset, chronic, remitting, involving principally injury to the skin, joints, kidney, and mucous membranes
- If include all mild forms, as common as 1:2500 in population, with F:M = 9:1.
- By definition, require 4 of 11 criteria: malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neurologic disorder (seizures, psychosis), hematologic disorder (hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia), immunologic disorder (LE cells, anti-DNA, anti-Sm, false positive VDRL), antinuclear antibody
- Genetic factors: 50-60% concordance in monozygotic twins, familial patterns, associated with HLA-DR-2 and DR-3 and with C2 deficiency
- Non-Genetic factors: drugs and UV light can induce or exacerbate symptoms
- Fundamental defect in immune regulation and self tolerance; B-Cell hyperactivity, with resulting increased production of both self and non-self antibodies. Mechanisms include: intrinsic defect in B-Cells, polyclonal activation of B-Cells, excessive stimulation of normal B-Cells by hyperactive T-Cells, and T-suppressor cell defects.
- Autoantibodies: DNA, histones, non-histone RNA binding proteins (Smith antigen, SS-A (Ro), SS-B (La)), nucleolar antigens. *Antibodies to dsDNA and Smith Antigen are strongly suggestive of SLE*.
- DNA is not very antigenic. Anti-DNA antibodies are likely to be cross reacting from antibodies to phospholipids, etc.
- Tissue injury mediated predominantly by DNA-anti-DNA immune complexes (Type III hypersensitivity) but also anti-RBC antibodies (Type II).
- LE bodies (hematoxylin bodies) are denatured nuclei following antibody attack; when mixed with phagocytic cells which engulf them, form LE cells. LE cell test positive in >70%.
- Highly variable clinical course

PATHOLOGY:

- Vasculitis of small arteries and arterioles, most common in skin and muscles, with fibrinoid deposits in vessel walls
- Onion-skinning of vessels of spleen by perivascular fibrosis
- Glomerulonephritis:
  - Class I: no recognized abnormality: rare
  - Class II: Mesangial Lupus GN: 10% patients
  - Class III: Focal Proliferative GN: typically segmental
  - Class IV: Diffuse proliferative GN: most serious; 40-50%
  - Class V: Membranous GN: 10%
  - All types caused by deposition of DNA-anti-DNA complexes
  - Subendothelial deposits are unusual outside of lupus
- Skin: immune complex deposition at dermal-epidermal junction; seen in both clinically involved & uninvolved skin
- Joints: non-erosive synovitis
- Pericarditis
- Heart: Libman-Sacks Endocarditis: non-bacterial verrucous endocarditis; vegetations predominantly on flow side of mitral and tricuspid valves, but may be on back; diffusely distributed over leaflets, small, may extend onto mural endocardium

Chronic Discoid Lupus Erythematosus

- Skin lesions; systemic manifestations rare
- Face and scalp most commonly; LE cell test rarely positive, positive ANA's in 35%; anti-dsDNA rare; NO Ag-Ab complexes in uninvolved skin

Subacute Cutaneous Lupus Erythematosus

- Intermediate between SLE and Discoid Lupus
- Widespread superficial skin involvement, mild systemic
- Anti-SS-A antibodies

Drug Induced Lupus Erythematosus

- Seen with hydralazine, procainamide, isoniazid, and D-penicillamine most commonly
- ANA's common, esp. anti-histones
- Renal and CNS involvement rare
- Associated with HLA-DR4

Sjögren's Syndrome

- Dry eyes and dry mouth resulting from autoimmune destruction of the lacrimal and salivary glands. May see dysphagia, fissuring of mouth, ulceration of cornea. Often see parotid gland enlargement
- 90% affected patients are women between 40-60 yrs.
- May occur as an isolated disorder (sicca syndrome or primary form) or in association with another autoimmune disease (secondary form), the most common being rheumatoid arthritis, but also SLE, polymyositis, scleroderma, etc.
- Histology shows infiltration of glands with predominantly T-Cells, predominantly CD4+, in a periductal distribution. A tubulointerstitial nephritis can also be seen in the kidney
- ANA's detected in most patients; most specific is antibodies to the ribonucleoproteins SS-A (Ro) and SS-B (La), especially the latter
- Lymph nodes often show pseudolymphomatous enlargement, but there is also a 40 fold increased risk of true lymphoma
- Associated with HLA-DR3

Scleroderma (Progressive Systemic Sclerosis)

- Progressive fibrosis of predominantly the skin, but also GI tract, kidney, heart, muscles, lungs. Death often from renal failure or cardiac failure
- F:M=3:1, mean age=40 yrs
- Often present with Raynaud's phenomenon (episodic vasoconstriction of the arteries and arterioles of the extremities)
- Fibroblasts of affected patients synthesize abnormally large amounts of collagen, although the collagen is normal
- Etiology involves cytokine activation of fibroblasts and/or damage and fibrosis of small blood vessels. Initiating factor is likely to be some as yet uncharacterized Ab-Ag interaction.
- Pathology: dermal fibrosis, atrophy of appendages, and thinning of epidermis; fibrous replacement of muscularis of the gut (particularly esophagus); inflammatory synovitis; renal vascular fibrosis; pulmonary alveolar fibrosis

Diffuse Scleroderma

- Widespread skin involvement at onset, with progression to internal viscera
- Antibody to DNA topoisomerase I (Scl-70) present in 70%
- Anti-centromere antibody seen in 20-30%

CREST Syndrome

- More limited involvement; more benign course; involvement of viscera only much later
- Calcinosis, Reynaud's, esophageal dysmotility, sclerodactyly, telangiectasia
- Anti-centromere autoantibody seen in 80-90%

"Localized Scleroderma"; e.g. Morphea

- Skin involvement only; no visceral involvement
- Usually limited in distribution, may be widespread
- Probably not related to progressive systemic sclerosis

Mixed Connective Tissue Disease

- Characterized by simultaneous features suggestive of SLE, polymyositis, and scleroderma
- Includes most cases of scleroderma
- High titer antibodies to nuclear ribonucleoproteins

Better long term prognosis than SLE or scleroderma alone; responds well to corticosteroids
May simply be a variant

Polymyositis-Dermatomyositis

Chronic inflammatory myopathies of uncertain cause
• Group I: Adult polymyositis (no skin involvement)
• Group II: Adult dermatomyositis
• Group III: I or II with malignancy
• Group IV: Childhood dermatomyositis
• Group V: Either associated with another immune disorder
Autoantibodies against tRNA synthetase (particularly histidyl) are seen in >25%
May be related to cross-reaction with Coxsackie B-group viruses, particularly in the childhood form
Myositis affects proximal muscles first: pelvic and shoulder girdle, then neck, posterior pharynx, intercostals). This is in contrast to most dystrophies (primarily distal muscles) and myasthenia gravis (ocular muscles)
Skin rash classically is a lilac discoloration of the upper eyelids with periorbital edema accompanied by a scaly erythematous eruption over the knuckles, elbows, knees
Visceral cancers more common in patients with dermatomyositis, approaching 15-20%, and involving the breast, ovary, lungs, and stomach

Amyloidosis

Probably a disease resulting from derangement of the immune apparatus
Proteinaceous substance insidiously deposited in tissues throughout the body, encroaching on structures and inducing pressure atrophy
Defect may be an inability to properly digest/degrade

Amyloid

Not a single compound; chemically, several types; derived from circulating precursor protein
All types have same structure and appearance
Homogenous, amorphous, pink hyaline on H&E; pink to red staining with Congo red which imparts an apple-green birefringence
EM: non-branching long 7.5-10nm diameter fibers (90% mass), accompanied by P component (10%): doughnut shaped pentagons with 9nm external and 4nm internal diameter composed of 180kD-220kD alpha-1 serum glycoprotein - homologous to C-reactive protein
Amyloid fibrils aggregate yielding a cross-β pleated sheet
Types:
• AL (amyloid light chain): Ig light chain derived (Bence Jones protein), usually λ; when partially cleaved, can accumulate
• AA (amyloid-associated): 8.5kD protein (76 amino acids) derived from 12kD SAA (serum amyloid associated protein) made by the liver
• AF: mutant form of transthyretin (formerly called prealbumin, since it electrophoreses just before albumin, but has no relation to it; involved in transport of thyroxin and retinol) seen in familial amyloid polyneuropathies and senile cardiac amyloidosis
• Hormones: calcitonin, proinsulin, etc.
• Others

Immunocyte Dyscrasia Associated (Primary) Amyloidosis

AL type; systemic in distribution
Most common form in US
Occurs in 5-15% of patients with multiple myeloma; also can be seen in Waldenström's macroglobulinemia, heavy chain disease, solitary plasmacytoma, follicular lymphomas
Most patients have no underlying overt B-Cell neoplasm; these cases are referred to as "primary amyloidosis"
Usually: heart, GI tract, peripheral nerves, skin, tongue

Reactive Systemic (Secondary) Amyloidosis

AA type; systemic in distribution
Occurs secondary to underlying chronic inflammatory condition such as TB, bronchiectasis, chronic osteomyelitis, rheumatoid arthritis (14-26%), IBD, heroin users; also seen with Renal Cell Ca and Hodgkin's disease
Most common sites: kidneys, liver, spleen, lymph nodes, adrenals, thyroid
Better prognosis than immunocyte associated amyloidosis

Endocrine Amyloid

Derived by enzymatic conversion of polypeptide hormones
Medullary carcinoma of thyroid, islet tumors of pancreas, pheochromocytoma, undifferentiated carcinoma of lung

Hemodialysis-Associated Amyloidosis

Deposition of beta-2-microglobulin in synovium, joints, and tendon sheaths; seen in patients on hemodialysis: cannot be filtered through dialysis membranes

Heredofamilial Amyloidosis

• Familial Mediterranean Fever: attacks of fever with inflammation of serosal surfaces; AA protein
• Familial amyloidotic polyneuropathies: autosomal dominant; AF protein (mutated transthyretin)

Localized Amyloidosis

Tumor like nodule
Lung, larynx, skin, urinary bladder, tongue, peri-orbital
At least some are AL protein

Amyloid of Aging

• Senile Cardiac Amyloidosis: usually asymptomatic, but can lead to heart failure; usually transthyretin (not mutated)
• Senile cerebral Amyloidosis: deposition of A4 (beta-amyloid) in "senile plaques" of Alzheimer's disease

PATHOLOGY:

Kidney: most common cause of death; enlarged, waxy, firm; involves primarily glomeruli but also peritubular interstitium, arteries, arterioles
Spleen: begin perifollicularly; two patterns of deposition:
• Sago spleen: splenic follicles - granular on gross
• Lardaceous: walls of sinuses, fusing
Liver: first in space of Disse, then hepatic parenchyma
Heart: interstitial deposits with pressure atrophy of myocytes

VIRUSES

GENERAL FEATURES OF VIRAL DISEASES

Can cause a wide variety of symptoms and diseases
The same virus can cause different diseases dependent upon the route of infection, and can cause disease of differing severity in different individuals.
Similar clinical and pathological presentations can be caused by different viruses
The presence of a virus does not necessarily mean that it is responsible for the observed disease.

DNA VIRUSES

Non-Enveloped

Parvovirus

18-26nm, defective (adeno-associated), icosahedral capsid, ssDNA
Adenosatellovirus

Papovavirus

45-55nm, icosahedral capsid, circular dsDNA
Papillomavirus
Human papilloma virus: many types, producing verruca vulgaris, condyloma acuminata, laryngeal papillomas
Polyomavirus
Polyoma virus
SV-40
Progressive multifocal leukoencephalopathy virus (JC virus)
BK virus: often isolated from urine samples, but not yet linked to any specific human clinical syndrome

Adenovirus

70-90nm, icosahedral capsid, dsDNA
Mastadenovirus
Adenovirus: conjunctivitis, pharyngitis, pneumonia; infected cells have enlarged nuclei and show two types of inclusions: clumped eosinophilic bodies with surrounding halo, or "smudge cell": large, ovoid nucleus filled with granular amphophilic to deeply basophilic mass and an indistinct nuclear membrane

Enveloped

Hepadnavirus

42nm, icosahedral capsule (28nm), dsDNA
Hepatitis B

Herpesvirus

120-200nm, icosahedral capsid (100nm), dsDNA
Alphaherpesvirus
Herpes Simplex I: predominantly oropharyngeal infections
Herpes Simplex II: predominantly urogenital infections
Varicella-Zoster Virus: Chicken pox and shingles
Betaherpesvirus
Cytomegalovirus (Salivary gland virus); Cytomegalic Inclusion Disease, when acquired perinatally, can (10%) develop into a full blown illness resembling erythroblastosis fetalis, involving salivary glands, kidneys, liver, lungs, gut, pancreas, thyroid, adrenals, and brain; CNS involvement can be fatal; get both large nuclear and smaller cytoplasmic inclusions
Gammaherpesvirus
Epstein-Barr Virus: Infectious Mononucleosis: Virus infects B-Cells and incorporates into it's genome; Expression of viral antigens on surface of B-Cells induces a marked expansion of T-Cells, many T-killer cells. These T-Cells are responsible for the atypical circulating cells and lymphadenopathy and splenomegaly (latter may be so enlarged as to rupture)

Poxvirus

250-400nm, complex structure (brick shaped), dsDNA
Orthopoxvirus
Variola (Small Pox)
Vaccinia
Cowpox
Molluscum Contagiosum
Paravaccinia (Milker's Nodules)
Contagious Pustular Dermatitis (orf)

RNA Viruses

Non-Enveloped

Picornavirus

24-30nm, icosahedral capsid, ssRNA
Enterovirus

Poliovirus	Polio, paralysis
Coxsackie A virus	meningitis, acute resp. infections
Coxsackie B virus	myocarditis of newborn, pericarditis
Echovirus	Usually local infections only
Enterovirus	

Rhinovirus
Many strains: Major cause of the "Common cold"
Generally remain confined to the upper respiratory tract
Aphthovirus
Foot and mouth disease virus
Hepatitis A

Reovirus

60-80nm, icosahedral capsid, dsRNA
Reovirus
Orbivirus
Colorado Tick Fever Virus
Rotavirus
Epidemic Acute Gastroenteritis: Can be visualized by negatively stained stool ultrafiltrates; Oral-fecal transmission; children & elderly most susceptible; Peak incidence in winter months; Mixed inflammation, shortening of villi, crypt hyperplasia

Enveloped

Togavirus

40-70nm, icosahedral capsid (30nm), ssRNA
Alphavirus (Group A arbovirus)
Eastern Equine Encephalitis virus: 70% mortality; survivors usually have mental defects; meningoencephalitis with acute vasculitis and fibrinoid necrosis
Semliki Forest Virus

Flavivirus (Group B arbovirus)
- St. Louis Encephalitis virus: 30-40% mortality; lesions most severe in substantia nigra and thalamus
- Dengue virus: fever, rash, muscle and joint pains; can cause severe hemorrhagic disease
- Yellow Fever virus: vicerotrophic for liver; midzonal necrosis
- Hepatitis C virus (see liver outline)

Rubivirus
- Rubella virus (German measles); Short, benign course, but when transmitted from mother to fetus, can cause severe congenital malformations, predominantly cardiac

Bunyavirus

90-120nm, helical capsid (9nm), ssRNA
- California Encephalitis Virus
- Crimean Hemorrhagic Fever
- Hantavirus: causes marked non-cardiogenic pulmonary edema; has recently caused several deaths in Southwestern US; natural reservoir: deer mouse

Retrovirus

80-140nm, icosahedral capsid (70nm), ssRNA

Cisternavirus A

Oncovirus B
- Mouse Mammary Tumor Virus

Oncovirus C
- Rous Sarcoma virus
- Murine sarcoma virus
- Human T-Lymphocyte Virus I and II

Oncovirus D

Lentivirus E
- Visna virus
- Human Immunodeficiency Virus (HIV)

Spumavirus F

Coronavirus

80-160nm, helical capsid(10-20nm), ssRNA
- Common cold syndrome

Arenavirus

50-300nm, complex capsid, ssRNA
- Lymphocytic Choriomeningitis virus
- South American hemorrhagic fever virus

Orthomyxovirus

80-120nm, helical capsid (9-15nm), ssRNA
- Influenza: generally remains confined to respiratory tract; evades host defenses by antigenic shift/drift

Paramyxovirus

125-250nm, helical capsid (18nm), ssRNA

Viruses enter body through respiratory tract; may produce local symptoms, or pass through without local reaction to cause systemic disease

Paramyxovirus
- Parainfluenza virus: most common cause of croup in children
- Mumps virus: Contagious childhood disease (peak incidence 5-15 yrs) characterized by swelling of parotid glands (bilateral in 70%) and occasionally other salivary glands; May involve pancreas, gonads (20%, usually unilateral), CNS; In adults, tissue destruction may be more marked; Salivary gland infiltrated by histiocytes, lymphocytes, plasma cells which compress acini and ducts, occasionally with focal necrosis. Similar pathology also seen in testis, where swelling can induce more necrosis.

Morbillivirus
- Measles virus: Measles (Rubeola): Acute febrile illness with spotty lesions inside the mouth (Koplik's spots - blister and ulcerate; diagnostic), conjunctivitis, lymphoreticular hyperplasia, blotch erythematous rash; Largely eliminated, but increasing in US; Lymphoid tissue shows multinucleated giant cells with eosinophilic nuclear inclusions (Warthin-Finkeldey cells)
- [Measles virus can also cause subacute sclerosing panencephalitis in children and young adults]

Pneumovirus
- Respiratory Syncytial Virus: croup or pneumonia; can also cause otitis media, meningitis, myelitis, myocarditis

Rhabdovirus

Bullet shaped (130-240 x 70-80 nm), helical capsid (15nm), ssRNA

Lyssavirus
- Rabies virus: primarily a disease of animals; transmitted to humans via bite from rabid animal; replicates locally and travels to brain via peripheral nerves; initial symptoms include malaise, fatigue, headache; this is followed by neurologic symptoms including disorientation, hallucinations, seizures, coma, death; cytoplasmic inclusions in neurons (especially Purkinje cells), called Negri bodies, are pathognomonic

Vesiculovirus
- Vesicular Stomatitis Virus

Unclassified

- Hepatitis Delta Virus: 36nm particle with an envelope ("viroid"); defective virus which requires co-infection with Hepatitis B virus; produces a fulminant hepatitis
- "Slow Viruses": Unclassified, unidentified infectious agents

Other Terms

Arboviruses *(arthropod borne viruses)*
- Sometimes used to refer collectively to the alphavirus and flavivirus genera of the togavirus family
- Sometimes also includes bunyavirus, reovirus, arenavirus, and rhabdovirus families

Pseudomyxovirus
- Refers collectively to the Morbillivirus and Pneumovirus genera of the Paramyxovirus family

BACTERIA

Gram Positive Cocci

Staphylococcus

Non-spore-forming gram + cocci, usually unencapsulated, in clusters
- S. aureus (coagulase positive)
- S. epidermidis (coagulase negative)
- S. saprophyticus (coagulase negative)

Staph aureus generally produces most severe disease, and when causes sepsis, often fatal; however, even Staph epidermidis can be fatal in immunocompromised
Normal inhabitant of nasopharynx and skin
Infective only following large dose inoculation
Most often form suppurative lesions with walled off abscesses or spreading cellulitis
Regional lymphadenitis usually mild
Staph aureus sepsis is a medical emergency - often fatal

Skin Infections
- Furuncles (Boil): Focal superficial suppurative inflammation of skin beginning in a single hair follicle
- Carbuncles: Deeper subcutaneous suppuration spreading laterally, generally involving skin of upper back or neck
- Impetigo: [see streptococcus]
- Surgical Wound Infection: Sutures and foreign bodies favor persistent infections; will not heal unless puss is drained

Pneumonia
Generally destructive bronchopneumonia which may rupture into pleura (empyema)

Endocarditis
Left or right sided
Most frequent destructive vegetative endocarditis

Toxin Related Diseases
- Staphylococcal Food Poisoning: Caused by toxin in contaminated food; Acute, self limited; onset 1-6 hrs after consumption
- Toxic Shock Syndrome: sporadic related to infected tampons; intractable shock, sometimes fatal
- Scalded Skin Syndrome (Toxic Epidermal Necrolysis): caused by exfoliation toxin; Subepidermal blistering and exfoliation with minimal inflammation; seen in children

Streptococcus

Gram positive cocci (slightly oval) in pairs and/or chains
- Beta-hemolytic (complete hemolysis on blood agar plates)
  - S. pyogenes: Group A; local and systemic invasion, poststreptococcal disorders
  - S. agalactiae: Group B; can cause perinatal infections
  - S. faecalis (AKA: enterococcus): Group D; UTI, cardiovascular infections, meningitis
- Alpha-hemolytic (partial hemolysis on blood agar plates)
  - S. viridans: Group H, K, others: endocarditis
  - S. pneumoniae (AKA: pneumococcus)

Two disease patterns: suppurative inflammation and poststreptococcal hypersensitivity disease (rheumatic fever, glomerulonephritis, erythema nodosum)
Asplenic patients particularly susceptible

Scarlet Fever
Acute strep pharyngitis accompanied by rash caused by erythrogenic toxin
3-15yrs of age
Raspberry or Strawberry tongue
Notoriously associated with post-streptococcal sequelae

Impetigo
Superficial skin infection, usually occurring in children
Can be caused by strep or staph
Strep often produces lymphangitic spread (red streaks)

Bronchopneumonia
Strep pneumoniae (diplococcus)
Causes most cases of lobar pneumonia
Polysaccharide capsule responsible for virulence
Same organism can also cause a bacterial meningitis

Gram Positive Bacilli

Bacillus

Large gram positive rods, square ended, in chains; spore forming; aerobic
- B. anthracis: major pathogen (anthrax)
- B. subtilis: [pathogenic only in immunocompromised]
- B. cereus: food poisoning

Anthrax
Organism itself produces minimal inflammation; hemorrhage and inflammation and edema due to exotoxin
Predominantly a disease of sheep
In humans, forms a malignant pustule at entry site, which blisters; necrosis, edema, inflammation
If becomes systemic (sepsis), usually fatal

Clostridia

Gram positive motile rods, anaerobic, spore forming, widely distributed in soil
Invade only under conditions of low oxygen tension, previous tissue damage, or poor phagocytosis
Disease usually due to a specific exotoxin that can be fatal even in the absence of tissue invasion - antitoxin only effective if given while toxin still circulating, before it binds to its target cells
Toxin liberation often requires growth without interference from competing flora

Clostridium tetani
Tetanospasmin: neurotoxin which disseminates through the blood stream, binds to peripheral nerve endings, ascends to cell body in CNS, all without causing any harm. When it passes into the presynaptic terminals of inhibitory spinal interneurons, it produce loss of sympathetic inhibition
Increased muscle tone, tachycardia, hypertension: muscles of face first, then trunk, producing tonic contractions
Minimal morphologic changes
Mortality today ~20%

Clostridium botulinum
Spores can resist boiling for many hours
Food poisoning caused by ingestion of preformed, heat labile toxin which is resistant to gastric acidity - readily absorbed into blood; attaches to synaptic vesicles of cholinergic nerves and blocks release of acetylcholine
Descending paralysis beginning with cranial nerves (ptosis, dysphagia, dysphonia, dry mouth, paralytic ileus, etc.)
15% mortality

Clostridium perfringens
Invasive infection
- Necrotizing cellulitis: Foul odor, thin serosanguinous exudate, sloughing of skin
- Myonecrosis (gas gangrene): produces gas bubbles in tissues (can cause crepitus) and extensive necrosis of muscle; Toxins induce active hemolysis: Hct can drop rapidly, even to 0!

Clostridium difficile
Pseudomembranous colitis, with inflammatory exudate spewing out from crypts

Seen particularly with clindamycin, lincomycin, and cephalosporins - treated with vancomycin

Corynebacterium

Gram positive rods, nonmotile, non-spore forming, club-shaped ends, often arranged in smears as "Chinese characters"

Corynebacterium diphtheriae

Acute communicable disease, usually of children 2-15 yrs old
Induces formation of an inflammatory 'pseudomembrane' in the respiratory tree overlying an ulcerated necrotic surface
Exotoxin (encoded by a lysogenic phage) is heat labile, 62kD, and can be lethal in a dose of only 0.1µg/kg. Fragment B required for transport into cell; Fragment A is enzymatically active: ADP-ribosylates elongation factor-2, causing necrosis. The toxin can have far reaching effect, especially myocardial fiber necrosis and polyneuritis with degeneration of the myelin sheaths

Gram Negative Cocci

Neisseria

Gram negative, non-motile diplococci, small (0.8µm), strict aerobes,

Neisseria meningitidis

Gram negative diplococcus
Colonizes upper respiratory tract - can invade
2/3 of all invasive infections produce meningitis
Characteristically produces cluster infections

Neisseria gonorrhoeae

Cause common gonorrheal urethritis ("clap")
Easily transmitted sexually or by other contact
Retrograde spread to internal genitalia where a chronic purulent inflammation is produced
If untreated, can spread into peritoneum in females (perihepatitis: Fitz-Hugh-Curtis Syndrome) or systemically (septic arthritis) in either sex, but this is rare
Most common cause of PID
In smears, often identified within phagocytes
Organisms under constant programmed genetic variation

Gram Negative Coccobacilli

Hemophilus

Encapsulated coccobacillary (pleomorphic) gram-negative

Hemophilus influenzae

Currently primary pathogen for children under 1 yr
Meningitis, URI, epiglottitis, pneumonia, endocarditis
Meningitis peaks at 1 yr (2 months - 7 yrs), usually sporadic, rapidly progressive, not infrequently fatal
Lesions are rich in neutrophils and fibrin, giving a plastic quality which resolves slowly and may scar
Acute epiglottitis is a pediatric emergency

Hemophilus ducreyi

Causes chancroid (soft chancre), a sexually transmitted disease

Bordetella

Small, pleomorphic gram negative coccobacillus

Bordetella pertussis

Causes Whooping cough, highly communicable usually self-limited childhood disease with violent coughing paroxysms
Organism does not invade but produces exotoxin
Extensive coughing spells can lead to subcutaneous emphysema or hypoxia induced convulsions

Brucella

Gram Negative Bacilli

The family Enterobacteriaceae, all facultative anaerobes or aerobes, includes the following genera: Enterobacter, Escherichia, Klebsiella, Proteus, Salmonella, Serratia, Shigella. All are found in the GI tract

Escherichia

Escherichia coli

Forms mass culture in human gut lumen, perhaps preventing colonization by more harmful bacteria
Most common cause of uncomplicated urinary tract infections; infections arising secondary to stone or obstruction are more likely due to Proteus, Pseudomonas, or Enterobacter
Also common: acute appendicitis, cholecystitis, diverticulitis
When it causes gram negative bacteremia, endotoxin induced DIC and/or shock ensues: 50% fatal
Enteroinvasive form produces a Shigella-like picture
Toxigenic form produces a watery diarrhea similar to that of cholera - causes 1/3rd cases of "Montezuma's revenge" in travelers not immune to the organism. No mucosal injury.
Most versatile source and recipient for gene exchanges

Klebsiella, Enterobacter, and Serratia

Klebsiella pneumoniae and Enterobacter aerogenes

Closely related organisms with similar disease spectrums
Severe pneumonia, UTI - not enterotoxic
Pneumonia is often lobar

Salmonella

Gram negative coliform organisms with flagella
Common cause of food and water borne enteric infections
Numerous serotypes and species
Lack enterotoxins, but invade mucosal cells inducing brush border degeneration, ulceration; can live in macrophages and neutrophils for a while

Salmonella typhi

Causes Typhoid fever
Penetrates into blood stream - bacteremia results in lymphoid proliferation, especially of Peyer's patches, which can subsequently ulcerate (form oval ulcers elongated in direction of stool flow, vs TB which produces circular or transverse ulcers)
Neutropenia in peripheral blood, hemophagocytosis in LN's, spleen, and liver
Culture of organism from blood in first week is diagnostic

"Food Poisoning"

Mildest expression of Salmonella disease spectrum
Short incubation period, superficial lesions limited to colon, with mixed inflammatory infiltrate

Salmonella typhimurium

Generally cause disease intermediate between food poisoning and typhoid fever

Shigella

Gram negative coliform facultative anaerobes
Infectious only for man; infectious even in small numbers
Cause bacillary dysentery: invade colonic mucosa, multiply in lamina propria and mesenteric LN's; unlike salmonella, do not cause bacteremia
Endotoxin release causes mucosal necrosis and a fibrinopurulent exudate forming a gray-yellow pseudomembrane - ulcerations usually remain superficial

Pseudomonas

Pseudomonas aeruginosa
- Low virulence in non-compromised hosts; readily phagocytosed
- Common secondary invader (when normal host barriers circumvented by other means)
- Number one source of sepsis in burn units
- Exotoxin A ADP ribosylates EF-2 (like diphtheria toxin)
- Histologically: necrotizing vasculitis with thrombosis, hemorrhage, large masses of proliferating organisms

Campylobacter

Campylobacter jejuni
- Responsible for 5-10% of hospital acquired dysentery
- Inflammation can involve entire gut from jejunum to anus with superficial erosions, crypt abscesses, villus atrophy

Campylobacter (now Helicobacter) pylori
- Causes an antritis

Vibrio

- Comma-shaped gram negative

Vibrio cholerae
- Does not invade
- Heat labile enterotoxin ADP-ribosylates a G-protein regulator of adenylate cyclase, generating excess cAMP, marked mucosal secretion, and a watery diarrhea
- Lymphoid hyperplasia often seen - may be due to other organisms

Yersinia

- Gram negative bacillus; safety pin appearance with methylene blue stain

Yersinia enterocolitica
- Major cause of enteritis in pediatric population
- Upper and lower GI tract involvement, with ulceration and spread to lymph nodes
- Lymph nodes and intestinal mucosa show 'granulomas' with stellate microabscesses rimmed by histiocytes - can mimic cat-scratch granulomas

Yersinia pestis
- Causes bubonic, pneumonic, and septicemic plague - total hemorrhagic necrosis of infected tissues
- Bubonic form limited to skin and LN's - most common - now mortality <20%; pneumonic and septicemic forms worse

Spirochetes

Borrelia

- Tick-borne, loosely wound spirochetes measuring up to 30µm
- Stain well with Wright-Giemsa stain

Borrelia recurrentis
- Relapsing fever caused by bouts of bacteremia with symptom-free intervals of about 1 wk duration
- Recurrences caused by programmed antigenic variation

Borrelia burgdorferi
- Lyme Disease
- Spreading, migrating erythema at inoculation site with sharp margins and central blanching
- Untreated, may progress to arthralgias, myocardial involvement, or central nervous system involvement

Treponema

- 10-13 µm corkscrew-shaped spirochete
- Produces minimal tissue damage, no known toxins
- Lesions linked to host immune response
- Low virulence, long latencies, but very high infectivity
- Two types of host antibody response
  - nonspecific antibodies; detected by STS, VDRL tests; can be falsely positive in mononucleosis, leprosy, autoimmune diseases, viral hepatitis, heroine users
  - specific antibodies - detected by FTA (fluor. treponemal Ab)

Treponema pallidum
- Causative agent of Syphilis (AKA lues)
- Sexually transmitted; also maternal-fetal transmission
- Three stages of disease, all marked histologically by plasmacytosis and proliferative (obliterative) endarteritis
  - Primary: chancre at site of inoculation
  - Secondary: generalized flat red-brown elevations (condylomata lata); contain numerous spirochetes
  - Tertiary: may occur years or decades later; only seen in about 1/3 untreated cases
    - Medial necrosis of aortic base and valve ring
    - Neurosyphilis
    - Syphilitic gumma, most common in liver
- Congenital Syphilis characteristically shows interstitial keratitis, Hutchinson's teeth (screwdriver shaped incisors), and eighth nerve deafness

Treponema pertenue and carateum
- Cause yaws and pinta, respectively

Others

Mycobacterium

- Slow dividers, facultative intracellular invaders
- Modest infectivity, but marked persistence in tissues
- Acid fast (Ziehl-Neelsen) staining due to waxy cell wall components
- Strict aerobes - do not grow in areas of low oxygen tension
- Grow slowly in culture (doubling time 48 hrs)

Atypical Mycobacteria
- M. avium-intracellulare most common in US
- Infection acquired from environment - not person to person
- Seen in immunocompromised, but also in COPD

Mycobacterium leprae
- Cause of leprosy, AKA Hansen's disease
- Obligate intracellular organism
- Low communicability
- Two forms of disease:
  - TT (polar tuberculoid form): vigorous T-Cell response with local activation of macrophages and granuloma formation
  - LL (polar lepromatous form): deficient T-Cell immunity, poor host response, macrophages stuffed with bacteria, bacteremia, seed cooler areas of body: skin, peripheral nerves, eyes, upper airways, testes, hands, feet

Mycobacterium tuberculosis
- AKA: Koch bacillus
- Infection used to be seen mostly in children and young adults; now more common in 50-60 yr old
- Two species: one predominantly infects humans (transmitted by inhalation); second is a bovine strain (now much less common but would cause GI infections from infected milk)
- Hallmark lesion is caseating granuloma (soft tubercle) although may have a cellular center (hard tubercle)
- Ghon focus: 1-1.5 cm gray-white inflammatory consolidation seen at the periphery of the upper part of lower lobe or lower part of upper lobe (greatest volume of air flow) which becomes granulomatous and then centrally necrotic by the 2nd week: primary infection focus, usually clinically silent
- Ghon complex: combination of primary lung lesion and ipsilateral lymph node involvement
- Rarely, primary focus will rapidly enlarge, erode into bronchi, giving rise to satellite lesions - may seed bloodstream resulting in miliary dissemination or meningitis

Secondary TB arises from reactivation of old primary lesions; presents as apical or posterior segment lesions (tubercul–oma), may be bilateral; can scar down, create progressive pulmonary TB, lead to tuberculous empyema, intestinal TB (if aspirated material is swallowed), or miliary seeding
Isolated distant organ involvement also seen (cervical LN, meninges, kidneys, adrenals, bones, fallopian tubes, epididymis
Secondary TB usually accompanied by fever, night sweats, weakness, fatigability, loss of appetite

Actinomycetes

Closely related to mycobacteria, with some similarity to fungi
Long, filamentous, gram-positive; don't stain on H&E

Nocardia

Infect chronically ill, immunosuppressed
Form necrotizing walled off abscesses (predominantly in lung) - no granulomata
Stains with acid fast stain (unlike Actinomyces)

Actinomyces

Chronic suppurative infection of neck, lung, or abdomen
Grossly visible yellow colonies: "sulfur granules"
Can infect normal hosts - invade only when tissue is devitalized by trauma (strict anaerobe)
Cervicofacial, thoracic, and abdominal Actinomycosis

FUNGI

Candida

AKA: Moniliasis; most common fungal infection
Non-branching boxcar-like chains of tubular cells (pseudohyphae) and small 2-4μm yeast forms
Infect oral cavity, GI tract, and vagina of normal individuals
Bacterial growth inhibits - when bacteria killed, Candida can proliferate and become invasive
Thrush: Candidal infection of oral cavity
Vaginal: more common during pregnancy and in oral contraceptive users
Invasive, systemic: renal (numerous microabscesses in both cortex and medulla), cardiac valves, lungs, meningitis

Aspergillus

Second most common infective fungus, esp. in hospitals
45° angle branching septate hyphae; 5-10μm
Three types of infection:
• Allergic: inhalation of large numbers of spores producing a hypersensitivity reaction in bronchi or alveoli
• Colonizing: growth of organisms in pulmonary cavity forming a mass (aspergilloma) without invasion
• Invasive: opportunistic infection involving primarily lung but also heart valves, brain, kidneys: targetoid lesions with necrotizing center and hemorrhagic border; propensity for invasion of vessel walls (like mucormycosis)

Mucormycosis (Phycomycetes)

Broad (6-50μm), irregular, empty looking non-septate hyphae with wide angle branching; ribbon-like
Opportunistic infections
Tendency to invade blood vessel walls (arterial)
Rhinocerebral, via nasal sinuses, seen in diabetics
Lung and GI involvement seen in advanced malignancy, leukemia, lymphoma, immunosuppressed

Histoplasma capsulatum

Tiny 2-5μm yeast forms with occasional unequal budding
Dust inhalation from soil contaminated with bird/bat droppings
Lesions and disease patterns are very similar to those of TB
Histologically, collections of macrophages filled with yeast

Blastomyces

Large 25μm yeast forms, thick refractile double contoured capsule, with broad based budding
M:F=9:1; limited to North America
Chronic focal suppurative or granulomatous lesions in lungs and skin (in skin, striking pseudoepitheliomatous hyperplasia)

Cryptococcus neoformans

5-10μm yeast with wide capsular halo and narrow based unequal budding - no hyphal forms in tissue
May infect healthy individuals, but usually opportunistic in patients with Hodgkin's, leukemia, lymphoma, AIDS
Capsule stains bright red with mucicarmine
Most frequent manifestation is meningitis or encephalitis
Small cysts filled with organisms and their mucinous secretions creating the "soap bubble" lesion

Coccidioides immitis

20-60μm spheres with endospores and capsule (spherule)
Infections seen in southwest US: "valley fever"
Primary pulmonary lesion similar to TB - suppurative or granulomatous
60% infections asymptomatic
Results in delayed hypersensitivity to coccidioidin antigen

PROTOZOA

Entamoeba histolytica

- 15-40µm trophozoite with small nucleus, foamy cytoplasm
- Often ingests red cells; very motile on wet preps
- Infects cecum and ascending colon;sometimes whole colon
- Can cause mild to very bloody diarrhea
- Invade lamina propria from deep in crypts; do not go past muscularis mucosa; spread out, undermining site of invasion (flask shaped lesion); as spread, cut into blood supply of overlying mucosa, causing liquefactive necrosis with minimal inflammatory response
- In ~40% cases, enter blood vessels and travel to liver where can form a unilocular cyst, often large, often hemorrhagic (chocolate colored anchovy paste; NOT malodorous)
- Lung and brain abscesses can also be formed

Naegleria fowleri

- Free-living ameboflagellate; large nucleus
- Enters arachnoid space through the cribriform plate while swimming in infected waters: causes meningoencephalitis
- Organism has large nucleus - easily mistaken for human cell

Giardia lamblia

- Worlds most prevalent gut protozoan
- Trophozoites (sickle shaped) live in brush border of duodenum and give rise to infective cysts
- Mucosa: normal to moderately inflamed with blunting of villi
- Can cause mild indigestion to copious watery diarrhea with flatulence, cramps, malodorous stools

Cryptosporidium

- Mild diarrhea in children to severe malabsorption in AIDS
- Live in intestine adherent to brush border and surrounded by host cell membrane (intracellular)
- Nuclei of infected cells become enlarged and hyperchromatic
- Intraepithelial lymphocytes common

Microsporidium

- Small protozoa which infect GI tract causing an intractable diarrhea in 60% AIDS patients

Enterotozoon bienneusi (discovered in 1985)

- Single organisms: infect only enterocytes
- Treated with metranidazole

Septata intestinalis (discovered in 1993)

- Infects all cells (enterocytes, fibroblasts, inflam cells, etc.)
- Multiple organisms found as clusters in all stages of maturation, but separated by "septa" of cytoplasm
- Treated with albendazol

Trichomonas vaginalis

- Most frequent venereal parasitic infection
- 15-18µm long turnip shaped flagellate
- Lives in postpubertal vaginas and male urethra (prepubertal vagina has wrong bacterial flora)
- Only small fraction of patients are symptomatic (itching, burning, especially during micturition)
- May be asymptomatic, even when present in large numbers

Pneumocystis carinii

- 4-6µm cysts
- Ubiquitous opportunistic parasite - essentially all children have acquired antibodies to it by age 2
- In protein malnourished children and immunosuppressed adults, can cause an interstitial pneumonia
- Foamy alveolar exudate with proliferating parasites

Plasmodia

- Four species, all cause different types of malaria
- Life cycle split between man and mosquito
- When infected into skin by bite of a carrier female mosquito, sporozoites travel to liver, enter hepatocytes, grow and transform to merozoites which reenter the blood and RBC's, and grow to become trophozoites. Some undergo sexual division into gametes which can then again be picked up by mosquitoes and transform into sporozoites
- Infected individuals show relapsing high fever with chills, rigor, headache, body ache, delirium; then sweating, break in fever, and lassitude
- Parasites can be found in the blood, and brown-black malarial pigment (hemozoin) can be found in histiocytes in the spleen and in Kupffer cells in the liver
- HbS carriers limit parasitemia by forcing parasite to leave the red cell as its heme starts sickling

P. vivax, P. ovale

- Benign tertian malaria: fever spikes 48 hrs apart; rarely fatal
- Vivax can only infect RBCs with the Duffy blood group factor

P. malariae

- Benign quartan malaria: fever spikes 72 hrs apart - long latency periods

P. falciparum

- Malignant tertian malaria: fever spikes at 48 hr intervals, progressive damage to RBC's, high parasitemias, can spread to CNS, accounts for most of the fatalities

Babesia microti

- Babesiosis: acute, sometimes prolonged illness with headache, fever, chills, myalgia, fatigue
- Commonly seen on Eastern seaboard, especially Nantucket and Martha's Vineyard
- Transmitted by tick

Trypanosoma

T. rhodesiense, T gambiense

- Acute febrile attack with purpura and DIC, then chronic episodic fever with lymphadenopathy and splenomegaly, then progressive brain dysfunction, "sleeping sickness", cachexia and death
- Transmitted by insect (Tsetse flies) - live in bloodstream
- Genetically programmed antigenic variation

T. cruzi

- Causes Chagas Disease, AKA American trypanosomiasis
- Intracellular parasite
- Acute: myocarditis; chronic: progressive cardiac failure
- In the heart, occasional cells stuffed with organisms; inflammation far out of proportion to number of organisms

Leishmania

- Tiny <3µm intracellular parasite - on smears, two basophilic dots (nucleus and kinetoplast)
- Limited cutaneous infection or generalized visceral infection

Toxoplasma gondii

- 3x6µm tachyzoites
- Definitive hosts are domestic cats - when shed in feces, oocysts are highly infective by any route
- In normal adults, produces a limited lymphadenopathy, often cervical, with follicular hyperplasia, monocytoid B-cells, and epithelioid histiocytes
- Fetal, neonatal, or immunocompromised infections rapidly lead to CNS involvement, progressive encephalitis, death

HELMINTHS

Effective infections rely upon longevity of individual worms rather than large reproduction rates - most helminths must cycle through the environment for reproduction
Individual worm burdens in humans tend to be stable and long-lasting; individuals harboring worms are generally more resistant to superinfection by the same worm
Only a small percentage of "infections" result in disease
Disease can be caused by:
• competition with host for essential nutrients
• mechanical obstruction
• blood-digestion
• inflammation and malabsorptive changes in the gut
• host hypersensitivity

Nematodes (Roundworms)

Ascaris lumbricoides

Largest (up to 35 cm) and most common intestinal roundworm
Fecal-oral transmission
In most infected individuals, remains commensally in gut not causing disease - eventually dies and is passed
Infections most common in children
Disease caused by hypersensitivity, GI obstruction, perforation of appendix or bile duct with peritonitis

Trichuris

AKA whipworm
Small intestine, up to 5cm long with attenuated anterior end
Rarely causes disease, and then only with massive infections, and then only mild disease

Enterobius vermicularis

AKA: Pinworm
Tiny, up to 1.3 cm long, prominent lateral ridges
Causes enterobiasis, AKA: oxyuriasis
Female worms migrate to anus at night to lay eggs; causes intense pruritus, insomnia and irritability in children
Not infrequently found incidentally in appendix

Necator americanus, Ancylostoma duodenale

AKA: Hookworms; 1 cm long
Sharp mouth-plates penetrate into duodenal or jejunal mucosa; worms feed on blood, most of which is excreted into the intestinal lumen (each worm uses 43ul blood/day)
Heavy infections needed to produce iron deficiency anemia
Eggs hatch in gut, deposited in feces, enter skin of human feet, travel to lungs, coughed up, swallowed, reenter gut

Strongyloides stercoralis

Very small (1mm long) intestinal luminal dweller
Burrow into mucosal crypts; can damage absorptive surface of gut leading to chronic enteritis
Only intestinal nematode which can reproduce within host
Larvae can invade and migrate to lung, liver, CNS

Dracunculus medinensis

AKA: Guinea worm
Long (120 cm) thin worm which enters by drinking larvae infested water; mature worms migrate to skin
Blistering, ulcerating skin lesions (often outer malleolus of foot; occasionally can see head or worm in fresh lesion
Worms used to be removed by winding it up on a stick; this is the probable origin of the caduceus

Trichinella spiralis

Trichinosis acquired by eating improperly cooked contaminated meat (pork, bear, wild game) - larvae released into stomach by digestion of cyst wall - attach to duodenal mucosa - mature to adult worms - produce numerous new larvae which invade bloodstream and spread to skeletal muscles where convert muscle cell to a nurse cell - encyst - in time, may die and calcify
Most common muscles: diaphragm, eye muscles, laryngeal muscles, deltoid, gastrocnemius, intercostals

Filaria

Long string-like nematodes whose fertilized females release tiny microfilariae into the lymph, blood, and skin
Can survive for many years, producing microfilariae
Mosquito borne

Wuchereria bancrofti

10 cm long; invade lymphatics producing lymphedema of scrotum, penis, vulva, leg, breast, or arm

Onchocerca volvulus

Largest of human filaria (50 cm)
Transmitted by black flies
Lives in skin - discharges microfilariae into subcutaneous tissue
In addition to skin lesions, can get blindness from millions of microfilariae accumulating in eye chambers

Cestodes (Flatworms)

AKA: tapeworms, platyhelminthes
Can achieve lengths of 3-6 meters
Scolex is head region - generates thousands of proglottids that articulate with each other and make up bulk of worm
Two types of infections: adult worm attached to intestinal wall or invasion by larval forms into various organs

Taenia

Ingestion of undercooked meat - larvae excyst and mature into adults - attach to bowel wall by scolex - can grow to great lengths
Can obstruct GI tract or lead to B12 deficiency
Diagnose by finding proglotids or eggs in stool
To cure, must remove scolex; a vermifuge can be used

Cysticercosis

Usually Taenia solium
Acquired by consumption of eggs; invade through gut and disseminate to brain, muscles, skin, heart
Can block spinal fluid reabsorption
Ovoid, white to opalescent
Often calcify or degenerate
Minimal inflammation when alive, extensive when die

Echinococcus granulosus

Main host is dog
Human ingestion of eggs leads to hatching in duodenum and invasive embryos which go usually to liver (66%) but also to lung (5-15%) or bones, brain, etc.
In target site, lodge within capillaries, incite an inflammatory reaction, and if survive encyst; this "hydatid cyst" grows in size over years and can reach 10cm or more
Cysts unilocular (E. multilocularis causes multilocular cysts)

Trematodes (Flukes)

Schistosoma
6 species, including S. mansoni, S. japonicum, S. haematobium
Infective form burrows through skin of feet into blood-stream; pause in lung at 4-14 days until reach liver; mature in intrahepatic portal radicals; eventually descend to mesenteric or pelvic venules where mate and lay eggs
Hypersensitivity granulomas in liver can lead to fibrosis
Generally minimal host tissue reactions to adults until die
Eggs produce significant inflammation; often calcify
Predisposes to squamous cell carcinoma of the bladder

Fasciola hepatica
Liver fluke
Worms migrate through liver (predominantly subcapsular); settle in gallbladder or bile ducts; can cause obstruction

Fasciolopsis bruski
Large Intestinal fluke (7 cm), principally small bowel
Attach to mucosa, hemorrhagic inflammation, can lead to abscesses and mucosal destruction

Paragonimus westermani
Lung fluke; small, 1.2 cm long
Cause cystic inflammatory lesions, usually in lung
Source: uncooked crayfish or crabs

OTHER INFECTIOUS AGENTS

Chlamydia
Obligate intracellular parasites with both RNA and DNA
Live within phagocytic vacuoles in cells - prevent fusion of lysosomes
Synthesize own nucleic acids, but not own ATP
Do not dictate host cell synthesis of new products
Inclusions can be identified with fluorescent antibodies
Giemsa stain can demonstrate either large "initial" (1 μm) bodies and smaller (.2-.3 μm) "elementary" bodies
Two species: psittaci and trachomatis, the latter with numerous serotypes

Ornithosis (Psittacosis)
Caused by inhalation of contaminated bird excrement
Infection can be asymptomatic, flu-like, serious, or fatal
Fatality has ranged from 5-40%

Urethritis
Asymptomatic in women
Often recognized by persistence following treatment for gonorrhea

Trachoma
Chronic suppurative eye disease
Mostly seen in dry, sandy regions
One of the leading global causes of blindness

Lymphogranuloma Venereum (LGV)
Venereally transmitted disease; marked lymphadenopathy
In males, invariably inguinal nodes; in females, can be deep pelvic or perirectal nodes
Stage I: small epidermal vesicle; granulomas; chlamydial inclusions
Stage II: suppurative granulomatous inflammation with stellate abscesses rimmed by epithelioid histiocytes
Stage III: chronic inflammatory infiltrates and dense fibrosis, plasma cells

Rickettsia
Small, gram-negative obligate intracellular bacteria; inhabit ticks, mites, fleas, lice - don't damage arthropod hosts
Infect humans either by arthropod bite or contact of abraded skin with arthropod excreta
In humans, multiply in small vessel endothelium; enter cell by induced endocytosis, escape into cytoplasm and begin dividing - can fill cell with organisms, may burst

Typhus Fever
Caused by Rickettsia prowazekii
Generally, no eschar is formed at site of inoculation
Limited to skin in milder cases, but can cause necrosis of fingertips, nose, ear lobes, scrotum, penis, vulva; internal hemorrhages involve brain, heart, testes, lungs, kidneys
Endothelial proliferation and swelling in capillaries, arterioles, venules; may narrow lumen or thrombose vessels but rarely destroy vessel walls
Cuff of inflammation, mixed leukocytes, surrounding vessels
In the brain, focal microglial proliferations mixed with leukocytes referred to as "typhoid nodule"

Rocky Mountain Spotted Fever
Caused by Rickettsia rickettsi
Organisms penetrate deeply into vessels, causing acute necrosis, fibrin extravasation, thrombosis - may mimic necrotizing vasculitis
Generally forms eschar at site of inoculation
Distribution of lesions similar to that for Typhus

Bacillary Angiomatosis and Peliosis Hepatis
Caused by Rochalimaea henselae or R. quintana species, or a related organism
Intracellular parasite which leads to death of infected cells and a degree of vascular proliferation

Mycoplasma
AKA: Eaton agents; Pleuropneumonia-like organisms (PPLOs)
Resemble L-forms of bacteria - tiny 0.125 to 0.35 μm polymorphous organisms
Extracellular human parasite
Frequent cause of primary atypical pneumonia
In 40%, elicits Ig production which agglutinate human Group O red cells at 4°C (cold agglutinins)

CONGENITAL SYNDROMES

TERMINOLOGY

- Pleiotropism: single gene with multiple effects
- Genetic Heterogeneity: multiple genotypes, same phenotype
- Variable expressivity: same genotype, variable phenotypes
- Penetrance: same genotype, same phenotype, but expressed to a varying degree
- Malformation: intrinsic developmental abnormality which occurs in <4% of the general population
- Variation: structural abnormality which occurs in >4% of the general population
- Deformation: structural abnormality due to external mechanical factors (e.g. oligohydramnios)
- Disruption: secondary destruction of an originally normal structure
- Syndrome: group of abnormalities which occur together, not clearly explainable by a single event but thought to be pathogenetically related
- Associations: non-random concurrence of multiple anomalies
- Sequence: varieties of causes producing a pattern of abnormalities
- Field Defects: pattern of anomalies resulting from disturbance of development of a single region/field
- Metacentric: centromere near center
- Submetacentric: centromere eccentrically placed
- Acrocentric: centromere near end
- Reciprocal Translocation: no genetic material lost
- Robertsonian translocation: fusion of long portions of two acrocentric chromosomes - small chromosome formed by two small portions is often lost
- Isochromosome: centromere divides in transverse plane, resulting in one chromosome with 2 p arms and one with 2 q arms
- Inversion: both break sites on same side (paracentric) or opposite sides (pericentric) of centromere
- Ring chromosome: loss of telomeres of p and q arm with fusion of resulting sticky ends
- Abnormalities of the sex chromosomes are more common and much better tolerated than autosomal abnormalities
- Lyonization: inactivation of all but one X (Mary Lyon, 1961).

GENERAL

- 13% newborns have 1 minor malformation, most in head, neck or hands
- 0.75% newborns have 2 minor malformations; 1/2000 have 3
- Causes of malformations: 8% single gene disorders; 6% chromosomal; 20% multifactorial; 5% environmental

Cytogenetic Disorders

Trisomy 21 (Down's Syndrome)
- Commonest chromosomal disorder (1/1000 newborns), commonest genetic cause of mental retardation
- Incidence increases with maternal age (1/1550 live births in mothers <20yrs, 1/25 in mothers >45 yrs)
- 95% are true trisomy; 4% are translocations (Robertsonian) of 21 to 14, 22, etc., 1% are mosaics
- Involves 21q22 band - this area includes the GART gene (purine biosynthesis)
- Clinical features: Mental retardation, flat facies, oblique palpebral fissures, congenital heart disease (40%), dysplastic ears, horizontal palmar creases
- Often see papillary muscle calcification and cystic dilatation of Hassall's corpuscles in the thymus
- Increased risk for Alzheimer's, infections, ALL
- Life expectancy: now ~30 yrs.

Trisomy 18 (Edward's' Syndrome)
- 1/3000-7000 live births
- 90% true trisomy, 10% mosaic
- Marked mental retardation, seizures, micrognathia, hypertonicity, flexion deformities of fingers, rocker-bottom feet, cardiac renal and intestinal defects, abnormal shaped head with low-set ears
- Usually die in first year of life

Trisomy 13 (Patau's Syndrome)
- 1/5000 live births
- 80% true trisomy, 10% translocation, 10% mosaic
- Marked mental retardation, microcephaly, arrhinencephaly, microphthalmia, retinal dysplasia, cleft lip, polydactyly, abnormal ears, cardiac dextroposition and defects, hyperconvex nails, club feet, flexed trigger thumbs, GI and GU abnormalities
- Usually die in first year of life

Chromosome 5p– (Cri du Chat Syndrome)
- Deletion of short arm of chromosome 5
- Most patients have a distinctive cry - sounds like a kitten
- Mental retardation, cardiac defects (VSD), microcephaly
- May survive to adulthood
- Adults develop myelodysplastic syndrome with picture similar to refractory anemia but which does not progress to AML

XO (Turner's Syndrome)
- XO in 57% (most common abnormal phenotype - only 3% of XO survive to birth), rest are partial deletions
- Primary cause of primary amenorrhea
- Short stature, streak (atrophied) ovaries, webbing of neck, peripheral lymphedema, coarctation of the aorta

XXX (Multi-X Syndrome)
- 1/1200 live female births
- XXX normal. Mental retardation increases with # of X's.

XXY (Klinefelter's Syndrome)
- 82% XXY; Occasionally XXXY, etc. or mosaics
- 1/850 live births - some increase with maternal age
- Most common cause of male infertility
- Hypogonadism, eunuchoid body habitus, gynecomastia, female distribution of hair. Mental retardation is seen increasingly with increasing numbers of X chromosomes

XYY Syndrome
- 1/1000 live male births
- Phenotypically normal
- May be excessively tall, have severe acne
- 1-2% show antisocial behavior

True Hermaphroditism
- Both testicular and ovarian tissue present, either separately or combined (ovatestis)
- Very rare; most are 46XX with translocation of part of the Y chromosome to one of the X's.

Pseudohermaphroditism
- By definition, a disagreement between gonadal (histology of gonad) and phenotypic sex
- Female pseudohermaphrodite: XX with normal internal genitalia but virilized external. Often due to increased androgenic steroids, usually from congenital adrenal hyperplasia
- Male pseudohermaphrodite: XY with testis, but external genitalia partially to completely female; most common cause is mutation of the androgen receptor (testicular feminization)
- Dihydrotestosterone directs development of male external genitalia; in absence -> female genitalia develops

Mendelian Disorders

Factors such as penetrance and variable expressivity often complicate strict dominant/recessive designations

Marfan's Syndrome
- Autosomal dominant, probably multiple genes involved, at least one localized to 15q21.1
- Some cases involve defect in fibrillin, an elastin binding scaffolding protein
- 70-85% are familial; in sporadic cases, risk increases with increasing paternal age
- Skeletal abnormalities: long extremities, lax joints, pectus excavatum or pigeon breast, kyphoscoliosis
- Ocular abnormalities: bilateral dislocation of lens (usually upward and outward); very rare except in Marfan's
- Cardiovascular abnormalities:
  - Cystic medionecrosis of the root of aorta causing dilatation and aortic incompetence. Rupture is cause of death in 40% patients with this disorder
  - Floppy mitral valve with regurgitation
- Average age at death 30-40 yrs

Neurofibromatosis Type I (von Recklinghausen's disease)
- AKA: Peripheral neurofibromatosis
- Autosomal dominant: gene on 17q11.2.; 100% penetrance
- 1/3000 live births; 50% of cases are spontaneous
- Multiple plexiform neurofibromas (superficial and deep); superficial lesions often with overlying hyperpigmentation; deep lesions become malignant in 3% of patients
- Cutaneous café au lait macules (>6), present in 90% patients
- Lisch nodules (pigmented iris hamartomas) in 95% of patients over 6 years
- Can also show erosive defects of bone and have a 2 fold increased risk of developing other tumors (e.g. Wilms', rhabdomyosarcoma, AML, unilateral acoustic neuromas, optic gliomas, meningiomas, pheochromocytomas)

Neurofibromatosis Type II (Acoustic form)
- AKA: Central neurofibromatosis
- Bilateral acoustic neuromas, café au lait spots, ± skin tumors; no Lisch nodules
- Autosomal dominant: gene on 22q11

Tuberous Sclerosis
- AKA: Bourneville's disease, Pringle's disease
- Adenoma sebaceum of face (actually are angiofibromas), seizures, and mental retardation
- Autosomal dominant with incomplete penetrance
- Also get numerous hamartomas: CNS-periventricular nodules ("tubers"), angiomyolipoma of kidney, subungual fibromas, cardiac rhabdomyomas, pulmonary lymphangioleiomyomatosis
- 30% fatal by age 5; 75% by age 20, usually from seizures

von Hippel-Lindau Syndrome
- Autosomal dominant: maps to 3p25
- Patients have a variety of benign and malignant neoplasms, including: hemangioblastoma of retina, cerebellum, medulla oblongata and spinal cord; angiomas of the liver or kidney; adenomas of the kidney and epididymis; renal cell carcinoma; pheochromocytoma; cysts of the pancreas, kidney, liver, and epididymis
- Over half die of hemangioblastomas of the CNS; renal cell carcinoma is another leading killer

Cystic Fibrosis (Mucoviscidosis)
- Autosomal recessive, variable penetrance; 1/20 whites are carriers; 1/2000 whites are affected
- Gene is on chromosome 7q32: encodes "CFTR" gene, a putative chloride transporter (1480 amino acids long)
- Most common (95%) mutation is deletion of amino acid Phe508, resulting in defective anion transport, particularly Cl^- and HCO_3^-, with subsequent abnormal water movement
- In sweat glands of skin, sweat ducts cannot take up Cl back from secretions: sweat high in NaCl
- In lungs, decreased Cl transport into lumen results in viscous secretions which plug airways. Infections by staph and pseudomonas common, often fatal (major cause of death)
- In pancreas, ducts do not secrete enough bicarbonate, resulting in viscous secretions, plugging of ducts, and eventually destruction of exocrine pancreas
- In liver, bile stasis leads to biliary cirrhosis in 5%
- Most affected males are sterile

Familial Hypercholesterolemia
- Normally, liver secretes VLDL which transports lipids to fat and muscle, being converted to IDL. IDL is then re-taken up by the liver, either before or after conversion to LDL in plasma and other sites, via the LDL receptor
- Patients have either reduced levels (heterozygous) or absent (homozygous) LDL receptor resulting in increased circulating LDL levels and increased cholesterol synthesis in the liver (less feedback inhibition)
  - Class I Absent receptors (macrophages pick up LDL by non-receptor mediated mechanism)
  - Class II Defective receptor binding
  - Class III Defective transport
  - Class IV Failure of receptor to aggregate in pits
- Brown and Goldstein won the Nobel Prize in 1985 for elucidating these pathways

Albinism
- Inability to synthesize melanin
- Two variants: oculocutaneous albinism (many types, all autosomal recessive) and ocular albinism (rare; limited to eye; usually X-linked recessive)
- Divided into tyrosinase positive and negative (more severe)

Fragile X Syndrome
- X-linked (Xq27.3) usually recessive, can occur in women
- Familial mental retardation, enlarged testes

Alkaptonuria (Ochronosis)
- Autosomal recessive
- Lack of homogentisic oxidase results in block of phenylalanine metabolism: buildup of homogentisic acid causes black discoloration of urine and cartilage of ears, nose, cheeks
- Accumulation in cartilage of joints results in a severe arthritis

Phenylketonuria (PKU)
- Autosomal recessive; characterized by lack of phenylalanine hydroxylase (PAH) leading to hyperphenylalaninemia and mental retardation
- PAH normally converts Phe to Tyr
- Metabolites of Phe can be found in the urine
- First clinical signs appear within 3-4 months: seizures, bizarre behavior
- Disease progression controlled by dietary restriction of Phe and supplementation of Tyr
- 3-10% cases have normal PAH activity but defects in other enzymes

Galactosemia
- Two forms, both autosomal recessive defects in galactose metabolism
- In one, absence of galactokinase, results only in cataracts
- Major form is lack of galactose-1-phosphate uridyl transferase, leading to accumulation of galactose in blood then in urine, with aminoaciduria
- 1/40-60,000
- Severe mental retardation results if galactose intake not restricted
- Histologically, also see fatty liver with bile stasis and eventually cirrhosis

Lysosomal Storage Diseases

Collection of disorders, usually autosomal recessive, resulting from deficiency of some enzyme needed for metabolism and leading to accumulation of secondary lysosomes in brain, heart, bones, liver, spleen

Commonly, infants are normal at birth (no products accumulated yet) and develop normally initially, but become symptomatic between 6 months and 2 yrs, depending on rate of accumulation

SPHINGOLIPIDOSES

Tay-Sachs Disease (G_{M2}-Gangliosidosis Type I)

Become symptomatic at 6 months - CNS deterioration; death by 2-3 yrs age

Most prominent among Ashkenazi Jews (1/30 are carriers)

Deficiency of hexosaminidase A (chromosome 15) resulting in accumulation of G_{M2}-ganglioside in neurons of CNS and retina (as well as liver, spleen, etc.).

Ballooning and loss of neurons with microglia proliferation

EM : whirled inclusions in lysosomes with onionskin layers

Retina shows cherry-red spot at macula

Fabry's Disease

AKA: angiokeratoma corporis diffusum universale

X-linked recessive

Skin lesions consist of slightly elevated red-blue nodules

Deficiency of lysosomal enzyme trihexosylceramide alpha-galactosidase, with systemic accumulation in blood vessel endothelial and smooth muscle cells, ganglion cells, reticuloendothelial, myocardial, and connective tissue

Gaucher's Disease

Lack glucocerebrosidase (chromosome 1q21) resulting in glucocerebroside accumulation in phagocytic cells throughout body (liver, spleen, bone marrow, lymph nodes, thymus, Peyer's patches, and neurons (types II and III)

Gaucher cells: enlarged, swollen (up to 100µm) cells with PAS positive 'crumpled tissue paper' inclusions

Three forms:

- Type I (classic): most common (80%); adult type (non-cerebral form); late onset
- Type II: infantile acute cerebral pattern; death at early age from CNS complications
- Type III: intermediate between I and II

Krabbe's Disease (Globoid Cell Leukodystrophy)

Deficiency of galactocerebroside B galactosidase

Early onset of symptoms (rigidity, instability) - fatal by 1 yr

Niemann-Pick Disease

Most common type (type A) shows lack of sphingomyelinase resulting in severe infantile onset neurologic involvement and death by 1-3 yrs of age

Sphingomyelin accumulates as foamy macrophages in liver, spleen, bone marrow

EM shows membranous cytoplasmic bodies resembling lamellated myelin (zebra bodies)

MUCOPOLYSACCHARIDOSES

Hurler's Disease (Type I MPS)

Lack of iduronidase

Normal development until 20months, then dementia begins

Usually fatal by 6-10 yrs, often due to involvement of cardiac valves resulting in stenosis or incompetence

EM shows zebra bodies (secondary lysosomes filled with lamellated inclusions)

Scheie's disease is a milder form

Hunter's Syndrome (Type II MPS)

X-linked recessive

Deficiency of L-iduronosulfate sulfatase, which circulates

Transplantation of normal fibroblasts subcutaneously has led to correction of the defect in some individuals

Sanfilippo Syndrome (Type III MPS)

Morquio Syndrome (Type IV MPS)

MUCOLIPIDOSES

Defect in transport of lysosomal enzymes into lysosomes

4 Types; Type II is also known as I-Cell disease

GLYCOGEN STORAGE DISEASES (GLYCOGENOSES)

Group of disorders of glycogen metabolism:

Types 0 and I result in hypoglycemia and accumulation

Types II - XI result in accumulation of glycogen in liver, spleen, heart, brain

Many of these disorders do not involve lysosomal enzymes, so glycogen storage diseases are often segregated from lysosomal storage diseases

von Gierke's Disease (Glycogenosis I)

Glucose-6-Phosphatase deficiency

Predominantly hepatic and renal accumulation

Pompe's Disease (Glycogenosis II)

alpha-L4-glucosidase (acid maltase) deficiency (a lysosomal enzyme)

Glycogen accumulates predominantly in skeletal and cardiac muscle, but also in other organs

Accumulation is in *membrane bound vacuoles* (lysosomes) unlike all other glycogenoses in which it is cytoplasmic

Progressive weakness, hypotonia, macroglossia, cardiomegaly

Death usually by age 2 from heart failure

McArdle's Syndrome (Glycogenosis V)

Muscle specific phosphorylase deficiency

Accumulation of glycogen in skeletal muscle only

Muscle cramps with exercise; persistent exercise can cause massive rhabdomyolysis

Debilitating, but usually not progressive

Multifactorial Inheritance

Usually multiple genes and environmental factors involved

2-7% risk of recurrence; (9% with two affected children)

20-40% concordance between identical twins

Ehlers-Danlos Syndromes

Heterogeneous group (10-12 types) of disorders of collagen synthesis and structure

Affects predominantly skin, ligaments, joints: hyperextensible and hypermobile; skin is stretchable but also fragile and vulnerable to trauma

Type I: Diaphragmatic hernia

Type IV: abnormalities of type III collagen, at least three distinct mutations/forms; spontaneous rupture of large blood vessels or intestines

Type VI: most common, autosomal recessive, reduced lysyl hydroxylase activity, affects only types I and III collagen; ocular fragility with corneal rupture and retinal detachment

Type VII: abnormal conversion of type I procollagen to collagen; two distinct mutations (autosomal recessive (enzyme) and autosomal dominant (structural gene))

Type IX: defect in copper metabolism, altering lysyl oxidase activity; X-linked recessive

Others

Beckwith-Wiedemann Syndrome

Macroglossia, omphalocele, characteristic ear creases, hemihypertrophy and/or visceromegaly; also see adrenal cytomegaly, pancreatic islet hyperplasia (often with associated clinical hypoglycemia), and renal medullary dysplasia

Cancer develops in 5%, usually Wilms' tumor

Association with 11p15 duplication, the site of the EGF-2 gene, a insulin-like growth factor. Receptors are present in large numbers in the tongue and adrenal cortex

Sturge-Weber Syndrome
- AKA: Encephalo-Trigeminal angiomatosis
- Variably described as autosomal dominant or recessive
- Must have at least two of:
  - Congenital port wine nevus of face (nevus flammeus) in distribution of trigeminal nerve
  - Leptomeningeal angiomatosis (may calcify)
  - Seizures
  - Mental Retardation
  - Hemiatrophy/hemiparesis (contralateral to facial nevus)
  - Eye or choroidal angiomas
- Abnormal development of vessels of head and neck; malformation occurs at 4-8 weeks gestation

Field Defects

Bilateral Renal Agenesis (Potter Syndrome)
- 1/3000-10,000; M:F=3:1
- Failure of development of early ureteric bud from mesonephric duct
- Usually sporadic, but somewhat higher than expected recurrence rate
- Absent kidney, renal artery, ureter; if bilateral, may have absent bladder
- Oligohydramnios: low set ears, limb deformities, club feet

Associations

VATER
- Frequently seen in stillborns, especially infants of diabetic mothers
- Vascular (75%): VSD, ASD, tetralogy of Fallot, PDA
- Vertebral (60%): hemivertebrae or absent pedicles
- Anus (60%): imperforate
- Tracheo-Esophageal fistula (60%)
- Renal (75%): hydronephrosis, agenesis, horseshoe kidney
- Radius (45%): hypoplastic radii and/or thumbs

Acquired Neonatal Syndromes

Respiratory Distress Syndrome
- AKA Hyaline membrane disease
- Most common in males, pre-term, appropriate for gestational age, maternal diabetes, cesarean delivery
- OK at birth, but within 30mins breathing becomes difficult, rate increases, oxygen requirement increases
- Due to deficiency of surfactant, the production of which by type II pneumocytes increases after 35wks and is stimulated by corticosteroids and thyroxin, inhibited by insulin
- Lungs are very solid with thickened septa, loss of lining cells, and formation of hyaline membranes if infant survives several hours
- Overall mortality is 20-30%

Complications:
- Bronchopulmonary Dysplasia (BPD): epithelial hyperplasia, squamous metaplasia, peribronchial and interstitial fibrosis due to mechanical ventilation and oxygen toxicity
- Patent Ductus Arteriosus (PDA): immaturity, hypoxia, acidosis delay closure; left to right shunt-> CHF
- Intraventricular hemorrhage (IVH): germinal matrix area has fragile vessels susceptible to increased cerebral blood flow accompanying hypoxia
- Necrotizing Enterocolitis (NEC): risk increases in RDS
- Retrolental Fibroplasia (RLF): destruction of the retina by oxygen toxicity

Erythroblastosis Fetalis
- Most common cause used to be due to Rh antigen (D antigen). Maternal antibodies (IgG) cross the placenta to react with the second Rh+ infant in an Rh- mother; in general, ABO incompatibility prevents sensitization of the mother by clearing Rh incompatible cells quickly
- Now that mothers are treated with anti-D Rh antibody to prevent sensitization, the most common cause is ABO incompatibility, seen almost exclusively in type O mothers. Even this is limited since A and B antigens are expressed only in low levels on fetal red cells.
- Infants develop hemolytic anemia, hyperbilirubinemia and jaundice, hypoxic damage to heart and liver, hypoalbuminemia, anasarca (hydrops fetalis)
- Kernicterus: deposition of unconjugated bilirubin in the basal ganglia, leads to significant dysfunction - pigment fades within 24hrs, even in formalin, so must cut brain immediately in suspected cases

Sudden Infant Death Syndrome (SIDS)
- AKA: Crib death, cot death
- Sudden unexpected death in otherwise healthy baby which remains unexplained even after a complete autopsy and examination of the death scene
- 0.5-2/1000 in US
- 90% occur before 6 months, most between 2 and 4 months
- Death usually occurs during sleep
- Factors associated with SIDS:
  - Maternal: <20yrs, unmarried, smoker, drug abuse, low socioeconomic status, short intergestational interval
  - Infant: premature, low birth weight, male, not first sibling, SIDS in a prior sibling, prone sleeping position, bottle feeding (vs breast feeding)
- May be multiple causes, may be related to sleep apnea
- 1-2% recurrence risk

Rubella Syndrome
- Occurs in mothers who become infected in first 16 wks
- Risks for malformations in the first, second, and third months are 50%, 20%, and 7%.
- Major triad: cataracts, heart disease, deafness
- Other defects include microphthalmia, microcephaly, mental retardation, hepatomegaly, splenomegaly

NEOPLASIA

Detection of Tumors
- 1,000,000 (10^6) cells weighs ~1mg; 1x1x1mm
- 10^9 cells weighs ~1 gm; 1x1x1 cm
- 10^{12} cells weighs ~1 kg; 10x10x10 cm - usually fatal

Metastatic Ability
- Attachment to matrix components (laminin, fibronectin) is important:
  - cells with increased numbers of laminin receptors have greater metastatic potential; some also secrete laminin which binds to own receptors and then to basement membrane
  - RGD containing peptides which block the fibronectin receptor on tumor cells can inhibit metastasis formation
- Tumor cells with higher levels of collagenase IV have increased metastatic potential
- Platelet coating of tumor cell aggregates in the bloodstream improves survivability and implantability

Karyotype Changes in Tumors

AML-M1	t(9:22)
AML-M2	t(8:21)
AML-M3	t(15:17)
CML (abl) Philadelphia chrom	t(9:22)(q34;q11)
ALL	t(9:22), t(1:19), t(4:11)
CLL	+12
Burkitt's (c-myc)	t(8;14)(q24;q32) [90%]
Follicular Small Cleaved (bcl-2)	t(14;18)(q32;q21)
Neuroblastoma	del 1p
Ewing's Sarcoma and PNET	t(11;22)(q24;q12)
Retinoblastoma	del 13q (band q14)
Meduloblastoma	del 17q
Small Cell Ca	del 3p
Renal Cell Ca	del 3p
Wilms' tumor	del 11p (band p13)
Colorectal Ca	del 17p, t(17;*)
Papillary cystadenoCa ovary	t(6;14)
Mesothelioma	del of 1p, 3p, or 22q
Meningioma	del 22
Leiomyoma	t(12;14); del 7
Leiomyosarcoma	del 1p
Liposarcoma (myxoid)	t(12;16)(q13;p11)
Liposarcoma (well diff)	ring chromosome 12
Fibrosarcoma (infantile)	+8, +11, +17, +20
Myxoid Chondrosarcoma	t(9;22)(q31;q12)
Synovial Sarcoma	t(X;18)(p11;q11)
Rhabdomyosarcoma (alveolar)	t(2;13)(q35;q14)
Rhabdomyosarcoma (embryonal)	+2q, +8, +20
Clear Cell Sarcoma	t(12;22)(q13;q12)
Desmoplastic small round cell tumor	t(11;22)(p13;q12)
Dermatofibrosarcoma Protuberans	ring chromosome 17

Predisposition to Cancer

Cancer Incidence
- Males: Prostate, Lung, Colorectal, Bladder, Lymphoma, Leukemia, Stomach, Pancreas
- Females: Breast, Colorectal, Lung, Endometrium, Lymphoma, Pancreas, Cervix, Leukemia
- Single most important environmental factor is smoking

Cancer Deaths
- Males: Lung, Colorectal, Prostate, Pancreas
- Females: Lung (recently passed breast), Breast, Colorectal, Ovary, Uterus, Pancreas
- Steady decrease in deaths from cervical, gastric, and hepatic carcinoma

Chemical Carcinogenesis

- Multi-step (≥2 stage) process: requires initiation & promotion
- Initiation is irreversible (permanent change in DNA of target cells) and rapid; results from exposure to a carcinogen; dose is cumulative over lifetime since irreversible
- Promotion is reversible, must follow initiation (cannot induce tumors by itself or before exposure to initiator), and probably also directly affect DNA
- Some carcinogens (complete) can both initiate and promote; others (incomplete) only initiate
- Chemical carcinogens can act either directly (eg alkylating or acylating agents: all are highly reactive electrophiles) or indirectly (procarcinogens: need to be modified, usually by P-450 mixed function monooxygenase)
- Ames Test: uses Salmonella typhimurium deficient in histidine synthesis; expose to potential carcinogen (usually with liver homogenate to activate if necessary) and grow on histidine free medium; count number of colonies which have acquired a mutation activating the histidine synthetase. This test relies on the fact that essentially all carcinogens are in fact mutagens
- There is not perfect correlation between in vitro mutagenicity and in vivo carcinogenicity. Many DNA insults can be repaired. Key mutations may involve the activation of proto-oncogenes
- Promoters: include phorbol esters, phenols, hormones, drugs; most widely used is TPA (12-O-tetradecanoyl phorbol-13-acetate); promoters are not electrophilic and do not damage DNA; TPA activates protein kinase C by acting as a diacylglycerol analog
- Promoter action seems to involve epigenetic alterations in expression of genetic information in cells

Carcinogenic Chemicals
- Alkylating Agents: (cyclophosphamide, Chlorambucil, busulfan; other anti-cancer drugs); activation independent; weak carcinogens; induce lymphoid neoplasms
- Polycyclic Aromatic Hydrocarbons: (benzo-a-pyrene, benzanthracene; produced by combustion of tobacco and from broiling or smoking animal fats); require activation to dihydrodiol epoxides; most potent carcinogens known; induce a wide variety of neoplasms
- Aromatic Amines and Azo Dyes: (food dyes); require activation in liver by P-450; hepatocellular carcinoma, bladder cancer (inactive form reactivated by glucuronidase in the bladder)
- Naturally occurring Carcinogens: aflatoxin B1 from Aspergillus flavus; potent hepatic carcinogen
- Nitrosamines: require activation
- Others: asbestos (bronchogenic carcinoma, mesothelioma, GI carcinoma); vinyl chloride (hemangiosarcoma of the liver); chromium and nickel (lung cancer); arsenic (skin cancer)

Radiation Carcinogenesis

Ultraviolet Radiation
- UVA (320-400nm); UVB (280-320nm); UVC (200-280nm)
- Causes SCC, basal cell Ca, melanoma in sun exposed areas
- Mechanism is due to formation of pyrimidine dimers in DNA
- Individuals with deficient excision repair pathways (e.g., Xeroderma Pigmentosum) have increased risk, as do other chromosome instability syndromes
- In mice, UV light also activates T-suppressor cells, permitting the emergence of highly antigenic tumors

Ionizing Radiation
- Electromagnetic radiation (x-rays, gamma rays) and particulate radiation (alpha, beta particles, neutrons) both cause cancer
- Dose, dose rate, radiation quality (linear energy transfer values), and host repair pathways all affect efficiency
- Leukemia is most common radiation induced malignancy (except for CLL, which never follows radiation)
- Thyroid Ca s/p radiation in children (~9%) is 2nd most common
- Others include breast, lung, salivary glands; more resistant are skin, bone, GI tract

Viral Oncogenesis

DNA VIRUSES
- Infection of a permissive cell results in full virus life cycle and cell death, so no transformation can occur
- Transformation occurs following integration in non-permissive cells in which expression of early genes is still possible (not damaged by integration)
- Mechanisms of oncogenesis are diverse
- T-antigens (3 in polyoma virus, two in SV-40); polyoma large T immortalizes cells in culture but does not confer malignant phenotype; subsequent action of middle T (binds to cellular src) results in malignancy

Human Papilloma Virus (HPV)
- 2,4,7: benign squamous papillomas of skin (warts)
- 6,11: anogenital and laryngeal papillomas; verrucous carcinoma (genital)
- 16,18,33: cervical and oral carcinoma
- 5,8,14: SCC of skin in patients with epidermodysplasia verruciformis (EV)

Epstein-Barr Virus (EBV)
- Associated with endemic form of Burkitt's lymphoma
- Binds C3 receptor on B-Cells
- Found in 100% of nasopharyngeal carcinoma

Hepatitis B Virus
- 200 fold increased risk of hepatocellular carcinoma

RNA VIRUSES
- All are retroviruses; have three groups of genes [gag (core proteins); env (envelope proteins); pol (reverse transcriptase)] flanked by two LTR's (long terminal repeats)

Acute Transforming Viruses
- All except rous sarcoma virus are deficient - need helper
- Contain a viral oncogene
- Rapid induction of tumors

Slow Transforming Viruses
- All are replication competent; contain no oncogenes
- Tumorigenicity requires integration near protooncogene
- Proto-oncogenes activated by increased expression or introduction of a mutation

Human T-Cell Leukemia Virus
- Only known human RNA Tumor virus
- Binds to CD4 on T-Cells
- Genome contains tat genes in addition to gag, env, pol
- tat genes (3) are tumorigenic; activate IL-2, IL-2R, etc.
- HTLV-I: associated with adult T-cell leukemia
- HTLV-II: implicated in Hairy cell leukemia

Oncogenes

- NOTE: Carcinogenesis is a multi-step process; no single oncogene will transform normal cells in culture; need combinations of two or more oncogenes

abl
- Chromosome 9q34
- Abelson murine leukemia virus
- CML: translocation of abl at 9q to 22q [Philadelphia Chromosome] forming a chimeric protein abl-bcr (breakpoint cluster region) with tyrosine kinase activity

bcl-1 (PRAD-1)
- Chromosome 11q13
- PRAD=parathyroid adenomatosis
- Protein has sequence similar to that of cyclins
- Intermediate (mantle zone) Lymphomas: translocation with Ig heavy chain region on 14q32

bcl-2
- Chromosome 18q21
- Outer mitochondrial membrane protein (25-26kD) which blocks programmed cell death when over-expressed
- Block of apoptosis occurs late in pathway since many causes of apoptosis can be blocked by bcl-2
- Follicular lymphomas (translocation with Ig region on 14q)

bcl-6
- Chromosome 3q27
- 706 amino acid protein, 90kD, 6 zinc fingers on C-terminus (DNA binding); localizes to nucleus
- Expressed in high levels in B-cells (mature); not present in pre-B or plasma cells
- Translocations show strong association with diffuse large cell lymphoma
- Appears to be involved in decision of B-cell to become memory cell, plasma cell, or undergo apoptosis

erb-A
- Chromosome 17
- Thyroid hormone receptor
- Associated with erythroleukemia

erb-B1
- Chromosome 7p11-12
- Avian erythroblastosis virus
- EGF receptor tyrosine kinase
- Squamous cell carcinoma (amplification)

erb-B2
- (see neu, below)

fes (fps)
- Chromosome 15q25-26
- Feline sarcoma virus
- Plasma membrane bound and cytoplasmic tyrosine kinase
- AML (translocation)

c-myc
- Chromosome 8q24
- Avian myelocytomatosis virus
- Nuclear protein which regulates transcription; can accelerate apoptosis as well as stimulate mitogenesis
- Burkitt's lymphoma (translocation of myc to Ig heavy chain gene at 14q32)
- Also rearranged in some glioblastomas

neu (erb-B2, Her-2)
- Chromosome 17q11-12; 185 kD phosphoprotein
- Resembles truncated EGF receptor; tyrosine kinase
- Appears to function in development and growth; increased expression makes cells more sensitive to growth factors
- Breast Cancer (amplification)

ras
- Chromosome 6q16-22
- Murine sarcoma virus
- Gene product is a 21kD, highly conserved GTP-binding protein with GTPase activity
- Activation of ras usually involves point mutation in the 12th, 61st, or 13th codon
- Most common mutation seen in human tumors; mutated in 10-15% of all human tumors, 90% pancreatic, 50% lung, 40% colonic adenocarcinoma; also in bladder carcinoma, leukemia, neuroblastoma
- H-ras (11p15) =Harvey
- K-ras (6p11-12; 12p12)=Kirsten
- N-ras (1p11-13)

src (pp60)
- src1: Chromosome 20q13; src 2: Chromosome 1p36
- Rous sarcoma virus
- Plasma membrane bound tyrosine kinase
- Interacts with vinculin; no known human tumor

Other Tyrosine Kinases
- fgr: (1p36) Gardner-Rasheed feline sarcoma
- fms: (5q34) feline sarcoma virus; macrophage colony stimulating factor-1 receptor analog; no human tumor
- mos: (8q11-22) Moloney murine sarcoma virus; serine/threonine kinase; cytoplasmic distribution
- raf: (3p25) serine/threonine kinase
- ret: Medullary and papillary carcinomas of the thyroid
- ros: Avian sarcoma virus; related to growth factor receptors
- yes: (18q21) Avian sarcoma virus; no human tumor

Other Nuclear Proteins
- ets: (21q22) supplements action of myb
- fos: murine osteosarcoma virus; nuclear transcription factor
- jun: AP-1 transcription factor
- myb: (6q22-24) Colon carcinoma (amplification)
- L-myc: (1p32) Small cell ca of lung (amplification)
- N-myc: (2p23-24) Neuroblastoma (amplification)
- rel: reticuloendotheliosis
- ski: (1q22-24) carcinomas

Others (Miscellaneous)
- erb-A: (17q11-12) thyroid hormone receptor; supplements action of erb-B
- int-2: (11q13) mouse mammary tumor virus; FGF like
- met: (7q22) Osteosarcoma
- sis: (22q13) Simian sarcoma virus; PDGF like, cytoplasm

Tumor Suppressor Genes (Anti-Oncogenes)

Rb (Retinoblastoma) Gene
- Chromosome 13q14
- Gene spans 150kb, transcribes as a 4.7 kb mRNA which encodes the 105 kD "RB protein" (a nuclear DNA binding protein)
- Prototype for Knudson's two hit model
- Patients with autosomal dominant hereditary disease carry one mutation in their genome (first hit)
- Mutations result in an increased frequency of retinoblastoma and also childhood osteosarcoma

p53
- Chromosome 17p13.1; 393 amino acids
- Negative regulator of cell cycle
- Normally present in low levels and with short half life
- Loss of function mutants have an increased half life; levels accumulate to 5-100x normal
- Some p53 mutants actually stimulate cell division and can act in a dominant fashion
- Mutations in region from amino acid 130-290
- Hot spots for mutations: 175, 248, 273
- Mutations seen in cancers of colon, breast, lung, and in leukemias, sarcomas
- Progression of follicular lymphoma to diffuse large cell lymphoma may be accompanied by p53 mutation

WT-1
- Chromosome 11p13
- 50kb gene; 52-54 kD nuclear protein; interacts with p53
- In embryo, expressed in kidney, mesothelium, gonadal ridge, spleen, CNS
- In adults: kidney, ovary, testis, uterus
- Binds same DNA sequence which is bound by a variety of growth factor receptors
- Translocations seen in Wilms tumor and in desmoplastic small round cell tumor

EWS
- Putative tumor suppressor gene
- Chromosome 22q12
- 40kb gene, 17 exons; 61kD protein
- Expressed ubiquitously in all tissues
- Translocations seen in: Ewing's sarcoma/PNET, soft tissue clear cell sarcoma, desmoplastic small round cell tumors, myxoid liposarcoma, AML

brca-1
- Chromosome 17q21
- Mutations in this gene seen in 5% of all breast cancers, but in 40% of breast cancers of patients from families with two or more individuals with breast cancer
- Large gene; different mutations seen in different patients
- The product of the altered gene is absent, supporting a role as a tumor suppressor

Others
- APC: (5q21) Familial adenomatous polyposis coli; carcinomas of colon, stomach, pancreas
- DCC: (18q21) Carcinomas of colon, stomach
- NF1: (17q11) Schwannomas, neurogenic sarcomas
- NF2: (22q12) Schwannomas (central), meningiomas

Paraneoplastic Syndromes

Symptom complexes in cancer-bearing patients not readily explainable by the local or distant effects of the tumor itself
- Hypercalcemia: most common paraneoplastic syndrome; can result from destruction of bone by tumor or by secretion of PTH like substances by the tumor: SCC (lung, cervix, ovary), clear cell carcinoma (ovary, kidney), dysgerminoma
- Cushing's Syndrome: lung (small cell), pancreatic, neural, thymic carcinoid; ectopic production of ACTH-like substance
- Syndrome of Inappropriate ADH: small cell carcinoma (lung), intracranial tumors
- Migratory Thrombophlebitis (Trousseau's): pancreas, lung
- Carcinoid syndrome
- Neuromyopathic syndromes (myasthenia gravis, cerebellar degeneration): lung, breast carcinoma, thymoma
- Acanthosis nigricans (gray-black patches of verrucous hyperkeratotic skin): stomach, lung, uterus
- Dermatomyositis: lung, breast
- Hypertrophic Osteoarthropathy (finger clubbing): lung
- Polycythemia: Hepatocellular carcinoma, cerebellar hemangioma
- Anemia: thymus

Tumor Antigens

No unequivocal human tumor specific antigens

However, there is evidence that immune defenses play a role in combating neoplasms:
- Immunodeficient individuals have 200 fold increase incidence of tumors (5% of congenital immunodeficients)
- In experimental animals, tumor resistance can be achieved by immunizing with killed tumor cells
- T-Cell sensitization occurs in melanomas, neuroblastomas, Burkitt's lymphoma, leukemia, osteosarcoma
- Treatment of patients with IL-2 (or IL-2 treatment of lymphocytes isolated from excised tumor) which induces proliferation of stimulated T-Cells can lead to partial or complete regression of metastases in patients with renal cell carcinoma or melanoma

HEAD AND NECK

Embryology

Head and neck structures develop largely from the branchial arches (numbered cranial to caudally)
Four branchial arches are well developed and visible on the external surface of the embryo by the 4th week, the 5th and 6th are small and internal
Branchial arches are separated by clefts called branchial grooves on the external surface and pharyngeal pouches on the internal surface; all branchial grooves but the 1st are obliterated
Each arch consists of mesodermally derived mesenchyme covered externally by ectoderm and internally by endoderm
Ectodermally derived neural crest cells migrate into the mesenchyme, proliferate, and give rise to many mesenchymal structures (bone, muscle, cartilage) in the head and neck
Each branchial arch is supplied by the appropriately numbered aortic arch and has an associated cranial nerve (5,7,9,10, respectively)

Branchial Arches
1: (Mandibular Arch) Splits into two prominences:
Smaller (maxillary) forms maxilla, zygomatic bone, part of temporal bone
Larger (mandibular) forms mandible
Cartilage of first arch (Meckel's) forms malleus and incus
2: (Hyoid Arch) overgrows 3rd and 4th to form cervical sinus; also forms part of hyoid bone, muscles of facial expression
Cartilage of second arch (Reichert's) forms stapes, styloid
3: Part of hyoid bone, stylopharyngeus muscle
4 + 6: Laryngeal cartilage, cricothyroid & pharyngeal muscles

Pharyngeal Pouches
1: Together with 1st branchial groove, forms external meatus, middle, and inner ear structures, Eustachian tube
2: Palatine tonsils
3: Inferior parathyroids and thymus (descend to below the 4th pouch structures)
4: Superior parathyroids
5: [Rudimentary]

Dental Lamina
Primitive epithelium overlying free margins of jaws; origin of primary and permanent teeth; epithelial rests are responsible for odontogenic cysts and tumors

Anomalies of the Branchial Structures

Branchial Sinus (Lateral Cervical Sinus)
Failure of obliteration of the second branchial groove
Usually a blind pit
If extents into pharynx, forms a "branchial fistula"

Branchial Cyst
Remnants of cervical sinus or second branchial groove
Often not symptomatic until early adulthood when enlarges owing to accumulation of fluid and cellular debris

First Arch Syndrome
Treacher Collins syndrome: autosomal dominant; malar hypoplasia, defects of lower eyelid, deformed external ear
Pierre-Robin syndrome: mandibular hypoplasia, cleft palate, eye and ear defects

Congenital Thymic Aplasia (DiGeorge Syndrome)
Failure of differentiation of the 3rd and 4th pouches
No thymus and no parathyroids

EAR

Inflammatory

External Ear

Keratinous Cysts
Some related to branchial cleft
Lined by keratinized squamous epithelium
Periauricular cysts may be of pilar type

Cauliflower Ear
Acquired deformity of auricle secondary to cartilage degeneration induced by trauma
Seen in boxers and wrestlers

Chondrodermatitis Nodularis Chronica Helicis
AKA: Winkler's disease
Small painful nodular lesion of the helix (usually upper) occurring in the elderly with a raised center containing a crust or scale; may be confused with basal cell carcinoma or actinic keratosis
Epithelial hyperplasia with inflammation of the underlying collagen and/or cartilage degeneration
No premalignant connotation; treat with simple excision

Relapsing Polychondritis
Episodic acute inflammatory destruction of the cartilage of the helix (not the tragus)
Can also involve nose, ribs, trachea (latter may be fatal)
May be autoimmune, mediated by antibody to type II collagen
Many cases associated with polymyalgia rheumatica

Malignant External Otitis
Necrotizing inflammation of external canal, often involving bone, caused by Pseudomonas
Occurs in diabetics and immunocompromised patients
If not aggressively debrided, will often lead to meningitis, brain abscess, osteomyelitis of base of skull, and death

Gout
Deposits of sodium urate crystals (tophus) in helix and anti-helix which can ulcerate
Urate will dissolve in water - not present in histologic sections

Middle Ear

Otitis Media
Acute form caused by Strep pneumonia or H. influenza; bulging hyperemic tympanic membrane
Chronic form: persistent drainage, tympanic membrane perforation, polypoid granulation tissue

Cholesteatoma
Tumor-like lesion of middle ear or mastoid area, grossly resembling a pearl; usually presents in 20's to 30's
Epidermal cystic structure filled with desquamated keratin debris and cholesterol crystals
Probably arises from ingrowth of squamous epithelium into middle ear following chronic otitis media with drum perforation; congenital form arises from squamous rests

Inner Ear

Otosclerosis
- Autosomal dominant, variably penetrant, most common cause of conductive hearing loss in young adults
- Bone deposition around stapes causing fixation to oval window

Neoplastic

External Ear

- All tumors of skin and skin appendages can occur here

Middle Ear

Choristoma
- Salivary Gland or Glial tissue

Paraganglioma (Chemodectoma)
- Glomus jugulare or glomus tympanicum
- Most common neoplasm of middle ear after squamous cell Ca

Middle Ear Adenoma
- Gray-white, firm lesion producing conductive hearing loss
- Solid, glandular, or trabecular growth pattern with cuboidal or cylindrical cells
- Benign, but may be locally aggressive with bone destruction

Meningioma
- 6% of all meningiomas arise from arachnoid villi of the petrous bone and may invade middle ear

Inner Ear

Acoustic Neuroma
- Benign tumor of Schwann cells of VIIIth cranial nerve
- Usually internal auditory canal and cerebellopontine angle regions

ORAL CAVITY

ODONTOGENESIS
- Epithelial buds on alveolar ridge grow down into primitive stroma
- The mandible grows around the developing teeth
- An invagination forms and deepens:
  - Epithelium: ameloblasts (form enamel of tooth)
  - Stroma: odontoblasts (form dentin of tooth)

Inflammatory/Non-Neoplastic

Non-specific Inflammatory Lesions

Gingivitis/Periodontitis
- Inflammation of soft tissue around teeth or surrounding alveolar bone, respectively
- Acute gingivitis can become necrotizing ("trench mouth"), particularly in setting of poor oral hygiene, smoking, stress

Aphthous Ulcers (Canker Sores)
- Single or multiple shallow fibrin coated ulcers with mononuclear underlying infiltrate
- Etiology unknown
- Painful

Pyogenic Granuloma (Lobular Capillary Hemangioma)
- Inflammatory "tumor" composed of granulation tissue
- Most commonly maxillary labial gingiva

Palatal Papillomatosis (Inflammatory Papillary Hyperplasia)
- Multiple foci of epithelial hyperplasia and pseudoepitheliomatous hyperplasia usually associated with poorly-fitting dentures
- Not a premalignant condition

Peripheral Giant Cell Tumor (epulis)
- Unusual inflammatory reaction (not neoplastic) characteristically protruding from the gingiva close to teeth
- Predilection for females
- Intact or ulcerated overlying mucosa
- Numerous multinucleated osteoclast-like foreign body giant cells with scant fibroangiomatous stroma
- Well delimited and easily excised

Specific Inflammatory Lesions

Oral Candidiasis
- AKA: Thrush, moniliasis
- Proliferates during extensive antibiotic therapy, immunosuppression, severe debilitation

Herpetic Stomatitis
- More commonly HSV-I
- Lesions can vary from isolated cold sore to blistering lesions over much of the oral mucosa
- Initially intra- and intercellular edema, ballooning degeneration, acantholysis, intraepidermal vesicle
- Intranuclear inclusions identifiable

Odontogenic Cysts

- Occur around teeth and are derived from remnants of the dental lamina epithelium
- Cysts are lined by hyperplastic squamous to thin squamous or cuboidal epithelium; often histologically similar to epidermal inclusion cysts; named most commonly by location (except Odontogenic Keratocyst)
- • Odontogenic Keratocyst: squamous lined cyst with parakeratosis and palisading basal cells; usually posterior, usually multilocular; can be aggressive or destructive; high recurrence rate; [NOTE: this histology overrides EIC-like cyst of any location because of its aggressiveness]
- • Radicular (Periapical) Cyst: most common, usually maxillary molars; occur at apex of tooth root due to severe pulp inflammation/death from infection or trauma
- • Dentigerous Cyst: surrounds the crown of an unerupted permanent tooth; can be destructive or deforming
- • Eruption cyst: forms over the site of a future tooth eruption; can prevent tooth from coming in
- • Primordial cyst: develops where a tooth never was
- • Paradental Cyst: laterally associated with the crown; essentially exclusively mandibular
- • Lateral Periodontal Cyst: develops in alveolar bone between teeth

- Calcifying Odontogenic Cyst (Gorlin cyst): painless enlargement of the mandible; may be a tumor, or may just be frequently associated with odontogenic tumors
- Gingival Cyst: whitish nodules in the gingiva of infants; looks most like an epidermal inclusion cyst

Fissural Cysts

Occur at junction points of developing structures, presumably arising from entrapped epithelial tissue
Lined by stratified squamous epithelium or pseudostratified columnar epithelium
- Nasopalatine Cyst: most common; usually 30's-50's; occurs in bone or soft tissues
- Median Palatine Cyst: occurs in posterior midline of palate
- Nasoalveolar Cyst (nasolabial): most commonly soft tissues of upper lip, lateral to midline
- Globulomaxillary Cyst: occur in bone at site where globar process and maxillary process fuse

Leukoplakia

Clinical term: "white plaque" - premalignant lesion
Sharply demarcated; can occur anywhere in oral mucosa
May be orderly mucosal thickening with epidermal hyperplasia and hyperkeratosis or disorderly hyperplasia with varying degrees of dysplasia up to carcinoma in situ
Erythroplasia (red plaque) more likely to be dysplastic

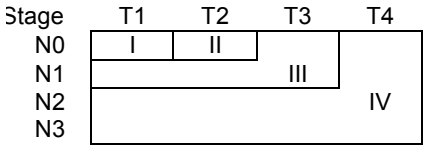
Neoplastic

Squamous Cell Carcinoma

<5% of all malignancies
>90% of all oral malignancies
More common in men
Sites include gingiva, buccal mucosa, floor or mouth, tongue, lip, palate
May have papillary, basaloid, small cell, or spindle cell (pseudosarcomatous) morphology

STAGING

T1	≤2 cm	N1	Single ipsilateral LN ≤3 cm
T2	2-4 cm	N2	Ipsilateral LN 3-6 cm or mult. LNs
T3	>4 cm	N3	LN>6 cm diameter
T4	Invades adjacent structures		



Odontogenic Tumors

EPITHELIAL

Ameloblastoma (Adamantinoma)
Most common odontogenic tumor with aggressive potential
Most commonly posterior mandible (80%) in middle 30's
May be associated with dentigerous cyst or impacted (20%) tooth
Almost always at least partially cystic, usually multilocular
Numerous histologic patterns: follicular (most common), acanthomatous, plexiform, unicystic, granular cell, desmoplastic, vascular, basal cell (least common); mixed pattern often seen
Outer-most cell layer of tall, columnar, palisading cells with reversed polarity (apically situated nuclei); inner layers of cells form variety of patterns often with "stellate reticulum cells"
Slow growing; curettage almost always results in recurrence, although may take 10-20 yrs; complete excision recommended
Radiation is contraindicated since it too frequently induces malignant transformation
When malignant cytologic features present, often referred to as Ameloblastic carcinoma

Adenomatoid Odontogenic Tumor (Adenoameloblastoma)
Anterior maxilla, usually in teens (mean=18 yrs); M:F=1:2
Slow growing, painless, well defined (often encapsulated) proliferation of pre-ameloblasts forming rosettes and duct-like tubules
Benign; conservative surgery usually curative

Calcifying Epithelial Odontogenic Tumor (Pindborg's tumor)
Most commonly mandible, usually 30-40 yrs old
Sheets of eosinophilic squamoid cells with nuclear pleomorphism and small cystic areas with amyloid-like material which often calcifies forming psammoma bodies (Liesegang rings)
Generally less aggressive than ameloblastoma

Squamous Odontogenic Tumor
Rare
Anastomosing nests and islands of mature stratified squamous epithelium in bland stroma

MESENCHYMAL

Odontogenic Fibroma
Children and young adults, usually mandible
Simple: fibrous connective tissue with plump fibroblasts and nests/strands of odontogenic epithelium
WHO type: very cellular fibrous connective tissue

Odontogenic Myxoma
20-30 yrs old, usually posterior mandible
Slow growing, expansile, can destroy bone
Honeycomb or multilocular, with delicate myxoid stroma containing scattered odontogenic epithelial rests (looks like immature dental pulp)

Cementoma
Includes true cementoma (cementoblastoma), periapical fibrous dysplasia, gigantiform cementoma, and central cementifying fibroma

MIXED

Odontoma
Usually maxilla; mean age 15yrs; usually asymptomatic
Multiple benign tumors (complex, compound, ameloblastic) which include "completely differentiated" components including calcification
Arises from enamel organ

Ameloblastic Fibroma
Posterior mandible; M≥F; mean age 15 yrs
Islands of odontogenic epithelium with typical reverse polarity in loose fibrous connective stroma which is often myxoid

Ameloblastic Fibrosarcoma
Similar to ameloblastic fibroma but with a malignant stromal component; epithelial component remains benign
Usually mandible; mean age 30 yrs

NASOPHARYNX and SINONASAL CAVITIES

Developmental

Nasal Glial Heterotopia
- AKA: Nasal glioma (misnomer - not a tumor)
- Firm, solid, polypoid mass composed of neuroglial tissue unconnected to the intracranial contents
- Usually present at birth; 1/3 are intranasal, 2/3 are extranasal
- No malignant potential

Nasal Encephalocele
- Herniation of brain through a bony defect in the skull

Nasal Dermoid
- "Teratomatous" cysts lined by squamous epithelium
- Occurs in midline

Inflammatory

Rhinitis
- Acute rhinitis almost always viral
- Chronic forms: allergic, non-allergic eosinophilic, vasomotor

Mucocele/Mucopyocele

Inflammatory (Allergic) polyps
- Unusual before age 20; if occurs in children, most likely indicates cystic fibrosis
- Loose edematous stroma with neutrophils, eosinophils, plasma cells, lymphocytes; can become quite large; may erode bone
- Stroma frequently contains isolated bizarre cells

Wegener's Granulomatosis
- Can produce a necrotizing sinusitis
- Necrotizing vasculitis with secondary granulomatous inflammation and epithelial ulceration
- Giant cells are also found unassociated with granulomas

Sarcoidosis

Neoplastic

Sinonasal Papilloma
- Benign but locally aggressive neoplasm occurring in nose and paranasal sinuses, usually of older (40-70 yrs) men
- Present with epistaxis or mass
- Proliferating squamous or columnar epithelium intermixed with mucin containing cells; mild to moderate atypia
- Recur if incompletely excised

Fungiform (Transitional-Cell) Type [50%]
- Exophytic lesions arise from septum
- Usually occurs in slightly younger age group
- HPV types 6 and 11 present in high proportion of cases
- Rarely become malignant

Inverted (Endophytic) Type [47%]
- Arise from middle meatus on lateral surface
- Also associated with HPV
- ~13% will progress to malignancy

Cylindrical Cell (Oncocytic Schneiderian) Type [3%]
- Do not appear to be associated with HPV
- Sharply defined cell borders, oncocytic cytoplasm, cilia on surface, mucin droplets, and intraepithelial spaces with inflammatory cells
- May destroy bone via pressure atrophy
- ~10% become malignant; does not metastasize

Nasopharyngeal Carcinoma
- Bimodal incidence with peaks at 20 and 65 yrs of age; M>F
- EBV implicated in pathogenesis of type III and some type II
- May be very difficult to detect grossly (most common presentation is unilateral LN metastasis) but may form an ulcerating, fungating growth
- Insidiously malignant lesions
- Vesicular nuclei with single large eosinophilic nucleolus
- Keratin positive, often EMA positive, may be CEA positive

Keratinizing (Epidermoid; Type I) [25%]
- Clear-cut keratinization
- Older age group; no association with EBV; less common
- 5yr survival 20%; NOT radiosensitive

Non-keratinizing (Type II) [10-15%]
- Polygonal cells with well defined cell margins; resembles transitional cell carcinoma
- 5 yr survival 35%; variable responsive to radiotherapy

Undifferentiated (Lymphoepithelioma; Type III) [60-65%]
- Common in southern Chinese males (Kwantung Province)
- Strongest correlation with EBV: PCR can demonstrate the viral genome in the tumor cells
- Abundant BENIGN lymphocytic infiltrate in stroma
- Indistinct cell borders
- Two patterns:
  - Reyaud's: well defined epithelial nests surrounded by fibrous tissue and lymphoid cells
  - Schmincke: epithelial & lymphoid cells diffusely intermingle
- 5 yr survival 60%; tumor is usually radiosensitive
- HLA-B17 associated with a poor prognosis

Sinonasal Carcinoma
- Rather rare, with a surprising left sided predominance
- Often detected late when has already destroyed bone
- Most are squamous cell type, but other types include transitional (cylindric), verrucous, adenocarcinoma, and undifferentiated carcinoma

Esthesioneuroblastoma
- AKA: olfactory neuroblastoma
- Median age 50, but wide range (3-79)
- Reddish gray, highly vascular polypoid mass
- Small round cells of neural crest origin, with round nuclei and indistinct cell borders , with or without Homer-Wright rosettes; may also have larger cells growing in solid nests
- Cytologic features not predictive of clinical behavior
- Highly malignant
- Translocation of 11 to 22 seen commonly (same as Ewing's)
- Very sensitive to radiation

Angiofibroma
- Present with nasal obstruction and epistaxis
- Almost exclusively in adolescent males; androgen dependent
- Non-encapsulated intricate mixture of blood vessels (with thin walls, no elastic laminae, minimal if any smooth muscle) and fibrous stroma (dense to edematous, often with stellate plump nuclei, can have giant cells)
- EM shows tight RNA-protein complexes forming dense round granules in the nuclei of fibroblasts
- Benign, but may bleed extensively during surgery

Polymorphic Reticulosis

Variant of Peripheral T-Cell lymphoma
Clinical Term: "Lethal midline granulomas", a syndrome with ulcerating mucosal lesions of the upper respiratory tract, unresponsive to antibiotic therapy
Extensive tissue necrosis, cartilage destruction, vascular thrombosis, large atypical cells in lymphoid aggregates, many of which mark as T-cells
Frequently lethal due to bacterial infection or hemorrhage

Others

Isolated "Extramedullary" Plasmacytoma
Often polypoid growths into nasal sinuses or nose
Overlying mucosa usually intact
Very radiosensitive (XRT often chosen over surgery)
Small Cell Carcinoma
Malignant Melanoma
Lobular Capillary Hemangioma
Hemangiopericytoma
~10% of all hemangiopericytomas occur in the sinuses
Solitary Fibrous Tumor of the Nasopharynx
Fibrous Histiocytoma
Embryonal Rhabdomyosarcoma
Giant Cell Tumor
Aneurysmal Bone Cyst
Meningioma
Usually transitional cell or menigothelial pattern
Myxoma

LARYNX

Non-Neoplastic Lesions

Acute Epiglottitis
Due to infection of Hemophilus influenza type B
Cherry red, markedly edematous epiglottis - can cause complete airway obstruction
Non-specific "Granulomas"
Usually unilateral vocal cord lesions composed of cellular granulation tissue, often with overlying ulceration
True granulomas are not seen
Believed to be caused by trauma
Contact Ulcers of Larynx
Pyogenic granuloma-like lesions occurring on the posterior aspect of the vocal cords with overlying epithelial ulceration or hyperplasia
Present with hoarseness, dysphagia, pain, sore throat
Caused by vocal cord abuse: shouting, intubation, gastric regurgitation, persistent coughing
Laryngeal Nodule
AKA: Singer's nodule, amyloid tumor, "Vocal Cord Polyp"
Non-inflammatory reaction of vocal cord to injury
Usually at junction of anterior 1/3 and posterior 2/3 of cord
Stromal edema with fibroblast proliferation, then dilated vessels and stromal hyalinization
Occasionally the term "polyp" is used to refer to a single lesion and "nodules" when bilateral
Telangiectatic, Fibrous, Hyaline, and Edematous-myxoid types

Papillomas

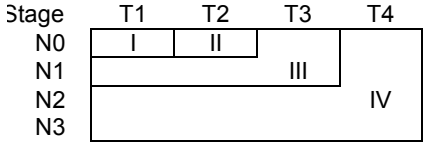
Juvenile Laryngeal Papilloma
Multiple tumors on true cords which may spread to the false cords, epiglottis, even tracheobronchial tree - often recur
Related to HPV-6 and 11
Papillary or acanthotic growth of well differentiated squamous cells with mild atypia and some mitoses overlying fibrovascular core
Repeated treatment may lead to destruction of the cords
Adult Laryngeal Papilloma
Male predominance; usually solitary
More inflammation
Dysplasia more significant; probably precursor to carcinoma
Does not spread or recur
Verruca vulgaris

Laryngeal Carcinoma

2.2% of all cancers in men, 0.4% in women; 96% are male
Most patients in 40's or older; mean age 55 yrs
Epidemiologically linked to tobacco and/or alcohol use
Histologically, >95% are squamous cell carcinomas which are either well, moderately, or poorly differentiated
Glottic (60-65%)
Arise from true vocal cords, almost always anterior 1/3
Remain localized for long period because surrounded by cartilage; few lymphatics
LN metastases unheard of for T1 lesions, rare even in T2 lesions
May be effectively treated with radiation
Supraglottic (30-35%)
False cord, epiglottis, arytenoid, aryepiglottic fold
Very rarely invades downward to the glottis; amenable to horizontal supraglottic partial laryngectomy
LN metastases in about 40%; 20-35% of clinically negative nodes will be positive
Transglottic (<5%)
Tumor involves laryngeal ventricle
Highest incidence of LN involvement (52%)
Subglottic (<5%)
Exclusively subglottic (rare) or true cord lesion extending more than 1 cm sub-glottically
Most aggressive site: cervical LN metastases in 15-20%, paratracheal nodes positive in 50%
Frequent extension to trachea and esophagus

STAGING

T1	Confined to site of origin; normal cord mobility
T2	Involves adjacent site; normal cord mobility
T3	Confined to larynx with cord fixation
T4	Extension beyond larynx
N1	Single ipsilateral LN ≤3 cm
N2	Single ipsilateral LN 3-6 cm or multiple LNs
N3	LN>6 cm diameter



Prognosis

5 yr survivals:	I	II	III	IV
Glottic	90%	85%	60%	20%
Supraglottic	85%	75%	40%	15%
Transglottic		50%		
Subglottic		40%		

Special Histologic Types

- Verrucous: 1-3%, most are glottic, pushing margin, better prognosis
- Basaloid: most commonly supraglottic; very aggressive with poor prognosis
- Spindle Cell (sarcomatoid): most commonly glottic; polypoid mass; stromal component may be truly malignant; epithelial component most commonly metastasizes
- Transitional
- Small Cell

Other Laryngeal Tumors

- Salivary Gland-Like Tumors
- Paraganglioma
- Chondrosarcoma
- Rhabdomyoma
- Synovial Sarcoma
- Lymphoma
- Granular Cell Tumor

SALIVARY GLANDS

Normal Anatomy

Major Salivary Glands:
- Parotid: largest, main duct (Stensen's) enters oral cavity opposite 2nd maxillary molar
- Submaxillary: 1/4 size of parotid, main duct (Whartan's) empties into floor of mouth
- Sublingual: 1/12 size of parotid; empties into floor of mouth

Minor Salivary Glands: oropharynx, gingiva, floor of mouth, cheek, hard and soft palates, tonsillar areas, tongue

Terminal portion (intercalated ducts and acini = ducto-acinar unit), especially reserve cells of intercalated ducts, probable source of most neoplasms

Xerostomia: dry mouth due to decreased salivary flow

Abnormal Location / Growth

Heterotopia: within lymph nodes in and near parotid, neck (often associated with cysts or sinuses)

Choristoma: nodule (usually gingival) of disorganized seromucinous salivary tissue plus sebaceous glands

Adenomatoid hyperplasia: localized nodule of hyperplastic glands, usually in hard palate

Inflammatory and Related Disorders

Sialolithiasis

Calculi can form in major ducts, sometimes multicentric

Most common in submaxillary gland (higher calcium content, largest duct)

Initially swelling and distention of ducts, then acini

Eventually, destruction of acini, chronic inflammation, induration

Chronic Sialadenitis

May be caused by obstruction of small ducts

In older females, related to rheumatoid arthritis; ?autoimmune

Granulomatous sialadenitis can result from TB, fungus, sarcoidosis, or secondary to duct obstruction/rupture

Necrotizing Sialometaplasia

Self-limited benign inflammation; lobular necrosis; central acini undergo squamous metaplasia

Most common in palate

Cysts

Benign lymphoepithelial cysts: epithelial lined with prominent lymphoid infiltrate in walls with germinal centers

Most common sites: lower lip, cheeks, tip of tongue

May be acquired (e.g. HIV), retention, or developmental

Also seen with Warthin's tumor, mucoepidermoid carcinoma, benign mixed tumor, sebaceous lymphadenoma

Mikulicz's Disease (Benign lymphoepithelial lesion)

Most common cause of Mikulicz's syndrome, the diffuse, enlargement of bilateral salivary and lacrimal glands

One manifestation of Sjögren's syndrome (also keratoconjunctivitis, rheumatoid arthritis, hypergammaglobulinemia, xerostomia)
- Lymphoid infiltration (often with germinal centers - mixed B and T-cell)
- Epimyoepithelial islands: collapsed acini with basal epithelial cells, modified myoepithelial cells, hyaline material (basement membrane), and lymphocytes

May progress to lymphoma, usually large cell, B-cell immunoblastic. Also small cleaved cell lymphomas

Others:

Keratinous cysts, amyloidosis, nodular fasciitis, cystic fibrosis

SALIVARY GLANDS - NEOPLASMS

GENERAL

Tumors 12x more common in the parotid than submaxillary

Only ~20% parotid tumors are malignant, vs ~40% for submaxillary gland and ~45% for palate - sublingual gland has highest incidence of malignancy

Tumors of submaxillary gland have worse prognosis than the same tumor in the parotid

Pain, facial nerve paralysis, rapid growth suggest malignancy

Benign or low-grade malignancy of superficial parotid can be treated with superficial parotidectomy, sparing facial nerve

Recurrence following excision - short survival

Radiation post-operatively may decrease local recurrence

STAGING

T1	≤2 cm	N0	None
T2	2-4 cm	N1	Single ipsilateral LN ≤3 cm
T3	4-6 cm	N2	Single LN 3-6 cm or multiple LNs
T4	a. >6 cm	N3	Any LN>6 cm
	b. Any size with local extension		

Stage	T1a, T2a	T1b, T2b	T3a	T3b	T4a	T4b
N0	I	II	II	III	III	IV
N1	III	III	III	III	III	IV
N2	IV					
N3						

Pleomorphic Adenoma

AKA: Benign Mixed Tumor

Despite its name, the entire tumor is of epithelial origin

Most common neoplasm of salivary glands (60-80%)

75% of all parotid neoplasms, <50% of all palatal neoplasms

Parotid : submaxillary : Sublingual = 10 : 1 : <<1

75% in superficial lobe of parotid, 25% deep

Most frequently seen in women in 30's; presents as painless persistent swelling

Gross: rubbery, well circumscribed, bosselated mass with small extensions; cartilage may be present

Wide variety of histologic appearances, including glandular, spindled, pseudovascular patterns, focal squamous metaplasia

May be focally very cellular, or be predominantly stroma

Stroma can be myxoid or hyalinized; usually some cartilage

Mesenchymal elements derived from myoepithelial cells

Two types of mucin (both actually epithelial in origin):
- Epithelial type: neutral glycoprotein
- Stromal type: highly sulfated glycosaminoglycans

Epithelium is keratin, EMA, CEA, lysozyme positive

Myoepithelium: keratin, actin, myosin, S-100 positive

Focal areas of penetration of surrounding tissue can result in a high recurrence rate, multifocally, if not widely excised

Recurrences may occur over 50yrs later - may be intractable

Malignant Mixed Tumor

Malignant Transformation of Pleomorphic Adenoma
- Occurs in 5-10% of benign mixed tumors
- Clinical indications: sudden increase in size, pain, paralysis
- Sometimes, only hyalinized scar may indicate former BMT
- Malignancy is limited to the epithelial component: can be any pattern; terminal duct type has best prognosis
- If malignancy confined to the BMT, excision usually curative; extension >8mm beyond capsule often die of tumor
- Metastases to regional LNs, lungs, bone, abdominal organs

True Malignant Mixed Tumor
- AKA: carcinosarcoma; carcinoma ex pleomorphic adenoma
- Both epithelial and "stromal" elements are malignant; both metastasize
- Aggressive, often rapidly lethal

Monomorphic Adenoma

- Includes benign tumors which are not pleomorphic adenomas
- Simple excision usually curative - malignant forms are rare

Warthin's Tumor
- AKA: Adenolymphoma, Papillary cystadenoma lymphomatosum
- More common in men, usually ~60 yrs old, often multicentric, bilateral in 10-15%, accounts for 70% of bilateral tumors
- Almost exclusive to the parotid
- Often cystic with papillary growth of two layers of oncocytic epithelial cells associated with numerous inflammatory cells with germinal centers (predominantly B-cells)
- May undergo hemorrhagic infarction with necrosis
- Epithelial cells, granular, loaded with mitochondria
- No myoepithelial cell component
- May arise in ectopic salivary gland tissue in lymph nodes

Oxyphilic Adenoma
- AKA: oncocytoma, mitochondrioma
- Solid, well circumscribed mass, tan
- Exclusively composed of oxyphilic cells; granular cytoplasm
- EM: cytoplasm packed with mitochondria with partitions (?dividing)
- Clear cell change can result from cystic dilatation of the mitochondria

Basal Cell Adenoma
- Some pathologists use the term monomorphic adenoma only for this entity, since it is the most monomorphic
- ~2% of all salivary gland tumors; 75% occur in parotid
- Mean age 58 yrs
- Grossly encapsulated, often cystic, generally smaller than benign mixed tumors; most common in parotid
- Uniform, monotonous cells with palisading at the periphery of the epithelial nests
- Growth patterns: tubular, trabecular, canalicular, solid, dermal eccrine; may be confused with adenoid cystic
- Abundant basal lamina material around and within epithelial nests
- Canalicular pattern much more common in upper lip

Sebaceous Adenoma
- When prominent lymphoid stroma: sebaceous lymphadenoma
- Malignant counterparts exist

Sialadenoma Papilliferum
- Papillary lesion of oral cavity, usually hard palate
- Exophytic mass of well differentiated squamous epithelium covering glandular component with cleft-like cystic spaces lined by cuboidal or columnar epithelium; cells may be oncocytic

Inverted Ductal Papilloma
- Small submucosal mass in oral cavity
- Well differentiated predominantly squamous epithelium associated with microcysts, occasional mucous cells, columnar lining

Myoepithelioma

- Tumor composed "exclusively" of myoepithelial cells: S-100+, SMA+, keratin+
- Some pathologists consider this a monomorphic adenoma, some a variant of benign mixed tumor
- Three major morphological types exist:
- • Spindle Cell Type: stroma like, scanty collagen, microcystic formations, myxoid change (most common)
- • Hyaline (plasmacytoid) Cell Type: eccentric nuclei, pleomorphic, no mitoses - diffuse (vs granular) eosinophilic cytoplasm, polygonal cell margins sharply outlined
- • Clear Cell Type (AKA: glycogen rich adenoma, tubular carcinoma, epithelial-myoepithelioma): tubules of clear cells with hyaline stroma; glycogen, but no fat or mucin; multinodular growth pattern, partial capsule
- Spindle cell and clear cell types occur usually in parotid; Hyaline type most common in palate
- Hyaline cell type usually benign, clear cell type often malignant (37% recur locally, 17% LN metastases, 9% die)

Mucoepidermoid Carcinoma

- Most common malignant tumor of parotid; most common malignant salivary gland tumor in children
- Can range from very indolent to overtly malignant
- Four cell types: mucinous, squamous, intermediate, clear
- • Low Grade: well circumscribed, cystic areas, predominantly well-differentiated mucinous cells
- • High Grade: ≥20% of the tumor is more solid, infiltrative; predominantly squamous, intermediate, and clear cells; marked nuclear atypia is generally NOT seen
- Mucin or keratin may escape, causing inflammatory reaction
- Prognosis: 5yr survival: 98% for low grade, 60% for high
- Recurrences/metastases usually occur within 5 yrs, or never

Adenoid Cystic Carcinoma

- AKA: cylindroma
- 3rd most common malignancy in parotid, 1st in minor salivary glands
- Grossly: solid, infiltrative
- Hyperchromatic angulated nuclei, clear cytoplasm
- 3 Histologic patterns: cribriform, tubular, solid; usually mixed with all three present; classify by most predominant pattern
- Pseudocysts with hyaline-like PAS+ material often seen in cribriform areas
- Marked propensity for perineural invasion; spread along nerves accounts for high recurrence rate
- Mesenchymal areas and squamous metaplasia consistently absent (unlike pleomorphic adenoma)
- Immunohistochemically, cells in ducts react like intercalated duct cells (positive for keratin, CEA, S-100), cells in pseudocysts like myoepithelial cells (positive for S-100, actin, ± keratin); amorphous material positive for laminin and type IV collagen
- Slow growing but highly malignant, with late recurrences (good 5yr survival, but much worse at 15 yrs)
- 15 yr survival based on pattern: 5% for solid, 26% for cribriform, 39% for tubular
- Prognosis better when in palate than when in parotid; worst in submaxillary gland
- Metastases most commonly to lung (often silent); LN metastases rare

Acinic Cell Carcinoma

- 1-3 % of all salivary gland tumors - majority in parotid
- Male predominance; peak incidence in the third decade
- Grossly: encapsulated, solid, friable, gray-white, ≤3cm
- Histologic patterns: solid ("classic"), microcystic (most common), papillary cystic, and follicular (least common); prognosis is independent of histologic pattern
- Frequently have a granular, basophilic cells with numerous zymogen granules
- Other cell types include: intercalated duct type, clear, vacuolated, nonspecific glandular
- When clear cell predominates: hypernephroid - glycogen
- May see peripheral lymphoid infiltrate, central psammoma bodies
- Survival: 89% 5 yr, 56% 20 yr - completeness of excision most important factor

Adenocarcinoma

Terminal Duct Carcinoma
- AKA: lobular carcinoma, polymorphous low grade adenocarcinoma
- Usually restricted to minor salivary glands / oral cavity
- Palate most common location (2nd most common type here)
- Uniform cell type (plump, columnar) with variable patterns: tubular, cribriform, papillary, solid, fascicular, Indian-file
- Background can be mucinous or fibrous
- Low grade malignancy: 12% recur, 10% LN metastases, no distant metastases

Salivary Duct Carcinoma
- Elderly males, usually parotid, sometimes submaxillary
- Micro: resembles ductal carcinoma of breast: comedo, solid, papillary, or NOS.
- Highly aggressive: 70% mortality

Papillary Adenocarcinoma (Papillary Cystadenocarcinoma)
- Less than 3% of all parotid tumors
- May become large - hemorrhage and necrosis common
- Well-defined papillary structures microscopically - mucinous component - often nuclear atypicality
- Low grade vs high grade based on stromal invasion

Adenocarcinoma, NOS
- 2/3 occur in major salivary glands
- Usually asymptomatic
- Designate as low grade or high grade based on cytologic atypia

Sebaceous Carcinoma

- Rare; most common in parotid
- Pleomorphic, atypical cells arranged in sheets and nests
- Often present as painful mass with facial nerve paralysis

Other Neoplasms

Malignant Lymphoma
- Prototypical location for MALT lymphomas
- Usually follicular center cell lymphomas, with slow evolution and good long-term prognosis
- Those arising in Mikulicz's disease usually immunoblastic with more rapid clinical course

Capillary Hemangioma (Benign Hemangioendothelioma)
- Most common salivary gland tumor in infants and children
- Permeate through glandular elements, often with mitoses
- Do not become malignant; often spontaneously regress

Neurilemoma

Pilomatrixoma

Embryoma
- Highly cellular epithelial parotid tumor of infancy with blastomatous appearance - rare

Giant cell tumors

Epidermoid Carcinoma
- Usually represent metastases to intraparotid lymph nodes

Small Cell (Anaplastic) Carcinoma
- Scanty cytoplasm, small cells, solid pattern, many mitoses
- Neuroendocrine features found in some

Lymphoepithelioma-like Carcinoma
- More frequent among Eskimos and Chinese
- Similar to Mikulicz's disease at low power, but epithelial islands are malignant cytologically
- As with lymphoepithelioma (nasopharyngeal carcinoma), may be EBV related
- Overall outcome not too bad

LUNG

Normal Anatomy

Average adult weight 350-435 gms
Right is trilobed; left is bilobed, the left "middle" lobe being assumed by the lingula
Bifurcation of trachea at level of 4th and 5th ribs: right mainstem bronchus more vertical and more direct: receives most aspirated material
Trachea and major bronchi have C-shaped cartilage rings; cannot be totally occluded by bronchoconstriction
Bronchi have discontinuous plates of cartilage and submucosal glands
First order bronchi = lobar bronchi
Second order bronchi (segmental bronchi) are numbered in order from proximal to distal: 10 on right, 9 on left

LUL: B1 - B4	RUL: B1 - B3
Lingula: B5	RML: B4 - B5
LLL: B6, B8-B10	RLL: B6 - B10

Bronchioles: no cartilage or submucosal glands: Clara cells secrete non-mucinous lining protein
Acinus: terminal bronchiole plus supplied respiratory bronchioles, alveolar ducts and alveolar sacs
Lobule: 3-5 terminal bronchioles and supplied acini
Pores of Kohn interconnect alveoli
Canals of Lambert: direct accessory bronchioloalveolar connections
Double arterial system: pulmonary and bronchial; single venous system: pulmonary
Pseudostratified ciliated columnar epithelium from larynx to bronchioles (except vocal cords: squamous)
Type I pneumocytes cover 95% alveolar surface
Type II pneumocytes contain lamellar bodies of surfactant
Inhaled particles over 10μm in size tend to impact on nasal or pharyngeal walls; 3-10μm impact in large airways; 1-5μm impact in terminal airways and alveoli; <1μm tend to remain suspended and are exhaled
Pulmonary Defense Mechanisms: Nasal clearance, mucociliary ladder, alveolar macrophages

Congenital Malformations

Tracheobronchial Malformations

Laryngeal Web
Incomplete recanalization of the larynx during the 10th wk
Membranous web forms at the level of the vocal cords, partially obstructing the airways

Tracheoesophageal Fistula (TEF)
Incomplete division of foregut into respiratory and digestive portions
Four types:
- Focal esophageal atresia: proximal esophagus ends as blind pouch (dilated); distal arises from trachea just above bifurcation; 85% of all TEFs
- [Both esophageal segments blind pouches (8%)]
- Both trachea and esophagus complete, but connected at level of bifurcation (4%)
- Focal esophageal atresia: proximal esophagus connects to trachea at level of bifurcation; distal arises as blind pouch
- Focal esophageal atresia: both proximal and distal esophageal segments communicate with the trachea

Tracheal Stenosis/Atresia
Rare
Usually associated with some tracheoesophageal fistula

Pulmonary Sequestration

Partial or complete separation of a portion of a lobe from the "surrounding" lung - sequestered segment has no connection to the main bronchial tree
Blood supply from aorta, not from pulmonary arteries
20% of patients have a histology of congenital cystic adenomatoid malformation

Intralobar Sequestration
Enclosed within pleura of "normal" lung
Usually lower lobe; 60% on the left
More likely to be symptomatic: recurrent infections or bronchiectasis
Usually large systemic arterial supply: 25% arise below diaphragm; may have shunts to pulmonary vessels; subclassified as Type I, II, or III for extensive, slight, absent overlap between circulations
Venous drainage is into pulmonary veins
Chronic inflammation, fibrosis, obliteration of vessels
May be congenital or acquired after multiple pneumonias

Extralobar Sequestration
Separated from pleural covering of lung - may be found anywhere in thorax or mediastinum; 90% occur on left
Associated with polyhydramnios and edema
Systemic arterial supply - usually small
Venous drainage is into azygous veins

Bronchogenic Cysts

May occur anywhere in lung; usually single, occasionally multiple; range from microscopic to >5 cm
Usually found adjacent to bronchi or bronchioles
Lined by bronchial-type epithelium; connective tissue may contain cartilage or mucous glands
Cavities usually filled with mucinous secretions or air; when infected; may lead to progressive metaplasia of lining or total necrosis of wall leading to lung abscess
May rupture into bronchi or pleural cavity

Congenital Lobar/Lobular Emphysema

Presents in very young children as sudden progressive respiratory distress
Affects upper lobe or RML most commonly
Massive over-distention of airways without tissue destruction

Congenital Cystic Adenomatoid Malformation

AKA: Cystic adenomatoid transformation
Seen in neonates with respiratory distress, but occasionally in older children
Solitary lesions, usually lower lobe
Various sized intercommunicating cysts with an adenomatoid cuboidal pseudostratified epithelium and smooth muscle proliferation; no cartilage
Classification based on size of cysts and "level of origin" base on histologic appearance (eg bronchial to alveolar)
Type 0 (<5%): main bronchus--like structures
Type I (65%): large cyst or cysts (~10cm), often surrounded by smaller cysts; bronchial-like
Type II (25%): medium sized (<2.5 cm) cysts surrounded by "normal" lung; bronchiolar-like
Type III (<10%): large number of small (<1.5 cm) cysts; terminal bronchiolar-like
Type IV (<5%): flattened epithelium; alveolar-like
Other associated anomalies, pulmonary and extrapulmonary, seen in 50% of patients with type II histology, 12% of patients with type I histology, but no patients with type III

Cystic Fibrosis

AKA: Mucoviscidosis
Autosomal recessive; 1/20 whites are carriers
Variable penetrance
Gene is on chromosome 7 (7q22-7q31): encodes "CFTR" gene, a putative chloride transporter
Results in defective anion transport, particularly Cl^- and HCO_3^-, with subsequent abnormal water movement
In sweat glands of skin, sweat ducts cannot take up Cl back from secretions: sweat high in NaCl
In lungs, decreased Cl transport into lumen results in viscous secretions which plug airways. Infections by staph and pseudomonas common, often fatal (major cause of death)

Pneumonias / Inflammation

Lobar Pneumonia

95% caused by pneumococci, most commonly types 1,3,7,2
Other agents: Klebsiella, staph, strep, H. influenza
Widespread fibrinosuppurative consolidation
Four stages:
• Congestion: (~24 hrs) vascular engorgement, intraalveolar fluid, numerous bacteria, few neutrophils
• Red Hepatization: Extravasated RBCs, fibrin, increasing numbers of neutrophils
• Gray Hepatization: Much more fibrin and neutrophils, disintegrating RBCs
• Resolution

Bronchopneumonia

Patchy consolidation of lung with foci of acute suppurative inflammation which are poorly defined grossly
Can be extensive, merging to involve an entire lobe

Aspiration
Usually right lower lobe, then RUL, then LLL
Can see significant destruction (out of proportion to inflammation), foreign body giant cells

Infectious
Most commonly basal
Staph, strep, pneumococcus, H. influenza, Pseudomonas

Complications
• Abscess: may be secondarily colonized by Mucormycosis or Aspergillus
• Empyema
• Organization

Lipoid Pneumonia

AKA: "Golden pneumonia"
Well circumscribed, firm
Lipid accumulation within foamy macrophages
Inflammation, proliferating pneumocytes, ± reactive endarteritis

Endogenous (obstructive)
Most commonly from obstruction by tumor, LN, abscess
Lipid derived from degenerating type II pneumocytes
Cholesterol clefts, giant cells

Exogenous
Aspiration of lipid materials
Right lung more commonly than left
Multinucleated giant cells

Infectious Granulomatous Inflammation

Can assume a variety of patterns and mimic any of the noninfectious granulomatous disorders
Vasculitis of infection more likely to show mural infiltrate of lymphocytes and plasma cells - few neutrophils

Histoplasmosis
Histoplasma capsulatum: oval shaped, 1-5μm - occasional buds
Necrotizing granulomas with cores composed of multiple concentric lamellae, frequently calcified, surrounded by palisading histiocytes and active inflammation, surrounded by zone of acellular collagen
Organisms identified by silver stain in necrotic cores

Coccidioidomycosis
Coccidioides immitis: numerous small (2-5μm) endospores within thick walled spherule 30-60μm
Necrotizing granuloma often with prominent eosinophilic infiltrate in surrounding tissue with organisms distributed throughout necrotic and viable zones

Cryptococcosis
Cryptococcus neoformans; soil, pigeon droppings; 2-15μm
Intracellular collections in histiocytes impart bubbly look
Bright red staining of capsule with mucicarmine
Varying dimensions
Usually necrotizing granulomas - some non-necrotizing

Blastomycosis
Blastomyces dermatitidis; 8-15μm; round
Initially acute inflammation followed by granulomas with centers containing necrotic neutrophils
Numerous round refractile organisms - stains strongly with mucicarmine

Mycobacterium tuberculosis
AKA: Koch bacillus
Infection used to be seen mostly in children and young adults; now more common in 50-60 yr old
Two species: one predominantly infects humans (transmitted by inhalation) and the second is a bovine strain, which is now much less common but would cause GI infections from infected milk
Histologically, hallmark lesion is caseating granuloma (soft tubercle) although may have a cellular center (hard tubercle)
Ghon focus: 1-1.5 cm gray-white inflammatory consolidation seen at the periphery of the upper part of lower lobe or lower part of upper lobe (greatest volume of air flow) which becomes granulomatous and then centrally necrotic by the second week - primary infection focus, usually clinically silent
Ghon complex: combination of primary lung lesion and ipsilateral lymph node involvement
Rarely, primary focus will rapidly enlarge, erode into bronchi, giving rise to satellite lesions - may seed bloodstream resulting in miliary dissemination or meningitis
Secondary TB arises usually from reactivation of old primary lesions - present as apical or posterior segment lesions (tuberculomas), may be bilateral - can either scar down, create progressive pulmonary TB, lead to tuberculous empyema, intestinal TB (if aspirated material is swallowed), or miliary seeding.
Isolated distant organ involvement is also seen (cervical lymph node, meninges, kidneys, adrenals, bones, fallopian tubes, epididymis
Secondary TB usually accompanied by fever, night sweats, weakness, fatigability, loss of appetite

Dirofilariasis
Dirofilaria immitis: canine heart-worm
Most patients asymptomatic
Well circumscribed coin lesion radiographically
Central "infarct" with surrounding granulomatous inflammation
Organisms within lumen of necrotic artery: ~200μm diameter with thick multilayered cuticle with transverse striations
Organisms may calcify with time

Additional Specific Infectious Agents

Pneumocystis Carinii
- Immunocompromised host
- Foamy or honeycombed intraalveolar exudate with an interstitial lymphoplasmacytic infiltrate
- Cysts identifiable by silver stain: 5μm in diameter with single or paired intracystic bodies (1-2 μm); some cysts may be folded or collapsed

CMV
- Immunocompromised host
- May be multifocal, miliary, or diffuse
- Predominantly mononuclear inflammation with edema and alveolar epithelial hyperplasia
- Foci of hemorrhagic necrosis can be seen
- Viral inclusions usually found; both nuclear and cytoplasmic

Adenovirus
- Bronchocentric; transmural bronchiolitis with marked destructive inflammation; bronchiolitis obliterans
- Smudge cells

Aspergillus
- 2nd most common infective fungus, especially in hospitals
- 45° angle branching septate hyphae
- Three types of infection:
  - Allergic bronchopulmonary aspergillosis: inhalation of large numbers of spores producing a hypersensitivity reaction in bronchi or alveoli (see below under Asthma)
  - Colonizing (secondary): growth of organisms in pulmonary cavity forming a mass (aspergilloma) without invasion
  - Invasive (primary): opportunistic infection involving primarily lung but also heart valves, brain, kidneys: targetoid lesions with necrotizing center and hemorrhagic border; angioinvasive hyphal forms

Diffuse Alveolar Damage (DAD)

- Severe acute injury from toxic insult: viruses (influenza), mycoplasma, inhalants (>70% oxygen, smoke, noxious gases), drugs (chemotherapeutic, heroin), ingestants (kerosene, paraquat), shock, sepsis, radiation (10% patients receiving chest radiation), acute pancreatitis, heat, burns, uremia, systemic lupus erythematosus, high altitude, molar pregnancy
- Etiology cannot be determined histologically
- Abrupt onset of severe arterial hypoxia which is not responsive to O_2 therapy
- Combination of endothelial and epithelial injury - bilateral and diffuse
- Exudative Stage:
  - First week following injury
  - Initially, edema (interstitial, intraalveolar), hemorrhage
  - Fibrin deposition and thrombi in small vessels/capillaries
  - Hyaline membrane formation (3-7 days)
  - Sloughing of alveolar cells, denudation of BM
  - X-ray often normal
- Proliferative Stage:
  - Begins in second week
  - Increasing interstitial inflammation
  - Fibroblast proliferation and interstitial fibrosis
  - Organization and phagocytosis of hyaline membranes
  - Proliferation of type II alveolar lining cells - hobnail
  - Bronchiolar damage with atypical squamous metaplasia
  - X-ray shows diffuse bilateral infiltrates
- Mortality 10-90%, depending on etiology - fibrosis is a bad prognostic sign, but not necessarily irreversible

Adult Respiratory Distress Syndrome
- AKA: ARDS, hyaline membrane disease
- Clinically: acute onset of dyspnea following known (by definition) inciting agent
- Severe hypoxemia and decreasing lung compliance
- 50% mortality with rapid course (days to weeks)

Acute Interstitial Pneumonia (AIP)
- AKA: Hamman-Rich disease, accelerated interstitial pneumonia
- Rapidly progressive interstitial pneumonia for which an identifiable initial insult cannot be found (relatively rare)
- Most often young adults (mean age 28)
- May follow flu-like illness
- Distinguish from UIP/IPF by diffuse fibroblast proliferation with relatively little collagen deposition - temporally synchronized
- No effective therapy, bad prognosis, 40-50% die within 2 months

Bronchiolitis Obliterans - Organizing Pneumonia (BOOP)

- AKA: cryptogenic organizing pneumonia
- Air space filling process combining bronchiolitis obliterans (inflammation of terminal bronchioles) and extension into alveolar ducts and spaces
- Pattern of injury seen in many conditions
- Etiology: often unknown, but also infections, inhalant, drugs, collagen vascular disease, chronic aspiration
- Acute onset of cough, dyspnea, fever, malaise; multiple patchy air space opacities, often bilateral; restrictive picture
- Distinctive type of fibrosis: lightly staining, oval to serpiginous, extending along air spaces, with elongated fibroblasts in a myxoid pale-staining matrix rich in mucopolysaccharides, with lymphocytes, macrophages, plasma cells, neutrophils
- Plugs or polyps may occlude distal bronchioles
- Foamy macrophages (obstructive lipid pneumonia)
- Excellent prognosis - complete recovery usually in few weeks

Obliterative Bronchiolitis

- Similar to BOOP, but disease restricted to bronchioles (i.e., pure bronchiolitis obliterans)
- Air flow obstruction, distended lung fields without infiltrates, poor prognosis
- Includes most cases occurring in bone marrow or heart/lung transplant patients and those with rheumatoid arthritis

Usual Interstitial Pneumonia (UIP)

- When no specific etiology (such as asbestosis, drug injury, radiation) can be identified, referred to as: Idiopathic Pulmonary Fibrosis (IPF), idiopathic (or diffuse) interstitial fibrosis, sclerosing alveolitis
- Most common of the idiopathic interstitial pneumonias
- Insidious onset of dyspnea, initially during exercise, later even at rest, (40-70 yrs age; M>F) with chronic progressive 4-5 yr downhill course to death
- X-ray shows bilateral infiltrates, more dense at base, but only minimal if any effusion; with progression, get fibrosis and shrinkage of lungs
- Pathogenesis may be related to activation of macrophages and "innocent bystander" destruction of pulmonary tissue
- Interstitial inflammation and fibrosis which *varies significantly from field to field* in both cellularity and degree of fibrosis, even with focal areas of honeycombed lung
- Lymphocytes (predominantly B), plasma cells, germinal centers, alveolar desquamation, cuboidalization of alveolar lining cells, narrowed airspaces, cystic changes
- Foci of fibroblasts in loose stroma represent active lesions
- Secondary pulmonary hypertensive changes and *smooth muscle hyperplasia*
- Tight intraalveolar aggregates of macrophages
- Steroid therapy widely used - less than 20% respond
- Cyclophosphamide therapy may be beneficial

Desquamative Interstitial Pneumonia (DIP)

- Some consider this an early form of UIP/IPF
- Occurs at mean age of 42yrs (90% cigarette smokers), 30% mortality with 12 yr mean survival; better prognosis than UIP; more responsive to steroid therapy
- Numerous large mononuclear cells in air spaces - most are actually macrophages vs desquamated cells
- Macrophages loosely aggregated, evenly dispersed, do not distend lumens
- Loss of type I pneumocytes with type II cells lining air spaces
- Blue bodies: laminated PAS+ iron containing bodies within or surrounded by macrophages
- Mild thickening of alveolar septa, less fibrosis than UIP
- Temporal uniformity vs heterogeneity of UIP
- Differential Dx: DIP like reactions seen in eosinophilic granuloma, asbestosis, around malignant tumors, respiratory bronchiolitis, collagen diseases, pulmonary alveolar proteinosis

Respiratory Bronchiolitis

- Similar to DIP but tends to be patchy, not diffuse, with macrophages predominantly in respiratory bronchioles and alveolar ducts; macrophages distend spaces
- Macrophages have finely granular yellow-brown pigment
- Almost always smoking history
- Predominantly lower lobes
- Self limited - corticosteroid therapy unnecessary
- May exist independently or as component of interstitial lung disease in continuum with DIP

Miscellaneous Interstitial Pneumonias

Chronic Interstitial Pneumonia (CIP)

- Temporally homogeneous lesions - don't fit others
- Cellular interstitial inflammation, many plasma cells, variable amounts of fibrosis (inactive)
- Associated with many underlying diseases: collagen vascular diseases, drug toxicity, hypersensitivity pneumonitis, severe pulmonary HTN, Mycoplasma

Lymphoid Interstitial Pneumonia (LIP)

- Mixed cellular infiltrate of lymphocytes, plasma cells, epithelioid histiocytes, germinal centers, granulomas
- Variable clinical and radiographic picture
- Probably early lymphoproliferative lesion of bronchial associated lymphoid tissue

Giant Cell Interstitial Pneumonia (GIP)

- Isolated multinucleated giant cells in alveoli and interstitium of lung otherwise showing changes of UIP
- Associated with heavy metals; rare

Granulomatous Interstitial Pneumonia

- Prominent epithelioid histiocytes as well as lymphocytes and plasma cells - may have loosely formed granulomas (vs sarcoid which has well formed granulomas)
- Many represent hypersensitivity pneumonia
- More responsive to steroids and better prognosis than UIP

End-Stage Fibrosis (Honeycomb Lung)

- Common end point for multiple causes and patterns
- Restructuring of distal air spaces, obliteration of small airways leading to macroscopic "emphysematous" cysts separated by areas of scarring (interstitial fibrosis)
- Enlarged air spaces lined by plump cuboidal or ciliated columnar cells (ingrowth of bronchial epithelium) with areas of squamous metaplasia
- Patients are at increased risk for developing peripheral carcinomas

Progressive Massive Fibrosis

- May complicate silicosis, asbestosis, coal workers pneumoconiosis, mixed dust fibrosis, etc.
- Large amorphous mass of fibrous tissue obliterating and contracting the parenchyma, usually upper lobes
- Central cavitation may be necrobiosis or sign of TB
- Clinically, patient is dyspneic, eventually even at rest
- Poorly localized chest pain is common
- May lead to right ventricular hypertrophy
- Caplan's Syndrome: development of rheumatoid nodules in setting of PMF: small firm tan nodules with central necrosis

Hypersensitivity Pneumonia

- AKA: Extrinsic Allergic Alveolitis
- Immunologic reaction to inhaled agents (fungus, mold, animal proteins) - combination of type III (immune complex) and type IV (cell mediated) reactions
- Acute: (large exposure): severe dyspnea, cough, fever - self limited; resolves in 12-18hrs (continued exposure can lead to permanent damage)
- Chronic: prolonged exposure to small doses; insidious onset of dyspnea and dry cough
- Patchy chronic interstitial pneumonia, accentuated around bronchioles, temporally synchronized, with uninvolved lung in between
- Lymphocytes predominate (most are CD8+ T-Cells), with plasma cells, histiocytes, rare eosinophils/neutrophils, minimal fibrosis without vasculitis - many will show loosely formed non-necrotizing granulomas
- BOOP-like changes can be seen in 2/3
- Steroids may help; best therapy is elimination of inciting agent

Farmer's Lung

Maple Bark Stripper's Disease

- Ovoid thick-walled brown spores (Cryptostroma corticale) in histiocytes or granulomas

Pigeon Breeder's Disease

- Small aggregates of foamy macrophages in interstitium and alveoli

Byssinosis

- Textile workers; inhalation of cotton fibers

Actinomycetes

Eosinophilic Pneumonias

- X-ray: patchy bilateral infiltrates, usually more prominent in periphery
- Filling of alveoli with eosinophils and large mononuclear cells or giant cells, necrosis of infiltrate, palisading histiocytes
- Interstitial infiltrate of eosinophils, plasma cells, lymphocytes
- Mild non-necrotizing vasculitis; bronchiolitis obliterans
- • Simple (Loeffler's syndrome): mild, self limited, resolves in 1 month, peripheral eosinophilia
- • Tropical: high fever, cough, wheezing, eosinophilia - usually caused by microfilaria within pulmonary capillaries
- • Chronic: variable clinical presentation; usually chronic asthma; eosinophilia, elevated IgE
- • Allergic Bronchopulmonary Aspergillosis: (see below under asthma)
- • Bronchocentric Granulomatosis (see below)
- Differential Dx: Churg-Strauss (PAN associated with asthma, Aspergillus related diseases)

Drug Induced Lung Disease

ALKYLATING AGENTS

Busulfan

- Used for CML - 1st agent shown to cause lung disease
- Pulmonary toxicity occurs in 4% pats receiving busulfan
- Latent periods 1 month to 12 yrs (mean 3.5 yrs)

Poor prognosis - most die within 6 months
Organizing diffuse alveolar damage with bronchiolar and alveolar epithelial atypia: cytomegaly, nuclear pleomorphism, prominent nucleoli
Chronic interstitial pneumonia, pulmonary ossification, and pulmonary alveolar proteinosis have also been reported

Cyclophosphamide
Unpredictable latent period
Organizing diffuse alveolar damage most common - less epithelial atypia than seen with busulfan
Have also seen chronic interstitial pneumonia, BOOP

Chlorambucil
Chronic interstitial pneumonia

NITROSOUREAS

Carmustine (BCNU)
Used to treat primary brain neoplasms
Direct relationship between cumulative dose and toxicity
20-30% overall incidence of toxicity; 50% for larger doses
Acute and organizing DAD most common lesion; less commonly CIP, veno-occlusive disease, pleural disease

ANTIBIOTICS

Bleomycin
3-5% incidence; higher for: higher doses, elderly, prior irradiation, recent previous use of Bleomycin
DAD most common, predominantly lower lobes, with alveolar hemorrhage, pleural fibrosis, eosinophilic pneumonia
BOOP, PVOD can be seen
Prognosis poor: rapidly progressive to death within 3 months

Mitomycin
8% patients; 50% overall mortality; full recovery possible
DAD with fibrinous pleuritis; BOOP, pulmonary edema, hemorrhage

ANTIMETABOLITES

Methotrexate
5-10% incidence; most recover completely, <10% die
Peripheral eosinophilia, diffuse pulmonary infiltrates
CIP with nodular interstitial infiltrates of lymphocytes, plasma cells, histiocytes, occasional giant cells
Hypersensitivity pneumonitis, BOOP, DAD can be seen

ANTIMICROBIALS

Nitrofurantoin
Commonly used, therefore causes most lung disease
Acute reaction in 90%: peripheral eosinophilia, pulmonary edema, DAD
Insidious onset in 10%: UIP, DIP, eosinophilic pneumonia

Sulfonamides
Eosinophilic pneumonia is underlying pathology

Amphotericin B
Diffuse alveolar hemorrhage when given in combination with leukocyte transfusion

ANTI-INFLAMMATORY DRUGS

Gold
1% patients: some MHC associations
Rheumatoid lung disease, DAD, CIP, BOOP

OTHERS

Antiarrhythmics: amiodarone, tocainide
Antihypertensives: hydrochlorothiazide, propranolol, hexamethonium, hydralazine, Captopril
Tocolytics: ritodrine, tertbutaline, albuterol, MgSO4
Anticonvulsants: phenytoin, carbamazepine
Psychotherapeutics: haloperidol, chlordiazepoxide, amitriptyline, imipramine
Opioids: morphine, methadone, codeine, heroin

Pneumoconioses

"Non-neoplastic reaction of the lungs to inhaled mineral or organic dust, excluding asthma, bronchitis, emphysema"
Extent of disease determined by amount of material retained in lungs and by the size, shape, and solubility of material
Particle sizes:

>5μm	Generally impact high in airway; cleared
<1μm	Generally remain suspended; exhaled
1-5μm	Reach terminal small airways; stay there

In general, concomitant cigarette smoking worsens disease
In general, pneumoconioses do NOT predispose to development of carcinoma (exception: asbestosis)

Silicosis

Silica: silicon dioxide, e.g. quartz

Acute Silicosis ("Accelerated Silicosis")
Heavy exposure over 1-3yrs
Looks like pulmonary alveolar proteinosis with variable amounts of interstitial fibrosis

Chronic Silicosis
After 20-40yrs exposure to dust containing up to 30% quartz (mining, sand blasting, metal grinding, tunneling, ceramics)
Onset and progression can be years after exposure
Proliferation of hyalinized nodules, usually peripheral, usually upper lobes, with variable amounts of black pigment (concomitant exposure to coal dust), well delimited, concentric lamellated hyaline, with rare giant cells or granulomas - necrosis rare
Nodules slowly but progressively expand - can obliterate small airways
Doubly refractile round particles may be seen (1-2μm)
Complications:
• Conglomerate nodules
• Progressive massive fibrosis
• TB (10-30x relative risk)
• Caplan's Syndrome

Asbestosis

Elongated fibrous particles in two groups:
• Serpentine group [90%] (e.g. chrysotile): long, flexible, curled, very thin; generally do not make it to small airways
• Amphibole group [10%] (e.g. amosite, crocidolite): brittle, straight, fracture; fragments carried into airways
Causes interstitial fibrosis similar to UIP, beginning as peribronchiolar fibrosis, preferentially lower lobes, with pleural fibrosis/calcification, parietal pleural plaques
Occurs 15-20yrs after exposure; generally requires >10yrs of exposure; insidious onset
Progression can lead to honey combed lung or PMF
Increased risk of bronchogenic carcinoma: risk relative to unexposed is 5x (relative risk for smokers: 11x ; relative risk for smokers exposed to asbestos: 55x)
Increases risk for mesothelioma (both pleural and peritoneal); still more rare than bronchogenic; smoking is not a factor

Coal Workers Pneumoconiosis

Simple CWP
Occurs after years of exposure to coal dust
Dust macule : interstitial dust filled macrophages surrounding dilated respiratory bronchioles and in the interlobular septa, usually upper portions of lobes, with minimal fibrosis
Coal nodule : discrete palpable <1cm lesion with central hyalinized collagen and pigment laden macrophages
Minimal functional deficits
2-8% will progress to complicated CWP

Complicated CWP
Progressive Massive Fibrosis with large black masses and central cavity
Immunologic mechanisms may be involved in pathogenesis

Mixed Dust Fibrosis

Low proportion of silica; silicotic nodules do not occur
Stellate interstitial fibrous lesion, predominantly in area of the respiratory bronchioles, spreading into surrounding parenchyma irregularly - fibrous zones remain discrete

Other Pneumoconioses

Pulmonary Mycotoxicosis
AKA: Organic dust syndrome
Caused by massive inhalation - probably toxic vs immune
Bronchiolitis with intraalveolar and interstitial neutrophils
Siderosis
AKA: arc-welder's lung, hematite lung
Results from exposure to inert metallic iron or its oxides
Macules and perivascular dust similar to CWP but with coarse brown-black particles of iron and gold-brown hemosiderin
Berylliosis
Acute form produces DAD
Chronic form is a systemic disease (lung, LNs, kidneys, liver, spleen) with a latent period up to 15 yrs: interstitial fibrosis with non-caseating subpleural, peribronchiolar, and perivascular granulomas which may have Schaumann bodies or asteroid bodies like sarcoidosis
Others
Talc, Aluminum powder, hard metal pneumoconiosis, alginate powder(dentists), PVC, fibrous glass

Chronic Obstructive Pulmonary Dz

AKA: Chronic Obstructive Airway Disease (COAD)
Pulmonary function tests show increased pulmonary resistance, limitation of maximal expiratory flow rates

Emphysema

Abnormal permanent enlargement of the distal air spaces due to destruction of the alveolar walls and loss of respiratory tissue
"Obstruction" caused by lack of elastic recoil
Most common cause is smoking: produces combination of emphysema and chronic inflammation (alpha-1-antitrypsin deficiency produces almost pure emphysema)
Most likely pathogenesis involves increased protease or decreased anti-protease activity

TYPES

Centroacinar (Centrilobar) Emphysema
Affects central (proximal) parts of the acini (respiratory bronchioles) but spares the distal alveoli
More severe in upper lobes, especially apical segments
Seen in smoking and secondary to coal dust
Panacinar (Panlobar) Emphysema
Uniform enlargement of all acini in a lobule
May not necessarily involve entire lung; predominantly lower lobes
Alpha-1-antitrypsin deficiency is prototype
Paraseptal (Distal Acinar) Emphysema
Proximal acinus normal, distal part involved
Most prominent adjacent to pleura and along the lobular connective tissue septa
Probably underlies spontaneous pneumothorax in young adults
Bullous Emphysema
Any form of emphysema which produces large subpleural blebs of bullae (>1 cm)
Localized accentuation of one of the above four forms
Interstitial Emphysema
Air penetration into the connective tissue stroma of the lung, mediastinum, or subcutaneous tissue
Compensatory "Emphysema"
Dilatation of alveoli in response to loss of lung substance elsewhere
Actually hyperinflation since no destruction of septal walls
Senile "Emphysema"
Change in geometry of lung with larger alveolar ducts and smaller alveoli
No loss of lung tissue; hence not really emphysema

Chronic Bronchitis

Clinically defined: persistent cough with sputum production for at least three months in at least two consecutive years
Can occur with or without evidence of airway obstruction
10-25% of urban dwelling adults qualify
Smoking is most important cause
Hypersecretion of mucous with:
• Increased numbers of goblet cells in small airways as well as large airways
• Increased size of submucosal glands in large airways (Reid index: ratio of thickness of mucous glands to thickness of wall between epithelium and cartilage)
Peribronchiolar chronic inflammation

Asthma

Increased responsiveness of tracheobronchial tree to various stimuli, leading to paroxysmal airway constriction
Unremitting attacks (status asthmaticus) can be fatal
Types: Extrinsic (atopic, allergic): most common; Intrinsic (idiosyncratic); now recognize mixed
Bronchial plugging by thick mucous plugs containing eosinophils, whorls of shed epithelium (Curschmann's spirals), and Charcot-Leyden crystals (eosinophil membrane protein); distal air-spaces become over distended
Thick basement membrane, edema and inflammation in bronchial walls with prominence of eosinophils, hypertrophy of bronchial wall muscle
Therapeutic agents are aimed at increasing cAMP levels either by increasing production (β_2-agonists, eg epinephrine) or decreasing degradation (methyl xanthines, eg theophylline). Cromolyn sodium prevents mast cell degranulation
Allergic Bronchopulmonary Aspergillosis
Occurs in chronic asthmatics; hypersensitivity to non-invasive Aspergillus
Bronchocentric granulomatosis, mucoid impaction of bronchi, eosinophilic pneumonia
Distinctive proximal bronchiectasis (?pathognomonic)

Bronchiectasis

Permanent abnormal dilation of bronchi and bronchioles, usually associated with chronic necrotizing inflammation
Patients have fever, cough, foul-smelling sputum
More common in left lung, more common in lower lobes
Causes:
• obstruction (tumor, mucous)
• intralobar sequestration
• immotile cilia syndrome
• Kartaganer's syndrome
• congenital
• cystic fibrosis
• necrotizing pneumonia

Miscellaneous Diseases

Pulmonary Atelectasis

Incomplete expansion of lungs or collapse of a previously expanded lung
Reversible disorder
Affected segment is prone to superimposed infections

Obstructive (Absorptive)
- Complete obstruction of an airway - oxygen trapped distal to obstruction is eventually absorbed, leading to collapse of the obstructed segment
- If large, mediastinum shifts towards the affected lung
- Usually caused by excessive secretions or inflammatory exudate within the smaller bronchi - most commonly seen in asthma, chronic bronchitis, bronchiectasis, aspiration, post-operative patients

Compressive
- Pleural cavity partially or completely filled by fluid, exudate, tumor, or air
- Most commonly seen in patients with cardiac failure
- If large, the mediastinum shifts away from the affected lung

Contraction
- Localized fibrosis increases the recoil of a focal area

Patchy
- Loss of surfactant (e.g., respiratory distress syndrome)

Alveolar Hemorrhage Syndromes
- Hemoptysis, pulmonary infiltrates, anemia, diffuse intraalveolar hemorrhage, necrotizing interstitial pneumonitis
- Generally not used to refer to hemorrhage secondary to necrotizing bronchopneumonia, renal failure, thrombocytopenia, venous congestion

Goodpasture's Syndrome
- AKA: anti-basement membrane disease
- Also get renal involvement due to glomerular destruction
- M:F=2:1
- Accumulation of RBCs and hemosiderin in alveoli and alveolar macrophages, some nonspecific thickening of alveoli, *vasculitis usually absent*
- Aggressive therapy needed
- Prognosis related more to renal disease

Idiopathic Pulmonary Hemosiderosis
- Similar to Goodpasture's syndrome but no renal involvement
- Almost exclusively children under 16, M=F
- Often improves without therapy, but may be fatal

Sarcoidosis
- Lungs frequently involved - may be only manifestation
- 60% cases will be positive on transbronchial biopsy
- Xray: interstitial infiltrates with hilar adenopathy
- Non-necrotizing granulomatous inflammation composed of tight clusters of epithelioid histiocytes, occasional giant cells, few lymphocytes - may become hyalinized
- Granulomas predominantly in interstitium vs air spaces, characteristically distributed along lymphatics
- Granulomatous vasculitis frequently present

Nodular Sarcoidosis
- Large coalesced areas of hyalinized granulomas
- Patients may not have hilar adenopathy

Necrotizing Sarcoid Granulomatosis
- First described by Leibow in 1973; rare
- May be a form of nodular sarcoidosis, a cross between sarcoid and Wegener's, or a discrete entity
- Extensive noncaseating granulomatous inflammation, vasculitis, and foci of parenchymal necrosis
- Confluent areas of cell-formed granulomas replace large areas of lung, and contain irregular zones of necrosis

Wegener's Granulomatosis
Classic Form
- Acute necrotizing granulomas of upper and lower respiratory tract (with giant cells and leukocytes); necrotizing vasculitis in lungs; focal or diffuse necrotizing glomerulonephritis
- Peak incidence is in 40's; M>F
- Persistent pneumonitis, chronic sinusitis, nasopharyngeal ulcerations, renal disease
- If untreated, 80% will die within 1 yr; if treated (immuno-suppression, eg cyclophosphamide), 90% respond
- Serum antineutrophil cytoplasmic antibodies serve as marker for disease activity
- Multiple bilateral nodules of liquefactive and coagulative necrosis in lung, creating large geographic lesions with eosinophils, giant cells (not forming well defined granulomas), leukocytoclastic angiitis (both arteries and veins); only scant numbers of lymphocytes or plasma cells
- Fulminant type: predominantly exudative changes
- Fibrous scar type: abundant collagen deposition

Limited Form
- Confined to lungs; no renal involvement
- Histology identical to classic form; more protracted course

Eosinophilic Granuloma
- AKA: Langerhans cell granulomatosis, Histiocytosis X
- 30% incidental finding; 25% present with pneumothorax
- Mean age 30 yrs, but large range - most are smokers
- Involvement limited to lung in 50%
- Patchy, nodular interstitial lesion with bronchiolocentric distribution, most commonly upper lobes - stellate nodules due to extension along alveolar septa
- Histiocytes with variable numbers of eosinophils, plasma cells, lymphocytes
- Macrophages often accumulate around lesions (DIP-like)
- EM shows characteristic Birbeck granules

Bronchocentric Granulomatosis
- Pathogenesis is immunologic
- Granulomatous inflammatory process beginning within bronchiole walls with destruction which may extend slightly into surrounding lung
- Histiocytes initially replace bronchiolar mucosa, palisading around lumen, eventually destroying entire wall with necrosis and cell debris and neutrophils surrounded by palisading histiocytes - necrosis often extends to involve cartilage
- Maintains peribronchiolar distribution
- Mucoid impaction of larger airways, often with fungal hyphae within the mucous, is common
- Closely related to chronic eosinophilic pneumonia
- Half patients have asthma, many allergic bronchopulmonary aspergillosis

Collagen Vascular Diseases
Rheumatoid Arthritis
- Interstitial pneumonia and fibrosis, often indistinguishable from UIP, may have prominent lymphoid aggregates with germinal centers (cellular CIP), BOOP, obliterative bronchiolitis, follicular bronchiolitis
- Necrobiotic nodules rare in parenchyma
- Vasculitis and/or pulmonary hypertension have been seen
- Pleural lesions include non-specific pleuritis and necrobiotic (rheumatoid) nodules
- Better prognosis than UIP

Systemic Lupus Erythematosus (SLE)
- Pleuritis, pleural effusion, pleural fibrosis
- Chronic interstitial pneumonia common, generally without much fibrosis
- DAD, intra-alveolar hemorrhage, pulmonary HTN, vasculitis

Scleroderma (Progressive Systemic Sclerosis)
- Interstitial fibrosis, more prominent in lower lobes, varying from UIP-like to honeycombing

Pulmonary Alveolar Proteinosis

AKA: pulmonary alveolar lipoproteinosis
Filling of alveolar spaces with PAS+ proteinaceous material with normal interstitial pulmonary architecture
Associated with immunodeficiencies, underlying malignancies (especially leukemia and lymphoma), infections agents, industrial or environmental exposures
Patients present with slowly progressive pulmonary infiltrates, dyspnea, cough, sputum, fever
Rx: pulmonary lavage

Amyloidosis

Generally an incidental finding rather than clinically significant

Diffuse Alveolar-Septal Amyloidosis
Most common in primary amyloidosis or multiple myeloma
Deposits in media of vessels and alveolar septa which may bulge into alveolar spaces

Nodular Pulmonary Amyloidosis
Generally not associated with deposits in other organs
Discrete peripheral tumor like nodules 1-3 cm composed of dense amorphous eosinophilic material often with aggregates of plasma cells, lymphocytes, giant cells

Tracheobronchial Amyloidosis
Rare - deposits confined to bronchial tree

Transplantation Related Disorders

Bone Marrow Transplantation
Pulmonary complications in ~50% patients
Usually infectious (CMV, bacteria) or interstitial pneumonia, obliterative bronchiolitis, lymphocytic bronchitis

Heart-Lung Transplantation
50% develop obliterative bronchiolitis after mean interval of 10 months - 50% mortality - probably type of chronic reject.
Acute rejection: w/in 3 months, perivascular mononuclear infiltrate affecting venules and small arteries: small lymphocytes, plasma cells, lymphoblasts

Other

Lymphomatoid Granulomatosis
(see Hematolymphoid Outline)

Pulmonary Alveolar Microlithiasis
Rare
Laminated calcospherites in the lung in the absence of any known abnormality of calcium metabolism

Pulmonary Hyalinizing Granuloma
Slowly enlarging nodules of thick collagen bundles with lymphocytes and plasma cells
Perivascular inflammation and mild vasculitis may be seen

Sclerosing Mediastinitis
Destructive and infiltrative proliferation of connective tissue in the mediastinum
May be exaggerated hypersensitivity reaction to infection in mediastinal lymph nodes

Mesenchymal Cystic Hamartoma
Multifocal bilateral small (<1 cm) cysts lined by metaplastic respiratory epithelium resting on a cellular cambium layer of mesenchymal cells

Pulmonary Vascular Disorders

Pulmonary Congestion and Edema

Hemodynamic
Increased hydrostatic pressure, as seen in congestive heart failure, causes increased interstitial fluid
Fluid accumulates only after lymphatic drainage has increased by about tenfold
Edema is initially interstitial but later becomes alveolar
Alveolar fluid accumulation more prominent in the lower lobes
Alveolar microhemorrhages and hemosiderin laden macrophages are common ("heart failure cells")

Microvascular Injury
Alveolocapillary membrane injury by inflammation, infection, toxins, shock
When diffuse, can lead to Adult Respiratory Distress Syndrome

Pulmonary Embolism / Infarction

Occlusions of pulmonary arteries by blood clot - almost always embolic in origin
In 95% cases, thrombi from deep veins of the leg
Large emboli (e.g., saddle embolus) often cause sudden death; if not, clinical picture may resemble myocardial infarction
If patient survives, clot may retract and eventually become totally lysed, leaving only small membranous webs
(NOTE: See also outline on Vessels)

Infarctions
When bronchial artery circulation is intact, embolization does not lead to infarction; thus, only ~10% emboli –> infarction
Infarction occurs with bronchial circulation is inadequate - therefore seen in elderly patients
Infarction most commonly lower lobe (75%), with a wedge shaped pleural based lesion, hemorrhagic at first, but then becomes pale as red cells lyse and fibrous replacement begins (at the margins)

Pulmonary Hypertension

Normally, pulmonary arterial pressures are only 1/8 of systemic levels
Atherosclerotic changes in pulmonary arteries generally indicative of pulmonary hypertension (except, can see mild atherosclerosis in elderly patients)

GRADING
Grades I-III are considered potentially reversible
Grades IV-VI are considered usually irreversible

Grade I
Medial muscular hypertrophy involving small arteries (media thickness exceeds 7% of external diameter of artery)
Extension of smooth muscle into small vessels in lung periphery

Grade II
Muscle hypertrophy plus intimal cell proliferation in small muscular arteries
Proliferating cells are not endothelial: smooth muscle or myofibroblast

Grade III
Concentric lamellar intimal fibrosis of muscular arteries
Eventually, fibrous tissue and reduplicated internal elastic lamina occlude the vascular lumen
Larger elastic arteries show atherosclerosis

Grade IV
Widespread dilatation of the small pulmonary arteries and arterioles
Plexiform lesions: aneurysmal expansion of the vessel wall of small muscular arteries usually just distal to their origin

from a larger vessel: proliferation of tiny vascular channels lined by myofibroblasts resembling endothelial cells

Grade V

Above changes plus vein-like branches of hypertrophied muscular arteries with minimal media

Angiomatoid lesions: exaggerated form of vein like branching in which a conglomeration of thin walled vessels is found adjacent to a muscular artery

Hemosiderin laden macrophages throughout the lung

Grade VI

Fibrinoid necrosis and necrotizing vasculitis with neutrophils and eosinophils

CAUSES

Primary cardiac disease - increased flow

Atrial septal defect, VSD, patent ductus arteriosus

Pulmonary Venous Congestion

(see below)

Primary pulmonary parenchymal disease

Increased pulmonary vascular resistance secondary to COPD, interstitial lung disease, recurrent emboli

Pulmonary Veno-occlusive disease

Obstruction of small pulmonary veins by concentric or eccentric intimal fibrosis

May overlook (interpret as interstitial fibrosis) unless do elastic stain to outline vessel walls

Can get medial hypertrophy in arteries

>50% of patients are ≤16 yrs old

Etiology unknown - ?venous thrombosis

Primary Pulmonary Hypertension

May be related to chronic vascular hyper-reactivity, chronic vasoconstriction, and resultant hypertension, intimal and medial hypertrophy

Lymphangiomyomatosis

AKA: lymphangioleiomyomatosis

Haphazard proliferation of smooth muscle cells throughout the interstitium of the lung involving walls of vessels, lymphatics, bronchioles, and septa

Extrapulmonary involvement (lymphatics, lymph nodes in thorax and/or abdomen) may be seen

Occurs exclusively in women in reproductive years

Associated with tuberous sclerosis - may be a limited form

Differential diagnosis: end stage UIP which can show smooth muscle proliferation

LUNG - Tumors

Inflammatory "Pseudotumors"

Almost always asymptomatic incidental findings on chest X-ray; small, solitary

Some of these entities may be or may progress to true neoplasms

Plasma Cell Granuloma

AKA: fibroxanthoma, histiocytoma

More common in children and young adults

Usually peripheral

Mature plasma cells and lymphocytes in a framework of fibrosis and granulation tissue

Mast cells and foamy histiocytes usually present

Sclerosing Hemangioma

Usually adult females; usually peripheral, lower lung fields

Well circumscribed but not encapsulated

Compact growth of polygonal cells lining sclerotic cores of papillary projections

EMA, keratin positive

No evidence for vascular etiology; probably type II pneumocytes

Pseudolymphoma

Similar to LIP but isolated masses vs diffuse infiltrate

Represents residuum of healing inflammatory lesion

Nodular mass which replaces a portion of the pulmonary parenchyma; scarring most prominent in the center with densely packed collagen, fibroblasts, and lymphocytes but no necrosis

May have germinal centers

Distinction from lymphoma: no hilar LN involvement, numerous germinal centers, mixed inflammatory cell population; lymphoma more monomorphous and has a lymphangitic distribution

Bronchogenic Carcinoma

GENERAL

Increasing in frequency over past 50 yrs

More common in males, but difference is decreasing

90% patients over 40; multiple tumors in 5%

60% incurable at time of detection

Some detected incidentally as coin lesion on chest X-ray; 35-50% coin lesions turn out to be carcinoma

Indisputable association with smoking, which increases relative risk by factor of 20 (increased risk for all types); also thought to be related to pulmonary fibrosis

Patients may present with extrapulmonary symptoms: clubbing of fingers (hypertrophic pulmonary osteoarthropathy), cortical cerebellar degeneration, encephalomyelitis

Many lung tumors are associated with ectopic secretion of hormones:

- Small Cell: ACTH, serotonin, ADH, HCG
- Carcinoids: ACTH, serotonin, HCG
- Squamous Cell: PTH

Bronchogenic carcinomas all presumably arise from bronchial epithelium; therefore, it is not uncommon for the tumors to have mixed or varied histological patterns

STAGING

Spread is by direct extension proximally and distally along bronchi; may seed pleura or mediastinum

Lymphatic spread first to hilar nodes, then mediastinal, lower cervical, and less commonly axillary and subdiaphragmatic

Metastases to liver, other area in lung, adrenal, bone, kidney, CNS - brain metastases most common for adenocarcinoma

T1: ≤3 cm; no invasion proximal to lobar bronchus
T2: >3 cm or pleural invasion or <2 cm from carina
T3: direct extension (parietal pleura, diaphragm, ...)
N1: Peribronchial or ipsilateral hilar nodes
N2: Ipsilateral mediastinal LNs

N3: Contralateral LNs or more distant LNs
M1: Distant metastases

Stage	T1	T2	T3
N0	I	I	III A
N1	II	II	III A
N2	III A	III A	III A
N3	III B	III B	III B

Stage I and II are operable, III is not

PROGNOSIS

60% of patients go to surgery; 60% of these are resectable
Radiation helps, but limited by the fact that 50% have metastases at time of diagnosis
TNM stage best prognostic indicator
Poor prognostic signs: age<40; F; vascular invasion, chest wall invasion, presence of a scar, aneuploid
Good prognostic sign: strong inflammatory response

Squamous Cell Carcinoma (35-50%)

AKA: Epidermoid carcinoma
>80% occur in males; most closely associated with smoking
Most are central (segmental bronchi) and present as hilar or perihilar masses
"Early carcinomas" can be polypoid, nodular, or superficially infiltrating
Generally larger than other lung carcinomas at diagnosis; grows more rapidly but tends to metastasize later
50% show signs of bronchial obstruction
Marked tendency to undergo central necrosis and cavitation
Squamous metaplasia or carcinoma in situ common in adjacent bronchial mucosa
Hypercalcemia due to PTH related protein is common
Calcification is extremely uncommon
High MW keratin staining is positive
Most curable of the lung cancers; 5 yr survival: 90% for "early lesions", 40% for well differentiated, 20% for moderately, 7% for poorly

Adenocarcinoma (15-35%)

50% of all tumors in females - increasing in prevalence (M=F)
Most commonly peripheral; often involve pleura
Usually poorly circumscribed gray-yellowish lesions
Many are associated with a "scar", but it is not always clear if the scar preceded the tumor or vice versa. Most tumor associated scars contain predominantly type III collagen, which is characteristic of a newly formed scar rather than established fibrosis, suggesting the scar follows the carcinoma
Traditionally, areas will exhibit gland formation, papillae, and/or secretion of mucin
Wide range of histologic patterns, merging with bronchioloalveolar carcinoma on one end and with undifferentiated large cell carcinoma on the other end. Major cell types are: bronchial surface cells (without mucus production), goblet cell, bronchial gland cell, Clara cell, type II alveolar cell, and mixed cell types
Low MW keratin, EMA, CEA positive; may be vimentin +
50% positive for surfactant apoprotein - can be used to distinguish primary from metastatic carcinoma
K-ras mutationally activated in some adenocarcinomas
Blood vessel invasion present at resection in >80%; resectability rate ~70% (twice other bronchogenic carcinomas)
5 yr survival 25%, independent of degree of differentiation or histologic type
Most important prognostic factors are metastases (LN or distant) and pleural involvement
Rarely, peripheral adenocarcinoma may spread massively into pleural space coating both pleural layers, simulating mesothelioma

Bronchioloalveolar Carcinoma

This term sometimes used to describe a pattern of adenocarcinoma; if restrict term to very well differentiated single lesions with no alveolar wall scaring and no other carcinoma pattern, accompanied by a slightly better prognosis (50-75% 5 yr survival if resectable solitary lesion)
If multiple lesions present, long term survival still very poor
Well differentiated cells lining respiratory spaces without stromal invasion
Can grow as a single peripheral nodule, multiple nodules, or a diffuse pulmonic-like infiltrate; tumor cells tend to grow along spaces: alveolar, perineural, sinusoidal in LNs. Generally does NOT form solid mass or invade structures
Three major histologic types:
• Clara cell type (38%)
• Type II pneumocytes (33%): mucin negative; slightly better prognosis
• Mucinous type (29%): more commonly multiple, therefore worst prognosis
Intranuclear inclusions can be present
Psammoma bodies are present in 13%

Small Cell Carcinoma (10-20%)

80% male, >85% smokers; typically central; may be small
Growth patterns: subepithelial, nodular, mixed, or peripheral; histologically: streaming, ribbons, rosettes, tubules, ductules
Hyperchromatic nuclei with finely dispersed chromatin (salt and pepper) with no obvious nucleoli and a thin nuclear membrane
Usually keratin positive; may also be positive for neural markers: neurofilaments, Leu 7, NSE
EM shows scattered dense core secretory granules
Tumor may derive from neuroendocrine cells of bronchi
Many of these tumors have a deletion of chromosome 3p
myc gene amplification may correlate with prognosis
Dismal prognosis: <2% 5 yr survival; chemotherapy helps in short term
Cytologic Types:
• Oat Cell (lymphocyte like): 42%; frequently see crush artifact; Azzopardi effect: basophilic deposits of chromatin surrounding blood vessels in areas of necrosis
• Fusiform: (29%); somewhat larger cell size
• Polygonal: (29%); medium sized cells with abundant cytoplasm; often confused with other lung carcinomas
Alternative Histologic Classification:
Oat cell, intermediate cell type (combines fusiform and polygonal), and combined

Undifferentiated Large Cell Carcinoma

10-15% of all lung tumors
Pleomorphic tumors without definite evidence of squamous or glandular differentiation (often diagnosis of exclusion)
Probably poorly differentiated variants of other tumor types
Ultrastructural and immunohistochemical features suggest a closer relationship to adenocarcinomas
Some associated with marked peripheral eosinophilia

Giant Cell Carcinoma

~1% of all lung tumors, ~5% of large cell carcinomas
Bizarre multinucleated giant cells and mononuclear forms growing in a solid fashion simulating sarcoma; nuclei are often so large as to suggest CMV infection
Heavy neutrophilic infiltrations between and within tumor cells
Most are peripheral and extensive at time of diagnosis
In some cases, foci of glandular differentiation can be found

LN metastases in nearly 100%; also tends to metastasize to adrenal glands and GI tract
Very aggressive tumor - incurable

Clear Cell Carcinoma
Term should be restricted to cases in which the entire tumor is clear (rare), rather than for other carcinomas which show focal clear cell change
Malignant, mitotically active cells
Keratin, EMA, and LeuM1 positive (just like renal cell carcinoma); however (unlike RCC) tend to be CEA+ and negative for lipid stains
Be sure to consider renal cell carcinoma and sugar tumor

Others

Adenosquamous Carcinoma
Unquestionable evidence of squamous and glandular differentiation found in the same neoplasm in roughly equivalent amounts
Less than 10% lung cancers; most are peripheral

Benign Clear Cell Tumor ("Sugar Tumor")
Rare tumor of unclear histogenesis
Small bland nuclei, no mitoses, well defined cell borders
Clear cytoplasm due to accumulation of glycogen; PAS +

Carcinosarcoma
Intermingling of carcinoma (usually squamous cell) with malignant spindle-shaped cells simulating fibrosarcoma or malignant fibrous histiocytoma
Osteoclast like giant cells may be present
Probably carcinoma with sarcoma-like stroma
Prognosis similar to routine bronchogenic carcinoma

Pulmonary Blastoma (Embryoma)
May present in adults or children; usually peripheral
Well differentiated glands in a cellular stroma composed of undifferentiated spindle cells - resembles fetal lung
Stromal component may differentiate toward skeletal muscle, smooth muscle, cartilage, or bone
May be related to carcinosarcoma

Other Tumors

Carcinoid Tumors

Formerly known as "bronchial adenoma"
Less than 5% of primary pulmonary neoplasms
Younger age of incidence (usually <40 yrs)
No association with smoking or other environmental factors
Generally divided into three major types, but there is much overlap - actually a continuum

Central Carcinoid
Most common type; usually adults, but most common primary lung neoplasm in children
Usually presents as a slow growing solitary endobronchial, often polypoid mass with high vascularity (hemoptysis)
Most hormonally silent, but may secrete serotonin, ACTH
Overlying mucosa usually intact; grayish yellow cut surface
Small uniform cells with central nuclei growing in compact nests, ribbons, festoons, pseudopapillary, papillary, or solid patterns
Dense core granules by EM
Variable reactivity for keratin, serotonin, NSE, chromogranin, synaptophysin, Leu 7, neurofilaments; CEA positivity may be associated with more aggressive behavior
Metastases to regional lymph nodes in 5%; rare distant metastases
70-80% 10 year survival
Oncocytic variant exists - similar behavior

Peripheral Carcinoid
More peripheral in origin, often subpleural
Tends to be multiple
Histologically, more spindled simulating smooth muscle, some pleomorphism, few mitoses
Amyloid and melanin may be found, and calcitonin reactivity may be present
Excellent prognosis, metastases rare
Tumorlet: nodular proliferation of small spindle cells around bronchioles - may be minute carcinoids or reactive process

Atypical Carcinoid
Either of above but with increased mitotic activity, nuclear hyperchromasia, or necrosis
LN metastases in 50-70%

Hamartoma

AKA: chondroid hamartoma; chondroid adenoma; chondroma
Benign - occurs in adults - usually solitary
Most commonly just beneath pleura
Usually presents as asymptomatic incidental X-ray finding
Composed of islands of cartilage (may calcify), fat, smooth muscle, and clefts lined by respiratory epithelium
An endobronchial variant exists with more adipose tissue and fewer epithelial cells and less cartilage

Paraganglioma (Chemodectoma)

May rarely occur in the lung - usually peripheral and benign
May be difficult to distinguish from carcinoid - look for S-100 positive sustentacular cells

Vascular Tumors

Kaposi's Sarcoma
Capillary Hemangioma
Angiosarcoma
Lymphangiomyomatosis

Intravascular Bronchioloalveolar Tumor (IV-BAT)
Pulmonary form of epithelioid hemangioendothelioma
Young adults; >80% female
Thin rim of plump acidophilic cells surrounding an eosinophilic mass of hyalinized stroma, sometimes calcified
Polypoid formations fill alveoli, arteries, veins

Salivary Gland-Type Tumors

Adenoid cystic carcinoma
Nodular (polypoid) and diffuse (subepithelial) types

Mucoepidermoid carcinoma
Low grade and high grade varieties

Acinic Cell Tumor

Lymphoma

Most are B-cell, most small lymphocytic type
Derived from bronchial mucosal associated lymphoid tissue
Differential diagnosis from LIP or pseudolymphoma can be very difficult

Metastases

PLEURA

Normal

Pleura (both visceral and parietal) is lined by mesodermally derived mesothelial cells
Mesothelial cells show apical tight junctions, desmosomes, surface microvilli, and a thick glycocalyx
Immunoreactive for low & high MW keratins
Most pleural pathology is secondary to some underlying pulmonary pathology

Pleural Effusions

Serous
Normally ~15mls
If more, usually bilateral and due to cardiac failure
Also seen with generalized edema (renal failure, cirrhosis)
Serofibrinous
Pleuritis: pneumonia, tuberculosis, lung infarcts, lung abscess, bronchiectasis
Rheumatoid arthritis, systemic lupus erythematosus
Radiation
Suppurative (Empyema)
Bacterial of mycotic seeding of pleural cavity, most commonly by contiguous spread from lung, occasionally by hematogenous spread
Hemorrhagic
Most commonly, small amount of blood due to procedure
When bloody serous effusion unrelated to procedure, most common cause is malignancy
Also consider hemorrhagic diathesis, rickettsial disease
Blood (Hemothorax)
Almost always ruptured aorta; almost always fatal
Chyle (Chylothorax)
Milky white material which, when allowed to stand, separates into layers, the upper of which is creamy and fatty
Usually indicates pulmonary lymphatic blockage, most commonly due to malignancy

Pleural Plaques

Hyalinized fibrous tissue usually but not always associated with asbestos exposure
Characteristically parietal or diaphragmatic; may calcify

Tumors

Mesothelial cells undergo hyperplastic response to injury or chronic irritation, which can be almost impossible to distinguish from well differentiated mesothelioma
p53 expression has been noted to be elevated in 70% of mesotheliomas, but is normal in reactive mesothelium

Solitary Fibrous Tumor of Pleura

AKA: solitary fibrous mesothelioma
Well circumscribed, sometimes encapsulated; usually visceral pleura
Usually asymptomatic
May present with pulmonary osteoarthropathy which vanishes upon tumor resection
No association with asbestos
Firm, lobulated, sometimes pedunculated, with whirled cut surface - mean diameter 6 cm
Tangled network of fibroblast like cells with deposition of abundant reticulin and collagen fibers; often referred to as the "patternless pattern"; cellularity varies from densely cellular to edematous to densely collagenous
Probably NOT mesothelial in origin
Tumor cells are CD34 positive
Usually cured by simple excision; may recur
15-20% behave "aggressively", with repeated recurrences
Aggressive signs include >5cm, absence of pedicle, high cellularity, and mitoses or necrosis

Benign Mesothelioma

AKA: Pleural fibroma
Relatively common in peritoneal cavity, more rare in pleural cavity
Soft friable mass, mottled, gray/pink/yellow
Papillary processes lined by one or several layers of cuboidal mesothelial cells
No atypia, solitary, well circumscribed

Malignant Mesothelioma

At least 2/3 are related to asbestos exposure
Chronic asbestos exposure caries a 2-3% risk of mesothelioma - risk is not increased by smoking (NOTE: risk of adenocarcinoma much higher); amphiboles (especially crocidolite) are most carcinogenic; chrysotile is least carcinogenic
Long latency between exposure and tumor: 25-45 years
Asbestos bodies more commonly found in lung
Multiple gray or white ill defined nodules diffusely thickening pleura - may grow extensively to fill pleural space and encase lung
Pleural effusion almost always present
Prognosis uniformly bad - 50% 1 year survival
Epithelial Type
Papillae or pseudoacini or even solid nests of cuboidal, columnar, or flattened cells
May be difficult to distinguish from pulmonary adenocarcinoma
Spindle Type (Sarcomatoid)
More nodular and less plaque-like
Often with hemorrhage, necrosis, cystic changes
Highly cellular, interweaving bundles of spindle cells
Nuclear atypia, mitotic figures common
When large amounts of collagen: desmoplastic mesothelioma
Worse prognosis than epithelial type; more often becomes diffuse
Associated with hypoglycemia which resolves upon removal of the tumor
Mixed (Biphasic)
Combination of epithelial and spindle types
Can resemble synovial sarcoma
Small Cell Mesothelioma
Very rare

DISTINGUISHING FROM PULMONARY ADENOCARCINOMA

Mesotheliomas produce hyaluronic acid (intracellular and extracellular) which can be stained with Alcian blue in a hyaluronidase sensitive manner
Mucicarmine or PAS positive droplets in cells favor adenocarcinoma
EM: mesothelial cells have long slender microvilli
Mesothelial cells are keratin, vimentin, EMA, S100 positive, and almost always CEA, Leu-M1, Ber-EP4 negative
Adenocarcinoma is consistently keratin, EMA, CEA, Leu-M1, Ber-EP4 positive
HMFG-2 stains only cell membranes of mesothelial cells but shows cytoplasmic staining for adenocarcinoma

HEART

Normal Anatomy

Weight: 300-350g (male); 250-300 g (female)
RV: 3-5mm ; LV: 13-15mm

Valves
- Lines of closure of semilunar valves marked by linear thickening, the centers of which have small fibrous nodules called corpora arantii
- Small fenestrations may exist on the downstream side of the closure line near the commisural attachments
- Papillary muscles for the mitral valve: Anterolateral is a single large column; posteromedial is divided into 3-4 pillars
- Histology: endothelial lined; thin layer of collagen and elastic tissue on atrial side, thick layer of dense collagen on ventricular side, loose myxoid connective tissue (zona spongiosa) in between

Conducting System
- SA Node: posterior wall of R atrium, adjacent to SVC
- AV Node: junction of median wall of right atrium with the interventricular septum
- Bundle of His: interventricular septum

Coronary Arteries
- LAD: apex, anterior LV, anterior 1/3 RV, anterior 2/3 septum
- RCA: lateral & posterior RV, posterior LV, posterior 1/3 septum
- LCx: lateral LV; in ~20% population, posterior circulation arises from this vessel ("left dominant")

Embryology

- The cardiovascular system is the first to function in the embryo; blood begins to circulate by the end of the third week
- Cardiac development begins on day 18-19 in the "cardiogenic area" of the splanchnic mesenchyme; heart forms as two side-by-side longitudinal cellular strands called cardiogenic cords
- Cardiogenic cords become canalized to form endocardial heart tubes - later fuse to form a single heart tube
- Formation of bulboventricular loop on day 23-24 introduces asymmetry
- Arterial system develops from paired aortic arches
- Venous system develops from venous end of heart

Aortic Arches
1: (Maxillary arteries)
2: (Stapedial arteries)
3: Common carotids / internal carotids
4: Proximal R subclavian — Aortic Arch
5: (nothing - may not even develop)
6: R pulmonary — L pulmonary / ductus arteriosus

- Note: left subclavian forms from the 7th intersegmental artery which migrates up the aorta to the arch

NON-NEOPLASTIC CARDIAC PATHOLOGY

Congenital Malformations

0.6-0.8% of live births
5% associated with chromosomal abnormalities
90% are "multifactorial" (unknown etiology)
2-10x more likely in sibling of an affected individual
However, monozygotic twins show only a 10% concordance of ventricular septal defects
Environmental causes: rubella, thalidomide, EtOH, smoking
Those producing right to left shunts (tetralogy of Fallot, transposition of the great vessels) also known as Cyanotic heart disease; paradoxical embolization may occur
Those producing left to right shunts (VSD, PDA, ASD) are also known as Late Cyanotic Heart disease; the shunt induces pulmonary hypertension, right ventricular hypertrophy, and eventually reversal of the flow through the shunt (Eisenmenger's syndrome)

Ventricular Septal Defect

Most common type: 30%
Frequency has been increasing in US
Small VSD's require no intervention; most close spontaneously
90% lie within or adjacent to the membranous septum

Patent Ductus Arteriosus

10% congenital cardiac anomalies
Joins pulmonary trunk to aorta just distal to left subclavian artery; functionally closes in first day or two of life
Prostaglandin E maintains ductus open
Closure stimulated by increased oxygen tension
Indomethacin induces closure by inhibiting prostaglandin E synthesis

Atrial Septal Defect

10% congenital cardiac anomalies
Three types:
- Ostium primum (5%): low in septum, adjacent to AV valves; common in Down's syndrome
- Ostium secundum (90%): at the site of the foramen ovale
- Sinus venosus (5%): high in septum near SVC

Pulmonic Stenosis / Atresia

7% congenital cardiac anomalies
With atresia, RV hypoplastic
Stenosis usually caused by fusion of the valve cusps

Coarctation of the Aorta

7% congenital cardiac anomalies
M:F=3:1, also common in Turner's syndrome
Accompanied by other defects in 50% cases (PDA, bicuspid aortic valve, AS, ASD, VSD, ...)
Usually occurs just distal (localized, adult type) or occasionally just proximal (diffuse, infantile type) to the ductus arteriosus
If not corrected, 60% die before age 40, often of aortic rupture

Aortic Stenosis

6% congenital cardiac anomalies
Most commonly bicuspid valve - predisposes to calcification later in life
Both valvular and subvalvular stenosis exist

Tetralogy of Fallot

6% congenital cardiac anomalies
• Ventricular septal defect, usually large
• Aorta which over-rides the septum
• Obstruction of right ventricular outflow, usually due to infundibular narrowing but occasionally pulmonic stenosis
• Right ventricular hypertrophy
Most common form of cyanotic heart disease
Can survive, even without surgical correction
Heart often boot shaped due to right ventricular hypertrophy
Pulmonic orifice generally does not grow with heart, so right to left shunting can increase with age; however, pulmonary changes do not occur (stenosis protects lungs), and RVH is limited since RV is decompressed into LV and aorta

Transposition of the Great Vessels

4% congenital cardiac anomalies; more common in infants of diabetic mothers
Cyanosis from birth - some interatrial communication is required for survival; 60% have PDA, 30% VSD
Most commonly, aorta arises from morphologic right ventricle and lies anterior to the pulmonary artery
Surgical correction: ventricles are inverted relative to the atria, so the right atrium supplies the left ventricle and thus the pulmonary artery
Often, other abnormalities of the AV canal are present

Truncus Arteriosus

2% congenital cardiac anomalies
Developmental failure of separation of the aorta and pulmonary artery: single large vessel with infundibular VSD

Tricuspid Atresia

1.5% congenital cardiac anomalies
Complete absence of tricuspid valve, underdeveloped RV, and an ASD

Anomalous Coronary Arteries

Left main arising from pulmonary trunk: early infarcts
Left main arising from right Sinus of Valsalva: associated with sudden death in adults

Cardiomyopathies

Congestive Heart Failure

Common end point for many forms of heart disease
Decompensation of cardiac function following failure to maintain sufficient output for metabolic needs

Left Sided Failure

Causes: Ischemic heart disease, Hypertension, Aortic or mitral valve disease, myocardial disease
Manifested most commonly by fluid accumulation in the lungs
Dyspnea, orthopnea, paroxysmal nocturnal dyspnea

Right Sided Failure

Causes: Left sided failure, increased pulmonary vascular resistance, myocarditis
Manifested by systemic congestion, especially in the liver, spleen, subcutaneous tissue

Ischemic Heart Disease

80% of all cardiac mortality (only slightly less than in 1970)
By far, the most common cause of sudden cardiac death
>90% cases caused by decreased coronary blood flow secondary to: atherosclerosis, thrombosis, vasospasm, arteritis, emboli, increased right atrial pressure

Angina

Chest pain just short of irreversible myocardial damage

Stable

Due to fixed stenosis, usually in first 2 cm of major coronary artery; 75% stenosis is sufficient to limit flow requirements during increased demand
ST depressions seen on ECG: subendocardial ischemia

Unstable (Crescendo)

Increasing frequency of pain, precipitated by decreasing efforts or occurring at rest
"Pre-infarction angina" - likely to progress to infarction
Probably represents thrombosis of a branch rather than a main coronary artery, with subsequent dilatation of collateral channels preventing infarction (if progresses slowly enough to allow collateral dilatation)

Prinzmetal's (Variant)

Due to coronary artery spasm
ST elevations seen on ECG: transmural ischemia

Myocardial Infarction

Predominantly a disease of the left ventricle
25-80% (depending on study) caused by thrombosis, often over an ulcerated plaque, in a main coronary artery
5% occur before age 40; incidence increases with age
M:F = 4-5:1 before age 50, then ratio decreases with age
Two types:
• Transmural ("Q-wave infarct"): most common, near full thickness (>60%), >2.5 cm
• Subendocardial: necrosis limited to inner 1/3 to 1/2 wall (systolic compression causes subendocardium to be most sensitive to ischemia)
Loss of contractility occurs with 1-2 minutes of ischemia, ATP is 50% depleted at 10 minutes, irreversible injury occurs at 20-40 minutes

Gross Changes

None in first 6-12 hrs, although treatment with triphenyl-tetrazolium chloride (TTC) can impart a red-brown color on non-infarcted myocardium (due to presence of dehydrogenases), thereby highlighting infarcted areas even at 3-6 hrs post infarct
18-24 hrs: pallor; red-blue cyanotic hue; then yellow
1 wk: hyperemic rim of vascularized connective tissue
7 wks: scarring complete

Histologic Changes

Waviness of fibers	1-3 hrs
Coagulative necrosis	4-12 hrs
Neutrophil infiltration	12-24 hrs
Contraction band necrosis (reperfusion)	18-24 hrs
Total coagulative necrosis	24-72 hrs

Complications

Post-infarct arrhythmia (most common cause of death) [90%]
Congestive heart failure [60%]
Hypotension / shock [10%]
Myocardial rupture [1-5%] (2-5 days)
Papillary muscle infarction/rupture
Subsequent infarct expansion
Fibrinohemorrhagic pericarditis
Mural thrombosis
Ventricular Aneurysm (1-2 days)

Chronic Ischemic Heart Disease

Diffuse myocardial atrophy (brown atrophy)
Patchy perivascular and interstitial fibrosis
Progressive ischemic necrosis

Hypertensive Heart Disease

- 2nd most common heart disease; affects 25% US population
- Result of pressure overload on heart
- Myocytes form new myofilaments and organelles; nuclei and cells enlarge; NO new cells are formed
- With time, myocyte irregularities, dropout, and interstitial fibrosis is seen

Cor Pulmonale

- Refers to right ventricular enlargement due to diseases of the lung and specifically excluding LVH as a cause
- Seen with: COPD, pulmonary fibrosis (any etiology), pulmonary embolism or vascular sclerosis, kyphoscoliosis or massive obesity restricting chest wall movement, chronic atelectasis
- Acute form produces RV dilatation
- Chronic form produces RV hypertrophy

Dilated Cardiomyopathy

- AKA: Congestive Cardiomyopathy
- Refers to disease of unknown etiology in theory, but some causal relationships are suspected
- Heart increased in weight, but walls are of normal or reduced thickness
- All four chambers usually dilated
- Presents as slowly developing congestive failure which is 75% fatal within 5 yrs

Alcoholic Cardiomyopathy
- Alcohol and its metabolites are directly toxic to myocardium
- Thiamin deficiency and cobalt toxicity (used to be added to beer) also contribute

Pheochromocytoma
- Patients may have foci of apparent ischemic necrosis in myocardium due to catecholamine release
- Mechanism appears related to vasomotor constriction in the face of an increase heart rate

Hemochromatosis
- Most commonly produces a dilated cardiomyopathy, but may produce a restrictive picture

Peripartum Cardiomyopathy
- Seen in month before or six months after delivery
- Likely to be secondary to some nutritional deficiency

Adriamycin (Doxorubicin)
- Vacuolization of myocytes due to dilation of sarcotubular system is earliest change
- "Adria cell": loss of cross striations, homogeneous basophilic staining, loss of myofilaments
- Minimal to no inflammation
- Occurs more frequently after a lifetime dose above 500mg/m^2
- Changes most pronounced in subendocardial region, and are enhanced by radiation

Cyclophosphamide
- Hemorrhagic necrosis, extensive capillary thrombosis, interstitial hemorrhage and fibrin deposition

Familial Cardiomyopathies

Postviral Myocarditis

Idiopathic Hypertrophic Cardiomyopathy

- AKA: Idiopathic Hypertrophic Subaortic Stenosis (IHSS), Asymmetric Septal Hypertrophy (ASH)
- May be restricted to septum (15-30mm thick), but often not
- Some degree of left ventricular outflow tract obstruction is often seen (obstructive hypertrophic cardiomyopathy)
- Myofiber hypertrophy, myofiber disarray and interstitial fibrosis; intramyocardial coronary vessels seen in 50%
- Endocardial fibrosis of outflow tract
- In 1/2 cases, autosomal dominant; in some, the mutation has been localized to myosin gene (chromosome 14)
- Often presents in young adults, either by asymptomatic murmur on routine physical exam or by sudden death during strenuous exercise (mean age 19 yrs)

Infiltrative/Restrictive Cardiomyopathies

- Any disorder resulting in restriction of ventricular filling

Amyloidosis
- As part of Systemic Amyloidosis (AA type of amyloid) or isolated as in Senile Cardiac Amyloidosis (AF type of amyloid [transthyretin])

Endomyocardial Fibrosis
- Disease of children and young adults in Africa
- Endocardial fibrosis extending from apex into outflow tracts of left and/or right ventricle
- Scarring may extend into inner 1/3 of myocardium and may involve tricuspid and mitral valves
- Varying amounts of inflammation, including eosinophils, often seen at edge of scarring

Loeffler's Endocarditis
- AKA: Fibroblastic parietal endocarditis with blood eosinophilia
- Similar to endomyocardial fibrosis - may be part of same spectrum
- Three stages: acute myocarditis (necrotic), organizing thrombus, endomyocardial fibrosis
- Eosinophilic infiltration of other organs often seen
- Rapid downhill course to death

Endocardial Fibroelastosis
- Pearly-white thickening of the endocardium due to increase in collagen and elastic fibers on the surface. Most commonly in the left ventricle, occasionally in the left atrium, right ventricle, right atrium
- Most often seen in children under 2yrs; etiology unclear; may be a common pathway from several injury types

Sarcoidosis
- Cardiac involvement in 25% of patients with systemic disease
- Often present with arrhythmia or other conduction abnormality

Glycogenosis and other Glycogen Storage Diseases

Hemochromatosis
- Normally, there is no stainable iron in the myocardium
- Iron deposits are greater in the epicardium

Myocarditis

- Need to see both inflammation (usually lymphocytic) and myocyte necrosis
- Most commonly result in a dilated cardiomyopathy
- Deaths are from acute heart failure or arrhythmias

Viral
- Accounts for most cases of well-documented myocarditis
- Coxsackie A and B, ECHO, polio, influenza A and B, HIV
- Cardiac involvement follows primary infection by days-weeks

Protozoal
- Chagas' disease (caused by Trypanosoma cruzi)
- In endemic areas, causes 25% of ALL deaths in 25-40 year old age group

Hypersensitivity
- Primarily perivascular inflammation; can see eosinophils and occasional giant cells
- Penicillin, sulfonamides, streptomycin

Giant Cell Myocarditis (Fiedler's)
- Rare, idiopathic
- Widespread myocardial necrosis with numerous giant cells
- Seen in young adults; rapidly fatal

Others
- Bacterial, fungal, parasitic, spirochetes (Lyme disease), chlamydial disease
- Collagen vascular disease, radiation, heat stroke, etc.
- Sarcoidosis, Kawasaki's disease

Arrhythmogenic Right Ventricle

AKA: Right ventricular cardiomyopathy, Uhl's anomaly, parchment right ventricle
Focal thinning to absence of the right ventricular myocardium due to replacement of muscle by adipose and fibrous tissue (Note: a small amount of fatty replacement is normal)
Often familial; usually affects men
Leads to RV dilatation, arrhythmias, and sudden death

Cardiac Transplantation

Myocardial biopsy most sensitive indicator of rejection
Need at least 4 pieces of tissue with myocardium to be an adequate sampling
Don't mistake a previous biopsy site as indicative of rejection
Quilty: dense subendocardial lymphocyte infiltrate, seen in 15% of post-transplant biopsies, often composed predominantly of B-cells (unlike rejection which is predominantly T-cells)
Comment on whether or not there is myocyte necrosis

Grading of Rejection

0: No rejection
I: Mild rejection
  IA: Patchy, perivascular inflammation
  IB: Diffuse, sparse interstitial infiltrate
II: Moderate rejection: Single focus of aggressive infiltrate, and/or isolated myocyte dropout
III: Moderate rejection
  IIIA: Multifocal aggressive interstitial infiltrates
  IIIB: Diffuse inflammation with necrosis
IV: Severe rejection: abundant myocyte death with vasculitis, hemorrhage, neutrophils, necrosis; usually not reversible

Valvular Heart Disease

Mitral Valve Prolapse

AKA: Floppy mitral valve
Very common: 5-7% US population; M:F=2:3; usually 20's-40's; also associated with Marfan's syndrome
Midsystolic click; if valve leaks, also late systolic murmur
Intercordal ballooning (hooding), occasionally elongated chordae tendineae
20-40% have concomitant involvement of tricuspid valve; pulmonic involvement in 10%
Histologically: myxoid degeneration of zona fibrosa, thickening of zona spongiosa (normal ratio 1:1)
Usually asymptomatic. However, can lead to infective endocarditis, mitral insufficiency (gradual or sudden), arrhythmias, or sudden death (rare)

Calcification of Mitral Annulus

Stony hard beading behind valve leaflets at base, without accompanying inflammation, rarely affecting valve function
Seen in elderly patients, usually women, often in association with ischemic heart disease

Calcific Aortic Stenosis

Commonly occurs with a congenital unicuspid valve (symptomatic before15 yrs) or a bicuspid valve (50's-60's), may also occur with a normal valve (70's-80's)
Calcified masses within the valve leaflets which protrude from both sides of the cusps, resulting in immobile leaflets and either stenosis, incompetence, or both
Unknown etiology and pathogenesis; more common in men
In bicuspid valves, begins at free ends and progresses toward base. In tricuspid valves, begins at base
Left ventricle undergoes secondary concentric hypertrophy
Rx: valve replacement, balloon valvuloplasty

Rheumatic Heart Disease

Incidence steadily declining - now accounts for <10% valvular heart disease, although still the most common cause of mitral stenosis and still a major cause of cardiac morbidity in the 15-25 yr age group
RF occurs 1-5 wks following a strep group A pharyngitis (streptococcal infections elsewhere are not rheumatogenic)
Etiology is immune, either due to antibodies which cross react with streptococcal antigens or autoantibodies triggered by streptococcal antigens; antibodies localize to the sarcolemmal membranes

Acute Rheumatic Fever

Acute, recurrent disease, usually in children (5-15 yrs old)
Fever, migratory polyarthritis (in adults), carditis, subcutaneous nodules (giant Aschoff bodies), erythema marginatum of skin (targetoid lesions), Sydenham's chorea
Edema, collagen fragmentation, and fibrinoid change dominate in early phase (2-4 weeks after pharyngitis)
Aschoff bodies: subendocardial or perivascular foci of fibrinoid necrosis with lymphocytes, later with macrophages which can become epithelioid (granulomatous); after many years, replaced by fibrous scar
Caterpillar cells: large multinucleated giant cells with chromatin clumping lengthwise in nucleus, appearing owl-eyed on cross section
MacCallum's plaques: map-like thickening of endocardium over lesions, usually in left atrium
Lesions in pericardium, myocardium, and on valves
Valve lesions not well formed Aschoff bodies: foci of fibrinoid necrosis along the lines of closure and on chordae tendineae; small vegetations may be present
Despite myocarditis, <1% patient die from ARF

Chronic Rheumatic Heart Disease

Develops in only a small number of patients with ARF, after 10 or more years, more commonly following recurrent ARF or if the initial ARF is severe or occurs early in childhood
Valve leaflets thickened; fibrous bridging across commissures; calcifications; "fish-mouth" deformity
Chordae tendineae thickened, fused, shortened
Mitral involvement alone in 65-70%, mitral and aortic in 25%; tricuspid only when both mitral and aortic involved; very rarely pulmonic

Cardiac Valve Vegetations

Infective Endocarditis

Colonization or invasion of the valves by infective organisms which lead to the formation of bulky, friable vegetations on flow side near free edge; often forms polypoid masses of thrombus laden with bacteria which hang from edge of valve; may extend to back of valve
Acute and subacute forms, depending on the virulence of the organism; acute form usually bulkier, more often on normal valves, and more often erodes or perforates (can be fatal within days); subacute form, though more indolent, is less responsive to antibiotics and blood cultures often negative
Bacteremia seems to be a prerequisite for development of infective endocarditis, but is clearly not sufficient
Cardiac abnormalities creating turbulent flow predispose: septal defects, valvular stenosis/reflux, prosthetic valves
Alcohol abuse, immunosuppression, and colon cancer are also predisposing conditions
~30% of cases occur on "normal" valves
65% caused by streptococcus (viridans, bovis, fecalis, etc.); relatively low virulence; principal cause of subacute
20-30% caused by staphylococcus aureus - more virulent - leading cause of acute disease

Others include strep pneumonia, E coli, N gonorrhoeae
IV drug users: S. aureus, Candida, Aspergillus

Valve involvement:	Left Sided	Right Sided
Acute	70%	25%
Subacute	90%	5-10%
IV Drug Use	40%	50%

Pulmonic valve almost never involved
In setting of artificial valve, often involve valve ring
Complications: valvular insufficiency or stenosis, abscess, embolization to lungs, brain, spleen, kidneys, metastatic infections, focal or diffuse glomerulonephritis

Nonbacterial Thrombotic Endocarditis (Marantic Endocarditis)
Precipitation of small sterile masses of fibrin on valve leaflets
Usually single vegetation on line of closure, loosely attached
Commonly involves multiple valves
Can become large; indistinguishable from infective endocarditis but without valvular destruction; may be precursor to it
More common in chronic diseases (e.g., malignant tumors, especially adenocarcinoma)

Endocarditis of SLE (Libman-Sacks Disease)
Mitral and tricuspid valvulitis occasionally seen in SLE
Multiple small vegetations of the leaflets, usually on the back side (particularly the posterior mitral leaflet) but may be on flow side; diffusely distributed over leaflets; may extend onto mural endocardium
Edema, fibrinoid change, small deposits of nucleic acid
Rarely of clinical significance

Lambl's Excrescences
Small, heaped up lesions on flow side of valves
Collections of fibrin at sites of endothelial damage

Carcinoid Heart Disease
Involves endocardium and valves of right heart, particularly right ventricular outflow tract (pulmonic valve)
Carcinoid syndrome: episodic flushing of skin, cramps, nausea, vomiting, diarrhea - cardiac involvement in 1/2, pulmonary involvement in 1/3
Plaque-like fibrous thickening of endocardium and valvular cusps with proliferation of smooth muscle and collagen deposition (there are no carcinoid tumor cells in the lesion)
No destruction of valve leaflet

Hurler's Disease
Lack of iduronidase (mucopolysaccharidosis type I)
Sulfated mucopolysaccharides accumulate intracellularly in macrophages in the aortic and mitral valves, resulting in marked thickening with stenosis or incompetence

Prosthetic Valves - Complications
6-9% per patient year
• Thrombosis and thromboembolism
• Infective endocarditis, most commonly staphylococcus
• Calcifications
• Tears in leaflets / structural breakdown of valve
• Paravalvular Leaks
• Occlusion or Dysfunction due to tissue overgrowth

CARDIAC TUMORS

Primary tumors are extremely rare - metastases much more likely (30 times more likely)
Most common primary tumors (4) are benign and account for 70% of all primary tumors of the heart

Benign Tumors

Myxoma
Most common primary cardiac tumor (50%)
Sporadic and familial types
Sporadic tend to be single and are more common in women; familial more likely to be multiple (1/3), are more likely to occur outside of left atrium, and present at an earlier age
90% located in atria, with 80% of those in the left atrium; favored site is the fossa ovalis
1-10 cm, sessile or pedunculated
Easily confused grossly and histologically with organizing thrombus, especially when sessile
May actually be a reactive process or a hamartoma
Myxoma cells: stellate or globular
Numerous small vessels in a myxoid acid mucopoly-saccharide matrix, hemosiderin
Uncommon findings: mucin producing glands, cartilage, EMA/CEA positivity

Lipoma
Well localized, poorly encapsulated, usually subendocardial or subpericardial, but may be within myocardium
Usually left ventricle, right atrium, or interatrial septum
Like myxoma, may represent hamartomas

Papillary Fibroelastoma
AKA: fibroelastic hamartoma, fibroma, papilloma
Usually located on valves, particularly ventricular surface of semilunar valves and atrial surface of AV valves
Right sided lesions more common in children, left sided in adults
Cluster of hair-like projections 2-5 mm in length covering a discrete region of the endocardial surface
Central fibroelastic stroma, myxoid matrix, and overlying hyperplastic endothelium
Probably organized thrombi

Rhabdomyoma
Most common primary cardiac tumor in children
Frequently discovered in first year of life; often multiple; can cause valvular obstruction
Small, gray white myocardial masses protruding into ventricular chamber
Mixture of large round and polygonal cells with glycogen rich vacuoles separated by strands of cytoplasm radiating from cell center - Spider Cells - these cells have myofibers
Probably a hamartoma
50% are associated with tuberous sclerosis
40% mortality by 6 months of age; 60% by 1 yr, 80% by 5 yrs

Others
Congenital Polycystic Tumor of the Atrioventricular Node
AKA: endodermal heterotopia, "mesothelioma of the AV node"

Ductular structures, cysts, and solid nests of epithelial-like cells with desmosomes and microvilli (keratin and CEA positive)
Because of location, may cause complete heart block

Epithelioid Hemangioma
Solid or microcystic aggregates of cells with vesicular nuclei (often with deep grooves) and abundant acidophilic cytoplasm, often with vacuoles
Probably metaplastic process
May be mistaken for metastatic carcinoma
Cells are keratin positive (?why)

Paraganglioma
AKA: Extra-adrenal pheochromocytoma
Left atrium most commonly

Schwannoma

Granular Cell Tumor

Malignant Tumors

Angiosarcoma
Typically in right atrium - large mass with intracavitary extension; may also infiltrate the myocardium
Appearance similar to angiosarcoma elsewhere, but tends to be more poorly differentiated

Others
Kaposi's Sarcoma
Liposarcoma
Rhabdomyosarcoma

Metastatic Tumors
In order of frequency: carcinomas of lung, carcinoma of breast, melanoma, lymphoma, leukemia, renal cell carcinoma, choriocarcinoma
Most often involve the pericardium, but may also be multifocal in the myocardium or produce an intracavitary lesion

PERICARDIAL DISEASE

Fluid Accumulation in Pericardial Sac
30-50 cc thin, clear, straw-colored fluid normally present

Pericardial Effusions
Effusions as large as 500 cc can be seen
Serous: congestive heart failure, hypoproteinemia
Serosanguinous: blunt chest trauma, CPR
Chylous: lymphatic obstruction (benign or malignant)
Cholesterol: rare; myxedema, usually idiopathic

Hemopericardium
Rupture of heart or intrapericardial aorta (MI, dissecting aneurysm, sharp chest trauma)

Tamponade
200-300 mls, accumulated rapidly, can cause cardiac compression and death

Pericarditis
An acute inflammation. The term "chronic pericarditis" actually refers to healed pericarditis

Fibrinous Pericarditis
Most frequent type
Seen following myocardial infarct, rheumatic fever, trauma, uremia, radiation, SLE, severe pneumonias
Clinically, hear a loud pericardial friction rub
Rubbery fibrin mass loosely gluing the parietal and visceral pleura together ("bread and butter")
Histologically: entangled mass of threadlike eosinophilic fibers or large amorphous mass
May resolve or become organized to produce an adhesive pericarditis

Serous Pericarditis
Rheumatic fever, SLE, systemic scleroderma, tumors, uremia, virus or TB can present this way
Mild inflammation of epicardial and pericardial surfaces: both acute and chronic inflammatory cells
Serous fluid, usually 50-200mls - exudative: thus, develops slowly and rarely alters cardiac function

Suppurative (Purulent) Pericarditis
Bacterial, mycotic, or parasitic invasion
M:F=3:1, 10-40 yrs
Enter pericardial space by: direct extension, seeding from blood, lymphatic spread, seeding by instrumentation
Inflammation may extend into surrounding mediastinum
Usually results in organization and thus a constrictive pericarditis with clinical sequelae

Hemorrhagic Pericarditis
TB or malignant neoplasm (from lung or breast)
Can also be seen following cardiac surgery

Caseous Pericarditis
Almost always TB

Constrictive Pericarditis
Usually idiopathic, but may follow suppurative of caseous pericarditis (classically TB) or after cardiac surgery of heavy irradiation
Pericardial space obliterated and transformed into a thick (0.5-1cm) mass of fibrosis and scar tissue, usually with calcification, encasing heart and causing tremendous restriction
When adhesion and fibrosis extends from parietal pericardium into the mediastinum, referred to as *Adhesive Mediastinopericarditis*
Increased workload on heart induces hypertrophy and dilatation. However, if tightly adherent to the heart, cardiac hypertrophy and/or dilatation cannot occur

Soldier's Plaque
Focal pearly thickened epicardial plaque - indicative of a healed pericarditis

BLOOD AND LYMPHATIC VESSELS

Normal Anatomy/Histology

Three layers: intima, media, adventitia
Veins and lymphatic have "valves" - endothelial folds

ARTERY TYPES

Large Elastic arteries:
- AKA: aorta, brachiocephalic, subclavian, early common carotid
- Intima initially very thin, but thickens with age as myointimal cells proliferate and matrix accumulates
- Media contains a large amount of elastic tissue (responsible for maintaining both blood pressure and blood flow during diastole); poor vascular supply (only outer third penetrated by vasa vasorum)
- Adventitia poorly defined; many vasa vasorum

Medium Size Muscular arteries:
- Media well demarcated by internal and external elastic lamina
- Elastic laminae are fenestrated, allowing smooth muscle migration into intima

Arterioles (<2 mm):
- Thickness of wall about equal to the diameter of lumen
- As caliber decreases, lose demarcation of layers
- Rich nervous supply - responsible for autonomic control of systemic blood pressure

CELL TYPES

Endothelial Cells
- Thromboresistant
- Contain numerous pinocytotic vesicles and Weibel-Palade bodies (rod-shaped cytoplasmic organelles 0.1-0.3µm in length containing an internal structure of parallel tubules - these bodies contain the factor VIII associated antigen AKA von Willebrand factor)
- Intercellular junction integrity can be adjusted by vasoactive substances
- Can actively contract

Smooth Muscle Cell
- Vasoconstriction and dilatation are major roles
- Can migrate, proliferate, and can synthesize collagen, elastin, and proteoglycans
- Have receptors for LDL
- Responsible for intimal collagenization in atherosclerosis

Embryology

- Vascular system develops in week three of fetal life from mesodermal cells of the "blood islands" (peripheral cells of islands form endothelium, central cells give rise to hematopoietic elements)
- Initially located in region of yolk sac, eventually spread throughout mesenchyme of fetus
- Later, pericytes from the surrounding mesenchyme join the primitive vessels and differentiate into the wall layers

Normal Hemostasis

- Sequence: vascular injury, brief vasoconstriction, binding of platelets to subendothelial connective tissue, activation of platelets with aggregation (primary hemostasis), activation of plasma coagulation cascade (secondary hemostasis)
- Balance between Anti-Thrombotic and Thrombotic activities

Anti-thrombotic
- Endothelial surface is non-thrombogenic
- Thrombomodulin (endothelial surface protein) binds thrombin converting it into a protein C activator, which, with protein S, is a potent anticoagulant
- Heparin like molecules on the endothelium accentuate the effects of anti-thrombin III
- Prostacyclin (PGI2) and ADPase activity inhibit platelet aggregation
- Tissue plasminogen activator (tPA) promotes fibrinolytic activity by activating plasmin
- Blood flow dilutes activated clotting factors - cleared by liver

Thrombotic
- Subendothelial connective tissue is very thrombogenic
- Thromboplastin (tissue factor) and other elements of clotting cascade
- von Willebrand factor, thromboxane A-2 (synthesized by platelets), and Platelet activating factor induce platelet aggregation
- tPA inhibitor limits fibrinolysis

Platelets
- Alpha-Granules: fibrinogen, fibronectin, PGDF, beta-thromboglobulin
- Dense bodies: rich in ADP and ionized calcium; also histamine, serotonin (5-HT), epinephrine

NON-NEOPLASTIC VASCULAR PATHOLOGY

Congenital Anomalies

Arteriovenous Malformations

- Abnormal communication between arterial and venous systems (without passing through capillaries)
- If large, can lead to right sided heart failure
- May be congenital or acquired (e.g., as a result of penetrating injury, inflammatory necrosis, aneurysmal rupture)

Berry Aneurysm

- Most common vascular malformation of cerebral vessels
- Accounts for 95% of cerebral aneurysms which rupture
- Occurs at bifurcation of major arteries:
  - 40% anterior communicating and anterior cerebral junction
  - 34% Bifurcation of middle cerebral in Sylvian fissure
  - 20% Internal carotid and posterior communicating junction
  - 4% Bifurcation of basilar into posterior cerebral arteries
- Multiple in 20-30% cases
- Although referred to as "congenital" most are not present at birth - develop because of a congenital weakness in wall (muscular discontinuity in media at carina of bifurcation)
- Straining at stool, lifting, sexual intercourse are associated with rupture - "Worst headache I've ever had"
- Likelihood of rupture increased when diameter > 1cm
- Most are sporadic, but increased association with polycystic kidney disease and other cerebral AV-malformations
- Rupture is fatal in 25-50%; some of the survivors will re-bleed

Fibromuscular Dysplasia

- Pathogenesis unknown: no necrosis, calcification, inflammation, arteriosclerosis
- Usually develop by 20-30 years of age
- Involves large and medium sized muscular arteries: renal, carotid, axillary, mesenteric

Abnormal arrangement cellular and extracellular elements of wall, particularly media, with disorderly proliferation and distortion of the lumen
Six distinct types:
- Intimal fibroplasia (1-2%): indistinguishable from proliferative stage of atherosclerosis, but no lipid
- Medial fibroplasia (60-70%): "string of beads" alternating stenosis (intimal fibrosis and medial thickening) and mural thinning/aneurysms
- Medial hyperplasia (5-15%)
- Perimedial fibroplasia (15-25%): Fibrosis of outer half of media - inner portion normal - with circumferential and uniform thickening of vessel and narrowing of lumen
- Medial dissection (5-15%): Medial fibrosis; dissecting aneurysms
- Periarterial fibroplasia (1%): perivascular fibrosis and inflammation

Degenerative Conditions

Arteriosclerosis

AKA: "Hardening of the arteries"
Three distinctive morphologic variants are recognized

Atherosclerosis
Term often used interchangeably with arteriosclerosis
Most common type; most common cause of death (myocardial infarcts, cerebral vascular accidents)
Atheroma (fibrofatty plaque): raised focal white to whitish yellow plaque within the intima; core composed of lipid (mainly cholesterol, also cell debris, crystals, foam cells, calcium); overlying fibrous cap (smooth muscle cells, macrophages, foam cells, collagen, lymphocytes [most of which are T-cells])
Most common sites: descending aorta, proximal coronary arteries, popliteal arteries, descending thoracic aorta, internal carotids, circle of Willis
Atheromas sparse at first, but can coalesce and become "complicated": calcification, necrosis, ulceration, thrombosis, aneurysmal dilatation, hemorrhage
Fatty Streak: *may* be precursor lesion of atheromas: yellow lesions composed of lipid filled smooth muscle cells and macrophages in lumen. Present in aortas of all individuals over 1 yr old; distribution different from atheromas

Risk factors:
- Age, male, familial predisposition
- Hyperlipidemia: risk correlates best with LDL levels (LDL contains ~70% circulating cholesterol - transports endogenously synthesized cholesterol), cholesterol >220mg/dl; most important risk factor in <45yr old
- Hypertension: >140/90; diastolic most important correlate
- Cigarette Smoking: >1 ppd. increases risk 70-200%
- Diabetes: 2 fold increase in myocardial infarctions; 150 fold increase in lower extremity ischemia
- Others: sedentary or stressful lifestyles, obesity, oral contraceptives, high carbohydrate intake

Multiple risk factors are more than additive

Theories of pathogenesis:
- Reaction to injury: leak of serum proteins and lipids, platelets, monocytes - in growth of smooth muscle cells
- Primary smooth muscle proliferation
- Encrustation of small thrombi

Arteriolosclerosis
Two types, both more severe in patients with hypertension

Hyaline Arteriolosclerosis:
Homogeneous pink hyaline thickening of walls with loss of underlying structure
Commonly seen in diabetes, especially in the kidneys
May be due to leakage of plasma components

Hyperplastic Arteriolosclerosis:
More common in severe hypertension (i.e., malignant)
Concentric thickening of wall and narrowing of lumen due to smooth muscle proliferation
Fibrinoid and acute necrosis can be seen
Kidney, periadrenal fat, gallbladder, peripancreatic, intestine

Mönckeberg's Arteriosclerosis
AKA: Medial calcific sclerosis
Calcifications in media of medium to small arteries with no associated inflammation - may ossify
Most commonly: femoral, tibial, radial, ulnar, genital tract
Rare before 50 yrs - completely unrelated to atherosclerosis

Cystic Medial Necrosis

Accumulation of amorphous material in the media often forming cysts or mucoid pools
Disruption of the structure of the tunica media by the appearance of small clefts filled with a slightly basophilic ground substance
Predisposes to dissections
Etiology unclear; seen in Marfan's syndrome

Aneurysms

Localized abnormal dilatation of any vessel
Most commonly caused by atherosclerosis and/or cystic medial necrosis; seen in Marfan's syndrome and Takayasu's arteritis
Classified grossly: berry (small), saccular, fusiform
By far, the most common site is the aorta, specifically abdominal; also in common iliacs, ascending aorta, descending thoracic aorta, and popliteal artery
When caused by atherosclerosis, rarely seen before age 50
Usually filled with mural thrombus
Thrombus may become superinfected by bacteria (usually salmonella, staph: embolization from endocarditis) or fungus (Aspergillus, Mucormycosis)
Complications include embolism of mural thrombus, rupture
Abdominal aneurysms >6cm carry a 50% chance for rupture within 10 yrs; rupture is fatal more than 50% time

Dissecting Aneurysms
AKA: Dissecting Hematoma, aortic dissection; both better terms since usually NOT associated with previous aneurysm
40-60yr age group, M:F=2-3:1; plus pregnant women
Hypertension is present in 95% patients
Sudden onset of excruciating pain beginning in the anterior chest and radiating to the back
Untreated, 35% fatal within 15 minutes, 75% within 1 week
Intimal tear usually (90%) in ascending aorta
Blood tracks through media and adventitia both distally and proximally - proximal dissections are most lethal
Fatalities usually follow secondary rupture into pericardial sac or pleural cavity

Types:	Classification System: Old	New
Ascending and descending aorta	I	A
Ascending aorta only	II	A
Descending only, above diaphragm	IIIA	B
Descending only, extending below diaphragm	IIIB	B

Syphilitic (Luetic) Aneurysms
Confined to thoracic aorta, usually ascending and transverse
Inflammation and destruction (endarteritis obliterans) of vasa vasorum leading to medial necrosis, inflammation, and scarring; scar retraction gives wrinkled "tree-bark" intima
Dilatation may involve aortic valve ring, leading to valve incompetence with thickening and rolling of the leaflets

Mycotic Aneurysm
Aneurysm secondary to weakening of wall from infectious vasculitis, most commonly bacterial (Salmonella)

Varicose Veins

Dilated, tortuous veins which lead to valvular incompetence, stasis, congestion, edema, and thrombosis
Most commonly involves the legs, often following pregnancy
Pathogenesis related to prolonged elevated intraluminal pressure
More important sites clinically are esophageal and hemorrhoidal varices following portal hypertension

Distal Aortic Thrombosis

AKA: Leriche's syndrome
Insidious onset and gradual progression of pain and fatigability of hips, legs, back; claudication, impotence
Often find absent pulses below umbilicus
Thrombotic occlusion of iliac arteries and distal aorta
Probably complication of atherosclerosis with ulceration

Cystic Adventitial Degeneration

Rare, almost always the popliteal artery
Mucinous degeneration in the wall leads to deposition of jelly like material which bulges into lumen and can cause obstruction
Probably related to pathogenesis of soft tissue ganglion

Phlebothrombosis / Thrombophlebitis

Terms are interchangeable since always see inflammation in thrombosed vessels
Three major predisposing factors:
- alteration in blood flow
- injury to endothelium
- hypercoagulability of the blood

Most common sites: calf (rarely embolize), femoral, popliteal, iliac, periprostatic / periuterine veins
Risk Factors:
- Prolonged bed rest; postoperative state; immobilization
- Myocardial Infarction and cardiac failure
- Pregnancy, post delivery, oral contraceptives
- Cancer
- Others: Tissue damage, Anti-thrombin III deficiency, Protein C deficiency, Prosthetic valves, Atrial fibrillation, Nephrotic Syndrome, Hyperlipidemia, Smoking

Phlegmasia Alba Dolens: AKA milk leg: iliofemoral venous thrombosis occurring in 3rd trimester of pregnancy; combination of venous thrombosis and lymphangitis leading to lymphedema

Vasculitides

Any inflammation of vessels which is not simply a direct extension from surrounding inflammation
Most are non-infectious immunologically mediated inflammations
Anti-cardiolipin antibodies present in most forms of vasculitis; probably a marker for vascular damage

Temporal (Giant Cell) Arteritis

AKA: Cranial arteritis, Horton's disease
Focal granulomatous inflammation (with or without necrosis) of medium and small arteries of the head and neck (although may be seen elsewhere, such as the aorta or mesenteric artery) with destruction of the internal and external elastic laminae
Most common vasculitis: ~1% of all people >80yrs old; M:F=1:3; associated with HLA-DR4
Headache, scalp tenderness, jaw pain, visual loss; markedly elevated erythrocyte sedimentation rate
Temporal artery biopsy positive in 60% of classic cases
Believed to be autoimmune in origin
Rapidly remits with steroid therapy

Polymyalgia rheumatica
Flu-like syndrome which accompanies 1/2 cases of TA
Visual symptoms in 40%

Polyarteritis nodosa

Classic PAN
Disease of young adults, M:F=2-3:1
Nodular lesions of small or medium-sized muscular arteries, [especially renal (85%), coronary (75%), hepatic (65%) and GI tract (50%); pulmonary circulation spared] with sharp demarcations (segmental lesions); most commonly at branch points
Often present with fever of unknown cause, hematuria, albuminuria, hypertension, abdominal pain and melena, muscular aches, motor peripheral neuritis
Lesions frequently scattered and of various ages
Frequently leads to aneurysms (especially in intestinal branches) and to thrombosis with infarction of supplied areas
Acute lesions show segmental fibrinoid necrosis which may be full thickness, with neutrophils, eosinophils, and lymphocytes
Healing lesions show fibroblastic proliferation - elastin stains show disruption of internal elastic lamina
30% patients have HepB antigen in serum
Anti-neutrophil cytoplasmic antibodies correlate with disease severity (usually P-ANCA [myeloperoxidase]; not specific)

Churg-Strauss Syndrome
AKA: allergic granulomatosis and angiitis
Variant of PAN with involvement of tracheal, pulmonary and splenic vessels (arteries, arterioles, capillaries, and veins)
Intra and extra-vascular necrotizing granulomas with eosinophils
Strong association with bronchial asthma and eosinophilia

Wegener's Granulomatosis

Acute necrotizing granulomas of upper and lower respiratory tract (with giant cells and leukocytes), with an accompanying necrotizing vasculitis of the pulmonary vessels and glomeruli, leading to persistent pneumonitis, chronic sinusitis, nasopharyngeal ulcerations, renal disease
Can be isolated to the lung
Peak incidence is in 40's; M>F
Involves predominantly arteries, but also veins
Serum anti-neutrophil cytoplasmic antibodies serve as marker for disease activity (usually C-ANCA [lysosomal enzymes])
If untreated, 80% will die within 1 yr; if treated (immuno-suppression, e.g. cyclophosphamide), 90% respond

Beurger's Disease

AKA: Thromboangiitis obliterans
Acute and chronic inflammation, often granulomatous, of intermediate and small muscular arteries and veins of extremities, usually the legs, leading to focal stenosing or occluding thrombosis
Begins before age 35 in most patients, M>>F
Strong correlation with smoking, including relapses
Neutrophil infiltration of wall, occlusive thrombosis, small microabscesses within the thrombus, Langhans' giant cells
Often leads to gangrene of extremities

Kawasaki's Disease

AKA: Mucocutaneous lymph node syndrome
Acute illness of infants and children with fever, conjunctivitis, lymphadenopathy, skin rash; M:F=1.5:1

70% show coronary artery involvement (1-2% mortality)
Acute necrotizing vasculitis (resembles PAN) which can lead to aneurysm formation
Some patients are ANCA positive
May be retroviral in origin

Takayasu's Arteritis

Chronic granulomatous arteritis involving adventitia and media and producing intimal fibrosis and fibrous thickening of the aortic arch with marked focal narrowing of the origins of the arch vessels
Common in Orient, M:F=1:3, 15-45 yrs old, often HLA-DR4
Ocular disturbances, weakened pulses in upper extremities ("pulseless disease"), subclavian bruits, hypertension, syncope, hemiplegia

Granulomatous Angiitis of the CNS

Dense inflammatory infiltrate with necrosis involving small and medium sized arteries of the cerebrum and meninges
Rare; affects individuals >40yrs old

Hypersensitivity Vasculitis

AKA: Leukocytoclastic vasculitis, Microscopic polyarteritis
Acute necrotizing inflammation of small vessels (arterioles, venules, capillaries); M=F
May be confined to skin or also involve mucous membranes, lungs, brain, heart, GI tract, kidneys, muscle
All lesions in a patient tend to be of same age
Drugs (penicillin), microorganisms, heterologous proteins, and tumor antigens have been implicated as triggers
Hypersensitivity vasculitis is the histologic pattern seen with the vasculitis of connective tissue diseases (SLE, rheumatoid arthritis), malignancies (lymphoproliferative), mixed cryoglobulinemia, Henoch-Schönlein purpura, drug reactions, serum sickness, amphetamine use, etc.

Infectious Arteritis

Usually suppurative or granulomatous
Bacterial: usually spread from nearby necrotizing inflammation
Fungal: aspergillosis and mucormycosis are angioinvasive and thus very prone to produce vasculitis and thrombosis

Other Non-Neoplastic Lesions

Raynaud's Disease/Phenomenon

Raynaud's Disease
Small arteries and arterioles in extremities undergo vasospasm in response to cold or emotional stress, producing pain and color changes from white to blue to red
Usually affects young healthy women
No anatomic abnormality seen
Raynaud's Phenomenon
Cold sensitivity, pain, color changes in skin secondary to an anatomic lesion in the vessel wall
Can be seen with arteriosclerosis, connective tissue diseases (scleroderma, SLE), vasculitis, etc.

Lymphedema

Any swelling, usually of extremity, due to increased interstitial fluid
Obstructive Lymphedema
From tumors, inflammation, surgery, postradiation fibrosis, filariasis, pregnancy, etc.
Rupture of dilated lymphatics can lead to chylous ascites, chylothorax, chylopericardium
Lymphedema Praecox
Swelling of feet and ankles in women 10-25 yrs old which may remain localized or progress upward throughout life
Unknown etiology
Milroy's Disease
Similar to lymphedema praecox but present at birth
Mendelian inheritance

VASCULAR TUMORS

Immunohistochemistry and Electron Microscopy
Endothelial cells: positive for Factor VIII-related antigen (most reliable and most specific), vimentin (especially epithelioid lesions), Ulex eruopeaus I lectin, collagen IV
Normal lymphatic vessels will be negative for Factor VIII and will not contain Weibel-Palade bodies
Pericytes (smooth muscle and glomus cells): cytoplasmic microfilaments, pinocytotic vesicles, reactivity for actin, vimentin, myosin. Desmin positive only in smooth muscle

Reactive Vascular Proliferations

Vascular Ectasias

Dilatation of preexisting vessels - not neoplasms
Nevus Flemmeus
AKA: nevus telangiectaticus, ordinary birthmark
Dilatation of vessels of middle and deep dermis
Most commonly middle forehead, eyelids, nape of neck
Most regress spontaneously, those of the neck more slowly
Nevus Vinosus (Port wine stain)
Specialized form of nevus flemmeus which grows with child and does not regress - overlying skin becomes thickened
Sturge-Weber syndrome (AKA encephalotrigeminal angiomatosis): port wine stain of face in distribution of trigeminal nerve associated with ipsilateral vascular malformations of the meninges and/or the retina
Nevus araneus (Arterial spider)
"Spider telangiectasias" with central feeder vessels and radiating smaller vessels - blanch with pressure
Acquired in pregnancy, liver disease, hyperthyroidism
Hereditary Hemorrhagic Telangiectasia
AKA: Osler-Weber-Rendu disease
Autosomal dominant, vascular anomalies of skin and mucosal membranes, especially face and mouth
Prone to bleeding (nose bleeds, GI bleeds, urinary bleeds)
Attempts to treat result in formation of satellite lesions

Papillary Endothelial Hyperplasia

AKA: Intravascular hemangioendothelioma, intravascular angiomatosis, Masson lesion
An unusual form of organizing thrombus
Most commonly excised from head, neck, fingers, trunk
Intraluminal papillary growth of plump endothelial cells overlying a thin collagenous core; simulates angiosarcoma
Pleomorphism and mitoses are minimal

Passive seeding into surrounding tissue may occur following rupture - does not signify malignancy
Excision is curative

Bacillary Angiomatosis

AKA: Epithelioid angiomatosis
Usually HIV infected patients; appearance similar to Kaposi's sarcoma and pyogenic granuloma
Multiple friable papules, usually dermal or subcutaneous, involving any site on the body; can involve liver, spleen, and lymph nodes as well
Lobular vascular proliferation with rounded vascular profiles and plump, protuberant, often epithelioid endothelium
Mitoses, necrosis common
Neutrophils present, usually in perivascular clusters (microabscesses)
Clusters of bacteria with tri-laminar structure consistent with gram negative Rickettsia-like bacilli; stain with silver stains
Rx: antibiotics (erythromycin)

Peliosis

[See Liver Outline]

Vascular Transformation of Lymph Nodes

AKA: Nodal angiomatosis
Occurs following obstruction of lymphatic outflow

Benign Tumors

Hemangiomas are among the most common soft tissue tumors
Comprise 7% of all benign tumors
Most common tumor in infancy and childhood
Skin is most common site, liver most common internal site
Many seem to be under hormonal control and fluctuate in size with pregnancy and menarche

Capillary Hemangioma

Proliferation of small, capillary-sized vessels lined by flattened endothelium; well defined but unencapsulated
Characteristically bright red to blue

Juvenile Capillary Hemangioma

AKA: strawberry nevus, cellular hemangioma, nevus vasculosus
Immature form of capillary hemangioma
1/200 live births; 20% are multiple
Most common on head and neck, especially parotid region
Grow following birth - may become elevated and protrude
Usually reach largest size by 6 months, then regress over years; 75-90% involute by age 7
Early lesions are cellular with plump endothelial cells - mature with age

Acquired Tufted Angioma

Similar to Juvenile hemangioma, but occurring in older group

Verrucous Hemangioma

Variant of capillary or cavernous hemangioma, the skin over which undergoes reactive hyperkeratosis
Usually lower extremity, childhood
Tendency to recur if incompletely excised

Cherry Angioma

AKA: Senile angioma, De Morgan spots
Small bright red papule with pale halo
Most commonly seen on trunk and extremities

Lobular Capillary Hemangioma

AKA: Pyogenic granuloma, granulation tissue hemangioma
Rapidly growing, purple-red friable polypoid lesion occurring on skin or mucosal surfaces: gingiva, finger, lips, face, tongue - all ages affected
1/3 linked to minor trauma
Each lobule has central vessel with numerous smaller vessels in an inflamed edematous stroma; numerous mitoses common
16% recur following excision

Granuloma Gravidarum

Specialized form occurring on gingiva during ~1% of pregnancies
Develop in first trimester; regress rapidly postpartum

Intravenous Pyogenic Granuloma

Usually neck or arm
Often mistaken for organizing thrombus

Cavernous Hemangioma

Large, cavernous vascular channels
Skin, usually of upper body; also liver, spleen, pancreas, CNS
May be engorged capillary hemangiomas, but usually larger, less circumscribed, more likely to be deep, don't regress, may be locally destructive
Thrombosis and calcification common
Kasabach-Merritt syndrome: thrombocytopenia and purpura seen in patients with a giant hemangioma, possibly due to platelet sequestration within tumor
Maffuchi syndrome: multiple cavernous hemangiomas and numerous enchondromas, usually of the fingers

Arteriovenous Hemangioma

AKA: cirsoid aneurysm, racemose hemangioma
Superficial and deep types
Symptoms related to degree of shunting - deep type tends to have more significant shunting
Usually young individuals; most commonly head, neck, legs
Medium sized arteries & veins amidst capillary hemangioma
Cure often requires deep surgical excision

Venous Hemangioma

AKA: large vessel hemangioma
Similar to cavernous hemangiomas but larger
Smooth muscle of venous wall often disorganized and blends into surrounding tissues
Thrombosis and calcification common

Epithelioid Hemangioma

AKA: Angiolymphoid hyperplasia with eosinophilia, Kimura's disease, histiocytoid hemangioma, inflammatory angiomatous nodule, pseudopyogenic granuloma
20-40 yrs old; F>M; head and neck, especially around ear
May be multiple, may even be intravascular
Circumscribed, usually subcutis or dermis, but may be deep
Multiple small peripheral vessels around a parent vessel; vascular spaces lined by epithelioid histiocytes, tomb-stoning into lumen and occasionally forming solid islands; surrounding stroma contains mixed inflammatory cell infiltrate with many eosinophils but also mast cells, plasma cells, lymphoid aggregates, even germinal centers
Controversial as to whether this is reactive or neoplastic
80% respond to radiotherapy; if excised, 1/3 will recur; only one reported case of metastasis

Deep Soft Tissue Hemangiomas

Uncommon

Skeletal Muscle Hemangioma

80-90% before age 30
Most commonly muscles of the thigh

Can be capillary, cavernous, or mixed type; mixed type most likely to recur
May have a significant amount of associated fat
Perineural involvement occurs; does not make malignant
18% will recur following excision

Synovial Hemangioma
Almost invariably around the knee
Cavernous hemangiomas with myxoid or hyalinized stroma separating the vascular spaces
Overlying synovium is often hyperplastic

Angiomatosis
AKA: Diffuse hemangioma
Multiple lesions involving large areas of the body, often the trunk or an extremity
Proliferation of small to medium sized vessels, usually thin walled, diffusely infiltrating the dermis, subcutis, or muscle, accompanied by a lots of mature adipose tissue

Lymphangiomatosis
Lymphatic counterpart - two can occur together
Principally children
3/4 have bone lesions (osteolytic)
Prognosis determined by extent of disease

Lymphangioma
Much less common than hemangiomas
Most are congenital and represent malformations with obstruction of outflow - rarely may be acquired
Most commonly head & neck, then trunk (axilla), extremities, may be intraabdominal
In mesentery, vessel walls may be thick

Cavernous lymphangioma
Congenital/infantile
Large, diffuse, doughy mass, prone to local recurrence
Dilated dermal and subcutaneous lymphatic channels without endothelial atypia

Cystic Hygroma
Large cystic mass, neck or inguinal region, infants, prone to local recurrence
Histology as for cavernous, but grossly dilated spaces

Lymphangiosum Circumscriptum
Numerous small vesicles or blebs; any age patient
Deep (subcutaneous) as well as superficial (papillary dermis) dilatation of lymphatics
Overlying papillomatous hyperplasia

Lymphangiomyomatosis
AKA: intrathoracic angiomyomatous hyperplasia
Proliferation of smooth muscle of the lymphatics and lymph nodes in the mediastinum, retroperitoneum, and lungs
Exclusively females; mean age 40
Progressive dyspnea due to chylous pleural effusions
In lung, proliferation of smooth muscle around arterioles, venules and lymphatics; alveolar septa become thickened
May be part of spectrum of tuberous sclerosis (like angiomyolipomas are) and thus hamartomas rather than true neoplasms

Hemangioendotheliomas
Vascular tumors of intermediate malignancy
Generally greater cellularity and mitotic activity than hemangiomas but lacking features of frank malignancy

Infantile Hemangioendothelioma
Almost always occur before 1 yr of age

Type I
Cellular proliferation of small vessels with plump walls occurring in skin
Benign lesions

Type II
Freely anastomosing vascular channels, solid areas, mitoses common
More commonly occur in internal sites (e.g., liver)
Can be aggressive; many consider this type to be equivalent to angiosarcoma
Occurrence in multiple sites could represent multifocality or metastases

Epithelioid Hemangioendothelioma
Can occur at any age; M=F; predominantly skin of extremities, liver, and lung
Solitary, slightly painful soft tissue mass often centered about a parent vessel
When vessel present (usually a vein), lumen often filled with tumor and necrotic debris
Epithelial appearing cells of the tumor cluster in small nests which do not form vessels but rather have intracellular lumina, frequently confused with mucin vacuoles
Stroma can be myxoid of hyalinized
15% recur; 30% metastasize to local nodes, lung, liver, bone
Significant atypia or high mitotic rate (>1/10 HPF) indicates a more aggressive course
Differential: melanoma, carcinoma, epithelioid sarcoma

"IVBAT"
In the lung, this lesion was originally mistaken as an intravascular bronchioloalveolar carcinoma
More common in women
Higher mortality than soft tissue counterpart

Spindle Cell Hemangioendothelioma
Occurs at any age; 1/2 cases less than 25 yrs old; M:F=2:1
Small red nodules in the subcutaneous tissue or dermis of the hand (or other distal extremity site)
Cavernous thin walled vessels with organizing thrombi, separated by proliferation of spindle cells suggestive of Kaposi's sarcoma but also containing epithelioid endothelial cells with intracytoplasmic lumina; minimal inflammatory response
Spindled cells are often Factor VIII negative
2/3 recur

Malignant Endovascular Papillary Angioendothelioma
AKA: Dabska tumor
Discrete mass or diffuse subcutaneous swelling in the skin of young children
Large almost cavernous vascular spaces, often without blood cells, with papillary projections containing hyaline cores of basement membrane material and lined by plump cells which may focally be columnar
Occasional LN metastases, but overall prognosis is good

Malignant Tumors

Angiosarcoma
Rare; <1% of all sarcomas
Most common sites: skin, soft tissue, breast, liver, bone, spleen - soft tissue lesions can arise from major vessels
Predisposing factors: chronic lymphedema, radiation; do NOT appear to arise in benign vascular lesions

Clinically, lesion is poorly defined; lateral extent in subcutaneous tissues often greatly exceeds superficial appearance
Can be very well differentiated - diagnosis based upon irregular channels, occasionally with papillary ingrowth of endothelium; lesion infiltrates rather than merely separating surrounding structures
May have epithelioid or spindle cell areas

Cutaneous
1/3 to 1/2 of all angiosarcomas
Usually elderly; M>F
Most common sites: head and neck (especially scalp), leg, trunk
1/2 are multifocal
5 yr survival: 12%; prognosis better if smaller than 5 cm
When occur in association with lymphedema (**lymphangiosarcoma**), almost always women following mastectomy - occurs on arm. This variant is often associated with premalignant proliferation of lymphatics at periphery of tumor; radical excision (e.g. forequarter amputation) only real hope for survival

Breast
1/2000 of breast malignancies
Always women; usually 20's - 30's
Rapidly growing mass diffusely enlarging breast
Deep, infiltrative, usually well differentiated

Hepatic
Rare
Associated with arsenic, Thorotrast, and polyvinyl chloride exposure, with long latent period

Kaposi's Sarcoma

Virally associated if not virally induced
Probably multifocal rather than metastatic process
Angiosarcomatous and fibrosarcomatous elements with numerous mitoses; when occurs in the skin, often a fibrinous exudate below the epidermis
Four clinical settings:
- Classic (chronic): skin of distal lower extremity, males, late adult, indolent course; 1/3 develop a second malignancy
- Lymphadenopathic: African children, sparse if any skin lesions, involves cervical, inguinal, hilar nodes, fulminant course
- Transplant Associated: Occur in 0.4% renal transplant recipients; relatively aggressive (30% fatal), dramatically improve if discontinue immunosuppression
- AIDS Related: 30% AIDS patients, with predilection for homosexuals; initially small, flat, pink - only later become blue-violet and papular; more aggressive course

Histologic Stages
Patch: flat lesion, circumferential proliferation of many small vessels around a larger central parent vessel
Plaque: elevation of skin, spindle cell component
Nodular: many spindle cells with slit like vascular spaces; PAS+ hyaline globules, peripheral inflammatory cells

Tumor Staging
I: cutaneous, locally indolent
II: cutaneous, locally aggressive, ± regional LN's
III: generalized mucocutaneous or LN involvement
IV: visceral

Tumors of Other Vascular Components

Hemangiopericytoma

Tumor of the pericyte: actin and vimentin positive, desmin and myoglobin negative
Occurs at all ages; peak incidence in 40's
Tumor is painless and therefore often presents clinically only after months or years
Some patients have hypoglycemia which resolves after removal of tumor
Most commonly thigh or pelvic retroperitoneum; also head and neck, trunk, arm - deep, usually in muscle
Relatively well defined mass due to presence of a pseudocapsule which is very vascular and can cause extensive hemorrhage during surgery
Tumor proper is composed of spindled cells with roundish nuclei; vessels penetrating the lesion have thin walls and irregular contours, often with an antler or staghorn pattern
Each tumor cells is individually surrounded by a reticulin meshwork; important in differentiation from other tumors
May have myxoid stroma, cell palisading, or solid areas; islands of tumor cells may be found outside pseudocapsule
So many tumors can have a similar "hemangiopericytoma-like pattern" that the diagnosis is essentially one of exclusion: must show negativity for epithelial, smooth muscle, and nerve sheath markers
Differential diagnosis: fibrous histiocytoma (more prominent spindle pattern), synovial sarcoma (not a broad a range of vascular patterns), mesenchymal chondrosarcoma (islands of cartilage)
Prognosis can be difficult to discern; in general, more than 4 mitoses/10HPF, necrosis, atypia are worrisome; recurrence is bad sign - most will later metastasize; metastases to lung and bone

Infantile Hemangiopericytoma
More superficial (subcutis)
Satellite nodules more common
Frequent endovascular proliferation
Increased mitotic activity and focal necrosis do NOT necessarily mean malignancy

Angiomyoma (Vascular leiomyoma)

Subcutaneous tissue, usually extremities, particularly lower leg; also arm, head, trunk; F>M
Generally small, slowly enlarging - often painful (one of the five ANGEL painful nodules of the skin with angiolipoma, traumatic neuroma, glomus tumor, eccrine spiradenoma)
Smooth muscle cells forming the tumor mass appear histologically to spread out from thick-walled vessels within or at the edge of the lesion
Myxoid areas, hyalinization, calcification, fat may be seen
Simple excision is curative

Glomus Tumor

[Unrelated to Glomus Jugulare et al. tumors of the Head and Neck, which are paragangliomas]
Glomus body is an arteriovenous anastomosis in the skin in which flow is regulated by a polypoid projection into the lumen of the shunt (Sucquet-Hoyer canals) composed of a mixture of traditional smooth muscle cells and glomus cells, specialized epithelial appearing smooth muscle cells; involved in thermal regulation
Tumor seen most commonly subungually in females, but also seen on palm, wrist, forearm, foot, head and neck, tip of spine (glomus cocygeum) and internal organs (stomach, patella, chest wall, bone) where normal glomus structures are not found
Small purple nodules usually <1cm which generally produce intense pain far out of proportion to the size of the lesion, elicited by even mild touch or temperature changes (especially cold)
Radiographically, may see erosion of terminal phalanx

Histologically: anastomosing collection of irregular vessels with intervening nests of glomus cells
Glomus cells: rounded cells with sharply demarcated round nuclei, eosinophilic cytoplasm, and poorly defined cell boundaries (can be visualized by PAS staining)
Immuno: desmin negative, SMA positive, Factor VIII negative
Essentially always benign - complete excision curative (10% recur)

Glomus Tumor Proper (75%)
Most commonly finger
Well defined cluster of small vessels, each sheathed by small nests or sheets of glomus cells

Glomangioma (20%)
Hand, forearm
Seen in patients with multiple or familial lesions
Less well circumscribed
Resemble cavernous hemangiomas with small nests of glomus cells in vessel walls

Glomangiomyoma (<10%)
Equally divided between upper and lower extremity
Composed of "transforming" glomus cells which have become elongated and more smooth muscle-like; merge with the outer smooth muscle layers of the larger vessels within the mass

Glomangiosarcoma
Debatable entity
Benign glomus tumor in association with more spindled fibrosarcomatous areas
Few reported cases; no reported metastases

Others

Neoplastic Angioendotheliomatosis
Originally thought to be a form of multicentric angiosarcoma
Actually a malignant lymphoma with tropism for vascular lumina

SOFT TISSUES

GENERAL INFORMATION ON SARCOMAS

In general affect males more frequently than females
Most occur in children under 13 or adults over 50; only a few occur between this age range: synovial sarcoma, alveolar soft part sarcoma, mesenchymal chondrosarcoma, alveolar rhabdomyosarcoma, angiomatoid MFH, extraskeletal Ewing's sarcoma, epithelioid sarcoma, and clear cell sarcoma
Generally do NOT evolve from benign tumors (exception: malignant schwannoma arising from neurofibroma in von Recklinghausen's disease)
Generally do NOT metastasize to lymph nodes (exception: synovial sarcoma)
Radiation induced lesions include MFH, extra-osseous osteosarcoma, and fibrosarcoma
Classified on a histogenetic basis by the adult tissue which tumor most closely resembles
Report must include size (especially < or > 5 cm) and location (subcutis vs deep soft tissues, compartment)

Immunohistochemistry

Keratin: usually positive in spindled carcinomas, monophasic synovial sarcoma, Merkel cell carcinomas (perinuclear spot)
HHF-35: muscle actin (smooth and skeletal)
Desmin: smooth and skeletal muscle
S-100: neural crest derived cells, but also fat, cartilage, myoepithelial cells; only expressed in 1/2 malignant schwannomas

Chromosomal Abnormalities

del 1p Leiomyosarcoma
t(2;13) Alveolar Rhabdomyosarcoma
t(9;22) Myxoid Chondrosarcoma
t(11;22) Ewing's sarcoma, PNET
t(11;22) Desmoplastic small round cell tumor
t(12;14) Leiomyoma
t(12;16) Myxoid Liposarcoma
t(12;22) Clear Cell Sarcoma
ring 12 Well Differentiated Liposarcoma
ring 17 Dermatofibrosarcoma Protuberans
t(X;18) Synovial sarcoma

Grading and Staging

Grading is usually three tiered (sometimes four), with most emphasis placed on necrosis (<15% vs >15%) and mitotic activity, but also including atypia
Some tumors receive automatic grades (eg, dermatofibro–sarcoma protuberans and well differentiated liposarcomas are all grade 1, and synovial sarcomas, angiosarcomas, and alveolar rhabdomyosarcomas are all grade 3)

T1 primary <5 cm
T2 primary >5 cm
N1 Regional LN's involved
M1 Distant metastases

	T1	T2
N0, Grade 1	IA	IB
N0, Grade 2	IIA	IIB
N0, Grade 3	IIIA	IIIB
N1	IVA	
M1	IVB	

Prognosis

Survival:	5 yr	10yr
Stage I	75%	63%
Stage II	55%	40%
Stage III	29%	19%
Stage IV	7%	3%

RETROPERITONEUM

One of the more common locations for sarcomas
Most frequent soft tissue sarcomas of the retroperitoneum, in descending order, are liposarcoma, malignant fibrous histiocytoma, leiomyosarcoma, and rhabdomyosarcoma

ADIPOSE TISSUE

Lipoma

Most common of the soft tissue tumors
Peak incidence in 40's and 50's; rare before 20
Most often in subcutaneous tissues of back, shoulder, neck
Delicately encapsulated in superficial soft tissue, poorly circumscribed when arise in deeper structures; in muscle, tend to be infiltrative; diffuse form exists which produces massive enlargement of an entire extremity
Most are indistinguishable from adult fat
Areas of infarction, necrosis, calcification, osseous metaplasia can occur
Fibrolipoma / myxolipoma if have increased amounts of fibrous or myxoid tissue, respectively

Angiolipoma

Well circumscribed small tumors; occur shortly after puberty
Often painful; subcutis of trunk or extremities
Vascular component prominent at periphery
Hyaline thrombi common in vessels

Myelolipoma

Lipoma with extramedullary hematopoiesis

Spindle Cell Lipoma

Characteristically shoulder or back of neck; rare on legs
45-65 yrs; M:F=9:1
Mixture of mature lipocytes and uniform, primitive, bland, S-100 negative spindle cells in a mucinous and fibrous background with frequent mast cells
May have a hemangiopericytic vascular pattern
Distinguish from myxoid liposarcoma by the thick collagen bundles and by the absence of lipoblasts and a plexiform vascular pattern

Pleomorphic Lipoma

Circumscribed lesion of the back of the neck or shoulder
Usually men; 60's; 1/10 as common as spindle cell lipoma
Lipoma containing hyperchromatic multinucleated (floret) giant cells (with a wreath-like arrangement of nuclei around cell periphery) within the fibrous septa; a few lipoblasts may be present, but still benign

"Atypical Lipoma"

Term often used to refer to a well differentiated liposarcoma which arises in the superficial soft tissues (the same tumor

occurring in the retroperitoneum or spermatic cord should be called a well differentiation liposarcoma)
Mature fat, floret-like cells, cellular fibrous septa
Often recur; generally don't dedifferentiate; don't metastasize

Hibernoma

Tumor of "brown fat"
Interscapular region, axilla, mediastinum, retroperitoneum
Brown cut surface
Nests of large cells with central nuclei and cytoplasm filled with many small neutral fat vacuoles which do not indent the nucleus

Lipoblastoma

Almost exclusively infants and young children (<3 yrs)
Proximal portions of upper and lower extremities; M>F
Well localized and superficial or diffusely infiltrating soft tissue (latter referred to as lipoblastomatosis)
Numerous lipoblasts, myxoid stroma
Distinguished from myxoid liposarcoma only by patient age, lobular growth pattern, absence of giant cells, less prominent capillary network

Liposarcoma

Located in deep soft tissues such as retroperitoneum and thigh; also mediastinum, omentum, breast, axilla
Most occur after age 50
Second most common soft tissue sarcoma in adults, most common sarcoma of the retroperitoneum
Often very large at diagnosis
Diagnostic cell is lipoblast: mononuclear or multinucleated cell with one or more cytoplasmic fat vacuoles which push aside and indent the nuclei ("mulberry cells")
>50% retroperitoneal liposarcomas, regardless of type, recur and often eventually dedifferentiate
Pleomorphic and round cell liposarcomas metastasize in 80-90% of cases; metastases are usually to the lung
Prognosis: 5 yr survival for well differentiated and myxoid types is 70%; for round cell and pleomorphic is 18%

Well Differentiated Liposarcoma (25%)
Often mistaken for lipoma; any "lipoma" in the deep soft tissues, especially the retroperitoneum or spermatic cord, should be diagnosed as a well differentiated liposarcoma
Three subtypes: lipoma like, sclerosing, inflammatory
Grade I by definition; does not metastasize
Treatment: retroperitoneal exenteration
Myxoid Liposarcoma (50%)
Primitive mesenchymal cells in a mucopolysaccharide rich matrix (hyaluronidase sensitive); mast cells common
Prominent arborizing vascular component (unlike myxoma) with a hypercellular zone around the larger vessels
Few to no mitotic figures
Often associated with chromosomal translocation t(12;16)
When pure, grade I (by definition)
When metastasizes, usually to the lung
Foci of pleomorphic or round cells which increase the cellularity to >25% decrease prognosis
Round Cell (Lipoblastic) Liposarcoma (15%)
AKA: "Cellular myxoid liposarcoma"
Similar to myxoid liposarcoma but with >25% cellularity due to a large number of small, non-descript round cells with acidophilic cytoplasm; cells may cluster
Scattered lipoblasts distinguish from Ewing's sarcoma
Moderate mitotic activity
Grade III by definition; more likely to metastasize
Pleomorphic Liposarcoma (10%)
Usually limbs and limb girdle soft tissues
Undifferentiated: tumor giant cells, often huge (>200 μm!)
Often, neutrophils around and within tumor giant cells
Still should be able to find at least focal S-100 positivity
Grade III by definition; aggressive; tends to metastasize
Dedifferentiated Liposarcoma
When liposarcomas recur, frequently are more poorly differentiated and can look like malignant fibrous histiocytoma, fibrosarcoma, or leiomyosarcoma
>5 mitoses/10 HPF
Don't see lipogenesis in the high grade component

FIBROHISTIOCYTIC LESIONS

Histiocytoma

Tight packing of polygonal cells with minimal stroma; inflammatory cells frequently present; fibrosis common in older lesions
Juvenile Xanthogranuloma
2/3 present by 6 months of age; rare after 3 yrs
Head, neck, extremities; 5-10% are deep
Ovoid-to-spindle cellular histiocytic proliferation with fibrosis, Touton giant cells, foam cells, lymphocytes, eosinophils
Benign
Reticulohistiocytoma
Generalize Eruptive Histiocytoma

Benign Fibrous Histiocytoma

Dermatofibroma
Middle adult life, limbs, trunk
Superficial cutaneous nodule, red-brown, slowly growing, painless
Interlacing fascicles of slender spindle cells
Foamy histiocytes, giant cells, branching vessels, chronic inflammation
Pseudoepitheliomatous hyperplasia of overlying epidermis

Giant Cell Tumor of Tendon Sheath (Nodular Tenosynovitis)
Predominantly tendons of fingers; also knees, hips
Solitary, circumscribed, lobulated, small (0.5 to 1.5 cm)
Slowly growing, painless
Sheets of rounded or polygonal cells with scattered benign appearing giant cells, lipid-laden macrophages, and hemosiderin-laden spindled cells
Well defined fibrous pseudocapsule
Collagenous stroma with cholesterol clefts
Local recurrence (15%), no malignant potential
Pigmented Villonodular Synovitis
Exuberant villous, heavily pigmented synovial overgrowth involving the majority of a joint surface, usually knee
Proliferation of surface synoviocytes and chronic inflammatory cells, thickening of synovial membrane, many pigment-laden macrophages, occasional giant cells
Cellular Fibrous Histiocytoma
Usually adults; deeper (often subcutaneous) soft tissue
Large (~5 cm); pushing margins
Ovoid to spindled cells, granular foamy cytoplasm, collagen, myofibroblasts; may see giant cells, hemorrhage, necrosis
May recur; does not metastasize

Borderline Fibrous Histiocytoma

Dermatofibrosarcoma Protuberans
- 20's-30's, M>F; usually trunk, most commonly shoulder or proximal extremity
- Slow, persistent growth
- Multinodular, reddish blue; poorly circumscribed (infiltrative)
- Local recurrence 33%, metastases rare
- Deep dermis; infiltrates subcutis (dermatofibromas are more superficial)
- Highly cellular lesion of well differentiated bland spindle cells in *storiform* pattern (interlacing bundles; basket weave); tumor cells insinuate between adipocytes and adnexal structures; myxoid areas accentuate the vascular pattern
- Moderate mitotic activity (no prognostic significance), abundant reticulin, hyperchromasia
- Do NOT see giant cells, foamy cells, hemosiderin laden cells
- Grade 1 lesion, by definition
- Some will undergo fibrosarcomatous transformation or progression to MFH; when this occurs, outgrows rest of tumor

Pigmented Dermatofibrosarcoma (Bednar's Tumor)
- Above plus population of dendritic cells heavily laden with melanin

Atypical Fibroxanthoma
- Head and neck (60's-70's) or limbs (30's-40's)
- Firm, often ulcerated nodule
- Predominantly dermal - may involve superficial fat
- Marked pleomorphism: "too bad to be malignant"
- Should NOT see storiform pattern, necrosis, myxoid degeneration

Malignant Fibrous Histiocytoma

- Most common soft tissue sarcoma of late adulthood (50-70 yrs); second most common sarcoma of retroperitoneum
- Mostly a tumor of soft tissues, but can occur in bone
- Of soft tissue tumors, 1/2 in lower extremities, 20% in upper extremities, 20% in abdomen and retroperitoneum
- Osseous tumors usually around knee; also pelvis, arms
- Any age, with peak incidence in 60's
- Cells show histiocytoid differentiation: lysozyme, Factor XIIIa, alpha-1-antitrypsin
- Almost all (except angiomatoid) are Grade 3; myxoid forms and densely hyalinized forms may be Grade 1 or 2
- Satellite lesions are common

Storiform-Pleomorphic (~70%)
- Polygonal histiocytoid cells, often with bizarre prominent oval nuclei, and spindled fibroblasts, myofibroblasts and smaller undifferentiated mesenchymal cells
- Tend to grow in a swirling, cartwheel, storiform pattern
- Pleomorphism, giant cells, slit-like vascular spaces common
- Metastases present at diagnosis in 50%

Myxoid (Myxofibrosarcoma) (15%)
- Loose myxoid stroma constituting >50% of the tumor mass, interspersed with areas of higher cellularity
- Abundant plexiform vascular network, scattered giant cells
- Distinguished from myxoid liposarcoma by presence of typical MFH growth pattern elsewhere in lesion
- Metastases present at diagnosis in 25%
- Second best prognosis of the variants (5 yr survival >50%)

Giant Cell (Malignant Giant Cell Tumor of Soft Parts) (10%)
- Spindled and polygonal cells arranged in vague nodules
- Giant cells are osteoclast like and are abundant

Inflammatory (Malignant Xanthogranuloma) (5%)
- Rare; predominantly in retroperitoneum
- Intense inflammatory infiltrate interspersed with, occasionally obscured by, tumor cells
- Tumor cells may contain phagocytosed neutrophils
- Very aggressive
- Differential diagnosis: malakoplakia, sarcomatoid renal cell carcinoma

Angiomatoid (<5%)
- Clinically and pathologically a completely different lesion
- Younger individuals; extremities, well circumscribed
- Very cellular areas (round, bland cells) interspersed with hemorrhagic cyst-like spaces and chronic inflammatory cells which may aggregate to form lymphoid follicles
- Much better prognosis than other variants: 12% recur, only 5% metastasize; only 1% die of disease

FIBROUS LESIONS

Benign

Nodular Fasciitis

- AKA: subcutaneous pseudosarcomatous fibromatosis
- Often misdiagnosed as fibrosarcoma or liposarcoma
- Peak incidence 40 yrs
- Unclear pathogenesis; probably reactive; some cases associated with trauma
- Upper extremities (flexor surfaces), trunk, neck
- Rapid growth, small size (2-3 cm), painful
- Zonal growth, with hypocellular center and hypercellular periphery
- Cellular tissue-culture like spindle cell proliferation (fibroblasts and myofibroblasts) in a myxoid matrix; may have many mitoses, but generally smooth nuclear contours and fine chromatin pattern
- Vascular proliferation, lymphocytic infiltration, extravasated RBCs, undulating wide bands of collagen which increase with the age of the lesion
- Focal metaplastic bone may be seen
- If <3 cm, may regress without treatment
- Generally do not recur, even if incompletely excised

Cranial Fasciitis
- Children; erosion of skull; may be related to birth trauma

Intravascular Fasciitis
- Involves walls of medium-sized vessels

Proliferative Fasciitis
- Rare. Adults (40-70 yrs)
- 66% occur on extremities
- Histology of nodular fasciitis, but with large basophilic cells resembling ganglion cells

Proliferative Myositis
- Muscles of shoulder, thorax, thigh
- Intramuscular variant of proliferative fasciitis
- Cellular proliferation of fibroblasts surrounding individual muscle fibers with *very large ganglion like basophilic cells with vesicular nuclei and very prominent nucleoli*

Eosinophilic Fasciitis
- Superficial soft tissues, usually thighs, often symmetrical
- Fibrosing inflammation with eosinophils, lymphocytes, and mast cells
- Sometimes associated with myalgias (eosinophilia-myalgia syndrome: caused by a toxin contaminating early preparations of L-tryptophan)

Myositis Ossificans

Solitary, non-progressive reactive condition often mistaken for osteosarcoma
Flexors of arm, quadriceps, adductors of thigh, gluteal muscles, soft tissue of hand most common - may not involve muscle
Occurs following trauma; usually young males
Highly cellular stroma associated with new bone with or without cartilage - usually no inflammation
As evolves, becomes zonal with cellular core, intermediate zone of osteoid, peripheral shell of highly organized, calcified bone

Elastofibroma

Poorly circumscribed; subscapular region (95%) of elderly adults (>55 yrs)
More common in women; more common in Japanese; no pain
Densely collagenized lesion with numerous thick eosinophilic extracellular refractile fibers which stain strongly for elastin

Fibroma

Ovarian Fibroma
Nuchal Fibroma
Nasopharyngeal Fibroma
Fibroma of Tendon Sheath
Usually males, 30-50 yrs old
Well circumscribed, lobulated; attached to tendon
Dense fibrous tissue with spindled mesenchymal cells (may be myofibroblasts) and dilated or slit-like channels resembling tenosynovial spaces
Numerous medium sized vessels
Probably a "burnt-out" giant cell tumor of tendon sheath

Keloid

Hypertrophic scar, thick collagen bands [See Skin Outline]

Tumors of Infancy and Childhood

Focal Myositis

Inflammatory pseudotumor of skeletal muscle in children
Usually lower extremity; painful
Degeneration / regeneration of muscle fibers with interstitial inflammation and fibrosis

Fibrous Hamartoma of Infancy

Tumor like (benign) condition seen during first 2 yrs of life
Usually boys; shoulder, axilla, upper arm
Solitary, poorly circumscribed, dermal to subcutaneous whitish mass with islands of fat
Organoid pattern composed of 1) well differentiated fibrous tissue, 2) mature adipose tissue, 3) immature cellular areas resembling primitive mesenchyme
Vimentin positive

Infantile Myofibromatosis

Solitary (50%)
Most cases in first month of life
Dermal, subcutis, muscle
Whirling pattern of benign fibrous tissue
Multicentric (50%)
May have extensive visceral involvement
May be fatal

Calcifying Aponeurotic Fibroma

AKA: Juvenile aponeurotic fibroma
Usually child (10-15 yrs old), usually hand or wrist (70%); occasionally feet
Nodule or ill defined infiltrating mass; slow growing, painless
May be attached to tendon; infiltrates fat and muscle
Diffuse proliferation of fibroblasts with focal calcifications
Often have scattered osteoclast-like giant cells
Proliferating cells have chrondrocyte features

Giant Cell Fibroblastoma

Almost exclusively children <10yrs; usually boys
Superficial soft tissues of back or thigh
Ill defined proliferation of fibroblasts in collagenized, focally myxoid stroma; hypocellular regions often alternate with hypercellular regions with prominent thick walled vessels
Multinucleated cells have floret-like appearance
Cystic or sinusoidal structures (pseudovascular spaces) lined by hyperchromatic giant cells is characteristic feature
May be juvenile version of Dermatofibrosarcoma protuberans

Aggressive/Malignant Lesions

Fibromatosis

Proliferation of well defined fibroblasts, focally very cellular but intermixed with more collagenous areas, with an *infiltrative* growth pattern and tendency to recur
Male predominance
Variety of names, patterns, associations
Uniformity of cells, rarity of mitoses

SUPERFICIAL

Palmar (Dupuytren's)
Bilateral in 50%; concurrent plantar disease in 10%
Results in fixed painless flexion contractures of digits
Plantar (Ledderhose's)
Middle of sole of foot; bilateral in 10-25%
Often some degree of pain / paresthesias
Usually present 10yrs earlier than palmar
Penile (Peyronie's Disease)
Usually dorsolateral penis; palpable induration

DEEP (MUSCULOAPONEUROTIC)

Desmoid (Abdominal)
Abdominal wall of women during or following pregnancy
Can be associated with Gardner's syndrome: 45% Gardner's syndrome patients develop desmoids
"Extraabdominal"
AKA: "Aggressive Fibromatoses"
Shoulder (22%), chest/back (17%), mesentery (10% [not really "extraabdominal"]), thigh (12%)
Mitoses up to 1 per 5 HPF allowed; must not be atypical
Characteristically have thin-walled elongated ectatic vessels
Initial recurrence rate ~50%; rate increases with each successive recurrence
Post radiation

FIBROMATOSES OF CHILDHOOD

Fibromatosis Coli
Infantile Digital Fibromatosis
Infantile Fibromatosis, Desmoid type
Gingival Fibromatosis
Hyalin Fibromatosis

Idiopathic Retroperitoneal Fibrosis

AKA: Ormond's disease, sclerosing fibrosis, sclerosing retroperitonitis
Ill defined mass composed of mixed inflammatory cells (lymphocytes and germinal centers, plasma cells, eosinophils) in a cellular fibrous stroma with foci of fat necrosis; mass surrounds the abdominal aorta and displaces the ureters medially
Polyclonal Ig production, predominantly IgA
Probably an immunologic hypersensitivity disorder
May be associated with mediastinal fibrosis, sclerosing cholangitis, Riedel's thyroiditis, pseudotumor of the orbit
Results in progressive renal failure from constriction and ultimately obliteration of the ureters

Solitary Fibrous Tumor

[See Lung Outline, under Pleura]

Fibrosarcoma

The frequency of this lesion is decreasing as most are reclassified as other entities, usually malignant fibrous histiocytoma; largely a diagnosis of exclusion
Most common in retroperitoneum, thigh, about the knee
Unencapsulated, infiltrative, soft "fish-flesh" masses
Areas of hemorrhage and necrosis
Classically a "herringbone" pattern of growth
Immunoreactive for vimentin and type I collagen
5yr survival 41%; 10yr survival 29%
Prognosis better for more superficial, better differentiated
Congenital fibrosarcomas and those occurring before 5 yrs of age are usually on extremities, usually painless, and tend not to metastasize
Often produce hypoglycemia secondary to elaboration of insulin like substances

SMOOTH MUSCLE

Leiomyoma

95% occur in female genital tract

Cutaneous Leiomyoma

Arise from erector pili muscles
Typically superficial, small, multiple, grouped

Genital Leiomyomas

Smooth muscle of superficial subcutaneous tissue of genital areas (nipple, areola, axilla, scrotum, penis, etc.)

Vascular Leiomyoma (Angioleiomyoma)

Smooth muscle of blood vessels
Generally in females, usually legs and feet
Often painful (painful nodules of skin and soft tissue are **A**ngiolipoma, traumatic **N**euroma, **G**lomus tumor, **E**ccrine spiradenoma, vascular **L**eiomyoma)
Often multiple vascular profiles

Symplastic Leiomyoma

AKA: Bizarre, atypical, apoplectic leiomyoma
An otherwise traditional leiomyoma with scattered cells containing large, atypical nuclei
Almost always uterus or skin
Prognosis determined by mitotic rate [See Uterus Outline]

Leiomyosarcoma

Most are in extremities, arising from wall of vessels
Large, soft, tendency for necrosis, hemorrhage, cystic degeneration - when arise from vessel, may be luminal
Fascicular pattern of growth (bundles intersect at right angles, unlike the herring bone pattern of fibrosarcoma); palisading of cigar shaped, blunt ended nuclei; mitoses
Often, cytoplasmic vacuoles are seen at both ends of nucleus, sometimes indenting it (unlike neural lesions)
Cutaneous and subcutaneous tumors have an excellent prognosis; deeper lesions are more likely to metastasize
Retroperitoneal and/or mesenteric tumors almost always malignant; prognosis worse when >5 cm

Leiomyoblastoma

AKA: Clear Cell (Epithelioid) Smooth Muscle Tumors
Uncommon in soft tissues; usually seen in stomach
[See GI Tract Outline]

STRIATED MUSCLE

TERMINOLOGY

Myofiber: skeletal muscle cell
Myofibril: array of actin (thin) and myosin (thick) filaments surrounded by sarcoplasmic reticulum; can have many myofibrils per myofiber
Sarcomere: collection of filaments between two Z-bands; the functional unit of the muscle cell
Banding pattern of a sarcomere:
- Z-band: electron dense discs; anchor the actin filaments
- A-band: central portion of sarcomere containing the thick myosin filaments
- H-band: central portion of A-band not overlapped by actin filaments
- M-line: inter-filament bridge at center of A band
- I-band: portion of actin filaments not overlapped by myosin

The term A-band stands for anisotropic and I-band for isotropic. Actually, both the A and I bands are anisotropic, meaning they can rotate plane polarized light, but the A-band is more anisotropic than the I-band
During sarcomere shortening, the A-band remains the same size; as the Z-bands approach each other, the I-bands and H-bands become shorter
Sarcolemma: cell membrane of a skeletal muscle cell
Sarcoplasmic reticulum: endoplasmic reticulum of a myofiber, specialized for transport and storage of calcium
Transverse Tubules: invaginations of the sarcolemma which extend to the sarcoplasmic reticulum of each myofibril of a myofiber, allowing rapid transmission of an electrical stimulus (depolarization)
Connective Tissue: epimysium surrounds entire muscle, perimysium separates groups of myofibers into muscle fascicles, and endomysium surrounds each individual muscle cell
Motor unit: refers to a single lower motor neuron (usually in anterior horn of spinal cord) and all of the muscle cells it

innervates (<10 for fine motor control, >1000 for large leg muscles); any given myofiber is innervated by only one neuron (except for the extraocular muscles)
Medial motor neurons tend to control proximal muscles

MUSCLE FIBER TYPES

Two "types" of muscle fibers, randomly intermixed within muscles; type determined by pattern of innervation from lower motor neuron; all myofibers in a given motor unit are of the same type; a fiber of one type can be converted to one of the other type by changing the pattern of stimulation (i.e., reinnervation with different nerve)

	Type I	Type II
Color:	Red	White
Speed:	Slow	Fast
Duration:	Prolonged	Quick
Fatigue:	Slow	Rapid
Prevalence:	1/3	2/3
Use:	Postural	Strength
Mitochondria:	Numerous	Fewer
Myoglobin:	High Concentration	Low
Glycogen Content:	Low	High
Lipid Content:	High	Low
Metabolism:	Aerobic	Anaerobic
ATPase (pH 9.4):	Unstained	Dark
ATPase (pH 4.6):	Dark	IIA: Light
("reverse ATPase")		IIB: Intermediate
NADH -TR	Dark	Light

NOTE: NADH is actually a stain for lipid, and is not as useful as the ATPase reaction since denervation causes both fiber types to stain dark
Type II muscles hypertrophy in response to training or anabolic steroids, and atrophy in response to disuse; type I fibers generally do not vary in size
Non-specific Esterase Reaction: stains type I fibers slightly darker then type II, but stains denervated fibers of either type very dark, owing to the diffuse distribution of acetylcholine esterase activity
Alkaline Phosphatase Reaction: stains regenerating fibers

HISTOGENESIS

Arise from fusion of myoblasts to form a multinucleated syncytium called a myotube which stimulates the formation of myofibrils
When becomes innervated, diffusely distributed acetylcholine receptors become concentrated at motor end plate

EVALUATING MUSCLE BIOPSIES

When evaluating muscle biopsies, need to first determine whether the changes are Neuropathic or Myopathic; in chronic conditions, there can be a mixture of these features making distinction difficult
Myopathic processes will show coexistent degeneration and regeneration
If process is myopathic, determine whether it is inflammatory or non-inflammatory: inflammatory processes show neutrophils and mononuclear cells within the muscle and often have an accompanying vasculitis; non-inflammatory processes show coagulative necrosis and "ragged-red" fibers
NOTE: variation in fiber size and internal nuclei are normal at the site of tendinous insertion

Regeneration
Regenerating fibers tend to have rounded edges, nuclei which may be central and have a prominent nucleolus, and stain strongly with the alkaline phosphatase reaction

Rhabdomyolysis
Diffuse destruction or lysis of skeletal muscle, which may be acute, subacute, or chronic
Cause is often unknown
Massive myoglobinuria can induce renal failure

Disuse (Non-specific) Atrophy
NOT caused by denervation
Selective loss of Type II fibers
Can also be seen secondary to large doses of steroids

Neurogenic Disorders

Denervation

Denervation results in atrophy (loss of myofibrils) of all the fibers in the motor unit associated with the lower motor neuron; loss of individual neurons will show small group atrophy, loss of larger nerves will show large group atrophy
Myofibers become angulated when viewed in cross section, and nuclei aggregate into hyperchromatic clumps
Both Type I and Type II fibers are lost; type II fibers lost first
Target fibers: central pallor with condensed eosinophilic rim surrounded by normal appearing muscle; seen in some cases of denervation; probably a transient state
Renervation usually occurs simultaneously with denervation, converting the previously "randomly" distributed type I and type II fibers into fibers of all one type: "Type grouping"

Werdnig-Hoffman Disease
AKA: Infantile Spinal Muscular Atrophy
Autosomal recessive congenital hypotonia with progressive group atrophy usually resulting in death by one year
Loss of lower motor neurons from the anterior horn of the spinal cord with widespread group atrophy

Amyotrophic Lateral Sclerosis
[See also CNS Outline]
Onset in 30's - 60's
Upper motor neuron loss results in fasciculations
Lower motor neuron loss results in group atrophy
Median survival 3 yrs

Myasthenia Gravis

Disorder of the neuromuscular junction
Autoimmune disease in which antibodies to the acetylcholine receptors at the post-synaptic membrane both block stimulation by acetylcholine and induce receptor down regulation
Increasing muscle fatigue with use; patients usually present with ocular muscle involvement
1/3 of patients have a thymoma; most of those without have thymic hyperplasia
Mortality in severe cases is due to respiratory compromise

Eaton-Lambert Syndrome
Myasthenia-like syndrome
2/3 of patients have a small cell carcinoma of the lung

Myopathic Disorders

Muscular Dystrophies

Inherited progressive primary degenerative diseases of skeletal muscle
Great variability in fiber size (compensatory hypertrophy of fibers not yet effected)
Diffuse endomysial fibrosis

Duchenne Muscular Dystrophy
AKA: Progressive Muscular Dystrophy
1/3500 live male births; 1/3 represent new mutation
X-lined recessive (affects primarily boys) inherited mutation mapped to defect in the dystrophin gene on chromosome

Xp21; this large gene product (430kD) is absent from affected patients
Involves primarily proximal muscles
Immobilization for even short periods of time can result in contractures
See "pseudohypertrophy" of calf muscles
Normal muscle strength at birth; weakness becomes apparent by age 3-4, usually wheelchair dependent at age 10 and bedridden by age 15; death due to involvement of respiratory muscles or heart
Serum creatine kinase levels elevated from birth
Breakdown of sarcolemma with degeneration of the muscle fibers (dark, hyalinized, over contracted), myophagocytosis, alkaline phosphatase positive regenerating muscle fibers with prominent nucleoli
Later, endomysial fibrosis and fibrofatty replacement of muscle as degeneration exceeds capacity for regeneration; eventually, near complete loss of myofibers

Becker's Muscular Dystrophy
Milder form of Duchenne muscular dystrophy (1/10 as common), with later onset (teens) which is also X-linked and which maps to the same locus
Affected individuals usually retain ability to walk into adulthood

Limb-Girdle Dystrophy
Group of diseases predominantly affecting the axial muscles
Most are autosomal recessive
Late onset (young adulthood)
Slow but progressive deterioration
Markedly increased numbers of central nuclei, with fiber splitting and dramatic fiber hypertrophy

Myotonic Dystrophy
1/20,000 live births
Autosomal dominant (linked to chromosome 19q13.2) but with variable penetrance
Syndrome which includes, usually, cataracts, frontal baldness, testicular atrophy, heart disease, and dementia
Onset often in 20's-30's; involves primarily facial and pharyngeal muscles
Myotonia: inability of muscle to relax once contracted
Increased number of central nuclei, many *ring fibers* (circumferential disposition of myofibers on cross section), chains of nuclei, type I fiber atrophy

Congenital Myopathies

Group of disorders which are not progressive but do restrict activity and are complicated by secondary skeletal problems such as kyphoscoliosis
Often present at birth with hypotonia, decreased deep tendon reflexes, and low muscle mass. With age, motor milestones are delayed
Biopsies reveal that morphologic abnormalities are restricted to the Type I fibers, which predominate; Type II fibers are decreased in number but structurally normal

Central Core Disease
Sporadic, autosomal recessive, and autosomal dominant forms
Type I fibers show a central core of lucency running the length of the cell (best demonstrated with the NADH-TR reaction) due to a loss of membranous organelles and often with disorganization of the surrounding myofibrils

Nemaline (Rod) Myopathy
Inclusions within the type I myofibers of rod-shaped structures which arise from the Z-bands and are stainable with trichrome stain or with PTAH (phosphotungstic acid hematoxylin)
Probably a group of disorders
Facial, pharyngeal, and neck muscle can be markedly involved
NOTE: rods can also be seen in muscular dystrophy, denervation atrophy, and inflammation: not specific

Central Nuclear Myopathy (Tubular Myopathy)
Autosomal dominant, recessive and X-linked varieties
X-linked form presents at birth, autosomal dominant is later onset
Predominance of small, Type I fibers with a single centrally located nucleus (normally, nuclei should be central in <3% of the fibers, unless near site of tendinous insertion)

Glycogen Storage Diseases

Some of these disorders, in particular Glycogenosis II (Pompe's disease) and Glycogenosis V (McArdle's disease) affect predominantly muscle
[See "Congenital Syndromes" outline]

Mitochondrial Myopathies

Inherited defects of mitochondrial metabolism
Examples include ATPase deficiency, carnitine metabolism defect, cytochrome deficiencies

Inflammatory Myopathies

Often see perifascicular atrophy, in which the peripheral fibers of a fascicle or group undergo degeneration/regeneration without involvement of the central fibers. This is often associated with a vasculitis

Polymyositis / dermatomyositis
Idiopathic disorder confined to striated muscle, often with exacerbations and remissions but slow, progressive weakness; ultimately fatal
Patients respond to corticosteroid therapy
May represent a paraneoplastic syndrome in some patients
[See "Inflammation and Immunology" outline under "Autoimmune Diseases"]

Viral Myositis

Neoplasms

Myxoma

Often a moderately well circumscribed gelatinous mass deep within muscle, usually of an extremity (especially thigh), but may be poorly circumscribed and infiltrating
Almost always adults; usually female
Proteoglycan matrix, slightly basophilic, with rare stellate cells; lacks the endothelial cell proliferation of a cardiac myxoma
Excellent prognosis: rarely if ever recurs

Rhabdomyoma

Cardiac and extracardiac types; cardiac "tumors" are probably hamartomatous rather than neoplastic
Extracardiac are probably true neoplasms and are divided into two types, with some overlap

Adult Type
Oral cavity and vicinity
Large, well differentiated, plump cells with abundant acidophilic cytoplasm and various amounts of clearing due to lipid and/or glycogen
Cross striations may be seen in some cells
Differential diagnosis: hibernoma, granular cell tumor

Fetal Type (Genital Type)
Head and neck in children under 3; vulvovaginal in middle aged women (latter also called genital rhabdomyoma)

Cellular, randomly intersecting bundles of immature skeletal muscle fibers, separated by strands of collagen with primitive mesenchymal cells
Lacks mitoses, cambium layer, and infiltrative margins of rhabdomyosarcoma

Rhabdomyosarcoma

More common than rhabdomyomas; relatively common soft tissue sarcoma in children
Except for pleomorphic type, 90% occur before age 20
M ≥ F; whites>blacks
Generally at least focally positive for muscle specific actin, desmin, myosin, myoglobin
MyoD: new antigen: 318 amino acid DNA binding protein which seems to initiate the commitment of undifferentiated mesenchymal cells to myoblasts; present in normal skeletal muscle and in all rhabdomyosarcomas, even those which are desmin negative (another factor needed for complete differentiation appears to be missing)
EM: thick + thin myofilaments, ribosomal-myosin complexes
All are Grade III by definition
Chemotherapy and in some cases radiotherapy can induce partial differentiation in childhood rhabdomyosarcomas
5 year survival by surgical stage:

I	Localized; completely excised	82%
II	Microscopic residual or + LN	78%
III	Gross residual tumor	64%
IV	Distant metastases	27%

Embryonal Rhabdomyosarcoma (50-60%)
Most commonly head and neck (orbit or nasopharynx), also retroperitoneum, bile ducts, urogenital tract
Generally 3-12 yrs old
Poorly circumscribed, white, soft
Rhabdomyoblasts take on many characteristic morphologies:
• Strap cells: elongated cells with one or several nuclei and long extended cytoplasmic processes with cross-striations
• Racquet shaped cells with a single nucleus in expanded end
• Spider cells: giant cells with peripherally arranged PAS+ vacuoles separated by thin strands of cytoplasm
• Broken strand sign: spindled rhabdomyoblast with focal cytoplasmic bend
Botryoid Rhabdomyosarcoma (5-10%)
Some pathologists consider this a subtype of embryonal rhabdomyosarcoma with grape-like gross appearance, but it occurs in a slightly younger age group (mean=7 yrs)
Seen in vagina, urinary bladder, nasal cavity, bile ducts
Dense collection of undifferentiated tumor cells immediately beneath the epithelium: Nicholson's *Cambium Layer*
Favorable prognosis
Alveolar Rhabdomyosarcoma (20%)
Generally 10-30 yrs old (mean=23); extremities, perineum, occasionally sinuses
Thin strands of fibrovascular stroma forming nests containing loose clusters of small, round, undifferentiated tumor cells which tend to "float free" in "lumen"
Occasional multinucleated giant cells
80% are associated with t(2;13)(q37;q14)
Solid variant exists in which cells remain better attached
Worst prognosis of all types; any alveolar component imparts the bad prognosis
Pleomorphic Rhabdomyosarcoma (<5%)
Tends to occur in individuals over 45 yrs (mean age=50 yrs)
Usually extremity, especially thigh
Large, atypical tumor cells, often giant cells
Difficult to distinguish from liposarcoma or MFH without immunohistochemistry
Spindle Cell Variant (<3%)
Rare. Newly recognized.

ALTERNATE CLASSIFICATION
Favorable: botryoid, well differentiated, embryonal
Unfavorable: alveolar, pleomorphic

Alveolar Soft Part Sarcoma

AKA: malignant organoid granular cell myoblastoma; malignant nonchromaffin paraganglioma
Deep soft tissues, usually thigh and leg, also head and neck (orbit, tongue); young adults (15-35 yrs)
Necrosis and hemorrhage common
Fibrous tissue strands forming nests of large, polygonal, loosely cohesive tumor cells with large vesicular nuclei, prominent nucleoli, granular cytoplasm
Often, cells near center of nests loose connection with surrounding cells, forming the alveolar pattern
Mitoses are rare
Probably an immature rhabdomyosarcoma; myo-D positive
Highly malignant, with blood borne metastases, most commonly to lung; lethal over protracted course of 5-10 yrs
Lesion is considered ungradable

PERIPHERAL NERVE LESIONS

Neuroma

Most occur following trauma (hence, traumatic neuroma)
Often very painful
Non-neoplastic overgrowth of nerve fibers and Schwann cells
Extensive perineural fibrosis common
Morton's Neuroma
Variant caused by repeated mild trauma
Typically interdigital plantar nerve between 3rd and 4th metatarsals; results in shooting pains upon standing
More common in women
Proliferation of Schwann cells and fibroblasts associated with fibrosis, nerve degeneration, endarteritis and thrombosis of the accompanying artery

Neurilemoma (Schwannoma)

Truly encapsulated neoplasm; grow eccentrically along periphery of nerve, compressing it; nerve usually does not penetrate tumor
Almost always solitary
Usually flexor surfaces of extremities, neck, mediastinum, retroperitoneum, posterior spinal roots
Larger lesions may be cystic
Antoni A areas: cellular, spindle cells, often palisading or in an organoid (Verocay bodies) pattern, predominate in smaller lesions
Antoni B areas: Tumor cells separated by abundant edematous myxoid stroma; occasional isolated bizarre cells
Blood vessels may be very prominent (fenestrated by EM) and are often thick walled

Mitoses can be seen
When arise from spinal nerve root, may have many melanocytes mixed in throughout tumor
Strongly S-100 positive; usually keratin negative

Ancient Schwannoma
Degenerative changes seen in "older" schwannomas, including cyst formation, hemosiderin, fibrosis, hyalinization of the vessels, calcification
These degenerative features all favor a benign diagnosis

Cellular Schwannoma
Antoni-A areas predominate

Neurofibroma

Solitary (90%) or multiple (10%); multiple usually means neurofibromatosis
20-30 yrs old most commonly
Tumors generally are NOT encapsulated
Nerve routinely runs through middle of tumor
May have diffuse, tortuous enlargement of nerve: plexiform
Combined proliferation of all nerve elements: Schwann cells, fibroblasts, axons, perineural cells; Schwann cells frequently predominate
Mast cells commonly present throughout stroma
Can have atypia, but should be no mitoses
Vessels are generally thin walled
Usually S-100 and GFAP positive, but often only weakly so

Plexiform Neurofibroma
Classic lesion of von Recklinghausen's disease
Diffuse enlargement of a nerve trunk by a neurofibroma causing a convoluted "bag of worms" appearance, appearing lobulated on cut section; may become very large
Prone to malignant degeneration: 5-10% of von Recklinghausen's disease patients develop malignant tumors arising in benign neurofibromas, almost always of deep large nerve trunks of neck or extremities

Granular Cell Tumor

AKA: Granular cell schwannoma
Almost always benign
Unknown histogenesis; originally thought to be myoblastic, but presence of S-100 positivity has suggested neural
Most common in the tongue and subcutaneous tissue, but can occur anywhere (any organ); young to middle age
Generally small, firm, gray-white to tan
Nests and sheets of round to polygonal cells with distinct borders, small central nuclei, occasional multinucleation or pleomorphism, scattered mitoses, and a prominent filling of the cytoplasm with PAS + diastase resistant granules which by EM are membrane bound autophagic vacuoles
When present in the skin of adults, often produce a pseudoepitheliomatous hyperplasia of the overlying epidermis, simulating squamous cell carcinoma
Because of infiltrative projections at periphery, 10% will recur

Malignant Granular Cell Tumor
Very rare
Large, rapidly growing, more infiltrative, numerous mitoses
May be very difficult to distinguish from benign counterpart

Ossifying Fibromyxoid Tumor of Soft Parts

Uncertain histogenesis; probably neural
Adults; M>F
Usually shell of mature bone enclosing bland, round to oval cells arranges in cords and nests in a myxoid to fibrous matrix with osteoid production
2/3 are S-100 positive
Recur; generally do not metastasize

Malignant Schwannoma

AKA: neurogenic sarcoma, neurofibrosarcoma, malignant peripheral nerve sheath tumor
50% arise de novo, 50% from preexisting neurofibroma in patients with von Recklinghausen's disease
Most commonly neck, forearm, lower leg, buttock
Cellular spindle cell tumor with abundant mitoses; some extremely bizarre cells may be present; metaplastic tissue present in 15%
Epithelioid and glandular variants exist
S-100 and Leu7 immunoreactive in only 50%
When arises in setting of von Recklinghausen's disease, very fulminant clinical course

Malignant Triton Tumor
Malignant schwannoma containing metaplastic skeletal muscle tissue

MISCELLANEOUS

Synovial Sarcoma

80% arise about the knee and ankle joints of young adults (15-35 yrs); M:F = 1.5:1
Also seen in shoulder, elbow, hip, retropharyngeal soft tissues, oral cavity, anterior abdominal wall
May be very aggressive or very indolent
Cell of origin unclear; probably primitive mesenchymal cell
Rarely involves synovial membrane or joint
Well circumscribed, firm, graying pink
Focal calcification frequent
Most show biphasic differentiation with a mixture of epithelial areas (glandular, papillary fronds, or nests of keratinizing squamous epithelium) and a sarcomatous spindle cell stroma
Spindle cells generally have plump nuclei, lobular growth pattern, focally whirled; numerous mast cells common; calcifications common; may have metaplastic bone or cartilage
Reticulin stains can highlight biphasic nature of tumor
May be predominantly or completely epithelial or spindled (monophasic variants)
Keratin reactivity is seen in both the epithelial (strong) and also the spindle cell component
Can also be immunoreactive for CEA, EMA, vimentin
LN metastases present in 10-15% (uncommonly high for a sarcoma)
5 yr survival now approaching 50%; prognosis better for younger age, *tumor <5cm* (single most important prognostic factor), <15 mitoses/10 HPF, diploid

Calcifying Synovial Sarcoma
Extensive calcification of stroma; most are <5 cm
Better 5 yr survival

Epithelioid Sarcoma

Usually extremities (hands, fingers (30%)) of adolescents and young adults (median age 26 yrs)
Inconspicuous appearing spindled and polygonal tumor cells, typically forming small nests with central comedo-

like necrosis; may be mistaken for necrotizing granulomas
Unknown histogenesis
Immunoreactive for keratin, vimentin, EMA, occasionally CEA
Favorable prognostic factors: <2 cm, female, few mitoses, no necrosis, diploid

Clear Cell Sarcoma

AKA: Malignant Melanoma of Soft Parts
Generally arises from large tendons or aponeuroses of extremities
Most commonly feet; usually young adults
Firm, well circumscribed, gray-white lesion with gritty texture
Pale cuboidal to fusiform cells with large prominent basophilic nucleoli forming nests or interlacing fascicles
Melanin may be present focally
Consistently S-100 positive; may be HMB-45 positive
Slow but relentless progression

Pigmented Neuroectodermal Tumor of Infancy (melanotic progonoma)

Occurs in children <6 months old; M=F
Anterior maxilla or other head and neck locations
Neuroblasts and melanoblasts in nests
Invades, but rarely metastasizes

Primitive Neuroectodermal Tumor (PNET)

AKA: peripheral neuroectodermal tumor, neuroepithelioma
Sheets of small-round-blue cells, often with rosette-like structures, with salt-and-pepper chromatin pattern
Related to Ewing's sarcoma (same t(11;22) translocation) but cells don't have the clear cytoplasm of Ewing's sarcoma
O-13 antibody to MIC-2 is a marker specific for both PNET and Ewing's sarcoma
[See also Bone and Cartilage Outline]

Malignant Small Cell Tumor of Thoracopulmonary Origin

AKA: Askin tumor
Same lesion occurring the in chest wall, probably originating from an intercostal nerve
Mean age 14; F>M

Desmoplastic Small Round Cell Tumor

Intra-abdominal (95%) mass with pain, ascites, and often obstruction of the colon, ureter, bile duct, or esophagus
M:F=4:1; wide age incidence with mean of 21 (7-48 yrs)
Usually large, multinodular to lobulated mass, often with many small implants
Small blue cells with round nuclei, dispersed chromatin growing in nests with angulated edges and peripheral palisading imbedded in a fibrotic bland stroma; relative amounts of cells and stroma can vary widely
Can see focal necrosis and cyst formation, glandular differentiation, ectatic vessels
EM characteristically shows bundles of intermediate filaments near the nuclei, often entrapping other organelles
Keratin, EMA, desmin (punctate perinuclear stain), vimentin, and NSE positive; LCA, actin, HHF-35, chromogranin negative; usually O-13 negative
>90% show t(11;22)(p13;q12), translocating the C-terminal DNA binding domain of WT-1 (11p13) to the N-terminus of EWS (22q12)
Poor prognosis: most patients dead of tumor within 5 yrs

Sacrococcygeal Teratoma

Most common teratoma in children; F>M
95% are benign, even when immature elements present
Risk of malignancy increases with age of patient

Mesenchymoma

Tumors with two of more mesenchymal elements (not counting fibrous tissue)
Benign and malignant forms exist
Most frequent is Angiomyolipoma

Others

Extragonadal Germ Cell Tumors
Extracranial Meningiomas
Myxopapillary Ependymomas
Extraskeletal Ewing's Sarcoma
Phosphaturic Mesenchymal Tumor
Rhabdoid Tumor

BONE and CARTILAGE

Normal Anatomy

- Bone and cartilage are composed of a matrix containing a fibrillar protein (collagen) and mucopolysaccharides; in cartilage, the latter predominates; in bone, the matrix becomes mineralized
- Epiphysis: endochondral ossification
- Metaphysis: also endochondral ossification; supplied by diaphyseal vessels; primary site of Ca and PO_4 exchange
- Diaphysis: supplied via Volkman's and Haversion canals
- Epiphyseal plate can act as barrier to tumor spread
- Periosteum: bone forming "membrane" surrounding bone; can become elevated and form new bone perpendicular to surface in primary tumors (Codman's triangle), but also in trauma, hematoma, TB, syphilis, metastases
- Osteoblasts: make osteoid; prominent golgi, abundant alkaline phosphatase activity; become osteocytes
- Osteoclasts: resorb bone, numerous mitochondria, abundant acid phosphatase activity; can remove bone 100x faster than osteoblasts can make it
- In adults, more than 1-2 osteoclasts per cm^2 is abnormal: Paget's, hyperparathyroidism, chronic osteomyelitis, tumor
- Parathormone receptors are located on osteoblasts; they secrete factors which activate osteoclasts; osteoclasts by themselves are NOT responsive to parathormone
- Osteoid: 90-95% type I collagen
- Mineralization: hydroxyapatite: $Ca_{10}(PO_4)_6(OH)_2$
- Mineralization normally lags behind osteoid deposition by 12-15 days, leaving a 15µm rim of unmineralized osteoid
- Woven bone: haphazard arrangement of fibers (vs. lamellar); occurs in fibrous dysplasia, high turnover states (healing)

Fractures

Healing:

- Hematoma forms
- Organized by influx of vessels
- Absorption of devitalized bone begins at ~3 days
- Intramembranous "pseudosarcomatous" bone growth begins at periosteum of two sides of fracture, and grows across the break, forming the primary callus (procallus)
- 1° callus absorbed - replaced by lamellar bone (2° callus)

- Exuberant callus usually means slow healing: infection, poor blood supply, delayed reduction, inadequate immobilization
- Sequestrum: dead bone; may be extruded through skin
- Involucrum: new bone formed sub-periosteally which envelops an inflammatory focus (reactive periosteal bone)
- Foreign material: (e.g. screws) eventually become isolated from bone by fibrous tissue continuous with periosteum; no foreign body giant cell reaction occurs

Necrosis

Infarct

- Seen following trauma; also seen in alcoholism, Gaucher's disease, decompression sickness, steroid use, sickle cell anemia, chronic pancreatitis
- No radiological abnormalities seen for 1-2 weeks
- Eventually get absorption with decreased density
- Commonly involves the femoral head: aseptic (avascular) necrosis: see "creeping substitution" of new bone for the non-viable bone; eventually get osteochondral collapse and secondary arthritis
- Increased incidence of malignancy

Osteochondritis Dissecans

- Articular cartilage and subchondral bone undergo necrosis with separation from the rest of the bone
- Usually medial femoral condyle; usually due to trauma

Osteomyelitis

Bacterial

- 70-80% Staphylococcus aureus, often penicillin resistant
- Also Klebsiella, E. coli, Proteus, Pseudomonas, Streptococcus, gonococcus
- Sickle cell patients prone to Salmonella osteomyelitis
- Newborns prone to Hemophilus influenza infection
- IV drug users prone to pseudomonas infection
- Hematogenous spread: most commonly ends of long bones (blood flow slowest in metaphyses)
- Children <1 yr old primarily have epiphyseal involvement

Plasma Cell Osteomyelitis: abundant plasma cells

Xanthogranulomatous Osteomyelitis: many foamy histiocytes

Chronic

- Cutaneous fistulas; surface may heal, forming an epidermal inclusion cyst
- Infection persists as long as dead bone with bacteria remain
- Sequestra are cortical

Tuberculous

- Formerly children/young adults; now more common in debilitated elderly
- Characteristically insidious, chronic, persistent, destructive, and resistant to management
- Vertebrae (Pott's disease), hip, knee, ankle, elbow, wrist
- Hematogenous spread: metaphysis, epiphysis, synovium
- Sequestra are cancellous

Syphilis

- Periosteal bone proliferation as well as destruction
- Vertebrae, hands, feet, Hutchinson's teeth
- When congenital, usually epiphyseal

Fungal

- Blastomycosis, Actinomycosis, histoplasmosis

Abnormalities of Production

Osteoporosis

- Decrease in mass of normally mineralized bones
- Usually due to increased absorption
- Occurs postmenopausally if no estrogen replacement; also seen in endocrine dysfunctions, neoplasms, immobilization
- Compression fractures of spine common

Osteomalacia

- "Rickets" in children with open epiphyseal plates (produces a characteristic cup-shaped deformity on X-ray)
- Accumulation of unmineralized bone matrix due to defective mineralization
- Decreased rate of mineralization (decreased serum calcium or phosphate, usually due to decreased levels of vitamin D)

Osteopetrosis

- AKA: Albers-Schönberg disease, Marble-bone disease
- Defect in remodeling by osteoclasts (lysosomal defect)
- Abnormal bone formation with excess lamellar bone and calcified cartilage
- Curable by bone marrow transplantation
- Malignant autosomal recessive form with obliteration of marrow cavity and early death from neutropenia/anemia
- Adult autosomal dominant form more benign (less severe)

Osteogenesis Imperfecta

- Disorder of type I collagen synthesis resulting in brittle bones
- Fractures common in the lower extremities, especially around the knees; leading to short stature
- Type I: Postnatal fractures, blue sclerae, hearing impairment, autosomal dominant, abnormality of pro-α1 chain
- Type II: Perinatal lethal; autosomal recessive
- Type III: Progressive deforming; abnormality of pro-α2 chain
- Type IV: Postnatal fractures, normal sclerae; autosomal dominant

Achondroplasia
- Autosomal dominant; normal longevity when heterozygous, lethal when homozygous
- Premature ossification of epiphyseal plates with normal appositional growth of bones, resulting in short but disproportionately wide bones

Renal Osteodystrophy
- Bone changes and hypocalcemia seen in setting of chronic renal failure due to hyperphosphatemia and secondary hyperparathyroidism
- Includes osteitis fibrosa cystica, osteomalacia, occasionally osteosclerosis

Hypertrophic Osteoarthropathy
- New periosteal bone formation at distal ends of long bones, especially the bones of the hands and feet, with arthritis of adjacent joints and clubbing of the digits
- Seen in patients with intrathoracic tumor, usually bronchogenic carcinoma
- Clubbing alone can also be seen in cyanotic heart disease, infective endocarditis, inflammatory bowel disease

BONE - Tumor-like Lesions

Paget's Disease (Osteitis Deformans)
- 90% patients >55 yrs old; very rare before 40 yrs; M=F
- More common in England, Australia, Northern Europe
- Many cases are monostotic and asymptomatic, usually affecting the axial skeleton (lumbosacral spine (70%), pelvis (65%); also femur, skull); some are polyostotic
- May be viral (slow virus): osteoclasts contain viral-like inclusions
- Initially lytic, followed by abnormal hyperplasia, thick trabeculae, disjointed and discontinuous lamellae, mosaic of cement lines (scalloped) - advances through bone at 1mm/month
- Increased incidence of sarcoma (femur, humerus, innominate, tibia, skull)
- Fractures are usually transverse
- Serum alkaline phosphatase often elevated (increased osteoblastic activity)

Osteitis Fibrosa
- Chronic hyperparathyroidism induced osteoclastic destruction of bone
- When cystic (osteitis fibrosa cystica), also known as von Recklinghausen's disease of bone
- Initially see only demineralization; later, reabsorption and fibrosis with bizarre osteoclasts tunneling within scalloped reabsorption cavities
- Microfractures lead to hemorrhage and hemosiderin laden macrophages ("*brown tumor*")
- Organization of hemorrhage creates mixture of macrophages, fibroblasts, osteoclasts, collectively forming a "*reparative giant cell granuloma*" (see also ABC)

Myositis Ossificans
- Solitary, non-progressive reactive condition often mistaken for osteosarcoma
- Flexors of arm, quadriceps, adductors of thigh, gluteal muscles, soft tissue of hand most common - may not involve muscle
- Occurs following trauma - usually no inflammation
- Highly cellular stroma associated with new bone, with or without cartilage
- As evolves, becomes zonal with cellular core, intermediate zone of osteoid, peripheral shell of highly organized bone

Fibrous Dysplasia
- Monostotic type (70%): older children, rib, femur, tibia
- Polyostotic type: rarer; can be seen without endocrine dysfunction (25%) or with endocrine dysfunction, skin hyperpigmentation, and precocious puberty (5%; AKA Albright's syndrome)
- Fusiform expanding mass arising in cancellous bone with thinning of overlying cortex
- Narrow, curved, misshapen (Chinese characters) metaplastic bone spicules (without lining osteoblasts) in sea of variably cellular fibrous tissue; with or without giant cells
- Cured by resection

Ossifying Fibroma
- AKA: Osteofibrous dysplasia
- Usually involves jaw
- Like fibrous dysplasia except osteoblasts line trabeculae, lamellar bone is present, tends to be cortical vs. medullary
- Greater tendency to recur

Metaphyseal Fibrous Defect
- AKA: Non-ossifying fibroma, "benign fibrous histiocytoma", fibrous cortical defect
- Adolescents, usually tibia or lower femur; bilateral in 50%
- Eccentric, sharply delimited lesions near epiphysis, often involving epiphyseal disorder
- "Non-ossifying fibroma" initially used to indicate variant which is loose and involves medullary space
- Cellular storiform fibrous tissue, scattered osteoclasts, foamy macrophages, hemosiderin
- Usually asymptomatic - found incidentally; may be painful
- Non-neoplastic; no malignant potential; often disappears spontaneously

Aneurysmal Bone Cyst
- Patients usually 10-20yrs old
- Usually vertebrae or flat bones, also diaphysis of long bones
- Often grow rapidly, mimicking a neoplasm
- Soft, sponge-like mass composed of large, blood filled spaces without endothelial lining, surrounded by a shell of reactive bone, producing an eccentric, often multicystic expansion of the bone, eroding the cortex, sometimes extending into the soft tissues
- Osteoclasts, reactive bone, degenerated calcifying fibromyxoid tissue
- ABC like areas can be seen in chondroblastoma, giant cell tumor, fibrous dysplasia; also nonossifying fibroma, osteoblastoma, chondrosarcoma, hamartoma of chest
- 20-30% will recur if treated with curettage alone

Solid Aneurysmal Bone Cyst
- Variant in which no cystic cavities are present
- Seen in small bones of hands and feet, jaw, vertebra, sacrum
- Spindle cell proliferation with osteoid, new bone formation, and giant cells
- Some equate this with a "giant cell reparative granuloma" (see also osteitis fibrosa)

Ganglion Cyst of Bone

Similar to soft tissue counterpart, but much rarer
When found in intraosseous location, close to joint space
Cyst surrounded by zone of sclerotic bone
Gelatinous content and wall of fibrous tissue
Ankle (especially tibia) most commonly affected

Unicameral Bone Cyst

AKA: solitary bone cyst, simple bone cyst
Usually upper humerus or femur; long or short bones
Most occur in males, almost all under 20yrs
Metaphyseal - with time, migrate away from epiphysis
Cyst contain clear or yellow fluid - lined by brown (hemosiderin stained) well vascularized connective tissue membrane, often with trapped cholesterol clefts
May see reactive changes; often present following fracture
Curettage and packing is treatment of choice

BONE and CARTILAGE - Tumors

CHARACTERISTIC LOCATIONS

Epiphysis: chondroblastoma, giant cell tumor
Metaphysis: giant cell tumor, enchondroma, chondrosarcoma, osteosarcoma, osteochondroma, osteoblastoma
Metaphyseal/Diaphyseal junction: fibrosarcoma, fibrous cortical defect, chondromyxoid fibroma, fibrous dysplasia, osteoid osteoma
Diaphysis: Ewing's, adamantinoma

GRADING

Low Grade
Grade I: well differentiated
Grade II: moderately differentiated
High Grade
Grade III: poorly differentiated
Grade IV: undifferentiated

STAGING

T1: confined by cortex
T2: extends beyond cortex
N1: regional lymph nodes involved

	T1	T2
N0, Low Grade	IA	IB
N0, High Grade	IIA	IIB
N1	IVA	IVA

IVB: M1
(NOTE: there is no Stage III)

Bone Forming

Osteoma

40-50 yrs old, M:F = 2:1
Bossellated lesion composed of dense, mature, predominantly lamellar bone, located usually on the flat bones of skull and face; may protrude into sinuses
May be reactive rather than a neoplastic process
Seen in patients with Gardner's syndrome

Osteoid Osteoma

M:F = 2:1; 10-30 yrs old
Can occur anywhere, most commonly femur, tibia, humerus
Intense, well localized pain (out of proportion to size of lesion) which is rapidly relieved by aspirin
Usually metaphyseal in long bones, pedicle in vertebrae
85% begin in cortex; 13% in medulla, 2% subperiosteal
Central radiolucent nidus (0.5-1.5 cm; osteoid growing in highly vascular osteoblastic connective tissue with some benign giant cells) surrounded by dense sclerotic bone
High levels of prostaglandins present, perhaps accounting for pain

Osteoblastoma

AKA: giant osteoid osteoma
Similar to osteoid osteoma, with larger (>1.5 cm by definition) nidus and minimal surrounding sclerotic bone
Most arise in medulla; metaphyseal; M:F=2:1; 10-30 yrs
Spine, large bones of legs; may be painless
May be difficult to distinguish from osteosarcoma; presence of infiltrative margin or *cartilage* suggests malignancy

Aggressive Osteoblastoma

AKA: malignant osteoblastoma, osteosarcoma resembling osteoblastoma
Atypical cytological features, wide irregular trabeculae lined by epithelioid osteoblasts, non-trabecular osteoid
Differentiation from osteosarcoma: low mitotic rate, osteoid not lace-like, tumor does not penetrate surrounding tissues

Osteosarcoma

Most common primary bone malignancy (except hematopoietic)
M:F = 3:2; usually 10-25 yrs old (second peak after 40 yrs)
Usually metaphyseal (~90%), particularly lower femur, upper tibia, upper humerus
Must identify irregularly contoured osteoid and/or bone produced by tumor cells - commonly anastomosing microtrabeculae
Most arise in medullary cavity and extend along marrow, to cortex, to soft tissues, to epiphysis, to joint; may elevate periosteum (Codman's triangle: new bone made by elevated periosteum); often have satellite nodules (skip metastases)
May destroy preexisting bone or grow around it
Spindle cell tumor; 50% are predominantly osteoblastic, 25% chondroblastic, and 25% fibroblastic; non-osteoblastic patterns can dominate histology - no effect on prognosis
Osteosarcoma cells may be alkaline phosphatase positive, usually vimentin positive, usually make type I collagen
Metastases via blood: lung (98%), other bones (37%), pleura (33%), heart (20%); regional LN's almost never involved

Predisposing Conditions

(NOTE: Most arise de novo)
- Paget's disease - accounts for many osteosarcomas in individuals >50 yrs old
- Radiation - 2nd most common post radiation sarcoma (after MFH). Usually 10 yrs after radiation - most high grade
- Chemotherapy - children with retinoblastoma or other malignancy; increased frequency of osteosarcoma in patients with mutations of the Rb gene
- Benign lesions: fibrous dysplasia, osteochondromatosis
- Foreign bodies: e.g. at site of total hip replacement - rare
- (Trauma: does not cause - merely brings to attention)

Therapy
- Often use preoperative chemotherapy - >90% response associated with good prognosis
- Excise entire biopsy tract with specimen
- Removal of metastases from lung appears to prolong survival

Prognosis
- 5 yr survival increased from 20% to 50% with advent of pre-adjuvant chemotherapy
- Good prognosis: Jaw or distal extremities; parosteal, periosteal, well differentiated intramedullary types
- Bad prognosis: Paget's, radiation induced (30% 5 yr), multifocal, focal dedifferentiation, telangiectatic
- No effect on prognosis: age, sex

VARIANTS / SPECIAL TYPES

Well differentiated Osteosarcoma
- AKA: intramedullary, central low-grade osteosarcoma
- Mostly adults, femur or tibia - very bland
- Hypocellular; resembles fibrous dysplasia, but with cortical destruction
- Recurrences common, metastases rare

Juxtacortical (parosteal) Osteosarcoma
- Infrequent; older age group (30-40's); F>M
- Metaphysis of long bones, usually distal femur (70%)
- Slow growing - some up to 15 yrs
- Large lobulated hypocellular mass, with spindle cells in a predominantly fibrous background; tends to encircle the bone; heavily calcified
- Very good prognosis if low grade
- Late in evolution, may become high grade (dedifferentiate) and penetrate medullary cavity - bad prognosis

Periosteal Osteosarcoma
- Grows on surface of long bones
- Upper tibial shaft or femur - usually limited to cortex
- Predominantly chondroblastic, usually high grade
- Prognosis better than conventional osteosarcoma

Osteosarcoma of the jaw
- Slightly older (average age 34)
- Prominent cartilaginous component
- Relatively good prognosis

Telangiectatic Osteosarcoma
- Prominent blood filled cystic formations (resembles an aneurysmal bone cyst)
- Malignant stroma in septa separating bloody cysts
- Pathologic fractures common
- May have more aggressive clinical course

Small Cell Osteosarcoma
- Often confused with Ewing's or lymphoma; but focally produces osteoid, sometimes mixed with cartilage
- Poor prognosis

Fibrohistiocytic Osteosarcoma
- Looks like MFH, especially in soft tissue

Anaplastic Osteosarcoma
- Marked pleomorphism - bizarre nuclei

Osteosarcoma in Paget's disease
- Occurs in <1% of patients with polyostotic Paget's
- Pelvis, humerus, femur, tibia, skull
- Usually many osteoclasts
- Extremely poor prognosis

Cartilage-Forming

Osteochondroma (Exostosis)
- Most common benign bone "tumor" (may be simply aberrant growth of cartilage rather than a true neoplasm)
- Young (~10 yrs old); M>F; usually asymptomatic
- Metaphysis, most commonly lower femur, upper tibia, upper humerus, pelvis
- Grows out in direction opposite that of the adjacent joint
- Usually ~4 cm, may get larger - larger tumors pedunculated
- Lobulated cap of cartilage (covered by fibrous membrane) with mature bone beneath making up the bulk of lesion; active endochondral ossification at interface
- Cap rarely exceeds 1 cm; in older lesions, cap may thin out or disappear
- Whole lesion may spontaneously regress
- If single, malignant transformation in 1-2%
- Signs of malignancy: >8cm, cap>3 cm, irregular cap
- Bursa may develop around head-can lead to chondrosarcoma

Osteochondromatosis
- AKA: Ehrenfried's hereditary deforming chondrodysplasia
- Multiple lesions; autosomal dominant
- Can be associated with Gardner's syndrome
- More likely to develop chondrosarcoma (10%)

Subungual Exostoses
- AKA: Dupuytren's exostoses
- Usually located on great toe
- Not really osteochondromas - different entity
- Invariably benign

Chondroma
- AKA: enchondroma when in center of diaphysis
- Common benign lesions
- Radiology: popcorn-like densities
- Usually small bones of hands or feet, especially proximal phalanges; unusual in ribs or long bones
- Mature well circumscribed lobules of hyaline cartilage, often with foci of myxoid degeneration, calcification, peripheral endochondral ossification; usually NOT painful
- In general, cellular myxoid areas should raise suspicion for low grade chondrosarcoma; however, lesions in the hands (which are often painful) can show cellular myxoid areas as well as double-nucleated lacunae and still behave in a benign fashion
- Non-hereditary syndromes of multiple chondromas have risk of malignant transformation (to chondrosarcoma):
  - Ollier's disease: predominantly unilateral, associated with ovarian sex-cord stromal tumors
  - Maffucci's syndrome: with soft tissue hemangiomas

Calcifying Enchondroma
- Massive calcification, present in metaphysis of long bones

Juxtacortical (Periosteal)
- Small (usually <3 cm) and well demarcated
- Like enchondromas of the hands, these lesions tend to be more cellular with occasional myxoid areas and atypical chondrocytes; may erode and induce sclerosis of contiguous cortex; still behave in a benign fashion

Cartilaginous and Vascular Hamartoma (mesenchymoma)
- Occurs in chest wall of infants - most are congenital
- Not strictly a chondroma
- Chondroid areas mixed with spindle areas in an aneurysmal bone cyst-like appearance

Chondroblastoma
- M:F=2:1; usually 10-20yrs old; characteristically painful
- Epiphyseal: distal femur, proximal humerus, proximal tibia
- Very cellular, occasional scattered collections of giant cells
- May have thick, sharply demarcated cell membranes; glycogen in cytoplasm; plump nuclei, characteristically with a longitudinal groove; reticulin fibers surround each cell (immature cartilage) and in small zones calcifies to form a lacy "chicken wire" pattern; S-100 positive
- 25-50% show areas resembling aneurysmal bone cyst with giant cells

Differential diagnosis: giant cell tumor, chondromyxoid fibroma
Treatment: curettage - may recur
Rarely, may behave aggressively - identical histology

Chondromyxoid Fibroma

Young adults, often long bones (most commonly tibia) or small bones of the feet; may become large
Radiographically, well defined lytic lesion of the lateral metaphysis, often with a sclerotic margin and thinned overlying cortex
Solid, yellowish to tan; bone is replaced rather than expanded
Large lobules of a hypocellular myxoid to chondroid matrix separated by a highly cellular stroma containing spindled cells and osteoclasts
Occasional pleomorphic giant cells can be seen; mitoses rare
Presence of binucleate or multinucleated cells, or multiple cells per lacunae, suggests a low grade chondrosarcoma
25% recur if curette - en bloc excision preferred

Fibromyxoma

Probably variant of chondromyxoid fibroma - older individuals

Chondrosarcoma

Most patients 30-60 yrs old - pelvis, ribs, shoulder
Can occur in children - usually extremities
Radiology: osteolytic lesions with spotty calcification, ill defined margins, expansive thickening of shaft, cortical thickening with areas of perforation or destruction - rarely grows beyond periosteum
Plump, hyperchromatic nuclei, two or more nuclei per cell, two or more cells per lacuna - cells are S-100 positive
Permeation of bone marrow with trapping of lamellar bone
Correlation with radiology essential: atypical cytology OK in lesion of fingers (enchondroma), but rapidly growing lesions of ribs or long bones which attain a size of >8cm are invariably malignant, regardless of cytology
Soft tissue implantation at biopsy common - en bloc excision or removal of biopsy tract important
Prognosis generally better than osteosarcoma
Microscopic grade (based on cellularity) important: 5 yr survival 78%, 53%, 22% for Grade I, II, III lesions
Recurrences usually of higher grade than primary, and may occur up to 20 yrs later
Metastases common, usually to the lung; never LN's

Three types by location:

- Central: Located in medullary cavity, usually of long bone
- Peripheral: Arise de novo or in preexisting osteochondroma; often have heavily calcified center
- Juxtacortical (Periosteal): Shaft of long bone, usually femur

VARIANTS

Clear Cell Chondrosarcoma

Often proximal femur, proximal humerus
Abundant clear cytoplasm, sharply defined cell borders, with interspersed fragments of lamellar bone
Similar to chondroblastoma - may be malignant counterpart
Usually entirely lytic, slightly expansile, sharply marginated
Behaves in low grade fashion

Mesenchymal Chondrosarcoma

10-30yr old; jaw, pelvis, femur, ribs; 30% arise in soft tissues
Dimorphic pattern: islands of well-differentiated cartilage intermixed with a highly cellular, undifferentiated stroma of small cells often with a lymphoma or hemangiopericytoma pattern - pleomorphism and/or mitoses rare
Small cells positive for vimentin, Leu 7; negative for S-100
Prognosis variable, generally poor

Myxoid Chondrosarcoma (Chordoid Sarcoma)

Can occur in bone or in soft tissue
Looks like chordoma, but is keratin negative

Dedifferentiated Chondrosarcoma

Focus of poorly differentiated sarcomatous element, usually at periphery of an otherwise low grade lesion
Focal areas may resemble MFH, rhabdomyosarcoma, fibrosarcoma, osteosarcoma
Marked acceleration of clinical course - very bad prognosis

Fibrohistiocytic Lesions

Benign Fibrous Histiocytoma

[See Metaphyseal Fibrous Defect, above]

Desmoplastic Fibroma

Rare benign to borderline neoplasm - most often long bones, pelvis, and mandible
Radiographically: purely lytic, honeycombed
Mature fibroblasts with abundant collagen
Probably represents osseous counterpart of fibromatosis
Often recurs, doesn't metastasize

Malignant Fibrous Histiocytoma

Similar to soft tissue counterpart
Long bones or jaw; mean age 40yrs
Bone infarcts, foreign bodies, irradiation, Paget's, dedifferentiation in chondrosarcoma account for 30%

Fibrosarcoma

Metaphyseal; 50% in distal femur or proximal tibia
Arises in medulla, destroys cortex, extends into soft tissues
Radiographically: lytic with soap-bubble appearance
If significant pleomorphism present, should diagnose as MFH
May be well differentiated - need radiology to call malignant
Cellular areas, mitoses, hyperchromasia favor malignancy
Survival correlates well with grade

Other Primary Bone Tumors

Giant Cell Tumor

AKA: Osteoclastoma; however, cells are NOT osteoclasts
F>M; usually 20's-30's; Oriental>Western - 95% at metaphyseal-epiphyseal junction growing into epiphysis (after plate closure)
Usually ends of long bones, particularly lower femur, upper tibia, lower radius, humerus, fibula; also sacrum
When occurs in an uncommon site, more likely to be an aneurysmal bone cyst
Radiographically: entirely lytic, expansile, usually without peripheral sclerosis or periosteal reaction (unless it recurs in soft tissue, where it usually is surrounded by an eggshell of ossification)
Variable size; solid, tan to light brown, often hemorrhagic
Giant cells with many central nuclei regularly distributed in a sea of somewhat spindled stromal cells (malignant cells)
Most likely, mononuclear cells arise from mesenchymal cells, and then fuse to form giant cells
Mitoses common, but atypia is not
Focal osteoid or bone seen in 1/3 cases
All potentially malignant: 30-50% recur, 5-10% metastasize
Recurrence rate: 35% for curettage, 7% for en bloc excision
Even 1-2% of low grade tumors will metastasize
Metastases (usually to lung) occur after surgical intervention
Radiation therapy often induces malignant transformation

Ewing's Sarcoma

- <5% of all malignant bone tumors
- Children and adults <30yrs; most 5-20 yrs old
- Usually long bones (femur, tibia, humerus, fibula), pelvis, rib, vertebra, mandible, clavicle; may be extra-osseous
- Arises in medullary cavity of diaphysis; widens the medulla and thickens the cortex; often extensive, and may involve entire bone; eventually penetrates cortex and invades soft tissues (bad sign) - may present as soft tissue lesion since permeation of medullary cavity may be non-destructive and radiographically inapparent
- As elevates periosteum and new bone is laid down, an onion-skin layering may be seen about the cortex on X-ray
- Grossly: white, fleshy
- Composed of sheets of small, uniform cells with indented nuclei (if nuclei are spindled, probably not Ewing's) and inconspicuous nucleoli; cell borders may be inapparent; occasional pseudorosettes (necrotic cells in center; no true lumen); strands of fibrous stoma separate tumor into irregular masses
- Cytogenetics: reciprocal translocation t(11;22)(q24;q12); the 22q12 locus is known as EWS, a putative tumor suppressor gene
- Glycogen usually present (PAS+); vimentin positive; may be keratin positive
- Anti-O13: stains Ewing's sarcoma and peripheral neuroectodermal tumors (PNET's) [reacts with MIC^2 gene product (~38kd); gene in "autosomal" region of X and Y chromosomes. Also expressed in pancreatic islets, ependyma, lymphoblastic lymphoma, some rhabdomyosarcomas]; Ewing's is probably a less differentiated form of PNET
- EM shows two cell types: large nuclei with open chromatin, small contracted nuclei with hyperchromatic chromatin
- All are high grade by definition
- 25% have multiple metastases at presentation: lungs, pleura, other bones (especially skull), CNS, regional LN's
- Becomes more pleomorphic following therapy
- Rx: surgery and radiation: 5 yr survival 5-8%. Multidrug chemotherapy has increased to 75%

Chordoma

- Arises from remnants of fetal notochord; malignant
- Most frequent in 40's and 50's, but can occur at any age; M>F
- Usually within vertebral bodies, intervertebral discs, sacrum
- 50% sacrococcygeal (older patients), 35% spheno-occipital (children), 15% cervicothoracolumbar spine
- Slow growing tumor - destroys bone, compresses structures
- Gelatinous, soft, areas of hemorrhage, may have bone/cart
- Cells grow in cords and *lobules* separated by a mucoid matrix
- Physaliferous cells: very large tumor cells with bubbly cytoplasm (some glycogen) and vesicular nuclei
- Mitoses scant or absent
- May simulate renal cell carcinoma
- EM: mitochondrial-endoplasmic reticulum complexes
- Immuno: S-100, vimentin, keratin, EMA positive; CEA –
- Repeated local recurrences, often for decades - can focally dedifferentiate - eventually fatal
- Metastases late in course: skin, bone
- Rx: surgery, radiation

Chondroid Chordoma

- Abundant cartilaginous component
- Usually spheno-occipital
- Better prognosis than ordinary chordoma
- Keratin stain usually only focally positive

Adamantinoma

- Predominantly Tibia; also femur, ulna, fibula; diaphysis or metaphysis; counterpart in jaw is referred to as ameloblastoma [see Head and Neck Outline]
- Poorly defined lytic lesion with marked sclerosis outlining single or multiple lucent areas; may extend to soft tissues
- Various microscopic patterns: fibrous dysplasia-like spindle cell component surrounding solid nests of usually basaloid cells with palisading at periphery but occasionally squamoid or tubular formations are seen; stroma probably reflects mesenchymal differentiation of epithelial tumor cells
- Low grade malignancy: local recurrences, occasional LN metastases

Miscellaneous Other Tumors

Plasma Cell Myeloma

- Most common primary tumor of bone (30%)
- Skull, spine, ribs
- [See Hematolymphoid Outline]

Malignant Lymphoma

- Patchy, cortical and medullary, diaphyseal and metaphyseal
- Most are large cell lymphomas, although Burkitt's can occur, as can Hodgkin's disease

Eosinophilic Granuloma

- [See Hematolymphoid Outline]

Vascular Tumors

- Hemangioma: common (12% at autopsy) - probably malformation
- Skull, vertebrae, jaw can be clinically significant
- Massive Osteolysis (Gorham's disease): reabsorption of whole or multiple bones and filling of residual spaces with heavily vascularized fibrous tissue - not a true neoplasm; unknown etiology
- Hemangiopericytoma: usually pelvis
- Epithelioid (Histiocytoid) hemangioendothelioma: often rich in eosinophils, often prominent inflammatory component
- Protracted clinical course
- Angiosarcoma

Peripheral Nerve Tumors

- Neurilemoma: predilection for mandible

Metastases

- Most common of all malignant tumors of bone (25-30 times more common than primary bone tumors)
- 80% are metastatic from breast, lung, prostate, thyroid, or kidney; 50% patients with these tumors will have bone metastases
- 70% involve axial skeleton, 30% extremities (usually from lung)
- Usually osteolytic, may be osteoblastic (prostate, breast, carcinoid) or mixed
- Generally does not destroy vertebral disc (unlike osteomyelitis)
- Most painful; local radiation effective for pain relief in 80%

ARTICULAR and PERIARTICULAR Diseases

Arthritis

Functional failure of the joint with pain and limitation on range of motion; may be a primary inflammatory lesion, but inflammation may also be minimal or purely secondary
Cartilage injury presents at loss of chondrocytes from lacunae, vertical or horizontal clefts within the cartilage (collagen injury) and/or depletion of proteoglycan from the matrix resulting in decreased basophilia
Cartilage proliferation/repair can be both intrinsic (islands of chondrocytes within the matrix) or extrinsic (new cartilage formation at the cartilage/bone interface)
Bone injury includes focal necrosis, microfractures, subchondral sclerosis, and development of subchondral cysts
Reactive synovium is often hyperplastic with increased cellularity and papillary projections into the joint space
Loose Bodies: fragments of bone or cartilage which become detached into the joint space; may continue to grow by surface apposition; centers eventually necrose and calcify

Osteoarthritis
AKA: degenerative joint disease
Disease of elderly, usually involving joints symmetrically
Most common sites: metatarsophalangeal joint of big toe, hip, knee
Damage to the cartilage and the underlying bone common, with areas of complete cartilage loss and a "polishing sclerosis" (eburnation) of the exposed bone
Marginal bony outgrowths (osteophytes) are commonly seen
Divided into primary and secondary:
• Primary: usually elderly women; affects "normal" joints; often asymptomatic
• Secondary: any age; affects previously damaged or congenitally abnormal joints; often involves weight bearing joints

Rheumatoid Arthritis
Usually women, 30's-40's
Initially involves small joints of hands and feet, then later wrists, elbows, knees; extension of disease is usually symmetric
Acute inflammatory infiltrate composed predominantly of neutrophils seen in acute effusions
Chronic disease shows marked proliferation of the synovium, often including rheumatoid nodules (seen in 25%: palisading histiocytes surrounding an irregular area of fibrinoid necrosis), lymphocytes, and many plasma cells, which extends over the articular surface to form the characteristic "pannus", destroying the underlying cartilage, occasionally leading to fibrous or osseous fusion of the joint
Hyperplastic synovium also seen outside the joint proper
Most likely an autoimmune disease: most patients have autoantibody against the Fc portion of IgG (rheumatoid factor)

Juvenile Rheumatoid Arthritis
AKA: Stills disease
Different disease than adult rheumatoid arthritis
Joint involvement more commonly acute, limited to one or a few joints, more commonly involves the knees, and is preceded by a febrile illness with generalized lymphadenopathy and hepatosplenomegaly
Rheumatoid factor often not present

Avascular Necrosis
Most commonly seen in the femoral head following infarction
Collapsed avascularized segment of bone results in secondary arthritis

Gout
Hyperuricemia leading to deposition of sodium urate crystals in joint and viscera (most patients have uric acid stones in the kidneys)
Recurrent attacks of acute gouty arthritis usually involve the lower extremities (especially big toe), usually monoarticular
Examination of aspirated fluid (in EtOH; crystal are water soluble) can show birefringent needle-shaped crystals
Granulomatous response to crystals seen in tissue sections
In chronic disease, large deposits (tophi) of urate crystals and chronic inflammatory cells in and around joints produces "tophaceous gout"
90% of cases are primary; secondary causes include increased nucleic acid turnover (leukemia), enzyme deficiency (Lesch-Nyhan syndrome: deficiency of hypoxanthine-guanine phosphoribosyltransferase), decrease renal secretion

Pseudogout
AKA: calcium pyrophosphate crystal deposition disease; chondrocalcinosis
Deposition within joints of chalky white calcium pyrophosphate crystals (small, rhomboid, weakly birefringent)
Most commonly affects knees, then ankles, wrists, hips, elbows

Ankylosing Spondylitis
AKA: rheumatoid spondylitis; Marie-Strümpell disease
HLA-B27 associated inflammation of the axial skeleton, always involving the sacroiliac joints and variably involving the hips and shoulders
Occurs most commonly in young men

Infectious Arthritis
Suppurative: usually gonococci, staphylococci, streptococci, Hemophilus influenzae
Tuberculous: most commonly spine (Pott's disease); also hip in children, knees in adults; organisms usually not demonstrable in the bone
Lyme Disease: caused by spirochete Borrelia burgdorferi; pathology similar to rheumatoid arthritis, with additional onion-skin thickening or arterioles

Bursitis

Clinical syndrome with pain, erythema, and swelling of one of the bursae associated with muscles, tendons, or joints
More common in men than women
Usually occurs in setting of chronic trauma, or less commonly infection, but may be a complication of rheumatoid arthritis
Thick wall, chronic inflammation, fibrinous exudate, focal vascular proliferations; may calcify

Baker's Cyst
Herniation of synovium of knee into the popliteal space
Wall is lined by synovium
Seen as a complication of increased intra-articular pressure due to degenerative joint disease or rheumatoid arthritis

Ganglion

Occur about joints (usually hands, feet) or in soft tissue; can cause pain, deformity, weakness, partial disability
Fibrous walled cyst (no epithelial lining), usually 1-2 cm diameter, containing a clear fluid, often mucinous
Etiology unclear: herniations of synovium or, more likely, mucinous degeneration of fibrous connective tissue
On rare occasion, may communicate with joint space or erode into bone

Morton's Neuroma

- Swelling of an interdigital nerve of the foot, usually between the third and fourth metatarsal, usually in a woman, resulting in shooting pains upon standing
- Proliferation of Schwann cells and fibroblasts associated with fibrosis, nerve degeneration, endarteritis and thrombosis of the accompanying artery

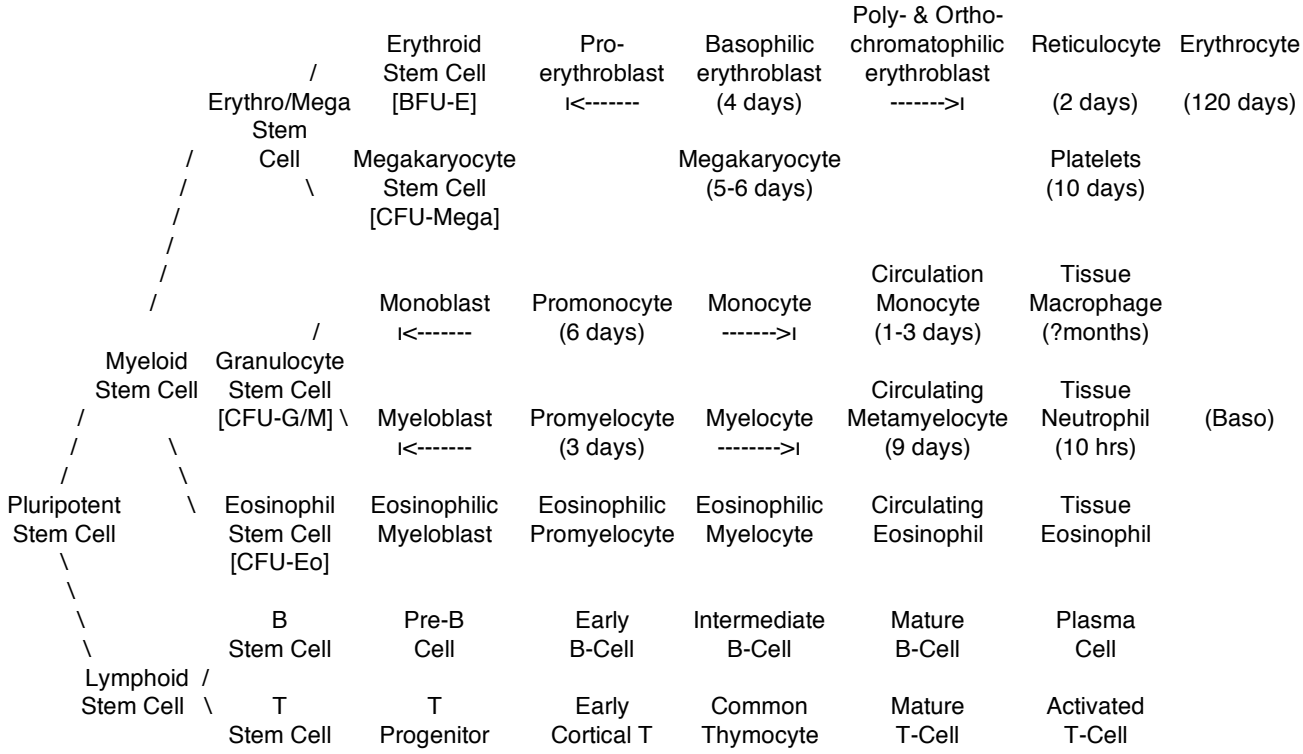
Pigmented Villonodular Synovitis

- Locally aggressive "tumor" of the synovium of the hand (swelling of tendon sheath) or knee (effusion), usually affecting only a single joint
- Proliferation of polygonal cells in a collagenous background, with scattered giant cells and often significant hemosiderin deposition
- Variable amounts of non-specific chronic inflammation accompanies the proliferation
- Probably similar entity to Giant Cell tumor of Tendon sheath occurring in association with a joint
- May recur locally
- [See also Soft Tissues Outline, Fibrohistiocytic lesions]

Primary Synovial Chondromatosis

- Lobulated overgrowth of cellular cartilage without an associated inflammation, often fragmenting into the joint space creating many loose bodies
- Chondrometaplasia of synovium occurs, often atypical
- Can also see cartilage proliferation secondary to osteoarthritis or loose bodies, but that is not atypical

HEMATOPOIETIC ONTOGENY



Marker Changes with Ontogeny

B-Cells

Lymphoid Pluripotent Stem Cell	→ B Lymphoid Stem Cell	→ Early Pre-B	→ Middle Pre-B	→ Late Pre-B	→ Early B Cell	→ Virgin Intermediate B-Cell	→ Mature B-Cell	→ Pre-Plasma	→ Plasma Cell
CD34 TdT	CD34 TdT HLA-DR	CD34 TdT HLA-DR CD19	-cd34- TdT HLA-DR CD19 CD10	-tdt- HLA-DR CD19 CD10 CD20	HLA-DR CD19 CD20 CD21	HLA-DR CD19 CD20 CD21	HLA-DR CD19 CD20 -cd21- CD25	HLA-DR CD19 CD20	HLA-DR
	Heavy: Light:	Rearranged	-	Expressed Rearranged	IgM Exp.	IgM,IgD	IgM,IgD,IgX		

Note: Separate lineage exists for which all cells are CD5+ (peritoneal B-Cells vs. CD5- B-Cells in lymph nodes and spleen)

T-Cells

Lymphoid Pluripotent Stem Cell	→ T Lymphoid Stem Cell	→ T Lymphoid Progenitor	→ Early Cortical Thymocyte	→ Common Thymocyte	→ Mature Medullary Thymocyte	→ Mature T-Cells	→ Activated T-Cell
CD34 TdT	CD34 TdT CD7	CD34 TdT CD7 CD2 CD5	TdT CD7 CD2 CD5	CD1a TdT CD7 CD2 CD5 CD3(cyto) CD4 + CD8	TdT CD7 CD2 CD5 CD3 ←--	CD7 CD2 CD5 CD3 -------- CD4,CD8,neither,both --------	CD7 CD2 CD5 CD3 --> CD25
		β: α:	Rearranged	- Rearranged	$TcR_{\alpha\beta}$ $TcR_{\alpha\beta}$	$TcR_{\alpha\beta}$ $TcR_{\alpha\beta}$	

Note: Separate lineage, beginning after T-lymphoid progenitor, of $CD4^-$,$CD8^-$ $\gamma\delta$-T cell (epidermis and intestinal epithelium) vs the $\alpha\beta$-T-cell of lymph nodes and spleen

Cluster Designation / Clusters of Differentiation

Identified immunologically: Cell surface markers were identified by monoclonal antibodies. Those which consistently recognized the same subsets of cells (clustered) were felt to most likely be reacting with the same molecule

	Synonyms	Cell Types	MW (kD)	Function
CD1a	T6, Leu6, Na1-34	early T, LC	49	MHC-I like
CD1b	WM-25, 4A76	early T, LC	43	MHC-I like
CD1c	L161, M241	early T, LC	45	MHC-I like
CD2	T11, Leu5	Pan-T, NK	50	CD58 receptor, Sheep RBC binding (rosette)
CD3	T3, Leu4, UCHT1	Pan-T (mature)	26,20,16	Associated with TcR
CD4	T4, Leu3a	Helper / Inducer T	60	MHC-II receptor, HIV receptor
CD5	T1, Leu1,UCHT2	Pan-T,B-Cell CLL	67	Present on subset of B-cells
CD6	T12, TU33, T411	T, rare B	100	
CD7	Leu9, OKT-16, WT1	Early+matureT, NK	40	IgM Fc receptor
CD8	T8, Leu2, UCHT4	Suppressor / Cytotoxic T, NK	32	MHC-I binding (2 chains)
CD9	ALB-6, J2	Pre-B, M, Plt	24	
CD10	J5, CALLA	Pre-B, pre-T, some mature B, G	100	Neutral endopeptidase
CD11a	LFA-1α chain	Leukocytes	180	adhesion (see CD18); binds CD54 (ICAM)
CD11b	Mo1, Mac1, Leu15	NK, M, G, T-suppressor	155	C3bi (CR3) receptor (see CD18)
CD11c	LeuM5, L29	M, G, NK, hairy cell leukemia cell	150	Cell adhesion (see CD18)
CDw12	M67	M, G,Plt	90-120	
CD13	My7, LeuM7	Myeloid	150	Aminopeptidase N
CD14	Mo2, My4, LeuM3	M, Mac, LC, immature G	55	
CD15	My1, LeuM1	G, M, Mac, Reed-Sternberg cells		
CD16	Leu11	NK, G, Mac	50-65	Fc_γIII receptor
CDw17	GO35	G,M,Plt		Lactosylceramide
CD18	M232, MHM23	Leukocytes		β-chain for LFA-1 (CD11a,b,c)
CD19	B4,Leu12	Pan-B (not plasma cells)	95	Ig-like
CD20	Leu16, L26, B1	Pan-B (not plasma cells)	37/32	Calcium channel
CD21	B2	B in blood, mantle zone	140	C3d (CR2) and EBV receptor
CD22	4KB-128, Leu14	Pan-B (cytoplasm + surface)	135	Homologous to myelin associated gp
CD23	Blast-2, Leu20	mantle zone B,activated M ,Eos	45-50	Fc_ε receptor
CD24	BA-1	Pan-B, plasma cells, G	41	
CD25	Tac, IL-2R	Activated T, B, M	55	α chain of IL-2 receptor
CD26	134-2C2	Activated T	120	Dipeptidylpeptidase IV
CD27	VIT14, OKT18a	T subset	55	
CD28	KOLT2	T subset, plasma cells	44	
CD29	K20	Many cells	130	Integrin β1-chain, Platelet GPIIa
CD30	Ki-1, Ber-H2	Act T, B, Reed-Sternberg cells	105-120	
CD31	SG134	Plt, M, G, B	140	Platelet GPIIa
CD32	C1KM5, 41H	M, G, B, eos, basophils	39	Fc_γII receptor
CD33	My9, LeuM9	immature myeloid	67	
CD34	My10	progenitors, vascular endothelium	105-120	
CD35	To5	G, M, B	160-250	CR1, C3b receptor
CD36	5F1, gp90	M, Plt, B	90	Platelet gpIV
CD37	HD28	B, (T, M)	40-52	
CD38	T16, Leu17	Activated T & B,NK, plasma cells	45	
CD39	AC2, OKT28	B subset, (M)	70-100	
CD40		B, carcinomas	50	Homologous to NGF-Receptor
CD41	CLB-thromb7, J15	Platelets, megakaryocytes	123,110	Platelet gpIIb/IIIa
CD43	Leu22, L60	T, G, M, NK, brain		Leukosialin, Altered in Wiskott-Aldrich
CD44	Pgp-1	RBC, many WBC,brain	80-95	lymphocytes homing receptor, memory marker?
CD45	LCA, T200, Leu18	T , B, G, M	180-220	memory marker?
CD45RO	UCHL-1	T, myeloid cells	205-220	
CD51		Platelets	125/25	Vitronectin receptor alpha chain (see CD61)
CD54	Leu54, My13	Many cells	90	Cell adhesion (ICAM-1)
CD56	NKH1, Leu19	NK, activated lymphs	220/135	Isoform of N-CAM
CD57	Leu7, HNK1	NK,T subset, B subset	110	
CD58	G26	Leukocytes, epithelial		LFA-3, Ligand for CD2
CD61		Megakaryocytes, platelets	110	β3 chain for CD41 and CD51
CD64		M	75	Fc_γ1 receptor
CD68	EMB11, KP-1	M, Mac	110	
CD69	Leu23	ActB, ActT, ActM, NK	32/28	
CD71	T9, OKT9, VIP-1	Proliferating cells	95	Transferrin receptor
CD74		B, M	41/35/33	MHC-II invariant chain

G: granulocytes, M: monocyte, LC:Langerhans cells, NK: Natural Killer Cells

HEMATOLYMPHOID SYSTEM - General

Development

"Blood islands" appear in yolk sac in 3rd wk of development
~3 months: migrate to liver (major hematopoietic site until birth)
Spleen, LNs, thymus contribute in the 2nd and 3rd trimesters
Bone marrow becomes active at ~4 months
Full term: bone marrow main site; liver nearly inactive
All marrow is active until puberty
By 18 yrs, active marrow is restricted to ribs, vertebrae, pelvis, skull, epiphyses of humerus and femur; rest becomes fatty and inactive
Marrow output can increase 7-8 fold if needed
When needed, extramedullary hematopoiesis reappears first in liver, then spleen, then LNs - never thymus

Growth Factors

GM-CSF: granulocyte/macrophage colony stimulating factor; made by T Cells, fibroblasts, endothelial cells
Erythropoietin: red cell maturation
IL-3: (AKA multi-CSF); growth factor for trilineage myeloid stem cell; made by T Cells

Bone Marrow

NORMAL

Cellularity: 90% for young children, 50-60% for adults, 40-50% after 60 yrs age
60% granulocytic; 20% erythroid; 10% lymphocytes and monocytes; 10% unidentifiable
M:E ratio 3:1 (base on spacing of red cell clusters)
Maturation: ~75% of myelocytic elements should be mature neutrophils, ~75% erythroid elements normoblasts
Early granulocytic precursors usually located next to bone spicules. Abnormally located granulocytic precursors can be a clue to preleukemic state. Paratrabecular lymphoid aggregates can indicate a lymphoma.
Megakaryocytes: normally 3-5 per 40x field
Macrophages: if you notice them, there are too many
Lymphocytic aggregates can be seen; increase in number with age; more prominent in AIDS, rheumatoid arthritis, IL-2 therapy
Iron: stored in macrophages: one iron-positive cell per 40x field is normal, 2 is increased, <1 is decreased; children under 14 yrs have no stainable iron
30-40% normoblasts have ferritin granules (sideroblasts); Iron overload → ring sideroblasts (ruptured mitochondria)

NON-NEOPLASTIC LESIONS

Serous Degeneration

AKA: Gelatinous transformation
Extremely malnourished patients (kwashiorkor, cachexia, AIDS)

Necrosis

Seen in tumors (metastatic and primary), sickle cell anemia, infectious processes, SLE, anorexia nervosa
Generalized bone pain
Aspirates tend to be gelatinous
Marrow replaced by amorphous granular eosinophilic debris

Granulomatous Inflammation

Fungus, TB, MAI, viral infections (e.g. mono), sarcoidosis
Also seen in Hodgkin's and non-Hodgkin's lymphomas
No etiology can be found in 80%
Lipid granulomas common - loosely spaced macrophages with fat vacuoles - giant cells seen in 5%

AIDS

Generally hypercellular with plasmacytosis
Serous degeneration, elevated reticulin
May have opportunistic infection even without granulomas (scattered macrophages is enough to get special stains)
Lymphocytic aggregates, both para and nonparatrabecular
Patients may develop a myelodysplastic picture

Spleen

Normally 150gm, ~12cm long
Functions: Filtration, immune, source of lymphoreticular or hematopoietic cells, storage for platelets
In an unstimulated spleen, see two layers of lymphocytes around central arterioles: central T-zone area (white pulp) and peripheral marginal zone (B and T cells). When stimulated, germinal centers form: get three layers: germinal center, mantle zone, and marginal zone

Congenital Anomalies

- Complete absence (rare)
- Hyposplenia
- Abnormal lobulation
- Polysplenia
- Accessory spleens - usually near hilum

Hypersplenism

Seen in minority of patients with splenic enlargement
- Enlarged spleen (usually secondary to another problem)
- Sequestration/loss of circulating RBC's, platelets, WBC's, or some combination
- Correction following splenectomy

DISORDERS OF WHITE PULP

Reactive follicular hyperplasia

Common among children and adolescents
Acute infections, ITP, rheumatoid arthritis, acquired hemolytic anemia, chronic hemodialysis, Castleman's disease

Reactive non-follicular lymphoid hyperplasia

Expansion of white pulp without formation of germinal centers
Viral infections, graft rejection, AILD

Chronic Lymphocytic Leukemia

Only leukemia which consistently and selectively involves the white pulp - irregular involvement

Malignant Lymphomas

Cannot distinguish nodular from diffuse in the spleen
Small cleaved, mixed small cleaved and large, and small noncleaved generally remain confined to white pulp
Small lymphocytic, mantle cell, marginal zone cell, large cell, Hodgkin's, and CTCL will bleed out into the red pulp as well

DISORDERS OF THE RED PULP

Congestion (1-5 kg)

Hemolytic anemias
Gandy-Gamna bodies: organized, fibrosed old hemorrhages with hemosiderin and calcium

Infection

Infectious mononucleosis, acute septic splenitis

Leukemias

Often diffusely infiltrate the red pulp making the white pulp barely discernible
CML: polymorphous infiltrate with eosinophilic myelocytes
Myeloid Metaplasia (Agnogenic or secondary): all three cell lines present for agnogenic, secondary may be limited to a single cell line
Hairy Cell Leukemia (see below under Other Leukemias)

Systemic Mastocytosis

Often relatively tight clusters of cells with clear cytoplasm and surrounded by fibrosis

Histiocytic Proliferations

Granulomatous inflammation, Gaucher's disease, Langerhans cells histiocytosis, malignant histiocytosis
Ceroid histiocytosis: accumulation of foamy macrophages laden with waxy material, predominantly sphingomyelin; seen most commonly in ITP and CML

OTHER NON-NEOPLASTIC CONDITIONS
- Inflammatory pseudotumor: spindle cell proliferation infiltrated by plasma cells, lymphocytes, eosinophils, and histiocytes; may be symptomatic
- Hyaline perisplenitis: collagenous thickening of capsule (sugar coating); no symptoms or sequelae
- Spontaneous rupture: always due to pathology (mononucleosis, malaria, typhoid fever, CML, acute splenitis) - can result in seeding of peritoneal cavity with spleens (splenosis)
- Peliosis: widespread, blood-filled cystic spaces, sometimes occurring independently of peliosis hepatis - usually patients with chronic wasting diseases (TB, carcinoma)

TUMORS

Benign: hemangiomas, lymphangiomas, splenic hamartoma (nodular lesion composed exclusively of red pulp elements), lipomas, fibromas, osteomas, chondromas

Malignant: hemangiosarcomas

Thymus

NORMAL

Embryologically derived from the third and occasionally fourth pair of pharyngeal pouches

Thymus weighs 10-35 gms at birth, grows to maximum size at puberty (20-50 gms), and then atrophies with replacement by fibrofatty tissue

Cortical and medullary regions; epithelial cells and lymphocytes (mostly T [medullary are mature, cortical are immature], some B)

Hassall's corpuscles: concentric aggregates of keratin surrounded by keratinized epithelial cells; found in the medulla

Parathyroids (arise from same pouches) may become entrapped in the thymus

NON-NEOPLASTIC LESIONS

Congenital Thymic Hypoplasia

Seen in a variety of congenital immunodeficiency syndromes, including reticular dysgenesis, severe combined immunodeficiency disease, ataxia-telangiectasia, DiGeorge syndrome

Thymus most commonly completely absent; a fibrous mass may be present in its place

Acquired Thymic Hypoplasia

Can occur in the young following severe stress, irradiation, chronic malnutrition, or associated with cytotoxic drugs or glucocorticoids

Thymic Hyperplasia

Difficult to evaluate by weight; therefore, use presence of lymphoid follicles within the thymus (thymic follicular hyperplasia) as indicator of hyperplasia

Germinal centers are located primarily in the medulla

Most frequently encountered in myasthenia gravis (seen in 85% patients with MG, more common in younger)

TUMORS

Thymoma

Neoplasm of thymic epithelial cells; most common tumor of the anterior mediastinum

Mean age = 50 yrs; incidence increases with age

Associated with myasthenia gravis, hematologic cytopenias, hypogammaglobulinemia, collagen vascular diseases

As the thymus can be present in atypical locations (e.g., neck), so can thymomas

Most (90%) are benign

Lobulated, weakly encapsulated (80%), gray-yellow-tan

Soft to firm; may have hemorrhages; cysts common

May be lymphocyte rich or lymphocyte poor

Epithelial component may be normal looking with poorly defined cell borders or may be oval to spindled

Spindled pattern more commonly associated with red cell aplasia; usually NOT associated with myasthenia gravis

Tumor cells are keratin, Leu-7, and CEA positive

Malignant Thymoma (Type I)

10% of thymomas

Histologically identical to benign thymoma but with invasion beyond the capsule or lymphatic or hematogenous spread

Thymic Carcinoma (Type II Malignant Thymoma)

Thymic epithelial cells are cytologically malignant

RED CELL PATHOLOGY

Erythropoietin

Stimulates red cell commitment (serum level: 0.01nM)

Glycoprotein (18.4kD protein plus 18kD sugars)

Believed to originate in kidney - may be enzyme

Responds to tissue oxygen tension, dependent on blood flow, Hgb concentration, Hgb saturation

Occasionally excessively produced in renal cell carcinoma, cerebellar hemangioblastomas, hepatic carcinomas, adrenal adenomas, and uterine leiomyomas

Hemoglobins

α-globins: 2/chromosome 16 (141amino acids); also, ζ–gene

$\beta,\delta,{}^{A}\gamma,{}^{G}\gamma$-globins: chromosome 11 (146 amino acids); γ: Ala vs Gly at amino acid 136

Embryonic: $\zeta_2\varepsilon_2$ (Gower 1); $\zeta_2\varepsilon_2$ (Portland); $\alpha_2\varepsilon_2$ (Gower 2)

Fetal: 75% HgF ($\alpha_2\gamma_2$), 25% HgA ($\alpha_2\beta_2$)

Adults: 96% HgA($\alpha_2\beta_2$),3% HgA_2($\alpha_2\delta_2$),1% HgF($\alpha_2\gamma_2$)

ANEMIAS

Blood Loss

Acute

Initially, there is no change in the hematocrit

Maximum hemodilution occurs at 48-72 hrs

Plasma proteins replaced more quickly, then red cells

When blood loss is internal, iron can be reclaimed

Reticulocyte count can reach 10-15% within 1 week

Chronic

Anemia occurs when rate of loss exceeds regenerative capacity, usually limited by availability of IRON

Results in iron deficiency anemia (see below)

Increased Hemolysis

Premature destruction of RBC's in the body, with retention of iron and expansion of marrow erythron, usually with increased number of circulating reticulocytes

Manifestations: hemoglobinemia, methemalbuminemia, jaundice, hemoglobinuria, hemosiderinuria:
- Hgb bound by α-2-globulin (haptoglobulin), preventing excretion in urine; cleared by reticuloendothelial system

- Some metabolized, releasing unconjugated (indirect) bilirubin; jaundice
- When haptoglobulin depleted, free Hgb oxidized to metHgb and both excreted in urine; red brown
- If renal excretion capacity exceeded, metHgb binds to albumin: methemalbuminemia: blood red-brown
- Metabolization of some by renal tubular cells results in hemosiderosis with shedding of these cells in urine

Marrow: increased number of normoblasts, with pressure atrophy of the inner cortical bone and new bone formation on the outside, especially in the ribs and facial bones
Chronicity: pigment gallstones, hemosiderosis, extramedullary hematopoiesis

Hemoglobinopathies

Sickle Cell Anemia
Mutation of Glu to Val at amino acid 6 of beta chain
8% black Americans are carriers (heterozygous) = sickle cell trait (40% Hg is HgS): protection against malaria
Deoxy-HgS "crystallizes" leading to hemolysis (anemia) and to obstruction of small vessels (vaso-occlusive crisis)
Sickling is initially reversible, but with repeated episodes, membrane damage occurs resulting in irreversible sickling
HgSC and HgSD have sickle cell anemia, but less severe
Not apparent at birth - HgF persists 1-2 yrs
Spleen: initially enlarged, then focal scarring with Ca and hemosiderin deposits (Gandy-Gamna bodies); get functional autosplenectomy: predisposes to Salmonella (osteomyelitis), Strep pneumoniae, H. influenza infections
Prenatal diagnosis possible by RFLP using MstII

Hemoglobin C Disease
Mutation of Glu to Lys at amino acid 6 of beta chain
HbC only 1/4th the prevalence of HbS
Splenomegaly, mild anemia
Target cells common

Thalassemia
Decreased synthesis of α or β chains, leading to excess of other chain; chain excess contributes to pathology
$\alpha\alpha/\alpha$- is silent carrier
$\alpha\alpha$/-- or α-/α- is alpha thalassemia minor (trait): hypochromic microcytic. Same seen in beta thal minor (β^0/β or β^+/β)
Beta thal minor accompanied by increased HgA_2 and HgF
Complete absence of alpha (Hg Barts - see below) is fatal
Most beta thalassemias caused by point mutations, most commonly leading to aberrant splicing; most alpha thalassemias caused by gene deletions
Beta thal major (complete absence [β^0] or reduced synthesis [β^+] genes) results in decreased production but also active hemolysis since excess alpha precipitates as Heinz bodies, causing 70-85% of precursor cells to be destroyed in the marrow (ineffective erythropoiesis)

Other Hemoglobins
HgD Los Angeles: Mutation of Glu 121 to Gln in beta chain
HgM: His to Tyr at iron binding site of alpha or beta chain
Iron stabilized in Ferric state - cannot bind oxygen
HgH (β_4): see in --/-α thal major, unstable, precipitates forming inclusions
HgBarts (γ_4): results in hydrops fetalis

Unstable Hemoglobins
Riverdale-Bronx: Gly to Arg at residue 6 of beta chain
Gun Hill: deletion of 5 amino acids from beta chain

Other Hereditary Hemolytic Disorders

Hereditary Spherocytosis
Autosomal dominant; 1/4500; 20% due to new mutations
Red cells spheroidal in shape - more fragile
Manifests at birth or later; Severe in infants; children/adults may compensate
Splenic enlargement is characteristic (500-1000 gm)
Cholelithiasis occurs in 40-50%
Defect in spectrin - many different types
Hemolytic crisis: fever, nausea, vomitting, jaundice
Aplastic crisis: usually triggered by parvovirus; worse anemia, loss of reticulocytes
Splenectomy prevents destruction - "curative"

Hereditary Elliptocytosis (Ovalocytosis)
Autosomal dominant; 1/4000-5000
Anemic and non-anemic varieties exist - most patients have only mild anemia

Hereditary Stomatocytosis
RBC's have a slit-like central zone of pallor on wet smears
Autosomal dominant
Red cells have an increased permeability to sodium and potassium, and increased active transport of these ions
- Overhydrated Form (Hydrocytosis)
  Stomatocytes seen even on dried smears
  Excess of ions and water; decreased MCHC
  Increased osmotic fragility
  Absence of band 7.2b (stomatin) from RBC membranes
- Dehydrated Form (Desiccytosis)
  Dried smears show target cells rather than stomatocytes
  Increased mean corpuscular hemoglobin concentration
  Decreased osmotic fragility

G-6-PD deficiency
Glutathione (GSH) prevents injury by exogenous oxidants
Glucose-6-P-dehydrogenase (X-linked) is enzyme in hexose monophosphate shunt which produces GSH
Many G6PD variants; 2 clinically significant:
•G6PD A^-: Mutant enzyme has shorter life than RBC
Hemolytic crisis affects older cells
Present in 10% American blacks
•G6PD Mediterranean: enzyme has lower activity throughout life - hemolytic crisis can be disastrous
Defect protects against malaria
Antimalarials (e.g. primaquine, quinacrine) can trigger hemolytic crisis
Hgb oxidizes to metHgb and precipitates in the cytoplasm, clumps (Heinz bodies) attach to cell membrane and increase osmotic fragility - Heinz bodies removed in spleen, decreasing size of RBC's and tendency to form spherocytes

Other enzyme deficiencies
•Other pentose phosphate shunt enzymes
•Glycolytic enzymes (eg, pyruvate kinase)

Acquired Hemolytic Disorders

Paroxysmal Nocturnal Hemoglobinuria (PNH)
Chronic intravascular hemolysis, worse at night in 25%
Abnormal sensitivity of RBCs to complement mediated lysis due to a deficiency of the membrane glycoprotein DAF (decay accelerating factor)
Similar defect seen in platelets and granulocytes; defect is in a multipotent stem cell
Significant risk of progression to leukemia

Autoimmune Hemolytic Anemias (AHA)
Warm antibody AHA:
Polyclonal IgG, does not fix complement, active at 37°C
Primary (60%) or 2° to lymphoma, neoplasm, drugs, SLE
RBCs sequestered in spleen leading to splenomegaly
Hemolysis is extravascular, usually in the spleen
Cold Agglutinin AHA:
Monoclonal IgM, fixes complement, agglutinates in cooler parts of body
Acute (Ab titers rise following mycoplasma pneumonia or mononucleosis) or chronic (lymphoma)
RBCs sequestered in liver
Hemolysis is extravascular, usually in spleen
Cold Hemolysin AHA

AKA: Paroxysmal Cold Hemoglobinuria (PCH)
Massive intravascular hemolysis, complement dependent, following exposure to cold
IgG autoantibodies against P-blood group antigens; bind complement at low temperatures
Occurs following infections (mycoplasma, measles, mumps)

Mechanical hemolysis (microangiopathic)
Schizocytes: sheared RBC's (helmet cells, burr cells)
- Prosthetic cardiac ball valves
- Advanced atherosclerosis
- Small vessel thrombi - D.I.C.
- Hemolytic Uremic Syndrome
- Malignant Hypertension
- TTP
- Ulcerative colitis

Isoantibody associated
Transfusion mismatch; Complement mediated destruction

Drug Induced, Infections, Hypersplenism

Diminished Erythropoiesis

Nutritional Deficiency

Pernicious anemia (megaloblastic anemia)
B_{12} malabsorption due to genetic defect (juvenile) or to chronic atrophic gastritis with loss of parietal cells, resulting in decreased Intrinsic Factor activity
Three autoantibodies associated with disease:
- blocks binding of IF to B_{12} (75% patients)
- binds to IF and IF-B_{12} complex (50%)
- binds to parietal cell brush border (85-90%)

Marrow: nests of darkly staining megaloblasts (immature nuclei, mature cytoplasm, larger than erythroblasts)
Myelin degeneration in dorsal and lateral tracts of spinal cord
In acquired form, also see atrophic glossitis and atrophic gastritis with intestinal metaplasia
In Folate deficiency, get all of above except CNS

Iron deficiency
Most common nutritional disorder in the world
Normal total body iron stores: M=3.5 gms, F=2.5 gms
Normally, 80% of total body Fe functional, 80% of that in Hgb
20% in storage form as ferritin (protein-iron complex) or hemosiderin within reticuloendothelial cells and in the liver
Iron is transported as ferritin, bound to transferrin (76kD divalent for Fe) which is normally 1/3 saturated
Iron reserves depleted before serum levels drop
Iron deficiency leads to Hypochromic Microcytic Anemia
Bone marrow:
- Increased erythropoietic activity
- Sideroblasts and stainable iron absent

Low iron levels also depletes iron from enzymes, resulting in oxidation of membrane proteins and decreased plasticity of the RBCs leading to POIKILOCYTOSIS
Plummer Vinson syndrome: microcytic hypochromic anemia, atrophic glossitis, esophageal webs
May take months to see response from iron supplements

Intestinal Malabsorption

Bone Marrow Failure (Aplastic Anemia)

Normochromic, normocytic anemia, usually with neutropenia and thrombocytopenia
Pure red cell aplasia rarely seen, although some association exists with thymoma
Marrow is hypocellular; replaced by fat and fibrous stroma
50% of cases are idiopathic
Other causes: Fanconi's anemia (autosomal recessive; associated findings: renal hypoplasia, absent or hypoplastic thumbs or radii, hyperpigmentation of skin, microcephaly), whole body irradiation, dose related or idiosyncratic drug reactions, post infectious
Can also see in tumors metastatic to the marrow (myelophthisic anemia), diffuse liver disease, chronic renal failure, endocrine disorders

POLYCYTHEMIA

Erythrocytosis

Relative polycythemia due to hemoconcentration
Total red cell mass is not increased
Seen in dehydration, vomiting, burns, electrolyte imbalance, and "stress polycythemia" (Gaisböck's syndrome)

Polycythemia Vera

Absolute increase in red cell mass (usually accompanied by increase in white cell count and especially platelet count) with a low erythropoietin level
Etiology appears to be related to increased sensitivity of myeloid stem cells to erythropoietin
M>F, 40-60 yrs old, whites>blacks
Marrow usually hypercellular, but not always
Reticulin increased in areas of megakaryocyte cellularity
Hyperviscosity of blood often leads to infarction of, most commonly, heart, spleen, kidney
20% develop peptic ulcers
30% die from thrombosis (usually brain), 10-15% from hemorrhage (often GI), 2 % AML (15% if irradiated)
15-20% long term survivors (>10 yrs) undergo transition to myeloid metaplasia with myelofibrosis
Associated with del20q11

Secondary Polycythemia

Usually normal white cell and platelet counts
Caused by increased production of erythropoietin

Appropriate
High altitude living
Carboxyhemoglobin
Chronic obstructive or other pulmonary disease
Right to left circulatory shunts (septal defects)
Low output cardiac failure
Hemoglobinopathies (high oxygen affinity)

Inappropriate
Erythropoietin secreting malignancies: renal cell carcinoma, cerebellar hemangioblastoma, hepatoma, adrenal adenoma, uterine leiomyoma
Hydronephrosis and renal cysts

Erythroleukemia

AKA: DiGuglielmo's syndrome, erythromyeloblastic leukemia
See below (M6 AML)
Marked anemia, leukopenia
If survive initial phase, gradual transition to immature myeloblastic leukemia
Course: months to 2 yrs, ending in death

LYMPH NODE PATHOLOGY

Non-Inflammatory

Inclusions/Lesions:

- Nevus cells: in capsule, usually axillary nodes
- Thyroid Follicles: marginal sinus of mid-cervical node; usually represent metastatic papillary carcinoma
- Ectopic thymus: supraclavicular LN's - differential is from metastatic epidermoid carcinoma
- Salivary gland tissue: common in high cervical nodes. If becomes neoplastic, usually get Warthin's tumor
- Mullerian epithelium: endosalpingiosis, endometriosis; decidual reaction may simulate carcinoma
- Breast tissue: normal mammary lobules in axillary LN
- Adipose metaplasia: up to 10cm, external iliac and obturator groups most common
- Silicone lymphadenopathy: side effect of breast reconstruction, nonbirefringent material in sinuses, giant cells
- Proteinaceous lymphadenopathy: like amyloid, but it isn't
- Hyaline material: especially aorto-iliac region, may become calcified, no clinical significance
- Infarction: painful swelling, necrosis, perinodal inflammation and granulation tissue
- Vasculitis: systemic vasculitides, AILD
- Hemangioma/lymphangioma: usually represent extension from primary soft tissue lesion
- Epithelioid hemangioma

Metastatic Tumors

Upper cervical: oropharynx, nasopharynx
Mid-cervical: thyroid, salivary glands, pharynx, larynx
Supraclavicular: lung, breast, (L: stomach, pancreas, prostate, testis)
Axillary nodes: breast, melanoma, lung
Inguinal: external genital organs, melanoma of legs - rarely internal pelvic organs or testis

Acute Lymphadenitis

Focal: usually direct drainage of infected areas
Generalized: viral, bacteremic, exotoxic diseases
Nodes: swollen, gray-red, engorged; large germinal centers with many mitoses; lymphocytes may penetrate capsule
Histiocytes with particulate debris
When pyogenic in origin, may see necrosis
Neutrophils frequently present

Chronic Lymphadenitis

Follicular hyperplasia

B-Cells stimulated
Large germinal centers with "blasts" bulging against well demarcated mantle zone - follicles expand at expense of mantle zone
Plasma cells, histiocytes, rare neutrophils in paracortex
Follicles vary in size and shape (vs lymphoma)

Nonspecific Reactive
May be limited to cortex or throughout
Follicles usually remain polarized; may coalesce
More florid in children

Toxoplasmosis
AKA: Piringer-Kuchinka
Typically posterior cervical nodes, younger woman
Triad: (not all three always present)
- Follicular hyperplasia, numerous mitoses, nuclear debris
- Small, epithelioid (non-sarcoid-like) granulomas, both within and at periphery of germinal centers - no giant cells
- Monocytoid B cell distention of marginal/cortical sinuses and paracortex

Rare to find organism: serological testing
Differential diagnosis: LP Hodgkin's (don't get granulomas)

Rheumatoid Arthritis or Sjogren's Disease
30-80% show generalized lymphadenopathy
Hyperplasia involves cortex and medulla with intense interfollicular plasmacytosis and numerous Russell bodies
Hyperplasia otherwise unusual in elderly
Identical changes in Sjogren's, Felty's syndromes
Long standing rheumatoid arthritis increased risk for lymphoma
Juvenile Rheumatoid Arthritis: above plus neutrophils

System Lupus Erythematosus
Predominantly cervical adenopathy: cortical follicular hyperplasia with interfollicular plasmacytosis
Often sharply circumscribed areas of paracortical necrosis with none or few neutrophils

Necrotizing Lymphadenitis (Kikuchi's)
Most common in Japan and Asian countries
Usually young women, painless cervical lymphadenopathy
Focal, well circumscribed, paracortical necrotizing lesions
Scattered fibrin deposits
Collections of large mononuclear cells
Scant numbers of neutrophils and plasma cells
EM: tubuloreticular inclusions, intracytoplasmic rodlets

Cat-scratch Disease
Primary cutaneous lesion with enlarged regional LN's
Early: follicular hyperplasia, histiocytic proliferation
Intermediate: Granulomatous changes
Late: large abscesses, with central stellate necrosis, neutrophils, and palisading histiocytes

Lymphogranuloma Venereum
Sexually transmitted: Chlamydia
Tiny necrotic foci; enlarge to form large stellate abscesses
Langhans' giant cells, fibroblasts, fistula tracts common

Kimura's Disease
Follicular hyperplasia, interfollicular eosinophilia, proliferation of thin walled vessels
LN changes accompany similar lesions in soft tissues

Syphilis
Generalized lymphadenopathy in 2°, localized in 1° and 3°
1°: capsular and pericapsular inflammation, fibrosis, diffuse plasma cell infiltrate, proliferation of blood vessels with endothelial swelling and inflammation, epithelioid histiocyte clusters, occasional sarcoid-like granulomas
2°: florid follicular hyperplasia, large clusters of epithelioid histiocytes, sarcoid-like granulomas
Look for spirochetes in wall of blood vessels

Castleman's Disease
AKA: Giant LN hyperplasia, LN hamartoma, angiofollicular mediastinal LN hyperplasia, follicular lymphoreticuloma
M=F, 8-70 yrs old
Two major histological types:
- Hyaline vascular (angiofollicular)

Large follicles with vascular proliferation
Hyalinization in center of follicles

Onion-skin layering of lymphocytes at follicle periphery
Prominent interfollicular stroma, plasma cells
Lymphoid Subtype: expansion of mantle zone with small regressed germinal centers
Polyclonal Ig production (vs lymphoma)
• Plasma cell type
Diffuse interfollicular plasma cell proliferation
Deposition of amorphous acidophilic material in follicles (probably fibrin and Ig)
Two major clinical presentations:
• Solitary form
Mass, usually mediastinal; also neck, lung, axilla, mesentery, retroperitoneum, extremities
Round, well circumscribed, up to 15 cm
90% hyaline vascular type (asymptomatic)
10% plasma cell type (fever, anemia, elevated ESR & Ig)
Rx: surgical excision
• Multicentric (systemic) form:
Patients tend to be older
Generalized lymphadenopathy - may involve spleen
Nearly always plasma cell type
Poor long term prognosis
Some association with spindle cell sarcoma development, presumably from vessels

Progressively Transformed Germinal Centers
Large (2-3x normal) centrally located follicles without follicle centers
Indistinct margin with surrounding mantle zone (mantle cells infiltrate into follicles)
May be seen concurrently or as an antecedent to Lymphocyte Predominant Hodgkin's disease

AIDS related Lymphadenopathy
Most commonly see "Florid Reactive Hyperplasia"
"Follicle lysis": collapse of the central portions of the germinal centers with invagination of mantle lymphocytes
May see advanced lymphocyte depletion (regressed germinal centers)

Diffuse (Paracortical) hyperplasia

Expansion of T-cell regions with effacement of follicles
Hypertrophy of endothelium - pseudolymphomatous
Seen in drug reactions (Dilantin), following smallpox vaccination, chronic dermatitis, viral infection

Postvaccinial Viral Lymphadenitis
Usually 1-10 wks post vaccination, usually supraclavicular
Diffuse or nodular paracortical expansion, immunoblast proliferation, vascular proliferation, sinusoidal dilatation, mixed cellular infiltrate (eosinophils, plasma cells, mast cells)
Immunoblasts may simulate Reed Sternberg cells

Infectious Mononucleosis
Variable, non-specific effacement of nodal architecture with infiltration of the trabeculae, capsule, and perinodal fat by immunoblasts and numerous plasma cells
Distinction from lymphoma: sinusoidal distribution of large lymphoid cells, increase in plasma cells, and vascular proliferation

Dermatopathic Lymphadenitis
AKA: Lipomelanosis reticularis of Pautrier
Lymphadenopathy secondary to itching and scratching dermatidities (psoriasis, MF, etc.)
Sometimes, no identifiable cutaneous lesion can be found
Pale yellow lymph nodes, often with black periphery (clumps of melanin)
Expansion of the T-dependent paracortical zone by a proliferation of the interdigitating reticulum S-100+ histiocytes with folded nuclei (Langerhans cells), compressing the follicles against the capsule

Sinus Pattern

"Sinus histiocytosis"
Seen in nodes draining cancer
Prominence of sinusoids - distended with histiocytes

Sinus Histiocytosis with Massive Lymphadenopathy
AKA: Rosai-Dorfman disease (1969)
[See below under Histiocytoses]

Lipophagic Reactions
Accumulation of phagocytosed fat in histiocytes
Many Types:
• Mineral Oil Ingestion: asymptomatic, periportal and mesenteric LN's, common (70% of all patients)
• Whipple's disease: mesenteric nodes; poorly formed granulomas with lipid in the macrophages and PAS+ particles in the cytoplasm; EM shows bacilliform bodies within the histiocytes; associated with intestinal malabsorption
• Lymphangiography: lipophagic granulomas may persist for months; neutrophils and then eosinophils common

Vascular Transformation of LN Sinuses
Subcapsular and interfollicular sinuses with blood filled endothelial lined spaces, variable fibrosis, and extravasated erythrocytes
Secondary to extranodal venous outflow obstruction
Vascular proliferation follows the sinuses (unlike Kaposi's)

Predominantly Granulomatous Pattern

Sarcoidosis
Diagnosis is always one of exclusion; rule out TB, atypical mycobacteria, fungus, leprosy, syphilis, Leishmania, brucella,...
Black:white = 10-15:1 (in US)
Lung (90%), LN's, eyes, skin most commonly affected
Often some degree of anergy - deficient peripheral T-Cell response; central T-Cell response still seems to work
Erythema nodosum often precedes or accompanies
Functional hypoparathyroidism is the rule
Non-caseating granulomatous inflammation in nodes/skin, with scattered Langhans' giant cells
Necrosis is absent or limited to small central fibrinoid focus
Schaumann bodies, asteroid bodies, and calcium oxalate crystals in cytoplasm of giant cells; none are specific
•Schaumann: round, concentric laminations, with Fe,Ca
•Asteriod: crisscrossing collagen fibers
Kveim test: 60-85% show granulomatous intradermal reaction following inoculation with extract of human spleen involved with sarcoidosis
Etiology unclear - mycobacteria or virus suspected
2/3 recover with minimal sequelae; 20% have some permanent loss of pulmonary function; 10% will die of cardiac, CNS involvement or progressive pulmonary fibrosis

Tuberculosis
Lymph nodes may become adherent to each other: matting, similar to that seen in metastatic carcinoma
"Scrofula": matted cervical lymphadenopathy
"Scrofuloderma": above forms draining sinus to skin
Small epithelioid granulomas to large caseous masses
Must demonstrate organisms

Atypical Mycobacteriosis
Typically lateral middle neck nodes of a child
Similar to TB with more of a suppurative component

Fungal Infections
Suppurative or granulomatous
Histoplasmosis: can cause widespread nodal necrosis and marked diffuse hyperplasia of sinus histiocytes
Sporotrichosis: may be suppurative

Chronic Granulomatous Disease
- Genetically determined enzymatic defect - cannot digest some microorganisms
- Granulomas with necrotic, purulent centers

Others / Mixed Pattern

Mucocutaneous LN Syndrome (Kawasaki's)
- Usually children, more common in Japanese
- Fever, cervical lymphadenopathy, pharyngeal and conjunctival inflammation, erythematous skin rashes
- Fatalities usually secondary to coronary arteritis
- LN: fibrin thrombi in smaller vessels, patchy infarcts

Leprosy
- Large, pale, round histiocytes; no granuloma formation; minimal necrosis

Mesenteric Lymphadenitis
- AKA: Masshoff lymphadenitis
- Caused by Yersinia
- Benign, self limited, may simulate appendicitis clinically
- LN: capsular thickening and edema, immunoblasts, plasma cells in cortical/paracortical region, germinal centers

Angioimmunoblastic Lymphadenopathy with Dysproteinemia (AILD)

- Polyclonal proliferation of immunoblasts and plasma cells
- Adults and elderly - fever, anemia, polyclonal hyperIg
- 27% occur after drug administration, particularly penicillin
- Systemic (spleen, liver, LN's, bone marrow...)
- LN: partial obliteration of nodal architecture by eosinophils, plasma cells, immunoblasts, some giant cells and proliferation of postcapillary venules, with amorphous eosinophilic interstitial deposits of a PAS+ material (probably cellular debris); no germinal centers
- BM: involved in 50-70%; usually focal, may be diffuse; increased reticulin in involved areas
- Rx: steroids ± combination chemotherapy
- 75% patients die; ability to achieve remission single most important prognostic factor
- Appearance of clones of tightly packed immunoblasts is bad sign - progress to immunoblastic sarcoma (usually T-Cell) and death

HODGKIN'S LYMPHOMAS

GENERAL

- 40% of all lymphomas in the US (much less in orient)
- Age: major peak in 20's, minor in 60's
- Male preponderance (especially in 5-11 yr old) except for NS
- Generally starts with involvement of a single node or group of contiguous nodes (most commonly cervical and/or supraclavicular) rather than generalized lymphadenopathy
- Fever, night sweats, weight loss common (alters stage)
- Patients have predisposition to opportunistic infections
- Microscopic typing should be done BEFORE Rx; necrosis, fibrosis, cellular changes alter histologic appearance
- May see only focal involvement of a LN early - don't type for this or only extranodal involvement unless NS type
- Non-caseating granulomas may be seen in involved and uninvolved nodes and organs (10%)
- Vascular invasion present in 6-14%
- Skin, GI, CNS, Waldeyer's ring are rarely involved; if they are, probably a non-Hodgkin's lymphoma
- Increased incidence in HIV, NHL, familial
- Unusual in setting of natural immune deficiency or suppression
- Almost never see leukemic transformation
- When spleen involved (40%), usually exclusively white pulp; multiple randomly distributed nodules 1-20mm diameter
- Rx: radiation (stage I /II) or chemotherapy + XRT (stage III/IV)

Reed-Sternberg Giant Cell
- Common feature of ALL Hodgkin's Lymphomas
- Classically binucleate or bilobed central nucleus with large acidophilic central nucleoli surrounded by clear halo
- Variants: mononuclear (Hodgkin's cell), mummified cell, lacunar cell, L/H cell
- Requirement of Reed-Sternberg cell for initial diagnosis is "absolute" (less strict for LP Hodgkin's or recurrent disease)
- Classic Reed-Sternberg cell:
  - +: CD15 (Leu-M1), CD30 (Ki-1), CD25 (IL-2R)
  - –: CD45 (LCA), pan-B, S-100, keratin, EMA
- 40% T-Cell, 20% B-Cell, 40% neither
- Rearrangements of immunoglobulin genes and of T-Cell receptor genes have been variably reported

SPREAD

- Generally see a well behaved spread of disease through contiguous LN groups, (especially NS and LP); <5% show non-contiguous spread
- May have direct extension into perinodal tissue
- 85% of Stage I/II disease are above diaphragm
- Spleen: if >400g, almost always positive
- Liver: if positive, spleen and retroperitoneal LN's positive

STAGING: (ANN ARBOR SYSTEM)

- I: Single LN region
  - I_E: single extralymphatic organ or site
- II: Two or more LN regions on same side of diaphragm
  - II_E: localized extralymphatic site and LN on same side
- III: LN regions on both sides of diaphragm
  - III_E: III plus involvement of extralymphatic site
  - III_S: III plus splenic involvement
  - III_{ES}: III plus extralymphatic site and spleen
- IV: Diffuse or disseminated involvement of one or more extralymphatic organs, ± LN involvement
  - A: asymptomatic
  - B: with fever, sweats, weight loss (>10% body weight) in 6 months preceding diagnosis
  - Liver: "indicative": RS variants in proper milieu; "suggestive": atypical histiocytes or reticular cells
  - BM: "strongly suggestive": focal/diffuse fibrosis in proper milieu

PROGNOSIS

- Clinical stage
- Pathologic stage:
  - Extranodal involvement bad (especially if distant rather than by direct spread)
  - Degree of splenic involvement: ≥5 nodules poor prognosis
  - Bulky disease unfavorable (mediastinal or abdominal)
- Age: >50 yrs unfavorable
- Sex and race: Black males worse than white females
- Microscopic type: LP and NS best, MC intermediate, LD worst (less important with current treatment protocols)

When recurs within radiation portal, frequently has altered histology: more malignant cells and fibrosis; original histology present outside radiation portal
70-90% advanced stage go into complete remission; 1/3 relapse, 1/3 of which salvageable: net 75% cure rate
Increased risk of developing acute nonlymphocytic leukemia (0.5-2%/yr; cumulative risk: 3.3-10%); non-Hodgkin's lymphoma (4-5% at 10yrs), especially Burkitt's like lymphoma; solid tumors in radiation field(13%/15 yrs)
Other risks: pneumococcal sepsis, azospermia (100%), amenorrhea, hypothyroidism (6-25%)

Microscopic Types (Rye Classification)

Nodular Sclerosis (60%)

Most common type in US by far
Distinct clinically and histologically from the other types
Typically, neck or mediastinum of young female - mediastinal involvement is almost always present
Usually presents in Stage I or II; 11yr median Stage I survival
Broad well organized (birefringent) collagen bands separating lymphoid tissue into well-defined nodules
Fibrosis often vasculocentric
Lacunar cell: large (40-50µm) cells with abundant clear cytoplasm (artifactual contraction from formalin fixation) and multiple convoluted nuclei with nucleoli smaller than classic R-S cell
Can see microabscesses with areas of necrosis surrounded by RS variants; mummified cells also seen
Cell types present can vary widely, and can include clumps of foamy macrophages, neutrophils, mast cells, etc.
EM: collagen fibers and myofibroblasts
3 subtypes based on cellularity of nodules: LP, MC, LD, with correspondingly increasing numbers of classic R-S cells, decreasing lymphocytes, lacunar cells, and prognosis
Differential diagnosis: Peripheral T-Cell lymphoma with sclerosis, agnogenic myeloid metaplasia (osteosclerosis with extramedullary hematopoiesis), nasopharyngeal carcinoma

Obliterative Total Sclerosis
Obliterative non-birefringent fibrosis of nodules with sparse residual cells (usually lacunar cells)

Cellular Phase
Minimal to no sclerosis but all other components present
This histology is common in relapses
Traditionally, worse survival than when collagen present
A nodular cellular variant exists

Syncytial Variant
Sheets and cohesive clusters of lacunar variants; can simulate carcinoma

Lymphocyte Predominant (5%)

Typically younger patient - usually presents Stage I
Usually high cervical nodes in young male (<35 yrs old)
Inguinal LN 2nd most common site (1st for nodular type)
Almost never involves spleen, liver, BM, mediastinum
Usually remain in isolated site unless progresses to another form of HD (62% progress)
Other LN's may show progressive transformation of the germinal centers
Lymphocytic and histiocytic forms
Diffuse and nodular forms - LN architecture effaced
Eosinophils, plasma cells, and fibrosis scanty or absent
Very few Reed-Sternberg cells - see many of the "L/H" (popcorn) variant with folded multilobed nucleus. Too many R-S cells suggest transition to mixed cellularity
Malignant cells are B-Cells (really is a follicular B-Cell lymphoma): monoclonal Ig, LCA+, CD20+, CD30-, CD15-
Prognosis increases with abundance of lymphocytes and presence of pseudonodules
Differential Diagnosis: Well differentiated lymphocytic lymphoma, mononucleosis, malignant melanoma, progressive transformation of germinal centers

Mixed Cellularity (30%)

Generally middle aged, usually presents Stage II or III
Median survival 5 yr even for Stage I
This category used by some to include all types which don't fit neatly into LP, NS, or LD, including partial node involvement
Often represents disease in transition between LP and LD
Large numbers of eosinophils, plasma cells, and atypical mononuclear cells admixed with classic Reed-Sternberg cells (which tend to be numerous; may be CD15–)
Differential diagnosis: Lennert's lymphoma (diffuse mixed T-cell ML with excessive histiocytes)

Interfollicular Hodgkin's disease
Frequently paracortical
Usually on a background of florid reactive follicular hyperplasia

"With epithelioid histiocytes"
Common
Scattered cohesive clusters of histiocytes to frank granulomas

Lymphocyte Depleted (5%)

Generally older individuals, usually men - extremely rare in children
Present as febrile illness with pancytopenia, hepatomegaly, and no peripheral lymphadenopathy
Usually presents in Stage IV
Predominance of R-S cells, disorderly fibrosis, lymphocyte depletion, and absence of RS variants (lacunar cells)
Necrosis more common than in other types
Highest incidence of vascular invasion
Differential Diagnosis: large cell non-Hodgkin's lymphoma, MF

"Diffuse fibrosis" type:
Decreasing number of cells secondary to heavy deposition of disordered, non-birefringent collagen
>90% have marrow involvement
Median survival = 39 months

"Reticular" type:
Numerous diagnostic Reed-Sternberg cells
Sarcomatous and non-sarcomatous subtypes, based on appearance of RS cells
<25% have bone marrow involvement
Median survival = 10 months

MALIGNANT NON-HODGKIN'S LYMPHOMAS

GENERAL

Normal maturation of follicular center B-cells to immunoblast proceeds through 1) small cleaved cell, 2) large cleaved cell, 3) small non-cleaved cell, 4) large noncleaved cell
Nucleoli normally present in noncleaved cells
Staging essentially same as for Hodgkin's lymphomas
Marrow involvement may be diffuse, interstitial, focal paratrabecular, or focal non-paratrabecular
In contrast to epithelial tumors, hematopoietic tumors tend to have single, non-random alterations and/or balanced translocations

Non-Hodgkin's lymphoma's (vs Hodgkin's):

- Are multiple diseases
- Show more variable, non-contiguous spread
- Involve peripheral LN's and mesenteric LN's
- Frequently present in extranodal sites

Tend to arise from B-cells (most common) or pre-thymic or thymic T-Cells

Childhood lymphomas:

- Lymphoblastic lymphoma and Burkitt's are almost exclusively childhood lymphomas
- Diffuse large cell and Diffuse large cell immunoblastic lymphomas occur in both children and adults

CLASSIFICATIONS

Rappaport Classification (1966)
First popularly used system
Divided growth patterns into nodular and diffuse; cells types into well differentiated, poorly differentiated (cleaved follicular center cells), histiocytic (large cells), and undifferentiated (round; between lymphocytes and histiocytic)

Lukes-Collins Classification (1973)
Based on proposed cell of origin; follicular center cells, cleaved or uncleaved; immunoblasts; B or T Cells

Kiel Classification (1973)
Similar to Lukes-Collins

Working Formulation for Clinical Use (1982)
Intended to establish a common language of communication between pathologists and clinicians rather than to represent specific disease entities
An individual patient can progress from one histologic type to another
Low Grade: Small lymphocytic, follicular small cleaved, follicular mixed
Intermediate Grade: follicular large cell, intermediate cell, diffuse small, mixed, or large cell
High Grade: Immunoblastic, lymphoblastic, small non-cleaved

Current
Monoclonal antibodies and gene rearrangement studies have shown that patterns formerly thought to represent different disease are actually part of the same process
New classification scheme is emerging based on immunophenotype and genotype of the malignant cells
This outline uses a modified version of the Working Formulation, incorporating new information from immunophenotyping

CLINICAL GRADES

Clinically Low Grade Lesions:
Indolent clinical course despite disseminated disease
Long survival with or without aggressive therapy
May be controlled by therapy, almost never cured
Nondestructive growth, well differentiated cytologically

Clinically High Grade Lesions:
Aggressive course: untreated, death in 1-2 yrs
Aggressive therapy can induce complete remission ("cure") in up to 50%
Destructive growth pattern, cellular atypia
Autonomous, will grow in culture, invade privileged sites

STAGING

Same as for Hodgkin's Disease

OVERVIEW BY IMMUNOPHENOTYPE

	B-Cell	T-Cell				
	CD19/CD20	CD5	CD43	CD23	CD10	bcl
Small Lymphocytic	+	+	+	+	–	-
Follicular	+	–	–	+/-	+	2
Mantle Cell	+	+	+	–	+/-	1
Marginal Zone	+	–	+/-	–	–	-
Burkitt's	+	–	–	–	+	-

Follicular Lymphomas

In the Working Formulation, the predominantly small cleaved and mixed cell types are low grade, and the predominantly large cell type is intermediate grade
Nodular pattern of growth
Arise from follicular center cells: B-Cells (CD19+, CD20+); CD10+ (most), CD5–
Comprise 50% of adult non-Hodgkin's lymphomas
Usually elderly (median age 60-65); unusual under 40 (especially small cleaved type), uncommon in blacks
Generally present with disseminated involvement (Stage III or IV) except for children (higher frequency of Stage I or II)
Distinction from reactive follicular hyperplasia:

- Effacement of LN architecture
- Filling of sinuses and capsular infiltration
- Numerous follicles with minimal variation in size/shape, evenly distributed at a high density throughout the cortex and medulla of the node
- Poorly defined follicle borders, no polarization, no mantle
- Monomorphic cells within follicles - few mitoses
- Minimal phagocytosis
- Atypical cells in interfollicular regions

Amorphous, eosinophilic material may be present extracellularly in follicles (PAS+, diastase resistant)
Interfollicular regions may show plasmacytosis
Often accompanied by T-Cells (30-60%) which are usually CD4+
Signet Ring Lymphoma: variant with prominent intracellular Ig (usually IgG or LC's, vs IgM of Russell bodies in lymphoplasmacytic malignancies)
Marrow: focal, relatively well defined lymphoid aggregates, commonly paratrabecular, with increase in reticulin; may be more "mature" than main lesion; follicular center cell lymphomas tend to be paratrabecular, large cell lymphomas frequently are non-paratrabecular
Peripheral blood may be involved (buttock cell), especially in small cleaved (BM involvement prerequisite)
Splenic involvement in 50%
Hepatic involvement in 50% (portal triads, encroaching on limiting plate without plasma cells - same as for diffuse lymphoma)
>80% have t(14;18)(q32;q21) translocation, juxtapositioning the bcl-2 oncogene (chromosome 18) next to the Ig heavy chain gene (chromosome 14)
bcl-2 expression absent in reactive follicles, but is expressed in *other* low grade lymphomas
With time, tendency to progress from SC → MC → LC

Rarely, blastic transformation with conversion to leukemic phase - median survival 2 months

With or without Sclerosis
- More common in retroperitoneal and inguinal LN's
- Both broad bands and fine reticular pattern
- Presence (independent of amount) means better prognosis

With or without Diffuse areas
- As disease progresses, becomes diffuse, but one follicle is enough to still call it follicular
- No alteration in prognosis except, perhaps, for large cell

Follicular, predominantly small cleaved

- AKA: Nodular poorly differentiated lymphocytic lymphoma
- 40-50% of all follicular lymphomas
- Cells slightly larger than normal lymphocytes, with cleaved nuclei with prominent indentations and infoldings
- Predominantly small cleaved = <20% large cells in nodules
- Mitotic rate low, lower than mixed or predominantly large cell
- Marrow: involved in 50-60%
- Spleen: evenly distributed, well defined similarly sized tumor nodules eccentrically placed in white pulp (B-cell area) Essentially every follicle involved
- Usually asymptomatic
- Tend to relapse when off chemotherapy
- Median survival, 7 yrs

Follicular, mixed small cleaved & large cell

- AKA: Nodular mixed cell type lymphoma
- 40-50% of all follicular lymphomas
- Large cells comprise 20-50% of cells in follicles (5-10/HPF)
- Large cells 2-3 x diameter of normal lymphocytes; round to oval vesicular nuclei with 1-3 peripheral basophilic nucleoli
- Bone marrow involved in 25-50%
- Spleen: involvement same as for SC variant
- When untreated, labile clinical course, but more rapid mitotic rate makes more responsive to aggressive chemotherapy, and can do better than SC subtype; survival strongly dependent on complete vs partial response

Follicular, predominantly large cell

- AKA: Nodular histiocytic lymphoma
- 10-15% of follicular lymphomas
- >50% cells in follicles are large cells
- Bone marrow involvement in <15%
- Spleen: when involved, large irregular tumors of unequal size, randomly distributed throughout parenchyma
- Cells are poorly mobile and rarely involve peripheral blood
- Tend to be localized at time of presentation, but have more aggressive clinical course than other follicular lymphomas
- Tend to progress to diffuse growth pattern - similar clinical course to diffuse large cell

Other Low Grade Lymphomas

Small Lymphocytic

- AKA: Well differentiated lymphocytic lymphoma
- Low grade lymphoma in the Working Formulation
- Typically middle-aged to elderly
- Prolonged evolution, scanty symptoms, good survival
- Most have blood and bone marrow involvement, as well as other organs, at presentation (Stage IV); marrow involvement is usually NOT paratrabecular
- B-lymphocytes (surface IgM, IgD, CD19+, CD20+) but 70% express T-cell marker CD5; most are also CD23+, CD10–
- 1% are T-cell neoplasms
- Chromosomal abnormalities likely: most common trisomy 12 (30%; 50% of CLL type) or 13q– (25%)
- LN: effacement by monotonous small lymphocytes with: clumped chromatin, inconspicuous nucleoli, few mitoses; PAS+ inclusions may be present in nuclei or cytoplasm; capsular invasion frequently present
- Proliferation centers: collections of blasts and prolympho-blasts, seen in 60%, may cause pseudofollicular appearance (focally less basophilia); distinguish from follicles by round nuclei, poor demarcation, no compression of surrounding reticulin fibers
- Some larger cells with vesicular nuclei may be present; no prognostic significance - don't confuse with LP Hodgkin's
- Splenomegaly in 25%: predominantly white pulp (asymmetric nodules, sometimes coalescing), extending into red pulp
- Hepatomegaly in 15% (portal); (sinusoidal involvement in CLL)
- Richter's transformation to large cell lymphoma or transformation to prolymphocytic leukemia may occur: accompanied by fever, weight loss, rapid LN enlargement, and a poor clinical course; cells have same surface markers as original lymphoma

Consistent with CLL
- Lymphoma represents tissue manifestation of leukemia
- Frequently see absolute lymphocytosis
- BM involved in 100% (focal or diffuse) - usually not paratrabecular
- A percentage will progress to systemic involvement (CLL)

Plasmacytoid
- AKA: Immunocytoma
- Usually associated with monoclonal gammopathy
- 30-50% have BM involvement - usually paratrabecular
- Frequently accompanied by increased # tissue mast cells
- If most cells are plasma cell like, more likely to be myeloma
- IgM or heavy chain producers tend to be lymphomas, IgG or light chain producers tend to be myelomas
- If IgM dysproteinemia present, "Waldenstrom's macroglobulinemia" (hyperviscosity, cryoglobulinemia, Coombs positive hemolytic anemia)
- Russell bodies: cytoplasmic Ig inclusions
- Dutcher bodies: "nuclear" Ig inclusions

Mantle Cell Lymphoma

- AKA: mantle zone lymphoma, intermediate lymphocytic centrocytic lymphoma
- Not part of the Working Formulation; most were best classified as diffuse small cleaved lymphoma
- Middle age to elderly (median = 58); M:F=3:1
- B-Cell lymphoma (most have sIgM, 50% also have sIgD; CD19+, CD20+)
- 50-90% have T-Cell markers CD5 and CD43 (Leu22); CD23–
- Immunophenotype most closely matches the B-cell of primary lymphoid follicles and the mantle-zone B-cells of secondary lymphoid follicles
- Usually see t(11;14)(q13;q32), which juxtaposes oncogene bcl-1 (chromosome 11; gene AKA PRAD-1 for parathyroid adenomatosis-1) with the Ig heavy chain (chromosome 14)
- Lymphadenopathy in 75%, B symptoms in 40%
- 95% stage III or IV at presentation
- BM involved in 76%; blood 21% - median survival 3 yrs
- Mixture of small round and small cleaved lymphocytes
- Generally modest mitotic rate
- Naked benign germinal centers (i.e., no mantle zone) surrounded by malignant cells
- Scattered large cells may be present
- Nodular and diffuse forms; diffuse behaves poorly
- Nodular configuration may be obvious or represented only by occasional small germinal centers

Spleen: residual germinal centers with marked expansion of mantle zones - massive splenomegaly (>1 kg) can result
Often occur in extranodal sites; when occurs in GI tract, distinct entity: multiple lymphomatous polyposis (straddles the muscularis mucosa but does not involve mucosa)
Most behave in a low grade fashion, but others are more aggressive

Marginal Cell Lymphoma

Not part of Working Formulation
B-cell malignancy: CD19+, CD20+; CD5–, CD23–, CD10–
30-35% are EMA positive
No rearrangements of the bcl-1 or bcl-2 genes
Cell of origin is unclear
Strong association with autoimmune disorders
Tend to be indolent lymphomas, but can transform to a large cell lymphoma which behaves much more aggressively; include low or high grade in diagnosis

Mucosa-Associated Lymphoid Tissue Lymphomas

AKA: MALT-omas
Includes the marginal-zone lymphoma of non-lymphoid tissue
Most common sites: salivary gland, GI tract
Tend to remain localized for long periods before progressing
Early lesions are probably antigen driven (e.g., Helicobacter pylori in the stomach) and are reversible by removal of the antigen; later, with dissemination, become antigen independent and although usually indolent, are no longer reversible
Lymphoepithelial lesions common (distinguishing feature) as are reactive follicles with germinal centers
Nodular and diffuse forms
Cells can be small cleaved (centrocyte-like), monocytoid, or plasmacytoid
Nodular form: perifollicular distribution, then may infiltrate lymphocytic cuff (mantle zone pattern) or may colonize germinal centers (follicular colonization)
Monotypic Ig expression seen (in frozen section material)

Monocytoid B-Cell Lymphoma

AKA: Parafollicular B-cell lymphoma
M:F=1:2; median age 60-65
Present commonly with enlarged peripheral LN's, usually around the parotid, often involving the parotid; frequently localized at presentation (Stage I or II), 10-20% of patients have Sjogren's disease
Extranodal presentation in 37%: salivary gland, breast, stomach, thyroid, soft tissue, bladder
Cells: small lymphocytes with bland, ovoid nuclei and abundant pale cytoplasm (similar to hairy cells)
LN: Sinusoidal and interfollicular/mantle pattern OR diffuse
Spleen: red pulp; Marrow: paratrabecular; Liver: sinusoidal

Diffuse Lymphomas

Account for 50% of adult and nearly all childhood non-Hodgkin's lymphomas (if include lymphoblastic and small non-cleaved)
More heterogeneous group than follicular; greater variability in immunophenotype and clinical behavior
In the Working Formulation, all three types are considered to be intermediate grade
May be T-Cell or B-Cell
Marrow involvement still frequently focal ("follicular")
If untreated, uniformly fatal within 2 yrs
Each may occur with or without sclerosis; prognostic significance is unclear
All respond to combination chemotherapy
Some (especially of the large cell type) represent progression from follicular lymphoma and are thus follicular center cell in origin; progression often accompanied by a mutation in p53

Diffuse, small cleaved cell

AKA: Diffuse poorly differentiated lymphocytic lymphoma
Generally B-Cell
Most of these have been reclassified as either Mantle Cell Lymphomas or Marginal Cell Lymphomas
2 yr survival ~40% (vs 80% for any follicular component)

Diffuse, mixed small and large cell

AKA: Diffuse mixed cell type lymphoma
Generally use this classification when 20-50% of the cells are "large"; criteria varies
Includes the diffuse counterpart of the follicular center cell origin (B-cell) as well as some peripheral T-cell lymphomas
[See also Peripheral T-cell Lymphomas, below]

With Epithelioid cell Component

Diffuse, large cell

AKA: Diffuse histiocytic lymphoma, Reticulum cell sarcoma
Occurs in both children and adults, mostly the latter (median age 57 yrs)
Not uncommonly seen in setting of AIDS
Grow as large bulky fleshy mass - may resemble carcinoma
Greater tendency for extranodal presentation (40%) including digestive tract, skin, skeletal system
~50% limited to one side of diaphragm (vs 90% for follicular)
Large cells with vesicular nuclei, subtle peripheral nucleoli
Bone marrow/liver involvement less common
When liver/spleen involved, usually large tumor masses rather than smaller nodules
50-60% B-Cell, 5-15% T-Cell, 5% histiocytic, 30-40% no markers (most B-Cell by gene rearrangement)
Associated with translocations involving the bcl-6 gene
Rapid progression, poor prognosis if untreated, but aggressive chemotherapy can yield good results
Distinguishing these from immunoblastic lymphomas may be academic
Median survival: 1-2 yrs

Cleaved Cell

Often accompanied by minority of small cleaved cells as well

Non-cleaved cell

More common
Vesicular nucleus but usually with small nucleoli
Difficult to distinguish from B-cell immunoblastic (nuclei more central in latter)
Generally higher mitotic rate than cleaved cell form

T-Cell Rich B-Cell Lymphoma

AKA: Pseudo-Peripheral T-Cell Lymphoma
Diffuse B-cell lymphoma, sometimes evolving from previous follicular lymphoma, in which >75% of the cells are actually reactive T-cells with normal helper:suppressor ratio obscuring the large malignant B-cells
M>F; generally in 60's
Despite the generally high stage of presentation and progression to a diffuse lymphoma, these patients tend to have an indolent course , perhaps because the large number of T-cells represents a host response

Histiocyte Rich B-Cell Lymphoma

Similar to T-cell rich B-cell lymphoma but with numerous non-epithelioid histiocytes
May be a variant of TCRBCL

High Grade Lymphomas

Large Cell, Immunoblastic

Plasmacytoid
- AKA: B-cell immunoblastic sarcoma (some actually T-cells)
- Immunoblast: large vesicular eccentric nucleus, single prominent central nucleolus, thick nuclear membrane; cells may be binucleate
- Intracytoplasmic Ig
- Most common lymphoma to arise in setting of immunodeficiency, Hashimoto's, Sjogren's, SLE (30%)
- Marrow involved in 25% at diagnosis
- Disseminates early, poor prognosis (median survival 14 months)

Clear cell
- AKA: T-Cell immunoblastic sarcoma (some are B-cells)
- [NOTE: See also Peripheral T-Cell Lymphomas]
- Less common than plasmacytoid
- Irregular nuclei, fine chromatin, small but distinct nucleoli, "water-clear" cytoplasm, interlocking plasma membranes (cohesive)
- Involves initially paracortical region
- Usually NOT preceded by an abnormal immune disorder
- Children and adults - may coexist with mycosis fungoides
- Generalized lymphadenopathy, polyclonal hyperIg
- Marrow involved in ~33% at diagnosis

Polymorphous
- AKA: pleomorphic histiocytoid lymphoma
- Most of these are Ki-1 positive and have been reclassified as "anaplastic large cell lymphoma"; [see below]

With epithelioid cell component
- AKA: Transformed Lymphoepithelioid T-cell lymphoma, Transformed Lennert's (see below)
- T-Cell lymphoma of adults, mostly
- 74% are stage IV at presentation
- Effacement of lymph node architecture, plasma cells, eos, proliferation of small vessels with plump endothelial cells
- May have Reed-Sternberg-like cells
- Small atypical lymphocytes between histiocytes
- Splenic involvement (this variant) similar to Lennert's

Lymphoblastic

- Usually children and adolescents (accounts for 1/3 of childhood non-Hodgkin's lymphomas)- also adults
- Anterior mediastinal mass in 50-80% (thymic region)
- CSF and skin involvement not uncommon
- Untreated: rapid dissemination, leukemia, death in months
- Gross: soft, white, foci of hemorrhage and necrosis
- Diffuse, monomorphic pattern of lymphocytes (round nuclei with "delicate" convolutions, fine chromatin, small nucleoli, and high mitotic rate) - focal "starry sky" areas
- Lymphocytes express terminal deoxynucleotidyl transferase (vs other lymphomas) and usually (80%) have T-cell markers (CD7, ±CD2), some are pre-B (intracytoplasmic μ), some B, some granulocytes
- In LN, predominantly paracortical
- T-cell tumors: usually male, always mediastinum
- May be a tumor of thymocytes (primitive T-cell precursors)
- Commonly progress to marrow involvement - acute lymphoblastic leukemia (especially T-cell type)
- In about 50% of cases, convolutions cannot be identified
- Differential diagnosis: small lymphocytic, LP Hodgkin's, small non-cleaved

Convoluted cell

Non-convoluted cell

Small Noncleaved Cell

- AKA: Diffuse undifferentiated lymphoma
- Cells intermediate in size between lymphocytes and histiocytes
- Usually positive for B-Cell markers (sIgM, CD19, CD20); CD5–, CD23–

Burkitt's
- Endemic in equatorial strip of Africa
- Most cases occur in children - mean age 10yrs
- Presentation: Africa (younger), jaw; US (older), ileum
- Peripheral lymphadenopathy rare
- Bulky, fleshy tumors, ± necrotic areas
- Micro: monotonous small (10-25μm) round cells (several prominent basophilic nucleoli) creating a dark "sky" with "stars" of non-neoplastic macrophages; high mitotic rate; may have follicular areas
- Numerous fat vacuoles in cytoplasm (Oil Red O positive)
- EM: abundant ribosomes, lipid inclusions, no glycogen, nuclear pockets/projections
- Bone marrow involvement late, leukemia rare
- Responsive to chemotherapy (especially African), 50% relapse
- Strong association with EBV (95% of African type; 20% of non-endemic type; 30% in AIDS patients)
- Usually CD10+
- Consistently see translocation of c-myc from chromosome 8q24 to the Ig heavy chain genes (90%) on chromosome 14q32 or the Ig light chain genes on chromosome 2p13 (kappa) or 22 (lambda)

Pleomorphic (non-Burkitt's)
- Occurs in older age group (mean 34 yrs)
- Larger tumor cells, more pleomorphic nuclei and cells than in Burkitt's, well-defined cytoplasm rim, large eosinophilic nucleoli, bi and multi nucleate
- GI involvement less common, marrow involvement more common than Burkitt's type
- Usually CD10–; c-myc gene rearrangements rare, but bcl-2 is rearranged in 30%
- More aggressive clinical course

Peripheral T-Cell Lymphomas

- All are diffuse - adults (rare <20 yrs)
- Constitute 30% of diffuse aggressive lymphomas in US
- Frequently classified as Large Cell Immunoblastic or Diffuse Mixed in the Working Formulation
- Most patients have generalized lymphadenopathy, most stage IV (involvement of skin, liver, peripheral blood, lungs), B-symptoms common
- 15% small irregular, 40% mixed cell type, 43% large cell
- <2% are small lymphocytic (WDL); tissue equivalent of T-CLL
- Small cells (slightly larger than normal lymphocytes): condensed chromatin, irregular nuclei, small nucleoli, may have abundant pale cytoplasm
- Large cells: vesicular nuclei, prominent eosinophilic nucleoli
- Both small and large cells show marked nuclear pleomorphism, lobulation, occasionally multinucleation
- Often inflammatory background: neutrophils, eosinophils, macrophages, plasma cells
- Skin involvement common - restricted to dermis
- Peripheral blood involvement only after skin involvement
- Cells contain at least one pan-T marker (CD2,3,4,7) but lack the markers of immature T-Cells (CD1a, TdT)
- 64% CD4+, 12% CD8+, 8% CD4+CD8+, 16% CD4–CD8–
- Most have α/β T-cell receptors

γ/δ Variant
- M>>F, usually younger adults
- Marked hepatosplenomegaly, minimal lymphadenopathy
- Usually CD4– and CD8–; CD3+, CD2+, CD16+
- Aggressive course; relapses common, usually fatal

Lymphoepithelioid Cell Lymphoma
- AKA: Lennert's Lymphoma
- Probably just a pattern and not a distinct entity
- Atypical large and small lymphocytes with a conspicuous epithelioid cell component, singly or in clusters, and a proliferation of vessels with plump endothelium, numerous plasma cells and eosinophils
- Patients are middle age to older, with generalized lymphadenopathy, often involving Waldeyer's ring, and hepatosplenomegaly and B symptoms
- Most are CD4+
- Spleen usually shows multiple randomly distributed nodules of varying size; collarettes of epithelioid histiocytes seen in marginal zone
- May undergo blastic transformation to immunoblastic ML

T-Cell Lymphoma Resembling AILD
- Preponderance of post-capillary venules
- May even get hypergammaglobulinemia
- Background of atypical lymphocytes, absent in AILD
- AILD may simply be a well differentiated form of this disease

Anaplastic Large Cell Lymphoma
- (AKA: Ki-1 lymphoma)
- Almost all are CD30+ (but not all)
- Usually CD2+, CD5+ (T-cells), CD45 (LCA) positive; usually LeuM1 (CD15) negative

Classic Type
- Usually presents in younger individuals, often involving skin, but may be seen in both children and adults
- Histologically, may mimic carcinoma, sarcoma, or malignant histiocytosis
- "Packman" nuclei common: large lobated to horseshoe shaped nuclei with pseudoinclusions
- Tumor cells often also positive for CD4 and EMA
- Erratic clinical course - long remissions ± chemotherapy
- Commonly show t(2;5)(p23;q35), especially when occurring in younger individuals
- Small cell and histiocyte rich variants exist

Primary Cutaneous Type
- Closely related to lymphomatoid papulosis (this is the malignant counterpart)
- Usually need clinical progression beyond the skin to make this diagnosis
- Usually EMA–; don't see t(2;5)

Adult T-Cell Leukemia/Lymphoma
- Associated with Human T-Cell Leukemia Virus (HTLV-I)
- Distinct clinical/pathological entity, although some consider this a variant of Peripheral T-Cell Lymphoma
- M=F; median age 40 yrs; acute to subacute course
- Most common in southwestern Japan, southeastern US; the majority of the US cases occur in blacks
- Probably long period between exposure to HTLV and development of disease
- Histology varies: pleomorphic, medium sized cell, mixed large and small cells are most common types, but also can get large cell or small cell variants
- Generalized lymphadenopathy, hepatosplenomegaly, leukemia; CSF involvement common
- Skin: can have epidermotropism with large Pautrier's microabscesses
- Hypercalcemia and bone lesions due to hormonal activation of osteoclasts rather than direct tumor involvement
- Markedly pleomorphic lymphoid cells in the peripheral blood with multilobated nuclei
- Cells are CD4+, IL2R + (CD25+)
- All present in Stage IV - prognosis poor, independent of histologic type - even with aggressive chemotherapy, median survival is less than one year

Miscellaneous Lymphomas

Cutaneous T-Cell Lymphoma (CTCL)
- AKA: Mycosis Fungoides / Sézary Syndrome
- Most cases have "helper" T-Cell characteristics: CD4+, IL2R- (CD25-)
- Sézary syndrome refers to triad of erythroderma, lymphadenopathy, and atypical lymphocytes in the peripheral blood
- Lymphocytes frequently show "cerebriform" appearance, although this may be lost in later stages
- Initially skin involvement, but later progresses
- Early disease progresses through various "stages":
  - Premycotic erythematous / exzematoid: focal oval or round circumscribed red flat macules
  - Patch: coalescence of macules into patches with scaling and intense pruritus, purple brown discoloration - some lesions may spontaneously regress
  - Plaque: palpable discrete, indurated papules which may arise in erythematous zones or de novo, may heal centrally while progress peripherally (T1-2)
  - Tumor: large elevated nodules >1 cm in diameter - may erode and ulcerate

Skin:
- Acanthosis or atrophy, focal parakeratosis
- Exocytosis of atypical lymphocytes
- Pautrier's microabscesses (also seen in Adult T-cell leukemia/lymphoma - almost pathognomonic)
- Clusters of atypical lymphocytes in superficial dermis
- Increased numbers of Langerhans cells
- May see mucinous degeneration of outer hair shafts

Lymph Nodes: 3 patterns
- Non-specific (rare): only reactive follicular hyperplasia
- Frank malignancy: partial or total replacement by monomorphic infiltrate of atypical lymphocytes, ± coagulative necrosis
- Dermatopathic Lymphadenopathy (80%): paracortical expansion by proliferating histiocytes with racket shaped granules on EM (Langerhans cells)

STAGING

TNM:
- T: Skin involvement
  - T0 Suspicious lesions
  - T1 Plaque stage - <10% body surface
  - T2 Plaque stage - >10% body surface
  - T3 Tumors
  - T4 Generalized erythroderma
- N: Nodal involvement
  - N0 None palpable, normal histology
  - N1 Palpable, normal histology
  - N2 Not palpable, abnormal histology
  - N3 Palpable, abnormal histology
- M: Visceral involvement (seen in 70% at autopsy)
  - M0 Absent • M1 Present (Stage IVB)

  Spleen (50%), lung (45%), liver (40%), BM (2%)

Clinical Staging:

	T1	T2	T3	T4
N0	IA	IB	IIB	IIIA
N1	IIA	IIA	IIB	IIIB
N2	IVA	IVA	IVA	IVA
N3	IVA	IVA	IVA	IVA

Angiocentric Immunoproliferative Lesions

Benign Lymphocytic Vasculitis (Grade I)
- Angiocentric mononuclear infiltrate (lymphocytes, plasma cells, immunoblasts) which involve vessel walls but without vascular destruction, lumenal compromise, or necrosis
- Most commonly lungs and skin
- Rx: Chlorambucil more successful than steroids
- May progress to more aggressive forms of AIL

Lymphomatoid Granulomatosis (Grade II)
- AKA: Polymorphic reticulosis, Lethal Midline Granulomas
- Commonly involve nose, lung, paranasal sinuses, nasopharynx; also skin, kidneys, CNS, GI tract
- Atypical angiocentric *angiodestructive* lymphoreticular infiltrate with *necrosis*, often extensive
- Mixed infiltrate: lymphocytes, plasma cells, immunoblasts, histiocytes, ± eosinophils
- Initially felt to be only locally invasive, but many progress to large cell immunoblastic lymphoma - prognosis worsens with increasing numbers of large lymphocytes and decreasing numbers of inflammatory cells
- Many patients respond to Rx (radiation if localized)

Angiocentric Lymphoma (Grade III)
- Neoplastic nature of angiocentric infiltrate usually obvious at presentation - atypia in both small and large cells.
- If large cells predominate, fulfill criterion for immunoblastic
- Vascular infiltration, destruction, extensive necrosis
- Discrepant histology at different sites common
- Primarily extranodal; may involve nodes - always diffuse
- In spleen, periarterial
- Lymphokine production by abnormal T-cells may induce a hemophagocytic syndrome

Lymphomas in Immunodeficiency

Primary (Genetic) Immunodeficiencies
- Increased incidence of malignancies, especially lymphomas
- Ataxia-telangiectasia: 10% die from lymphomas, usually B-immunoblastic sarcoma
- Wiskott-Aldrich syndrome: 10% die from lymphomas, both Hodgkin's (50% LD type) and non-Hodgkin's
- X-linked recessive lymphoproliferative syndrome (immunodeficiency to EBV): Burkitt's, immunoblastic

Post Transplant Lymphoproliferative Disease
- 4-6% renal transplant patients develop malignancies: Skin tumors, ML, Kaposi's, cervical carcinoma
- Lymphoma frequency 350x general population (higher in cardiac transplant patients)
- Initially a polyclonal B-cell hyperplasia; later evolves into a B--cell lymphoma, often retaining a polyclonal phenotype; etiology may be similar to MALT lymphomas
- 50% involve CNS (vs 1% for general population)
- 30% involve the allograft
- Pleomorphic, rapid clinical course; must remove the graft

AIDS
- Malignancies: Kaposi's sarcoma, malignant lymphoma
- Usually extranodal, involving GI tract, CNS, BM, heart
- Usually non-Hodgkin's, usually diffuse large cell (B-cell)

Others
- Rheumatoid arthritis, Sjogren's, Hashimoto's, and group of "atypical immunoproliferative processes", including AILD

Other

Composite
- Patient has two distinct lymphomas at same anatomic site
- Most common: Hodgkin's and Follicular small cleaved or diffuse large cell
- More likely, less differentiated is a blastic form of other

Large Cell Lymphoma with Filopodia
- AKA: Microvillous Lymphoma of B-Cell Origin; probably same as "Anemone cell tumor", "porcupine cell tumor"
- Large cell lymphoma with sinus growth pattern; CD45+
- By EM, abundant filiform cytoplasmic projections

Malignant Angioendotheliomatosis
- Systemic lymphoma with marked tropism for blood vessels
- Usually B-Cell phenotype
- Involves skin and CNS most commonly

PLASMA CELL DYSCRASIAS

GENERAL
- AKA: Monoclonal gammopathies, paraproteinemia
- Need two components:
  - • Uncontrolled proliferation of plasma cells or related cell
  - • Abnormally elevated blood and/or urine levels of a homogeneous Ig and/or one of its constituent chains
- Free light chains are small enough to be effectively excreted in urine (Bence Jones proteins) - may occur alone or in combination with any hyper-Ig syndrome

Multiple Myeloma (60%)

- AKA: Plasma cell myeloma
- Multiple masses of immature plasma cells scattered primarily throughout the skeletal system
- Peak incidence 50-60yrs ; M>F (slightly)
- More common in long-standing chronic infections
- Patients present with unexplained anemia, proteinuria, infections (impaired immunity)
- Later: bone pain, fractures, renal failure
- Generally: 3gm Ig/100cc serum or 6 mg Ig/100cc urine

IgG	60%	IgM	10-15%	Light chains only	5-10%
IgA	15-20%	IgD/IgE	rare		

- IgD secretors have more aggressive clinical course
- Most are CD19–, CD20–, CD38+
- 10% show systemic amyloidosis
- X-ray: multiple destructive bone lesions, initiating in medullary cavity and eroding cortex, forming sharply punched out defects (1-4 cm) - "soap bubble"

Vertebrae	66%	Femur	28%
Ribs	44%	Clavicle	10%
Skull	41%	Scapula	10%
Pelvis	28%		

- Soft tissue lesions may appear later: spleen, liver, kidneys, lungs, lymph nodes: fleshy, red-brown masses
- Mature to very immature plasma cells, bi- and trinucleate, Russell bodies
- Plasma cells may account for 15-90% of cells in marrow; patchy or diffuse involvement
- Myeloma nephrosis (60-80%): abnormal interstitial plasma cell infiltrate plus distal tubule and collecting duct casts
- Rarely, non-secreting variant (no serum protein peak)
- Survival: 1-2 yrs without treatment
- Bad Prognosis: serum β-2 microglobulin >4 ng/µl, extensive or diffuse marrow involvement, highly immature plasma cells or anaplastic conversion, plasma cell leukemia
- Patients have increased risk of developing other cancers

Solitary Myeloma (3-5%)

AKA: Solitary plasmacytoma
Two types: Bone (see multiple myeloma) or soft tissues (lungs, oronasopharynx, nasal sinuses)
Peak incidence 40-50 yrs old; M>F
50% have monoclonal protein in urine and/or serum; but level generally <2 gm/100cc, and non-monoclonal Ig normal
For those with bone involvement, 50% of those with dysproteinemia and 25% of those without progress to multiple myeloma - therefore, may be early stage of same disease
For those without bone involvement, only 10-20% progress to multiple myeloma

Plasma Cell Leukemia

Plasma cells in peripheral blood (>20% or absolute plasma cell count >2000)
Variant of Multiple Myeloma
Usually small numbers of leukemic cells
Tissue involvement rare

Waldenstrom's Macroglobulinemia (5%)

AKA: Plasmacytoid lymphoma
Monoclonal gammapathy generally (85%) occurring in a setting of a lymphoproliferative disorder
Rare before 60 yrs of age
Diffuse marrow infiltration by plasma cells, plasmacytoid lymphocytes, and lymphocytes (all from same clone). Cells do not form tumor masses or produce lytic lesions
Lymphocytes commonly contain Dutcher bodies (intranuclear inclusions)
Similar infiltrate may be seen in LNs, spleen, liver
Usually IgM, rarely IgG or IgA
Symptoms: weakness, fatigue, weight loss
In 90%, total protein in serum >6.5 gm/100cc; IgM 1-3 gm
IgM >15% of all Ig (usually 5%)
Bence Jones proteins found in 20-30%
Mean survival: 2-5 yrs

Heavy Chain Disease

Rare - Heavy chains only are produced
Can get hepatosplenomegaly and soft tissue tumors
Can get at any age, although median age is 61

Alpha
Children
Two patterns:
• Massive infiltrate of lamina propria of intestine with villous atrophy, malabsorption, diarrhea; abdominal LNs involved; AKA: "Mediterranean Lymphoma" [see GI Outline]
• Similar infiltrate in respiratory tract

Gamma
Elderly
More like malignant lymphoma than myeloma - no lytic lesions
May be associated with TB, rheumatoid arthritis, autoimmune
Course: months to years

Mu
Rare - usually seen in patients with CLL

Monoclonal Gammopathy of Undetermined Significance (MGUS) (30%)

Ig peak in blood, but no apparent associated cellular proliferation
Seen in ~3% of people over 70yrs; most are asymptomatic
Bence Jones proteins generally NOT seen

MYELODYSPLASTIC SYNDROMES

Heterogeneous group of stem cell disorders with abnormal hematopoiesis and varying potential to evolve into AML (1/3 will ultimately progress)
Older individuals (60-75), M>F, present with fatigue
50% hypercellular, 25% normocellular, 25% hypocellular
May see increased reticulin
ALIP (abnormal localization of immature precursors) may be seen - may indicate increased risk of progression
A picture identical to myelodysplastic syndrome can be seen in patients with AIDS

Cytogenetics
May also be seen in chromosome deletion syndromes:
5q–:RA-like picture; does not progress
7q–:Presents 6-8mos; leukemia by 3-6 yrs
50% of all patients have some chromosome deletion, most commonly 5q– (good prognosis), then 8+ (intermediate prognosis), 7– or 7q– (poor prognosis); also see 20q–, 12p–, abnormalities of 17, y–.

Refractory Anemia (RA)

<1% blasts in peripheral blood, <5% in marrow
Hypercellular marrow with erythroid hyperplasia and/or dyserythropoiesis
Normal granulocytes and megakaryocytes

Refractory Anemia with Ringed Sideroblasts (RARS)

RA plus ≥15% of nucleated RBCs are ringed sideroblasts (iron in mitochondria)
Marked increase in erythroid precursors
Significant iron accumulation in macrophages

Refractory Anemia with Excess Blasts

Cytopenia affecting two or more cell lines
1-5% blasts in peripheral blood, 5-20% in marrow
Hypercellular marrow with erythrocyte or granulocyte hyperplasia
Dysgranulopoiesis, dyserythropoiesis, and/or dysmegakaryocytopoiesis

RAEB in Transformation (RAEB-T)
5-30% blasts in peripheral blood, 20-30% in marrow
Auer rods may be present
60% progress to AML with median survival of 6 months

Chronic Myelomonocytic Leukemia

Hypercellular marrow with increase in both monocytic and granulocytic lines
Monocytes: >1 x 10^9/L, often with mature granulocytosis
<5% blasts in peripheral blood, 5-20% in marrow

CMML in Transformation (CMML-T)
5-30% blasts in peripheral blood, 20-30% in marrow

LEUKEMIAS

GENERAL

Diffuse (begins focally) replacement of the bone marrow (rarely, older patients with AML or ALL may present with hypocellular marrow)
Abnormal numbers and forms of immature WBC's in peripheral blood
Widespread infiltrates in the liver, spleen, LN's and other sites throughout the body
Symptoms, complications, and death arise from anemia, thrombocytopenia, and loss of normally functioning leukocytes
Acute leukemias present aggressively: WBC<10K in 50%, >100K in 10%
Chronic leukemias are insidious, often detected only on routine physical exam
Beyond acute or chronic, typing of the leukemia is better done on smears of peripheral blood or marrow aspirate
Leading cancer killer of children <15 yrs in US
Rate of cell growth actually slower than normal, but get accumulation due to apparent block in differentiation

Primary Changes:

BM replacement can erode cancellous and cortical bone
Myelofibrosis may be present: ALL>AML>>CLL or CML
Lymphadenopathy common, especially in lymphocytic
Splenomegaly common, especially in CML (generally <2.5kg in CLL, <1 kg in monocytic) - firm parenchyma - expansion of red pulp
Hepatomegaly, especially in CLL

Secondary Changes:

Anemia (NOTE: as marrow recovers, fat cells regenerate first, then erythroids (in islands, often with dyseryhropoietic changes), granulocytes, megakaryocytes)
Hemorrhages and hematomas, most frequently in brain
Infection
Vascular sludging/infarcts

CHLOROMA (GRANULOCYTIC SARCOMA):

Extramedullary tumor mass composed of myeloblasts with or without neutrophil promyelocytes
More common in children
Undifferentiated, intermediate, and differentiated types
Look for eosinophilic myelocytes; increase in number with increasing differentiation of lesion
Frequently misdiagnosed as large cell lymphoma
May be isolated or associated with AML, CML, agnogenic myeloid metaplasia, polycythemia vera - may predate AML or be first evidence of relapse
Associated with subperiosteal bone (especially of the skull, sinuses, sternum, ribs, vertebrae, pelvis), LN's, skin
If occurs within orbit (common) usually presents with proptosis
Gross: fresh cut surface is often green (peroxidase)

Acute Lymphoblastic (Lymphocytic) Leukemia (20%)

Most frequent cancer in children <15 yrs (peak age=4yrs)
Generalized lymphadenopathy, splenomegaly, hepatomegaly
80% are of B-Cell origin; most are pre-B (CD19+ but often CD20 and Ig–). Prognosis best for pre-B phenotype
High levels of terminal deoxynucleotidyl transferase
Intense therapy induces remission in > 50%
Often, Rx makes cells smaller - more like lymphocytes
Cytogenetic abnormalities seen in 60%:
- Good prognosis: hyperdiploidy (seen in 25-30%)
- Poor prognosis: Philadelphia chromosome (15% adults, 5% children); t(1:19) (20-25%)

Subtypes:

- L1 (85%): Small cells predominate, homogenous, little cytoplasm, round regular nuclei, nucleoli not visible. Some cells up to twice size of small lymphocytes
- L2 (13%): Features of L1 and L3. Nuclei have clefts. Nucleoli present, more cytoplasm - T or B Cell, adults
- L3 (1-2%): Homogeneous population of large cells (3-4x size of small lymphocytes), round nuclei, prominent nucleoli, abundant deeply basophilic cytoplasm; leukemic form of Burkitt's lymphoma (cells have t(8;14) translocation)

Chronic Lymphocytic Leukemia (25%)

Most common leukemia in adults >60yrs; M:F=2:1
Extremely uncommon among Orientals
Defined as >15K lymphocytes/mm^3 with ≤10% blasts
4-15K = early low count CLL, subleukemic CLL
Usually B-cell, with weak sIg but also CD5+; rare cases (2%) of T-Cell (see below)
Generalized lymphadenopathy (65%), splenomegaly (40%), hepatomegaly (25%)
Homogenous population of small mature lymphocytes
Reticulin increased in 25%
Often associated with Small Lymphocytic Lymphoma
With therapy, survival of 10-15 yrs not uncommon

T-Cell CLL

Rare; accounts for <2% of all cases of CLL
Circulating cells may (60%) show cytoplasmic azurophilic granules (large granular lymphocytes) suggesting T-CLL
Beta-glucuronidase and acid phosphatase activity almost always elevated (rarely elevated in B-CLL)
CD3+, usually CD8+ (suppressor T-cell); CD56–; clonal rearrangement of T-cell receptor gene(s)
If CD4+, usually a prolymphocytic variant (see below)
Lymphocytosis may range from 3K to 500K; white count may remain stable for years
Cutaneous involvement may be seen, but without epidermal involvement
May get neutropenia, pure red cell aplasia, hypogamma–globulinemia due to production of gamma interferon

NK-Cell CLL

Even more rare than T-Cell CLL; comprise only 1/5 of the non-B-cell CLL's
Cells usually CD2+ but CD3–; CD16+, CD56+; usually CD4–, CD8–
No rearrangements of the T-cell receptor genes is seen

Prolymphocytic

Larger, predominantly immature lymphocytes
Usually older males
Usually B-Cell (80%) with strong sIg expression
Remainder are T-Cell (20%); usually CD4+ (as well as CD2+, CD3+, CD5+)
Markedly elevated WBC with >55% prolymphocytes
Usually massive splenomegaly without lymphadenopathy
Generally low mitotic rate
More aggressive clinical course than typical CLL

Intermediate (CLL/prolymphoctic leukemia)

10-55% prolymphocytes in blood

TRANSFORMATION

Prolymphocytoid (de-differentiation) (5%)

Increase in prolymphocytes to >20% of marrow or blood lymphocytes
Often focally in BM, surrounded by well-differentiated lymphocytes
Prominent, single eosinophilic nucleoli

Richter's (large cell transformation) (3-10%)
Pleomorphic, usually B-immunoblastic lymphoma; occasionally Hodgkin's disease
Increased symptoms, frequent lymphopenia, downhill course
Lymphoma cells usually not seen in peripheral blood

STAGING

Rai Staging		Median Survival
0:	Lymphocytosis only	150 mos
I:	Lymphadenopathy	101 mos
II:	Enlarged liver or spleen, ± LN's	71 mos
III:	Anemia ± organomegaly	19 mos
IV:	Thrombocytopenia, ± organomegaly	19 mos

Alternate Staging		
A:	Enlargement of 1 or 2 of spleen, liver, cervical LN's, axillary LN's, inguinal LN's	Gen popul.
B:	3 or more	7 yrs
C:	Anemia or thrombocytopenia	2 yrs

Acute Myelocytic (Myeloblastic) Leukemia (40%)

>30% blasts (NOTE: for M3-5, include promyelocytes and promonocytes when counting blasts)
Most common leukemia in the 15-59 yr age group
Etiology may be linked to oncoviruses
Azurophilic granules (appear at promyelocyte stage) are modified 1° lysosomes
Myeloperoxidase stain distinguishes myeloblasts from lymphoblasts
Esterases: Naphthyl AS-D chloroacetate esterase (NCE) specific for myeloids; Alpha-naphthyl acetate esterase (ANE) specific for monocytes
Auer bodies: red rod shaped abnormal lysosomes (derived from 1° granules) principally seen in myelocytic leukemias (also some monocytic)
Remissions can be achieved, but in general are short-lived
All trans retinoic acid can induce some differentiation
Presence of Philadelphia chromosome (3%) is a bad prognostic sign

Subtypes:
- M0: **Minimally differentiated**. No myeloperoxidase staining; <3% blasts
- M1 (20%): **Myeloblastic without maturation**. blasts without Auer rods or granules (≥30% of non-erythroid cells in marrow are myeloblasts)
- M2 (30%): **Myeloblastic with maturation**. many blasts (≥30%), but some maturation to promyelocytes (>10%) or beyond, few monocytic elements (<20%); 20-25% have t(8;21)
- M3 (5%): **Promyelocytic** - mostly promyelocytes with many Auer rods (Faggot cells: numerous Auer rods like sticks in a fireplace) and peroxidase-positive granules; frequently present in DIC; microgranular (hypogranular) variant exists without Auer Rods; >90% show t(15;17)
- M4 (30%): **Myelomonocytic** - both myeloid (M2) and monocytic elements (20-80% monocytic elements in marrow, or serum lysozyme level ≥3 x normal). Present with leukocytosis;
  M4EO: Myelomonocytic with bone marrow eosinophilia 100% have inversion of chromosome 16; better prognosis than standard M4
- M5 (10%): **Monocytic** - monoblasts and monocytes >30%; must confirm diagnosis with fluoride inhibited esterase reaction; urine/serum lysozyme usually elevated; present with gingival infiltration; 30% have abnormality of chromosome 11
  M5A (poorly differentiated): ≥80% monocytic elements are blasts
  M5B (differentiated): <80% monocytic elements are blasts;
- M6 (5%): **Erythroleukemia** - erythroid elements constitute >50% of the cells and have bizarre multilobated nuclei; ≥30% of non-erythroid elements are blasts
- M7 (5%): **Megakaryoblastic** - immature and abnormal megakaryocytes (≥30% in aspirate or circulating); myelofibrosis usually present

Chronic Myelocytic Leukemia (15%)

90% have Philadelphia chromosome [Ph': translocation from 22q11 to 9q34, forming chimeric protein c-abl/bcr (breakpoint cluster region)]
Ph' negative CML has worse prognosis than Ph' positive (different disease)
White count invariably elevated, usually >100K
Huge spleens common
BM: usually less than 5% myeloblasts
Mostly neutrophils with scattered myelocytes and promyelocytes - increased number of basophils typical
Leukemic cells usually have markedly decreased alkaline phosphatase activity
2-3 yr course without treatment
May develop myelofibrosis late in course
Treatment induces 2-5 yr remission, usually followed by blast crisis (usually myeloblasts, but 30% are immature B-Cells) and death

Other Leukemias

Hairy Cell Leukemia
AKA: Leukemic Reticuloendotheliosis
Most commonly male (may be young, but median age 50)
Insidious onset with massive splenomegaly, no lymphadenopathy, usually pancytopenia
Hairy cell: 10-14µm, clear to lightly basophilic cytoplasm with numerous delicate cytoplasmic projections, perinuclear halo (formalin artifact); delicate nuclear chromatin
Marrow: usually hypercellular (may be hypocellular) with loosely packed hairy-cells (vs tight packing in lymphomas); reticulin invariably increased; erythroid hyperplasia common
Spleen: disease of red pulp - diffuse infiltration by monotonous population of small mononuclear cells, usually with invasion into vascular walls (subendothelial)
Contain Tartrate Resistant Acid Phosphatase (TRAP)
EM: 50% have ribosome-lamella complex
Monoclonal B lymphocytes, CD5-, CD19+, CD20+, CD10-, IgM+, IL2R+, CD11c+, CD25+
Two types:
- Leukopenic (WBC <3K)
  Most common form in US
  Reticulin almost always increased
- Non-leukopenic (WBC >3K)
  Most common form in Japan

Rx: splenectomy, alpha-interferon, deoxycoformycin
Differential Diagnosis: Mastocytosis

Histiocytic Leukemia
Controversial whether or not this exists

Stem Cell Leukemia
Highly acute, extremely immature
Rapidly fatal (months)

Erythroleukemia
AKA:DiGuglielmo's syndrome., erythromyeloblastic leukemia
See above (M6 AML)
Marked anemia, leukopenia
If survive initial phase, gradual transition to immature myeloblastic leukemia
Course: months to 2 yrs, ending in death

MEGAKARYOCYTES / PLATELETS

NORMAL HEMOSTASIS
Vasoconstriction at the site of endothelial injury
Platelet adhesion / degranulation / aggregation (primary hemostasis)
• Promoted by: exposed subendothelial connective tissue, thromboxane A_2, ADP, thrombin
• Inhibited by: prostacyclin, ADPase, anti-coagulants (heparin)
Later, platelet plug undergoes a "viscous metamorphosis" due to activation of ADP and thrombin (secondary hemostasis)

Thrombocytopenia

Decreased Platelet Production

Aplasia
Myelophthisic Anemias
Metastatic carcinoma, leukemia
Folate or Vit B_{12} deficiency
Dilution by multiple transfusions

Abnormal Platelet Activity

Bernard-Soulier syndrome
Inherited deficiency of platelet membrane glycoprotein required for platelet-collagen interaction
Thrombasthenia
Defective platelet aggregation in response to ADP, collagen, epinephrine, or thrombin
Fanconi's anemia
Wiskott-Aldrich syndrome
Aspirin abuse

Increased Platelet Destruction

Drug reactions
Seen with quinine, quinidine, chloramphenicol, alkylating agents, antimetabolites, thiazide diuretics, methyldopa
Mechanical injury
Prosthetic valves, microangiopathic anemia, malignant HTN
Hypersplenism
Normally, spleen sequesters 30-40% of platelets; when enlarged, can increase to 90%
Isoimmune Thrombocytopenia
Seen in neonates and post-transfusion
Most platelets contain specific antigens
PL^{A1} negative mothers with PL^{A1} positive fetus create antibodies - similar to Rh disease

Idiopathic Thrombocytopenic Purpura (ITP)
AKA: Autoimmune thrombocytopenia
Acute ITP:
Children, usually following viral infection
Believed that viral antigens adsorbed onto platelets
Chronic ITP:
Adults, usually women
Primary or associated with another autoimmune disorder
Appears related to antibody production against platelet surface antigens
Spleen: usually normal size, congested sinuses, enlarged follicles, megakaryocytes often found in sinuses, masses of agglutinated platelets
Bone Marrow: mild increased numbers of megakaryocytes, may have increased numbers of plasma cells
Hemorrhages in skin, epicardium, GI tract, urinary tract
70-80% patients markedly improve following splenectomy
Thrombotic Thrombocytopenic Purpura (TTP)
Thrombocytopenia, microangiopathic anemia, fever, transient neurologic deficits, and renal failure
Widespread microthrombi in arterioles, capillaries, venules
More common in young females (30's)
Once invariably fatal, but many survive now with therapy
Rx: steroids, splenectomy, exchange transfusions
Disseminated Intravascular Coagulation (DIC)
AKA: Consumption coagulopathy, defibrination syndrome
Acquired thrombohemorrhagic disorder 2° to a variety of diseases
Activation of clotting and thrombolytic cascades, with consumption of platelets, fibrin, and coagulation factors
Major initiating mechanisms are release of tissue factors and widespread damage to endothelium
Thrombi found (in order of frequency): brain, heart, lungs, kidneys, adrenals, spleen, liver

Thrombocythemia

Primary Thrombocythemia

AKA: Essential, idiopathic
Increased number and size of megakaryocytes in bone marrow, with peripheral thrombocytosis
Closely related to polycythemia vera, but lacks necessary red cell mass
Marrow is normal to hypocellular with mildly increased reticulin staining

Megakaryoblastic Leukemia

AKA: M7 AML
Related to acute myelofibrosis

MYELOFIBROSIS

Myeloid Metaplasia

AKA: Myelofibrosis; when etiology unknown: "agnogenic" or "primary"
Appearance of extramedullary hematopoiesis (in agnogenic form) or malignant myeloid cells in another organ, usually spleen, with fibrosis in the marrow
Primarily adults (mean age 60 yrs); younger age when follows polycythemia vera or CML
Hepatosplenomegaly 2° to extramedullary hematopoiesis
Spleen weight usually ~2 kg
Normal to increased neutrophil alkaline phosphatase activity (decreased in 90% patients with CML)

Marrow: 3 stages: hypercellular, patchy fibrosis, and obliterative myelosclerosis; degree of fibrosis does not always reflect duration of disease
Hypocellular marrow with condensed nuclear chromatin; megakaryocytes tend to persist but are dysplastic
Osteosclerotic changes present by X-ray in 40%
Extramedullary hematopoietic tumors not uncommon
Indolent, prolonged clinical course - median survival 10 yrs

Acute Myelofibrosis

AKA: Acute myelosclerosis, malignant myelosclerosis, acute myelodysplasia with myelofibrosis
Little to no RBC poikilocytosis, no splenomegaly
Marrow: hyperplasia of all three lines (usually most notable in megakaryocytes) with a significant left shift - PANMYEOLOID disorder
Nuclear chromatin more open (vs agnogenic)
Increased reticulin fibers - may be dense
Closely related to Acute Megakaryoblastic Leukemia
Rapid clinical course - median survival 2 yrs

HISTIOCYTOSES

Glycogen Storage Diseases

[See Congenital Syndromes Outline]

Hemophagocytic Syndrome

Associated with both viral (EBV, CMV, adenovirus) and bacterial infections, as well as some peripheral T-cell lymphomas
When occurs in children, high mortality rate
Generally peripheral pancytopenia
Bone Marrow: pink areas at low power, containing collections of mature histiocytes, many showing phagocytosis of erythroid cells (both mature and nucleated) - phagocytosis often more prominent on smears
Frequently decreased erythroid and granulocyte precursors
Spleen: may be enlarged with prominent histiocytic infiltrate
Coagulation abnormalities in most patients
Unlike histiocytic medullary reticulosis, cells have low N:C ratio and abundant cytoplasm with large vacuoles

Sinus Histiocytosis with Massive Lymphadenopathy

AKA: Rosai-Dorfman disease (1969)
Massive, painless, bilateral cervical LN enlargement; mean age 20 yrs
Nodes matted by perinodal fibrosis
Dilatation of lymphatic sinuses with architectural effacement
Numerous histiocytes with large vesicular nucleus and abundant clear lipid containing cytoplasm
Lymphocytophagocytosis common
Capsular and pericapsular inflammation/fibrosis
Histiocytes S-100 positive, KP-1 (CD68) positive
May involve extranodal sites (30%): eyes, ocular adnexae, upper respiratory tract, skin, CNS - spleen and BM spared

Langerhans' Cell Histiocytosis

AKA: Histiocytosis X, differentiated histiocytosis, Langerhans' cell granuloma, Hashimoto-Pritzker's (self limited, congenital)
Proliferation of Langerhans' cells: antigen presenting "histiocyte" with irregular nuclei containing prominent grooves and folds and abundant acidophilic cytoplasm; occasionally multinucleated
S-100, Leu-6 (CD1a), sialylated Leu-M1, and vimentin positive; usually LCA, EMA, Leu-M1 negative
Langerhans' cells of Histiocytosis X are CD4 positive (normal Langerhans' cells are not)
EM: Birbeck's granule (intracytoplasmic, pentalaminar rodlike tubular structure with a periodicity and a dilated terminal end: tennis racket)
Variable numbers of eosinophils, lymphocytes, plasma cells, neutrophils are present
Necrosis not uncommon
LN involvement (sinus distention with Langerhans' cells and eosinophils) can occur alone or as a part of a systemic disease
Marrow involvement late - generally focal with granulomatous appearance

<u>Unifocal Langerhans' Cell Histiocytosis</u>
AKA: Eosinophilic Granuloma
Benign - usually children and young adults, M>F
Usually in bone: skull, jaw, humerus, rib, femur
Asymptomatic to bone eroding with pain, pathologic fractures
May spontaneously heal by fibrosis
Very radiosensitive - excellent prognosis
No systemic involvement
Must follow to rule out early presentation of multiple form

<u>Multiple Bone Langerhans' Cell Histiocytosis</u>
AKA: Polyostotic EG, Hand-Schuller-Christian's Disease
Onset usually before age of 5
Fever, seborrhea like rash, frequent otitis media, URI's
50% have granulomatous involvement of posterior pituitary stalk or hypothalamus → diabetes insipidus
30% have orbital granulomas with exophthalmos
Good prognosis: spontaneous remission in half - other half respond to chemotherapy

<u>Multiple Organ Eosinophilic Granuloma</u>
Involves skeleton, skin, lungs
Poor prognosis for young (<18mos), hepatomegaly, anemia, marrow involvement, hemorrhagic skin lesions
Aggressive form of Multiple Bone EG

<u>Acute Disseminated Langerhans Cell Histiocytosis</u>
AKA: Progressive Differentiated Histiocytosis, Letterer-Siwe Syndrome
Progressive systemic proliferation of differentiated histiocytes
Infants and children under 3 yrs - may be present at birth
Initially fever, then diffuse maculopapular eczematous skin rash, then splenomegaly, hepatomegaly, lymphadenopathy, cystic lesions in skull, pelvis, long bones
Cells are mature, abundant cytoplasm, occasionally multinucleated
EM: occasional Langerhans' granules (rod-like tubular structures)
Minimal erythrophagocytosis
Infants <6mos generally rapid downhill course
Older children: 1-2 yrs without treatment, a little better with aggressive therapy

Histiocytic Medullary Reticulosis

AKA: Malignant Histiocytosis
When in marrow and blood, "leukemic reticuloendotheliosis"
Progressive systemic proliferation of somewhat immature, morphologically atypical histiocytes and/or precursors
Usually children and young adults
Patient usually acutely ill when first seen
Fever, lymphadenopathy, constitutional symptoms early
Lymphadenopathy, hepatomegaly, splenomegaly, skin involvement common
Anemia, leukopenia, thrombocytopenia, increased serum ferritin
Erythrophagocytosis common, plasma cells common
Infiltration of capsule rare - individual cells
Lysozyme (muramidase), alpha-1-antichymotrypsin positive
Usually rapidly fatal (2/3rds die within months)

True Histiocytic Lymphoma

Very rare - only 6 well documented cases in the literature
All cases are male
No common histologic features
Need markers and absence of T or B rearrangements

SYSTEMIC MASTOCYTOSIS

Round to spindled, monotonous, polygonal cells with inconspicuous nuclei, clear or granular cytoplasm, well defined cell outlines; granules stain with Giemsa, toluidine blue, Leder
Scattered eosinophils usually present
Median age: 75 w/o skin lesions; 45 with
LN: partial or complete effacement
Spleen: always involved
• Ill defined granuloma like nodules grossly, scattered throughout parenchyma
• Angiocentric fibrotic nodules with small clusters of mast cells embedded within
Skin: Urticaria Pigmentosa
Osteoblastic and osteoclastic lesions
Marrow: most frequent non-cutaneous site (90%); increased reticulin, focal (more common) or diffuse involvement; any distribution, both monocellular and polycellular [eosinophils, lymphocytes, histiocytes] lesions
Horny et al classification:

Type	Marrow Involvement	Uninvolved Marrow	Associations
I	Focal	Normal	Urticaria Pigmentosa
II	Focal	Granulocytic hyperplasia	Myeloproliferative disorders
III	Diffuse	-	Mast Cell Leukemia

Types II and III have more aggressive course than type I

TUBULAR GASTROINTESTINAL TRACT

(Esophagus, Stomach, Small Intestine, Colon, Appendix)

Disorders Common to All Levels of the GI Tract

Carcinoid Tumors

- Tumors of "APUD-cells" (amine precursor uptake and decarboxylation)
- All are potentially malignant tumors
- More carcinoid tumors occur in the GI tract than elsewhere
- 60-80% occur in "midgut", i.e., appendix or ileum; 10-20% in "hindgut" (mostly rectum), 10-25% in "foregut" (stomach or proximal duodenum)
- Tumors in appendix and rectum are rarely malignant, despite extensive local spread
- Tumors in the duodenum tend to be low grade and may be associated with Zollinger Ellison syndrome (gastrinoma) or neurofibromatosis (somatostatinoma)
- Tumors in ileum, stomach, and colon are frequently malignant
- Most common malignant tumor of the small bowel
- Gastric and ileal lesions are frequently multicentric
- By convention, 0.1 mm is division between microcarcinoid (hyperplasia) and carcinoid (neoplasia); submucosal invasion warrants diagnosis of carcinoid regardless of size
- Usually small, well defined submucosal elevations, often yellowish in color, covered by a flattened mucosa which may ulcerate or form a polypoid projection
- Monotonous round cells with pale pink cytoplasm, minimal mitotic activity or pleomorphism; infiltrating tumor cells induce a desmoplastic response
- Growth pattern tends to vary with location: trabecular or microglandular in the foregut and hindgut, solid nests or insular in the midgut
- All are argyrophilic (Grimelius stain); midgut carcinoids are also usually argentaffilic (Fontana-Masson)
- Immunoreactive for keratin, CEA (apical or luminal), NSE, chromogranin, synaptophysin, Leu 7, serotonin
- Usually S-100 negative except in the appendix
- Often are multihormonal by special stains
- Indicators of aggressive behavior include size >2cm, spread beyond submucosa (except in the appendix), mitoses, ulceration, necrosis
- 5 yr survival drops markedly once tumor invades into serosa or beyond (85% down to 5%)
- When >2cm, 2/3 will have already metastasized; when <1cm, <5% will have metastasized

Classic Carcinoid
- Solid nests of small monotonous cells
- Often invade nerves, muscle, lymphatics, even serosa

Adenocarcinoid (tubular adenocarcinoid)
- Glandular formation without solid nests; abundant stroma
- Often misdiagnosed as adenocarcinoma
- Usually lack seratonin; often positive for glucagon
- Seen in small intestine and appendix (tip)
- Prognosis same as classic type and depends on location

Atypical Carcinoid
- Obvious endocrine features but with invasion, necrosis, mitoses
- Better prognosis than adenocarcinoma, but worse than classic carcinoid

Mucinous Carcinoid / Clear Cell Carcinoid
- Essentially unique to the appendix (see below)

CARCINOID SYNDROME
- Paroxysmal flushing, asthma-like wheezing, right sided heart failure, attacks of explosive watery diarrhea, abdominal pain, edema
- Seen in 1% patients with carcinoid tumors, 10% of those with gastrointestinal carcinoids
- Principle agent responsible for symptoms appears to be serotonin
- Serotonin (5-hydroxytryptamine; 5-HT) formed by hydroxylating tryptophan to 5-hydroxytryptophan (5-HTP) and then decarboxylating to 5-HT
- Foregut carcinoids lack the decarboxylase, and therefore produce mostly 5-HTP rather than 5-HT
- Liver usually metabolizes 5-HT and 5-HTP to 5-HIAA; for distal gastrointestinal carcinoids to produce the carcinoid syndrome, generally need liver metastases

Smooth Muscle Tumors

- Gastric, esophageal, and rectal tumors are more likely to be benign, small intestinal and proximal colonic tumors are usually malignant

Leiomyoma
- Small, well defined, <4 cm
- Common, often multiple
- May ulcerate overlying mucosa - still benign
- Smooth muscle tumors in the stomach often have unusual features: extreme cellularity, occasional large cells with bizarre hyperchromatic nuclei, marked diffuse vascularity, palisading of nuclei, clear cytoplasm
- ≤1 mitosis per 10 high power fields
- Myofibrils may be sparse or even absent - some prefer to refer to these as *Stromal Tumors*

Smooth Muscle Tumors of Undetermined Malignant Potential
- AKA: "STUMP"
- Generally high cellularity, necrosis, hemorrhage
- Fewer than 5 mitoses per 10 high power fields
- Some will behave in a malignant fashion, others benign

Leiomyosarcoma
- 5 or more mitoses per 10 high power fields
- Usually >5cm with areas of necrosis, hemorrhage, extreme cellularity, and marked atypia
- Often sufficiently poorly differentiated by be diagnosable as a smooth muscle tumor only by immunostain - may even be negative for smooth muscle actin: "Malignant Stromal Tumor"
- Most commonly metastasize to liver and lung
- Metastases can develop ≥10 yrs after removal of primary

Leiomyoblastoma
- AKA: clear cell or epithelioid leiomyoma / leiomyosarcoma
- Round cells with a central nucleus and abundant clear cytoplasm (probably fixation artifact)
- Majority are benign, some are malignant
- Almost all of these occur in the stomach; malignant ones tend to be on the posterior wall (vs anterior), have smaller cells, anaplasia, alveolar arrangement, less reticulin, and *higher mitotic rate*

Lymphoproliferative Disorders

- 90% of GI tract lymphomas are diffuse, 10% are follicular
- Most are large B-Cell lymphomas; second most common type is small cleaved

Lymphomas in the GI tract tend to remain localized for prolonged periods before progressing
Overall survival good compared to carcinomas (5yr=45%); however, once becomes disseminated, essentially always fatal within 2yrs
Lymphomas used to be classified as "Western Type (Sporadic)" or "Mediterranean"; the former included large cell lymphomas, Burkitt's, and others; the latter most closely approximated what are now called MALT lymphomas
Currently, it seems more reasonable to use the conventional (although constantly evolving) classification for nodal lymphomas to subdivide GI tract lymphomas, with some special considerations

Localized Lymphoid Hyperplasia
AKA: "Pseudolymphoma" in the stomach, "rectal tonsil" in the rectum
Lymphoid proliferation usually is diffuse (stomach, proximal small intestine, rectum), although can be follicular (nodular) in the terminal ileum and appendix
Distinguish from "true lymphomas" by polymorphous infiltrate, presence of well formed reactive lymphoid follicles, proliferation of vessels, associated dense collagenous fibrosis, or ulceration (more common when benign)
Many of these may actually be low grade MALT lymphomas while still in their reversible state (see below)

Diffuse Large Cell Lymphoma
Most common type - almost all are B-Cell; may show immunoblastic cytology
Men affected more commonly than women
Usually found in the stomach (50-60%); 20-30% in the small intestine (usually ileum), 10-20% in the colon
Often are Ki-1 (CD30) positive
Most of these may represent the high-grade form of MALT lymphoma

Mucosal Associated Lymphoid Tissue (MALT) Lymphomas
Men and women affected equally
Cell morphology varies from diffuse small cleaved to intermediate "centrocytic" type
These lesions appear to initially represent an over-reaction to persistent or recurrent antigenic stimulation (e.g., Helicobacter pylori in the stomach); at this stage, the "lymphoma" (since often monoclonal) is treatable and reversible by elimination of the antigen (e.g., antibiotics); later, with dissemination, disease becomes antigen independent and although usually indolent, is no longer reversible
Lymphoepithelial lesions common (distinguishing feature) as are reactive follicles with germinal centers and plasma cells
Low and High grade types exist, the later often arising in the setting of a lower grade lesion

Immunoproliferative Small Intestine Disease (IPSID)
AKA: Mediterranean lymphoma
Probably a subtype of the MALT lymphomas, in that this disease appears to be reversible with antibiotics or antihelminthics in early stages, but not later
Presents at 40-45yrs usually with malabsorption
Usually involves the proximal small bowel
Diffuse proliferation in the lamina propria of initially mature plasma cells and lymphocytes associated with increased serum IgA levels
When undergoes transition to a lymphoma, often a large cell histology with immunoblastic and plasmacytic features and a rapid downhill course

Multiple Lymphomatous Polyposis
Extranodal mantle zone lymphoma involving the GI tract
Accounts for <5% of all GI lymphomas; most common in stomach and small intestine
Proliferation of intermediate size lymphocytes, usually straddling the muscularis mucosa
Distinguish from MALT lymphomas by lack of lymphoepithelial lesions and absence of germinal centers

Burkitt's Lymphoma
Non-endemic form usually affects older individuals and involved the ileum
[See Hematolymphoid Outline]

Enteropathy Associated T-Cell Lymphoma
Wide age range (30-70yrs)
Usually preceded by a 20-30 yr history of malabsorption, most commonly celiac sprue
Seen in association with the 10% of celiac sprue patients who do NOT have antibodies to alpha-gliatin
Most commonly proximal small bowel
Often CD30+ (large, bizarre multinucleated cells - mimics Hodgkin's disease)

ESOPHAGUS

NORMAL ANATOMY
Extends from C6 to T11 or T12
10-11 cm long in newborn, 25 cm in adult (on average)
Endoscopists measure distances in the esophagus from the incisors (the gastroesophageal junction is therefore usually located at 38-41cm)
Three points of luminal narrowing:
• Cricoid cartilage
• Where left mainstem bronchus crosses anterior to the esophagus (midway down)
• Diaphragm
Upper and lower sphincters defined manometrically; no mophological landmarks
Outer longitudinal muscle layer is striated for the first 6-8 cm
No serosa - lesions can easily spread into mediastinum

Malformations (Congenital & Acquired)

Tracheoesophageal Fistulas
[See Lung Outline]

Heterotopic Tissue
Gastric Mucosa
Seen in both children and adults, most commonly just distal to cricoid cartilage
May be detected as a filling defect
Resembles gastric mucosa grossly - may ulcerate
Mostly mucin secreting cells; chief and parietal cells rare
May give rise to adenocarcinoma

Salivary Gland
Rare; Middle or distal esophagus

Esophageal Rings / Webs

Either fold of mucosa (most commonly) or localized annular thickening of muscle
Generally designated webs when above the aortic arch and rings when below
Often asymptomatic or episodic dysphagia

Webs
Usually women, usually >40 yrs old, usually upper esophagus
Can be seen in association with iron deficiency anemia (Plummer-Vinson syndrome)

Rings
AKA: Schatzki's rings
Found in distal 5 cm of esophagus, usually at squamo-columnar junction (squamous mucosa on upper surface, gastric on lower)
2-4 mm thick, protrude <5 mm

Diverticula

Zenker's (Pulsion)
Upper esophagus at junction with pharynx

Traction
Usually lower third of esophagus near hilum of lungs

Hiatal Hernia

Sac-like dilatation of stomach present above the diaphragm

Sliding Hernia (90%)
Congenitally short esophagus or acquired from esophageal scarring induced with traction on the stomach
Extent of herniation and degree of symptoms accentuated by swallowing
Predisposes to reflux

Rolling (Paraesophageal) Hernia (10%)
Portion of cardia protrudes through the diaphragm into the thorax along side the esophagus
Vulnerable to strangulation and infarction

Lacerations

AKA: Mallory-Weiss Tears
Linear irregular lacerations oriented longitudinally usually at the GEJ
Occur following fits of vomiting; most commonly in alcoholics
May involve only mucosa or even the full wall
Usually not massive, but do account for 5-10% of cases of massive hematemesis

Varices

Dilatation of vascular channels (coronary veins) in lower esophagus to divert flow out of the portal system in patient with portal hypertension, usually secondary to cirrhosis
Difficult to visualize post-mortem because varices collapse
Massive hematemesis
40% fatality rate; of those who survive, half will re-bleed, and 40% of those will die

Esophageal Dysmotility

Achalasia
Motor dysfunction resulting in: decreased peristalsis, incomplete relaxation of LES, increased basal LES tone
Progressive dilatation of the esophagus above the LES
In sporadic form, myenteric plexus may be absent from upper portion of esophagus but is present in region of LES
Cause is usually unknown
2-7% of patients will develop esophageal carcinoma
Can occur in Chagas' disease, in which the trypanosome infection causes destruction of the myenteric plexus of the esophagus, duodenum, colon and ureter

Plummer-Vinson Syndrome
Anemia, atrophic gastritis, dysphagia; usually affects women
Increase risk of squamous cell carcinoma of the upper esophagus, oropharynx, or tongue
Associated with upper esophageal webs

Progressive Systemic Sclerosis
Part of CREST syndrome (calcinosis, Reynaud's, esophageal dysmotility, sclerodactyly, telangiectasias)
Vasculitis with muscle wall degeneration

Idiopathic Muscular Hypertrophy
Primary abnormality of neural control of the distal esophageal musculature, resulting in esophageal spasm
Affects predominantly inner circular muscle layer

Leiomyomatosis

Inflammatory Lesions

Reflux Esophagitis

Produced by recurrent or prolonged reflux; promoted by elevated acidity and disordered esophageal motility
Often associated with sliding hiatal hernia, Zollinger-Ellison syndrome, scleroderma
Histologic changes include basal hyperplasia (>15-20% of the epithelial thickness), elongation of the vascular papillae to >1/2-2/3 mucosal height, intraepithelial eosinophils, numerous intraepithelial neutrophils

Infectious Esophagitis

Bacterial

Viral
CMV: Submucosal cells with inclusions
Herpes: Epithelial cells with ground-glass nuclei; often form multinucleated giant cells

Fungal
Candida: White plaques usually in middle to distal esophagus; budding blastospores and pseudohyphae
Mucormycosis
Aspergillosis

Other Causes of Esophagitis

Ingestion of irritants
Prolonged gastric intubation
Radiation / Anticancer therapy
Crohn's disease
Pemphigus Vulgaris
Uremia
Graft-vs-Host disease

Barrett's Metaplasia

Conversion of stratified squamous epithelium to columnar epithelium in the lower portion of the esophagus
Complications: ulceration, stricture, adenocarcinoma (~10%)
Barrett's Type I: no residual squamous islands are present
Barrett's Type II: squamous islands persist among the columnar mucosa

TYPES

Specialized Type (Intestinal or Colonic)
Goblet cells and columnar cells (goblet cells contain sialomucin [acid mucin] and stain positively with Alcian blue at pH 2.5)
Most common type seen in adults
Incomplete: gastric foveolar cells intermixed with intestinal goblet, absorptive, Paneth and endocrine cells
Complete: Only intestinal-type cells present

Cardiac or Junctional Type
- Almost entirely mucin cells
- Generally need to see ≥3 cm above the GEJ (i.e., <35cm) to be comfortable calling this more than an irregular Z-line
- Some pathologists do not consider this Barrett's at all, but rather simply a very irregular Z-line

Atrophic Fundal Type
- Contains few parietal and chief cells
- Rare - usually the type seen in children

DYSPLASIA
- Hyperchromatic and crowding nuclei = low grade dysplasia
- Glandular distortion and nuclear hyperchromasia extending to upper portions of epithelium = high grade dysplasia
- In general, when high grade dysplasia present in a biopsy, there is a 70% chance that carcinoma is already present

Neoplasms

Benign Lesions

- Uncommon; usually small and asymptomatic

Inflammatory Fibrous Polyp
- AKA: fibrovascular polyps, inflammatory pseudotumors
- Usually pedunculated and solitary
- 85% located in upper third of esophagus
- Submucosal proliferation of vascularized, inflammed fibrous stroma with eosinophils frequently present
- Similar to lesion in stomach

Squamous Papilloma
- Usually lower esophagus; men over 40yrs; may be multiple

Adenoma
- Arises in Barrett's mucosa

Leiomyoma

Granular Cell Tumor

Localized Amyloidosis

Squamous Cell Carcinoma

- 80-85% of esophageal carcinomas
- 10% of all cancers of the GI tract
- More common among blacks and males
- Risk factors: lye strictures (1000x risk), chronic *alcohol* (20-30x risk, especially hard liquor) and *tobacco* (10-20x risk) use, consumption of foods rich in Aspergillus, nitrites, or nitrosamines; chronic vitamin deficiency, achalasia, esophagitis, Plummer-Vinson syndrome
- 20% upper third, 50% middle third, 30% lower third
- May present as hemorrhage, sepsis, tracheoesophageal fistula
- Most commonly fungating polypoid lesion (60%), less commonly necrotic deeply ulcerating lesion (35%), rarely diffusely infiltrating wall with thickening, rigidity, luminal narrowing
- Extensive circumferential and/or longitudinal spread common due to rich lymphatic supply
- Usually well into wall or beyond by time of diagnosis; only about 1/2 cases ressectable
- 30% 1 yr survival, 5-10% 5 yr survival

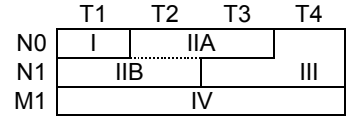
Superficial (early) Squamous Carcinoma
- Limited to mucosa or submucosa (Stage I)
- May be inapparent grossly
- 5yr survival good: 65-90%

Verrucous Carcinoma
- Rare
- Predominantly exophytic growth with pushing margins
- Slow growing; rarely if even metastasizes

Epidermoid Carcinoma with Spindle-cell Stroma
- AKA: pseudosarcoma, carcinosarcoma, spindle cell carcinoma
- Usually large (~6cm) polypoid lesion of the middle to lower esophagus, often with very inconspicuous epithelial component which is usually squamous
- Spindle component resembles MFH; may have focal cartilage or bone or skeletal muscle differentiation
- Prognosis actually better than traditional squamous cell carcinoma: 3 yr survival ~40%

STAGING

T1	lamina propria or submucosal invasion
T2	muscularis propria invasion
T3	adventitial invasion
T4	adjacent structures
N1	regional nodes involved



Adenocarcinoma

- 5-10% of esophageal carcinomas
- Almost always white; M:F=5:1; median age 50
- Usually middle or lower third, often GEJ
- Vast majority probably arise in setting of Barrett's mucosa
- Gross: mass or nodular elevation in otherwise intact mucosa
- Histologic types:
  - Intestinal: as seen in stomach or intestines
  - Diffuse: diffuse infiltration of mucin producing cells
  - Adenosquamous: mixture of squamous cell and adenoCa
- Same staging as for squamous cell carcinoma
- As with SCC, most are high stage at diagnosis

Other Tumors of the Esophagus

Basaloid Type Carcinoma
- Thought by many to be a type of adenoid cystic carcinoma
- Small, blue cells with peripheral pallisading, round glandular lumina, abundant basal lamina material
- Extremely aggressive behavior

Small Cell Carcinoma
- Highly malignant; neuroendocrine carcinoma
- Usually fungating grossly
- Distinguish from better differentiated carcinoid tumor

Other Malignant Tumors
- Adenosquamous carcinoma
- Mucoepidermoid carcinoma
- Leiomyosarcoma
- Malignant Melanoma
- Malignant Lymphoma
- Plasmacytoma

STOMACH

Normal Anatomy

Mucosal surface and gastric pits lined by surface mucous cells
Neck mucous cells are the progenitor cells for the glandular epithelium and the pit and surface epithelium
Glands of cardia and antrum are similar to neck mucous cells
The fundic glands contain the parietal (HCl and intrinsic factor) and chief (pepsinogen) cells
The antrum contains endocrine cells, variably designated as enteroendocrine, enterochromaffin, Kulchitsky, or APUD (amine precursor uptake and decarboxylase) cells

Malformations (Congenital and Acquired)

Hiatal Hernias

(see above under Esophagus)

Heterotopic Pancreas

Relatively common: 1-2% of the general population
Dome-shaped mass (1-2cm), nipple-like projection, or symmetric cone
75-85% occur in submucosa, rest in muscularis
61% are in the antrum, 24% in the pylorus
Endocrine pancreas (islets) present in only one third

Pyloric Stenosis

Congenital Hypertrophic Pyloric Stenosis
Familial malformation; seen in 1/300-900 births; M:F=4:1; most common in first born
Hypertrophy and perhaps hyperplasia of the circular muscle of the muscularis propria of the pylorus
Present with regurgitation and vomiting in 2nd or 3rd week
Acquired Pyloric Stenosis
Long-term complication of chronic antral gastritis and/or peptic ulcer disease
Can also be seen in carcinomas of the pylorus, head of pancreas, or lymphomas

Gastric Antral Vascular Ectasia

AKA: "Watermelon stomach"
Persistent blood loss; may be severe
Prominent radiating mucosal stripes arising in the pylorus
Unknown etiology

Inflammatory / Non-Neoplastic

Acute Gastritis

Acute mucosal inflammation, usually transient
Continuum including acute gastritis, acute hemorrhagic gastritis, acute erosive gastritis, and acute stress erosions
Usually only partial erosion of the mucosa, not penetrating the muscularis mucosa
Often accompanied by focal hemorrhage into mucosa
In severe forms can have sloughing of the mucosa and extensive lamina propria hemorrhages
Can be caused by excessive EtOH consumption, chronic aspirin (of other non-steroidal anti-inflammatory drug) use, heavy smoking, shock, severe stress (see below)
When severe (acute hemorrhagic erosive gastritis), mortality can exceed 50%

Chronic Gastritis

Infiltration of lamina propria by lymphocytes and plasma cells combined with varying degrees of gastric atrophy
Many classification schemes used
Immune Gastritis (Type A; Fundal)
Involves fundic mucosa preferentially; antrum usually spared
Patients have circulating antibodies to parietal cells and/or intrinsic factor
Hypochlorhydria, loss of parietal cells, hypergastrinemia
Significant gastric atrophy and intestinal metaplasia
10% will develop pernicious anemia after several years
Associated with other autoimmune disorders (Hashimoto's thyroiditis, Addison's disease)
Non-Immune Gastritis (Type B; Antral)
No associated parietal cell antibodies or pernicious anemia
Four times more common than Type A
Helicobacter pylori implicated in many cases as causal agent. It is present on the surface of the epithelium and is NOT seen in areas of intestinal metaplasia
• Hypersecretory Subtype:
Restricted to the Antrum; usually minimal fundic atrophy
Hyperacidity, often leading to duodenal ulcers
Normal gastrin levels
• Environmental Subtype:
Most common form of chronic gastritis
Involves both fundus and antrum
Initially patchy in antrum, later diffuse in antrum and fundus
Strong association with atrophy, metaplasia, carcinoma
Begins as superficial gastritis, progresses to atrophic
Etiologically related to EtOH use, but NOT to smoking

HISTOLOGIC CLASSIFICATION

Chronic Superficial Gastritis
Inflammation confined to superficial mucosa (upper 1/3)
Mild flattening of mucosa
Chronic Atrophic Gastritis
More obvious thinning of mucosa - may appear red grossly since submucosal vessels more visible
Full thickness inflammation involving the glandular portion of mucosa as well as more superficial areas
Graded mild, moderate, severe based on thickness of glandular portion in relation to mucosa
With atrophy, glands become cystically dilated, commonly metaplastic (see below); in type A, there is an absence of parietal cells
Gastric Atrophy
Thinning of gastric mucosa in absence of inflammation, usually seen as an end stage of chronic gastritis

SYDNEY SYSTEM

Need at least two biopsies each from the fundus and antrum
Diagnosis is given a multi-part name including following:
Etiology: (if known) e.g., autoimmune
Type: Acute, chronic, special (granulomatous, eosinophilic)
Distribution: antral, fundic, or pangastritis
Graded Variables: inflammation, activity (mild=1/3 pits, moderate=1/3-2/3 pits, severe=>2/3 pits), metaplasia, atrophy, Helicobacter pylori density

Specific Gastridities

Granulomatous Gastritis
Seen in sarcoidosis but also as an isolated disorder
Generally 40yrs or older
?TB, mycosis, Crohn's
Lymphocytic Gastritis
T-Cell infiltration of foveolae and surface epithelium
Frequently seen in patients with Celiac sprue

Eosinophilic Gastritis
- Infiltration of the mucosa and sometimes submucosa by eosinophils
- Usually involves distal stomach and proximal duodenum
- Necrotizing vasculitis may be present
- Probably allergic reaction to ingested material

Gastritis in Immunosuppressed
- CMV, HSV, cryptosporidiosis, mycobacteria

Gastric Ulcers

Stress Ulcers
- Multiple small lesions, mainly gastric, sometimes duodenum
- Shedding of superficial epithelium to full thickness ulceration
- Occurs in setting of "severe stress", e.g. shock, sepsis, severe trauma, etc.
- Pathogenesis usually unclear
- Cushing's Ulcers: in setting of elevated intracranial pressure; increased acid secretion due to increased vagal tone
- Steroid Ulcer: following steroid use
- Curling's Ulcers: associated with extensive burns

Peptic Ulcers
- Chronic, usually solitary lesion (80%) occurring at any level of GI tract exposed to acid-peptic juices
- Most commonly 1st portion duodenum (~80%), antrum of stomach (~20%), Barrett's esophagus, Meckel's
- Remitting and relapsing course; M:F=3:1 (duodenal); 1.5-2:1 (gastric); pain after eating
- 50% <2 cm, 75% <3 cm, 10%> 4 cm
- Oval, sharply delimited defect with tendency for overhanging mucosal margins, especially proximally
- Minimal if any heaping up of margins (common in carcinoma)
- Gastric folds radiate out from ulcer
- Nearly all patients have concurrent chronic antral gastritis (e.g., Helicobacter pylori); those who don't are usually habitual aspirin users
- Fatal in ~5%: 70% due to perforation, 10% due to bleeding
- Duodenal:
  - Genetic influences appear to be involved
  - Increased incidence in alcoholic cirrhosis, chronic renal failure, COPD, hyperparathyroidism
  - Increase in both the basal and stimulated level of acid secretion, and more rapid gastric emptying are common
  - Anterior wall more commonly than posterior
- Gastric:
  - Genetic influences to not appear to be involved
  - Low to normal acidity; probably abnormal mucosal resistance
  - Usually lesser curve
  - 1-3% will develop gastric carcinoma

Gastric Hyperplasias

- AKA: Hypertrophic Gastritis
- Neither hypertrophic nor inflammatory - hyperplastic
- Giant, cerebriform enlargement of the rugal folds
- Roentographically, can be confused with lymphoma

Menetrier's Disease
- Hyperplasia of the surface mucous (foveolar) cells with tortuous, cork-screw cystic dilatation extending to the base of the glands
- Hypochlorhydria, often hypoproteinemia
- Usually chronic and severe; progressive
- Antrum usually uninvolved
- May show slightly increased risk of carcinoma

Zollinger-Ellison Syndrome
- Hyperplasia predominantly of the glandular cells (mainly parietal cells which tend to crowd out the chief cells; sometimes enterochromaffin-like cells also proliferate) secondary to gastrin secreting tumor (20% are associated with Multiple Endocrine Neoplasia I)
- Gland lumen size is normal; no cyst formation
- Hyperchlorhydria

Hyperplasia of Parietal and Chief Cells
- AKA: Hypertrophic Hypersecretory Gastropathy
- Two variants of unknown etiology:
  - Protein loosing:
    - Patient's are often hypergastrinemic
    - Histology mimics that of Menetrier's disease
  - Non-protein loosing:
    - Patients are hyperchlorhydric but NOT hypergastrinemic
    - Histology mimics Zollinger-Ellison syndrome

Metaplasia

- Most commonly, but not exclusively, seen in the setting of atrophic gastritis

Pyloric Metaplasia
- With age, fundic gland mass decreases and is replaced by pyloric glands

Ciliated Cell Metaplasia

Intestinal Metaplasia
- Replacement by mucosa with goblet cells, absorptive cells, Paneth cells, etc.
- Small bowel (intestinal) and large bowel (colonic) types
- Both may be either complete or incomplete:
  - Complete (Type I): Sialomucin predominates (goblet cells)
  - Incomplete (Type II): absorptive cells absent; gastric foveolar cells retained
    - Type IIA: foveolar cells contain neutral mucins
    - Type IIB: foveolar cells contain sulphomucins
- When incomplete, special stains needed to detect the different staining properties of the mucins

Polyps

Hyperplastic (85%)
- AKA: Inflammatory, regenerative
- Exaggerated regenerative response to injury
- Usually multiple, most sessile, <1 cm, randomly distributed
- Elongated and distorted glands, tubules, microcysts with a single layer of regular cells, predominately foveolar
- Stroma often inflamed, edematous, with patchy fibrosis
- Often seen coexisting with gastric carcinoma elsewhere

Adenomatous (10%)
- Neoplastic lesion
- Usually single, antral, up to 3-4 cm; larger are pedunculated
- Closely packed gland-like tubular structures or villi with dysplastic cells - probably arise in intestinal metaplasia
- Tubular, villous, and tubulovillous varieties; 10% are flat or depressed (higher rate of malignant transformation)
- Estimated risks of synchronous and metachronous gastric adenocarcinomas has varied widely among different studies: 4-50% and 3-75%, respectively

Fundic Gland Polyps
- Multiple small polyps with cystically dilated fundic glands forming microcysts lined by fundic epithelium
- Can arise secondary to omeprazole therapy

Inflammatory Fibroid Polyp
- Can occur anywhere in GI tract, ~75% occur in stomach, usually the antrum
- Mean age 53; presents with pain and/or obstruction
- Proliferation of loose connective tissue in the submucosa with small caliber thin walled vessels surrounded by hypo-cellular stroma; inflammatory cells - can become quite large
- Overlying mucosa is stretched and eventually ulcerates

Hamartomatous
- Peutz-Jeghers
- Juvenile (retention) polyps

Polypoid Mucosal Prolapse
- AKA: polypoid cystic gastritis; polypoid hypertrophic gastritis
- Occurs on the gastric side of a gastroenterostomy stoma
- Same histology as hyperplastic polyps

Neoplasms

STAGING

T1 lamina propria or submucosal invasion
T2 muscularis propria or subserosal invasion
T3 penetration of serosa
T4 adjacent structures
N1 perigastric nodes within 3cm of primary involved
N2 perigastric nodes >3cm from 1° or other local LN's

	T1	T2	T3	T4
N0	IA	IB	II	IIIA
N1	IB	II	IIIA	IIIB
N2	II	IIIA	IIIB	IV
M1	IV			

Adenocarcinoma

85-90% of gastric malignancies
Incidence particularly high in Japan, Chile, Scotland, Finland; lower in US, UK, Canada, Greece; more common in blacks
Overall incidence in US has been steadily dropping over past several years, but the incidence of carcinoma in the cardia ins increasing; currently, 50% of gastric cancers in white men are in the cardia (M:F=8:1)
Risk factors: dietary/environmental (still unidentified) [salt, low intake of animal fat/protein, complex carbohydrates, nitrates]; chronic gastritis and pernicious anemia; gastric adenomatous polyps
Accompanied by hypochlorhydria in 85-90% cases, and chronic atrophic gastritis is usually present
Lesser curvature involved 3x more frequently than greater
Cells generally positive for keratin, EMA, CEA
Often present in advanced stage; may present with metastases; only about 50% resectable at diagnosis; 80-90% have local LN metastases
Virchow's node: isolated metastasis to left supraclavicular LN (also called Trousseau's sign)
Overall 5yr survival still 5-15%

Superficial Spreading (Early) Carcinoma
10-35% of gastric carcinomas
Limited to mucosa and submucosa
Less than 20% have LN metastases; 5 yr survival 80-95%

HISTOLOGIC TYPES:

Intestinal Type
AKA: Expanding carcinoma
Relatively cohesive mass of tumor cells; pushing margins
May be nodular, polypoid, or ulcerated
Usually well demarcated grossly
Can be composed of foveolar cells, intestinal columnar, and/or goblet cells
Arise from metaplastic epithelium
Used to be the more common type, but incidence has been decreasing relative to the diffuse type

Diffuse Type
AKA: Infiltrative carcinoma; Linitis Plastica
Individually invading tumor cells with intracellular mucin vacuoles, often forming signet ring cells
Extent of tumor cannot be appreciated grossly
Does not appear to be related to environmental factors; occurs at a younger age than the intestinal type; incidence has been steady for many years
Marked degree of inflammation and desmoplasia and the inconspicuous tumor cells may lead to missed diagnosis

PROGNOSTIC FACTORS

Good: distal gastric involvement (vs proximal), pushing margin, small size, intestinal type, inflammatory infiltrate
Poor: young age, deep invasion, infiltrative margin, diffuse type, positive margins, LN involvement

METASTASES

Liver metastases most common with intestinal type
Diffuse type: peritoneum, lung, adrenal gland, ovary
Krukenberg Tumor: bilateral ovarian involvement

Carcinoid Tumors

[See also beginning of this Outline]
5% of GI carcinoids occur in stomach
Slow growing, but always malignant
When metastasize (30%), usually regional LNs only
Much better prognosis than adenocarcinoma, but clearly more aggressive than carcinoid tumors of the appendix
Two Subtypes:
• G-Cell Tumor (gastrinoma): antral, immunoreactive for gastrin, sometimes associated with peptic ulcer
• Enterochromaffin-like cells (ECL tumor): multiple, often polypoid, fundic; believed to result from gastrin stimulation

Other Carcinomas

Small Cell Carcinoma
Highly malignant; neuroendocrine carcinoma
Adenosquamous and Squamous Cell Carcinoma
Less than 1% gastric carcinomas
Mucinous Carcinoma
Relatively good prognosis
Hepatoid Adenocarcinoma
Parietal Gland Carcinoma

Lymphoma

[See also beginning of this Outline]
3-5% of all gastric malignancies
Most common site for primary lymphomas in GI tract
Some of the MALT type lymphomas are associated with Helicobacter pylori
Much better prognosis than gastric adenocarcinomas
Can be treated with radiation alone - if transmural, risk gastric perforation

Smooth Muscle Tumors

[See also beginning of this Outline]
Most smooth muscle tumors in the stomach are benign
Smooth muscle tumors in this location often have bizarre features (extreme cellularity, occasional large cells with bizarre hyperchromatic nuclei, marked diffuse vascularity, palisading of nuclei, clear cytoplasm) and still be benign; base determination on mitotic rate

Other Tumors

Glomus Tumor
Clear epithelioid cells arranged around dilated vessels
Morphologically similar, perhaps histogenetically, to leiomyoblastoma
Lipoma
Granular Cell Tumors
Neurofibroma, Schwannoma
Usually well demarcated, firm, <4 cm; arise in muscularis
May be leiomyomata with minimal to no myofibers
Many prefer to refer to all such tumors as *stromal tumors*

SMALL INTESTINE

Normal

Length: in an adult, averages 6-7 meters (20 feet)
Epithelium regenerates every 72-96 hrs (3-4 days)
Cell types: Undifferentiated, Paneth, Goblet, endocrine

Malformations (Congenital and Acquired)

Atresia/Stenosis

Atresia: failure to canalize; blind pouch or fibrous cord
85-90% are solitary
Radiographically: "string of pearls"
May be related to in utero mechanical injury
Types of Atresia:
- Type I: 20%, continuous bowel lumen interrupted by a mucosal septum and an intact mesentery
- Type II: 35-40%, blind proximal and distal ends connected by a fibrous cord; mesentery intact
- Type III: 40-45%, blind proximal and distal ends; unattached
- (Type IV: subset of Type III (~1/3) with V-shaped mesenteric defect)

"Apple Peel" atresia: interruption in distal duodenum or proximal jejunum with absence of the dorsal mesentery and obliteration of the superior mesenteric artery; the distal small intestine is shortened and has a spiral configuration
Stenosis: narrowing of canalized lumen (by fibrosis, stricture)

Abdominal Wall Defects

Omphalocele
1/5000 live births
Amnion enclosed extra-abdominal sac contains intestines and sometimes the liver
Arises in midline and involves the umbilical stump
Failure of intestines to return to abdomen at 10-11 weeks
50% mortality

Gastroschisis
1/12,000 live births
Non-enclosed paraumbilical abdominal wall defect
Abdominal contents (usually just bowel) externalized

Diverticula

Mesenteric
Congenital defects in the muscular wall (thinned)
Pseudodiverticula (muscle wall not present in outpouching)
Rare; most common in duodenum

Meckel's
Persistence of omphalomesenteric (vitelline) duct (connection between GI tract and umbilicus present at 4wks and which normally becomes obliterated to form a fibrous band which is subsequently absorbed)
Solitary; antimesenteric; usually ileal (~30cm from cecum)
Present in 2% of population, more commonly males
50% have some gastric mucosa; peptic ulceration may occur, usually in adjacent intestinal mucosa
Ectopic pancreas may also be seen in wall
Complications: perforate, ulcerate, bleed, intussusception

Heterotopic Tissue

Pancreas
1-2 cm mucosal elevation
Ducts and acini, usually without islets
Can occur anywhere in small bowel; most common in duodenum (periampullary); least common in jejunum
May serve as a lead point for intussusception

Gastric Mucosa
Discrete small nodules or sessile polyps in the duodenum
Fundic type mucosa with chief and parietal cells

Endometriosis

Intussusception

Usually of infants or children; one segment of small bowel (the intussesceptum) becomes telescoped into the immediately distal segment of bowel (the intussescipiens) and is propelled further inward by peristalsis, taking the mesentery with it - can lead to infarction
When occurs in adults, usually due to a mass lesion which forms the leading point of traction
In children, lymphoid hyperplasia often serves as the mass which forms the leading edge
Barium enema may reduce the lesion

Inflammatory Disorders

Ischemic Bowel Disease

Mesenteric artery successively branches; intermediate branches have numerous anastomoses with each other
May mimic Crohn's disease

Obstruction of a main branch:	extensive infarction
secondary branch:	no effect (collaterals)
terminal branch:	localized infarction

TRANSMURAL INFARCTION (GANGRENE)
Short segment or more commonly substantial length
Grossly hemorrhagic, whether arterial or venous in origin
Arterial occlusions tend to have sharper margins; venous occlusions tend to fade gradually into normal bowel
Intense congestion, subserosal and submucosal hemorrhages, edema, later blood in lumen
Perforation likely within 3-4 days

Arterial Thrombosis
Usually associated with / triggered by atherosclerosis
Other etiologies: vasospasm, dissecting aneurysm, tumor, fibromuscular hyperplasia of the intestinal arteries (seen in some patients on digoxin), acute arteritis (polyarteritis nodosa)

Embolic Occlusions
Usually superior mesenteric since inferior has a more oblique take-off from aorta
Intracardiac or intraaortic mural thrombi most commonly

Venous Thrombosis
25% cases of transmural infarction
Following surgery, cardiac failure, polycythemia, mass

HEMORRHAGIC GASTROENTEROPATHY
Usually related to hypoperfusion (eg shock)
Superficial layers affected first; extends deeper with increasing severity
Similar histology to transmural, but less severe

CHRONIC ISCHEMIA
Fibrosis most pronounced in mucosa
Fibrotic narrowing can occur

Malabsorption Syndromes

Abnormal absorption of fat, fat soluble vitamins, or other vitamins, proteins, carbohydrates, minerals, usually with abnormal fecal excretion of fat (steatorrhea: >6gm/day)
Can be due to defective intraluminal hydrolysis, mucosal abnormality, lymphatic obstruction, infection, etc.

Appearance of mucosa under dissecting scope can be correlated, roughly, with histology. Patterns:

Appearance	Histology
Villous, fingerlike	Normal
Villous, leaflike	Normal
Convoluted (cerebroid)	Partial villous atrophy
Mosaic	Subtotal villous atrophy
Flat	Near total villous atrophy

Celiac Disease

AKA: celiac sprue; non-tropical sprue; gluten sensitive enteropathy

Affects predominantly the proximal small bowel

Etiology is almost certainly a hypersensitivity response to gliadin (gluten) in the diet

80-90% are HLA-B8 or DR3

Associated with dermatitis herpetiformis: 60-80% of patients with DH have abnormal intestinal villi; 75% show improvement of the skin lesions when placed on a gluten free diet

Absence of villi (or marked flattening [should be 3x depth of crypts]) resulting in a flat mucosa, with plasma cells, absence of alpha-1-antitrypsin from crypt cells, and accumulation of large fat globules

Not diagnostic: same changes can be seen in kwashiorkor, dermatitis herpetiformis, and severe tropical sprue

90% of patients contain circulating antibodies to alpha-gliadin; antibody level does not correspond well to the severity of disease

The course of the disease can be followed by monitoring serum IgA anti-smooth muscle endomesium levels

When increased lamina proprial accumulation of hyaline material occurs, some refer to a *collagenous sprue*

Complications:

- Intestinal Malignant Lymphoma: [see also beginning of this outline] following long standing disease in the 10% of patients who do NOT have antibodies to alpha-gliadin
- Chronic nonspecific ulcerative duodenojejunoileitis: may be an initial stage of the lymphoma described above
- Gastrointestinal Carcinoma: rare; usually in jejunum; usually adenocarcinoma

Tropical Sprue

Unrelated to gluten ingestion

Almost exclusively limited to tropics (living in or visiting)

May be related to enterotoxigenic E coli

Responds to folic acid, Vitamin B_{12}, and tetracycline

Partial villous atrophy seen in most cases, more prominent in the distal small bowel

Inflammatory infiltrate has large numbers of lymphocytes and occasional eosinophils

Whipple's Disease (Intestinal Lipodystrophy)

Large macrophages (stuffed with diastase resistant PAS positive 'bacilliform bodies') packing the lamina propria and distorting the villi, alternating with dilated lymphatic channels and empty spaces containing neutral lipids (occasionally with giant cells: lipogranulomas)

No significant inflammatory response

Organism not consistently identified on culture

Usually whites, M:F=10:1, 30's-40's

Not restricted to bowel; similar macrophages can be seen in other parts of GI tract, LN's, heart, lung, liver, spleen, adrenals, nervous system

Other Causes of Malabsorption

- Biliary obstruction with bile acid deficiency
- Chronic pancreatitis
- Amyloidosis
- Reduced small bowel length after surgical resection
- Infections
- Lymphatic obstruction

Peptic Ulcer Disease

[See above under stomach]

Infectious Enterocolitis

[See also Infectious Agents Outline]

Organisms associated with Enteroinvasion

Usually ulceroinflammatory

- Shigella: (see below under colon)
- Salmonella

Invades and produces endotoxin (like Shigella) but generally does not ulcerate

Immune response produces massive lymphoid hypertrophy (e.g. typhoid fever)

May have secondary necrosis of mucosa overlying the lymphoid follicles

Involves both the small and large intestine

- Others:

Campylobacter jejuni, some strains of E. coli, TB, Yersinia

Also viral, fungal, protozoal

Organisms which adhere but do not Invade (Toxin Producing)

Vibrio cholera and toxigenic E. coli produce toxin which activates adenylate cyclase; no histopathologic changes

Preformed Clostridium toxins or staphylococcal toxins can produce pathology without the organism

Radiation Enteritis

Grossly, thickening of bowel wall due to fibrosis, particularly in the submucosa

Mucosal ulceration

Early changes: increased mucus production, nuclear changes in the lining epithelium

Later: submucosal edema, then fibrosis and ulceration

Subendothelial accumulation of lipid-laden macrophages in vessels, with thrombosis and calcification

Non-Steroidal Anti-Inflammatory Drug Induced Gut Lesions

Can see erosions or ulcers

Most characteristically, see strictures of the small intestine with diaphragm formation

Crohn's Disease (Regional Ileitis)

Idiopathic, chronic and recurrent inflammatory bowel disease with variably distributed but usually sharply delimited, typically transmural involvement of bowel at any level by non-caseating granulomatous inflammation, ulceration, and fibrous constriction

Onset usually in 20's and 30's; higher incidence in US, UK, and Scandinavia than in USSR, South America

White>Blacks; F≥M

Often intermittent attacks of diarrhea, fever, abdominal pain; attacks can be triggered by physical or emotional stress

Most commonly affects terminal ileum (65-75%) and/or colon (50-70%); colonic involvement alone in only 20-30%

Frequently "skip lesions" in GI tract, with intervening unaffected segments

Related lesions may be seen in skin, bone, muscle, lung

Pathogenesis unknown: theories include infectious, immunologic, vasculitis, etc.

Inflammation in wall initially edematous, but then becomes fibrous with longitudinal mucosal ulcerations, creeping fat, luminal narrowing, fissure formation (25-30%), and fistulous tracts

Histologically, transmural inflammation, relatively poorly formed noncaseating granulomas (present in only 65%), lymphoid aggregates and germinal centers, dilation or sclerosis of lymphatic channels

Complications: strictures, fistulas, abscesses, protein-losing enteropathy, vitamin B_{12} malabsorption, ankylosing spondylitis
Increased risk of carcinoma (3%)

Neoplastic Diseases

Account for less than 5% of the tumors of the GI tract
Malignant tumors are about 50% more common than benign
Most of the malignant tumors are in the ileum

Adenoma

Most often in duodenum and ileum
Similar to those of the colon
Larger ones, particularly villous adenomas, frequently undergo malignant transformation

Brunner's Gland Adenoma

AKA: polypoid hamartoma, brunneroma
Nodular proliferation of all elements of normal Brunner's glands (ducts, stroma)
Probably not true neoplasm; hyperplasia

Peutz-Jegher's Syndrome

Hamartomatous Polyps
Glands supported by broad bands of smooth muscle
Columnar and goblet cells on surface, Paneth and endocrine cells near base

Adenocarcinoma

Can grow in napkin ring or polypoid fashion
Most arise in the duodenum
40-60 times less common than in the colon
Staging is similar to that in the colon EXCEPT:
- Only N0 and N1 for regional nodes uninvolved/involved
- Tis is intraepithelial only; intramucosal is T1

Ampullary Carcinoma

Often arises from pre-existing villous adenoma, often with "benign" glands in villi but malignant cells in base
Intraampullary, periampullary, and mixed forms
Usually poorly differentiated adenocarcinoma
Metastatic at diagnosis (regional LN's) in 35-50%
Distinction from bile duct carcinoma or pancreatic carcinoma important since prognosis better: 25% 5 yr, 50% if node negative
Prognosis relates to size

Other Carcinomas

Small Cell Carcinoma
Adenosquamous Carcinoma
Anaplastic (Sarcomatoid) Carcinoma

Carcinoid Tumor

[See also beginning of this Outline]
Most common malignant tumor of the small bowel
~30% of patients with small intestine carcinoids will have either concurrent malignancies (intestinal or extra-intestinal) elsewhere, most commonly GI adenocarcinoma

Gangliocytic Paraganglioma

AKA: nonchromaffin paraganglioma, paraganglioneuroma
Benign tumor; almost exclusively 2nd portion of duodenum, especially near ampulla of Vater
Most are small, submucosal, pedunculated; frequently ulcerate and bleed
Composed of a mixture of three cell types: endocrine cells (carcinoid-like, usually positive for pancreatic polypeptide), ganglion cells, and spindle-shaped S-100 positive Schwann-like cells

Smooth Muscle Tumors

[See also beginning of this Outline]
Much more likely to be malignant than esophageal or gastric
10% duodenal, 37% jejunal, 53% ileal
Leiomyoblastoma type very uncommon

Malignant Lymphoma

[See also beginning of this Outline]

Enteropathy Associated T-Cell Lymphoma

Immunoproliferative Small Intestine Disease

De novo Lymphomas

80-90% solitary, usually ileum
Diffusely infiltrating, often bulky
Most are large B-cell, followed by small lymphocytic

Other Tumors

Lipomas
Hemangioma
Neurofibroma
Granulocytic Sarcoma

Metastatic Tumors

By far, the most common tumor in the small intestine
Can often involve as multiple polypoid lesions
Most common primaries: malignant melanoma, lung carcinoma, breast carcinoma, choriocarcinoma

COLON

Normal

Colon retroperitoneal along most of its length
Rectum ~6 inches long; proximal portion in peritoneal cavity; distal is extraperitoneal with peritoneal reflection forming the pouch of Douglas (common site for tumor implantation)

Vascular Supply:

- Superior Mesenteric: cecum, right colon, transverse colon
- Inferior Mesenteric: descending (left) colon, sigmoid colon, proximal rectum
- Hemorrhoidal branches of internal iliac: distal rectum

Watershed areas:

- Splenic flexure: between superior and inferior mesenteric arteries
- Rectum: between inferior mesenteric and hemorrhoidal arteries

Collateral blood supply from posterior abdominal wall makes transmural infarction uncommon
Superior hemorrhoidal veins (drain to portal system) anastomose with the inferior hemorrhoidal veins (drain to inferior vena cava) - become dilated in portal hypertension

Nervous Supply:

Auerbach's plexus (within muscularis) and Meissner's plexus (submucosal) form from neuroblasts which migrate in a cephalocaudal direction during development; usually reach rectum by 12 weeks gestational age

Malformations (Congenital and Acquired)

Miscellaneous Malformations

- Malrotation
- Duplication
- Imperforate Anus

Hirschsprung's Disease

- AKA: Congenital megacolon
- Failure of neuroblasts to migrate to the end of the bowel, resulting in an aganglionic segment which always involves the rectum and extends varying distances proximally
- 80% patients are male; 10% have Down's syndrome
- 4% risk in sibling of an affected patient
- Usually manifests early in neonatal period
- Absence of ganglion cells accompanied by erratic hyperplasia of nerves within the submucosa and increased acetylcholinesterase activity in the lamina propria and muscularis mucosa
- Restricted to the rectum in 90%
- Lack of peristalsis results in a functional obstruction and dilatation to form "megacolon"
- Surgical correction required; 5-10% mortality from electrolyte disturbances and infections

Diverticular Disease

- AKA: Diverticulosis
- Outpouchings of mucosa and submucosa through a weakened area in the muscularis, often with hypertrophy of adjacent muscularis
- Symptomatic in only ~20% affected patients
- Symptoms of lower abdominal discomfort and/or cramping pains may or may not be present, independent of whether or not inflammatory changes (diverticulitis) are present
- >95% diverticula are located in the sigmoid colon
- Pathogenesis involves both focal weakness in the muscularis and increased intraluminal pressure
- When inflamed, peridiverticular acute and chronic inflammation is seen with fibrosis and sometimes abscess or fistula tract formation

Hemorrhoids

- Variceal dilations of the anal and perianal venous plexi
- Affects ~5% population; unusual before 30 yrs of age except in pregnant women
- Predisposing factors: constipation with straining at stool, venous stasis of pregnancy, increased portal hypertension
- External: inferior hemorrhoidal plexus; below anorectal line
- Internal: superior hemorrhoidal plexus; above anorectal line

Angiodysplasia

- Dilatation and increased tortuosity of the submucosal veins in the cecum and occasionally ascending colon
- Can cause lower GI bleeding in elderly
- Probably acquired
- May develop in the cecum because, since it has the largest diameter, it's wall tension is the greatest, compressing the veins in the muscularis and thereby shunting more blood through the submucosal veins

Inflammatory Disorders

Necrotizing Enterocolitis

- Acute necrotizing inflammation of small and large intestine
- Affects 10% full term infants; more common in prematurity
- Peak incidence is 2-3 days of age following initiation of oral feeding
- More common among formula fed vs breast fed infants
- Symptoms vary from mild abdominal tenderness to frank bleeding, perforation, and sepsis
- Radiography may reveal air in bowel wall (pneumatosis intestinalis)
- Most common sites: terminal ileum, cecum, ascending colon
- Mucosal necrosis with fibrinous exudate, sometimes pseudo-membrane formation, neutrophils, lymphocytes

Ulcerative Colitis

- Idiopathic; Inflammatory Bowel Disease
- Recurrent acute and chronic inflammatory disorder affecting principally the rectum and left colon, but often extending more proximally; never beyond the cecum
- Patients often present with attacks of bloody mucoid diarrhea which may persist for days, weeks, or months
- 4-6/100,000 in US; whites>black; F>M; peak onset 20-25yrs
- Like Crohn's, patients may also have migratory polyarthritis, ankylosing spondylitis, uveitis, skin lesions
- Continuous involvement from rectum (in untreated cases); no skip lesions, although different segments may be in different stages of healing / activity; with treatment, can have patchy involvement, even in the rectum
- Active lesions marked by mucin depletion, crypt abscesses, ulcerations which tend to be broad based and may extend deep into submucosa but usually not far into muscularis, extensive mucosal destruction, islands of residual mucosa (pseudopolyps), undermining and mucosal bridging
- Chronic changes include distortion of crypt architecture (branching and irregular glands), basal lymphoplasmacytic infiltrate, Paneth cell metaplasia, adipose islands in lamina propria
- Dysplasia should be graded on every biopsy as absent, indefinite, low grade, or high grade
- 2-5% will develop primary sclerosing cholangitis
- 25% are P-ANCA positive: more likely to develop PSC
- Fulminant UC: 25% cases; sudden onset of intractable bloody diarrhea, fever, electrolyte imbalances; can be fatal

Complications:

- Toxic Megacolon: sudden cessation of bowel function with dilatation and potentially rupture
- Carcinoma: Incidence of carcinoma is 1% at 10 yrs, 3.5% at 15 yrs, 10-15% at 20 yrs, 30% at 30 yrs duration (when majority of colon involved; lower for limited disease); tumors may be multiple; usually preceded by dysplasia; tumors tend to be higher grade/stage than those arising in uninflamed mucosa

Crohn's Disease

(see above under Small Intestine)

Ischemic Colitis

- Most commonly splenic flexure, descending, sigmoid; occurs in elderly
- Edema, hemorrhage, later ulcerations, fibrosis, pseudomembranes, pseudopolyps; not uncommonly with adjacent normal mucosa
- Hemosiderin usually abundant
- Lymphoid follicles and granulomas are absent
- Differential diagnosis includes Crohn's disease, ulcerative colitis, and pseudomembranous colitis

Infectious Colitides

Acute Self-Limited Colitis
- AKA: Nonspecific bacterial colitis
- Edema, inflammation, hyperemia, hemorrhage
- Most commonly Campylobacter, Salmonella, Shigella
- Salmonella and Shigella can simulate Ulcerative Colitis
- E coli can cause an acute hemorrhagic colitis
- Shigella
  - Bacillary dysentery
  - Penetrates mucosa; replicates within lamina propria; elaborates cytotoxic endotoxin
  - Shallow ulcerations
  - Preferentially involves large bowel
- Salmonella (see above under Small Intestine)

Pseudomembranous Colitis
- Acute colitis in which the inflamed, focally necrotic mucosa is covered by pseudomembranes composed of fibrin and inflammatory cells spewing out from the crypts
- Caused by toxin of Clostridium difficile, which overgrows normal flora usually following treatment with a broad spectrum antibiotic, particularly clindamycin or lincomycin
- More often involves the right colon; may occasionally involve the distal small bowel
- Membranes gray-yellow; may coalesce and become greenish
- Differential diagnosis: ischemic colitis

Other Infectious Colitides
- Amebic: predilection for cecum and ascending colon, flask shaped ulceration with minimal inflammation
- TB: most commonly ileocecal; mass (tuberculoma) present in 50% cases
  - Currently, most commonly acquired from swallowing infected pulmonary secretions
- CMV: most commonly ileocecal; extensive ulceration, inclusion bodies most prominent in vascular endothelial cells
- Cryptosporidiosis: most common cause of severe watery diarrhea in AIDS
  - Organism present in large numbers; difficult to treat

"Microscopic Colitis"

- Chronic or episodic watery diarrhea with radiographically and endoscopically normal bowel
- Patients almost always >30 yrs age (mean age 55); M:F = 1:6; may have autoimmune disease
- Histologic features vary from field to field - patchy

Lymphocytic Colitis
- Surface epithelium is somewhat flattened with loss of mucin and cytoplasmic vacuolization, and is infiltrated by lymphocytes, neutrophils, eosinophils
- Occasional crypt abscesses may be present

Collagenous Colitis
- Lymphocytic colitis with deposition of ≥10μm thick hypocellular collagenous band beneath surface mucosa, occasionally with trapped congested capillaries

Other Colitidies

Diversion Colitis
- Occurs in distal bowel isolated from fecal stream by diversion colostomy
- Marked lymphoid follicular hyperplasia with germinal centers, acute cryptitis, and crypt abscesses

Radiation Colitis
- Acute: within 2 weeks; epithelial injury with inflammation
- Chronic: 2 months-20 yrs; proliferative endarteritis, fibrosis

Other Non-Neoplastic Lesions

Colitis Cystica Profunda
- Intramural mucus-containing cysts in colon and rectum
- Localized form typically occurs in rectum; AKA hamartomatous inverted polyp
- Diffuse form results from inflammation and ulceration

Melanosis Coli
- Brown-black discoloration of the colonic mucosa due to accumulation within the lamina propria of macrophages filled with pigmented material composed of melanin and lipofuscin; usually PAS and Fontana Masson positive
- Attributed to use of anthracene type laxatives which damage the mucosal cells; macrophages phagocytose debris
- No clinical or physiologic significance

Neoplasms

Polyps

NON-NEOPLASTIC POLYPS

Hyperplastic Polyps
- Most common non-neoplastic polyp in the GI tract
- Generally sessile, <5 mm; single or multiple
- Found in 25-50% individuals at autopsy; account for 90% epithelial polyps at autopsy, but only 20% biopsied polyps
- 60-80% in rectosigmoid
- Epithelium has normal mucinous component with a scalloped saw-tooth pattern, especially on the surface

Juvenile (Retention) Polyps
- Most frequent polyp in children; 1/3 cases seen in adults
- Most common in rectosigmoid; Autoamputation is common
- Granular, red grossly; mucus-filled cystic glands
- Stroma is inflamed and edematous (crypt rupture)

Hamartomatous (Peutz-Jeghers-type) Polyps
- May be single or multiple (in the Peutz-Jeghers syndrome)
- Glands supported by broad branching bands of smooth muscle which extend upward from the muscularis mucosa into the lamina propria
- Columnar and goblet cells on surface, Paneth and endocrine cells near base
- Minimal to no atypia

Pseudopolyps
- Islands of residual mucosa surrounded by ulceration, seen in Ulcerative Colitis

Inflammatory Fibroid Polyps
- Mainly occur in the small intestine and stomach (see above)
- Broad based, 1-15 cm, ulcerated surface
- Fibroblasts, inflammatory cells (often eosinophils) in collagenous or myxoid stroma
- May present as intussusception

Solitary Rectal Ulcer
- AKA: Benign idiopathic recurrent rectal ulceration
- Solitary (may be multiple), ulcerated (may have intact overlying mucosa), polypoid lesion 4-18 cm from anal margin (may be anal or in sigmoid colon), often associated with mucosal prolapse
- Obliteration of lamina propria by fibrosis, smooth muscle proliferation within and extending up from the muscularis mucosa, decreased numbers of lymphocytes
- **Inflammatory Cloacogenic Polyp** and **Mucosal Prolapse Syndrome** are probably variations on this

Lymphoid Polyps
- Mucosal protrusion secondary to lymphoid hyperplasia, most commonly seen in the rectum

NEOPLASTIC POLYPS

Adenomatous Polyps (Tubular Adenomas)
- May be pedunculated; stalk usually has normal epithelium; stalks longer in left colon
- 75% of all neoplastic polyps; M:F=2:1
- 0.3-3.5 cm; the majority are located in the sigmoid colon and rectum, but 25-40% are found in the right colon

- Thicker mucosa with goblet cell depletion, multiple cell layers, mitoses off basal layer
- Superficial areas affected first
- Dysplasia can be graded as mild, moderate, severe
- Although "premalignant", few adenomatous polyps progress to cancer; risk of malignancy only 1-3%; increases with number and size (especially if >2cm) of polyps
- Larger lesions usually have some villous component: "Villo-glandular polyps" or "tubulovillous polyps"; increased risk of malignant progression
- Pseudoinvasion of the stalk distinguished from carcinoma by similarity to surface glands, presence of lamina propria between glands, lack of a desmoplastic response, hemosiderin granules or hemorrhage

Villous Adenoma
- Account for <10% of all neoplastic polyps
- >50% villous in architecture
- Tend to occur in elderly patients, usually single, rectosigmoid, sessile, large
- Associated with hypoproteinemia and hypokalemia
- Much more prone to undergo progression to malignancy than tubular adenomas (30-70%)

Serrated Adenoma
- Uncommon (<1% of all polyps)
- Mixed hyperplastic and adenomatous polyp
- On low power, contains the serrated surface and glands of a hyperplastic polyp, but has the cellular immaturity of an adenoma
- Probably represents a transitional state

POLYPOSIS SYNDROMES

Cowden's Syndrome
- Multiple hamartomatous polyps, but not Peutz-Jegher's type (disorganization and proliferation of muscularis mucosa)
- Autosomal dominant
- Facial trichilemomas, acral keratoses, oral mucosal papillomas
- Increased incidence of malignancy in various sites (especially breast, thyroid)

Cronkhite-Canada Syndrome
- Non-hereditary
- Multiple juvenile polyps associated with alopecia, nail atrophy, and hyperpigmentation

Familial Polyposis
- Autosomal dominant, gene on chromosome 5q21 (APC gene)
- Polyps not present at birth
- Early development (teens-20's) of numerous tubular adenomas throughout GI tract (including small intestine and stomach) - usually need 100 polyps to make diagnosis
- High incidence of malignant transformation; almost 100% will develop carcinoma by early 30's

Gardner's Syndrome
- Autosomal dominant
- Colonic polyposis in association with multiple osteomas of the skull and mandible, keratinous cysts of the skin, soft tissue tumors (especially fibromatosis)
- Risk of colonic carcinoma as high as for familial polyposis

Multiple Juvenile Polyposis Syndrome
- Autosomal dominant
- Associated with development of adenomatous polyps and adenocarcinoma

Peutz-Jegher's Syndrome
- Autosomal dominant
- Multiple hamartomatous (juvenile) polyps in colon (30%), small bowel (100%) and stomach (25%); melanotic mucosal and cutaneous pigmentation around the lips, mouth, face, genitalia, palmar surfaces of hands
- Increased risk of developing carcinomas of the pancreas, breast, lung, ovary, and uterus

Turcot's Syndrome
- Autosomal recessive
- Colonic adenomatous polyps seen in association with brain tumors, usually glioblastomas

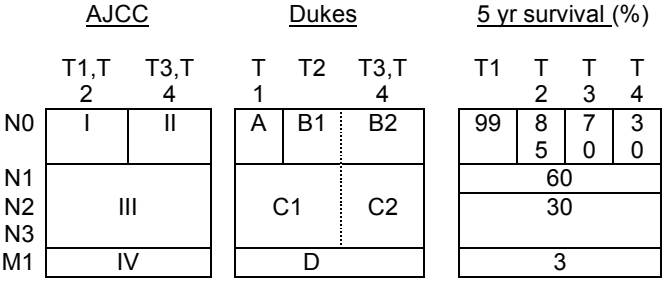
Adenocarcinoma

- Second leading cancer killer in the United States; 15% of all cancer deaths
- Account for 98% of all cancers of the large intestine
- 50-70% are rectosigmoid
- Incidence appears to parallel socioeconomic status
- Cecum and ascending colon in low incidence areas, more frequently rectum and sigmoid in higher incidence areas
- Increasing use of sigmoidoscopy has led to decreased frequency in rectosigmoid recently
- Dietary factors predisposing to carcinoma include low content of unabsorbable vegetable fiber, high content of refined carbohydrates, high fat content
- Peak incidence in 60's; <20% in patients <50
- On the left side, tend to grow as annular encircling lesions with early obstruction; on the right: polypoid, fungating masses, generally don't obstruct, diagnosed later
- Usually well to moderately differentiated adenocarcinoma, often with T-Cell inflammatory response at leading edge
- Tumor is keratin and CEA positive (latter equally distributed vs. apical distribution in normal mucosa)
- ras, p53 (17p13), DCC (18q21) mutations common

STAGING

(Lamina propria of colon lacks lymphatics. Therefore, even if tumor invades lamina propria, it is still considered in situ)

Tis	Intraepithelial carcinoma or lamina propria invasion
T1	submucosal invasion
T2	muscularis propria or subserosal invasion
T3	subserosal or other pericolic invasion
T4	adjacent structures or through peritoneum
N1	1-3 pericolic or perirectal nodes
N2	≥4 pericolic or perirectal LN's
N3	LNs along vascular trunk or apical node involvement



PROGNOSTIC FACTORS

- Metastases most commonly to liver, often as a single or small number of large well defined lesions, often central necrosis
- Good prognostic factors: females, low stage, pushing margins and inflammatory infiltrate, eosinophil infiltration
- Bad prognostic factors: very young or very old, males, obstruction, perforation; mucinous, small cell, or signet ring cell; vascular or perineural invasion

SPECIAL HISTOLOGIC TYPES

Mucinous
- Collections of tumor cells suspended in lakes of extracellular mucin
- 15% of colorectal carcinomas, most commonly rectum, commonly associated with villous adenomas
- Slightly worse prognosis, independent of histologic grade

Signet Ring
- Rare, usually younger patients
- Signet ring cells with diffuse infiltration and thickening of wall

Metastases more likely to LNs, peritoneal surface and ovary rather than liver
Extremely poor prognosis

Squamous
More common in cecal neoplasms
Usually adenosquamous; rarely purely squamous

Neuroendocrine Features
If scattered cells in otherwise typical adenocarcinoma, usually mucinous type, does not influence prognosis
Small cell pattern caries a poor prognosis

Others
Clear cell change
Basaloid (cloacogenic)
Choriocarcinomatous

Carcinoid Tumor

[See also beginning of this Outline]
Most commonly in rectum, sometimes in distal sigmoid
Generally are well behaved
In the rectum, >70% are positive for Prostatic Acid Phosphatase (in both men and women) but are negative for Prostate Specific Antigen

Carcinoma of the Anal Canal

Present with bleeding (50%), pain (40%)
More common in women, but increasing frequency among homosexual men
Most are epidermoid (squamous cell) carcinomas
~20% will show a basaloid appearance with areas of palisading; this has been variably termed basaloid, transitional, or cloacogenic, but is probably a variant of squamous cell carcinoma
May be massively infiltrated by eosinophils
HPV is strongly suspected in pathogenesis

Other variants/carcinomas include:
- Sarcomatoid carcinoma
- Verrucous carcinoma
- Mucinous Adenocarcinoma
- Basal cell carcinoma
- Bowen's disease
- Paget's disease

Other tumors of the anal canal
Malignant melanoma
Embryonal rhabdomyosarcoma
Malignant Lymphoma

Other Neoplasms

Lipoma
Lipomatosis of the Ileocecal Valve
Smooth Muscle Tumors
Most are in the rectum, are small, and are benign
Proximal tumors tend to be larger; more likely to be malignant
Kaposi's Sarcoma

APPENDIX

NORMAL
Extremely rich in lymphoid tissue in young individuals
Lymphoid tissue and epithelium undergoes atrophy during life; may result in complete fibrous obliteration of the lumen (may be a schwannoma related lesion, since often there is associated hypertrophy of the nerves)

Acute Appendicitis

Mainly a disease of adolescents - may affect any age
Classically, pain is initially periumbilical, then migrates to right lower quadrant, fever, nausea/vomiting, abdominal tenderness, leukocytosis - rarely are all elements present
Most commonly arises in setting of obstruction by fecalith, vermicularis, foreign body, cecal tumor
Obstruction and continued mucin secretion leads to increased luminal pressure, collapse of drainage veins, ischemic injury, bacterial invasion, further ischemia, etc.
Most surgeons accept a 20% false-positive rate of operating for acute appendicitis, since rupture carries a 2% mortality
Usually require neutrophils in muscularis to make diagnosis, since neutrophils in mucosa or submucosa can result from drainage from an infection higher in bowel
Some divide degree of inflammation into early (focal), suppurative, gangrenous, and perforative

Eosinophilic Appendicitis
Diffuse eosinophilic infiltration often with granulomas
Correlated with present of Strongyloides stercoralis in stool

Appendiceal "Infections"

Oxyuris Vermicularis
Seen in about 3% of appendices removed surgically
Most common in children between 7 and 11 yrs
May induce granulomatous inflammation

Campylobacter
Measles
Infectious Mononucleosis
Adenovirus

Neoplasms

Mucinous Cystadenoma

AKA: Mucocele
Diffuse globular enlargement of appendix by large amount of tenacious mucus; lumen lined by atypical mucinous epithelium with at least focal papillary growths
Four times more common than malignant counterpart
20% will be associated with appendiceal perforation and implantation of mucin within the peritoneum - malignant cells will NOT be found in the mucin
May have coexisting mucinous cystadenoma of the ovary with identical histology
Some pathologists reserve the term mucocele for mucinous distention secondary to non-neoplastic obstruction

Mucinous Cystadenocarcinoma

Similar to benign counterpart except cells are more atypical, often invade bowel wall, and viable tumor cells can be found in the mucin lakes
When mucin is present in the peritoneal cavity associated with malignant cells, called **pseudomyxoma peritonei**

Adenocarcinoma

May be secondarily involved by a cecal carcinoma
Histology same as for colonic tumor
Signet ring variant exists

Carcinoid Tumor

[See also beginning of this Outline]
Most common site for carcinoid tumor in the body
Found in 1/300 routine appendectomies
Tip of appendix most common site (70%); when more proximal, may cause obstruction and appendicitis
Large majority are benign
Rarely cause carcinoid syndrome
Immunoreactive for seratonin and S-100

Classic Type
Solid nests of small monotonous cells; insular growth pattern
Often invades nerves, muscle, lymphatics, even serosa

Tubular Adenocarcinoid
Glandular formation without solid nests
Usually tip of appendix
Usually lacks seratonin; often positive for glucagon
Often misdiagnosed as adenocarcinoma; important distinction since behavior is benign

Clear Cell Carcinoid
Cells have clear cytoplasm but lack mucin and glycogen
Behaves like classic type

Mucinous Carcinoid
AKA: Goblet cell carcinoid, microglandular carcinoma, crypt cell carcinoma
Unique to the appendix
Cells may have signet ring configuration
Grows in a concentric pattern within the submucosa
More aggressive than other two types with 10-20% metastasizing, often to bilateral ovaries

PERITONEAL CAVITY

Peritoneum

NORMAL
Lined by mesodermally derived keratin positive mesothelium
Subserosal cells are vimentin positive, fibroblast-like, and believed to be pluripotent

Peritonitis

May completely resolve, become walled off (abscess), or heal as fibrous adhesions
• Chemical: bile, pancreatic juices, gastric juice, barium
• Meconium: intrauterine perforation of small bowel
• Bacterial: primary infections: streptococci, usually children secondary infections: perforation of viscus, TB
• Foreign body: granulomatous inflammation

Cysts

Pseudocyst
No lining; result from inflammatory processes

Solitary Cyst
1-6 cm
Attached to wall of lying loose
Usually watery fluid in lumen, single layer of cuboidal to flat mesothelial cells

Multicystic Benign Mesothelioma
Usually adult females
Cysts are microscopic to >15 cm diameter
Flattened cuboidal mesothelium, clear fluid, mild chronic inflammation in walls
Probably reactive process; frequently recur

Müllerian Cysts
Usually fallopian tube type epithelium
Seen in males - residual Müllerian structures

Hyperplasia/Metaplasia

Mesothelial Hyperplasia
Reaction to irritation
Nodular or papillary; Psammoma bodies may be present

Metaplasia
Squamous
Müllerian (endometriosis, endosalpingiosis, ectopic decidual reaction)
Cartilaginous

Mesothelioma

[See also "Pleura" in Lung Outline]

Fibrous
<25% peritoneal tumors (much less common than in pleura)
May arise from submesothelial connective tissue
May be associated with hypoglycemia
Generally benign

Benign Epithelial Mesothelioma
Small, solitary, papillary structure
Resembles choroid plexus
May be extension of mesothelial hyperplasia

Malignant Epithelial Mesothelioma
Most are in males over 40 yrs
~50% associated with (heavy) asbestos exposure
Multiple plaques / nodules on visceral and parietal peritoneum
Ascites almost always present
Advanced lesions may obliterate peritoneal cavity
Histology is variable: papillary, tubular, solid; psammoma bodies; may have sarcomatoid component
Generally keratin positive; CEA and LeuM1 negative
EM: long microvilli

Omentum

Hemorrhagic Infarct (Torsion, strangulation)
Cystic Lymphangioma
Most tumors are metastatic implants

Mesentery

Panniculitis
Mesenteric Cysts (Same as peritoneal "Solitary cysts")
Giant lymph node hyperplasia (Castleman's disease)

LIVER

Normal Anatomy

Averages 1400-1600 gm in adult
Covered by Glisson's Capsule
Receives 70% blood flow from portal vein, 30% hepatic artery
Grossly divided into left, right lobes; right is 6x larger and contains quadrate (inferior) and caudate (posterior) lobes
Enormous reserve and regenerative capacity; regenerated liver often has abnormal biliary connections
Microscopically divided into "lobules", 1-2 mm in diameter
- Classical: hexagonal: central vein in middle
- Portal: triangular: portal tract in middle and 3 central veins
- Acinar: diamond: 2 central veins + 2 portal tracts
  - Zone 1) periportal; most sensitive to toxins
  - Zone 2) intermediate
  - Zone 3) pericentral vein; stellate, not circular; most active P-450 oxidase system; most sensitive to ischemic injury

Portal tracts contain: portal vein, hepatic artery, bile duct (one per artery), lymphatics, nerves, connective tissue
Limiting plate: lineup of hepatocytes surrounding portal tract
Cords are 1 cell thick in adult; 2 in newborns (and in regenerating liver)
Nuclear size in hepatocytes varies significantly; ploidy ranges up to octaploid
Sinusoids lined by discontinuous, fenestrated endothelium
Lymphatic flow: Perisinusoidal space of Disse, periportal space of Mall, portal tract lymphatics, etc.
Bile flow: canaliculi, Canals of Herring (cells intermediate between hepatocytes and duct cells), portal bile ducts, left and right hepatic ducts, common hepatic bile duct, etc.
Bile flow is energy dependent (probably active transport of ions is required)
Little variation in hepatocyte size; significant anisonucleosis
Kupffer cells: monocyte/phagocyte system - in sinusoids; can be visualized by staining with Cam56
Perisinusoidal "Ito" cells: fat containing mesenchymal cells in space of Disse; important for vitamin A storage (become swollen in hypervitaminosis A)
Iron accumulation is predominantly periportal, vs lipofuscin accumulation which is predominantly peri-central vein

Immunohistochemistry
KP-1 (CD68) stains Kupffer cells
Low MW keratin stains bile ducts
EMA/CEA stains canaliculi

Biopsy
Blind percutaneous liver biopsy: mortality rate 1/5-7000 bxs
For patients with clotting abnormalities, use transjugular approach
Indications: mass lesion, abnormal/unexplained chemistries, failure of unknown cause, staging of known disease

Embryology

Arises as ventral bud from caudal foregut early in 4th week
Hepatic diverticulum separates from primitive gallbladder
Hepatocytes & intrahepatic bile ducts endodermally derived
Initially, R and L lobes same size; then R enlarges, develops caudate and quadrate lobes
Hematopoiesis begins during the 6th week - continues to term
9 wks: liver represents 10% fetal weight (5% at term)
12th wk: bile formation begins
Extrahepatic biliary tree initially occluded with endodermal cells, later recanalized

Heterotopia
Has rarely been seen in gallbladder, spleen, pancreas, umbilicus, adrenal glands, omentum

Jaundice (Icterus)

Yellow-green discoloration of skin or sclerae by bilirubin; pruritus common (due to bile acids in serum, not bilirubin)
Kernicterus: deposition of bilirubin in brain (disappears within 24 hrs of death; to diagnose, need to cut brain fresh)
Not clinically evident until serum bilirubin exceeds 2mg/dL
70% bilirubin derived from catabolism of hemoglobin
Heme (red) → biliverdin (green) → bilirubin (yellow) → conjugated (glucuronidated) in liver, secreted in bile → converted to urobilinogen by bacteria → most oxidized to urobilin (stercobilin) and excreted; 10% reabsorbed, returns to liver, some excreted by kidneys
Unconjugated bilirubin not water soluble (binds albumin in serum, cannot be excreted by kidneys); toxic to tissues

UNCONJUGATED (INDIRECT) HYPERBILIRUBINEMIA

Increased production
AKA: hemolytic jaundice
Pernicious anemia, thalassemia

Decreased uptake by liver
Constitutional hepatic dysfunction = Gilbert's syndrome; affects 7% population

Impaired conjugation
Physiologic jaundice of the newborn
Crigler-Najjar Syndrome
- Type I: autosomal recessive deficiency of glucuronyl-transferase; progressive kernicterus; invariably fatal
- Type II: autosomal dominant with variable penetrance, moderate decrease in glucuronyltransferase; normal liver histology

CONJUGATED (DIRECT) HYPERBILIRUBINEMIA

Liver damage (intrahepatic cholestasis)
Secretion of bilirubin into canaliculus is compromised before ability to conjugate is lost

Dubin-Johnson Syndrome
Autosomal recessive defect in canalicular transport of organic anions, including conjugated bilirubin
Liver becomes black due to accumulation of an unknown pigment (not related to bilirubin)

Extrahepatic Duct Obstruction
(see below)

Inflammatory / Non-Neoplastic Disorders

Genetic / Childhood Disorders

Neonatal Hepatitis Syndrome
Onset of jaundice between 1 wk and 2 months
Usually idiopathic (may be caused by sepsis, Listeria, Toxoplasma, HepB, CMV, HSV, alpha-1-AT, galactosemia, cystic fibrosis, tyrosinemia...)
Lobular disarray, focal liver cell necrosis, prominent giant cell transformation, mononuclear infiltrate into portal areas, cholestasis, reactive changes in Kupffer cells
Long term prognosis generally not good - surgery to rule out biliary atresia can further increase morbidity/mortality
Usually don't see bile duct proliferation (vs. in atresia)

Alpha-1-Antitrypsin Deficiency
- May present as liver disease, lung disease, or both
- More than 30 variants exist
- Abnormal allele is "Z" vs. M for the Pi (protease inhibitor) locus (chromosome 14); mutant protein (single amino acid change: glu342→lys) is not secreted
- ZZ individuals (1 in 2-4000) have 10-15% normal level of AAT; 2/3rds develop liver disease; 2.5% die by 4 yrs
- May present later in adult life with cirrhosis and liver failure; usually shows massive accumulation of AAT
- Increased risk for hepatocellular carcinoma in males
- PAS+, diastase resistant round to oval cytoplasmic globules in periportal regions; by EM, these are in the endoplasmic reticulum; composed of the mutant protein
- May also see giant cell formation, cholestasis, portal fibrosis

Cystic Fibrosis
- Liver usually unaffected at birth - worsens through life
- Steatosis most common lesion, panlobular
- Focal biliary cirrhosis with inspissated granular eosinophilic material within portal bile ductules is pathognomonic
- 10% develop cirrhosis by age 25
- [See Congenital Syndromes Outline for more details]

Reye's Syndrome
- Encephalopathy and fatty degeneration of liver, usually lethal
- Associated with elevated serum ammonia
- Linked in children to the use of aspirin for viral illnesses
- Panlobular steatosis, microvesicular, without inflammation
- May lead to zonal or massive hepatic necrosis
- EM: enlarged, pleomorphic mitochondria with swollen matrix
- Microvesicular fat also accumulates in proximal tubules of kidney and in myocardium and skeletal muscle

Hemochromatosis
- Autosomal recessive (chromosome 5p): incidence 1-2/1000; M:F=7:1
- Hepatic Iron Index: µmoles Fe / gm dry weight liver / age
  - Homozygotes: >2, may be >20
  - Heterozygotes: 0.2 - 2
  - Normal: 0.1 - 1
- Quantitative iron can help distinguish primary hemochromatosis from secondary hemosiderosis (iron overload without associated tissue damage; iron preferentially accumulates in the Kupffer cells)
- If cirrhosis (usually micronodular) develops, increased risk of hepatoma, decreased life span
- Associated with HLA-A3 and HLA-B14

• Familial (idiopathic) Hemochromatosis
- Excessive iron absorption
- Iron accumulates in Kupffer cells, periportal hepatocytes
- Some fibrosis may be present - not related to amount of iron

• Neonatal Hemochromatosis
- Not familial: affects premature infants
- Progressive iron deposition in liver and other tissues

Wilson's Disease
- AKA: Hepatolenticular degeneration
- Autosomal recessive inability to excrete copper into the bile
- Present late childhood/early adulthood with neurologic dysfunction, hepatic disease, or hemolytic anemia
- Variable liver picture: acute hepatitis, CAH, fulminant, cirrhosis; typically CAH with fibrosis and glycogen nuclei
- Histochemical stains for copper inadequate as screening test; need chemical determination of serum or liver biopsy
- Patients usually have Kayser-Fleischer rings on cornea

Congenital Hepatic Fibrosis
- Bands of fibrous septa (with numerous bile ducts) surrounding islands of normal parenchyma
- Not cirrhosis: no inflammation, no regenerative nodules
- May belong to spectrum of diseases including Caroli's disease and polycystic liver disease

Intrahepatic Biliary Atresia
- Absence or loss of intrahepatic ducts with minimal if any regenerative effort
- Usually need <0.5 ducts per portal tract (normal=1) to make diagnosis
- Alagille's Syndrome (arteriohepatic dysplasia): autosomal dominant syndromic form with vertebral arch anomalies, pulmonic stenosis, abnormal facies, hypogonadism; progressive loss of bile ducts with age
- Non-syndromic form: usually congenital absence of the ducts

Circulatory / Vascular Changes

- May be due to obstruction of blood inflow (hepatic artery or portal vein) or blood outflow (central or hepatic vein)

Infarction
- Rare - requires sudden obstruction of hepatic artery

Portal Vein Thrombosis
- Abdominal cancers, peritoneal sepsis, pancreatitis, post-surgery; cirrhosis, metastatic cancer
- Abdominal pain and ascites

Chronic Passive Congestion
- Slightly enlarged, blood filled, rounded edges
- Nutmeg appearance, with central congested areas and relative pallor of the periportal zones
- Distention of central veins and periveinular sinusoids
- Erythrocytes may be extruded into the cords where they become trapped

Centrilobular Necrosis
- Seen in prolonged congestive heart failure
- Grossly, nutmeg appearance with central depressions
- Necrosis of liver cells around central veins - may bridge
- May also be seen in left heart failure alone - ischemic

• Cardiac Sclerosis: CLN with delicate central fibrous scarring, extending out into surrounding liver

Veno-occlusive disease
- Sclerotic occlusion of the central veins with associated sinusoidal congestion; sclerosis may extend into outflow veins, simulating Budd-Chiari
- Can be seen with pyrrolozidine alkaloids, azathioprine, thioguanine, hepatic radiation, bone marrow transplantation with graft vs. host reaction

Budd-Chiari Syndrome
- Unexplained partial or complete thrombosis and/or fibrous obliteration of the major hepatic veins or inferior vena cava, usually with membranous webs
- Can be seen with polycythemia vera, pregnancy, oral contraceptives, hepatoma, intraabdominal malignancies
- Acute form is rapidly lethal; chronic is 50% lethal at 5 yrs

Peliosis Hepatis
- Caused by ricketsial organism: Rochalimaea henselae or Rochalimaea quintana (related to agent which causes bacillary angiomatosis in the skin)
- Hepatocytes die and drop out; red cells are extruded into the space of Disse, occupying the space where the hepatocytes used to be; eventually walls of the now empty sinusoids break down producing cystic pools of blood lined by hepatocytes rather than endothelial cells
- Can be seen with anabolic steroid use, exposure to vinyl chloride, following renal transplants, hematologic disorders

Viral Hepatitis

VIRUSES

Hepatitis A
- Nonenveloped ssRNA, icosahedral, 27nm (Picornavirus)
- Not cytopathic directly
- ~1 month incubation period; Ab's begin to appear ~2 wks later
- Most infections are anicteric; self-limited illness

Inflammation tends to be restricted to portal and periportal areas (in contrast to Hep B,C which tend to be panlobular)
IgG indicates exposure to HAV at some point in life; IgM is marker for acute infection; IgM may persist for 1 year
Fatalities in <0.5%; no chronic carrier state exists

Hepatitis B:
Enveloped (42nm) "Dane Particle"; 27nm hexagonal inner core with circular dsDNA genome
Present in blood near end of incubation period (1-6 months); can be transmitted by blood exposure
Most cases subclinical; 10% symptomatic cases develop acute fulminant hepatitis or chronic disease
Virus is NOT cytopathic (integrates into host DNA) - injury due to inflammation
May cause "*ground glass*" cytoplasm - distention of SER with virions; indication of chronic carrier state
Incubation period ~2 months
HBsAg appears first, followed shortly by HBeAg which peaks early and then disappears with IgM-anti-HBc and anti-HBe. HBsAg drops after ~2mos, and there is a 1-4 month "window period" before anti-HBs appears
Persistence of HBeAg indicates continued active infection and probable progression to chronic hepatitis
Progression to chronic hepatitis more common in immunocompromised patients
Symptoms appear with IgM-anti-HBc

Hepatitis C (non-A/non-B)
Enveloped ssRNA 9.4kb flavivirus
Causes most (80-90%) cases of transfusion related hepatitis; also common in IV drug users
Directly cytopathic
Seropositivity occurs late in infection
Tends to produce a greater degree of fat accumulation (macro- and microvesicular) and eosinophilic changes in the hepatocytes
Inflammation may involve the bile ducts
Insidious progression; chronic hepatitis may develop in ~50% of patients
May progress to cirrhosis even without significant piecemeal necrosis

Hepatitis delta
Defective RNA virus (small, only 1.7kb, requires concurrent infection with HepB)
Can be directly cytopathic; tends to be more severe than other hepatitis infections (marked intralobular involvement)
Microvesicular fat and many acidophil bodies are seen
IgM anti-D is a reliable marker

Hepatitis E
RNA virus (calcivirus)
Uncommon - not much known
Commonly produces cholestasis
Causes high mortality in pregnancy
HepE antigen can be detected in hepatocytes

ACUTE VIRAL HEPATITIS
May be icteric or non-icteric
Panlobular disease with irregular cords, lobular disarray, variation in hepatocyte size, inflammation (predominantly mononuclear, some neutrophils and eosinophils)
Ballooning degeneration: rapid swelling of pre-terminal hepatocytes with rarefaction of the cytoplasm
Acidophil (Councilman) bodies: Eosinophilic apoptotic degeneration of hepatocytes; shrunken cells are extruded into the sinuses
Typically, multiple small foci of hepatocyte dropout
Histologic changes essentially independent of etiologic agent
Bridging necrosis: when present, indicates greater likelihood of atypical outcome: progressive failure and death, cirrhosis

Fulminant Hepatitis
Severe form with submassive to massive necrosis
2-3 wk downhill course to death
50-60% cases caused by virus; with drugs (INH, halothane, acetaminophen) and chemicals can also cause

Acute Cholestatic Viral Hepatitis
To distinguish from obstructive cause, must identify hepatitis in areas without cholestasis

Infectious Mononucleosis
Less hepatocellular injury but marked lymphocytosis and plasmacytosis within the portal tracts, often in an "Indian-file" configuration

AIDS Hepatitis
Wide variety (any) of histologic patterns, plus often see MAI, CMV, cryptosporidium, Microsporidium, Kaposi's sarcoma, malignant lymphoma

CHRONIC HEPATITIS (Traditional Classification)
Distinction of chronic from acute hepatitis is made clinically (not histologically); usually need persistent elevation of liver aminotransferase levels in the serum for >6 months

Chronic Persistent Hepatitis
Inflammatory infiltrate restricted to portal tracts
Most common long term sequelae of viral hepatitis (B or C)
Can tolerate minimal erosion of the limiting plate, but must have no cell necrosis

Chronic Lobular Hepatitis
Patchy inflammation within the lobules with only minimal portal tract inflammation
May mimic acute hepatitis - need clinical history
Some pathologists consider this a variant of CPH

Chronic Active Hepatitis
AKA: chronic aggressive hepatitis
Piecemeal necrosis: destruction of the liver cells at the interface between the parenchyma and the portal tracts
Bridging necrosis: collapse of reticulin network due to coalescence of islands of focal necrosis
Pattern ranges from minimal to widespread necrosis
More likely to progress to end stage liver disease, especially if associated with HepBsAg
• Autoimmune chronic hepatitis: variant with clinical hypergammaglobulinemia, autoantibodies to smooth muscle and/or mitochondria, no evidence of HepB infection

ALTERNATE CLASSIFICATION FOR CHRONIC HEPATITIS
The traditional CPH, CLH, CAH terminology has several problems: subject to sampling error, little correlation with tendency for progression, misleading to clinicians
Increasing knowledge of the nature of hepatitis C infection has further damaged the utility of the traditional classification: with chronic Hep C infection, the histologic picture fluctuates between CPH and mild CAH, and can progress to cirrhosis, often suddenly, without "significant" piecemeal necrosis; hepatitis B may behave similarly
Proposed Alternate Classification scheme has three parts:
• Etiology: Viral, autoimmune, drug induced, idiopathic
• Grade: mild, moderate, severe based on portal and/or lobular activity
• Stage: (degree of fibrosis): none, portal, bridging, cirrhosis

Granulomatous Hepatitis

Often misused term, since most cases show only granulomas but no hepatitis
Granulomas seen in 3-10% of all liver biopsies, usually portal
Most common causes: infection (viral, rickettsial, mycobacterial, fungal); lipogranulomas; sarcoidosis, intrinsic liver disease (PBC), lupus, Crohn's
Drug induced causes: phenylbutazone, sulfonamides

Drug Induced Hepatitis

Response of liver to toxic injury is markedly variable - any pattern can be seen
Many responses are idiosyncratic (not related to dosage)
- Microvesicular fat: tetracycline (more marked in pregnancy)
- Cholestasis (no inflammation): contraceptives, anabolic steroids
- Cholestatic Hepatitis: phenothiazines
- Chronic active hepatitis: oxyphenisatin, isoniazid, methyldopa
- Zonal Hepatic Necrosis: yellow phosphorus (zone 1), carbon tetrachloride (zone 3), acetaminophen (zone 3); zone 3 has highest concentration of P450 oxidase
- Panlobular hepatitis: methyldopa, halothane, MAO inhibitors, antiTB agents, mycotoxins of Amanita phalloides

Alcoholic Liver Disease

Most common cause of liver disease in the US (by far)
Variety of changes seen - can never conclusively diagnose alcoholic etiology
Fatty change most common, usually macrovesicular; only finding in 40%; accumulates first in centrilobular area (zone 3); may involve entire lobules
Pericentral vein fibrosis initially involves just the wall, but then progresses to occlusion and insinuates into surrounding parenchyma in a *chicken wire* pattern, encasing individual and groups of hepatocytes
Alcoholic Hepatitis develops in 20-25% of heavy drinkers: includes inflammation and hepatocellular degeneration, predominantly in centrilobular area, with:
- Mallory bodies: refractile condensation of PAS positive material (keratin) in cells - not pathognomonic
- Neutrophilic infiltrate (attracted to Mallory bodies)
- Giant mitochondria: like Mallory bodies; PAS negative

Most common cause of cirrhosis in US (although only ~25% of heavy drinkers show progression to cirrhosis); initially large fatty micronodular, then progresses to shrunken, non-fatty, macronodular liver

Non-Alcoholic Steatohepatitis

NOTE: True microvesicular fat is too small to be seen on H&E (unlike mixed micro and macrovesicular fat, which usually indicates waxing or waning macrovesicular fat deposits)
Non-alcoholic steatohepatitis can be indistinguishable from alcoholic, including the presence of hepatitis, Mallory bodies, neutrophils, central sclerosis, fibrosis, and cirrhosis in addition to the steatosis
Obesity / rapid weight change, diabetes (often see glycogen nuclei), tuberculosis, ulcerative colitis, Reye's syndrome, anoxia

Total Parenteral Nutrition-Associated Liver Disease
Seen in patients, especially neonates, on prolonged TPN
Pathogenesis not understood: probably combination of toxic effects of amino acids, increased hepatic lipoprotein synthesis, and bowel rest with lack of luminal hormone secretion
Increased transaminases seen at 5 days
Steatosis and canalicular cholestasis begins within 2 wks
Moderate to severe portal fibrosis after 90 days

Acute Fatty Liver of Pregnancy
Usually 30th to 40th week, usually primigravidas
Grossly, pale yellow small liver
Microvesicular steatosis involving zone 3, sometimes 2 and 3, sometimes panacinar or zonal
Marked ballooning of hepatocytes also seen
May see intrahepatic cholestasis, liver cell necrosis
Resolves following delivery

Nonspecific Reactive Hepatitis

Nonspecific reaction to variety of infections/toxins; frequently seen in AIDS patients
Mild intralobular ± portal inflammation, mild proliferation of bile ducts, rare necrotic hepatocytes
Usually spares some portal tracts
May be variant of chronic lobular hepatitis

Lesions Affecting Primarily Bile Ducts

NOTE: Bile duct proliferation is also seen as a secondary process in a number of hepatic diseases
Bile plugs strongly suggest obstruction at some level
Bile plugs in regenerating ducts seen in sepsis, cholangitis, post-transplantation
Regenerating ducts (small, no lumen, peripherally located in triads) are chemotactic for neutrophils - not indicative of infection unless neutrophils are within the ducts
Copper accumulates in hepatocytes in all chronic cholestatic diseases (normally secreted in bile)
Cholestasis produces feathery degeneration of peri-portal hepatocytes (cholate injury)

Intrahepatic Biliary Atresia
[See above under Genetic / Childhood Disorders]

Extrahepatic Biliary Atresia
[See below under Gallbladder; Congenital Abnormalities]

Extrahepatic Biliary Obstruction
Acute cholestasis produces bile pigment accumulation initially in zone 3 (peri-central vein) which later extends toward the periportal canaliculi
Initially "bland" (i.e., no inflammation) centrilobular cholestasis (intrahepatocyte and canalicular)
Bile "Infarct": not really an infarct; rupture of duct with local spillage of bile, resulting in hepatocellular ballooning degeneration ONLY in areas of cholestasis; may form small bile lakes; pathognomonic for large duct obstruction
Acute "cholangitis" with periductal edema (predominantly large ducts), neutrophilic and mononuclear portal inflammation, ductular proliferation at periphery of triads (chemotactic for neutrophils; neutrophils should not be in duct lumen unless associated with an ascending infection)

Acute Cholangitis
Usually bacterial in nature (E. coli, Klebsiella, Enterobacter)
Almost never occurs without partial or complete biliary obstruction
Fever, chills, jaundice, sepsis, RUQ pain
Distention of bile ducts with neutrophils in lumen of ducts; inflammation extends into periductal tissue
May progress to liver abscesses

Primary Biliary Cirrhosis
AKA: Chronic nonsuppurative destructive cholangitis
Progressive, protracted destruction of small bile ducts
Middle age female (M:F=1:9)
Elevated alkaline phosphatase with normal transaminases
Increasing incidence recently; normal life expectancy
Antimitochondrial antibodies found in 90-95% (also seen in 20% patients with chronic active hepatitis). 4 types of anti-mitochondrial antibodies are seen, most commonly against pyruvate dehydrogenase subunit on inner membrane
Patients frequently have polyclonal IgM peak in serum
Associated with HLA-DR8
Four stages: Schuer (Ludwig)
- I Florid duct lesion (portal)
- II Ductular proliferation (periportal)
- III Scarring (bridging fibrosis)
- IV Cirrhosis

Patchy distribution and asynchronous progression: may see areas of stage I-III in same biopsy
Florid duct stage: pathognomonic: lymphocytic and plasma-cell infiltrate centered on the bile ducts; degeneration of

ductal epithelium, foamy macrophages, granulomas, minimal extension of inflammation into surrounding parenchyma with "cholate injury" (mildly pale swelling) to surrounding hepatocytes
Decrease in number of ducts, proliferation of ductules
Later, fibrosis, eventually cirrhosis
May be difficult to distinguish from chronic active hepatitis, since may see piecemeal necrosis in PBC and bile duct injury in CAH. Copper accumulation suggests PBC (normally secreted in bile)
Granulomas, generally poorly formed, may indicate a favorable prognosis
Associated autoimmune disorders unfavorable
Rx: liver transplantation

Primary Sclerosing Cholangitis
Progressive inflammatory destruction of the extrahepatic and later intrahepatic biliary system, leading to biliary cirrhosis
Rare disorder; unknown etiology, most likely autoimmune
M:F=2:1, usually <45 yrs
Involves intrahepatic and left, right, and common hepatic bile ducts (10% are intrahepatic only; none are extrahepatic only)
Patients present with progressive fatigue, pruritus, jaundice
Cholangiogram shows focal strictures, producing an apparent beading
Early lesion: pericholangitis
Later: uneven thickening of extrahepatic ducts by fibrosis and sparse mixed inflammatory infiltrate, spares epithelium
Late: fibrous obliteration of intrahepatic ducts with replacement of duct segments by solid cords of connective tissue, leading ultimately to biliary cirrhosis
Ulcerative colitis seen in 60-90% patients; UC usually develops first; PBC more common in P-ANCA positive UC
Association with UC suggest PBC may be caused by draining of bacterial or other products through the portal system
Also seen in association with Riedel's thyroiditis, retroperitoneal fibrosis, orbital pseudotumor
Associated with HLA-B8 and DR3
Increased risk of cholangiocarcinoma
Differential diagnosis: schistosomiasis (involves veins, not ducts); cholangiocarcinoma, CMV

Pericholangitis
May not be unique entity; may be early stage of PSC
Chronic inflammatory infiltrate of portal tracts surrounding bile ducts with duct damage

Cirrhosis

Scarring of the *entire* liver with diffuse fibrosis, loss of lobular architecture, and nodular regeneration
Final common pathway for many diseases - often, the specific etiology cannot be determined histologically
Vascular reorganization with formation of abnormal arteriovenous connections is common
Ductular proliferation is seen regardless of etiology - does not necessarily indicate PBC
It is important to evaluate the level of activity: look for on-going necrosis at border between septa and parenchyma

Micronodular Cirrhosis
Almost all parenchymal nodules ≤3 mm diameter
Fibrous septa are thin (2 mm) and uniform
Nodules lack portal tracts and hepatic veins
Regularity suggests a uniform pathogenesis
Used to be referred to as Laennec's, portal, or nutritional cirrhosis; these terms are no longer used because their etiological implications are not always accurate
Associated with alcoholism and chronic biliary obstruction

Macronodular Cirrhosis
Many nodules >3 mm diameter - some up to 3 cm
Broad fibrous septa as well as some delicate septa
Nodules contain portal tracts and hepatic veins
Variability suggests irregular preceding insult
May evolve from micronodular cirrhosis
Greater association with hepatocellular carcinoma
• Incomplete septal fibrosis: subtype with delicate septa forming portal-portal connections

Mixed Cirrhosis
Combination of above two processes
May represent livers in transition from micronodular to macronodular cirrhosis

Liver Disease in Pregnancy

Portal hypertension, chronic active hepatitis, Dubin-Johnson syndromes are disease exacerbated by pregnancy

Acute fatty liver of pregnancy (see above)

Viral Hepatitis
Most common cause of jaundice in pregnancy (as well as in non-pregnant women of childbearing age)
Treatment of newborn with hyperimmune serum and HBV vaccine will decrease risk of: acute infection, chronic carrier state, hepatocellular carcinoma

Intrahepatic Cholestasis of pregnancy
2nd most common cause of jaundice in pregnancy
May occur anytime during gestation - more common later
Pruritus and jaundice persist till delivery
Bland cholestasis, predominantly zone 3
Presumably related to pregnancy associated steroids
Greater risk is to fetus: fetal distress, premature delivery, fetal death in utero

Liver disease in toxemia (pre-eclampsia) of pregnancy
Usually third trimester, usually primigravida
May see diffuse or confluent hemorrhage, parenchymal or capsular
Areas of infarction common - may be massive
Hemorrhage, fibrin deposition, hepatocellular necrosis in periportal regions
May also see sinusoidal fibrosis, steatosis, portal lymphoplasmacytic infiltrate, bile inspissation in canaliculi

HELLP Syndrome
Severe form of toxemia
Combination of hemolysis, elevated liver tests, low platelets
May result in hepatic rupture

Cystic Liver Disease

Adult Polycystic Liver Disease
Autosomal dominant
Multiple variable sized cysts (mm's to >10 cm) usually (90%) lined by a cuboidal epithelium
Do NOT communicate with biliary tree
Frequently accompanied by medullary renal cysts
Usually asymptomatic

Caroli's Disease
AKA: communicating cavernous biliary ectasia
Autosomal recessive
Multiple, large, ectatic ducts communicating with biliary tree
Patients may have recurrent cholangitis
Often seen in conjunction with congenital hepatic fibrosis or choledochal cysts

Solitary Non-Parasitic Cyst
Etiology unclear - probably retention cyst of bile ductule origin; flattened cuboidal epithelial lining

Echinococcus Cyst
AKA: Hydatid cyst
Rare in US, frequent in Iceland, Australia, South America
Caused by larval or cystic stage of dog tapeworm, most commonly Echinococcus granulosus
Liver and lung most common sites for cysts
Eosinophilia present while parasite is alive
When parasite dies, wall of cyst collapses and calcifies

Rupture into peritoneum can cause death by anaphylaxis
Usually unilocular cyst, 1-7 cm diameter; 75% right lobe
Cyst filled with colorless fluid, daughter cysts
Wall has outer chitinous (fibrous) layer and inner germinal layer - inner layer calcifies

Abscess (Amebic / pyogenic)
Originally, used to be more common in young adults, caused by ameba or secondary to pylephlebitis
Now, more commonly seen in older patients, usually enteric bacteria
30-80% mortality
Amebic cysts: odorless "anchovy paste" composed of necrotic hepatic tissue
Pyogenic cysts: foul smelling contents with necrosis and neutrophils
Predisposing factors: biliary tract obstruction/infection, bacteremia, direct extension, trauma, pylephlebitis
Multiple lesions seen in 50% pyogenic, 25% amebic

Mesenchymal Hamartoma
[See below under Neoplasia, Other]

Liver Transplantation

First one performed in 1963
Indications: idiopathic cirrhosis, primary biliary cirrhosis, sclerosing cholangitis, biliary atresia, alpha-1-antitrypsin deficiency
~75% recipients have one or more episodes of rejection
~15% require re-transplantation due to graft failure
Graft rejection most common reason for failure; usually occurs 1-4 wks after transplant; earlier failure usually due to technical problems; later more commonly infectious
Harvesting/reperfusion injury: microsteatosis, ballooning degeneration, central canalicular cholestasis; later: acidophil bodies, hemorrhage, increased numbers of Kupffer cells; finally: centrilobular necrosis
Hyperacute rejection (necrotizing arteritis) very unusual; immediate graft failure usually secondary to occlusive or non-occlusive ischemia or infection
Acute Rejection: triad: mixed lymphocytic-neutrophilic portal infiltrate, bile duct injury, endothelialitis:
Grade I: <50% bile ducts damaged, endothelialitis
Grade II: >50% bile ducts damaged, ± endothelialitis
Grade II: Larger vessel arteritis
Treated Rejection: mononuclear cell infiltrate disappears first, leaving acute inflammation
Chronic Rejection: obliterative endarteritis, portal fibrosis with bridging, paucity of bile ducts, cirrhosis, foam cell accumulation within intima of large vessels
Acute vanishing bile duct syndrome: irreversible loss of bile ducts within 100 days following transplantation due to a destructive cholangitis
Lymphoproliferative Disorder: affects 3-4% of patients

Hyperplasia / Neoplasia

Nodular Regenerative Hyperplasia

AKA: Nodular transformation
Formation of cirrhosis-like nodules but without intervening fibrosis; nodules separated by compressed atrophic "normal" liver
May represent compensatory hyperplasia following diffuse chronic injury such as ischemia or chemical injury
Cell plates usually 2 cells thick, indicating regeneration
Generally involves the entire liver

Partial Nodular Transformation
Variant in which changes are confined to the area of the porta hepatis
Probably an early stage of nodular transformation

Focal Nodular Hyperplasia

Any age, usually 20-40's, but all ages; F:M=2-4:1
Asymptomatic in 80%; multiple in 20%
Arteriographically: hypervascular with centrifugal filling and a dense capillary blush
Grossly: gray-white, unencapsulated, solid mass (usually <5cm) beneath capsule, sometimes pedunculated; often central fibrosis with radiating, stellate bands of fibrosis
Histology: all components of the normal liver lobule present; may have eccentrically thickened vessels in septa secondary to fibromuscular hyperplasia; septa may divide lesion into lobules, simulating cirrhosis
Arteriolar occlusion in central scar often seen: presumably etiologic: small area infarcts and scars; surrounding areas undergo compensatory hyperplasia

Liver Cell Adenoma

Usually female (M:F=1:9), 20-40's; definite relationship to oral contraceptives (80-90%), often regress when discontinue
Most are solitary, right lobe, usually >10cm at presentation
More often symptomatic; hemorrhage common: 25% present with hemoperitoneum
Well defined capsule, well-differentiated hepatocytes with abundant cytoplasm, 2 cell layers thick, but NO portal triads, central veins, or fibrosis, and no bile ducts or connection with the biliary system
Largest vessels are at the periphery and show intimal thickening and smooth muscle proliferation
Absence of vascular invasion differentiates from carcinoma. Also, hepatoma often shows "nodule within nodule", infiltrative growth pattern, thick cords to sheets of cells

Multiple Hepatocellular Adenomatosis
M=F; no association with contraceptives, patients are older
Usually >10 nodules of varying size
May be a **very** well differentiated hepatocellular carcinoma

Macroregenerative Nodule

AKA: Adenomatous hyperplastic nodule
Small numbers of nodules, usually >1cm, usually occurring in the setting of cirrhosis, with a thin fibrous rim
Two types:
• Nodules similar to surrounding smaller nodules
• "Dysplastic Nodule" with small cell dysplasia, a basophilic cytoplasm, monomorphous histology; borderline lesion; nodule within nodule appearance suggests hepatoma

Hepatocellular Dysplasia

Controversial subject
Even when correctly diagnosed, no clear indications for therapy

Large Cell Dysplasia
Isolated large cells with enlarged nuclei but normal N:C ratio
Normal nuclear contours
Commonly seen in cirrhosis
No evidence for pre-malignant condition

Small Cell Dysplasia
Clusters of normal sized cells with larger nuclei (increased N:C ratio) and irregular nuclear contours
Architecture reasonably normal
DNA ploidy shows an increased number of peaks, most centered around 2n and 4n
Proliferating cell nuclear antigen and Ki-67 are both increased, although not as much as in hepatocellular Ca
Pre-malignant

Hepatocellular Carcinoma

AKA: Hepatoma
Any age; M>F, especially when associated with cirrhosis
Usually presents with abdominal pain ascites, hepatomegaly
Alpha-fetoprotein levels often elevated in serum
Predisposing factors: cirrhosis, hepatitis B and C, Thorotrast (thorium dioxide), anabolic or progestational steroids (may be adenomas), alcohol, radiation, alpha-1-antitrypsin deficiency, aflatoxins from fungus Aspergillus flavus, ataxia-telangiectasia syndrome, hemochromatosis
May be single large mass ("massive"), multiple discrete masses ("nodular") or numerous small nodules scattered throughout the liver ("diffuse")
May be encapsulated, pedunculated, any size
Histologic patterns: trabecular (most common), solid, pseudoglandular (acinar), pelioid, giant cell, sarcomatoid, clear cell
Network of sinusoidal vessels surrounds tumor cells
Stroma usually scanty
Hepatocytes may be well differentiated to very bizarre
Vascular invasion common
Portal vein thrombosis found in a large percentage of cases
Intranuclear pseudoinclusions, Mallory's hyaline, bile pigment, even significant clear cell change can all be seen
AFP, AAT, transferrin, Cam 5.2 positive; CEA, AE1 negative
Prognosis poor: 10% survival at 5 yrs
Good prognosis: low stage, encapsulation, single lesions, absence of cirrhosis, perhaps those associated with OCP
No effect on prognosis: tumor size, age, sex, present of HBV

Sclerosing Hepatic Carcinoma

3% of primary hepatic tumors; M=F; usually in 60's
2/3 of the patients have hypercalcemia and hypophosphatemia without bone metastases
Only 50% of cases associated with cirrhosis
Cords of tumor cells in a dense fibrotic stroma
Most show hepatocellular histology; 1/3 show partial to complete cholangiocarcinoma histology
Aggressive: mean survival = 6 months

Fibrolamellar Variant

AKA: Polygonal cell type; oncocytic type
Predominantly young patients (~25 yrs); M=F; 2/3 in left lobe
1-2% of hepatomas, but ~40% of the under 40yrs population
No association with cirrhosis or hepatitis virus
Fibrosis arranged in a lamellar fashion around polygonal, deeply eosinophilic hepatocytes (packed with mitochondria) which form sheets and occasional trabeculae
Calcification may be seen on plain films
More amenable to resection (60%)
Cure rate of 50% much better than conventional hepatoma

STAGING

	# tumor masses	Size	Vascular Invasion
T1:	1	<2 cm	–
T2:	1	<2 cm	+
	multiple in 1 lobe	<2 cm	–
	1	>2 cm	–
T3:	1	>2 cm	+
	multiple in 1 lobe	<2 cm	+
	multiple in 1 lobe	>2 cm	+/–

T4: multiple lesions of any size in multiple lobes or involving major vessels
N1: regional lymph nodes involved
M1: Distant metastases

Stage	T1	T2	T3	T4
N0	I	II		IV A
N1			III	
M1			IVB	

Hepatoblastoma

Almost exclusively in children, usually in first 3 yrs; may be congenital; may be familial
Single, usually encapsulated
Can be associated with Wilms' tumor, glycogen storage dz, hemihypertrophy, virilization (ectopic steroid production), Beckwith-Wiedemann syndrome, polyposis coli
Tumor cells reactive for EMA, keratin, vimentin, AFP, CEA
Immunohistochemistry suggests the small "anaplastic" cells mature first to embryonal cells, which may then undergo ductular differentiation or progress to fetal type cells
Locally invasive; metastases to regional LNs, lung, brain
40-70% are unresectable at diagnosis
Prognosis better than hepatocellular carcinoma (especially for the fetal type) but is still <40% long term survival

Pure (Epithelial) Type (75%)

Fetal: small monotonous hepatocytes arranged in irregular two-cell thick cords with sinusoids, recapitulating fetal liver; extramedullary hematopoiesis common
Embryonal: predominantly solid growth pattern with ribbons, rosettes, and papillary formations; cells smaller, immature, usually more mitoses, higher N:C ratio; may represent ductular differentiation
Macrotrabecular type: resembles hepatocellular carcinoma

Mixed Type (25%)

Epithelial cells plus primitive stromal component which may be undifferentiated or develop into bone or cartilage

Anaplastic Type (rare)

AKA: undifferentiated, small cell
Sheets of loosely cohesive small blue cells

Benign Bile Duct Tumors

Bile Duct Hamartoma

AKA: von Meyenburg complex, Moschowitz complex, ductal plate anomaly
Multiple small white nodules scattered throughout the liver
Focal (usually periportal) disorderly collection of bile ducts and ductules, slightly dilated and containing bile, surrounded by abundant fibrous stroma
Some may be ischemic in origin
May be associated with adult polycystic hepatorenal disease

Bile Duct Adenoma

Firm, white, discrete subcapsular nodules, usually <1 cm
80% of true adenomas are single; almost never bile stained
Multiple small cuboidal epithelium lined ducts with small lumens, without bile, in a scant to abundant connective tissue stroma
CEA, EMA, keratin positive

Biliary Cystadenoma

Multilocular cysts with mucinous or clear fluid lined by a simple cuboidal to columnar epithelium
Usually right lobe; 25-30 cm diameter, F>>M
Malignant transformation can occur: pleomorphism, anaplasia, stromal infiltration

Biliary Papillomatosis

Dilated intrahepatic or extrahepatic ducts with exophytic, papillary proliferations of duct lining cells on fibrovascular cores
Although cytologically benign, often recurrent, progressive, and ultimately fatal

Cholangiocarcinoma

5-30% of primary hepatic malignancies
Most seen >60yrs of age; M=F
Some arise within congenitally dilated intrahepatic bile ducts, after Thorotrast, anabolic steroids, intrahepatic lithiasis, primary sclerosing cholangitis

No relationship with cirrhosis
Marked heterogeneity of neoplastic cells within same gland
Tendency to spread between hepatocyte plates and along ducts and nerves, and to invade lymphatics
Usually marked desmoplastic response
Mucin stains usually positive; occasionally signet ring cells
Keratin (Cam 5.2 and AE1), EMA, CEA positive; AFP negative
Klatskin tumor: cholangiocarcinoma arising at confluence of left and right hepatic ducts
Adenosquamous and mucoepidermoid variants have been described
Staging is same as for hepatocellular carcinoma

Vascular Tumors

Hemangioma
Most common benign tumor of liver; usually cavernous
M:F=1:5; may enlarge during pregnancy

Infantile Hemangioendothelioma
Solitary or multiple
Two histologic types:
• Type I: small, well formed vessels with plump endothelial lining cells; may progress to cavernous hemangioma
• Type II: marked nuclear pleomorphism, mitoses, papillary projections of endothelial cells into lumen of cystic spaces
High mortality, often due to hepatic failure or CHF

Epithelioid Hemangioendothelioma
Mostly adult females, perhaps related to oral contraceptives
Tumors often multiple, involving entire liver
Dendritic and epithelioid tumor cells infiltrate sinusoids and veins
Abundant stroma which is variably myxoid to sclerotic; dystrophic calcification can be seen
Better prognosis than angiosarcoma; 28% metastasize, but does not preclude long term survival

Angiosarcoma
AKA: Malignant hemangioendothelioma
Freely anastomosing vascular channels; varying degrees of differentiation
Usually Factor VIII immunoreactive
Increased risk factors: cirrhosis, vinyl chloride exposure, thorium dioxide exposure, arsenic exposure
Most patients die within 6 months of liver failure or abdominal hemorrhage

Other Tumors

Focal Fatty Change
Not a tumor
Steatosis confined to a discrete area of the liver from a few millimeters to 10 cm in diameter
No clinical significance, but often mistaken at ultrasound or CT for something more ominous

Mixed / Combined Hepatocellular and Cholangiocarcinoma
Both malignant hepatocytes and malignant bile duct cells
<5% of primary hepatic carcinomas
Presumably arise from common precursor cell (both the bile ducts and hepatocytes arise from same precursors)

Mesenchymal Hamartoma
Usually infants
Solitary, spherical, reddish nodule 5-20 cm in diameter; may be pedunculated; may show cystic accumulation of fluid in stroma
Well vascularized loose mature connective tissue intermixed with irregular, elongated, branching bile ducts, vessels, occasional islands of hepatocytes or hematopoiesis
Looks like breast fibroadenoma at low power

Malignant Mesenchymoma
AKA: undifferentiated sarcoma, embryonal sarcoma
Usually children 6-10 yrs old; present with abdominal swelling
Highly atypical mesenchymal cells with entrapped hyperplastic and dilated bile ducts near periphery
Large, solitary, well circumscribed, necrosis, hemorrhage
Very poor prognosis

Angiomyolipoma
Generally solitary, 1-20 cm, tan to yellow, well demarcated
Hematopoietic islands seen in 2/3

Carcinoid Tumor

Teratoma

Metastatic Tumors

Most common malignant tumor in liver (>90%!; drops to <50% in cirrhotic livers)
Frequent primary sites include gallbladder, bile ducts, pancreas, stomach, large bowel, lung, breast, kidney
Leukemias and lymphomas often involve the liver
Sarcomas also frequently metastasize to liver

GALLBLADDER

Normal

In 60-70% individuals, common bile duct joins the pancreatic duct and empties into duodenum at a single site
Gallbladder has no muscularis mucosa or submucosa; mucosal lining and lamina propria directly above muscularis
Some glands penetrate into wall
Bile is 97% water
Liver secretes 0.5 to 1.0 L bile per day; gallbladder can hold 50ml - concentrates bile 5-10 fold
Bile acids (cholates, deoxycholates, chenodeoxycholates) make up 70% of solutes in bile, phospholipids 22%, cholesterol 4%, bilirubin 1%
Most bile salts excreted into duodenal lumen are reabsorbed in the small intestine and colon: enterohepatic circulation

Congenital Abnormalities

Extrahepatic Biliary Atresia
Partial/total absence of permeable bile ducts between porta hepatis and duodenum; may have fibrous cords without patent lumen
1/20,000 live births; most common cause of persistent neonatal cholestasis
Etiology may be developmental (persistence of solid stage of duct development) or acquired (in utero destruction of duct system by viral / other injury)
Intrahepatic ducts initially proliferate (peaks at 205 days), fibrose, then regress (most rapid at ~400 days)
• Correctable (10%): patent proximal ducts; perform biliary enteric anastomosis
  • Type I: involves only common bile duct
  • Type II: common bile duct and hepatic duct absent

- Uncorrectable (Type III) (90%): no patent portion of the extrahepatic system; 2/3 will have no gallbladder, 1/3 will have patent gallbladder and cystic duct, but no ducts between liver and cystic duct; perform Kasai procedure (hepatic porto-enterostomy) before 10wks age can restore bile flow - large failure rate - presence of bile ducts larger than 200μm diameter in resected portion is a positive prognostic sign

Choledochal cyst
- Most common cause of obstructive jaundice in children beyond infancy
- Focal fusiform or diverticular dilatation of common bile duct
- May secondarily obstruct extrahepatic biliary tree
- Cyst wall fibrous, sometimes calcified, with 1-2 liters bile
- Increased incidence of carcinoma

Heterotopic Tissue
- Gastric mucosa, intestinal, pancreas, adrenal, thyroid
- Most occur as well defined nodules in neck or cystic duct

Cholelithiasis

Only 10% gallstones are pure:
- Pure cholesterol stones: pale yellow, round/ovoid, granular surface, often single, crystalline core, radiolucent
- Pure calcium bilirubinate stones (pigment stones) are black oval, numerous; associated with cirrhosis and hemolytic disorders; when develop in setting of infection, brown rather than black and softer
- 80% of all gallstones are mixed with varying combinations of cholesterol, calcium bilirubinate, and calcium carbonate; usually multiple and laminated
- Some designate any stone with >70% cholesterol as a cholesterol stone and any with <30% cholesterol as a pigment stone
- Combined stones (10%) have either pure nucleus with a mixed shell or vice versa
- ~20% stones have enough calcium to be radio-opaque
- Bile salts and, to a lesser extent, lecithin (phospholipid) increase solubility of cholesterol in bile
- Lithogenesis promoted by excess of cholesterol relative to amount of bile salts, followed by nucleation precipitation and then growth of aggregates
- Biliary sludge with mucus and small crystals usually precedes stone formation
- Risk factors: female, age >40, obesity, multiple pregnancies; any drugs or hormones which increase cholesterol excretion or decrease bile salt levels promote stones

Inflammatory Disorders

Acute Cholecystitis

- 90% cases caused by impaction of gallstone in neck of gallbladder or cystic duct ("calculus cholecystitis")
- Often sudden onset; surgical emergency
- E. coli or other gram negative bacilli can be cultured from bile in 80% cases - probably secondary event
- Acalculus cholecystitis much less common; seen more frequently in men and in association with previous surgery, bacteremia, trauma, systemic arteritis, diabetes, prolonged labor, intravenous hyperalimentation
- Grossly, gallbladder enlarged and tense - may be bright red
- Serosa may be coated by fibrin
- Contents may be turbid with fibrin or pus
- Wall thickened and edematous, but in severe cases may be gangrenous - infiltrated by neutrophils
- In rare cases, may heal by calcifying → porcelain gallbladder

Chronic Cholecystitis

- Virtually always associated with cholelithiasis; F:M=3:1
- May result from repeated mild acute inflammatory events, but usually seen in absence of history of acute events
- Wall often has some degree of chronic inflammation, but may be minimal; subserosal fibrosis, entrapped epithelial crypts (cholecystitis glandularis), dystrophic calcification
- Acute and chronic features may be seen together

Follicular cholecystitis
- Lymphoid follicles present transmurally

Eosinophilic Cholecystitis
- Large number of mature eosinophils

Xanthogranulomatous cholecystitis

Other Non-Neoplastic Disorders

Cholesterolosis
- No clinical significance
- Yellow flecks studding mucosal surface
- Mucosa usually congested ("strawberry gallbladder")
- Focal accumulation of lipid laden macrophages in the lamina propria at the tips of mucosal folds

Adenomyoma and Adenomyomatosis
- Proliferation of both glandular and smooth muscle elements with extension of the surface epithelium deep into the wall

Inflammatory Polyps
- Fibrous stroma covered by a usually intact epithelium creating a sessile mucosal projection; stroma infiltrated with chronic inflammatory cells

Mucocele (Hydrops)
- When outflow obstructed by a stone but acute inflammation does not develop
- Gallbladder distended with clear, watery, mucinous secretion
- Wall often becomes stretched and atrophic

Neoplasms

Benign Lesions

Papillomas and Adenomas
- Rare
- Localized benign overgrowths of lining epithelium
- Papilloma usually has stalk-like connection; adenoma connected via broad base

Paraganglioma

Granular Cell Tumor

Carcinoma of Gallbladder

- More frequent in females (3-4:1)
- 90% patients >50 yrs old
- May be diffuse (70%) or polypoid (30%) mass
- 80-90% cases also have gallstones
- Diffuse form may be grossly indistinguishable from chronic cholecystitis
- Most are adenocarcinomas; may be papillary, usually deeply invasive, poorly differentiated cytologically
- Keratin and CEA positive
- Focal intestinal metaplasia common
- Squamous metaplasia can give rise to adenoacanthoma or adenosquamous carcinoma
- Undifferentiated (anaplastic, pleomorphic, sarcomatoid) histology also exists
- Most have invaded the liver by time of diagnosis (Stage V); uniformly fatal

STAGING

Nevin Scheme

Stage		5 yr survival
I	Intramucosal	90%
II	Mucosa and muscularis	55%
III	Full thickness of wall	15%
IV	Cystic lymph node	15%
V	Liver or other organs	3%

American Joint Committee on Cancer

T1a	Mucosal
T1b	Muscularis
T2	Perimuscular connective tissue
T3	Perforates serosa or extends into adjacent organ (if liver, <2 cm)
T4	>2 cm into liver, or into 2 or more adjacent organs
N1	Cystic duct, pericholedochal, or hilar LNs
N2	Peripancreatic, periduodenal, periportal, celiac, or superior mesenteric LNs

Stage	T1	T2	T3	T4
N0	I	II	III	IV A
N1	III	III	III	IV A
N2	IV B	IV B	IV B	IV B

Carcinoma of Extrahepatic Bile Ducts

AKA: Cholangiocarcinoma
Equal frequency in males and females; usually >60 yrs
90% present with jaundice
In order of frequency, most common sites in biliary tree are gallbladder, papilla of Vater, common bile duct, left or right hepatic ducts, common hepatic duct
Can be polypoid or superficial, but most are nodular or sclerosing with deep penetration into wall
Heterogeneity of cells within the same gland, increased N:C ratio, nucleolar prominence, and stromal and perineural invasion
Choledochal cysts, cholangitis, and Giardia predispose
Overall survival rate <10%

Embryonal Rhabdomyosarcoma

Usually in children <5 yrs old
Arise in extrahepatic bile ducts (>75% in common bile duct); patients present with obstruction and jaundice
Botryoid morphology with cambium layer subjacent to the bile duct epithelium

PANCREAS

Normal Anatomy

Averages 15cm length, 60-140gm in adult
Close proximity to duodenum, ampulla of Vater, common bile duct, superior mesenteric artery, portal vein, spleen and its vessels, stomach, transverse colon, left lobe of liver
Large reserve of function, so damage detected only when advanced or when involves surrounding structures
At birth, the islets represent a greater fraction of the whole gland than in the adult, since with age the exocrine pancreas "overgrows" the endocrine pancreas

Exocrine

Acini separated by scant connective tissue stroma
Ductal system: centroacinar cells, then cuboidal, columnar
Duct cells are mucin secreting; intercalated ducts to intralobular to interlobular, etc.
Main ducts: Wirsung (main) and Santorini (accessory)
In 60% adults, major pancreatic duct does not empty into duodenum directly but rather into the common bile duct
Secretion occurs in response to secretin from duodenum

Endocrine

Islets of Langerhans (10^6); more in tail; 1-1.5 gms total
Cell types: Granules by EM
- Alpha (20%; peripheral; glucagon) round with gray halo
- Beta (70%; central; insulin) rectangular, halo, matrix
- Delta (5-10%; somatostatin: large, pale, no halo suppresses insulin + glucagon)
- PP cell (1-2%; pancreatic polypeptide; small, dark also in exocrine pancreas)
- D1 cells (P cells) (Vasoactive Inhibitor Peptide)
- EC cells (serotonin)

Dorsal derived islets have more alpha cells than PP cells; Ventral derived islets have abundant PP cells

Embryology

Both exocrine and endocrine pancreas form from endodermally derived tubules
Islets form from cells which separate from tubules (~9 weeks)
Arises from two duodenal buds: dorsal and ventral pancreas
Ventral (uncinate process and inferior portion of head) arises near the entry of the common bile duct and grows more slowly, eventually swinging around posteriorly with the bile duct as the duodenal C-loop forms (5-6 wks) to fuse with the larger dorsal portion (body and tail)
Wirsung duct formed from ventral duct and distal portion of the dorsal duct; the proximal portion of the dorsal duct, if it persists, becomes the Santorini (accessory) duct
In 10%, the ducts fail to fuse - double duct system persists

Heterotopia

Approximately 2% incidence
Most common sites are duodenum, stomach, jejunum, Meckel's diverticulum, gallbladder, large bowel
Firm, yellow, lobulated - often central umbilication
Islet tissue found in only 1/3
May become inflamed or neoplastic

Annular Pancreas

Rare malformation, more prevalent in males
May result from growth of bifed ventral bud both anterior and posterior to the duodenum, each fusing with dorsal bud
May cause duodenal obstruction shortly after birth

Congenital Islet Hyperplasia

Children of diabetic mothers
Islets infiltrated by eosinophils
Also see asymmetric septal hypertrophy and sacral agenesis
Neisidioblastosis: diffuse beta cell hyperplasia both within islets and throughout the pancreas

Inflammatory / Non-Neoplastic Disorders

Acute Pancreatitis

Etiology controversial: most likely transient/partial obstruction (calculus or sphincter spasm) resulting in bile reflux into pancreatic duct system with activation of pancreatic enzymes and subsequent tissue destruction
80% of cases are associated with either biliary tract disease (M:F=1:3) or alcoholism (M:F=6:1)
Postoperative pancreatitis usually related to surgical trauma
10-20% patients with parathyroid adenoma/carcinoma develop acute pancreatitis - ?hypercalcemia
Other etiologies include idiopathic hypercalcemia, thiazides, furosemide, and estrogen use
Acinar cell homogenization, ductal dilatation, diffuse edema, acute inflammation, fibrosis, fat necrosis, calcification
May result in large abscess formation
Severe form referred to as acute hemorrhagic pancreatitis or acute pancreatic necrosis
20% mortality (10-15% for swollen, edematous gland; 50% if hemorrhagic and necrotic gland)

Chronic Pancreatitis

AKA: Chronic relapsing pancreatitis
Usually not associated with acute pancreatitis
Duct and islets are spared initially

Chronic obstructive pancreatitis

Narrowing or occlusion of the duct, usually from carcinoma or stone, most commonly cholelithiasis
Less severe changes than calcifying form, with relative sparing of the duct epithelium
With large duct obstruction, pancreatic damage is relatively uniform throughout the gland

Chronic calcifying pancreatitis

Most commonly seen in alcoholics
Damage is irregular and patchy: dilatation of ducts with squamous metaplasia and intraluminal protein plugs (which often calcify), acinar dilatation and atrophy, interlobular fibrosis
Pseudocyst formation common
Calcifications range from microscopic to stones several centimeters in diameter

Complications

- Widespread metastatic fat necrosis: presumably related to release of lipase - involves subcutaneous tissue, mediastinum, pleura, pericardium, liver, etc.
- Erythema nodosum like panniculitis
- Initially a marked proliferation of islet cells, and then later a preferential loss of insulin secreting cells
- Avascular bone necrosis

Cystic Lesions of the Pancreas

Congenital Cysts

Anomalous development of pancreatic ducts
Related to similar diseases in liver and kidney
May be single or multiple, microscopic or large
Von Hippel-Lindau disease: pancreatic cysts associated with angiomas in the retina, cerebellum, brain stem

Cystic Fibrosis

AKA: Mucoviscidosis
Cysts form secondary to duct obstruction with thick, tenacious secretions

[See also Congenital Syndromes Outline]

Pseudocysts
- Account for >75% of all cystic lesion in the pancreas
- Seen in pancreatitis, trauma, and occasionally neoplastic duct obstruction
- Amylase rich fluid in cysts
- Can extend well beyond pancreas; multiple in 15%
- Cysts characteristically have no epithelial lining or connection with the duct system
- Complications include rupture, hemorrhage, erosion into surrounding structures (e.g. splenic artery)

Diabetes Mellitus

- Most common disease process affecting the pancreas
- Islets may be normal , but may see amyloid deposition (40%), fibrosis (25%), or vacuolation /destruction of beta cells
- Other associated findings:
  - Microangiopathy
  - Retinopathy (nonproliferative [exudative] and proliferative types)
  - Nephropathy (nodular Kimmelstiel-Wilson glomerulosclerosis, pyelonephritis, papillary necrosis)
  - Neuropathy (usually symmetric polyneuropathy)

PRIMARY

Type I
- AKA: Juvenile onset, insulin dependent; ketoacidosis prone
- Genetic susceptibility (50% concordance among identical twins)
- Autoimmune destruction of islets
- Increased association with rubella and coxsackie viruses, and with cow-milk allergy

Type II
- AKA: Adult onset, non-insulin dependent
- Obese and non-obese subtypes
- 90% concordance among identical twins
- Decreased secretion of insulin without loss of islets

SECONDARY

- Hemochromatosis, drugs, tumors, chronic pancreatitis

Other

Hemochromatosis
- Hemosiderin deposition in acinar and islets cells leads to brown discoloration ("bronze diabetes")

Fatty Infiltration (Lipomatosis)
- Non-destructive infiltration - no clinical significance

Pancreatic Atrophy
- If ischemic, will affect both endocrine and exocrine
- Obstruction of ducts (ligation) can cause complete destruction of exocrine pancreas with sparing of islets (allowed the initial isolation of insulin)

Pancreas Transplant

- Sparse inflammatory infiltrate (lymphocytes) always seen
- For rejection, need to have patchy inflammation in acinar tissue and ducts, with cell drop-out, interstitial fibrosis, cellular atypia, and a capilaritis
- Chronic rejection shows endarteritis with foam cell accumulation

TUMORS of the Exocrine Pancreas

STAGING

T1	limited to pancreas	Ia: ≤2 cm
		Ib: >2 cm
T2	extension to duodenum, bile ducts, soft tissue	
T3	extension to stomach, spleen, colon, major vessels	
N0	No regional nodes	
N1	Positive regional nodes	

	T1	T2	T3
N0	I	I	II
N1	III		
M1	IV		

Infantile Pancreatic Carcinoma

- AKA: pancreatoblastoma
- Common pancreatic tumor in children, but not only kind
- Well formed glands arranged around solid nests of cells which may have squamoid features
- Looks like islet cell tumor or carcinoid, but no granules by EM
- Actually, acinar cell tumor
- Relatively favorable prognosis, but can be large, direct extension, metastases

Papillary & Solid Epithelial Neoplasm

- AKA: papillary-cystic carcinoma, cystic-solid papillary carcinoma (depending on proportion of components)
- Probably begins as a solid tumor; degeneration of cells far from vessels with sparing of the perivascular cells leads to a pseudopapillary pattern and cystic spaces
- Most cases in young women (20's)
- Usually large and hemorrhagic/necrotic on cut section
- Solid areas are very cellular, simulating islet cell tumor; cells have ovoid nuclei with folds, indistinct nucleoli, few mitoses; cytoplasmic PAS positive hyaline globules
- Papillae: thick edematous (sometimes mucinous with foamy cells) fibrovascular cores covered by a multilayered epithelium
- Can see focal reactivity for a number of antigens, most commonly NSE; usually vimentin positive, keratin negative
- Ultrastructurally, features of acinar, ductal, and endocrine differentiation
- Most likely tumor of primitive cells with the capacity for dual differentiation
- Excellent prognosis

Microcystic Cystadenoma

- AKA: glycogen rich, serous cystadenoma
- Patients usually elderly; usually head of pancreas
- Associated with von Hippel-Lindau syndrome
- Large; numerous small cysts (most <1 cm) lined by flat cuboidal cells with abundant glycogen, minimal mucin, microvilli; myoepithelial cells still present
- Prominent vascularization, central scar (may be calcified); islet cells in trabeculae
- Invariably benign

Mucinous Cystic Tumors

- AKA: mucinous cystadenocarcinoma
- Younger age group (40's), female predominance
- More commonly body or tail; may be confused w/ pseudocyst
- Large, often encapsulated, with multilocular or unilocular cysts, tall mucin producing cells; may have intermixed endocrine or Paneth cells

Cellular stroma (similar to ovary), often calcification in wall; hypovascular
Invasion of wall or frank anaplasia indicates malignancy, but all mucinous tumors are potentially malignant
Overall 5yr survival 50%

Ductal Adenocarcinoma

85% of all pancreatic malignancies, even though duct cells account for only 4% of pancreatic mass
4th most common cancer killer in US
Increased incidence in Peutz-Jeghers syndrome, exposure to betanaphthylamine or benzidine, cigarette smoking (2x), diabetes, gastrectomy
Most patients are elderly, slight male predominance
2/3 cases in head of pancreas, 1/3 in body or tail
Multiple tumors found in 20%
Poorly delineated, firm, white/yellow
Well to poorly differentiated; occasionally papillary
Well differentiated tumors can be very difficult to diagnose; look for nuclear pleomorphism (size variation >4:1), loss of polarity, incomplete glandular structures, disorganized duct distribution, prominent nucleoli, mitoses
Diagnosis by cytology even more problematic: success rate varies with source: pancreatic secretions: 50-85%; duodenal secretions: 66%; percutaneous or intraoperative FNA: 90%; transduodenal biopsy avoids the risk of fistula formation
Desmoplastic stromal reaction common
Immunoreactive for keratin, EMA, CEA, CA19-9, laminin
Carcinoma in situ present in 20-30%, often far from tumor mass - may be at surgical margin
Obstruction of the duct can lead to a background of chronic pancreatitis
Islet tissue preserved longest, but when destroyed creates diabetic picture clinically
Trousseau's Syndrome: migratory peripheral thrombophlebitis seen in 10-25% of patients

Microscopic Variants

Adenosquamous, oncocytic, clear cell, signet ring, mucinous (colloid) carcinoma

Spread

Perineural invasion in 90% - beware of benign epithelial inclusions
85% cases are beyond pancreas at the time of diagnosis
88% to peripancreatic LN's, 33% to more distant nodes
Liver, peritoneum, lung, adrenal, bone, skin, CNS
Liver metastases most common in tumors of body or tail

Prognosis

10% 1 yr survival; 2% 5 yr survival
Even T1 lesions have only a 15% 5 yr survival

Acinar cell carcinoma

1-2% of all pancreatic cancers
May arise from acinar hyperplasia, benign form may exist
Generally solid mass obliterating architecture without duct dilatation - occasionally multicystic
Acinar cells with numerous zymogen granules, often prominent nucleoli, usually immunoreactive for trypsin
May be associated with widespread subcutaneous fat necrosis
Very poor prognosis

Anaplastic Carcinoma

7% of non-endocrine pancreatic malignancies
Most involve body or tail
Most patients >50yrs; male predominance
Extremely poor prognosis
Three subtypes:
• Pleomorphic: bizarre multinucleated giant tumor cells
• Sarcomatoid: spindle cells
• Undifferentiated: small cell

Giant Cell Tumor

Two cell types: uniform spindle cells with atypical features and multinucleated osteoclast-like giant cells (not atypical)
Prognosis more like ductal than anaplastic

TUMORS of the Endocrine Pancreas

GENERAL

Much less common than tumors of the exocrine pancreas
Mostly adults, some in infants (even newborns)
Most commonly body or tail (more islets)
May arise from pleuripotential precursor (terminal ducts) rather than islets themselves
May be non-functioning or secrete one or several peptides: if multiple tumors, each may be same peptide, different peptide, or mixture
Grossly: solid, pink, vascular, may show extensive fibrosis, calcification, bone; may be partially cystic
Generally, monotonous proliferation of small cells with central nuclei, occasional small nucleoli, and a finely granular cytoplasm; Grows in one of four patterns:
• Solid (A, I): most common pattern; any cell type
• Gyriform (B, II): alpha or beta cells
• Glandular (C, III): G or VIP cells
• Nondescript (D, IV)
Amyloid may be seen in stroma of insulin secreting tumors
Cells generally immunoreactive for NSE, chromogranin, synaptophysin, neurofilament, plus specific peptides (may be focal) including insulin, glucagon, somatostatin, pancreatic polypeptide, serotonin, vasoactive intestinal peptide, ACTH, ADH, MSH, calcitonin, parathormone, GH

Malignancy

Stromal invasion, vascular invasion, metastases best criteria
Nuclear pleomorphism and mitoses common in benign lesions
Malignant tumors are more likely to be functional - may also secrete chorionic gonadotropin
Beta cell tumors usually benign, all others usually malignant
Slow growing tumors - resection of unresectable tumors or metastases (liver most common site) is warranted

Beta Cell Tumor

AKA: insulinoma
Most common functioning islet cell tumor
Clinically: Whipple triad:
• mental confusion, weakness, fatigue, convulsions
• fasting blood sugar <50mg%
• symptoms relieved by glucose
>90% are solitary; 0.3 to 1.5 cm diameter
Use angiography to localize - 70% successful
Micro: solid or gyriform; glands usually NOT seen
EM: dense-core granules ± crystalline material
Immuno: insulin (less than normal islets); minimally reactive for chromogranin
In children: may see neisidioblastosis (direct transformation of ductal epithelium into neoplastic islet tissue)
Only 10% are malignant

Alpha Cell Tumor

AKA: glucagonoma
Glucagonoma Syndrome:
• mainly adult females (perimenopausal)

- abnormal glucose tolerance test
- normocytic normochromic anemia
- skin rash: necrolytic migratory erythema
- weight loss, depression, DVT's, frequent infections

Associated with Glucagonoma Syndrome
- Large, solitary
- Non-descript microscopic pattern, atypical granules by EM
- Focal reactivity for glucagon
- Usually malignant

Not Associated with Glucagonoma Syndrome
- Small, multiple
- Gyriform growth pattern, typical granules by EM
- Strongly reactive for glucagon
- Nearly always benign

G-cell Tumor

- AKA: gastrinoma
- Zollinger-Ellison syndrome: gastric hyperacidity with gastric, duodenal, jejunal ulcers; diarrhea in 1/3 patients
- Located in pancreas in 75%, duodenum 23%, stomach rarely
- Without other endocrine abnormalities, usually solitary and malignant; as component of MEN I [see Endocrine Outline], often multiple, benign
- Non-neoplastic pancreas usually shows islet cell hyperplasia
- If localized tumor, remove; otherwise, remove stomach

Others

Delta Cell Tumor
- AKA: somatostatinoma
- May present with diabetes, steatorrhea, hypochlorhydria (somatostatin is inhibitory of other islet cells)
- Psammoma bodies common

VIP producing tumors
- AKA: vipoma
- Watery diarrhea without gastric hypersecretion (hypokalemia, achlorhydria)
- Indistinguishable histologically from G-cell tumor - use immuno (may also be positive for PP, calcitonin, alpha HCG)

PP Cell Tumor
- Rare if count only those exclusive for PP
- Pancreatic polypeptide common in other islet tumors

Carcinoid Tumor
- Similar to carcinoid tumors elsewhere
- Probably arise from Kultschitsky cells in exocrine ducts

Small Cell Carcinoma
- Similar to counterpart in lung
- May secrete ACTH or parathyroid hormone

KIDNEY

Anatomy / Physiology

~150gm each in adult; left higher than right
Unit of function: nephron (1.3 million / kidney)
Receives 20-25% of the cardiac output (1700 L per day)
Arteries: renal, interlobar, arcuate, interlobular, afferent, glomerular capillaries, efferent...
Renal lobules demarcated by interlobular arteries, contain medullary ray (collecting ducts)
Renal columns of Bertin between renal pyramids
Lobe: pyramid plus overlying cortex (6-18 lobes / kidney)
10-25 papillary ducts (of Bellini) per papilla

Juxtaglomerular Apparatus

- JG cells (modified smooth muscle cells within afferent arterioles)
- Macula Densa (specialized region of distal convoluted tubule where it adjoins its parent glomerulus)
- Lacis (non granular) Cells (mesangial-like cells situated between afferent arteriole, macula densa, and glomerulus

ULTRAFILTRATION

Glomerular capillaries composed of fenestrated endothelium
Filtration barrier: Glomerular basement membrane (~3.5nm, negatively charged matrix: polyanions and acidic glycoproteins)
180L filtrate / day; ~1 L final excretion per day

REABSORPTION

First Third (Proximal Convoluted Tubules)
65% reabsorbed - output isotonic
All glucose + amino acids via Na symport
Secretion of acids; bicarbonate reabsorption

Middle Third (Loop of Henle)
15% reabsorbed - output hypotonic
Descending: low salt permeability, high water
Ascending: high salt permeability, low water
Thick Ascending: Active NaCl Transport establishes Counter current multiplier

Distal Third (Distal Convoluted., Collecting tubules)
Output variable
NaCl transport controlled by ALDOSTERONE
Water permeability controlled by ADH

HORMONES

Aldosterone
Increases NaCl transport
98% resorbed routinely - modulates remaining 2%
Can vary urine secretion by up to 3 L per day

Anti-Diuretic Hormone (Vasopressin)
Increases water permeability of Distal 1/3
Diabetes Insipidis: no ADH - lose 10L/day
SIADH: high ADH - oliguric

Renin
Secreted by Juxtaglomerular apparatus in response to hypotension; Macula densa cells may provide JGA with information about the content of fluid in the distal tubule
Converts hepatic angiotensinogen to angiotensin I
ACE in lung converts angiotensin I to angiotensin II
Angiotensin II increases aldosterone production and causes vasoconstriction

Natriuretic Hormone
Uncharacterized agent to explain how nephrons ↑ GFR to compensate for nephron destruction

Erythropoietin
Source not precisely known
Secreted in response to low oxygen tension, either as a result of low flow or low oxygen concentration

Clinical Terminology

Clearance: Amount of plasma cleared of a substance per minute to account for appearance in urine (C=mg/ml in urine x ml/min urine / mg/ml in plasma)
Azotemia: ↑BUN/Cr; may be prerenal, renal, postrenal
Uremia: azotemia + clinical signs/symptoms
Sina qua non of chronic renal failure
Selective Proteinuria: low molecular weight proteins
Acute Renal Failure: abrupt oliguria/anuria with rapidly progressive azotemia (increase in blood urea/ammonia)
Nephrotic Syndrome: massive proteinuria (>3.5 gm/day), hypoalbuminemia, severe edema (anasarca), lipiduria, hyperlipidemia
Nephritic Syndrome: (i.e., acute glomerulonephritis) acute hematuria, RBC casts, mild proteinuria, hypertension, edema, oliguria
Rapidly Progressive GN: acute hematuria, profound oliguria, renal failure in weeks

Embryology

Pronephros (forekidney)
Wolffian duct based
Non-functional kidneys, but most of the ducts are retained to form collecting system

Mesonephros (midkidneys)
Analogous to kidneys of fish and amphibians
Appear in 4th week
Function for a while in rabbit, cat, pig, ...?human?
Form complete nephron like tubules, but degenerate

Metanephros (hindkidneys)
Begin to form in 5th week, function by 11-13 wks
Metanephric diverticulum (ureteric bud) forms ureter, pelvis, calyces, and collecting tubules, penetrating into the metanephric mesoderm, which forms the metanephric vesicles, then tubules (S-shaped) - proximal ends invaginated by glomeruli to form nephron

Congenital Anomalies

Renal Agenesis
Bilateral: rare; severe oligohydramnios, early death
Unilateral: 1/1000; other kidneys hypertrophies

Hypoplasia
Usually unilateral
Term collectively refers to truly insufficient development (minority of cases) and to small kidneys secondary to vascular / infectious insult
True hypoplasia will show decreased number of lobules (<5 vs >10)

Ectopic Kidneys
Usually pelvic, malrotated, smaller

Horseshoe Kidney
1/600 persons
Fusion of upper (10%) or lower (90%) poles, anterior to the great vessels

Miscellaneous
Malrotation; multiple renal vessels; duplications of the upper urinary tract

Cystic "Diseases"

Cystic Renal Dysplasia

"Multicystic kidney"; Potter's Types 2 and 4
Sporadic (non-hereditary)
Developmentally abnormal kidney, with persistence within the kidney of undifferentiated mesenchyme, immature and cystically dilated collecting ductules, and most diagnostically cartilage (20% - pathognomonic),
Can be unilateral (60-70%) or bilateral (30-40%)
Enlarged, usually cystic organ, often irregular contour, with disorganized parenchyma; can't distinguish cortex from medulla grossly or histologically
90% of cases are associated with (caused by?) outflow obstruction from ureteral atresia or urethral valves

Autosomal Recessive Polycystic Disease

"Infantile"; Potter's type 1, Perinatal, Juvenile
Cysts usually begin to develop at 19-20 wks gestation
Most present in utero or neonatally; some in childhood
When severe, may result in pulmonary hypoplasia secondary to compression during development
Bilateral
Multiple small cysts derived from saccular or cylindrical dilatation of the *collecting ducts* which completely replace the medulla and cortex
Associated with some form of hepatic cysts, bile duct proliferation (actually collapsed but interconnected sacs) and "congenital hepatic fibrosis"

Autosomal Dominant Polycystic Disease

"Adult"; Potter's type 3
Relatively common (1/500)
Always bilateral eventually (may be unilateral or focal early)
Symptoms (flank pain, hematuria, renal failure) usually appear in 30's-40's, although may range from early childhood to 70's or 80's
Urine concentrating defect is an early marker
Huge kidneys, almost entirely replaced by cysts, although some functioning nephrons may remain
Cysts have a variable lining (arise from *all parts of nephron*)
Two types:
• Type I (90%): linked to mutation in collagen IV gene of chromosome 16p; 100% penetrance
• Type II (10%): no linkage to 16p; milder form; later onset
Accounts for 5-8% renal transplants
50-60% will have asymptomatic hepatic cysts; cysts may also occur in pancreas, spleen, lungs, ovary
Floppy mitral valve commonly seen
1/6 will have Berry aneurysms
1/3 die from renal failure, 1/3 from hypertension

Medullary Sponge Kidney

Multiple cystic dilatations restricted to collecting ducts
Usually asymptomatic, but increased risk of infection, calcifications, calculi
Cysts lined by cuboidal or transitional epithelium

Uremic Medullary Cystic Disease

AKA: Familial juvenile nephronophthisis, hereditary tubulointerstitial nephritis
Often hereditary (65%: juvenile onset, autosomal recessive; 15%: adult onset, autosomal dominant)
Onset in childhood - progressive (5-10yr to renal failure)
Renal insufficiency results from tubulointerstitial damage
Contracted, granular; medullary cysts, most prominent at cortical-medullary junction; tubular atrophy, thickening of basement membranes, interstitial fibrosis

Simple Cysts

Very common
Probably result from isolated dilatation of a single nephron
May be hemorrhagic, but always avascular

Acquired Polycystic Disease

Seen in chronic dialysis patients (3-4 yrs)
In most florid extent, may resemble adult polycystic
Flattened epithelium with foci of papillary hyperplasia

Hydronephrosis

Obstruction of urinary outflow leading to cystic dilatation of the ureter, pelvis, and calyces
When occurs early in gestation, invariably produces some degree of cystic renal dysplasia
In adults, get progressive atrophy of renal cortex until only a thin rim remains

Glomerular Diseases

Glomerulonephritis: renal disease in which the major pathologic changes are confined to the glomeruli
Diffuse: involves all glomeruli (vs. focal)
Global: involves entire glomerulus (vs. segmental)
Major pathogenic mechanisms:
• Deposition of preformed immune complexes in glomeruli
• Formation of immune complexes by interaction of circulating antibodies with antigens deposited in the glomeruli
• Direct interaction of circulating antibodies with glomerular components
Focal involvement suggests secondary renal involvement in a systemic disease
Glomerular hypercellularity more common in nephritic patients (post-streptococcal, membranoproliferative, crescentic) than in nephrotic patients (minimal change disease, diffuse mesangial proliferative, focal and segmental, membranous)
Abbreviations:
GN: glomerulonephritis
LM: light microscopic appearance
IF: immunofluorescence localization of immune complexes
EM: electron microscopic findings
(G)BM: (glomerular) basement membrane

"Primary" Glomerular Diseases

NOTE: Minimal change disease, diffuse mesangial proliferative, and focal and segmental glomerulosclerosis may be all part of a spectrum of the same disease process (significant clinical and pathologic overlap)

Minimal Change Disease

AKA: lipoid nephrosis, nil disease, foot process disease, primary nephrotic syndrome
10-15 x more common in children than adults (>80% children with nephrosis vs. 20% adults)
Incidence increased in Hodgkin's disease
Selective proteinuria (nephrotic syndrome) usually without hematuria, HTN, or loss of renal function

Generally responsive to glucocorticoid therapy
Some require immunosuppression (e.g. cyclosporin)
Relapsing or polycyclic course; 70-80% will completely remit, 1-2% will die
LM: Essentially normal; tubules may show hyaline droplets
IF: Usually negative (occasionally, complement and fibrinogen in peripheral capillary walls)
EM: Foot process "fusion" (actually represents loss of foot processes with swelling of those remaining); microvillus transformation of epithelial cells

Diffuse Mesangial Proliferative

Idiopathic Form (IgM Nephropathy)
Probably variant of minimal change (similar clinical course) but may be seen in Lupus or Henoch-Schönlein purpura
Clinical presentation varies with etiology
LM: Mild mesangial hypercellularity and sclerosis
IF: Occasional IgM and C3 in small mesangial deposits; IgG seen in post-infectious or latent form
EM: mesangial sclerosis; occasional small mesangial deposits; foot process fusion

Berger's Disease (IgA Nephropathy)
Different clinical entity: recurrent hematuria, mild proteinuria, elevated IgA; chronic and persistent course
LM and EM: as above
IF: IgA and C3 in mesangial distribution

Focal & Segmental Glomerulosclerosis

10% of childhood and 15% of adult nephrotic syndrome
80% have nephrotic syndrome, although proteinuria usually non-selective
Etiology: ?reflux, obstruction, HTN, radiation, aging; also associated with heroine use
Not a specific disease entity but rather a pattern of response
When present early in clinical course, bad prognosis
When present late in clinical course, not always bad
Usually steroid resistant, hematuria, HTN
50% will die within 10 years of diagnosis
Often recurs in patients receiving allografts
LM: Segmental sclerosis of focal glomeruli, more common in juxtamedullary glomeruli; focal tubular atrophy with interstitial fibrosis
IF: IgM and C3 in sclerotic segments (non-specific; only occasionally seen)
EM: Foot process fusion; mesangial sclerosis with increased matrix; collapsed glomerular capillary loops

Special form seen in AIDS
Seen more commonly in black IVDA's
Rapid progression to renal failure
LM: large hyalin casts in tubules; active interstitial nephritis; marked hyperplasia of glomerular epithelial cells
EM: tubuloreticular structures in endothelial cells

Membranous Glomerulonephropathy

25-40% of adults with nephrotic syndrome
<5% of nephrotic syndrome in children
Idiopathic, but almost certainly an immune complex GN
Associated with: malignancies, viral hepatitis, malaria, parasites, penicillamine, nonsteroidals, heavy metals (gold, mercury), autoimmune diseases (rheumatoid arthritis, Hashimoto's thyroiditis, myasthenia gravis, lupus)
Can lead to persistent proteinuria; 50% will progress to renal failure over many years; corticosteroid therapy may help
Some will transform to anti-GBM type picture: rapid progression to renal failure
LM: uniform diffuse capillary wall thickening (loops appear stiff); spike and dome silver stain pattern; varying degree of interstitial scarring
IF: granular peripheral capillary deposits: IgG>IgM>IgA; ±C3
EM: Four stages:
• Stage I: scattered subepithelial deposits
• Stage II: more deposits with BM material deposited in between (*spike and dome*)
• Stage III: intramembranous deposits
• Stage IV: dissolution of deposits, rarefaction, irregular thickening of GBM

Post-Infectious Glomerulonephritis

AKA: Acute Diffuse Intracapillary Proliferative GN
Most associated with certain strains of group A hemolytic strep, less commonly with protozoa (malaria, toxoplasmosis), viruses (hepatitis B, EBV), spirochetes, other bacteria (salmonella, enterococcus, staph)
Immune complex mediated
Onset of renal symptoms 1-4 wks after "illness"; classically present with nephritic syndrome
Darkening of urine, malaise, oliguria, edema, proteinuria, occasionally nephrotic syndrome
Marked decrease in GFR with salt and water retention
Pale cortex with petechial hemorrhages
95% children recover spontaneously (histology usually returns to normal in 6 months to 3 yrs)
~60% adults recover; some develop rapidly progressive GN
LM: diffuse global glomerular hypercellularity; partial capillary obliteration by endocapillary proliferation; mesangial and epithelial proliferation, with or without crescents
IF: granular ("lumpy-bumpy") deposition of IgG, C3 in peripheral loops; fibrinogen in a mesangial pattern
EM: *Subepithelial* "humps" (deposits); may have small subendothelial deposits early ; foot process effacement over deposits

Diffuse Crescentic Glomerulonephritis

AKA: rapidly progressive, extracapillary proliferative GN
Oliguria, azotemia, proteinuria, hematuria, hypertension, unresponsive nephrotic syndrome; eventually: anuria, end stage failure (a few stabilize)
Rapid, generally irreversible course
Steroids, cyclophosphamide, plasmapheresis do not help

THREE SUBTYPES: (same LM appearance)
Glomerular crescents (proliferation of parietal epithelium and infiltration of monocytes; later fibrin deposition, collagen); segmental necrosis, glomerular capillary collapse, atrophic tubules, interstitial inflammatory infiltrate
Crescents may be associated with focal disruption of the GBM and/or of Bowman's capsule

Post-infectious (severe)
Slightly better prognosis than other two variants
IF: Granular IgG and C3
EM: subepithelial "humps", mesangial deposits, fibrin deposition associated with breaks in GBM

Anti-Glomerular Basement membrane antibodies
With lung involvement = Goodpasture's Syndrome
IF: diffuse linear staining of GBM with IgG>IgM>IgA, granular staining for C3; fibrinogen focally within glomerular capillary loops; linear staining of tubular BM's for Ig's may be seen
EM: fibrin associated with breaks in GBM; no deposits

Idiopathic
AKA: Pauci-immune crescentic GN
Occasionally associated with a vasculitis; many patients are anti-neutrophil cytoplasmic antibody positive (see below)
IF: No Ig staining. Complement and fibrinogen may be present associated with crescents
EM: as for Anti-GBM

Membranoproliferative Glomerulonephritis

AKA: Hypocomplementic(C3), lobular
Variable presentation, but typically acute nephritis, nephrotic syndrome, HTN
Primarily affects children and young adults
Course generally progressive with intermittent remissions and gradual loss of renal function
High recurrence in transplants (especially type II), but usually does not compromise graft function for a while

THREE SUBTYPES: (same LM appearance)
Glomerular enlargement with lobular accentuation; increase in mesangial cell number and matrix
Irregular thickening of capillary wall by interposition of mesangial cells between the endothelium and the BM: "tram track" or "reduplication of the GBM"
Crescents seen in ~20%

Type I - "Classical", "Mesangiocapillary" (2/3 of cases)
IF: IgG, IgM, C3,± IgA deposition - lumpy bumpy; Granular fibrin deposition
EM: *Subendothelial* and mesangial deposits; occasional subepithelial deposits; Increased mesangial matrix; *mesangialization* of the capillary loops; foot process fusion

Type II - "Dense Deposit GN" (1/3 of cases)
Familial, associated with partial lipodystrophy
Abnormal activation of alternate complement pathway
C3 Nef (C3 nephritic factor - antibody) in serum
Poorer prognosis than type I
IF: Extensive C3 in mesangium and peripheral capillary loops; Ig's usually absent - fibrin occasionally seen
EM: Very dense deposits *in lamina densa* of GBM, forming a long ribbon of hazy material which may be discontinuous

Type III - "Mixed"
Rare; Probably an advanced form of type I (Classical)
Both subendothelial and subepithelial deposits by EM

"Secondary" Glomerular Diseases

Lupus Nephritis

Renal involvement in 50-80%
Prognosis correlates with extent of renal disease
Subendothelial deposits correlate with renal failure
Tubulointerstitial infiltrate common: lymphocytes, plasma cells, eosinophils
Pathogenesis: deposition of DNA-anti-DNA complexes
World Health Organization Classification:

WHO Class I
No lesions, no symptoms

WHO Class II (Mesangial)
Mild to moderate proteinuria, good prognosis
LM: IIA: no significant changes
IIB: mild mesangial hypercellularity centered away from vascular pole
IF: Mesangial IgG, C3; occasionally other Igs
EM: Mesangial deposits

WHO Class III (Focal Segmental)
Proteinuria, sometimes aggressive course
LM: focal and segmental necrosis / proliferation (<50% involvement of <50% glomeruli); mild diffuse mesangial prominence; segmental capillary proliferation with obliteration of lumen; hyaline wire loops; focal crescents
IF: more diffuse involvement with granular capillary Ig and C3
EM: subendothelial deposits and mesangial deposits; occasionally subepithelial deposits

WHO Class IV (Diffuse Proliferative) - most common type
Majority to all of glomeruli are involved
Worst prognosis, progressing to renal failure (unless treated)
LM: Mesangial proliferation; membranoproliferative and/or crescents; condensed nuclear debris ("hematoxyphil body"); thickened wire capillary loops; 25% show lobular accentuation
IF: Ig, coarsely granular pattern in mesangium and capillary loops; Full house pattern: multiple Ig's: IgG+IgM>IgA>IgE (Presence of IgE associated with poorer prognosis)
EM: Large subendothelial deposits - "fingerprint"; mesangial, subepithelial, and intramembranous deposits common; tubuloreticular structures seen in endothelial cells

WHO Class V (Membranous)
Identical to lesions of idiopathic membranous
Indolent progression

WHO Class VI (Sclerosing)
LM: Global glomerulosclerosis, usually fibrous crescents, interstitial fibrosis, nephron loss with tubular atrophy
EM: Irregular thickening of capillary BM with intramembranous deposits

Diabetic Nephropathy

More common in early onset or poorly controlled diabetes
Recurrent proteinuria, often nephrotic, with slow progression to chronic renal failure
Papillary necrosis seen
Diffuse and Nodular types
LM: diffuse thickening of capillary wall, nodular (Kimmelstiel-Wilson) sclerosis, arteriolar nephrosclerosis, "insudative" glomerular lesions (fibrin cap, capsular drop)
Global sclerosis (related to duration, not severity)
IF: diffuse thin linear staining for IgG, C3, and albumin
EM: diffuse even thickening of GBM (up to 5-10 x normal!); increased mesangial matrix; ± subendothelial granular deposits

Amyloidosis

[see also Inflammation and Immunology Outline, under Autoimmune Diseases]
Deposits of Amyloid protein A (stains with Congo-red)
Massive proteinuria (12-20 g/24hrs!)
Glucocorticoid therapy unsuccessful, outlook poor
LM: Homogenous deposits in glomeruli, tubular basement membranes, and vessel walls
IF: Ig may be present in non-specific pattern
EM: Amyloid fibrils (β-pleated sheet, 7-12nm) widely present in mesangium and peripheral capillary BM

Light Chain Disease

7-10% of patients with multiple myeloma
LM: capillary wall thickening, nodular sclerosis; "amyloid" deposits of AL type
IF: monoclonal κ or λ light chain - linear deposition
EM: granular deposits in glomerular and tubular BM

Cryoglobulinemia

Renal lesions seen in 50% patients; can be seen in lymphoma
Anatomically, same as Type I membranoproliferative (mesangiocapillary) GN
LM: diffuse proliferation / lobular accentuation / neutrophils; intraluminal eosinophilic occlusive thrombi; ± crescents
IF: large peripheral capillary deposits with IgG and IgM; granular staining for C3, C1, C4
EM: subendothelial and mesangial deposits, with parallel arrays of fibrils or tubules

Henoch-Schönlein Purpura

Purpuric skin lesions (leukocytoclastic vasculitis) characteristically involving the extensor surfaces of the arms, legs, buttocks; also joint pain, melena, abdominal pain; episodic
Most common in children 3-8 yrs old, but renal disease is more severe when occurs in adults
Renal involvement in 25%: nephritis to asymptomatic hematuria/proteinuria
Usually self limited; morbidity/mortality due to renal disease
Wide range of histopathology, most similar to IgA nephropathy, but often crescentic GN when severe
Healed lesions may be present (episodic nature)

Hereditary/Familial Nephropathies

Alport's Syndrome

Type I: dominant, associated with deafness, males sterile
Others: X-linked dominant, autosomal recessive, ± deafness
Appears to be some defect in GBM
May or may not progress to renal failure
Glomerulosclerosis, tubular atrophy, interstitial foam cells
IF: no specific staining. Does NOT stain with anti-GBM
EM: thinning, thickening, and splitting of GBM in an irregular pattern

Nail-Patella Syndrome

Similar to Alport's
EM: thickening of GBM with fibrillar collagen

Congenital Nephrotic Syndrome

Autosomal recessive
Occur before 1 yr of age - often fatal

Finish Type:

Premature, low birth weight infants
Enlarged placenta (1/3 body weight)
Immature glomeruli with sclerosis
Tubular cyst formation = "Microcystic disease"
Arteriolar medial hypertrophy
EM: obliteration of foot processes

French Type:

Usually develops between 3 months and 1 yr
Renal insufficiency within 1-3 yrs
Glomeruli show mesangial, then global sclerosis
Tubular atrophy with interstitial fibrosis
Increased mesangial matrix

Thin Glomerular BM Disease

AKA: Benign familial hematuria
Autosomal dominant; onset in childhood
Similar to Alport's clinically; usually no uremia or renal insufficiency; microscopic hematuria (persistent or intermittent); proteinuria is unusual
More common in women (thinner BM to begin with)
LM: Normal, except for hematuria
IF: Small amounts of Ig and C3 deposited along BM
EM: Thin GBM (~200nm vs 300nm in normal adults); focal capillary wall collapse with thickening; ± mesangial deposits

Tubulointerstitial Diseases

Acute Interstitial Nephritis

Interstitial inflammation almost always involves the tubules to some extent, due to the intimate interrelationship between the tubules and the interstitium

Acute Pyelonephritis

Flank pain, fever, malaise, dysuria, pyuria
Gram negative bacilli of GI tract account for >85% of cases (E. coli, Proteus, Klebsiella, Enterobacter)
Most common in pregnant women and men with obstructive prostatic hypertrophy
Mechanism of infection:
• Hematogenous spread: predominantly corticomedullary junction; kidney usually resistant unless damaged
• Ascending Infection: M:F=1:8 in non-instrumented patients
• Vesicoureteral Reflux (during micturition)
Patchy, often wedge shaped suppurative inflammation, usually predominantly cortical, with *edema*, *neutrophils* in interstitium and tubular lumina, and areas or necrosis/abscess formation in cortex
Inflammation rapidly spreads throughout tubules; glomeruli, arterioles, and arteries are spared

Pyonephrosis

Caused by near complete obstruction
Pus, unable to drain, fills kidney

Acute Hypersensitivity Nephritis

AKA: Drug induced nephritis
Seen with beta-lactam antibiotics, NSAID's, diuretics, dilantin, rifampin, amphotericin, gentamycin
Non-drug related causes include viral (Hantavirus, EBV, HSV, CMV, adenovirus, HIV) and autoimmune disease (SLE, Sjögren's, rheumatoid arthritis)
Predominantly interstitial inflammation with edema, lymphocytes (mostly helper T-cells), macrophages, *eosinophils*, plasma cells; may have granulomas
Tubular epithelial damage with regeneration, tubulitis; glomeruli and vessels usually normal
With NSAIDs, also get glomerular foot process fusion

Renal Papillary Necrosis

Most common in obstructed patients with: diabetes (synchronized lesions), alcoholism, sickle cell disease, analgesic abusers (usually affects papilla of upper and lower pole; lesions at various stages; seen with acetaminophen, phenacitin, aspirin, codeine)
3 Stages of progression:
• I: Papillae firm with gray streaks, interstitial homogenization, thickening of basement membranes, focal cell necrosis, fine calcification - cortex normal
• II: Papillae shrunken, brown; confluent necrosis, focal tubular atrophy in overlying cortex
• III: Kidneys decrease in weight, total papillary necrosis, extensive calcification (may have metaplastic bone), overlying tubular atrophy and interstitial fibrosis (cortical changes more marked if papillae fails to slough)

Chronic Interstitial Nephritis

Hallmark of chronic injury is interstitial fibrosis
Often, the etiology cannot be unequivocally determined once fibrosis is extensive; most common causes are obstruction, vesicoureteral reflux, and idiopathic (non-obstructive)
Irregular, asymmetrical scarring involving the calyces and pelvis as well as the cortex
Get predominantly tubulointerstitial damage with "normal" glomeruli; *tubular atrophy* or dilatation, thyroidization; *fibrosis*, periglomerular fibrosis; predominantly lymphocytes in interstitium

Drug Induced

Interstitial fibrosis and tubular atrophy

Seen with lithium (nephrogenic diabetes insipidus), cyclosporin (see below under Renal Transplant), and analgesics

Xanthogranulomatous Pyelonephritis
- Large yellow orange nodules replace normal renal parenchyma - can mimic renal cell carcinoma
- Infiltrate of foamy macrophages and giant cells, plus granulomas, lymphocytes, plasma cells
- Associated with E. coli, Proteus, Staph aureus (urea-splitting organisms)

Malakoplakia
- AKA: megalocytic interstitial nephritis
- Confluent yellow-tan nodules replacing renal parenchyma
- Few lymphocytes, many histiocytes
- Michaelis-Gutmann bodies (partially digested bacteria, calcified) in stroma and in cells

Tuberculosis
- Frequently unilateral
- May be miliary (numerous small tubercles scattered throughout the cortex) or isolated to urinary tract, with progressive destruction of the renal parenchyma

Pelvic Lipomatosis
- Replacement of pelvis by adipose tissue following atrophy

Ask-Upmark Kidney
- Extensive scarring of a kidney lobule, resulting in apparent focal hypoplasia

Acute Tubular Necrosis
- Major cause of acute renal failure (<400cc urine/24 hrs)
- Complete anuria rare
- Acute renal failure probably due to tubular obstruction by debris
- 4 Clinical phases:
  - Onset (36 hrs)
  - Oliguric (days-weeks): fluid overload, uremia, hyperkalemia
  - Early diuretic: steady inc. urine volume, hypokalemia, electrolyte imbalance, inc. vulnerability to infection
  - Late diuretic: recovery of function
- Gross: swollen and pale kidneys

Ischemic
- AKA: Tubulorrhectic, shock kidney, hemoglobinuric nephrosis
- Proximal tubules and thick portion of the ascending limb are most vulnerable to ischemic injury (greatest ATPase activity)
- Usually following hypotension secondary to bacteremia, burns, etc.; unusual following hemorrhage alone
- Focal tubular necrosis at multiple points along the nephron with skip lesions
- Basement membrane rupture (tubulorrhexis)
- Casts in distal tubules (eosinophilic and granular; contain Tamm-Horsfall protein)
- Interstitial edema, leukocytes in dilated vasa recta
- Later, epithelial regeneration with flattening of tubule cells
- Can also be seen following massive hemolysis or massive rhabdomyolysis: "pigment associated ATN"

Nephrotoxic
- Usually involves proximal convoluted tubules, sparing distal
- No basement membrane destruction
- Seen with heavy metals, organic solvents, sulfonamides, neomycin, methecillin, anesthetics
- Can have non-oliguric ATN
- Ethylene glycol not truly nephrotoxic; large accumulation of calcium oxalate crystals in tubules

Chronic Renal Failure
- Volume regulation: dehydration early, then systemic edema (anasarca): lose concentrating ability, then filtration rate
- Acid/Base: metabolic acidosis, Kussmaul breathing
- GI: N/V, ?bleeding
- Cardiovascular: CHF, HTN (↑ volume, renin, or both)
- Hematopoietic: anemia (decreased erythropoietin + bleeds)
- Bone metabolism: ↓Ca,↑PO_4,↑PTH→renal osteodystrophy

Nephrolithiasis
- 1% of all US population will develop a kidney stone
- "Primary" = occurs without renal abnormality or infection
- 4 kinds of stones, all with an organic matrix of mucopolysaccharides comprising <5% stone weight
- 65-75% are calcium oxalate and Ca phosphate (sarcoidosis, hyperparathyroidism, excess Vitamin D, multiple myeloma)
- 5-20% are uric acid, xanthine (gout, Lesch-Nyhan, glycogen storage disease, excess dietary protein)
- 15% are magnesium ammonium phosphate ("Triple stones" or "struvite stones")
- 1-2% are Cystein
- May form at area of ulceration on surface of papillae

Miscellaneous

Osmotic Nephrosis
- Foamy clearing of cytoplasm of the proximal tubular epithelium secondary to sucrose or mannitol injection
- No clinical significance

Hyaline Change
- Proximal tubular epithelium contains cytoplasmic eosinophilic PAS positive droplets
- Seen in patients with marked proteinuria; represents reabsorption of filtered proteins

Hypokalemic (Vacuolar) Nephropathy
- Secondary to chronic protein depletion (e.g. GI disease)
- Coarse "vacuolization" of tubule cells, mainly proximal, caused by dilatation of intercellular spaces

Urate Nephropathy
- Precipitation of uric acid crystals in renal tubules, principally collecting ducts
- Common in leukemia/lymphoma patients on chemotherapy

Myeloma Kidney
- Insidious and progressive renal failure, or ARF caused by precipitation of Bence-Jones protein in tubules with obstruction
- Normal to shrunken and pale kidneys, with pink to blue amorphous casts, giant cells, tubular necrosis, interstitial inflammation ± granulomas

Nephrocalcinosis
- Calcification in renal parenchyma, typically on tubular basement membranes and in interstitium, associated with hypercalcemia and hypercalcuria
- Tubular atrophy, interstitial fibrosis, periglomerular fibrosis

Vascular Lesions

Benign Nephrosclerosis
- Always associated with hyaline arteriolosclerosis
- Fine, even granularity to cortical surface
- Cortical narrowing with mildly decreased renal mass
- Focal tubular atrophy, interstitial fibrosis
- Fibroelastic hyperplasia: reduplication of elastic lamina of interlobular and arcuate arteries, with fibrosis of media

Malignant Nephrosclerosis
- Associated with malignant hypertension (rapidly rising BP, with diastolic pressure >130 mmHg, developing over 3mos to 2 yrs, usually ending in death)
- Fibrinoid necrosis of arterioles, often with inflammatory infiltrates in vessel wall (necrotizing arteriolitis)
- Hyperplastic arteriolitis: intimal thickening by proliferation of concentric smooth muscle cells ("onion skinning")

Renal Artery Stenosis
- 70% caused by atheromatous plaque at origin; M>F
- Fibromuscular dysplasia of renal artery accounts for many of the remaining cases, especially those occurring in younger patients [see Vessels Outline]; F>M
- Diffuse ischemic atrophy of ipsilateral kidney with minimal arteriolosclerosis
- Enlargement of contralateral kidney, often with marked arteriolosclerosis

Infarcts
- Usually embolic in origin (look for cholesterol crystals)
- Wedge shaped, with base at capsule
- Typically pale-white with hyperemic rim
- With time, replaced by fibrous tissue - forms contracted scar

Vasculitis
- Hypersensitivity response to antigens (drugs) and various clinical syndromes (e.g., Wegener's Granulomatosis, Polyarteritis nodosa)
- Distinction based on other organ involvement
- LM: Focal and segmental necrotizing to diffuse crescentic GN; Can see granulomas in Wegener's, extending through Bowman's capsule into the interstitium
- Tubulointerstitial infiltrate with eosinophils
- IF: Mesangial and subendothelial fibrin, ± IgG, IgM, C3
- EM: Mesangial deposits, fibrin in capillaries, capillary rupture

Anti-Neutrophil Cytoplasmic Antibodies
- Cytoplasmic (C-ANCA) pattern seen in Wegener's
- Perinuclear (P-ANCA) pattern seen in small vessel vasculitides, polyarteritis nodosa, rheumatoid disorders

Hemolytic Uremic Syndrome
- Microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure
- More common in children
- 75% patients infected with verocytotoxin producing E. coli
- Adults: post-partum women, oral contraceptive users
- Prognosis better in children
- LM: Thrombi in glomeruli; focal necrosis without leukocyte infiltration; bloodless glomeruli; fragmented RBC's; thickening of capillary walls (tram tracks); myointimal proliferation in small arterioles
- IF: Fibrin, occasional Ig's
- EM: Separation of endothelium from BM with light granular material in the new subendothelial space

Thrombotic Thrombocytopenic Purpura
- Identical to HUS, with perhaps more prominent platelets

RENAL TRANSPLANTATION

Preservation Injury
- Swelling of tubular epithelial cells with occlusion of the lumen by cytoplasmic "blebs"; necrosis
- EM: mitochondrial and lysosomal swelling

Hyperacute Rejection
- Minutes to hours after transplant; rarely may take 1 week
- Mediated by preformed antibodies vs donor endothelium
- Fibrin thrombi in glomeruli and other vessels, infarction, tubular necrosis, widened/congested interstitial capillaries, interstitial hemorrhage

Acute Imminent Rejection
- Occurs in first month; usually due to preservation injury
- ≥3 neutrophils in glomerular capillaries; dilated intertubular capillaries (with mononuclear cells)
- Edematous interstitium, swollen tubular epithelium and vascular endothelium
- Suggests graft will likely be rejected within three months

Acute Rejection
- May occur at any time after ~7 days (including years)

Interstitial (cellular):
- Interstitial edema and chronic inflammatory cell infiltrate, initially at the corticomedullary junction with immunoblasts, lymphocytes, plasma cells, and scattered neutrophils and eosinophils; lymphocytes often migrate into the tubular epithelium
- Predominantly T-cells, both CD4+ and CD8+ cells
- Reversible with immunosuppression; in particular, OKT-3, a monoclonal antibody to T-cells, is quite effective at reversing cellular rejection

Vascular (hormonal):
- Endothelial cell swelling, subendothelial inflammatory cells (predominantly chronic), interstitial hemorrhage, infarcts
- Severe cases: necrotizing arteritis, fibrinoid necrosis
- Less easily reversible

Chronic Rejection
- Several months to years after transplantation
- Clinically, slow gradual decrease in renal function
- Glomeruli, vessels, interstitium, and the tubules are all involved

Vasculopathy
- Myointimal proliferation of vessels
- Interstitial scarring
- Tubular atrophy or loss
- Mononuclear cell infiltration

Glomerulopathy
- Glomerular hypercellularity, sclerosis, irregular basement membrane thickening, ischemic glomerular capillary collapse

Cyclosporin Toxicity
Acute
- Related to high levels
- May have no lesions or mild tubular and vascular changes (tubular degeneration with vacuolization and eosinophilic inclusions, peritubular capillary congestion)
- Vacuolization of endothelial and smooth muscle cells

Chronic
- Stripes of interstitial fibrosis, atrophic tubules in cortex, tubular de-differentiation, glomerulosclerosis

Recurrence of Glomerulonephritis
- Occurs in 10-20%; accounts for 2% of graft failures
- Most commonly seen in patients with focal and segmental GN, but greatest frequency of recurrence is with membranoproliferative glomerulonephritis

TUMORS: Pediatric Cortex/Medulla

Nephrogenic Rests

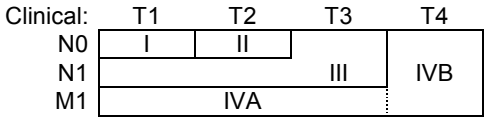
Predominantly to exclusively epithelial cells forming disorganized structures
Considered abnormal development rather than a neoplasm
Presumably, all Wilms' tumors arise from nephrogenic rests
• Perilobar Rests:
  At periphery of renal lobe
  Found in 30-40% of kidneys with Wilms' tumors
  Type seen in Beckwith-Wiedemann syndrome
  Associated with *synchronous* bilateral Wilms' tumors
• Intralobar Rests:
  Inner portions of cortex or medulla
  Seen with Wilms' tumors presenting at younger age
  Associated with *metachronous* bilateral Wilms' tumors
Both types of rests may be further subclassified as:
  • Dormant: no change for many years; older patients
  • Regressing/Sclerosing: maturing; most common subtype for perilobar rests
  • Obsolescent: primarily hyalinized stroma
  • Hyperplastic: macroscopic; may progress; if Wilms' tumor arises within one, causes a spherical expansion

Nephroblastomatosis
Multiple nodules or diffusely distributed nephrogenic rests
Single/multifocal, uni/bi-lateral, usually subcapsular; may be limited to a small region
Perilobar, intralobar, combined, and panlobar types
Found in 1% of neonatal kidneys
Similar to Wilms' histologically

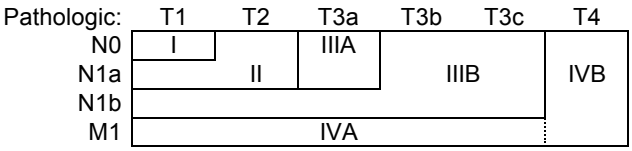
Wilms' Tumor (Nephroblastoma)

50% occur <3 yrs of age, 90% <10 yrs
Only rarely congenital, but 15-30% are associated with genitourinary malformations and genetic syndromes (e.g., deletion of 11p13 (WT-1): Wilms' with aniridia; deletion of 11p15 (WT-2): Beckwith-Wiedemann syndrome)
5-10% bilateral; can also occur outside the kidney
Presentation: abdominal mass (rarely as hematuria, hypertension, proteinuria)
Large, white, well circumscribed, solid, hemorrhage, necrosis
3 components histologically; can have one, two, or all:
• Epithelial tissue: embryonic tubular structures (with or without glomeruli) to small, round cell rosettes
• Undifferentiated Blastema: cellular, small round-oval primitive cells, scanty cytoplasm
• Mesenchymal Tissue: spindle cell (fibroblast-like); may differentiate toward smooth or skeletal muscle (if large amount of skeletal muscle, always young children, 50% bilateral)
"Teratoid Wilms' Tumor": differentiation to ganglion cells, adipose tissue, bone, etc.
Grade histology as "favorable" or "unfavorable"; unfavorable histology requires (must have all 3): anaplasia (nuclei 3x size of neighbors); hyperchromasia; abnormal mitoses
Spread: local to peri-renal soft tissue, adrenal, bowel, liver; Renal pelvis or ureter invasion rare
Metastases: regional LN in 15%; distant: lungs, liver, peritoneum
Therapy depends on stage: chemotherapy ± radiation; therapy induces massive necrosis of the immature component but spares the mature portions
Prognosis: overall cure for unilateral: ~90%; survivors have increased risk for second neoplasm; unfavorable histology (seen in ~5%) increases mortality from 5% to 50%
Good prognostic signs: age<2; low stage, no anaplastic regions, tubular differentiation
Pure blastemal tumor may have worse prognosis
Pure rhabdomyomatous tumors do very well

Clinical Staging
T1: Unilateral, intact, ≤80cm^2, including kidney
T2: Unilateral, intact, >80cm^2, including kidney
T3: Unilateral, ruptured
T4: Bilateral
N1: Regional LNs M1: Metastases



Pathologic Staging
T1: Confined to kidney, capsule intact
T2: Beyond kidney, but completely excised
T3a: Microscopic residual tumor
T3b: Macroscopic residual tumor or ruptured
T3c: Not resected
T4: Bilateral
N1a: Regional LNs, resected
N1b: Regional LNs, incompletely resected
M1: Metastases



Multicystic Nephroma

AKA: multilocular cystic nephroma
Early infancy; nearly always unilateral
Presents as abdominal mass, ureteral obstruction
Sharply demarcated, 5-15cm, coarsely nodular, white, serous cysts
Tubular epithelium lining cysts; hobnail cells; spindle cell stroma between cysts
Some refer to this entity as multilocular cysts - require the presence of blastemal cells in wall to call multicystic nephroma
Probably just a well differentiated variant of nephroblastoma
Curable by simple excision

Mesoblastic Nephroma

AKA: fetal, mesenchymal, or leiomyomatous hamartoma
<5% of pediatric renal tumors, but most common tumor before 1 yr (congenital: usually discovered before 6 months)
Solid, yellow-gray to tan, whirled configuration, usually infiltrative growth pattern (occasionally well circumscribed); no hemorrhage or necrosis
Spindled cells which look like smooth muscle cells; infiltrate and entrap tubules; no capsule
Usually benign, but will recur if not completely excised
Atypical variant: many mitoses, infiltrates pelvis or perirenal tissue, metastasizes

Intrarenal Neuroblastoma

Invades from adrenal or arises as primary
Can be confused with Wilms'
[See Endocrine Outline, Adrenal Medulla]

Clear Cell Sarcoma

AKA: Bone-metastasizing renal tumor
4% of childhood renal tumors; peaks at 2-3 yrs
Well demarcated, homogeneous tan, cystic; always unilateral
Small cells, round nuclei, clear cytoplasm in only 20%, prominent fibrovascular stroma

Growth patterns: epithelioid, spindled, sclerosing, myxoid, palisading, cystic, pericytoma-like, and pleomorphic
Very malignant

Rhabdoid tumor

Young infants (median age 18 months)
Soft, solid, infiltrative margins
Monomorphic proliferation of medium sized round/oval cells (can be spindled); large cytoplasmic eosinophilic globule displacing nucleus laterally; involves medulla and cortex
Looks like rhabdomyosarcoma (negative for muscle markers)
Should NOT find well differentiated skeletal muscle; if do, probably a Wilms' tumor
EM: whirled array of intermediate filaments in the cytoplasm
Strong association with meduloblastoma of brain
Very malignant: mortality >75%

TUMORS: Adult Cortex/Medulla

Adenoma

Found in 20% adult kidneys, generally <6mm
May be tubular or papillary
Probably nodular hyperplasia vs neoplasm
Some pathologists consider all proliferations of renal tubule cells in the kidney to be renal cell carcinomas, since lesions as small as 1cm have metastasized; others prefer to use the "3cm rule", calling lesions with low grade histology which are <3cm adenomas

Renal Cell Carcinoma

AKA: Renal Adenocarcinoma, Hypernephroma
Median age 55-60yrs; M:F=2-3:1; Bilateral 1%
Account for 85-90% of all renal malignancies; 2% of all cancers in adults
RCC may develop in setting of: von Hippel-Lindau's (multiple and cystic tumors), acquired cystic disease (secondary to long term dialysis), adult polycystic disease (or multicystic nephroma)
Patients present with a triad of hematuria (59%), flank pain (41%), abdominal mass (45%). Also: weight loss (28%), anemia (21%), fever (7%)
Often produce hormones resulting in polycythemia, hypercalcemia, HTN, femininization, Cushing's syndrome
Well demarcated, centered in cortex, often extending outside kidney but extending to pelvis only late in course; golden yellow; fibrous capsule; hemorrhage, necrosis, calcification, cystic change; multiple nodules in 5%
Cystic changes can be extensive; any multicystic lesion with hemorrhage needs to be thoroughly sampled
Large, optically clear ("Clear Cell") or granular ("Granular Cell") cytoplasm; may have hyaline droplets, central nuclei
Clear cells contain fat, glycogen, few organelles
Tubular, papillary, solid, alveolar, or trabecular pattern
Believed to be a tumor of the renal tubular epithelial cell
Immunochemistry: reactive for keratin, vimentin, EMA (adrenal cortical tumors are EMA negative), ±CEA
Often see deletion/rearrangement of chromosome 3p (except in papillary renal cell carcinoma - see below)
Occasionally regresses without treatment
Most common recipient of metastasis into a tumor (most common donor is lung)

Spread/Metastases

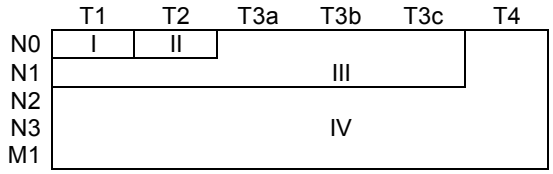
1/3 have invaded perinephric fat or regional LNs
Renal vein and inferior vena cava invasion common
1/3 have distant metastases: lung, bones(pelvis, femur), adrenal gland, liver
Frequently solitary metastases
Metastases may develop years after primary removed
Rare in tumors <3 cm diameter

Grading

1: Small, round, uniform nuclei
2: Larger nuclei, small nucleoli
3: Even larger nuclei, prominent nucleoli
4: Pleomorphic/multilobated nuclei, cells may be spindled

Staging

T1: Confined to kidney, ≤ 2.5cm
T2: Confined to kidney, > 2.5 cm
T3a: Extends to adrenal or soft tissue
T3b: Extends into renal vein or lower inferior vena cava
T3c: Extends into inferior vena cava above diaphragm
T4: Beyond Gerota's fascia
N1: Single LN, ≤ 2cm
N2: Single LN, 2-5cm or multiple LNs, all <5cm
N3: Any LN >5cm
M1: Metastases



Prognosis

5 yr: I: 60-80%; II: 40-70%; III: 10-40%; IV: 5%
Metastases most important bad sign
Tumor size (<3 cm best, prognosis decreases with size up to 10cm, then plateaus)
Clear cell less aggressive than granular cell

SPECIAL HISTOLOGIC TYPES OF RENAL CELL CARCINOMA

Tubulopapillary Renal Cell Carcinoma (5-15%)

Predominantly papillary (>75%); hypovascular on arteriography, necrosis, inflammation, cyst formation
Cores of papillae often have foamy macrophages
Papillary adenomas may also be present
Does not show changes in chromosome 3p; instead, see gains of chromosome 7 or 17 and, in men, loss of Y chromosome
If pure, usually localized to kidney: better overall prognosis

Chromophobe Renal Cell Carcinoma (<5%)

Sharply defined cell borders, lightly staining cytoplasm but not completely clear
Low nuclear grade, well defined nuclei
Will stain with colloidal iron, alcian blue
Vimentin negative; keratin and EMA positive
EM: peculiar vesicles
Better overall prognosis

Oncocytic Renal Cell Carcinoma

Similar to oncocytoma but higher nuclear grade or mixed with other histologic patterns

Collecting Duct Carcinoma (1-2%)

Differentiates toward collecting (Bellini's) ducts
Centered in medulla, tubulopapillary, desmoplastic reaction

Sarcomatoid Carcinoma (1%)

AKA: Spindle cell, anaplastic, carcinosarcoma
Spindle and/or pleomorphic giant cells; simulate sarcoma
Cytology: Grade 4 (by definition)

Oncocytoma

Mahogany-brown, solid, central stellate scar; may be large (>10cm)
Solid sheets or nests of regular cells with abundant acidophilic granular cytoplasm (mitochondria - often swollen); small, round, regular nuclei

Must be grade 1-2 with no other histologic patterns and no necrosis; otherwise, diagnose as RCC with oncocytic change
Some multi-centric, few bilateral
May be a tumor of the collecting duct cells
Most are negative for vimentin
Lack the cytogenetic abnormalities of renal cell carcinoma
Invasion of capsule or renal vein possible, although most behave in a benign fashion, regardless of size
Some pathologists do not make the diagnosis of oncocytoma, preferring instead to call all of these lesions "Renal Cell carcinoma, oncocytic variant"

Juxtaglomerular Cell Tumor

Presents with HTN, secondary to renin production
Looks like hemangiopericytoma with oval to spindled cell background, small vessels, ± tubules
EM shows characteristic large rhomboid crystals in membrane bound granules
Usually benign

Angiomyolipoma

Rare; may be hamartomas rather than neoplasms
<1cm-20cm in size; well circumscribed, yellow to gray-tan; frequently multifocal, 15% bilateral; may be confused grossly with renal cell carcinoma
Mixture of fat, thick walled tortuous blood vessels without elastic lamina, and smooth muscle; marked variability in appearance, based on relative proportions of each component; spectrum includes capsular leiomyoma
Cells are HMB-45 positive with a granular staining pattern
PAS^+ crystalloid structures in some cells
20-50% of cases are associated with tuberous sclerosis; also with lymphangiomyomatosis (often multiple)
Capsular invasion in 1/4; local recurrences
Does not metastasize (LN involvement = multifocality)
Sometimes fatal hemorrhage
Can coexist with RCC

Medullary Fibroma

AKA: Renal Medullary Interstitial Cell Tumor
Probably hamartomatous rather than neoplastic
Usually <1 cm; gray-white; composed of fibroblast-like cells and collagenous tissue; cells are derived from medullary interstitial cells
May "trap" small cords of tubular cells
Benign

Other Tumors

Benign: Hematoma, teratoma, lipoma, leiomyoma, hemangioma
Malignant: Carcinoid, sarcomas (various types), lymphoma, plasmacytoma
Metastatic tumors usually bilateral

Tumors of the Pelvis and Ureter

Transitional Cell Carcinoma

Mostly in adults
1/4 cases have history of analgesic abuse and/or renal papillary necrosis
Associated with Thorotrast, cyclophosphamide
Presentation: hematuria
Soft, white to grayish red masses with glistening surfaces
Histology can show glandular or squamous metaplasia (see below), or can acquire sarcomatoid appearance
May have small pools of mucin
May diffusely involve entire pelvis - can involve parenchyma
Frequently multicentric; 40% have tumors elsewhere in urinary tract

Epidermoid Carcinoma (5-10%)

Associated with squamous metaplasia (leukoplakia)

Adenocarcinoma (<1%)

Reserve for rare tumors with mucin and well formed glands
Related to glandular metaplasia of transitional epithelium secondary to long-standing chronic inflammation

URETER

Normal

Approximately 30 cm in length, 5 mm in diameter
Three points of narrowing:
• Ureteropelvic junction
• Where cross anterior to the iliac vessels
• Entry into the bladder

Congenital Anomalies

2-3% of all autopsies

Double (Bifed) Ureters

Usually accompanied by partial or complete duplication of the renal pelvis

Ureteropelvic Junction Obstruction

Usually males, more commonly on left
Abnormal organization of and/or excess stromal deposition of collagen between smooth muscle bundles
Results in Hydronephrosis

Diverticula

Inflammation

Changes arise only in long-standing ureteritis

Ureteritis follicularis

Accumulation of subepithelial lymphoid aggregates, imparting a fine granularity to the mucosa

Ureteritis Cystica

1-5 mm fine cysts protruding from luminal mucosa
Dilated Brunn's nests with clear contents

Tumors

Very rare; most tumors are metastases
Primary tumors are of same type as seen for the renal pelvis and urinary bladder

BLADDER

Normal

Epithelium derived from endoderm of urogenital sinus; epithelium of renal pelvis and ureter are mesodermally derived
Only the most superior/anterior aspect is covered by peritoneum
Urothelium is a transitional epithelium, usually 5-8 cells thick, divided into three layers:
• Superficial zone: single layer of large, flattened cells that cover relatively large areas - "umbrella cells"
• Intermediate zone: 4-5 layers when maximally stretched, 6-8 layers when fully contracted
• Basal zone: single layer of small cells, cylindrical to flattened
Lamina propria is juxtaposed to the muscularis propria; there is no submucosa
EM shows scalloped concave rigid membrane plaques (Asymmetric unit membrane plaque). Cytoplasmic "fusiform vesicles" contain similar plaques - this allows increase in surface area of membrane

Congenital & Acquired Malformations

Exstrophy
Developmental defect of closure of the anterior wall of the abdomen and the bladder so that the bladder communicates with the exterior of the body through a large defect or as an open sac
Often associated with other abnormalities of GU tract
Increased incidence of malignancy (Adenocarcinoma)
Urachus
5-6 cm vestigial structure located between the apex of the bladder and the umbilicus
In the embryo, this connected the bladder to the allantois
Tubular urachal remnants are found in 32% individuals; lining may be transitional or columnar
Cystocele
Protrusion of the bladder into the vagina, creating a pouch
Caused by relaxation of the pelvic support in females leading to uterine prolapse; this pulls the bladder floor downward
Diverticula
Pouch-like evagination of the bladder wall
Congenital: due to focal muscular defect - some muscle is retained within the wall
Acquired: more common; arise following persistent urethral obstruction; only mucosa and lamina propria in the pouch (no muscle); more commonly multiple; posterior wall above trigone most common location
Diverticula represent sites of urinary stasis, with potential for infection

Cystitis

General Acute and Chronic Cystitis

Frequently precedes pyelonephritis
Most common organisms: E. coli, then Proteus, Klebsiella, Enterobacter; also Tuberculosis, Candida albicans, Cryptococcus, schistosomiasis, Adenovirus, Chlamydia, mycoplasma
Also seen following cytotoxic antitumor drugs, radiation, or trauma
Present clinically with frequency, lower abdominal pain, dysuria (pain or burning on urination)
Hemorrhagic Cystitis
Often following radiation or chemotherapy; also Adenovirus
Marked epithelial atypia (more bizarre than carcinoma)
Suppurative Cystitis
Accumulation of large amounts of puss in lumen
Granulomatous Cystitis
Frequently seen following BCG therapy for papillary TCC
Also seen with TB
Chronic Cystitis
More extreme heaping of mucosa
Red, friable, granular, sometimes ulcerated surface
Lymphoplasmacytic infiltrate
Fibrous thickening of the muscularis
Cystitis Follicularis
Variant of chronic cystitis with aggregation of lymphocytes into follicles

Special Forms of Cystitis

Interstitial (Hunner's) Cystitis
Persistent, chronic cystitis, most frequent in middle aged women (M:F=1:10), very painful hematuria, urgency; unresponsive to medical (antibiotic) therapy
Clinical-pathological correlation required; histology may be normal
Inflammation and fibrosis of all layers of the wall
Localized ulcer is often present
Lamina propria shows edema, hemorrhage, granulation tissue, mononuclear inflammation, often perineural
Often, numerous mast cells are present beneath the ulcer, *within the detrusor muscle*, and between the epithelial cells in the mucosa
Eosinophilic Cystitis
Two clinical settings:
• women and children, associated with allergic disorders and eosinophilia
• older men following bladder injury
Dramatic, recurrent episodes of frequency, dysuria and hematuria
Grossly: broad based polypoid growths
Chronic cystitis with dense inflammation, abundant eosinophils in lamina propria (numbers decrease with increasing fibrosis), fibrosis, muscle necrosis, occasionally giant cells; overlying epithelium often metaplastic or proliferative
Polypoid Cystitis
Benign, inflammatory process which simulates neoplasm
Usually dome or posterior wall, secondary to catheter trauma
Stromal edema, congestion, chronic inflammation, normal epithelium without atypia
Emphysematous Cystitis
Occurs most frequently in diabetics (50% cases)
Gas bubbles in the submucosal connective tissue, presumably caused by gas forming bacteria
Giant cells surround gas bubbles
Tuberculosis
Most frequent cause of granulomatous cystitis
Usually secondary infection from kidney; initially involves the area around the ureteral orifices
Malakoplakia
Soft yellow 3-4cm mucosal plaques composed of closely packed, large, foamy macrophages with occasional giant cells and interspersed lymphocytes
Macrophages contain basophilic PAS positive granules filled with bacterial debris
Michaelis-Gutmann bodies: laminated mineralized concretions within and between macrophages
Most likely represents a defective host response to bacterial infection, usually from Gram negative bacilli
Probably same as Xanthogranulomatous cystitis

Miscellaneous

Obstruction
- Usually due to prostatic hypertrophy in males, cystocele in females
- Other causes: congenital urethral narrowing, inflammatory strictures, mechanical obstructions, neurogenic paralysis
- Thickening of wall due to hypertrophy of smooth muscle, resulting in marked trabeculations of the wall
- With time, crypts between muscle bundles may form diverticula (see above)

Lithiasis
- Bladder calculi much more common in men than women
- Majority are solitary and composed of phosphate salts

Amyloidosis
- May be part of a systemic process or nodular and localized to the bladder (amyloid tumor)
- Deposits in interstitium of lamina propria, often penetrating into the muscularis
- Minimal inflammation unless ulcerated
- Can also be seen in the ureter, renal pelvis, or urethra
- Most are AL protein

Endometriosis

Proliferative / Metaplastic Lesions

- Occurs in setting of long-standing chronic inflammation

Brunn's Nests, Cystitis Cystica and Cystitis Glandularis
- Invagination of transitional epithelium into the underlying lamina propria (Brunn's nests)
- May lose connection with the surface and become cystic with a flattened transitional to cuboidal lining (cystitis cystica)
- Cyst lining may undergo metaplasia to columnar, mucous secreting cells (cystitis glandularis)
- Probably not premalignant

Squamous Metaplasia
- Non-keratinizing: most commonly seen in trigone of women; responsive to estrogen
- Keratinizing: seen secondary to trauma, diverticula, bladder stones, or schistosomiasis

BLADDER TUMORS

Tumor-Like Lesions

Amyloid Tumor
- [See above]

Inflammatory Pseudotumor
- AKA: Plasma cell granuloma
- Well defined mass; may be encapsulated
- Lymphocytes, histiocytes, plasma cells

Spindle Cell (Pseudosarcomatous) Nodule
- Occurs following instrumentation (TUR)
- Small, sessile, friable nodule; ulceration of overlying epithelium, hemorrhage
- Simulates sarcoma (usually leiomyosarcoma) with high cellularity, high mitotic activity; may "invade" and destroy muscle
- No pleomorphism, ulcerated surface, RBC extravasation, and history distinguish from true sarcoma

Benign Tumors

Condyloma acuminatum

- HPV induced papillomas, almost always associated with lesions of the perineum

Inverted Papilloma

- AKA: Brunnian adenoma
- Most commonly adults, males, located in trigone, neck, or prostatic urethra; usually solitary
- May be a reactive lesion
- Presents with hematuria and/or obstruction
- Often a polypoid, usually sessile mass, showing invagination of the epithelium without atypia, without papillae, few mitoses, normal maturation
- Must distinguish from TCC involving Brunn's nests

Nephrogenic adenoma

- AKA: Adenomatoid Tumor, Mesonephric adenoma
- May be localized or diffuse metaplasia rather than neoplasm
- Occurs in response to chronic infection, calculi, prolonged catheterization; 20% multiple
- Papillary, polypoid, or sessile; generally small
- Small tubules (microcysts) lined by cuboidal and hobnail cells, often with a prominent basement membrane
- No atypia, not premalignant
- Differential diagnosis: mesonephroid (clear cell) adenocarcinoma

Other Benign Tumors

Paraganglioma (Extra-adrenal pheochromocytoma)
- Can occur as a primary bladder lesion, localized within wall
- Patients present with fainting during micturition
- Not all are necessarily benign

Leiomyoma

Hemangioma

Granular Cell Tumor

Neurofibroma

Malignant Tumors

Transitional Cell Carcinoma

- 90% of all primary tumors of the bladder; 3% of cancer deaths
- Most patients >50yrs old; M:F = 3:1; present with hematuria
- Risk factors: exposure to aniline dyes (especially benzidine), *smoking* (4x relative risk), cyclophosphamide ingestion, phenacitin, schistosomiasis
- 75% arise from trigone region; partial or complete ureteral obstruction common
- Papillary and non-papillary (in-situ or "flat") forms; >70% of patients have multiple recurrences of papillary TCC before progression to a more invasive lesion; some patients present with high grade lesion from the start
- Foci of glandular or squamous metaplasia common
- Immunoreactive for keratins, CEA (esp. high grade), Leu-M1
- Tumors can be graded on scale of I-IV or 0-III, where lowest grade is essentially equivalent to benign papilloma
- Many of these tumors, especially higher grade, are multifocal; most common in presence of dysplasia

Grading
- Grade I: papillary structures, uniform cells, >7 layers
- Grade II: pedunculated or sessile; more crowding/layering of cells; enlargement of nuclei, more than occasional mitosis
- Grade III: Sessile or cauliflower-like, often with necrosis and ulceration, smaller masses of cells, many mitoses
- Grade IV: Most sessile with necrosis; marked atypia and pleomorphism, frequent mitoses, often atypical

Stage

AJCC		Alternate Staging
Ta	Non-invasive, papillary (Stage 0a)	
Tis	Non-invasive, flat (Stage 0is)	
T1	Subepithelial connective tissue	A
T2	Superficial muscle (<50%)	B1
T3a	Deep muscle (>50%)	B2
T3b	Perivessicle fat	C
T4a	Prostate, uterus, vagina	D1
T4b	Pelvic wall, abdominal wall	D2
N1	Single LN, <2 cm	
N2	Single LN 2-5cm or multiple LNs <5cm	
N3	Any LN>5cm	

	T1	T2	T3a	T3b	T4a	T4b
N0	I	II		III		
N1-3	IV					
M1						

LN metastases in 25%; distant sites: lung, liver, bone

Treatment
- Carcinoma in situ: total cystectomy - usually multifocal
- Grade I-II: transurethral resection
- Grade III-IV or any grade with Stage >A: radical cystectomy
- Radiation works well for papillary component but has little effect on invasive component
- Bacillus Calmette-Geurin (BCG) therapy has been effective at decreasing recurrence rates

Prognosis
- Poor: High stage (muscle invasion), LN involvement, grade, dome or anterior wall, dysplasia elsewhere in bladder, vascular invasion
- Good: young patient, inflammatory response

Squamous Cell Carcinoma
- ~5% of primary bladder tumors
- Association with schistosomiasis, chronic irritation (eg calculi)
- M:F = 3:2
- More commonly fungating and invasive
- Somewhat worse prognosis than TCC, but probably due to higher stage at presentation

Adenocarcinoma
- Rare (~2% primary bladder tumors)
- Develop in setting of cystitis glandularis, exstrophy, or in urachal remnant
- Unlike transitional cell carcinoma, most are solitary lesions
- Generally deeply invasive
- Restrict term to pure adenocarcinomas; focal glandular changes or mucin production by a TCC is still a TCC
- Poor prognosis

VARIANTS

Clear Cell (Mesonephric, Mesonephroid) Type
- Usually papillary
- Mixture of glands, ducts, papillae, cysts, solid areas
- Cells have abundant cytoplasmic glycogen and a hobnail morphology
- Marked pleomorphism, infiltration, and mitoses distinguish from adenomatoid tumor

Signet Ring Cell Carcinoma
- Diffuse infiltration of wall (linitis plastica pattern)

Small Cell Carcinoma
- As with its pulmonary counterpart, frequently shows some neuroendocrine features
- May be pure or combined with invasive TCC
- Extremely aggressive

Sarcomatoid Carcinoma
- AKA: Carcinosarcoma
- High grade tumor: epithelial component (transitional, glandular, squamous, or undifferentiated) and sarcomatous component (spindle cell to specific types of differentiation)
- Generally, even sarcomatoid regions are keratin positive

Rhabdomyosarcoma
Adult form
- Usually >40 yrs old
- Similar to rhabdomyosarcoma of skeletal muscle

Sarcoma Botryoides
- Generally infants and children
- Embryonal rhabdomyosarcoma
- Grows as large grape like polypoid projections into lumen

Leiomyosarcoma
- More common in adults
- Usually well circumscribed, may protrude into lumen, may ulcerate

TESTIS

Normal

Adult: 12-18g; 5x3x3 cm
Capsule composed of 3 layers:
- Tunica vaginalis (outer serosa)
- Tunica albuginea (fibrous capsule)
- Tunica vasculosa

250 lobules each with up to 4 seminiferous tubules (each ~200µm long)
Germ cell : Sertoli cell ratio usually 13:1
Sertoli cells form the blood-testis barrier; basal spermatogonia are on the blood side of the barrier
Spermatogenesis: spermatogonia (two types: pale, dark), primary spermatocytes, secondary spermatocytes, spermatids, spermatozoa
~1/2 germ cells should be in late spermatid stage
Spermatogenesis stimulated by FSH; Leydig cells produce testosterone in response to LH
Leydig cells contain Reinke crystalloid (hexagonal prisms by EM, tapered ends, moderately electron dense)

Development

3 Phases of development:
- Static (birth to age 4 - seminiferous tubules compactly filled with small undifferentiated cells; Leydig cells present in newborn, but then disappear)
- Growth (4 - 10 yrs: minimal growth, lumen forms, increased tortuosity of tubules)
- Development and maturation (age 10 to puberty: gonadotropin driven growth; mitoses, Leydig cells reappear; primary and secondary spermatocytes appear at age 8-11, spermatids by age 12)

Failure of Pubertal Maturation
- Hypoganadotrophic eunuchoidism (60%)
  Low LH+FSH levels, small tubules, few Leydig cells
- Klinefelter's syndrome (30%)
  XXY, fibrosis of tubules, prominent basement membrane thickening, Leydig cell hyperplasia, increased incidence of breast carcinoma
- Testicular Aplasia (10%)
  Absent testicular tissue; elevation in urinary LH and FSH

Congenital / Acquired Malformations

Cryptorchidism
In 10% males at birth: 80% inguinal, 20% abdominal
90% descend in 1st year, leaving <1% cryptorchidism
Should be corrected by age 2-3 yrs (earlier if bilateral)
Unilateral: 100% fertile if corrected before age 10
Bilateral: 50% fertile if corrected before age 5
If uncorrected by puberty:
Small, brown testis with atrophic tubules, thickened basement membrane, foci of Sertoli cell hyperplasia, prominent interstitial cells
10-50x more likely to develop malignancy (usually seminoma) unless corrected by age 6; some increased risk persists even after correction
Increased incidence of malignancy in contralateral testis of patient with unilateral cryptorchidism

Ectopic Spleen
Splenogonadal fusion syndrome: congenital malformation occurring when two organs in close proximity
Always left sided
Continuous Variant: cord of fibrous or splenic tissue
Discontinuous Variant: no connection

Polyorchism

Adrenal Cortical Rests

Epidermoid Cysts
Intraparenchymal keratin filled cysts with squamous lining
Squamous metaplasia or monodermal teratoma - unknown
Sample thoroughly for adnexal structures (rule out teratoma)

Hydrocele
Accumulation of fluid in tunica vaginalis
May occur following trauma or epididymitis

Spermatocele
Cystic dilatation of efferent ducts, lined by tall ciliated cells

Varicocele
Abnormal dilatation of veins in the spermatic cord
90% occur on left
Often results in decreased fertility

Torsion

Spermatic Cord
Peak incidence in first year, second peak near puberty
Enlarged, painful
Intense congestion to hemorrhagic infarction (veins occlude first; arteries may or may not occlude)
Usually minimal inflammation (impaired blood flow)
If reduce within 6 hrs, usually no infarction; if >24 hrs, almost always infarcted

Appendix testis or epididymis
Pain well out of proportion to size of structure
- Testis: Paramesonephric duct remnant (92%)
- Epididymis: Mesonephric duct remnant (8%)

Causes of Infertility

Azospermia
- Germ cell aplasia (Sertoli cell only syndrome) (29%): Thickening of BM with fibrosis
- Spermatocytic Arrest (26%): usually at 1° spermatocyte; Leydig cells normal
- Generalized Fibrosis (18%)
- Normal Spermatogenesis (27%): total bilateral obstruction causing secondary spermatocytic arrest with sloughing of immature spermatocytes into the lumen

Oligospermia
- Incomplete Arrest
- Spermatogenic hypoplasia (no specific arrest, just decreased production)
- Regional (incomplete) fibrosis
- Tubular hyalinization (e.g., Klinefelter's syndrome)
- Normal Spermatogenesis: partial obstruction

Testicular Atrophy
(Note: if elastic fibers present, puberty was reached before disease developed)
- Atherosclerosis
- Hypopituitarism
- Irradiation
- Uncorrected cryptorchidism
- Semen outflow obstruction
- Generalized malnutrition
- Chemotherapy (especially cyclophosphamide)
- End stage inflammatory orchitis (e.g., postpubertal mumps)
- Exogenous estrogen or GnRH for prostatic carcinoma
- Exhaustion atrophy following persistent elevated FSH
- Hepatic cirrhosis (increased endogenous estrogens, not metabolized by liver)

Inflammatory Orchitis

Mumps
Orchitis occurs in 20% of postpubertal patients

Edema of tunica albuginea and the interstitium, with vascular congestion, necrosis of spermatocytic cells (largely sparing the Sertoli cells), interstitial lymphocytic aggregates, neutrophils
10% of postpubertal patients with orchitis become infertile

Pyogenic Epididymoorchitis
Congestion, edema, neutrophils (interstitium, then tubules)
May lead to venous thrombosis, septic infarction
E. coli most commonly (for children and men>35 yrs); when sexually active: Neisseria gonorrhea, Chlamydia
Other infections agents: Toxoplasma, fungi, parasites, syphilis, TB (hematogenous or via prostate; former usually spares tail of epididymis), atypical mycobacteria
Most infectious agents (especially TB) infect epididymis first, then spreads to testis; however, syphilis usually begins in testis

Non-Specific Granulomatous Orchitis
Solid, nodular enlargement of testis
History of trauma usually present
Granulomatous inflammation surrounding the seminiferous tubules; probably secondary to acid fast products of disintegrating sperm
Can be secondary to sarcoid or infectious
Non-infectious autoimmune form also exists

Malakoplakia
Abscess formation, tubular atrophy
Michaelis-Guttmann bodies (intracellular and extracellular round bodies which stain for iron and calcium)
Bacterial in origin, usually E. coli

Other Non-Neoplastic Lesions
Juvenile Xanthogranuloma
Sinus Histiocytosis with Massive Lymphadenopathy

TESTICULAR TUMORS

Germ Cell Tumors
Account for 90-95% of all testicular tumors
Arise from germinal epithelium; 60% are mixed tumors
Most common malignancy in males 25-29yrs
Increased risk in patients with cryptorchidism, a positive family history, previous germ cell tumor, intersex syndrome, or oligospermic infertility
Presents usually with painless unilateral enlargement
1-3% bilateral (15% if both undescended) - usually metachronous
Many germ cell tumors, regardless of type, show isochromosome 12
Histologic types: originally it was thought that these tumors followed either a seminomatous or a non-seminomatous pathway; it is now known that the sequence appears to be Intratubular Germ Cell Neoplasm, then seminoma, then others, usually via embryonal; however, can progress to others without an embryonal or even a seminoma stage, and most of the subtypes appear to be able to interconvert

Spread
Lymphatic: First, periaortic and iliac nodes (80% ipsilateral, 20% bilateral), then mediastinal, left supraclavicular nodes. Inguinal nodes involved only if skin or scrotum invaded
Blood: lungs, liver, brain (especially choriocarcinoma), bone (especially seminoma)
Histology of metastases may be completely different from that of the primary tumor

Staging
Tis Intratubular tumor
T1 Limited to testis
T2 Beyond tunica albuginea or into epididymis
T3 Spermatic cord involvement
T4 Scrotal involvement
N1 Single LN <2cm
N2 Single LN 2-5cm or multiple LNs all <5cm
N3 Any LN >5cm

	Any T
N0	I
N1-3	II
M1	III

Therapy and Prognosis
Initially, inguinal orchiectomy. Get histology, then:
• Seminoma: radiation of retroperitoneum (very sensitive)
• NSGCT: lymphadenectomy if vascular invasion identified; chemotherapy if metastases present
Prognosis: Cure rate is >95% without LN involvement; 40-90% with positive LN's (except choriocarcinoma, which is almost always fatal)
If alive at 2 yrs, 90% chance of cure; at 6 yrs, ~100%
Bad prognostic signs: extension into spermatic cord, Leydig cell hyperplasia in residual testis, vascular invasion
Follow serum: HCG elevated in 72% (may present as gynecomastia), AFP elevated in 75%

Intratubular Germ Cell Neoplasia
Seen in 80% testis with invasive malignancy
Can be seen in contralateral testis
Histology is usually independent of the histology of the invasive component

IGCN, unclassified
Atypical germ cells at base of otherwise normal seminiferous tubules, with clear cytoplasm (glycogen), PLAP+
Thickened lamina propria with hyalinization

IGCN with extratubular extension ("Microinvasive")
Atypical germ cells in interstitium
?invasion vs. ectopic germ cell elements

Intratubular Seminoma

Intratubular Embryonal Carcinoma

IGCN, other forms

Seminoma
30-40% of all testicular tumors
Most common type in men >60 yrs
Rare in prepubertal male
Tend to remain localized a long time before metastasizing

CLASSICAL SEMINOMA (95%)
Mean age 42 yrs
Solid, homogeneous, light yellow; often replaces entire testis; may show some necrosis; cystic changes or hemorrhage suggest non-seminomatous component

Clear cells (abundant glycogen) with sharp borders, central hyperchromatic nuclei with 1-2 prominent nucleoli; cells arranged in sheets, nests, trabeculae, or dispersed throughout the interstitium; nests are surrounded by fibrous bands infiltrated by inflammatory cells (lymphocytes, plasma cells, granulomas)
20% show no inflammatory response (may have worse prognosis)
Serum shows elevated PLAP in 40-50%
May occur in extra-testicular sites (pineal, anterior mediastinum, retroperitoneum); worse prognosis
Immunoreactive for Placental Alkaline Phosphatase (PLAP), vimentin; generally negative for keratin

Seminoma with trophoblastic giant cells
10-20% classical seminomas contain isolated or syncytial masses of large cells, often perivascular, with associated hemorrhage
Cells contain chorionic gonadotropin, ± elevation in serum
May be more aggressive
If serum HCG does not fall after orchiectomy, suggests there are metastases with the same histology or that the patient has choriocarcinoma

Anaplastic seminoma
Initially defined as >3 mitoses/HPF; need other pleomorphism
Poorly defined; unclear significance

SPERMATOCYTIC SEMINOMA (5%):
Mean age 65yrs (older age group)
Never occurs in combination with teratoma; never occurs outside of testis; no association with cryptorchidism or IGCN
Soft, pale gray, homogeneous; ~10% are bilateral
Three cell types (small, medium, and large), all with perfectly round nuclei (medium sized cells predominate)
Cells have dense cytoplasm, numerous mitoses
Prominent intratubular growth pattern at periphery
Few lymphocytes
Excellent prognosis unless sarcomatous transformation

Non-Seminomatous Germ Cell Tumors (NSGCT)

Mean age 30 yrs; Rare beyond 60 yrs of age

EMBRYONAL CARCINOMA
Metastasize early: poor prognosis
Heterogeneous solid gray mass with foci of hemorrhage and necrosis
Sheets, glands, tubules, papillae, or alveolar nests of undifferentiated cells with vesicular nuclei, prominent nucleoli, numerous mitoses, pleomorphism
Immunoreactive for keratin, although may be only focal
When pure, AFP negative
Most occur mixed with other histologic types, only 3-7% pure

TERATOMA (MATURE, IMMATURE)
5-10% of all testicular tumors
Heterogeneous tumor: multiloculated cysts, cartilage
Most common tissues: nerve, cartilage, epithelium
Immature components of unclear significance
In children, never metastasize
In adults, may have metastases even if all mature

Teratocarcinoma
Teratoma plus embryonal carcinoma
Appearance depends on relative amounts of each
Can get sarcomatous elements

Teratoma with malignant transformation
Malignancy (e.g. adenocarcinoma) arising in a mature component

Primitive neuroectodermal tumor
All immature neural tissue

CHORIOCARCINOMA
5% of all testicular tumors
Usually very small, hemorrhagic, partially necrotic
Giant syncytial trophoblasts with large atypical nuclei intermixed with cytotrophoblasts (must have both) in a biphasic, plexiform pattern; no intermediate trophoblasts
Syncytial component positive for chorionic gonadotropin
Almost always disseminated at presentation, thus fatal
Primary may regress leaving only hemosiderin laden scar

YOLK SAC TUMOR
AKA: Endodermal sinus tumor, juvenile embryonal carcinoma, embryonal adenocarcinoma, orchidoblastoma
Monomorphic teratoma mimicking embryonal yolk sac
Homogeneous, soft, microcystic, yellow-white, mucinous
Organoid intermingling epithelial and mesenchymal elements (microcystic, glandular alveolar, papillary); hyaline intracytoplasmic inclusions, PAS+, diastase resistant
Perivascular Schiller-Duval bodies (endodermal sinuses: mesodermal core, central capillary, visceral and parietal layers; resembles primitive glomerulus)
Immunoreactive for keratin and AFP (alpha-fetoprotein)

Pure form
Infants and children (<2 yrs old); excellent prognosis

Mixed form
Adults; worse prognosis

Polyembryoma
Multiple embryoid bodies (amnion-like cavity with embryo-like cellular invagination overlying a yolk sac-like structure)
Considered a mixed tumor with yolk sac, embryonal

Diffuse embryoma
Embryonal, yolk sac, and trophoblastic elements in orderly arrangement

Sex-Cord Stromal Tumors

~4% of all testicular tumors

Leydig (Interstitial Cells)

Testosterone producing cells

Nodular Leydig Cell Hyperplasia
Usually multiple nodules, almost always <0.5 cm
Seen in cryptorchid testes

Leydig Cell Tumor
3% bilateral
Presentation: mass or gynecomastia
Small (average 3 cm), sharply demarcated, dark brown
Well defined cell borders, acidophilic to clear cytoplasm, round to oval nucleus, nuclear pleomorphism; solid growth, occasionally trabecular
EM: smooth ER, Reinke's crystalloid (elongated, often tapered crystals; moderately electron dense)
10% metastasize (larger (7.5 cm), other malignant features)

Sertoli Cells

Sertoli Cell Hyperplasia
AKA: hypoplastic tubules, tubular adenomas
Seen in half of the cryptorchid testes and in 20% patients with testicular tumors
Frequency decreases with age

Sertoli Cell Adenoma
Not uncommon in testicular feminization syndrome
Elongated tubules lined by Sertoli-like cells

Sex-cord tumor with Annular Tubules
Closely related to Sertoli cell adenomas
Seen in patients with Peutz-Jeghers syndrome

Sertoli Cell Tumors
AKA: androblastoma
1/3 associated with gynecomastia

Well circumscribed, white or yellow, firm, focally cystic
Sertoli cells form tubules or solid sheets
10% behave malignantly - metastasize

Sclerosing Sertoli Cell Tumor
Mean age 35
Well circumscribed, firm, white
Solid and hollow tubules in a hypocellular fibrous stroma
Generally well behaved

Large Cell Calcifying Sertoli Cell Tumor
Usually <20yrs old; frequently bilateral or multifocal
Associated with Leydig cell tumors, pituitary tumors, adrenal cortical hyperplasia, cardiac myxomas, Peutz-Jeghers
Sheets to cords of tumor cells with abundant cytoplasm separated by abundant fibrous tissue with calcifications

Other Sex Cord - Stromal Tumors
Granulosa Cell tumor (juvenile form in infants <6 months; abnormal chromosomes and ambiguous genitalia)
Counterparts of ovarian surface epithelial tumors (serous, mucinous, endometrioid, clear cell, Brenner)

Other Testicular Tumors

Gonadoblastoma
Mixed Germ cell - Sex Cord - Stromal Tumor
Arises in individuals with underlying gonadal disorder, usually chromosomal abnormality, with occasional exceptions
Calcifications; hyaline bodies surrounded by malignant cells

Lymphoma
5% of all testicular malignancies; 50% of the bilateral tumors
Most common testicular tumor in elderly
Large cell type most common (non-cleaved, immunoblastic)
If primary, good prognosis; if not, bad prognosis
Involvement interstitial with relative sparing of the seminiferous tubules, especially at periphery

Leukemia
Usually ALL; Similar pattern to lymphoma
Clinically evident in 8% children with ALL, microscopically evident in 20% - often first sign of relapse

Others
Carcinoid Tumor
Well circumscribed, firm yellow masses
Orchiectomy usually curative

Spindle Cell Tumor
May have islands of squamous metaplasia

Paratesticular Rhabdomyosarcoma
Most common non-germinal tumor of scrotal contents in children and adolescents
Nearly always of embryonal type
Metastases to retroperitoneal nodes in 40%

Metastatic Tumors
Most common primaries: lung or prostate

Epididymal Tumors

Adenomatoid Tumor
Most common type; 20-30 yrs peak incidence
Presents as mass with or without pain
Small (~2 cm), solid, firm white, occasional small cysts
Unencapsulated, cords of flattened to cuboidal epithelium, often with vacuolated cytoplasm, with dilated channels and prominent stroma with smooth muscle and elastic fibers
Hyaluronidase sensitive mucin staining
Immunoreactive for keratin and EMA; negative for CEA, factor VIII
Histogenesis unclear - may be special form of mesothelioma
Invariably benign

Mesothelioma
Usually fibrous type
Arises from tunica vaginalis testis
Differential includes adenocarcinoma of rete testis

Papillary Cystadenoma
Unilateral or bilateral
Familial incidence: part of von Hippel-Lindau syndrome
1-5 cm, well circumscribed, cystic or solid
Papillary infoldings with clear cytoplasm
Malignant counterpart, rare

PROSTATE

Normal

- Approximately 20 gm in normal adult
- Retroperitoneal; encircles neck of bladder
- No distinct capsule
- Classically, 5 lobes: posterior, middle, anterior, two lateral
- Urethra enters from bladder on superior surface of gland and exits anteriorly
- Glands lined by two cell layers: low cuboidal basal layer and cuboidal to columnar secretory layer
- Epithelial cells immunoreactive for PSA (prostate-specific antigen), PAP (prostate-specific acid phosphatase), keratin, Leu-7, EMA (80%), CEA (25%)
- Basal cell layer immunoreactive for keratin 903 (difficult stain to do correctly)

Prostatitis

Acute Bacterial Prostatitis
- Usually a localized process involving small number of ducts or acini
- Formerly, gonorrhea most common cause
- Now, E. coli infection associated with some degree of urinary obstruction and urinary retention is most common
- Abscess formation can be seen
- Usually not biopsied

Chronic Prostatitis
- Can be bacterial or non-bacterial
- Lymphocytes, plasma cells, macrophages
- Can result in mild elevations of PSA

Tuberculosis
- Prostate involved in ~10% of patients with systemic infection
- Usually lateral lobes, usually bilateral
- Confluent foci of caseous necrosis common
- Some cases occur following treatment with Bacillus Calmette Guérin (BCG) therapy for TCC; these cases tend to remain localized

Non-specific Granulomatous Prostatitis
- Firm prostate with dense fibrosis and granulomas
- No necrosis
- Unknown etiology; probably duct rupture and leakage of contents

Eosinophilic Prostatitis

Malakoplakia
- Usually associated with similar disease in bladder

Nodular Hyperplasia

- AKA: Benign Prostatic Hypertrophy
- Often results in some degree of urinary obstruction
- Occurs in 50% men by 40's, 75% by 70's; ~4% of men over 70 have prostates larger than 100gms
- Intact testes required, since hormonal stimulation necessary
- Average size is 100gm; up to 800gm has been reported
- Begins on inner portion of gland (peri-urethral)
- Both glandular and stromal (fibrous and smooth muscle) hyperplasia
- Inspissated secretions, calcifications, calculi (7%), corpora amylacea, infarction (20-25%)

Basal Cell Hyperplasia
- Small, generally solid nests of benign-appearing epithelial cells with a somewhat clear cytoplasm
- Can mimic PIN, but generally is NOT papillary
- Always an accompanying usual hyperplasia
- Keratin 903 positive
- May be ischemic in origin

Tumor-Like Conditions

Sarcoma-Like Nodules
- Usually few weeks to months following TUR procedure
- Exuberant stromal reaction
- May have high mitotic activity, extreme cellularity

Melanosis
- Can occur in epithelium or in stroma (blue nevus)

Urethral Polyps
- Tall columnar cells - cause hematuria in young

Amyloid Nodule

Sclerosing Adenosis
- AKA: fibroglandular nodule
- Relatively well circumscribed aggregate of smaller glands in the middle and larger glands to the periphery
- Nucleoli generally present but small
- S-100 stains myoepithelial cells in this lesion, but not elsewhere (i.e., not in normal prostate)

Atrophy
- Small basophilic glands with open lumina, often lined by a single cell layer, but cells are flattened (atrophic)
- Sclerotic stroma
- May be confused with adenocarcinoma

Prostatic Intraepithelial Neoplasia (PIN)

- Identifiable on low power: glands with normal architecture but with papillary projections into the lumen and darker staining due to hyperchromasia and enlargement of the nuclei with overlapping and stratification; cells may contain pigment
- Almost exclusively confined to peripheral zones
- Four histologic patterns: micropapillary, tufted, cribriform, flat
- Graded as PIN I, II, or III: some use Low (I) and High (II or III)
- Prominent nucleoli make PIN II (at least)
- PIN I or II can be found in 70% of "normal" patients
- Keratin 903 staining may be scanty
- PIN III indicates up to a 70% chance of a coexisting adenocarcinoma elsewhere in the gland

Adenocarcinoma

- Second most common malignancy in men in US
- Responsible for 10% cancer deaths
- Black:white = 2:1; hormonally related
- Unlike BPH, most carcinomas arise peripherally
- 75-85% are multifocal
- Most arise from peripheral ducts and acini; a few arise in the larger primary ducts
- Gray or yellowish grossly
- Variable growth patterns: cribriform, diffuse, glandular, papillary, etc.
- Morphologic variants include small cell, mucinous (more aggressive; less responsive to hormonal therapy), squamous, adenoid cystic, and large duct adenocarcinoma (papillary or cribriform; prostatic, endometrioid, transitional cell, mixed)
- 10-25% show protein crystals in glandular lumina; strong indicator of malignancy; crystals are deeply eosinophilic, often rhomboid, and are immunoreactive for Ig light chain (κ or λ)
- Other indicators or probable malignancy: necrosis in secretions, deeply eosinophilic secretions, basophilic mucinous secretions
- When nucleoli exceed 3μm, always malignant; 1-3μm is suggestive of carcinoma

Can use keratin 903 to look for presence of basal cell layer; because of the variability in staining, absence does not necessarily mean carcinoma

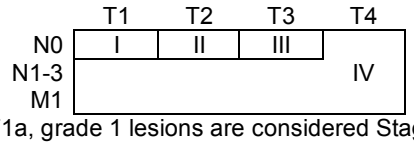
Spread
- Marked propensity for perineural invasion
- "Capsular" invasion very common
- Seminal vesicles involved in 30%
- Metastases most commonly to bone and LNs
- Bone lesions usually multiple, osteoblastic or osteoclastic
- LN involvement is first pelvic, then retroperitoneal

Clinical Staging

A: No palpable lesion:	A1: <5%	A2: >5% or high grade
B: Confined to prostate	B1: 1 lobe	B2: both lobes
C: Periprostatic:	C1: <70g	C2: >70 gm tumor or seminal vesicle
D: Metastatic:	D1: pelvic LN's	D2: distant

- 35% males >50 and 60% >80 have stage A1 disease
- <10% individuals with stage A1 disease progress
- 30-50% stage A2 lesions progress within 5 yrs, 20% fatal
- 75% patients are Stage C or D when present clinically

Pathologic Staging
- T1a: Not palpable; ≤5% of resected tissue
- T1b: Not palpable; >5% of resected tissue
- T1c: Not palpable; positive needle biopsy
- T2a: Confined to prostate; ≤1/2 lobe
- T2b: Confined to prostate; 1/2 - 1 lobe
- T2c: Confined to prostate; both lobes
- T3a: Unilateral extracapsular extension
- T3b: Bilateral extracapsular extension
- T3c: Involves seminal vesicle
- T4a: Bladder neck, external sphincter, rectum
- T4b: Levator muscles, pelvic wall
- N1: Single LN, <2cm
- N2: Single LN, 2-5cm; or multiple LNs, all <5cm
- N3: Any LN >5cm



NOTE: T1a, grade 1 lesions are considered Stage 0

Grading (Gleason)
- Score two most predominant patterns
- 1: Single, separate, uniform glands, closely packed, round, well delimited
- 2: Single, separate, less uniform glands, loosely packed, less well delimited
- 3a: Single, separate, variable glands, irregularly separated, poorly delimited
- 3b: Like 3a, but very small glands or tiny cell clusters
- 3c: Cribriform tumor, well circumscribed
- 4a: Raggedly outlined, infiltrating, fused glands
- 4b: Large pale cells (hypernephroid)
- 5a: Comedocarcinoma pattern
- 5b: Anaplastic cell masses or single cells

Therapy and Prognosis
- Stage A1 lesions are treated conservatively (followed)
- Radiotherapy or radical prostatectomy for A2
- Radical prostatectomy for B
- Stage C and D are treated with radiation and anti-androgen therapy
- Stage and grade most important prognostic indicators
- Age is NOT a factor in prognosis
- Weak reactivity for PSA and PAP may indicate a more aggressive tumor

Flutamide Therapy
- Flutamide is an anti-androgen which blocks peripheral conversion of estrogens to androgens (primary stimulation for prostate growth is androgens from the adrenal gland)
- (Note: patients treated with Flutamide are often given Lupron, a LHRH agonist, to maintain testicular function)
- Flutamide induces atrophy of both the normal and malignant prostatic glands
- Prominent basal cell layer, immature squamous metaplasia, shrinking of secretory layer with vacuolization of cells which may become difficult to find; pigment may be present
- May need keratin stain to find residual tumor
- Don't give a Gleason grade to treated tumor - inaccurate
- Same histologic changes are seen in LN metastases

Endometrioid Carcinoma of the Prostate
- Arises from utricle
- Usually papillary
- Generally does not metastasize to bone; normal serum acid phosphatase level
- May have relatively good prognosis

PENIS

NORMAL
- Erectile tissue: 2 corpora cavernosa, 1 corpus spongiosum containing the urethra and extending into the glans
- Urethral meatus normally at the central ventral glans
- Covered by a squamous epithelium, non-keratinized on the glans

Congenital and Acquired Malformations

Abnormalities of Size
- Almost always associated with other abnormalities of the genitourinary tract
- Aphalalia: Penile agenesis (very rare)
- Hypoplasia
- Hyperplasia
- Diphalalia: duplication of penis

Abnormalities of Urethral Meatus
- Epispadias: opens on dorsum of glans
- Hypospadias: opens on ventral surface of penis
- Accessory Urethral canals:

Phimosis
- Orifice of prepuce too small to allow normal retraction
- May be caused by congenital anomaly or chronic infection
- Paraphimosis: prepuce retracted but too tight to be re-extended
- Treated with circumcision

Infections

[See also Infectious Agents Outline]

Balanoposthitis
- Infection of glans and prepuce
- Most commonly seen in uncircumcised newborns
- Strep, staph, Neisseria gonorrhea, gardnerella vaginalis, Trichomonas
- Inflammation is non-specific

Syphilis
- Usually on glans
- Initially firm, erythematous papule which ulcerates (hard chancre)
- Plasma cells and lymphocytes underlying ulcer, with endothelial cell proliferation and capilaritis
- Secondary syphilis: condyloma lata (flat, maculopapule)
- Tertiary syphilis: gummas (granulomas)

Lymphogranuloma Venereum
- Chlamydia trachomatis
- Short-lived painless papule or ulcer, followed by suppurative inflammation of the inguinal lymph nodes

Others
- Granuloma Inguinale, Herpes, Molluscum Contagiosum

Miscellaneous Inflammatory Lesions

Balanitis Xerotica Obliterans
- Equivalent to Lichen Sclerosis et Atrophicus of the Vulva
- Gray white geographic areas of atrophy, which histologically show loss of lamina proprial structures, thinning of the epidermis, and diffuse fibrosis
- Predominantly lymphocytic infiltrate deep

Balanitis Circumscripta Plasmacellularis
- AKA: Zoon's balanitis
- Unknown etiology; usually uncircumcised men
- Epidermal atrophy; plasma cell rich inflammation, histiocytes with hemosiderin pigment

Peyronie's Disease
- Fibrous thickening of the tissue between the corpora cavernosa and tunica albuginea limiting the movement of these structures past each other during an erection (curvature toward side of lesion)
- Histology is that of fibromatosis
- May be inflammatory in etiology
- May lead to ossification

Non-Invasive Squamous Lesions

Condyloma Acuminatum
- Sexually transmitted disease caused by human papilloma virus, most commonly types 6 and 11
- Accounts for ~1/3 of all polypoid lesions of the male urethra
- Most commonly urethral meatus or fossa navicularis
- Exophytic, fungating wart-like lesion
- Hyperkeratosis, hypergranulosis, acanthosis, koilocytosis

Bowenoid Papulosis
- Occur in patients <35yrs, usually skin of the shaft or glans
- Multiple small rapidly developing shiny erythematous lesions which histologically are very similar to squamous cell carcinoma in situ but with slightly more orderly background, and some maturation toward the surface
- 80% of cases have been shown to have HPV-16
- Often spontaneously disappear without treatment

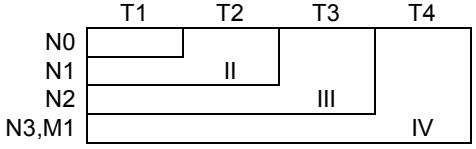
Bowen's Disease
- AKA: Squamous cell carcinoma in situ
- Usually shaft or scrotum of patient >35yrs
- Slowly enlarging, sharply demarcated, single lesion, scaly
- Full thickness dysplasia with hyperchromasia, mitoses
- 5-15% will progress to invasive squamous cell carcinoma
- Nearly 1/3 of patients will have some "unrelated" visceral malignancy (lung, GI tract, or urinary tract)

Erythroplasia of Queyrat
- AKA: Squamous cell carcinoma in situ of the glans
- Asymptomatic, well defined shiny red lesions of the glans and foreskin of uncircumcised men
- Histology same as Bowen's disease
- No association with visceral malignancy

Squamous Cell Carcinoma

- 1% of male cancers in US; much higher elsewhere; appears to be significant decreased incidence among circumcised population
- Patients usually 40-70yrs old; usually arises on glans
- May be some association with HPV 16 and 18
- Predominantly two growth patterns: exophytic papillary and ulcerating flat
- Slow growing
- ~15% have metastasize at diagnosis
- If limited to the glans, >95% survival; with involvement of shaft and regional LNs, survival at 3yrs <50%

Staging
- Tis Carcinoma in situ
- Ta Noninvasive verrucous carcinoma
- T1 Subepithelial connective tissue
- T2 Corpus spongiosum or carvernosum
- T3 Urethra or prostate
- T4 Adjacent structures
- N1 Single superficial inguinal LN
- N2 Multiple or bilateral superficial inguinal LNs
- N3 Deep inguinal or pelvic LNs



HISTOLOGICAL TYPES

~50% of SCC of the penis fall into the NOS category

Verrucous Carcinoma

5% of penile cancers
Large, warty exophytic growth
Extremely well differentiated histology throughout, with pushing borders
Does not metastasize
Very good prognosis

Superficially Spreading
Vertical Growth
Multicentric
Basaloid
Inflammatory
Spindle-Cell

OVARY

NORMAL
- Follicles: primordial, primary, secondary, tertiary, graafian, atretic; also corpora lutea and corpora albicantia
- Hilus cells (counterpart of Leydig cells) are intimately associated with nerves; more prominent in older women
- Walthard cell nests may be cystic or solid
- Germ cells develop from endoderm; rest of ovary is mesodermal in origin

Congenital Malformations

Mesonephric (Wolffian Duct) Remnants
- Small duct-like structures at ovarian hilus
- May become cystically dilated
- Mesonephric ducts have cuboidal epithelium, predominantly non-ciliated, on a well developed basement membrane
- (In contrast, paramesonephric (Müllerian) ducts are taller, contain a mixture of ciliated and non-ciliated cells, and have an inconspicuous basement membrane)

Gonadal Dysgenesis
- May be "pure" or associated with Turner's syndrome
- Ovaries represented by a streak of fibrous tissue

Mixed Gonadal Dysgenesis
- One streak ovary and the other with testicular tissue
- Particularly prone to develop gonadoblastoma

Inflammatory Lesions

Nonspecific Inflammation
- Usually ascending, practically always associated with salpingitis resulting in a tubo-ovarian abscess (see below)
- Heals with fibrous scarring and by conversion to a tubo-ovarian cyst

Granulomatous Inflammation
- TB, Actinomycosis, Schistosomiasis, Enterobius vermicularis
- Sarcoidosis, Crohn's disease

Torsion
- Usually secondary to inflammation or tumor of tube or ovary, but both are normal in 20% of cases
- Hemorrhagic infarction
- If reduce quickly enough, may be able to recover
- Non-operated cases may calcify

Non-Neoplastic Cystic Lesions

Germinal Inclusion Cysts
- Small, multiple; probably invaginations of surface epithelium
- Flattened epithelium, tubal metaplasia, psammoma bodies

Follicular Cysts
- Distention of developing follicles - may occur at any age
- Generally call "follicular cyst" only if >2 cm; if smaller, simply a "cystic follicle"
- Lined by theca layer, frequently luteinized, ± granulosa layer

Corpus Luteum Cyst
- Reproductive age patients
- Bright yellow convoluted thick rimmed hemorrhagic cyst
- Lined by luteinized granulosa cells surrounded by theca lutein cells
- May rupture into peritoneum

Polycystic Ovaries
- 3-5% of all women
- Multiple subcapsular follicular cysts (usually <1cm) covered by a dense fibrous capsule
- Stein-Leventhal Syndrome: polycystic ovaries, amenorrhea, and sterility
- Follicular cysts produce androgens, which are converted to estrogens which leads to endometrial hyperplasia and anovulation (by suppression of FSH)

Epidermoid Cysts

Non-Neoplastic Proliferations

Endometriosis
- "Ectopic" proliferation of endometrial glands and stroma with hemosiderin
- Ovary is most common site; associated with infertility
- May be small focal lesions or convert entire ovary into a "chocolate cyst" from repeated hemorrhages

Endosalpingiosis
- Proliferation of tubal epithelium without stroma
- Usually 1 cell layer, obvious lumen; cells may be ciliated
- Increased frequency in presence of serous ovarian tumors

Stromal Hyperplasia
- Bilateral diffuse (single cells or clusters) or nodular proliferation within the cortex and medulla of plump ovarian stromal cells, often with patchy or extensive luteinization (hyperthecosis, diffuse thecomatosis)
- True thecomas may develop in this background

Hilus Cell Hyperplasia
- Multiple nodules, usually <2mm each

Ectopic Decidual Reaction

Massive Edema of the Ovary
- Patients present with pain and an abdominal mass
- Usually unilateral massively enlarged soft, boggy ovary; may be in excess of 2kg!
- In addition to diffuse edema, cystic follicles usually present
- Partial torsion may have an etiologic role
- Differential diagnosis: ovarian fibroma

Fibromatosis
- Usually younger age group (13-40yrs) than fibroma
- Firm, white cut surface with residual follicles

OVARIAN NEOPLASMS

GENERAL
- 5th leading cancer killer in women; most common cause of death from GYN malignancies
- Predominantly disease of older white women
- Pregnancy and oral contraceptives DECREASE risk
- ~10% of tumors in women <45yrs are malignant; ~50% in women >45yrs
- Most common sites of spread: contralateral ovary, peritoneal cavity, pelvic LNs, paraaortic LNs
- Overall survival: 35% at 5 yrs, 28% at 10 yrs, 15% at 25 yrs
- Prognosis for borderline tumors generally good, even with involvement of the peritoneal cavity

FIGO Staging
- (NOTE: TNM staging same: T2c=FIGO IIc)
- I: Limited to the ovaries
  - Ia: one ovary, no ascites
    - Ia1: intact capsule, no tumor on surface
    - Ia2: tumor on external surface or ruptured capsule
  - Ib: both ovaries, no ascites
    - Ib1: intact capsule, no tumor on surface
    - Ib2: tumor on external surface or ruptured capsule
  - Ic: ascites or malignant washings

II: Pelvic extension
IIa: uterus or tubes
IIb: other pelvic tissues
IIc: IIa or b with ascites or positive washings
III: Intraperitoneal metastases outside pelvis, retroperitoneal nodes, or small bowel or omentum
IIIa: microscopic peritoneal seeding
IIIb: implants larger, but <2 cm
IIIc: >2 cm implants or positive lymph nodes
IV: Distant metastases or liver metastases

Stage and Prognosis

Stage	Frequency	5 yr Survival
I	26%	61%
II	21%	40%
III	37%	5%
IV	16%	3%

Surface Epithelial Tumors

2/3 of ovarian tumors; ~90% of all malignant ovarian tumors
Believed to arise from the epithelium lining the outer surface of the ovary, variably termed "surface", "coelomic" or "germinal" epithelium - continuous with the mesothelium
Actually, tumors probably arise from an invaginated portion of this epithelium
Not infrequently tumors can be mixture of multiple types
All of these tumors are divided into benign, borderline, and malignant categories
Borderline tumors also go by the terms "low malignant potential" or "indeterminate malignant potential"
Both borderline and malignant tumors are treated with total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) and surgical staging; if preservation of fertility is desired and tumor is stage 1 and borderline, can limit surgery to unilateral salpingo-oophorectomy
In general, 1 tissue block per 1-2 cm of maximum tumor dimension is recommended

Serous Tumors

Comprise 25-30% of all ovarian tumors, most in adults, 30-50% are bilateral
Usually cystic spaces with papillary formations protruding into the cavities which are filled with a clear (sometimes viscous) fluid
Cuboidal to columnar cells line cyst wall and papillae
Psammoma bodies seen in 30%
Immunoreactive for keratin, EMA, sometimes vimentin
Negative for CEA (unlike mucinous tumors)

Serous Cystadenoma / Cystadenocarcinoma

Benign (~70%): single layer of cells, no atypia, no invasion
Borderline (10-15%): stratification and glandular complexity, often with cytologic atypia and mitotic figures but NO definite destructive stromal invasion (i.e., no associated stromal edema and reactive fibroblastic response)
Malignant (15-20%): high mitotic rate, atypical cells, stratification, glandular complexity, branching papillary fronds, *destructive stromal invasion*
Bilateral in 10% of benign, 25% borderline, 70% malignant
Borderline lesions tend to occur in a slightly younger age group than carcinoma, and tend to be lower stage at presentation

Cystadenofibroma

Prominent fibrous stromal component surrounding benign glands
Solid, white lesion grossly
Malignant counterpart (cystadenofibrocarcinoma) is rare

Serous Surface Papillary Carcinoma

Grows exophytically on surface of ovary with little involvement of underlying ovary
Most are bilateral; rapidly spread throughout abdomen

Mucinous Tumors

15-25% of ovarian tumors
Bilateral in 10-20% (most commonly when malignant)
Most common surface epithelial tumor in children, perhaps due to its unclear recurrent relationship with teratoma
Tend to grow larger than serous type
Usually at least partially cystic, most commonly multiloculated; cysts contain mucinous material
Papillae, solid areas, necrosis, hemorrhage more common in malignant form
Tall, columnar, non-ciliated cells with intracellular mucin overlying basal nuclei
Tumors can be endocervical type or intestinal type (latter with goblet cells, Paneth cells, etc.)
Stroma often cellular, may be luteinized; stromal invasion is often difficult to assess because of gland complexity
Benign: most common (80%)
Borderline (15%): increased layering, but ≤4 cells
Malignant (5%): cell atypia, increased layering of cells (>4 cells thick), complex glands, stromal invasion
Tendency to implant on peritoneal structures; if extensive, "pseudomyxoma peritonei"; may be impossible to distinguish from appendiceal primary when both involved
CEA positivity seen in 15% benign, 80% borderline, and 100% malignant mucinous tumors
Not uncommonly seen concurrently with Brenner tumor or with teratoma

Endometrioid Tumors

5-10 % of ovarian tumors
10-20% have coexistent endometriosis
Generally large cystic mass with solid areas, often hemorrhagic, usually *without* papillary structures
Resemble endometrial adenocarcinomas
Areas of squamous metaplasia are common
Borderline variant exists, but it is very rare
Prognosis generally twice as good as serous or mucinous carcinoma, but because most are stage I and well differentiated

Clear Cell (Mesonephroid) Tumors

Usually 40's to 50's
Spongy, often cystic appearance
Tubular-cystic, papillary, and solid growth patterns
Cores of papillae often hyalinized
Large tumor cells with clear cytoplasm and hobnail appearance; cytoplasm may be oncocytic
Probably a variant of Endometrioid Carcinoma
5 yr survival 40-50%

Brenner Tumor

1-2% of all ovarian tumors
Average age at presentation is 50 yrs; 3/4 over 40 yrs
Usually unilateral, firm, white, solid
Solid and cystic nests of cells resembling transitional epithelium with distinct cell borders, oval nuclei with small but distinct nucleolus and longitudinal grooves
Stroma is dense and fibroblastic
Not infrequently seen with mucinous cystadenoma

Metaplastic Brenner Tumor

Prominent cystic formations with mucinous changes

Proliferating Brenner Tumor

Presence of papillary fronds and nuclear atypia
Resembles papillary TCC (low grade)

Malignant Brenner Tumor

Stromal invasion, cytologically malignant (resembles high grade transitional cell carcinoma)

Mixed Mesodermal Tumor

Benign
- Papillary adenofibroma

Malignant
- Same as counterpart in uterus
- Carcinomatous component may be serous, endometrioid, squamous, or clear cell
- Extremely poor prognosis, especially heterologous type
- Most common heterologous element is chondrosarcoma

Germ Cell Tumors

- 20-30% of all ovarian tumors
- Most are seen in children or young adults; the younger the patient, the more likely tumor will be malignant
- 95% are benign cystic teratomas
- ~10% of germ cell tumors are of mixed type (most common is dysgerminoma and yolk sac tumor)

Dysgerminoma

- <1% of all ovarian tumors; 5% of malignant ovarian tumors
- 80% of patients are under 30yrs old, 40% under 20yrs
- Bilateral in 15%; when unilateral, more common on right
- Female counterpart of classical seminoma
- Large, encapsulated, smooth, often convoluted surface
- Gray solid cut surface; foci of hemorrhage and necrosis may be seen, but not as commonly as in other ovarian tumors
- Well defined nests of tumor cells separated by fibrous stroma infiltrated by lymphocytes
- Tumor cells have clear cytoplasm, oval uniform large nuclei, one or more prominent nucleoli
- 10% will have other germ-cell components - worse prognosis
- Metastases most commonly to other ovary, retroperitoneal nodes, peritoneal cavity
- When encapsulated, 95% 5yr survival; 33% with metastases

Dysgerminoma with Multinucleated Giant Cells (3%)
- Scattered HCG positive syncytiotrophoblast-like cells
- No change in prognosis

Anaplastic Dysgerminoma
- Marked mitotic activity (often >30 per HPF!)

Yolk Sac Tumor

- AKA: Endodermal Sinus Tumor
- Tumor of children and young adults (mean age 19)
- Serum AFP invariably elevated; HCG levels normal
- Smooth, glistening surface
- Reticular and microcystic growth patterns are most common; may also see papillary and solid
- Schiller-Duval bodies: glomeruloid structures with bulbous pseudopapillary processes containing central vessels
- Intracytoplasmic PAS positive hyaline droplets
- Subclinical metastases common
- 3yr survival was only 13%; multidrug chemotherapy has markedly improved this

Polyvesicular Vitelline Pattern
- Small cystic structures with eccentric constrictions separated by a dense spindle cell stroma
- When pure, good prognosis

Hepatoid Pattern
- Resembles hepatocellular carcinoma (large, polygonal cells in cords or sheets)

Glandular Pattern
- May resemble endometrioid carcinoma

Embryonal Carcinoma

- Rare in the ovary; median age 15 yrs
- Serum HCG levels always high; AFP levels often elevated
- Solid sheets and nests of large primitive cells often with abortive glandular formations, frequently admixed with syncytiotrophoblast-like giant cells
- Necrosis, hemorrhage common
- Poor prognosis

Polyembryoma

- Very rare
- Preponderance of embryoid bodies in various stages of development

Choriocarcinoma

- Most are metastases from uterine tumors
- When primary to ovary, usually part of mixed germ cell tumor
- Biphasic cell population with cytotrophoblasts and syncytiotrophoblasts
- When pure, usually lethal

Immature (Malignant) Teratoma

- Mixture of embryonal and adult tissues from all three germ layers; main component usually neural
- Grade I: mostly mature tissues (immature neural tissue comprises <1 high power field), loose mesenchymal stroma, immature cartilage, occasional mitoses
- Grade II: fewer mature tissues, foci of neuroepithelium not exceeding 3 low power fields on any one slide
- Grade III: little to no mature tissue; numerous neuroepithelial elements occupying 4 or more low power fields
- When yolk sac pattern also present, worse prognosis

Malignant Neuroectodermal Tumor
- Nearly exclusively composed of neuroectodermal elements

Ependymoma

Mature Cystic Teratoma

- 20% of all ovarian tumors; bilateral in 12%
- Most occur in women <30 yrs old
- >98% are benign (unlike counterpart in testis)
- Usually multiloculated with large cysts containing sebum, hair, keratin, teeth
- Microscopic foci of immature tissue are allowed
- Rokitansky's protuberance: central area containing bone and well formed teeth

Mature Solid Teratoma
- Rare; young women
- Predominantly solid mass grossly (may have small cystic areas microscopically)
- Some prefer to refer to this as Grade 0 immature teratoma
- Entirely adult tissue; excellent prognosis

Epidermoid Cyst
- Absence of other elements
- Probably arises from epithelial cell nest

Struma Ovarii
- Dominant growth of thyroid component of teratoma
- Can be seen in combination with mucinous cystadenoma, Brenner tumor, or carcinoid tumor

Carcinoid Tumor
- May be component of teratoma, primary tumor without other teratomatous components (good prognosis), or metastasis from some other primary (bad prognosis)
- Most primary carcinoids are unilateral, often symptomatic

Strumal Carcinoid
- Combination of carcinoid and thyroid elements

Mucinous Carcinoid
- Analogous to the appendiceal tumor with goblet cell-like cells growing in nests or glands
- Differential diagnosis: Krukenberg tumor

Malignant Transformation
- Usually to SCC, then carcinoid, then adenocarcinoma

Sex Cord - Stromal Tumors

5% of all ovarian tumors

Granulosa Cell Tumor

5% before puberty, 40% postmenopausal
<5% are bilateral
3/4 produce estrogen in excessive amounts; 1/4 are associated with endometrial hyperplasia
Usually encapsulated, solid, lobulated, gray
May contain cysts with straw-colored fluid
Variable microscopic appearance: microfollicular, macrofollicular, trabecular, insular, solid
Call-Exner bodies: small gland like "follicles" filled with acidophilic material; not always present
May have a thecal cell component; may luteinize, but less commonly than juvenile variant
Reticulin fibers surround groups of cells
Coffee-bean nuclei with folds or grooves
Can have bizarre multinucleated cells; probably degenerative rather than sign of malignancy
Immunoreactive for vimentin; usually keratin negative
Most are low stage (FIGO I) at presentation
Prognosis related to tumor size and stage; most deaths occur after 5yrs, so 5yr survival rates are not meaningful

Juvenile Granulosa Cell Tumor

Nearly 80% of patients are <20yrs old; most present with isosexual precocity
Larger tumor cells, extensive luteinization, paucity of nuclear grooves, nuclear atypia, often high mitotic rate; Call-Exner bodies are rare
Cysts are usually larger than in conventional variety
Better prognosis than typical granulosa cell tumor

Thecoma / Fibroma

Most patients are >40yrs old
Usually unilateral, well defined, firm, solid
Thecoma is yellowish, fibroma white
Both have spindle cells with central nuclei and a moderate amount of cytoplasm
Oil red O staining of fresh (frozen) tissue can show intracytoplasmic fat in thecomas
Reticulin fibers surround individual cells
Differential diagnosis: massive edema, fibromatosis

Cellular fibromas

High cellularity, ≤3 mitoses / 10 HPF (if more, fibrosarcoma)
May recur

Sclerosing Stromal Tumor

Younger age group (15-30 yrs)
Gray-white to yellow variegated cut surface
Multiple pseudolobules of cellular stroma with prominent extatic vessels separated by anastamosing hypocellular regions which vary from fibrous to edematous
Dual cell population: collagen-producing spindle cells, round or oval cells with clear cytoplasm (lipid)

Sertoli-Leydig Cell Tumor

AKA: Arrhenoblastoma; androblastoma
Uncommon; <0.2% of ovarian neoplasms
Young patients (average age 25 yrs)
Despite name, EM shows that the Sertoli-like cells are actually more granulosa cell like
Testosterone and estradiol are found in both cell types
Relatively good prognosis

Well Differentiated (Meyer type I) (11%)

Tubules lined by Sertoli-like cells separated by fibrous stroma with variable numbers of Leydig-like cells
100% survival

Intermediate (Meyer type II) (54%)

Cords, sheets, or other aggregates of Sertoli-like cells growing in lobules separated by spindled stromal cells and intermixed Leydig-like cells
~90% survival

Poorly Differentiated (Meyer type III) (13%)

Masses of spindled cells arranged in a sarcomatoid pattern
~40% survival

With Heterologous Elements (22%)

Mucinous epithelium, liver, skeletal muscle, cartilage

Retiform (15%)

Occurs in children (10-25 yrs)
May have papillary appearance grossly
Sertoli-Leydig elements mixed with irregular cleft-like spaces lined by low cuboidal cells, occasionally with blunted papillae (looks like rete testis)
20% die of disease

Pure Sertoli Cell Tumor

Rare - almost always at least some Leydig cell component
Solid and hollow tubules lined by Sertoli-like cells which usually lack atypia
Abundant lipid may be present in the cytoplasm

Gynandroblastoma

Sex-cord stromal tumor with a mixture of similar amounts of granulosa-thecal elements and Sertoli-Leydig elements

Lipid Cell Tumors

Includes: Leydig (Hilus) cell tumor, luteoma, etc.
Usually unilateral, yellow or yellow-brown nodules separated by fibrous trabeculae
Aggregates of large rounded or polyhedral cells with features of steroid hormone secreting cells
~40% of these tumors are negative for intracellular fat
Most patients have a virilizing syndrome
When Reinke's crystals are visualized, subclassify as Leydig cell; if located at the hilus of the ovary (most common location), designate as Hilus cell tumor
Almost all behave in benign fashion, especially when less than 8cm diameter

Sex Cord Tumor with Annular Tubules

1/3 cases associated with Peutz-Jeghers syndrome
Growth pattern of Sertoli cells but cells which appear more like granulosa cells - may be a variant of either
Simple and complex annular tubules containing eosinophilic, often calcified, hyaline bodies

Other Tumors

Gonadoblastoma

AKA: dysgenetic gonadoma
Combination of germ cell elements and sex-cord stromal elements
Usually nests containing multiple small round gland-like spaces filled with hyaline material; nests surrounded by fibrous bands
Occurs almost exclusively in sexually abnormal individuals, most commonly XY gonadal dysgenesis and XO-XY mosaicism
Never seen in normal ovaries
36% are bilateral
Hyalinization and marked calcification common

Germ Cell-Sex Cord-Stromal Tumors, NOS

Waste-basket diagnosis for mixed tumors which don't neatly fit into any of the well characterized types

Endometrioid Stromal Sarcoma
Proliferation of malignant stromal cells
Resembles endometrial stroma
Most cases represent spread from the uterus

Small Cell Carcinoma
May be confused with granulosa cells tumor
Large, solid tumor with areas of necrosis and hemorrhage
Diffuse proliferation of small cells with small nuclei and minimal cytoplasm; clusters of larger , more pleomorphic cells may be present; follicle-like structures may be seen
Immunohistochemistry is variable: sometimes keratin, vimentin, laminin, all, none
Unknown histogenesis

Hypercalcemic Type
Usually unilateral
Generally young women (mean age 22)
Patient has hypercalcemia; resolves after tumor resection

Pulmonary Type
~50% are bilateral
Generally older women (mean age 59)

Hepatoid Adenocarcinoma
Hepatoid histology may occur in the absence of yolk-sac differentiation (similar tumor also seen in the stomach)
Most patients are older
Usually at least focally positive of AFP
Very aggressive

Krukenberg Tumor
Metastatic adenocarcinoma, nearly always bilateral
Diffusely infiltrating signet ring cells with marked stromal proliferation
Primary sites include stomach, stomach, stomach, and also breast and large bowel

FALLOPIAN TUBES

NORMAL
3 distinct cell types: secretory, ciliated, intercalated (peg)
Immunohistochemical stains for amylase are positive
Lymphatic drainage joins that of ovary and uterus; ampulla also drains via broad ligament to superior gluteal nodes

Inflammation
Acute Suppurative Salpingitis (Pelvic Inflammatory Disease)
Common, usually ascending
Neisseria gonorrhoeae (~45%), Chlamydia (~20%)
May result in fusion of tubal plicae, obliteration of ostium, and subsequent infertility
Pyosalpinx: lumen filled with acute inflammation
Tubo-ovarian abscess: inflammation involves both fallopian tube and ovary; more commonly polymicrobial (enteric)

Granulomatous Salpingitis
Tuberculosis: Hematogenous, therefore usually bilateral
Actinomycosis, Schistosomiasis, fungal
Foreign Bodies: e.g. lubricant or other therapeutic agents

Other Non-Neoplastic Abnormalities
Tubal Pregnancy
Incidence increased markedly following PID
Trophoblastic invasion of wall of tube occurs - vessels usually rupture causing hematosalpinx
Significant hemorrhage if tube ruptures into peritoneum

Walthard Cell Nests
Small collections of flat to cuboidal cells on the tubal serosa
Probably focal mesothelial hyperplasia

Paratubal Cysts
AKA: Hydatids of Morgagni, paraovarian cysts
Small, round, attached by pedicle, thin wall, serous contents

Endometriosis
Focal replacement of tubal epithelium by uterine mucosa

Endosalpingiosis
Presence of tubal epithelium outside of fallopian tube
Most common site is ovary, close to fimbria of tube

Salpingitis Isthmica Nodosa
Usually young women (~25yrs), usually bilateral
Well delimited nodular enlargement of isthmic portion
Cystically dilated gland-like formations surrounded by hypertrophied muscle and occasionally endometrial-like stroma; glands do connect to tube lumen
May be inflammatory or related to adenomyosis
Approximately 50% patients are infertile

Tumors

Adenomatoid Tumor
Usually small, solid, firm white, unencapsulated
Dialted channels lined by a flattened to cuboidal epithelium, often with vacuolated cytoplasm, and separated by a stroma rich in smooth muscle and elastic fibers
Immunoreactive for keratin and EMA; – for CEA, factor VIII
Alcian blue positive, hyaluronidase sensitive mucin
Benign - probably represents a special form of mesothelioma

Carcinoma
Rare, <1% of GYN tract malignancies
1/10 as common as extension from endometrial primary
By convention, extensive involvement of uterus and tube is a uterine primary; ovary and tube is an ovarian primary
Most patients are postmenopausal
Usually invasive papillary adenocarcinoma, often solid areas
Any of the endometrial variants may also be seen
Prognosis determined more by stage than by grade
5 yr survival: Stage I: 77%, II: 40%, III: 20%

FIGO Staging

I: Confined to one or both tubes	Ia: One tube, no ascites
	Ib: Both tubes, no ascites
	Ic: Ascites with malignant cells
II: Pelvic extension	IIa: Involves uterus or ovary
	IIb: Involves other pelvic structures
III: Widespread intraperitoneal metastases	
IV: Extraperitoneal extension	

Others
Papillary Cystadenoma
Teratoma
Leiomyoma
Malignant Mixed Müllerian Tumor
Choriocarcinoma

UTERUS

GENERAL

Uterus weighs 50gms, 8cm long during reproductive life
Postmenopausally, atrophies to 5-6 cm
Zona basalis (deepest layer) is unresponsive to hormones
Zona functionalis (responsive layer) is subdivided into the superficial zona compacta and the deeper zona spongiosis

EMBRYOLOGY

During 6th week, an invagination of the coelomic lining epithelium forms the paramesonephric (müllerian) ducts
Müllerian ducts form high on dorsal wall (8th-9th week) and grow caudally, fusing caudally and extending to the urogenital sinus
Unfused portions form the fallopian tubes, fused portion forms the uterus and upper 1/3 of vagina

Endometrial Dating

Generally give a two day range
In normal cycle, the secretory phase is always 14 days
The proliferative phase is usually ~14 days, but may vary from individual to individual and cycle to cycle (up to 2 days); therefore, secretory endometrium dated either based on a 14 day proliferative phase, or simply as "Post-ovulatory day" (e.g., POD 1 = Day 15; POD 14 = Day 28)

Proliferative Phase

Columnar cells, pseudostratified, with cigar shaped nuclei with coarse (clumpy) chromatin, mitoses
Increasing tortuosity of glands as progress
Early (4-7): short, narrow straight glands, compact stroma
Mid (8-10): peak stromal edema, numerous mitoses, curving, coiled glands
Late (11-14): Tortuous glands with pseudostratification, moderately dense stroma

Interval (Day 15)

Subnuclear secretory vacuoles present, but in <50% cells

Secretory Endometrium

Single layer of cuboidal cells with round nuclei and fine chromatin; tortuous glands, secretions in glands
Day 16: Subnuclear vacuoles, pseudostratification
Day 17: Orderly row of nuclei, subnuclear vacuoles
Day 18: Vacuoles above and below nuclei, smaller
Day 19: Decreased number of vacuoles, orderly nuclei
Day 20: Peak secretion; ragged luminal border
Day 21: Early stromal edema; still significant secretion
Day 22: Peak stromal edema; "naked" stromal nuclei
Day 23: Spiral arterioles become prominent
Day 24: Periarteriolar cuffing of predecidua
Day 25: Predecidua beneath surface, inspissated secretions
Day 26: Coalescence of decidual islands, few neutrophils
Day 27: Many neutrophils, focal necrosis and hemorrhage
Day 28: Prominent necrosis and hemorrhage
Menstrual: Stromal clumping, glandular breakup

Other Endometrial Patterns

Arias-Stella Reaction: hypersecretory glands with marked enlargement of nuclei with hyperchromasia; changes usually focal; cytoplasm cleared or eosinophilic
Estrogen Therapy: proliferative endometrium, often to point of endometrial hyperplasia if unaccompanied by progestin
Progestational Agents: decidualized stroma; initially glands are secretory, then with time become weakly proliferative

Abnormal Bleeding

Definitions

Dysfunctional (anovulatory) Uterine Bleeding: excessive bleeding without demonstrable cause (e.g., estrogen breakthrough bleeding, estrogen withdrawal bleeding)
Menorrhagia: prolonged (>7 days) or excessive (>80mls) bleeding at normal time in cycle
Metrorrhagia: bleeding at irregular intervals
Menometrorrhagia: prolonged or excessive bleeding outside of normal cycle
Luteal Phase Defect: histologic date >2 days behind clinical date
Dyssynchrony: >4 day variation between glands and stroma

Causes

- Anovulation
- Pregnancy Related
- Endometritis
- Endometrial Polyp or hyperplasia
- IUD
- Exogenous Hormones
- Leiomyoma
- Thyroid Dysfunction
- Carcinoma

Endometritis

Acute Endometritis

Usually seen following abortion, delivery, or instrumentation
Neutrophils predominate

Chronic Endometritis

Lymphocytes and plasma cells (only need one plasma cell) in a stroma which tends to be spindled and edematous
Usually vaginal bleeding and pelvic pain
May be accompanied by mucopurulent cervicitis or pelvic inflammatory disease
Do not attempt to date endometrium in endometritis (usually can't, which is a clue to the diagnosis)
Intrauterine Device: induces chronic endometritis, sometimes with necrosis and squamous metaplasia; Actinomycosis, Entamoeba histolytica infections common

Endometrial Metaplasia

Squamous Metaplasia

- Adenoacanthosis: diffuse metaplasia
- Morules: berry-like aggregates of squamous cells without keratinization
- Ichthyosis uteri: rare; keratinization

Seen most commonly in women on exogenous estrogens
Often continuous with surface glands

Ciliated Cell (Tubal) Metaplasia

Scattered ciliated cells normally present in endometrium
When increased in number, resembles fallopian tubes (may have peg cells)

Syncytial Papillary Metaplasia

Papillary growth of an eosinophilic syncytium replacing the surface epithelium, associated with prolonged estrogen stimulation; nuclei are pyknotic; neutrophils common

Mucinous Metaplasia

May be endocervical or intestinal type

Eosinophilic (oxyphilic) Metaplasia

Hobnail and Clear Cell (Mesonephroid) Metaplasia

Common in gestational endometrium or in repair

Stromal Metaplasia

Rare; metaplasia is in the stroma rather than the epithelium
Islands of foam cells, smooth muscle, cartilage, bone

Adenomyosis and Endometriosis

Presence of islands of endometrial glands and stroma within the myometrium (adenomyosis) or outside of the uterus (endometriosis - can occur essentially anywhere)
Can both be present or occur independently
To make diagnosis, need two of glands, stroma, hemosiderin
Adenomyosis generally produces myometrial hypertrophy
When adenomyosis involves a leiomyoma, frequently referred to as an adenomyoma

Adenomyosis is generally non-functional basal type endometrium, whereas endometriosis is frequently functional and cycles similar to orthotopic endometrium
Pathogenesis still unknown; proposals include regurgitation, metaplasia, and lymphatic dissemination

Abnormal Endometrium

Atrophic
Nonstratified, flattened to cuboidal cells, aligned pyknotic nuclei
Glands often cystically dilated
Stroma spindled
Weakly Proliferative
Nonstratified to mildly pseudostratified columnar, thin and elongate nuclei with coarse to dense chromatin
Low gland to stroma ratio
Disordered Proliferative
Relatively common in perimenopausal women
Normal proliferative endometrium lining glands which are cystically dilated or budding or show irregular branching
Endometrium may be stratified, but there should be no atypia
Gland to stromal ratio is normal (1:1) but there is non-uniformity from field to field
Stromal cells spindled with plump nuclei
Endometrial Hyperplasia
Absolute increase in endometrial volume for the patient's age
Background endometrium is PROLIFERATIVE
Classified as simple (cystic) or complex (adenomatous) and with or without atypia
Adenomatous indicates branching or budding glands or tightly packed glands with loss of intervening stroma; occurs at older age than simple
Cytologic Atypia: Nuclear clearing (prominent euchromatin), irregular nuclear size and shape, prominent nucleoli, atypical mitoses
Architectural Atypia: Increased epithelial thickness, loss of radial orientation, glandular bridging
Risk of progression to carcinoma higher for complex and higher when cytologic atypia present

Simple without atypia:	5%
Complex without atypia:	25%
Atypical:	>50%

Endometrial Polyps

Hyperplastic Polyp
Localized irregular hyperplasia of endometrium
Endometrium and stroma unresponsive to progesterone
Stroma composed of spindle, fibroblast like cells with abundant extracellular connective tissue
Large blood vessels with thick walls
Atrophic Polyp
Involuted hyperplastic polyp; cystically dilated glands
Secretory (Functional) Polyp
Cycles with the surrounding endometrium
Adenomyomatous Polyp
Hyperplastic polyp with smooth muscle fibers separating the glands
No atypia
Mixed Endometrial-Endocervical Polyp
Atypical Polypoid Adenomyoma
Sessile or pedunculated lesion
Irregular atypical glands with enlarged nuclei, thick nuclear membranes, and prominent nucleoli, in a cellular stroma with smooth muscle bundles (≤2-3 stromal mitoses per 10 high power fields)
Commonly see squamous metaplasia

Tumors of the Endometrium

Endometrial Carcinoma

Most common invasive GYN malignancy in the US
80% occur in postmenopausal women
Major risk factors: excessive estrogen stimulation, obesity, diabetes, hypertension, infertility
Non-neoplastic endometrium often hyperplastic
80% are adenocarcinomas
Positive for keratin, vimentin, IgA, ±CEA
Extension into cervix occurs in 10%
Invasion of myometrium corresponds to grade
Lymph node metastases to pelvic and periaortic LN's
Histological Grading
Grade I: highly differentiated adenocarcinoma (≤5% solid)
Grade II: moderately differentiated with 6-50% solid areas
Grade III: >50% solid or entirely undifferentiated
NOTE: significant nuclear atypia raises grade by I
50%, 35% and 15% of adenocarcinomas are Grade I, II, and III, respectively
Nuclear Grading
Using the four criteria:
• prominent nucleoli
• irregular nuclear contour
• clumped chromatin
• nuclear size 3-4x normal
Grade I: fewer than two
Grade II: any two
Grade III: three or four
Staging (FIGO; equivalent to AJCC):
• I: confined to corpus
  Ia: limited to endometrium
  Ib: invasion ≤50% thickness
  Ic: invasion >50% thickness
• II: corpus and cervix but not outside uterus
  IIa: endocervical gland involvement only
  IIb: cervical stromal invasion
• III: outside uterus, but not outside true pelvis
  IIIa: Serosa or positive cytology
  IIIb: Vaginal metastases
  IIIc: Pelvic or periaortic LN involvement
• IV: outside true pelvis of to bladder or rectum
  IVa: adjacent organs (bladder or bowel)
  IVb: distant organs

MORPHOLOGIC VARIANTS:

Villoglandular
Well differentiated villiform variant of endometrioid carcinoma
Don't confuse with papillary serous
Secretory
Rare; NOT a variant of clear cell carcinoma
Neoplastic glands with subnuclear vacuolization and secretory pattern in adjacent, uninvolved endometrium
Lack of polarization distinguishes this lesion from hyperplasia with secretory changes
Very low grade; good prognosis
Ciliated Cell
Very rare
Solid areas and nucleoli distinguish from ciliated metaplasia
Very low grade; good prognosis
Adenoacanthoma
Squamous metaplasia (benign) in an endometrioid adenocarcinoma
Do NOT include squamous areas in determining FIGO grade
Slightly better prognosis than endometrioid, NOS
Adenosquamous
Both endometrioid and squamous components are malignant
Probably somewhat worse prognosis than endometrioid, NOS
Glassy Cell Carcinoma
Variant of adenosquamous carcinoma
Pink cytoplasm, complicated nuclei with nucleoli

Aggressive; poor prognosis

Serous Adenocarcinoma
- AKA Papillary Serous, Uterine Papillary Serous (UPSC)
- (Does not always have papillae, so renamed simply "Serous")
- Generally small, short papillae line by highly atypical cells with hob-nailing; necrosis; psammoma bodies in 30%
- Lymphatic and myometrial invasion common
- Don't grade - prognosis is uniformly dismal
- Spread mimics ovarian carcinoma: omentum, peritoneum, colon, ascites
- If isolated focus in a polyp without vascular invasion, still equally bad
- Probably a multifocal disease
- Not very responsive to either chemotherapy or radiation

Clear Cell
- 1-5% of all endometrial carcinomas; usually older patients
- No association with diethylstilbestrol exposure
- Small papilla lined by hobnailed cells with clear cytoplasm
- Stroma usually hyalinized
- Tubular, tubulocystic or solid patterns focally; often all three
- Hyaline globules are characteristically seen
- Very poor prognosis: However, if stage I, survival slightly better than serous carcinoma; stage II or higher very bad
- Closely related to serous carcinoma; two often occur together

Mucinous
- Usually need >25% of cells to have intracellular mucin to make this diagnosis
- No significant difference in prognosis relative to endometrioid

Squamous Cell Carcinoma
- Pure epidermoid carcinoma is rare

Mixed

Undifferentiated
- Small cell (oat cell); poor prognosis

Endometrial Stromal Tumors

- Occur in middle age women (~45 yrs)
- Present with vaginal bleeding, pelvic pain
- Soft, yellow to orange, foci of hyalinization
- When <4cm, usually don't recur; when larger or extend outside uterus, may be lethal; can metastasize

Stromal nodules (<25%)
- Well circumscribed, pushing margins, no invasion
- Often protrude into endometrial cavity
- Benign; do not recur, do not metastasize

Low Grade Stromal Sarcomas
- AKA: endolymphatic stromal myosis
- Cut surface shows worm-like protrusions of tumor
- Histologically similar to stromal nodule, but infiltrates myometrium, invades and permeates lymphatic vessels, broad ligament
- <10 mitoses / 10 HPF
- 50% of patients present with Stage I disease
- 20% recur, but may not be for many years

High Grade Stromal Sarcoma
- Patients generally over 50yrs old
- Soft mass fills uterine cavity and invades myometrium
- Similar to low grade but usually has larger pleomorphic cells and must have >10 mitoses per 10 HPF
- Poor prognosis: frequently recur; often multiple metastases

OTHER VARIANTS

Stromomyoma
- AKA: Combined Smooth Muscle - Stromal Tumor
- Rare; reproductive age women
- More than 1/3 of the tumor is smooth muscle
- Benign

Uterine Tumors Resembling Ovarian Sex-cord Tumors
- Nests, cords, tubules or islands of epithelioid cells
- Benign vs Low Grade vs High Grade determined by pushing vs infiltrative margins and < or > 10 mitoses per 10 HPF

Extrauterine Endometrial Stromal Sarcoma
- Presumably arises in endometriosis
- Same histology as uterine counterpart

Mixed Mesodermal Tumors

Uterine Adenofibroma

- AKA: Papillary adenofibroma, adenomyomatosis
- Occurs in postmenopausal women
- Benign counterpart of Müllerian adenosarcoma (both epithelium and stroma are benign)
- Lobulated or papillary; superficial; does not invade myometrium
- Fewer than 4 mitoses per 10 high power fields

Müllerian Adenosarcoma

- Elderly individuals (median age 58)
- Low grade variant of MMT
- Bulky, polypoid lesion filling endometrial cavity
- Benign appearing epithelium (similar to phylloides tumor of breast), often appearing as large irregular glands with more worrisome stroma
- Very cellular stroma which condenses around glands; ≥4 mitoses per ten high power fields

Malignant Mixed Müllerian (mesodermal) Tumor

- Rare; Practically always in postmenopausal (median age 68)
- ~10% of cases have history of prior radiation exposure
- Present as large polypoid growth, usually arising from the posterior uterine fundus
- Foci of necrosis and hemorrhage
- BOTH carcinomatous and sarcomatous elements
- Restriction to inner half of myometrium only hope of cure
- On rare occasions, may arise in extra-uterine site (ovary, tube, peritoneum)
- Overall 5yr survival ~20-30%

Homologous variety
- Malignant stroma formed by round cells resembling endometrial stroma or spindle cells resembling leiomyosarcoma or fibrosarcoma

Heterologous variety
- Often more bulky than homologous
- Malignant stroma forms skeletal muscle (most common), cartilage, bone, fat
- Rarely see skin appendages, glia, or thyroid (unlike teratoma)
- Slightly worse prognosis

Tumors of the Myometrium

Leiomyoma

- Present in 20% of women 30-50 yrs old and in 40% of women over 50yrs
- Much more common in blacks (usually multiple)
- When multiple, more likely to all be benign
- Benignancy or malignancy determined by mitotic rate and cellularity (see table) [Note: for proper mitotic count, must section and fix rapidly or cells undergoing mitosis will complete telophase and falsely depress the count]
- Tumor is sensitive to compromise of vascular supply: secondary changes present in 65%: hyaline degeneration (63%), myxomatous degeneration (19%), calcification (8%)
- Can be infiltrated by lymphocytes: inflammatory pseudotumor

Cellular Leiomyoma
- More cellular than surrounding myometrium, no atypical features, <5 mitoses/10 HPF
- In pregnancy or women on oral contraceptives, may undergo central hemorrhage ("hemorrhagic cellular leiomyoma"); most are subserosal; 1/3 rupture into peritoneum

Atypical Leiomyoma
- AKA: Bizarre, Symplastic, Pleomorphic
- Variation in cell size and shape, hyperchromatic nuclei, multinucleated cells, but normal number of mitoses

Leiomyolipoma
- Mature adipose tissue intermixed with smooth muscle

Leiomyoblastoma
- AKA: Epithelioid, clear cell, or plexiform leiomyoma
- Tend to be solitary
- Rounded, polygonal cells (rather than spindled), often with clear cytoplasm (glycogen), growing in nests or compartments separated by hyalinized stroma
- Usually blends into more mature smooth muscle at periphery

Intravenous Leiomyomatosis
- Rare; wide age range
- Coiled, lobulated, well defined myometrial mass with "worm-like" growths into the uterine veins in the broad ligament; may extend up the inferior vena cava to the right atrium
- Histology is that of a normal leiomyoma

Diffuse Leiomyomatosis
- Involvement of nearly the entire myometrium by innumerable <1cm poorly-defined leiomyomata
- Associated with pregnancy or oral contraceptives
- Involute when hormone source removed

Benign Metastasizing Leiomyoma
- Patients usually 20-40yrs old, usually black women, usually following a hysterectomy or myomectomy
- Multiple smooth muscle tumors in lung, peritoneum, LNs
- Diagnosis of exclusion
- May actually be a very low grade leiomyosarcoma

	Mitoses per 10 high power fields				
	<2	2-5	6-10	11-15	>15
Atypical or Epithelioid	B	U	M	M	M
Cellular	B	B	U	M	M
Normal (Typical)	B	B	Leiomyoma with ↑# mitoses		U

B=Benign (Leiomyoma) U=Uncertain Malignant Potential
M=Malignant (Leiomyosarcoma)

Leiomyosarcoma
- Median age: 54 yrs
- Rare; only one for every 800 leiomyomata
- In general do not arise from pre-existing leiomyomata
- Diagnosis based on mitotic activity and cellularity (see chart)
- Hypercellular; 67% are solitary; 25% have infiltrating margins; 10% show vascular invasion
- 5yr survival 40-50% if limited to uterus; 20% overall

Myxoid Leiomyosarcoma
- Gelatinous appearance; appears well defined grossly
- Invasive with spindled muscle cells in a myxoid matrix
- Behave malignantly, regardless of mitotic count

Malignant Leiomyoblastoma
- AKA: Clear cell (epithelioid) leiomyosarcoma
- Rare; frequently infiltrating margin, necrosis
- Mitotic rate still key distinguishing feature

Adenomatoid Tumor
- AKA: Adenomatoid Mesothelioma
- Median age 42; BENIGN
- Usually solitary, subserosal proliferation of mesothelial-lined capillary-like spaces intermixed with smooth muscle
- Similar lesions may occur in fallopian tubes, ovary, omentum

Gestational Trophoblastic Disease

Implantation Site Changes
- Gold standard is chorionic villi
- In absence of this, immunohistochemically confirmed intermediate trophoblasts surrounding hyalinized vessels is presumptive evidence of intrauterine gestation

Arias-Stella Reaction
- Seen with both intrauterine and ectopic pregnancies
- Cellular stratification, enlarged cells, bizarre large hyperchromatic nuclei

Immunohistochemistry:	keratin	HPL	HCG
Cytotrophoblasts	++	-	-
Intermediate Trophoblasts	++	++	+
Syncytiotrophoblasts	++	+	++

(HPL=human placental lactogen)
(HCG=human chorionic gonadotropin)

Placenta Accreta
- Placental villi adhere to underlying myometrium
- Placenta increta: villi invade into myometrium
- Placenta percreta: villi invade through myometrium

Exaggerated Placental Site
- AKA: Syncytial endometritis
- Extensive *syncytiotrophoblastic* invasion of endometrium and mesentery
- Rare if any mitoses

Placental Site Nodule
- AKA: Placental Site Plaque
- Nodules of *intermediate trophoblasts* in a hyalinized stroma

Partial Hydatidiform Mole
- 25-40% of all moles
- Fetus often present, almost always anomalous
- Vesicular changes in some of the villi with edema, irregular scalloped contours, trophoblast inclusions, trophoblast hyperplasia
- Similar histology can also be seen in trisomies of chromosomes 13 or 18
- Most are triploid (58% XXY, 40% XXX, 2% XYY); some are tetraploid; result from fertilization of normal egg with 2 sperm; 2:1 paternal:maternal chromosomes
- 4-10% have persistent trophoblastic disease, usually intrauterine; much less likely to invade than complete mole

Complete Hydatidiform Mole
- Vesicular hydropic swelling of all of the villi, trophoblast hyperplasia, usually with absence of any identifiable embryo; "bunch of grapes"
- Large, bizarre mass fills and distends uterus
- Total weight often >200 gms
- Significant degree of trophoblast hyperplasia
- >90% are diploid; 85-90% are XX, 10-15% are XY
- All of the chromosomes are paternal; results from fertilization of an egg which has lost its chromosomes by either one or two sperm (if one, duplicates itself)
- Patients who have had a mole have increased risk for a 2nd
- Villi usually lack identifiable vessels
- Note: similar histology with trophoblast hyperplasia and small sheets of trophoblasts is normal at 5wks gestation; key is numerous nucleated RBC's (hence fetus, hence not complete mole)
- 10-30% will have persistent trophoblastic disease: persistent complete mole (10-15%), invasive mole (10-20%) or choriocarcinoma (2-3%)

Invasive Mole
AKA: Chorioadenoma destruens
Mole, usually complete mole, in which the *villi* penetrate the myometrium or the vessels of the myometrium
Occurs in 16% of all moles
Serosa usually intact
Vascular invasion may lead to embolization of villi
Rx: chemotherapy

Placental Site Trophoblastic Tumor
AKA: atypical choriocarcinoma; trophoblastic pseudotumor
75% follow a normal pregnancy
Grossly, well localized but ill-defined myometrial mass
Histologically, consists of intermediate trophoblasts; some syncytiotrophoblasts may be present as well
Locally invasive but usually self-limited
10% metastasize widely and are fatal

Choriocarcinoma
Highly malignant neoplasm
Dual cell population: cytotrophoblasts and syncytiotrophoblasts; do not see intermediate trophoblasts and NEVER see villi
Most commonly occurs following a complete mole (50%); 25% occur following an abortion; 22% follow normal pregnancy
Hemorrhagic tumor masses which are nodular and well defined; vascular invasion common
Metastasize early: lung (50%) vagina (35%), bone, brain, liver, kidney, bowel
Immunoreactive for HCG and keratin
Exquisitely sensitive to chemotherapy: has improved survival from <20% to nearly 100%

Other Tumors
Chorangioma
Hemangiomas of placenta
Common: found in 1/100 placentas
Usually well circumscribed; degenerative changes common
Larger lesions (>5 cm) can be associated with hydramnios, hemorrhage, premature delivery, premature placental separation
Chorangiosis
Diffuse increase in vascularity (increased number of vascular channels per villus)
May be associated with neonatal morbidity

CERVIX

Reactive Changes
Squamous Metaplasia
Begins basally
Cells acquire nucleoli and polygonal appearance on cytology
May involved glands, giving appearance of invasion
In essence, causes retreat of transitional zone into cervix
Nabothian Cysts
Blockage of endocervical glands
Usually secondary to inflammation
Endocervical Polyps
Probably chronic inflammatory or hamartomatous in nature
Edematous, inflamed, fibrotic stroma with dilated glands
May have multinucleated giant cells in stroma
Herpes Simplex Infection
Intense non-specific inflammation with ulceration
Only rarely are diagnostic multinucleated cells with inclusions seen in biopsy
Human Papilloma Virus
Condyloma acuminatum, flat condyloma, papilloma
Most commonly HPV-6 and 11, also 16
Simple koilocytic changes (binucleate cell with surrounding halo and denser peripheral cytoplasm) without disruption or expansion of the basal cell layer (latter indicates dysplasia)
Chlamydia trachomatis
Most common venereal disease
Chronic non-specific inflammation, reactive epithelial atypia, occasionally prominent lymphoid follicles
Cervical Ectropion
Presence of glandular epithelium in ectocervix
Strong correlation with in utero exposure to DES
Microglandular Hyperplasia
Seen with oral contraceptive use, sometimes pregnancy; usually younger women
Complex proliferation of tightly packed small glands with flat epithelial cells and little if any atypia, often with squamous metaplasia
CEA negative (unlike endocervical adenocarcinoma)
Atypical variant exists with predominantly solid sheet-like growth pattern
Diffuse Laminar Endocervical Hyperplasia
Proliferation of endocervical glands, typically with inflammatory infiltrate
Very well demarcated lower extent
Benign
Decidual Reaction
Often multiple, yellow or red elevations, friable
Endometriosis
Mesonephric (Gartner's Duct) Rests
Usually lateral wall, deep to the endocervical glands
Single cell layer, usually cuboidal
Clear cells, but no hob-nailing

Cervical Dysplasia
Enlargement of cells, increased nuclear:cytoplasmic ratio, irregular nuclear borders, chromatin clumping, and LOSS of BASAL POLARITY
Most often occurs at the transition zone between the columnar endocervical mucosa and the squamous ectocervical mucosa
Graded as mild, moderate, severe based on degree of atypia
Cervical Intraepithelial Neoplasia (CIN) graded as I, II, or III based on the degree of dysplasia and the thickness of involvement (<1/3; 1/3-2/3; >2/3)
When full thickness changes without any differentiation at any level, Carcinoma in Situ
Of mild to moderate lesions, 62% will regress, 22% will persist, and 16% will progress
Of severe dysplasia, invasive carcinoma will develop in 11% within 3 yrs, 22% in 5 yrs, and 33% in 9 years
HPV types 6 and 11 correlate with low grade lesions; types 16,18, 31, 33, and 35 with high risk for progression to carcinoma

Cervical Epidermoid Carcinoma

- Most common malignancy of GYN tract
- Second most common cause of cancer death in US women
- Usually older age groups, but increasing frequency <40 yrs
- Single most important risk factor is age of first intercourse
- Almost certainly HPV related
- May be bulky (exophytic) or infiltrative (or both)
- Major subtypes include: large cell non-keratinizing (65%), keratinizing (25%), small cell (probably worst prognosis), basaloid, verrucous
- Microinvasion suggested by the presence of desmoplastic stromal reaction with metachromatic staining
- Keratin and CEA immunoreactive
- Microinvasive carcinoma caries a 1% risk of LN metastases
- Endometrial extension decreases prognosis 10-20%
- LN metastases: first paracervical, hypogastric, obturator, external iliac; then sacral, common iliac, aortic, inguinal
- Distant metastases to lungs (9%) and bones (4%)

FIGO Staging (Same as AJCC)

- 0: CIS
- I: Confined to cervix and/or uterus
  - Ia1: Minimal microscopic microinvasion
  - Ia2: Invasion <5mm (some use 3mm) over area of <7mm
  - Ib : Invasion >5mm (some use 3mm) into cervical stroma
- II: Beyond cervix, but not pelvic wall or lower 1/3 of vagina
  - IIa: No parametrial involvement
  - IIb: Obvious parametrial involvement
- III: To pelvic wall, lower 1/3 vagina, rectum, hydronephrosis
  - IIIa: No extension to pelvic wall
  - IIIb: Pelvic wall and/or hydronephrosis
- IV: Beyond true pelvis or mucosa of bladder or rectum
  - IVa: Adjacent organs
  - IVb: Distant organs
- NOTE: Regional LN involvement (N1) makes lesion at least Stage IIIB, regardless of size or local extent of primary

Prognosis

- 5 yr survival: Stage I: 80-90%; II: 75%; III: 35%; IV: 10-15%

Adenocarcinoma

- 5-15% of all carcinomas of the cervix
- Association with long term use of oral contraceptives; also with HPV 16 and 18
- Alcian blue, mucicarmine, and CEA reactive material found intracellularly in almost all cells, unlike endometrial adenocarcinoma in which reaction is only focal and superficial
- Most are well differentiated and mucin producing
- Dysplasia, atypical hyperplasia, CIS, malignant cells in more than one gland, and microinvasion (budding and branching with stromal reaction and inflammation) can all be seen
- In general, overall prognosis is worse than for epidermoid carcinoma

VARIANTS

- ~50% of endocervical adenocarcinomas show typical mucinous endocervical glandular appearance
- Another ~25% appear endometrial or intestinal
- The remaining ~25% are divided among the following

Minimal deviation Adenocarcinoma (Adenoma Malignum)

- 1% of adenocarcinomas; very well differentiated
- Architectural features of malignancy, but cytologically "benign"
- Can only be diagnosed by location deep in cervix

Villoglandular Carcinoma

- Papillary carcinoma occurring in young women (~30 yrs old)
- Surface papillary growth pattern
- Good prognosis

Adenosquamous (Mixed) Carcinoma (~15%)

- Particularly common during pregnancy (~20% of cases)
- Squamous component often well differentiated
- Worse prognosis than pure squamous cell carcinoma

Glassy Cell Carcinoma (<5%)

- Many consider this a variant of adenosquamous carcinoma
- Younger age group (mean 41 yrs); often during pregnancy
- Ground glass or granular cytoplasm, prominent eosinophilic and PAS positive cell rim, large nuclei, prominent nucleoli
- Solid nests of cells, Numerous mitoses, prominent inflammatory infiltrate, often rich in eosinophils
- Poor prognosis

Basaloid

- Older women; very good prognosis

Adenoid Cystic Carcinoma

- Generally elderly multigravid black women
- Similar in appearance to salivary gland counterpart
- Very poor prognosis

Clear Cell Carcinoma

- Müllerian derivation
- Most common cervical carcinoma in young women; 50% of cases are related to in utero diethylstilbestrol exposure
- Usually exophytic growth pattern
- Large cells, abundant clear cytoplasm, hob-nailing
- 85% are stage I or II at presentation
- Relatively good prognosis

Mesonephric Carcinoma

- Rare
- Clear cells, but no hob-nailing
- Occur deep in cervix, almost always lateral walls

Neuroendocrine Carcinoma

- Spectrum from carcinoid-like to small cell carcinoma
- Frequently immunoreactive for NSE, chromogranin
- Even carcinoid-like tumors are more aggressive here than similar tumors elsewhere; small cell very aggressive

VAGINA

Congenital & Acquired Malformations

Tubal Fimbria
- May become entrapped in vaginal scar tissue following vaginal hysterectomy

Endometriosis

Vaginal Adenosis
- Any Müllerian-type glandular epithelium in the vagina, usually occurring in the upper third of the vagina
- Usually become clinically detectable only after puberty
- May be subdivided into "Mucinous" (endocervical), "Tubo-ovarian", and mixed types
- Accompanying chronic inflammation and squamous metaplasia are common, occasionally replacing most of the adenosis
- Oral contraceptives can induce microglandular hyperplasia within these lesions
- Seen in nearly 100% of patients exposed to diethylstilbestrol in utero prior to the 8th week of gestation

Cysts
- Epithelial inclusion cysts
- Müllerian Cyst: simple lining of endocervical type cells
- Gartner's duct (mesonephric) cysts: cuboidal, no mucin

Vaginal (Fibroepithelial) Polyps
- May have atypical cells in stroma
- Do not call botryoid rhabdomyosarcoma without well formed cambium layer or invasion

Microglandular Hyperplasia
- [See Cervix, above]

Benign Neoplasms

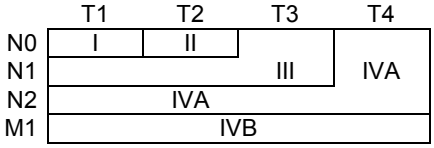
- Papillomas
- Tubulovillous Adenoma
- Leiomyoma
- Rhabdomyoma (always in adults)

Malignant Neoplasms

Vaginal Intraepithelial Neoplasm (VAIN I-III)

Epidermoid Carcinoma
- Most carcinomas represent extension of cervical carcinoma
- 95% primary carcinomas are conventional squamous cell
- Can also see Verrucous, Small Cell variants

Staging (FIGO and AJCC):
- T1 Confined to Vagina
- T2 Invades paravaginal tissues
- T3 Extends to pelvic wall
- T4 Invades mucosa of bladder / rectum or beyond pelvis
- N1 Pelvic LN metastases for upper 2/3 of vagina
  Unilateral inguinal LNs for lower 1/3 of vagina
- N2 Bilateral inguinal LNs



Clear Cell (mesonephroid) Carcinoma
- Seen in children or young adults; average age 17 yrs
- Anterior or lateral wall of upper vagina
- 2/3 of patients have history of in utero exposure to DES
- Tubules and cysts lined by clear cells alternating with more solid and papillary areas
- Hobnail-shaped cells protrude into glandular lumen
- Usually are NOT mucin positive
- Few mitoses, clear cytoplasm due to glycogen

Botryoid Rhabdomyosarcoma
- AKA: sarcoma botryoides
- Special type of embryonal rhabdomyosarcoma
- 90% in girls <5 yrs; 2/3 <2 yrs
- Polypoid invasive tumor, usually anterior vaginal wall
- Grossly appears as "bunch or grapes"
- Proliferation of myxomatous stroma with undifferentiated round or spindle cells, some with bright red cytoplasm
- Tumor cells crowd around vessels and beneath the squamous epithelium ("cambium layer" of Nicholson)
- Foci of neoplastic cartilage may be present (older patients)
- Extensive local spread; most do not metastasize

Malignant Melanoma

Endodermal Sinus Tumor

Leiomyosarcoma

Malignant Fibrous Histiocytoma

Epithelioid Sarcoma

VULVA

Cystic Lesions

Epidermoid Cyst

Pilonidal Cyst
- Most commonly clitoral area

Skene's Duct Cyst
- AKA: Paraurethral cyst

Hymenal Cyst
- Newborns

Mucinous Cyst of the Vestibule

Endometriosis

Bartholin Gland Cyst/Abscess
- Result from obstruction and/or chronic bacterial infection, especially gonorrhea
- Lining (transitional or squamous) may be destroyed

Inflammatory Lesions

Syphilis
- Plasma cells, lymphocytes, histiocytes underlying an ulcer containing neutrophils and necrotic debris
- Endarteritis common

Granuloma Inguinale
- Chronic infection by Calymmatobacterium granulomatis (gram negative encapsulated bacillus)
- Dense dermal infiltrate of histiocytes and plasma cells with islands of necrosis (small abscesses) and overlying pseudoepitheliomatous hyperplasia
- Donovan bodies: small round encapsulated bodies inside cytoplasm of histiocytes (best seen on Giemsa or Warthin-Starry)

Crohn's Disease
- May be contiguous with rectal lesions or independent

Lymphogranuloma Venereum
- Chlamydia trachomatis infection of lymphatic vessels
- Small ulcer at contact site, involvement of inguinal lymph nodes by stellate abscess with epithelioid histiocytes

Hydradenitis Suppurativa
- Chronic inflammation of the apocrine glands following duct occlusion by keratin plugs
- Peri-folliculitis, abscesses, sinus tracts
- Usually polymicrobial

Vulvar Dystrophies

- Post menopausal atrophy of vulvar skin and subcutaneous tissue producing thickened white skin clinically, often with severe pruritus

Keratosis and Chronic Inflammation
- Clinically referred to as "leukoplakia"
- Squamous hyperplasia, thick keratin layer, acanthosis, prominent stratum granulosum, dermal inflammation
- Foci of atypia or dysplasia not uncommon

Lichen Sclerosis et Atrophicus
- May occur anywhere on skin, most commonly vulva
- Clinically referred to as "kraurosis"
- White or ivory angulated macules or papules
- Hyperkeratosis with epithelial atrophy; edema and sclerotic homogenization of upper dermis (loss of elastin); underlying dense lymphocytic infiltrate may be present
- Telangiectatic vessels common

Benign Neoplasms

Condyloma
- HPV, usually type 6 or 11
- Condyloma acuminatum: soft elevated mass(es) composed of papillary arrangement of well-differentiated squamous epithelium overlying connective tissue cores
- Flat condyloma: not exophytic; slightly more common
- In both, see koilocytosis and lymphocytic infiltration of stroma
- Not specifically part of sequence including dysplasia and carcinoma, but often coexists with dysplastic areas

Melanocytic Nevi
- Particularly on the labia majora
- Almost always intradermal or compound

Hidradenoma Papilliferum (Papillary Hidradenoma)
- Small, well circumscribed subcutaneous nodule
- Papillary and glandular patterns with stratification and some degree of pleomorphism
- May arise from apocrine sweat glands of vulva or perhaps ectopic breast

Angiomyofibroblastoma
- Small, well circumscribed proliferation of vessels and a myxoid stroma
- May be an early form of Aggressive Angiomyxoma
- Does not recur after excision

Ectopic Mammary Tissue
- Occurs along the primitive milk line (extends from axilla to groin in embryo)
- Can undergo any changes seen in normal breast tissue, from lactational changes to benign and malignant tumors

Other Benign Lesions
- Syringoma
- Chondroid Syringoma

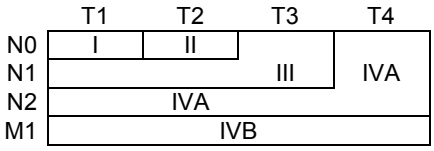
Bowenoid Papulosis
- Usually multiple pigmented papules on vulva of young patients, resembling warts or nevi
- Histologic appearance very similar to Bowen's disease, but some normal organization persists
- Some pathologists consider this a clinical diagnosis only, with the corresponding pathologic diagnosis being VIN
- May spontaneously regress

Malignant Neoplasms

Vulvar Intraepithelial Neoplasia (VIN)
- Intraepithelial dysplasia with a progression of atypia and disorder from basal third (VIN-I) to full thickness (VIN-III)
- HPV (especially types 16 and 18) present in >90% cases
- This lesion is more likely to progress to invasive carcinoma, and in fact may invade even before full thickness dysplasia is attained (NOTE: only ~5% progress)

Bowen's Disease
- AKA: Carcinoma in situ
- Some pathologists include these with VIN III
- Slightly elevated, plaque-like, red - may involve perineum
- Full thickness involvement of epidermis by large dyskeratotic cells and abnormal mitoses, with acanthosis and parakeratosis, hyperchromatic nuclei
- Only 10% become invasive (more if immunosuppressed)
- Strong association with HPV-16

Squamous Cell Carcinoma
- Usually arises on labia minora
- Grows slowly, but eventually ulcerates and spreads widely
- Usually very well differentiated
- Microinvasive: <1mm of invasion; <1% have LN metastases
- FIGO (AJCC) Staging:
  - T1 Confined to vulva, ≤2cm
  - T2 Confined to vulva, >2cm
  - T3 Invades lower urethra, vagina, or anus
  - T4 Invades bladder mucosa, upper urethral, or rectal mucosa, or fixed to bone
  - N1 Unilateral regional LNs
  - N2 Bilateral regional LNs
  - M1 Distant metastases (includes pelvic LNs)



Verrucous Carcinoma
- Typical warty appearance, generally large, locally infiltrative with pushing margin, does not metastasize

Basal Cell Carcinoma
- Chiefly labia majora
- May recur; does not metastasize

Paget's Disease
- Crusting, elevated scaling erythematous rash
- Epidermis contains large, pale-clear cells, tending to lie along the basal layer, occasionally forming clusters or glands; often involves appendages
- Tumor cells are PAS positive and immunoreactive for CEA, EMA, and Cam-5.2
- Usually NOT associated with underlying invasive component (unlike mammary Paget's disease)

Malignant Melanoma
- Most common non-epidermoid malignancy of vulva (5-10%)
- Need to distinguish from Paget's disease

Aggressive Angiomyxoma
- Soft tissue tumor which may simulate Bartholin gland cyst
- Gelatinous and ill-defined mass of hypocellular myxoid stroma with vessels having dilated lumina; no mitoses, no atypia
- Most patients are in teens to 20's
- Recurrences common

Bartholin Gland Carcinoma
- Can be squamous, adenocarcinoma, adenoid cystic carcinoma, transitional cell carcinoma, etc.

BREAST

Normal Anatomy / Physiology

Gland = large duct system + terminal duct-lobule unit (latter responsible for fibrocystic disease & most carcinomas)
Lactiferous (collecting) ducts empty into nipple; 1 per lobe; ~20 lobes per breast
Lactiferous sinus: Fusiform dilatation beneath nipple
Terminal duct-lobule unit (TDLU) surrounded by specialized myxoid appearing hormone responsive stroma - absent elastic fibers
Two cell layers:
• Epithelium: keratin, EMA, milk fat globule membrane antigen, alpha lactalbumin positive
• Myoepithelial cells: actin, other keratins, weak S-100
Nipple contains sebaceous glands, smooth muscle bundles
Marked hyperplastic changes in pregnancy; isolated lobules can undergo similar changes without pregnancy, cause unknown
Ectopia: within axillary nodes and along "milk line" (axilla to inguinal region)

Inflammatory and Related Disorders

Duct Ectasia
AKA: varicocele; comedo- , periductal-, or stale milk-mastitis
May produce nipple retraction or inversion; discharge in 20%
Large duct dilatation containing necrobiotic material; wall is thickened by fibrosis
If material escapes into tissue, florid inflammatory response
Calcification common; on mammogram, appears as tubular and/or annular shadows
Fat Necrosis
Can produce skin retraction, simulating carcinoma
Foamy macrophages infiltrating partially necrotic fat
Seen in ruptured ectatic ducts or fibrocystic disease and following trauma (often superficial subcutaneous tissue)
Calcifications
Calcium Oxalate: birefringent; faint, almost always benign
Calcium Phosphate: blue, sharp; may be benign or malignant
Others:
Abscess
Granulomatous mastitis: TB, Foreign body reaction (e.g., silicone), sarcoidosis
Breast infarct
"Mondor's disease" (thrombophlebitis of breast & chest wall)

Fibrocystic Disease

AKA: cystic mastopathy, Schimmelbusch's disease, mammary dysplasia, chronic cystic mastitis...
Preferred term: "fibrocystic changes"; not necessarily premalignant
Usually 25-45 yrs old; white
Usually bilateral, but may be asymmetrical
Long term contraceptive use may decrease incidence
Disease of the Terminal Duct-Lobule Unit
Features/histological appearance includes:
• Stromal Fibrosis: probably secondary to cyst rupture, mild to dense hyalinization
• Formation of cysts: microscopic to grossly visible, cloudy yellow or clear fluid, "blue dome cysts", typically clustered, flattening or loss of epithelium, thick fibrous wall
• Chronic inflammation: secondary to cyst rupture
• Fibroadenomatoid change: stromal proliferation and slit like spaces
• Apocrine Metaplasia: eosinophilic, snout cells, PAS positive, prominent nucleoli
• Epithelial hyperplasia: (see below)

Adenosis

"Any hyperplastic process that primarily involves the glandular component of the breast"
Term generally used to refer to multifocal or diffuse process (unlike adenoma, which is usually solitary and localized)
Sclerosing adenosis
Average age 30yrs; typically confused with carcinoma
Most important feature of benignancy is preservation of lobular architecture seen at low power, despite the absolute increase in the number of glands
More cellular centrally than peripherally
Two cell layers; dense stroma; no mitoses; no necrosis
Can see apocrine metaplasia, perineural "permeation"
Smooth muscle actin or collagen IV immunostain can help distinguish from carcinoma; often reveals more extensive proliferation of myoepithelial cells than is evident on H&E
May become involved by lobular carcinoma in situ
Radial Scar
AKA: Sclerosing duct lesion, nonencapsulated sclerosing lesion, indurative mastopathy, infiltrating epitheliosis, benign sclerosing ductal proliferation
Adenosis, epithelial hyperplasia, and sclerosis which mimics carcinoma mammographically, grossly, and often histologically
Stellate shaped; central area shows sclerosing adenosis like lesion with fibrosis and elastosis; as move further out from center, ducts show cystic dilatation and often increased epithelial hyperplasia
Entirely benign; relative cancer risk greater only with atypical hyperplasia
When larger than 1cm, often referred to as **"Complex Sclerosing Lesion"**
Blunt duct adenosis
Dilatation of small ducts with blunting of the ends, hyperplasia of both luminal and basal epithelium, and an increase in the associated surrounding specialized connective tissue
Nodular adenosis
Combination of blunt duct adenosis and sclerosing adenosis
Get increased cellularity without significant sclerosis
Microglandular adenosis
Irregular distribution in fat or fibrous tissue of small, uniform ducts with open lumina containing eosinophilic secretions
No associated sclerosis or stromal reaction
Myoepithelial layer may be absent!
Thick basement membrane present
Differential diagnosis: tubular carcinoma
Adenomyoepithelial (apocrine) adenosis
Microglandular adenosis in which the glands enlarge, undergo apocrine metaplasia, and have prominent myoepithelial cell layer
Atypical Apocrine Sclerosing Lesion
Sclerosing adenosis with apocrine metaplasia and thus large nucleoli
Virginal Hypertrophy
AKA: Gigantomastia
Unilateral or bilateral
Proliferation of ducts and stroma with little to no lobular involvement
Histologically, very similar to gynecomastia

Adenoma

Generally refers to a focal, usually solitary proliferation of predominantly the epithelial component of the breast
In some cases, it is unclear whether these are true neoplasms or localized hyperplasias

Lactating adenoma
- Solitary or multiple movable masses, during pregnancy
- Localized hyperplasia - may occur in ectopic breast tissue
- Gray-tan cut surface, well circumscribed; necrosis and lymphocytic infiltrate common

Tubular adenoma
- Present in young adults
- Solitary, well-circumscribed, firm tan-yellow mass
- Closely packed regular small tubules, decreased numbers of myoepithelial cells, minimal stroma

Intraductal Papilloma
- Can arise in large or small ducts; average age 48
- Bloody nipple discharge common; solitary in 90%
- Usually <3 cm (unlike papillary carcinoma, which is larger)
- Complex, cellular, arborescent
- Features favoring benign: well developed fibrovascular cores, myoepithelial cell layer, normochromatic oval nuclei, minimal mitoses, apocrine metaplasia, lack of cribriform or trabecular pattern
- May see: hemorrhagic infarct, squamous metaplasia, focal necrosis, pseudoinfiltration at base
- Intracystic papilloma (papillary cystadenoma): variant within a large cystic (tension) duct
- Single papilloma has no association with higher cancer rates
- Multiple papillomas (papillomatosis) more likely to recur and associated with increased risk of malignancy

Nipple Adenoma
- AKA: Florid papillomatosis of nipple ducts, erosive adenomatosis
- Usually 30's-40's; unilateral, bloody or serous discharge
- Proliferation of epithelial and myoepithelial cells, often extending into the epidermis
- Three patterns: sclerosing papillomatosis, papillomatosis without sclerosis, and adenosis
- Use criteria for papilloma to distinguish from malignancy

Fibroadenoma

- Most common benign "tumor" of breast
- Probably not neoplasm but rather localized nodular hyperplasia of both stromal and glandular tissue
- Typically young adults (20-35 yrs)
- Enlarge during pregnancy, regress with age
- Usually single; multiple in 20%
- Sharply demarcated, firm, <3 cm, with solid grayish white cut surface with a bulging, whorl-like pattern & slit like spaces
- Stroma usually loose with acid mucopolysaccharides
- Elastic tissue absent; presumably derived from the terminal duct-lobule unit
- Two microscopic types, of no particular significance:
  - Intracanalicular: stroma invaginates glands, appears to be within them
  - Pericanalicular: oval glandular configuration maintained

Histological Variations:
- Hemorrhagic infarction (more common in pregnancy)
- Degenerative changes: hyalinization, calcification, ossification
- Stromal changes: high cellularity, dense fibrosis, prominent myxoid change
- Apocrine metaplasia (15%), squamous metaplasia (rare)
- Sclerosing adenosis (10%)
- Lactational change
- Fibroadenomatosis: merges with surrounding fibrocystic disease
- Stromal multinucleated giant cells
- Hamartoma (choristoma): presence of adipose tissue, smooth muscle, or cartilage in the stroma

Juvenile (giant, massive, fetal, cellular) fibroadenoma
- Young age, large (>10cm), hypercellular stroma; may be bilateral, often in blacks

Malignant Transformation
- Occurs in 0.1%
- Most are lobular carcinoma in situ
- If limited to fibroadenoma, excellent prognosis
- Sarcomatous transformation even more rare

Hyperplasia, Ductal and Lobular

AKA: Papillomatosis, epitheliosis

Grading scheme:		Relative risk for Invasive Cancer
I	No or mild hyperplasia	1
II	Moderate or florid hyperplasia	1.5 to 2
III	Atypical ductal or lobular	4-5
IV	In situ ductal or lobular carcinoma	8-10

Features of benignancy:
- Elongated clefts separate intraluminal mass from basal cells
- Streaming alignment of nuclei and cells creating irregular, non-rigid bridges
- Indistinct cytoplasmic borders
- Acidophilic, finely granular cytoplasm (vs pale, homogeneous)
- Apocrine metaplasia, complete or incomplete
- Presence of myoepithelial cells
- Oval, normochromatic (vs round hyperchromatic) nuclei with slight overlap and small, single nucleolus; only few mitoses
- Foamy macrophages in lumen & associated with epithelium
- Intraluminal or stromal (vs basal) calcifications; no psammoma bodies
- No necrosis

Atypical Hyperplasia, Ductal and Lobular
- Hyperplasia, seen usually in a background of fibrocystic changes, which show some but not all of the features of in situ carcinoma

Breast Carcinoma

General

- Most common malignant tumor among women; affects 1/9 women; accounts for 20% of cancer deaths in women

Risk Factors
- Geographic (US > Japan)
- First degree relative with breast cancer increases risk 2-3x; familial breast carcinoma linked to a gene at 17p21 (brca-1)
- Risk increases with age
- Early menarche / late menopause / nulliparity
- Removal of ovaries before age 35 reduces risk to 1/3
- Women who have their first child before 18 yrs of age have 1/3 risk of women who have first child after age 30
- Exogenous estrogen may increase risk, especially in presence of fibrocystic disease - contraceptive use shows no change in risk
- Increased risk with exposure to radiation
- Obesity
- Atypical epithelial hyperplasia
- Risk of carcinoma in contralateral breast of patients with invasive carcinoma is 5 x risk of general population, reaching 25-50% for lobular carcinoma in situ
- High lipid diet; moderate EtOH consumption
- Multicentricity more common in lobular vs ductal

Diagnosis
- 40% of mammographically detectable cancers not palpable; 20% of palpable cancers not detected by mammography
- Clinical evaluation of axillary nodes is wrong 30% of the time
- Mammography can detect tumors 1-2 cm in size
- Only 20% of mammographically "suspicious" lesions are Ca
- MRI cannot detect microcalcifications
- 50% occur in upper outer quadrant, 20% central/subareolar, 10% each of the other three quadrants

90% carcinomas are ductal

Molecular Biology

p53 (17p13) mutations are the most common alterations seen in both familial and sporadic breast carcinoma

neu (erb-B2, Her-2; 17q11-12) often amplified; second most common change

brca-1 (17q21) is third most common mutation; see decreased level of expression (hence it is a putative tumor suppressor gene); mutations seen in 5% of breast cancers, but in 40% of breast cancers from patients in families with two or more breast cancers

Amplification of c-ras and c-myc has also been seen, as has mutations in Rb

Spread

Direct spread, lymphatic, hematogenous

Can "recur" months, years, or decades after initial therapy

11% of cancers grossly <1cm had tumor outside 2cm margin

2/3 patients have LN metastases at time of diagnosis

1% of patients with apparently "intraductal" carcinoma will have LN metastases

Nodes: axilla (40-50%), internal mammary (22%), supraclavicular (20%; zero if no axillary nodes)

Enlarged axillary LN in adult female with no known primary will be breast cancer or malignant melanoma in >90%; caution: breast cancer can be S-100+

Metastases: bone, lung, pleura, liver, adrenal, CNS; invasive lobular also goes to stomach, bowel, spleen, heart

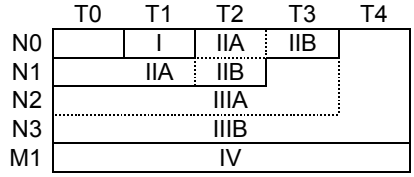
Grading

Histologic: I-III based on score for each of percent tubule formation, nuclear pleomorphism, and mitotic count; histologic grade only used for infiltrating ductal carcinoma

Nuclear: I-III based on pleomorphism and mitoses

Staging

T0 No primary
T1 2 cm or less a. ≤0.5cm b. 0.5-1cm c. 1-2cm
T2 2-5 cm
T3 >5 cm
T4 Any size with a. extension to chest wall
b. edema or ulceration of the skin
c. a and b
d. Inflammatory carcinoma
N0 None
N1 Moveable ipsilateral axillary nodes
a. all LN metastases <0.2cm
b. LN metastasis >0.2cm
i. 1-3 LNs, all <2cm
ii. ≥4 LNs, all <2cm
iii. Beyond LN capsule, <2cm
iv. any LN>2cm
N2 Fixed ipsilateral axillary nodes
N3 Ipsilateral internal mammary nodes positive



Therapy

• Surgery

• Radiation

Post-op adjunct, primary therapy, or Rx for local recurrence

Bizarre nuclear changes, extensive tumor necrosis

• Hormonal

The effectiveness of anti-estrogen therapy is well correlated to the presence of estrogen and/or progesterone receptors in nuclei of the tumor cells (~2/3 of all breast tumors are ER/PR+, including most lobular carcinomas and ~50% of ductal carcinomas, especially mucinous; medullary and comedocarcinoma are usually negative)

Castration (30-40% respond), adrenalectomy (30-40%), hypophysectomy (40-50%), medical anti-estrogen

Results in prominent, sometimes focal fibrosis, hyalinization, degenerative changes (tumor cell vacuolization, necrosis)

• Chemotherapy

Improve survival in metastatic disease, improve cure post-op in patients with positive nodes

Prognosis

Overall 5 yr survival: 60% for LN–; 34% for LN + (therefore, 50% reduction in survival with LN involvement)

Favorable:

• Age < 50 yrs
• Early diagnosis (88% 5 yr survival if detected prior to development of symptoms)
• Small size (<1 cm) (for node negative disease, recurrence rate in 1/2 the rate when the primary is 1-2cm)
• Tubular, cribriform, medullary, pure mucinous, papillary, juvenile, adenoid cystic
• Pushing vs infiltrating margin
• Absence of inflammatory response (!) (except medullary)

Unfavorable:

• Ca manifesting during pregnancy (15-35% 5 yr survival)
• *Presence of invasion / proportion of invasive component*
• *High nuclear or histologic grade*
• Number of LNs: 0, <4, ≥4; 5yr survival: 80, 50, 21% (in premenopausal women, two LNs significantly decreases survival; also, at any age, single LN >2cm equivalent to ≥3 small positive LNs)
• Signet ring, inflammatory, comedocarcinoma
• Tumor necrosis
• Skin or nipple invasion
• Vascular invasion
• Aneuploid tumor
• Local recurrence
• High S-phase
• Extensive intraductal carcinoma

No effect (or unclear effect) on prognosis:

• Oral contraceptives
• Site in breast
• CEA positivity
• Paget's disease
• ? erb-B2 status
• ? cathepsin D status
• ? Degree of sinus histiocytosis in nodes
• ER/PR status: meaningful if strongly negative or strongly positive; intermediate levels do not correlate with outcome

Ductal Carcinoma In Situ

Comedocarcinoma

May reach large size - palpable - >60% are larger than 2 cm

>50% are centrally located

1/3 are multifocal; 10% are bilateral

Solid inward growth of large high grade pleomorphic tumor cells, mitoses, central necrosis ± calcification

Myoepithelial cells may be present

Stroma: concentric fibrosis; mild to moderate chronic inflammation

20-50% recurrence rate after local excision (vs <5% for other intraductal lesions)

Even if no invasion is identified, can have LN metastases

Solid

Solid filling of duct with uniform cells, larger than LCIS but smaller than comedocarcinoma, with sharp cytoplasmic borders and no necrosis

Neuroendocrine variant with mixture of spindled cells and round cells filling the duct

Cribriform

Round, regular glands within the monomorphous epithelial proliferation; "rigid" trabeculae; no nuclear atypia

Papillary Carcinoma

Most papillary breast lesions are benign (see above)

Features of malignancy: older patient, uniformity of cells, no myoepithelial cells, nuclear hyperchromasia, mitoses, lack of apocrine metaplasia, minimal stroma, eosinophilic look
Intracystic variant: occurs within large cyst

Micropapillary
Elongated epithelial projections into lumen without connective tissue support, ± cavity at base, bulbous expansion at tip; no nuclear atypia

Cystic Hypersecretory
Cystic formations, abundant secretory material, single cell type, cribriform spaces (not as regular as in cribriform carcinoma)

Clinging
One or two layers of malignant cells lining large, empty lumen with occasional individual cell necrosis

Lobular cancerization
Presence within a lobule of cytologically ductal carcinoma

Infiltrating Ductal Carcinoma

Classic
AKA: ordinary, NOS; "breast cancer"
75% of all invasive ductal carcinomas
Yellowish-gray, gritty, stellate, necrosis, hemorrhage, cystic degeneration, "chalky streaks" (duct or vessel elastosis), calcifications in 60%
Tremendous variability in microscopic appearance
Invasion of lymphatics (33%), perineural space (28%), blood vessels (5%)
Immunohistochemistry: + low MW keratin, EMA, milk fat globule; lactalbumin and CEA positive in 70%, 10-45% S-100 positive
May be positive for high MW keratin if squamous metaplasia

Tubular Carcinoma
Mean age 50 yrs
Characteristically small (mean diameter of 1 cm)
Well differentiated glands, no necrosis, no mitoses, mild pleomorphism (simulates radial scar, microglandular adenosis)
Haphazard arrangement of glands in stroma, infiltration of fat, open lumina, basophilic secretion, apocrine-type apical cytoplasm, formation of trabecular bars
2/3rds have intraductal carcinoma, micropapillary or cribriform
56% multicentric, 10% metastasize
Excellent prognosis (<5% recur in 7 years) if pure

Cribriform Carcinoma
Often seen with tubular carcinoma
Well differentiated, low nuclear grade, excellent prognosis

Mucinous Carcinoma
AKA: mucoid, colloid, gelatinous
Usually in postmenopausal women
Well circumscribed; crepitant, currant jelly mass
Small clusters of tumor cells (solid or acinar) floating in sea of mucin (neutral or acid; almost entirely extracellular)
Approximately 1/4 show features of endocrine differentiation
When pure, only 2-4% have LN metastases; good prognosis
May recur many years later (e.g. 12 yrs!)
Some consider this an in situ lesion - only mucin is invasive

Juvenile (secretory)
Seen primarily in children, also in adults
Well circumscribed, small, pushing margins, central hyalinization
Tubuloalveolar, focally papillary growth pattern; cells with vacuolated cytoplasm, eosinophilic PAS+ secretion
100% five year survival

Medullary Carcinoma
More common in women <50yrs; particularly in Japanese
~1% of breast carcinoma
Well circumscribed, may become large (5-10 cm)
Homogenous gray cut surface with small foci of hemorrhage or necrosis
Pushing borders, diffuse growth pattern, no glandular differentiation, cytologically high grade (large pleomorphic cells, large nucleoli, many mitoses), indistinct cell borders, spindle cell metaplasia; minimal fibrosis (tend to be soft)
Prominent lymphoplasmacytic infiltrate at periphery (T-cells; IgA), often with germinal centers
Axillary metastases usually few in number
Slightly better survival vs classic (84 vs 63% 10 yr survival)
Prognosis better for tumors smaller than 3 cm

Invasive Papillary
Rare; most papillary carcinomas are in situ
Pushing growth pattern, excellent prognosis

Apocrine
Very rare (<1% breast cancers)
Large cells, abundant acidophilic, granular PAS+ cytoplasm

Carcinoid
AKA: Invasive ductal carcinoma with endocrine differentiation
Carcinoid syndrome not present clinically
Solid nests of cells, ribbons, rosettes, fibrous stroma
Prognosis same as for classic type
Dense core secretory granules present

Metaplastic
Well circumscribed
Predominantly sarcomatoid appearance (any sarcoma), usually vimentin positive, may maintain epithelial markers
25% metastasize
More aggressive than classic; tumor size most important
Subtypes:
- Epidermoid: Rare; elderly women; extensive squamous metaplasia
- Spindle Cell Carcinoma
- Acantholytic epidermoid: poorly cohesive; pseudoglandular
- Adenosquamous

Inflammatory Carcinoma
Clinically, breast frequently red and warm with edema of skin
Undifferentiated carcinoma with extensive dermal lymphatic invasion
Ominous prognosis; perhaps should be considered "inoperable"

Paget's Disease
Crusted lesion of the nipple with underlying intraductal carcinoma, ± invasion
Large clear cells within epidermis, concentrated along basal layer; may form small glandular structures
Underlying tumor always ductal; may be focally continuous with skin
30-40% have metastases at time of diagnosis
EMA, milk fat globule, CEA, low MW keratin +; S-100 –
Origin of the cells is still unclear

Lobular Carcinoma in Situ

AKA: Lobular neoplasia
Generally is a disease of premenopausal women
Multicentric in 70%, bilateral in 30-40%
Generally not identifiable grossly
Filling and distention of lobules by uniform, round, loosely cohesive small cells with low nuclear grade (round normochromatic nuclei, minimal mitoses, minimal necrosis, minimal atypia)
3/4 will show scattered positivity for mucin
Myoepithelial cells generally still present
Can occur within fibroadenomas or sclerosing adenosis
Risk of invasive carcinoma 25-30% (10x control population); invasive component may be of ductal or lobular type and may occur in either breast; thus, LCIS is a fundamentally different disease than DCIS: it is a marker for overall increased risk; this is why some pathologists prefer the term lobular neoplasia
Close follow-up usually sufficient

Invasive Lobular Carcinoma

Classic type
- May be diagnosed without lobular carcinoma in situ
- Often multicentric; 20% are bilateral
- Small, relatively round uniform cells growing singly in an Indian file pattern, often concentric around lobules with in situ lobular
- Dense, fibrous stroma with periductal and perivenous elastosis
- Prognosis slightly better than for classic infiltrating ductal

Signet ring
- Must have classic signet ring cells with intracytoplasmic mucin
- May coexist with mucinous, classic ILC or invasive ductal
- Poor prognosis

Others
- Different growth pattern; still small cells, low nuclear grade
- • Alveolar: sharply outlined groups separated by fibrous septa
- • Tubulolobular: typical ILC merging with small, "closed" tubules

Sweat-Gland Type Carcinomas

Benign
- Eccrine spiradenoma (sharply circumscribed lobules, small lumens, basaloid cells)
- Papillary clear cell hidradenoma (pedunculated, intracystic, papillary; two epithelial cells types: clear and granular)
- Benign mixed tumor (pleomorphic adenoma, chondroid syringoma; adenomyoepithelioma with heterologous stroma (myxoid or chondroid))

Adenoid Cystic Carcinoma
- Most common of this rare group
- Often confused with much more common intraductal cribriform carcinoma
- Two types of cavity formations: true glands, and eosinophilic "cylinders" containing PAS+ basement membrane material (collagen IV)
- May show foci of sebaceous differentiation
- Relatively good prognosis: LN metastases in 6%; pulmonary metastases in 12%

Other Malignant
- Mucoepidermoid Carcinoma
- Apocrine Carcinoma

Myoepithelial Malignancies

Adenomyoepithelioma
- Small (~1 cm diameter), firm, well circumscribed
- Polygonal cells, optically clear cytoplasm, arranged in nests
- Some cells spindled, hence tumor is biphasic
- No instances of metastases

Clear Cell Carcinoma
- Glycogen rich large clear cells - not biphasic
- True carcinoma: prognosis same as invasive ductal Ca

Spindle cell myoepithelioma
- Nonencapsulated, cellular, fascicular growth pattern
- Round, firm, well circumscribed, with solid gray-white cut surface containing cleft-like spaces - may have hemorrhage, necrosis
- Many are very large, but some remain <5cm
- Benign glandular elements with very cellular stroma ranging from predominantly periductal fibroblastic appearance with foci of mature adipose tissue (benign end of spectrum) to marked nuclear atypia and mitoses extending even distant from glands
- Can have metaplastic cartilage, bone, rarely skeletal muscle, or can take on the appearance of any malignant sarcoma; overgrowth of glands can be seen
- Stromal cells have progesterone but not estrogen receptors
- Indicators of malignancy: >10 mitoses/10HPF, marked atypia, stromal overgrowth relative to glands, infiltrating margin, necrosis, hemorrhage
- Better differentiated tumors have tendency for local recurrence, but rarely metastasize
- Cytologically malignant tumors have 3-12% incidence of metastases (usually lung or bones - rarely axillary nodes)

Vascular Tumors

Pseudoangiomatous Hyperplasia
- Clinically and grossly simulate fibroadenoma
- Benign lesion

Angiosarcoma
- Characteristically young women
- Highly malignant to very benign appearing
- Key is "freely anastomosing vascular channels"
- Prognosis poor: 33% five year survival

Hemangioma

Angiolipoma

Miscellaneous "Tumors"

Stromal Sarcoma
- Lack the epithelial component of phylloides tumor
- Usually fibrosarcoma-like; may be very anaplastic

Granular Cell Tumor
- May simulate invasive carcinoma
- Usually small, but may be up to 10cm - Benign

Fibromatosis

Nodular Fasciitis

Malignant Lymphoma
- May be primary
- Right breast more common than left; 25% bilateral
- Soft, grayish white, no associated skin retraction
- Almost always diffuse non-Hodgkin's, most common is large cell; nearly all are B-cell - MALT lesion
- Don't confuse with pseudolymphoma: reactive, germinal centers

Granulocytic Sarcoma
- Look for eosinophilic myelocytes or metamyelocytes

Other Tumors of the Breast

Phylloides Tumor

- AKA:
- Despite its alternate name (cystosarcoma phylloides), most of these lesions are benign, but often locally aggressive
- Median age 45; very rare below 25 yrs

MALE BREAST DISEASE

Gynecomastia

- Often result of increased estrogens or decreased androgens
- After age 25, may be caused by hormonally active tumors
- Usually centered below the nipple (unlike more eccentric carcinoma)
- Unilateral (left breast more common) or bilateral

- Oval, disc shaped mass, elastic consistency, well circumscribed
- Proliferation of ducts and surrounding edematous stroma; no glands
- Stromal fibrosis increases with age of lesion

Other Benign Lesions

- Duct ectasia, sclerosing adenosis
- Nipple adenoma
- Myofibroblastoma

Carcinoma

- 1% of breast cancers in US occur in males (10% in Egypt)
- Increased incidence in Klinefelter's syndrome
- Probably some relation with gynecomastia - not clear
- Usually elderly male - nipple discharge usually indicates carcinoma
- Paget's disease/skin involvement common
- All types seen - invasive lobular is most uncommon
- 40% 10 year survival (79 and 11% for node negative and positive)

ENDOCRINE ORGANS

Multiple Endocrine Neoplasias

Autosomal dominant syndromes with high degree of penetrance
Hyperplasias almost always precede neoplasia, especially in the thyroid (C-cells) and adrenal medulla

MEN type I
AKA: Werner's syndrome
Mapped to chromosome 11
• Pituitary adenoma
• Parathyroid gland (chief cell hyperplasia)
• Pancreas (50% G-cell tumors, 30% beta cell, 12% VIP cell)
Other: adrenal cortex; nodular hyperplasia of thyroid; carcinoid tumors of lung, thymus, GI tract; lipomas; Menetrier's disease; Zollinger-Ellison syndrome with peptic ulceration and hypersecretion

MEN type II (IIA)
AKA: Sipple's syndrome
Mapped to chromosome 10
• C-cell hyperplasia/medullary carcinoma of thyroid
• Pheochromocytoma of adrenal medulla
• Parathyroid chief cell hyperplasia
Occasionally also seen adrenal cortical tumors
MEN type III (IIB)
AKA: Gorlin's syndrome
• Medullary carcinoma of thyroid
• Adrenal Pheochromocytoma
• Mucosal neuromas (ganglioneuromas) of corneal nerves, lips, GI tract (main distinguishing factor from MEN IIa)
Also: skeletal abnormalities, Marfanoid habitus
Occasionally adrenal cortical tumors, parathyroid tumors

Pancreatic Islets, Testis, and Ovary

[Endocrine lesions of these organs are discussed in their respective Outlines]

THYROID

Normal Anatomy

Averages 15-25gm in adult, but varies significantly with sex and iodide intake
Two lateral lobes connected by isthmus - a pyramidal lobe may protrude superiorly from isthmus
Follicular Cells
Follicles vary in size: average 200µm
Single layer of cuboidal to columnar cells
Some cells have abundant mitochondria: acidophilic; referred to as Hürthle cells or Askanazy cells
Immunoreactive for thyroglobulin, T3, T4, low molecular weight keratin, EMA, vimentin
Thyroglobulin (650kD) synthesized and stored extracellularly as "colloid"; calcium oxalate crystals can be seen in the colloid in ~50% of patients
Tyrosyl residues iodinated to monoiodotyrosine (MIT) and diiodotyrosine (DIT). MIT and DIT couple to form T3 or T4
In response to TSH, T3 and T4 pinocytosed and released
Both T3 and T4 are bound by thyronine binding protein; T4 binds tighter, less is available; therefore, T3 is more active
Parafollicular (C) cells
Between and within follicles, especially upper and middle portions of lateral lobes; neural crest derived
Immunoreactive for calcitonin, CEA (CEA more prominent in hyperplasia or neoplasia)
Secrete calcitonin (directly inhibits osteoclasts) in response to high serum calcium

Embryology

Develops as tubular invagination (thyroglossal duct) from base of the tongue called the foramen cecum
Grows downward in front of trachea and thyroid cartilage
Distal end becomes adult gland, proximal part regresses by the fifth to seventh week of gestation
Joined by tissue derived from the 4th and 5th pharyngeal pouches, which contributes to the parafollicular cells
Hyoid bone forms from second branchial arch
Thyroglossal Duct Cyst
Localized persistence of duct, usually in region of hyoid bone
May become clinically evident at any age
Pseudostratified ciliated or squamous epithelium lined, with mucous glands and follicles in stroma with inflammation
Papillary carcinoma may form: excellent prognosis; can preserve main thyroid gland
Surgical excision must include the middle third of the hyoid bone of the lesions will likely recur
Heterotopia
Approximately 10% incidence, most subclinical
Most common sites are base of tongue (50%), anterior tongue, larynx, mediastinum, heart
In 70% patients with grossly evident lingual thyroid, main gland is absent

Clinical Syndromes

Goiter
Any enlargement of the thyroid gland
May be nodular or diffuse, hyper or hypofunctioning
Hyperthyroidism
Warm skin, exophthalmos, tachycardia, muscle atrophy
Causes: Grave's disease, toxic multinodular goiter, adenoma
Less common causes: acute/subacute thyroiditis, functioning carcinoma, pituitary adenoma, struma ovarii, choriocarcinoma
Treatment: propylthiouracil blocks iodide to iodine conversion, preventing thyroid hormone synthesis; get decrease in T3/T4, increase in TSH, glandular hyperplasia and hypervascularity
Prior to surgery (1-2 wks), give iodide: gland becomes firmer and less vascularized
Hypothyroidism
Cretinism: hypothyroidism present during development and infancy, resulting in physical and mental retardation
Myxedema: hypothyroidism in older child/adult: lethargy, cold intolerance, apathy, edema, dry skin
Causes: surgical/radiation ablation, agenesis, Hashimoto's, hypopituitarism

Thyroiditis

Acute Thyroiditis

Usually infectious; associated with upper airway infections
Strep hemolyticus, Staph aureus, Pneumococcus
Suppurative and non-suppurative forms; may have abscess formation
May also be fungal or viral

Granulomatous Thyroiditis

de Quervain's thyroiditis
AKA: subacute thyroiditis, Giant cell thyroiditis
Typically young women with sore throat, odynophagia
Associated with HLA-B35
Initially, elevated T3 and T4, suppression of Iodine uptake
Later, may become hypothyroid
Involvement of entire gland, but often asymmetrical
Gland typically 2x normal size; fibrosis limited to gland
Inflammation, foreign body giant cells, granulomas; giant cells engulf colloid
Etiology unknown - may be viral

Palpation Thyroiditis
AKA: Multifocal granulomatous thyroiditis
Common, clinically insignificant
Focal inflammation with epithelial loss from isolated or small groups of follicles; lymphocytes, histiocytes (±foamy), few giant cells scattered in small collections about gland
Caused by local trauma; seen in most removed glands

Other granulomatous thyroididites
TB, mycoses, syphilis (tertiary)

Autoimmune Thyroiditis

Lymphocytic Thyroiditis
Common cause of goiter in children: low iodine uptake
May be focal, or present with diffuse enlargement of the gland with extensive lymphocytic infiltration and germinal centers, but no Hürthle cell change
Squamous metaplasia can be seen, as can fibrosis

Hashimoto's Thyroiditis
AKA: struma lymphomatosa
Predominantly women over 40 yrs; M:F = 1:10
Associated with HLA-DR5
Probably genetic deficiency in antigen specific suppresser T-Cells, resulting in cytotoxic T-Cell attack on follicular cells; later develop circulating Ab's to thyroglobulin and/or TSH receptor; in most cases, ~50% of lymphocytes are B-Cells
Initially mild hyperthyroidism, later hypothyroidism
Diffuse, firm enlargement ± tracheal/esophageal compression, without adherence to surrounding structures
May be asymmetric or nodular
Lymphocytic infiltration with germinal centers PLUS oxyphilic (Hürthle cell) change of (>50%) follicular epithelium; polyclonal plasma cell infiltrate
Follicles become small and atrophic; may show nuclear clearing and overlapping nuclei (similar to papillary carcinoma)
Usually only mild fibrosis
Complications: lymphoma; less commonly: leukemia, papillary carcinoma, Hürthle cell tumors
• Fibrosing Variant: 12% of all cases
Extensive fibrosis of hyaline type, limited to gland

Reidel's Thyroiditis

AKA: Reidel's struma, invasive thyroiditis
Member of group of idiopathic "inflammatory fibroscleroses" including retroperitoneal fibrosis, sclerosing cholangitis
Not really a disease of the thyroid but rather a disease of the neck which happens to involve the thyroid
Rare; adults and elderly; M:F = 1:3
Extremely firm, involves soft tissue, profound dyspnea
Asymmetrical and multifocal
Dense active proliferative fibrosis extending into surrounding soft tissues - patchy inflammation (lymphocytes and IgA plasma cells), no giant cells
Inflammation in walls of medium sized vessels
Usually require surgery, which can be difficult

Other Non-Proliferative Lesions

Hemochromatosis
Amyloidosis
"Black Thyroid": seen in patients on minocycline (tetracycline derivative); pigment deposition in apical surface of the follicular cells

Hyperplasias

Dyshormonogenetic Goiter

Seen in abnormal iodination
Often small follicles with scanty colloid
Nodular and trabecular microfollicular patterns, focally papillary, moderate cellular pleomorphism
Differential diagnosis: papillary carcinoma

Diffuse Hyperplasia (Grave's Disease)

AKA: thyrotoxicosis, exophthalmic goiter, autoimmune hyperthyroidism
Typically young females (M:F = 1:5) with muscle weakness, weight loss, tachycardia, pretibial myxedema
Associated with HLA-DR3
Generally 80-90 gms (3 fold increase in size) with symmetric diffuse enlargement, reddish or gray, consistency of pancreatic tissue
Marked follicular hyperplasia with papillary infolding, columnar cells, clear to foamy cytoplasm, some oxyphilic cells, depleted colloid (note: hyperplastic changes may be less marked if patient treated prior to surgery)
Lymphocytic infiltration of stroma, occasional germinal centers, mostly T-cells, mild fibrosis
Proliferating follicles may extend beyond gland into neck
Incidental papillary carcinomas found in 1-9% of cases
Rx: propylthiouracil (results in florid hyperplasia), methimazole, subtotal thyroidectomy (if leave ~5gm on each side, will regenerate to euthyroid state)
The more lymphocytes and oxyphil cells at surgery, more likely to become hypothyroid
70% patients have anti-TSH receptor antibody

Nodular Hyperplasia

AKA: multinodular goiter, adenomatous hyperplasia

Endemic Goiter
Low iodine intake leads to low levels of T3 and T4, elevated TSH levels, and hyperactive gland (parenchymatous goiter) which later undergoes cellular atrophy with storage of large amounts of colloid (diffuse or nodular colloid goiter)

Sporadic Nodular Goiter
Unknown pathogenesis
3-5% incidence clinically, 50% at autopsy
Some cases associated with Hashimoto's or lymphocytic
Clinically euthyroid
Multinodular gland, often very large, occasionally with a large, firm, dominant nodule which may be functional
Gland often asymmetric; capsule usually intact
Hemorrhage into a nodule can cause rapid enlargement/pain

Some cases present as mediastinal mass
Range of microscopic appearances which may vary significantly from nodule to nodule: large follicles with flattened epithelium, cellular and hyperplastic nodules, Hürthle cells, papillae, granulomatous inflammation, hemorrhage, calcification
Papillary or pseudopapillary lesions distinguished from carcinoma by lack of nuclear features, line walls of cyst
Highly atypical nuclei - ? exposure to radioactive iodine

Sequestered Thyroid Nodule
AKA: parasitic nodule, lateral aberrant thyroid
Peripherally located thyroid nodule, disconnected from gland
Usually results from nodular hyperplasia or nodular Hashimoto's thyroiditis
Should exhibit same histology as main gland - no lymph node tissue
Differential diagnosis: metastatic papillary carcinoma, follicular variant

C-Cell Hyperplasia
Precursor lesion of familial medullary carcinoma
Most pronounced in central part of lateral lobes
May be diffuse or nodular
C-cells within follicles and between them
Arbitrarily, >6 C-cells/follicle = hyperplasia
Greater CEA reactivity than normal C-cells

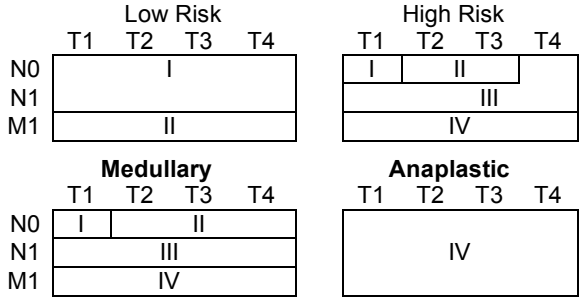
Epithelial Tumors
Follicular and undifferentiated may be more common with iodine deficiency, papillary with high iodine uptake
Radiation exposure usually leads to benign thyroid lesions, but also an increased incidence of papillary carcinoma
Distinguishing benign from malignant clinically: more likely to be malignant for: young or old, male, single nodule, ipsilateral adenopathy, cold nodule, solid (vs. cystic)

Fine Needle Aspiration
Three recommended diagnoses:
- Probably benign: colloid, histiocytes, lymphocytes
- Follicular lesion: high cellularity, no nuclear features of pap.
- Papillary carcinoma: nuclear features (grooves and pseudo-inclusions), papillae, psammoma bodies

Therapy
Nodulectomy no longer considered adequate
Lobectomy with isthmusectomy for follicular adenoma
Lobectomy or subtotal for minimally invasive follicular carcinoma and papillary carcinoma
Near total thyroidectomy for widely invasive follicular, high risk papillary, poorly differentiated; total thyroidectomy for medullary carcinomas
Radical neck dissection for medullary, but not papillary carcinoma
Post-operative suppression with exogenous Synthroid
Post-operative radioactive iodine usage (for treatment of metastases) is controversial

Staging
T1 <1 cm, limited to thyroid
T2 1-4 cm, limited to thyroid
T3 >4 cm, limited to thyroid
T4 Extension beyond thyroid capsule
N0 No regional nodes
N1 Positive regional nodes a: ipsilateral cervical nodes
b: bilateral or contralateral

Follicular or Papillary Carcinoma



Low risk: men <40; women <50 (alternatively, anyone <45)
High risk: men ≥40, women ≥50 (alternatively, anyone ≥45)

Follicular Adenoma
Euthyroid patients; cold to slightly warm nodule, rarely hot
Usually solitary; surrounded by intact capsule; unlike uninvolved gland, compression of adjacent tissue
Variety of patterns:
- normofollicular (simple)
- macrofollicular (colloid)
- microfollicular (fetal)
- trabecular/solid (embryonal)
- pseudopapillary structures

Mitoses rare to absent, no capsular invasion
Secondary changes: hemorrhage, edema, fibrosis, calcification, cystic degeneration, ossification
1/4 of cases show aneuploidy by flow cytometry
Treatment: lobectomy

Variants
- Hürthle cell adenoma: >50% Hürthle cells
- Atypical adenoma: cellular proliferation but no capsular or vascular invasion
- Hyalinizing trabecular adenoma: well defined, organoid trabeculae simulating paraganglioma
- Adenoma with bizarre nuclei: huge, hyperchromatic nuclei, usually in clusters
- Clear cell adenoma
- Adenolipomas: adipose metaplasia of the stroma

Follicular Carcinoma
Uncommon (15-20% of thyroid malignancies), female predominance, older patients
Well formed follicles, cribriform areas, trabecular formations, solid growth pattern; nuclear atypia and mitoses
Psammoma bodies absent, squamous metaplasia very rare
Reactive for thyroglobulin, low MW keratin, EMA, S-100
Full thickness capsular and/or blood vessel invasion indicates carcinoma; invasion partially into capsule doesn't
May be related to iodine deficiency

Minimally invasive
Grossly encapsulated with microscopic invasion in vessels within or just outside capsule - intravascular tumor nodules often covered by endothelium
Metastases in 5% with vessel invasion, 1% with only capsular invasion

Widely invasive
Widespread infiltration of vessels and/or adjacent tissue
Metastases common

Metastases
Blood borne: lung, bones (shoulder, sternum, skull, iliac)
Metastases often better differentiated than primary

Papillary Carcinoma
Most common thyroid malignancy: 65-60% of thyroid malignancies in adults, >90% in children
Female predominance, mean age 40yrs
Increased incidence in Hashimoto's thyroiditis or following radiation

Clinical presentation: thyroid nodule (cold) in 67%, thyroid nodule and LN in 13%, LN only in 20%
Size varies widely - may be quite small
Solid, white, firm, often infiltrating; 10% show cystic change
Well developed branching, complex papillae with edematous or hyalinized fibrovascular cores, ± lymphocytes, hemosiderin, some follicles (irregular to tubular)
Nuclear features (may have some, none, all; focal or diffuse):
- Ground glass (optically clear) nuclei, large, overlapping (note: often absent in frozen section/cytologic material)
- Nuclear pseudoinclusions (cytoplasmic invaginations)
- Nuclear grooves

Mitoses rare; fibrosis common
Psammoma bodies present in 30-50% cases
May see solid/trabecular pattern or squamous metaplasia (common; most common at periphery of lesion)
Multifocal in 25-75% cases; vascular invasion in 5%
Immunoreactive for low and high molecular weight keratin (note: normal thyroid usually negative for high MW), thyroglobulin, EMA, vimentin, ±CEA
Associated with RET oncogene and PTC (papillary thyroid carcinoma) oncogene

Variants:
- Follicular Variant: almost entirely follicles but with nuclear features, fibrous trabeculae, psammoma bodies - behaves as conventional papillary carcinoma
- Papillary Microcarcinoma: 1cm or less in diameter, usually incidental, cervical LN metastases in 1/3, distant metastases rare, excellent prognosis
- Encapsulated variant: totally surrounded by capsule; may still have LN metastases, but no distant metastases; excellent prognosis
- Diffuse Sclerosing Variant: diffuse involvement of one or both lobes, dense sclerosis, numerous psammoma bodies, squamous metaplasia, heavy inflammation; widespread LN metastases usually present, lung metastases common; worse prognosis than conventional papillary carcinoma; differential diagnosis: Hashimoto's thyroiditis
- Tall cell variant: abundant eosinophilic cytoplasm; often lymphocytic infiltrate; worse prognosis
- Columnar Variant: like tall cell, but with nuclear stratification
- Oxyphilic Variant: (see Hürthle cell carcinoma)

Spread
Extrathyroid extension in 25%
Cervical LN involvement in ~50%; often cystic changes
Hematogenous spread less common than other thyroid carcinoma

Prognosis
Poor prognosis: >40yrs old, male, extrathyroid extension, large tumor size, non-encapsulated, multicentricity, distant metastases, aneuploidy
Anaplastic foci develop in 1% - essentially all die
Not related to prognosis: relative amounts of papillae vs. follicles, history of irradiation, fibrosis, squamous metaplasia, positive cervical LN's

Medullary Carcinoma

AKA: parafollicular cell, solid, hyaline, C-cell carcinoma
5-10% of thyroid carcinomas
Solid, firm, well circumscribed, nonencapsulated
More common in upper half of gland (more C-cells)
Marked variation in cytologic appearance: round to polygonal cells with granular cytoplasm in carcinoid-like nests, trabecular, glandular, or pseudopapillary configurations; highly vascular stroma, hyalinized collagen, amyloid, coarse calcification, may see psammoma bodies
Most produce calcitonin; some also produce prostaglandins, histaminase, ACTH, VIP, or serotonin, CEA
May have many neutrophils (inflammatory type)
Cells be spindle shaped or even anaplastic
Immunoreactive for keratin, NSE, chromogranin, synaptophysin, calcitonin, CEA; negative for thyroglobulin
Spread via lymphatic and blood; metastases to LN's, lung, liver, bone
Sporadic and MEN III more prone to metastasize than MEN II
Treatment is surgical; 5yr survival 70-80%; 10yr ~50%
Prognosis better for young, female, familial, confined to gland, extensive amyloid

Sporadic form
Accounts for 80% cases
Adults, mean age 45, solitary, cold thyroid mass

Familial
Younger (mean age 35), often multiple and bilateral
C-cell hyperplasia in residual gland
Autosomal dominant inheritance
Belongs to MEN type II and III; also von-Hippel Lindau, neurofibromatosis
Treatment: total thyroidectomy

Hürthle Cell Tumors

More than 50% Hürthle cells
Some consider this a variant of follicular carcinoma
Usually adult females
Solid, tan, well vascularized, usually encapsulated
Usually follicular, may be trabecular/solid or papillary
Granular, acidophilic cytoplasm (filled with mitochondria)
Tumors with follicular pattern should be assessed (benign or malignant) as follicular lesions: capsular/vascular invasion; solid/trabecular areas and small cells favor carcinoma
Carcinomas tend to be aggressive: 20-40% 5yr survival

Poorly Differentiated Carcinoma

AKA: Insular carcinoma
Older age group, usually grossly invasive
Nesting pattern of growth, small uniform cells, necrosis
Not immunoreactive for thyroglobulin or calcitonin
May arise in well differentiated carcinoma
60% mortality

Anaplastic Carcinoma

AKA: undifferentiated or sarcomatoid carcinoma
Rapidly growing mass, elderly, with dyspnea/dysphagia
Highly necrotic/hemorrhagic mass
Three major patterns:
- Squamoid: may even keratinize
- Spindle Cell: storiform; may form bone/cartilage
- Giant Cell: usually scattered among spindle cell pattern

Usually arise within pre-existing tumor, usually papillary carcinoma
Essentially 100% mortality (mean survival 6 months), usually from local extension into neck structures

Other Epithelial Tumors

Clear cell tumors
Can see clear cell change in any of the thyroid tumors
Most common in Hürthle cells (swelling of mitochondria) but can also see in papillary (glycogen accumulation)
No change in prognosis
Differential diagnosis: metastatic renal cell, parathyroid

Epidermoid carcinoma
Usually represents extensive squamous metaplasia or anaplastic carcinoma

Mucoepidermoid carcinoma
Probably variant of papillary with mucinous and squamous metaplasia

Thymoma
Perhaps arises from intrathyroid ectopic thymus tissue

Small Cell Carcinoma
Probably poorly differentiated form of medullary carcinoma
Paraganglioma
Not primary to thyroid, but to nearby carotid body
May be confused with medullary carcinoma
S-100 positive sustentacular cells at periphery or zellballen

Non-Epithelial Neoplasms

Malignant Lymphoma
Most common in elderly females; often arise in setting of lymphocytic or Hashimoto's thyroiditis
Often rapid enlargement
Euthyroid; one or more cold nodules
Solid white fish-flesh
Example of MALT (mucosa-associated lymphoid tissue) lymphoma; most are diffuse large cell, follicular center cell origin; immunoblastic, lymphoplasmacytic are also seen
Packing of follicles with lymphocytes is a diagnostic feature; usually not seen in thyroiditis
Better prognosis if restricted to thyroid; if recurs, may recur in GI tract

Plasmacytoma
Local disease or manifestation of widespread myeloma
Reserve for tumors composed entirely of plasma cells

Teratoma
Infants or children - cystic and benign
Rarely in adults - usually malignant

Metastases
Most common primary sites:
- Skin (melanoma) 39%
- Breast 21%
- Kidney 12%
- Lung 11%

PARATHYROID

Normal Anatomy
Normally, four glands, each 4x3x1.5mm, with an average aggregate weight of 120mg (slightly higher in women)
25% individuals have >4 glands, usually 5; 6 or <4 is rare
Chief Cell: predominant cell type; centrally located nucleus, pale granular cytoplasm, ill defined cell margins
Oxyphil Cell: more cytoplasm, oncocytic, mitochondria
Clear (Wasserhelle) cells: not present in normal gland
Oxyphil cells appear soon after puberty and increase in number with age, forming islands after 40; probably derived from chief cells
Fat infiltration also begins at puberty
Follicles with "colloid" may be present; can be distinguished from thyroid by presence of glycogen in cells and absence of oxalate crystals
Parathormone: Regulates calcium metabolism (in conjunction with Vitamin D and calcitonin) secreted in response to low calcium; increase renal excretion of phosphate, renal and intestinal reabsorption of calcium, and activate osteoclasts via osteoblasts (receptors are on the osteoblasts; they secrete factors which activate the osteoclasts)

Embryology
Upper pair arises from fourth branchial cleft; descends into neck with the thyroid; resides in middle third of postero-lateral part of thyroid
Lower pair arises from third branchial cleft (initially above superior pair); descends with thymus to lie near inferior thyroid artery at lower pole of thyroid
Anomalous locations include carotid sheath, behind the esophagus, anterior mediastinum, intrathyroidal

Clinical Syndromes
HYPERPARATHYROIDISM
Primary Hyperparathyroidism
Increased parathormone secretion almost always due to adenoma or chief cell hyperplasia - carcinoma in <4%
Usually adults, can be familial, seen in MEN-I and IIa
Relationship exists with neck radiation and with sarcoidosis
Hypercalcemia, hypophosphatemia, duodenal peptic ulcers
- Osteitis fibrosa cystica (brown tumor, Recklinghausen's disease): expansile multilocular mass, often jaw, alternating solid and cystic areas, hemosiderin deposition, giant cells; reversible with removal of hyperfunctioning gland(s)
- Renal changes: renal stones, nephrocalcinosis

Secondary Hyperparathyroidism
Chronic renal disease (more common; Vitamin D resistant) or intestinal malabsorption, increased serum phosphorus, decreased serum calcium; chief cell hyperplasia results
Tertiary Hyperparathyroidism
Patients with secondary hyperparathyroidism in whom one or more parathyroid has become autonomous

THERAPY FOR HYPERPARATHYROIDISM
Identify all four glands; if all appear normal, look for fifth, usually in the mediastinum; if can't find four, consider intrathyroid location
If one enlarged, remove (probably adenoma) and biopsy at least one other to rule out chief cell hyperplasia
For chief cell hyperplasia, subtotal parathyroidectomy (remove all of 3 glands, all but 30-50mg of fourth)
Alternatively, remove all glands with auto-transplantation of tissue into forearm muscle

HYPOPARATHYROIDISM
Hypocalcemia, mental changes, calcification of lens, calcification of basal ganglia (Parkinson's), cardiac conduction defects
Usually results from accidental surgical ablation

Hyperplasia / Neoplasia

Chief Cell Hyperplasia
AKA: Primary nodular hyperplasia
Classically, all glands are enlarged (10g or more!), tan to reddish, with superior glands larger than inferior glands
Pseudoadenomatous: one gland much larger than others
Parathyromatosis: numerous microscopic foci of hyperplastic parathyroid in neck; rare

Mostly chief cells, often grouped in nodules; may see fibrous septa, giant nuclei
In secondary hyperparathyroidism, can have significant variability; usually fewer giant nuclei and more oxyphil cells
Only reliable distinguishing feature from adenoma is presence of some normal parathyroid tissue in patients with adenoma

Water-Clear Cell Hyperplasia

Rare, no familial incidence
Extreme enlargement of all glands (>100gm!), in which the superior glands are distinctly larger than the inferior glands
Optically clear cytoplasm (numerous clear vacuoles) - cells vary significantly in size - giant nuclei are not seen
Associated with primary hyperparathyroidism
Entity has essentially disappeared in past few decades

Adenoma

M:F = 1:3; usually in 30's; usually too small to be palpable
75% involve inferior gland, 15% superior, 10% anomalous (of these, 70% mediastinal, 20% intrathyroid)
Encapsulated, very cellular, often with rim of compressed normal parathyroid tissue
Usually chief cells predominate, other cell types can be seen
Marked variation in nuclear size and hyperchromatic nuclei favor benign rather than malignant diagnosis
Mitoses rare
Diffuse growth usually; may be nesting, follicular, papillary
By EM, may see both large amounts of glycogen and secretory vacuoles (in normal cells, only one or other)

Oxyphil Adenoma

Variant composed almost entirely of oxyphil cells
Most are non-functioning

Lipoadenoma

AKA: lipohyperplasia, hamartoma, adenoma with myxoid stroma
Abundant mature adipose tissue; usually circumscribed
Usually functioning

Parathyroid Carcinoma

Typically presents with hyperparathyroidism
If non-functioning, more aggressive
May coexist with chief cell hyperplasia or adenoma
Very high serum calcium, palpable mass, vocal cord paralysis favor carcinoma
Trabecular arrangement of cells, dense fibrous bands, spindled tumor cells, mitotic figures, capsular invasion, vascular invasion
Rx: removal of lesion, surrounding soft tissue, ipsilateral lobe of thyroid
Recurrence within 2 years ominous prognostic sign

ADRENAL CORTEX

NORMAL

Normal adult weight 4-5 gms
Derived from urogenital ridge; mesodermal in origin
Before birth: white "fetal zone": large plump eosinophilic cells
After birth, fetal zone involutes leaving only outermost layer which differentiates into a 1mm thick three zone cortex:
• Zona glomerulosa: 10-15% cortex; few lipid droplets, anastomosing network of smooth endoplasmic reticulum, normal mitochondrial cristae (lamellar); mineralocoriticoids, most importantly aldosterone (major regulator of ECF volume and potassium metabolism)
• Zona fasciculata: 80% cortex; cords of cells with lipid vacuoles (grossly yellow), elaborate SER, stacks of granular ER, prominent Golgi apparatus, mitochondria have tubulovesicular cristae
• Zone reticularis: similar to fasciculata but much less lipid and therefore more eosinophilic (grossly brown)
Fasciculata and reticularis both responsible for producing glucocorticoids (e.g. cortisol) and androgens (testosterone) under control of pituitary ACTH (39 amino acid peptide derived from proopiomelanocortin)

Congenital Abnormalities

Ectopic Adrenal

Usually in retroperitoneum, anywhere along the urogenital ridge from diaphragm to pelvis
Usually composed only of cortex
Small rests also occasionally found subcapsularly in kidney, in the hilar region of the testis or ovary, or in hernia sacs

Congenital Adrenal Hypoplasia

Anencephalic Type

Only provisional cortex; no fetal zone
Infants are anencephalic and still born

Cytomegalic Type

Adrenals have combined weight < 1 gm
Cortex consists of large (3-5x normal) eosinophilic cells
Unknown etiology; possibly X-linked or autosomal recessive

Congenital Adrenal Hyperplasia

Most common congenital adrenal disorder
Actually ≥8 distinct clinical syndromes, all with congenital deficiency of a specific enzyme (autosomal recessive)
Most common is deficiency of 21-hydroxylase
Completed cortisol cannot be produced; elevated ACTH results in adrenal hyperplasia; shunting of intermediates to other pathways often results in virilization of external genitalia in girls (adrenogenital syndrome)

Hypoadrenalism

Primary Chronic Adrenocortical Insufficiency (Addison's Disease)

Any conditions which destroys >90% of the adrenal cortex produces this clinical picture
Insidious development of weakness, fatigability, anorexia, nausea and vomiting, weight loss, hypotension, hyperpigmentation (from elevated proopiomelanocortin peptides)
Two most common causes are idiopathic adrenitis/atrophy (probably autoimmune) and tuberculosis. Others include amyloidosis, hemochromatosis, metastatic carcinoma

In general, cortex is atrophic with variable amounts of chronic inflammatory cells
Autoimmune Addison's Disease divided into two types:
• Type I: at least two of Addison's disease, hypoparathyroidism, mucocutaneous candidiasis; defect in suppresser T-Cell function
• Type II (Schmidt's syndrome): Addison's disease, autoimmune thyroid disease, and/or insulin-dependent diabetes mellitus; associated with HLA-A1 and B8

Primary Acute Adrenocortical Insufficiency

Can develop as a crisis in patients with Addison's disease, (precipitated by stress), following too rapid withdrawal of steroids (suppressed endogenous production recovers slowly), or result from massive hemorrhage
In neonates, can see massive hemorrhage following prolonged or difficult delivery, presumably secondary to hypoxia or trauma

Waterhouse-Friderichsen Syndrome
Hemorrhagic destruction of the adrenals related to bacterial infection
Meningococcemia by far most common cause; others include pneumococci, staphylococci, Hemophilus influenzae
Widespread petechiae, purpura, hemorrhages throughout body, particularly skin and mucosal surfaces
Adrenals hemorrhagic and necrotic; sometimes merely sacs of blood clot

Secondary Adrenocortical Insufficiency

Any disorder of hypothalamus or pituitary resulting in decreased levels of ACTH
Since tropic hormones are low, do NOT see hyperpigmentation
May also seen in setting of exogenous corticosteroids

Hyperadrenalism

Cushing's Syndrome

Clinical features include impaired glucose tolerance (overt diabetes in 20%), moon facies, "buffalo hump", abdominal striae, loss of libido, vascular fragility with skin hemorrhages

Pituitary Cushing's Syndrome (60-70%)
Bilateral adrenal hyperplasia due to an elevation of ACTH levels, usually due to a pituitary adenoma (Cushing's disease)
Suppressible by high doses of dexamethasone
Hyperplasia is usually diffuse but sometimes nodular

Adrenal Cushing's Syndrome (20-25%)
Functioning neoplasm of adrenal cortex, usually adenoma
Low serum ACTH, symptoms not suppressible by high doses of dexamethasone

Ectopic Cushing's Syndrome (10-15%)
ACTH or compound with similar biological activity elaborated by a non-endocrine neoplasm, most commonly bronchogenic carcinoma (60%), malignant thymoma (15%)
Not suppressible by high doses of dexamethasone

Iatrogenic Cushing's Syndrome
Patients on chronic steroids, usually transplant recipients or with autoimmune disorders

Primary Hyperaldosteronism

AKA: Conn's Syndrome
Hypertension, neuromuscular symptoms, renal potassium wasting, elevated aldosterone levels IN THE ABSENCE OF ELEVATED RENIN LEVELS
Unlike secondary hyperaldosteronism, generally do NOT see edema with Conn's syndrome
Almost invariably caused by adrenocortical adenoma
Aldosterone secreting adenomas usually <2 cm, bright yellow, nonencapsulated, mixed cell types (see below)

Adrenal Virilism

Most readily recognized in females
Caused by androgen secreting adenomas; generally larger than adenomas associated with Cushing's syndrome, often highly pigmented

Adrenal Cortical Neoplasms

Adenoma / Carcinoma

Bright yellow tumors
Varying mixtures of clear and compact cells similar to those of the normal zona fasciculata; compact cells may predominate
Adenomas generally weigh 40-60gms and measure <5cm; carcinomas >100gms and/or >5cm
Adenomas may be difficult to distinguish from hyperplastic nodule; if residual cortex is normal or atrophic, probably an adenoma
Carcinomas are more likely to show necrosis, broad fibrous bands, nuclear anaplasia, high N:C ratio, high mitotic activity, vascular invasion, capsular invasion; rapidly lethal
Many adenomas and carcinomas are functional, but not all

Myelolipoma

Usually asymptomatic and benign
Sharply circumscribed unencapsulated pale yellow cortical lesion
Fat cells admixed with myeloid cells and lymphocytes

Other Tumors

Adenomatoid Tumor
Ovarian Thecal Metaplasia
Metastatic Tumors: usually from lung, breast, GI tract, thyroid, kidney

ADRENAL MEDULLA

NORMAL

Derived from neural crest
A component of the sympathetic paraganglia
Body's major source of epinephrine (adrenaline)
Epinephrine : norepinephrine ratio is usually 5-6:1
Tyrosine → Dihydroxyphenlyalanine → dopamine occurs in cytoplasm; dopamine then enters granules and is converted to norepinephrine; norepinephrine must then

reenter the cytoplasm for conversion to epinephrine, which then reenters the secretory granules
Major breakdown products of catecholamines include metanephrine, normetanephrine, vanillylmandelic acid (VMA), and homovanillic acid (HVA)

Neuroblastoma

One of the most common solid tumors of childhood (7-10% of all childhood malignancies); equal frequency with Wilms' tumor, but occurs at an earlier age
80% occur in children under 5yrs; 35% in children under 2yrs
50-80% of neuroblastomas occur in adrenal or adjacent retroperitoneal tissues; posterior mediastinum is second most common location (15-20%), cervical sympathetic chain (5%)
Large tumors (6-8cm on average), soft, white lobular cut section with focal to extensive hemorrhage, necrosis, cyst formation; dystrophic calcification common
Small cells with hyperchromatic nuclei arranged in solid sheets or in small nests separated by fibrovascular septa; Homer-Wright pseudorosettes around tangled eosinophilic fibrils
90% tumors will produce catecholamines; urinary VMA elevated in ~3/4 of cases
NSE positive; stroma contains S-100 positive Schwann cells
Often, deletion of chromosome 1p is seen
N-myc amplified in ~30% of tumors (often as double minutes or homogeneously staining regions; associated with translocation to tip of 1p); when present at >10 copies, associated with a poor prognosis
trk oncogene expression seen in lower stage, younger patients; good prognosis: tumors more likely to differentiate, regress, or respond to therapy
Metastases occur early and widely
Hutchinson-type Neuroblastoma: extensive bony metastases, particularly to the skull and orbit, producing exophthalmos
Pepper-type Syndrome: massive metastases to the liver

Ganglioneuroblastoma

>5% maturation to ganglion cells, with residual areas of immature blastoma
Two types:
• Composite: nodules of neuroblastoma in a ganglioneuroma
• Diffuse: both elements distributed throughout tumor; better prognosis than composite type

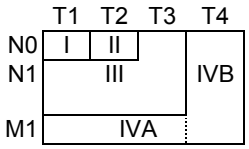
Ganglioneuroma

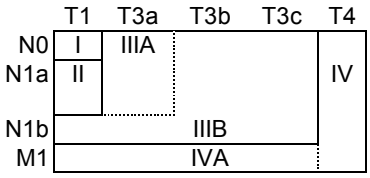
All mature elements: fibrous and Schwann cell-rich stromal background with scattered ganglion cells

STAGING

Commonly Used Staging Scheme		% 2yr Survival
Stage I:	confined to structure/organ of origin	95-100
Stage II:	Beyond site of origin; don't cross midline	85-90
Stage III:	Across midline, ± LN metastases	50-60
Stage IV:	Metastatic disease, usually to skeleton	10-15
Stage IVs:	I or II with microscopic metastases to skin, liver, marrow; usually <1 yr old; good prognosis	60-65

Clinical TNM:		Pathologic TNM:	
T1	Single tumor ≤5cm	T1	Completely excised
T2	Single tumor 5-10cm	T2	N/A
T3	Single tumor >10cm	T3	Residual Tumor
T4	Multicentric tumors		T3a: microscopic
			T3b: macroscopic
			T3c: unresected
N1	Regional LNs	T4	Multicentric tumors
		N1a	Resected regional LNs
		N1b	Incomplete resection





PROGNOSIS

Good: Better differentiated tumors; high ratio of urinary VMA:HVA; Stage IVs; young age (<1yr); extraadrenal, aneuploidy
Bad: High levels of ferritin or NSE; N-myc amplification; adrenal; >5 yrs old

Pheochromocytoma

AKA: Intra-adrenal paraganglioma
Usually induces marked hypertension secondary to catecholamine production
Usually secrete more norepinephrine than epinephrine
Peak incidence in 30's - 40's
When same tumor occurs outside of the adrenal medulla, it is referred to as an extra-adrenal paraganglioma; 70-90% of paragangliomas are intra-adrenal; 10-20% are bilateral
5% of the adrenal tumors are malignant; 10-50% when extra-adrenal
80-90% are sporadic; rest associated with familial syndromes (MEN IIA or IIB)
1gm - 4000gm; average weight is 100gm
Usually well demarcated; well vascularized fibrous trabeculae divide tumor into lobular pattern; pale gray to light brown
Hemorrhage, necrosis, cysts common
Cytologic appearance varies widely from mature chromaffin cells with abundant basophilic cytoplasm and secretory granules to marked cellular and nuclear pleomorphism
Tumor cells often grow in small clusters (zellballen) separated by thin fibrovascular stroma
Mitotic figures are rare but do not imply malignancy
Vascular invasion may be seen; does not necessarily make it malignant
Features of malignancy: capsular invasion, numerous mitoses, necrosis, solid/diffuse growth pattern without nests or with large nests, spindled cells, aneuploidy; however, diagnosis of malignancy cannot be made by histologic criteria alone
Complications include catecholamine cardiomyopathy
Metastases may occur very late in disease

Extraadrenal Paraganglioma

Same tumor as pheochromocytoma, but occurring outside of the adrenal gland
Generally named by site:
• Chemodactoma: carotid body
• Jugulotympanic Paraganglioma (glomus jugulare; glomus tympanicum)
• Vagal Paraganglioma (glomus vagale)
• Mediastinal

PITUITARY

NORMAL

0.5 gm in adult; 10-15 mm in greatest dimension
Three "lobes": anterior (adenohypophysis), intermediate, and posterior (neurohypophysis)
Anterior lobe derived from evagination of the roof of the primitive oral canal known as Rathke's pouch
Posterior lobe develops as an outpouching of the floor of the third ventricle near the hypothalamus
Pharyngeal pituitary gland: ~90% of autopsies can show small amount of pituitary tissue in roof of nasopharynx; comprises <1% of total adenohypophyseal mass in body
Portal blood supply: first capillary bed in floor of third ventricle (hypothalamus) and second in anterior lobe
In general, each cell of the anterior pituitary secretes only one hormone (exception: FSH and LH made by same cells)
25-50% of anterior pituitary cells do not stain for any specific hormones or with H&E (chromophobes) and have only a few granules by EM
Acidophils: somatotrophs (30%) and mamotrophs (20%); more concentrated in lateral portions of the anterior lobe
Basophils: corticotrophs (15%), gonadotrophs (20%), and thyrotrophs (10%); more numerous in central portion of anterior lobe
Anterior pituitary hormones:
Glycoproteins: α and β subunits; α's same, β's unique:

TSH	Thyrotropin (thyroid stimulating hormone)
LH	Luteinizing Hormone
FSH	Follicle Stimulating Hormone

Non-glycosylated proteins:

PRL	Prolactin
ACTH	Adrenal-corticotrophin
GH	Growth Hormone

Hormone release from the anterior pituitary is controlled by releasing hormones from the hypothalamus:

TRH	Stimulates TSH and Prolactin release
GnRH	Stimulates LH and FSH release
Dopamine	Inhibits Prolactin
Somatostatin	Inhibits GH and TSH

Posterior pituitary releases vasopressin (ADH) and oxytocin, which are synthesized by cell bodies in the hypothalamus and travel along axons to the posterior pituitary
During pregnancy,
Tumors of the pituitary often result in enlargement of the sella turcica by X-ray, CT, or MRI; visual disturbances (bilateral homonymous hemianopsia); rarely increased intracranial pressure

Hyperpituitarism

Generally age 20-50; rarely (3%) associated with MEN I
Hyperpituitarism may be hypothalamic in origin; however, almost all cases are due to a secreting tumor, almost always an adenoma:

Prolactinoma	30%	amenorrhea, galactorrhea
Growth Hormone	17%	gigantism, acromegaly
Mixed GH, Prolactin	10%	
ACTH	14%	Cushing's disease
LH and FSH	3%	
TSH	<1%	
Nonfunctional	23%	

Adenomas account for ~10% of intracranial tumors
Adenomas may be <1 cm or >10 cm
Microadenomas (<1cm) can be found in 25-40% of patients at autopsy
Generally poorly encapsulated, if at all; may invade surrounding structures, even bone
Monomorphous population of cells in sheets, cords, nests, sometimes pseudoglandular or papillary; obliterate the normal acinar pattern; cells may show marked nuclear pleomorphism
Invasion into surrounding structures (seen in 35%) does not necessarily mean malignancy; carcinomas of the anterior pituitary are very rare; in general, to call a lesion malignant, need evidence of metastasis
Occasionally, completely infarct ("apoplexy"): clinical picture changes from hyperpituitarism to hypopituitarism

Prolactinoma
M:F=1:2; present with amenorrhea/galactorrhea or impotence
Cells are granular by H&E
EM shows misplaced exocytosis of granules

Growth Hormone Secreting Adenoma
Produces acromegaly and/or gigantism, depending on whether develops before or after closure of epiphyseal plates
Most cases present in 30's; decreases life span by 10yrs
30% of patients are hypertensive
Cells are granular by H&E
EM shows "fibrous body" composed of 7-8nm filaments and granules, near the nucleus

Adrenal-corticotropinoma
>80% of patients have Cushing's Syndrome (Disease)
80-90% are microadenomas; rarely see visual disturbances
EM shows 7nm filaments throughout the cytoplasm
- Nelson's Syndrome: adenomatous enlargement of pituitary with a carcinomatous histologic picture including local invasion and metastases, hyperpigmentation, expansion of sella-turcica; occurs in patients from whom an ACTH secreting pituitary tumor cannot be resected and who are therefore treated with bilateral adrenalectomy

Gonadotropinoma
Almost always male
Present with visual impairment, impotence, loss of libido
See elevation of FSH most commonly

Hypopituitarism

Generally caused by destruction of >75% of anterior lobe
Occasionally, results from hypothalamic destruction or malfunction
Usually results in pan-hypopituitarism
Clinically, sequence of detection of dysfunction is usually gonadotropins, GH (before puberty), TSH, ACTH, lastly PRL

Nonsecretory (Chromophobe) Adenoma
Hormone deficits develop slowly over years, so tumors generally large at time of diagnosis
Both null (clear) cell adenomas and oncocytic adenomas

Sheehan's Syndrome
AKA: Post partum pituitary necrosis
Sudden infarction following obstetric hemorrhage or shock, perhaps because enlarges with pregnancy and requires a greater blood supply
Incidence increased in patients with long-standing diabetes
Occasionally seen in non-pregnant females or in males (in setting of disseminated intravascular coagulation, sickle cell anemia)

Pituitary Infarction
Can occur independent of pregnancy; seen with hypertension, diabetes, arteriosclerosis, trauma
Usually does not involve the posterior pituitary (different blood supply)
As long as ~1/3 of gland remains viable, usually asymptomatic

Lymphocytic Hypophysitis
- Rare; associated with postpartum hypopituitarism, but can be seen in men
- May be autoimmune in origin
- Present with amenorrhea, galactorrhea, thyroiditis
- Atrophic acini separated by lymphocytes

Empty Sella Syndrome
- Primary: herniation of arachnoid through defect in sellar diaphragm with increased CSF pressure and atrophy of pituitary; most commonly obese, middle age, multiparous females; often asymptomatic
- Secondary: Sheehan's syndrome, apoplexy, surgery

Craniopharyngioma
- AKA: adamantinoma or ameloblastoma
- Derived from Rathke's pouch
- Anastomosing epithelial islands with cysts, straw colored fluid, giant cells, often calcifications

Crooke's hyaline degeneration of the basophils
- Glassy perinuclear cytoplasm displacing the basophilic cytoplasm to the periphery
- Seen in ACTH producing cells of the pituitary in setting of Cushing's syndrome or exogenous cortisol therapy with chronically elevated cortisol levels and subsequent feedback inhibition to corticotrophs

Other Causes
- Metastatic tumors
- Disruption of blood supply (vasculitis, thrombosis)
- Inflammatory destruction
- Rathke's cleft cyst
- Surgical or radiation ablation

Posterior Pituitary Syndromes

ADH deficiency (diabetes insipidus)
- Polyuria and excessive thirst
- Neoplastic or inflammatory destruction; surgical or radiation injury, severe head injury, idiopathic

Syndrome of Inappropriate ADH release (SIADH)
- Abnormal retention of water with expansion of extracellular fluid volume, hyponatremia, hemodilution
- Usually paraneoplastic in origin

SKIN

The numerous environmental agents to which the skin is continuously exposed, and the easy accessibility of this organ to the biopsy knife has lead to a tremendous number of pathologic "entities" with names ranging from the mundane to the exotic
This outline does not pretend to represent in anyway a comprehensive coverage of these entities but rather more of a sampling of the diversity which exists
The reader is referred to any of a number of texts specifically on the skin for a more detailed coverage

GENERAL TERMINOLOGY

Macule	flat discoloration ≤1 cm
Patch	flat discoloration >1 cm
Papule	solid elevation ≤1 cm
Plaque	flat, solid elevation >1 cm
Nodule	round solid elevated lesion >1 cm
Vesicle	small fluid filled blister ≤1 cm
Bulla	fluid filled blister >1 cm
Telangiectasia	dilated vessels
Scale	Visible cornified cells
Crust	serum within scale
Acanthosis	thickening of the epidermal layer
Lichenification	thickening of skin from chronic rubbing
Hyperkeratosis	increased thickness of cornified layer
Parakeratosis	hyperkeratosis & residual pyknotic nuclei
Hypergranulosis	thick granular cell layer (slow turnover)
Hypogranulosis	thin granular cell layer (fast turnover)
Spongiosis	intercellular edema
Ballooning	intracellular edema
Acantholysis	loss of cell-cell adhesion
Vacuolar ∆'s	small separations above and below BM
Dyskeratosis	premature keratinization in spinous layer
Papillomatosis	elongation of dermal papillae

Inflammatory Dermatoses

Acute Dermatitis (Eczema)

Gross and histologic appearance varies with site and duration
Early: erythema, aggregates of tiny pruritic vesicles which rupture easily exuding clear fluid, crusted
Chronic lesions: scaly, thickened
Spongiosis, vesicularization, exocytosis are key features
Mild acanthosis to psoriasiform epidermal hyperplasia
Parakeratosis over spongiotic foci, hyperkeratosis over chronic lesions
Superficial perivascular mixed inflammation
An important differential diagnosis is CTCL

Atopic Dermatitis
Associated with asthma and hay fever (excess IgE)
Usually starts ~6 wks age on head and neck
Progresses to flexural aspects of limbs; often symmetrical
Intense pruritus, lichenification, vesiculation rare

Seborrheic Dermatitis
Infants to early teens onward
Scalp, forehead, eyebrows, eyelids, ears, cheeks, chest
Erythema and scaling
Similar to psoriasis, but spongiosis is present

Nummular (Discoid) Dermatitis
Pruritic coin shaped plaques on lower legs, backs of hands, forearms
Women (15-30yrs) and middle aged males
Pronounced spongiosis

Stasis (Varicose) Dermatitis
Usually medial lower ankle; impaired venous return
Ulceration with increased risk of malignancy at margins
Hemosiderin deposition, fibrosis, new blood vessels

Contact Dermatitis
Allergic (e.g. poison ivy, nickel) and irritant (e.g. soaps) types (irritant does not require prior sensitization)
Distribution initially confined to areas of exposure

LICHEN SIMPLEX CHRONICUS
Chronic form of any of above with irritation and trauma
Epidermis undergoes a psoriasiform thickening but with an increased thickness of the granular layer
Scarring and broadening of dermal papillae

Psoriasis

Common; affects 1-2% population; chronic relapsing
Typically ~27 yr old; elbows, knees, scalp
Plaque (sharply demarcated, scaly surface, removing scales with fingernail results in small droplets of blood: Auspitz's sign - diagnostic)
Guttate (eruptive: small lesions on trunk, proximal extremities)
Pustular (sterile 2-3 mm pustules over trunk and limbs following fever, with surrounding generalized erythema)
Parakeratosis, hyperkeratosis: cells undergoing rapid turnover with thinning or absence of granular cell layer
Flaky scale with inflammatory cells in groups in scale
Acanthosis with long rete ridges and thinning of epidermis over dermal papillae
Extravasated RBCs in dermis
Pustular variant: Intraepidermal (between granular and cornified layers) vesicle with essentially all neutrophils (Munro's microabscesses)

Lichen Planus

Itchy flat-topped purple papules with white dots (fine scale)
Most common on extremities: wrist, elbow, glans penis
4th-6th decades, idiopathic, self limited
Hyperplasia of stratum granulosum (slowed turnover)
Basal cell hydropic changes / liquefaction - eosinophilic "colloid" bodies
Saw-toothed rete ridges (irregular epidermal hyperplasia)
Tight superficial dermal *band-like* chronic inflammation, filling papillary dermis

Lichen Planopilaris
Variant which preferentially affects epithelium of hair follicles

Vesicular and Bullous Diseases

[See also Acute Dermatitis]

MILIARIA
Caused by eccrine duct obstruction
Most commonly seen on trunk and intriginous regions

Miliaria Crystallina
Obstruction in stratum corneum, with subcorneal vesicles containing a few neutrophils
Tiny vesicles ("water droplets")

Miliaria Rubra
Obstruction in "prickle" cell layer creating an intraepidermal spongiotic vesicle
Multiple tiny erythematous papules

PEMPHIGUS
Rare autoimmune disorder with blistering which results from loss of integrity of the normal intercellular attachments within the epidermis
Usually 40-60 yrs old, M=F

Blisters induced by rubbing "normal" skin (Nikolsky sign)
Histologic common denominator is acantholysis

Pemphigus Vulgaris
Most common type (accounts for 80% cases)
Mucosa and skin, especially scalp, face, axilla, groin, trunk
Fragile blisters which readily rupture leaving a painful crusted bloody erosion
Preferentially involves layer immediately above basal layer, creasing a *suprabasal* cleft or bullae; remaining basal cells tombstone into lumen of blister
Antibody to adherens junction
Rx with high dose corticosteroids has reduced mortality

Pemphigus Vegetans
Rare form; large moist warty plaque studded with pustules
Similar histology to vulgaris but with overlying epidermal hyperplasia

Pemphigus Foliacious
More benign form, endemic in South America
Scalp, face, trunk - mucous membranes rarely involved
More *superficial* blisters seen, selectively involving the stratum granulosum or subcorneal layer
Numerous neutrophils may be present
Antibody to desmoglian

Pemphigus Erythematosus
Localized and less severe form of pemphigus foliacious
Restricted to malar region of face

OTHER VESICULAR AND BULLOUS DISEASES

Grover's Disease
AKA: Transient Acantholytic Dermatitis
Self limited acantholysis of unknown etiology
Intensely pruritic linear pattern of papules, vesicles, plaques, excoriations on chest, back, thighs.
Suprabasal splitting - can mimic Pemphigus Vulgaris, Darier's, Hailey-Hailey

Toxic Epidermal Necrolysis
AKA: Lyell's Syndrome (Note: term originally used to refer to scalded skin syndrome in infants)
Probably extreme form of erythema multiforme
Widespread tender erythematous rash, flaccid fluid filled bullae which rupture
Positive Nikolsky sign (blister on rubbing)
Some cases may be related to drug, sepsis, lymphoma
Appreciable mortality
Extreme epidermal necrosis with *subepidermal* blistering
Mild dermal perivascular monocytic infiltrate

Bullous Pemphigoid
May present at any age, usually in 70's
Typically inner thighs, flexor surfaces of arms, groin, axilla, abdomen; spares face and scalp
Large, tense bullae, some with blood, on "normal" skin
Anti-basement membrane Ab in serum (usually IgG) resulting in a linear direct immunofluorescent pattern for Ig and complement
Subepidermal fluid filled blister with eosinophils and serum without acantholysis
Inflammatory cell rich and cell poor variants
Edema in dermis
Increased risk of other autoimmune diseases
Usually controllable by corticosteroids

Dermatitis Herpetiformis
Intensely pruritic papulovesicular eruption involving the extensor surfaces, scalp, shoulders, buttocks, 25-50yr old
Granular deposits of IgA at dermal epidermal junction at the tips of the dermal papillae
Subepidermal (blister forms below the basement membrane), multilocular vesicles with neutrophils and eosinophils; dermal papillary neutrophilic microabscesses
All patients have some form of gluten sensitive enteropathy, 65-75% fulfilling the criteria for celiac sprue
Long term gluten free diet can cure both the enteropathy and the skin lesions
Skin lesions respond to Dapsone (enteropathy does not)
Patients (especially males) have an increased risk of developing a non-Hodgkin's lymphoma

Epidermolysis Bullosum Aquisita
Acquired predisposition to blistering following mild trauma
Onset in adulthood; NOT inflammatory
Vesicles/bullae on dorsal fingers, wrists, feet, elbows, knees
Blood or fibrin, generally in subepidermal blisters
Dermal papillae retained (no dermal edema)
Non-inflammatory - responds poorly to steroids

Porphyria Cutanea Tarda
Can be autosomal dominant, but usually sporadic
Subepidermal bulla with "festooning" of the dermal papillae into the bullus
Eosinophils, hyalinized perivascular deposits in dermis

Granulomatous Diseases

Granuloma Annulare
Dorsum of hands and arms, young females (2:1)
4 types: localized, generalized (associated with diabetes), perforating (ulcerates the overlying epidermis), subcutaneous (usually occurs in children)
1 to several skin-colored to red papules in an annular or arcuate pattern
Spontaneously resolve in ~2 yrs, may recur
Discrete palisading granulomas, generally superficial, with a well defined zone of disintegrating collagen and *mucin* positivity; occasional giant cells

Necrobiosis Lipoidica
M:F=1:3, most in 4th decade; 60% have diabetes mellitus
Sclerotic, round, circumscribed, slightly elevated plaque; initially red brown, then yellow with violaceous border
Predilection for lower extremities; may be symmetrical
Dermal granulomas with palisading histiocytes (arranged in tiers), plasma cells, poorly defined areas of disintegrating collagen but *no mucin*
Widespread changes in collagen; more extensive vascular changes than with granuloma annulare
May be a primary vascular disease or a primary collagen disease with secondary vascular changes

Rheumatoid Nodules
Develop at sites of trauma/pressure points in 30% of patients with rheumatoid arthritis
Erythematous plaques/nodules, often fixed to bone/fascia
Histology: Deep dermis and subcutaneous fat
Large, multinodular granulomas in deep dermis and subcutaneous fat with palisading histiocytes, occasional giant cells, and central fibrinoid degeneration (fibrin, Ig's, lipid)

Sarcoid
Cutaneous involvement in 20-35%
Widespread, asymptomatic maculopapular eruption
Associated with increased incidence of pulmonary fibrosis
"Lupus pernio": chronic violaceous plaque, usually on nose
Deep (subcutis) non-necrotizing granulomata: lobular panniculitis; small lymphocytes with Langhans giant cells
Stretched but intact overlying skin

Inflammation of Hair Follicles/Adnexae

Acne Vulgaris (Comedones)
Cystically dilated hair follicle
May be inflamed or not inflamed

Folliculitis
Papulopustules centered about hair follicles
Neutrophilic infiltrate (also lymphocytes) with dilatation and often rupture of the infundibulum of the follicle
Special stains may reveal the organism

Follicular Mucinosis
- AKA: Alopecia Mucinosis
- Hairless edematous plaques, usually on the head and neck of children
- Mucin pools within the hair follicle infundibulum dissect and separate the keratinocytes
- Eosinophils usually present in benign, childhood form
- When occurs in adults, may be a precursor lesion for CTCL

Rosacea
- Crops of papules over forehead, malar areas, nose, chin
- Persistent lymphedema and sebaceous hypertrophy result in rhinophyma
- Etiology unknown - can follow prolonged use of topical steroid
- Nonspecific perivascular inflammation with telangiectasia
- Enlargement of sebaceous glands

Focal Epidermal Atrophy

Lichen Sclerosis et Atrophicus
- Rare, females 45-60, genital area
- White or ivory angulated macules or papules
- Pathogenesis unknown
- Hyperkeratosis with epithelial atrophy edema and homogenization of upper dermis (loss of elastin)
- Underlying dense lymphocytic infiltrate may be present
- Telangiectatic vessels common
- In postmenopausal women, progressive and unresponsive to therapy; ~5% will develop squamous cell carcinoma

Balanitis Xerotica Obliterans
- Same disease in men, occurring on the glans penis
- Can lead to phimosis or squamous cell carcinoma
- More commonly associated with extragenital LSA

Panniculitis

Erythema Nodosum
- Commonest nodular panniculitis; often associated with infections, drug administration, IBD, some malignancies, sarcoidosis, pregnancy
- M:F= 1:9, usually anterior and lateral lower legs
- Pyrexia, malaise, joint pain
- Predominantly septal inflammation; septal widening due to edema, fibrin, and infiltration of neutrophils (later lymphocytes)
- Granulomatous inflammation with giant cells may develop

Erythema Induratum
- More chronic form of panniculitis; unknown cause, although probably vasculitis
- Presents as erythematous, slightly tender nodule; often ulcerates
- Necrosis and inflammation within the fat lobules; a necrotizing vasculitis of medium sized vessels often seen

Infectious Lesions

Wart (Verruca vulgaris)
- Caused by HPV types 2,4,7 (plantar: 1,2; condylomata acuminata: 6,11,16)
- Persist for months to years
- "Papillary" acanthosis with parakeratosis over the tips of the exophytic component
- Marked orthokeratosis with prominent granular cell layer

Herpes Simplex
- Cutaneous lesion appears after nerve involvement
- Lesions recur, but become less florid and less frequent
- Multinucleated giant cells, nuclear inclusions (ground glass, blue speckled nucleus); necrosis with vesicle formation

Molluscum contagiosum
- Self limited poxvirus infection
- Lobulated, endophytic hyperplasia -> circumscribed intradermal pseudotumor
- Keratinocytes contain a large intracytoplasmic inclusion

Impetigo
- Staph infection of mild abrasions - children most commonly
- Neutrophil filled intraepidermal vesicles (split beneath stratum granulosum)
- May progress to cellulitis, glomerulonephritis, erythema nodosum, or erythema multiforme

Syphilis
- Genital chancre develops 20-30 days after exposure to Treponema pallidum; painless ulcer, resolves by itself
- Secondary cutaneous lesions - head and neck common
- Variable appearance
- Intense perivascular infiltrate with plasma cells

Candida
- Tight, protective scale with neutrophils in epidermis and chronic inflammation in dermis

Miscellaneous External Agents

Urticaria (Hives)
- Most commonly 20-40 yrs old
- Individual lesions usually develop and fade within 24 hrs; new lesions appear elsewhere
- Very subtle histology: mild superficial perivascular chronic inflammation, dermal edema, dilated lymphatics

Erythema Multiforme
- Predominantly young individuals; may be recurrent
- Etiology usually unknown, but can be caused by infectious agents or drugs
- Groups of maculopapules, often with annular configuration, on elbows, knees, acral regions; sometimes face and trunk, mouth
- Keratinocyte necrosis, spongiosis, vacuolization of basement membrane
- Both epidermal and dermal involvement
- Can see either intraepidermal or subepidermal bullae, or both
- Inflammatory infiltrate in high papillary dermis; eosinophils; RBC extravasation

Steven's-Johnson Syndrome
- Severe form of erythema multiforme with mucosal involvement, conjunctivitis, high fever
- 5% of cases are fatal
- [See also Toxic Epidermal Necrolysis]

Arthropod Bite
- Superficial and deep perivascular mixed chronic inflammation
- Eosinophils
- Edematous dermis; mild acanthosis of overlying epidermis

Fixed Drug
- Seen with trimethoprin sulfamethoxazole, ASA, tetracycline, barbiturates; recur at same site with each administration
- Hydropic degeneration of basal cells; pigment incontinence

Photo-Drug
- Sun exposed areas
- Allergic Type: eosinophils, contact dermatitis picture
- Toxic Type: sunburn type picture

Polymorphous Light Eruption
- Papular, papulovesicular, plaque, or diffuse type eruptions occurring on sun exposed skin 4-24 hrs after sun exposure
- Onset after puberty
- Histology is nonspecific

Congenital Diseases

Ichthyosis
- Multiple types: most common: autosomal dominant (vulgaris)
- Dryness to fine fish-like scale, involving predominantly extremities but sparing flexures
- Believed to be secondary to increased adhesiveness
- X-linked recessive disorder has larger coarse scales
- Hyperkeratosis on normal/atrophic epidermis with thin to absent granular layer

May get keratin plugging of hair follicles

Urticaria Pigmentosa
- Round to oval erythematous macules to nodules which weal after slight stroking or rubbing
- Lesions present at birth or appear in first year; darken with time (increased melanin); usually regress within 5-6 years
- Adult form: pigmented, usually on trunk, systemic involvement common (bone marrow)
- Many mast cells (± eosinophils) in dermis; associated edema

Darier's Disease
- AKA: Keratosis Follicularis
- Plaques of greasy, crusted, sometimes warty yellow-brown papules on scalp, forehead, upper chest, back
- Usually autosomal dominant; also see palmar pits, longitudinal splitting of nails
- Marked hyperkeratosis, acantholysis (suprabasal clefts)
- Corps ronds: dyskeratotic cells in granular layer with surrounding halo

Hailey-Hailey Disease
- AKA: Benign Familial Chronic Pemphigus
- Autosomal dominant, appears in early adolescence
- Massive acantholysis with suprabasal vesicles/bullae on normal to erythematous skin at friction sites on neck, axilla, groin; erode and crust; adnexae are spared
- Acantholysis incomplete - some connections preserved
- Superinfection by Candida and Staph common
- Symptoms worsened by trauma or sun

Xeroderma Pigmentosum
- Autosomal recessive defect in repair of thymidine dimers
- Extreme photosensitivity (freckles to blistering rash)
- Eventually develop widespread cutaneous tumors
- Solar damage, hyperkeratosis, epidermal atrophy, pigment incontinence

Tuberous Sclerosis
- Autosomal dominant, although most new mutation
- "Adenoma sebaceum": pink papules/nodules in butterfly pattern over nose and cheeks, sparing the upper lip
- Fibrovascular hamartomatous proliferation with prominent sebaceous glands; later perifollicular concentric fibrosis
- "Shagreen Patch": flat raised lesion on the lower back
- Periungual fibromas

Lupus

Discoid Lupus
- Cutaneous form of LE with no systemic manifestations
- Generally face, earlobes, neck, scalp
- A vacuolar and interface dermatitis
- Acute: Lichenoid perivascular inflammation (always superficial, may also be seen deep); hydropic degeneration of basal cells; edema in papillary dermis
- Chronic: hyperkeratosis with follicular plugging, epidermal atrophy, thick basement membrane
- Direct immunofluorescence shows granular band of immunoglobulin and complement along the dermal-epidermal junction

Lupus Erythematosus
- M:F = 1:9, 20's to 40's, prevalent in blacks
- Butterfly rash, multisystem involvement
- Histology similar to discoid lupus
- In patients with systemic disease, granular band of Ig and complement deposition can also be seen in clinically normal skin - can help distinguish discoid from systemic

Primary Vascular Diseases

[See also Vessels Outline]

Leukocytoclastic Vasculitis
- Most common vasculitis
- Polymorphic, but palpable purpura most common
- Necrotizing vasculitis of small superficial vessels with fibrinoid necrosis and Ab-Ag complexes (autoimmune)

Polyarteritis Nodosa
- Systemic necrotizing vasculitis of medium sized to small arteries; overlaps with leukocytoclastic vasculitis
- 50% 5 yr mortality
- Joint, PNS, CNS, Renal involvement common

Wegener's Granulomatosis
- Necrotizing granulomas of upper airway, glomerulonephritis, granulomatous vasculitis
- Before treatment, 80% 1 yr mortality

Lymphocytic Proliferative Lesions

Mycosis Fungoides
- Dense lymphocytic infiltrate with epidermotropism of lymphocytes without spongiosis
- Lymphocytes in epidermis ± Pautrier's microabscesses
- Plasma cells

Lymphomatoid Papulosis
- M:F=2:1, usually 30's; unknown etiology
- Erythematous dermal papules, hemorrhagic, necrotic, scars
- Dermal and epidermal infiltrate of atypical lymphoid cells
- Mostly T-helper cells; may mimic PLEVA histologically
- Looks malignant, but usually benign course

Graft-vs-Host
- Acute: basal cell hydropic degeneration, degenerate keratinocytes, exocytosis, mild dermal perivascular lymphocytic infiltrate
- Chronic: lichenoid infiltrate, hyperkeratosis, hypergranulosis, basal cell hydropic degeneration
- Late chronic: epidermal atrophy, abolition of ridges, loss of adnexal structures, scarring of superficial and deep dermis

Miscellaneous

Calcinosis Cutis
- Dystrophic calcification

Prurigo Nodularis
- Chronic, intensely pruritic nodules: globular, dark, with a warty or excoriated surface
- 5-75yrs at onset, lasting average of 9 years
- Compact orthokeratosis, acanthosis, pseudoepitheliomatous hyperplasia, vascular hyperplasia in dermis

Erythema Annulare Centrifugum
- Annular erythematous bands, well circumscribed
- May remain stationary or spread outward
- Trunk most common, then lower limbs, arms, hands
- Tight dermal perivascular mononuclear infiltrate with normal overlying epidermis

Pityriasis Rosea
- 10-35 yr old, "rose colored scale"
- Starts as herald patch, single red papule enlarges over 48hrs
- After incubation period (1-2wks), generalized eruption of pink elliptical lesions 1 cm long along skin tension lines
- Focal alternating hyperkeratosis/parakeratosis; slight acanthosis; focal spongiosis and dermal edema
- Superficial loose lymphohistiocytic infiltrate with extravasation of RBC's into dermis

PLEVA
- Pityriasis Lichenoides et Varioliformis Acuta (Mucha-Haberman disease)
- M:F=3:1, late childhood to early adult
- Pink papules on trunk and extremities which ulcerate and then heal without scarring
- Acute ulceronecrotic lesions with wedge-shaped keratinocyte necrosis, spongiosis, exocytosis of lymphocytes & RBCs
- Obscured dermal-epidermal junction
- Extravasated RBC's in dermis

Kawasaki's
- AKA: Mucocutaneous lymph node syndrome

SKIN - Proliferative Lesions

Keratinocyte "Tumors"

Cutaneous Horn
Protuberant column of keratin
May be found over other lesions

Achrochordon
AKA: Fibroepithelial papilloma/polyp, skin tag
Histology: normal skin, seborrheic keratosis, etc.

Acquired (digital) fibrokeratoma
Collagenous protrusions with hyperkeratotic epidermis
Usually around interphalangeal joints

Seborrheic Keratosis
Very common, developing in middle aged to elderly
Sharply delineated, round, tan to black, mostly on face, arms, upper trunk - never palms or soles
Leser-Trelat Sign: sudden increase in size or number associated with internal malignancy
Full thickness proliferation of keratinocytes with horn cysts, thick basal cell layer, hyperkeratotic
Multiple variants:
- Keratotic (papillomatous): verrucous; flat bottom
- Adenoid: thin strands of proliferating basal cells
  Horn cysts may not be present
- Acanthotic: Rounded, smooth surface
  May have marked melanocyte proliferation
- Inverted (irritated) follicular: penetrating but circumscribed lower border

Pseudoepitheliomatous Hyperplasia
Occurs at sites of trauma, chronic irritation, ulcers
Can be produced by fungal infections
Thin, elongated anastomosing ridges
Inflammatory cells, dermal vascular proliferation

Lichenoid (Lichen-Planus-like) Keratosis
Asymptomatic, 0.5-2cm slightly verrucous or scaly
Sun exposed skin, bright red to brown
Basket-weave hyperkeratosis
Similar histology to lichen planus but tends to be solitary, contains eosinophils or plasma cells, and hash focal areas of parakeratosis or epithelial atypia

Acanthosis Nigricans
Hyperkeratosis and papillomatosis
80% occur in children
When occurs in adults, usually associated with underlying malignancy, most commonly gastric

Hyperplastic Vulval Dystrophy
[See also Uterus and Vulva Outline]
Clinical term: Leukoplakia
Hyperkeratosis, irregular acanthosis, hyalinization of the papillary dermis, mild chronic inflammatory cell infiltrate
With or without atypia

Keratoacanthoma
Rapidly growing benign skin tumor of pilosebaceous origin, occurring on sun exposed skin of face, back of hands, wrists, forearms; M:F=3:1
Clinical stages: rapid growth (over couple of months), maturation, resolution (spontaneous regression)
Round, reddish nodule with central cup-shaped crater filled with keratin; symmetrical, well differentiated squamous cells
Perineural invasion of small nests of squamous cells can be seen
Differentiation from squamous cell carcinoma is based on the fact that a keratoacanthoma grows rapidly, has an exophytic component, abundant glassy cells, and a mixed inflammatory cell infiltrate

Clear Cell Acanthoma
Rare, usually solitary, elderly; most commonly lower limbs
Well demarcated lateral border with abundant glycogen
May arise from intraepidermal eccrine ducts

Noninvasive Squamous Lesions
Actinic (Solar) Keratosis
Yellow brown, scaly lesions on sun exposed skin (face, upper back, arms)
Stratum corneum replaced by parakeratotic scale: alternating parakeratotic/orthokeratotic horn; (follicular areas spared)
Granular layer absent; focal basal cell proliferation
Chronic inflammation in papillary dermis with basophilic degeneration of collagen
Hyperplastic and atrophic variants
Only a small proportion progress to invasive SCC

Bowenoid Actinic Keratosis
Similar to, but smaller than, Bowen's disease
Occurs on sun exposed skin
Usually not full thickness involvement

Intraepidermal Epithelioma
Nests of enlarged, atypical keratinocytes in the epithelium, but with normal underlying basal layer

Bowenoid Papulosis
Glans penis of circumcised men, vulva of women
20-40yrs old, multiple red papules; rapidly developing
Histology is very similar to Bowen's disease but more orderly background with some surface maturation

Bowen's Disease
AKA: Squamous Cell Carcinoma in situ
Slowly enlarging, scaly, erythematous sharply demarcated lesion occurring anywhere on skin or mucous membranes; devoid of adnexae
Middle-aged to elderly; may be associated with arsenic exposure; not related to sun exposure
Full thickness dysplasia (carcinoma in situ) with cytoplasmic vacuolization, nuclear hyperchromasia, multinucleated keratinocytes, dyskeratosis, mitoses, parakeratosis
~5% will develop invasive SCC

Erythroplasia of Queyrat
Squamous cell carcinoma in situ of the glans penis
Occurs in uncircumcised men
Asymptomatic, erythematous, well defined

Squamous Cell Carcinoma
2nd most common cutaneous malignancy (after BCC)
Occurs at sites of "trauma" (sun exposure, burns, chemical exposure, PUVA, renal transplantation)
Prognosis related to depth of invasion and tumor thickness
Tumors >2 cm thick: <5 % LN metastases

HISTOLOGIC VARIANTS:

Well differentiated (80%): large amount of keratin and involucrin, dermal invasion required
Spindle Cell: sun exposure (lip), spindled, differential diagnosis: malignant melanoma, atypical fibroxanthoma
Acantholytic (adenoid, pseudoglandular): sun exposed areas, desmosome defect with loss of cohesiveness and false glands
Verrucous: usually sole of foot, extremely well differentiated, ulcerates, locally invasive on a broad front to bone (metastases rare)
Clear cell: rare, primarily head and neck, males, clear cells in foci or throughout lesion, differential diagnosis: sebaceous carcinoma

Staging
NOTE: Same staging scheme used for all carcinomas of the skin (including those arising from appendages); Melanomas and lesions of the eyelids are specifically excluded

T1 Tumor ≤2cm
T2 2-5cm
T3 >5 cm
T4 Invades muscle, bone, cartilage

N1 Regional LNs
M1 Distant metastases

	T1	T2	T3	T4
N0	I	II		
N1	III			
M1	IV			

Basal Cell Carcinoma

Most common cutaneous malignancy
Predominantly sun exposed skin, in proportion to # of pilosebaceous units; slow and indolent growth
Prevalent in transplant patients
Synchronous and metachronous tumors common
Proliferation of basal cells with peripheral palisading, separation artifact, stromal mucin, incomplete differentiation toward adnexal (usually pilar) structures
Mitotic rate unrelated to prognosis
Immunohistochemistry: Keratin +, EMA -, CEA -
If untreated, may invade subcutaneous fat; only 1/3 of incompletely excised lesions recur
Metastases rare (<.002%); if does metastasize, usually fatal within 1 year

MULTIPLE VARIANTS:

Superficial
Arises in skin with thin epidermis and fine hairs
Chiefly lateral growth; high recurrence rate

Localized-ulcerative
75% lesions - non healing ulcer
Telangiectatic vessels

Localized-cystic
Lobulated, smooth, pearly nodule

Diffuse Sclerosing Type (Morpheaform)
Poorly defined margins
Extent often far beyond clinical appearance
Loss of peripheral palisading, dense stroma
Tend to be more aggressive

Basosquamous (metatypical)
Atypical squamous cells - more aggressive

Clear Cell
Clear vacuoles - occasional signet ring cells

Basal Cell Nevus Syndrome
AKA Gorlin's syndrome
Multiple BCC's, starting at an early age
Autosomal dominant
Jaw cysts, skeletal abnormalities, falx cerebri calcification, palmar pits

Fibroepithelial Tumor of Pinkus
Back, abdomen and thigh - look like skin tags
2-3 cell thick basaloid epithelial strands anastomosing to compartmentalize fibrous stroma

Paget's Disease

Most common extra-mammary sites: vulva, penis, scrotum, anus, axillae, umbilicus, eyelids
Mammary Paget's: associated with underlying carcinoma
Paget cells cluster; pink cytoplasm, vesicular nuclei
Large cells, PAS positive, pseudoglandular
CEA positive; usually keratin and S-100 negative

Appendage "Tumors"

Cutaneous Cysts

Epidermal Inclusion Cysts
Pilosebaceous units or implantation trauma
Unilocular, granular cell layer present

Milia
Subepidermal blisters or plugged eccrine ducts
Miniature epidermoid cysts

Tricholemmal (pilar) cysts
Scalp, yellowish, intradermal swellings
No granular cell layer, cholesterol clefts

Proliferating Tricholemmal cysts
Slow growing, large tumor on scalp of elderly female
Lobulated intradermal mass of squamous epithelium
Peripheral palisading, thick refractile basement membrane
Mitoses limited to basal layer

Hair Follicle Lesions

Pilar Sheath Acanthoma
Upper lip, solitary, central pore with keratinaceous material
Multiloculated lobulated tumor masses radiating into surrounding dense stroma

Trichilemmoma
Small warty or smooth papule on face of older adults
Proliferation of outer root sheath with uniform small cells forming one or more lobules arising from epidermis
Peripheral palisading; thickened basal membrane

Pilomatricoma
Slowly growing, firm chalky nodule, usually on face
Biphasic population of basaloid and ghost cells (hair matrix differentiation); 75% show calcification

Trichofolliculoma
Dome shaped; central pore with silky white thread-like hairs
Dilated hair follicle with numerous secondary (mature and immature) follicles arising from its stratified squamous wall

Trichoepithelioma
Small, flesh colored nodule
Lobules of basaloid cells and keratinocytes disconnected from the epidermis; peripheral palisading; horn cysts; cellular fibrotic stroma surrounding lobules is part of tumor
Differential diagnosis: basal cell carcinoma

Piloleiomyoma
Small, firm, intradermal nodules
Groups or linear arrays on trunk or extremities

Sebaceous Glands

Nevus sebaceous (of Jadassohn)
Single, round, usually head/neck, yellow, flat;becomes warty
Acanthotic, abortive hair papillae, ectopic apocrine glands in 50%; Prone to evolve into BCC

Sebaceous hyperplasia
Face of older adults, yellowish dome shaped papule
Hyperplastic glands high in dermis, drain into central duct

Sebaceous adenoma

Rare - yellow papule, looks like BCC's
Individual lobules, collagenous pseudo capsules peripheral small germinative cells with round to oval vesicular nuclei and eosinophilic cytoplasm

Sebaceous carcinoma
Aggressive periocular variant and relatively non-aggressive extraocular form
Irregular lobular pattern in upper dermis with basophilic sebaceous cells containing small granular nuclei with eosinophilic nucleoli

Eccrine Glands

Syringoma
Multiple symmetrically distributed small papules on lower eyelids which appear at puberty; female predominance
Intraepidermal eccrine sweat duct tumor (acrosyringium)
Interconnecting eccrine strands + ducts in a fibrous stroma
Small ducts with 2 rows of cells
Lumens, lined by cuticle, with eosinophilic granular material

Eccrine Acrospiroma
AKA: Eccrine hidradenoma, clear cell hidradenoma
Arises from distal excretory duct of the eccrine gland
Superficial dermal nodules with monomorphic cuboidal cells with a basophilic cytoplasm mixed with clear cells

Eccrine Poroma
This may be a specialized form of eccrine acrospiroma
Solitary, slightly red scaly nodule, usually sole, sides of foot
Tumor of upper dermal eccrine duct (outer acrosyringium)
Tumor replaces epidermis (sharp demarcation) and grows down into dermis; monomorphic, cuboidal cells; occasionally with duct differentiation
Malignant form: rare, marked nuclear pleomorphism

Cylindroma
99% head, neck, scalp; F:M=9:1; Slow growing, red
Multiple lobules in a *jig-saw pattern* in upper dermis, no connection to epidermis
Each lobule: *thick PAS+ basement membrane*, basal cells (hyperchromatic nuclei) and central cells (vesicular nuclei)

Eccrine Spiradenoma
Solitary intradermal lesion, blue overlying skin: PAINFUL
Basophilic nests of tumor cells in dermis: peripheral small cells with round hyperchromatic nuclei surrounding large cells with vesicular nuclei and eosinophilic nucleoli
Rich vascular supply

Chondroid Syringoma (Benign Mixed Tumor of the Skin)
Firm, lobulated nodules in dermis or fat; solitary, asymptomatic, usually head and neck
Multilobulated, well circumscribed mass with nests or cords of polygonal cells with basophilic nuclei and lots of eosinophilic cytoplasm
Stroma has a pseudocartillagenous appearance

Eccrine Carcinoma
Classical, syringoid, microcystic adnexal, mucinous, and adenoid cystic variants

Apocrine Glands

Apocrine Nevus (Syringocystadenoma Papilliferum)
Solitary, usually scalp, gray to brown papillary, moist
Double layered "apocrine" epithelium lining glandular spaces and papillae; Fibrovascular core typically with plasma cells

Tubular Apocrine Adenoma
Dermal nodule, long duration, may be large; scalp, axilla
Poorly circumscribed dermal tumor within foci of ductular communication with the epidermis
Lobular masses of tubular structures
Columnar epithelium, myoepithelial layer, apocrine secretion

Hidradenoma
Females only - asymptomatic nodule in genital/perianal region
Well demarcated dermal nodule composed of papillary fronds with columnar cells and underlying myoepithelial cells
Fibrous pseudocapsule common

Merkel Cell Carcinoma

Highly aggressive firm, raised, painless nodule
Occurs on sun damaged skin: head and neck (44%), leg, arm, buttock
Epidermis: normal, tumor, SCC not uncommon
Predominantly dermal tumor with trabecular growth pattern, dissection of collagen by small basophilic cells with small eccentric nucleolus, nuclear molding
EM: 100-150nm neurosecretory granules, paranuclear filament whorls
Recurrence common (36%), metastasizes (28%)
50% 2 yr mortality

Aggressive Digital Papillary Adenocarcinoma

Appendage tumor seen almost exclusively on the digits
Papillary projections into cystic spaces and tubular structures intermixed with more solid, poorly differentiated areas with necrosis
Tends to metastasize to lungs

Fibrous Proliferation

Hyperplastic Scar

Increased amount of collagen, in thin fibers

Keloid

Exuberant scars, predominantly in blacks
Large eosinophilic collagen fibers; unusually large fibroblasts

Fibromatosis

Juvenile hyalin type, Dupuytren's type
Round plump spindle cells in collagenous stroma with hyalinization

Nodular Fasciitis

Reactive, unknown etiology, usually limbs
Rapidly growing subcutaneous nodule - painful
Plump spindle cells in loose myxoid and collagenous stroma
Numerous thin walled vessels with prominent endothelium
Sparse chronic inflammation

Morphea (Localized Scleroderma)

White, indurated area(s)
Sclerotic hyalinized thickening of the dermis; epidermis normal
Superficial and deep perivascular infiltrate
Sclerosis extends into fibrous septa of deeper adipose tissue

Dermatofibroma (Fibrous Histiocytoma)

Middle adult life: trunk, proximal extremities
Firm cutaneous nodule, reddish brown, slowly growing, painless
Interlacing fascicles of slender spindle cells with foamy histiocytes, giant cells, vessels, hemosiderin, chronic inflammation
Infiltrative margins; superficial; overlying pseudo-epitheliomatous hyperplasia separated from the underlying lesion by a think zone of normal dermis (Grenz zone)

Fibrocartillagenous Type ("Typical")
- Plump capillaries, fibroblasts, foamy histiocytes
- Cellular (histiocytoma) and angiosiderotic (sclerosing hemangioma) variants

Pleomorphic Type ("Atypical")

Atypical Fibroxanthoma
- Firm, often ulcerated nodule on sun exposed head and neck (60's-70's) or limbs (30's-40's)
- Predominantly dermal - may involve superficial fat
- Marked pleomorphism: "too bad to be malignant"
- Should NOT see storiform pattern, necrosis, myxoid change
- Proliferation of Factor XIIIa positive histiocytes

Dermatofibrosarcoma Protuberans
- Multinodular, reddish blue nodule, 20's-30's, usually trunk
- Deep dermis to subcutis (dermatofibroma more superficial)
- Well differentiated spindle cells in storiform, interlacing bundles - basket weave
- Moderate mitotic activity, abundant reticulin
- Pigmented and myxoid variants exist
- Local recurrence 33%, metastases rare

Giant Cell Tumor of Tendon Sheath
- Slow growing, painless nodule of hands, feet, usually fingers
- Fibrous pseudocapsule, lobulated; Pleomorphic histiocytes, giant cells, hemosiderin; collagenous stroma with cholesterol clefts
- Local recurrence (15%), no malignant potential

Neurilemoma (schwannoma)
- Solitary, painless mass, head, neck, limbs
- Encapsulated, biphasic
- Antoni A: Tightly packed spindle cells, tapering elongated wavy nuclei; nuclear palisading (Verocay bodies)
- Antoni B: irregularly scattered spindle or stellate cells in abundant loose myxoid stroma; small blood vessels with hyalinized walls

Neurofibroma
- Generally young individuals; any site; solitary or multiple (von Recklinghausen's)
- Irregular, spindle shaped cells in loose matrix within superficial dermis; No capsule, no mitotic activity
- Mast cells
- Variants: Myxoid, plexiform, epithelioid, Pacinian

MELANOCYTIC LESIONS

MELANOCYTES
- Neuroectodermally derived cells
- Stain with silver stains (melanin), S-100, vimentin, DOPA reaction. Negative for keratin, neurofilament, GFAP
- Melanoblast: immature form
- Melanophage: macrophages which have phagocytosed pigment (pigment incontinence)
- Color depends on melanin location: epidermis, brown; superficial dermis (clumped), black; deep dermis, blue

Benign Disorders of Pigmentation
Freckles (ephelis)
- Reactive to sunlight, 1-10 mm, irregular borders
- Increased melanin deposition, melanocyte hypertrophy, normal or decreased numbers or melanocytes

Melasma
- "Mask of pregnancy"; can also occur outside of pregnancy
- Increased pigmentation but normal number of melanocytes

Vitiligo
- Hypopigmentation, often irregular, hyperpigmented border
- Complete absence of melanocytes (unlike albinism, in which melanocytes are present but don't make melanin)

Lentigo (lentigo simplex, nevus spilus)
- Usually seen in children; unresponsive to sunlight
- 5-10mm, tan-brown with smooth, well demarcated borders
- Melanocyte hyperplasia and hyperpigmentation of basal epidermis, with elongation of rete ridges but generally without melanocyte nesting

Nevi (melanocytic, nevocellular)
- Any localized benign abnormality of melanocytes
- Most appear at 2-6yrs of age, nearly all by age 20
- Nevus cells and melanocytes are derived from the same lineage (neural crest) but show different biological behavior and may in fact be different cells

Junctional
- Flat or slightly elevated, non-hairy, fawn colored
- Melanocytic nests (theques) on epidermal side of dermal-epidermal junction
- May give rise to malignant melanomas

Intradermal
- Papillary, pedunculated, or flat; often hairy
- Small nests or bundles of melanocytes in papillary dermis (if deeper, think congenital)
- Not circumscribed, but surrounded by basement membrane
- Degree of pigmentation varies
- Lower half of lesion less cellular, spindled, neuroid
- Almost never give rise to melanoma

Compound
- Junctional plus intradermal features
- Junctional component tends to decrease with age (except on palms, soles)
- A prominent junctional component indicates "activity": activation occurs from sunlight, pregnancy, recurrence following excision, melanoma elsewhere

Blue Nevus
- Usually head, neck, upper extremity
- Abundant melanin pigment
- Band of uninvolved dermis between epidermis and lesion

Cellular Blue Nevus
- Usually buttock, lower back, back of hands or feet
- Large, intensely pigmented, very cellular, pushing margins, dermal sclerosis, elongated dendritic processes with fine melanin granules
- No junctional activity or inflammation
- 25% are congenital
- Usually benign

Spitz Nevus (Spindle Cell and/or Epithelioid Cell Nevus)
- 50% occur before puberty, but can occur at any age
- Pink red papule on face, prepubertal
- Compound (70%), intradermal (20%), junctional (10%)
- Generally scanty pigment (except pigmented variant)
- Symmetrical, sharp lateral demarcation, mature with depth (become more neural looking)
- Overlying epidermal hyperplasia, telangiectasia
- Intraepidermal hyaline globules (Kamino bodies)
- Almost always benign

Giant Congenital Pigmented Nevi
- Bathing-trunk distribution
- Large, coarse skin with folds, often satellite lesions
- Histologically: deep lesions
- Prior to surgery, need to expand skin since need to cover a large defect to achieve resection; nevertheless, still usually requires multiple surgeries

~50% of patients show an extra chromosome 7 when grown in culture (may all be an artifact of cell culture); similar change seen in some smaller congenital nevi
Figures for risk of malignant transformation range from 2%-40%

Bulky Perineal Neurocytoma
Congenital, large, polypoid or pedunculated hyperpigmented mass in the genital area, often obscuring the genitals
Histology is that of a benign congenital nevus; often have cystic structures lined by nevus cells
Large numbers of small neuratized bodies (look like Meissner's corpuscles)
HMB-45 positivity extends deep into lesions and include the cystic structures but not the neural structures
S-100 positivity in all structures
Probably an uncommon variant of giant congenital pigmented nevus
May have aggressive histology in newborn; however, malignant transformation is rare before 6 months of age

Deep Penetrating Nevus
10-30 yrs old, usually face or upper trunk
Darkly pigmented, dome shaped nodule
Nests of nevus cells with scattered melanocytes which fill the dermis; may infiltrates erector pili muscles
May extend through the dermis into the subcutis
Benign lesion; does not recur or metastasize

Other Nevi
- Halo: surrounded by unpigmented skin, secondary to regression
- Balloon: large foamy melanocytes
- Congenital (non-giant): involve reticular dermis, subcutaneous tissue, and skin adnexae

DYSPLASTIC NEVUS
Familial - predisposed to melanoma
Some atypical melanocytes
Lymphocytic infiltrate in papillary dermis
Bridging of rete ridges by melanocyte nests
Junctional component extends beyond intradermal
Eosinophilic concentric/lamellar fibrin deposition
Believed by some to be precursor for malignant melanoma

Lentigo Maligna (Hutchinson's Freckle)
AKA: Malignant melanoma in situ
Sun exposed areas, most common on cheek of elderly
Tan to black; solar elastosis; individual (± nesting) atypical junctional melanocytes; minimal transepidermal migration; often involves adnexae
Slow growing, 30-40% invade if untreated (premalignant)

Malignant Melanoma
Most associated with sunlight, especially in red haired whites
Almost always have junctional component. Therefore, if intradermal, probably metastatic
~20% are believed to arise from a pre-existing nevus
Markedly varied histologic appearance, often with some areas of nesting
Nucleoli commonly present and large; nuclear pseudoinclusions composed of cytoplasm very common

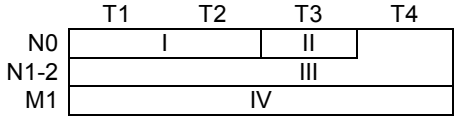
Types:
- Lentigo Maligna Melanoma
  Arises from Lentigo Maligna
  Atypical cells present in dermis (vertical growth phase)
  Better prognosis than other types
- Superficial Spreading Melanoma
  Most common form
  Blue with admixed tan and brown (early)
  White, pink, blue = areas of regression
- Nodular Melanoma
  Younger age group - usually shorter duration
  Elevated lesion
- Acral-lentiginous
  Intraepidermal with hyperplastic epidermis
- Desmoplastic

Growth Phase:
Radial: restricted to epidermis, or individual cells or small, regular nests in the dermis
Vertical: large or atypical nests in dermis

Features of Malignancy:
Large, High mitotic rate, Poorly circumscribed/ low cohesiveness in nests, Lateral extension of individual cells (trailing off), Extension within adnexal epithelium, Variation in size/shape, Lack of maturation, Prominent nucleoli, Fine dusty melanin granules, Melanocyte necrosis (if not related to ulceration), Lymphocytes in tumor

Regression:
Primary can spontaneously regress (metastases do not)
Clinically: white, often with a bluish hue
Irregularities along dermal-epidermal junction, focal necrotic cells, band-like lymphocytic infiltrate, melanophages, subepidermal fibrosis, atrophy of rete ridges
For two lesions of the same size, regression is a bad prognostic sign, since it indicates lesion was once larger

Staging
Tis In situ (Clark Level I)
T1 ≤.75mm thick; invades papillary dermis (Clark Level II)
T2 .75-1.5mm; fills papillary dermis (Clark Level III)
T3 1.5-4mm thick; into reticular dermis (Clark Level IV)
T3a 1.5-3mm T3b 3-4mm
T4 >4mm thick; into subcutaneous tissue (Clark Level V)
T4a No satellite lesion T4b Satellites within 2cm
N1 Regional LN metastasis ≤3cm
N2 Regional LN metastasis >3cm or in transit metastasis



Breslow Level: measure depth in mm from overlying stratum granulosum or ulcer bed to deepest extension IN THE PRIMARY TUMOR

CENTRAL NERVOUS SYSTEM

Normal Anatomy

BRAIN

The cerebrum is divided, on each side, into the frontal, parietal, occipital, and temporal lobes
Sylvian Fissure: marks the upper border of the temporal lobes; sparates from parietal lobes
Rolando Fissure (central sulcus) separates the frontal from parietal lobes, and is bounded by the precentral motor cortex and the postcentral sensory cortex
Convolutions are termed gyri for the cerebrum, folia for the cerebellum
Cranial nerves 1 and 2 are CNS extensions and are myelinated by oligodendrocytes; the other 10 cranial nerves are "peripheral" and are myelinated by Schwann cells
Perikarya: neuronal cell bodies
Stria of Gennari: prominent horizontal layer of myelinated fibers in the visual cortex
Bergmann glia: elongated astrocytes of the cerebellum
Rosenthal fibers: intracytoplasmic hyaline structure, sometimes corkscrew shaped, found in pilocytic astrocytes
Corpora Amylacea: argyrophilic and PAS positive polyglucosan globules in the terminal processes of astrocytes

Cerebral Spinal Fluid

CSF produced in the choroid plexus which projects into the lateral, third, and fourth ventricles
Lateral ventricles connect to third ventricle via the foramina of Monro, which then connects to the fourth ventricle via the aqueduct of Sylvius
There is no lymphatic system in the brain to drain excess fluid; therefore, the brain is very sensitive to edema
Hydrocephalus: increase in the volume of the ventricles and thus of the CSF

Meninges

- Dura mater (pachymeninx): mostly collagenous; reduplicated in the midline to form the falx cerebri and rostral to the cerebellum to form the tentorium cerebelli; contain branches of the middle meningeal artery
- Arachnoid: delicate web-like membrane
- Pia mater: lies along surface of brain, tightly adherent to it

Cells

- Neurons: large nuclei, prominent nucleolus; neurofilaments
- Astrocytes: large, vesicular nuclei; cytoplasm usually not evident unless become reactive; markedly GFAP positive
- Oligodendrocytes: small round nuclei usually with surrounding halo (artifact) giving a fried egg appearance
- Microglia: elongated cigar-shaped nuclei
- Ependyma: epithelial layer lining ventricles; S-100 positive; GFAP negative

SPINAL CORD

Dorsal portion predominantly sensory
Ventral portion predominantly motor
Central canal becomes discontinuous by puberty
Tapered at caudal end to form the filum terminale, a fibrous extension containing nests of glia and ependymal cells; adipose tissue may be present in 10% of individuals

Embryology

Arises in the midline of the developing embryo as the primitive neural groove, which bulges up and fuses in the mid dorsal region (neural tube); this tube fuses rostral to caudal
Cylindrical neural tube develops focal constrictions to form four segments:

- Prosencephalon (forebrain):
  - Diencephalon: thalamus and hypothalamus
  - Telencephalon: lateral ventricles and cortex
- Mesencephalon (midbrain): aqueduct of Sylvius
- Rhombencephalon (hindbrain):
  - Metencephalon: pons and cerebellum
  - Myelencephalon: medulla
- Spinal Cord

Inflammatory / Non-Neoplastic Disorders

Developmental Defects

Ectopia

Nodular, mature; predominantly astrocytic
Most common site: nasal "glioma"
Can also see neural tissue in occipital bone
Other tissue may also be ectopic to the CNS:
Thyroid tissue in sellar region
Salivary gland in cerebellopontine angle

NEURAL TUBE DEFECTS

Any failure of closure of midline structures over the neural tube: ranges from occult spina bifida to craniorachischisis (completely open neural tube)

Anencephaly

1/1000 live births

Encephalocele

1/8000 live births
Usually occipital

Spina Bifida

1/800 live births; F>M
Occult spina bifida is present in 1-25% of the population
70% are lumbosacral; cervical-occipital is second most common site
Associated malformations include hydrocephalus (25%) and Arnold-Chiari malformation (elongation of the brainstem and cerebellum)
Classification of defect is based upon where the defect is and what is contained in the resulting "sac"

Meningocele	Meningomyelocele
Syringomyelocele	Lipomeningomyelocele
Myelocele	Encephalocele

91% have motor disability
50-70% have urinary or anal sphincter involvement
35% of patients survive

Cerebrovascular Disease

Accounts for ~50% of patients on neurology service
Mostly a disease of the elderly (>60yrs old)

Cerebrovascular Accident

Causes:		
	Atherosclerosis	40-60%
	Embolism	15-40%
	Intracerebral Hemorrhage	10-15%
	Subarachnoid Hemorrhage	10-15%
	Others	5-20%

Brain has an absolute requirement for oxygen; following cessation of blood flow:

11 seconds	Unconscious
40 seconds	EEG flat

3 minutes	Glucose gone; irreversible
5-7 minutes	Tissue ATP gone

- Different cell types show different sensitivities to ischemia; in order: neurons, oligodendrocytes, astrocytes, microglial cells, vessels
- Different regions of the brain show different sensitivities to global ischemia; in order: hippocampus (Sommer sector [CA-I], CA-II spared), external pyramidal layer (layer 3) of the neocortex, Purkinje cells of the cerebellum, inferior olivary neurons, subthalamic nucleus
- Histologic evidence of neuronal anoxic/ischemic injury: acidophilic degeneration, glassy cytoplasm, loss of Nissel substance, hyperchromatic nuclei, shrinkage of neuron with increase in peri-neuronal space

Infarct
- May be hemorrhagic or anemic, depending upon whether or not blood flow is re-established

Gross:	6 hrs	No changes
	8-48 hrs	Swelling
	>48 hrs	Mushy, friable
	2nd week	Liquefaction
	≥3 weeks	Cavitation (1cc/3 months)
Micro:	8-12 hrs	Classical ischemic changes
	12-48 hrs	Macrophages appear
	48 hrs	Macrophages become foamy
	3rd day	Astrocytes proliferate, become gemistocytic; nuclei enlarge
	7th day	Capillary walls thicken
	>30 days	Only astrocytes remain

Hematoma

Epidural (Extradural) Hematoma
- Between the skull and the dura
- Localized; usually large angle edges
- Bleeding is from torn meningeal arteries, usually associated with a skull fracture
- Patient typically recovers from initial unconsciousness, but over the next few hours regresses into a deepening coma
- High pressure bleed; must be surgically drained

Subdural Hematoma
- Between the dura and arachnoid space
- Sharp angle borders as extends outward over a larger area
- Bleeding from bridging veins; occurs at sites where brain is able to move (often contra coup)
- Slower, low pressure bleed: patient shows a gradual decline in their level of consciousness over days to weeks
- May be self contained; clot eventually reabsorbed leaving a yellow-stained "membrane"

Subarachnoid Hemorrhages
- Generally NOT related to trauma but rather to vascular insult: hypertension, aneurysm, embolus, infarct
- [See below]

Vascular / Hemorrhagic Diseases

Hypertensive Hemorrhage
- >60% occur in the basal ganglia
- Other common locations include thalamus, pons, and midbrain

Durét Hemorrhage
- Secondary brainstem hemorrhage, usually due to a supratentorial mass
- Results in punctate hemorrhages throughout the tectum of the pons
- Basilar artery is anchored at the tentorium. As the brainstem is forced downward by a mass lesion, pulls on the penetrating arteries, inducing ischemia; when restore blood flow, get multiple small hemorrhages into the brainstem

Saccular (Berry) Aneurysm
- [See also Vessels Outline]
- Most commonly at branch point between anterior and middle cerebral arteries; caused by a defect in the vessel wall
- Aneurysms are present in 5% or adults (25% are multiple, 20% are bilateral)
- Only 12/100,000 rupture per year; 30% mortality within the first 24 hrs; 60% within the first 30 days

Arteriovenous Malformation
- 1.5% of intracranial "tumors"
- Most common location is distribution of the middle cerebral artery
- Presentation: hemorrhage (86%), seizure (8%), headache (6%)
- Irregular thickening of the vessel walls; elastin stain shows duplication or triplication of the internal elastic lamina alternating with areas lacking any elastic lamina

Infectious Lesions

- Major routes of infection:
  - direct extension from neighboring structures
  - retrograde extension from other neural structures
  - hematogenous dissemination
  - inoculation following trauma or iatrogenic

Meningitis
- Inflammation predominantly limited to the meninges
- Acute pyogenic: E. coli (neonates), H. influenza (children), N. meningitidis (adolescents), pneumococcus (very young and very old)
- Acute lymphocytic: usually viral
- Chronic: TB, syphilis, cryptococcus

Cerebritis
- Focal inflammation of the brain parenchyma
- Usually bacterial, less commonly fungal or parasitic
- Some pathologists to not distinguish this from encephalitis

Brain Abscess
- Arise in necrosis resulting from cerebritis or encephalitis, often 1-2 weeks following infarction
- Most commonly streptococci, E. coli, Staph. aureus (trauma), Bacteriodes, fungi (especially in immunocompromised)

Encephalitis
- Diffuse inflammation, often involving the meninges as well (meningoencephalitis)
- Usually viral or rickettsial
- Herpes Simples: temporal or frontal lobes; early lesions mimic ischemia; later perivascular chronic inflammation, focal necrosis, hemorrhage
- Post-infectious: following Varicella or influenza; prominent demyelination
- Herpes Zoster: predominantly unilateral vasculopathy causing contralateral hemiparesis
- Subacute Sclerosing Panencephalitis: measles virus
- AIDS: markedly varied histologic picture, including encephalitis, leukoencephalopathy, vacuolar myelopathy, toxoplasmosis, Candida, cryptococcus
- Transmissible Subacute Spongiform Encephalopathy: i.e., Creutzfeldt-Jakob disease; see below under Dementia

Progressive Multifocal Leukoencephalopathy
- Multifocal destruction of oligodendrocytes resulting in demyelination with minimal inflammation and minimal damage to axons
- Caused by DNA papovavirs, usually JC virus
- Occurs in setting of underlying disease: AIDS, CLL, carcinoma, TB, SLE, s/p transplant
- Ground glass oligodendroglial nuclei (filled with virions), large pleomorphic astrocytes, perivascular chronic inflammation

Dementias

Alzheimer's Disease
- Accounts for 50% of dementia in pure form, 70-75% in combination with other forms

- Marked atrophy, especially of the frontal lobes
- Cell loss, senile plaques, neurofibrillary tangles, granulovacuolar degeneration, amyloid angiopathy
- Hirano body: eosinophilic, football shaped structure; part of normal aging, but more numerous in Alzheimer's disease
- NOTE: neurofibrillary tangles are also seen with postneoplastic parkinsonism, progressive supranuclear palsy, and Down's syndrome

Multi-infarct dementia
- Pure multi-infarct dementia accounts for only 15% of all dementias, but probably plays a significant role in 30%

Pick's Disease
- Rare; peak incidence at 60yrs of age, M=F; familial cases are autosomal dominant
- Profound dementia which shows a time course similar to Alzheimer's Disease
- Sharply demarcated focal atrophy of the anterior frontal and temporal lobes
- Pick Bodies: subtle, swollen, filamentous, eosinophilic bodies in the cytoplasm of neurons

Creutzfeldt-Jakob Disease
- AKA: Transmissible Subacute Spongiform Encephalopathy
- Related to "Kuru" and the sheep model "Scrapie"
- Rapidly progressive dementia, ataxia, myoclonus; specific clinical picture depends upon which portions of the brain are involved
- 85% of cases are sporadic; 10-15% are familial (autosomal dominant); 5% are iatrogenic
- CSF usually normal
- EEG shows characteristic changes in 2/3's of patients: generalized bilateral short interval periodic sharp wave complexes
- Vacuolar spongiform degeneration of the neuronal processes (neuropil) with neuronal loss and glial proliferation
- Amyloid plaques composed of PrP (prion protein) seen
- Infectious agent is not clearly molecularly defined; the term "Prion" for "proteinaceous infectious agent" has been coined by advocates of the theory that nucleic acid is not needed for transmissibility; others favoring a more traditional agent refer to it as a "slow virus"
- The prion protein gene is localized on chromosome 20p; the gene product in normal individuals is 33-35kD and is completely digested by proteinase K; in affected patients, the gene product (PrP 33-35sc) is degraded only to a 27-30kD protein by proteinase K digestion, and this smaller protein can polymerize into rods with amyloid features; in the disease, this product is what accumulates in and around neurons
- Mutations in the prion protein gene have been linked to familial forms of this disease
- Formalin does not inactivate infectivity; however, treating formalin fixed material with >90% formic acid does inactivate it
- Always fatal, usually within six months

Parkinsonism

- Expressionless facies, pill-rolling tremor, rigidity, slowed voluntary movements
- Can be caused by a number of agents, including adverse drug reactions and postencephalitic

Parkinson's Disease
- Idiopathic form or Parkinsonism
- Prevalence: 1-2/1000; most common in 50-60 yr old range
- Lewy bodies: round, concentrically laminated, pale eosinophilic cytoplasmic inclusion
- Loss of pigmented neurons from the substantia nigra, with pigment in macrophages and a reactive astrocytosis

Multiple Sclerosis

- Onset usually in 20-40's; slightly more common in women
- Relapsing episodes of paresthesias, visual disturbances, incoordination
- Genetic susceptibility: 25% concordance among monozygotic twins
- May have an infectious etiology (?viral)
- Multiple subtypes: Charcot (classical), Marburg (acute), Schilder (diffuse sclerosis), Balo (concentric), Devic (neuromelitis optica)
- Tan gray plaques of demyelination in the white matter, typically just off the lateral angle of the ventricles

Primarily Motor Disorders

Amyotrophic Lateral Sclerosis (ALS)
- Disease linked to chromosome 21; 10% of cases are autosomal dominant
- Lower motor neuron and upper motor neuron loss; little if any sensory deficits
- Weakness of the extremities (pyramidal tract involvement), muscle atrophy (hands first), labioglossolaryngeal paralysis (bulbar disturbances)
- On exam, see fasciculations (rapid fine repetitive spontaneous movements of a part of a muscle; manifestation of denervation hypersensitivity, i.e., upper motor neuron lesion), exaggerated deep tendon reflexes
- Histology: pyknosis, swelling, and loss of motor neurons; demyelination in the white matter
- Median survival: 3yrs (1.5 yrs with bulbar involvement)

Huntington's Disease
- Autosomal dominant inheritance (chromosome 4p16.3) with complete penetrance
- Symptoms appear at ~35-40yrs of age; progress ~10-15 yrs to death
- Chorea, psychiatric changes (promiscuousness, violence, sociopathic behavior, depression); later confusion, memory deficits, dementia
- Juvenile form: rigidity, seizures, dementia
- Marked primary atrophy of the caudate nuclei bilaterally; may involve the putamen
- Large neurons remain, but all of the small ones are gone
- Gene encodes a 348kD protein of unknown function
- Terminal CAG repeats in the gene; the more repeats, the earlier the presentation

Werdnig-Hoffman Disease
- Autosomal recessive
- "Floppy infant syndrome"
- Rapidly progressive muscle weakness secondary to loss of lower motor neurons from anterior horns of the spinal cord

Leukodystrophies

- Abnormalities of myelin metabolism leading to ineffective myelination and subsequent demyelination
- Most are autosomal recessive enzyme defects

Metachromatic Leukodystrophy
- Deficiency of cerebroside sulfatase
- Leads to accumulation of sulfatides in and around neurons
- Progressive motor impairment

Krabbe's Disease
- AKA: Globoid cell leukodystrophy
- Onset usually by 6 months of age: rigidity, decreased alertness; fatal by age 2
- Deficiency of galactocerebroside B galactosidase
- Demyelination, plus multinucleated histiocytes (Globoid cells) around blood vessels

Adrenoleukodystrophy
- X-linked recessive
- Accumulation of long chain fatty acids

Patients have a concurrent adrenal insufficiency
Juvenile form: boys ~10yrs old; large plaques of demyelination; fatal within 3 yrs
Adult form: slowly developing spastic paralysis, cerebellar ataxia, peripheral neuropathy

Tumors of the Central Nervous System

GENERAL

15% CNS tumors are in the spinal cord, 85% in the brain
Metastatic tumors are usually extradural
Account for 2% of all cancer deaths, but ~20% of cancer deaths prior to age 15 (second only to leukemias)
Most are idiopathic; radio waves from cellular phones have been implicated by some
CNS tumors seen with von Recklinghausen's, von Hippel-Lindau, Turcot's familial polyposis, tuberous sclerosis, and the multiple nevoid basal cell carcinoma syndromes
70% of intracranial tumors are supratentorial in adults (most commonly astrocytomas (40-50%), metastases, meningiomas(~15%)), but 70% are infratentorial in children (most commonly astrocytoma (45%), medulloblastoma, (40%) ependymoma, and craniopharyngioma)
Even "benign" tumors can be lethal; lethality more commonly due to compression and herniation rather than actual destruction of brain tissue by the tumor itself
Rarely metastasize out of CNS

Gliomas

Most common type - account for 50% of all CNS tumors

Glioblastoma Multiforme

Account for more than half of the gliomas
Originally used to represent grade IV (or III) astrocytoma, but often so poorly differentiated that no astrocytic features persist
Most commonly occur in cerebrum, usually >40yrs of age
Key distinguishing feature from lower grade lesions is necrosis
Other characteristic histologic features include peripheral pseudopalisading of tumor cells around necrosis, multinucleated giant cells, gemistocytes, glomeruloid endothelial cell proliferation, infiltrative growth pattern
Tend to evolve toward small cell malignancy
Median survival decreases with patient age, but is very poor (without treatment, median survival ~2 weeks)
[See discussion of Grading under Astrocytoma]

Gliosarcoma

Rare tumor; occurs in ~2% of glioblastomas
Glioblastoma with sarcomatous changes, most commonly arising from fibroblasts of the hyperplastic blood vessels
Sarcomatous component most common MFH-like

Astrocytoma

Account for 20% of gliomas
Unencapsulated; infiltrate surrounding parenchyma; margins can be very difficult to define, even microscopically
With time, astrocytomas tend to progress in grade

Grading

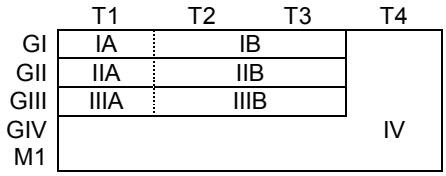
Three and four tiered grading systems exist; in general, grades I and II of a 4 tiered system are grouped into grade I in the three tiered system
3 tiered (World Health Organization): astrocytoma, anaplastic astrocytoma, glioblastoma
4 tiered: astrocytoma, cellular astrocytoma, anaplastic astrocytoma, glioblastoma
Prognosis correlates well with grade (median survival with radiation therapy):

Grade	Overall	<50 yrs	>50 yrs
I	[50% survive]	-	-
II	4 yrs	5.5 yrs	0.5 yrs
III	1.6 yrs	2.5 yrs	0.7 yrs
IV	0.7 yrs	1 yr	0.5 yrs

Frequency of mitoses, vascular proliferation, and cellular atypia increase with grade; necrosis needed to advance to highest grade

Staging

Supratentorial		Infratentorial	
T1	≤5cm, unilateral	T1	≤3cm, unilateral
T2	>5cm, unilateral	T2	>3cm, unilateral
T3	Invades ventricular system		
T4	Crosses midline or invades infra- (supra-) tentorially		



SPECIAL TYPES

Cerebellar Astrocytoma

Cells are fibrillary and fusiform, resembling reactive astrocytes
Better prognosis than cerebral astrocytomas

Juvenile Pilocytic Astrocytoma

Occur usually in children surrounding the third ventricle or cerebellum
Slow growing, usually well circumscribed
Tight clustering of astrocytes around blood vessels, with loose infiltration of tumor cells into surrounding tissue
Dual cell population: spindled, "pilocytic" cells admixed with microcystic areas
Most are low grade
Prognosis is good unless the brainstem is involved

Gemistocytic Astrocytoma

Occur at an earlier age, on the average
Most will progress to glioblastoma multiforme within 5 yrs of presentation
Poor survival (mean=2.5 years)

Diffuse Astrocytoma

AKA: Gliomatosis cerebri
Diffuse enlargement without grossly or microscopically identifiable tumor margins
Perineuronal tumor cell aggregates
Relatively poor survival (though not as bad as gemistocytic astrocytoma)

Subependymal Giant Cell Astrocytoma

Largely intraventricular lesion seen in tuberous sclerosis

Oligodendroglioma

- Comprise ~5% of gliomas; more common in adults
- Classically, monotonous proliferation of small cells with central round nuclei and a clear cytoplasm (artifact) creating a "fried egg" appearance; calcifications common
- Small thin-walled vessels may separate tumor into lobules creating a "chicken wire" appearance
- Although more aggressive lesions tend to show greater cellular atypia, mitoses, vascular hyperplasia, or necrosis, there are no reliable histologic features upon which a prediction of prognosis can be made

Ependymoma

- Account for ~5% of gliomas
- Most commonly seen in children and young adults
- Most common tumor occurring in the spinal cord
- Arise from ependymal cells in spinal cord (central canal, filum terminale) or the ventricular system of the brain
- Grow in a perivascular pattern, with uniform elongated cells aligned perpendicular to vessels with their nuclei polarized away from the vessels; may also form small tubules or rosettes with a central lumen
- EM reveals basal bodies and cilia
- Seeding through CSF can occur; malignant forms can also occur

Myxopapillary Ependymoma

- Variant occurring in the filum terminale of the spinal cord
- Papillae with core composed of a dilated vessel; grow in a myxoid stroma
- GFAP positive
- Generally very good prognosis
- Differential diagnosis: chordoma

Subependymoma

- Multiple small nodules in the wall of ventricles
- Almost always asymptomatic; usually an incidental finding

Choroid Plexus Papilloma

- Constitute <2% of gliomas
- Most commonly seen in children and young adults
- Most commonly arise in lateral ventricles or fourth ventricle
- Hemorrhagic, friable mass

Mixed Gliomas

- Most commonly astrocytoma and oligodendroglioma
- Less commonly oligodendroglioma and ependymoma

Other Primary CNS Tumors

Neuronal and Glio-Neuronal Tumors

Ganglioneuroma

- AKA: Gangliocytoma
- Tumor of differentiating neuronal cells with reactive glial stroma

Ganglioglioma

- Mixture of both neoplastic neural and glial elements

Central Neurocytoma

- AKA: Central neuroblastoma
- Arise in paraventricular area, often forming an intraventricular mass; usually younger patients
- Geographic clusters of small blue cells separated by perivascular zones of fibrillar stroma
- Histology similar to oligodendroglioma but with fibrillar areas
- Very good prognosis

Medulloblastoma

- Located in midline or lateral cerebellum, most frequently in children (5-10 yrs) with a second peak in 20's
- Small blue cell tumor composed of undifferentiated cells in sheets, occasionally aggregating into Homer-Wright rosettes without a lumen
- N-myc gene product overexpressed in ~30% (gene is NOT amplified); associated with a poorer prognosis
- Malignant; 5 yr survival is 40%

Desmoplastic Medulloblastoma

- Invade the meninges and induce a fibroblastic proliferation

Meningiomas

- Account for ~20% of all CNS tumors (10-15% of intracranial tumors, 25% of spinal cord tumors)
- Usually occur in adults, most commonly in women
- Usually attached to the dura, encapsulated, pushing margins
- Tumor cells are spindled but plump and at least focally arranged in circular whirls which may calcify and form psammoma bodies
- Tumor cells are EMA and vimentin positive
- 3 major histologic divisions: Syncytial (meningotheliomatous), Fibroblastic, Transitional (includes psammomatous)
- Most recurrences due to incomplete excision
- Angioblastic and papillary variants have worst prognosis

Atypical Meningioma

- Cellular lesion with numerous mitoses and micronecrosis

Malignant Meningioma

- Malignant cytology and presence of cerebral invasion

Tumors of Ancillary Structures

Schwannoma (Neurilemoma)

- Account for 10% of intracranial tumors, 25% of spinal cord tumors
- Arise from cranial and spinal nerve roots, predominantly sensory nerves: thoracic for spinal cord, cranial nerves VIII (acoustic) and V (trigeminal) for head
- Encapsulated eccentric enlargement of nerve root with cellular areas (Antoni A) alternating with more myxoid areas (Antoni B). Reticular fibers surround each individual tumor cell

Neurofibroma

- Rare except for patients with von Recklinghausen's disease
- Diffuse, concentric enlargement of the nerve; enlargement often extends into nerve branches (plexiform neurofibroma)

Craniopharyngioma

- 2-3% of CNS tumors; most commonly child or young adult
- Circumscribed, slow growing tumors arising at base of brain; generally does not invade brain, but reactive astrocytic proliferation often present
- Epithelial in origin: clusters of squamous cells in pituitary stalk (Rathke pouch remnant)
- Thick brown fluid, keratin and cholesterol in cysts surrounded by and containing nests of epithelial cells which are columnar at periphery and more squamoid toward center; calcifications common
- Rupture of cysts or escape of contents induces a vigorous inflammatory response
- Benign tumor, but survival (overall ~70%) related to ability to completely remove surgically; will usually recur if not completely excised

Hemangioblastoma

- 2-3 % of CNS tumors; most commonly 20-50 yrs of age, especially in association with von Hippel Lindau syndrome
- Cerebellum most common site; also see in spinal cord

Thin walled vessels anastomosing within a "stroma" composed of plump oval to polygonal cells of uncertain histogenesis
Good prognosis

Pituitary Adenoma
[See Endocrine Handout]

Hematopoietic Tumors
Lymphomas may be primary to the CNS; 1% of CNS tumors; 1% of non-Hodgkin's lymphomas; increased incidence in setting of immunosuppression
Usually B-Cell, most commonly diffuse large cell type

Pineal Gland Tumors

Germ Cell Tumors
Most commonly in males near pineal gland or base of brain
Seminoma (dysgerminoma) most common type
Used to be referred to as "Pinealomas"

Pinealoma
Rare
Tumor of pineal parenchymal cell

Metastases

~20% of all CNS tumors; usually multiple
Most common primary sites: lung, breast
Favored metastatic site for some less common tumors: renal cell carcinoma, choriocarcinoma, melanoma

SYNDROMES

Addison's disease: primary chronic adrenocortical insufficiency, with weakness, fatigability, anorexia, weight loss, and hypotension

Adrenogenital: group of disorders caused by adrenocortical hyperplasia: masculinization in women; feminization in men; precocious puberty in children

Agammaglobulinemia of Bruton: X-linked primary immunodeficiency syndrome with defective B-Cell maturation and near total absence of Ig's in serum

Alagille's: autosomal dominant; jaundice due to progressive loss of bile ducts, vertebral anomalies, hypogonadism, pulmonic stenosis

Albright's: polyostotic fibrous dysplasia with skin pigmentation, endocrine dysfunction, and precocious puberty

Arthus reaction: localized form of type III (immune complex mediated) hypersensitivity reaction

Ataxia-Telangiectasia: autosomal recessive cerebellar ataxia and telangiectasias resulting from defective repair of X-ray damage leading to chromosome instability; patients prone to develop lymphoma, leukemia, gastric carcinoma

Beckwith-Wiedemann: Macroglosia, omphalocele, hemihypertrophy, and/or visceromegaly; also see adrenal cytomegaly and islet hyperplasia; cancer develops in 5%, usually Wilms' tumor; association with 11p15 duplication

Bloom's: Spontaneous chromatid breakage; leukemia, GI carcinoma

Caplan's: development of pulmonary rheumatoid nodules in a background of progressive massive fibrosis

Carcinoid: combination of symptoms produced by serotonin release from carcinoid tumors which have metastasized to the liver: mottled blushing, angiomas of the skin, acquired pulmonary and tricuspid stenosis, diarrhea, bronchial spasm, mental aberration

Caroli's disease: communicating cavernous biliary ectasia; may be seen in conjunction with congenital hepatic fibrosis

Chediak-Higashi: several defects in leukocytes, including impaired chemotaxis; autosomal recessive

Churg-Strauss: variant of polyarteritis nodosum associated with bronchial asthma, pulmonary vessel involvement, and granulomatous inflammation

Conn's: primary hyperaldosteronism due to an adrenocortical adenoma

Cowden's: multiple non-Peutz-Jegher's colonic hamartomatous polyps with facial trichilemomas and oral mucosal papillomas

CREST: calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia: a limited form of scleroderma

Cri du Chat: chromosome 5p-; see Congenital disorders

Crigler-Najjar: impaired conjugation of bilirubin by the liver, leading to an unconjugated hyperbilirubinemia

Cronkhite-Canada Syndrome: Gastrointestinal polyposis, alopecia, hyperpigmentation, and dystrophic changes in fingernails and toenails

Cushing's: increased adrenocortical secretion of cortisol due to elevated ACTH levels; moon facies, acne, abdominal striae, hypertension, amenorrhea and hirsutism; when associated with pituitary adenoma, called Cushing's disease

DiGeorge's: Selective T-Cell immunodeficiency resulting from failure of development of the third and fourth pharyngeal pouches (thymus, parathyroids, C-cells of thyroid)

DiGuglielmo's: erythromyeloblastic leukemia (M6 AML)

Down's: Trisomy 21

Dubin-Johnson: autosomal recessive defect in bile canalicular transport producing a conjugated hyperbilirubinemia and a black liver

Edward's: Trisomy 18

Ehlers-Danlos: heterogeneous group of disorders of collagen synthesis/structure

Eisenmenger's: right ventricular hypertrophy and pulmonary hypertension caused by a left to right shunt which results in reversal of the flow through the shunt (right to left)

Fabry's disease: X-linked lysosomal storage disease (sphigolipidosis)

Fanconi's Anemia: autosomal recessive chromosomal breakage; associated findings: renal hypoplasia, absent or hypoplastic thumbs or radii, hyperpigmentation of skin, microcephaly; patients at risk for ANLL, SCC, Hepatoma

Fitz-Hugh-Curtis: stabbing right upper quadrant pain secondary to perihepatitis caused by spread of untreated gonorrheal cervicitis into the peritoneum

Gardner's: autosomal dominant; colonic polyposis, osteomas, keratinous cysts of the skin, soft tissue fibromatosis; high risk of colon cancer

Gaucher's disease: autosomal recessive lysosomal storage disease (sphigolipidosis)

Gilbert's Syndrome: constitutional hepatic dysfunction; decreased uptake of bilirubin by the liver; produces unconjugated hyperbilirubinemia

Goodpasture's: anti-basement membrane antibody mediated destruction of glomerular and pulmonary basement membranes leading to a rapidly progressive glomerulonephritis and a necrotizing, hemorrhagic pneumonia

Gorham's disease: AKA: massive osteolysis: reabsorption of whole or multiple bones and filling of residual spaces with heavily vascularized fibrous tissue

Hansen's disease: leprosy

HELLP: combination of hemolysis, elevated liver function tests, and low platelets; seen in severe toxemia of pregnancy

Horton's disease: Temporal (giant cell) arteritis

Hunter's: Type II mucopolysaccharidosis; X-linked recessive

Hurler's: Type I mucopolysaccharidosis

Kartaganer's: congenital absence of cilia leading to situs inversus, chronic sinusitis, bronchiectasis

Kasabach-Merritt: thrombocytopenia complicating a giant hemangioma

Klinefelter's: XXY

Krabbe's disease: AKA globoid cell leukodystrophy; lysosomal storage disease (sphigolipidosis)

Löeffler's: eosinophilic pneumonia with granulomas; usually self limited

Maffucci's: AKA dyschondroplasia with vascular hamartomas: multiple hemangiomas and enchondromas

Marfan's: autosomal dominant defect in connective tissue integrity

McArdle's: Type V glycogenosis

Menke's: X-linked recessive disorder of intestinal copper absorption, needed by lysyl-oxidase, resulting in changes in aortic collagen and elastin

Mikulicz's: originally used to refer to what is now called Sjögren's syndrome, not used to refer to any swelling of the salivary gland and lacrimal gland.

Milroy's Disease: resembles lymphedema praecox but present from birth and inherited as Mendelian trait

Morquio's: Type IV mucopolysaccharidosis
Nelson's: adenomatous enlargement of the pituitary with a carcinomatous histologic picture occurring in patients with unresectable pituitary tumor treated with bilateral adrenalectomy
Nezelof's: absent thymus and cell mediated immunity (like DiGeorge's) but with normal parathyroids
Niemann-Pick disease: autosomal recessive lysosomal storage disease with zebra bodies
Ollier's disease: multiple unilateral enchondromas; often associated with ovarian sex-cord stromal tumors
Osler-Weber-Rendu: autosomal dominant hereditary hemorrhagic telangiectasias of the face and oral mucosa
Parinaud's: AKA oculoglandular syndrome; swelling of the eye, jaw, and high cervical LN's
Peutz-Jegher's: autosomal dominant; multiple gastrointestinal hamartomatous polyps, melanotic mucosal and cutaneous pigmentation around the lips, mouth, face, genitalia, palmar surfaces of hands
Plummer Vinson syndrome: microcytic hypochromic anemia, atrophic glossitis, esophageal webs
Pompe's disease: glycogenosis II, a lysosomal storage disease
Pott's disease: tuberculous spondylitis
Ramsay Hunt: involvement of the geniculate ganglion by Herpes Zoster, resulting in facial paralysis
Reiter's: triad of conjunctivitis, urethritis, and arthritis
Reye's: fatty degeneration of the liver and encephalopathy seen in children treated with aspirin for a viral illness
Reynaud's disease: Reynaud's phenomenon occurring in the absence of an anatomic lesion in the vessel walls
Reynaud's phenomenon: pain and color changes in the skin, usually of distal extremities, in response to cold
Sanfilippo: Type III mucopolysaccharidosis
Schmidt's: Type II autoimmune Addison's disease
Sheehan's: post-partum pituitary infarction and necrosis
Sicca: Sjögren's syndrome occurring without another autoimmune disorder (like rheumatoid arthritis)
Stein-Leventhal: polycystic ovaries, amenorrhea, and sterility
Steven's-Johnson : severe form of erythema multiforme with mucosal involvement, conjunctivitis, high fever
Sturge-Weber: port wine stain of face in distribution of trigeminal nerve associated with ipsilateral vascular malformations of the leptomeninges and/or the retina
Tay-Sachs disease: lysosomal storage disease (sphigolipidosis)
Trousseau's: migratory thrombophlebitis seen in patients with a malignancy; first described for pancreatic carcinoma
Turcot's: autosomal recessive; colonic adenomatous polyps and glioblastomas of the CNS
Turner's: XO
Vanishing bile duct: irreversible loss of bile ducts due to a destructive cholangitis within 100 days following liver transplantation
von Gierke's: Type I glycogenosis
von Hippel-Lindau: cavernous hemangioblastomas of cerebellum or brain stem, hemangiomas and cysts of pancreas, liver, kidneys; autosomal dominant
von Recklinghausen's disease: autosomal dominant disorder with multiple plexiform neurofibromas, cafe au lait macules, and Lisch nodules
Waterhouse-Friderichsen: hemorrhagic destruction of the adrenals, usually secondary to meningococcemia
Werdnig-Hoffman disease: Infantile Spinal Muscular Atrophy; autosomal recessive congenital hypotonia due to absence/loss of lower motor neurons from the anterior horns of the spinal cord
Wiskott-Aldrich: X-linked recessive immunodeficiency of T-Cells associated with thrombocytopenia and eczema
Zollinger-Ellison: gastric hyperplasia secondary to a gastrin secreting tumor

BODIES

Acidophil bodies: see Councilman bodies
Adria cell: cardiac myocyte which has lost its cross-striations and myofilaments secondary to Adriamycin toxicity
Aschoff bodies: foci of fibrinoid necrosis within the myocardium of a patient with acute rheumatic fever
Asteroid bodies: acidophilic, stellate inclusions in giant cells in sarcoidosis and berylliosis
Auer Rods: red-rod shaped lysosomes (abnormal) seen in malignant cells of predominantly M3 acute myelogenous leukemia
Barr Bodies: inactivated X chromosome - dark staining mass in contact with the nuclear membrane
Birbeck granules: "Tennis racket" shaped granules in cytoplasm of Langerhans cells (histiocytosis X) with trilaminar "handle"
Blue-Blobs: atrophy in Pap-smears
Blue bodies: laminated PAS+ iron containing bodies in alveolar macrophages of desquamative interstitial pneumonia
Call-Exner bodies: small gland like "follicles" filled with acidophilic material often seen in ovarian granulosa cell tumors
Caterpillar cells: large multinucleated giant cells with lengthwise chromatin clumping in nucleus; appear owl eyed on cross section; seen in heart in acute rheumatic fever
Charcot-Leyden crystals: crystals shaped like double pyramids; found in sputum of asthma patients; made by eosinophils
Councilman Bodies: apoptotic, eosinophilic hepatocytes extruded into the sinuses
Corpora Amylacea: argyrophilic and PAS positive polyglucosan globules in terminal processes of astrocytes
Corpora Arantii: small fibrous nodules at the centers of the semilunar valve cusps along the lines of closure
Cowdry type A inclusions: acidophilic intranuclear inclusion separated from the nuclear membrane by an artifactual cleft - typical of Herpes infected cells
Curschmann's spirals: twisted mass of mucus seen in sputum of patients with asthma
Donovan body: intracellular bacillus (Calymmatobacterium donovani) seen in histiocytes in the genital skin of patients affected with granuloma inguinale
Dutcher bodies: "intranuclear" inclusions of immunoglobulin in plasmacytoid cells

Faggot cells: malignant promyelocytes of M3 AML containing numerous Auer rods like "sticks in a fireplace"
Gandy-Gamna bodies: calcium and hemosiderin deposits in the spleen: seen in setting of increased hemolysis
Glomus bodies: regulated arteriovenous anastomoses in the skin which play a role in thermoregulation
Guarneri bodies: Epidermal cells with eosinophilic cytoplasmic inclusions in skin of patients with smallpox
Hassall's corpuscles: concentric aggregates of keratinized epithelial cells and keratin in the medulla of the thymus
Heinz bodies: clumps of precipitated oxidized hemoglobin in the cytoplasm of red cells
Hematoxylin bodies: see LE bodies
Hirano body: eosinophilic, football shaped inclusion seen in neurons of the brain; part of normal aging, but more numerous in Alzheimer's disease
Hutchinson's teeth: inflammatory destruction of the teeth seen in tertiary syphilis
Kamino bodies: Intraepidermal hyaline globules seen in a Spitz nevus
Kayser-Fleischer rings: rings of discoloration on cornea of patients with Wilson's disease
Koplik's Spots: spotty lesions that blister and ulcerate deep in the cheek mucosa; diagnostic for measles
Lambl's excrescences: small fibrin vegetations overlying sites of endothelial damage of flow side of cardiac valves
LE bodies (AKA hematoxylin bodies): nuclei of damaged cells with bound anti-nuclear antibodies which become homogeneous and loose chromatin pattern. When phagocytosed, form LE cells
Lewy bodies: round, concentrically laminated, pale eosinophilic cytoplasmic inclusions seen in neurons in Parkinson's disease
Libman-Sacks nodules: non-bacterial verrucous cardiac valve leaflet vegetations seen in SLE
Lipofuscin Granules: polymers of lipid complexed with proteins - responsible for brown atrophy
Lisch Nodules: pigmented iris hamartomas seen in patients with type I neurofibromatosis
Loose Bodies: fragments of bone or cartilage which become detached into the joint space; may continue to grow by surface apposition; centers eventually necrose and calcify
MacCallum's plaques: map-like thickening of the endocardium over myocardial lesions in acute rheumatic fever
Mallory Bodies: alcoholic hyalin - eosinophilic intracytoplasmic inclusions in hepatocytes: intermediate filaments, predominantly prekeratin
Michaelis-Gutmann bodies: partially digested bacteria, (calcified) in stroma and in cells; seen in Malakoplakia
Negri Bodies: bullet shaped cytoplasmic inclusions in neurons (especially Purkinje cells); pathognomonic for rabies infection
Nemaline Bodies: Z-bands seen by EM in degenerative skeletal muscle diseases
Neurofibrillary Tangles: microtubule-associated proteins and neurofilaments, seen in Alzheimer's disease
Physaliferous cells: very large tumor cells with bubbly vacuolated cytoplasm (some glycogen) and vesicular nuclei, seen in chordomas
Reinke crystalloid: crystals found in Leydig cells of testes: hexagonal prisms, tapered ends, moderately electron dense
Rokitansky's protuberance: central area of an ovarian mature cystic teratomas containing bone and well formed teeth
Rosenthal fibers: intracytoplasmic hyaline structure, sometimes corkscrew shaped, found in pilocytic astrocytes
Russell Bodies: cytoplasmic immunoglobulin inclusions in plasma cells or plasmacytoid cells
Schaumann bodies: concentrically laminated inclusions (up to 50μm) in giant cells seen in sarcoidosis? and berylliosis
Schiller-Duval bodies: endodermal sinuses: glomeruloid structures seen in yolk sac tumors
Smudge cell: cell with a large, ovoid nucleus filled with granular amphophilic to deeply basophilic mass and an indistinct nuclear membrane; seen in Adenovirus infected cells
Soldier's plaque: white thickening of the epicardium from a healed pericarditis
Sulfur Granules: yellow foci of Actinomyces
Sucquet-Hoyer canals: shunts of Glomus bodies, involved in thermal regulation
Verocay bodies: palisades of nuclei at the end of a fibrillar bundle in a Schwannoma (Neurilemoma)
Warthin-Finkeldey cells: multinucleated giant cells with eosinophilic nuclear and cytoplasmic inclusions found in lymphoid organs of patients with measles
Weibel-Palade bodies: Rod-shaped cytoplasmic organelles in endothelial cells containing von Willebrand factor
Zebra Bodies: palisaded lamellated membranous cytoplasmic bodies seen by EM in macrophages of patients with Niemann-Pick disease, Tay-Sachs disease, or any of the mucopolysaccharidoses
Zellballen: clusters of tumor cells surrounded by a thin fibrovascular stroma, seen in pheochromocytoma and extra-adrenal paragangliomas

REFERENCES

This following is a list of the major sources used in compiling these outlines. Additional sources such as individual lectures, journal articles, etc. have been omitted. The reader is encouraged to consult these references for additional information, photographs, or simply for a prose discussion of any of the topics covered in these outlines. The references used are by no means the only texts available on this subject. After all, pathology is pathology, and what makes one text different from another is the selection of material, the organization of that material, and the style of the presentation. The reader may find any of a number of other excellent works preferable. The selections here represent the bias imposed by my personal collection of texts and the references readily available to me during my training. I particularly recommend the Robbins text for its discussion of non-neoplastic pathology, and have found the Ackerman text invaluable for tumor pathology.

General Texts

Cotran, R., Kumar, V., and Robbins, S. Robbins Pathologic Basis of Disease, 4th edition (1989). W.B. Saunders Company, Philadelphia.

Kissane, J., editor. Anderson's Pathology, 9th edition. (1990) C.V. Mosby Company, St. Louis.

Rosai, J. Ackerman's Surgical Pathology, 7th edition (1989) C.V. Mosby Company, St. Louis.

Sternberg, S., editor. Diagnostic Surgical Pathology, 2nd edition (1994) Raven Press, New York.

Specialized Texts

Alberts, B., Bray, D., Lewis, J., Raff, M., Roberts, K., Watson, J. Molecular Biology of the Cell, second edition. (1989) Garland Publishing, Inc., New York

Beahrs, O., Henson, D., Hutter, R., and Kennedy, B., editors. The American Joint Committee on Cancer's Manual for Staging of Cancer, fourth edition (1992) J. B. Lippincott Company, Philadelphia

Enzinger, F. and Weiss, S. Soft Tissue Tumors, second edition (1988). C.V. Mosby Company, St. Louis.

Jaffee, E. Surgical Pathology of the Lymph Nodes and Related Organs (Major Problems in Pathology, 2nd edition, Volume 16). (1995). W.B. Saunders Company, Philadelphia.

Jawetz, E., Melnick, J., and Adelberg, E. Review of Medical Microbiology, 17th edition. (1987). Appleton and Lange, Norwalk

Katzenstein, A., and Askin, F. Surgical Pathology of Non-Neoplastic Lung Disease (Major Problems in Pathology, 2nd edition, Volume 13). (1990). W.B. Saunders Company, Philadelphia.

Knowles, D., editor. Neoplastic Hematopathology. (1992). Williams and Wilkins, Baltimore.

McKee, P. Pathology of the Skin with Clinical Correlations. (1989). J.B. Lippincott Company, Philadelphia.

Moore, K. The Developing Human; Clinically Oriented Embryology, 3rd edition. (1982) W.B. Saunders Company, Philadelphia.