

**UNIVERSITY OF CALIFORNIA
SAN FRANCISCO
SCHOOL OF MEDICINE
DEPARTMENT OF PATHOLOGY**

GENERAL PATHOLOGY

COURSE SYLLABUS

FOR

**PATHOLOGY 135
Physical Therapy**

FALL of 2016

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UNIVERSITY OF CALIFORNIA,
SAN FRANCISCO
DEPARTMENT OF PATHOLOGY

Mon 8AM-10AM
Tues 9 AM-10 AM

LECTURE SCHEDULE
2016
PATHOLOGY 135

<u>Lec. #</u>	<u>Date</u>	<u>Day</u>	<u>Lecturer</u>	<u>Room</u>	<u>Topic</u>
1-2	09/19	M	Sánchez	HSW303	Introduction / Cell Injury: Mechanisms and Adaptations / Acute Inflammation I
3	09/20	Tues	Sánchez	HSW300	Acute Inflammation II
4-5	09/26	M	Sánchez Sánchez	Cole Hall	Chronic Inflammation Tissue Repair: Regeneration and Healing I
6	09/27	Tues	Sánchez	Cole Hall	Tissue Repair: Regeneration and Healing II
7-8	10/03	M	Sánchez Sánchez	HSW303	Immunopathology I Immunopathology II
9	10/4	Tues	Sánchez	HSW300	Fluid and Hemodynamic Derangements I
	10/11-12	Tues	Sánchez	NO CLASSES	
10-12	10/17	M	Sánchez Sánchez Sánchez	Cole Hall	Fluid and Hemodynamic Derangements II Principles of Neoplasia I Principles of Neoplasia II 8:00-11:00 am
13	10/18	Tues	Sánchez	Cole Hall	Cardiovascular Diseases I
14	10/25	Tues	Sánchez	HSW300	Cardiovascular Diseases II
15-16	10/31	M	Sánchez Sánchez	HSW303	Respiratory Diseases I Respiratory Diseases II
17	11/01	Tues	Sánchez	Cole Hall	MIDTERM EXAM

<u>Lec. #</u>	<u>Date</u>	<u>Day</u>	<u>Lecturer</u>	<u>Room</u>	<u>Topic</u>
18-19	11/07	M	Sánchez Sánchez	Cole Hall	Kidney and Urinary Tract I Kidney and Urinary Tract II
20	11/08	Tues	Sánchez	Cole Hall	Bone and Joint Diseases I
21	11/15	Tues	Sánchez	Cole Hall	Bone and Joint Diseases II
22-23	11/21	M	Sánchez Sánchez	Cole Hall Cole Hall	Diseases of the Skin I Diseases of the Skin II
24	11/22	Tues	Sánchez	Cole Hall	Central & Peripheral Nervous System Pathology I
25-26	11/28	M	Sánchez Sánchez	Cole Hall	Central & Peripheral Nervous System Pathology II Anemia I
27	11/29	Tues	Sánchez	Cole Hall	Anemia II
28	12/06	Tues	Sánchez	Cole Hall	FINAL EXAMINATION 9-12

PATHOLOGY 135
Lecturers - Fall of 2016

Course Director: Henry C. Sánchez, M.D.

Clinical Professor of Pathology

GLOSSARY OF WORDS COMMONLY MISUSED, ABUSED, OR CONFUSING

<u>Autolysis</u>	Digestion of cells (especially dead or degenerating) by enzymes contained within them and by enzymes released from neighboring cells.
<u>Caseous</u>	Cheesy, a term descriptive of a lesion's texture, not its appearance.
<u>Clot</u>	The mass formed outside a leaking blood vessel (or after death, inside the vessel), composed of fibrin and trapped blood cells. Unlike thrombus #1, which forms in a moving blood stream, a clot does not contain platelets as a major component.
<u>Diapedesis</u>	Passage of blood cells through the intact walls of blood vessels.
<u>Edema</u>	Accumulation of excessive fluid in tissues.
<u>Embolus</u>	An embolus is an intravascular mass that is carried by the blood to a site distant from its point of origin. The relationship between an embolus and a thrombus is that emboli can arise from a dislodged thrombus. However, an embolus can be any foreign body (air, fat, or even a piece of plastic tubing).
<u>Epithelioid cell</u>	See Granuloma for definition.
<u>Exudate</u>	Material such as fluid, cells, or cellular debris that has escaped from blood vessels, usually as the result of inflammation. An exudate, in contrast to a transudate, is characterized by a high content of protein and cells, and has a higher specific gravity than a transudate.
<u>Granuloma</u>	Any one of a rather large group of focal, nodular lesions formed as part of a defensive reaction against a number of biological, chemical, or physical agents. Granulomas are characterized at some stage in their development by macrophage accumulations. Often, these phagocytes have ingested some foreign material and developed abundant cytoplasm, so that they vaguely resemble squamous cells, in which case they are called epithelioid cells. Other macrophages in a granuloma develop into multinuclear cells. Granulomas generally also contain numerous mononuclear macrophages, as well as lymphocytes and fibrous tissue. These lesions ordinarily persist in the tissue as slowly smoldering inflammations. Despite their "defensive" role, they can be very tissue-destructive and may become fibrotic, calcified, or necrotic. Morphologically, granulomas tend to be fairly typical of certain diseases, and structurally they afford valuable clues to diagnosis. However, they are not diagnostically definitive, since granuloma structure reflects both the causal agent and the immune status of the host. The granuloma of one specific disease may closely resemble that of an etiologically unrelated disorder; and in some diseases, considerable variations in granuloma morphology exist.

<u>Histiocyte</u>	See Macrophage.
<u>Hyaline</u>	Glassy, homogeneous, and translucent in appearance. Does not refer to a chemically specific substance.
<u>Inflammation</u>	The body's response to injury. Inflammation is a dynamic complex of cellular, humoral, and tissue reactions occurring in vascularized tissues.
<u>Ischemia</u>	Local decrease of O ₂ supply to tissue. Ischemia is produced by decreased perfusion and also by increased functional demand exceeding O ₂ available.
<u>Karyolysis</u>	Dissolution and destruction of nucleus. Karyolysis is microscopically visible as loss of chromatin affinity for basic dyes.
<u>Karyorrhexis</u>	Refers to the clumping of nuclear materials forming discrete balls of dense, intensely staining materials with an intact nuclear envelope.
<u>Kupffer cell</u>	See Macrophage.
<u>Lymph</u>	A clear, transparent fluid that collects in the lymphatic vessels from tissues throughout the body. Lymph consists of water, various salts and protein, leukocytes (mainly lymphocytes), and a few red blood cells. In small lymphatic vessels, its composition is very similar to that of fluid in tissue interstices.
<u>Lyse</u>	To break up, to disintegrate.
<u>Lysosome</u>	A cell organelle containing a number of acid-active hydrolytic (lytic) enzymes.
<u>Macrophage</u>	A large, mobile, phagocytic cell. During maturation, these cells reside in the bone marrow and blood as monocytes. Later, in tissue, they are called histiocytes. When they form part of the lining of liver cells, they are called Kupffer cells. They may be either mononuclear or multinuclear (probably because of cellular fusion). When multinuclear, macrophages are often called giant cells, which have a variety of descriptive names (such as "foreign body giant cells") reflecting the situation evoking their presence or the scientist who first discovered them.
<u>Mast cell</u>	A tissue cell containing coarse, basophilic, metachromatic granules ordinarily undetectable in H&E-stained sections. Among other components, it contains heparin and histamine.
<u>Monocyte</u>	A stage in the development of the macrophage, between its formation in the bone marrow and its ultimate life in the tissues. During this stage, the cell exists in the blood.

<u>Necrosis</u>	The conversion to debris of circumscribed areas of dead cells within the living body.
<u>Pus</u>	A suspension of leukocytes, debris of dead cells, and tissue elements, which has been liquefied by lytic enzymes (probably elaborated by polymorphonuclear (PMN) leukocytes). Microscopically, it appears as a host of PMN leukocytes.
<u>Thrombus</u>	A thrombus is a mass formed from the constituents of the blood within the vessels or heart during life. Unlike a clot, it is initiated by platelet activity and contains many platelets.
<u>Transudate</u>	A collection of fluid formed from blood, lymph, or tissue fluid, produced by passage through an intact epithelial or endothelial layer. In contrast to exudates, it contains a low concentration of protein and few cells.

Mechanisms Of Disease

INTRODUCTION

PATHOLOGY: A clinical subspecialty primarily concerned with diagnosis.

Anatomic Pathology: Diagnosis is made through the use of morphologic techniques, especially the gross and microscopic evaluation of tissues and organs.

Clinical Pathology (Laboratory Medicine): Diagnosis through the use of laboratory-based techniques, including biochemical assays, culture of microorganisms, etc., in the evaluation of tissues and body fluids.

Anatomic Pathology**--Surgical Pathology**

General subspecialties:

Neuropathology

Dermatopathology

Renal pathology

Transplant pathology

Pulmonary pathology

Gastrointestinal pathology, etc.

Special techniques

Immunohistochemistry

Electron microscopy

--Cytology

Exfoliative cytology

Fine needle aspiration

--Autopsy Pathology

Forensic pathology

Clinical Pathology**--Clinical Chemistry**

--Hematology

--Medical microbiology

--Blood banking

Experimental Pathology

Research in the biology of disease

PATHOLOGY: Two Departments at UCSF:

Anatomic Pathology

Laboratory Medicine

PATHOLOGY: THE COURSE

The course will provide you with a thorough understanding of anatomic pathology and survey diseases of selected organ systems. The first half of the course before the midterm will cover the mechanisms of disease, and the second half of the course will cover systemic pathology (e.g.,

cardiovascular system). The audio of each lecture and review session before each exam will be posted within 36-48 hours after the lecture or review session.

Two exams will be given. The first exam will cover the mechanisms of disease and the test is fifty multiple-choice questions and the final exam is one hundred multiple-choice questions (30% covering mechanisms of disease relating to systemic pathology and 70% covering the systemic pathology – a. etiology, b. pathogenesis, c. most common symptoms/signs, d. classic morphologic changes [gross and/or histopathology], and e. complications). 10% of the questions will involve a picture (gross or microscopic specimen), graph or diagram. Grades will be based upon the mean and standard deviation for each class (mean equals a “B” grade within +/- one standard deviation, “A” grade will be greater than 1 standard deviation, “C” grade will be 1 to 1 ½ standard deviation, “D” will be 1 ½ to 2 standard deviations, and “F” grade will be greater than 2 standard deviations. When students fail, the student will meet with the course director to plan a make-up exam and/or require remedial work.

PATHOLOGY SERVICES AT UCSF SURGICAL PATHOLOGY

Surgical Pathology is concerned with the diagnostic evaluation of solid tissue specimens removed from living patients. The tissues may have been removed as a means of treatment or simply to establish a diagnosis; in the latter case, they are known as biopsy specimens. Regulations of the Joint Commission on Hospital Accreditation, the by-laws of the University of California Hospitals, and the principles of responsible clinical practice require that all tissues removed from patients must be examined by a surgical pathologist. This is done primarily in the interests of better patient care, as a diagnosis based on thorough histological examination of isolated tissues (the tissue diagnosis) generally provides the most reliable and verifiable means of establishing a diagnosis. In addition, this process provides objective documentation to help protect against improper operations and possible medicolegal problems.

Approximately 25,000 surgical pathology specimens are examined at UCSF each year; an additional 8,000 and 3,800 are seen at San Francisco General Hospital and the San Francisco Veterans Hospital, respectively. UC physicians and surgeons submit the vast majority to Pathology; a substantial minority is sent here by outside physicians. Sites commonly biopsied for diagnostic purposes include the skin, oropharynx, bronchial and GI mucosae, uterine cervix, endometrium, breast, lymph nodes, prostate, liver, and brain. Some of the organs more commonly removed for the treatment of disease include the appendix, gall- bladder, colon, stomach, uterus, breast, kidneys, and lower extremities. Portions of non-diseased organs, such as the Fallopian tubes, vasa deferens, and vagus nerves, are often submitted to document their removal.

Clinicians who submit specimens to Surgical Pathology must ensure that these specimens are unambiguously labeled to indicate the patient and the tissue removed and must provide sufficient clinical information to allow meaningful interpretation of the specimen. The gross appearance of the tissue is examined and recorded by the pathologist who then selects appropriate samples for the preparation of one or more microscope slides. Very small biopsies may be examined in their entirety, but only tiny portions of any large specimen can be examined microscopically. Selection of the appropriate regions to be examined requires a skilled pathologist with complete and reliable data provided by the clinicians. Microscopic slides are prepared by technicians and examined by the pathologist who then interprets the gross and microscope findings. The pathologist's final report can provide information about diagnosis, adequacy of treatment, documentation of surgery, or the extent of surgery or disease.

Standard Procedures - Most specimens submitted from the clinics and operating rooms are delivered to the Surgical Pathology Laboratory (M-576). The pathological consultation for such specimens typically includes the gross examination; selection and removal of appropriate samples for microscopy; formalin fixation, paraffin embedding, sectioning, staining and preparation of microscope slides by a technician; interpretation of the gross and microscopic findings by an attending pathologist; and the preparation of a typed final report. This process takes a minimum of 24 hours, largely because of the time required for fixation and preparation of the slides. A longer time may be needed if the specimen is large and requires more fixation, if special stains are needed, or if inadequate clinical information accompanies the specimen. Typed reports are usually available 48 to 72 hours after surgery and are placed in the patient's permanent records.

The cost of Surgical Pathology consultation at UCSF depends upon the complexity and diagnostic difficulty of the case and the techniques used to evaluate it. Complex cases, involving large or multiple specimens, include radical breast surgery, complete neck dissection, and radical pelvic or abdominal surgery, especially where lymph node dissection is performed. Hematoxylin and eosin stained (H&E) sections are sufficient for examination of most specimens. Special chemical stains are commonly used when appropriate for identification of iron, lipid, amyloid, mucin, fibrous tissue, fungi, bacteria, and acid-fast organisms. Monoclonal antibody stains can be used to identify specific macromolecules, such as immunoglobulins or keratin. Electron microscopy is used in some cases to evaluate intracellular inclusions or to find ultrastructural evidence of the tissue of origin in poorly-differentiated neoplasms. Obviously, these special studies entail additional costs. Special studies are routine for certain types of specimens; for example, a renal biopsy for glomerular disease is routinely evaluated by H&E stain, PAS stain, six different monoclonal antibodies stains, and electron microscopy.

Frozen Section Consultation - The pathologist is often called to the operating room to examine tissue and consult with the surgeon. In cases where a rapid diagnosis is required during surgery, a frozen section can be performed. In this procedure, a tissue sample is quick-frozen to permit sectioning, then stained and examined by light microscopy. By this means, a diagnosis can usually be rendered within 15 minutes to aid the surgeon in deciding how to proceed. This technique is used to save the patient the danger and expense of a second operation, guide exploratory surgery, or allow definitive therapy. Although frozen section diagnoses are generally accurate, it is important to realize that the inherently poorer quality of frozen sections limit the resolution of this technique, and that immediate decisions cannot always be made because of difficulty in obtaining adequate tissue, limited sampling, lack of time for consultation, or difficulty in defining the nature of the disease process. Interpretation of a frozen section always requires close cooperation between the pathologist and the surgeon. Paraffin sections of the specimens are also made subsequently. More than 1,200 frozen sections are performed annually at UCSF, an average of five each working day.

Sample Collection - Tissue morphology is extremely delicate, and improper handling can easily destroy any irreplaceable biopsy specimen. Most specimens for routine handling should be placed immediately in a 10% formalin solution. For adequate fixation, the specimen should remain immersed in 20 times its own volume of formalin for a time sufficient to permit the fixative to diffuse throughout the specimen (usually several hours or more). Air drying and excessive handling of the tissue should be avoided. Contrary to popular belief, immersion of specimens in "physiological" saline solutions leads to rapid tissue destruction. Large specimens are ordinarily examined before fixation should be refrigerated to prevent autolysis.

Certain types of specimens require special handling and must not be exposed to formalin. Frozen sections, lipid stains and many antibody techniques require fresh unfixed tissue, whereas specimens for electron microscopy or enzyme histochemistry must be placed immediately in special fixatives. Microbial cultures, when indicated, must of course be taken under sterile conditions prior to fixation; this should be done by the clinician prior to submitting the specimen to Pathology. For certain biopsies (notably those from lymph nodes, kidneys, and unusual neoplasms) the pathologist should be notified in advance and should be present when the biopsy

is taken. Advice on handling of individual specimens is available 24 hours each day through the Surgical Pathology Laboratory.

Problems, Pit-Falls and Interpretation - The histologic evaluation of tissue is widely recognized as the most reliable and objective means of establishing a diagnosis in most organic disorders. Nevertheless, the histological findings are often non-specific and non-quantitative, and are strongly influenced by the site and timing of the biopsy. An accurate interpretation therefore requires a skilled and experienced pathologist working in close cooperation with the clinician. Even the best pathologist can be led astray by inaccurate or incomplete clinical data. In some cases, different pathologists may disagree on the nature or significance of a particular lesion. Clinicians are encouraged to contact the pathologist to request a clarification of a diagnosis, discuss its implications for therapy, or request a second opinion. Frequent problems that arise prior to the pathologist receiving the specimen include unlabeled or mislabeled specimens, improper handling, and the removal of a portion of the specimen without permission of the pathologist.

Surgical Pathology in Community Practice - All accredited hospitals must have a pathologist. In smaller communities, the pathologist may live in another city and visit the hospital only on certain days of the week to do scheduled frozen sections and supervise the laboratory. Tissues removed in a physician's private office should be sent to a pathologist for evaluation.

In keeping with the role of UCSF as a tertiary care center, our Pathology Department frequently receives tissues or slides from community physicians or outside institutions for special studies, confirmation of a diagnosis, or expert consultative advice. Slides from prior biopsies at outside hospitals are always reviewed when a patient is referred to UCSF for specialized treatment. For example, oncologists will not treat a tumor mass without a confirmed biopsy diagnosis of malignancy. Clinical evidence alone, or a verbal report of the biopsy diagnosis, is inadequate to protect the physician and the patient from mistaken radical treatment of a benign lesion.

PATHOLOGY SERVICES AT UCSF

AUTOPSY PATHOLOGY

The autopsy (also known as "necropsy" or "post-mortem examination") is a powerful diagnostic and investigative technique that has served a critical role throughout the history of medicine and will continue to do so in the future. Examination of the dead provides a unique opportunity to perform diagnostic and investigative techniques with a thoroughness that would not be possible in the living patient. One important goal of the autopsy is to determine the cause of death, but this procedure serves other functions as well. For example, post-mortem examination provides an opportunity to confirm clinical diagnoses, to evaluate the effectiveness of therapeutic interventions, to correlate clinical findings with anatomic lesions, and to search for undiagnosed disease processes. Surveys have found that 10-15% of autopsies reveal one or more clinically unsuspected diagnoses that would have significantly altered the patient's management. Autopsy also provides a chance to study disorders that are incompletely understood (a category that includes essentially all human diseases); this is especially important in the case of new diseases, as illustrated in the early years of the AIDS epidemic. Finally, the autopsy is an invaluable tool in teaching students, residents and faculty, and provides a source of data for statistical analyses of disease incidence.

Standard Procedures - A physician, generally the patient's attending physician, is responsible for determining the death of the patient, for filling out the death certificate, and for obtaining permission to perform an autopsy. In most cases, autopsy is an elective procedure and cannot be performed without the written consent of the next of kin. Occasionally, written consent is obtained from the patient prior to death; although this is legally acceptable, autopsies usually are not performed if the family objects. In certain circumstances, however, autopsy is required by law and must be performed by the county medical examiner or coroner. Autopsy is legally required when the patient dies:

1. from homicide, suicide, accident, poisoning, injury or as the result of a criminal act;
2. with no physician in attendance. This includes solitary deaths, patients who have not seen a physician for twenty days prior to death, and those with medical attendance for less than 24 hours;
3. if the physician is unable to state the cause of death;
4. of occupational causes, in an operating room, or before having fully recovered from an anesthetic;
5. after having been comatose throughout the period of physician's attendance, whether in home or hospital;
6. an unidentified person.

It is the legal responsibility (punishable by imprisonment and fine) of the attending clinician to establish whether these criteria are met; if any doubt exists, the Coroner's Office should be notified.

At UCSF, nurses supervise delivery of the body to the autopsy room, and morgue attendants and administrative personnel employed by the hospital coordinate such activities as

making arrangements with funeral directors. For the convenience of the families, and to minimize delays in disposition of the body, autopsies at UCSF are performed seven days a week.

At UCSF, gross dissection is performed by an intern or resident, usually with the aid of an assistant. A complete autopsy involves the examination of all thoracic, abdominal and pelvic viscera, as well as the brain and spinal cord. Less extensive autopsies (limited to certain organs or body cavities) can also be performed according to the wishes of the family. Some organs, such as the eyes, are not ordinarily examined. The gross findings are reviewed by an attending pathologist and a written preliminary report is prepared, usually within 24 hours. Tissue samples are then taken from all significant lesions and all major organs for preparation of microscope slides by the technical staff. After review of these slides by the attending pathologist, a final report is prepared. The report includes a list of all diagnoses, a brief summary of the clinical course, a detailed description of gross and microscopic findings, and a narrative summary correlating the clinical and pathological findings. The final report is sent to the attending clinician, who is responsible for reporting and interpreting the autopsy findings to the family. Copies of the report may also be sent to other physicians or relatives on written request.

In addition, a copy of the autopsy report becomes the final entry in the patient's medical record.

Although the autopsy is best suited to obtaining morphological information, any chemical or microbiological test could, in principle, be done. The results of such tests, however, must be interpreted with caution. Widespread hemolysis, cytolysis and blood clotting occur soon after death and dramatically alter blood chemistry, while the demise of the immune system permits enteric bacteria to spread rapidly throughout the body.

The medicolegal autopsy requires special training and experience as well as special toxicologic assays. This procedure is the domain of the San Francisco Medical Examiner's Office and is not performed at UCSF.

Autopsy facilities must be available in every hospital to maintain accreditation. Autopsies are performed on approximately 20% of patients who die at UCSF (approx. 160-180 autopsies per year). The percentage is usually much lower in community hospitals, and some institutions send bodies to larger centers. Any licensed physician may perform an autopsy; though optimal interpretation requires considerable training. The gross dissection can usually be completed in from 1 to 4 hours depending upon the complexity of the case, restrictions, and the skill of the prosecutor. Final reports are available a minimum of two weeks after autopsy, although verbal reports may be available much sooner. If the brain is examined, a minimum time of 3 weeks is required because the brain must be hardened in fixative for 10 days before cutting.

Because of variability in the time and effort required to complete each autopsy, and the high fixed costs of operating the hospital morgue, the cost of an autopsy is hard to determine. Typical estimates range from \$800-\$3400. These costs are paid from general operating funds of the hospital; the patient's relatives are not charged unless they request an autopsy on someone who has not been a patient at this hospital.

Problems, Pitfalls and Interpretation - If the autopsy is performed in a timely and careful fashion, it does not significantly delay funeral preparations nor preclude display of the deceased

at the funeral. The problems most frequently encountered relate to obtaining informed consent from relatives, coordination of efforts with those of funeral directors, and medicolegal entanglements which may become very complex, time-consuming, and expensive.

The morphologic findings detailed in an autopsy report are generally highly reliable. In contrast, the death certificate may be very misleading, even on a patient who has been autopsied. Clinicians ordinarily fill out these certificates shortly after the patient's death, before autopsy findings are available. In completing the death certificate, the clinician must first specify the immediate cause of death, followed by two or three less immediate causes. In many cases, however, the immediate cause is not apparent even after gross autopsy (e.g., in patients dying of cardiac arrhythmia or hypoventilation). Many physicians incorrectly put down a definition of death ("cardiorespiratory arrest") rather than its cause. In many cases, death results from a complex sequence of events, which may be incompletely reflected, in the death certificate. Consequently, statistics and interpretations based on death certificates should be regarded as highly suspect, even when autopsies have been performed.

PATHOLOGY SERVICES AT UCSF DIAGNOSTIC CYTOLOGY

Diagnostic cytology is concerned with the interpretation of cells. These cells may exfoliate freely from epithelial surfaces, may be collected by brushing or scraping parts of the body, may be collected by washing lesions with saline, or may be collected by inserting a needle into a mass or organ and aspirating cells. Cytology is used both to screen asymptomatic patients and as a means to establish a primary diagnosis in patients with specific lesions. An example of how cytology is used to screen asymptomatic patients is the Papanicolaou smear, where cells from the uterine cervix are examined to screen for cervical cancer. An example of how cytology is used to make a primary diagnosis of a mass lesion is the use of fine needle aspiration biopsy (FNAB) to sample a palpable breast lump. In some cases, the cytologic finding is confirmed by open surgical biopsy before therapy is instituted; in other cases, the cytologic diagnosis serves as the basis for definitive medical or surgical therapy without further histologic confirmation.

Approximately 27,000 cytology specimens are seen at UCSF each year; there are about 10,000 cytologic preparations examined annually at the San Francisco General Hospital. Common types of cytologic specimens include Papanicolaou smears from the uterine cervix; urine, sputum, ascites fluid, and pleural fluids; endoscopic brush biopsies of the GI mucosae; and bronchial brushes or washes. Most of these samples are collected by clinicians such as obstetrician/gynecologists, urologists, pulmonary internists, and gastroenterologists. The samples are submitted to the pathologist, who looks at the specimen under the microscope and renders a diagnosis. Another type of cytologic specimen is a FNAB, which at UCSF and SFGH is usually performed, smeared, and interpreted by a pathologist. FNAB refers to sampling, without anesthesia, mass lesions with a 22-gauge needle. This procedure is less expensive, less invasive, and faster than open surgical biopsy. The pathologist performs the procedure, prepares the smear, and interprets the microscopic appearance of the smear because studies have shown that the highest accuracy rates are achieved with pathology-based FNAB services. FNAB is commonly used to sample palpable masses of the thyroid gland, lymph nodes, salivary glands, breast, and prostate. Nonpalpable masses of the lung, liver, pancreas, and pelvic organs are routinely sampled by FNAB with the help of ultrasound or CT guidance.

Clinical history is very important for accurate cytologic diagnosis. The pathologist can provide a more accurate and more meaningful analysis of a specimen when he or she knows the clinical history, pertinent physical examination findings, x-ray results, laboratory results, and clinical differential diagnosis. It is vitally important that the clinicians provide the pathologist with all of the above data on the cytology requisition form. The idea that the pathologist should render an accurate diagnosis based only on the microscopic appearance of the specimen is a dangerous attitude that can hamper patient care. The accurate use of diagnostic cytology requires good communication between clinicians and cytopathologists.

Standard Procedures - Most cytology specimens, with the exception of FNABs, are delivered by messenger service to the Cytology Department. When specimens are received in cytology, technologists prepare, fix and stain the smears. When large volumes of fluid are submitted, it is important to concentrate the cells by use of filtration or centrifuge techniques. After the slides are fixed and stained, the technologists screen the slides and mark any suspicious cells.

Screening entails looking at every cell for evidence of abnormalities. All slides are then sent to the pathologist who reviews the entire smear and renders a diagnosis.

FNABs are performed by the cytopathologist on call. After palpating the mass carefully, the cytopathologist introduces a 22-gauge needle, attached to a syringe, into the mass. The biopsy is performed by exerting full suction and moving the needle back and forth within the mass. The procedure is terminated when any material is seen in the hub of the needle. Termination is accomplished by releasing the suction before pulling the needle out of the patient. While an assistant applies pressure to the puncture site to avoid hematoma formation, the pathologist carefully prepares the smears. Some of the smears are immediately fixed in alcohol for Papanicolaou staining and some are air dried for May-Grunwald-Giemsa staining.

Many of the specialized staining techniques discussed under the surgical pathology section can also be applied to cytology smears. Special stains for microorganisms, mucin, amyloid, and fibrous tissue are sometimes useful. Immunoperoxidase (IPOX) stains can also be used to establish a very specific diagnosis.

STAT Cytology Specimens - At times an immediate cytologic diagnosis is required. Intraoperative FNABs of pancreatic lesions are interpreted while the patient is anesthetized. For example, FNAB of the pancreas might reveal adenocarcinoma, if no metastases are identified, radical surgery can be performed to affect a cure. When the FNAB is negative for malignancy, no further surgery may be required. FNABs are sometimes performed on patients with suspected metastases to the spinal cord so that emergency radiotherapy can be instituted as quickly as possible. In most cases, radiotherapists are reluctant to treat patients emergently without a microscopic diagnosis of malignancy.

Problems, Pit-falls and Interpretation - All of the comments listed in the surgical pathology section also apply to cytology. When cytologic diagnoses are different from the clinical impression, it is important that the cytopathologist and clinician discuss the case. The apparent inconsistencies can usually be cleared up with discussion, repeat cytologic examination, open surgical biopsies, or special studies.

Cytology in Community Practice - Most pathologists have training in cytology and considerable experience in interpreting cervical and body fluid specimens. Many pathologists, however, have much less experience with FNAB interpretation and may not offer it as a routine service. As this procedure is used more frequently, and as more pathologists trained in this procedure go into private practice, FNAB will become more readily available at community hospitals.

Cell Injury: Mechanisms and Adaptations**OBJECTIVES**

- *Describe the terminology and traditional concepts upon which general pathology is based.*
- *Describe the etiologies and mechanisms of cell injury.*
- *Define necrosis and the different types.*
- *Define apoptosis and describe its importance in normal and abnormal cellular processes.*
- *Describe cellular adaptive mechanisms and types of pathologic calcifications.*

Reading: Robbins Basic Pathology; Kumar, Abbas, Mitchell, 9th Ed., 2013, pp. 1-26.

"We must focus on those events that precede the development of focal cytoplasmic degradation, identify the first manifestation of injury, determine what injuries are critical in causing death, and discover the extent to which those injuries are reversible. Only such an approach can help the physician reach his ultimate goal: to prevent and cure disease."

OVERVIEW

<u>Causes</u>		<u>Responses: Adapt or Death</u>
Physical - temperature, pH, trauma	Cell	Cell Injury - reversible & irreversible
Nutrients - lack of O ₂ , Vitamin A		Inflammation - acute & chronic
Biological Agents - bacteria, viruses, fungi		Repair
Immune Mechanisms		Regeneration
Genetic - mutations, rearrangements, oncogenes, repressive genes		Disorders of Growth - hypertrophy, hyperplasia, dysplasia - including
Ionizing radiation		Neoplasia (cancer)

I. OVERVIEW OF PATHOLOGY

- A. Definition: Pathology (*patho* or "suffer" + G. *logos*, study) = "medical science and specialty practice concerned with all aspects of disease, but with special reference to the essential nature, causes, and development of abnormal conditions, as well as the structural and functional changes that result from the disease processes." -- Stedman's Medical Dictionary 28th Ed.
- B. Etiology or cause:
1. Congenital - genetic, malformation.
 2. Acquired - infectious, nutritional, chemical, physical, etc.
- C. Pathogenesis:
- Represents those biochemical reactions and cellular events that lead to disease. Multiple etiologies or causes can give similar morphologic changes or very unique morphologic alterations. Think of any disease like reading a good book, watching a movie, or going to the opera, there is a beginning, middle, and an end.
- D. Morphologic Changes:
1. Structural and accompanying functional alterations in cells, tissues, and organs that are characteristic or diagnostic of the etiology or cause.
- E. Functional Derangements and Clinical Significance:
1. Type of morphologic changes and their distribution in different tissues or organs will affect normal function and determine clinical manifestations including symptoms (patient's complaints) and signs (objective data obtained by the practitioner), course of the disease, and prognosis.

II. CAUSES OF CELL INJURY

- A. Hypoxia - decreased availability of oxygen (most common form of cell injury).
- Causes of oxygen deprivation:
 - Ischemia (insufficient blood supply) - most common cause of hypoxia
 - Cardiopulmonary failure
 - Loss of oxygen carrying capacity of the blood - anemia.
- Thus, the severity of oxygen deprivation will produce a spectrum of alterations from biochemical (aerobic to anaerobic metabolism) to morphologic (atrophy to cell death) changes

B. Physical Agents:

Mechanical trauma, deep cold to burns, sudden changes in atmospheric pressures, ionizing radiation, and electric shock

C. Chemical Agents and Drugs:

A large list of chemicals can produce cell injury include elements (mercury), salts, simple molecules (oxygen), poisons, air pollutants, insecticides, herbicides, industrial and occupational chemical, recreational drugs (alcohol and narcotic drugs), and therapeutic drugs.

D. Infectious agents:

Viruses, rickettsiae, bacteria, fungi, and parasites

E. Immunologic reactions:

Anaphylaxis, deposition of immune complexes, reactions to self-antigens, etc.

F. Genetic Derangements:

Congenital malformations - e.g., Down syndrome
Insertions, deletions, translocations, frameshift and point mutations are responsible for inborn errors of metabolism
Neoplasia

G. Nutritional Imbalances:

Protein-calorie deficiencies - marasmus (total calorie deficiency) and kwashiorkor (total protein deficiency)
Vitamin (cofactor) deficiencies and excesses
Dietary excesses - fat

III. MECHANISMS OF CELL INJURY

A. General characteristics of cell injury:

1. Cell reactions to injury are the basis of disease –
ABILITY TO ADAPT OR DIE.
2. Four intracellular systems are particularly susceptible:
 - a. Integrity of cell membranes.
 - b. Aerobic respiration involving oxidative phosphorylation and production of ATP.

- c. Synthesis of enzymes and proteins.
 - d. Preservation of genetic apparatus of the cell.
- 3. The diagnostic and traditionally recognized morphologic changes are frequently due to accumulation of cell metabolites in the cytoplasm: water and electrolytes, carbohydrates, lipid, or proteins.
- 4. These cytoplasmic accumulations generally revert to normal if the injurious stimulus is removed or if the cell can adapt to the noxious agent.
- 5. Some sublethal cell injuries; e.g., chromosome damage, may have a more deleterious effect on the host than do lethal injuries to individual cells.
- B. Cellular metabolism is highly integrated and cell injury can have multiple secondary effects when one cellular function is disrupted.
- C. Morphologic changes at any level is preceded only after some critical biochemical system within the cell is damaged.
- D. Morphologic reactions are dependent upon the type of injury, duration, pattern, and severity.
- E. Type, metabolic state, and adaptability of the cell will affect the changes due to cell injury.
- F. Ischemic and hypoxic injury:
 - 1. Reversible cell injury:

Oxidative phosphorylation is first point of the attack resulting in acute cellular swelling (e.g., hydropic change or ballooning).
 - 2. Irreversible cell injury:
 - a. Injury to lysosomes with leakage of their enzymes into the cytoplasm.
 - b. In the living host, the injured cells die and are converted to debris even if the injurious stimulus is removed. The debris is removed by phagocytes
 - c. The most easily recognized morphologic changes occur in the nucleus--the nucleus shrinks (pyknosis), fades (karyolysis), or nuclear material clumps (karyorrhexis).
 - d. Mechanisms of Irreversible Injury:
 - ATP depletion
 - Cell membrane damage:

This is the central factor in the pathogenesis of irreversible cell injury through the progressive loss of phospholipids, cytoskeletal abnormalities, toxic oxygen free radicals, and lipid breakdown.

- G. Apoptosis (Gr. “*falling off*”) - programmed cell death or destruction without an inflammatory response.
1. Physiologic:
 - a. During embryogenesis including implantation, organogenesis and developmental involution
 - b. Hormone-dependent involution (e.g., sloughing off of endometrial cells during the menstrual cycle; ovarian follicular atresia during menopause; decreased breast size following the cessation of breast feeding)
 - c. Deletion of a portion of proliferating cells (e.g., intestinal crypt epithelia)
 - d. Selective death of immunocytes (T and B lymphocytes) - e.g., developing thymus
 2. Pathologic:
 - a. Viral diseases leading to cell death (e.g., acidophil or Councilman bodies in toxic or viral hepatitis; T4 helper lymphocytes in HIV disease)
 - b. Pathologic atrophy (e.g., prostatic atrophy after castration)
 - c. Duct obstruction leading to pathologic atrophy (e.g., organs containing ducts - kidney, pancreas, parotid)
 - d. Cell death induced by T8 (cytotoxic) lymphocytes (e.g., graft-versus-host disease and cellular immune rejection)
 - e. Injurious agents (e.g., cytotoxic anticancer drugs, mild thermal injury, radiation)
 3. Morphologic characteristics:
 - a. General cell shrinkage
 - b. Chromatin condensation (most common)
 - c. Cytoplasmic bleb formation and apoptotic bodies (cytoplasm plus condensed and packed organelles with or without nuclear fragments)
 - d. Phagocytosis of apoptotic cells by unaffected parenchymal cells or

macrophages

- e. Lack of an inflammatory response compared to different types of necrosis (see below)

4. Mechanisms:

Activation of endonuclease (DNA fragmentation and possibly leading to chromatin condensation), protease cytoskeleton disruption and cell shrinkage) and transglutaminase (cytoplasmic protein cross-linking). Also changes in cell surface leading to phagocytosis without an inflammatory response.

IV. RESPONSE TO LETHAL INJURY: NECROSIS

The events occurring after death of tissue. Autolysis is self-digestion by lytic enzymes. Necrosis is the conversion of dead cells to debris within a living organism. The form of necrosis depends on the nature of the tissue, which enzymes remain active, and the cause of the injury.

- A. Coagulative necrosis (ischemia leading to an infarct - heart, kidney, liver): Histologic-acidophilic clumping and opacification of cytoplasm, with preservation of cell outline. Loss of nuclear staining secondary to karyolysis and karyorrhexis. Denaturation of enzymes, lack of water for hydrolytic enzyme function, decrease pH.
- B. Liquefactive necrosis (extensive release of lytic enzymes - abscess, infarct of brain, pancreas, intestinal epithelium): Complete lysis of cells by catalytic enzymes. In part autolytic, but largely heterolytic from PMN and macrophage lysosomes.
- C. Caseous necrosis (granulomatous diseases – e.g., tuberculosis): White, cheesy texture and appearance in gross specimen. Amorphous, granular debris in histologic preparation. A combination of coagulative and liquefactive necrosis.
- D. Fat necrosis (injury to fat - pancreatitis): Gross: small, chalky-white necrotic areas. Histologic: Amorphous, basophilic deposits of calcium-fatty acid complexes (saponification = production of soap).
- E. Fibrinoid necrosis: Histologic: Pink, amorphous, sometimes granular deposits (plasma proteins, especially fibrin) superimposed on dead or injured cells. Fibrinoid necrosis is associated with acute immunologic injury and vascular diseases.
- F. Gangrenous necrosis: Usually applied to the lower limb which has lost its blood supply and the resulting dead tissue (coagulative necrosis) becomes secondary infected with bacteria leading to liquefactive action of the bacteria and proteolytic enzymes released by leukocytes. Other sites that can become gangrenous includes the gastrointestinal tract, gallbladder and testis.

Dry gangrene: coagulative necrosis is the predominant pattern.
Wet gangrene: liquefactive process is the dominant pattern.

V. CELLULAR ADAPTATIONS

Overview

1. Potentially reversible once the stimulus is removed.
2. Those involving growth (plasia) can increase the risk for neoplasia (autonomous growth).

A. Atrophy

Definition: Shrinkage in the size of the cell by loss of structural components.

Causes:

1. Decreased work load (e.g., hospitalization)
2. Loss of innervation (e.g., alpha-motor neuron disease)
3. Diminished blood supply (e.g., atherosclerosis)
4. Inadequate nutrition (e.g., protein-caloric deficiencies)
5. Loss of endocrine stimulation (e.g., menopause)
6. Aging (most common cause of atrophy)

B. Hypertrophy

Definition: Increase in the size of cells due to the synthesis of more structural components; therefore, an increase in the size of the organ.

Caused by increased functional demand or by specific hormonal stimulation.

Physiologic:

Growth of the uterus during pregnancy (hypertrophy of myometrium - smooth muscle cells)

Pathologic:

Left ventricular hypertrophy due to hypertension (hypertrophy of cardiac myocytes)

C. Hyperplasia

Definition: Increase in the number of cells in an organ or tissue.

Hormonal hyperplasia:

Glandular epithelium of the female breast at puberty and during pregnancy; pregnant uterus

Compensatory hyperplasia:

Regeneration of an organ or tissue (partial hepatectomy)

Pathologic hyperplasia:

The majority of pathologic hyperplasias are due to excessive hormonal stimulation or the effects of growth factors on target cells - hyperplasia of the endometrium in some post-menopausal women can give rise to neoplasia (endometrial adenocarcinoma)

D. Metaplasia

Definition: Reversible change in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type.

If the factor(s) responsible for the change persists then cancerous transformation in the metaplastic epithelium may occur (e.g., squamous metaplasia in chronic bronchitis can give rise to dysplasia or squamous cell carcinoma)

E. Dysplasia

Definition: Epithelial or mesenchymal cells that have undergone proliferation and atypical cytologic alterations involving cell size, shape, and orientation.

In the cervix and respiratory tract is strongly implicated as a precursor of cancer.

VI. CALCIFICATION

A. Dystrophic calcification

Definition: Deposition of calcium salts in nonviable or dying tissues either intracellular, extracellular or both.

Examples:

Heterotopic bone may form at the site of calcification (e.g., Mönckeberg's medial calcific sclerosis, a form of arteriosclerosis – hardening of the artery)

Single necrotic cells may give rise to lamellated concretions called psammoma (sand) bodies (papillary carcinoma of the thyroid and ovary, and meningioma [brain])

B. Metastatic calcification

Definition: Deposition of calcium in normal tissues due to hypercalcemia (increased serum calcium greater than 10.5 mg/dL).

Causes:

1. Hyperparathyroidism
2. Vitamin D intoxication
3. Systemic sarcoidosis
4. Addison disease (chronic adrenal insufficiency)
5. Hyperthyroidism
6. Idiopathic hypercalcemia of infancy.
7. Increased bone catabolism associated with disseminated bone tumors
8. Leukemia
9. Immobilization

Primarily affects the interstitial tissues of the blood vessels, especially kidneys, lungs, and gastric mucosa.

VI. HYALINE CHANGE

A. Definition: Any alteration within cells or in the extracellular space, which gives a homogeneous glassy, pink appearance in routine histologic sections stained with H&E.

B. Intracellular hyaline:

Hyaline droplets in the proximal tubular epithelial cells of the kidney (e.g., nephrotic syndrome)

2. Russell bodies (accumulation of cytosol immunoglobulins) in plasma cells

3. Viral inclusions in either the cytoplasm or the nucleus which often represents viral nucleoproteins

Alcoholic hyaline in liver cells - aggregates of prekeratin (intermediate filament found in epithelial cells)

C. Extracellular hyaline:

1. Walls of blood vessels especially in the kidney in longstanding hypertension
2. Hyalinization of glomeruli with chronic damage
3. Amyloidosis (condition of abnormal deposition of extracellular protein) has a hyaline appearance

Acute Inflammation**OBJECTIVES**

- *Describe the sequence of events that occur in blood vessels, endothelial cells and leukocytes during an acute inflammatory response, and how these account for the cardinal clinical signs of inflammation*
- *Describe, with illustrative examples, the beneficial and harmful consequences of inflammation*
- *Describe where the mediators of inflammation are produced and what their main actions are*
- *Describe the processes by which neutrophils recognize, phagocytose, and eliminate bacteria or other foreign substances from the tissues*
- *Describe the mechanisms by which circulating leukocytes recognize and invade an injured or infected tissue*
- *Describe the local and systemic manifestations of inflammation*

READING

Chapter 2 in *ROBBINS BASIC PATHOLOGY* (V. Kumar, A. K. Abbas, R. Mitchell), 9th Ed., 2013; pages 29-53.

MAIN IDEAS

- Inflammation is a concerted group of defensive reactions that occur, to varying degrees, in response to most types of tissue injury or distress. It is fundamentally beneficial, but can have deleterious effects including tissue damage and thus have pathological consequences.
- The inflammatory response consists of changes in the caliber and permeability of blood vessels; endothelial activation; and recruitment and activation of leukocytes, which function to eliminate the offending agent.
- The inflammatory response is induced by molecules referred to as mediators, which are produced by host cells (tissue macrophages, endothelial cells, mast cells) or from plasma proteins, in response to microbes, dead cells, and other toxic substances.
- Inflammation is associated with characteristic local and systemic signs and symptoms and changes in plasma proteins, all of which are used to diagnose inflammatory disorders.

I. OVERVIEW OF INFLAMMATION

The goal of the inflammatory response is to get rid of external invaders (e.g. microbes in tissues) and internal dangers (e.g. necrotic tissue) by bringing the body's defenders to the invaders. The most powerful defenders are circulating white blood cells (leukocytes) and several plasma proteins, all of which are normally in the blood in an inactive state (so they don't cause any harm). The invaders are typically in tissues, outside the blood vessels.

Therefore, the reactions in inflammation first involve blood vessels (slowing of blood flow, and increased permeability, promoting exit of proteins and cells), and this is followed by the active recruitment of blood leukocytes and their activation in the tissues.

We commonly think of inflammation as a pathologic process (cause of disease), whose consequences range from the nuisance of the common cold to the seriousness of meningitis, pneumonia, arthritis, and the like. The components of the inflammatory reaction that destroy and eliminate microbes and dead tissues are capable of also injuring normal tissues. Therefore, injury may accompany entirely normal, beneficial inflammatory reactions, and inflammation may even be the cause of a disease if the reaction is very strong (e.g. in severe infections), prolonged (e.g. when a microbe resists eradication), or inappropriate (e.g. when it is directed against self-antigens – in autoimmune diseases – or against usually harmless environmental antigens – in allergic disorders). Some of the most vexing diseases of humans are disorders in which the pathophysiologic basis is inappropriate, often chronic, inflammation. This is why understanding the process of inflammation is fundamental to virtually all of clinical medicine. It is also the basis for understanding anti-inflammatory drugs and their value and risks.

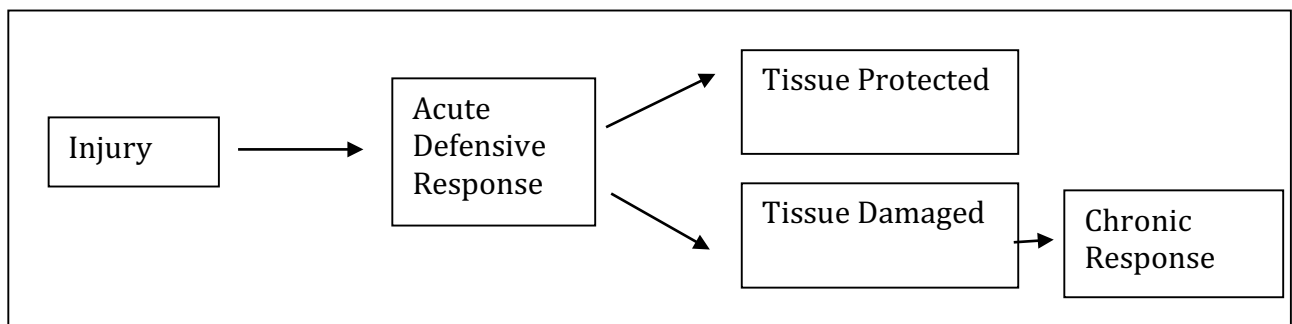
II. PATHOGENESIS OF INFLAMMATION

A. Causes of Inflammation

Most types of tissue injury or infection trigger a concerted array of active defensive responses in the affected tissue that are collectively known as inflammation.

Inflammation commonly occurs at sites of:

- Physical trauma (blunt or penetrating)
- Infection (bacterial, viral, parasitic)
- Tissue necrosis (from any cause)
- Immune reactions
- Thermal injury (e.g., burns, sunburn, frostbite)
- Foreign bodies (splinters, dirt, talc, suture material) inoculation of certain normal host-derived materials (hair, sebum, etc.) into tissue



2. A great many different phenomena can occur as part of an inflammatory response, depending on the nature, severity, and duration of the injury, the tissue involved, and the status of the host. In any given instance, fever, sleepiness (somnolence), runny nose

(rhinorrhea), itching, local blood clotting, or other signs and symptoms might or might not be present. However, the three events that occur most commonly and are most central to the inflammatory response are:

- changes in local microvascular blood flow and permeability;
- activation of endothelial cells; and
- migration of blood leukocytes into the affected tissue.

3. The five cardinal signs of inflammation are:

- pain
- redness (erythema)
- warmth
- swelling (edema)
- loss of function

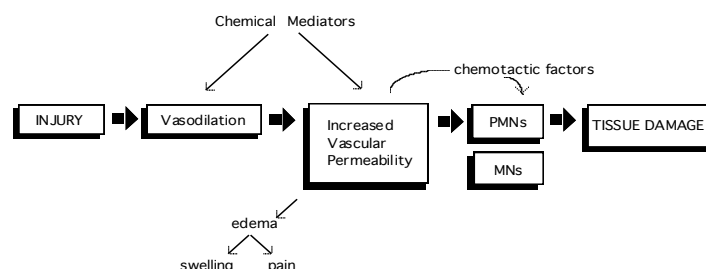
These are perhaps the most useful and ubiquitous diagnostic clues in all of clinical medicine, so it is important to know how they arise.

4. Inflammation is a defensive response that is fundamentally beneficial to the host. Excessive or inappropriate inflammation, however, can be detrimental. For this reason, medications that can suppress various aspects of inflammation – including NSAIDs (non-steroidal anti-inflammatory drugs), corticosteroids, antihistamines, and many others – are central to the practice of medicine.

5. Classification of Inflammation: Acute vs. Chronic

	Onset	Predominant Cells in Infiltrate	Cardinal Signs
Acute	Fast (seconds to hrs., days)	Neutrophils	More prominent
Chronic	Slow (days, weeks, months)	Lymphocytes/ Macrophages	Less prominent

Diagram of the Main Features of Acute Inflammatory Response



A few types of injuries or infections cause only acute or only chronic inflammation, and this may provide a clue to diagnosis, but often both occur together. Sometimes an initial acute response gradually wanes and is replaced by chronic inflammation, and this can enable us to estimate when the injury occurred.

We will focus on acute inflammation in this lecture and on chronic inflammation in the next.

6. The suffix “-itis” means “inflammation of,” as in meningitis, arthritis, rhinitis, pneumonitis, conjunctivitis, etc. These can be further modified; e.g.: acute meningitis, chronic meningitis, acute allergic rhinitis, etc.

B. Chemical Mediators of Inflammation

Each aspect of the inflammatory response is controlled by diffusible extracellular signaling molecules, including many proteins, peptides, and small organic compounds, that are collectively called “mediators of inflammatory.” It follows that in order to understand the reactions of inflammation, you have to appreciate the mediators. This is also important because you will be using drugs that inhibit one or more of these mediators every day in your medical practice. The list of inflammatory mediators is overwhelming (as is the list of anti-inflammatory medications occupying pharmacy shelves). The problem of understanding (and remembering) this long list is compounded by the fact that many mediators have overlapping actions. Descriptions of the individual mediators are in the BASIC PATHOLOGY textbook.

It is important to remember the general properties of these chemical mediators of inflammation:

Mediators of inflammation are produced by (1) injured or distressed host cells, (2) byproducts of tissue injury and/or host responses derived from plasma proteins – such as coagulation cascade (blood clotting), generation of bradykinin and complement activation, and (3) unique microbial products.

Biologically active mediators are produced only when needed, i.e. in response to external stimuli. Cell-derived mediators are either pre-formed and secreted rapidly (histamine), or newly synthesized and secreted (prostaglandins and leukotrienes; cytokines). Plasma-derived mediators circulate in an inactive form and need to be activated to do their job. Most of the mediators act for brief periods and close to where they are produced.

Together, these mediators of inflammation ensure that inflammation is triggered whenever there is tissue damage, infection, or distress, regardless of its specific cause.

The principal mediators of inflammation and their actions are summarized in Table 1.

Table 1. Summary of the major mediators of inflammation

	Vascular Dilatation	Vascular Permeability	Endothelial Activation	Leukocyte Attraction	Pain	Fever
<u>Secreted by Host Cells</u> Histamine Prostaglandins, leukotrienes Nitric Oxide Chemokines Cytokines	XXX XXX XXX	XXX XXX	XXX XXX	 XXX	 XXX XXX	 XXX XXX
<u>Byproducts of</u> Complement activation Coagulation, e.g.: fibrin, thrombin Collagen degradation		XXX	XXX XXX	XXX XXX XXX		
<u>Uniquely Microbial Products</u> Bacterial lipopolysaccharide N-formylated peptides			XXX	XXX		

C. Microvascular Reactions in Inflammation

The vascular reactions of inflammation are designed to bring oxygen and circulating molecules of host defense (antibodies, complement proteins, others) to sites of infection or tissue necrosis (vasodilatation), increased vascular permeability, and make vessels permissive for the exit of leukocytes (increased vascular permeability).

The main vascular reactions are:

- Dilation of small vessels: slows down blood flow (stasis); seen externally as erythema (redness), felt as warmth.

An acute inflammatory response begins with vasodilatation of small vessels around the injury due to relaxation of smooth muscle in vessel walls affecting arterioles, capillaries, and venules due to the release of key chemical mediators of inflammation including:

1. Neurotransmitters (e.g., substance P) released from autonomic neurons.
2. Histamine from mast cells - marrow-derived cells (granulocytes) that reside in connective tissue throughout the body, especially around blood vessels. They store abundant histamine in cytoplasmic granules, and discharge it (degranulate) within seconds after many types of physical or chemical stimuli.
3. Arachidonic acid (AA) metabolites produced by mast cells, leukocytes, endothelial cells and platelets – vasodilation (PGI₂, PGE₁, PGE₂, PGD₂), while other AA metabolites (thromboxane A₂, leukotrienes C₄, D₄, E₄) cause vasoconstriction.
4. Bradykinin derived from the kinin system leads to vasodilatation.

The physiological effects of vasodilatation lead to increased volume of local blood flow, and leukocytes flow more slowly along the length of the vessels, and collide more

frequently and at lower velocity with the endothelium facilitating transmigration/diapedesis through the vessel wall (primarily, post-capillary venules).

- Increased local vascular permeability: due to retraction of endothelial cells from one another, creating microscopic, temporary gaps in the lining, and occurs primarily in the smallest venules (called “postcapillary venules”). The physiological effects include protein-rich fluid from the serum leaks out into the extracellular space, a condition called edema. (results in swelling!).
- The benefits to the host is:
 - a. Diluting any injurious material (toxins, etc.) in the tissue
 - b. Releasing serum immune proteins into the tissues
 - c. Increasing local lymphatic drainage (promotes immune responses)The blood cells tend to accumulate in the leaky vessels (called “sludging”).
- Endothelial activation: increased expression of adhesion molecules and secretion of chemokines, preparing the endothelium to attract and hold leukocytes. This begins within seconds, complete within hours and occurs primarily in the postcapillary venules. This is triggered by numerous mediators that indicate distress (see above), and results in expression of specific proteins on endothelial surface including ICAM-1 and VCAM-1 (which can bind to integrins [transmembrane heterodimeric glycoproteins] on leukocytes [LFA-1 and MAC-1]) and selectins (receptors on endothelial cells – E-selectin and P-selectin and leukocytes – L-selectins [which can bind to sugar residues on mucins and other glycoproteins]). Together, these adhesion molecules make the endothelium “sticky” for leukocytes and act like cellular brakes!

Some selectins are normally stored in secretory granules (called “Weibel-Palade bodies”) in the endothelium, and can be transferred to the surface within seconds after activation. Other selectins, as well as ICAM-1 and VCAM-1, must first be synthesized and then expressed, a process that may take hours.

D. Reactions of Leukocytes

Neutrophils (also called polymorphonuclear leukocytes, PMNs) are the first leukocytes to arrive at sites of acute inflammation but are short-lived (24-48 hours). Monocytes arrive later and in the tissues they develop into macrophages, which live longer (60-120 days). This is why as inflammation becomes prolonged or chronic, the dominant leukocyte population changes from neutrophils to macrophages.

The response of white blood cells, the body’s principal cells of host defense, consists of:

1. **Recruitment from blood into tissues**: A multi-step process involving various adhesion molecules and chemical attractants (mainly chemokines). An inflamed tissue tends to attract circulating leukocytes because the cells flow slowly through the distended microvessels, and collide frequently against the endothelium. The activated endothelium expresses selectins that can bind to leukocytes when they collide. The distressed tissues produce an assortment of diffusible molecules that serve as leukocyte chemotactic factors. These chemoattractants that can attract and cause other changes in one or more classes of leukocytes by binding receptors on

their surfaces.

They include:

chemokines – A diverse group of “chemoattractant cytokines,” proteins produced by endothelial cells and many other cells types when distressed. Some chemokines selectively attract neutrophils, others monocytes, others lymphocytes, etc., depending on the receptors they express; many attract more than one cell type. Though soluble, chemokines tend to adhere to endothelial cells and to extracellular matrix, so they eventually form an immobilized concentration gradient that starts at the endothelial surface, rises through the tissue, and peaks at the site of injury.

- a. Fragments of fibrin or collagen (as occur in a wound)
 - b. Complement byproducts (especially, C5a)
 - d. N-formylated peptides – found in bacterial, but not human, proteins; a telltale sign of infection.
2. Leukocyte/endothelial interactions: a leukocyte attaches to vessels of an inflamed tissue in a 3-step process:
- a. **Selectin-mediated phase** – When a leukocyte randomly collides with venular wall, selectins on the activated endothelium bind to sugar residues on the leukocyte. This first attachment is weak and short-lived, so leukocyte may initially skip or roll along the endothelium under force of the flowing blood.
 - b. **Activation phase** (chemoattractant-mediated) – Once attached, the leukocyte detects chemotactic factors (see above) on the endothelium. In response, it begins to express functional integrin proteins on its surface.
 - c. **Integrin-mediated phase** – The leukocyte integrins bind to ICAM-1 and VCAM-1 on the activated endothelium. This binding is very tight, so the leukocyte stops rolling and flattens out against the vessel wall. Seen under light microscope, this phenomenon is called **margination**.

Once attached, leukocytes actively crawl between endothelial cells into the tissue (a process called emigration), then migrate up the gradient of chemotactic factors to the site of injury or infection.

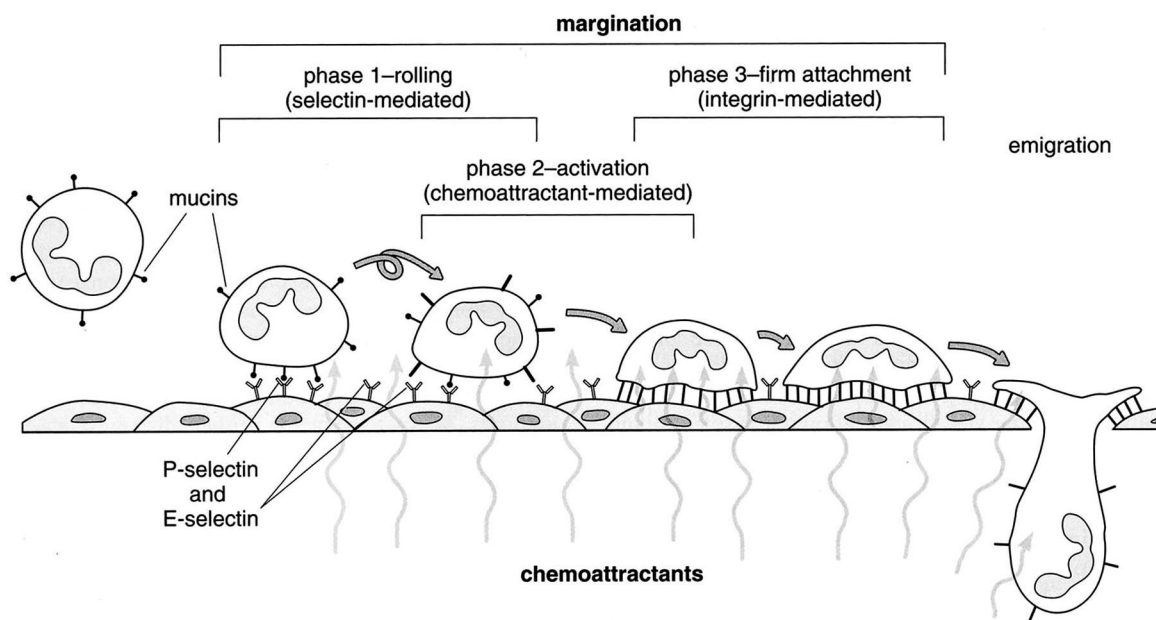


Figure 2.

3. Activation: Leukocytes sense microbes via several types of receptors and are activated to produce substances that destroy microbes and necrotic debris.
- a. The first leukocyte to arrive are neutrophils, which are also commonly called polymorphonuclear leukocytes, PMNs, “polys,” or “segs” (in each case referring to their segmented nuclei). A tissue infiltrate composed mainly of neutrophils is, by definition, an acute inflammatory infiltrate. Such infiltrates occur in many settings and so are not very helpful for specific diagnosis, but it is worth considering two common etiologies:
 - Microbial infection
 - Acute tissue necrosis from any cause
 - Neutrophil morphology and lifecycle:
 - Bone-marrow-derived, granulocyte lineage
 - Most abundant leukocyte in the blood (normally 50-75% of White Blood Cells - WBCs)
 - Characteristics of a mature neutrophil:
 - i. Multi-lobed nucleus
 - ii. Numerous cytoplasmic granules (specialized lysosomes) containing antimicrobial proteins and enzymes
 - iii. Minimal rough ER and Golgi, so limited ability to synthesize new secretory or membrane proteins
 - iv. Few mitochondria, so anaerobic metabolism
 - v. Terminally differentiated – cannot replicate by cell division
- b. Lifecycle:
 - Develop to maturity in the bone marrow
 - Stored in marrow for about 5 days, in a large reserve pool
 - Released into bloodstream, circulate for about 10-12 hrs., then die by apoptosis
 - UNLESS they circulate into an inflamed tissue, in which case they marginate, emigrate, chemotaxis to the site of injury, and ATTACK! They can reside in tissue for 24-48 hours before they will die.
 -
- c. Neutrophil Effector Mechanisms (e.g., how they defend the host)
 - When exposed to inflammatory mediators, neutrophils become activated and become voracious phagocytes, engulfing bacteria, cell debris, or foreign particulate matter.
 - How do they recognize so many targets?
 - i. There are lots of different receptors on each neutrophil
 - ii. The receptors tend to have broad specificity, recognizing many related ligands or ligands found on many different microbes or foreign substances

iii.

phagocytosis

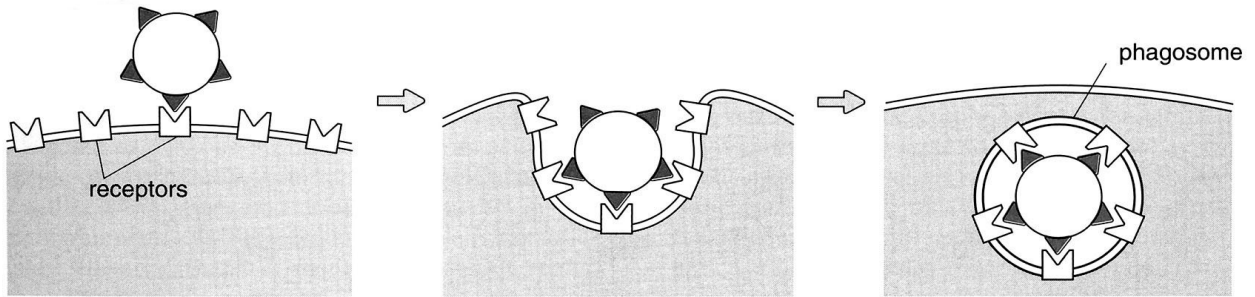


Figure 3a.

4. Phagocytosis: Phagocytes (neutrophils, macrophages) ingest microbes and dead cells. The efficiency of this process is greatly increased if the particle to be ingested is coated with antibodies (IgG, IgM), complement proteins (C3b), or mannose binding lectin (lectins are sugar-binding proteins) called “opsonization”, because phagocytes (neutrophils and macrophages) have receptors for antibody and complement (MAC-1/C3b receptor).

opsonization

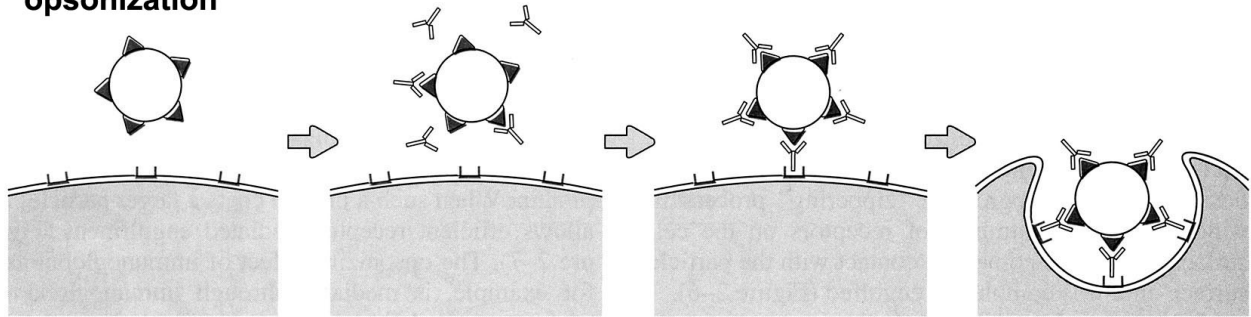


Figure 3b.

5. Destruction: Activated leukocytes destroy what they have eaten, using the microbicidal substances see below. Much of this destruction happens within phagocytic vesicles, to prevent damage to the leukocyte itself.
 - a. Storage granules fuse with the phagosome (“degranulation”), disgorging their contents onto the particle. These contents include:
 - α -defensins – small antimicrobial proteins that kill by creating pores in bacterial, viral, or yeast membranes
 - Lysozyme – enzyme that digests bacterial surface
 - Lactoferrin – sequesters iron needed for microbial growth
 - Many proteases (e.g., collagenase and elastase) and other hydrolytic enzymes (e.g., acid hydrolases)
 - b. Acid is pumped into the phagolysosome. This process hydrolyzes the particle and enhances activities of antimicrobial enzymes.
 - c. Oxidative killing – two enzymatic pathways generate powerful oxidants inside the phagolysosome (see Figure 5):
 - NADPH-dependent oxidase - during neutrophil degranulation, 3 cytosolic and 2 membrane subunits come together at the membrane to form an active oxidase, which, together with the granule enzyme myeloperoxidase (verdoperoxidase), uses oxygen and NADPH to produce hypochlorous acid (“bleach”) and organic chloramines.
 - Inducible nitric oxide synthetase (iNOS) – activated neutrophils express iNOS, which uses oxygen and arginine to generate peroxynitrite ions.

Together, yield a sharp rise in oxygen consumption (called a metabolic burst or respiratory burst) by the neutrophil. This continues up to 3 hours after phagocytosis.

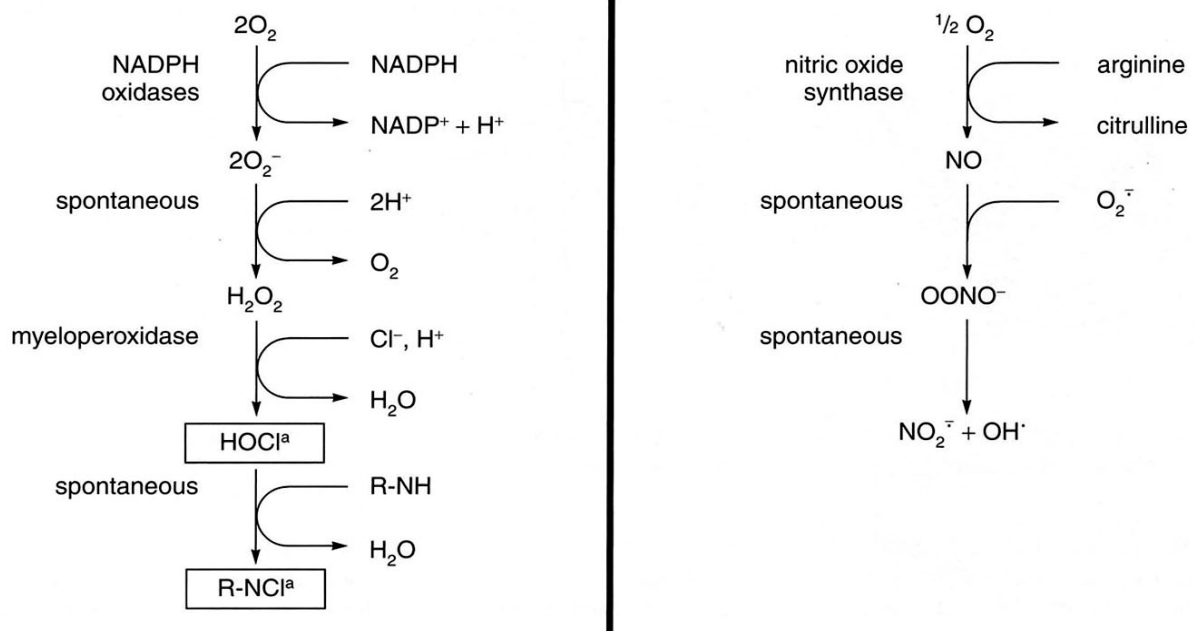


Figure 5.

6. Damage to surrounding tissues: Activated leukocytes can liberate microbicidal substances into the extracellular space, where these same substances can damage normal tissues. This is why inflammation can itself cause injury.

III. MORPHOLOGY OF ACUTE INFLAMMATION

Common features: vasodilation, edema, leukocyte (mostly neutrophil) infiltration in tissues.

In different tissues, and in response to different external stimuli, the reaction assumes particular forms that often suggest the underlying pathophysiology.

- Serous inflammation: outpouring of clear fluid in a confined space, e.g. a blister; also in cavities like the pleural cavity.
- Fibrinous inflammation: rich in fibrin; often seen on serosal surfaces (pericardium, peritoneum, pleura)
- Purulent (suppurative) inflammation: abundant pus (thick, usually green-yellowish and white fluid consisting of neutrophils, cellular debris and microbes); indicates infection.
- Cellulitis: dense infiltrate of leukocytes through tissue, usually subcutaneous, accompanied by erythema (redness); strongly suggestive of infection.
- Ulcer: discontinuity in epithelium with underlying inflammation and different stages of tissue repair; acute or chronic. Note: an erosion is a local area of denudation of surface epithelial cells to the level of the basement membrane; a type of superficial ulceration.
- Abscess: a localized collection of inflammatory cells (primarily, neutrophils); initially, walled off by fibrin and eventually, by a fibrous capsule; acute or chronic.
- Empyema: a collection of pus in a body cavity.

IV. CLINICAL CORRELATIONS

Physicians have learned to appreciate the clinical manifestations of acute inflammation because this may be the telltale sign of a life-threatening (and treatable) infection. Several of these manifestations are virtually diagnostic of acute inflammation (although the presence of inflammation will not necessarily reveal the underlying cause). In acute injury, neutrophils become detectable as early as 30 min, accumulate significantly by 8-12 hrs., and continue to arrive until chemotactic signals subside.

Local manifestations: heat, redness, swelling, pain and loss of function (the five “cardinal signs” of inflammation)

Systemic manifestations:

Fever (mediated by cytokines [primarily, TNF and IL-1], prostaglandins)

Leukocytosis (mediated by cytokines, e.g. G-CSF, GM-CSF): increased numbers of WBCs in the blood; in severe reactions, incompletely differentiated (immature) neutrophils may spill out of the bone marrow into the blood (because the nuclei are not multilobed, these are called “band” forms) -- this phenomenon is called “shift to the left”.

"Acute phase response": change in levels of several plasma proteins; caused by cytokines (especially IL-6) mediated increase in synthesis of these proteins in the liver; proteins affected include some that increase Rouleaux formation of RBCs (measured as the erythrocyte sedimentation rate), C-reactive protein, serum amyloid A precursor protein

Inflammation is the cause of clinical problems in many diseases. Sometimes, it is a minor nuisance (e.g. a sore throat – acute pharyngitis); sometimes it causes chronic and debilitating diseases (e.g. rheumatoid arthritis – chronic inflammation); and at other times it is acute and life-threatening. An example of the last group is septic shock, seen in some severe disseminated bacterial infections, especially with some gram-negative bacilli and some gram-positive cocci. In this syndrome, massive leukocyte activation leads to a “cytokine storm” (TNF, IL-1 and others), causing low blood pressure (hypotension), disseminated intravascular coagulation (DIC), and metabolic disturbances.

Clinical Outcomes of Acute Inflammation:

- a. Complete resolution
- b. Abscess formation (localized collection of pus)
- c. Scarring (fibrosis) – see Tissue Repair lecture
- d. Chronic inflammation (see next lecture)

Chronic Inflammation

OBJECTIVES

- **Compare and contrast acute vs. chronic inflammation in terms of: etiology (causes), time course, pathogenesis, and morphologic changes**
- **List the components of the mononuclear phagocyte system, and describe how macrophages are activated and what functions are performed by activated macrophages**
- **Describe the features of a granuloma, and list the major diseases in which granulomatous inflammation is a prominent feature**
- **Describe the relationships between immune responses and acute and chronic inflammation**

REQUIRED READING

Chapter 2 in *ROBBINS BASIC PATHOLOGY* (V. Kumar, A. K. Abbas, R. Mitchell), 9th edition, 2013; pages 53-58.

Main Ideas

- Inflammation becomes chronic when the offending agent cannot be eliminated.
- Chronic inflammation is characterized by co-existing active inflammation, immune response (usually), tissue destruction, and attempted repair (fibrosis, or scarring).
- Blood monocytes colonize tissues, where they differentiate into resident macrophages. Though slower and less numerous than neutrophils, they are longer-lived and relentless phagocytes, and also are able to attract and regulate many other defensive cell types, including lymphocytes.
- The principal cells in chronic inflammation are macrophages and lymphocytes, where they collaborate in carrying out intricate defensive reactions known as acquired cell-mediated immune responses; other cells that may be involved are fibroblasts, eosinophils, plasma cells.
- A granuloma is a specialized form of chronic inflammation consisting mainly of macrophages in a nodular aggregate surrounding an inciting agent that is particularly large or resistant to digestion, such as a foreign body, fungus, mycobacterium, or multicellular parasite.

I. OVERVIEW OF CHRONIC INFLAMMATION

In many respects, chronic inflammation represents a failure of the initial (acute) response to deal with the offending agent. As the offending agent persists, the adaptive immune system kicks in. Therefore, chronic inflammation often has a large component of adaptive immunity (hypersensitivity). Not surprisingly, the causes of chronic inflammation are agents that are difficult to eradicate, the most important being:

Microbes that resist clearance (mycobacteria, some viruses and fungi); and

Self-antigens, the targets of autoimmune diseases (such antigens obviously being impossible to get rid of). We have referred previously to “immune-mediated inflammatory diseases”; most of these diseases are characterized by chronic inflammation.

Chronic inflammation is largely a cellular response, with a minor (if any) role of vascular dilation and permeability.

II. PATHOGENESIS OF CHRONIC INFLAMMATION

Persistent stimuli recruit circulating cells by the same mechanisms as those described in the previous lecture. The principal cells involved in chronic inflammation are:

- Blood monocytes and their tissue counterpart, macrophages (the cells of the mononuclear phagocyte system), the body's most powerful phagocytes
- Lymphocytes, including effector T lymphocytes (CD4⁺ helper and CD8⁺ CTLs), which enhance recruitment and activation of macrophages, and antibody-secreting cells (plasma cells)
- In special cases, eosinophils predominate
- Fibroblasts and blood vessels involved in the repair reaction (discussed in the next lecture, on Tissue Repair)

A. The Monocyte/Mononuclear/Macrophage Series Nearly all tissues, organs, and internal body cavities contain resident phagocytes. May be rare or very abundant (e.g., Kupffer cells make up 10% of the liver), and may have specialized morphology and specific names in some tissues, but all are derived from blood monocytes and all belong to a single cell lineage called the mononuclear phagocytes or the monocyte/macrophage series.

1. Monocytes and Macrophages

- a. Moderately large, with kidney-shaped nucleus, loose chromatin, fairly abundant cytoplasm containing lysosomal granules.
- b. Unlike neutrophils, monocytes:
 - are not very numerous in peripheral blood (1-6% of WBCs);
 - do not have conspicuously large and numerous granules in their cytoplasm, BUT
 - have abundant rough ER and Golgi, so they can synthesize new granules and new membrane or secretory proteins as needed;
 - have numerous mitochondria;
 - are not terminally differentiated – i.e., they have at least some capacity to divide;
 - are not fully mature cells; and
 - do not normally circulate throughout their lives.

2. Life cycle:
 - a. Produced, but not stored, in bone marrow
 - b. Released to blood, circulate for about 24 hrs.
 - c. Migrate into a tissue and take up permanent residence. How they choose the tissue is not known; probably involves chemokines. Once settled, they are “tissue macrophages” or “histiocytes.”

Cells of the Monocyte-Macrophage Lineage

<u>TISSUE</u>	<u>CELL TYPE DESIGNATION</u>
Blood	Monocytes
Bone marrow	Monocytes & monocyte precursors (monoblasts, promonocytes)
Any solid tissue	Resident macrophages (histiocytes) & myeloid dendritic cells
Skin	Langerhans' cells
Liver	Kupffer cells
Lung	Alveolar macrophages
Bone	Osteoclasts
Synovium	Type A synovial cells
Central nervous system	Microglia
Pleural cavity	Pleural macrophages
Peritoneal cavity	Peritoneal macrophages
Chronic inflammatory exudate	Exudate macrophages
Granuloma	Epithelioid cells multinucleated giant cells

- d. Live 2-4 months (60-120 days) in tissue, either stationary or wandering around by amoeboid motion.
- e. Constantly sampling their surroundings by phagocytosis, pinocytosis, and receptor-mediated endocytosis.

3. MACROPHAGE ACTIVATION

- a. If a macrophage encounters certain signals of tissue distress, it undergoes activation, characterized by increased:
 - size (especially cytoplasm)
 - motility
 - metabolic rate
 - effector functions (see below)
- b. Signals for macrophage activation include:
 - Interferon- γ , a cytokine secreted by lymphocytes and other cells (Note: lymphocyte/macrophage collaboration!)

- Byproducts of tissue injury and/or host responses such as: complement activation, blood coagulation, and collagen breakdown
- Unique microbial products such as: bacterial lipopolysaccharide (LPS) and other lipid-rich foreign macromolecules as well as bacterial DNA

4. MACROPHAGE EFFECTOR FUNCTIONS

a. Phagocytosis

- Like neutrophils, each macrophage has numerous surface receptors that enable it to recognize and engulf a wide range of particles. A partial list includes:
Toll-like receptors – a family of receptors that recognize bacterial lipopolysaccharide and other lipophilic microbial macromolecules. Upon binding, they transmit powerful activation signals to the macrophage.

Scavenger receptors – a family of broad-specificity receptors that mediate binding and endocytosis, especially of negatively-charged ligands. Probably important for recognizing apoptotic cells (via surface phosphatidylserine); also many other ligands.

Receptors for opsonins – especially complement byproducts, mannose binding lectin, and immunoglobulin proteins secreted by lymphocytes.
 (Note: lymphocyte/macrophage collaboration!)

- Mechanisms of engulfment, degranulation, and killing are as described for neutrophils, EXCEPT:
 Metabolic burst is less pronounced; digestion occurs more slowly (because fewer granules available at any moment)

Digestion continues much longer (because the macrophage lives much longer and can synthesize new granules as needed)

Indigestible material can be sequestered inside the macrophage, sometimes for decades (e.g., carbon particles in smokers' lungs; talc; tattoos)

- When necessary, multiple macrophages can either fuse to form a multinucleate giant cell that is able to engulf larger particles, such as splinters, surgical sutures, or multicellular parasites; or link together through complex folds of their surfaces, forming a continuous sheet of macrophages (called epithelioid cells) that can entrap the foreign material.

b. Secretion – Activated macrophages can secrete a diverse array of products that are useful for host defense and/or wound repair, including:

- Antimicrobial enzymes – e.g., lysozyme
- Proteases and other hydrolytic enzymes – e.g., elastase and collagenase
- Reactive oxygen species, nitric oxide, hydrogen peroxide

- Complement and blood coagulation proteins
- Proteins that regulate other host defensive cells and activities, including:
Chemokines – attract other leukocytes, including lymphocytes
(Note: lymphocyte/macrophage collaboration!)

Cytokines — such as interleukin-1, -6 (which induces fever), granulocyte-monocyte colony-stimulating factor (GM-CSF, which prolongs survival of neutrophils in an inflamed tissue by preventing their apoptosis), and interleukin-12 (which controls lymphocyte differentiation).
(Note: lymphocyte/macrophage collaboration!)

Other inflammatory mediators, e.g., prostaglandins, nitric oxide

- c. Antigen presentation – macrophages are among a small number of cell types that functional as “professional” antigen-presenting cells (APCs), e.g., cells that can capture and display foreign substances in a form that can be recognized and responded to by lymphocytes. APCs are essential for many types of host defense and will be discussed in great detail next year.
(Note: macrophage/lymphocyte collaboration!)

B. Lymphocytes and Other Cells

T lymphocytes: CD4⁺ helper cells (usually of the Th1 subset) and CD8⁺ CTLs, responding to peptides derived from microbial or self-antigens. Both Th1 cells and CTLs secrete the cytokine IFN-gamma, which activates macrophages. It is easy to understand how this reaction can become a vicious cycle – macrophages display peptide antigens to T-cells and secrete the T-cell-activating cytokine IL-12 – T-cells develop into Th1 cells and secrete the macrophage-activating cytokine IFN-gamma – and so on. This “cross-talk” between macrophages and T lymphocytes sets up an internal amplification (positive feedback) loop, because of which chronic inflammatory diseases are often persistent, progressive, and difficult to treat.

B-lymphocytes and plasma cells

In special circumstances, other cells such as **eosinophils** (e.g., in persistent allergies and infection by helminthic parasites).

III. MORPHOLOGY OF CHRONIC INFLAMMATION

Chronic inflammatory reactions show variable mixtures of macrophage and lymphocyte infiltration, tissue necrosis, and scarring.

Granulomas (type of chronic inflammation)

1. Certain organisms and foreign substances typically provoke a specialized form of chronic inflammation known as granulomatous inflammation. This is characterized as follows:
 - a. The infiltrate is composed mainly of macrophages, with a variable minority of lymphocytes and other cells.

- b. The macrophages accumulate as dense nodules around the inciting agent. The nodules themselves are whitish masses, often visible with the naked eye.
 - c. Multinuclear giant cells are common due to the fusion of modified macrophages.
 - d. Under the microscope, the inciting agent can often be identified inside the granuloma.
- 2. Agents that induce granulomas tend to be large, insoluble, and hard to digest. Major etiologies include:
 - a. Mycobacteria, notably *M. tuberculosis*
 - b. Fungi
 - c. Foreign bodies (e.g.: talc, suture material, hair, carbon, etc.)
 - d. Sarcoidosis (a disease whose cause is unknown)
- 3. Caseation – Necrosis of the center of a granuloma, usually due to *M. tuberculosis* or, less often, to other mycobacterial or fungal organisms. Produces a semi-solid, friable, “cheesy” slurry of lipid-rich debris at the core. Think tuberculosis until proven otherwise!
- 4. Resolution – After the initial threat is controlled, macrophages stay on the scene to eliminate (by phagocytosis and by secreting hydrolytic enzymes) any remaining cellular or foreign debris from the tissue, thus setting the stage for tissue repair.

IV. CLINICAL CORRELATES

- A. Macrophages and lymphocytes collaborate in many ways, and so tend to be found together.
- B. Because of their relative scarcity in the bloodstream, limited replicative capacity, and slow migration, macrophages accumulate slowly in inflamed tissues, requiring about a week to reach significant numbers. The lymphocytes arrive shortly thereafter.
- C. An inflammatory infiltrate composed mainly of macrophages and lymphocytes (in any proportion) is, by definition, a chronic infiltrate.
- D. In chronic inflammation, the cardinal signs and associated features of inflammation (e.g.: fever and night sweats due to TNF and IL-1) tend to develop more slowly and are less prominent than in acute inflammation, but may persist for decades.
- E. Even when demand is high, the number of monocytes circulating in peripheral blood rarely increases significantly.

V. SUMMARY

Acute and chronic inflammatory infiltrates represent two distinct patterns of host defense, each best suited for particular purposes. The neutrophils of an acute infiltrate are abundant, rapidly available, and identical, and they respond quickly and intensely to generic signals of tissue injury or infection. Their repertoire of responses, however, is very limited, and their lives very short. Macrophages, on the other hand, respond more slowly but are much more durable and versatile, and are able to control the activities of

other effector cell types. In particular, chronic infiltrates represent a collaboration between macrophages and lymphocytes – the cells responsible for many of the body's most elegant and specific immune responses.

Tissue Repair: Regeneration and Healing I & II**OBJECTIVES**

- *Compare and contrast repair, regeneration and healing*
- *Classify the regenerative capacity of various tissue types in terms of labile, stable, or permanent cells*
- *Describe the components of tissue repair involved in wound healing, including the cells, growth factors/cytokines and components of the extracellular matrix*
- *Describe the sequence of cutaneous wound healing referred to as primary or secondary healing, as well as the factors that retard these processes*

READING: Robbins Basic Pathology, Kumar, Abbas, Mitchell, 9th Ed., 2013, pp. 58-73.

I. INTRODUCTION

Cells, tissues and organs are constantly being exposed to some type of potential injury; therefore, multicellular organisms have evolved a complex array of biochemical and cellular responses to help repair and restore the normal anatomic architecture and function that was initially altered and/or lost from an injurious insult. The **reparative process** covers a spectrum from **regeneration** where anatomic structures are completely replaced by the growth of new cells and tissues (e.g., growth of a new tail from a lizard whose tail was lost to a predator) to **healing** (a tissue response to a wound, inflammation, or necrosis) leading to collagen deposition and scar formation (**fibrosis**). In mammals, the reparative process has a limited capacity for regeneration and a greater propensity for healing with fibrosis, which is dependent upon the cell type, and the duration, severity and depth of the injury.

II. DEFINITIONS

A. **An injury or a wound** may result from a pathologic process that is either external or internal to the body. It is the disruption of normal anatomic structure and function. It can include:

a cut or burn	infarction	chemical injury	tumor invasion
immune reaction	infection	mechanical injury	genetic defect

B. **Classification of Wounds** into two broad categories: **acute** and **chronic**

Acute wounds proceed through an orderly and timely reparative process that results in complete or partial restoration of anatomic structure and function (e.g., acute bacterial pneumonia).

Chronic wounds have failed to proceed in an orderly and timely reparative process to produce restoration of anatomic structure and function (e.g., non-

healing diabetic foot ulcer), or proceeded through the repair process without establishing a sustained anatomic structure and function (e.g., severe cutaneous burn leading to extensive fibrosis/scarring, cirrhosis of the liver due to chronic alcohol use).

III. CLASSIFICATION OF TISSUE TYPES ACCORDING TO REGENERATIVE CAPACITY

- A. **Labile tissues (continuously dividing tissues)**: Cells are constantly proliferating throughout life. These include blood-forming or hematopoietic cells of the bone marrow and hematopoietic tissues; surface epithelial cells such as stratified squamous epithelium of the skin, oral cavity, esophagus, anus, vagina and cervix; columnar epithelium of the gastrointestinal tract and uterus; the lining epithelium of all the excretory ducts of the glands of the body including the sweat glands, salivary glands, pancreas and biliary tract; the transitional epithelium of the urinary tract and sperm-forming cells of the testes. In most of these examples, the differentiated cells are derived from tissue **stem cells** (an unlimited capacity to proliferate and the ability to generate progeny that can undergo different lines of differentiation) located in a unique site called a **niche** (e.g., bulge of a hair follicle, crypts of the intestine).
- B. **Stable tissues (quiescent tissues)**: Cells with normally a low level of replication that can undergo rapid division in response to stimuli. These tissues have the capacity to reconstitute the tissue of origin; this regeneration depends on the maintenance of a normal connective tissue framework, e.g., an intact basement membrane. Once connective tissue framework is disrupted, regeneration does not occur. Replacement is by mitosis of more differentiated cells, e.g., epithelial cells of liver including hepatocytes and bile duct cells, kidney, adrenal, and thyroid glands; fibroblasts of connective tissue, smooth muscle, chondrocytes, osteocytes and the endothelium of blood vessels. Stem cells can also contribute to cell proliferation.
- C. **Permanent tissues (nondividing tissues)**: cells that have lost the ability to replicate and no apparent stem cells exist, e.g., cardiac muscle cells, germ cells of ovary and most populations of neurons. The apparent loss of most permanent tissues is often replaced with collagen deposition or fibrosis (scar formation). However, the central nervous system contains a paucity of fibroblasts except around blood vessels and will not produce a fibrous scar but a “glial scar” surrounding a cystic space following infarction.

III. THE COMPONENTS OF HEALING

- A. **Overview**: Classic steps of **wound healing** involves multiple overlapping processes leading to wound closure. It refers to a sequence of biological events including: hemostasis (platelets and fibrin); inflammation (neutrophils,

macrophages and lymphocytes); regeneration (re-epithelization); fibrosis (angiogenesis, fibroblasts), synthesis of extracellular matrix including fibronectin, laminin, proteoglycans and collagen deposition); and remodeling (collagen fibril crosslinking and degradation, scar formation) and ultimately, complete or partial restoration of anatomic structure and function. Throughout these overlapping processes, many different cytokines are being released that help modulate and control the healing process (see Table 2).

B. The Contribution of the Circulation - review Hemostasis and Blood Lectures

At the site of injury, hemorrhage occurs and injured blood vessels undergo immediate vasoconstriction due to the release of catecholamines. Other vasoactive compounds (bradykinin, serotonin, histamine) are released from mast cells leading to diapedesis, the passage of intravascular constituents through the blood vessel wall. Coagulation cascade is initiated and platelets aggregate to form a blood clot (fibrin, platelets and red blood cells and leukocytes) overlying the wound which will later become the **eschar** (“scab”), provides a protective cover. The blood clot becomes a provisional extracellular matrix for cell migration (leukocytes and fibroblasts). The platelets secrete several mediators including platelet-derived growth factor, that will attract and activate macrophages and fibroblasts. However, hemorrhage and platelets are not essential to wound healing because vasoactive mediators and chemotactic factors are generated from coagulation and activated complement pathways as well as injured parenchyma cells.

C. Inflammatory Response - review Acute and Chronic Inflammation Lectures

INJURY → INFLAMMATION → REPAIR

The cells of wound healing include the cells of inflammation (leukocytes including neutrophils, macrophages, lymphocytes). The infiltrating neutrophils will remove the bacteria and foreign material within the wound by extruding them into the scab or by activated macrophages. The activated macrophages release growth factors (see Table 1) which will initiate the formation of **granulation tissue** (collection of activated fibroblasts and new blood vessels (neovascularization) through the process of angiogenesis.

Of all of the inflammatory cells, the **MACROPHAGE** is key. The macrophage secretes numerous cytokines important repair (see Table 1 below) and is phagocytic.

D. Regeneration (Re-epithelization)

Re-epithelization of wounds occurs within hours after injury. The re-epithelization process involves two mechanisms: migration and mitosis (replication). Migration is the dominant process followed by replication. The

more superficial the wound or injury the re-epithelization is hastened. The epithelial cells migrate as sheets of cells with the leading cells phagocytizing the debris in front of them. These cells secrete collagenase and plasminogen activator. When there are no further cells for migration then mitosis begins.

E. Extracellular Matrix Deposition, Fibrosis and Angiogenesis

The Extracellular Matrix (ECM) - review Extracellular Matrix and Connective Tissue Lecture

The ECM consists primarily of adhesion and fibrous proteins embedded in a hydrated polysaccharide gel. The two main classes of extracellular macromolecules that make up the matrix are (1) proteoglycans; and (2) fibrous structural proteins (e.g., collagen (Table 1) and elastin) 3) laminin and fibronectin for cellular migration. The proteoglycans form a highly hydrated, gel-like “ground substance” in which the fibrous proteins are embedded. The gel permits diffusion of nutrients, metabolites, growth factors and hormones; the collagen fibers strengthen and help to organize the matrix, and rubberlike elastin fibers give it resilience. Growth factors are also embedded in this gel.

TABLE 1 MAJOR COLLAGENS

Collagen	Location	Cells
Type I	Skin, bone, tendon: hard mature scar tissue late in fibrosis and in late cirrhosis, constituting 90% body collagen	Primarily fibroblasts, but in other cells also
Type II	Cartilage	Chondrocytes
Type III	Blood vessels, smooth muscle as in uterus, GI tract, and other hollow organs; in rapidly proliferating tissues; during embryogenesis, wound healing, organ regeneration; early cirrhosis and fibrosis	Smooth muscle cells, primitive fibroblasts and stem cells
Type IV	Basement membranes	Epithelial cells and highly specialized stromal cells such as endothelial and muscle cells.

Fibrosis - Collagen in Early vs. Late Wound Healing

In nature, it is common for a temporary scaffolding to be made before the permanent structure is laid down. Collagen synthesis is increased due to growth factors (PDGF, FGF, TGF- β) and interleukins-1 and -13. In scar

formation, Type **III** collagen is deposited in early wound healing (granulation tissue), forming thin, soft, collagenous fibers. Tough type **I** collagen forms thick fibers, and is deposited in mature scar (see Tissue Remodeling below), associated with wound contraction. The permanent, hard, white, fibrous type I collagen scar takes about 10 days to 2 weeks to form, but lasts for years.

Elastin is a cross-linked random-coil protein that gives tissues their elasticity. Tissues such as skin, blood vessels, gastrointestinal tract, uterus, and lung require elasticity in order to function. A network of elastic fibers in the ECM of these tissues gives them the required ability to recoil after transient stretch. Elastin is usually associated with a glycoprotein called fibrillin. Together they make up the elastin fiber.

Proteoglycans are proteins decorated with straight chain sugars called GAGs (glycosaminoglycans). They control collagen fiber diameters, bind growth factors, and have general regulatory functions in the extracellular matrix.

Angiogenesis (neovasculation) occurs with the secretion of VEGF (vascular endothelial growth factor) by mesenchymal cells and stromal cells. VEGF stimulates new blood vessels by 1) stimulating proliferation and migration of endothelial cells from pre-existing local vessels and 2) the mobilization of endothelial cell precursors from the bone marrow. The new blood vessels are leaky and need to be stabilized with the requirement of pericytes and smooth muscle cells, and the deposition of extracellular matrix proteins. This stabilization process is dependent upon the secretion of angiopoietins, PDGF and beta-TGF.

Another important event in wound healing is **wound contraction**, which is one of the most powerful mechanical forces in the body. The exact mechanism is unknown. However, specialized fibroblasts with smooth muscle cellular components appear in the wound called **myofibroblasts**. The myofibroblasts are located in the center of the granulation tissue and at the margins of the wound. These cells are at the greatest number during and after wound contraction.

F. Tissue Remodeling

Tissue remodeling is the time when granulation tissue evolves into scar formation and changes in the extracellular matrix. A balance between extracellular matrix synthesis and degradation begins. Matrix metalloproteinases (MMPS) are interstitial collagenases (cleave collagen types I, II, and III), gelatinases (degrade collagen and fibronectin) and stromelysins (degrade proteoglycans, laminin, fibronectin, and amorphous collagens). These proteases are secreted into the healing wound and require zinc as a cofactor. There is also a family of specific tissue inhibitors of metalloproteinases (TIMPs) which are produced by most mesenchymal cells.

TGF- inhibits the synthesis of MMPS and stimulates TIMP synthesis. This tissue remodeling eventually slows down to a quiescent state once scar formation is complete.

E. The Signals of Wound Healing

Table 2: Cytokines Affecting Wound Healing

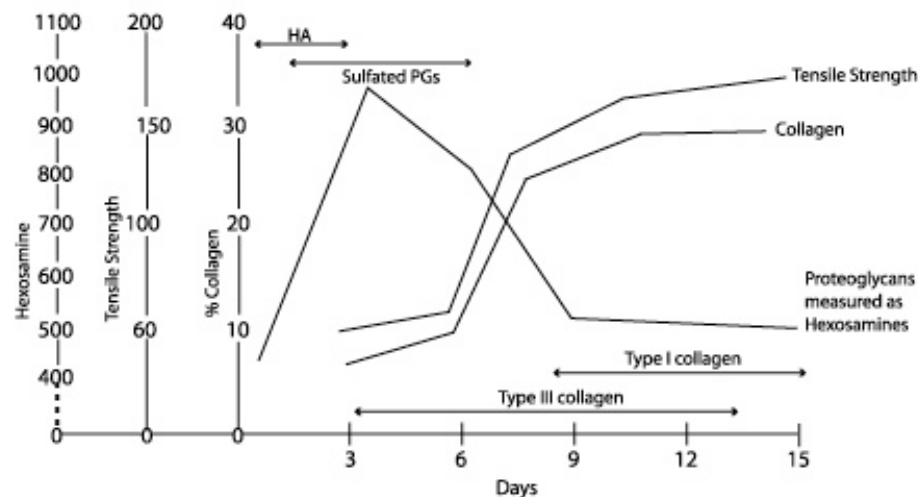
Cytokine	Symbol	Source	Target Cells and Major Effects
Platelet-derived growth factor	PDGF	Platelets, macrophages , endothelial cells, keratinocytes, smooth muscle cells	Chemotactic for neutrophils, macrophages, fibroblasts, and smooth muscle cells; activates neutrophils, macrophages, and fibroblasts; mitogenic for fibroblasts, endothelial cells, and smooth muscle cells; stimulates production of MMPs, fibronectin, and hyaluronic acid; stimulates angiogenesis and wound contraction; remodeling; inhibits platelet aggregation; regulates integrin expression
Transforming growth factor beta family (1, 2 and 3)	TGF-beta	Platelets, T lymphocytes, macrophages (3), endothelial cells, keratinocytes, smooth muscle cells, fibroblasts	Chemotactic for neutrophils, macrophages, lymphocytes, fibroblasts, and smooth muscle cells, stimulates TIMP synthesis, keratinocyte migration, angiogenesis, and fibrosis; inhibits production of MMPs and keratinocyte proliferation; regulates integrin expression and other cytokines; induces TGF-beta production
Epidermal growth factor	EGF	Platelets, macrophages , saliva, urine, milk, plasma	Mitogenic for keratinocytes and fibroblasts; stimulates keratinocyte migration and granulation tissue formation
Transforming growth factor alpha	TGF-alpha	Macrophages , T lymphocytes, keratinocytes, and many tissues	Similar to EGF
Fibroblastic growth factor family (basic and acidic forms)	FGF	Macrophages , mast cells, T lymphocytes, endothelial cells, fibroblasts, and many tissues	Chemotactic for fibroblasts; mitogenic for fibroblasts and keratinocytes; stimulates keratinocyte migration, angiogenesis, wound contraction and extracellular matrix deposition
Keratinocyte growth factor (FGF-7)	KGF	Fibroblasts	Stimulates keratinocyte migration, proliferation, and differentiation
Insulin-like growth factor-1	IGF	Liver, macrophages , fibroblasts, epidermal cells, and other cells	Stimulates synthesis of sulfated proteoglycans and collagen, keratinocyte migration, and fibroblastic proliferation; endocrine effects similar to growth hormone

Connective tissue growth factor	CTGF	Endothelial cells, fibroblasts	Chemotactic and mitogenic for various connective tissue cells
Vascular endothelial cell growth factor	VEGF	Epidermal cells, macrophages	Increases vasopermeability; mitogenic for endothelial cells; angiogenesis
Tumor necrosis factor alpha	TNF-alpha	Macrophages , mast cells, T lymphocytes	Activates macrophages; mitogenic for fibroblasts; stimulates angiogenesis; regulates other cytokines
Interleukins	IL-1, etc.	Macrophages , mast cells, keratinocytes, lymphocytes, and many tissues	Chemotactic for neutrophils (IL-1) and fibroblasts (IL-4); stimulates MMP-1 synthesis (IL-1), angiogenesis (IL-8), TIMP synthesis (IL-6); regulates other cytokines
Interferons	IFN-alpha, etc.	Lymphocytes and fibroblasts	Activates macrophages; inhibits fibroblast proliferation and synthesis of MMPs; regulates other cytokines
Colony-stimulating factor -1	CSF-1	Multiple cells	Activates macrophages and stimulates granulation tissue formation

V. THE ACTUAL SEQUENCE AND TYPES OF CUTANEOUS WOUND HEALING

A. **Primary Union** (“healing by first intention”): Clean wound, with edges brought into contact. (**Figure 1**)

1. **First 24 hours:**

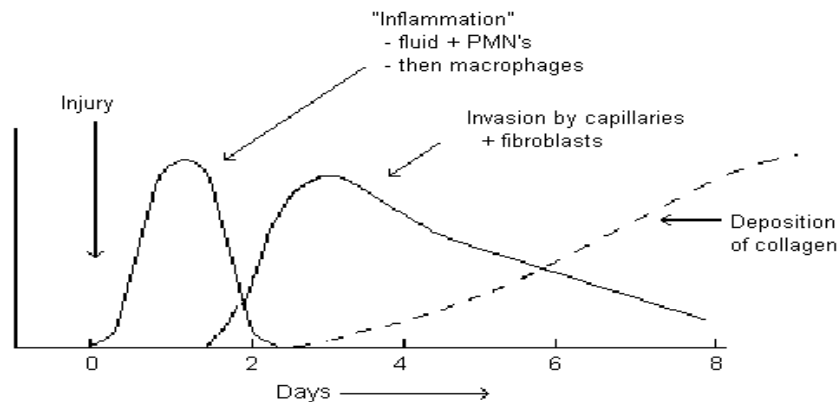


- a. Blood clot fills wound; platelets contract and thus reduce the defect; the fibrin-containing scab protects against desiccation, drying and bacterial penetration.
 - b. Acute inflammation: Primarily neutrophils in the wound (PMNs).
 - c. Epithelial migration: Begins at 1 hr., approximately 1 mm/day.
2. **By 3 days:**
- a. Macrophages digest fibrin, red blood cells and tissue debris.
 - b. Fibroblasts enlarge, proliferate and migrate.
 - c. Endothelial cells of nearby vessels proliferate and extend toward the wound. Capillary sprouts advance 0.2 mm/day as solid columns and anastomose with neighbors to form a plexus of vessels.
3. **By 5 days:**
- a. Fibroblasts and small blood vessels bridge the defect.
 - b. Granulation tissue is weak, mostly collagen III; new blood vessels are weak and bleed easily.
 - c. Epidermis regenerated.
4. **Between 6 and 12 days:**
- a. Collagen I synthesis:
 - b. Day 7, wound at 10-20% strength
 - c. Day 12-14, collagen increased to give enough strength to have sutures removed (70-80% strength).
5. **From 12 days to 1 year:**
- a. Remodeling phase: Collagen also becomes increasingly insoluble as it becomes more cross-linked.

B. Secondary Union (“healing by second intention” a gaping wound)

Definition: Granulation tissue—a combination of lymphocytes, macrophages, fibroblasts, and growing blood vessels. In healing by primary union, granulation tissue is minimal; in secondary union it can be extensive.

SCHEMATIC OF WOUND HEALING



General scheme for deposition of collagen during wound healing.

Figure 2.

1. Distinctive features
 - a. Amount of granulation tissue is greater than in primary union.
 - b. Wound contraction is prominent. Myofibroblasts are fibroblasts that contain smooth muscle filaments in their cytoplasm. Their contraction is important in reducing size of defect (contraction).
 - c. Bacterial contamination is inevitable.
 - d. Epidermis migration is slow: Upward growth of granulation occurs as the defect is filled.
2. Advantages are that:
 - a. Large defects may be closed.
 - b. Severely contaminated wounds may heal.

C. Complications of Cutaneous Wound Healing

- a. Inadequate formation of granulation tissue or scar can lead to **wound dehiscence** (rupture of a wound) and ulceration.
- b. Wound **contraction** may result in severe disfigurement and local immobilization due to the formation of a contracture; commonly seen in severely burned patients.
- c. Exuberant granulation tissue may protrude from the wound ("proud flesh") impeding wound healing (e.g., re-epithelization) and lead to greater scar formation and/or increased risk for infection.
- d. Excessive collagen formation and/or decreased degradation:

Hypertrophic scar – exuberant scar formation remains within the boundaries of the original wound and almost always regress over a period of time.

Keloid – scar tissue that extends beyond the boundaries of the original wound and usually does not regress.

VI. PATHOLOGY OF HEALING

Table 3 Factors that Retard Healing

Local Factors	Systemic Factors
Blood supply	Age
Denervation	Anemia
Local infection	Drugs (e.g., steroids, cytotoxic medications, intensive antibiotic therapy)
Foreign body	Genetic disorders (e.g., osteogenesis imperfecta, Ehlers-Danlos syndromes, Marfan's syndrome)
Hematoma	Hormones
Mechanical stress	Jaundice
Necrotic tissue	Malignant disease
Protection (dressings)	Malnutrition
Surgical technique	Obesity
Type of Tissue	Systemic infection
	Temperature
	Trauma, hypovolemia and hypoxia
	Uremia
	Vitamin deficiency (e.g., vitamin C)
	Trace metal deficiency (e.g., zinc, copper)

B. Organization: Replacement of wound healing exudate by granulation tissue leading to fibrosis is called organization.

1. In body cavities, such organization causes fibrous adhesions.
2. On heart valves, organization leads to stenosis (thickening of valves, makes them rigid, keeps them from opening fully) or insufficiency (scar contraction keeps valve from closing fully).
3. In lungs, organization reduces total lung capacity.
4. In joint cavities, such organization can immobilize/fuse a joint (ankylosis).
5. When a localized collection of pus (abscess) in organs and tissues is walled off by a fibrous capsule.

VII. Summary

Tissue repair is a very important biological process in all organ systems in response to injury. Each tissue in the human body has evolved a complex array of biochemical and cellular reparative responses to injury including regeneration, healing, and fibrosis.

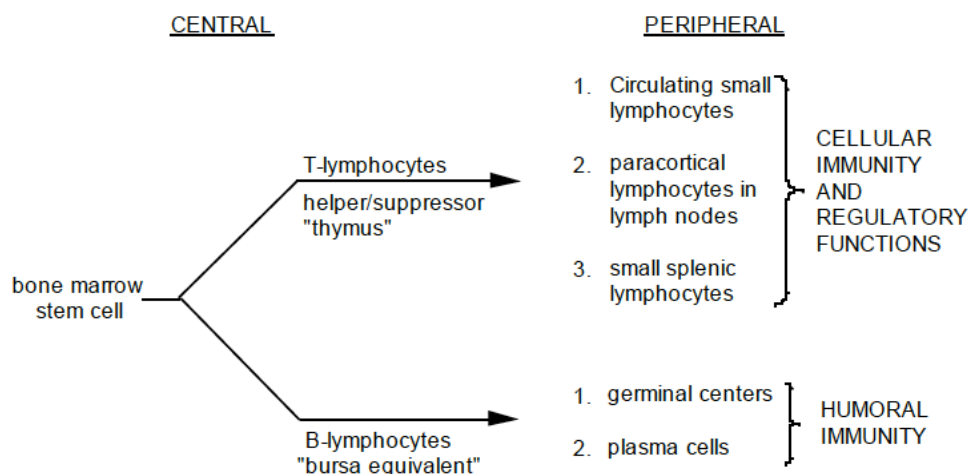
Immunopathology I and II**Objectives:**

- *Define and explain fundamental primary (congenital) immunodeficiencies.*
- *Compare and contrast the mechanisms and patterns of tissue damage due to hypersensitivity reactions.*
- *Describe the causes and types of autoimmune diseases.*

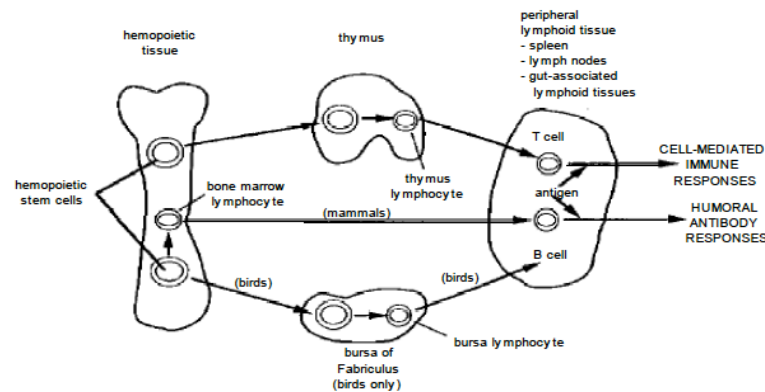
READING: Robbins Basic Pathology, Kumar, Abbas, Mitchell, 9th Ed., 2013, pp.139-143, 109-120, 120-135.

I. Immunological Deficiency Diseases**A. The thymus and bursa of Fabricius of the chicken: Original experimental model**

1. Suggested two morphologically and functionally distinct populations of immunocytes.
2. Thymectomized chicks are deficient in cellular immunity, i.e., delayed hypersensitivity and graft vs. host reactions are diminished and graft rejection is impaired. They are lymphopenic and lack small lymphocytes in the spleen (chicken lack lymph nodes).
3. Bursectomized chicks are deficient in humoral immunity, i.e., their circulating levels of immunoglobulins are severely depressed and they do not respond with antibody production, even when hyperimmunized. They lack plasma cells and germinal centers.

B. Probable development of the mammalian immune system, based on the chicken model:

1. The thymus and the bursa equivalent are CENTRAL lymphoid organs providing cells and stimulatory factors for the immunologically active PERIPHERAL immune system.
2. The mammalian bursa equivalent has not been directly demonstrated, but is thought to be either gut-associated lymphoid tissue (Peyer's patches, etc.) or a cell population within the bone marrow.



II. Primary immunologic deficiency diseases:

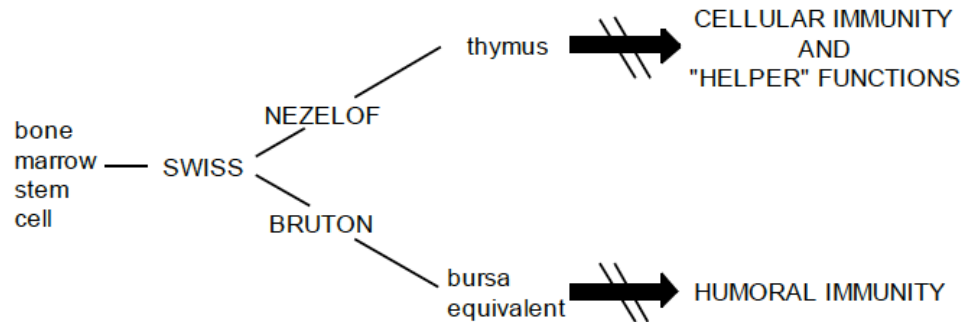
1. General: It was noted in the 1950's that infants born with anatomical defects of their lymphoid organs (i.e., thymus, lymph nodes, spleen) were immunological "cripples" subject to overwhelming infection. Often the anatomical defect correlated with a specific clinical syndrome and with infection by a specific category of microorganisms, such as fungi, viruses, or bacteria.
2. Severe Combined Immunodeficiency: Swiss agammaglobulinemia (autosomal recessive) and X-linked recessive forms:
 - a. Thymus vestigial, circulating lymphocytes below 600/cu. mm. and paracortical areas of lymph nodes depleted.
 - b. Germinal centers and plasma cells essentially absent.
 - c. These children almost completely lack immune defenses, both humoral and cell-mediated.
 - d. The most severe of the primary immunological deficiency diseases, with essentially complete absence of B- and T-lymphocytes. Characterized by early death due to bacterial, fungal and viral infections of the respiratory and gastrointestinal tracts as well as of the skin.
 - e. Subset of patients have single enzyme defect-adenosine deaminase. Therapies include enzyme replacement, bone marrow transplant, and recently gene therapy--insertion of gene into lymphocyte genome.

3. DiGeorge (22q11.2 deletion) Syndrome: Cellular Immunodeficiency with Abnormal Immunoglobulin Synthesis:
 - a. The thymus is essentially nonlymphoid, paracortical areas of lymph nodes are depleted, and there is lymphopenia.
 - b. Germinal centers are variable, ranging from absent to nearly normal. B-lymphocytes and plasma cells are present.
 - c. Cellular immunity is severely impaired due to lack of T-lymphocytes. Immunoglobulin levels are generally low and there may be dysglobulinemia.

NOTE: The imperfect humoral system in these children probably reflects lack of T-lymphocyte helper function and/or thymic factors which are necessary for normal humoral responses.

- d. These patients are subject to overwhelming virus and fungal infections, particularly candidiasis. Severe recurrent viral infection or candidiasis have, in fact, become clinical signs suggesting of thymic disorder.
 - e. Condition is not unlike a "congenital AIDS."
4. X-linked infantile hypogammaglobulinemia (Bruton type):
 - a. Thymus essentially normal, with normal numbers of circulating and paracortical lymphocytes; normal population of T-lymphocytes.
 - b. Germinal centers and plasma cells completely lacking; B-lymphocytes "absent" in that immunoglobulin-bearing cells are reduced greatly in numbers. However, lymphocytes with surface receptors for complement (a B cell characteristic) are present in normal numbers. This suggests a maturational defect in the B-lymphocyte population rather than a complete lack of this cell type.
 - c. Striking defect in humoral response with extreme deficiency of all major immunoglobulins. Response to hyperimmunization is nil. Cellular immunity is essentially normal.
 - d. High susceptibility to bacterial infections. Survival directly related to availability of antibiotic and gamma globulin administration.

5. Suggested pathogenesis of primary immunological deficiency diseases based on chicken model.



NOTE: The three examples given fit this scheme well. Primary immunological deficiency disease of greater complexity is more difficult to classify. An excellent example is the Wiskott-Aldrich syndrome. Affected children have lymphopenia and lack of delayed hypersensitivity, as assayed by skin testing; but they also have a partial humoral immune defect in that their response to carbohydrate (but not to protein) antigens is impaired.

6. Phagocytic defects: Chronic granulomatous disease of childhood

Male infants who are susceptible to infection with unusual organisms. Neutrophil and monocyte phagocytosis is defective.
7. Complement defects: Several are known leads to decreased resistance to infection
8. Inability to control Epstein Barr Virus (EBV), lethal infectious mononucleosis syndrome

III. Secondary immunological deficiency diseases

1. HIV disease and AIDS (see later lecture)
2. Iatrogenic:
 - a. X-irradiation
 - b. Immunosuppressive drugs
 - i. transplantation
 - ii. anti-neoplastic
 - iii. anti-autoimmune
3. Secondary to malignancy
 - a. Hodgkin lymphoma (may already be an underlying immune deficiency)
 - b. Myelophthistic phenomena - neutropenias

IV. Hypersensitivity - Immunological responses leading to tissue injury.

A. Immediate (Type I) Hypersensitivity (Anaphylactic type)

Definition: antigen reacting to sensitized mast cells or basophils causing subsequent degranulation.

Sensitization: binding of Ig usually IgE to mast cell surface after T_H2 releases cytokines stimulating B-cells to secrete IgE. The allergen or antigen specifically binds to the binding site surface Ig on the mast cell resulting in degranulation.

Degranulation: the vasoactive amines and other biologically active substances such as ECF (eosinophil chemotactic factor) and heparin are packaged in mast cell granules. Crosslinking of surface IgE by antigen causes adenylate cyclase activation and subsequent increases in intracellular Ca. The mast cell degranulates and releases the contents, the so-called primary mediators of anaphylaxis.

Secondary mediators: these include leukotrienes and prostaglandins produced by the activation of the arachidonic acid metabolism in the mast cell membrane. These substances cause smooth muscle contraction (bronchospasm), chemotaxis of neutrophils, macrophages and eosinophils, vasodilation and modify platelet function.

Eosinophils are the regulators of anaphylaxis by releasing such substances as histaminases. The eosinophil is the histological hallmark of Type I reactions such as asthma and parasitism.

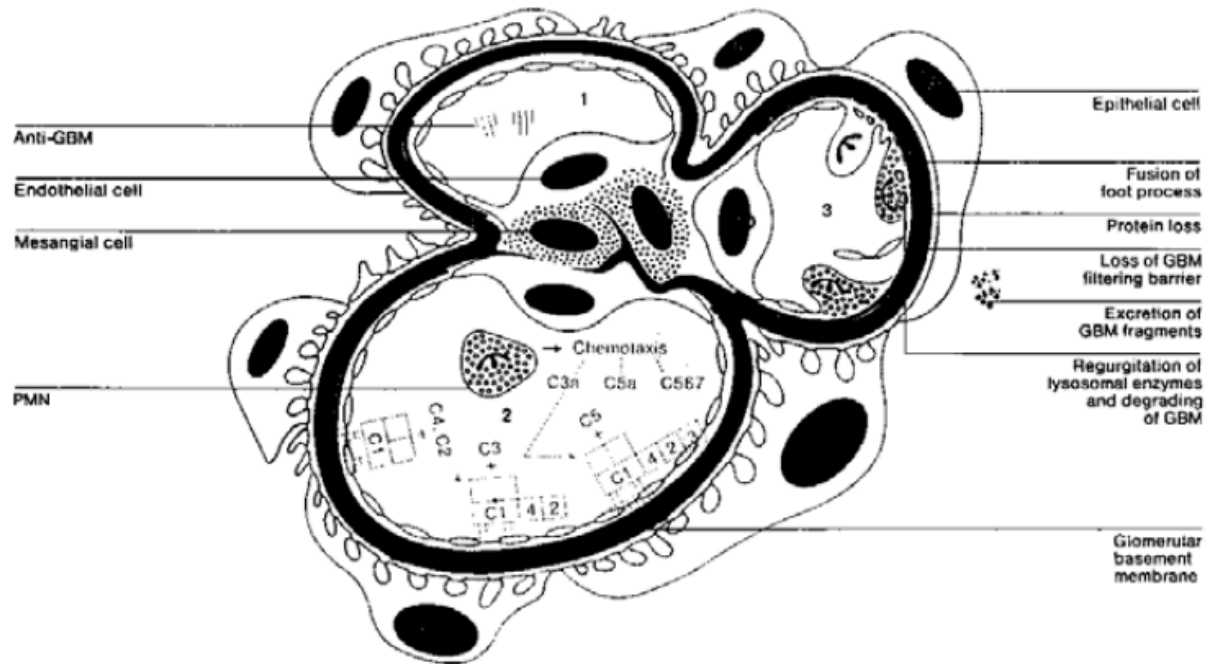
B. Antibody—Mediated (Type II) Hypersensitivity (Cytotoxic)

Definition: formation of antibody with subsequent binding of antibody to a cell or tissue surface leading to lysis, phagocytosis or tissue damage (fibrinoid necrosis).

Illustrative Example - Goodpasture syndrome (autoantibodies against the glomerular basement membrane)

1. Anti-GBM antibodies form against basement membranes in the renal glomeruli and lung.
2. The anti-GBM antibodies bind to the GBM and trigger the complement cascade (complement C2 and C4 are consumed).
3. Chemotactic factors such as C5a attract neutrophils to glomerular capillaries.
4. PMN's attempt to phagocytize the anti-GBM and complement bound to the GBM and release lysosomal enzymes.
5. GBM disintegrates and allows plasma protein escape.
6. The reaction of the plasma protein escape in fusion of the epithelial foot processes and subsequent coverage of the GBM with a continuous sheet of epithelium.
7. Consequences: hemoptysis, hematuria, renal failure.

The pathogenesis of anti-glomerular basement membrane nephritis



Other Examples- auto-immune hemolytic anemia

C. Immune Complex-Mediated (Type III) Hypersensitivity (Immune Complex Disease)

Definition: deposition of antibody-antigen complexes in tissue with subsequent inflammation and tissue damage (fibrinoid necrosis).

Illustrative Example: post-streptococcal glomerulonephritis

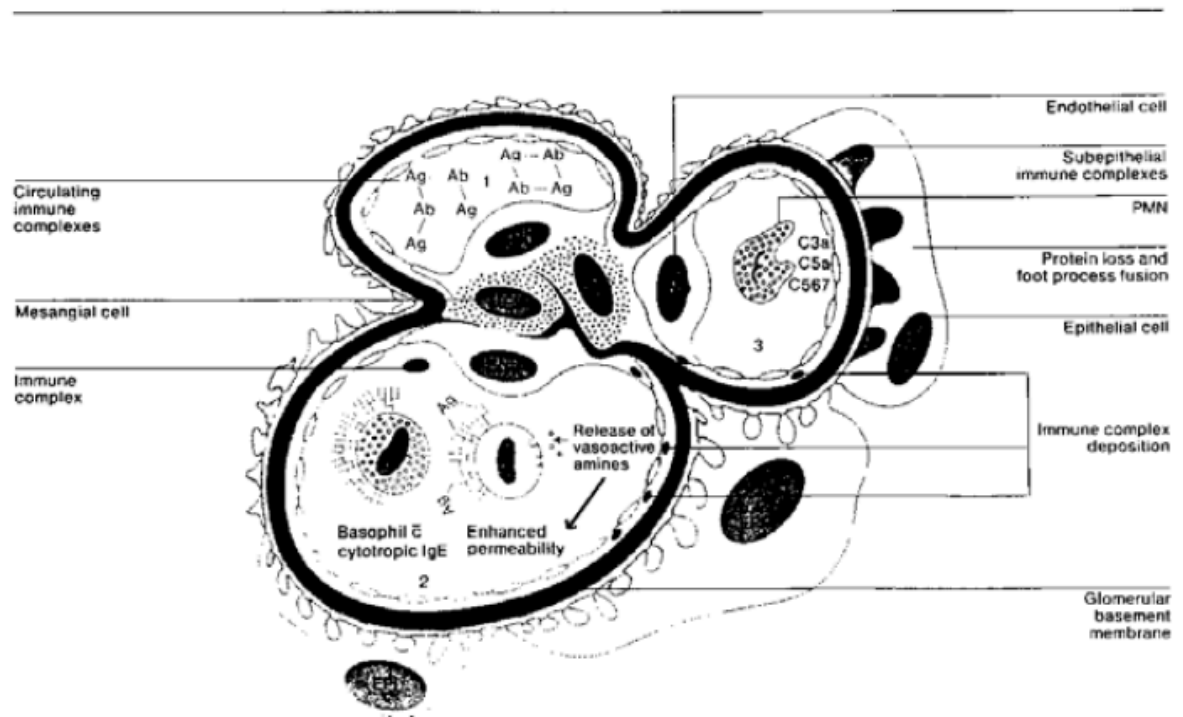
1. Infection with a nephrogenic strain of group A beta-hemolytic streptococcus (skin infections account for 2/3 of cases).
2. Buildup of anti-streptococcal antibodies over the course of weeks.
3. Deposition of immune complexes in the subepithelial-GBM space and on the GBM.
4. Activation of complement (depletion of C2, C4) and chemotaxis of neutrophils
5. Immune complexes and the lysosomal enzymes of the activated neutrophils damage the GBM and lead to plasma protein loss.
6. Protein loss causes foot pad fusion of the epithelial membrane.
7. Huge subepithelial immune complexes now form, the so-called “humps.”
8. Consequences: hematuria and mild proteinuria, hypertension and oliguria. Usually self-limited but can lead to chronic renal failure (CRF). Severe cases

leading to CRF can feature “crescent” formation (deposition of fibrin, damaged epithelial cells and monocytes in Bowman space).

Other Examples:- SLE rapidly progressive glomerulonephritis

- chronic infections (hepatitis B, syphilis, HIV)
- cryoglobulinemia, multiple myeloma
- inflammatory vasculitides secondary to immune complexes formed in autoimmune disease, chronic infection and malignancy.

The pathogenesis of immune complex nephritis



D. Cell-Mediated (Type IV) Hypersensitivity (Delayed, Cell Mediated)

Definition: reaction of sensitized T lymphocytes with subsequent release of interleukins, lymphokines and cytotoxins. Histological hallmark is infiltration of tissue with lymphocytes.

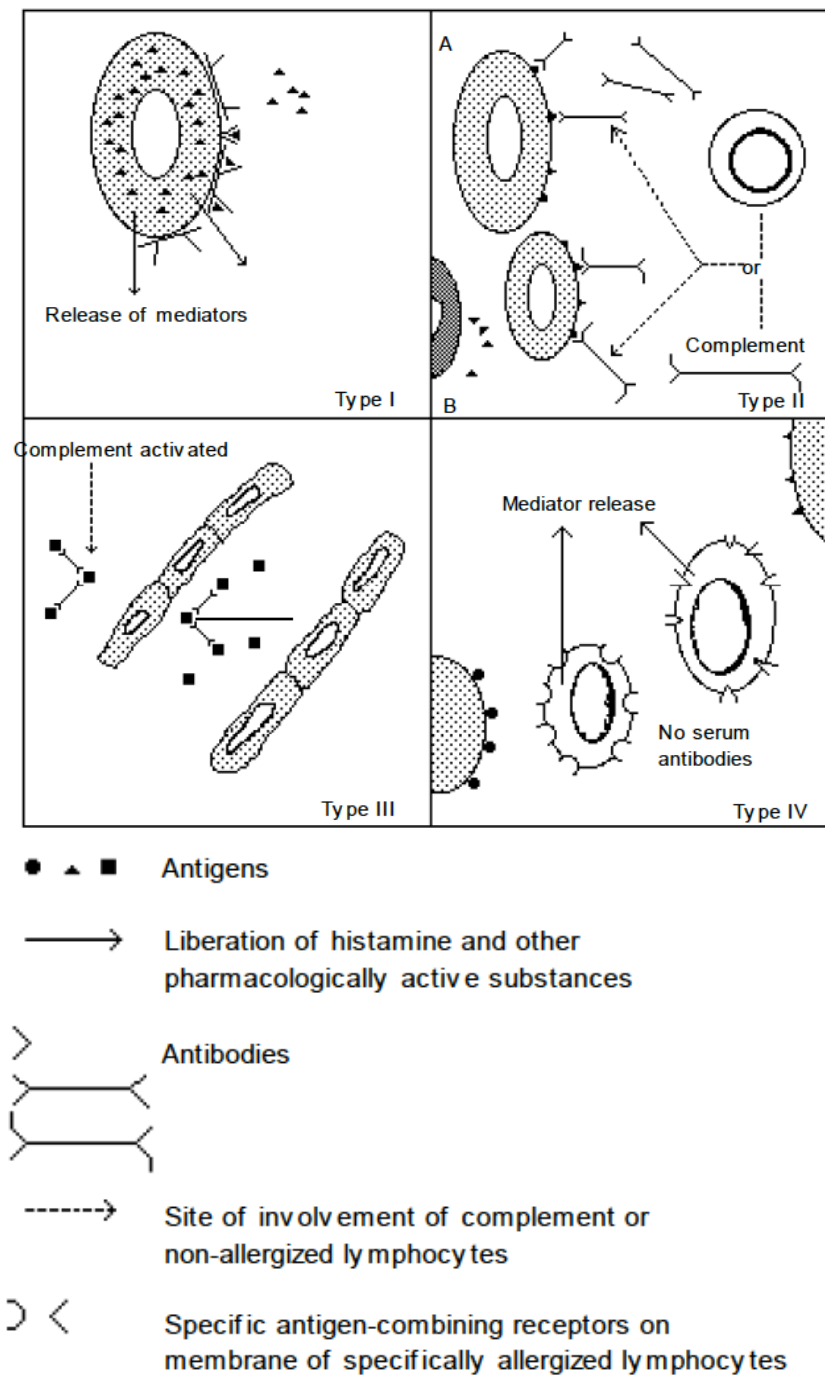
Illustrative Example: renal allograft rejection

1. Blood borne graft cells (dendritic cells, monocytes serve as the initial “antigen presenting cells.”
2. CD4 or helper cells recognize HLA-D antigen differences between the graft and the host via the T-cell receptor (CD4 also binds class II antigens in a general manner).

3. CD8 or suppressor/cytotoxic cells recognize HLA-A, B, C differences between the graft and the host also via the T-cell receptor (CD8 also binds class I antigens in a general manner).
4. The sensitized CD4 cells secrete IL-2 which cause proliferation of the cytotoxic CD8 cells and enhances the B-cell humoral response.
5. The sensitized cytotoxic CD8 cells recognize the original graft via the HLA-A, B, C antigens and specifically kill graft cells.
6. The CD8 cells during graft attack also release interferon alpha, a substance that activates macrophages causing non-specific damage to the graft.
7. Antibodies recognizing the graft can initiate Class II Reactions via ADCC and complement.

Other Examples: tuberculin test, granulomatous diseases, contact dermatitis, poison ivy dermatitis, graft-versus-host disease, etc.

V. The Mechanisms Involved



VI. Autoimmunity: Process by which immunocompetent cells and/or their products (i.e. autoantibodies recognize and interact with self-constituents).

A. Examples

Graves' syndrome	TSH receptor
idiopathic adrenocortical insufficiency	adrenal cortex
autoimmune hemolytic anemia	red cells
myasthenia gravis	acetylcholine receptor
idiopathic thrombocytopenia purpura	platelets
primary biliary cirrhosis	"mitochondria"
Sjogren syndrome	"nucleoproteins"
rheumatoid arthritis	immunoglobulin/CD8
lymphocytes	
systemic lupus erythematosus (SLE)	nucleic acids
Goodpasture syndrome	basement membrane
Hashimoto thyroiditis	thyroglobulin

B. Tissue Damage

Type II cytotoxicity - cell mediated antibody dependent

Type III immune complex disease

Type IV cytotoxicity - cell mediated T-cell dependent

e.g., multiple sclerosis

type I diabetes mellitus

C. Systemic Lupus Erythematosus (SLE)

- a) Incidence of 1/2500
- b) Female to male ratio = 10:1
- c) Second or third decade of life
- d) Disease is more common and severe in black Americans
- e) Pathogenesis - failure of the regulatory mechanisms that sustain self-tolerance
 - (1) Antibodies are directed towards DNA, histones, nonhistone proteins bound to RNA, and nucleolar antigens (ANA [$>95\%$], anti-dsDNA [40-60%], anti-SM [20-30%], and antiphospholipid antibody)
- f) Clinical Presentation
 - (1) Joint pain, skin rash, renal disease, pleuritis and pericarditis, neurological disorders, hematologic (type II hypersensitivity reaction)
- g) Pathology
 - (1) Skin
 - (a) Malar rash "butterfly pattern"
 - (b) Maculopapular lesion - discoid lupus
 - (c) Urticaria
 - (d) Bullae
 - (e) Ulcerations

- (2) Renal
 - (a) Class I - No morphologic changes on LM, IF, or EM
 - (b) Class II - Mesangial lupus nephritis
 - (c) Class III - Focal glomerulonephritis
 - (d) Class IV - Diffuse proliferative glomerulonephritis (most common [45-50%])
 - (e) Class V - Membranous glomerulopathy (second most common glomerular lesion)
- (3) Heart
 - (a) Nonbacterial verrucous endocarditis (Libman-Sacks endocarditis)
 - (b) Myocarditis
- (4) Pericardium and other serosal surfaces
 - (a) Pericarditis - acute, subacute, chronic
- (5) Spleen
 - (a) Moderately enlarged
- (6) Lungs
 - (a) Pleuritis
 - (b) Pleural effusions
 - (c) Interstitial pneumonitis
 - (d) Diffuse fibrosing alveolitis
- (7) Central nervous system
 - (a) Unclear
- h) Clinical Course
 - (1) Variable and unpredictable
 - (2) Therapy - steroids and immunosuppressive
 - (3) 86% survival at 5 years
 - (4) Death from renal failure and opportunistic infections

D. Scleroderma (Progressive Systemic Sclerosis)

- a) Female to male ratio = 3:1
- b) Third and fifth decades of life
- c) Excessive fibrosis throughout the body via fibroblast activation (IL-1, TNF-a, TGF-b, PDGF)
- d) Two Types
 - (1) Diffuse scleroderma
 - (a) Anti-DNA topoisomerase I antibody (Scl-70 [40-70%])
 - (b) Widespread involvement of skin at onset, with rapid progression and early visceral involvement
 - (c) Clinical course - renal failure, pulmonary insufficiency, intestinal malabsorption, cardiac failure

- (2) CREST syndrome (Calcinosis, secondary Raynaud phenomenon, Esophageal dysmotility, Sclerodactyly, Telangiectasis)
 - (a) Anticentromere antibody (90%)
 - (b) Limited skin involvement often confined to face and fingers
 - (c) Visceral involvement occurs late
 - (d) Clinical course is relatively benign

Fluids and Hemodynamic Derangements I & II**OBJECTIVES:**

- *Define edema and congestion.*
- *Describe the hemostatic mechanism.*
- *Describe the pathobiology of the thromboembolism.*
- *Define and describe the pathology of an infarct.*
- *Explain the pathophysiology of shock.*

READING: Robbins Basic Pathology; Kumar, Abbas, Mitchell, 9th Ed., 2013, pp.75-98.

I. Edema and Congestion

A. Edema - abnormal accumulation of water in tissue spaces and serous cavities

1. Causes of edema:

- a. Endothelial damage e.g., burns, inflammation, allergic reactions, trauma
- b. Increased hydrostatic pressure e.g., congestive heart failure, constrictive pericarditis, cirrhosis, venous obstruction
- c. Increased osmotic tension of interstitial fluid e.g., sodium retention due to excess salt intake, increased renin/angiotensin/aldosterone secretion
- d. Reduced oncotic pressure of plasma e.g., nephrotic syndrome, cirrhosis, malnutrition, protein losing gastroenteropathy
- e. Lymphatic obstruction e.g., inflammatory, neoplastic, post-surgical

2. Local edema

- a. Obstruction of venous outflow
- b. Inflammation (exudate vs. transudate)

3. Generalized edema (“anasarca”)

- a. Hepatic origin - due to decreased synthesis of plasma proteins, especially albumin.
- b. Cardiac origin - due to retention of Na^+ and water, and increased capillary blood pressure.
- c. Renal origin - due to increased glomerular capillary permeability and loss of plasma albumin in the urine.

- B. Congestion - an increased volume of blood within dilated vessels.
- a. Active hyperemia (dilation of arterioles, i.e., inflammation) --Causes increased redness in the affected part due to arterial and arteriolar dilatation brought about by sympathetic neurogenic mechanisms or the release of vasoactive substances (e.g., histamine and serotonin)
 - b. Passive (obstruction of venous outflow, i.e., heart failure, chronic passive congestion of liver, lungs)

II. **The Hemostatic Mechanism** includes those processes which act together to arrest bleeding. It has three components:

A. Vascular wall

1. Endothelial lining - endothelial cells contain potent thrombogenic and anti-thrombogenic substances:
 - a. Potent thrombogenic factor (tissue thromboplastin), von Willebrand's factor [source = endothelial cells] causing platelet adhesion to subepithelial collagen; thromboxane A₂ (vasoconstrictor).
 - b. Anti-thrombogenic substances - plasminogen activator, anti-platelet aggregating prostaglandins, for example, prostacyclin (PGI₂) inhibits platelet aggregation and is a vasodilator]; thrombomodulin - binds thrombin and activates protein C (cofactor protein S) which inhibits clotting by enzymatic cleavage of factors Va and VIIIa.
2. Subendothelial connective tissue - promotes platelet adherence and release reactions
3. Muscular layer - causes constriction of blood vessels. Induced by pain reflexes and vasoactive amines (histamine and serotonin) released from platelets. The degree of vasoconstriction depends on the amount of muscle in the vessel wall, so that arteries constrict more than veins.

B. Platelets - The normal number of circulating platelets is 150,000 - 450,000/mm³. They are derived from megakaryocytes in the bone marrow. Thrombocytopenia (decreased numbers of platelets) may be due to decreased production or increased destruction. When vascular endothelium is damaged, platelets:

1. Adhere to the underlying collagen. The initial biochemical mechanism which induces platelets to adhere to collagen is not fully known. At first platelets are loosely adherent and contain many intracytoplasmic granules, but within a minute or two, they form a closely packed aggregated mass

(the hemostatic plug) in which individual platelets lose their granules and cytoplasmic outlines.

2. Release vasoactive amines (histamine, serotonin), platelet aggregating agents (ADP, prostaglandin endoperoxidases, thromboxane A₂), and various platelet clotting factors like platelet factor 3 (platelet thromboplastin), platelet factor 4 (heparin neutralizing factor), platelet thrombosthenin (causes clot retraction).
3. Laboratory tests for platelet function:
 - a. Bleeding time - skin puncture (normal range: 2 - 7 minutes)
 - b. Platelet count (normal = 150K to 400K per mm³)
4. Platelet Disorders
 - a. Immune Thrombocytopenic Purpura (ITP)
 - (1) Thrombocytopenia is mediated by humoral antibodies or Ag-Ab complexes
 - (2) Acute - self-limited, post viral infection in children
 - (3) Chronic - adults as primary disease or in association with other conditions like SLE or AIDS
 - (4) 90% of patients have platelet associated immunoglobulins (IgG) against Gp IIb-IIIa and Gp Ib-IX on platelets.
 - i) Platelets are destroyed in the reticuloendothelial system (splenic macrophages) predominantly after antibody coating of platelets
 - (5) Symptoms are related to thrombocytopenia such as petechial hemorrhage, excessive bleeding
 - (6) Laboratory findings
 - i) Decreased platelets (increased bleeding time)
 - ii) PT and PTT are normal
 - iii) Fibrinogen is normal
 - b. Thrombotic Thrombocytopenic Purpura (TTP)
 - (1) Pathogenesis involves a deficiency/inactive form of a protease that cleaves von Willebrand factor resulting in platelet aggregates surrounded by intravascular hyaline thrombi throughout the microcirculation producing thrombocytopenia and leading to microangiopathic hemolytic anemia (schistocytes/helmet cells).
 - (2) Clinical
 - i) Pentad (TTP) - fever, thrombocytopenia, microangiopathic hemolytic anemia, transient neurologic deficits and renal failure. Most frequently seen in females.
 - c. Hemolytic uremic syndrome (HUS) - thrombocytopenia, microangiopathic hemolytic anemia, dominance of acute renal failure and

onset in childhood as well as in adulthood

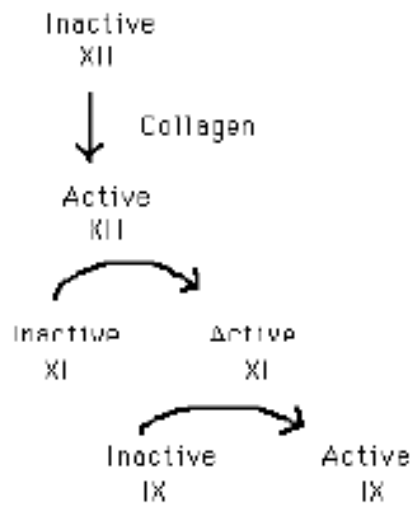
- (1) Cause - Often HUS follows gastroenteritis caused by E. coli 0157:H7
- (2) Laboratory findings
 - i) Decreased platelets (increased bleeding time)
 - ii) PT and PTT are normal
 - iii) Fibrinogen is normal

C. **Coagulation** - fluid blood transformed into a gel

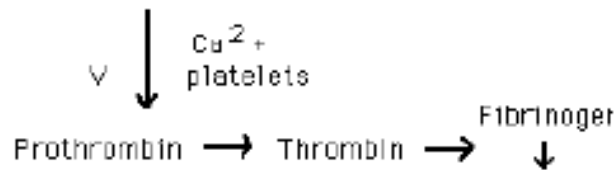
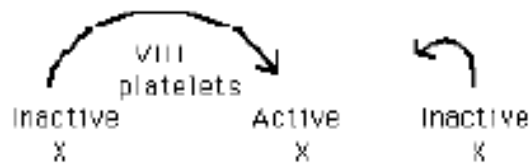
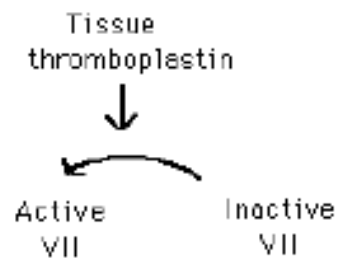
1. Extrinsic System of Blood Coagulation - Following tissue injury, a phospholipid protein complex (called tissue factor [old term: tissue thromboplastin]) gains entrance into the circulation to activate the extrinsic system (converts inactive factor VII to active factor VII).
2. Intrinsic System of Blood Coagulation - All the substances necessary for clotting are already present in circulating blood. This system is activated by contact with a foreign surface (usually collagen), but also Ag-Ab complexes, glass, etc. The contact-sensitive protein is factor XII or Hageman factor.
3. Laboratory tests for coagulation function:
 - a. Partial thromboplastin time (PTT) screens the intrinsic system assessing the adequacy of factors XII, HMWK, PK, XI, IX, and VIII. Normal range: comparable to control (25 to 35 seconds).
 - b. Prothrombin time (PT) screens the extrinsic system. Normal range: comparable to control (10-15 seconds).
 - c. Fibrinogen conversion is assessed by thrombin time (TT) or fibrinogen level (9-13 seconds).

SCHEMATIC DIAGRAM OF BLOOD COAGULATION

Intrinsic System



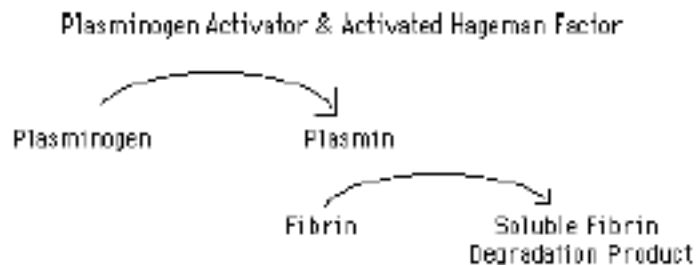
Extrinsic System



NOTE: The different coagulation factors are present in the plasma as inactive precursors. Following activation each newly formed enzyme reacts with its specific substrate to generate another active enzyme until fibrinogen is converted to fibrin. The next chart lists some synonyms of the different clotting factors.

<u>Factor</u>	<u>Synonyms</u>
I	Fibrinogen
II	Prothrombin
III	Tissue extract, thromboplastin
IV	Calcium
V	Proaccelerin, labile factor
VI	No longer used (contaminant)
VII	Proconvertin, stable factor
VIII	Antihemophilic factor, AHF
IX	Christmas factor, autoprothrombin II
X	Stuart-Power factor
XI	Plasma thromboplastin antecedent
XII	Hageman factor
XIII	Fibrin stabilizing factor

3. The body has many checks and balances which prevent too much clotting or which act to dissolve fibrin after it is formed.
 - a. Increased levels of circulating anticoagulants (heparin from mast cells) after an episode of clotting. Also increased levels of enzymes which inactivate each of the clotting factors after they are activated.
 - b. The reticuloendothelial system removes particulate procoagulants like tissue thromboplastin from the circulation.
 - c. The fibrinolytic enzyme system lyses fibrin after it is formed. Plasmin is a powerful protease which splits insoluble fibrin into soluble fibrin split products (D-dimers).



Plasmin is derived from plasminogen, an inactive precursor in blood. Plasminogen is activated by a combination of activated Hageman factor (XII) and tissue plasminogen activator (which is derived from damaged vascular endothelium), and fibrin (insoluble).

4. Bleeding Disorders Related to Clotting Factor Abnormalities

(1) Acquired

- (a) Vitamin K deficiency - leads to decreased synthesis of factors II, VII, IX and X and protein C
- (b) Liver failure or disease - makes virtually all clotting factors

(2) Disseminated Intravascular Coagulation (DIC)

- a) Causes - obstetric complications (abruptio placentae, retained dead fetus, septic abortion, amniotic fluid embolism, toxemia), infections (Gram-negative sepsis, meningococcemia, Rocky Mountain spotted fever, histoplasmosis, aspergillosis, malaria), neoplasms (carcinomas of the pancreas, prostate, lung, and stomach, acute promyelocytic leukemia), massive tissue injury (traumatic, burns, extensive surgery) and others (acute intravascular hemolysis, snakebite, giant hemangioma, heat stroke, vasculitis, aortic aneurysm, liver disease)
- b) Laboratory findings
 - i. Decreased platelets (increased bleeding time)
 - ii. PT and PTT are abnormal
 - iii. Fibrinogen is decreased and fibrin split products increased
 - iv. Intravascular microthrombi

(3) Inherited

- a) von Willebrand disease – deficiency or defect in vWF factor
 - i. Characterized clinically by spontaneous bleeding from mucous membranes, excessive bleeding from wounds, menorrhagia
 - ii. Platelet counts are normal
 - iii. Patients have a prolonged bleeding time
 - iv. VWF factor is necessary for platelet adhesion to the endothelium
 - v. Ristocetin aggregation test is negative
 - vi. Bleeding into joints is not common

b) Hemophilia A (Classic hemophilia)

- i. Factor VIII deficiency
- ii. X-linked recessive
- iii. Clinical manifestations are spontaneous hemorrhage especially in joints.
- iv. Platelets count is normal
- v. Bleeding time is normal

- c) Hemophilia B (Christmas disease)
 - i) Factor IX deficiency
 - ii) X-linked recessive
 - iii) Clinically indistinguishable from hemophilia A
- 5. There are several points where the clotting and fibrinolytic systems and the inflammatory response interact. Hageman factor is a common activator for all 3 systems. Platelets contain clotting factors, vasoactive agents, and other activators of inflammation. Fibrin degradation products are vasoactive agents. Plasmin activates complement (alternative pathway via C3). Fibrin, the end product of clotting, is an important component of the acute inflammatory response.

III. **Thromboembolism**

A. **Thrombus**

Definition: A thrombus is a mass formed from the constituents of the blood within the vessels or heart during life.

1. Dependent upon three factors (**Virchow triad**):
 - a. **Injury to endothelium:**
 - Damaged vascular endothelium (particularly atherosclerosis).
 - This is the most important cause of arterial thrombosis.
 - b. **Changes in laminar flow:**
 - i. Increased viscosity of the blood (polycythemia)
 - ii. Stasis of blood (most important cause of clotting in deep leg veins)
 - iii. Turbulence (aneurysms)
 - c. **Hypercoagulability:**
 - i. Increased coagulability of the blood (increased levels of platelets or clotting factors)
 - ii. Disseminated cancer
 - iii. Nephrotic syndrome
 - iv. Severe trauma or burns
 - v. Decreased fibrinolytic activity (late pregnancy and post-partum)
 - vi. Disseminated intravascular coagulation (DIC)
2. Differences between a true thrombus and a post-mortem blood clot
 - a. Early - Lines of Zahn (strands of fibrin bordered by the formed elements of the blood). For this reason, a true thrombus is mottled gray-red and friable.
 - b. Later - Adherent to vascular endothelium. If the person survives the thrombotic event, over a period of time the thrombus stimulates an

inflammatory and reparative response called organization during which fibrin is removed and collagen is laid down. The term recanalization refers to the formation of a new channel through an organizing thrombus.

3. Fate of a thrombus

- a. Organization and recanalization (large thrombi).
- b. Fibrinolysis (small thrombi).
- c. Give rise to an embolus.

B. Embolus

Definition: An embolus is a detached intravascular mass (gas, liquid or solid) that is carried by the blood to a site distant from its site of origin. Differences between an embolus and a thrombus:

1. An embolus may be composed of "foreign" material (amniotic fluid, bacteria, tumor cells).
2. An embolus may not conform to the shape of a blood vessel while a thrombus usually does.
3. The underlying artery under a thrombus usually shows atherosclerosis, but is normal under an embolus until organization occurs.

4. Types of Emboli

- a. Thrombus (98% of all emboli) - deep leg veins
- b. Bone marrow - fractures, cardiopulmonary resuscitation
- c. Atheromatous debris - severe atherosclerosis
- d. Fat--fractures, extensive crushing injuries of soft tissues
- e. Bacteria - infectious endocarditis
- f. Tumor cells - renal cell carcinoma, metastasis
- g. Amniotic fluid - labor and delivery
- h. Gases (barotrauma):
 - i. Acute form - the bends or "the chokes", e.g., scuba divers
 - ii. Chronic form - Caisson's disease (decompression sickness) leads to multiple foci of ischemic necrosis affecting the heads of the femur, humeri and tibia.
- i. Pulmonary (most common type of embolus):
 - i. Most (80%) are clinically silent.
 - ii. Origin: Deep leg veins, prostatic venous plexus
If more than 50% of vasculature is obstructed, it can lead to sudden cardiac death.
 - iii. Obstruction of small sized pulmonary branches usually causes infarction.

- iv. Medium sized pulmonary vascular obstruction leads to hemorrhage.
- v. Outcome:
 - Resolution in 70 to 80%
 - Infarction in 10 to 15%
 - Chronic pulmonary hypertension in 5%
 - Death in 10%
- j. Systemic types:
 - i. 80% arise within the heart
 - ii. Always causes infarction
 - iii. Amniotic fluid - embolism
 - iv. Air or gas embolism
 - v. Fat embolism

IV. **Infarction**

1. Definition: An infarct is a localized area of necrosis resulting from circulatory insufficiency (ischemia).
2. Infarcts of the heart, brain, and lungs collectively account for more deaths than all forms of cancer and infectious disease put together in the United States.
3. Etiology--Thrombus and embolus.
4. Whether or not infarction occurs depends on several factors:
 - a. The degree of obstruction
 - b. Acuteness of occlusion
 - c. Presence or absence of collateral circulation
 - d. Pre-existing disease in the organ
 - e. Whether the patient survives long enough to develop an infarct
 - f. The kind of tissue involved
5. Gross Pathology
 - a. Wedge-shaped
 - b. Apex of wedge points to the occlusion

Classified by color as:

- a. Hemorrhagic, or red
 - i. Loose tissues
 - ii. Dual blood supply
 - iii. Venous occlusion
- b. Anemic; pale or white

- i. Solid organs or tissues
- ii. Single blood supply
- iii. Arterial occlusion (most common)

6. Clinical significance depends on the organ involved. Arterial occlusions giving rise to infarction are common in the:

- a. Heart (usually anemic) - generally due to thrombus of atherosclerotic coronary artery
- b. Brain (may be hemorrhagic or anemic) - thrombotic occlusions are usually anemic or pale; embolic occlusions are usually hemorrhagic
- c. Lung (hemorrhagic) - usually due to embolism rather than thrombus
- d. Intestine (hemorrhagic) - may be thrombotic or embolic
- e. Spleen (anemic) - may be thrombotic or embolic
- f. Kidneys (anemic) - may be thrombotic or embolic
- g. Relatively rare in other organs (i.e., liver)

NOTE: Venous occlusions are relatively rare causes of infarction. When it occurs, the infarct is hemorrhagic.

7. Healing - most infarcts heal by organization by the ingrowth of fibroblasts and collagen from the periphery toward the center (provided the person lives long enough for this to occur).

V. **Hemorrhage** - escape of blood from the vascular system

A. Terminology

- 1. Petechiae
- 2. Ecchymosis
- 3. Purpura
- 4. Epistaxis - bleeding from the nose
- 5. Hematemesis - vomiting blood
- 6. Hemoptysis - coughing blood
- 7. Melena - refers to dark color of partially digested blood in stool
- 8. Hematuria - blood in the urine



refers to size
of the
hemorrhagic lesion

9. Hemothorax, hemopericardium, hemoperitoneum - bleeding into the various serous cavities
10. Hematoma - a localized hemorrhage into the tissues or tissue spaces

B. Serious effects of hemorrhage are due to:

1. Location
2. Amount of blood lost

VI. Shock

Definition: Widespread hypoperfusion of cells and tissues due to reduction in the blood volume or cardiac output, or redistribution of blood resulting in an inadequate effective circulating volume leading to systemic hypoxic injury.

A. Causes:

1. Shock may be due to decreased blood volume. Examples include:
 - a. Loss of whole blood (hemorrhage)
 - b. Loss of plasma (severe burns and peritonitis)
 - c. Loss of fluids and electrolytes (diarrhea and vomiting; anaphylaxis)
2. Shock may also occur in the presence of a normal blood volume. The three most common examples are:
 - a. Myocardial infarction, myocarditis, etc.
 - b. Massive pulmonary embolism
 - c. Endotoxin shock
 - i. Vasoconstriction of arterioles and venules due to the release of endothelin-1 from injured endothelial cells
 - ii. Disseminated intravascular coagulation (DIC)
 - d. Neurogenic shock due to brain trauma or general anesthesia
 - e. Sepsis

B. Stages of shock:

1. Stage 1 - due to low cardiac output, or vasodilatation/compensated hypotension
2. Stage 2 - decreased tissue perfusion
3. Stage 3 - Endothelial damage, release of endothelin-1 (potent vasoconstrictor) and microcirculatory failure leading to cellular membrane injury and cell death

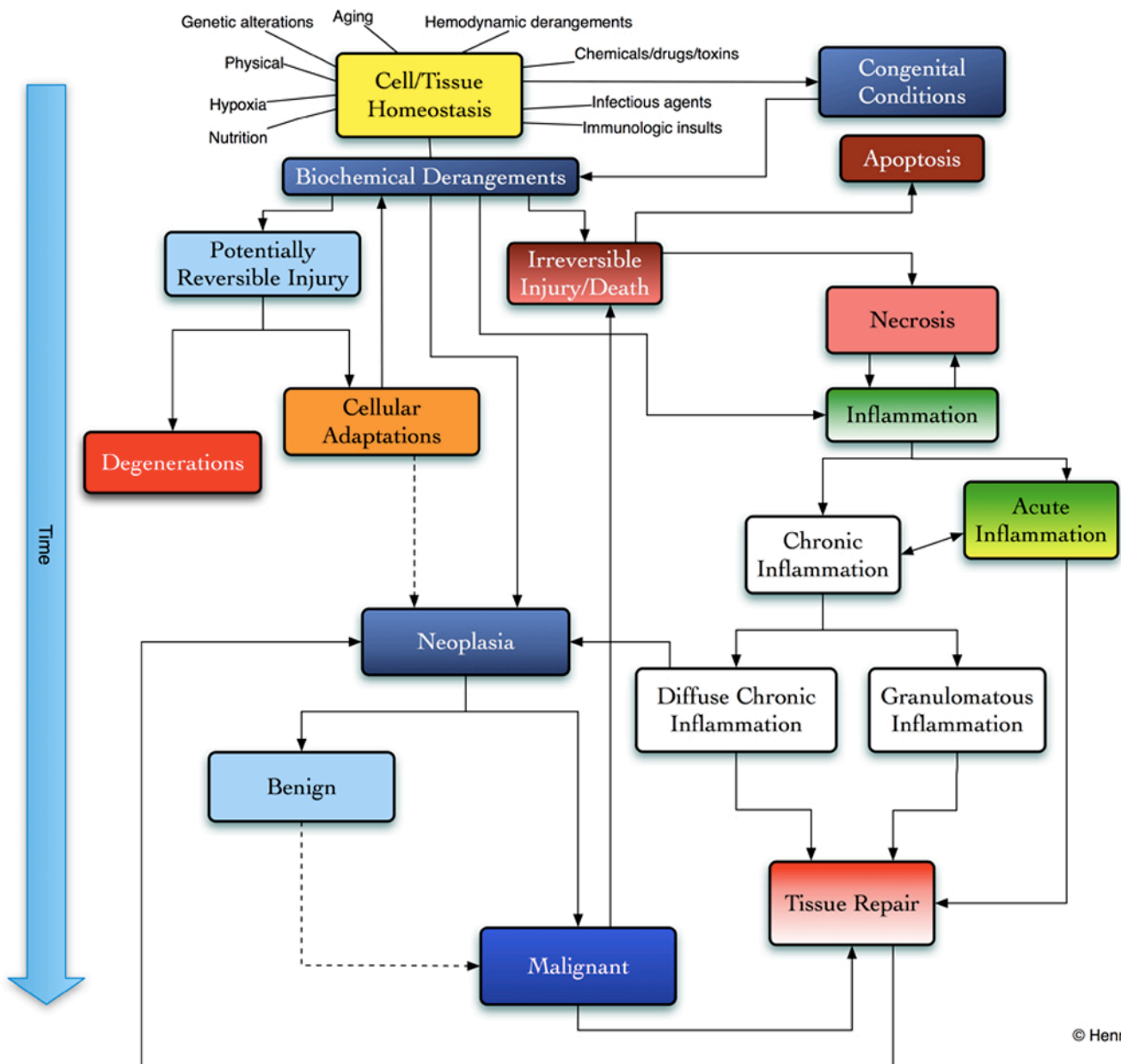
C. Irreversible shock--does not respond to therapy.

D. Pathology of shock--nonspecific

1. Congestion of the viscera
2. Focal tubular necrosis or acute tubular necrosis (shock kidney)
3. Diffuse alveolar damage (shock lung or ARDS--adult respiratory distress syndrome)
4. Centrilobular hemorrhage and necrosis (shock liver)
5. Thrombotic lesions (more common in endotoxin shock than in shock due to other causes)

NOTE: In many cases, there is good clinical evidence that the patient died as a result of shock, but there are no pathologic lesions suggestive of shock.

Framework of the Pathologic Mechanisms of Disease



Systemic Pathology

Principles of Neoplasia

OBJECTIVES

- *Define neoplasia*
- *Define non-neoplastic growths and neoplasia*
- *Compare and contrast anaplasia, hyperplasia, neoplasia and dysplasia*
- *Recognize the critical distinction between benign and malignant neoplasias*
- *Describe the ways cancers spread*
- *Define grade and stage*
- *Describe the causes of cancer*
- *Compare and contrast proto-oncogenes and tumor suppressor genes*
- *Define and describe tumor progression*
- *Define serum tumor markers and clinical use*

READING

Chapter 5 in ROBBINS BASIC PATHOLOGY (V. Kumar, A. K. Abbas, R. Mitchell), 9th edition, 2013, Elsevier; pages 161-173; pages 192-195 (metastasis); 198-204 (causes); 207-213 (clinical aspects).

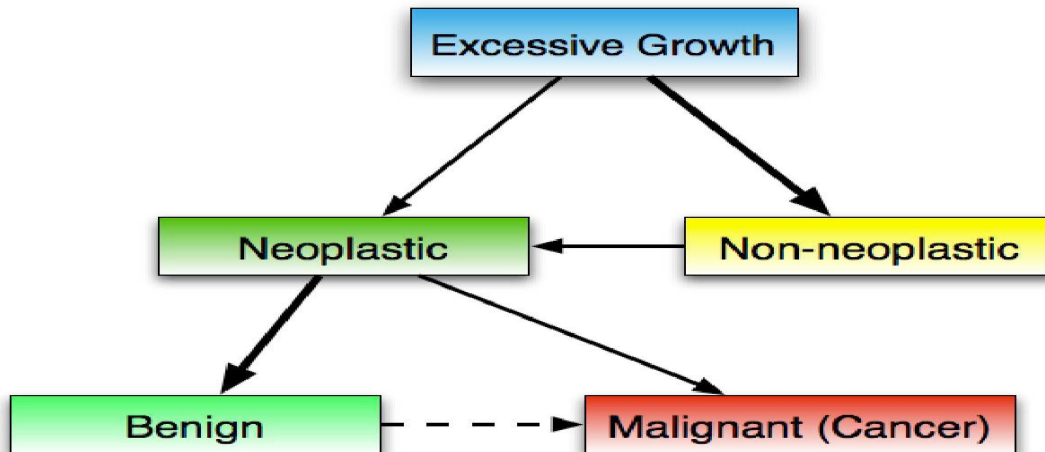
I. NOMENCLATURE

Neoplasm: An abnormal tissue mass whose growth exceeds and is uncoordinated with that of adjacent normal tissue and whose growth persists after cessation of the stimuli that provoked it.

II. . EPIDEMIOLOGY

Second leading cause of death in the U.S. in both adults and children

- More than 1,685, 210 estimated new cancer cases in 2016.
Females = 843,820 and Males = 841,390
- More than 595,690 deaths in 2016.
- One of every four deaths in the U.S. will be due to cancer.
- Most common cancer in women is breast and in men is prostate.
- Most common cancer leading to death in both women and men is lung (smoking).
- In general, the risk for cancer increases with age. However, each type of cancer has a characteristic age distribution, and certain cancers occur most commonly in children or other specific age groups.



A. Non-Neoplastic Growth Disturbances

Choristoma (= ectopia, heterotopia): An ectopic focus of mature tissue found at an abnormal location. Examples: islands of pancreatic tissue in the intestinal wall; foci of grey matter in white matter of the brain.

Hamartoma: A focal overgrowth of cells or tissue elements that occurs in an organ where such elements are normally present. Examples: congenital nevi in the skin; bile duct hamartoma of liver.

Hyperplasia: Cellular proliferation in an organ or tissue, which results in an increased number of cells while generally, preserving the normal tissue architecture. Examples: mammary glands in pregnancy (progesterone-dependent); lymph nodes in infection; fibrous tissue in tissue repair. Occurs only in cells capable of mitotic division.

Hypertrophy: Increase in the size of individual cells, which may result in enlargement of the organ but preserves normal architecture. Example: myocardium in hypertension.

Metaplasia: A process in which fully-differentiated cells of one type are replaced by fully-differentiated cells of another type. Usually seen in epithelia in response to chronic irritation. Example: squamous metaplasia in respiratory epithelium of smokers or glandular metaplasia in the esophagus due to gastric reflux.

Dysplasia: A proliferation of epithelial cells which show some cytologic features of malignancy and distort the epithelial organization to some degree, but which differentiate fully by the time they reach the upper layers of the epithelium and do not invade downward through the basement membrane.

Why are these not considered neoplasms? Choristomata and hamartomata are congenital lesions whose growth parallels that of the body as a whole. Hyperplasia, hypertrophy, metaplasia and dysplasia are stimulus dependent and

typically cease when the stimulus is withdrawn.

- | | | |
|----------------------|-------------|--|
| B. Benign: | “-oma” | -- adenoma (glandular)
-- squamous papilloma (squamous, e.g. a wart) |
| C. Malignant: | “carcinoma” | -- epithelial tissues
-- adenocarcinoma (glands)
-- squamous carcinoma |
| | “sarcoma” | -- nonepithelial tissues |

Some important generalizations:

- 1) Carcinomas (90%), as a group, are much more common than sarcomas (10%).
- 2) Leukemias and lymphomas are the most common forms of sarcoma, and together account for about 8% of cancer incidence and mortality. Most other types of sarcoma are very rare.
- 3) Benign neoplasia is usually not a precursor of cancer: most benign neoplasms are no more likely to become malignant than the adjacent normal tissue.

Important exceptions: certain types of nevi (mole) and colonic adenomas.

III. MORPHOLOGIC PROPERTIES

A. Benign neoplasms

1. **Gross features:** expansile (compress adjacent tissue), small, encapsulated, well differentiated, slow rate of growth (years), non-invasive and never metastasize.
2. **Microscopic features:**
Architecture - well-circumscribed, encapsulated, and expansile growth.

Cytologic features - close resemblance to its normal counterpart and usually diploid

B. Malignant neoplasms

1. **Gross features:** rapid growth (days to months), large, infiltrative, invasive, necrosis, hemorrhage, and metastasis.
2. **Microscopic features:**
Architecture - infiltrative, invasive, necrosis, and destruction of normal

architecture

Cytologic features - discohesion, pleomorphism (various changes in size and shape), anaplasia (very poorly differentiated), loss of polarity, increase in nucleus/cytoplasm, hyperchromasia (increased overall chromosome content, irregularly granular chromatin, prominent nucleoli (increased rRNA synthesis), tumor giant cells, and increased and/or abnormal mitoses.

Spread of malignant tumors:

Progressive infiltration, invasion and destruction of adjacent normal tissue

C. Invasion

Mechanism: degradation of extracellular matrix by collagenases, plasmin and other proteolytic enzymes.

D. Metastasis

The process by which malignant cells migrate (usually through the blood or lymphatic system) from the site of origin of the neoplasm to other sites in the body, where they resume growth and form new malignant lesions (called metastases).

Carcinoma-in-situ	vs.	Invasive carcinoma
Involves surrounding tissue		No invasion
Limited to epithelial cells		Extends beyond the basement membrane above the basement membrane

Pathway of Spread:

1. Seeding of body cavities and surfaces

Example: gallbladder and pancreatic carcinomas

2. Lymphatic spread

Most common pathway for the initial dissemination of carcinomas, however sarcomas can also spread by this route

Example: breast, colon and lung carcinomas

3. Hematogenous spread

Invasion into venous vessels leading to distant metastases

Examples: sarcomas, renal cell carcinoma, hepatocellular carcinoma (hepatoma), follicular carcinoma of the thyroid, choriocarcinoma (germ cell tumor) and osteogenic sarcoma

4. Mechanism:

- a. Tumor cells adhere to and invade basement membrane and pass through extracellular matrix by degrading its components which consists of collagen, laminin, proteoglycans and fibronectin
- b. Intravasation and form tumor embolus
- c. Adhere to vascular basement membrane
- d. Extravasation
- e. Form metastatic deposit

IV. GRADING AND STAGING

- A. Grading** is based on the degree of differentiation of the tumor cells and the number of mitoses.

Low grade tumor = typically well-differentiated

High grade tumor = poorly differentiated (anaplastic)

- B. Staging** is based on the size of the primary lesion, its extent of spread to regional lymph nodes, and the absence or presence of blood-borne metastasis (TNM system or Tumor Nodes Metastasis).

V. COMPLICATIONS OF CANCER

- A. Mass effects (e.g., glioblastoma multiforme)
- B. Pain (e.g., gastric carcinoma)
- C. Pathologic fractures (e.g., osteogenic sarcoma)
- D. Infection (e.g., opportunistic infections)
- E. Anemia (e.g., anemia of chronic disease)
- F. Fever (e.g., Hodgkin lymphoma)
- G. Jaundice (e.g., pancreatic carcinoma of the head of the pancreas)
- H. Obstruction of viscera (e.g., myxoma of the heart)
- I. Cachexia- general wasting (e.g., many malignant tumors)

VI. DIAGNOSIS OF MALIGNANCY

A reliable diagnosis of cancer absolutely requires microscopic evaluation of the lesion via a biopsy; this is known as the tissue diagnosis, and is generally rendered by a pathologist.

A. Diagnostic Features of Malignancy:

- 1. Metastasis
- 2. Invasion of adjacent normal tissue
- 3. Loss of normal tissue architecture

B. However, when the cytologic features of malignancy are present, a diagnosis of cancer can be made by examining individual cells that have been scraped or sloughed from a tissue -- this is a basis of the Pap smear for cervical cancer and other cytological techniques (e.g., fine needle aspiration).

VII. CAUSES OF CANCER (SEE SLIDES)

- A. Chemical carcinogens
- B. Physical carcinogens/ionizing radiation
- C. Viruses
- D. Inflammation and cancer
- E. Familial gene alterations

VIII. CARCINOGENESIS IS A MULTISTEP PROCESS

- A.** Most tissues are thought to contain a subpopulation of stem cells that retain the ability to replicate, though they may or may not be replicating at any given moment. Mitotic division of stem cells gives rise to two classes of cells: cells that are committed to terminal differentiation (and so lose the ability to divide) and new stem cells that replenish the replicative pool.

Thus, cells in a normal tissue are heterogeneous with respect to their ability to either proliferate or differentiate.

- B.** Growth Fraction: the proportion of a cell population that is involved in replication; this varies over time and in response to physiologic demands.
- C.** Current View:
 - 1. Cancers arise by mutation of a cell that has the ability to proliferate (stem cell).
 - 2. As in normal tissues, the progeny of this mutant cell are heterogeneous with respect to their ability to differentiate or proliferate.
- D.** When we say that a particular cancer is well-differentiated or poorly-differentiated, we are describing the population as a whole -- the proportion of cells that have undergone differentiation and the extent to which they resemble normal cells. In general, the more cells differentiate, the smaller the replicative pool. Hence, differentiation tends to be inversely proportional to growth rate.
- E.** Popular Misconception: "Cancer is characterized by an abnormally high rate of cell division."
 - 1. In fact, average cell generation times may be the same or even much longer than in corresponding normal cells. Growth rates vary enormously among different normal or neoplastic cells, even among tumors of the same type and within an individual tumor.
 - 2. Very few cancers grow as quickly as a normal fetus. It can take years (even decades) to produce a detectable tumor mass:
 - a. In theory, a single cell 10 μm in diameter would take 30 generations to produce a mass 1 cm^3 in diameter. With a 12-hr generation time, that could occur in about a week. But, in reality:
 - growth fractions vary widely (6% - 95% in various cancers)
 - 80-90% of cells die or are otherwise lost
 - doubling times tend to lengthen as tumor enlarges, due to suboptimal growth conditions and other factors
 - b. Some factors that limit cancer growth:
 - failed mitoses (wildly abnormal cells are less likely to prosper!)

- exfoliation of cells at surfaces
- inadequate blood supply
- host factors: immune response, nutrition, endocrinologic factors, therapy

Example: Cancer of the uterine cervix:
 Peak incidence of carcinoma-in-situ is at 25-35 years of age
 Peak incidence of overtly invasive cancer is at 40-45 years of age
 Thus, 10-15 years of evolution are required for invasion to occur even after cancer is present!

IX. MUTATIONS

- A. Many different mutations are implicated in human tumorigenesis. Some occur in a wide variety of cancers; others are specific to particular types of malignancies. Most of the genes involved can be assigned to one of two broad categories:
 1. Proto-Oncogenes: the normal products of these genes are thought to be involved in promoting cell proliferation or survival. Mutations that lead to excessive or dysregulated expression of the gene products are carcinogenic. Examples: growth factor receptors, intracellular signaling molecules, cell-cycle regulatory proteins.
 2. Tumor Suppressor Genes: normally act to inhibit cell growth, invasion, or other aspects of the malignant phenotype. Mutations that inactivate these genes are carcinogenic. Examples: retinoblastoma (Rb) gene product and p53.
- B. Some mutations alter properties of the cell itself; others affect its interactions with other cells and tissues.
 1. Example: Cancers produce angiogenic factors that stimulate the local capillary proliferation needed to support cancer growth.
- C. In general, multiple different mutations must occur in a cell to make it malignant -- no single alteration is necessary or sufficient, but together they produce full-blown cancer.

X. TUMOR PROGRESSION (SEE SLIDES)

Tendency of neoplastic cells to evolve over time by changing their biological behavior (e.g., rapid growth and metastasis = aggressive clinical behavior) and phenotype (e.g., increased anaplasia). Most tissues are thought to contain a subpopulation of stem cells that retain the ability to replicate, though they may or may not be replicating at any given moment. Mitotic division of stem cells gives rise to two classes of cells: cells that are committed to terminal differentiation (and so lose the ability to divide) and new stem cells that replenish the replicative pool. Thus, cells in a normal tissue are heterogeneous with respect to their ability to either proliferate or differentiate. Many different mutations are implicated in human tumorigenesis. Some occur in a wide variety of cancers; others are specific to particular types of neoplasias. These genes involve promoting cell proliferation or survival (e.g., growth factor receptors, intracellular signaling molecules, cell-cycle regulatory proteins) and others that act to inhibit cell growth, promote cell death (e.g., apoptosis), invasion, or other aspects of the neoplastic phenotype. These mutations occur due to genetic instability of these neoplastic cells, which are more prone to mutate compared to normal cells.

A. Adenocarcinoma of the Colon

Adenomatous Polyp -- Though this lesion is not itself a cancer, there is a significant risk that cells within it will become malignant. Hence, it is an example of a pre-malignant lesion.

B. Squamous Carcinoma of the Uterine Cervix

1. Dysplasia -- A proliferation of epithelial cells which show some cytologic features of malignancy and distort the epithelial organization to some degree, but which differentiate fully by the time they reach the upper layers of the epithelium and do not invade downward through the basement membrane. This is another example of a pre-malignant lesion. When superficial differentiation is lost and the process extends through the full thickness of the epithelium, it is known as:
2. Carcinoma-in-situ -- Carcinoma confined within the intact basement membrane, i.e., not yet invasive. Over time, can progress to invasive and metastatic cancer.

C. Endometrial Carcinoma

1. Hyperplasia -- Unopposed estrogen on the endometrial cells will lead to hyperplasia and this increases the risk of endometrial carcinoma.

D. Squamous Cell Carcinoma of the Lung

1. Metaplasia -- Smokers damage delicate respiratory epithelium leading to squamous metaplasia and the metaplastic squamous cell can evolve into carcinoma-in-situ, invasive and metastatic squamous cell carcinoma.

XI. SERUM TUMOR MARKERS (SEE SLIDES)

CARDIOVASCULAR DISEASES I**ARTERIOSCLEROSIS****OBJECTIVES:**

- *Explain the important risk factors for atherosclerosis.*
- *Describe the pathobiology of atherosclerosis.*
- *Describe the complications of atherosclerosis.*

READING: Robbins Basic Pathology, Kumar, Abbas, Mitchell, 9th Ed., 2013, pp.335-344.

I. Introduction

The term arteriosclerosis actually means hardening of the arteries (skleros = hard), but we use the word to include several degenerative diseases of the arteries. These may be classified as follows:

- A. Atherosclerosis (athere = soft; skleros = hard) - This disease involves the intima of medium-sized (muscular), and large-sized (elastic) arteries. It is characterized by intimal fibrosis and lipidosis.
- B. Medial calcification or Monckeberg sclerosis. Characterized by the deposition of calcium in the media of muscular arteries.
- C. Arteriolosclerosis - Refers to degenerative changes in the arterioles like "intimal hyaline-thickening." This is an important lesion in the kidney in hypertension, also seen in diabetes mellitus, and to some extent in older people without hypertension or diabetes.

Atherosclerosis (type of chronic inflammatory disease) is by far the most important entity in this classification, especially in relation to obstruction of blood flow. Monckeberg sclerosis has no clinical significance. Arteriosclerosis will be discussed in detail in the cardiovascular and renal lectures in relation to hypertension. For the remainder of this lecture, we will be concerned only with atherosclerosis; with its gross and microscopic appearance, its pathogenesis and, most important: how the disease affects the flow of blood to certain vital organs.

II. Gross pathology of atherosclerosis

- A. Fatty streaks - yellow lines in intima. Seen in early childhood at point of branching.
- B. Atheromas - soft, elevated, yellow plaques. Seen in adolescents. Fatty streaks and atheromas are reversible.
- C. Fibrous plaques - firm, white. Seen in young men. On the average 10 years later in women compared to men.
- D. Most plaques contain both elements, lipid and fibrous tissue.

E. Complicated lesions.

1. Ulceration
2. Thrombosis-impairs distal arterial circulation
3. Aneurysm
4. Necrosis, hemorrhage, and calcification

III. Microscopic pathology of atherosclerosis (light and EM)

- A. The basic lesion is a proliferation of smooth muscle cells which migrate into intima from the media through penetration of the internal elastic membrane. By electron microscopy, these cells have myofibrils in their cytoplasm. For this reason, they have been called smooth muscle cells, but they have the ability to lay down collagen and accumulate lipid. NOTE -- these cells have surface binding sites for the low density lipoprotein-cholesterol complex, and an internal (metabolic) pathway for synthesizing cholesterol.
- B. Many of these lipid-laden cells disintegrate releasing their lipid contents into the intercellular spaces of the intima.
- C. This incites a secondary inflammatory response characterized by severe fibrosis which forms a cap of collagen over a central core of lipid. Some plaques are mainly collagen with very little lipid.
- D. A mass of lipid and necrotic debris forms which may narrow the lumen, ulcerate and give rise to thrombosis, or encroach on the media and give rise to aneurysm formation.

IV. Factors influencing atherosclerosis (risk factors)

- A. Age and Sex (usually male and middle age to elderly)
- B. Primary Risk Factors
 1. Diabetes mellitus
 2. Hypertension
 3. Smoking
 4. Hyperlipidemia (e.g., hypercholesterolemia)
 5. Obesity
- C. Secondary Risk Factors
 1. Lack of exercise
 2. Aggression (competitiveness)
 3. Diet
 - a. Cholesterol rich
 - b. Beta-lipoproteins (high density lipoproteins protect against atherosclerosis; low density lipoproteins, if increased, are a risk factor).

V. Clinical significance of atherosclerosis

- A. Ischemic heart disease. The underlying lesion is atherosclerosis of the coronary arteries. The disease process may narrow or obstruct the vascular lumen sufficiently to cause a discrepancy between oxygen demand and supply and give rise to angina pectoris, lethal cardiac arrhythmias, and myocardial infarction (necrosis of heart muscle).
- B. Cerebrovascular accidents (stroke). Many are secondary to thrombosis of atherosclerotic carotid arteries and branches including the circle of Willis.
- C. Peripheral vascular disease and gangrene of the lower extremities. Secondary to atherosclerotic obstruction lesions in the distal aorta, iliac arteries and branches (the vessels supplying the upper extremities are not affected by the disease).
- D. Atherosclerosis of the aorta may give rise the aortic aneurysms (with rupture), renal failure (if the renal arteries are compromised), and cholesterol embolization.

CARDIOVASCULAR DISEASES II**DISEASES OF THE HEART****OBJECTIVES:**

- *Describe the pathogenesis of a myocardial infarct and its complications.*
- *Define acute and chronic rheumatic heart disease and describe its pathogenesis and complications.*
- *Explain the risk factors, pathogenesis and complications of infective endocarditis.*
- *Define and describe hypertension and its complications.*

READING: Robbins Basic Pathology, Kumar, Abbas, Mitchell, 9th Ed., 2013, pp. 374-386, 391-385, 332-334, 386-388.

I. INTRODUCTION

Heart disease is the leading cause of death in the United States today, accounting for almost 24% of all deaths. The relative risk of different kinds of heart disease varies to a great extent with age. In infants and young children, congenital heart disease is most important. Rheumatic fever and rheumatic heart disease are more common in older children and young adults. With increasing age, these diseases become less common as the incidence of arteriosclerotic coronary disease rises to dominate the mortality picture. More people die of myocardial infarction than any other disease. Hypertensive heart disease and bacterial infective endocarditis, also important on a statistical basis, span multiple ages.

II. ISCHEMIC HEART DISEASE

The heart is particularly vulnerable to diseases which compromise its blood supply.

A. Anatomy of the coronary circulation

1. Left coronary circulation
 - a. anterior descending artery
 - b. circumflex artery

2. Right coronary artery

B. Relation of coronary atherosclerosis to ischemic heart disease

1. Coronary blood flow is not reduced until 75% of the lumen is compromised.
2. The disease process involves the epicardial coronary arteries and does not extend into the intramural coronary arteries.

3. Arteriosclerotic plaque is most common and most severe in the proximal portion of the anterior descending artery.
4. A thrombus is found in 50% of cases of all types of myocardial infarction (subendocardial and transmural), while 90% incidence of thrombosis in patients with transmural infarction.
5. Angina pectoris -- a clinical syndrome characterized by sporadic episodes of chest pain. The pain is secondary to coronary insufficiency, but the degree of ischemia is insufficient to induce infarction.
6. Sudden death (death in one hour or less) in the absence of myocardial infarction (sudden coronary death). Death cannot be explained on any basis other than coronary atherosclerosis often with acute thrombus formation over an atherosclerotic plaque. Presumably, death is caused by ventricular fibrillation due to acute hypoxic injury.
7. Myocardial infarction
 - a. Clinical symptoms and laboratory findings
 - i. Pain, leukocytosis
 - ii. Electrocardiographic changes
 - iii. Abnormalities in serum enzyme levels (CPK-MB fraction, **troponin I**)
 - iv. Complications: Congestive heart failure, cardiogenic shock, arrhythmias (90%)
 - b. Pathology-ischemic necrosis of heart muscle
 - i. Histologic criteria for dating an infarct
 - a) Neutrophils - hours to days
 - b) Macrophages - weeks
 - c) Fibroblasts and collagen - weeks to months
 - c. Complications of infarction (50% mortality over a 5 year-period)
 - i. Cardiac rupture. Most common during first week. Incidence: 5-8% of infarcts. Three types: free wall, I.V. septum, papillary muscle.
 - ii. Ventricular aneurysm. Incidence varies from 5-35% of infarcts. Complications: refractory heart failure, secondary rupture, mural thrombosis.
 - iii. Mural thrombosis. Predisposing factors: ventricular aneurysm, extension of the infarct to the endocardium, congestive heart failure. The risk of embolization after myocardial infarction is 6%.
 - iv. Massive pulmonary embolism. Related to prolonged bed rest.

III. ACUTE RHEUMATIC FEVER

Rheumatic fever is an acute, recurrent, inflammatory disease, principally of children (peak age incidence between 5 and 15 years), that follows a pharyngeal infection with group A streptococcus. Over a period of years, the mitral or mitral and aortic valves, which are the

sites of the acute attacks, may become damaged permanently. Especially in persons who have had three or more attacks of acute rheumatic fever in the past. The valve leaflets are deformed by chronic inflammation, fibrosis and vascular proliferation (remember heart valves are avascular structures). Evidence strongly suggests that the damage incurred by the valves is due an immune response to streptococcal antigens (streptolysin O and DNAase B), which results in either a cross reaction to tissue antigens primarily in the heart, or an autoimmune response to tissue antigens. Rheumatic fever is an inflammatory disease of heart, joints and small blood vessels.

A. Pathogenesis

1. Relationship to infection with beta hemolytic Group A streptococcus.
2. Known rheumatic subjects have an increased susceptibility to streptococcal infection.
3. Incidence of residual heart damage increases with repeated attacks of acute rheumatic fever.
4. Rationale of penicillin prophylaxis.
5. Widely disseminated, focal, inflammatory lesions involve several organ systems in acute rheumatic fever:

Heart - Foci of fibrinoid necrosis surrounded by lymphocytes and macrophages (large histiocytes with vesicular nuclei and abundant basophilic cytoplasm are called Anitschkow cells) with an occasional plasma cell are called **Aschoff bodies**. In acute rheumatic fever, Aschoff bodies can be found in all layers of the heart (pericardium, myocardium and endocardium).

Joints - Acute nonspecific arthritis (migratory arthritis); largest joints are primarily affected, especially the knees

Skin - Subcutaneous nodules or erythema marginatum which are essentially giant Aschoff bodies with a large central area of fibrinoid necrosis encircled by chronic inflammatory cells as described above in the heart

Arteries - A form of hypersensitivity angiitis (infiltration of leukocytes in vessel wall)

6. Jone Criteria of Rheumatic Fever

Major:

- Migratory polyarthritis (knee)
- Pancarditis
- Subcutaneous nodules
- Erythema marginatum
- Sydenham's chorea

Minor:

- Fever
- Arthralgia
- Increase in acute reactions

Diagnosis is based upon preceding streptococcal Group A infection plus two major, or one major and two minor criteria

IV. CHRONIC RHEUMATIC HEART DISEASE

Over a period of years, the mitral or mitral and aortic valves, which are the sites of the acute attacks, become damaged permanently (many persons with only one or two attacks of acute rheumatic fever escape any permanent damage to the heart valves)

A. Mitral stenosis. Most common type of chronic deformity.

1. Pathologic changes in heart

- a. Fibrous adhesions between the free edges of the cusps, and thickening and fusion of mitral valve leaflets
- b. Shortening, thickening, and fusion of chordae tendineae
- c. Dilatation of left atrium (arrhythmias)
- d. Mural thrombosis of left atrium
- e. Increased risk for bacterial endocarditis

2. Pathologic changes in lungs (secondary to elevated pulmonary venous pressure)

- a. Pulmonary congestion and edema
- b. Hemorrhage and infarction
- c. Hemosiderosis
- d. Hyperplasia of pulmonary arterioles
- e. Fibrosis of alveolar septa
- f. Right ventricular hypertrophy and failure

B. Mitral insufficiency - leads to left ventricular failure

C. Aortic stenosis - leads to left ventricular failure

D. Aortic insufficiency - leads to left ventricular failure

V. INFECTIVE ENDOCARDITIS

This is one of the more serious infections encountered in humans. Endocarditis can be divided into two broad categories: acute and subacute infectious endocarditis. These subdivisions represent a clinical spectrum of infectious endocarditis. Risk factors include rheumatic heart disease, congenital heart disease (a small interventricular septal defect, patent ductus arteriosus, and tetralogy of Fallot), mitral valve prolapse, degenerative calcific valvular stenoses, bicuspid aortic valve, artificial valves, indwelling pulmonary artery catheters, neutropenia, immunodeficiency, immunosuppression, and IV drug abuse.

A. Acute infectious endocarditis:

1. *Staphylococcus aureus* (high virulence) is the leading cause of acute infectious endocarditis.
2. Large vegetations (few millimeters to several centimeters) form usually on previously normal valves. The acute vegetations are composed of fibrin, bacteria, and neutrophils.

B. Subacute infectious endocarditis:

1. Various streptococci (low virulence) - viridians group, and others - are responsible for the majority of the cases of infectious endocarditis.
2. Smaller vegetations are usually formed on abnormal or diseased valves.

C. Cardiac Complications:

1. Valvular insufficiency or stenosis with cardiac failure
2. Myocardial abscess with possible perforation of interventricular septum or free wall
3. Suppurative (purulent) pericarditis
4. Dehiscence of artificial valve

D. Embolic complications:

1. With left-sided lesions - brain, spleen, kidneys, and other sites
2. With right-sided lesions - lungs
3. Osler's nodes - tender, red, raised punctate lesions of the hands and feet
4. Janeway lesions - painless hemorrhagic raised areas on the palms and soles
5. Roth spots - round white retina spots surrounded by hemorrhage

E. Metastatic Infections:

1. With acute staphylococcal endocarditis to almost any organ or tissue resulting in abscess formation
2. With subacute streptococcal endocarditis(rare)

F. Renal complications:

1. Embolic infarction
2. Focal glomerulonephritis
3. Diffuse glomerulonephritis
4. Multiple abscesses with acute staphylococcal endocarditis

VI. HYPERTENSION

- A. Definitions - Hypertension can be simply defined as elevated arterial blood pressure leading to end-organ damage. About 12% of persons die as a direct result of hypertension. Arterial blood pressure can be defined as the product of cardiac output X peripheral resistance ($BP = CO \times PR$).
- B. Classification of systemic hypertension (pulmonary hypertension will be discussed in the lecture on lung)
1. Essential (primary, idiopathic). The cause of the hypertension is not known. Any person having an arterial pressure greater than 140/90 mm Hg and who has no known cause for the hypertension is considered to have essential hypertension. Account for 90% of cases.
 2. Secondary - Due to known causes (renal, endocrine, neurogenic, cardiovascular)
- C. Effects of hypertension
1. Hypertrophy of the left ventricle and left ventricular failure
 2. Blood vessels
 - a. Accelerates atherosclerosis
 - i. Myocardial infarction
 - ii. Aortic aneurysms
 - iii. Cerebral vascular accidents (hemorrhage and/or infarct)
 - b. Small blood vessels (arterioles) of the kidney and retina especially prone to damage (to a lesser degree other vessels in the adrenals and pancreas are involved).
- D. Main causes of death in hypertension
1. Renal failure
 2. Heart failure
 3. Cerebral vascular accidents

E. Clinical manifestations of hypertension

<u>Organ</u>	<u>Symptoms</u>	<u>Physical or Laboratory Findings</u>
Eye	Visual acuity Transient or permanent blindness	Arteriolar narrowing, A-V crossing defects, hemorrhage or exudates, papilledema
Brain	Severe headache, drowsiness or stupor, transient ischemic attacks, cerebrovascular accident (hemorrhage or thrombosis)	<u>Hypertensive encephalopathy</u> - often lateralizing neurologic findings (may be transient) <u>Cerebrovascular accident</u> - often lateralizing, nuchal rigidity with hemorrhage into C.S.F.
Cardiac	Heart failure Angina pectoris Myocardial infarction	Cardiac enlargement, pulmonary edema, left ventricular hypertrophy and/or ischemia or infarction pattern on the EKG
Renal	Uremic syndrome Hematuria	Proteinuria, serum creatinine and B.U.N., hematuria (in malignant phase)
Circulatory	Intermittent claudication (Leriche syndrome) Aortic dissection	Diminution of peripheral pulses, bruits over arteries, evidence of decreased flow

Pulmonary Diseases I**OBJECTIVES:**

- *Distinguish between different types of pneumonia - acute vs. chronic; alveolar vs. interstitial bacterial vs. fungal vs. viral*
- *Describe the general categories of diffuse infiltrative lung disease*
- *Explain the "alveolitis" hypothesis of pathogenesis of diffuse interstitial lung disease*
- *Compare and contrast acute, chronic and end-stage diffuse interstitial lung disease*
- *Explain the pathogenesis of pulmonary embolism*
- *Define and describe the pathogenesis of pulmonary hypertension and clinical presentation*

READING: Robbins Basic Pathology, Kumar, Abbas, Mitchell, 9th Ed., 2013
pp. 486-504, 460-463, 472-482, 482-485.

I. Structure of the respiratory system**A. Airways**

1. Cartilaginous airways - trachea and bronchi
2. Non-cartilaginous airways - bronchioles

B. Lung parenchyma

1. Pulmonary lobule - structures derived from a small bronchiole (terminal bronchioles, respiratory bronchioles, alveolar ducts and alveolar sacs).
2. Pulmonary acinus - structures derived from a single terminal bronchiole (respiratory bronchioles, alveolar ducts and alveolar sacs).

C. Pleura**D. Blood supply--dual blood supply from pulmonary arteries and bronchial arteries.****II. Pulmonary defense mechanisms****A. Airways**

1. Mucus--forms a physical barrier to organisms contains IgA, antibacterial substances (e.g. lysozyme, lactoferrin)
2. Cilia--push secretions out of lungs

B. Alveoli

1. Alveolar macrophages--phagocytic, chemotactic mediators
2. Antibody--mainly IgG
3. Complement

III. Pulmonary infections - Introduction

Pneumonia refers to inflammation of the lungs, particularly of the respiratory portion, synonym=pneumonitis. Pneumonia is an important health problem. It is the cause of 8.5% of the hospitalizations in the U.S. Nosocomial pneumonia develops in 0.7% of all hospital patients but in as many as 13% of those admitted to intensive care units. Pneumonia develops in as many as one third of immunosuppressed patients.

A. Routes of pulmonary infection.

1. Airways
 - a. Inhaled aerosols
 - b. Aspiration of oropharyngeal secretions
2. Bloodstream
3. Traumatic implantation
4. Direct spread via lymphatics from chest wall, abdomen or mediastinum

B. Classification of pneumonias

1. Acute versus chronic pneumonia
2. Alveolar versus interstitial pneumonia
3. Primary (previously healthy individual) versus Secondary (underlying disease predisposing to lung infection)
4. Etiology

IV. Etiologic types of pulmonary infections

A. Bacterial pneumonia

Bacterial organisms cause intra-alveolar exudate resulting in consolidation of the lung parenchyma. Two types of bacterial pneumonia occur:

1. Lobar pneumonia--infection of a large portion of a lobe or an entire lobe.
 - a. Etiology

- i. 90% *Streptococcus pneumoniae*
(most commonly types 1, 2, 3, 7)
 - ii. Other bacterial organisms causing lobar pneumonia include *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Hemophilis influenzae*, *Pseudomonas aeruginosa*, *Proteus* species
 - b. Morphology (untreated)
 - i. Congestion (earliest finding) - vascular engorgement and serous exudate
 - ii. Red hepatization (days 1-3) - neutrophils, fibrin, extravasated RBC's, and bacteria
 - iii. Gray hepatization (days 4-8) - formation of a fibrinous network, degenerating WBC's
 - iv. Resolution (day 9) - dissolution of fibrin
 - c. Clinical manifestations--sudden onset of shaking chills, fever, prostration, chest pain, cough, dyspnea, rusty sputum, leukocytosis
- 2. Bronchopneumonia - patchy, peribronchial and peribronchiolar consolidation of lung
 - a. Etiology
 - i. Most pathogenic bacteria but particularly staphylococci, streptococci, *Hemophilis influenzae*, *Pseudomonas aeruginosa*, *Proteus* species
 - ii. Secondary to lung congestion, aspiration, debilitation, other respiratory tract disease
 - b. Morphology
 - i. Consolidation around small bronchi and bronchioles
 - ii. Lesions are slightly elevated, dry, granular, gray-red to yellow
 - iii. May become confluent
 - iv. Airway lumens filled with neutrophils, fibrin, macrophages
 - c. Clinical manifestations--variable including fever, cough, sputum production
- 3. Complications of pneumonia
 - a. Abscess formation--occurrence rate varies with etiologic agent
 - b. Pleuritis, pleural effusion--fibrinous pleuritis in 2/3 of cases
 - c. Empyema (pus in a body cavity) --15-25% of cases
 - d. Organization
 - e. Bacteremic dissemination--20-35% of patients with lobar pneumonia, less with bronchopneumonia leads to sepsis

B. Tuberculosis (chronic, primary or secondary)

Tuberculosis (TB) is a communicable disease which results in necrotizing granulomatous inflammatory reactions. World-wide, TB remains a leading cause of death and currently TB is the leading cause of death of AIDS patients in the world. Until recently, the death rate from TB in the U.S. was decreasing from 200 per 100,000 in 1900 down to 2 per 100,000 in 1980. The incidence of TB is currently increasing and strains of drug-resistant *Mycobacterium tuberculosis hominus* have been identified.

1. Etiology.

- a. TB is caused by *Mycobacterium tuberculosis hominus* which like all mycobacteria is an obligate aerobe. These organisms are acid fast, i.e., complex lipids contained in the organisms take up carbol fuchsin stain and resist decolorization from acid wash
- b. "Atypical" infections are caused by other mycobacteria
- c. The route of infection is usually by direct inhalation of the organism. Oropharyngeal and intestinal infection may occur by ingestion of unpasteurized milk contaminated with *M. bovis*

2. Pathogenesis.

- a. Primary TB
 - i. Develops in previously unexposed, nonsensitized individuals
 - ii. Inhaled bacilli implant in distal air spaces of lower part of upper lobe or upper part of lower lobe.
 - iii. Initially, there is nonspecific inflammatory reaction, but by 2-3 weeks there is development of delayed hypersensitivity.
 - iv. The primary infection appears as a 1-1.5 cm gray-white area of consolidation and is called the Ghon focus.
 - v. Drainage of bacilli, either free or within macrophages to regional lymph nodes forms secondary areas of infection. The combination of the Ghon focus and nodal involvement is referred to as the Ghon complex.
 - vi. The histopathological features of these lesions consist of granulomatous inflammatory reactions forming both caseating and noncaseating tubercles.
 - vii. With resolution, the lesions become fibrocalcific scars but may harbor viable organisms for years.
 - viii. Clinically, primary TB is usually asymptomatic and is recognized only by positive TB skin test or focus of calcification on chest x-ray. Rarely primary TB may evolve without interruption into secondary TB.

- b. Secondary (reactivation, post-primary) TB
 - i. Arises in a previously sensitized host (less than 5% of patients with primary TB develop secondary TB).
 - ii. Normally results from reactivation of dormant primary lesions but may occur after reinfection with exogenous bacilli.
 - iii. Localized to apices of upper lobes.
 - iv. Consists of 1-2 cm areas of consolidation with central caseation and peripheral fibrotic reaction. Regional lymph nodes may be involved.
 - v. Either spontaneously or with treatment, secondary lesions may resolve by progressive fibrous encapsulation and calcification.
 - vi. In unfavorable cases, the disease may persist and progress along one of the following pathways: 1) cavitory pulmonary TB; 2) endobronchial, endotracheal, and laryngeal TB; 3) pulmonary miliary TB; 4) systemic miliary TB; 5) isolated organ TB 6) intestinal TB.
 - vii. Clinical manifestations: patients may be asymptomatic or have a gradual onset of malaise, anorexia, weight loss fever, night sweats. Later the disease localizes and patients may have cough, sputum production, or pleuritic pain. Miliary TB may present as a fever of unknown origin.

C. Fungal infections of the lungs.

Fungi are obligate saprophytes or parasites with nutritional requirements similar to those of bacteria. Many pathogenic fungi affect only the skin; however, some also involve the viscera (deep mycoses), particularly the lung. The deep mycoses may occur in otherwise healthy individuals but most frequently occur as opportunistic infections in during chronic diseases, during cancer chemo- or radiotherapy, prolonged antibiotic therapy, or immunosuppressive treatment. The type of lung disease produced by these agents varies from acute pneumonitis to chronic granulomatous infection similar to TB.

- 1. Fungal infections occurring in both normal and immunocompromised individuals.
 - a. Histoplasmosis (*Histoplasma capsulatum*).
 - i. Produces a disease similar to TB
 - ii. Endemic in the Ohio and central Mississippi River Valleys, Appalachian Mountains and southeastern U.S
 - iii. Budding intracellular yeast, 2-4 μm in diameter

- b. Coccidioidomycosis (*Coccidioides immitis*).
 - i. May cause asymptomatic pulmonary infection (60%), progressive pulmonary disease, or miliary disease
 - ii. Endemic in southwestern and far western U.S., particularly the San Joaquin Valley (valley fever)
 - iii. Spherules, 20-200 μm in diameter
 - c. North American Blastomycosis (*Blastomyces dermatitidis*).
 - i. May cause asymptomatic pulmonary infection, progressive pulmonary disease, or rarely, miliary disease
 - ii. Round yeast, 8-20 μm in diameter
 - d. Cryptococcus (*Cryptococcus neoformans*).
 - i. Rarely occurs in normal individuals
 - ii. Progressive pneumonia often with dissemination to meninges in immunocompromised patients
 - iii. Pigeon droppings serve as reservoir of infection. It is not transmitted from man to man
 - iv. Budding yeast 12-25 μm
2. Fungal infections occurring mainly in the immunosuppressed.
- a. Candidiasis (*Candida* species).
 - i. Among fungi, *Candida albicans* is the most frequent cause of disease. In the non-immunocompromised patient candidiasis causes superficial infections of the epithelial surfaces of intertriginous areas of the skin, mouth, urinary tract and vagina
 - ii. In immunocompromised hosts, it may involve the lungs, heart valves, kidney, liver, GI tract and central nervous system
 - iii. Invasive hyphae
 - b. Aspergillosis (*Aspergillus* species)
 - i. Three types of infection: 1) bronchial; 2) mycetoma; and 3) necrotizing pneumonia
 - ii. Branched, septate and nonseptated hyphae

D. Viral infections of the lung

Viruses are common causes of respiratory tract infections. They may cause considerable morbidity and mortality among infants, the elderly and immunocompromised patients.

1. Types of viral respiratory tract infection.

- a. "Common cold"--tonsillopharyngitis, pharyngitis, sinusitis, otitis media and epiglottitis
- b. "Flu"--fever, headache, myalgia, malaise
- c. "acute bronchitis"--productive cough without pneumonia
- d. "pneumonia"--diffuse interstitial infiltrates

2. Common viral pathogens of the respiratory tract

- a. Orthomyxoviridae--influenza A, B, C
- b. Paramyxoviridae--measles, parainfluenza 1-4, respiratory syncytial virus
- c. Picornaviridae--rhinovirus, enterovirus, Coxsackie B, echovirus
- d. Coronaviridae--coronavirus
- e. Adenoviridae--adenovirus, herpes simplex 1 and 2, varicella-zoster, cytomegalovirus

V. Diffuse Infiltrative Lung Disease

A. Introduction

Diffuse infiltrative lung disease is a term used to characterize a large group of lung diseases that share some common clinical and radiologic features. However, from the standpoint of etiology, pathogenesis and pathologic anatomy, they often have little in common. These disorders share dyspnea as the predominant clinical manifestation. Chest radiographs are characterized by diffuse "infiltration" by irregular linear, nodular or diffuse ("ground glass") shadows. Laboratory studies reveal hypoxemia, impaired oxygen exchange (diffusing capacity), and in advanced stages of the diseases, decreased lung volumes and compliance.

Despite the fact that these are a diverse group of diseases, their clinical similarities, the fact that pathologic abnormalities involve the lung periphery, and their contrasts with chronic obstructive lung diseases, make their grouping convenient. However, subclassifying them becomes a problem because of their number (more than 150 separate diseases have been described¹); because identical pathologic reactions may have multiple causes, and conversely, many individual diseases may elicit similar pathologic reactions. Be that as it may, a partial listing of diffuse infiltrative lung diseases is given in Table 1 for your interest rather than as an aid to memorization. You may find that a familiarity with the general categories will be useful clinical knowledge.

Table 1. Diffuse infiltrative lung disease (reference only).

1. Infections	6. Pulmonary vascular diseases
Miliary TB	Arteriolitis
Fungal	Pulmonary veno-occlusive disease
Viral	Multiple/Recurrent pulmonary embolism
Parasitic (<i>Pneumocystis carinii</i>)	
2. Neoplasms	7. Specific disorders of unknown etiology
Leukemia	Sarcoidosis
Lymphoma	Wegener's granulomatosis
Adenocarcinoma-bronchoalveolar type	Chronic eosinophilic pneumonia and related disorders
Metastatic carcinomatosis	Goodpasture syndrome
3. Occupational and environmental diseases	Idiopathic pulmonary hemosiderosis
Allergic alveolitis (organic dusts)	Pulmonary alveolar proteinosis
Silicosis (coal and graphite)	Pulmonary alveolar microlithiasis
Other silicates	Eosinophilic granuloma (Histiocytosis X)
Asbestosis	Tuberous sclerosis
Berylliosis	Lymphangioleiomyomatosis
Toxic gases (NO ₂ , SO ₂ , Br, Cl)	8. Interstitial pneumonias
Fumes (toluene)	Acute
Smoke inhalation	Diffuse alveolar damage (acute respiratory distress syndromes)
4. Drugs, toxins and therapeutic agents	Bronchiolitis obliterans organizing pneumonia (BOOP)
Chemotherapeutic agents (busulfan, bleomycin)	Chronic
Antibiotics (nitrofurantoin)	Idiopathic pulmonary fibrosis (IPF)
Other drugs (gold, penicillamine, amiodarone)	(Usual interstitial pneumonia-UIP)
Toxins (paraquat)	Lymphocytic interstitial pneumonic. (LIP)
Radiation	
Oxygen	
5. Connective tissue disease	
Scleroderma	
Systemic lupus erythematosus	
Rheumatoid arthritis	
Mixed connective tissue disease	
Other connective tissue diseases	

B. Pathogenesis

Current hypotheses directed towards understanding the pathogenesis of diffuse infiltrative lung diseases generally subscribe to the theory that injury to the lung, whether it is due to shock, toxic effects on cells, infectious agents or immune-mediated mechanisms, causes alveolitis. The alveoli are composed of endothelial and epithelial cells, collagen fibers, elastic tissue, proteoglycans, fibroblasts, mast cells, and inflammatory cells. The resident inflammatory cells consist of macrophages (93%), lymphocytes (7%), and eosinophils and neutrophils (less than 1%). During alveolitis these inflammatory cells increase in number and change in their relative proportions. Mediators of inflammation, proteases, oxidants, and other cell products are released from these cells as well as from injured endothelial, epithelial and mesenchymal cells. The net result is a perturbation of the delicate connective tissue framework of the lung. Continual injury may lead to progressive and irreversible scarring.

C. Examples of some diffuse infiltrative lung diseases

1. Acute diffuse infiltrative lung disease (example: diffuse alveolar damage).
 - a. Diffuse alveolar damage (DAD) has many synonyms including acute or adult respiratory distress syndrome (ARDS), acute alveolar injury, diffuse alveolar injury, shock lung, etc.
 - b. Gross pathology--heavy, firm lungs with boggy, red parenchyma.
 - c. Microscopic pathology--
 - i. *early stages*--edema, congestion and fibrin deposition. 24 hours after injury hyaline membranes become evident. These are composed of protein- and fibrin-containing edema fluid and cytoplasmic and lipid cellular debris from necrotic alveolar epithelial cells. Hyaline membranes increase in number for the next several days, but then begin to disappear at a somewhat variable rate. The loss of alveolar epithelial cells affects gas transport and surfactant production. With the loss of surfactant there is considerable atelectasis and this combined with the edema makes the lungs "stiff" or noncompliant. Additionally, the lung injury causes an inflammatory response.
 - ii. *healing*--If the cause of diffuse alveolar damage is removed, pulmonary edema resolves, Type II pneumocytes proliferate and repair the alveolar lining and atelectatic areas re-expand.

- iii. *organization*--However, with progression of the disease, there is organization of the fibrin exudate and interstitial fibrosis can develop.

2. Chronic diffuse infiltrative lung disease (some important examples).

- a. Idiopathic pulmonary fibrosis (IPF) also called usual interstitial pneumonia (UIP)
 - i. accounts for majority of cases.
 - ii. chronic clinical course ending in respiratory failure.
 - iii. corticosteroids have been tried but response is variable, often poor.
 - iv. microscopically, there may be edema, hyperplasia of Type II pneumocytes, interstitial inflammation and even hyaline membranes. With progression (and the time when biopsy is most likely to be considered) one finds organization of the alveolar exudate and thickening of the interstitium due to inflammation and fibrosis.
- b. Hypersensitivity pneumonitis (extrinsic allergic alveolitis)
 - i. interstitial reaction to numerous different antigens.
 - ii. responsive to corticosteroids and removal of offending antigen.
- c. Connective tissue diseases.
 - i. Interstitial inflammation and fibrosis may occur as part of the connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, and scleroderma.
 - ii. The pathology is often indistinguishable from UIP.
- d. Pneumoconiosis
 - i. Infiltrative lung diseases caused by inorganic dusts such as asbestosis, silicosis, anthracosis (coal), berylliosis.
 - ii. Diagnosis is dependent on recognizing or quantitating the suspected particles in the lung.

3. End-stage diffuse infiltrative lung disease (“honeycomb lung”).

At this stage of diffuse infiltrative lung disease, it may be difficult or impossible to make a diagnosis on pathological grounds alone.

- a. Gross pathology--the lung is composed of multiple small cysts resembling honeycombs. The lung tissue is firm and the pleural surface is irregular and nodular.
- b. Microscopic pathology--there is extensive interstitial fibrosis and scarring with remodeling of airspace's. Some of these spaces may be filled with accumulations of mucoid secretions. The thickened interstitium may contain lymphoid aggregates. Pulmonary arteries tend to have hyperplastic intima.

D. Clinical manifestations and clinical approach to these diseases

The most important complaint from patients presenting with diffuse infiltrative lung disease is dyspnea. Other important symptoms include cough, sputum production, and weight loss. Fever, night sweats, and joint pains are other chief complaints. Medical history is important at arriving at a correct diagnosis in diffuse infiltrative lung disease. Particularly important is thorough investigation of patient's occupational and environmental history. Review of previous chest radiographs can help determine the chronicity of the disease. Physical examination is often nonspecific but may help when the lung disease is a manifestation of a systemic disorder.

VI. Pulmonary embolism

A. Introduction

Embolism refers to occlusion of some part of the cardiovascular system by impaction of some mass (embolus) which has been transported through the blood stream. Pulmonary embolism refers to an embolism that lodges in the pulmonary arterial system. It is a major cause of death either as a sole cause or as a major contributing cause. Its annual incidence in the U.S. is 650,000, and it carries a 40% mortality.

B. Origins of pulmonary emboli

1. Pulmonary emboli arise most frequently from thrombi which form in the deep veins of the legs.
2. Venous thrombosis and pulmonary emboli occur secondary to:
 - a. Immobilization of an extremity
 - b. Congestive heart failure
 - c. Following trauma (blunt trauma, fractures, burns)
 - d. During delivery or postpartum

C. Clinical manifestations

The consequences of pulmonary embolism depend on the size of the emboli, the state of the occluded arteries, and the state of the general pulmonary circulation.

1. Sudden death - occurs with massive pulmonary embolism that occludes the main pulmonary arteries (saddle embolism) or the blood supply to 4 of the 5 pulmonary lobes.
2. Sudden chest pain, syncope, dyspnea - occlusion to large lobar vessels or multiple smaller vessels. Hemoptysis may occur if there is pulmonary hemorrhage or infarction. Death may also occur in elderly or debilitated patients.
3. Asymptomatic - smaller emboli may be asymptomatic or produce a transient episode of chest pain, cough and hemoptysis

VII. Pulmonary hypertension (pulmonary vascular sclerosis)

A. Primary pulmonary hypertension

1. Only about 1% of the total cases of pulmonary hypertension
2. Etiology unknown
3. Occurs in young individuals--more commonly women
4. No successful treatment, only symptomatic therapy
5. Clinically manifestations include fatigue, syncope, dyspnea on exertion, and occasionally chest pain

B. Secondary pulmonary hypertension

1. Occurs in conditions in which the resistance to flow in the pulmonary arterial bed is increased or when there is prolonged blood volume overload
2. May develop at any age and present with respiratory insufficiency and right heart failure

C. Morphology

1. Main pulmonary arteries - atheromas
2. Medium sized pulmonary arteries - intimal thickening and medial hypertrophy
3. Smaller arteries and arterioles - intimal thickening, reduplication of the internal and external elastic laminae, medial hypertrophy, fibrinoid necrosis

Pulmonary Diseases II**OBJECTIVES:**

- *Recognize the gross and microscopic pathology of the four main types of chronic obstructive lung diseases.*
- *Compare and contrast between the two major types of emphysema.*
- *Explain the protease-antiprotease hypothesis of emphysema pathogenesis.*
- *Describe the pathogenesis of chronic bronchitis.*
- *Describe the different pathogenic mechanisms involved in asthma.*
- *Describe the most common types of lung carcinoma.*
- *Explain how the pathology and biology of lung cancers produces different types of clinical manifestations.*

READING: Robbins Basic Pathology, Kumar, Abbas, Mitchell, 9th Ed., 2013
pp.463-472, 505-511

I. Obstructive Lung Disease**A. Introduction**

As the title of the topic implies, the group of lung disorders included in this category are related by a functional abnormality - a decreased ability to expire. Several terms have been used to describe these diseases. They include chronic obstructive lung disease, chronic obstructive pulmonary disease, chronic airway disease, chronic obstructive airway disease, chronic airflow obstruction, etc. In this country, chronic obstructive lung disease (C.O.L.D.) and chronic obstructive pulmonary disease (C.O.P.D.) are used most frequently. The four major types of obstructive lung diseases are listed below with their definitions.

1. **Emphysema**-a condition of the lung characterized by abnormal enlargement of air spaces distal to the terminal bronchiole, arising from destruction of their walls.
2. **Chronic bronchitis**-chronic excessive production of mucus in the airways not due to known specific causes (i.e. bronchiectasis, tuberculosis). In this definition "chronic" means on most days for more than three months a year for two or more successive years.
3. **Asthma (reactive airway disease)**-a disease characterized by increased irritability of the tracheobronchial tree, potentiating paroxysmal narrowing of bronchial airways and airflow obstruction. The obstruction to airflow may reverse spontaneously or as a result of treatment with bronchodilator drugs. At least some asthmatic conditions appear to be related to allergy.

4. **Bronchiectasis**-chronic necrotizing infection of the bronchi and bronchioles leading to or associated with abnormal dilation of these airways.

B. Emphysema

1. Types of emphysema

Emphysema can be classified by its anatomical distribution within the lung acinus (Figure 1). There are three types: centriacinar, panacinar, and paraseptal¹. Clinically, centriacinar and panacinar are the most important.

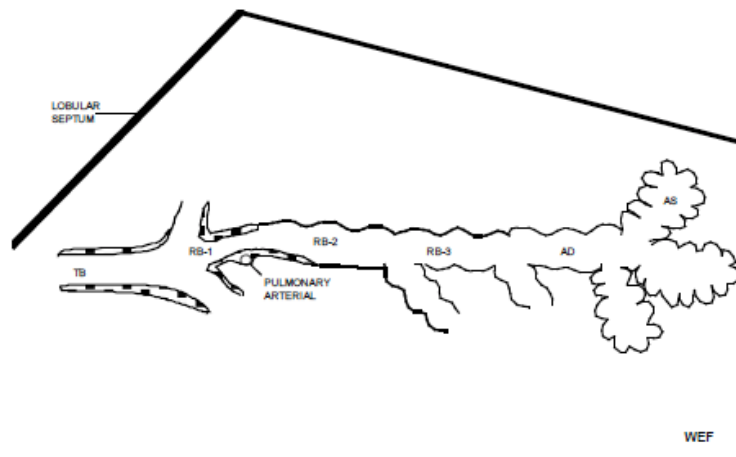


Figure 1. Normal lung acinus.

- a. **Centriacinar emphysema** (synonym: centrilobular emphysema). In this type of emphysema, the proximal portions of the acini (respiratory bronchioles) are affected and the distal portions of the acini (alveolar ducts and alveoli) are usually spared (Figure 2). In centriacinar emphysema the second- and third-order respiratory bronchioles are more severely affected than the first order respiratory bronchiole. In severe centrilobular emphysema, the distal acinus may be involved making its differentiation from panacinar emphysema difficult. There is generally variation in the severity of centriacinar emphysema among lobules and even within the same lobules. The lesions are more common and more severe in the upper lobes. Chronic inflammation of the airways supplying the emphysematous areas and chronic inflammation and fibrosis of the walls of emphysematous spaces can usually be seen. Centriacinar emphysema is the most common type of emphysema. It is the type of emphysema associated with smoking.

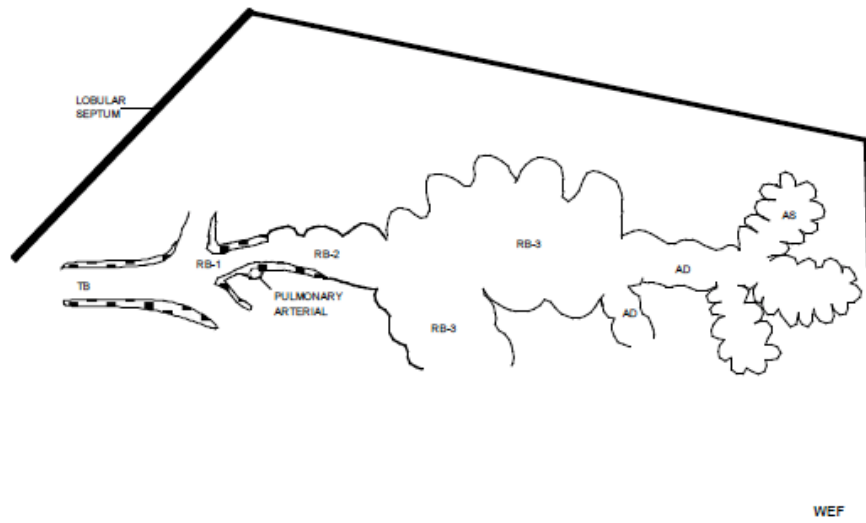


Figure 2. The lung acinus in centriacinar emphysema

- b. **Panacinar emphysema** (synonym: panlobular emphysema). In this type of emphysema, the acini are more or less uniformly affected from the level of the respiratory bronchiole to the terminal alveoli (Figure 3). Panacinar emphysema tends to be more frequent in the lower zones of the lung. It is the type of emphysema associated with **alpha-1-antitrypsin deficiency**. It can also be found in 5-10% of random autopsies and up to 20% in autopsies performed on persons over the age of 70. It may occur in patients with chronic bronchitis, and in these cases, centrilobular emphysema is usually present as well, making precise classification difficult.

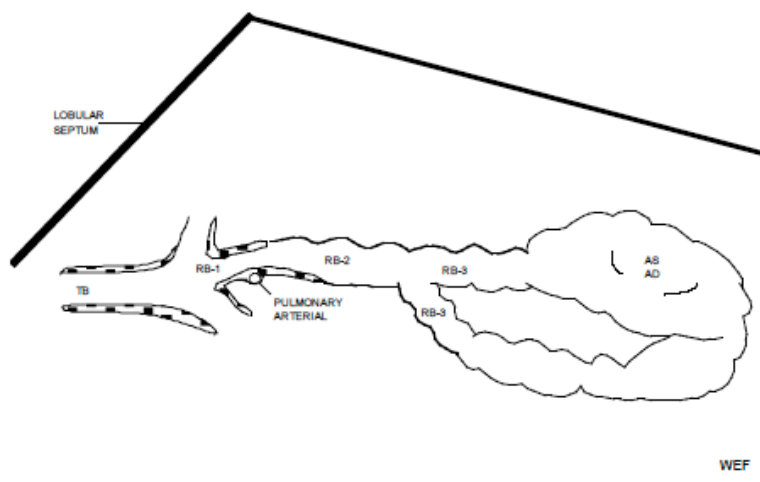


Figure 3. The lung acinus in panacinar emphysema.

2. Pathogenesis of emphysema (**protease-antiprotease hypothesis**)

The pathogenesis of the destruction of the lung parenchyma in emphysema is believed to be due to the actions of proteolytic enzymes or proteases, particularly the protease elastase (Figure 4). This theory has evolved from clinical observations in patients with a deficiency in alpha-1-antitrypsin, a protease inhibitor, and from studies of chronic bronchitis due to smoking. In both alpha 1-antitrypsin deficiency and smoking, the elastase destroys the elastin framework of the lung resulting in emphysema.

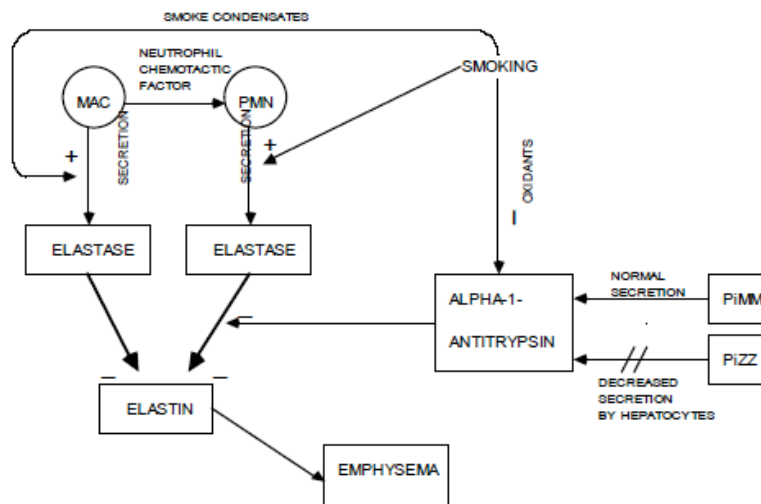


Figure 4. Pathogenesis of emphysema - the protease-antiprotease hypothesis.

3. Clinical manifestations of emphysema (see section B-3 below).

C. Chronic bronchitis (productive cough for 3 consecutive months for 2 or more years)

Chronic bronchitis is common among smokers and people who dwell in smog.

1. Pathogenesis of chronic bronchitis

The development of chronic bronchitis is due to chronic irritation of the airways by inhalation of substances and the development of microbiologic infections. Tobacco smoke is, of course, the major irritating inhalant; however, pollutants including sulfur dioxide, nitrogen dioxide, etc. can exert similar effects. Airway irritants activate neurohormonal pathways that stimulate airway secretory cells to release their products. Additionally, they act on inflammatory cells that normally reside in the airways to release various mediators that both attract additional leukocytes and stimulate airway mucous secretion.

How does this cause airways obstruction? Excessive production of mucous by goblet cells lining the small airways can result in mucous plugging of the bronchiolar lumen. Additionally, inflammatory infiltrates and clustering of pigmented alveolar macrophages contribute to lumen narrowing. As the disease progresses, fibrosis of the bronchiolar wall may develop. Narrowing of airways less than 2-3 mm in diameter contribute to the development of obstructive airway physiology.

The development of infection in this fertile environment of narrowed and obstructed airways is a secondary phenomenon that probably contributes to disease progression and certainly to acute exacerbations. *Hemophilus influenzae*, pneumococci, and *Streptococcus viridans*, adenovirus, and respiratory syncytial virus are the most common pathogens.

2. Morphology of chronic bronchitis

The pathological finding that most consistently correlates with chronic bronchitis is not inflammation as one would suspect by its name but rather **enlargement of tracheobronchial submucosal glands and an increase in the number of surface goblet cells**. Hypertrophy and hyperplasia of the mucous secretory apparatus is associated with the increased sputum production so clinically apparent in this disease. Reid² described a simple light microscopic technique for measuring tracheobronchial gland enlargement (Figure 5). This measurement, now known as the **Reid index** correlates well with the clinical presence of chronic bronchitis. The mean Reid index in normal individuals is roughly one-third while in bronchitics it averages one-half.

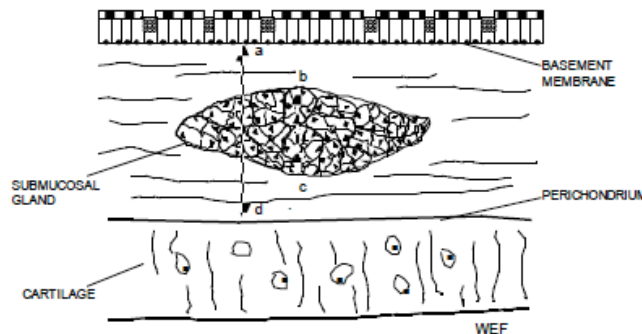


Figure 5. The Reid index is obtained by determining the ratio of the thickness of the submucosal glands (b-c) to the distance between the perichondrium and the basal lamina of the bronchial lining epithelium (a-d).

3. Clinical manifestations of emphysema and chronic bronchitis.

The clinical features of COPD developing in patients with emphysema and chronic bronchitis differ. These differences are summarized below in Table 1. It should also be noted that the distinctions between chronic bronchitis and emphysema can be blurred since emphysema is about twice as frequent in subjects with chronic bronchitis than without.

Table 1. Clinical features of chronic bronchitis and emphysema.

	Predominant Bronchitis	Predominant Emphysema
Appearance	"blue bloater"	"pink puffer"
Age	40-50	50-75
Dyspnea	mild; late	severe; early
Cough	early; copious sputum	late; scanty sputum
Infections	common	occasional
Respiratory insufficiency	repeated	terminal
Cor pulmonale	common	rare; terminal
Airway resistance	increased	normal or slightly increased
Elastic recoil	normal	low
chest radiograph	prominent vessels; large heart	hyperinflation; small heart

D. Asthma

Asthma is a common condition with an incidence of approximately 4% in the U.S. Patients with asthma have hyperresponsive airways and their disease is characterized by **reversible bronchoconstriction** in response to varied stimuli. Asthma can be classified based on these stimuli or more traditionally, into two types: **extrinsic** (immunologic or allergic) and **intrinsic** (non-immunologic or idiosyncratic). The types of asthma, precipitating factors and pathogenic mechanisms are listed in Table 2.

Table 2. Asthma, types, precipitating factors and pathogenic mechanisms.

<u>Types of asthma</u>	<u>Stimuli</u>	<u>Pathogenic mechanism</u>
Extrinsic		
Atopic (allergic)	specific allergens (dusts, pollens, etc.)	Type I (IgE) immune reaction
Intrinsic		
Nonreaginic	respiratory tract infection	Unknown; hyper- reactive airways
Aspirin sensitive	aspirin	Decreased prosta- glandins; increased leukotrienes
Occupational/ air pollution	chemicals	Types I and III immune reactions
Allergic broncho- pulmonary asper- gillosis	antigen (fungal spore) challenge	Types I and III immune reactions
Exercise; cold air	increased ventilation; low temperature	Unknown
Psychogenic	emotional factors	Activator of vagal efferent pathways

1. Pathogenesis of asthma

The exact mechanisms in the pathogenesis of asthma have not been elucidated with certainty. Several mechanisms could certainly be operative. Basically, studies have focused on two major areas:

- (1) Interaction of allergens with IgE antibodies bound to mast cells from which are released mediators that potentiate bronchoconstriction, mucous secretion, and recruitment of inflammatory cells.
- (2) Hyperreactivity or imbalance of the neurohumoral (autonomic) control of airway constriction and mucous secretion.

The pathogenesis of asthma is summarized below in Figure 6.

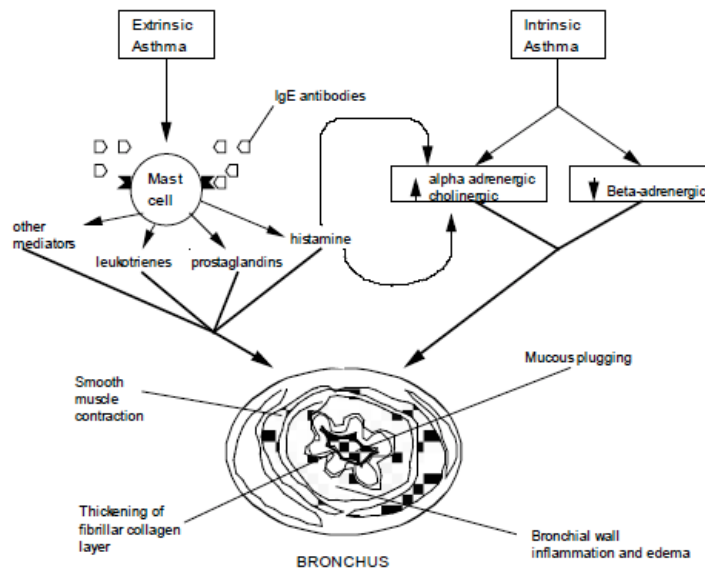


Figure 6. Pathogenesis of asthma.

2. Morphology of asthma

The pathologic changes in asthma have been primarily described in patients dying of asthma, fortunately a rare occurrence. Nonfatal cases demonstrate similar if somewhat milder alterations.

- a. **Mucus plugging.** This is the most dramatic finding in asthma. Bronchi and bronchioles are occluded by plugs of mucus. The plugs are composed of mucous containing an inflammatory cell exudate. Eosinophils predominate. Also, the mucous plugs contain whorls of sloughed bronchial or bronchiolar epithelium admixed with proteinaceous secretions (Curschmann spirals) and collections of crystals derived from eosinophils (Charcot-Leyden crystals).
- b. **Thickening of the basement membrane** of the airway epithelium. Although referred to as basement membrane thickening, it is actually a thickening of the sub-epithelial fibrillar collagen layer. This layer is usually 7.5 μm thick but in asthma it averages 17.5 μm in thickness.
- c. **Edema and inflammation of bronchial walls.** Again, eosinophils are prominent. Studies of mast cells in asthmatics suggest that they are reduced in number and that they appear degranulated.

d. **Hypertrophy and hyperplasia of submucosal mucous glands.**
Hyperplasia of epithelial goblet cells also may be found.

e. **Hyperplasia of airway smooth muscle.**

3. Clinical manifestations of asthma

Extrinsic asthma usually develops in children and young adults with histories of atopy and family histories of multiple allergies. These patients frequently have elevated serum IgE levels and peripheral blood eosinophilia. Typically, this type of asthma abates in adulthood. Intrinsic asthma generally develops in adulthood. IgE levels and eosinophil counts are normal. This group of patients may have chronic bronchitis upon which airway hyperreactivity develops.

In either case, asthmatic attacks are characterized by the sudden development of bronchoconstriction which results in dyspnea and wheezing. Patients have difficulty with both inspiration and expiration, although more so with expiration since the airways widen and lengthen during inspiration. The constricted airways cause wheezing, principally during expiration. Hyperinflation of the lung results as air is trapped distal to mucus plug obstructions. The attacks typically last from one to several hours and subside spontaneously or with therapy. As mentioned above, asthma is rarely fatal; however, it may cause death when bronchoconstriction fails to reverse for days or weeks (**status asthmaticus**). In these cases, death from acute respiratory failure or superimposed infection may occur.

E. Bronchiectasis (dilated airways)

Before the introduction of antibiotics and immunizations, bronchiectasis frequently developed during childhood as a complication of childhood infections. Today it is less common, but it remains clinically important in several conditions.

1. Pathogenesis of bronchiectasis

Bronchiectasis occurs in a variety of diseases (Table 3) that have in common **obstruction of airways, impaired mucociliary clearance and persistent infection**. In some cases, infection develops in bronchiectatic areas while in others, infection is the precipitating cause of the airway injury and dilatation.

Table 3. Causes of bronchiectasis

<u>Causes</u>	<u>Pathogenesis</u>
Post-infective measles, pertussis, adenovirus, TB, suppurative pneumonias	impaired drainage of secretions
Congenital abnormalities intralobar sequestration	infection
Hereditary conditions Cystic fibrosis	abnormal chloride channel (CFTR) function leading to mucus hyperviscosity and superimposed infection
Immotile cilia syndrome (Kartagener)	impaired ciliary activity leading to impaired mucociliary clearance
Immunodeficiency states	infection
Congenital bronchiectasis	defect in bronchial wall cartilage

2. Morphology of bronchiectasis

- a. Bronchiectatic airways are dilated, sometimes up to four times normal size, and can usually be seen to reach the pleural surface.
- b. Bronchiectatic airways are filled with suppurative exudate composed of acute and chronic inflammatory cells. There may be squamous metaplasia or pseudostratification of the remaining epithelium.
- c. There may be destruction of bronchial and bronchiolar walls, and this may result in abscess formation.
- d. With healing there may be regeneration of normal epithelium; however, dilatation and scarring persist.
- e. The adjacent lung parenchyma may show patchy emphysema, atelectasis, and fibrosis.

3. Clinical manifestations

The most prominent symptom of bronchiectasis is chronic cough with the production of copious, purulent sputum. Lung abscesses may develop, as may parenchymal infections. Erosions into bronchial arterioles and arteries may lead to hemoptysis or occasionally frank hemorrhage. Long-standing, severe

bronchiectasis may lead to severe obstructive ventilatory insufficiency, dyspnea, cyanosis and digital clubbing.

II. Lung Cancer

A. Introduction

Cancer of the lung is usually referred to as "bronchogenic carcinoma" despite the fact that not all lung cancers arise in the bronchi. Over 90% of tumors of the lung are included in this group and they are all malignant. The remaining lung tumors consist of a variety of benign and malignant tumors arising from both epithelial and mesenchymal tissues.

B. Epidemiology

1. Incidence

At the turn of the century it was a relatively rare disease; however, it is now the second most common visceral malignancy in men and women, and accounts for 13% of all cancers in men and 12% in women in 2005. Its incidence has been increasing steadily in females so that it is now the second most common visceral malignancy and accounts for 12% of all cancers in women. Generally, lung cancer occurs between ages 40-70 with a peak incidence in the 6th-7th decade.

2. Etiology

- a. **Tobacco smoking.** The association of tobacco smoking with lung cancer was established by epidemiologic studies done in the 1950s and 1960s.
 - i. There is a reduced risk of lung cancer in nonsmokers.
 - ii. There is an increased risk of lung cancer with number of cigarettes smoked.
 - iii. In ex-smokers' lung cancer rates decline to near normal after 10 years.
 - iv. Smokers develop changes in their respiratory epithelium. These include loss of cilia, basal epithelial hyperplasia, and nuclear abnormalities (atypia and dysplasia).
- b. **Industrial hazards.** Several industrial exposures increase the risk of developing cancer.
- c. **Air Pollution.** There is a slightly higher risk of developing lung cancer for people living in urban areas.

- d. **"Scar Cancer."** There is an increased incidence of lung cancer in areas of scarring due to lung injury from infarcts, infections, or infiltrative lung disease.

C. Classification of major types of lung cancer.

1. Histologic classification.

<u>Type</u>	<u>Cox and Yessner</u>	<u>Frequency (%)</u>	
		<u>UCSF</u>	<u>Today</u>
Squamous carcinoma	33	31	25-30
Adenocarcinoma	28	30	30-35
Combined squamous carcinoma and adenocarcinoma			
Small cell carcinoma	22	12	20
Large cell carcinoma	17	24	5-15

D. Classification by site. Seventy-five percent of lung cancers arise in first three generations of bronchi.

1. Central (bronchogenic) - Majority are squamous or small cell carcinomas.
2. Peripheral - Twenty-five percent of lung cancers. Arise in relation to small bronchi, bronchioles, or alveoli. Most are adenocarcinomas.

E. Spread of lung cancer.

1. Local invasion
 - a. Central carcinomas - invade mediastinum
 - b. Peripheral carcinomas - invade pleura
2. Lymphatic metastasis
 - a. Hilar scalene lymph nodes
 - b. Pleural lymphatics
3. Bloodstream (hematogenous) metastasis - common

Sites of metastasis include:
 adrenal glands (50%)
 liver (30%)
 brain (20%)
 bone (20%)
 kidney (15%)

F. Clinical Manifestations.

Symptoms from lung cancer are quite variable and depend on site of tumor and the presence or absence of metastasis.

1. Intrathoracic effects of lung tumors.
 - a. Local effects of lung tumors.
 - i. Cough and sputum production--Since most patients with lung cancer are smokers, cough and sputum production have often been present for years. Local irritation by tumor may result in a change in the cough or sputum.
 - ii. Wheezing
 - iii. Hemoptysis
 - iv. Dyspnea
 - v. Chest pain
 - b. Infections distal to tumor--Obstruction of airways by tumors may result in the development of pneumonia. The infections tend to resolve slowly, recur and lead to chronic pneumonia and bronchiectasis.
 - c. Pleural effusions--These develop as a result of metastasis to pleura, infection or lymphatic obstruction.
2. Extrathoracic effects of lung tumors.
 - a. Due to metastases
 - i. Superior vena caval obstruction
 - ii. Recurrent nerve paralysis
 - iii. Painful bone lesions
 - iv. Neurologic symptoms resulting from brain metastases
 - b. Paraneoplastic syndromes
 - i. Endocrine: Ectopic hormone production. Cushing's syndrome (ACTH), inappropriate ADH secretion, hypercalcemia (PTH), carcinoid syndrome (5-hydroxytryptamine), gynecomastia (gonadotropins).
 - ii. Neuromuscular: polymyositis, carcinomatous myopathy, Eaton-Lambert syndrome, peripheral neuropathy, subacute cerebellar degeneration, leukoencephalopathy.
 - iii. Skeletal: clubbing, hypertrophic osteoarthropathy.
 - iv. Cutaneous: acanthosis nigricans, dermatomyositis
 - v. Cardiovascular: migratory thrombophlebitis, nonbacterial thrombotic (marantic) endocarditis.

G. Staging

- Occult: Malignant cells in bronchopulmonary secretions without evidence of primary tumor or metastases.
- Stage I: Tumor less than or larger than 3 cm without metastasis; tumor less than 3 cm with metastasis to local hilar lymph nodes only.
- Stage II: Tumor larger than 3 cm with local hilar lymph node metastases only.
- Stage III: Tumor within 2 cm of the carina or invading adjacent structures outside the lung; tumor of any size with metastasis to mediastinal lymph nodes or distant metastases.

H. Prognosis.

The overall prognosis of lung cancer is poor with five-year survival rates around 10-20%. Less than 30% of patients present with lesions sufficiently localized to permit surgical resection. For localized solitary tumors, surgical resection results in up to 50% five-year survival, excepting small cell and large cell anaplastic tumors.

	<u>5-year Survival Rate (with therapy)</u>
Stage I	50%
Stage II	20%
Stage III	5%

I. Tumors of the pleura

1. Primary neoplasms of the pleura are rare.
2. They may be benign or malignant.
 - a. Localized fibrous mesothelioma (benign)
 - b. Malignant mesothelioma (see Environmental Pathology Lecture)
 - i. incidence of malignant mesothelioma increased with heavy exposure to asbestos
 - ii. Uniformly fatal

Kidney and Urinary Tract / Male Reproductive Diseases**OBJECTIVES:**

- *Describe the various glomerular, tubular, interstitial and vascular diseases.*
- *Describe polycystic kidney diseases.*
- *Compare and contrast the various tumors that arise within the kidney and urinary tract.*

READING: Robbins Basic Pathology, Kumar, Abbas, Mitchell, 9th Ed., 2013, pp. 517-549, 663-671.

I. INTRODUCTION

- A. Classification of renal disease according to parenchymal structures primarily or predominantly involved:

1. Glomerular diseases
2. Tubular diseases
3. Interstitial diseases
4. Vascular diseases

Regardless of which tissue component is primarily affected, secondary involvement of other components commonly occurs either simultaneously or sequentially.

- B. Major clinicopathologic syndromes associated with renal diseases

1. Uremia -- A clinical syndrome due either to destruction of parenchyma or functional loss of renal tissue. Often referred to as renal failure or insufficiency. May be acute or chronic, reversible or irreversible.
 - a. Biochemical disturbances -- Most important are: sodium and water retention with hypertension and edema; azotemia (increased BUN and serum creatinine); acidosis, hyperkalemia, and hyperphosphatemia due to excretory failure of H^+ , K^+ , and phosphate.
 - b. Pathology -- Multiple organs and tissues involved due to widespread capillary damage.

Skin: uremic dermatitis

C.V. system: myocardial hypertrophy, uremic pericarditis

Lungs: uremic pneumonitis

G.I. tract: uremic colitis

Nervous system: uremic encephalopathy, retinopathy, and peripheral neuropathy

Skeleton and endocrine: parathyroid hyperplasia, renal osteodystrophy

Soft tissues: metastatic calcification.

II. GLOMERULAR DISEASES

A. Inflammatory diseases: Glomerulonephritis that typically produces a nephritic syndrome (mild to moderate hypertension, proteinuria, hematuria, azotemia, oliguria).

1. There are several clinical types which may occur as primary renal disease or as secondary renal manifestations of infectious (i.e., post-streptococcal glomerulonephritis) or systemic immunological diseases (i.e., systemic lupus erythematosus).
2. Glomerular lesions consist of cell proliferation, margination of inflammatory cells, and sometimes necrosis, usually associated with deposition of immune complexes.
3. Clinical manifestations may be limited to urinary findings in mild cases (i.e., slight to moderate proteinuria and hematuria). In other cases, they consist of nephrotic syndromes when alterations of capillary permeability predominate; uremia when capillary obstruction by proliferated cells is most severe; or a combination of symptoms of the two syndromes in intermediate cases.
4. Clinical evolution varies depending on type:
 - a. Resolution (i.e., post-streptococcal glomerulonephritis)
 - b. Progression toward end-stage renal disease within several months (i.e., rapidly progressive glomerulonephritis) or several years (i.e., lupus nephritis).

B. Non-inflammatory diseases:

1. Nephrotic syndrome -- A clinical syndrome due to increased permeability of glomerular capillary walls to plasma proteins. Loss of albumin induces mobilization of lipids with hyperlipemia and lipiduria.
 - a. Cardinal features and criteria for diagnosis:
 - i. Proteinuria: urinary excretion of proteins (mostly albumin) in excess of 3.5 gm/24 hr/1.73 m² of body surface.
 - ii. Hypoproteinemia: plasma levels of albumin 3.0 gm% or less
 - iii. Hyperlipemia: serum cholesterol in excess of 300 mg%/dl
 - iv. Lipiduria: free fat droplets, oval fat bodies, fatty casts in urine.
 - v. Edema: Due to decreased plasma oncotic pressure allowing more water and solutes to remain in interstitial tissues.
2. Most common types:

- a. Minimal change disease (Lipoid nephrosis or Nil disease): More often seen in children and characterized by reversible alterations of glomerular epithelial cells (loss of foot processes and microvillous transformation).
- b. Diabetic glomerulosclerosis: Develops 5-15 years after onset of diabetes mellitus. Characterized by thickening of basement membrane material in glomerular capillaries. Manifested by proteinuria and nephrotic syndrome followed by progressive renal failure in 50% of patients.

III. TUBULO-INTERSTITIAL DISEASES

A. Acute Tubular Necrosis (acute kidney injury, "ATN," "acute renal failure," "vasoactive nephropathy")

1. Etiology:
 - a. Acute ischemia: Many conditions producing hypotension and renal ischemia of sufficient severity and duration (i.e., transfusion reactions, shock, hemorrhage, crush injuries).
 - b. Chemicals: HgCl₂, CCl₄, uranium, diethylene glycol.
 - c. Drugs: especially antibiotics (kanamycin, gentamicin, amphotericin B, degraded tetracyclines).
2. Clinical aspects:
 - a. Rapidly developing oliguria or anuria (renal shut-down) and uremia.
 - b. Death or full recovery of renal function possible if patients supported until tubular regeneration occurs (1-3 weeks) and normal renal blood perfusion reestablished.
3. Mechanisms of anuria:
 - a. Generally poor correlation between degrees of histologic change or necrosis and total cessation of renal function.
 - b. Implicated mechanisms:
 - i. Failure of glomerular filtration due to vasoconstriction. with preferential reduction of cortical blood perfusion.
 - ii. Tubular obstruction by accretion of cell debris in tubular lumen.
 - iii. Tubular disruption with passive back-flow of glomerular filtrate.

Combination of mechanisms (i.) and (ii.) seems most important.

4. Histology: - variable and dependent on etiology.
 - a. Spotty tubular cell necrosis and hemoglobin pigment casts in ischemic type of injury.
 - b. Extensive proximal tubular cell necrosis in heavy metal poisoning.
 - c. Marked proximal tubular cell swelling and vacuolation in diethylene glycol poisoning.
 - d. Phospholipidosis (granular cytoplasmic degeneration) of proximal and distal tubular cells in gentamicin toxicity. Cytoplasmic granules are due to injury to the membranes of cellular organelles and develop from

secondary autophagic lysosomes within which the altered organelles (i.e., mitochondria) are digested. Residual phospholipids surviving digestion form dense bodies characterized by concentric myelin-like layers.

Sufficiently severe degrees of this type of injury will result in cell death.

- e. Tubular cell regeneration begins after 3-5 days and is completed in two to three weeks.

B. Allergic Tubulo-Interstitial Nephritis

Acute interstitial inflammation with numerous eosinophils and neutrophils due to production of antibodies against tubular antigens consisting of tubular proteins and chemicals acting as haptens. Methicillin ("methicillin nephritis") most commonly involved; other penicillin derivatives, cephalosporins, and thiazide diuretics may cause the reaction. Tubular damage is caused by and correlates with the severity of the interstitial inflammation.

C. Acute and Chronic Pyelonephritis

1. Inflammation of renal pelvis extending to renal parenchyma usually from lower urinary tract, particularly urinary bladder (cystitis).
2. Acute episodes often self-limited but leave residual scarring and tend to recur.
3. Chronic pyelonephritis results from repeated bouts of acute infection and may lead to extensive scarring with loss of renal function.
4. Etiology: Bacteria from intestinal tract contaminate the perineal region and invade the urinary bladder via the urethra.
 - a. *E. coli* most important.
 - b. *Proteus vulgaris*, *Pseudomonas* and *Aerobacter* species increasingly important in iatrogenic and hospital-acquired infections due to catheterization and instrumentation in lower urinary tract.
5. Pathogenesis: Ascending route of infection most important.

Predisposing factors:

- a. Functional or mechanical urinary obstruction with stasis of urine.
- b. Vesico-ureteral reflux.
- c. Caliculi.
- d. Pregnancy and diabetes.
- e. Catheterization, instrumentation of lower urinary tract.
6. Pathology: Swollen, congested kidneys with multiple small abscesses in severe acute cases.

Contracted, coarsely granular kidneys in chronic cases.

Microscopically: Interstitial inflammation
 Tubular atrophy with colloid protein casts
 Glomerular pericapsular fibrosis

Fibromuscular hyperplasia of arteries

IV. POLYCYSTIC KIDNEY DISEASE

The most important entity among inherited tubular developmental abnormalities is Polycystic Kidney Disease. Two distinct forms are seen:

- a. Adult Form: More common (1:500 persons affected; responsible for 5-8% of cases of renal failure) and inherited as autosomal dominant.
 - Associated with cysts in liver in 50% of patients.
 - Associated with cerebral berry aneurysms in 15% of cases, rupture of which accounts for 10% of fatal subarachnoid hemorrhages.
 - Saccular and cystic dilatations of tubules affect all portions of nephrons in both kidneys. There is an admixture of normal and cystic nephrons in varying portions in each patient.
 - The percent of nephrons involved determines the age of onset of symptoms (usually 3rd and 4th decades) and the longevity of patients thereafter.
- b. Infantile Form: Rare and inherited as autosomal recessive.
 - Invariably associated with multiple hepatic cysts and portal fibrosis.
 - Characterized by saccular or cystic dilatation of 60-90% of collecting tubules in both kidneys, giving them a sponge-like appearance.
 - Symptomatic in early infancy and usually fatal.

V. VASCULAR DISEASES

- A. Renal Infarction:
 - Embolism.
 - Severe atherosclerosis of renal arteries and their main branches with or without thrombosis.
- B. Arteriolar Nephrosclerosis: Sclerosis and narrowing of renal arterioles due to essential hypertension causing chronic ischemia and progressive atrophy of renal parenchyma.

- C. Renal Hypertension: due to partial stenosis of renal arteries, usually unilateral. In the ischemic kidney juxtaglomerular cells respond by increasing secretion of the vasopressor hormone Renin.

VI. RENAL TRANSPLANT REJECTION

Immunological rejection of a transplanted kidney is associated with two main lesions usually occurring in combination, but each with variable intensity:

1. Vasculitis: Inflammation of arterial walls with or without necrosis and thrombosis. Mediated by circulating antibodies already present in recipient prior to transplantation and reacting with vascular antigens, particularly endothelial. Therefore, the reaction occurs immediately or soon after transplantation. Predominantly seen in acute and hyperacute rejection. Causes renal ischemia and hemorrhagic infarction.
2. Interstitial Nephritis: Inflammation of interstitial tissue with tubular damage due to cell-mediated immunity involving lymphocytes sensitized to tubular antigens. Reaction requires several days to develop and is characterized by infiltration of interstitial tissue by numerous lymphocytes and monocytes. The process may continue for several years after transplantation and leads to gradual destruction of renal tubules and progressive parenchymal fibrosis.

VII. COMMON TUMORS AND TUMOR-LIKE LESIONS OF URINARY TRACT

A. Renal Cell Carcinoma

1. Tumor of adults (6th-7th decade); more common in males; 80-90% of renal malignant tumors; 3% of visceral cancers.
2. Three to 12 cm in size. Yellow. Necrosis and hemorrhage frequent.
3. Origin from tubular epithelium. Cells frequently filled with fluid, lipids, and glycogen ("clear cells" pattern). Early invasion of veins.
4. Metastasis: Often first sign due to early hematogenous spread to lungs, brain, bones.
5. Variability of presenting symptoms and signs (in order of frequency):
 - Painless hematuria, flank pain, palpable mass.
 - Fever of unknown origin may be the only manifestation.
6. Polycythemia may be a special manifestation due to the production of erythropoietin-like material.
7. Radioresistant.
8. Five-year survival: 50%.

B. Nephroblastoma (Wilms tumor)

1. Common renal tumor of children (usually under 6 years); 20% of visceral childhood cancers.
2. May attain huge size. Spread to other kidney and metastasis to lungs most frequent.
3. Histologic pattern: Tumor of renal mesoderm, admixture of epithelial and mesenchymal cells of many types.
4. Signs and symptoms (in order of frequency): abdominal mass, pain, hematuria.
5. Radiosensitive
6. Five-year survival, 40%; with radiotherapy and chemotherapy, 90%.

C. Urothelial (transitional cell) carcinoma of urinary bladder

1. Neoplasm of adults (5th-7th decade), twice as frequent in males.
2. 90% originate in urinary bladder; 5-10% in renal pelvis.
3. Etiology: beta naphthylamine in workers in aniline dye industry; schistosomiasis (associated with squamous cell carcinoma of the urinary bladder); tobacco.
4. Histologic grading based on cellular differentiation and invasion; Grade I (papillary, well-differentiated, non-invasive), to Grade IV (anaplastic, invasive).
5. Invasion most important factor affecting prognosis: five-year survival 85% without invasion; 20% with invasion.
6. Presenting symptoms (in order of frequency): hematuria, frequency of urination, dysuria (pain on urination).
7. Marked tendency to recur after removal.
8. Metastasis via lymphatics first to external iliac nodes.

D. Nodular hyperplasia of the prostate ("Benign Prostatic Hypertrophy")

Nodular enlargement of prostate, common in men over the age of 60 years, due to hyperplasia of prostatic glands and surrounding fibromuscular tissue. Prostatic nodular hyperplasia does not increase the risk for prostatic adenocarcinoma.

Usually arises in central and transitional zones of the prostate thereby causing early discomfort and urinary obstruction due to impingement on urethra and outflow of urinary bladder.

E. Carcinoma of the prostate

1. The prostatic carcinoma is the most common cancer in men (overall).
2. Firm tumor, usually in peripheral zone (posterior lobe), subcapsular, not obstructive until late stage (by contrast, benign prostatic hypertrophy: soft nodules, central and transitional zones, obstructive in early stage of development).
3. Elevated serum levels of prostate-specific antigen normally produced by prostatic glandular cells is evidence of tumor size, capsular invasion and/or metastasis.
4. Metastasis:
 - a. Pelvic, para-aortic, and mediastinal lymph nodes
 - b. Viscera: kidney, adrenals, liver, lungs
 - c. Bones in area of distribution of vertebral venous plexus: lumbar spine, femora, pelvic bones; osteoblastic rather than osteolytic type of bone metastases
5. Frequent hormone (androgen) dependency: basis for palliative treatment with orchiectomy and/or estrogens.
6. Five-year survival about 35%.

Bone and Joint Diseases**Objectives:**

- *Briefly describe the characteristics and the pathology of the conceptually or clinically important bone and joint diseases.*

READING: Robbins Basic Pathology, Kumar, Abbas, Mitchell, 9th Ed., 2013
pp. 765-790.

Bone: The two principle types of bone formation are membranous (e.g. calvarium) where bone is formed directly from connective tissue, and endochondral (e.g. long bones), where bone is formed from a cartilaginous precursor. Bones are classified into long bones (e.g. femur), short bones (e.g. bones of hands) and flat bones (e.g. pelvic bones). Longitudinal growth of bones formed by endochondral formation occurs at the epiphyseal plate where longitudinal cartilage columns of the epiphyseal plate are transformed into bony columns. With cessation of growth in the teens, the plate closes and becomes ossified. Important metabolic afflictions, neoplasms and other diseases occur in the area of the growth plate.

Long bones are divided into epiphysis (end), metaphysis (on the central side of the growth plate) and diaphysis (the central part of the shaft). Bone has a dense cortex and on the inside trabeculae, which extend along the lines of stress add support. The trabecular structures are relatively light but add strength along the lines of stress.

Bone has an organic matrix containing collagen, acid mucopolysaccharides and other proteins. The matrix under normal conditions is almost entirely calcified. The bone is a living tissue responsive to various conditions e.g. changes in stress, to injury etc. and can be remodeled to adapt to changes. The bone cells include osteoblasts (bone forming cells), osteocytes and osteoclasts (bone resorption cells – specialized multinucleated macrophages).

A large number of diseases affect bones and joints. These can be classified into the following broad categories:

Bone:

Developmental lesions
Post-traumatic lesions
Metabolic diseases
Infectious diseases
Cysts
Benign and malignant tumors
Others

Joints:

Degenerative arthritis
Rheumatoid arthritis
Metabolic diseases, e.g., gout, etc.
Infectious diseases
Proliferative/metabolic diseases
Neoplasms
Others

Since each of these categories of bone and joint diseases consist usually of several entities about which, frequently a great deal of information is available, they cannot all be discussed. Therefore, several clinically important entities or syndromes will be selected and briefly described.

METABOLIC BONE DISEASES

Osteopenia is a term describing the loss of bone mass (radiological density) and can be due to various disorders such as osteoporosis or osteomalacia (soft bones with deficiency in only calcification like in rickets).

Osteoporosis is a disease of the osteoid matrix with decrease in bony mass (density) showing thinning of osseous trabeculae and cortex but usually no defect in calcification. There is neither osteoblastic rimming (suggesting appreciable active bony deposition) nor resorption lacunae (indicating active bone removal by osteoclasts). Bony matrix, under normal circumstances, is slowly deposited and resorbed, these processes being in equilibrium. However, in osteoporosis, there is a very slight imbalance, with slightly increased resorption of matrix, although in other cases there may be also a decrease in matrix formation. As indicated above, there is usually no lack of calcification, although superimposed calcium deficiency will aggravate the condition. It often occurs in post-menopausal women, probably in part related to estrogen deficiency, but also in elderly males and under still other circumstances, e.g., prolonged administration of glucocorticoids (steroids). Fracture(s) may occur on relatively slight provocation. The hip is a frequent site of such fracture, but compression fractures of vertebral bodies occur not infrequently.

Osteomalacia is due to incomplete calcification of the normally formed osteoid matrix and leads to weakness and deformity of bone because of a variety of causes such as vitamin D deficiency (decreased GI absorption of Ca^{++}) lack of sun light (decrease conversion of precursor to active vitamin D) renal disease (renal loss of Ca^{++}), and others. When occurring in children, it is termed "rickets." There are only partially calcified osseous trabeculae and the periphery of the lamellae are non-calcified. (In contrast, normal bone is almost entirely calcified.) Serum calcium and/or phosphorous levels are decreased while serum alkaline phosphatase activity is increased.

INFECTIOUS DISEASES

Acute osteomyelitis is due to infection of bone by organisms such as staphylococcus or streptococcus, pseudomonas, klebsiella and other organisms. Infection may be due to either direct introduction (e.g., commuted fracture) or by hematogenous route. There is an acute inflammatory reaction with necrosis of bone. There may be local pain, and the patient may be febrile and have leukocytosis. The disease can become chronic with separation of the necrotic bone (sequestrum), which may be discharged, usually in fragments, via a fistulous tract to the skin. In chronic osteomyelitis plasma cells and lymphocytes predominate. Osteomyelitis may also be caused by mycobacteria and fungi and then may assume a granulomatous character.

BONE TUMORS

There are many types of primary bone tumors, benign or malignant, often occurring preferentially at particular sites and at different ages. Different tumors require entirely different forms of treatment and have different outcomes. A relatively common primary benign neoplasm is enchondroma with its malignant counterpart chondrosarcoma. One of the more frequent primary malignant tumors osteosarcoma will also be described. In addition, metastatic tumors

extending to bone are frequent from sites such as breast, prostate and other sites, particularly late in the course of the disease.

Enchondromas are benign cartilaginous tumors of bone, occurring over a wide age range with a peak incidence in midlife. Most commonly they appear as solitary lytic lesions, arising probably from ectopic cartilaginous rests in the metaphysis. They occur in many long bones, e.g., femur and humerus, but they also occur in small bones such as those of the hand. They are well circumscribed, with a sharply defined margin on radiologic examination and often have small calcifications. Microscopically, they are non-infiltrative, are composed of well-differentiated cartilage cells, and lack mitotic activity. Rarely, such enchondromas may turn gradually into secondary chondrosarcomas. Primary chondrosarcomas arise *de novo* without underlying known benign cartilaginous tumor. The better differentiated chondrosarcomas represent local problems often successfully treated by resection, but the higher grade tumors may metastasize to various sites including the lung. Chondrosarcoma infiltrate adjacent bone, show mitotic activity, may show nuclear enlargement, and double nucleated cells are frequent.

Osteosarcomas are most often highly malignant tumors of osteoblasts that have a peak incidence in teenagers and most often involve the distal metaphysis of the femur, but other long bones may also be involved. Microscopically, one sees infiltrating malignant spindle cells with mitotic activity producing osteoid. In the past, these tumors, even with radical surgery, had a poor prognosis (10% survival), but with the addition of chemotherapy to surgical removal of the neoplasm, the survival rate has now improved (60-70% survival). These tumors have a tendency to spread via hematogenous route to the lungs. Less frequently, osteosarcomas occur in jaw bones with a peak incidence in the third decade of life. These are thought by some, but not all authors to have a better prognosis than osteosarcomas in long bones. If death occurs in osteosarcoma of the jaw, it is often due to uncontrolled local disease, rather than distant metastasis.

DISEASES OF JOINTS

Degenerative joint disease (Osteoarthritis) is one of the most common diseases of old age, but it can also occur earlier in life, e.g. secondary to trauma or congenital hip disease. Involvement of the hip and knee joints may cause severe disability. There is degeneration of the articular cartilage without appreciable inflammation, and there is deformity of the supportive bony elements may occur. Fissures may extend through the cartilage and are often associated with cysts in the underlying bone. Many patients now receive considerable symptomatic relief by removal of the diseased joint surface and replacement by a prosthesis.

Rheumatoid arthritis (autoimmune disease) is less common than osteoarthritis with preponderance in females. It is a debilitating and destructive disease of the larger and smaller joints with development of an inflamed fibrous membrane (pannus) covering and destroying the articular surface. Various chronic inflammatory cells, including plasma cells, infiltrate the synovial membrane; lysosomal enzymes and cytokines participate in the destructive process. Areas of necrosis, surrounded by chronic inflammation develop in the connective tissues in many sites; such lesions, often grossly nodular, are called rheumatoid nodules. The cause is thought to be an autoimmune reaction. In most cases an antigammaglobulin (Rheumatoid factor) can be demonstrated in the serum.

Gout is less frequent than osteoarthritis or rheumatoid arthritis. It is caused by hyperuricemia, which may be due to an inborn metabolic defect, due to administration of drugs that raise the uric acid level in the serum or other causes. Monosodium urate crystals are deposited in joints, viscera, kidney, and other tissues and uric acid stones may be formed in the urinary tract. The deposition in joints shows a preference for the lower extremities and clinically, many patients present with sudden, very painful involvement of the phalangeal-metatarsal joint of the great toe. Microscopically, the tissue has an accumulation of needle-like crystals, usually occurring in masses which initially invoke an acute inflammatory reaction, soon to be replaced by histiocytes (macrophages), multinucleated giant cells and proliferating fibrous tissue. Nodules of uric acid crystals in connective tissue are termed "tophy" and not only involve the soft tissue of the joint, but may also erode the articular cartilage and the bone.

Infectious arthritis. Joints may become infected by a variety of organisms either by direct penetration, extension from infected adjacent bone (osteomyelitis) or by the hematogenous route. Inflammation can be acute, chronic, or granulomatous, in part dependent on the organism and timing of the event.

Diseases of the Skin**Objectives:**

- *Describe the important structures of the skin and nomenclature of skin neoplasms.*
- *Describe benign and malignant epithelial neoplasms of the skin and discuss clinicopathological correlation.*
- *Explain the importance of solar skin damage due to irradiation within the ultraviolet spectrum.*
- *Define and describe benign melanocytic neoplasms (melanocytic nevi).*
- *Describe the pathobiology of melanoma and discuss clinicopathological factors important in prognosis and therapy.*
- *Define and give an example for each prototypical pattern of inflammatory skin disease.*

READING: Robbins Basic Pathology, Kumar, Abbas, Mitchell, 9th Ed., 2013, pp.851-870-857.

Key microanatomical structures

1. *Epidermis*, largely composed of keratinocytes, with intercalated melanocytes and Langerhans cells
2. *Dermis*, a connective tissue matrix containing vessels and nerves
3. *Adnexal structures*, consisting of eccrine (sweat) glands, apocrine glands, sebaceous glands, and hair follicles

Diseased skin

Cutaneous disorders can be divided into *malformations*, *inflammatory diseases*, *infections*, *hyperplasias*, and benign or malignant *neoplasms*. Most conditions fit into one category, but occasional ones span two or more categories. Consider a verruca vulgaris (wart). Verrucae represent an infection by human papillomavirus, yet verrucae are also hyperplasias, in the sense that the virus induces epidermal proliferation which can abate after the virus disappears. In a clinical sense, verrucae can also be considered as benign neoplasms, as they present as noninvasive growths that can persist indefinitely.

The language of clinical dermatology has evolved so that diseased skin can be described as precisely as possible. Important terms to remember include:

<i>Macule:</i>	<1 cm flat area of discoloration, without change in texture
<i>Patch:</i>	>1 cm flat area of discoloration, without change in texture
<i>Papule:</i>	<1 cm, elevated, palpable skin lesion
<i>Plaque:</i>	>1 cm, elevated, palpable skin lesion
<i>Nodule:</i>	a rounded skin lesion of roughly equal diameter and depth
<i>Vesicle:</i>	an intracutaneous fluid-filled space, <1 cm in diameter
<i>Bulla:</i>	an intracutaneous fluid-filled space, >1 cm in diameter
<i>Pustule:</i>	an intracutaneous pus-filled space, often within a hair follicle

Approach to Diagnosis of Skin Diseases

Clinical history

Physical examination

Diagnostic tests: skin scrapings (KOH preparation), Woods lamp (UV light) examination, skin biopsy (by curettage, shave technique, punch technique, or complete excision)

SKIN NEOPLASMS

Skin neoplasms, like neoplasms in other organ systems, are classified with reference to the cell type or structure that the proliferation resembles microscopically. Pathologists refer to this resemblance as *differentiation toward* the native cell or structure. It is common for students and physicians to think of the classification of neoplasms in terms of the *cell of origin* of a process, but keep in mind that many if not most neoplasms arise from primitive cells or proliferating cells that are often less than perfectly committed to a particular type of differentiation. Differentiation toward a structure can also be thought of as the cell's *lineage*. Thus, squamous cell and basal cell carcinomas of the skin, the two most common types of skin cancer, are malignancies with epithelial differentiation that arise from proliferating keratinocytes, presumably as a consequence of genetic mistakes made in mitosis under the influence of environmental and host genetic influences. Basal cell carcinoma (BCC) exhibits some of the microscopic features of the epidermal basal layer and squamous cell carcinoma (SCC) resembles spinous (squamous) layer keratinocytes, but to think of BCC and SCC as malignancies that strictly arose from basal cells and squamous cells is a misconception.

Neoplasms are named using essentially the same system employed in other organs. Malignancies with epithelial differentiation (of epithelial lineage) are collectively called *carcinomas*. Malignancies with mesenchymal differentiation (of mesenchymal lineage) are collectively called *sarcomas*. The specific names of benign and malignant neoplasms are generally determined by the cell or cells toward which microscopic differentiation is observed. For example, a benign proliferation resembling adipocytes (lipocytes) is known as a lipoma, a benign proliferation resembling endothelial cells (angiocytes) is known as an angioma or hemangioma, and a malignant proliferation resembling keratinocytes of the spinous (squamous) layer of the epidermis is known as squamous cell carcinoma. Some exceptions to these rules include the following:

1. benign neoplasms with epithelial differentiation, which are often referred to as *keratoses*
2. adnexal neoplasms and cysts, which are sometimes classified with regard to the structure (rather than the cell) that the lesion's differentiation resembles. For example, a benign adnexal neoplasm with sweat gland differentiation is known as a hidradenoma (literally, "water gland neoplasm").
3. benign neoplasms of melanocytes, which are known as melanocytic nevi. Melanocytic nevi must of course be contrasted with the malignant neoplasm of melanocytic lineage, known as melanoma. Nevi and melanoma are discussed in the second section of this handout.

Benign and pre-invasive neoplasms with epidermal differentiation (keratoses)

Verruca vulgaris (common wart) and condyloma (genital wart). Warts are technically a *hyperplasia* in a pathological sense, as they are a proliferation induced by a stimulus (namely viral DNA) that can be withdrawn, thus leading to abatement of the proliferation. Nevertheless, the clinical presentation is usually as a slowly growing, persistent, non-invasive growth, similar to a benign neoplasm, and thus warts are considered as neoplasms for the purposes of this discussion. The causative stimulus of the proliferation is human papillomavirus (HPV) DNA. Clinically, warts are rough, scaly papules, usually only a few mm in diameter, although larger lesions can develop. Warts develop at any age, and warts occur with increased frequency in immunocompromised patients, as would be expected in a viral process. Microscopically, warts are characterized by marked thickening of the epidermis, often in a papillated configuration. Clumping of keratin filaments in the cytoplasm and a wrinkled nuclear outline are characteristic viropathic alterations.

The causative virus, HPV, has a variable genetic structure with more than 60 different HPV types identified to date. The manifestations of a given HPV type depend on both host and viral factors, but in general, specific HPV types tend to be associated with specific types of lesions. For example, HPV types 2 and 4 are often found in common warts, and types 6, 11, 16, and 18 are common in condylomas. Some HPV types, including HPV 16 and 18, are said to be "oncogenic", and are associated with a risk of transformation to squamous cell carcinoma (SCC). HPV 16 DNA has been identified in both cervical and digital (finger) SCC. Warts are typically treated by destructive modalities, including application of acid, cryotherapy, or laser ablation. Microscopic examination of large and persistent warts is warranted, in light of the small risk of transformation into SCC.

Seborrheic keratosis (SK). Also known as a seborrheic wart, an SK is a greasy, brown, scaly growth that is common in older patients. Although an SK can clinically resemble a common wart, the lesions are not induced by papillomavirus. SKs have no biological significance, although they are extremely common, as they are completely benign. It is important to have an awareness of the neoplasm, however, as it is common, poses a cosmetic concern to many patients, and serves as a clinical simulator of malignant melanoma.

Solar keratosis (historically actinic keratosis, or AK). Solar keratosis (AK) is an extremely common, scaly papular skin lesion that develops on sun-damaged skin, typically in an older adult. There are no reliable figures for the incidence of AKs, but a conservative estimate of several million new neoplasms annually is reasonably accurate. As many as 50% of adults with light skin will develop AKs. Cumulative ultraviolet (UV) radiation exposure is established as the primary factor in lesional development. AKs represent squamous cell carcinoma at an embryonic stage, when the atypical keratinocytes that comprise a lesion are entirely intraepithelial and probably before all of the necessary molecular events to permit invasive dermal growth have taken place. Pathologically, an AK consists of foci of abnormal keratinocytes, alternating with normal

keratinocytes, within the epidermis. It is important to have AKs treated, as they are unstable lesions that can progress to form invasive carcinoma, although the risk of malignant transformation is low (<10%).

Malignant neoplasms with epithelial differentiation (carcinomas).

Basal cell carcinoma (BCC). BCC is not only the most common skin cancer but is also the most common type of human malignancy, with approximately 500,000 newly diagnosed tumors annually. The clinical morphology of BCC can be extremely variable, ranging from thin reddish papules to densely indurated and ulcerated plaques, but the prototypical BCC is a pearly, translucent, telangiectatic papule. The risk of developing BCC is roughly proportional to one's cumulative UV exposure and inversely proportional to one's degree of skin pigmentation. Histologically, BCC is characterized by "basaloid" cells which display peripheral palisading and adjacent mucinous stroma. The morbidity of BCC is largely due to relentless local growth, with invasion of contiguous structures. Metastasis of BCC is extremely rare.

Squamous cell carcinoma (SCC). SCC is the second most common type of skin cancer, with more than 100,000 newly diagnosed tumors annually. As is the case for BCC, the development of cutaneous SCC is primarily related to cumulative UV radiation exposure, but squamous cell carcinoma can also develop in patients with other risk factors, including persistent chronic inflammation (such as at the site of a nonhealing wound or at a sinus tract due to underlying osteomyelitis) or radiation injury. Microscopically, SCC consists of clusters of abnormal (malignant) keratinocytes that invade the dermis. The malignant keratinocytes have irregular, hyperchromatic nuclei, and the cytoplasm of the cells usually show evidence of keratinization. SCC is a more aggressive malignancy than BCC, although the risk of metastasis is still very low. SCC of the lip has a higher risk of metastasis than SCC of other skin sites.

A note about solar damage. Not only do the tanning (mostly UVA) and burning (mostly UVB) rays of the sun cause AKs, BCCs, SCCs and melanomas that become manifest when humans are old, the rays of the sun cause wrinkles that are manifest when humans are relatively young. Most adults receive the majority of their lifetime dosage of UV irradiation during childhood and adolescence. Even though you and your patients may have already received a big dose of UV light, it is never too late to begin a healthy relationship with the sun. Tanning salons boast they are safe since they only use UVA spectrum lamps, but these not only cause skin aging, they are linked to increased risk of all skin cancers (albeit less than UVB exposure). Avoid sunburn. Wear sunscreen when in bright midday sun and use a sunscreen or block that is good for UVA as well as UVB. The SPF indicator only refers to UVB protection and there is yet no number protection factor used for UVA protection. Wear a hat. Wear sunglasses. It's fine to be outdoors, but it's a mistake to bake! Unless, of course, you want to be a raisin. If you can then avoid being in the direct sunlight, if not then wear sun blocking clothing and a hat, and finally if in the direct sunlight without clothing protection, use sunscreen or sunblock that is applied and reapplied according to the manufacturers instructions. Needless exposure of skin to direct sunlight, even with sunprotection creams is not recommended.

Selected benign neoplasms with mesenchymal differentiation.

Hemangioma. Benign vascular neoplasms come in a variety of flavors, the most common of which are cherry and pyogenic. Cherry angiomas are small, reddish-purple papules that can develop at any age. The double misnomer "pyogenic granuloma" (PG) refers to a lesion now known pathologically as lobular capillary hemangioma. Clinicians still prefer the term PG, however, despite the fact that the lesions are neither purulent or granulomatous. PG presents as an ulcerated, reddish papule, frequently on the hand or foot, and often there is a history of recent bleeding. PG is a vascular proliferation that occasionally develops at the site of an injury, and is thought to represent either an abnormal wound healing reaction or a neoplasm induced by an abnormal wound healing reaction. Microscopically, PG consists of aggregations of thin-walled blood vessels. The aggregations of vessels are known as lobules, a fact which serves as the basis for the correct pathological name of lobular capillary hemangioma.

Dermatofibroma is the most common neoplasm of fibrocytic lineage, and typically presents as a firm papule or nodule on the extremity. Since dermatofibromas sometimes develop at sites of trauma or after insect bites, some authorities have considered dermatofibroma as a reactive, inflammatory condition, but the lesions generally persist and thus display the biological behavior of a benign neoplasm. Dermatofibromas are often hyperpigmented. Microscopically, the neoplasm consists of a nodular proliferation of spindled and dendritic cells, usually positioned between markedly thickened collagen bundles. The neoplastic cells are believed to actively secrete either cytokines or growth factors that induce hyperplasia and hyperpigmentation of the overlying epidermis. The induced epidermal changes are the explanation for the hyperpigmented clinical appearance.

MELANOCYTIC NEVI (INFORMALLY KNOWN AS MOLES) AND MELANOMA

MELANOMA

Melanoma is the most important cutaneous malignant neoplasm, as it is the most lethal. The recognized incidence of melanoma is presently increasing, but it is not entirely clear that the increase in incidence figures is entirely due to an expanded presence of the disease, as there have been significant changes in the microscopic criteria used by pathologists over the past 2 decades. Some of these criteria have enabled earlier recognition of melanoma, and thus some of the increase in diagnosis may merely be attributable to earlier recognition of the disease. It is important to have a keen awareness of melanoma because virtually all examples of melanoma can be diagnosed by a clinician at an early stage, when surgical removal can effect a cure. Typically, lesions suspicious for malignant melanoma can be recognized by their large size, asymmetry, irregular borders, and irregular coloration. Changes in long-standing pigmented lesions or the development of new pigmented lesions late in life are clinical events that should be viewed with great suspicion, and a biopsy for precise diagnosis is probably warranted.

1. *Incidence.* The diagnosis of melanoma is increasing rapidly. Mortality from melanoma remains only slightly increased, however, suggesting that earlier diagnosis yields the bulk of the newly diagnosed neoplasms.
2. *Epidemiology.* Individuals with light skin have an increased risk of developing all skin cancers, including melanoma. Large numbers of melanocytic nevi, and/or the presence of dysplastic nevi, also seem to be risk factors for the development of melanoma.

Prognostication of melanoma

Clinical Stage I disease (confined to the skin) has an overall 5-year survival rate of over 80%, while clinical Stage II disease (with regional lymph node metastases) has a 5-year survival rate less than 50%. Clinical Stage III (systemic) disease is usually fatal within a few months or years. Conventional chemotherapy and radiation therapy are of only limited benefit. There is some promise that biologic response modifiers such as interleukin-2, G-CSF and melanoma vaccines may modify the poor prognosis of metastatic melanoma.

Effect of invasion and tumor thickness.

If the melanoma has not infiltrated or invaded the underlying dermis then it is called melanoma in situ, which is a completely curable disease if it is adequately excised to prevent recurrence.

*The most important prognostic indicator for a primary invasive melanoma is the thickness of the primary neoplasm (how far it has invaded into the underlying dermis), a figure which is usually recorded in portions of millimeters. This measurement is referred to as the *microstage measurement* (or *thickness* or *Breslow's level*). Although it seems somewhat curious that thickness would serve as a reliable prognostic indicator, keep in mind that the measurement represents a crude estimate of the volume of the primary neoplasm and its access to lymphatic vessels of the dermis. Thus, the larger the primary neoplasm, the worse the prognosis, which is a common sense relationship.*

Effect of gender.

Women tend to have a better prognosis than men, at all body sites and for all thicknesses of melanoma.

Effect of site.

In general, the best prognosis occurs in extremity lesions, followed by the trunk. In general, head and neck primary neoplasms have the least favorable prognosis.

Surgical therapy and re-excision of melanoma

A conservative but total excision of a suspicious pigmented lesion, with histologic evaluation, should be the first step in the evaluation of any suspected melanoma. Consultation with an experienced pathologist or a dermatopathologist is mandatory, as there are many pitfalls in the correct microscopic diagnosis of melanoma. After a confirmed diagnosis of melanoma has been made, re-excision of the site of the primary neoplasm is usually recommended, to ensure complete local removal of the malignancy. Although wide surgical margins of several cm were obtained in the relatively recent past, present guidelines recommend reexcision with a

surrounding border of 5 mm of clinically normal skin for melanoma in situ (melanoma confined to the epidermis), and reexcision with a surrounding border of 1 cm of clinically normal skin for most invasive melanomas. In the past, inappropriately large, mutilating re-excisions and amputations have been performed for primary malignant melanomas. These procedures have been abandoned in the face of careful controlled studies, which demonstrated that extensive surgery does not improve a patient's prognosis

MELANOCYTIC NEVI

The term nevus is used to describe certain congenital malformations. Epidermal, vascular, and connective tissue nevi all can occur as "birthmarks". The term melanocytic nevus was originally used in reference to congenital melanocytic nevi, which are birthmarks composed of melanocytes. Although some melanocytic nevi are congenital, most melanocytic nevi are acquired benign neoplasms. Both congenital and acquired melanocytes are composed of clusters (nests) of bland, uniform cells with rounded or oval nuclei. Other variants of nevi include halo nevi (nevi with an inflammatory reaction that yields a perinevic zone of decreased pigmentation); blue nevi (nevi composed of heavily pigmented, dendritic or spindled melanocytes); Spitz's nevi (benign nevi composed of enlarged melanocytes, which sometimes can histologically simulate melanoma); and dysplastic (Clark's) nevi. Mixtures of melanocytic cell types (e.g., ordinary melanocytic nevus cells and blue nevus cells) can occur, and are referred to as combined melanocytic nevi. These unusual patterns of melanocytic nevi will not be discussed further in this setting.

1. *Acquired melanocytic nevi* evolve from a "junctional" pattern (consisting of flat clinical lesions, with melanocytes in nests at the dermal/epidermal junction), progress to a "compound" pattern (consisting of slightly elevated, papular lesions, with clusters of melanocytes both at the junction and in the superficial dermis), and continue to progress to an "intradermal" pattern (elevated or polypoid clinical lesions, with clusters of melanocytes only in the dermis). Acquired nevi increase in number through childhood, adolescence, and early adulthood, with a peak prevalence in the 4th decade of life. Melanocytic nevi often involute throughout later adulthood, so that in patients above the age of 70, nevi are relatively uncommon. Virtually all acquired nevi are small (less than 6 mm), symmetrical, and evenly colored. Microscopically, acquired nevi consist of clusters of melanocytes with bland nuclear features.
2. *Congenital melanocytic nevi* are present at birth or become evident in early childhood. Congenital nevi tend to be larger than acquired ones, typically being greater than 1.5 cm in diameter, and giant congenital nevi that involve the skin of an entire extremity or body region can be seen. It is difficult to get accurate data regarding the risk of melanoma developing in a congenital nevus, but the risk appears to be very low. Although the risk is low, there appears to be a significant risk of melanoma developing in giant congenital nevi (those greater than 20 cm in diameter), and thus prophylactic removal is usually pursued. The risk of melanoma may merely be proportional to the tremendous number of melanocytes in these large lesions. Congenital nevi show the same histologic pattern as acquired nevi, although the lesions are typically larger and extend more deeply into the dermis, where melanocytes are often found surrounding hair follicles

3. *Clark's or Dysplastic nevi* were first characterized in families that had an inherited genetic defect leading to increased incidence of melanomas (inherited melanoma families), but later were found to be a type of melanocytic nevus that occurs quite commonly outside of this setting, in normal individuals. These type of nevi have a distinctive histologic or microscopic appearance and an "atypical" clinical appearance that often causes them to be biopsied.

Please note:

Not all pigmented lesions are melanocytic neoplasms. Keratoses and other skin cancers (such as BCC) may be incidentally pigmented, due to a small population of intercalated, non-neoplastic melanocytes. Metabolized blood pigment, such as in traumatic blood blisters, can also contribute to a black or hyperpigmented clinical appearance. Thus, a variety of neoplasms, both melanocytic and non-melanocytic, as well as benign or malignant, can produce the clinical morphology of a changing pigmented lesion. Diagnosis usually depends on histological examination, and thus biopsies of suspicious pigmented lesions are warranted.

Because melanoma is a potentially lethal disease, but occurs on the skin where it can be detected early, both physician and patient education regarding melanocytic nevi and melanoma is important. ALL PATIENTS WITH CLINICALLY SUSPICIOUS PIGMENTED LESIONS SHOULD BE REFERRED TO A DERMATOLOGIST OR ANOTHER TRAINED INDIVIDUAL. YOU MAY SAVE A LIFE AND/OR AVOID A LAWSUIT.

INFLAMMATORY SKIN DISEASES (DERMATITIS OR SKIN RASHES)

It is impossible to understand the pathology of skin rashes without a rudimentary knowledge clinical dermatology. It is also impossible for me to teach you all the dermatology you need to know to appreciate the dermatopathology of rashes in 1 hour. Therefore, we will cover the clinical and microscopic features of selected prototypical dermatoses.

The curse of history. There are hundreds of rashes. Dermatologists have been looking at skin for decades, and for most of that time rashes were named and grouped based on clinical appearance. This yielded a burgeoning nomenclature laden with peculiar Greek and Latin names unrelated to pathogenesis. As an example, consider some of the "erythemas:" erythema multiforme, a dermatitis triggered by herpes virus in which the epidermis is attacked immunologically; erythema annulare centrifugum, a dermatitis with lesions resembling hives, which is often triggered by superficial fungal infections; and erythema nodosum, a panniculitis (inflammation of the subcutaneous fat) that is often triggered by oral contraceptives and recent strep infections. The only thing these dermatoses have in common is redness. As with all bad medical nomenclature, the nomenclature of dermatology is firmly entrenched and will remain inviolate.

Why are there so many rashes and skin problems?

You can see your skin, but you can't see your liver. Therefore, every little permutation of skin redness and scaliness is analyzed carefully, but inflammation in the liver and most other organ systems remains occult unless organ dysfunction or failure occurs.

Your skin is "wired for sound." The skin has an incredibly delicate and complex neural network, with the capability to produce symptoms such as itching and burning. These symptoms motivate the patient and doctor to classify, diagnose, and treat even minor skin diseases. In other (less innervated) organ systems, minor disorders may remain asymptomatic and occult.

Your skin is in constant contact with the environment. The skin and bowel are exposed to a steady stream of insults from our often noxious surroundings. Other organ systems have a more filtered and thus safer view of the world.

Eight prototypical patterns of inflammatory skin disease

1. *Spongiotic dermatitis*, also known as eczema. Spongiosis refers to fluid between keratinocytes, and the eczematous skin rashes all show this pathologic feature, which is manifest microscopically as widened intercellular spaces between keratinocytes. The fluid leaking between keratinocytes corresponds to a weepy, oozing clinical appearance. The prototypical form of spongiotic dermatitis is poison oak dermatitis, a variant of allergic contact dermatitis (ACD) triggered by a plant allergen. ACD is a type IV hypersensitivity reaction to an exogenous allergen that contacts the skin. In the first phase of the reaction, the allergen (hapten) is bound and presented by Langerhans cells (antigen presenting cells) in the presence of HLA. In the second phase of the reaction, T-helper cells bind the antigenic complex, thus triggering a cytokine cascade. ACD can be triggered by hundreds of different molecules in addition to the agent found in poison oak leaves, including a variety of topical medications. The diagnosis is usually made on clinical grounds, based on a good history and typical "geometric" clinical distribution. The diagnosis can be confirmed through "patch testing", which consists of applying the allergen to the skin in a controlled fashion and then observing the site for a reaction. There are a tremendous number of other rashes that show a spongiotic histologic pattern, and this group of diseases is referred to by the broad and nonspecific clinical term "eczema". The different variants of eczema are usually separable based on clinical appearance and history, but the microscopic findings are always similar. Why is spongiosis (eczema) important? Keep in mind that eczema is the single most common reason people seek dermatologic medical care.
2. *Psoriasiform dermatitis*: The term "psoriasiform" refers to a very regular thickening of the epidermis, which can be induced by certain cutaneous inflammatory reactions. The prototypical dermatitis with epidermal thickening is psoriasis. The "heartbreak" of psoriasis is that up to 2% of Americans have this chronic, scaly, treatment-resistant rash. The tendency to get psoriasis is inherited, but the genetic expression of the disorder is quite variable, and thus patients with psoriasis may have a negative family history. In addition, some patients will never get more than scaly elbows, while other individuals

may develop life-threatening, diffuse involvement, known as erythroderma. Psoriasis primarily affects the skin, but the disorder can also show systemic manifestations, including an oligoarticular, deforming arthritis. In psoriasis, the epidermis is hyperplastic, with proliferation driven by a chronic inflammatory reaction that is not yet understood. Bacterial infections can be a triggering or exacerbating factor. In contrast to eczema, psoriasis has a characteristic histologic pattern, and we can render an unequivocal diagnosis under the microscope. The key features are thickening of the epidermis, vascular dilatation of superficial vessels, and overlying crust that contains neutrophils. Many patients will tell you that they have “psoriasis” and “eczema”, but keep an open mind. Because these dermatoses are so common, these terms have nearly become synonyms for “rash” in lay circles.

3. *Vesiculobullous dermatitis (blistering disorders)*. Blistering rashes are characterized by a pathological separation of adjacent tissues in the skin. The most common level of separation is at the junction of the epidermis to the underlying dermis, and the prototypical disorder is bullous pemphigoid (BP). BP is a blistering disease that primarily affects older patients, usually has an indolent course, and the prognosis is favorable unless the disease is extensive. Under the microscope, there is a subepidermal cleft, and there are usually numerous eosinophils in the blister cavity and in the adjacent dermis. BP is an immune-mediated (“autoimmune”) disease. Antibodies that react with a unique protein (which is now known as the “BP antigen”) in the basement membrane zone can be identified in these patients. These antibodies bind the target antigen and trigger the complement cascade, and the ensuing inflammatory reaction apparently damages the basement membrane leading to blistering.
4. *Interface dermatitis* refers to a group of rashes in which an inflammatory reaction is focused on the basal layer of the epidermis. The prototypes are erythema multiforme (EM) and lichen planus (LP). Patients with EM develop flat red lesions that often develop dusky centers, creating a target-like appearance. The lesions are often acral, but involvement of mucous membranes is common and the process may generalize. When generalization occurs, the syndrome is known as toxic epidermal necrolysis (TEN) or Stevens-Johnson Syndrome. In generalized cases, the disease may be life threatening due to metabolic imbalance and patients are generally admitted to a burn unit for care. Under the microscope, we see vacuolization of the basal layer of the epidermis with necrosis of single keratinocytes. The individual keratinocytes are “bumped off” by a cell-mediated immune response. This reaction is commonly triggered by herpes virus, and episodes of EM may occur soon after a cold sore. EM may also be triggered by drugs, including antibiotics. EM is an acute and episodic reaction, with exacerbations that last only briefly (at most 2-3 weeks) and then resolve; the eruption can recur if the offending stimulus is encountered again. In contrast, LP is a chronic cell-mediated reaction directed against the basilar keratinocytes. Patients with LP develop pruritic, polygonal, purplish papules that can occur anywhere but are often acral in distribution. The papules of LP can last many weeks to months. Similar to EM, LP is the result of a cell-mediated immune reaction directed against the keratinocyte, but the triggering reactions are not understood. Some lichen planus-like reactions are induced by medications; most are idiopathic. Both EM and LP can be treated with topical and systemic corticosteroids.

5. *Vasculitis* refers to inflammation of blood vessels. There are several different clinicopathologic varieties: the inflammation may be predominantly neutrophilic or predominantly lymphocytic, and the affected blood vessels may be small or large. The prototype is so-called allergic vasculitis or small vessel leukocytoclastic vasculitis (LCV). Clinically, one sees hemorrhagic papules in LCV, and under the microscope one sees necrosis of dermal capillary walls by a neutrophilic infiltrate. Fibrin, red cells, and nuclear debris surround the damaged vessels. LCV is an example of a type III hypersensitivity reaction, in which antigen and complementary antibody are present in proper proportions to permit immune complex formation. The immune complexes are deposited in capillary walls, and the complement cascade is triggered with resultant vascular inflammation and damage. Depending on the type of vasculitis and the extent of the inflammatory reaction, viscera may also be involved. The same type of inflammatory mechanism is operational in neutrophilic vasculitides that affect larger vessels, such as polyarteritis nodosa, but the clinical manifestations and lesional morphology differs substantially, with nodular rather than papular skin lesions and with a greater tendency to systemic involvement.
6. *Granulomatous dermatitis* is a diagnostic group characterized by inflammatory infiltrates rich in macrophages. Granulomatous rashes include both infectious and sterile conditions. Typically, firm nodular lesions are present on the patient. The prototype is sarcoidosis. The microscopic appearance of sarcoid is characterized by "naked tubercles", which consist of clusters of macrophages, some of which are multinucleate. In contrast to the mononuclear cell infiltrate seen in sarcoidosis, cutaneous infections often show a mixture of macrophages and neutrophils, a pattern referred to as "suppurative and granulomatous." When considering a diagnosis of sarcoidosis, it is important to remember it is a diagnosis of exclusion; therefore, polarized microscopic examination to rule out foreign body reaction and special stains and cultures to exclude infection are routinely part of the diagnostic workup.
7. *Folliculitis* is the medical term for "zit." There are infectious and inflammatory causes of inflamed hair follicles. The prototypes are suppurative (bacterial) folliculitis and acne vulgaris. Suppurative folliculitis is a follicular infection generally caused by staphylococci. Patients present with red papules and pustules, often itchy, on the trunk, thigh, face, and scalp. A short course of oral antibiotics is usually curative, although some scalp folliculitis is resistant to therapy. Microscopically, we see a follicle filled and surrounded by a mixture of inflammatory cells, and neutrophils are often abundant. In folliculitis the follicles are merely infected and inflamed; in contrast, there are 2 fundamental pathogenic processes in acne. The follicles keratinize abnormally and thus have a tendency to get "clogged" (a process known as comedo formation), and the clogged follicles are subsequently prone to becoming inflamed, which is the basis for the papules and pustules seen clinically. Both pathogenic mechanisms are treatable. The abnormal keratinization is usually treated using vitamin A derivatives known as retinoids. The topical retinoid of choice is Retin-A, which has also been utilized as an anti-wrinkle cream, and the systemic retinoid most commonly employed is Accutane®. It is important to realize that Accutane is teratogenic. The inflammatory component of acne

usually responds to antibiotics, either through alteration in follicular flora, through an anti-inflammatory mechanism, or through both. It is the inflammatory response to acne that triggers scarring, and thus treatment of acne is important. Acne is unrelated to diet and the consumption of chocolate, but can be exacerbated by hormonal influences, which is why acne is so common in the peripubertal period.

8. *Panniculitis* refers to inflammation of the subcutaneous fat, which consists of *lobules* of adipocytes separated and supported by fibrous *septa*, and thus inflammatory reactions are divided into lobular panniculitis and septal panniculitis based on the zone in which the inflammation predominates. Based on this distribution of inflammation and the composition of the infiltrate, the dermatopathologist can make decisions regarding the diagnosis. The prototypical panniculitis is a septal panniculitis, erythema nodosum (EN). Patients with EN develop red, indurated, warm, deep nodules and plaques, most commonly on the lower extremities. Recent infections and medications (especially oral contraceptives) are the most common triggers. Immune complexes and vasculitis have long been thought to play a pathogenic role, but the precise pathogenesis remains uncertain. Under the microscope, EN displays granulomatous inflammation in a septal distribution.

Please note:

There is a science to diagnosing rashes, and microscopic examination can aid precise classification. Once the rash is correctly classified, a range of behavior can be expected, and therapeutic options are more clearly defined. The dermatopathologist assesses the pattern of the inflammatory reaction, sees which skin structures are involved, and examines the composition of the infiltrate before arriving at a diagnosis.

There are several dermatoses, including psoriasis, eczema, and folliculitis, that are so common that nearly all medical professionals should have some basic knowledge regarding them.

CENTRAL & PERIPHERAL NERVOUS SYSTEM PATHOLOGY

Reading: Robbins Basic Pathology, Kumar, Abbas and Aster, 9th ed., pp. 812-849.

Objectives:

1. *Define and describe the different types of inflammatory conditions of the CNS involving the meninges and brain parenchyma*
2. *Define and describe the major types of cerebrovascular diseases involving the CNS.*
3. *Define and describe important developmental conditions of the CNS including neural tube defects, Arnold-Chiari malformations, syringomyelia and perinatal brain injury.*
4. *Compare and contrast common demyelinating diseases of the CNS (multiple sclerosis) and PNS (Guillain Barre syndrome)*
5. *Compare and contrast common neurodegenerative diseases including Parkinson disease, Huntington disease, Alzheimer disease, Lewy body dementia, Friedreich ataxia, and amyotrophic lateral sclerosis*
6. *Define and describe important CNS tumors*
7. *Describe the different types of mass lesion effects on the CNS*

A. Inflammation

- a) Portals of entry of infectious agents
 - (1) Hematogenous - lungs and pharynx (common)
 - (2) Direct implantation - trauma
 - (3) Local extension - mastoid, nasal sinuses, skull fracture
 - (4) Peripheral nervous system - rabies and leprosy (Herpes and CMV in AIDS patients)
 - (5) Indirect effects - e.g., bacterial exotoxins (tetanus and diphtheria toxins)
- b) Meningitis (**See Table 1**)
 - (1) Definition: an inflammatory process confined to the meninges and subarachnoid space
 - (a) Infectious - bacterial, viral, fungal, parasitic
 - (b) Chemically induced - procaine, methotrexate, bleeding
 - (2) Acute pyogenic meningitis
 - (a) Causative organisms
 - i) Group B hemolytic streptococcus or *Streptococcus agalactiae* (most common), *Escherichia coli* (second most common), Enterobacteriaceae (Proteus spp.), *Listeria monocytogenes*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*: neonates

- ii) *Haemophilus influenzae* type b is the most common cause of meningitis in young infants between 1 month and 2 years, but an infrequent cause of meningitis in neonates and persons older than 6 years
 - iii) *Neisseria meningitidis*: majority of cases under 5 years of age and a slightly increased prevalence in adolescence and young adults, but can occur throughout life
 - iv) *Streptococcus pneumoniae*: adolescents and adults with or without previous skull fracture due to trauma
- (3) Gross
 - (a) Brain and spinal cord swollen (edema) and congested
 - (b) Subarachnoid space is filled and distended with a fibrinopurulent exudate
- (4) Microscopic features
 - (a) Subarachnoid space - fibrinopurulent exudate
- (5) Complications
 - (a) Acute manifestations
 - i) Cerebral edema leading to herniation
 - ii) Abscess formation
 - iii) Arteritis leading to arterial vascular occlusion and stroke
 - iv) Venous thrombosis resulting in venous infarction and sinus thromboses
 - (b) Chronic manifestations:
 - i) Adhesive arachnoiditis leading to blockage of CSF resorption and obstructive hydrocephalus
 - ii) Cranial nerve palsies
 - iii) Seizures
 - iv) Mental retardation
- (6) Chronic meningitis (bacterial or fungal)
 - (a) Causative agents include *M. tuberculosis*, *T. pallidum*, *Brucella* sp., *Coccidioides*, *Candida*
 - (b) Prototype: Tuberculosis (base of the brain, primarily)
 - (c) Pathology
 - i) Gross - cloudy meninges which may localize to the base of the brain
 - ii) Microscopic features - mixed inflammatory infiltrate (lymphocytes, plasma cells, macrophages, fibroblasts; multinucleated giant cells and granulomas involving the subarachnoid space and leptomeninges)
 - (d) Complications
 - i) Cranial nerve neuropathy secondary to adherent

- arachnoiditis
- ii) Obstructive hydrocephalus secondary to adherent arachnoiditis
- iii) Vasculitis leading to thrombosis and infarction
- iv) Meningoencephalitis

c) Brain Abscess (**See Table 1**)

- (1) Major organisms: anaerobes, Streptococcus frequent; also fungi
- (2) Routes of infection
 - (a) Hematogenous (50%)
 - i) Infective endocarditis
 - ii) Congenital heart disease
 - iii) Pneumonia
 - (b) Spread from adjacent focus (40%)
 - i) Ear to temporal lobe
 - ii) Mastoid to cerebellum
 - iii) Sinuses to adjacent brain
 - (c) Penetrating wound (10%)
- (3) Pathology
 - (a) Gross
 - i) The abscess is walled off with a fibrous capsule, which is dependent upon duration of abscess (10 to 24 days to be walled off)
 - (b) Microscopic features
 - i) Fibrous capsule walls off necrotic brain and organisms
- (4) Complications
 - (a) Rupture into subarachnoid spaces leading to purulent meningitis
 - (b) Rupture into ventricular system resulting in ventriculitis
 - (c) Mass effect leading to increased intracranial pressure and herniation
 - (d) Viral encephalitis (**See Table 1**)

Table 1: Cerebrospinal Fluid in Different Conditions

Condition	Opening Pressure (mm H ₂ O)	WBC (cells/mm ³)	Differential	Glucose mg/dL	Protein (mg/dL)
Normal	70-180	< 5 lymphs	Mon	45-85	15-45
Bacterial infection	400	8500	90%Polys	15	120
Brain abscess	450	5	90%Lym	60 (Normal)	60 (Normal)
Viral infection	100	120	90%Lym	83 (Normal)	17
Tuberculosis	250	250	90%Lym	35	100
Aseptic Reaction	350	80	85%Lym	70 (Normal)	40 (Normal)
Cryptococcal infection (India ink)					500

- d) Acute Viral Encephalitis
- (1) Arthropod-Borne Encephalitis - eastern and western equine encephalitis
 - (2) Herpes Simplex Type I (labialis) - most common in children and young adults; neonates develop a panencephalitis compared to adults. In adults, an acute necrotizing encephalitis involves the limbic system, especially the temporal lobes (epilepsy and memory loss often results)
 - (3) Herpes Simplex Type II (genitalis) - responsible for most cases of herpetic viral meningitis and produces a generalized, severe encephalitis in neonates
 - (4) Herpes Zoster-Varicella
 - (a) Unilateral vasculopathy - delayed contralateral hemiparesis following shingles [Cranial Nerve V (V1)]
 - (b) AIDS - multifocal encephalitis; inclusion bodies in astrocytes, oligodendrocytes, and neurons
 - (5) Poliomyelitis - enterovirus which attacks only lower motor neurons
 - (6) Rabies - Negri bodies (cytoplasmic location) are pathognomonic for rabies and is almost always fatal
 - (7) Cytomegalovirus (CMV) - occurs in fetuses and immunocompromised individuals resulting in necrotizing periventricular infection
 - (8) Human Immunodeficiency Virus 1 (HIV-1, HTLV III, LAV)
 - (a) Aseptic meningitis - 10% of patients with HIV infection
 - (b) Subacute encephalitis - multinucleated giant cells, macrophages and lymphocytes, microglial cells, and reactive astrocytes (pathognomonic for HIV infection); correlated with AIDS dementia complex
 - (c) Vacuolar myelopathy
 - (d) Peripheral neuropathy

- e) Slow Viral Diseases
 - (1) Subacute sclerosing panencephalitis - due to measles virus in children and adolescents with previous measles attack; inclusions in oligodendrocytes, neurons and astrocytes. Death occurs 6 to 9 months after infection.
 - (2) Progressive multifocal leukoencephalopathy (PML)
 - (a) Produces demyelination due to two related papovaviruses (JC [accounts for most cases]) infecting oligodendrocytes
 - (b) Associated with advanced hematologic malignancies, and immunocompromised states including AIDS

- f) Prion Diseases (Old terms: Unconventional Agent [Spongiform] Encephalopathies)
 - (1) Creutzfeldt-Jakob Disease (Subacute Spongiform Encephalopathy, Transmissible Agent Dementia)
 - (a) Incidence = 1-2 per 1,000,000
 - (b) Peak incidence = 50 to 65 years of age
Mad Cow Disease - a new variant of Creutzfeldt-Jakob Disease that occurs earlier in adulthood
 - (c) Rapidly progressive dementia, myoclonus, and cerebellar/extrapyramidal signs
 - (d) Mode of transmission is not well understood; however, iatrogenic transmission has been demonstrated (e.g., corneal transplantation, deep implantation electrodes, and contaminated preparations of human growth hormone [not possible with recombinant form])
 - (e) Spongiform changes without inflammation - gray matter
 - (f) Disease will typically result in death within seven months due to acute aspiration pneumonia as a consequence of diminished gag/cough reflex
 - (2) Gerstmann-Sträussler-Scheinker Syndrome
 - (a) Very rare autosomal dominant disorder
 - (b) Clinical - dementia and extrapyramidal, pyramidal and/or cerebellar signs
 - (c) Amyloid plaques always are present
 - (3) Fatal Familial Insomnia
 - (a) Very rare autosomal disorder
 - (b) Nerve cell loss in different portions of the thalamus
 - (4) Kuru
 - (a) Disease confined to a tribe in New Guinea where the disease is transmitted by cannibalism
 - (b) Affects primarily the cerebellum and striatum. In 60% of cases, kuru plaques composed of amyloid are found in the cerebellum.
 - (c) Clinical presentation: cerebellar ataxia and shivering tremor
 - (d) Death from infection and/or malnutrition within 1 year

B. Cerebrovascular Diseases

1. Definitions

- a) Stroke (clinical term) = Sudden loss of one or more neurologic functions due to cerebrovascular diseases
- b) Complete stroke = The deficit is stable
- c) Transient ischemic attack (TIA) = Loss of neurologic function which recovers within 24 hours
- d) Reversible ischemic neurologic deficit (RIND) = Loss of neurologic function, which is restored within 7 days

2. Pathology

- a) All vascular diseases can have only three outcomes
 - (1) Infarct - pale or hemorrhagic
 - (2) Hemorrhage - macroscopic or microscopic
 - (3) Mass lesion effect - a result of pressure on adjacent structures

3. Infarcts:

- a) Most common causes of cerebral infarction are atherosclerosis or arteriolosclerosis
- b) Sites of infarcts
 - (1) Structures supplied by the middle cerebral artery, but can occur anywhere
- c) Pathology
 - (1) 65% are pale (artery associated with a thrombus)
 - (2) 35% are hemorrhagic (associated with embolus or venous thrombosis)
 - (a) Emboli go to cortical grey matter and are hemorrhagic
 - (3) Recent infarct
 - (a) Gross: soft and edematous (not well demarcated for several days).
 - (b) Microscopic features
 - i) Neurons - die within minutes and become pyknotic and shrunken (red cytoplasm) with 8 to 10 hours. These dead neurons will be eaten by neurons (neuronophagia)
 - ii) Oligodendrocytes - become eosinophilic and homogeneous
 - iii) Edema - spongiosis
 - iv) Macrophages - migrate into the tissue within 3-5 days from the venules and begins to eat for months until necrotic tissue has been removed
 - v) Astrocytes - reactive (nuclei enlarge and cytoplasm becomes visible) and appear within three weeks. They proliferate and

form a “glial scar” at the periphery of the infarct which takes 6-9 months.

- (4) Remote (old) infarct
 - (a) Gross: cystic change
 - (b) Microscopic features
 - i) Glial scar surrounding the cystic defect

Note: Fibroblasts are not found in normal brain except in perivascular spaces. Three situations in the CNS that will produce fibrosis: fibrous wall of an abscess, healed intraparenchymal hemorrhage and radiation therapy of brain tumors.

- 4. Intracerebral hemorrhage
 - a) More likely to kill than infarcts
 - b) Common precipitating conditions
 - (1) Increased incidence in African-Americans
 - (2) Hypertension (most common cause)
 - (3) Diabetes mellitus
 - (4) Aneurysm (5% of the population have aneurysms - defect in the internal elastic lamina)
 - (5) Atherosclerosis of cerebral arteries
 - c) Arterioles are thought to be the most common sources of hemorrhage
 - d) Locations
 - (1) Basal ganglia, internal capsule, thalamus, brain stem, and cerebellum
 - e) Increased intracerebral pressure leading to brainstem herniation
- 5. Trauma
 - a) Contusion (recent or remote) - “bruise”
 - (1) Coup - directly related to a blow or injury
 - (2) Contrecoup - a site on the brain opposite to the site of injury
 - (a) Most common kind
 - (b) Common sites include orbital surface of the frontal lobes, and the frontal and temporal tips
 - b) Epidural Hematoma
 - (1) Fracture temporal or parietal bone
 - (2) Rupture middle meningeal artery and/or branches
 - (3) “Lucid interval”; headache, vomiting, confusion, seizures, hemiparesis and death
 - (4) Requires emergent neurosurgery to decrease intracranial pressure
 - c) Subdural hematoma (chronic hematomas)
 - (1) Blunt trauma, alcoholism, and elderly
 - (2) Bridging veins (draining into the superior sagittal sinus) are

- torn
 - (3) Clinical manifestations - delayed onset of symptoms
 - (a) Rigidity, hemiparesis, and hemiplegia
 - 6. Outcome to CNS trauma - diffuse axonal injury
 - a) Can involve many areas of the brain
 - b) Probably represents diffuse tearing or fracturing of axons which is believed to be the important cause of “persistent vegetative state” post trauma
 - 7. Subarachnoid Hemorrhage
 - a) Causes
 - (1) Rupture of aneurysm (i.e., berry aneurysm)
 - (a) Bifurcation of anterior communication artery - common site for a berry aneurysm
 - (b) Second most common site is the proximal portion of the middle cerebral artery
 - (2) Arteriosclerosis
 - (3) Inflammation
 - (4) Trauma
 - (a) Clinical manifestations - severe headache, meningism, and bloody spinal tap
- C. Developmental Conditions
 - 1. Neural tube defects
 - a) Neural tube defects are the most common type of congenital malformation of the central nervous system, which result from failure of closure of the neural tube at the rostral and caudal ends and is related to folate deficiency during pregnancy.
 - b) Types
 - (1) Rostral end of the neural tube – anencephaly (lack of brain development)
 - (2) Caudal end of the neural tube
 - (a) Spina bifida occulta – bony defect of the vertebral arch
 - (b) Meningocele – bony defect of the vertebral arch with outpouching of the meninges
 - (c) Myelomeningocele – bony defect of the vertebral arch with cystic outpouching of the meninges, spinal cord and spinal roots
 - (d) Myelocele – bony defect of the vertebral arch and opening of the overlying skin with complete exposure of the spinal cord and spinal roots
 - 2. Arnold-Chiari malformations
 - Type 1 – downward displacement of the cerebellar tonsils and the medulla oblongata through the foramen magnum, which is common and often asymptomatic
 - Type 2 – due to a faulty craniospinal junction resulting in a small posterior

fossa and abnormal development of the cerebellum and medulla oblongata leading to downward displacement through the foramen magnum and obstruction of CSF in the fourth ventricle leading to obstructive hydrocephalus

3. Syringomyelia – an ependymal cell-lined, CSF-filled channel parallel to and connected to the central canal of the spinal cord about 90% of cases are associated with Arnold-Chiari malformation type 2. Syringomyelia leads to paralysis and loss of sensory functions.
4. Perinatal brain injury due to hypoxic injury to the CNS during prenatal or immediately postnatal period. Most frequently occurs in premature neonates.
 - a) Germinal matrix hemorrhage – hemorrhage localized to the germinal matrix due to the rupture of fragile blood vessels
 - b) Periventricular leukomalacia (softening of the white matter) is due to ischemic necrosis of the periventricular white matter from decreased blood flow to the watershed areas in the white matter
 - c) Multicystic encephalopathy due to multiple remote infarcts occurring early in pregnancy

D. Degenerative and Demyelinating Diseases

1. Demyelination
 - a) Multiple sclerosis
 - (1) Epidemiology
 - (a) Higher prevalence in northern latitudes
 - (b) Epidemics: Faroe Islands (post-WWII)
 - (c) Age = 10-50 years old with peak incidence of 30-35
 - (2) Clinical Course
 - (a) Initial symptoms include 25% partial or total loss of vision and 50% weakness or numbness in one or more limbs
 - (b) 90% of cases are relapsing and remitting, and 10% are rapidly progressive
 - (c) Duration of symptoms - several weeks to months
 - (d) Frequency of relapses - about 1 every 2 years
 - (3) Pathology
 - (a) Gross
 - i) Bilateral distribution of plaques (periventricular predilection); widely distributed involving the brain, cerebellum, brain stem, spinal cord, and optic nerve
 - (b) Microscopic features
 - i) Evidence of remyelination only at the edge of the plaque
 - ii) Plaque shows perivenous inflammation, demyelination with loss of oligodendrocytes, preservation of axons, and

- exuberant reactive astrocytic gliosis
 - iii) Active lesion shows cellular border composed of macrophages with myelin debris
 - iv) Earliest lesion shows perivascular inflammation and demyelination
 - (4) Pathogenesis
 - (a) Hypothesis: An autoimmune disease triggered by a viral infection in a genetically susceptible individual
 - (5) Prognosis
 - (a) 75% survive at 25 years
 - (b) After 25 years, 2/3 are active

2. Neural degeneration

- a) Alzheimer disease
 - (1) Most common cause of dementia in the United States (second most common cause of dementia is multi-infarct)
 - (2) Incidence is exponential from ages 60 to 90 (3% at age 60, 10% at 75, 40% at 85)
 - (a) Females more susceptible than males (2-3X)
 - (3) Three Forms of the Disease
 - (a) Down syndrome (Trisomy 21) – early onset before the age of 40 years of age
 - (b) Familial (single genetic locus) - autosomal dominant inheritance
 - i) Chromosome 21 - familial Alzheimer disease gene and b-amyloid precursor protein (beta-APP) gene (10% of cases)
 - ii) Chromosome 19 - apolipoprotein-E gene (3 alleles)
 - iii) Chromosomes 14 (40% of cases) presenilin I gene and 1 (presenilin II gene)
 - iv) Also called presenile dementia - early onset (<65 years of age)
 - (c) Sporadic Alzheimer Disease
 - i) Accounts for 85-90% of all Alzheimer disease
 - ii) Also called senile dementia - late onset (65> years of age)
 - (4) Protective factors
 - (a) Level of education (inverse relationship)
 - (b) Smoking
 - (5) Pathology:
 - (a) Gross - cortical atrophy of the frontal, temporal and parietal lobes, hippocampus, and cerebral nuclei (Basal nucleus of Meynert [major cholinergic input])

- and Locus coeruleus [major norepinephrine input to the cerebral cortex and hippocampus])
- (b) Microscopic features - neuritic plaques, neurofibrillary tangles (abnormally phosphorylated tau protein - a microtubule associated protein) within neurons, amyloid angiopathy, granulovacuolar degeneration of hippocampal neurons, and Hirano body (crystal-like aggregates of actin filaments) formation in hippocampal neurons
- (6) Definitive diagnosis is made based upon clinical features (loss of recent memory and progressive dementia) and neurohistological examination of the brain at autopsy
 - (a) Neurohistological diagnosis is defined as demonstrating an age-adjusted number of senile plaques and neurofibrillary tangles in the hippocampus and at least three other neocortical regions
- b) Picks - atrophy of frontal and temporal lobes (knife blade atrophy or “walnut brain”) and leads to progressive dementia
- c) Huntington - basal ganglia (caudate) – see Genetic Disorders lecture
- d) Parkinsonisms - basal ganglia and substantia nigra
 - (1) Clinical - cogwheel or “lead pipe” rigidity, festinating gait, expressionless face, and resting tremor
 - (2) All forms of Parkinsonism (Lewy Body Parkinsonism, Postencephalitic Parkinsonism, Atherosclerotic [ischemic] Parkinsonism, or manganese and MPTP poisonings) share a minimum 80% loss of nerve cells in the substantia nigra
 - (3) Pathology - Lewy body degeneration (alpha-synuclein and ubiquitin) affecting substantia nigra, locus coeruleus, sympathetic ganglia, basal nucleus of Meynert and cerebral cortex
 - (4) Treatment - L-dopa and anticholinergic drugs are necessary because there is marked depletion of dopamine in the caudate nucleus and putamen
- e) Lewy body dementia – a progressive neurodegenerative disease (second most common after Alzheimer disease) where Lewy body formation occurs in the neurons of the neocortex (limbic system and cingulate gyrus) and subcortical nuclei (basal nucleus of Meynert, amygdala and substantia nigra).
 - (1) Clinical manifestations include memory loss, parkinsonism and visual hallucinations
- f) Amyotrophic lateral sclerosis (Lou Gehrig disease)
 - (1) Degeneration of motor neurons in the spinal cord (lower motor neurons) and corticospinal tracts (upper motor

- neurons including brain stem, motor nuclei and primary motor cortex)
- (2) Clinical - neurogenic muscular atrophy with associated weakness, fasciculations, hyperreflexia, spasticity
- g) Friedreich ataxia
 - (1) An autosomal recessive disorder with early onset in childhood due to the degeneration of neuronal tissue, especially in the spinal cord
 - (2) Genetics – expansion of an unstable triple nucleotide repeat (GAA repeats in the first intron) of the frataxin gene on chromosome 9. The frataxin protein is essential in the mitochondrial iron regulation; the absence of frataxin leads to the accumulation of mitochondrial iron, free radical formation and mitochondrial damage
 - (3) Pathology – degeneration of the following neurons
 - (1) Dorsal root ganglia
 - (2) Clarke column (origin of spinocerebellar tract)
 - (3) Posterior column of the spinal cord
 - (4) Cranial nerve nuclei of VII, X, and XII
 - (5) Dentate nucleus and Purkinje cells of the cerebellum
 - (6) Betz neurons (large motor neurons [upper motor neurons) of the primary motor cortex
 - (4) Clinical manifestations – gait ataxia, dysarthria, hand clumsiness, loss of sense of position, impaired vibratory sensation, and loss of tendon reflexes. The affected children become wheelchair dependent by the age of 5

E. Peripheral Nerves

1. Mechanisms of Peripheral Neuropathy
 - a) Wallerian degeneration
 - (1) Transection (physical injury) or infarction (polyarteritis nodosa) of axons and myelin degeneration distal to the site of injury leading
 - b) Axonal/neuronal degeneration
 - (1) Degeneration of the whole neuron with secondary demyelination. Axonal conduction remains relatively normal for a variable period of time then ceases abruptly.
 - (2) Causes - toxins, dietary deficiency states, metabolic abnormalities, hereditary degenerative disorders and idiopathic
 - c) Segmental demyelination
 - (1) Primary destruction of the myelin sheath leaving the axon intact; however, Wallerian degeneration may occur secondary to segmental demyelination. Conduction is slowed and conduction block may occur.

- (2) Causes - genetic, immunologic (Guillain-Barré syndrome), toxins and metabolic disorders
 2. Neuropathy
 - a) Nutritional - pyridoxine or vitamin B6 deficiency
 - b) Toxic - vincristine
 - c) Diabetic -microvascular disease (diabetic mononeuropathies) and disordered glucose metabolism (polyneuropathies)
 - d) Mechanical
 - (1) Compartment syndromes - carpal tunnel syndrome
 - e) Systemic - uremia; amyloidosis
 - f) Autoimmune
 - (1) Guillain-Barré syndrome (acute idiopathic polyneuritis) - acute demyelinating disease (loss of Schwann cells) of peripheral nerves
 - (2) Infection - leprosy and herpes
- F. CNS and PNS Neoplasias
1. Approximately, 50% of neoplasms of the brain are primary, and the other 50% are secondary or metastatic tumors
 2. Comparing any one primary CNS tumor (e.g., glioblastoma multiforme) to secondary tumors of the CNS (malignant melanoma, breast, lung and renal cell carcinoma), metastatic tumors are more common
 3. Glioblastoma multiforme (type of anaplastic astrocytoma)
 - a) Most common primary brain neoplasm in adults
 - b) Age: Adults - 40-50 yr. with male:female (2:1)
 - c) Cerebral - most common site but can occur in the brain stem
 - d) Gross
 - (1) Infiltrative border, necrosis, hemorrhages, and may cross midline as a “butterfly” glioma via the corpus callosum
 - (2) Can seed the CSF
 - (3) Rapid growth
 - e) Microscopic features
 - (1) High cellularity
 - (2) Necrosis and pseudopalisading - critical feature
 - (3) Mitoses
 - (4) Pleomorphism
 - (5) Neovascularity
 - (6) +/- GFAP positive cells
 - f) Prognosis is poor
 4. Astrocytoma
 - a) Age: Adults - 30-40
 - b) Gross: not well demarcated, most commonly cerebral
 - c) Micro: fibrillary cells with a neuropil background
 - (1) GFAP positive cells
 - d) Variants

- (1) Circumscribed
 - (a) Second most common primary brain tumor in children
 - (b) Most common type = Juvenile pilocytic astrocytoma
 - (c) Age: children 5 to 10 years old
 - (d) Clinical - cerebellar or obstructive symptoms and signs
 - (e) Gross
 - i) Cerebellum - Classic cyst with mural nodule
 - ii) Also seen in optic nerve, hypothalamus, cerebrum, and spinal cord
- 5. Ependymoma
 - a) Age
 - (1) Children and adolescents: fourth ventricle
 - (2) Adults: spinal cord
 - b) Gross: Most common intramedullary spinal cord tumor
 - (1) Well circumscribed solid masses, arise from floor of the fourth ventricle
 - (2) May be associated with a syrinx (tunnel-shaped) cavity in spinal cord
- 6. Oligodendroglioma
 - a) Often associated with protracted history of seizures
 - b) Age: adults- 30-40 yr.
 - c) Gross: Cerebral, superficial, calcified and circumscribed
 - d) Microscopic features:
 - (1) “Fried egg” cells - really fixation artifact “chicken wire” vessels
 - (2) Look for partitioning of uniform cells into discrete groups by the capillary-like vessels
 - (3) Anaplastic if necrotic and neovasculature may spontaneously hemorrhage
 - (a) Note:
 - i) Primary brain tumors with hemorrhage = oligodendrogliomas and glioblastoma multiformes
 - ii) Metastases with hemorrhage = choriocarcinoma, melanoma, renal and breast
- 7. Primitive Neuroectodermal Tumors (PNET)
 - a) Cerebellum - Medulloblastoma
 - (1) Age: most common primary CNS tumor in children
 - (2) Incidence: male to female (3:1)
 - (3) Clinical - cerebellar and obstructive symptoms and signs
 - (4) Gross
 - (a) Usually midline in the cerebellum

- (b) Rapid growth with infiltration
 - (5) Microscopic features
 - (a) Sheets of poorly differentiated carrot-shaped cells
 - (b) Homer-Wright rosettes - actually pseudorosettes as there is no true lumen
 - (c) May see astrocytic differentiation, rarely neuronal, muscle, connective tissue
 - (d) Frequently seeds CSF
- 8. Meningioma
 - a) Age: adults - women > men
 - b) Clinical - symptoms and signs dependent upon site
 - c) Gross: Parasagittal most common, also spinal, intraventricular; firm tumors that push into the parenchyma - extra-axial; often involves the dura. Slow growing tumor.
 - d) Microscopic features
 - (1) Arises from arachnoidal cells
 - (2) Classical pattern - psammoma bodies and whorls or sheet-like growth (meningotheiomatous)
- 9. Metastatic:
 - a) Usually multiple tumors at the grey-white matter junction, circumscribed, may be necrotic
 - b) Cancers that frequently metastasize to the brain: lung, breast, GI, skin (malignant melanoma) and kidney (renal cell carcinoma)
 - c) Hemorrhagic - choriocarcinoma, melanoma, renal and breast
 - d) Frequency: Lung >>> Breast > GI > Other
- 10. Pituitary Adenomas
 - a) Acidophilic, basophilic, chromophobic - no longer utilized
 - b) Most common secreting adenoma - prolactinoma (30% of surgically removed adenomas)
 - c) Variable growth pattern, enlarged sella eventually resulting in suprasellar extension
 - d) Variants
 - (1) Growth Hormone producing - acromegaly
 - (2) ACTH-cell adenoma - Cushing disease; usually this is a microadenoma, associated with Crookes Hyalinization - down regulation of remaining normal corticotrophs
 - (3) Nelson's Syndrome - Unrecognized adenoma followed by an adrenalectomy to treat Cushing's disease. Leads to uncontrolled growth of the adenoma which becomes an invasive macroadenoma.
- 11. Nerve Sheath Tumors
 - a) Schwannoma
 - (a) Usually involves sensory roots; spinal or VIII nerve (acoustic neuroma), less often cranial nerve V
 - (1) Age: adults (female>male); except for Von Recklinghausen disease

- (2) Gross: encapsulated, nerve often at periphery of mass
 - (3) Microscopic features: Biphasic
 - (a) Antoni A - dense, compact areas with palisades around acellular zones (Verocay bodies)
 - (b) Antoni B - Loosely associated areas
 - (4) Bilateral acoustic schwannomas associated with von Recklinghausen Disease, type 2
 - b) Neurofibroma:
 - (1) Associated with von Recklinghausen Disease, also sporadic
 - (2) Gross: Usually well encapsulated, incorporates the nerve
 - (3) Malignant change more common in variant – sarcoma
12. Others
- a) Craniopharyngioma
 - (1) Common in first two decades of life
 - (2) Arises from Rathke pouch
 - (3) Gross: cystic, oily, variegated tumor
 - (4) Microscopic features
 - (a) “Adamantinomatous” pattern or cystic change with keratinizing squamous epithelium and calcification
 - (5) Associated with hypothalamic dysfunction
 - b) Colloid cyst
 - (1) Location: third ventricle
 - (2) Gross: encapsulated, contains colloid
 - (3) Micro: lined by low cuboidal secretory epithelium
 - (4) Associated with obstructive signs and symptoms
 - c) Lymphoma - multifocal, periventricular; often associated with minimal edema
 - (1) Sporadic cases in older adults (60-70's)
 - (2) Cases associated with immunodeficiency - originally most often in renal transplant patients now seen in AIDS patients (1-2%)
 - (3) Microscopic features: malignant lymphoid cells in the tissue with perivascular collections and “onion-skin” reticulin
 - d) Germ Cell Tumors
 - (1) Pineal gland and third ventricle locations
 - (a) Microscopic features
 - i) Seminoma pattern (germinoma) most common and can see all patterns as in gonadal tumors

F. Mass Lesion Effects

1. Types of mass lesions
 - a) Congenital - cysts
 - b) Traumatic - hematoma
 - c) Vascular - hematoma or infarct with associated edema
 - d) Infectious - abscess
 - e) Toxic-metabolic - edema from poison
 - f) Neoplasms - glioblastoma or meningioma
2. Types of herniation
 - a) Fungus cerebri
 - (1) Definition
 - (a) Herniation of brain through defect in skull
 - (2) Usually associated with trauma or following surgery
 - (3) Uniformly associated with death
 - (4) Rare
 - b) Subfalcial
 - (1) Definition
 - (a) Brain pushed under falx cerebri usually by one-sided mass lesion
 - c) Transtentorial
 - (1) Definition
 - (a) Cerebrum pushed down through incisura due to a mass in cerebrum
 - (2) Most common type of herniation (complex)
 - (3) Components
 - (a) Hippocampus or its anterior part (uncus) can be pushed over the edge of the tentorium leading to infarction
 - (b) Third nerve(s) can be compressed or stretched leading to pupillary miosis or mydriasis
 - (c) Posterior cerebral artery or arteries can be compressed leading to infarction of the visual cortex
 - (d) Crus cerebri (one or both) can be compressed resulting in contralateral body paresis or paralysis
 - (e) Midbrain can be pushed down through tentorial notch leading to stretching of arteries causing rupture and hemorrhage (Duret hemorrhages). These hemorrhages are almost always fatal.
 - d) Tonsillar
 - (1) Definition
 - (a) Cerebellar tonsils pushed down through foramen magnum which is almost always due to a posterior fossa mass (cerebellar mass); rarely a cerebral mass
 - (2) Tonsils are compressed and become infarcted
 - (3) Medulla oblongata becomes infarcted and is most often rapidly fatal

ANEMIA I & II**OBJECTIVES:**

1. *Define the anemia.*
2. *Describe the difference between microcytic, normocytic and macrocytic anemias.*
3. *Describe the pathogenesis and clinical presentations of each major type of anemia with specific examples including iron deficiency anemia, anemia of chronic disease, thalassemias, sickle cell disease, G6PD deficiency, hereditary spherocytosis, vitamin B12 and folate deficiencies.*
4. *Describe the red blood cell morphologic changes associated with each type of anemia.*

READING: Basic Pathology, Kumar, Cotran and Robbins, 9th Ed., pp. 407-425

A. Definition: Anemia is a decrease in total circulating red cell mass

B. Terms to describe the red blood cells under the microscope:

1. Variation in **color**:
 - a) Normochromic - normal staining intensity
 - b) Hyperchromic - increased staining intensity
 - c) Hypochromic - decreased staining intensity
 - d) Polychromatophilia - blue-gray color to red cells indicate of the presence of RNA (immature red cell) often seen in reticulocytosis due to severe hemolysis and acute blood loss
2. Variation in **size**:
 - a) Microcytes (cell volume)
 - b) Macrocytes (cell volume)
 - c) Anisocytosis - abnormal variation in size, which is a feature of most anemias
3. Variation in **shape**:
 - a) Poikilocytosis - variation in shape
 - (1) Example: A variety of anemias
 - b) Elliptocytes - cells are elliptical
 - (1) Examples: Iron deficiency anemia, megaloblastic anemia, and sickle cell anemia

- c) Spherocytes - nearly spherical erythrocytes (lack of a central pale area)
 - (1) Example: hereditary spherocytosis
- d) Target cells - a peripheral rim of hemoglobin with a dark, central, hemoglobin-containing area
 - (1) Example: Thalassemia
- e) Schistocytes - cell fragments secondary to hemolysis (helmet cells)
 - (1) Examples: Megaloblastic anemia, severe burns, and microangiopathic hemolytic anemia (DIC)
- f) Acanthocytes - spiculated red cells
 - (1) Example: abetalipoproteinemia (hereditary or acquired)

4. Variation in **structure**:

- a) Basophilic stippling - abnormal instability of RNA within developing red blood cell
 - (1) Examples: lead poisoning, megaloblastic anemia, thalassemias, and other severe forms of anemia
- b) Siderocytes - inorganic iron-containing granules within red cells
 - (1) Example: After splenectomy
- c) Howell-Jolly bodies - smooth, round fragments of nuclear chromatin
 - (1) Examples: megaloblastic anemia, hemolytic anemia and after splenectomy (single Howell-Jolly body); megaloblastic anemia (multiple Howell-Jolly bodies)

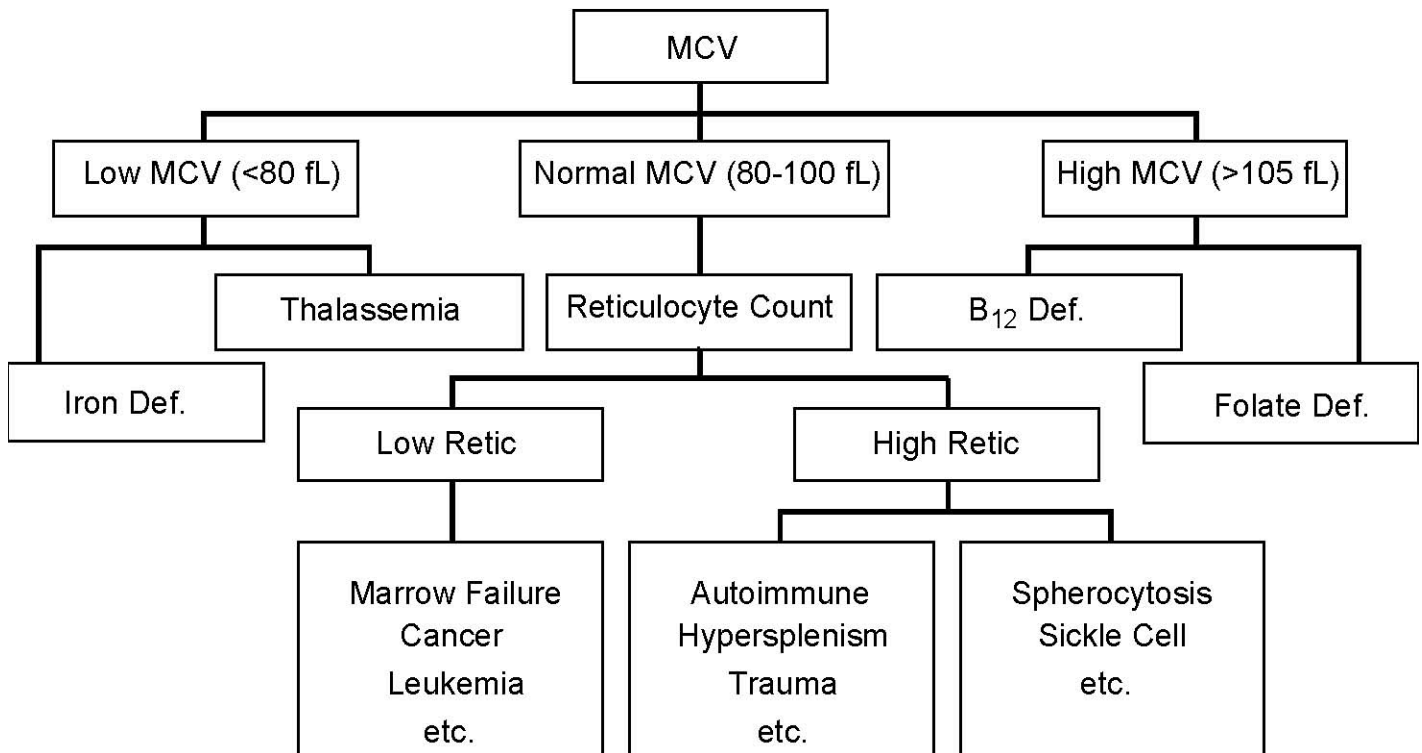
C. Polycythemia

- 1. Reactive - any process that decreases O_2 or increase erythropoietin production
- 2. Neoplastic - Polycythemia rubra vera, autonomous proliferation of RBC precursors and related to chronic myelocytic leukemia

D. Anemias

- 1. Patients rarely die of anemia but frequently die of the cause of anemia. Most important test in diagnosis of anemia is the mean corpuscular volume [MCV] (**See Figure 1**).

Figure 1. Anemia Workup



2. Hypochromic, Microcytic Anemias

- (1) Definition: Decreased mean corpuscular hemoglobin concentration [MCHC] which can occur with a reduced mean corpuscular volume [MCV = < 80 fL] due to impaired hemoglobin synthesis
- (2) Disorders of iron metabolism
 - (a) Iron deficiency anemia
 - i) Low iron but high TIBC (Total Iron Binding Capacity) because of stimulated transferrin synthesis
 - ii) Low serum ferritin
 - iii) Usually high red cell dispersion width (RDW) is the standard deviation of MCV and an estimate of erythrocyte anisocytosis.
 - (b) Anemia of chronic disease (osteomyelitis, bacterial endocarditis, lung abscess, rheumatoid arthritis, regional enteritis, Hodgkin Lymphoma, and breast and lung carcinomas) due to the release of IL-1 (macrophages) leading to increased lactoferrin sequestering iron stores.

- i) Normal or increased storage iron in marrow macrophages
 - ii) Normal or low TIBC
 - iii) Normal or high serum ferritin
- (3) Disorders of porphyrin and heme synthesis (sideroblastic anemias) - drug or toxin induced [ethanol, INH, lead], hereditary [x-linked and autosomal recessive]
- (4) Disorders of globin synthesis - thalassemias (see below) and hemoglobinopathies
- (5) Hemoglobin defects (synthesis) - **Thalassemias** (α and β) [*sea of blood*]:
 - (a) Lack of either alpha (one functional pair of genes on each chromosome 16), or beta chain (one functional gene on each chromosome 11)
 - (b) Autosomal co-dominant trait:
 - i) Heterozygous form - thalassemia minor or thalassemia trait) can be asymptomatic or mildly symptomatic
 - ii) Homozygous form - thalassemia major is associated with severe hemolytic anemia.
 - (c) Hypochromatic anemias with basophilic stippling and target cells
 - (d) β -Thalassemia is the most common and is due to abnormal RNA splicing (most common underlying mechanism):
 - i) Thalassemia major (β^0/β^0 = absent b-chain; β^+/β^+ = severely deficient):
Homozygous (β^0/β^0 or β^+/β^+) - severe anemia requiring blood transfusions
Clinical - cardiac failure due to secondary hemochromatosis from multiple transfusions. Average of death = 17 years
 - ii) Thalassemia minor: Heterozygous (β^0/β^+ or β^+/β^0) - asymptomatic with or without anemia; red cells are abnormal
Clinical - mild microcytic hypochromatic anemia with normal life expectancy
 - (e) α -Thalassemia is due to reduced alpha synthesis (deletion of α -globin gene loci):
 - i) Silent ($-\alpha/\alpha\alpha$) - asymptomatic without red cell abnormality
 - ii) α -Thalassemia trait ($--/\alpha\alpha$ [Asian] or $-\alpha/-\alpha$ [black African]) - asymptomatic and resembles thalassemia minor
 - iii) HbH disease ($--/-\alpha$) - severe anemia

- iv) Hydrops fetalis (---) -*in utero* death
- v) Non α -chains (b-chain) are less toxic and more soluble than α -chains, which would explain why the clinical manifestations in α -thalassemia tend to be less severe.

3. Normochromic, Normocytic Anemias

- (1) Definition: Mean corpuscular volume [MCV = 80-100 fL] and mean corpuscular hemoglobin concentration [MCHC] are normal. The retic (new RBC's) count is very important in this type of anemia.
 - (a) Examples:
 - i) Acute post-hemorrhagic anemia. The retic count is high.
 - ii) Marrow hypoplasia - aplastic anemia. The retic count is low.
 - iii) Marrow infiltration - metastatic disease, myelofibrosis, inherited storage diseases (e.g., Gaucher disease). The retic count is low.
 - (iv) Decreased erythropoietin production - kidney and liver diseases, endocrine disorders, malnutrition, anemia of chronic disease (e.g., chronic infections, inflammatory diseases [rheumatoid arthritis], and cancers). The retic count is low.
- (2) Reticulocyte Count in Anemia (**See Figure 1**)
 - (a) Low reticulocyte count
 - i) Marrow failure - metastatic cancer, leukemia, malnutrition
 - ii) Chronic disease or infection
 - iii) Inflammatory disease (rheumatoid arthritis)
 - iv) Decreased erythropoietin production (kidney and liver diseases)
 - (b) High reticulocyte count = hemolytic anemias

Definition: In a steady state bone marrow must produce reticulocytes at the same rate that they are being destroyed, therefore reticulocyte levels are inversely proportional to red cell survival.

 - i) Extrinsic (acquired) hemolytic disorders
 - 1) Immune (alloimmune, autoimmune, drug-induced) - elevated Coombs test and spherocytes which is the most common cause of hemolytic anemia
 - 2) Hypersplenism - enlarged spleen due to any cause
 - 3) Paroxysmal nocturnal hemoglobinuria
 - 4) Toxins (clostrial) and metabolic abnormalities (hepatocellular

disease - end-stage cirrhosis leads to spur cell hemolytic anemia) – Coombs negative

- 5) Red cell parasites - malarial infections, babesiosis (protozoan), bartonellosis (gram-negative bacterium) - Coombs negative.
- 6) Red cell trauma - prosthetic heart valves, DIC (microangiopathic hemolytic anemia), malignant hypertension, vasculitis (rickettsial infections, polyarteritis nodosa, Wegener's granulomatosis) - Coombs negative

ii) Intrinsic hemolytic disorders (Coombs negative)

(1) **Sickle cell anemia**

- (a) An autosomal recessive trait (co-dominant)
- (b) Homozygous condition is called sickle cell disease or anemia
- (c) Heterozygous condition is called sickle cell trait
- (d) Molecular basis - Substitution of normal glutamic acid with valine at codon 6 on the β chain
- (e) Pathology:
 - (i) Chronic anemia
 - (ii) Jaundice leading to cholelithiasis

Vascular occlusions (account for most of the clinical manifestations):

- (i) Microthrombi
- (ii) Autosplenectomy
- (iii) Aseptic necrosis of the femoral head
- (iv) Ocular complications: retinopathy, vitreous hemorrhage, and neovascularization
- (v) Bronchopneumonia (pneumococcal and H. influenzae) and pulmonary vascular occlusions (i.e., infarction, chronic hypoxia, pulmonary hypertension with cor pulmonale)
- (vi) Chronic osteomyelitis - increased susceptibility to Salmonella infections
- (vii) Neurologic manifestations - infarction, and subarachnoid hemorrhage

- 2) **Glucose-6-phosphate dehydrogenase deficiency**
 - (a) X-linked recessive disorder
 - (b) Abnormality - deficiency or impaired enzyme in the hexose monophosphate shunt or in glutathione metabolism which provides protection against oxidation injuries induced by drugs in red blood cells
 - (c) 150 variants worldwide
- 3) **Hereditary spherocytosis**
 - (a) Autosomal dominant disorder
 - (b) Deficiency in ankyrin and spectrin (cytoskeletal proteins responsibility for the maintenance of the normal shape, strength, and flexibility of the red blood cell) leads to spheroidal erythrocytes and spontaneous loss of red cell membrane which are less deformable and predisposes to splenic sequestration and destruction
 - (c) Clinical manifestations: chronic hemolytic anemia, jaundice, splenomegaly (500 to 1000 gm), and cholelithiasis (pigmented) leading to cholecystitis

4. **Megaloblastic Anemias**

- (1) Definition: Due to defects in DNA synthesis (cell division) as a result of tetrahydrofolate reductase pathway leading to bone marrow and peripheral blood abnormalities (morphologic changes of cell nuclei of hemopoietic cells) leading to macrocytes [MCV = > 105 fL].
- (2) Cobalamin deficiency (Vitamin B₁₂)
 - (a) Decreased ingestion - poor diet, strict vegetarianism
 - (b) Impaired absorption - pernicious anemia (atrophy of gastric mucosa with autoantibodies directed against parietal cells and intrinsic factor) leading to decreased production of intrinsic factor required for resorption in the terminal ileum [most common cause of cobalamin deficiency in the Western Hemisphere]
 - (c) Impaired utilization - congenital enzyme deficiencies, nitrous oxide administration
 - (d) Chronic deficiency (15 to 30 years) - dyspnea, congestive heart failure, gastrointestinal tract (sore tongue and cheilosis) and neurologic

manifestations (symmetric numbness, tingling, and burning in hands or feet).

- (3) Folate deficiency
 - (a) Decreased ingestion - lack of vegetables, alcoholism
 - (b) Impaired absorption - tropical sprue, celiac disease, anticonvulsants, congenital malabsorption
 - (c) Impaired utilization - folic acid antagonists (methotrexate, ethanol, triamterene), congenital enzyme deficiencies
 - (d) Increased requirement - pregnancy, infancy, hyperthyroidism, neoplastic disease
 - (e) Increased loss – hemodialysis
 - (f) Clinical manifestations include no neurologic manifestations, similar to vitamin B₁₂ deficiency involving the gastrointestinal tract and increase the risk of neural tube defects in pregnant women
- (4) Metabolic Inhibitors
 - (a) Purine synthesis - methotrexate, azathioprine, etc.
 - (b) Pyrimidine synthesis - methotrexate, 6-azauridine
 - (c) Thymidylate synthesis - methotrexate, 5-fluorouracil
 - (d) Deoxyribonucleotide synthesis - hydroxyurea, etc.
- (5) Inborn Errors of Metabolism:
 - (a) Lesch-Nyhan syndrome - deficiency of hypoxanthine-guanine phosphoribosyltransferase (HPRT)
 - (i) Incidence - 1 in 100,000 births
 - (ii) X-linked recessive
 - (iii) Clinical - hyperuricemia, and neurologic manifestations including self-mutilation, choreoathetosis, spasticity and mental retardation

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