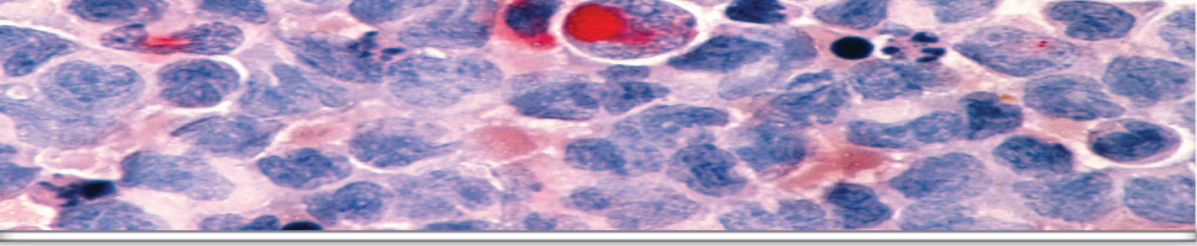

Pathology Flash Cards

SECOND EDITION

277 High-Yield Cards...
Every One with a Clinical Vignette!

Suzanne J. Baron • Christoph I. Lee

Mc Graw Hill LANGE

Lange Pathology Flash Cards

Second Edition

Suzanne J. Baron, MD
Cardiology Fellow
Department of Medicine
Cardiology Division
Massachusetts General Hospital
Boston, Massachusetts

Christoph I. Lee, MD
Resident Physician
Department of Radiology
Stanford University Hospital
Palo Alto, California

New York / Chicago / San Francisco / Lisbon / London / Madrid / Mexico City
Milan / New Delhi / San Juan / Seoul / Singapore / Sydney / Toronto

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Preface

When we began to prepare for the USMLE Step 1 early in our second year at Yale Medical School, we discovered that a myriad of sources was available for pathology review but none that were both comprehensive and organized in a fashion conducive to repetitive review. We found that the material in many of the resources was presented in outline form, which failed to organize the etiology, pathology, clinical findings, and treatment options of each disease in a consistent manner. Although we used the most highly rated pathology reviews, we still found ourselves combining information from multiple sources to create a more comprehensive and convenient review tool.

Lange Pathology Flash Cards are the result of our trials and tribulations while trying to learn pathology and review the subject for the boards. These cards offer the most complete, concise, and relevant high-yield information for the major diseases tested on the USMLE Step 1 and in the second-year pathology course. The content covers the most current and board-relevant information that can otherwise only be found by combining the content of several review sources. In this second edition, we have added more, up-to-date high-yield disease processes and key information that is currently being tested on the Step 1.

We are excited to present this high-yield pathology content in a format designed for active review. Each card provides a structured presentation of a specific disease and allows students to easily compare and contrast diseases. The introductory cards for each system describe the basic physiologic and/or pathophysiologic principles of the relevant structures and organs. Each disease-specific card contains both a clinical vignette and the characteristics of the disorder. The vignette appears on the front side of the card and frames the pertinent information in the context of a clinical application. The reverse side of the card includes information related to the etiology and epidemiology of the disease; classical or defining pathologic, pathophysiologic, or histologic

findings; clinical manifestations, classical presentations, and current medical treatments; and pearls. In addition, the most salient features of each disease are highlighted in bold throughout each card for rapid review purposes.

We would suggest using these cards as an adjunct to your pathology course materials early in your second year. Familiarizing yourself with these cards as you tackle your course will be immensely helpful to you during your Step 1 review. We would like to encourage you to jot down your own notes in the margins and make these cards your personal pathology review. We also encourage you to make your own cards for low-yield conditions that you identify.

We hope that this second edition of the *Lange Pathology Flash Cards* will help prepare you for the boards and serve as a resource that will bridge your basic pathology knowledge with the clinical aspects of disease that you will soon be encountering firsthand on the wards.

Best of luck with Step 1, and feel free to contact us with any suggestions to improve this study tool in the next edition.

Suzanne J. Baron, MD
sbaron@partners.org

Christoph I. Lee, MD
stophlee@stanford.edu
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Finally, we thank all of our family and friends who have provided constant reassurance and moral support throughout this enriching experience. Special thanks to Fran and Joe Baron, John and Jay Lee, Monique Mogensen, Bart Kenney, Bettina Lee, and Elena Paul.

About the Authors

Suzanne J. Baron, MD, earned an AB magna cum laude in psychology and biology from Harvard University and her MD from Yale University School of Medicine. She completed her internal medicine residency at Massachusetts General Hospital and is currently a cardiology fellow at Massachusetts General Hospital. Suzanne is an accomplished pianist and has published her research in peer-reviewed journals including JAMA and Circulation Research.

Christoph I. Lee, MD, earned an AB cum laude in English from Princeton University and his MD from Yale University School of Medicine. He is currently completing a residency in diagnostic radiology at Stanford University Hospital. In the past, Dr. Lee managed a global tuberculosis initiative for Ralph Nader and has published several original research articles regarding health policy and diagnostic radiology in peer-reviewed journals.

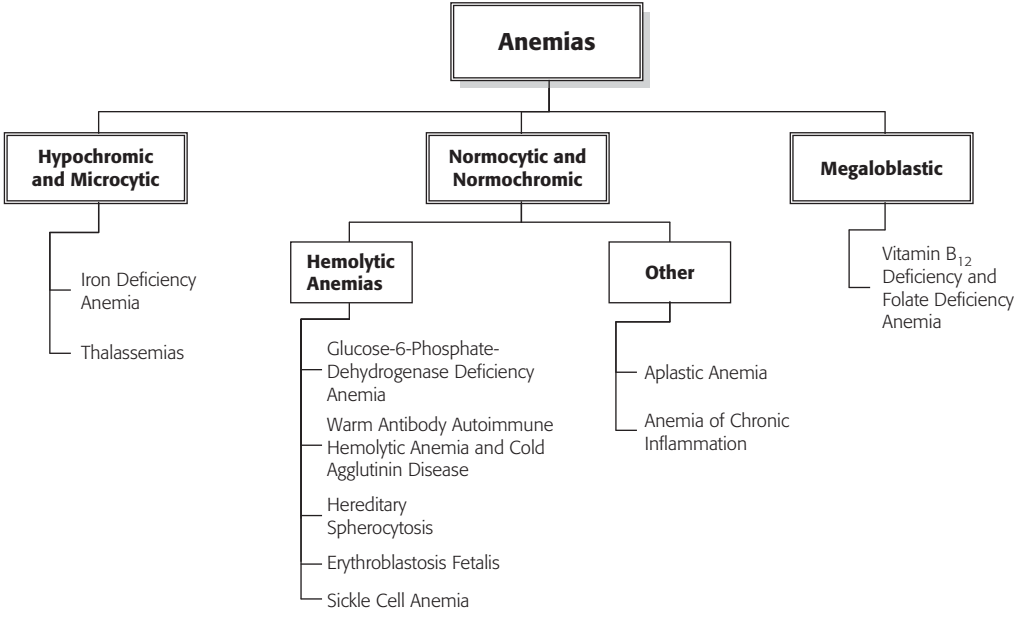
Abbreviations

5-HIAA: 5-hydroxyindoleacetic acid
ACA: anterior cerebral artery
ACE: angiotensin-converting enzyme
ACTH: adrenocorticotropic hormone
ADH: antidiuretic hormone
AFP: alpha-fetoprotein
AIHA: autoimmune hemolytic anemia
ALL: acute lymphoblastic leukemia
ALP: alkaline phosphatase
ALS: amyotrophic lateral sclerosis
ALT: alanine transaminase
AML: acute myelogenous leukemia
ANA: antinuclear antibody
ANCA: antineutrophil cytoplasmic antibody
Anti-TTG: Anti-transglutaminase
APC: antigen presenting cells
APKD: adult polycystic kidney disease
ARDS: acute respiratory distress syndrome
ARF: acute renal failure
ASD: atrial septal defect
ASO: antistreptolysin O
AST: aspartate transaminase
AZT: Zidovudine
BP: blood pressure
BPH: benign prostatic hypertrophy
BUN: blood urea nitrogen
CAD: coronary artery disease
CALLA: common acute lymphoblastic leukemia antigen
c-ANCA: cytoplasmic antineutrophilic cytoplasmic antibodies
CCK: cholecystokinin
CD4: clusters of differentiation
CEA: carcinoembryonic antigen
CF: cystic fibrosis
CFTR: cystic fibrosis transmembrane conductance regulator
CHF: congestive heart failure
chr: chromosome
CK: creatinine kinase
CK-MB: creatine kinase-myocardial band
Cl^-: chloride ion
CLL: chronic lymphocytic leukemia
CML: chronic myelogenous leukemia
CMV: cytomegalovirus

CNS: central nervous system
CO: cardiac output
COPD: chronic obstructive pulmonary disease
CRF: corticotropin releasing factor
CSF: cerebrospinal fluid
CVA: costovertebral angle
CXR: chest x-ray
DES: diethylstilbestrol
DEXA: dual energy X-ray absorptiomety
DHT: dihydrotestosterone
DIC: disseminated intravascular coagulation
DIP: distal interphalangeal
DM: diabetes mellitus
DNA: deoxyribonucleic acid
dsDNA: double-stranded DNA
DVT: Deep venous thrombosis
EBV: Epstein-Barr virus
ECG: electrocardiogram
EDV: end-diastolic volume
EEG: Electroencephalogram
EPO: erythropoietin
ESR: erythrocyte sedimentation rate
ESRD: end-stage renal disease
FEV_1: forced expiratory volume in 1 second
FNA: Fine needle aspiration
FSH: follicule-stimulating hormone
FVC: forced vital capacity
GABA: Gamma-aminobutyric acid
GBM: glomerular basement membrane
G-CSF: granulocyte colony stimulating factor
GERD: gastroesophageal reflux disease
GFR: glomerular filtration rate
GGT: gamma glutamyl transpeptidase
GH: growth hormone
GHRH: growth hormone releasing hormone
GI: gastrointestinal
GnRH: gonadotropin releasing hormone
GU: genitourinary
HAV: hepatitis A virus
HBcAg: hepatitis B core antigen
HBeAg: hepatitis B e antigen
HBsAg: hepatitis B surface antigen
HBV: hepatitis B virus
hCG: human chorionic gonadotropin
HCO_3^-: bicarbonate ion
Hct: hematocrit
HCV: hepatitis C virus
HDV: hepatitis D virus
HEV: hepatitis E virus
HGPRT: hypoxanthine-guanine phosphoribosyltransferase

HLA: human leukocyte antigen
HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A
HPV: human papilloma virus
HSV: Herpes simplex virus
HTN: hypertension
HUS: hemolytic uremic syndrome
IBD: inflammatory bowel disease
IgA: immunoglobulin A
IgE: immunoglobulin E
IgG: immunoglobulin G
IgM: immunoglobulin M
INH: isonicotinic acid hydrazide
IPKD: infantile polycystic kidney disease
IV: intravenous
IVC: inferior vena cava
JVD: jugular venous distention
JVP: jugular venous pressure
KSHV: Kaposi's sarcoma-associated herpesvirus
LA: left atrium
LAD: left anterior descending coronary artery
LAP: leukocyte alkaline phosphatase
LDH: lactate dehydrogenase
LDL: low-density lipoprotein
LES: lower esophageal sphincter
LFTs: liver function tests
LH: luteinizing hormone
LLQ: left lower quadrant
LV: left ventricle
MAO: monoamine oxidase
MCA: middle cerebral artery
MCHC: mean corpuscular hemoglobin concentration
MCP: metacarpophalangeal
MCV: mean corpuscular volume
MDS: myelodysplastic syndrome
MEN: multiple endocrine neoplasias
MHC: major histocompatibility complex
MI: myocardial infarction
MLF: medial longitudinal fasciculus
MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI: magnetic resonance imaging
MS: multiple sclerosis
MSH: melanocyte-stimulating hormone
MTP: metatarsopharyngeal
NADPH: nicotinamide adenine dinucleotide phosphate (reduced form)
NHL: non-Hodgkin lymphoma
NSAIDs: nonsteroidal anti-inflammatory drugs
OCP: oral contraceptive pills
OSA: obstructive sleep apnea

P-ANCA: perinuclear pattern of antineutrophil cytoplasmic antibodies
PAS: periodic acid-Schiff
PCA: posterior cerebral artery
PCP: *Pneumocystis carinii* pneumonia
PDA: patent ductus arteriosus
PGE: prostaglandin E
PIP: proximal interphalangeal
PNS: peripheral nervous system
PPD: purified protein derivative
PSA: prostate-specific antigen
PT: prothrombin time
PTH: parathyroid hormone
PTHrP: Parathyroid hormone related peptide
PTT: partial prothromboplastin time
PV: pemphigus vulgaris
RA: rheumatoid arthritis
RBC: red blood cell
RHD: rheumatic heart disease
RLQ: right lower quadrant
RNP: ribonucleoprotein
RPR: Rapid plasma reagin
RSV: respiratory syncytial virus
RUQ: right upper quadrant
RVH: right ventricular hypertrophy
RV: right ventricle
SIADH: syndrome of inappropriate antidiuretic hormone secretion
SLE: systemic lupus erythematosus
STDs: sexually transmitted diseases
STEMI: ST-elevation myocardial infarction
SVC: superior vena cava
t(#;#): chromosomal translocation
TB: tuberculosis
TH: thyroid hormone
TIBC: total iron-binding capacity
TLC: total lung capacity
TMP-SMX: trimethoprim-sulfamethoxazole
TRAP: tartrate-resistant acid phosphatase
TRH: thyrotropin-releasing hormone
TSH: thyroid-stimulating hormone
UDP: uridine diphosphate
URI: upper respiratory infection
UTI: urinary tract infection
VDRL: venereal disease research laboratory
VHL: von Hippel-Lindau
VMA: vanillylmandelic acid
VSD: ventricular septal defect
VZV: varicella zoster virus
WBC: white blood cell


Anemias
Hypochromic and Microcytic
Iron Deficiency Anemia
Thalassemias
Normocytic and Normochromic
Hemolytic Anemias
Glucose-6-Phosphate-Dehydrogenase Deficiency Anemia
Warm Antibody Autoimmune Hemolytic Anemia and Cold Agglutinin Disease
Hereditary Spherocytosis
Erythroblastosis Fetalis
Sickle Cell Anemia
Other
Aplastic Anemia
Anemia of Chronic Inflammation
Megaloblastic
Vitamin B_{12} Deficiency and Folate Deficiency Anemia

Erythrocytes

Development

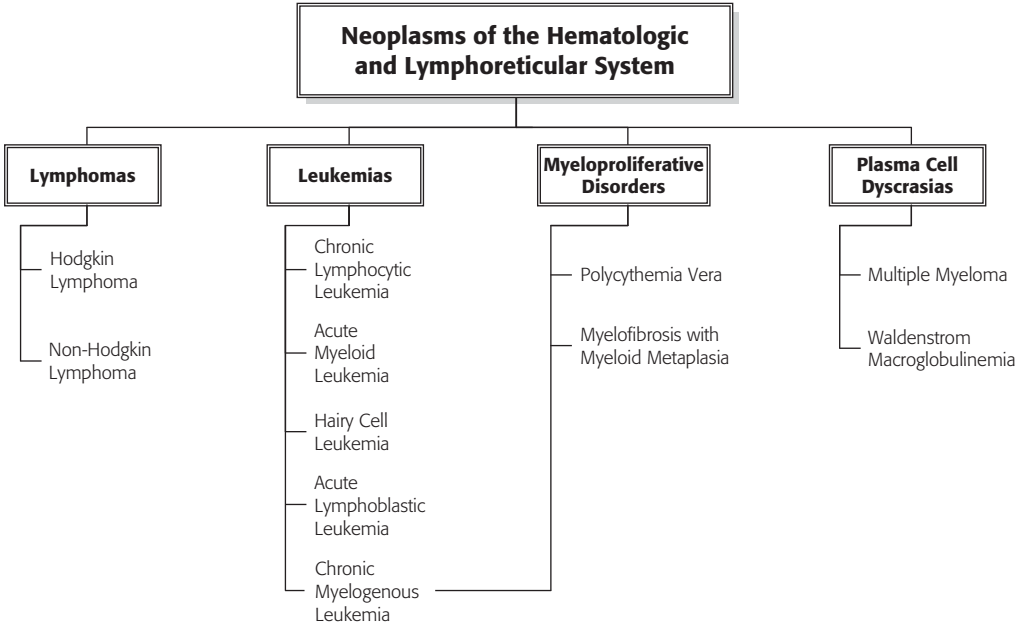
- Hematopoietic stem cell → proerythroblast → → reticulocyte → erythrocyte.
- Mature erythrocytes contain no nucleus or cytoplasmic organelles; thus, energy is derived from anaerobic degradation of glucose.
- Lifespan is 120 days; old erythrocytes are removed from circulation by spleen and liver.

Structure

- Biconcave disk shape is maintained by submembrane cytoskeleton composed of spectrin, ankyrin, protein 4.1, and other proteins.
- Biconcave shape results in increased surface area to volume ratio, thereby enhancing gas exchange.

Function

- Involved in oxygen and carbon dioxide transport via hemoglobin.


Neoplasms of the Hematologic and Lymphoreticular System
Lymphomas
Hodgkin Lymphoma
Non-Hodgkin Lymphoma
Leukemias
Chronic Lymphocytic Leukemia
Acute Myeloid Leukemia
Hairy Cell Leukemia
Acute Lymphoblastic Leukemia
Chronic Myelogenous Leukemia
Myeloproliferative Disorders
Polycythemia Vera
Myelofibrosis with Myeloid Metaplasia
Plasma Cell Dyscrasias
Multiple Myeloma
Waldenstrom Macroglobulinemia

Leukocytes

GRANULOCYTES

Neutrophil

- *Structure:* multilobed nucleus; granules containing lysozyme, myeloperoxidase, and hydrolytic enzymes
- *Function:* involved in acute inflammatory response

Basophil

- *Structure:* bilobed nucleus; dark blue granules containing heparin, histamine, leukotrienes
- *Function:* involved in mediating allergic reactions

Eosinophil

- *Structure:* bilobed nucleus; pinkish granules containing major basic protein, histaminase, and arylsulfatase
- *Function:* defends against parasitic infections; levels increased in asthma, allergic processes, neoplasm, collagen vascular disease

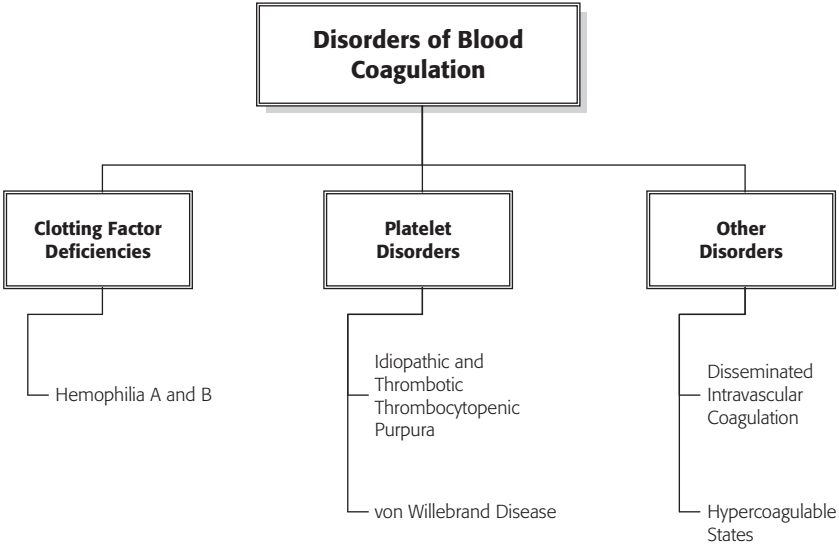
LYMPHOCYTES

B Cell

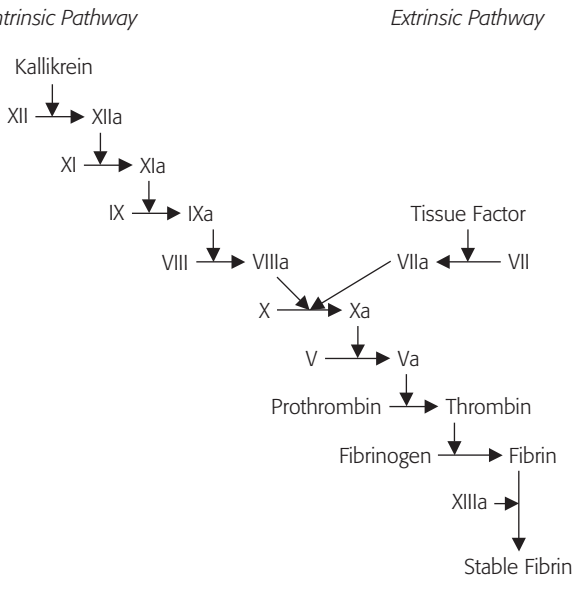
- *Development:* develops from lymphoblast in bone marrow; matures in bone marrow
- *Structure:* small cell with large, darkly staining nucleus
- *Function:* mediates humoral immune response; differentiates into antibody-producing plasma cells; can function as antigen-presenting cell via MHC II

T Cell

- *Development:* develops from lymphoblast in bone marrow; matures in thymus
- *Structure:* small cell with large, darkly staining nucleus
- *Function:* mediates cellular immune response; differentiates into cytotoxic T cells (MHC I, CD8), helper T cells (MHC II, CD4), and suppressor T cells


Disorders of Blood Coagulation
Clotting Factor Deficiencies
Platelet Disorders
Other Disorders
Hemophilia A and B
Idiopathic and Thrombotic Thrombocytopenic Purpura
von Willebrand Disease
Disseminated Intravascular Coagulation
Hypercoagulable States

COAGULATION CASCADE



PLATELETS

- *Development:* derived from megakaryocytes in the bone marrow
- *Function:* involved in thrombogenesis; forms platelet plugs via adhesion and aggregation reactions; activates the coagulation cascade

A 26-year-old pregnant woman presents to your office for a checkup. She states that her pregnancy has been proceeding smoothly, although she has been feeling more tired than she expected. Her physical examination is largely unremarkable except for marked pallor. You order serum studies and find that she has decreased hematocrit, decreased ferritin, and increased total iron-binding capacity. Her peripheral blood smear shows red blood cells that are both microcytic and hypochromic. You reassure her that these findings are most likely associated with her pregnancy status and recommend iron supplements.

Iron Deficiency Anemia

Etiology	**Chronic blood loss,** most often caused by **gastrointestinal bleeding** or menorrhagia; dietary deficiency (rare); malabsorption; pregnancy
Pathology	*Peripheral blood smear:* **Hypochromic microcytic** erythrocytes
Clinical Manifestations	**Fatigue, pallor,** and dyspnea during exercise *Lab findings:* Decreased hematocrit, **decreased serum iron, decreased serum ferritin, increased TIBC**, decreased Fe/TIBC ratio (< 15%)
Treatment	Iron supplementation; identification of source of occult blood loss
Notes	**Plummer-Vinson syndrome** is a disease in which patients present with iron deficiency anemia, esophageal webs, and glossitis. It is associated with an increased risk for developing esophageal cancer. **Sideroblastic anemia** is the result of defective heme biosynthesis within erythrocyte precursor cells. It can be caused by hereditary enzymatic defects or acquired defects (ie, alcohol or lead, MDS). Laboratory studies reveal increased iron and ferritin levels, but a normal TIBC. Ringed sideroblasts are present in the bone marrow. Treatment is directed at underlying cause as well as supportive with blood transfusions.

A 46-year-old man presents to your office complaining of weakness and a “pins and needles” feeling in his extremities. You note that he is ataxic and has decreased vibration and position sense in both his arms and legs. Upon further examination, you also observe that his tongue is red and enlarged. When laboratory tests reveal a positive Schilling test and a macrocytic anemia, you question the patient’s diet habits, drinking habits, and history of abdominal surgery.

Megaloblastic Anemias

Etiology

Vitamin B_{12} deficiency anemia (pernicious anemia): Autoimmune gastritis (results in the **failure to produce intrinsic factor);** malabsorption or vegetarian diet; gastric resection or resection of the ileum

Folate deficiency anemia: Malabsorption or dietary deficiency (often seen in alcoholics); pregnancy; pharmacologic agents (methotrexate, sulfa drugs, phenytoin, AZT)

Pathology

Vitamin B_{12} deficiency: Demyelination of the posterior and lateral columns of the spinal cord. *Peripheral blood smear:* pancytopenia; **hypersegmented neutrophils; macrocytic erythrocytes**

Folate deficiency: *Peripheral blood smear:* pancytopenia; **hypersegmented neutrophils; macrocytic erythrocytes**

Clinical Manifestations

Vitamin B_{12} deficiency: Neurologic abnormalities (ataxia, impaired proprioception, and vibratory sensation); glossitis; symptoms of autoimmune gastritis. *Lab findings:* Decreased Hct, **decreased serum vitamin B_{12}, anti-intrinsic factor antibodies, abnormal Schilling test** (tests for decreased absorption of oral vitamin B_{12}).

Folate deficiency: Glossitis and diarrhea. *Lab findings:* **Decreased Hct, decreased red blood cell folate levels.**

Treatment

Vitamin B_{12} deficiency: Vitamin B_{12} supplementation; intrinsic factor supplementation if anemia caused by autoimmune gastritis

Folate deficiency: Folic acid supplementation

Notes

A 7-year-old girl is referred to your hematology practice by her pediatrician after several abnormal blood tests, which include an increased mean corpuscular hemoglobin concentration and increased red blood cell osmotic fragility. You discover that one of the child's parents suffers from a genetic blood disorder and you begin to suspect that the child will most likely have to undergo surgery to treat her disorder.

Hereditary Spherocytosis

Etiology	**Autosomal dominant** condition that causes a defect in an erythrocytic membrane protein (usually **spectrin or ankyrin**)
Pathology	*Peripheral blood smear:* **Spherocytes** (sphere-shaped erythrocytes with no central pallor)
Clinical Manifestations	**Splenomegaly; hemolytic anemia,** which can lead to **jaundice** *Lab findings:* **Increased erythrocyte osmotic fragility, increased MCHC, reticulocytosis,** normal MCV, normal Hgb
Treatment	Splenectomy; folate supplementation
Notes	**Paroxysmal nocturnal hemoglobinuria** is a stem cell disorder characterized by increased sensitivity of RBCs to complement-mediated lysis. Patients present with episodic morning hemoglobinuria (increased urine hemosiderin), hemolytic anemia, and venous thrombosis. Diagnosis is confirmed by positive Ham (acid serum) test and flow cytometry.

A 35-year-old African American man comes to your office after noticing that his urine has become tea colored. He tells you that he has just returned from a trip to Africa where he had taken primaquine to guard against contracting malaria. Upon finding Heinz bodies on his peripheral blood smear, you suspect that his dark urine will likely resolve on its own shortly. You reassure the patient that his current condition is likely related to the primaquine and recommend no further testing.

Glucose-6-Phosphate Dehydrogenase Deficiency Anemia

Etiology and Epidemiology	**X-linked recessive** disorder resulting in a **deficiency of *glucose-6-phosphate dehydrogenase*** (G6PD) Affects 10%–15% of African Americans
Pathology and Pathophysiology	*Peripheral blood smear:* **Bite cells; Heinz bodies** (clumps of oxidized hemoglobin within the RBC) *Pathophysiology: G6PD* is an enzyme involved in the production of NADPH in the hexose monophosphate shunt pathway. NADPH is necessary for reduced glutathione, which protects hemoglobin from oxidative damage. When *G6PD* is deficient, reduced glutathione is absent. Without reduced glutathione, hemoglobin is oxidized and forms Heinz bodies in the RBC. Heinz bodies cause damage to the RBC membrane and these damaged RBCs are removed in the spleen, leading to anemia.
Clinical Manifestations	**Episodic hemolytic anemia** with hemoglobinuria occurring with ingestion of **oxidant drugs** (eg, primaquine, quinidine, quinine, sulfonamides, anti-TB drugs) or certain foods (ie, fava beans)
Treatment	Avoid oxidant drugs
Notes	Increased malarial resistance is noted with G6PD deficiency

An 8-year-old African American boy presents to the emergency department complaining of severe pain in both legs. The pain began after the boy attended a pool party and spent much of the day swimming. He reports that he has suffered from severe bouts of back and chest pain in the past owing to a pre-existing medical condition. Routine laboratory studies demonstrate a severe anemia. You place the child on oxygen, begin aggressive intravenous fluid hydration and call the blood bank to prepare for a blood transfusion.

Sickle Cell Anemia

Etiology and Epidemiology	**Autosomal recessive** disorder resulting in the production of **Hgb S.** Hgb S arises from a mutation (substitution of valine for glutamine) in the gene coding for the β-globin chain of Hgb 8% of African Americans carry the gene for Hgb S
Pathology and Pathophysiology	*Peripheral blood smear:* **Crescent-shaped RBCs; Howell-Jolly bodies;** reticulocytosis *Pathophysiology:* Hgb S polymerizes in hypoxic environments (as caused by infection, exercise, or dehydration), causing the RBC shape to become distorted and more susceptible to hemolysis
Clinical Manifestations	Chronic **hemolytic anemia,** which may lead to jaundice and leg ulcers; **vaso-occlusive crises** (Severe pain in the back or limbs because of microvasculature blockage by sickled cells.); **autosplenectomy** caused by repeated infarction; **aplastic crises,** usually provoked by B19 parvovirus infection; increased susceptibility to **infection** by encapsulated organisms (*Salmonella*) *Imaging:* "Crew cut" on skull x-ray because of marrow expansion
Treatment	Transfusions, fluid resuscitation, pain control, and oxygen during hemolytic and vaso-occlusive crises; plasma exchange for severe vaso-occlusive crises (ie, stroke, acute chest syndrome); hydroxyurea (increases Hgb F levels) and bone marrow transplant for severe disease
Notes	Patients with **hemoglobin C disease** (different mutation in β-chain of Hgb) and **sickle cell trait** (heterozygous for the Hgb S gene) tend to have milder versions of sickle cell anemia. The Hgb S gene provides resistance to *Plasmodium falciparum* malaria.

A 10-month-old boy from Greece presents with pallor and failure to thrive. During physical examination, you find that his spleen is enlarged and that he has an abnormal facial structure. You order a peripheral blood smear, which shows a microcytic, hypochromic anemia with target cells. You begin to suspect that this child may need blood transfusions for the rest of his life.

Thalassemias

Etiology and Epidemiology	**α-Thalassemias: Deletion of one or more of four genes coding the α-globin chain of Hgb** **β-Thalassemias:** Point **mutation in the β-globin gene** resulting in reduced or absent synthesis of β-globin chain of Hgb All thalassemias are relatively more common in people of **Mediterranean** ancestry
Pathology	**α-Thalassemias:** *Peripheral blood smear:* hypochromic, microcytic erythrocytes; **target cells** **β-Thalassemias:** *Peripheral blood smear:* hypochromic, microcytic erythrocytes; **target cells;** anisopoikilocytosis
Clinical Manifestations	**α-Thalassemias:** Four clinical variants: (1) α-thalassemia trait with 3–4 normal genes present—asymptomatic; (2) α-thalassemia trait with 2 normal genes present—mild anemia with decreased MCV; (3) **Hemoglobin H disease** with 1 normal gene present—**severe hemolytic anemia** with **decreased MCV (< 70),** presence of Hgb H (aggregation of excess β-chains), **splenomegaly;** (4) hydrops fetalis with 0 normal genes present—stillborn fetus **β-Thalassemias:** Two clinical variants: (1) β-thalassemia minor (heterozygosity)—mild anemia with decreased MCV; (2) **β-thalassemia major** (homozygosity)—**severe hemolytic anemia** with decreased MCV, presenting in infancy, **increased Hgb F, splenomegaly, bony abnormalities** (marrow expansion), **hemosiderosis** (owing to chronic transfusions), heart failure (owing to hemosiderosis)
Treatment	**α-Thalassemias:** No treatment needed for α-thalassemia trait; transfusions for hemoglobin H disease **β-Thalassemias:** No treatment needed for β-thalassemia minor; transfusion and/or bone marrow transplantation for β-thalassemia major
Notes	

A 30-year-old woman arrives at the emergency room complaining of fatigue and dark-colored urine. While obtaining the history of her present illness, you learn that she has been recovering from a recent bout of pneumonia, for which she had been treated appropriately by her primary care physician with a course of antibiotics. Physical examination reveals an enlarged spleen and slight scleral icterus. You obtain a blood sample and decide to order a direct Coomb test.

Autoimmune Hemolytic Anemias

Etiology	**Warm antibody autoimmune hemolytic anemia (WAIHA):** Caused by **IgG antibodies that react against the RBC membrane;** reason for formation of IgG antibodies may be idiopathic, or underlying disease such as SLE, CLL, or lymphomas **Cold agglutinin disease (CAD):** Caused by **IgM antibodies that react against the I antigen on RBCs** leading to phagocytosis of the RBC; reason for formation of IgM antibodies is often idiopathic, or may be a result of Waldenstrom macroglobulinemia, mononucleosis, or *Mycoplasma pneumoniae* infection Besides WAIHA and CAD, autoimmune hemolytic anemia can also be induced by pharmacologic agents (sulfa drugs, quinidine, rifampin)
Pathology	**WAIHA:** *Peripheral blood smear:* **spherocytes** (sphere-shaped erythrocytes with no central pallor); reticulocytosis **CAD:** *Peripheral blood smear:* **spherocytes** (sphere-shaped erythrocytes with no central pallor); reticulocytosis
Clinical Manifestations	**WAIHA:** Severe **hemolytic anemia,** which may lead to jaundice; splenomegaly. *Lab findings:* **Positive direct Coomb test,** decreased Hct. **CAD:** Mild **hemolytic anemia** (which may lead to jaundice) upon exposure to cold. *Lab findings:* **Positive cold agglutinin test.**
Treatment	**WAIHA:** Treat underlying disease; steroids and/or splenectomy **CAD:** Avoid cold environments
Notes	The direct Coomb test checks for the presence of antibodies on the surface of RBCs. The indirect Coomb test assesses for the presence of free antibody in the patient's serum.

A 28-year-old woman presents to the hospital in labor with her second child. As you prepare for the delivery, you discover that this woman had pregnancy complications associated with tearing of the placenta during the delivery of her first child. The mother and first child had been blood typed for Rh antigen during their stay at the hospital and records show that the mother is D-negative and the first child was D-positive. Concerned, you decide to administer anti-D IgG antiserum to the mother during her delivery to prevent the possibility of a serious hematologic complication for the second child.

Erythroblastosis Fetalis

Etiology	ABO incompatibility or **Rh antigen incompatibility** (usually **fetal D** antigen) between mother and fetus
Pathology and Pathophysiology	*Peripheral blood smear:* Erythroblasts; reticulocytosis *Pathophysiology:* **Maternal alloimmunization** to fetal red blood cell antigens (usually caused by exposure to fetal Rh antigens during prior pregnancy) results in maternal antibodies reacting against fetal RBCs
Clinical Manifestations	Severe **fetal hemolytic anemia;** extramedullary hematopoiesis; increased indirect bilirubin, resulting in jaundice and **kernicterus**; severe cases may result in **fetal heart failure** with generalized edema or in a stillbirth
Treatment	Transfusion Preventive measures include giving **anti-D IgG** to D-negative mothers during delivery of a D-positive child
Notes	

A 15-year-old girl presents to the emergency department with a petechial rash, bleeding of the oral mucosa, fatigue, and a history of recurrent sinus infections over the past 2 months. She does remember having had a bad flu-like virus about 3 months ago that caused her to miss 4 days of school. There is no hepatosplenomegaly on examination. Laboratory tests reveal anemia, neutropenia, and thrombocytopenia. There are no abnormal cell types seen on peripheral blood smear. You decide to admit the patient to the hospital and you schedule a bone marrow biopsy.

Aplastic Anemia

Etiology	Idiopathic; radiation, **benzene,** or **drugs** (chloramphenicol, alkylating agents); **idiopathic** autoimmune dysfunction of cytotoxic T cells; viral infection (parvovirus B19, EBV, HIV, hepatitis C); auto-immune disorders (ie, SLE)
Pathology	*Bone marrow:* **Hypocellular** and demonstrating fatty change with no hematopoietic cells *Peripheral blood smear:* **Pancytopenia**
Clinical Manifestations	Anemia presenting with **fatigue,** malaise, and **pallor;** neutropenia presenting with **infections;** thrombocytopenia presenting with **mucosal bleeding,** purpura, or **petechiae;** no hepatosplenomegaly
Treatment	Transfusion; administration of G-CSF or GM-CSF; allogenic bone marrow transplant; cessation of causative drug; immunosuppression with cyclosporine

Notes

A 57-year-old woman with a history of rheumatoid arthritis presents to your office complaining of fatigue upon exertion. You note that she is pale and decide to send her for serum studies. Laboratory results reveal an anemia as well as low serum iron levels, a low TIBC, and mildly increased serum ferritin levels. You tell the patient your diagnosis and begin to discuss whether treatment is necessary.

Anemia of Chronic Inflammation

Etiology	Secondary to **chronic systemic disorders,** including rheumatoid arthritis, chronic infection (ie, HIV), or malignancy
Pathology and Pathophysiology	*Peripheral blood smear:* **Normochromic, normocytic** erythrocytes *Pathophysiology*: Increased cytokines and hepcidin in setting of inflammatory state leads to impaired iron utilization by bone marrow with resulting decreased erythropoiesis
Clinical Manifestations	Fatigue and pallor associated with **anemia** *Lab findings:* Mildly decreased Hct, **low serum iron, low TIBC, normal to increased serum ferritin** (increased storage iron in marrow macrophages)
Treatment	Treat underlying disease; synthetic erythropoietin or blood transfusions if severe
Notes	

A 6-year-old boy presents to your office complaining of fatigue, fever, and a history of recurrent epistaxis (nose bleeds) and urinary tract infections. He has an enlarged liver and spleen and a petechial rash over his entire body. Concerned, you send him for some blood tests, which demonstrate pancytopenia with the presence of multiple blast forms. You fear that a bone marrow biopsy may demonstrate cells that would stain positive for TDT and CALLA.

Acute Lymphoblastic Leukemia (ALL)

Etiology and Epidemiology	Risk factors include prior exposure to radiation and chemotherapy Occurs most often in **children** with a median peak age of 10, but may also occur in the elderly
Pathology	ALL can be classified as either T cell or early B cell. Lymphoblastic surface antigens indicate the origin of the leukemia. B-cell antigens include **CALLA** (CD10), CD19, and CD20. T-cell antigens include CD2, CD5, and CD7. *Terminal deoxynucleotidyl transferase* **(TDT)** is a marker of immature T and B lymphocytes and is present in 95% of cases. *Bone marrow:* **Hypercellular;** composed mostly of **lymphoblasts;** distorted architecture of marrow *Peripheral blood smear:* **Pancytopenia** with lymphocytosis (excess **lymphoblasts**)
Clinical Manifestations	**Fatigue;** infections; **mucosal bleeding;** lymphadenopathy; hepatosplenomegaly; **bone pain;** cranial neuropathies
Treatment and Prognosis	Chemotherapy or bone marrow transplant, Very responsive to therapy with a good prognosis
Notes	ALL is the most common childhood cancer. It also accounts for 80% of all childhood leukemias.

A 52-year-old woman presents to your clinic complaining of a 2-week history of low-grade fever and weakness. Further evaluation reveals that she has suffered from various infections over the past 3 months. Upon physical examination, you note that she is pale with a petechial rash and that she has an enlarged spleen and liver. After a peripheral blood smear demonstrates pancytopenia with multiple myeloblasts, you immediately refer this patient to a hematologist/oncologist.

Acute Myelogenous Leukemia (AML)

Etiology and Epidemiology	Risk factors include Down syndrome and exposure to ionizing radiation, benzene, or chemotherapy Associated with chromosomal translocations: **M3-t(15;17),** M2-t(8;21) Occurs most frequently in **middle-aged adults**
Pathology	There are **8 subgroups (M0-M7),** each associated with a specific neoplastic myeloid lineage (myelocyte, monocyte, megakaryocyte, erythrocyte) and a level of maturation *Bone marrow:* **Hypercellular** with distorted architecture; **myeloblasts** specific to the subtype; **Auer rods** (cytoplasmic granules) especially with M3 (acute promyelocytic leukemia) *Peripheral blood smear:* **Pancytopenia** with **myeloblasts**
Clinical Manifestations	**Fatigue; infection; bleeding** (menorrhagia, nose bleeds); lymphadenopathy; hepatosplenomegaly; stroke caused by leukostasis (elevated blast count leads to occluded microcirculation)
Treatment and Prognosis	Chemotherapy or bone marrow transplant; **all-trans retinoic acid for M3** with t(15;17) Prognosis fair: 60% remission, but only 25% of these patients remain disease free for 5 years
Notes	

A 55-year-old man presents to your office complaining of a feeling of heaviness in his abdomen. He has had several infections over the past 6 months. Physical examination demonstrates a massively enlarged spleen and a peripheral blood smear reveals abnormal cells with filamentous projections. As you refer this patient to a hematologist/oncologist, you reassure him that his disease is very sensitive to treatment.

Hairy Cell Leukemia

Etiology and Epidemiology	Etiology unknown Occurs mostly in **middle-aged men**
Pathology	*Bone marrow:* Interstitial infiltrate of **hairy cells** (B cells with hairlike projections that stain positive for **TRAP**) *Peripheral blood smear:* **Pancytopenia** with hairy cells
Clinical Manifestations	Massive **splenomegaly;** hepatomegaly; **infections**
Treatment and Prognosis	Very sensitive to chemotherapy and other agents (2-chlorodeoxyadenosine)
Notes	Other peripheral T-cell leukemias/lymphomas include the **cutaneous T-cell lymphoid neoplasms** (mycosis fungoides and Sézary syndrome), which are characterized by neoplastic CD4 T cells with cerebriform nuclei, and **adult T-cell leukemia/lymphoma,** which is associated with HTLV-1 infection.

A 67-year-old man presents to your office for his annual checkup. You learn that he has been rather tired as of late and has had several nose bleeds over the past 6 months. Physical examination reveals shotty lymphadenopathy and mild hepatosplenomegaly. A complete blood count reveals an extremely high white blood cell count. You order a peripheral blood smear, which demonstrates multiple smudge cells, helping you to make a diagnosis.

Chronic Lymphocytic Leukemia (CLL)

Etiology and Epidemiology	Associated with chromosomal abnormalities (trisomy 12, deletions of 13q, deletions of 11q) Most often occurs insidiously in **men over the age of 60**
Pathology	*Bone marrow:* Infiltration with **small lymphocytic cells** resembling normal mature **B lymphocytes** (they express **CD5,** which is normally seen in T lymphocytes) *Peripheral blood smear:* **Smudge cells** (leukemic cells are sensitive to mechanical disruption occurring during slide preparation); lymphocytosis; normochromic, normocytic erythrocytes
Clinical Manifestations	**Lymphadenopathy,** hepatosplenomegaly, mucosal bleeding, and fatigue May have few symptoms (indolent course) Complications include warm **AIHA,** thrombocytopenia, and **hypogammaglobulinemia,** which lead to infections
Treatment and Prognosis	Chemotherapy to relieve symptoms, but **cure is rare** Mean survival is 3–25 years after diagnosis depending on cytogenetic status
Notes	CLL is very similar to SLL (small lymphocytic lymphoma)

A 44-year-old man presents to your clinic complaining of severe fatigue. Physical examination is relatively unremarkable except for an enlarged spleen. You send him to the laboratory for blood tests, which reveal multiple immature granulocytes on peripheral blood smear, a high WBC count, and low *leukocyte alkaline phosphatase* activity. Based on these test results, you begin to suspect that he may have a chromosomal abnormality.

Chronic Myelogenous Leukemia (CML)

Etiology and Epidemiology	Associated with the **Philadelphia chromosome t(9;22),** which forms a hybrid gene (***bcr-abl***) that codes for a protein with tyrosine kinase activity Occurs mostly in **middle-aged people**
Pathology	*Bone marrow:* Hypercellular; **increased myeloid precursor cells** *Peripheral blood smear:* Leukocytosis with a mixture of mature and immature myeloid cells
Clinical Manifestations	Presents with low-grade fever, **fatigue,** night sweats, and **splenomegaly** *Lab findings:* **Leukocytosis** (neutrophils and metamyelocytes)**, decreased LAP,** increased serum B_{12}, hyperuricemia
Treatment and Prognosis	Chemotherapy (hydroxyurea, imatinib [a tyrosine kinase inhibitor]) or bone marrow transplantation Death usually occurs because of transformation into AML **(blast crisis)**
Notes	CML is considered a **myeloproliferative disorder** along with polycythemia vera, essential thrombocythemia, and myelofibrosis.

A 54-year-old overweight man presents to your office complaining of headache and worsening vision over the last month. His past medical history includes hypertension and a recent hospital admission for deep vein thrombosis. He has no history of COPD, smoking, renal disease, or endocrine abnormalities. Physical examination demonstrates a blood pressure of 130/80, but is otherwise unremarkable. Blood tests reveal an increased hematocrit and increased RBC mass. To confirm your suspicions, you decide to order a test to determine serum erythropoietin levels.

Polycythemia Vera

Etiology	Myeloproliferative disorder of unknown etiology Occurs most often in middle-aged, obese, hypertensive men
Pathology	*Bone marrow:* **Hypercellular** with marked **increase in erythroid precursor cells;** increase in other hematopoietic elements (megakaryocytes, myelocytes) also present
Clinical Manifestations	**Splenomegaly;** pruritus; symptoms associated with hyperviscosity (headache, blurry vision); **thrombosis; bleeding** *Lab findings:* **Increased Hct, increased RBC mass, decreased erythropoietin levels,** increased WBCs, increased platelets, increased LAP, increased serum vitamin B_{12} levels, hyperuricemia
Treatment	Phlebotomy; aspirin; hydroxyurea if thrombosis occurs
Notes	Polycythemia vera is considered a **myeloproliferative disorder** along with CML, essential thrombocythemia, and myelofibrosis. **Essential thrombocythemia** is characterized by **thrombocytosis** and megakaryocytosis and presents with bleeding and thrombosis. **Secondary polycythemia** refers to increased RBC mass owing to **increased erythropoietin** production caused by chronic hypoxia, renal disease, or Cushing syndrome.

A 51-year-old man presents to the clinic with a chief complaint of increasing fatigue over the past 8 months. He states that he used to be very active, but finds that he tires now from walking up the stairs in his house. Blood tests demonstrate a low hematocrit and a peripheral blood smear reveals teardrop-shaped erythrocytes, large platelets, and granulocytic precursor cells. You suspect that he may also have extensive extramedullary hematopoiesis in his liver and spleen and fear that he may eventually have to undergo a bone marrow transplant.

Myelofibrosis with Myeloid Metaplasia

Etiology	**Increased secretion of platelet-derived growth factor (PDGF)** and transforming growth factor-β (TGF-β) results in **fibroblastic proliferation** in the bone marrow
Pathology	*Bone marrow:* **Replacement of bone marrow cavity with fibrous tissue;** loss of hematopoietic precursor cells except for megakaryocytes (which are actually increased) *Liver and Spleen:* **Extramedullary hematopoiesis** (owing to loss of bone marrow) *Peripheral blood smear:* **Teardrop-shaped erythrocytes;** granulocyte precursor cells; nucleated RBCs; thrombocytosis with abnormal-looking platelets
Clinical Manifestations	**Anemia** presenting with fatigue and pallor; massive **splenomegaly** *Lab findings:* **Decreased Hct**
Treatment	Bone marrow transplant; supportive care with transfusions
Notes	

A 22-year-old man presents to your office complaining of a painless lump in his neck. Upon further questioning, you discover that he has had a low-grade fever and drenching night sweats for the past 2 months. He also has lost 14 pounds over the past 8 weeks. Physical examination reveals unilateral cervical lymphadenopathy and splenomegaly. A lymph node biopsy reveals large multinucleated cells with prominent nucleoli resembling owl's eyes. You immediately refer the patient to a hematologist/oncologist.

Hodgkin Lymphoma

Etiology and Epidemiology	Etiology unknown, but EBV infection has been implicated Classic presentation is in a **20-year-old man,** although Hodgkin actually has a bimodal age distribution of patients with a peak between 20–30 and a peak over age 50
Pathology	*Lymph node:* **Reed-Sternberg cell** (**multinucleated giant cell** with eosinophilic nucleoli resembling **owl's eyes,** believed to be of CD 30+ and CD 15+ B-cell origin) **Four histologic variants: (1) Lymphocyte predominance:** many lymphocytes, few Reed-Sternberg cells; **(2) Nodular sclerosis:** fibrous bands, variants of Reed-Sternberg cells called lacunar cells; **(3) Mixed cellularity:** eosinophils, plasma cells, Reed-Sternberg cells, fibrosis; **(4) Lymphocyte depletion:** few lymphocytes, many Reed-Sternberg cells, necrosis
Clinical Manifestations	**Painless lymphadenopathy** usually in the neck (localized, single group of nodes); pruritus; splenomegaly Constitutional symptoms (**B symptoms**): Low-grade fever, night sweats, weight loss
Treatment and Prognosis	Radiation and chemotherapy **Good prognosis** (80% cure) associated with nondisseminated disease, absence of B symptoms, and certain histologic types (lymphocyte predominance and nodular sclerosis), although patients with Hodgkin lymphoma are at risk for **second malignancies** (acute leukemia, breast cancer)
Notes	Hodgkin lymphoma tends to spread to **contiguous lymph nodes.** The Nodular Sclerosis histologic variant of Hodgkin lymphoma is more commonly seen in women.

A 57-year-old man presents to your office after noticing a large painless lump in his neck. Upon questioning, he tells you that he has been suffering from a low-grade fever over the past 3 months. He has also lost 10 pounds during that time. Physical examination reveals painless cervical and inguinal lymphadenopathy and hepatosplenomegaly. Blood tests reveal a mild anemia as well as elevated LDH levels. You decide to send him for a lymph node biopsy.

Non-Hodgkin Lymphoma (NHL)

Etiology and Epidemiology	**Chromosomal translocations: Burkitt lymphoma: t(8;14),** results in **overexpression of c-*myc*; follicular lymphoma: t(14;18),** results in **activation of *bcl-2*,** most common **Viral infection: HIV, EBV** (EBV associated with **Burkitt lymphoma** of the jaw) Median age at diagnosis is 65; more common in males
Pathology	*Lymph node:* **(1) Follicular:** proliferation of **cleaved cells in nodular pattern; (2) Burkitt: starry-sky** appearance, noncleaved cells; **(3) Small lymphocytic:** widespread effacement of lymph node architecture by small mature lymphocytes, related to **CLL** (also positive for CD5 marker); **(4) Diffuse large B cell:** large cells with large, round nucleus; **(5)** other variants include mantle cell, marginal cell, and MALT lymphoma
Clinical Manifestations	**Hepatosplenomegaly; painless lymphadenopathy;** fewer **B symptoms** than Hodgkin lymphoma *Lab findings:* **Increased LDH** (used as prognostic marker), no hypergammaglobulinemia
Treatment and Prognosis	Chemotherapy and radiation; bone marrow transplantation for relapsing disease Median survival is 6–8 years; prognosis worse for the elderly, those with disseminated disease and those with aggressive forms
Notes	NHL does not spread contiguously. EBV infection is also associated with an increased risk for nasopharyngeal carcinoma.

A 69-year-old man presents to the emergency department complaining of pain in his neck and back. Upon directed history, he also reveals that he has been extremely tired and has suffered from two urinary tract infections over the past 4 months. An x-ray of his back reveals fractures in the L2 and L3 vertebrae as well as punched-out lytic bone lesions in the posterior skull. Laboratory studies reveal a mild anemia as well as an elevated BUN and creatinine. You decide to admit him to the hematology/oncology service for further evaluation.

Multiple Myeloma

Etiology and Epidemiology	Tumor cell arises from proliferation of **monoclonal plasma cells,** which produce **IgG** Most common in people over the age of 60
Pathology	*Bone marrow:* Neoplastic plasma cells with **fried egg** appearance derived from B lymphocytes *Peripheral blood smear:* **Rouleaux formation** of erythrocytes *Long bones:* **Lytic lesions** (produced by osteoclast-activating factor secreted by neoplastic cells)
Clinical Manifestations	**Bone pain** and fractures; renal insufficiency; recurrent infections; primary amyloidosis *Imaging:* **Punched-out lytic lesions** on radiographs *Lab findings:* Monoclonal immunoglobulin spike **(M protein)** on serum protein electrophoresis, **Bence-Jones protein** (IgG light chains) **in urine, anemia,** increased ESR, **hypercalcemia,** hyperglobulinemia (IgG), azotemia
Treatment	Chemotherapy and autologous stem cell transplantation
Notes	**Monoclonal gammopathy of undetermined significance (MGUS)** is an **asymptomatic** disease characterized by a **monoclonal M protein spike < 3 g/dL** and is associated with no Bence–Jones proteinuria, no lytic bone lesions, and no renal insufficiency. Patients with MGUS should be closely monitored since they are at higher risk to develop multiple myeloma or another lymphoproliferative disease.

A 72-year-old man presents to your office complaining of fatigue, blurry vision, headaches, and weight loss over the past 6 months. Physical examination reveals hepatosplenomegaly, generalized lymphadenopathy, and retinal vascular dilatation. An abdominal x-ray and urinalysis are normal, although blood tests demonstrate anemia and increased serum viscosity. You decide to send this patient for a bone marrow biopsy.

Waldenstrom Macroglobulinemia

Etiology and Epidemiology	Hyperviscosity syndrome most often associated with **IgM-producing plasmacytic lymphocytes** (hybrids of plasma cells and B lymphocytes) Most frequently occurs in men over the age of 50
Pathology	*Bone marrow:* Mixture of **small lymphoid cells** showing differing degrees of plasma cell differentiation; **Dutcher bodies** (eosinophilic inclusion bodies in nucleus); **Russell bodies** (eosinophilic inclusion bodies in cytoplasm) *Peripheral blood smear:* **Rouleaux formation** of erythrocytes
Clinical Manifestations	Fatigue; weakness; weight loss; **anemia; hepatosplenomegaly;** lymphadenopathy Complications include **hyperviscosity syndrome** from circulating IgM (blurry vision, neurologic abnormalities, heart failure), bleeding, and **peripheral neuropathy** (from IgM deposition) *Lab findings:* Monoclonal **IgM spike** seen on serum protein electrophoresis, **increased serum viscosity,** decreased Hct
Treatment	Chemotherapy; periodic plasmapheresis
Notes	

A 32-year-old woman is brought to the emergency room by a friend because of the onset of confusion and disorientation over the past day. Upon physical examination, you discover a generalized petechial rash, fever, and bilateral positive Babinski sign. You immediately order several blood tests, which show an elevated LDH, increased indirect bilirubin, thrombocytopenia, and anemia. Examination of a peripheral blood smear yields multiple reticulocytes and schistocytes. You admit the patient to the intensive care unit and you prepare for emergency plasmapheresis.

Idiopathic and Thrombotic Thrombocytopenic Purpura

Etiology and Epidemiology

Idiopathic thrombocytopenic purpura (ITP): Antiplatelet IgG antibodies coat platelets, leading to phagocytosis by splenic macrophages. Occurs in children as acute self-limited reaction to viral infection, or can occur in adults as chronic disease.

Thrombotic thrombocytopenic purpura (TTP): Etiology unknown although viral infection, drugs, and autoimmune diseases have been implicated. Occurs most commonly in women between age 20 and 50.

Pathology

ITP: *Bone marrow:* occasionally there are **increased megakaryocytes;** *Peripheral blood smear:* **thrombocytopenia** with slightly enlarged platelets

TTP: Widespread hyaline **microthrombi in the microvasculature** with no inflammation; *Peripheral blood smear:* **thrombocytopenia; schistocytes;** reticulocytosis

Clinical Manifestations

ITP: Mucous membrane bleeding; epistaxis; petechiae; no splenomegaly. *Lab findings:* Decreased platelets, **antiplatelet antibodies,** increased bleeding time.

TTP: Neurologic deficits; fever; renal insufficiency; petechiae; **microangiopathic hemolytic anemia.** *Lab findings:* **Decreased platelets,** increased LDH and indirect bilirubin, azotemia, increased bleeding time, decreased Hct.

Treatment

ITP: Prednisone; splenectomy

TTP: Plasma exchange; steroids

Notes

An 8-year-old boy presents to the emergency department with a swollen right knee. He denies a history of trauma to the knee. Physical examination reveals a warm, swollen, erythematous joint with a significant effusion. Upon taking a family history, you learn that two of the boy's maternal uncles suffer from a bleeding disorder. Laboratory tests reveal a prolonged PTT, a normal PT, and a normal bleeding time. To provide the proper treatment, you immediately order a clotting factor assay.

Hemophilias A and B

Etiology	**Hemophilia A: X-linked recessive** disorder resulting in a **deficiency of factor VIII** **Hemophilia B: X-linked recessive** disorder resulting in a **deficiency of factor IX**
Pathophysiology	Lack of clotting factor VIII or IX results in an **ineffective intrinsic pathway** of coagulation
Clinical Manifestations	**Bleeding** into muscles and joints (hemarthrosis); easy bruising; GI bleeding *Lab findings:* **Prolonged PTT, normal PT, normal bleeding time,** normal thrombin time
Treatment	Replace deficient clotting factor
Notes	**Vitamin K deficiency** is most commonly caused by liver disease, malabsorption, or warfarin administration. It results in a deficiency of factors II, VII, IX, and X and laboratory studies demonstrate a prolonged PT.

A 7-year-old girl is brought to the emergency department because of uncontrollable bleeding following a deep laceration to her palm. Further questioning reveals that she has been taking aspirin for a viral illness, that she has a history of prolonged bleeding, and that her brother and mother both suffer from a bleeding disorder. Laboratory tests reveal a prolonged bleeding time, a prolonged PTT, and a normal PT. You suspect that this girl and her family are affected with the most common hereditary bleeding disorder and advise them all to avoid aspirin.

von Willebrand Disease

Etiology and Epidemiology	**Autosomal dominant** disease marked by a **deficiency in von Willebrand factor (vWF).** Acquired von Willebrand disease is associated with malignancy and autoimmune diseases and is related to decreased synthesis and increased clearance of vWF. von Willebrand disease is the **most common hereditary bleeding disorder** (affects 1% of all people)
Pathophysiology	Lack of vWF results in **impaired platelet adhesion** to the subendothelium during vascular injury, thereby resulting in deficient platelet plug formation. Because vWF also acts as a carrier protein for factor VIII, deficient vWF results in a **functional deficiency of factor VIII,** thereby impairing the intrinsic pathway of coagulation.
Clinical Manifestations	Mucosal bleeding *Lab findings:* **Prolonged PTT, prolonged bleeding time, normal PT,** normal thrombin time
Treatment	Avoid aspirin and other anticoagulants; desmopressin or factor VIII replacement if necessary
Notes	There are two bleeding disorders that result from **deficiencies in platelet aggregation:** (1) **Glanzmann thrombasthenia**, which results from a deficiency of glycoproteins IIb and IIIa, which are receptors for fibrinogen, and (2) **Bernard–Soulier disease**, which results from a deficiency of glycoprotein Ib, which serves as a receptor for vWF factor. Both disorders present with mucosal bleeding, a prolonged bleeding time, and normal PTT and PT.

A 33-year-old woman presents to your office because of a swollen, painful left calf. She denies any sort of recent trauma or fevers. She has no significant past medical history and her only medication is an oral contraceptive. Her family history is notable for the death of her mother at age 55 from a pulmonary embolism. During physical examination, you elicit a positive Homan sign with pain on dorsiflexion. Concerned, you order a Doppler ultrasound of the left lower extremity.

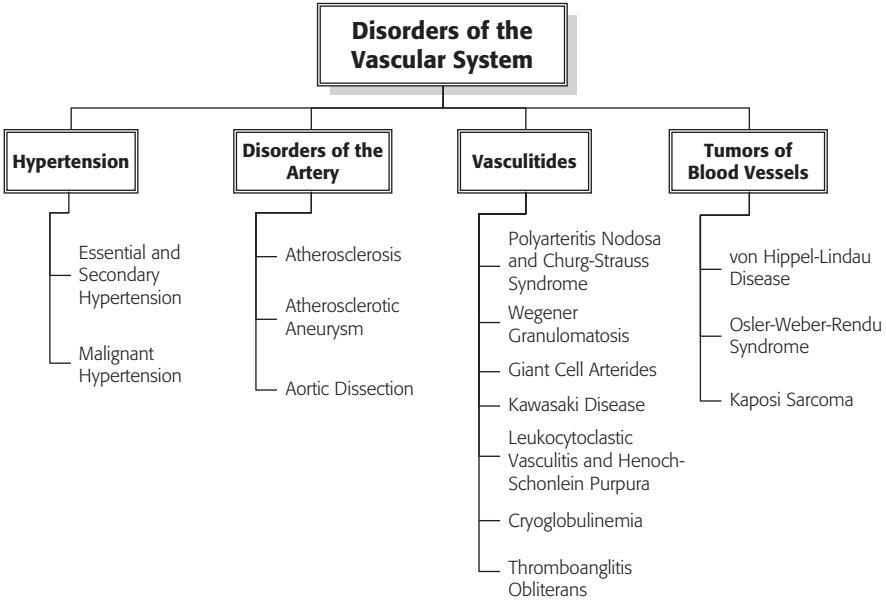
Hypercoagulable States

Etiology	Causes of inherited hypercoagulable states include **Factor V Leiden** (resistance to activated protein C), prothrombin mutation, protein C or S deficiency, antithrombin III deficiency, or antiphospholipid syndrome Causes of acquired hypercoaguable states include cancer, myeloproliferative disorders, pregnancy, nephrotic syndrome, or estrogens
Pathology	*Vein:* **Venous thrombus (dark red** with pale gray fibrin strands, firm and **attached to the vessel wall); venous inflammation**
Clinical Manifestations	**Symptoms of DVT** or **pulmonary embolism;** stroke; recurrent miscarriages *Lab findings:* **Increased D-dimer levels,** increased PTT levels in antiphospholipid syndrome
Treatment	**Anticoagulation** (heparin for short term, warfarin for long term)
Notes	**Virchow triad (endothelial injury, hypercoagulable state, venous stasis)** predisposes to the formation of a deep vein thrombosis.

A 28-year-old woman, who is at 33-week gestation, presents to the emergency department with heavy vaginal bleeding. Ultrasound evaluation reveals that she is suffering from abruptio placentae (premature separation of the placenta from the uterus wall). As she is being prepared for delivery, you notice that there is blood seeping from her IV and venipuncture sites and that she has a petechial rash. Concerned, you immediately order several blood tests, which reveal a prolonged PT, prolonged PTT, prolonged bleeding time, prolonged thrombin time, thrombocytopenia, and elevated D-dimer levels. You begin transfusing platelets and fresh frozen plasma in the hope of stabilizing this life-threatening complication.

Disseminated Intravascular Coagulation (DIC)

Etiology	Seen in connection with **obstetric complications** such as abruptio placentae or amniotic fluid embolus, malignancy, **sepsis,** trauma, acute pancreatitis, shock, and hemolytic transfusion reactions
Pathology and Pathophysiology	*Peripheral blood smear:* **Schistocytes; thrombocytopenia** *Pathophysiology:* Excess thrombin activity leads to **activation of the coagulation and fibrinolytic cascades** and microthrombi, which subsequently **leads to consumption of platelets, fibrin, and clotting factors,** and thereby leads to bleeding *Vasculature:* **Microthrombi** in microvasculature of multiple organs
Clinical Manifestations	**Bleeding and thrombosis** (manifested by bleeding from venipuncture sites, petechiae, and ischemia of the fingers and toes); microangiopathic hemolytic anemia *Lab findings:* **Prolonged PT and PTT, prolonged bleeding time and thrombin time, increased D-dimer levels, decreased fibrinogen, decreased platelets,** decreased Hct
Treatment	Platelet transfusion, fresh frozen plasma and cryoprecipitate transfusion to replenish depleted clotting factors and fibrinogen
Notes	Prolonged PT, PTT, bleeding time, and thrombin time also occur in **coagulopathy of liver disease.** This disorder is not associated with microthrombi and can be treated with vitamin K.


Disorders of the Vascular System
Hypertension
Essential and Secondary Hypertension
Malignant Hypertension
Disorders of the Artery
Atherosclerosis
Atherosclerotic Aneurysm
Aortic Dissection
Vasculitides
Polyarteritis Nodosa and Churg-Strauss Syndrome
Wegener Granulomatosis
Giant Cell Arterides
Kawasaki Disease
Leukocytoclastic Vasculitis and Henoch-Schonlein Purpura
Cryoglobulinemia
Thromboanglitis Obliterans
Tumors of Blood Vessels
von Hippel-Lindau Disease
Osler-Weber-Rendu Syndrome
Kaposi Sarcoma

Arteries

- Thick walled vessels under high pressure that carry the stressed volume.
- Divided into three types: (1) large, elastic arteries (eg, aorta); (2) medium-sized, muscular arteries comprising branches of aorta; and (3) small arteries within tissues and organs.
- Atherosclerosis affects largely elastic and muscular arteries.

Arterioles

- Smallest branches of the arteries.
- Principal sites of physiologic blood flow resistance.
- Site of the highest reduction in blood pressure and velocity.
- Hypertension affects primarily small muscular arteries and arterioles.

Capillaries

- Arise from arterioles and comprise the largest total cross-sectional area and surface area in the cardiovascular system.
- Lined by endothelial cells and supported by a thin basement membrane. Of the note, the media is absent.
- Slow flow, high surface area, and thin walls allow rapid exchange of materials between the blood and tissue.

Veins

- Large-caliber, thin-walled vessels under low pressure.
- Contain the highest proportion of blood in the cardiovascular system, and carry the unstressed volume.
- Have poor support and are predisposed to compression, dilatation, and invasion by tumors and inflammation.

A 45-year-old obese white man presents to the clinic for an annual checkup. He has no complaints other than occasional headaches. During the history, you find that he is a smoker and has a family history of heart disease. His physical examination is significant for mild obesity and a blood pressure of 160/100. You suggest lifestyle changes including weight loss, a low-salt diet, and smoking cessation, and you also prescribe hydrochlorothiazide to treat his condition.

Essential and Secondary Hypertension

Etiology and Epidemiology	**Primary (idiopathic) (90%):** Risk factors include old age, race, diabetes, smoking, obesity, and positive family history **Secondary (10%):** Caused by renal parenchymal disease, renovascular disease, Conn syndrome, Cushing syndrome, pheochromocytoma, OSA, and drug reactions (OCP, NSAIDS, steroids)
Pathology and Pathophysiology	*Microscopic:* Hyaline thickening of vessels; atherosclerosis *Pathophysiology*: Primary (essential) HTN has been associated with increased cardiac output and increased total peripheral resistance
Clinical Manifestations	Usually **asymptomatic;** can be associated with occasional headaches or palpitations Complications include CAD, MI, CVA, CHF, peripheral vascular disease, aortic dissection, retinopathy, and renal failure
Treatment	Reduce blood pressure to < 140/90 mm Hg with lifestyle changes and antihypertensive therapy; treat underlying causes of secondary hypertension **Lifestyle changes:** Weight loss, exercise, reduce salt intake, smoking cessation, and moderate alcohol intake **Pharmacologic agents:** ACE inhibitors, calcium antagonists, β-blockers, thiazide diuretics, α-blockers
Notes	**Hypertensive renal disease** can present with nephritic syndrome and is associated with overstimulation of the renin-angiotensin system.

A 30-year-old African American man presents with recent-onset headaches, blurred vision, and dyspnea. On physical examination, he appears very ill and has difficulty concentrating and answering your questions. You see cottonwool spots on a funduscopic examination, a displaced forceful heart beat, and a blood pressure reading of 190/130. You immediately place the patient on IV sodium nitroprusside treatment.

Malignant Hypertension

Etiology and Epidemiology	Results from an accelerated course of essential or secondary hypertension More common in young **African American men**
Pathology	*Arteriole:* **Hyperplastic arteriosclerosis** (concentric, laminated **onionskin thickening** of arterial walls accompanied by necrotizing arteriolitis [fibrinoid deposition in arteriole walls with necrosis and inflammation]) Can result in other pathologic conditions including LV hypertrophy and failure and **malignant nephrosclerosis** (ruptured glomerular capillaries causing flea-bitten kidney)
Clinical Manifestations	Presents with **headache,** altered mental status, blurred vision, and dyspnea Physical examination shows displaced forceful cardiac apex beat, presence of S4, **papilledema, retinal hemorrhages** and exudates, and **marked diastolic pressure increase (> 120 mm Hg)**
Treatment and Prognosis	Initial lowering of blood pressure with IV agents (Nipride, hydralazine, labetalol) followed by strict blood pressure control with oral agents Often can result in an early death
Notes	**Hyaline arteriosclerosis** is associated with essential HTN or diabetes and involves hyaline thickening or proliferative changes of small arteries and arterioles, especially in the kidney (benign nephrosclerosis).

A 40-year-old white man presents to your office complaining of sharp chest pains radiating to his shoulder during strenuous physical activities. On further questioning, he divulges that he has painful muscle cramps in his legs when running on the treadmill. Both his chest pains and leg cramps are relieved by rest. Taking a full history, you find that his father died of an MI in his early 50s and two paternal uncles experienced the same fate. On physical examination, you find yellow nodules under both eyelids. You send him for laboratory studies including triglyceride and cholesterol levels to confirm your diagnosis.

Atherosclerosis

Etiology	Risk factors include **smoking,** HTN, diabetes, **hypercholesterolemia** (increased LDL), positive family history, **old age, male gender, postmenopausal status in women,** hyperuricemia, and oral contraceptive use
Pathology	*Artery:* Progresses from **fatty streaks** (lipid-laden foam cell accumulations in intima) to proliferative plaques to complex atheromas *Atheroma:* Central core of cholesterol and foam cells (lipid-laden macrophages) covered by fibrous cap; atheromas may be complicated by overlying thrombus formation, ulceration, or calcification of plaque; usually present in elastic arteries and medium/large muscular arteries
Clinical Manifestations	Often asymptomatic; can present with **angina** or **claudication** (pain in muscles during exercise, relieved by rest) Complications include aneurysms, MI, stroke, bowel ischemia, renal artery ischemia, peripheral vascular occlusive disease, and emboli of overlying thrombus or of plaque itself
Treatment	Lipid-lowering agents (eg, HMG-CoA reductase inhibitor)
Notes	**Xanthomas** are yellow plaques or nodules of the skin. They are composed of lipid-laden macrophages and are associated with hypercholesterolemia.

A 55-year-old man presents to the emergency room with intense pain in the back, abdomen, and groin. He was brought by ambulance after feeling nauseated and suddenly fainting. On physical examination, he is pale, sweating profusely, and hypotensive. You also note a pulsatile mass in the mid-abdomen. As you begin to give the patient fluids and prepare him for emergency imaging, you call for a vascular surgery consult to evaluate this patient for surgery.

Atherosclerotic (Abdominal Aortic) Aneurysm

Etiology and Epidemiology	Associated with **atherosclerosis,** CAD, trauma, familial predisposition, and cystic medial necrosis Occurs more frequently in **men** over the age of 50
Pathology	*Artery:* Usually found in the **descending aorta** below the renal arteries; occurs in areas of **wall weakening** (atherosclerotic plaque can destroy media) or in localized dilatations of arteries and veins; saccular outpouching often filled with atherosclerotic plaque or thrombus
Clinical Manifestations	Usually asymptomatic until rupture; may present with pulsating, painless upper abdominal mass; if ruptured, will present with **severe tearing abdominal pain radiating to the back** and hypotension Complications include occlusion of renal, iliac, and/or mesenteric arteries with thrombus, emboli, or rupture *Imaging:* Double-barrel lumen of aorta
Treatment	Surgical repair if rapidly growing aneurysm of if > 5.5 cm; blood pressure control with β-blockers and ACE-inhibitors; smoking cessation; lipid-lowering treatment
Notes	**Syphilitic aneurysm** is associated with tertiary syphilis. The blood supply of the aorta (vasa vasorum) is disrupted, resulting in aneurysm of **ascending aorta** or aortic arch with a **tree-bark** gross appearance of aorta and aortic valve incompetence.

A 30-year-old man with Marfan syndrome presents to the emergency room with severe, sudden, tearing chest pain radiating to the abdomen and back. The pain has progressively shifted downward over the last several hours. On physical examination, he is found to have asymmetric pulses and a pericardial friction rub. ECG studies are normal and angiography shows an ascending aortic abnormality. You schedule the patient for immediate surgical repair.

Aortic Dissection

Etiology	Associated with **hypertension,** trauma, Marfan syndrome, Ehlers-Danlos syndrome, coarctation of the aorta, bicuspid aortic valve, and last trimester of pregnancy; there is no association with atherosclerosis
Pathology	*Gross:* Tear in aortic intima allowing formation of intramural hematoma; possible presence of **cystic medial necrosis** (lesion predisposing to aortic dissection characterized by separation of elastic and muscular elements of media)
Clinical Manifestations	Presents with **sudden, severe, tearing left chest pain,** often radiating through the back; **pain shifts downward** with time Complications include aortic rupture, causing hemopericardium, cardiac tamponade, and death
Treatment	Surgical repair if dissection involves ascending aorta or if there is significant branch artery involvement; strict heart rate and blood pressure control with β-blockers and ACE-inhibitors

Notes

A 45-year-old man presents to the clinic complaining of 1 month of diffuse abdominal pain with occasional nausea and vomiting. He also reports generalized malaise and a weight loss of 15 pounds over the last 4 months. Upon further history, you discover that he has hepatitis B. Physical examination is notable for palpable purpura. Serum studies show an elevated ESR and an increased WBC count. You suspect that a vessel biopsy would reveal necrotizing arteritis and you decide to start the patient on prednisone.

Polyarteritis Nodosa

Etiology and Epidemiology	Etiology unknown, but associated with **HBV** infection in 30% of patients Primarily affects **middle-aged men,** but can occur in any age group of both sexes
Pathology	*Gross:* Affects **small- or medium-sized muscular arteries,** especially at branch points of vessels of the kidney, heart, liver, or GI tract; lesions are of **different ages** *Microscopic:* **Transmural** inflammation of arterial wall with neutrophil, eosinophil, and mononuclear infiltrate; **fibrinoid necrosis** may be present
Clinical Manifestations	Fever**; weight loss**; malaise; **abdominal pain** with associated nausea and vomiting; **arthralgia;** renal failure; **peripheral neuropathy**; hypertension; cottonwool spots (retinal occlusion); myocarditis; pericarditis; palpable purpura *Lab findings:* **Elevated ESR,** leukocytosis
Treatment	Corticosteroids; azathioprine; cyclophosphamide; antiviral therapy for HBV related disease
Notes	**Churg-Strauss syndrome** is another necrotizing vasculitis affecting small and medium vessels. Clinically, it presents with the triad of pulmonary vasculature involvement, peripheral fluctuating eosinophilia, and late-onset asthma unresponsive to bronchodilators. Laboratory studies reveal a positive ANCA (c-ANCA or p-ANCA) and eosinophilia. It is treated with high-dose corticosteroids.

A 40-year-old man presents to the emergency room after coughing up blood. He has a history of chronic sinusitis and recurrent otitis media over the past decade. CXR reveals multiple nodules and multilocular, irregular cavities. Urinalysis demonstrates hematuria. When serum studies reveal a markedly elevated ESR and the presence of c-ANCA, you decide to start the patient on a combination of cyclophosphamide and prednisone.

Wegener Granulomatosis

Etiology and Epidemiology	Caused by an immunologic mechanism (perhaps hypersensitivity reaction) Tends to affect men between the ages of 30 and 60, but can occur at any age
Pathology	*Gross:* Vascular granulomatous lesions in the **upper respiratory tract, lungs,** and **kidney** *Microscopic:* **Necrotizing granulomas** with necrotic center surrounded by lymphocytes, macrophages, and giant cells in vascular walls; granulomatous vasculitis with inflammatory infiltrate surrounded by fibroplastic proliferation; rapidly progressive glomerulonephritis
Clinical Manifestations	Perforation of nasal septum; **chronic sinusitis;** otitis media; dyspnea; **hemoptysis; hematuria;** rash; myalgias; increased risk of DVTs Complications include renal failure (nephritic syndrome) and deafness *Imaging:* CXR shows large nodular densities *Lab findings:* **c-ANCA** positive, RBCs and/or RBC casts in urine
Treatment	Cyclophosphamide and prednisone for initial therapy; methotrexate as maintenance therapy
Notes	**Microscopic Polyangiitis** is a necrotizing small-vessel vasculitis that presents with glomerulonephritis and pulmonary involvement. Biopsy demonstrates a necrotizing pauci-immune inflammation of small vessels without granulomas. This disease is associated with a positive p-ANCA and is treated with cyclophosphamide and corticosteroids.

A 70-year-old white woman presents to the clinic complaining of severe unilateral headaches and transient blurry vision. Upon physical examination, you find that there is pain upon palpation of her temples. When laboratory tests reveal an elevated ESR, you initiate treatment with prednisone to prevent possible blindness. You also ask for an ophthalmological consult and you order a temporal artery biopsy, which you suspect will reveal granulomatous inflammation and the presence of giant cells.

Giant Cell Arteritides—Takayasu Arteritis and Temporal Arteritis

Etiology and Epidemiology	**Takayasu arteritis (Tak):** Etiology unknown, although immune mechanisms are suspected; mostly affects **young Asian women** **Temporal arteritis (Temp):** Etiology unknown, although T-cell–mediated injury has been suggested; usually affects **elderly women**
Pathology	**Tak:** *Gross:* disease of medium and large arteries resulting in **thickening of aortic arch** or proximal great vessels and thus vascular insufficiency. *Microscopic:* mononuclear infiltrate with perivascular cuffing of vasa vasorum in adventitia and media and **granulomatous changes** with giant cells. **Temp:** *Gross:* affects small- and medium-sized arteries, usually **branches of carotid artery** (especially temporal artery). *Microscopic:* **granulomatous inflammation** of media with mononuclear infiltrate; **giant cells.**
Clinical Manifestations	**Tak:** Fever; weak pulses in upper extremities **("pulseless disease");** arthralgias; syncope; skin nodules; night sweats; claudication; **visual and neurologic disturbances** **Temp:** Unilateral **throbbing headache;** tender nodules along temporal artery course; **jaw claudication** (pain when chewing); impaired vision (because of occlusion of ophthalmic artery); 50% of patients have systemic **polymyalgia rheumatica** (proximal muscle pain and morning stiffness, most commonly seen in elderly) *Lab findings:* Markedly **elevated ESR** (for both Tak and Temp)
Treatment	Corticosteroids
Notes	

A 6-year-old Japanese boy presents to the emergency room with high fever, malaise, and severe conjunctivitis. Physical examination is significant for congested conjunctiva, oral mucosa lesions, cervical lymphadenopathy, and erythema of the palms and soles of his feet. To prevent possible coronary aneurysm, you admit the child to the hospital and begin treatment with IV gamma globulin, but you reassure the mother that this condition usually resolves on its own.

Kawasaki Disease (Mucocutaneous Lymph Node Syndrome)

Etiology and Epidemiology	Etiology unknown, although defect in immune system regulation is suspected Usually affects **infants and young children**
Pathology	*Gross:* Affects **small- and medium-sized vessels** (including coronary arteries) *Microscopic:* Transmural inflammation and necrosis of vessel wall with inflammatory infiltrate
Clinical Manifestations	**Fever;** congested conjunctiva; **mucocutaneous lesions** (oral mucosa); cervical lymphadenitis (usually 1 neck node); edema of hands and feet; **erythema of palms and soles of feet** Complications include **coronary artery aneurysms,** which can rupture and lead to death
Treatment and Prognosis	Aspirin; IV gamma globulin (prevents coronary aneurysm) Disease is usually self-limited
Notes	

A 32-year-old male presents to your clinic complaining of arthralgias and palpable purpura on his lower extremities. He had been recovering from a recent bout of cellulitis, for which he had been taking amoxicillin. Laboratory studies demonstrate an elevated ESR as well as decreased complement levels. As you prepare the patient for a skin biopsy to confirm your suspicions, you inform him that you suspect that his cellulitis and antibiotics may be related to his current condition.

Leukocytoclastic (Hypersensitivity) Vasculitis

Etiology	Exact etiology unknown, but thought to be caused by immune complex deposition in small vessels precipitated by drug reactions, bacterial infections, tumor, or other antigens; may be component of other diseases (Henoch-Schönlein purpura, connective tissue disorders)
Pathology and Pathophysiology	*Pathophysiology:* Caused by type III hypersensitivity reaction *Gross:* Affects **small vessels** (arterioles, capillaries, venules) especially of **skin, lungs,** heart, GI tract, muscle, and **kidneys;** lesions of **same age** *Microscopic:* **Fibrinoid necrosis** of vascular media with neutrophil infiltration, which become fragmented (leukocytoclasia); no immune deposits
Clinical Manifestations	**Palpable purpura; hemoptysis; arthralgias; hematuria** and proteinuria; GI bleeding; myalgias *Lab findings:* Elevated ESR, decreased complement levels
Treatment	Withdrawal of offending agent; steroids
Notes	**Henoch-Schönlein purpura** is a vascular disorder affecting children and typically follows a viral URI or a streptococcal infection. It is histopathologically similar to leukocytoclastic vasculitis and is also associated with IgA nephropathy with mesangial IgA deposits. Clinically, it is manifest as palpable purpura on the arms, legs, and buttocks, colicky abdominal pain, arthralgias, and renal involvement, which varies from mild proteinuria to ESRD. It is treated supportively in mild cases or with steroids in severe cases with significant renal involvement.

A 52-year-old female presents to an urgent care clinic complaining of weakness and joint aches. Her past medical history is notable for hepatitis C infection. Review of systems reveals the presence of diffuse abdominal pain, dark urine, and peripheral neuropathy. Physical examination is notable for a lacy rash on bilateral calves as well as 1+ pitting edema. A urinalysis reveals the presence of hematuria and proteinuria. As you send off more laboratory studies to confirm your suspected diagnosis, you start the patient on immunosuppressive therapy with prednisone.

Cryoglobulinemia

Etiology and Epidemiology	Causes include **lymphoproliferative disorders** (multiple myeloma, CLL, NHL), **HCV infection**, autoimmune syndromes, infections (EBV, CMV), or idiopathic Tends to affect **middle-aged women**
Pathology	*Gross:* Affects **small vessels (**arterioles, capillaries, venules), especially of the skin and kidney *Microscopic:* Inflammation of the vascular wall with cryoglobulin immune deposits
Clinical Manifestations	Weakness; **livedo reticularis;** purpura; **arthralgias; glomerulonephritis with nephritic syndrome;** anemia; abdominal pain; peripheral neuropathy *Lab findings:* **Positive cryocrit, decreased C4 levels**
Treatment	Treat underlying disorder; steroids or other immunosuppressant agents for visceral organ involvement
Notes	

A 30-year-old man presents to the emergency room with a cold, pale left foot with absent pedal pulse. He complains of loss of feeling in his left foot after several months of painful bouts in the involved area. He has smoked two packs of cigarettes a day for the past 10 years. You order an arterial biopsy of the affected region, which demonstrates intimal proliferation and thrombi with inflammatory infiltrates. You explain to the patient that the condition is associated with his smoking and that the most effective treatment is smoking cessation.

Thromboangiitis Obliterans (Buerger Disease)

Etiology and Epidemiology	Etiology unknown, although there is a strong association with **smoking** Most frequent in **young men** between the ages of 25 and 50
Pathology	*Gross:* Segmental **vasculitis** of **small- and medium-sized peripheral arteries** (especially the tibial and radial arteries) and veins *Microscopic:* **Transmural inflammation** with acute and chronic inflammatory infiltrate; thrombosis of lumen with **microabscesses** surrounded by granulomatous inflammation
Clinical Manifestations	Intermittent claudication; superficial nodular phlebitis; Raynaud phenomenon; severe painful **ischemic attacks in extremities** leading to ulceration or even **gangrene**
Treatment	**Smoking cessation;** sympathectomy to prevent vasospasm
Notes	

A 20-year-old man presents to the clinic with a several-month history of headaches, ataxia, and deteriorating vision. Concerned about a CNS process, you order an emergency MRI of the head and find multiple cysts throughout the cerebellum and brainstem consistent with hemangioblastomas. You begin to suspect that this patient has a genetic disorder involving chromosome 3 that will predispose him to renal cell carcinoma and other neoplasms.

von Hippel-Lindau Disease

Etiology	**Autosomal dominant** disorder, resulting in deletion of VHL gene (tumor suppressor gene) on chromosome **3p**
Pathology	**Hemangioblastomas** (vascular neoplasm associated with large cyst) or cavernous hemangiomas of the **cerebellum, brain stem,** and **retina** Adenomas and cysts of liver, kidneys, and pancreas
Clinical Manifestations	Initially presents with headaches, ataxia, or loss of vision Associated with increased incidence of **renal cell carcinoma,** pheochromocytoma, and ocular and CNS hemangioblastomas
Treatment	Surgical removal of tumor and radiation therapy
Notes	**Capillary hemangioma** is a malformation of a cluster of capillary-like channels filled with blood. It is the most common tumor of infancy and is responsible for port wine stain birthmarks. **Cavernous hemangioma** consists of a large vascular space filled with blood.

A 2-year-old Mormon girl in Utah is brought into your office by her mother for the first time since birth. She presents with multiple small telangiectasias of the skin and oral and nasal mucosa. Her nasal lesions are open and bleeding. The patient's mother divulges that the girl has had more frequent dark black stools over the past couple of months. When questioned about family history, the mother reports that the child's father suffers from frequent nose bleeds and blood in his stools. You suspect that this child's condition is caused by an autosomal dominant genetic disorder.

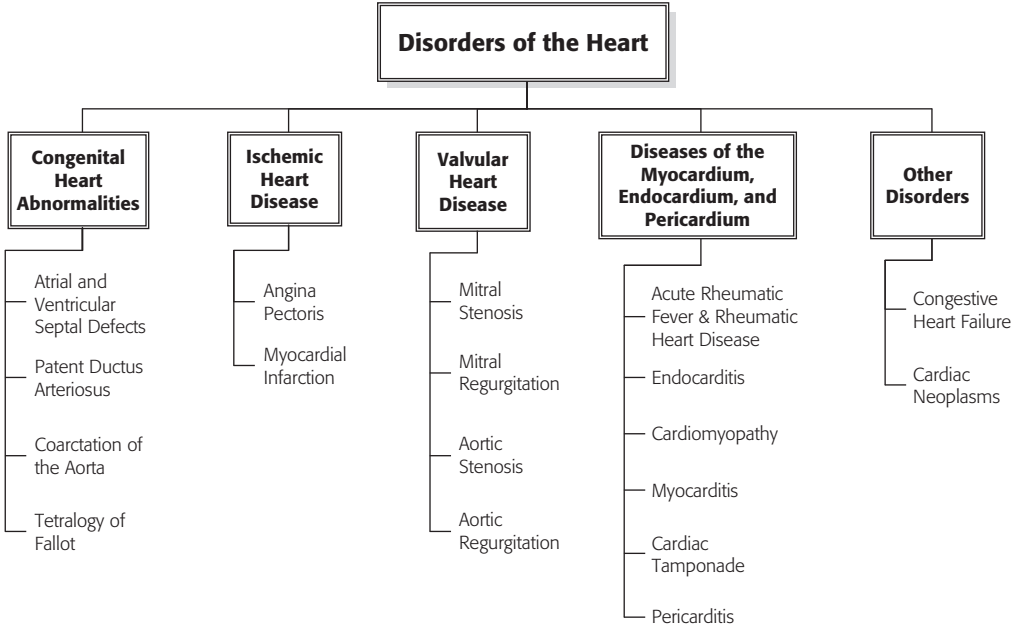
Osler-Weber-Rendu Syndrome (Hereditary Hemorrhagic Telangiectasia)

Etiology and Epidemiology	**Autosomal dominant** disorder resulting in mutations in TGF-β binding proteins Seen with increased frequency in Utah Mormons
Pathology	Localized **dilatation and convolution of venules and capillaries** of the skin and mucous membranes of the oral cavity, respiratory tract, GI tract, and urinary tract
Clinical Manifestations	Recurrent hemorrhage from skin and mucous membrane lesions Complications include **GI bleeding and epistaxis** *Lab findings:* Normocytic, normochromic anemia
Treatment	Nasal packing; cautery; estrogens to control epistaxis
Notes	**Sturge-Weber syndrome** is a congenital disorder associated with ipsilateral port wine stain of the face, glaucoma, and hemangiomatous masses on the meninges. It is manifest clinically by severe mental retardation, seizures, and retinal detachment.

A 35-year-old HIV-positive man presents to the clinic with a 10-pound weight loss and widely disseminated, painless, reddish-purple skin lesions on his face, arms, and trunk. He also notes dark stool recently and states that he has been coughing up blood. You immediately recognize the condition and set the patient up for both a colonoscopy and bronchoscopy to assess possible visceral involvement. Meanwhile, you decide to adjust his HIV therapy to try and reduce his HIV viral load and you explain to him that he will most likely need chemotherapy to treat this condition.

Kaposi Sarcoma

Etiology and Epidemiology	Etiology unknown; however, viral origin and association with immune status are being investigated. Three variants: (1) *Classic KS*: seen in older men of Ashkenazi Jewish or Mediterranean descent; (2) *Endemic (African) KS*: seen in young African men and children; (3) *Epidemic KS*: caused by **human herpes virus type 8;** associated with AIDS, especially in homosexual men with low CD4 counts.
Pathology	*Gross:* Reddish macules that become raised plaques and nodules over time; begins in skin, but can spread to lymph nodes and viscera (ie, lungs and GI tract) *Microscopic:* Dilated blood vessels with an endothelial mononuclear infiltrate; will progress to see spindle cells with hyaline globules, mitotic figures, and hemosiderin pigment
Clinical Manifestations	**Painless, reddish-purple, raised plaques** and firm nonpruritic nodules; lymphadenopathy; hemoptysis; dyspnea; abdominal pain and GI bleeding *Lab findings:* Specific KSHV antibodies present 70%-90% of time
Treatment	Reduce HIV viral load and raise CD4 count with antiviral therapy. Treat limited disease with intralesional vinblastine or topical treatments. Treat systemic disease with chemotherapy.
Notes	Kaposi sarcoma, non-Hodgkin Lymphoma, CNS lymphomas, and cervical cancer are cancers commonly associated with AIDS.


Disorders of the Heart
Congenital Heart Abnormalities
Atrial and Ventricular Septal Defects
Patent Ductus Arteriosus
Coarctation of the Aorta
Tetralogy of Fallot
Ischemic Heart Disease
Angina Pectoris
Myocardial Infarction
Valvular Heart Disease
Mitral Stenosis
Mitral Regurgitation
Aortic Stenosis
Aortic Regurgitation
Diseases of the Myocardium, Endocardium, and Pericardium
Acute Rheumatic Fever & Rheumatic Heart Disease
Endocarditis
Cardiomyopathy
Myocarditis
Cardiac Tamponade
Pericarditis
Other Disorders
Congestive Heart Failure
Cardiac Neoplasms

Cardiac Output (CO)

- CO is equal to the product of stroke volume (SV) and heart rate (HR); thus, changes in either the SV or HR cause a change in the CO.
- SV is dependent upon contractility, preload, and afterload.

Contractility (inotropism)

- Increases with sympathetic stimulation, increased intracellular calcium concentrations, decreased extracellular sodium concentrations, and administration of digitalis.
- Decreases with parasympathetic stimulation, heart failure, acidosis, hypoxia, and hypercapnia.

Preload

- *Preload* is the ventricular end-diastolic volume and is related to the right atrial pressure.
- Increases with increased venous return caused by exercise, blood transfusion, and sympathetic stimulation
- Venous dilators (eg, nitroglycerin) work by decreasing the preload.

Afterload

- *Afterload* is the diastolic arterial pressure and is proportional to the peripheral resistance.
- LV afterload corresponds to the aortic pressure and RV afterload corresponds with pulmonary artery pressure.
- Vasodilators (eg, hydralazine) work by decreasing the afterload.

Starling Curve

- The *Starling curve* relates the preload (or ventricular end-diastolic) volume with the CO (or SV).
- It shows that the force of contraction is proportional to the initial length of cardiac muscle fiber.
- An increase in preload will cause a corresponding increase in CO.

A 14-year-old boy with Down syndrome presents to your clinic with gradual onset of shortness of breath over the last several months. Physical examination reveals a systolic ejection murmur, a widely fixed split S2 sound and an oxygen saturation level of 93% on room air. As you schedule the boy for several cardiac tests, you worry that he may need surgery to correct his condition.

Atrial Septal Defect and Ventricular Septal Defect

Etiology	**Atrial septal defect (ASD):** Congenital abnormality; associated with trisomies and rubella syndrome **Ventricular septal defect (VSD): Most common congenital cardiac anomaly;** caused by failure of fusion of the interventricular septum with the aortic septum; associated with fetal alcohol syndrome and Down syndrome; may also result as complication from MI
Pathology and Pathophysiology	**ASD:** Defect in atrial septum allowing communication between right and left atria; several variants including **septum secundum** (90%) resulting from defective fossa ovalis, **septum primum** (5%) associated with Down syndrome, and **septum venosus** (5%) **VSD:** Defect in ventricular septum allowing communication between right and left ventricles; several variants including **membranous VSD** (90%), infundibular VSD, and muscular VSD *Pathophysiology for both ASD and VSD:* **Left-to-right shunt** results from lower pulmonary vasculature resistance as compared to systemic vasculature resistance
Clinical Manifestations	**ASD:** Often presents in adult life; **wide fixed split S2;** systolic ejection murmur **VSD:** If large, may cause **holosystolic murmur** at left lower sternal border and RVH Complications of ASD and VSD include pulmonary hypertension, **late cyanosis,** and paradoxic embolism
Treatment	Small VSDs may close spontaneously; surgery for large ASDs and VSDs
Notes	**Eisenmenger syndrome** refers to cyanosis occurring in adulthood owing to a shunt shift from left-to-right to right-to-left. It is caused by uncorrected VSDs, ASDs, and PDAs.

A 6-month-old boy is brought to the emergency room by his mother, who notes that he appears to be having trouble breathing. Upon speaking with the mother, you discover that she suffered from rubella during her pregnancy and that the child has not been seen by a doctor since birth. On physical examination, a continuous “machine-like” murmur is heard and you note signs of pulmonary congestion. You make a preliminary diagnosis and schedule the patient for an echocardiogram.

Patent Ductus Arteriosus (PDA)

Etiology	Congenital anomaly caused by **failure of closure of fetal ductus arteriosus;** associated with congenital rubella; increased risk in patients at high altitudes (fetal oxygen deprivation)
Pathology and Pathophysiology	*Vasculature:* Persistence of communication between pulmonary arteries and aorta after birth (normally closes within 24 hours of birth) *Pathophysiology:* **Left-to-right shunt** results from lower pulmonary vasculature resistance as compared to systemic vasculature resistance
Clinical Manifestations	Presents with **continuous "machine-like" murmur** Complications include RV hypertrophy and heart failure
Treatment	**Indomethacin closes PDA;** misoprostol (PGE) keeps PDA open
Notes	**Eisenmenger syndrome** refers to cyanosis occurring in adulthood owing to a shunt shift from left-to-right to right-to-left. It is caused by uncorrected VSDs, ASDs, and PDAs.

A 20-year-old man presents to your clinic complaining of progressive dyspnea. His lung examination is normal, but you note that he has significantly weak femoral pulses bilaterally and a blood pressure of 160/110 in both arms. When a chest x-ray reveals notching of the ribs, you refer the patient to a cardiologist for further evaluation.

Coarctation of Aorta

Etiology and Epidemiology	Etiology unknown; associated with **Turner syndrome** (infantile type) Occurs more frequently in **men**
Pathology	**Infantile type:** Narrowing of aorta proximal to ductus arteriosus **Adult type:** Narrowing of aorta distal to ductus arteriosus Both types may be accompanied by bicuspid aortic valve, aortic stenosis, ASD, VSD, berry aneurysm, or mitral regurgitation
Clinical Manifestations	**Adult type:** Noncyanotic disease; **weak femoral pulse; hypertension in upper extremities** versus lower extremities; **left ventricular hypertrophy;** holosystolic murmur. *Lab findings:* **Notching of ribs** on x-ray resulting from collateral circulation **Infantile type:** Heart failure
Treatment	Surgical resection
Notes	

A newborn boy, born to a diabetic mother, is found to be blue. Physical examination reveals a holosystolic murmur, consistent with the presence of a large ventricular septal defect. A chest x-ray demonstrates a boot-shaped heart. As you schedule several cardiac tests for the baby, you suspect that the child will most certainly need surgery to correct the myriad of defects associated with his condition.

Tetralogy of Fallot

Etiology	Caused by anterosuperior displacement of infundibular septum resulting in unequal division of aorta and pulmonary artery
Pathology	Tetralogy includes **pulmonary stenosis, RV hypertrophy, VSD,** and **aorta overriding VSD**
Clinical Manifestations	Results in right-to-left shunt leading to **early cyanosis** at birth, hypercapnia, and restlessness *Imaging:* X-ray shows **boot-shaped heart**
Treatment and Prognosis	Surgery to close VSD and relieve pulmonary stenosis Clinical prognosis is dependent on the severity of pulmonary stenosis
Notes	**Transposition of great vessels** also presents with **early cyanosis** and is associated with offspring of diabetic mothers. It is caused by **failure of aorticopulmonary septum to spiral,** resulting in aorta arising from RV and pulmonary trunk arising from LV. The disorder is fatal unless associated with VSD, ASD, or PDA. Treatment is immediate surgery.

During a routine physical examination, a 60-year-old man mentions to you that he occasionally experiences chest discomfort that radiates to his left shoulder. He describes that discomfort as a "weight on his chest" and notes that the pain tends to come on after he shovels his driveway and dissipates with rest. He denies any chest pain at rest. You schedule him for an exercise stress test, write him a prescription for nitroglycerin, and warn him against performing any strenuous exercise until further consultation with a cardiologist.

Angina Pectoris

Etiology	**Stable angina**: Caused by atherosclerosis **Prinzmetal (variant) angina**: Associated with coronary artery vasospasm **Unstable (crescendo) angina**: Caused by disruption of atherosclerotic plaque with partial thrombosis in coronary artery
Pathophysiology	All types of angina are caused by transient ischemia resulting in inadequate myocardial oxygenation
Clinical Manifestations	**Stable**: Precordial chest discomfort associated with **exertion;** pain is relieved by rest and nitroglycerin; nonspecific ST-T changes on ECG **Prinzmetal**: Episodic chest pain occurring at rest; may see ST elevation on ECG **Unstable**: Progressively frequent chest pain initially occurring with activity but later occurring at **rest;** considered indication for acute MI in near future; may see ST depressions on ECG
Treatment	**Stable:** Nitrates; β-blockers; statins; aspirin **Prinzmetal:** Vasodilators (nitrates, calcium channel blockers) **Unstable:** β-blockers; statins; aspirin; coronary evaluation with catheterization in near future; consider heparin treatment
Notes	Angina pectoris may be clinically silent in diabetics.

A 60-year-old man presents to the emergency department complaining of 2 hours of crushing substernal chest pain that radiates to his left shoulder and jaw. He appears fatigued and is breathing heavily and sweating profusely. You order an ECG, which demonstrates ST elevations across the precordium. You immediately activate the cardiac catheterization laboratory in the hopes of minimizing tissue damage caused by his condition. You worry that this patient may be at significant risk for ventricular rupture in 5–7 days.

Myocardial Infarction

Etiology

Caused by vasospasm, embolus, or **atherosclerotic thrombus resulting in coronary artery occlusion**

Risk factors include increasing age, hypertension, smoking, diabetes, male gender, postmenopausal women, and hyperlipidemia

Pathology

Heart: Progression from wavy fibers with **edema** and hemorrhage (4-12 hours) to **coagulative necrosis** with muscle hypereosinophilia and **neutrophilic infiltration** (12-36 hours) to **macrophage infiltration** with phagocytosis of dead cells and formation of granulation tissue (5-10 days) to **scar formation** (10 days to 2 months)

Clinical Manifestations

Crushing, substernal **chest pain with radiation to jaw and left arm;** dyspnea; nausea; diaphoresis.

Complications include **cardiac arrhythmia** (can cause sudden death within first few days), fibrinous pericarditis (within 3-5 days), pulmonary edema, CHF, shock, thromboembolism, **rupture of ventricular free wall or septum (VSD)** (within 7-10 days), rupture of papillary muscle leading to mitral regurgitation, and **Dressler syndrome** (autoimmune fibrinous pericarditis several weeks post-MI)

Lab findings: Diagnosis with **ST elevation (STEMI)** and permanent **Q wave** on ECG (within hours); **elevated cardiac troponin** (seen within 4 hours to 10 days); elevated CK-MB, LDH-1, and AST

Treatment

Thrombolytic therapy and/or coronary angioplasty for early MI

Notes

A 23-year-old woman presents with dyspnea on exertion and orthopnea. She has no significant past medical history, although she does recall having had strep throat 10 years ago, which was not treated with antibiotics. On physical examination, you hear a late, low-frequency, rumbling, mid-diastolic murmur following a high-pitched opening snap heard best at the apex of the heart. You order an echocardiogram and refer her to a cardiologist for further treatment of her condition.

Mitral Stenosis

Etiology	Usually caused by rheumatic heart disease
Pathology	*Mitral valve:* **Fish-mouth** appearance; fibrous thickening; calcification of leaflets; fusion of commissures; shortening of chordae tendineae
Clinical Manifestations	Tends to **present 10+ years after rheumatic fever** with dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea. Other findings include delayed, low-frequency, **rumbling, mid-diastolic murmur** following a high-pitched **opening snap** after S2 best heard at apex, and left atrial dilation. Complications include atrial fibrillation, predisposition to subacute endocarditis, and right heart failure
Treatment	Valve replacement if severe; treatment of heart failure if needed
Notes	

A 20-year-old woman presents to your clinic for her annual checkup. She is a new patient and on physical examination, you note that she has a holosystolic, high-pitched, blowing murmur with a mid-systolic click heard best at the apex with radiation to the axilla. You mention this finding to your patient and reassure her that it is a benign condition that affects at least 3% of adults in the United States.

Mitral Regurgitation

Etiology	Causes include rheumatic heart disease, **mitral valve prolapse,** infective endocarditis, papillary muscle damage after MI, and LV dilatation
Pathophysiology	*Pathophysiology:* Results from distortion of normal alignment of mitral valve and/or papillary muscles
Clinical Manifestations	**Holosystolic high-pitched blowing murmur** best heard at apex with radiation to axilla; S3 may be present. Acute cases may present with pulmonary edema while chronic cases may present with fatigue and weakness on exertion. Complications include pulmonary hypertension and RV failure.
Treatment	Endocarditis prophylaxis; mitral valve replacement
Notes	Mitral valve prolapse is the most common heart valve murmur presenting in young women as a late systolic murmur with midsystolic click. On pathology, there is an enlarged mitral leaflet that balloons into the left atrium during systole. There is also annular dilation, thinned chordae tendineae, and fibrous thickening of valve leaflets. It is usually benign, but it may be associated with connective tissue diseases (eg, Marfan syndrome).

A 70-year-old man presents to your office for a new patient visit. He has not seen a doctor in 25 years. On review of systems, he reports progressive dyspnea with exertion and he admits that he has passed out on occasion. On physical examination, a coarse, late-peaking crescendo-decrescendo, systolic ejection murmur heard best at the base of the heart is detected. You also note that his carotid pulses are quite weak. You make a preliminary diagnosis based on your physical examination and order an echocardiogram to confirm your suspicions.

Aortic Stenosis

Etiology	Causes include senile/degenerative **calcific aortic stenosis** (occurs in patients > 60 years old), **congenital bicuspid valve,** and rheumatic heart disease
Pathology and Pathophysiology	*Aortic valve:* Calcific deposits on aortic cusps (calcific aortic stenosis); fibrosis of cusps; commissural fusion (if associated with rheumatic heart disease) *Pathophysiology*: Increased afterload from increased gradient across narrowed aortic valve leads to LV hypertrophy and decreased LV compliance. Eventually, LV failure occurs. Angina results from mismatch of myocardial oxygen supply (decreased compliance leads to compression of intramyocardial vessels) and demand (increased oxygen need from increased LV wall stress).
Clinical Manifestations	Presents with **angina, syncope, and CHF;** patients have coarse, late-peaking **crescendo-decrescendo systolic ejection murmur** following ejection click which radiates to the apex and the neck; **pulsus parvus et tardus** (peripheral pulses are weak and delayed compared to heart sounds); carotid bruit; S4 often present; may see left ventricular hypertrophy
Treatment	Control of hypertension; primary prevention of coronary artery disease with statins; valve replacement if severe
Notes	

A 25-year-old man presents with increasing shortness of breath and dyspnea on exertion. He is very tall with long, wiry limbs and hyperextensible joints. On physical examination, there is marked pulsatile blushing of his nail beds. You also hear an immediate, high-pitched, blowing, diastolic, decrescendo murmur over the left sternal border while the patient is leaning forward. You order an echocardiogram to determine whether the patient is a candidate for valve replacement.

Aortic Regurgitation

Etiology	Causes include rheumatic heart disease, infective endocarditis, dilation of ascending aorta associated with hypertension and increasing age, nondissecting aortic aneurysm, Marfan syndrome, syphilitic aortitis, ankylosing spondylitis, and prosthetic aortic valve replacement
Pathophysiology	Insufficient valve results in volume overload of LV leading to simultaneous LV hypertrophy and dilatation. Volume overload also results in increased stroke volume, leading to hyperdynamic pulses and widened pulse pressure.
Clinical Manifestations	Presents with dyspnea on exertion, shortness of breath, and forceful heart beat. Patient has immediate **high-pitched, blowing, diastolic, decrescendo murmur** heard best at left sternal border with patient leaning forward; presence of S3; **wide pulse pressure; hyperdynamic pulses** often associated with pulsatile blushing of nail beds; LV hypertrophy and dilatation. Complications include **severe LV failure**
Treatment	Control of hypertension; treatment of heart failure if present with diuretics; eventual valve and aortic root replacement

Notes

A 10-year-old girl presents to the clinic with fever, malaise, migratory polyarthritis, and a blanching erythematous ring-shaped rash over her proximal extremities. On further questioning, you find out that she suffered from a severe sore throat 2 to 3 weeks ago. Serum studies demonstrate an ESR of 100 and a positive anti–streptolysin O titer. You worry that she may suffer from valvular heart disease during her adult years as a result of her current condition.

Acute Rheumatic Fever and Rheumatic Heart Disease

Etiology	**Acute rheumatic fever (ARF):** Antibodies formed against **group A β-hemolytic streptococci** cross-react against patient's tissues; usually presents in children 5-15 years of age **Rheumatic heart disease (RHD):** Late sequelae of acute rheumatic fever; presents 20+ years after ARF
Pathology	**ARF:** Presence of **Aschoff bodies** (inflammatory foci surrounded by lymphocytes) and **Anitschkow cells** (macrophages which may become multinucleated) producing a pancarditis in heart tissue; serofibrinous pericardial exudate **RHD:** Mitral stenosis with fish-mouth deformity; may also affect aortic valve
Clinical Manifestations	**ARF:** Onset of symptoms 2-3 weeks after streptococcal pharyngitis; major Jones criteria include **carditis, migratory polyarthritis,** chorea, **erythema marginatum** (blanching, ring-shaped rash), and subcutaneous nodules; minor Jones criteria include fever, arthralgia, or evidence of previous streptococcal infection **(positive anti–streptolysin O [ASO] titer)**. *Lab findings:* Elevated ESR. **RHD:** Presents with valvular heart disease (usually **mitral stenosis,** but may have aortic stenosis as well); valvular disease may lead to hypertrophy of heart, arrhythmias, and heart failure
Treatment	Penicillin for streptococcal infection; salicylates for fever and arthritis; endocarditis prophylaxis if indicated
Notes	

A 30-year-old man presents to the emergency room with sudden high fever and shaking chills. A new murmur localized to the mitral valve is heard. The patient has bilateral nail-bed hemorrhages, painful nodules on the tips of his fingers and toes, an erythematous rash on his palms and soles, and white spots surrounded by hemorrhage in his retina. You immediately begin the patient on broad spectrum antibiotics and order blood cultures and an echocardiogram to confirm the diagnosis.

Acute and Subacute Endocarditis

Etiology	**Acute:** Often caused by ***Staphylococcus aureus***
	Subacute: Often caused by **viridians streptococci** (eg, *S mutans*); often occurs after dental procedures
Pathology	**Acute:** Large vegetations consisting of fibrin, inflammatory cells, and bacteria on previously normal valves
	Subacute: Small vegetations consisting of fibrin, chronic inflammatory cells, and fibrosis on abnormal valves
Clinical Manifestations	**Acute:** Sudden **high fever** with chills; new onset of murmur
	Subacute: Insidious onset with **low-grade fever**
	Both types can present with **Osler nodes** (painful nodules on digit pads), **Janeway lesions** (red rash on palms and soles), **Roth spots** (white spots on retina with surrounding hemorrhage), nail-bed **splinter hemorrhages,** and bacteremia
	Complications include **chordae tendineae rupture,** perforation of valvular leaflet, heart failure, suppurative pericarditis, and septic emboli
Treatment	**Acute:** Broad spectrum antibiotics; may need surgical treatment if severe
	Subacute: Broad spectrum antibiotics; prophylaxis of SBE with antibiotics in susceptible individuals before dental procedures
Notes	**Tricuspid valve endocarditis** is associated with **IV drug use.**
	Nonbacterial endocarditis is associated with **sterile emboli** and seen with cancer metastasis or renal failure **(marantic endocarditis),** SLE (**Libman-Sacks endocarditis,** which demonstrates vegetation on *both sides* of valve), DIC, or carcinoid syndrome.

A 20-year-old man from Panama presents to your clinic complaining of dyspnea, orthopnea, bilateral leg swelling, and a bloated belly. He denies any history of a congenital heart disease, rheumatic fever, or valvular disease. As you prepare to admit him to the hospital for further testing and treatment, you wonder if a parasitic disease may be causing his condition.

Myocarditis

Etiology and Epidemiology	Usually caused by viruses (ie, Coxsackievirus A, **Coxsackievirus B),** or *Trypanosoma cruzi* (Chagas disease); other causes include fungi (eg, *Candida*), helminthes (eg, trichinosis), parasites (eg, toxoplasmosis), bacteria (eg, Lyme disease), postviral syndrome, SLE, drug hypersensitivity, hyper/hypothyroidism, and sarcoidosis Seen most commonly in young men
Pathology	*Gross:* Hemorrhages visible on ventricular myocardium *Microscopic:* Diffuse myocardial degeneration and necrosis with **mononuclear inflammatory infiltrate**
Clinical Manifestations	May be asymptomatic or may present as **biventricular heart failure,** fever, dyspnea, fatigue, new onset of systolic murmur, palpitations, or **pleuropericardial pain** Complications include arrhythmias or sudden death
Treatment	Usually supportive
Notes	

A 20-year-old college football player suddenly collapses and dies during a practice session. His father had suffered a similar fate in his early 30s. On autopsy, he is found to have a hypertrophied heart with an enlarged intraventricular septum. On histologic examination of the myocardium, you see disoriented, tangled, hypertrophied myocardial fibers and you suspect that his death was related to an autosomal dominant condition resulting in a mutation of beta-myosin heavy chain protein gene.

Cardiomyopathy

Etiology	**Dilated:** Most common cardiomyopathy (90%); causes include **alcoholism,** chronic ischemia, wet beriberi (vitamin B_1 deficiency), postmyocarditis, cocaine abuse, **doxorubicin toxicity,** peripartum cardiomyopathy, and muscular dystrophies **Hypertrophic:** Idiopathic or resulting from **autosomal dominant mutation in β-myosin heavy chain gene** **Restrictive:** Can be idiopathic or caused by sarcoidosis, amyloidosis, Löffler endomyocardial fibrosis, systemic sclerosis, and endocardial fibroelastosis
Pathology and Pathophysiology	**Dilated:** Dilation of all chambers; hypertrophy of muscle cells; interstitial fibrosis; results in **systolic dysfunction** **Hypertrophic:** Hypertrophy of interventricular septum and myocardium; banana-shaped LV lumen; haphazard arrangement of hypertrophied myocytes; results in **LV outflow tract obstruction** and **impaired diastolic filling** leading to decreased CO **Restrictive:** Bi-atrial dilation; diffuse interstitial fibrosis; results in decreased ventricular compliance with **decreased diastolic filling** and decreased CO
Clinical Manifestations	**Dilated:** Signs of CHF. *Imaging:* CXR demonstrates **balloon heart** **Hypertrophic:** Dyspnea; angina; syncope with exertion; palpitations; sudden death **Restrictive:** Dyspnea; exercise intolerance; weakness; edema
Treatment	**Dilated:** ACE inhibitors; anticoagulants; diuretics; transplant **Hypertrophic:** β-blockers; refrain from strenuous exercise **Restrictive:** Treatment of underlying cause
Notes	

A 35-year-old woman presents with acute chest pain and a nonproductive cough. Review of systems reveals a history of malar rash, fatigue, and migratory polyarthritis. On physical examination, she is found to have a friction rub and distant heart sounds and she complains of increased pain when supine. An increased jugular venous pressure is noted with inspiration and diffuse ST elevations are seen on most ECG leads. You initiate therapy with corticosteroids and refer her to a rheumatologist and a cardiologist.

Pericarditis

Etiology	**Acute:** Can be **serous** (caused by SLE, RA, scleroderma, renal failure, viral infection, or tumors), **fibrinous** (caused by renal failure, MI, ARF, radiation, or postsurgical trauma), **hemorrhagic** (caused by TB or malignancy), or **suppurative** (caused by bacteria such as **TB,** *Staphylococcus*, or *Pneumococcus*) **Constrictive:** Previous history of acute pericarditis
Pathology and Pathophysiology	**Acute: (1) Serous:** protein-rich exudate in pericardial space with inflammatory reaction on tissue surfaces; **(2) Fibrinous:** fibrin-rich exudate in pericardial space, which may resolve or organize into scar; **(3) Suppurative:** purulent exudate with massive inflammatory reaction on tissue surfaces, which usually organizes into scar; **(4) Hemorrhagic:** fibrin-rich exudate with associated hemorrhage in pericardial space **Constrictive:** Heart encased by fibrous scar with **loss of pericardial space,** resulting in reduced cardiac contraction and venous return
Clinical Manifestations	**Acute: Chest pain** worsening with inspiration and supine position; **friction rub;** pulsus paradoxus; distant heart sounds; fever; nonproductive cough; Kussmaul sign (increased JVP with inspiration). *Lab findings:* **Diffuse ST elevations** in most ECG leads and normal CK-MB. **Constrictive:** Quiet heart sounds; Kussmaul sign; S3; may mimic right-sided heart failure
Treatment	**Acute:** Treat any underlying causes if known; NSAIDs; corticosteroids if necessary **Constrictive:** Pericardiectomy
Notes	

A 75-year-old woman with a history of metastatic breast cancer presents to the emergency department complaining of weakness and difficulty breathing. On physical examination, her blood pressure is 90/50 and her heart sounds are distant and faint. You also note that she has an increased JVP. When an ECG reveals a QRS complex height that varies from one heart beat to the next, you prepare for an immediate pericardiocentesis.

Cardiac Tamponade

Etiology	Can be caused by hemopericardium (accumulation of blood in pericardial sac) resulting from traumatic perforation of heart or aorta, cardiac rupture resulting from acute MI, or aortic dissection. May also result from accumulation of inflammatory effusions in pericardial space as caused by malignancy, connective tissue disorders, or infections.
Pathophysiology	Compression of heart leads to restriction of cardiac filling and equilibration of pressure in heart chambers, resulting in decreased CO
Clinical Manifestations	Presents with **Beck Triad (hypotension, distant heart sounds, increased venous pressure);** pulsus paradoxus; cyanosis; Kussmaul sign (increased JVP with inspiration); can be fatal if not promptly treated *Lab findings:* **Electrical alternans** on ECG (beat-to-beat alterations of QRS complex height), enlarged cardiac silhouette on CXR
Treatment	Immediate pericardiocentesis
Notes	

A 55-year-old woman presents to your clinic complaining of ankle swelling and increasing shortness of breath with exertion. Upon directed questioning, she reveals that she also experiences shortness of breath when she is lying down. Physical examination reveals marked hepatosplenomegaly, distended neck veins, and pedal edema. A chest x-ray is suggestive of cardiomegaly. You start the patient on an ACE inhibitor, diuretic, and a low-sodium diet and you refer her to a cardiologist.

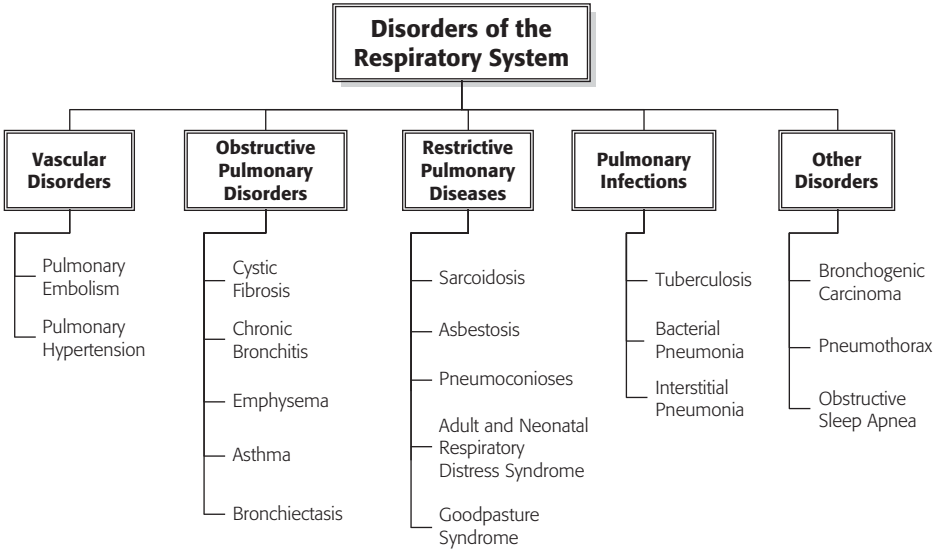
Congestive Heart Failure

Etiology	**Left-sided (LS):** Ischemic heart disease (especially MI); hypertension; aortic/mitral valve disease; cardiomyopathies; myocarditis **Right-sided (RS): Left-sided heart failure;** mitral stenosis; cor pulmonale; cardiomyopathies; myocarditis; tricuspid/pulmonary valve disease
Pathology and Pathophysiology	**LS: Hypertrophied and dilated LV;** dilated LA; pulmonary congestion with presence of **hemosiderin-laden macrophages** or "heart failure" cells **RS: Hypertrophied and dilated RV;** usually hypertrophied and dilated LV; hepatic congestion (nutmeg liver) with centrilobular necrosis; congested spleen *Pathophysiology for both left- and right-sided failure:* LV failure leads to decreased cardiac output, resulting in dyspnea. Pulmonary edema results from LV failure to keep up with RV output, leading to increased fluid transudation from pulmonary vessels. RV failure leads to increased central venous pressure, causing hepatomegaly and peripheral edema.
Clinical Manifestations	**LS: Dyspnea; orthopnea;** paroxysmal nocturnal dyspnea; **pleural effusion;** cerebral anoxia; salt and water retention **RS:** Fluid retention and **peripheral edema; hepatosplenomegaly;** ascites; **distention of neck veins**
Treatment	Diuretics; low-sodium diet; ACE inhibitors; nitrates; beta-blockers; digoxin
Notes	**Cor pulmonale** refers to isolated right-sided heart failure caused by chronic pulmonary hypertension.

A 40-year-old woman presents to the emergency room complaining of dyspnea on exertion and fainting spells. Physical examination is significant for a low-grade fever and a regurgitant murmur localized in the left atrium near the mitral valve. Two-dimensional echocardiography shows a tumor near the mitral valve that moves with the cardiac cycle. You schedule surgery to excise the lesion.

Cardiac Neoplasms (Atrial Myxoma and Rhabdomyoma)

Etiology and Epidemiology	**Myxomas:** Etiology unknown although 10% of cases are caused by autosomal dominant trait; seen in **adults** **Rhabdomyomas:** Associated with tuberous sclerosis; seen in **infants and young children**
Pathology	**Myxoma:** Usually found in **LA** near the fossa ovalis; often in **pedunculated form;** composed of globular myxoma cells and smooth muscle cells in a mucopolysaccharide ground substance **Rhabdomyoma:** Grayish myocardial mass that protrudes into ventricle; composed of **spider cells** (polygonal cells with glycogen-laden vacuoles separated by cytoplasmic strands)
Clinical Manifestations	**Myxoma:** Presents when mitral valve function is compromised by **ball-valve obstruction** causing dyspnea or syncope, when a stroke occurs because of an embolus, or when a regurgitant valvular murmur is found on physical examination; systemic manifestations includes fever, wasting, arthralgias, malaise, and anemia **Rhabdomyoma:** Presents with symptoms of obstruction of cardiac chamber
Treatment	Myxomas are usually benign and can be surgically excised.
Notes	Metastasis is the most common cause of cardiac tumor. Cardiac sarcomas are rare, but when they occur, they are malignant tumors that often metastasize.


Disorders of the Respiratory System
Vascular Disorders
Pulmonary Embolism
Pulmonary Hypertension
Obstructive Pulmonary Disorders
Cystic Fibrosis
Chronic Bronchitis
Emphysema
Asthma
Bronchiectasis
Restrictive Pulmonary Diseases
Sarcoidosis
Asbestosis
Pneumoconioses
Adult and Neonatal Respiratory Distress Syndrome
Goodpasture Syndrome
Pulmonary Infections
Tuberculosis
Bacterial Pneumonia
Interstitial Pneumonia
Other Disorders
Bronchogenic Carcinoma
Pneumothorax
Obstructive Sleep Apnea

LUNG VOLUMES AND CAPACITIES

Lung Volume/Capacity	Definition
Tidal Volume (TV)	Air expired or inspired after a single, normal breath
Inspiratory reserve volume (IRV)	Air that can be inspired above the tidal volume
Expiratory reserve volume (ERV)	Air that can be expired after expiration of the tidal volume
Residual volume (RV)	Air remaining in lungs after maximal expiration
Forced expiratory volume at 1 second (FEV_1)	Air expelled in the first second of forced expiration
Vital capacity (VC)	TV + IRV + ERV
Inspiratory capacity (IC)	TV + IRV
Functional reserve capacity (FRC)	RV + ERV
Total lung capacity (TLC)	TV + IRV + ERV + RV

PULMONARY FUNCTION TEST: SPIROMETRY

- Measures lung volumes and capacities; cannot measure RV or any capacity that includes RV (FRC or TLC)
  → Ratio of FEV_1/FVC is used to assess pulmonary function. In obstructive disease, FEV_1 and FVC are both decreased, but FEV_1 is decreased more, so FEV_1/FVC is decreased. In restrictive disease, both FEV_1 and FVC are decreased to a similar extent so FEV_1/FVC is either normal or increased.

A 63-year-old man presents to your office complaining of worsening shortness of breath over the past year. You know that this patient has smoked two packs of cigarettes a day for the past 45 years. As you are talking to the patient, you notice that he is using his accessory muscles of respiration to breathe, that his chest is barrel shaped and that he is breathing carefully through pursed lips. Using a spirometer, you determine that he has a decreased FEV_1/FVC ratio and an increased TLC. You tell the patient that it is imperative that he stop smoking and prescribe him a tiotropium inhaler.

Emphysema

Etiology	Associated with smoking and hereditary α_1-antitrypsin deficiency
Pathology and Pathophysiology	*Pathophysiology:* Enzymes (elastase) destroy elastin in alveolar wall, unless neutralized by α_1 antitrypsin; smoking inactivates α_1-antitrypsin and attracts neutrophils (source of elastase) *Gross:* **Enlargement of air spaces; destruction of alveolar wall;** 4 patterns seen: **(1) Centriacinar—**respiratory bronchioles dilated especially in **upper lobes,** seen in **smokers; (2) Panacinar—**entire acinus is dilated in **entire lung,** seen with **α_1-antitrypsin deficiency; (3) Paraseptal—**distal alveoli dilated near pleura and interlobar septa, may see large blebs; **(4) Irregular—**acinus is irregularly involved, associated with scarring and inflammation
Clinical Manifestations	**"Pink puffers"** (slowing of forced expiration through pursed lips); **dyspnea;** cyanosis; tachycardia; **barrel-shaped chest;** use of accessory respiratory muscles Complications include pneumothorax caused by bullae rupture, chronic bronchitis; and **cor pulmonale** *Imaging:* Hyperinflation and bullae with flattened diaphragm on CXR *Lab findings:* Hypoxia, **increased residual volume** and TLC, **decreased FEV_1/FVC ratio**
Treatment	Smoking cessation; oxygen; bronchodilators (anticholinergics, beta-agonist); inhaled steroids
Notes	Emphysema is a chronic obstructive pulmonary disease (**COPD**) Hereditary α_1-antitrypsin deficiency also causes hepatic cirrhosis

An 8-year-old girl is brought into an urgent-care clinic complaining of shortness of breath. Her past medical history is significant for multiple allergies. Upon physical examination, you hear expiratory wheezes and you observe that the patient is using her accessory muscles of respiration. You decide to administer an inhaled β_2-adrenergic agonist for relief of her symptoms.

Asthma

Etiology	**Extrinsic:** Associated with **type I hypersensitivity reaction;** seen in **children** **Intrinsic:** Associated with chronic bronchitis, exercise, or cold; seen in **adults**
Pathology and Pathophysiology	*Pathophysiology:* Hypersensitivity of bronchial airways results in symptomatic bronchospasm *Lung:* **Hypertrophy of bronchial smooth muscle; hyperplasia of bronchial submucosal glands; mucous plugs** containing Curshmann spirals and Charcot-Leyden crystals
Clinical Manifestations	**Dyspnea; expiratory wheezing;** cough; use of accessory muscles of respiration; pulsus paradoxus Complications include status asthmaticus (prolonged asthma attack) *Lab findings:* Hypoxia, **decreased FEV_1/FVC ratio,** eosinophilia in children
Treatment	**Inhaled β_2-adrenergic agonists** (albuterol) for quick relief; inhaled or systemic corticosteroids, leukotriene modifiers (zileuton), cromolyn, or theophylline for long-term control
Notes	

A 44-year-old man presents to your office complaining of a persistent cough, which is productive of copious sputum. He admits that he is a heavy smoker and has suffered from similar coughs for several years. Physical examination reveals diffuse wheezing and crackles. You suspect that this patient will have a decreased FEV_1/FVC ratio and strongly suggest that he stop smoking.

Chronic Bronchitis

Etiology	Chronic irritation caused by **smoking,** air pollution, or infection
Pathology	*Lung:* **Hyperplasia of submucosal glands** leading to increased mucus secretion; increase in goblet cells
Clinical Manifestations	**Productive cough** for at least 3 months over 2+ years; **"blue bloaters"** (refers to cyanosis); dyspnea; wheezing Complications include **cor pulmonale** *Lab findings:* **Increased residual volume** and TLC, **decreased FEV_1/FVC ratio, Reid index > 50%** (refers to increased mucous gland size)
Treatment	Smoking cessation; oxygen; bronchodilators (anticholinergics, beta-agonist); inhaled steroids
Notes	Chronic bronchitis is a chronic obstructive pulmonary disease (**COPD**).

A 25-year-old man presents to the emergency department with hemoptysis associated with a chronic productive cough. He reports suffering from chronic sinusitis and has had several bouts of severe pneumonia that have required hospitalization in the past. Pulmonary function tests reveal a decreased FEV_1/FVC ratio. When CT scan reveals dilated bronchioles with signet-ring appearance, you decide to check for situs inversus because his present condition may be associated with a rare genetic disorder.

Bronchiectasis

Etiology	Caused by bronchial **obstruction** (tumor, foreign body, mucus), chronic necrotizing **infections of bronchi,** or **cystic fibrosis**
Pathology	*Lung:* **Dilated airways** usually in **lower lobes;** inflammation within bronchial walls; fibrosis of bronchial walls in chronic disease
Clinical Manifestations	Chronic **cough** with copious **purulent sputum; hemoptysis; cyanosis;** anemia Complications include lung and brain abscesses or cor pulmonale *Imaging:* Dilated bronchioles with signet-ring appearance on CT scan *Lab findings:* **Decreased FEV_1/FVC** ratio, decreased Hct
Treatment	Antibiotics; bronchodilators; surgical resection for localized disease
Notes	**Kartagener syndrome** is caused by a defect in dynein, leading to immotile cilia. Clinical manifestations include bronchiectasis, sterility, recurrent sinusitis, and situs inversus (dextrocardia).

A 2-year-old girl is brought to the emergency department because of shortness of breath and a productive cough. Upon questioning her parents, you discover that this patient has a history of pulmonary infections and bulky stools that float. Physical examination reveals a thin girl with a barrel-shaped chest, crackles over both lungs, and digital clubbing. Later, a sweat test demonstrates high levels of chloride ions. You realize that this girl will have a severely shortened life span owing to her condition.

Cystic Fibrosis

Etiology

Autosomal recessive disorder that is caused by a mutation (most common is ΔF508) on **chromosome 7.** This mutation results in a **defective membrane Cl^- channel (CFTR),** causing defective chloride and water transport in epithelial cells.

Pathology and Pathophysiology

Pathophysiology: Mutated Cl^- channel leads to **secretion of thick mucus,** which lodges in lungs, liver, and pancreas

Lung: **Mucus plugs** obstructing bronchioles; hyperplasia and hypertrophy of goblet cells

Liver: **Mucus plugs** obstructing bile canaliculi; biliary cirrhosis

Pancreas: **Mucus plugs** obstructing pancreatic ducts; fibrosis of exocrine glands

Clinical Manifestations

Chronic lung disease causing productive cough, **pulmonary infections, bronchiectasis,** cyanosis, and barrel-shaped chest; **pancreatic insufficiency** causing **steatorrhea, diabetes,** and malabsorption; **meconium ileus** (small bowel obstruction in newborn); infertility in men

Lab findings: **High Cl^- concentrations in sweat test,** hypoxia, **increased ratio of residual volume to TLC**

Treatment and Prognosis

Antibiotics; bronchodilators; techniques to clear airway secretions; **lung transplantation**

Median age of survival is 31. Death occurs from pulmonary complications.

Notes

A 63-year-old man is hospitalized for a severe case of lobar pneumonia with sepsis. Within the first 24 hours of his hospitalization, he develops worsening respiratory failure and requires intubation. A chest x-ray reveals bilateral patchy opacities. He becomes progressively hypoxemic even with increased oxygen delivery via the ventilator. You continue to treat the patient's pneumonia, but you worry that he will have up to a 40% mortality rate given his current condition.

Adult and Neonatal Respiratory Distress Syndrome

Etiology	**Adult respiratory distress syndrome (ARDS):** Lung infections; toxin inhalation; **sepsis, trauma;** pancreatitis; **shock;** DIC **Neonatal respiratory distress syndrome (NRDS):** Predisposed by **prematurity,** maternal diabetes, and birth by C-section; caused by **deficiency of pulmonary surfactant**
Pathology and Pathophysiology	**ARDS: Damage to alveolar capillary walls and alveolar walls** by cytokines and endotoxin leads to increased vascular permeability and decreased surfactant, which leads to pulmonary edema and alveolar collapse. *Gross:* Heavy, red lung. *Microscopic:* **Intra-alveolar edema** and inflammation with **hyaline membranes;** if nonfatal, results in chronic **scars.** **NRDS:** Surfactant deficiency results in **increased surface tension in the lung,** causing alveolar collapse. *Gross:* Heavy, purple lung; engorged pulmonary vessels. *Microscopic:* **Eosinophilic hyaline membranes within alveoli.**
Clinical Manifestations	**ARDS:** Dyspnea; tachypnea; cyanosis. *Imaging:* Diffuse **bilateral infiltrates on CXR;** mismatch on ventilation-perfusion scan. *Lab findings:* **Hypoxia; $Pa_{O_2}/F_{IO_2} < 200$.** **NRDS:** Dyspnea, tachypnea, and cyanosis soon after birth; if nonfatal, complications include bronchopulmonary dysplasia, PDA, intraventricular brain hemorrhage, and necrotizing enterocolitis
Treatment	**ARDS:** Treat underlying cause; positive-pressure mechanical ventilation **NRDS:** Exogenous surfactant at birth to infants under 28 weeks; corticosteroids to mother before birth; oxygen therapy (carries risk of oxygen toxicity, damage caused by oxygen free radicals)
Notes	ARDS carries a 40% mortality rate.

A 49-year-old man presents to your clinic complaining of mild shortness of breath over the past year. He does not smoke, although he has worked in a glass-manufacturing factory for over 20 years. A chest x-ray reveals eggshell calcification of the hilar lymph nodes. You make a diagnosis and suggest that he have a PPD placed because his condition is associated with increased susceptibility to tuberculosis.

Pneumoconiosis (Silicosis, Coal Worker, Anthracosis)

Etiology	Inhalation of inorganic dust particles, including carbon dust (**anthracosis**), coal dust (**coal worker**), and silica dust (**silicosis**)
Pathology	**Coal worker pneumoconiosis:** *Simple:* **Coal macules** around bronchioles in upper lobes. *Complicated:* **Progressive massive fibrosis; blackened fibrotic nodules** with necrotic center in lung. **Silicosis: Silicotic nodules** in lungs that may **obstruct airways** or blood vessels; nodules may become collagenous scar; honeycomb lung **Anthracosis:** Irregular black patches (carbon-ingesting macrophages) along lung lymphatics
Clinical Manifestations	**Coal worker pneumoconiosis:** *Simple* is asymptomatic; *complicated* can result in **bronchiectasis,** pulmonary hypertension, or **cor pulmonale.** *Imaging:* Small opacities in upper lung seen on CXR. **Silicosis:** Dyspnea; **increased susceptibility to TB.** *Imaging:* Nodularity in the upper lung and **eggshell calcification** of hilar lymph nodes seen on CXR. **Anthracosis:** Asymptomatic *Lab findings:* **Decreased TLC** for all forms
Treatment	Symptomatic relief; withdrawal of offending agent
Notes	

A 59-year-old man presents to your office with a productive cough and dyspnea. He has smoked heavily for many years and works in construction. A CT scan reveals interstitial lung fibrosis and calcified pleural plaques. You inform him that his condition has placed him at great risk for both bronchogenic carcinoma and malignant mesothelioma of the pleura.

Asbestosis

Etiology	**Inhalation of asbestos fibers;** aggravated by cigarette smoking
Pathology and Pathophysiology	*Pathophysiology:* Alveolar macrophages engulf asbestos fibers, which cause a fibroblastic response *Lung:* Diffuse **interstitial fibrosis;** asbestos bodies (yellow-brown ferruginous bodies in lungs reflect asbestos fibers coated with hemosiderin); collagenous **plaques on pleura and diaphragm**
Clinical Manifestations	**Dyspnea;** productive cough *Imaging:* Interstitial fibrosis and pleural plaques on CT, mainly affects lower lobes *Lab findings:* **Decreased TLC**
Treatment	No effective treatment
Notes	Patients with asbestosis are at increased risk of developing bronchogenic carcinoma and **malignant mesothelioma of the pleura.** On histology, malignant mesothelioma presents as dense sheet of white tumor that has both a fibrous and glandular epithelial component and encases the lung.

A 26-year-old man presents to the emergency room after coughing up blood. He also reports progressive fatigue, occasional headaches, and bouts of tea-colored urine. Physical examination reveals a blood pressure of 160/100, bilateral pulmonary crackles, and lower extremity edema. When his urinalysis demonstrates hematuria, you begin to suspect that he may be suffering from an autoimmune disorder and you order a serum study looking specifically for antiglomerular basement membrane antibodies, which will confirm your suspected diagnosis.

Goodpasture Syndrome

Etiology and Epidemiology	Caused by **antibodies against the glomerular basement membrane (GBM)** (type II hypersensitivity reaction) Most commonly seen in **men** between the ages of 20 and 30
Pathology	**Lung: Intra-alveolar hemorrhages;** fibrosis thickening of the septa; hemosiderin-laden macrophages in alveoli **Kidney: Rapidly progressive crescentic glomerulonephritis** (macrophages, proliferating parietal cells and fibrin coalesce to form crescents in Bowman space, which eventually destroy Bowman space and compress the glomerular capillaries) **Immunofluorescence studies: Linear deposits of immunoglobulins** along alveolar and glomerular basement membranes
Clinical Manifestations	**Hemoptysis; nephritic syndrome** (edema, hypertension, hematuria) *Lab findings:* **Antiglomerular basement membrane antibodies,** iron deficiency anemia
Treatment	Plasma exchange and corticosteroids
Notes	**Anti-GBM glomerulonephritis** is characterized by nephritic syndrome mediated by anti-GBM antibody deposition in the kidney without involvement of the lung.

A 32-year-old African American woman presents to the urgent-care clinic complaining of fever, rash, and dyspnea. Upon questioning her further, you discover that she has been suffering from arthralgias in both of her knees and her right hip. Physical examination is notable for a red, nodular rash on all of her extremities. A chest x-ray reveals interstitial lung infiltrates and massive bilateral hilar lymphadenopathy. Serum studies reveal an increased ESR, increased ACE activity, and hypercalcemia. You suspect that you will see noncaseating granulomas on a biopsy of her hilar lymph nodes.

Sarcoidosis

Etiology and Epidemiology	Cause unknown, although immune dysfunction has been postulated Highest incidence in African American women between the ages of 20 and 40
Pathology	Involved tissues most commonly include **lung, lymph nodes, spleen, liver,** bone marrow, skin, eyes, and salivary glands *Microscopic:* **Noncaseating granuloma** with fibrotic center surrounded by epithelioid cells and Langhans giant cells; asteroid bodies (inclusions within giant cells) and Schaumann bodies (calcium concretions) are also present, although they can be present in other granulomatous diseases as well
Clinical Manifestations	Malaise; fever; hepatosplenomegaly; dyspnea; **interstitial lung disease; erythema nodosum;** polyarthritis; uveitis; CNS and peripheral neuropathy *Imaging:* **Bilateral hilar lymphadenopathy** and **interstitial lung infiltrates** on CXR *Lab findings:* Decreased TLC, increased ESR, **increased ACE activity, hypercalcemia** and hypercalciuria, hypergammaglobulinemia, reduced sensitivity to skin test antigens
Treatment	Corticosteroids
Notes	

An 82-year-old woman presents to the emergency department complaining of severe shortness of breath. She tells you that her right calf has been sore as well. On directed history, you discover that she suffered a stroke 6 months ago and has been bedridden ever since. Further evaluation reveals that she is hypoxic and has elevated D-dimer levels. You decide to begin empiric anticoagulant therapy and you order a ventilation-perfusion scan on this patient.

Pulmonary Embolism

Etiology	Emboli can be air, amniotic fluid, fat, foreign bodies, or tumor cells. The most common emboli (95%) are **thromboemboli,** which usually originate from **deep vein thrombosis** in the leg
Pathology	*Gross:* **Hemorrhage** or **infarct** of the lung (usually of the lower lobes); infarct only occurs in patients with inadequate circulation due to lung or heart disease; may see **venous thrombus (dark red** with pale gray fibrin strands and firm) lodged in pulmonary vessel
Clinical Manifestations	**Tachycardia; dyspnea;** pain on inspiration; may have symptoms of **DVT** (sore, swollen calf); may have syncope or hypotension if massive PE *Imaging:* **Mismatch seen on ventilation-perfusion scan,** filling defect seen on high resolution CT scan of the chest *Lab findings:* Hypoxia**, elevated D-dimer levels** (seen with thromboembolus)
Treatment	Anticoagulation; consider thrombolysis if patient is hypotensive or if signs of right heart strain
Notes	Pulmonary embolism is the third leading cause of death among hospitalized patients. **Virchow triad** (venous stasis, hypercoagulable state, vessel wall injury) predisposes to deep vein thrombosis and thus to pulmonary embolism.

A 35-year-old woman presents to the clinic complaining of a several month history of progressive shortness of breath with exertion. She has no history of respiratory illnesses. Physical examination reveals an oxygen saturation level of 92% on room air, a systolic ejection click, and narrow splitting of the S2 heart sound. An electrocardiogram demonstrates signs of right ventricular hypertrophy. You order an echocardiogram to further evaluate the pressures in her pulmonary vasculature, but you begin to worry that this patient may have a very poor prognosis.

Pulmonary Hypertension

Etiology	**Idiopathic;** connective tissue disorders (SLE, CREST); congenital heart disease with left-to-right shunts; left heart failure; **interstitial lung diseases** (COPD, OSA, sarcoidosis); pulmonary embolism
Pathology	*Lung:* **Medial hypertrophy and intimal fibrosis of the pulmonary arterioles** *Heart:* **Right ventricular hypertrophy;** right ventricular dilatation (seen with acute cor pulmonale)
Clinical Manifestations	**Dyspnea, fatigue,** and **chest pain;** systolic ejection click; narrow splitting of S2 Complications include cyanosis, **thrombosis,** right ventricular hypertrophy, and **cor pulmonale** (right-sided heart failure secondary to pulmonary hypertension)
Treatment	**Oxygen;** diuretics for right heart failure; anticoagulation; phosphodiesterase inhibitors
Notes	

A 68-year-old man presents to the emergency department complaining of a fever, dyspnea, and a cough productive of green sputum. Physical examination reveals an ill-appearing man, breathing heavily. On lung examination, you note bronchial breath sounds and dullness to percussion over the right lower lung lobe. A chest x-ray demonstrates circumscribed opacity over the region of his right lower lung lobe. You obtain sputum and blood cultures and then admit this patient to the hospital for antibiotic treatment.

Bacterial Pneumonia

Etiology	**Lobar pneumonia: Pneumococcus** accounts for 90%-95% of cases **Bronchopneumonia:** *Staphylococcus aureus, Haemophilus influenzae, Klebsiella, Streptococcus pyogenes*
Pathology	**Lobar:** Generally **intra-alveolar exudate leading to consolidation;** 4 stages: (1) congestion: heavy red lung, intra-alveolar fluid; (2) red hepatization: RBCs, fibrin and neutrophils within alveoli; (3) gray hepatization: fibrin and neutrophils within alveoli; (4) resolution: intra-alveolar exudate is reabsorbed **Bronchopneumonia:** Often is bilateral and **multilobar; neutrophil exudate extends from bronchi** and bronchioles into adjacent alveoli
Clinical Manifestations	Malaise, **fever, dyspnea,** and **productive cough.** Bronchial breath sounds and rales on auscultation and dullness to percussion over affected lung areas. Complications include abscess, empyema, or sepsis *Imaging*: CXR shows **radio-opaque lobe** for lobar pneumonia or **patchy opacities** for bronchopneumonia
Treatment	Antibiotics; respiratory support
Notes	Hospital-acquired pneumonias may be caused by gram-negative microorganisms *(Klebsiella, Escherichia coli, Pseudomonas)* as well as gram-positive organisms *(S aureus)* and can be fatal.

A 21-year-old woman presents to the university health clinic complaining of general weakness and a low-grade fever of 3 days' duration. Upon directed history, you learn that she has had an occasional cough and dyspnea and that her two roommates have been suffering from similar symptoms. When a chest x-ray reveals patchy infiltrates, you prescribe her a course of azithromycin and schedule her for a follow-up visit to make sure that her symptoms have resolved.

Interstitial Pneumonia

Etiology	***Mycoplasma pneumoniae;*** **viruses** (influenza, RSV, adenovirus); *Chlamydia psittaci; Coxiella burnetii; Legionella pneumophila*
Pathology	*Lung:* Often **multilobar; patchy infiltration** of mononuclear inflammatory exudate into **alveolar walls;** may see pink hyaline membranes lining alveoli
Clinical Manifestations	Malaise; **fever;** muscle aches; **occasional cough** (clinical picture appears less severe than bacterial pneumonias) *Imaging:* CXR reveals **patchy infiltration** *Lab findings:* Leukocytosis, elevated cold agglutinin levels in *M pneumoniae* infection
Treatment	Antibiotics; supportive care
Notes	***Pneumocystis carinii*** **pneumonia (PCP)** is the most common opportunistic infection seen in AIDS patients. It demonstrates an interstitial pattern of lung pathology and can be diagnosed by silver stain of a bronchial lavage.

A 42-year-old HIV-positive man presents to the emergency department with hemoptysis. He states that he has lost 15 pounds over the last 2 months and has had an intermittent fever, cough, and chills. He has not been taking any of his HIV medications and his CD4 count is 130. A chest x-ray reveals a lesion in his apical right lung. He is able to cough up green mucous coated with blood. You send the sample off for staining and culture. The sample reveals acid-fast bacilli and you decide to admit this patient to an isolation room and begin him on a multidrug treatment regimen while drug susceptibility tests are run.

Tuberculosis (TB)

Etiology	Inhalation of droplets containing ***Mycobacterium tuberculosis***
Pathology and Pathophysiology	*Pathophysiology:* TB bacilli are phagocytosed by alveolar macrophages, inducing a T-cell-mediated immune response. Macrophages and T cells kill most of bacilli, but a few residual bacilli lay dormant in the Ghon complex (primary TB). Upon reinfection or immunosuppression, these organisms become activated (secondary TB). TB may spread via lymphatics or blood and result in miliary TB (seeding of distal organs) or other extrapulmonary TB manifestations (include meningitis and Pott disease of the spine). **Primary TB: Ghon complex** (lesion in upper part of lower lobe that becomes calcified); enlarged caseous hilar lymph nodes **Secondary TB:** Tubercle formation **(cavitary lesion)** in **lung apex** or hilar lymph nodes; **caseating granuloma** made of epithelioid cells, fibroblasts, and giant cells
Clinical Manifestations	Primary TB is asymptomatic, but secondary TB produces constitutive symptoms (fatigue, **weight loss,** fever, and **productive cough** with **hemoptysis**) *Lab findings:* **Positive PPD test,** calcified Ghon complex on CXR, **acid-fast bacilli** in sputum and confirmed by culture
Treatment	**4-drug TB regimen:** INH, rifampin, pyrazinamide, ethambutol/streptomycin; add 2 more drugs at a time for drug-resistant strains
Notes	**PPD test:** Represents delayed hypersensitivity after primary TB infection

A 63-year-old man presents to your office after noticing that his left eyelid is droopy. Upon further questioning, he admits to some shortness of breath over the past 2 months, but attributes that to his 40-year-long heavy smoking habit. Physical examination reveals ptosis and miosis of the left eye and extremely dry skin of the left face. A chest x-ray demonstrates an irregular mass in the apex of his left lung. You admit the patient to the hospital for a biopsy of the mass, but you fear that the prognosis is not good.

Bronchogenic Carcinoma (Part 1)

Etiology

Cigarette smoking (especially linked with squamous cell and small cell carcinoma); air pollution; ionizing radiation; asbestos; nickel; chromium exposure

Pathology

Squamous cell: Central location; hilar mass with **cavitation; keratinization** of squamous cells

Adenocarcinoma: Peripheral location; includes **two forms:** (1) *Bronchial derived:* develops on **scar site,** glandular elements with mucin cells; (2) *Bronchioloalveolar:* multiple **mucinous nodules** (which appear on CXR), tall columnar epithelial cells, which line the alveolar walls

Small cell: Central location; small, round, basophilic cells with little cytoplasm (**oat cell** is a neoplasm of neuroendocrine Kulchitsky cells)

Large cell: Peripheral location; large polygonal **undifferentiated cells** (pleomorphic giant cells with leukocyte fragments in cytoplasm)

Metastases of all types often occur to adrenals, brain, liver, bone

Notes

Metastases of other cancers to the lung are more common than primary lung cancer and may spread to lung hematogenously, via lymphatics or through contiguous growth.

Carcinoid tumor can also occur in the lung.

A 71-year-old man presents to your office because of water retention. He states that he keeps himself well-hydrated, but he does not feel that his intake matches his output. Pertinent past medical history includes shortness of breath and weight loss of 15 pounds over the past 3 months. He has smoked 2 $^{1}/_{2}$ packs of cigarettes per day for 50 years. Besides looking into possible causes of urinary obstruction and other diagnoses, you decide to send the man for a chest x-ray, which reveals a central coin lesion. Based on the patient's history, you expect to see small, round cells with scant cytoplasm on a biopsy of the mass.

Bronchogenic Carcinoma (Part 2)

Clinical Manifestations

Hemoptysis; chest pain; **dyspnea;** cough; weight loss; **pleural effusion** (usually bloody); **hoarseness** (from recurrent laryngeal nerve paralysis)

Pancoast tumor: apical lung tumor resulting in **Horner syndrome** (ptosis, miosis, anhidrosis) owing to tumor involvement of cervical sympathetic plexus

Superior vena cava syndrome: facial swelling and dilation of veins of head and upper limbs from tumor compression of SVC

Cushing syndrome (caused by ACTH-like protein production), **SIADH** (caused by ADH-like protein production), and **Lambert-Eaton syndrome** (myasthenia gravis-like illness resulting from defect in acetylcholine release) are all seen in **small cell carcinoma**

Imaging: CXR demonstrates **pneumonic coin lesion**

Lab findings: Hypercalcemia **(**caused by **PTH-like protein production)** seen in squamous cell carcinoma

Treatment and Prognosis

Surgery, radiation, and chemotherapy for nonsmall cell lung carcinoma; radiation and chemotherapy for small cell carcinoma

Overall 5-year survival rate is 10%–15%

Notes

A 22-year-old man presents to the emergency department complaining of severe chest pain and shortness of breath. Physical examination reveals a tall, thin man with decreased breath sounds, decreased tactile fremitus, and hyperresonance to percussion over the right chest. His ECG appears normal, but a supine chest x-ray reveals a deep sulcus sign over the right costophrenic angle. You immediately place him on oxygen and prepare him for chest tube placement.

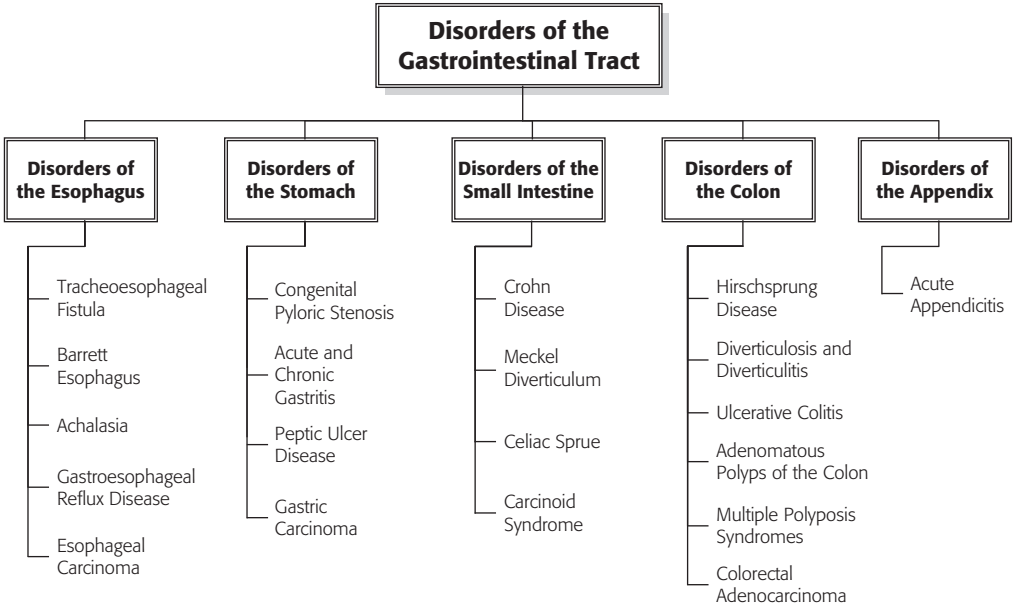
Pneumothorax

Etiology and Epidemiology	**Primary spontaneous: Rupture of subpleural bleb;** penetrating or blunt trauma **Secondary spontaneous:** Complication of prior lung disease (PCP, TB, CF, COPD) **Tension:** Positive pressure mechanical ventilation; lung infection Spontaneous pneumothorax is most common in **young, tall, thin men** who smoke.
Pathophysiology	**Compression and collapse of the lung** resulting from air in the pleural space
Clinical Manifestations	**Chest pain; dyspnea;** hypoxia; **diminished breath sounds;** decreased tactile fremitus; **lung hyperresonance to percussion** on side of pneumothorax *Imaging:* **Tracheal deviation away** from side of pneumothorax, visceral pleural line on upright CXR, **deep sulcus sign** (abnormally radiolucent costophrenic sulcus) on supine CXR
Treatment	Drainage of pleural air with chest tube or aspiration needle; surgical resection of blebs to prevent future recurrence if appropriate
Notes	Besides air, the pleural space can also become filled with serous fluid **(hydrothorax),** blood **(hemothorax),** inflammatory exudate **(empyema),** or lymphatic fluid **(chylothorax).** These fluids may need to be drained and the instigating factors treated to relieve respiratory distress.

A 63-year-old overweight male presents to your clinic because his wife has noticed that he stops breathing for up to 15 seconds at a time during the night. She is concerned and hopes that something can be done. On further questioning, he admits to often feeling sleepy during the day. You suggest that the patient start a weight loss program and that he consider using a CPAP machine to treat his condition.

Obstructive Sleep Apnea

Etiology and Epidemiology	Risk factors include obesity, hypothyroidism, cigarette smoking, and hypertension Most commonly affects **middle-aged men**
Pathophysiology	Loss of normal pharyngeal muscle tone **allows pharynx to collapse** during inspiration with resulting upper airway obstruction during sleep
Clinical Manifestations	**Daytime sleepiness** and cognitive impairment; thrashing movements during sleep Complications include pulmonary hypertension with right heart failure and cardiac arrhythmias *Lab findings:* **Apneic events** on sleep study (**polysomnogram**), erythrocytosis
Treatment	Weight loss; continuous positive airway pressure (**CPAP**); surgery to resect pharyngeal soft tissue (uvulopalatopharyngoplasty)
Notes	Breathing is interrupted by *lack of effort* in **central sleep apnea**.

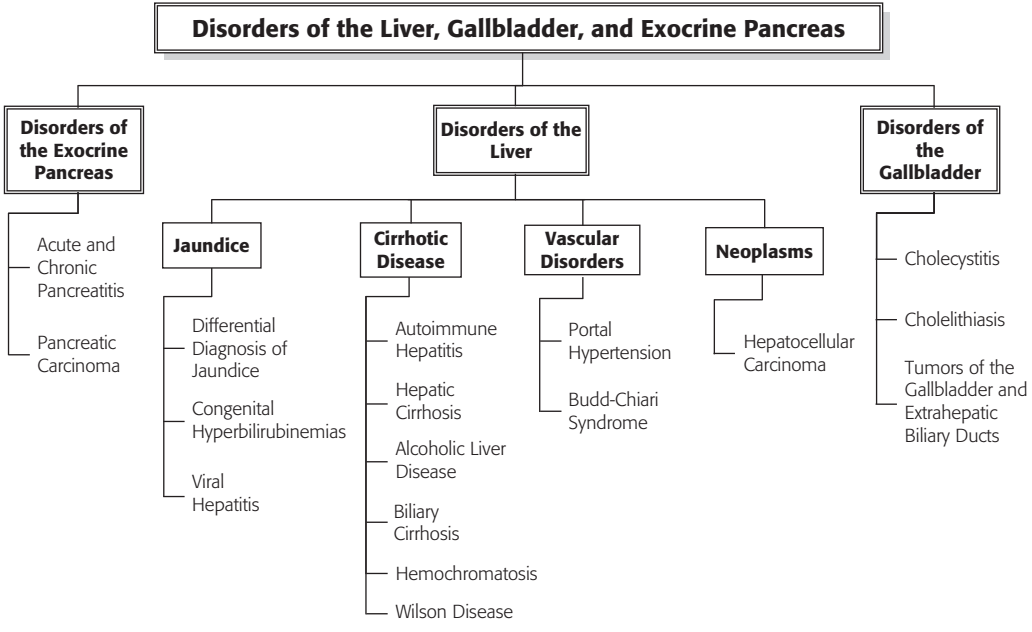

Disorders of the Gastrointestinal Tract
Disorders of the Esophagus
Tracheoesophageal Fistula
Barrett Esophagus
Achalasia
Gastroesophageal Reflux Disease
Esophageal Carcinoma
Disorders of the Stomach
Congenital Pyloric Stenosis
Acute and Chronic Gastritis
Peptic Ulcer Disease
Gastric Carcinoma
Disorders of the Small Intestine
Crohn Disease
Meckel Diverticulum
Celiac Sprue
Carcinoid Syndrome
Disorders of the Colon
Hirschsprung Disease
Diverticulosis and Diverticulitis
Ulcerative Colitis
Adenomatous Polyps of the Colon
Multiple Polyposis Syndromes
Colorectal Adenocarcinoma
Disorders of the Appendix
Acute Appendicitis

DIGESTION AND ABSORPTION

Nutrient	Digestion	Absorption in Small Intestine
Carbohydrates	α-Amylase in saliva; α-amylase from pancreas; oligosaccharide hydrolases at brush border of small intestine	Na^+-dependent cotransport of glucose, galactose in duodenum, proximal jejunum; facilitated diffusion of fructose
Proteins	Trypsin; chymotrypsin; carboxypeptidases; elastase	Na^+-dependent cotransport of amino acids, dipeptides, tripeptides
Lipids	Lingual lipase in saliva; mechanical breakdown in stomach; CCK slows gastric emptying; pancreatic lipases (lipase, phospholipase A, colipase)	Micelle formation in lumen; diffusion of fatty acids, monoglycerides, cholesterol into cell

MALABSORPTION

- Patients may present with steatorrhea (greasy, foul-smelling stools) and fat-soluble vitamin deficiencies caused by inability to absorb lipids.
- Causes include pancreatic enzyme deficiencies because of cystic fibrosis, pancreatitis, gastrin hypersecretion, ileal resection, and bacterial overgrowth.


Disorders of the Liver, Gallbladder, and Exocrine Pancreas
Disorders of the Exocrine Pancreas
Acute and Chronic Pancreatitis
Pancreatic Carcinoma
Disorders of the Liver
Jaundice
Differential Diagnosis of Jaundice
Congenital Hyperbilirubinemias
Viral Hepatitis
Cirrhotic Disease
Autoimmune Hepatitis
Hepatic Cirrhosis
Alcoholic Liver Disease
Biliary Cirrhosis
Hemochromatosis
Wilson Disease
Vascular Disorders
Portal Hypertension
Budd-Chiari Syndrome
Neoplasms
Hepatocellular Carcinoma
Disorders of the Gallbladder
Cholecystitis
Cholelithiasis
Tumors of the Gallbladder and Extrahepatic Biliary Ducts

LABORATORY TESTS OF THE LIVER AND PANCREAS

Aspartate and Alanine Aminotransferase (AST, ALT)

- Elevated levels result from hepatocellular necrosis or inflammation.
- ALT is more specific to the liver than AST.
- An AST/ALT > 2/1 is typical of alcoholic hepatocellular damage.

Alkaline Phosphatase

- Elevated levels suggest cholestasis or infiltrative liver disease (eg, tumor or abscess).
- Can be elevated in diseases of the liver, bone, intestine, or placenta.

Gamma-Glutamyl Transpeptidase (GGT) or 5′-Nucleotidase (5′-NT)

- Elevated levels concomitant with elevated alkaline phosphatase suggest a hepatic origin of disease.

Amylase and Lipase

- Released into the serum with pancreatic damage.
- Lipase is the more specific enzyme marker for pancreatitis.

You are called emergently to see a newborn baby boy in the nursery. The mother reports that the baby started choking and coughing up breast milk upon her first attempt to feed him. On physical examination, the baby is excessively salivating and appears slightly blue in color. You order laboratory studies, expecting to find severe fluid and electrolyte imbalances, and you order a chest x-ray to look for signs of a gastric air bubble. You also call a pediatric surgical consult as you suspect that the child will need immediate surgical repair of his condition.

Tracheoesophageal Fistula

Etiology	Congenital abnormality
Pathology	Multiple variants; the most common variant (90%) is lower esophagus communicating with trachea near tracheal bifurcation, resulting in the upper esophageal end becoming a blind pouch
Clinical Manifestations	Presents with **newborn choking,** coughing, and vomiting with each attempt to feed; **excessive salivation;** cyanosis and pulmonary symptoms; **aspiration** and paroxysmal suffocation and severe fluid and electrolyte imbalances may occur *Imaging:* CXR shows presence of gastric air bubble
Treatment	Surgical repair
Notes	Tracheoesophageal fistula can be associated with other abnormalities, including maternal **polyhydramnios** (excessive amniotic fluid), congenital heart disease, and GI malformations.

A 45-year-old male patient with a 3-year history of gastroesophageal reflux presents to a gastroenterologist with the chief complaint of increasing heartburn and regurgitation after meals. He has been taking antacids and proton pump inhibitors daily for the last year with reasonable relief of symptoms before the recent increase in heartburn and regurgitation even with antacid use. You, as the gastroenterologist, perform an endoscopy and find orange, gastric-type epithelium extending upward from the stomach into the distal esophagus in a circumferential fashion. You take a biopsy and send it to the laboratory for histologic studies, but you fear that this man is now at an increased risk for developing esophageal adenocarcinoma.

Barrett Esophagus

Etiology	Complication of chronic **gastroesophageal reflux**
Pathology	*Gross:* Orange, gastric-type epithelium extending upward from the stomach into distal tubular esophagus in a tonguelike or circumferential fashion on endoscopy *Microscopic:* Squamous epithelium of esophagus is replaced by **metaplastic columnar epithelium** with mucosal glands containing goblets cells. Columnar cells may display signs of dysplasia (enlarged, hyperchromatic nuclei).
Clinical Manifestations	Symptoms are a consequence of gastroesophageal reflux; history of **heartburn** (retrosternal burning), regurgitation, and belching after meals; dysphagia is common Complications include ulcerations, stricture formation, and **increased risk** (30- to 40-fold) of **esophageal adenocarcinoma**
Treatment	Long-term proton pump inhibitors or H_2-receptor antagonists and antacids
Notes	

A 55-year-old Caucasian man presents to your gastroenterology clinic. He reports that he has had difficulty keeping down both solids and liquids over the last several months. After obtaining a more detailed history, you find that the patient has regurgitated small amounts of undigested food after almost every meal for the last 3 weeks. He also complains of substernal pain even hours after eating small meals. A barium esophagography reveals a characteristic “bird-beak” at the lower esophageal sphincter. The patient asks what can be done to stop the pain and you answer that botulinum toxin can be injected directly into the affected esophageal site with relief that can last for months.

Achalasia

Etiology and Epidemiology	Idiopathic motility disorder Steady increase of incidence with age
Pathology and Pathophysiology	*Gross:* Dilation of esophagus above LES *Microscopic:* Absence of ganglionic cells of myenteric plexus in esophageal wall *Pathophysiology:* Loss of myenteric plexus results in loss of peristalsis in distal two thirds (smooth muscle) of the esophagus and **impaired relaxation of the LES**
Clinical Manifestations	Gradual, progressive difficulty swallowing both solids and liquids; regurgitation of undigested food; substernal pain and fullness after eating Complications include an increased risk of **squamous cell carcinoma** of the esophagus *Imaging:* **Barium esophageal swallow** shows dilated esophagus with distal stenosis (**"bird-beak"** or rat-tailed LES)
Treatment	Botulinum toxin injection (for pain); pneumatic dilation of LES; surgical myotomy
Notes	Esophageal dysfunction is also seen in Chagas disease, esophageal tumors, systemic sclerosis, and esophageal spasm.

A 42-year-old African American man presents to the clinic complaining of heartburn 30 minutes after eating many meals. His pain is worst when he lies down after eating. He has been treating himself with baking soda with good results, but he is wondering if some pill could be prescribed instead. On further questioning, the patient denies any regurgitation or dysphagia. You prescribe omeprazole (a proton pump inhibitor) in lieu of the baking soda and suggest that he does not recline for at least 3 hours after eating a large meal.

Gastroesophageal Reflux Disease

Etiology	Associated with hiatal hernia, alcohol, tobacco, obesity, pregnancy, and scleroderma
Pathophysiology	Gastric acid refluxes into esophagus because of **incompetent LES** (decreased muscular tone); untreated GERD can lead to Barrett esophagus
Clinical Manifestations	Characterized by **heartburn,** which worsens after meals, when lying down, and when bending; symptoms usually **reduced by antacids**
Treatment	H_2-receptor antagonists; proton pump inhibitors; antacids
Notes	

A 56-year-old man presents to the clinic with decreased ability to swallow solid foods even with extensive chewing. After taking a complete history, you learn that he has been avoiding large meals and has lost nearly 30 pounds over the last 6 months. He has smoked two packs of cigarettes a day for 20 years and has a history of heavy alcohol use as well. He complains of pain in his throat when swallowing and has been coughing up small amounts of blood on occasion. On physical examination, you notice both cervical lymphadenopathy and hepatomegaly, as well as a hoarse voice when the patient responds to your questions. You order an endoscopy with biopsy to establish your suspected diagnosis.

Esophageal Carcinoma

Etiology and Epidemiology	Risk factors include **Barrett esophagus,** achalasia, **smoking,** corrosive esophagitis, diverticula, esophageal webs, **alcohol use,** and genetic predisposition Occurs most frequently in men between the ages of 50 and 70
Pathology	**Squamous cell carcinoma:** *Gross:* arises in upper and middle thirds of esophagus; may be polypoid lesion or diffuse infiltrating lesion or necrotic ulceration. *Microscopic:* tumor cell clusters composed of dysplastic squamous epithelium with keratin pearls. **Adenocarcinoma:** *Gross:* arises in lower third of esophagus, usually from Barrett esophagus; appears as raised patch that may become a nodular mass with ulceration. *Microscopic:* glandular formation with mucin-producing cells.
Clinical Manifestations	Progressive solid food **dysphagia;** weight loss; anorexia; hoarseness; pain; hematemesis. Coughing or pneumonia may be a presenting sign owing to formation of tracheoesophageal fistula. Most patients present with advanced, incurable disease
Treatment and Prognosis	Palliative care; surgical resection; chemotherapy; radiation therapy Overall 5-year survival is < 15%
Notes	Squamous cell carcinoma accounts for 90% of esophageal cancers across the world, but in the United States, there is roughly equal incidence of squamous cell carcinoma and adenocarcinoma of the esophagus.

A mother brings her 2-week-old baby girl into your clinic. She reports that her child was feeding normally at first, but recently has developed projectile vomiting after feeds. After taking a more detailed history, you learn that the child has also not passed stool for the last 4 days. On physical examination, you notice an olive-like epigastric mass. You call for a surgical consult, as you suspect that the child will need a myotomy.

Congenital Pyloric Stenosis

Etiology and Epidemiology	Congenital abnormality with a multifactorial pattern of inheritance; often associated with Turner syndrome or **polyhydramnios** Tends to affect men more often than women
Pathology	*Pylorus:* Hypertrophy and hyperplasia of muscularis propria
Clinical Manifestations	**Projectile vomiting** beginning at 2 weeks of age **Palpable** olive-like **mass** in epigastric region
Treatment	Surgical incision of hypertrophied muscle **(myotomy)**
Notes	**Diaphragmatic hernia** is the incomplete development of the diaphragm resulting in abdominal contents herniating through the diaphragm malformation and compressing developing lung buds, thereby causing pulmonary hypoplasia. Clinical manifestations include breathlessness, cyanosis, and unusually flat abdomen in a newborn. This condition can be repaired surgically.

A 66-year-old woman presents to the emergency room complaining of several bouts of bloody vomit. Further history reveals that she has also been suffering from some epigastric pain. Past medical history is significant for osteoarthritis, for which she has been taking high-dose Motrin daily. You admit her for endoscopic evaluation and you suspect that she will need to consider alternative therapy for her osteoarthritis.

Acute and Chronic Gastritis

Etiology	**Acute:** Drugs (eg, NSAIDs); alcohol; smoking; severe stress; systemic infections; uremia **Chronic: Type A** is an autoimmune disorder while **type B** is caused by *Helicobacter pylori* infection
Pathology	**Acute:** *Gross:* subepithelial hemorrhages, petechiae, and punctate erosion. *Microscopic:* **neutrophilic infiltration** with purulent and hemorrhagic exudate. **Chronic:** *Gross:* thickened and reddened rugal folds in **fundus (type A) or antrum (type B);** with long-standing disease, **mucosa may become atrophic.** *Microscopic:* **lymphocytic infiltrate** in lamina propria; lymphoid aggregates; presence of *H pylori* among microvilli (type B); hyperplasia of G cells (type A); presence of intestinal metaplasia or dysplastic cells.
Clinical Manifestations	**Acute:** Anorexia; **epigastric pain;** nausea; vomiting; **hematemesis** (coffee ground emesis) **Chronic: Type A:** fatigue; indigestion and diarrhea; pallor; mild splenomegaly. *Lab findings:* **autoantibodies to parietal cells; pernicious anemia;** macrocytic anemia; B_{12} deficiency; positive Schilling test. **Type B:** asymptomatic; associated with **peptic ulcer.** *Lab findings:* **positive *H Pylori* serology or stool antigen.** Complications of both types include an increased risk of **gastric carcinoma**
Treatment	**Acute:** H_2-receptor antagonists or proton pump inhibitors **Chronic:** Parenteral vitamin B_{12} (type A); triple therapy (bismuth, metronidazole, tetracycline, or amoxicillin) (type B)
Notes	

A 65-year-old man presents to the clinic complaining of epigastric pain after meals. After taking a more thorough history, you learn that he is a heavy smoker and that he has lost 10 pounds over the last 4 months because of a decreased appetite connected with the pain associated with meals. He denies any frank blood in his stools, but he has noticed that his stool has been darker recently. You schedule an upper endoscopy to evaluate the patient further, but in the meantime, you start him on a high-dose proton pump inhibitor.

Peptic Ulcer Disease

Etiology and Epidemiology	**Gastric (G):** *H pylori* infection (70%); NSAIDs; seen in **older** patients **Duodenal (D):** ***H pylori*** infection; seen in **younger** patients and in patients with blood group O Development of peptic ulcer disease is also associated with chronic gastritis, **smoking,** Zollinger-Ellison syndrome, hyperparathyroidism, and MEN type I
Pathology and Pathophysiology	*Gross:* Mucosal defect with clean, **punched-out margins** occurring in antral and prepyloric regions **(G)** or in duodenum (usually the first part) **(D)** *Microscopic:* Varies depending on stage of ulcer; active ulcers demonstrate necrotic fibrinoid debris with neutrophilic infiltrate and eventually granulation tissue; **hypertrophy of Brunner glands (D)** *Pathophysiology:* **G:** arises because of decreased mucosal protection against gastric acid. **D:** arises because of increased gastric acid and pepsin secretion in combination with decreased mucosal protection.
Clinical Manifestations	**Gastric: Epigastric pain greater with meals;** weight loss. *Lab findings:* decreased H^+ secretion, increased gastrin levels. **Duodenal: Epigastric pain decreases with meals;** weight gain. *Lab findings:* increased H^+ secretion Complications include GI bleed, perforation, and obstruction.
Treatment	Proton pump inhibitors or H_2-receptor antagonists. Treat *H pylori* infection with **triple therapy** (bismuth, metronidazole, and tetracycline or amoxicillin).
Notes	Peptic ulcer disease is not a precursor to gastric carcinoma.

A 54-year-old Japanese American man presents to the clinic complaining of a gnawing epigastric pain. Upon taking a complete history, you learn that he has lost 20 pounds over the last 2 months and has been vomiting after meals. The pain has not been relieved by the use of over-the-counter antacids. On physical examination, you note supraclavicular lymph node swelling and darkened, thickened skin in the flexural areas of the patient's legs and arms. You schedule the patient for an upper endoscopy with cytologic brushings and biopsies of any suspicious lesions as you fear that this patient may have a very serious condition.

Gastric Carcinoma

Etiology and Epidemiology	Risk factors include **chronic gastritis,** dietary nitrosamines, and excessive sodium intake More common in **men > 50 years** of age and in patients with blood group A
Pathology	**Intestinal type:** *Gross:* lesion with irregular necrotic base and **heaped-up margins,** usually located in the lesser curvature of the antrum or prepyloric region. *Microscopic:* glandular formation of mucin-producing cells. **Diffuse type:** *Gross:* infiltrative process producing rigid stomach wall (**linitis plastica** or leather bottle stomach). *Microscopic:* clusters of gastric-type mucous cells **(signet-ring cells)** within gastric wall. Can see early, aggressive, local metastasis to the lymph nodes and liver
Clinical Manifestations	Presents with anorexia, weight loss, vomiting, and gnawing epigastric pain not relieved by antacids *Lab findings:* Hypochromic microcytic anemia
Treatment	Surgical resection
Notes	**Virchow node** is involvement of the left supraclavicular node by metastasis of stomach or other GI cancer. **Krukenberg tumor** is bilateral metastasis of GI (usually stomach) cancer to ovaries. Histologically, the tumor has abundant mucus and signet-ring cells. **Acanthosis nigricans** refers to hyperpigmentation and epidermal thickening of the flexural areas. It is suggestive of a visceral malignancy, including cancer of the stomach, lung, breast, or uterus.

A 25-year-old man presents to the clinic complaining of intermittent bouts of diarrhea and RLQ pain not associated with meals. The patient reports that he has been constipated for several days. Your physical examination is significant for a temperature of 100°F, several oral aphthous ulcers, and a palpable RLQ mass. The patient also complains of migrating joint pains and a periodic burning sensation in his eyes with blurred vision, although his eye examination is normal. The perianal region is normal upon examination, but the guaiac test for occult blood is positive. You order an upper GI series with small bowel follow-through to look for evidence of ulcers, strictures, or fistulas as you suspect that this patient's symptoms may be associated with a chronic disease.

Crohn Disease

Etiology and Epidemiology	Idiopathic, although infectious causes have been suggested Occurs most frequently in women between the **ages of 15 and 30**
Pathology	*Gross:* Changes located to **terminal ileum,** small intestine, and colon; not found in rectum; **creeping fat** over bowel surface; thickened bowel wall leading to a **narrow lumen;** linear ulceration of the mucosa; **cobblestone mucosa** (submucosal edema with elevation of surviving mucosa) *Microscopic:* **Transmural inflammation; skip lesions** (areas of normal bowel interspersed with diseased bowel); fissures; **noncaseating granulomas;** atrophy of crypts; mucosal metaplasia
Clinical Manifestations	Intermittent bouts of **low-grade fever, diarrhea (often with blood),** and RLQ pain; may have RLQ mass on physical examination *Extraintestinal manifestations:* Oral aphthous ulcers; **erythema nodosum; migratory polyarthritis;** uveitis; sacroiliitis; ankylosing spondylitis *Complications:* Fibrous **strictures** causing intestinal **obstruction** or perforation; **perianal fistulas;** and malabsorption syndrome *Imaging:* **String sign** on x-ray after barium swallow (represents narrowed bowel lumen); evidence of ulceration, stricturing, or fistulas of the small intestine or colon on endoscopy
Treatment	Antidiarrheals; glucocorticoids; sulfasalazine; immunosuppressants
Notes	Crohn disease is considered an **inflammatory bowel disease** along with ulcerative colitis.

A 1-year-old boy is brought to the emergency room by his concerned mother after she found bright red stool in his diapers. On physical examination, the child has a tender abdomen and you note a sausage-like mass in the right lower quadrant of the abdomen. You make a diagnosis of intussusception and treat the patient with an air enema. You suggest that the child undergo a lower GI series to determine if he has any bowel abnormality that may predispose him to developing intussusception.

Meckel Diverticulum

Etiology and Epidemiology	Derived from remnant of **vitelline duct** (yolk stalk) Occurs in 2% of population
Pathology	*Gross:* Blind pouch on antimesenteric border of ileum within 2 feet of the ileocecal valve causing tubular outpouching of small intestine *Microscopic:* True diverticulum with all 3 layers of the bowel wall (mucosa, submucosa, muscularis propria); may contain **acid-secreting gastric mucosa** and/or pancreatic tissue
Clinical Manifestations	Presents in first 2 years of life. Usually asymptomatic, but can cause peptic ulcerations leading to a **GI bleed, intussusception** (invagination of a bowel segment into a more distal bowel segment), or **volvulus** (twisting of one bowel portion around its own mesentery). Intussusception presents with red currant jelly stools owing to bowel ischemia. Volvulus presents with acute abdominal pain, constipation, gas, and sigmoid distention.
Treatment	Surgical excision
Notes	Meckel diverticulum is the most common congenital abnormality of the GI tract.

A 23-year-old Irish immigrant presents to the clinic complaining of diarrhea that has been bothering him for 4 weeks. He tells you that he has bowel movements upward of 10 times a day. He describes his stools as soft, pale, large, floating, greasy, and foul smelling. On further questioning, he reveals that he also lost 7 pounds over the past month even though his appetite has been greater than usual. Physical examination reveals loss of muscle mass and marked pallor and the abdominal examination is significant for distention and hyperactive bowel sounds. Your suspicions are confirmed when serum studies reveal the presence of antigliadin antibodies.

Celiac Sprue

Etiology and Epidemiology	**Autoimmune-mediated intolerance to gluten** (present in wheat, oat, rye, and barley) More common in people of northern European descent; also associated with HLA-DR3 and HLA-DQw2
Pathology	*Gross:* Blunting and **atrophy of small intestinal mucosal villi** *Microscopic:* **Increased lymphocytes** and plasma cells in the lamina propria; loss of brush border
Clinical Manifestations	May become symptomatic in **infancy** with growth retardation and **failure to thrive**, but may present in young adulthood**.** Also may see **steatorrhea** (pale, bulky, frothy, foul-smelling stool), abdominal distention, weight loss, or **dermatitis herpetiformis** (symmetric, recurrent, pruritic, subepidermal blisters usually occurring over extensor surfaces of the extremities or over the trunk, scalp, and neck); 10%–15% of patients will develop enteropathy-type T-cell lymphoma. *Lab findings:* Abnormal D-xylose test, **antigliadin and antiendomysial and anti-TTG antibodies**
Treatment	**Gluten-free diet;** dapsone for dermatitis herpetiformis
Notes	**Tropical sprue** is a malabsorption syndrome caused by overgrowth of enterotoxigenic organisms found in the tropics and is treated with broad-spectrum antibiotics. **Whipple disease** is caused by a rare multisystemic infection with PAS-positive actinomycete, *Tropheryma whippelii.* It presents with a malabsorption syndrome, arthralgias, and CNS, cardiac, and ocular involvement.

A 40-year-old male patient presents to the clinic complaining of abdominal cramps and watery diarrhea. Upon taking a more complete history, you learn that he has had recurrent, watery diarrhea for nearly 2 months and has lost nearly 10 pounds during the same period. On physical examination, you find a red, flushed face, expiratory wheezes audible on both lower lung fields, and a right-sided murmur consistent with pulmonic regurgitation. You order a 24-hour urine collection looking for elevated levels of 5-HIAA and you explain to the patient that he will need a CT scan in an attempt to locate the anatomic source of his symptoms.

Carcinoid Syndrome

Etiology and Epidemiology	Caused by **serotonin release** from certain carcinoid tumors Occurs in 1% of patients with carcinoid tumors
Pathology and Pathophysiology	**Carcinoid Tumor:** *Gross:* yellowish-tan intramural or submucosal mass most commonly present in the **appendix,** but also present in GI tract, pancreas, respiratory tract, gallbladder, thymus, and reproductive organs. *Microscopic:* derived from **neuroendocrine cells** of the GI tract; tumor cells have pink granular cytoplasm with stippled nucleus. *Pathophysiology:* Carcinoid syndrome is caused by **hepatic metastases** of carcinoid tumor. Carcinoid tumors of the bowel release serotonin into the portal circulation, where it is metabolized and removed. Hepatic metastases release serotonin into the hepatic vein and thus into systemic circulation, thereby leading to carcinoid syndrome.
Clinical Manifestations	Recurrent **watery diarrhea; facial flushing;** asthma (**bronchospasm); right-sided valvular disease** (pulmonic, tricuspid valves) leading to endocarditis and right-sided heart failure *Lab findings:* Increased levels of **5-HIAA in the urine**
Treatment and Prognosis	Cyproheptadine (histamine-receptor antagonist) for diarrhea; octreotide acetate (somatostatin analog) reduces urinary 5-HIAA; surgery for localized carcinoid Overall 5-year survival rate for carcinoid tumors is 90%
Notes	Carcinoid tumor is the most common tumor of the appendix. Left-sided heart disease in carcinoid syndrome is seen in fen-phen diet pill users.

A 2-day-old baby boy with Down syndrome is examined in the neonatal ward because the child has failed to pass meconium. On examination, the child has abdominal distention consistent with an obstruction of the bowel. Realizing that the patient may experience a possible bowel perforation with resulting peritonitis if not treated immediately, you put the newborn on parenteral alimentation while you order a rectal biopsy in which you expect to see absence of ganglion cells in the muscle wall and submucosa of the rectal tissue.

Hirschsprung Disease

Etiology and Epidemiology	Caused by **failure of neural crest cell migration during embryogenesis** Occurs in 1 in 5000 births; affects boys more than girls; associated with Down syndrome
Pathology	*Gross:* **Dilation of colon** proximal to aganglionic segment (**megacolon**); involvement of **rectum** *Microscopic:* Absence of ganglion cells of Auerbach and Meissner plexuses
Clinical Manifestations	Presents as **failure to pass meconium** or chronic constipation with abdominal bloating early in life; may also present as acute enterocolitis with watery, foul-smelling stool, or perforation of colon
Treatment	Surgery and anastomosis
Notes	

A 65-year-old man presents to the clinic complaining of a mild aching abdominal pain in the left lower quadrant. Upon taking a more detailed history, you learn that he has been constipated, while passing loose stools every other day for the past 2 weeks. He has vomited 3 times over the same period of time. On physical examination, he has a low-grade fever, a palpable left lower quadrant mass with tenderness, and a positive stool guaiac test. Plain abdominal films find no evidence of free abdominal air. You decide to start the patient on an antibiotic regimen to treat his current symptoms and you inform the patient that a high-fiber diet will be necessary to treat his underlying disease.

Diverticular Disease (Diverticulosis and Diverticulitis)

Etiology and Epidemiology	**Diverticulosis:** Development of diverticula is associated with increased pressure in the bowel and bowel wall weakness; commonly seen in people > 60 years; associated with low-fiber diet **Diverticulitis:** Caused by inflammation of diverticula, usually by impacted fecal material
Pathology	**Diverticula:** *Gross:* **blind pouches** leading off the alimentary tract that communicate with gut lumen; most commonly false (pulsion) diverticula resulting from herniation of mucosa through defects in muscular layer; less commonly true (traction) diverticula consisting of mucosa, muscularis, and serosa. *Microscopic:* atrophic mucosa with **thin muscularis propria.** **Diverticulosis: Presence of multiple diverticula** most commonly in the sigmoid colon **Diverticulitis: Inflammation of diverticula** with inflammatory infiltrate with edema
Clinical Manifestations	**Diverticulosis:** Usually **asymptomatic,** but can present with vague abdominal discomfort and frank blood in the stool with no leukocytes or epithelial cells **Diverticulitis:** Presents with **fever,** a chronic colicky **LLQ abdominal pain,** and possibly bright red **blood in the stool;** complications include perforation, abscess formation, peritonitis, and bowel stenosis
Treatment	**Diverticulosis:** High-fiber diet; psyllium fiber laxatives **Diverticulitis:** Antibiotics; high-fiber diet; consider colonic resection if multiple episodes of diverticulitis occur
Notes	

A 32-year-old woman presents to the clinic complaining of blood-tinged diarrhea. She reports that she had 4 episodes of loose stool per day with intermittent rectal bleeding for the last 2 weeks. On further questioning, you learn that she frequently sits on the toilet with the urge to defecate, but does not actually have bowel movements. On physical examination, the patient has LLQ tenderness and red blood is visible on digital rectal examination. You decide to order a flexible sigmoidoscopy, expecting to see continuous inflammation of the colon with rectal involvement and friable mucosal pseudopolyps.

Ulcerative Colitis

Etiology and Epidemiology	May be related to immune system dysfunction Occurs **most commonly in women between ages of 20 and 25,** but affects all ages
Pathology	*Gross:* **Continuous lesions** of the colon with **rectal involvement; friable mucosal pseudopolyps** (mucosal remnants of previous ulcerations) with free-hanging mesentery *Microscopic:* Mononuclear inflammatory infiltrate in lamina propria; **crypt abscesses** and ulcers (neutrophilic infiltrate in crypt lumen); **dysplastic changes** in epithelial cells; submucosal fibrosis and glandular atrophy results from healed disease
Clinical Manifestations	May present with **tenesmus** (urge to defecate with ineffectual straining) or chronic **diarrhea with blood** and mucus. *Extraintestinal manifestations:* Pyoderma gangrenosum (painful ulcerating boils) and **primary sclerosing cholangitis** (fibrosing chronic cholestasis that can lead to portal hypertension). Complications include severe colonic stenosis, **toxic megacolon** (inflammation of myenteric plexuses leading to gangrene), and **increased risk for colorectal adenocarcinoma** *Imaging:* Loss of haustrations causes **lead-pipe** appearance
Treatment	Antidiarrheals; sulfasalazine; glucocorticoids; immunosuppressants; proctocolectomy (with placement of ileostomy) is curative
Notes	Ulcerative colitis is considered an **inflammatory bowel disease** along with Crohn disease.

A 55-year-old man with a family history of colon cancer comes into the clinic for his annual colon cancer screening. You perform a routine fecal occult blood test that results in a positive reading. A flexible sigmoidoscopy is ordered during which several pedunculated polyps are visualized and biopsied. You inform the patient that you think that the chance of malignant progression of these neoplasms is not high, but you will have to await the results of the biopsies to be certain these polyps are benign.

Adenomatous Polyps of the Colon

Etiology and Epidemiology	Associated with familial predisposition (possible connection to mutation of tumor suppressor gene on chromosome 5) Present in 35% of adults > 50 years of age
Pathology	**Tubular adenomas (75%):** Usually found in colon; small and pedunculated with stalk; dysplastic epithelium with hyperchromatic nuclei and loss of cell orientation **Tubulovillous adenomas (15%):** Resemble tubular adenomas but surface is covered by fingerlike villi, similar to villous adenomas **Villous adenomas (10%):** Usually found in rectum or sigmoid colon; broad-based (sessile) polyps with large numbers of fingerlike villi; villi have dysplastic columnar epithelium
Clinical Manifestations	Usually asymptomatic but can result in **rectal bleeding,** which may cause an iron deficiency anemia Associated with **increased risk for colorectal adenocarcinoma** (especially with villous adenomas).
Treatment	Colonoscopic removal of adenomatous polyps; primary surgical resection of large sessile lesions Aspirin and NSAIDs used to decrease incidence of adenomas and colorectal cancer
Notes	

A 20-year-old male patient presents to the gastroenterologist's office for his annual sigmoidoscopy screening. He has been coming to your office every other year for the last 10 years because he has an immediate relative with a familial polyposis syndrome. You perform the flexible sigmoidoscopy and find over100 adenomas in the colon. You order genetic testing, which confirms your presumptive diagnosis. After informing the patient of your findings, you suggest that he undergo total colectomy with ileoanal anastomosis to prevent the development of colorectal cancer.

Multiple Polyposis Syndromes

Familial Adenomatous Polyposis	*Etiology:* Autosomal dominant condition caused by mutation of APC gene on chromosome 5 *Clinical manifestations:* 500–2500 colonic adenomas present at puberty *Treatment:* Prophylactic colectomy (**100% evolve into colon cancer** if not resected)
Hereditary Nonpolyposis Colorectal Cancer	*Etiology:* Autosomal dominant condition caused by defect in DNA mismatch repair genes on chromosome 2, 3, or 7 *Clinical manifestations:* Appearance of **colonic adenomas in early adulthood;** increased risk for colorectal cancer and other cancers (especially endometrial cancer) *Treatment:* Surgical resection
Peutz-Jeghers Syndrome	*Etiology:* Autosomal dominant condition *Clinical manifestations:* Palpable **hamartomatous (nonneoplastic) polyps** of the colon and small intestine; **melanotic macules** in the mouth, lips, hands, and genitalia; no increased risk for colorectal cancer, but there is an increased risk of stomach, breast, ovarian, pancreatic, uterine, or lung cancer *Treatment:* Routine surveillance for malignancy
Gardner Syndrome and Turcot Syndrome	*Etiology:* Autosomal dominant conditions associated with defects in APC gene on chromosome 5 *Clinical manifestations:* **Gardner: adenomatous polyps** along with **osteomas** and soft-tissue tumors. **Turcot: adenomatous polyps** with **CNS tumors.** Both conditions carry increased risk for colorectal cancer. *Treatment:* Surgical resection

A 55-year-old white man presents to the clinic complaining of weakness and fatigue. After taking a detailed history, you learn that he has been suffering from intermittent rectal bleeding and loose stools and that he has lost 15 pounds over the last 2 months. His family history is significant for colon cancer. On physical examination, the patient has marked pallor and a positive stool guaiac test. Laboratory tests reveal an iron deficiency anemia and elevated CEA levels. You schedule a colonoscopy with biopsy for pathologic confirmation of your presumptive diagnosis.

Colorectal Adenocarcinoma

Etiology and Epidemiology	Risk factors include adenomatous polyps, long-standing ulcerative colitis, low-fiber diet, old age, positive family history, hereditary nonpolyposis colorectal cancer (HNPCC), and familial adenomatous polyposis (FAP) Most commonly occurs between the ages of 60 and 80
Pathology	*Gross:* Appearance varies from polypoid mass (proximal colon) to lesions with ulcerated centers and irregular margins that circumscribe bowel (distal colon) *Microscopic:* Dysplastic columnar cells in glandular formation; may produce mucin, some tumors may be anaplastic
Clinical Manifestations	Can be asymptomatic; if symptomatic, presents with **pallor, weight loss, intermittent diarrhea, LLQ pain,** or obstruction *Lab findings:* **Positive stool guaiac test; increased serum CEA;** microcytic, hypochromic anemia (iron deficiency anemia secondary to GI bleed)
Treatment	Surgical resection; chemotherapy (5-FU)
Notes	Colorectal cancer is the second leading cause of death owing to malignancy in the United States. Preventive measures include screening all patients > 50 years of age with colonoscopy every 10 years.

A 13-year-old girl presents to the emergency room with RLQ pain, nausea, and vomiting. Just 12 hours earlier, she was experiencing vague, colicky periumbilical pain. On physical examination, you find that the patient has a low-grade fever and localized tenderness with guarding in the RLQ when palpated. Laboratory studies show mild leukocytosis. You call the pediatric surgery team to prepare this patient for immediate surgery.

Acute Appendicitis

Etiology and Epidemiology	Caused by **obstruction of the appendix** by a fecalith, inflammation, foreign body, or neoplasm Peak incidence is between **10 and 30 years of age**
Pathology	*Gross:* Red, **swollen appendix** with fibrinous exudate *Microscopic:* **Neutrophilic infiltrate** extending through to muscularis; abscess formation; ulcerations; congested vasculature
Clinical Manifestations	Vague **periumbilical pain** that later localizes to **RLQ pain; fever;** anorexia; nausea; **vomiting; psoas sign** (pain on passive extension of right hip); **obturator sign** (pain with passive flexion and internal rotation of right hip) Complications include gangrene and perforation leading to peritonitis *Lab findings:* Leukocytosis
Treatment	Appendectomy
Notes	Appendicitis is the most common abdominal surgical emergency, affecting 10% of population.

A 50-year-old man presents to the emergency room complaining of abdominal discomfort. Upon taking a complete history, you find that he has had a dull ache in the RUQ for nearly a week and that he had a low-grade fever and a sense of malaise during the same period. He also complains that his urine has progressively become darker and darker even though he has kept himself well-hydrated. On physical examination, you notice a yellow discoloration of the skin and yellowing of the whites of the eyes. His liver is tender and enlarged and he has appreciable ascites, gynecomastia, and asterixis. You order laboratory studies, specifically expecting to find increased urine bilirubin, decreased urine urobilinogen, and increased AST and ALT.

Jaundice

Etiology	Caused by hepatocellular disease, biliary obstruction, hemolytic anemia, and congenital hyperbilirubinemias
Pathophysiology	Bilirubin is formed by the degradation of heme. When heme is degraded outside the liver, bilirubin is bound to albumin **(unconjugated bilirubin)** and transported to the liver for processing. Hepatocytes normally conjugate bilirubin **(conjugated bilirubin)** and excrete it into bile. Bile enters the GI tract where it is eventually converted into urobilinogen by intestinal bacteria, reabsorbed and excreted in the urine. Only conjugated bilirubin is soluble and can be reabsorbed from the intestine. Pathologic processes cause increased production of bilirubin, decreased hepatic uptake or secretion of bilirubin, deficient conjugation, or impair the flow of bile that cause the accumulation of bilirubin, which leads to jaundice.
Clinical Manifestations	Jaundice presents with yellow discoloration of skin, sclera, and tissues, and dark urine *Lab findings:* Depends on etiology of jaundice: (1) *hepatocellular disease jaundice:* **conjugated and unconjugated hyperbilirubinemia,** increased urine bilirubin, normal or decreased urine urobilinogen, increased ALT and AST, increased ALP; (2) *biliary obstructive jaundice:* **conjugated hyperbilirubinemia,** increased urine bilirubin, decreased urine urobilinogen, **increased ALP,** hypercholesterolemia; (3) *hemolytic anemia jaundice:* **unconjugated hyperbilirubinemia,** absent urine bilirubin (acholuria), increased urine urobilinogen
Treatment	Treat underlying cause
Notes	

A 1-month-old boy presents to the clinic with jaundice. To determine the cause of his jaundice, you order a panel of liver function tests. Results from the studies show an increased unconjugated bilirubin level in the serum and low fecal urobilinogen. Further genetic testing shows the child has a lack of bilirubin *UDP glucuronyl transferase,* an autosomal recessive condition. Although you place the child on plasmapheresis and phototherapy, he inevitably develops CNS deterioration and dies within the year.

Congenital Hyperbilirubinemias

Gilbert Syndrome	*Etiology:* Autosomal dominant condition resulting in decreased *UDP-glucuronyl transferase* activity and decreased bilirubin uptake by liver *Clinical manifestations:* Usually **asymptomatic;** mild scleral icterus, may be triggered by stress; **unconjugated hyperbilirubinemia**
Crigler-Najjar Syndromes Types I and II	*Etiology:* Autosomal recessive (type I) or autosomal dominant with variable penetrance (type II) conditions resulting in absent *UDP-glucuronyl transferase* activity *Clinical manifestations:* Type I more severe than type II; presents early in life with jaundice; **kernicterus and CNS deterioration; unconjugated hyperbilirubinemia** *Treatment:* Plasmapheresis and phototherapy (type I); phenobarbital (type II)
Dubin-Johnson Syndrome and Rotor Syndrome	*Etiology:* Autosomal recessive conditions resulting from defective bilirubin transport out of liver *Clinical manifestations:* Intermittent jaundice; RUQ and epigastric pain; **conjugated hyperbilirubinemia;** mildly elevated LFTs; **black liver** (D-J syndrome); Rotor syndrome is less severe
Notes	Make sure to differentiate hereditary hyperbilirubinemias from physiologic jaundice of the newborn **(neonatal hyperbilirubinemia),** which appears in the first week of life and is caused by increased bilirubin production and relative deficiency of *UDP-glucuronyl transferase* in the immature liver

A 30-year-old man presents to the clinic complaining of abdominal pain and dark urine. While taking a history, you note that the pain is localized to the RUQ and has been present for over 6 months. On physical examination, you notice yellowing of the skin as well as of the whites of the eyes. Hepatomegaly is present on abdominal palpation. The patient states that he is sexually active and has, on occasion, not practiced safe sex. He also admits to IV drug use. You order serum studies expecting to find elevated ALT and AST levels. You also order studies looking for serologic markers specific to this patient's most likely diagnosis.

Viral Hepatitis

Etiology	**HAV** and **HEV** are transmitted fecal-orally. **HBV, HCV, HDV** are blood-borne viruses
Pathology	**Acute hepatitis (all strains):** *Gross:* enlarged, red liver (green if cholestatic). *Microscopic:* **swelling of hepatocytes; ground-glass hepatocytes (HBV);** cholestasis; macrophage aggregation; bridging necrosis; portal tract inflammation; hyperplasia of Kupffer cells. **Chronic hepatitis (HBV, HCV, HDV):** *Gross:* **cirrhotic liver** with fibrous septa and irregular nodules. *Microscopic:* **bridging fibrosis** of the portal and periportal regions; lymphoid aggregates.
Clinical Manifestations	Abdominal pain; dark urine; hepatomegaly; jaundice; scleral icterus **HBV and HCV** have a strong association with chronic active hepatitis, cirrhosis, and **hepatocellular carcinoma** *Lab findings:* **Elevated ALT and AST levels** *Serologic markers:* IgM antibody to HAV detects active HAV infection. IgG antibody to HAV indicates old HAV infection and is protective. **HBsAg** indicates infection (prolonged in **carrier state**). Antibody to HBs provides immunity to HBV. **IgM antibody to HBcAg** is important for diagnosis of acute disease during **window period. Antibody to HBeAg** indicates low **transmissibility.**
Treatment	Vaccinations for HAV and HBV. HBV treated with antivirals (ie, entecavir). HCV treated with PEG-interferon and ribavirin.
Notes	HCV is a common cause of hepatitis among IV drug users. HEV causes increased mortality among pregnant women.

A 33-year-old female presents to the clinic complaining of abdominal bloating and yellowing of her skin. She has a past medical history significant for Hashimoto thyroiditis and takes Synthroid for this condition. On physical examination, you notice jaundice as well as the appearance of multiple spider nevi and hepatomegaly. Initial laboratory studies reveal elevated bilirubins and transaminases as well as elevated globulin levels. While you order a panel of autoimmune studies and arrange for a liver biopsy, you begin to suspect that this patient may benefit from treatment with steroids.

Autoimmune Hepatitis

Etiology and Epidemiology	**Autoimmune disorder,** often found in conjunction with other autoimmune disorders (Sjögren syndrome, thyroiditis, ulcerative colitis, arthritis) Most common in young women, although can affect all ages
Pathology	*Gross:* **Cirrhotic liver** with fibrous septa and nodular appearance *Microscopic:* **Bridging fibrosis** of the portal and periportal regions; hepatocyte necrosis
Clinical Manifestations	May be asymptomatic initially or may present with acute hepatitis, hepatomegaly, spider nevi, and amenorrhea *Lab findings:* **Elevated gamma-globulin levels,** elevated bilirubins and transaminases, positive antinuclear antibody (ANA), **positive anti-smooth-muscle antibody (ASMA) (type 1),** positive anti-liver-kidney microsome antibody (LKM-1) (type 2)
Treatment	Prednisone with or without azathioprine
Notes	

A 52-year-old man presents to the clinic complaining of fatigue, abdominal bloating, and loss of sex drive. Upon taking his history, you learn that the symptoms have come on slowly over the last year and that he is a recovering alcoholic. On physical examination, you note painful swelling of the breasts bilaterally, ascites, scleral icterus, jaundice, abnormally strong halitosis, several capillary telangiectasias on his face, loss of sexual hair, and 3+ ankle edema bilaterally. While awaiting laboratory studies, you start diuretic therapy and encourage continued abstinence from alcohol.

Hepatic Cirrhosis

Etiology	**Micronodular:** Alcoholism; hemochromatosis; Wilson disease **Macronodular:** HBV and HCV; drug-induced hepatitis; biliary cirrhosis; Wilson disease; α_1-antitrypsin deficiency; progressed alcoholic micronodular cirrhosis
Pathology and Pathophysiology	*Gross:* **Micronodular** cirrhosis has **uniform nodules < 3 mm; macronodular** cirrhosis has broad fibrous bands dividing liver into **irregular nodules > 3 mm** *Microscopic:* **Diffuse fibrosis** of the liver followed by nodular regeneration lacking normal hepatic architecture; reorganization of vascular architecture *Pathophysiology:* Liver destruction leads to increased portal venous pressure, decreased plasma oncotic pressure (hypoalbuminemia), and decreased degradation of aldosterone, resulting in peripheral edema and ascites
Clinical Manifestations	Weakness; weight loss; **ascites;** vomiting; **jaundice;** fetor hepaticus (corpse-smelling breath); **spider nevi** (capillary telangiectasias of face); **gynecomastia;** loss of sexual hair; testicular atrophy; **asterixis** (coarse hand tremor); ankle **edema.** Complications include **hepatic encephalopathy** (ammonia acts as neurotoxin), **hepatorenal syndrome,** and **increased risk of hepatocellular carcinoma** *Lab findings:* Anemia; **prolonged PT** (resulting from coagulation-factor deficiency); **hypoalbuminemia; hyperbilirubinemia; increased ALT, AST, and ALP;** high blood ammonia levels
Treatment	Alcohol abstinence; low-salt diet; diuretic therapy; vitamin supplementation
Notes	

A 48-year-old woman presents to the clinic with nausea and abdominal pain after a weekend of binge drinking. She complains that she has lost her appetite and you notice that she is jaundiced and has mild hepatomegaly upon palpation. You order serum studies that show an AST:ALT ratio of 2.5, as well as leukocytosis. Her serum ALP is also slightly elevated. You suspect that a liver biopsy would demonstrate macrovesicular fat, neutrophil infiltration with hepatic necrosis, Mallory bodies, and perhaps micronodular cirrhosis.

Alcoholic Liver Disease

Etiology and Epidemiology	Ethanol consumption Occurs more commonly in women
Pathology	**Hepatic steatosis (fatty liver):** Early and reversible change; yellow greasy liver; **accumulation of lipid droplets** in centrilobular hepatocytes **Alcoholic hepatitis:** Hepatocyte swelling and necrosis; **Mallory bodies** (intracytoplasmic eosinophilic hyaline bodies); neutrophilic infiltration of hepatocytes; sinusoidal and perivenular fibrosis **Alcoholic cirrhosis:** Late change; fatty enlarged liver that may become brown and shrunken; irregular nodularity with **hobnail** appearance; **fibrosis of liver** with loss of hepatic architecture
Clinical Manifestations	**Hepatic steatosis:** Mild hyperbilirubinemia; increased ALP **Alcoholic hepatitis:** Occurs after bout of heavy drinking; anorexia; abdominal pain; hepatomegaly; **AST:ALT > 1.5;** leukocytosis **Alcoholic cirrhosis:** Portal hypertension; jaundice; ascites; elevated LFTs
Treatment	**Abstinence from alcohol;** vitamin supplementation (especially folate and thiamine); methylprednisolone in severe cases of alcoholic hepatitis
Notes	**Fatty liver** is also seen in Reye syndrome (viral infection and salicylate use in children), tetracycline toxicity, diabetes, malabsorption syndromes, Kwashiorkor, and hepatic failure in pregnancy.

A 48-year-old woman presents to the clinic complaining of increased itching. She has a 10-year history of Sjögren syndrome that is well-managed with symptomatic relief. On physical examination, you note severe jaundice, evidence of intense scratching, xanthomas in her skin and eyelids, and mild hepatosplenomegaly. You order serum studies that show hypercholesterolemia, elevated ALP, antimitochondrial antibodies, and an elevated IgM level. You prescribe cholestyramine for her itching and you worry that her condition may eventually progress to liver failure.

Biliary Cirrhosis

Etiology and Epidemiology	**Primary biliary cirrhosis (PBC):** Autoimmune origin; can occur with other autoimmune diseases (Sjögren syndrome, thyroiditis, rheumatoid arthritis); most common in **women 40–60 years old** **Secondary biliary cirrhosis (SBC):** Caused by extrahepatic biliary obstruction
Pathology and Pathophysiology	**PBC:** *Gross:* progressive **green tint to liver.** *Microscopic:* destruction of bile ducts by **periportal granuloma formation;** lymphocytic infiltrate in portal tract; **eventual destruction of hepatic parenchyma** leading to hepatic cirrhosis. **SBC:** *Gross:* **yellow-green liver.** *Microscopic:* fibrous septa; variation in bile duct size; **bile lakes** (accumulation of bile in hepatic parenchyma); bile stasis. *Pathophysiology:* extrahepatic biliary obstruction leads to an increase in intrahepatic duct pressure leading to ductal injury and eventual fibrosis; can be complicated by ascending cholangitis (bacterial infection of intrahepatic ducts).
Clinical Manifestations	Severe **obstructive jaundice; pruritus; xanthomas;** hepatosplenomegaly; eventual liver failure *Lab findings:* **Hypercholesterolemia, increased ALP, antimitochondrial antibodies** (PBC)
Treatment	Ursodeoxycholic acid; cholestyramine for itching; liver transplant in severe disease
Notes	**Primary sclerosing cholangitis** occurs in young men and is often associated with ulcerative colitis. It is characterized by fibrosis and stricturing of intra- and extrahepatic ducts with resulting cholestasis. It presents with jaundice, RUQ pain, and elevated ALP and bilirubins. Treatment includes endoscopic dilation of bile ducts, ursodeoxycholic acid, and transplant for severe cases.

A 55-year-old man presents to the clinic complaining of weakness, fatigability, weight loss, and anorexia. He notes that he is more thirsty and is urinating more frequently than usual. On physical examination, you note scleral icterus, jaundice, gynecomastia, and hyperpigmentation of the skin on his trunk and extremities. You order serum studies, which reveal mildly elevated LFTs, increased serum iron, decreased TIBC, a transferrin saturation of 85%, and a serum ferritin level of 1500 μg/L. You explain to the patient that his disease will need to be treated with weekly phlebotomy and deferoxamine and that members of his family should consider undergoing genetic testing to see if they are susceptible to this condition.

Hemochromatosis

Etiology and Epidemiology	**Primary hemochromatosis:** Autosomal recessive condition involving a mutation on chr 6 causing excessive absorption of iron in the intestinal mucosa; associated with HLA-A3. Most commonly seen in northern Europeans with onset of disease after age 50. **Secondary hemochromatosis:** Acquired disease caused by chronic transfusion therapy combined with ineffective erythropoiesis. It is seen in thalassemia major and iron overload syndromes.
Pathology	**Accumulation of iron as hemosiderin** in liver, pancreas, heart, adrenals, testes, pituitary, kidneys, and skin *Liver: Gross:* large; deep-brown; **micronodular.** *Microscopic:* accumulations of parenchymal hemosiderin beginning in periportal hepatocytes; eventually progresses to cirrhosis.
Clinical Manifestations	Classic triad of **cirrhosis, diabetes,** and **skin hyperpigmentation (bronze diabetes);** arthropathy; hepatomegaly; cardiac disease. Complications include increased risk of infection with *Vibrio vulnificus, Listeria,* and other iron-loving organisms and **increased risk of hepatocellular carcinoma** *Lab findings:* Mildly elevated LFTs, **increased serum iron, decreased TIBC, transferrin saturation > 80%, serum ferritin > 1000 μg/L**
Treatment	**Weekly phlebotomy** and **deferoxamine** Prevention of primary hemochromatosis by screening for increased transferrin saturation in neonatal period
Notes	

An 8-year-old boy presents to the clinic because his parents have noticed strange, jerky movements and drastic changes in his behavior and personality. His parents tell you that he has become much more emotionally labile and has been making statements that are out of context and incomprehensible. On physical examination, you see a brownish ring around the superior and inferior poles of the cornea. He has a resting tremor in both arms and hands. You order laboratory studies, which show a decreased serum ceruloplasmin and elevated levels of copper, amino acids, and glycogen in the urine. You begin the patient on penicillamine to increase urinary excretion of chelated copper.

Wilson Disease

Etiology and Epidemiology	Rare **autosomal recessive** disorder involving a mutation of copper-transporting protein leading to defective conjugation of copper to ceruloplasmin Onset of disease occurs between first and third decades
Pathology and Pathophysiology	*Pathophysiology:* **Increased copper absorption in the gut** and **decreased excretion via bile** leads to **copper accumulation throughout the body,** especially in the parenchymal cells of the liver, kidney, brain, and cornea *Liver:* Varies from acute and chronic hepatitis to (micronodular or macronodular) **cirrhosis;** Mallory bodies (intracytoplasmic hyaline bodies) are apparent on biopsy *Brain:* Atrophy and cavitation of basal ganglia
Clinical Manifestations	Hepatitis; hypersplenism; hemolytic anemia; portal hypertension; **psychosis** or dementia; **Kayser-Fleischer rings** (thin brown rings around corneas on eye examination); **choreiform movements** (extrapyramidal motor signs similar to those in Parkinson disease) Complications include an **increased risk of hepatocellular carcinoma** *Lab findings:* **Decreased serum ceruloplasmin,** hypercupriuria (copper in urine), aminoaciduria, glycosuria
Treatment	**Penicillamine**
Notes	

A 45-year-old woman presents to the clinic complaining of spitting up red blood. After taking a complete history, you learn that she has also recently started suffering from hemorrhoids with red blood found on the toilet paper after bowel movements. She had been previously healthy and she denies any significant alcohol use, history of hepatitis, or drug use. Her vital signs are notable for a blood pressure of 100/50. On physical examination, you note that she has pallor, ascites, and marked splenomegaly. Varices are seen around her belly button and external hemorrhoids are visible on rectal examination. You order laboratory studies that show normal LFTs, but evidence of hypersplenism. While awaiting imaging testing, you begin to suspect that a splenectomy would be curative for the underlying disease, which is causing her symptoms.

Portal Hypertension

Etiology	**Pre-hepatic portal venous obstruction:** caused by portal vein thrombosis or splenic vein obstruction **Intra-hepatic portal venous obstruction:** caused by **cirrhosis,** metastatic tumor, or schistosomiasis **Post-hepatic portal venous obstruction:** caused by constrictive pericarditis, tricuspid insufficiency, CHF, or Budd-Chiari syndrome
Pathophysiology	Portal venous obstruction results in increased use of venous collaterals of the portal-systemic anastomoses, leading to varices in the submucosal veins of the esophagus, rectal veins, and paraumbilical-inferior epigastric veins. Furthermore, increased portal vein pressure results in decreased capillary fluid resorption, leading to collection of fluid in the peritoneal cavity (ascites).
Clinical Manifestations	Splenomegaly; **esophageal varices; hemorrhoids; caput medusae** (periumbilical varicose veins), **hematemesis;** spider angiomas; hypotension; pallor; **ascites**
Treatment	Splenectomy is curative for portal hypertension caused by splenic vein thrombosis. Band ligation or sclerotherapy for variceal bleeding. **Anticoagulation** for isolated portal vein thrombosis. Treatment of cirrhosis.
Notes	

A 45-year-old white man with a history of paroxysmal nocturnal hemoglobinuria presents to the clinic with severe RUQ abdominal pain. He tells you that he has been vomiting off and on for the last 2 weeks. On physical examination, you note jaundice, painful hepatic enlargement, splenomegaly, mild ascites, visible abdominal and back veins when standing, and pedal edema. You order serum studies that are noteworthy for elevated LFTs. When a duplex Doppler ultrasonography reveals evidence of a thrombosis of the hepatic veins, you immediately begin this patient on thrombolytic therapy.

Budd-Chiari Syndrome

Etiology and Epidemiology	Caused by **thrombotic occlusion of the hepatic veins** Associated with polycythemia vera, pregnancy, hepatocellular carcinoma, blunt abdominal trauma, oral contraceptive use, and paroxysmal nocturnal hemoglobinuria
Pathology	*Liver:* **Centrilobular congestion and necrosis** with sinusoidal dilatation; eventual development of centrilobular fibrosis; thrombi in major veins
Clinical Manifestations	Tender, **painful hepatic enlargement**; jaundice; scleral icterus; splenomegaly; vomiting; ascites; **visible abdominal and back veins** when standing; pedal edema; absence of JVD (versus right heart failure); may lead to eventual liver failure *Imaging:* Detection of hepatic venous or IVC thrombosis on Doppler ultrasound or CT scan *Lab findings:* Elevated LFTs
Treatment	Balloon angioplasty; thrombolytic therapy into hepatic vein; surgical bypass of obstruction; diuretics and salt restriction (for ascites)
Notes	

A 53-year-old African American man with known alcoholic cirrhosis presents to the clinic with increased abdominal girth and a fever. He tells you that he has noticed a fever for the last 2 weeks and that he has lost 10 pounds over the last month. On physical examination, you note jaundice, scleral icterus, hepatomegaly, and increased ascites. Laboratory studies reveal leukocytosis, anemia, and a sudden increase in serum ALP that did not exist previously. An elevated AFP level is also detected. When a CT scan of the abdomen reveals a large hepatic mass, you order a liver biopsy to confirm your suspected diagnosis.

Hepatocellular Carcinoma

Etiology	Risk factors include **alcoholic cirrhosis**, **HBV**, **HCV**, hemochromatosis, Wilson disease, α-1-antitrypsin deficiency, and hepatic carcinogens (eg, aflatoxin B1)
Pathology	*Gross:* May appear as single mass, multiple masses, or infiltrative carcinoma; pale and green tinted *Microscopic:* Tumors range from cords or sheets of cells roughly resembling hepatic parenchyma to anaplastic masses; may invade portal veins or IVC Commonly spread by **hematogenous dissemination,** often to the lungs, vertebrae, adrenals, or brain
Clinical Manifestations	Fever; weight loss; **worsening hepatomegaly; worsening or bloody ascites;** cirrhotic symptoms *Lab findings:* **Elevated AFP,** leukocytosis, anemia, sudden elevation of ALP
Treatment and Prognosis	Surgical resection; chemotherapy; radiotherapy; liver transplantation Death often occurs within 10 months of diagnosis
Notes	Hepatocellular carcinoma is the most common primary malignant tumor of the liver in adults. **Cholangiocarcinoma** is an aggressive tumor arising from the intrahepatic biliary ducts. It is associated with *Clonorchis sinensis* infestation and primary sclerosing cholangitis. **Liver adenomas** are related to oral contraceptive use and can result in intraperitoneal hemorrhage. **Liver angiosarcomas** are related to polyvinyl chloride (Thorotrast) exposure.

A 48-year-old woman with a history of gallstones presents to the clinic complaining of a 1-day history of nausea, vomiting, and abdominal pain. She characterizes the abdominal pain as severe and steady and localized to the epigastric and RUQ region of her abdomen. Her vital signs are notable for a temperature of 101.1°F and you note inspiratory arrest on RUQ palpation. You order serum studies that demonstrate increased ALP, leukocytosis, and mild hyperbilirubinemia. You start her on antibiotics, but you suspect that she likely will need surgical intervention in the future to treat her condition.

Acute and Chronic Cholecystitis

Etiology and Epidemiology	**Acute:** Usually of **infectious origin** (CMV, *Cryptococcus*); trauma or burns; postoperative state **Chronic:** Frequent complication of **gallstones** (most common cause of cholecystitis); repeated bouts of acute cholecystitis Cholecystitis is most commonly seen in **women over the age of 40**
Pathology	**Acute:** *Gross:* **enlarged and discolored gallbladder;** may see obstructing stone at neck; cloudy or purulent bile in lumen. *Microscopic:* thickened and edematous wall; **inflammatory infiltrate** with vascular congestion. **Chronic:** *Gross:* **thickening of gallbladder wall** as a result of extensive fibrosis. *Microscopic:* subepithelial fibrosis with **mononuclear infiltrate;** outpouching of mucosal epithelium through wall (Rokitansky-Aschoff sinuses).
Clinical Manifestations	**Acute:** Nausea; vomiting; fever; **RUQ pain upon palpation; Murphy sign** (inspiratory arrest on RUQ palpation). *Lab findings:* **increased ALP;** leukocytosis; mild hyperbilirubinemia. **Chronic:** Nausea; vomiting; recurrent episodes of colicky **RUQ pain; intolerance to fatty foods** Complications include bacterial superinfection and gallbladder perforation or obstruction
Treatment	Antibiotics; cholecystectomy
Notes	

A 60-year-old Native American woman presents to the clinic complaining of a 3-month history of severe RUQ pain. On history, you learn that she has given birth to 5 children, is postmenopausal, and is currently taking HRT. She reports that the pain is exacerbated after she takes her grandchildren out for fast food and indulges in greasy foods herself. She also confesses that she does drink quite a bit on the weekends and feels abdominal pain shortly afterward as well. On physical examination, you note mild tenderness in the RUQ. You order an ultrasound, which you are confident will confirm your suspected diagnosis.

Cholelithiasis (Gallstones)

Etiology and Epidemiology	**Cholesterol stones:** Associated with obesity, older age, Crohn disease, cystic fibrosis, multiparity, rapid weight loss, clofibrate use, estrogen use, and native American heritage **Pigment stones:** Associated with alcoholic cirrhosis, hemolytic anemia, biliary tract infection, and older age Cholelithiasis is most commonly seen in **obese, multiparous women over the age of 40**
Pathology and Pathophysiology	*Pathophysiology:* Stones form when cholesterol and bilirubin overwhelm solubilizing bile acids and lecithin in the gallbladder **Cholesterol stones: Radiolucent**, although 10%–20% may be opaque owing to calcification **Pigment stones: Radio-opaque;** composed of bile pigments **Mixed stones:** Radiolucent; composed of both cholesterol and bile pigments; most common type
Clinical Manifestations	Usually asymptomatic, but may present with **Charcot triad:** severe colicky epigastric and RUQ pain (especially after fatty meal), spiking fever, and jaundice Complications include biliary colic, common bile duct obstruction, cholecystitis, acute pancreatitis, gallstone ileus, ascending cholangitis, and possible adenocarcinoma of the gallbladder
Treatment	**Cholecystectomy** if symptomatic; no treatment if asymptomatic
Notes	

A 52-year-old woman presents to the clinic with epigastric and RUQ pain, which is especially severe after a fatty meal. She also reports that her appetite has decreased and that she has lost 10 pounds over the last month. Physical examination reveals a fever of 102°F, jaundice, and scleral icterus. An ultrasound is suggestive of cholecystitis and a cholecystectomy is performed. Histologic examination of the gallbladder reveals an adenocarcinoma with an infiltrating pattern of growth with diffuse thickening of the wall of the gallbladder. You inform the patient of this diagnostic finding and suggest that she return for a follow-up visit immediately.

Tumors of Gallbladder and Biliary Ducts

Etiology and Epidemiology	**Adenocarcinoma of the gallbladder (AGB):** Associated with **gallstones;** most common primary tumor of the gallbladder; most commonly presents in women after age 60 **Carcinoma of extrahepatic biliary ducts and the ampulla of Vater (EBD):** Rare; associated with *Clonorchis sinensis* infection, primary sclerosing cholangitis or IBD; most commonly presents in elderly men
Pathology	**AGB:** *Gross:* infiltrating pattern of growth shows diffuse thickening of gallbladder wall; exophytic pattern grows into lumen as irregular cauliflower mass. *Microscopic:* adenocarcinoma with varying degrees of differentiation; often invades liver. **EBD:** *Gross:* small gray nodules in wall of bile duct. *Microscopic:* adenocarcinoma with mucin-secreting cells; fibrous stroma; epithelial proliferation.
Clinical Manifestations	**AGB:** Presenting symptoms are insidious and **indistinguishable from gallstones** (abdominal pain, jaundice, anorexia, and nausea and vomiting) **EBD:** Presents with **progressive, relentless obstructive jaundice,** nausea/vomiting, weight loss, and a painless, **palpably enlarged gallbladder** (not seen in gallstone disease) *Lab findings for both types:* Elevated LFTs, prolonged PT
Treatment	**AGB:** Cholecystectomy; chemotherapy; radiotherapy **EBD:** Ductal cancers are not amenable to surgical resection and are treated with chemotherapy and/or radiotherapy; ampullary cancers are usually resected
Notes	

A 42-year-old man presents to the emergency room with severe epigastric and LUQ abdominal pain radiating to the back. He reports nausea and vomiting for the last 24 hours. He also confesses to binge drinking over 2 days prior to the onset of symptoms and he admits to similar symptoms after binge drinking in the past. His past medical history is significant for hyperlipidemia. On physical examination, you note diaphoresis, a fever of 102.8°F, and that the abdomen is distended and tender to palpation of the epigastric and LUQ regions. You order serum studies that are significant for leukocytosis and elevated serum lipase and amylase. You put the patient on pancreatic rest, involving IV fluids and no oral intake, and you allow him to have Demerol as needed for his pain.

Acute and Chronic Pancreatitis

Etiology	**Acute:** Caused by **activation of pancreatic enzymes resulting in organ autodigestion;** associated with **alcohol, gallstones,** hyperlipidemia, hypercalcemia, drugs (thiazides, sulfonamides), mumps infection, and autoimmune disease **Chronic:** Caused by repeated bouts of pancreatic inflammation; associated with **alcoholism** and cystic fibrosis
Pathology	**Acute:** *Gross:* **hemorrhagic** areas with areas of white **fat necrosis.** *Microscopic:* interstitial edema and inflammation; necrosis of parenchyma with vascular damage; **calcium soap deposition.** **Chronic:** *Gross:* fibrotic bands producing a lobular appearance; **calcified concretions; pseudocyst formation.** *Microscopic:* destruction of acini (islets of Langerhans spared) with **fibrous replacement;** mononuclear inflammatory infiltrate.
Clinical Manifestations	**Acute:** Severe epigastric and **LUQ abdominal pain radiating to the back;** nausea; vomiting; fever; may occur after increased **alcohol intake** **Chronic:** Recurrent attacks of **abdominal and back pain;** development of **pancreatic insufficiency** and diabetes *Lab findings for both acute and chronic:* Leukocytosis, **elevated serum lipase and amylase** Complications include DIC, ARDS, diffuse fat necrosis, tetany, and acute renal failure
Treatment	Food restriction and IV fluids; Demerol for pain control; enzyme and insulin replacement for pancreatic insufficiency
Notes	

A 55-year-old man presents to the clinic complaining of generalized malaise and weakness, a 15-pound weight loss over the last 6 weeks, and anorexia. On physical examination, you note marked jaundice. There is also redness and tenderness on palpation of his extremities, which is consistent with the finding of migratory thrombophlebitis. You order laboratory studies that show increased direct bilirubin, increased ALP, as well as a positive CA 19-9 marker. You begin to fear that this patient may have a very severe disease with an extremely poor prognosis.

Pancreatic Carcinoma

Etiology

Risk factors include chronic pancreatitis, smoking, alcohol, high-fat diet, chronic gallbladder disease, and diabetes

Associated with mutation of K-*ras* oncogene and p53 tumor suppressor gene

Pathology

Gross: May arise in head (60%), body (15%), or tail (5%) of pancreas, or involve whole organ (20%); grayish mass that may block ampullary region leading to bile duct obstruction and **dilated intrahepatic ducts**

Microscopic: **Adenocarcinoma** with variable degree of differentiation; tumor cells form clusters or tubular structures with invasive growth pattern; malignant glands may be formed by anaplastic cuboidal epithelium; **stromal fibrosis**

Clinical Manifestations

Often **clinically silent until widespread metastasis,** usually to lung or bone. Presents with **upper abdominal pain radiating to the back,** weight loss, anorexia, migratory thrombophlebitis **(Trousseau syndrome), painless obstructive jaundice,** and a palpable gallbladder (because of common bile duct obstruction).

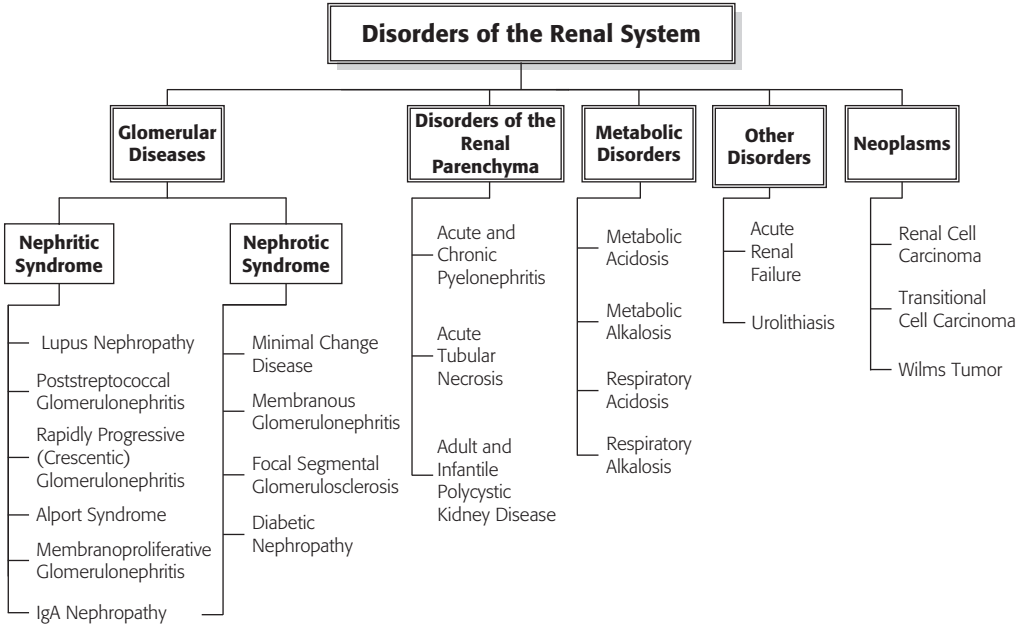
Lab findings: Increased direct bilirubin, **increased ALP, increased CEA levels, increased CA 19-9 levels**

Treatment and Prognosis

Radical pancreaticoduodenal resection (Whipple procedure) in 30% of patients; adjuvant radiotherapy and chemotherapy

Overall 5-year survival rate is < 4%

Notes


Disorders of the Renal System
Glomerular Diseases
Nephritic Syndrome
Lupus Nephropathy
Poststreptococcal Glomerulonephritis
Rapidly Progressive (Crescentic) Glomerulonephritis
Alport Syndrome
Membranoproliferative Glomerulonephritis
IgA Nephropathy
Nephrotic Syndrome
Minimal Change Disease
Membranous Glomerulonephritis
Focal Segmental Glomerulosclerosis
Diabetic Nephropathy
Disorders of the Renal Parenchyma
Acute and Chronic Pyelonephritis
Acute Tubular Necrosis
Adult and Infantile Polycystic Kidney Disease
Metabolic Disorders
Metabolic Acidosis
Metabolic Alkalosis
Respiratory Acidosis
Respiratory Alkalosis
Other Disorders
Acute Renal Failure
Urolithiasis
Neoplasms
Renal Cell Carcinoma
Transitional Cell Carcinoma
Wilms Tumor

GLOMERULAR FILTRATION

Filtration Barrier

- Composed of the fenestrated capillary endothelium, the fused glomerular basement membrane, and the podocyte foot processes epithelial layer
- The capillary endothelium serves as a size barrier while the basement membrane contains heparin sulfate, which leads to a negative charge barrier preventing protein filtration

Glomerular Filtration Rate (GFR) and Filtration Fraction

- GFR can be estimated by the clearance of creatinine ($C_{creatinine}$)
- The effective renal plasma flow (RPF) can be estimated by the clearance of para-aminohippuric acid (C_{PAH})
- The filtration fraction (fraction of RPF filtered across glomerular capillaries) is equal to GFR/RPF

CLINICAL MANIFESTATIONS OF NEPHROTIC AND NEPHRITIC SYNDROME

Nephrotic Syndrome

- *Proteinuria:* because of disruption of glomerular charge barrier
- *Hypoalbuminemia:* because of proteinuria
- *Edema:* because of decreased plasma oncotic pressure from proteinuria
- *Hyperlipidemia* and *hypercholesterolemia:* because of increase in lipoprotein synthesis

Nephritic Syndrome

- *Oliguria* and *Azotemia:* because of renal inflammation
- *Hypertension:* results from decreased clearance of sodium and water
- *Hematuria:* because of leakage of blood into Bowman capsule

A 4-year-old boy presents to the emergency room with a 1-week history of generalized edema and fatigue. Your history reveals that he suffered from a viral URI 1 week before this visit. Serum and urine studies reveal massive proteinuria, hyperlipidemia, and hypoalbuminemia. You suspect that a renal biopsy would show normal-appearing glomeruli on electron microscopy except for fusion of the epithelial foot processes and you begin the child on prednisone.

Minimal Change Disease (Lipoid Nephrosis)

Etiology and Epidemiology	Etiology unknown, but usually occurs following a viral URI; associated with Hodgkin disease and hypersensitivity reactions Most often seen in **young children,** but can occur in older children and adults
Pathology	*Light microscopy:* **Normal-appearing glomeruli;** can see **lipid accumulation** in renal tubular cells *Electron microscopy:* **Fusion of epithelial foot processes**
Clinical Manifestations	**Nephrotic syndrome** Complications include infection by gram-positive organism, thromboembolism, and protein malnutrition
Treatment and Prognosis	**Prednisone;** cyclophosphamide or chlorambucil for steroid-resistant cases Response is excellent
Notes	Minimal change disease is the prototype of the nephrotic syndrome.

A 40-year-old white woman with a history of SLE presents to your office with a chief complaint of increased swelling in her legs. She had been referred by her primary care physician, who suspected a secondary illness to her lupus. Recent laboratory studies show proteinuria, hypoalbuminemia, hyperlipidemia, and hypercholesterolemia. You suspect that a renal biopsy would demonstrate immune complex deposition on electron microscopy as well as a "spike and dome" appearance on silver methenamine stain.

Membranous Glomerulonephritis

Etiology and Epidemiology

An immune complex disease of unknown etiology

Secondary disease seen in 10% of SLE patients (type V Lupus Nephritis) and is sometimes associated with infections (eg, hepatitis B and C, syphilis, malaria), drugs (eg, gold salts, penicillamine, NSAIDs), or malignancy

Incidence is highest in adults

Pathology

Light microscopy: Diffuse capillary wall thickening and basement membrane thickening

Immunofluorescence: Granular pattern of IgG or C3 deposits (lumpy-bumpy)

Electron microscopy: Electron dense **immune complex deposition** in **subepithelial locations** within the basement membrane of glomerular capillary walls

Silver methenamine stain: A **spike-and-dome appearance** resulting from the extension of basement membrane between and around the immune deposits (spikes = basement membrane, domes = immune complex deposits)

Clinical Manifestations

Nephrotic syndrome accompanied by **azotemia**

Complications include **renal vein thrombosis** and higher incidence of occult neoplasms of lung, stomach, and colon

Treatment

Cyclophosphamide or steroids; ACE inhibitors (reduce urinary protein loss); renal transplantation for severe cases

Notes

Membranous glomerulonephritis is a common cause of adult nephrotic syndrome.

A 40-year-old HIV-positive white man is admitted to the hospital complaining of generalized edema and fatigue. A complete history reveals that he is a habitual IV drug user. Laboratory studies show hypoalbuminemia, hyperlipidemia, proteinuria, and microscopic hematuria. You suspect that his current presentation is related to his HIV and you prepare the patient for a renal biopsy to determine the exact diagnosis.

Focal Segmental Glomerulosclerosis

Etiology and Epidemiology	Often idiopathic, but has been associated with heroin use, morbid obesity, and HIV infection Most often occurs in older patients
Pathology	*Light microscopy:* Sclerosis within capillary tufts of deep juxtaglomerular glomeruli with **focal distribution** (involves some, but not all, glomeruli) and **segmental distribution** (involves only a part of the glomerulus); hyalinosis (deposition of hyaline masses) also seen *Immunofluorescence:* IgM and C3 seen in sclerotic lesions *Electron microscopy:* Fusion of epithelial foot processes
Clinical Manifestations	**Nephrotic syndrome;** more severe disease in HIV and IV **drug users** *Lab findings:* 80% have microscopic **hematuria** at presentation
Treatment and Prognosis	Prednisone Most patients progress to ESRD in 5–10 years
Notes	

A 60-year-old African American man with a 20-year history of type II DM presents for a nephrology consult after his primary care physician found a progressive increase of proteinuria in recent laboratory studies. These laboratory studies also showed hyperlipidemia and hypercholesterolemia. On physical examination, the patient has bilateral diabetic retinopathy and 2+ edema in both legs. You start the patient on an ACE inhibitor and you suspect that a renal biopsy would show Kimmelsteil-Wilson nodules.

Diabetic Nephropathy

Etiology and Epidemiology	Associated with long-standing diabetes Type I diabetes carries 30%–40% chance of diabetic nephropathy after 20 years; type II diabetes carries 15%–20% chance after 20 years; however, because there are more patients with type II diabetes, ESRD is more prevalent among type II diabetics There is a higher risk of developing diabetic nephropathy among men, African Americans and Native Americans with diabetes.
Pathology	*Light microscopy:* **Increase in mesangial matrix,** resulting in either diffuse glomerulosclerosis (diffusely distributed increase in mesangial matrix) or nodular glomerulosclerosis (**Kimmelstiel-Wilson nodules**—nodular accumulations of mesangial matrix material) *Electron microscopy:* Striking increase in glomerular basement membrane thickening
Clinical Manifestations	**Nephrotic syndrome;** diabetic retinopathy is invariably present *Lab findings:* Microalbuminuria (early sign), proteinuria (late sign)
Treatment and Prognosis	Strict glycemic control; treatment of hypertension and microalbuminuria with ACE inhibitors during early stages to slow progression Often progresses to ESRD and dialysis
Notes	Diabetic nephropathy is the most common cause of ESRD in the United States.

A 45-year-old white woman with a 15-year history of SLE presents to the nephrologist after her primary care physician found hematuria and proteinuria on a routine urinalysis. The patient has edema of the ankles on physical examination and she is experiencing a SLE flare-up with an extensive malar rash visible over her face. A renal biopsy is obtained and examination by light microscopy reveals wire-loop abnormalities. You examine the patient's current immunosuppressive therapy to see what additional therapies should be added.

Lupus Nephropathy

Etiology	Renal component of **SLE**
Pathology	Five distinct renal histologic patterns: **(1) Type I:** normal; **(2) Type II** *(mesangial form):* focal and segmental glomerular involvement with increase in mesangial matrix; **(3) Type III** *(focal proliferative form):* involves less than half of glomeruli, causing extensive damage to individual glomeruli; **(4) Type IV** (*diffuse proliferative form*): most severe form involving all glomeruli with marked inflammation, mesangial proliferation, and scarring. *Light microscopy:* **wire-loop abnormality** caused by immune complex deposition and gross thickening of glomerular basement membrane. *Electron microscopy:* **endothelial cell proliferation**. *Immunofluorescence:* marked **subendothelial immune complex deposition. (5) Type V** *(membranous form):* similar to membranous glomerulonephritis.
Clinical Manifestations	**Type I:** No clinical findings **Types II and III:** Mild to moderate proteinuria and hematuria **Type IV:** Combination of **nephrotic and nephritic** syndromes **Type V: Nephrotic syndrome**
Treatment	**Types I and II:** No treatment **Types III, IV, and V:** Immunosuppression (corticosteroids, cyclophosphamide, and/or azathioprine)
Notes	Renal lesion severity often determines overall prognosis of SLE patients.

A 10-year-old girl presents to the clinic complaining of eye swelling. You note that the child was seen 3 weeks ago in clinic for a chief complaint of sore throat. Upon taking a history and performing a physical, you find that the patient has pronounced periorbital edema, has been urinating very little despite adequate fluid intake, and has a blood pressure of 150/90. Laboratory findings include azotemia, hematuria, red cell casts in the urine, and an elevated ASO antibody titer. You reassure the parents that their child's condition will likely resolve on its own.

Poststreptococcal Glomerulonephritis (Acute Proliferative Glomerulonephritis)

Etiology and Epidemiology	Most frequently seen in **children** following infection with nephritogenic strains of **group A β-hemolytic streptococci**
Pathology	*Gross pathology:* Characterized by **intense inflammatory reaction** involving all glomeruli in both kidneys, resulting in **punctate hemorrhages** on kidney surfaces *Light microscopy:* Enlarged, hypercellular, swollen glomeruli with proliferation of mesangial and endothelial cells; normal glomerular basement membrane thickness *Electron microscopy:* **Electron-dense humps** on the epithelial side of the basement membrane **(subepithelial localization)** *Immunofluorescence:* Coarse granular immunofluorescence for IgG or C3 **(lumpy-bumpy)**
Clinical Manifestations	**Nephritic syndrome** and periorbital edema *Lab findings:* Urinary RBCs and/or red cell casts, decreased serum C3, elevated ASO antibody titer (evidence of recent streptococcal infection)
Treatment and Prognosis	Resolves spontaneously
Notes	Poststreptococcal glomerulonephritis is an **immune complex disease** with the antigen-antibody complex of streptococcal origin and is the prototype of the nephritic syndrome.

A 40-year-old white man is admitted to the hospital with complaints of blood in his sputum and urine. A thorough history also reveals fever, malaise, and a 10-pound weight loss over the past month. On physical examination, you find that his blood pressure is 160/95 and that he has several abnormal lung sounds. A urine dipstick demonstrates hematuria. CXR reveals several nodular lesions and blood tests show the presence of C-ANCA and an elevated ESR. You start the patient on a high dose of corticosteroids and you suspect that a renal biopsy would demonstrate crescent-moon shapes between the Bowman capsule and the glomerular tuft.

Rapidly Progressive (Crescentic) Glomerulonephritis

Etiology	**Type 1:** Idiopathic or **Goodpasture syndrome** **Type 2 (immune complex):** Idiopathic; postinfectious causes; SLE; **IgA nephropathy; Henoch-Schönlein purpura** **Type 3 (pauci-immune type):** Idiopathic; **Wegener granulomatosis;** microscopic polyangiitis
Pathology	*Light microscopy:* Formation of **crescent-moon shape** between Bowman capsule and glomerular tuft, resulting from deposition of fibrin in the Bowman space and from proliferation of parietal epithelial cells of the Bowman capsule
Clinical Manifestations	**Nephritic syndrome;** progressing rapidly to renal failure within months Signs and symptoms specific to each etiology (eg, hemoptysis and antiglomerular basement membrane antibodies in Goodpasture syndrome)
Treatment and Prognosis	Treat with diuretics and often eventual dialysis; immunosuppression if appropriate for underlying cause; may require transplantation Rapid course to renal failure
Notes	RPGN refers to a syndrome associated with severe and progressive glomerular injury. It encompasses many different etiologies.

A 10-year-old boy presents to the clinic complaining of a red tinge to his urine. A more detailed history reveals that he was diagnosed with mild nerve deafness 2 years earlier and also developed posterior cataracts 1 year ago. Laboratory studies confirm hematuria as well as the presence of erythrocyte casts. You begin to wonder if his conditions may be related to a genetic disorder.

Alport Syndrome

Etiology	Genetic disorder with heterogenous inheritance (usually X-linked dominant) that results in the mutation of α-5 chain of **type IV collagen**
Pathology	*Electron microscopy:* Irregular foci of thickening or attenuation in the glomerular basement membrane with **longitudinal splitting** of the lamina densa
Clinical Manifestations	Triad of **nephritis, nerve deafness,** and various eye disorders (**cataracts,** lens dislocation, corneal dystrophy); often initially presents with hematuria and erythrocyte casts
Treatment	ACE inhibitors; renal transplantation
Notes	

A 25-year-old woman with a history of SLE is admitted to the hospital with generalized edema, malaise, and fatigue. You take a thorough history, which reveals that she had cold symptoms 2 weeks earlier. Laboratory studies show hypoalbuminemia, hypercholesterolemia, proteinuria, and low complement levels. When a renal biopsy shows reduplication of the basement membrane on electron microscopy, you adjust the patient's current corticosteroid dose and decide to add an antiplatelet drug to her regimen.

Membranoproliferative Glomerulonephritis

Etiology and Epidemiology	Associated with inherited complement component deficiency **Type I** is seen in SLE, hepatitis B and C, and involves classic and alternative pathway activation **Type II** involves only alternative pathway activation Most patients are under the age of 30
Pathology	**Types I and II:** *Light microscopy:* reduplication of basement membrane **(splitting)** and expansion of mesangial matrix into the capillary loops (**tram track** appearance) **Type I:** *Electron microscopy:* subendothelial electron-dense deposits **Type II:** *Electron microscopy:* characteristic **dense deposit** of homogeneous material within glomerular basement membrane
Clinical Manifestations	**Type I:** Commonly presents with **nephrotic** syndrome **Type II:** Commonly presents with hematuria and chronic renal failure *Lab Findings*: Decreased C3 levels, **elevated BUN and Cr, RBCs and/or RBC casts in urine**
Treatment and Prognosis	Corticosteroids and immunosuppression if appropriate for underlying cause Slowly progresses to renal failure with a high recurrence rate after transplantation
Notes	

A 15-year-old Asian American boy presents to the emergency room complaining of blood in his urine. Upon taking a complete history, you learn that he has also been suffering from fevers, myalgias, and arthralgias for the last 2 days. Serum studies reveal increased serum IgA levels and normal serum complement levels. You begin him on prednisone and you suspect that he is afflicted with the most common form of acute glomerulonephritis in the United States.

IgA Nephropathy (Berger Disease)

Etiology and Epidemiology	Primary renal disease of **IgA deposition** in the glomerular mesangium that can manifest after infection (viral URI, GI infection, flu-like syndrome) or can be a component of **Henoch-Schönlein purpura** Most commonly seen in children and young adults with men affected more often than women
Pathology	*Light microscopy:* Focal proliferative glomerulonephritis with diffuse mesangial widening *Electron microscopy:* **Mesangial deposits of IgA**
Clinical Manifestations	Presents with **recurrent hematuria** (red or cola-colored urine) 1–2 days after an infection *Lab findings:* Increased serum IgA level (50% of cases), normal serum complement levels
Treatment and Prognosis	Prednisone Can progress to chronic renal failure
Notes	Berger disease is the most common form of acute glomerulonephritis in the United States and is also prevalent in Asia.

A 25-year-old woman presents to the emergency room with fever, severe flank pain, and costovertebral angle tenderness. After taking a complete history, you find that she is sexually active and has had a 2-week history of burning pain while urinating and increased urinary frequency. Urinalysis reveals white cell casts in the urine and a urine sample is sent for culture. While you await the culture results, you start her on broad spectrum antibiotics.

Acute and Chronic Pyelonephritis

Etiology and Epidemiology	**Acute:** Caused by infection of renal parenchyma; more frequent among women **Chronic:** Results from chronic urinary tract obstruction and recurrent UTIs
Pathology	**Acute: Affects renal cortex with sparing of glomeruli;** neutrophilic infiltration and abscess formation within renal interstitium; abscesses may rupture introducing WBCs into tubular lumen **Chronic: Asymmetric corticomedullary scarring;** tubules contain eosinophilic, proteinaceous casts resulting in gross appearance reminiscent of thyroid follicles **(thyroidization of the kidneys);** in later stages, results in tubular atrophy and interstitial fibrosis
Clinical Manifestations	**Acute: Fever; flank pain with CVA tenderness;** polyuria and dysuria; nausea, vomiting, and diarrhea **Chronic:** Recurrent episodes of acute pyelonephritis can lead to renal hypertension and ESRD *Lab findings:* **WBC and/or WBC casts in urine**
Treatment	**Acute:** IV antibiotics **Chronic:** Renal transplantation if progresses to ESRD
Notes	**Renal papillary necrosis** is a complication of acute pyelonephritis in diabetics or chronic phenacetin users and is characterized by ischemic necrosis of tips of renal papillae. **Diffuse cortical necrosis** is an acute generalized infarction of renal cortices (medulla is spared) usually because of a combination of DIC and end-organ vasospasm in association with obstetric catastrophes or septic shock.

A 60-year-old man is admitted to the intensive care unit with hypotension and severe sepsis. His hypotension gradually resolves with aggressive fluid resuscitation and pressor support. Over the next couple of days, he becomes progressively oliguric. Laboratory studies reveal worsening renal failure and hyperkalemia. His urine sediment demonstrates muddy brown casts. You worry that this patient may become progressively fluid overloaded and hyperkalemic and eventually need dialysis.

Acute Tubular Necrosis

Etiology	Precipitated by **renal ischemia** (eg, prolonged hypertension, shock), **crush injury** (eg, intense exercise, myoglobinuria), **contrast** or **nephrotoxic drugs** (eg, aminoglycosides)
Pathology	*Kidney:* **Focal tubular epithelial necrosis;** rupture of basement membranes; eosinophilic hyaline casts in collecting ducts; interstitial edema; **evidence of epithelial regeneration** (flattened epithelial cells with mitotic figures)
Clinical Manifestations	Presents with signs of acute renal failure Death owing to arrhythmia from hyperkalemia can occur during the initial oliguric phase *Lab findings:* **Oliguria,** elevated urinary sodium (> 40 mEq/L), azotemia, **tubular epithelial cell casts** (**muddy-brown casts**) in urine, hyperkalemia
Treatment and Prognosis	Loop diuretics for diuresis; electrolyte and fluid level management (may require dialysis) May recover renal function or may lead to ESRD
Notes	Acute tubular necrosis is the most common cause of acute renal failure. **Acute drug-induced interstitial nephritis** is caused by penicillin derivatives (eg, methicillin), NSAIDs, and diuretics, and is characterized by acute interstitial renal inflammation with resolution after withdrawal of offending agent.

A 25-year-old man presents with blood in his urine. After taking a complete history, you learn that his father had died of kidney failure in his late 30s and that the patient is very concerned about having the same fate. Physical examination reveals a blood pressure of 170/110 mm Hg and bilateral, palpable renal masses. A murmur is heard on the chest examination that is consistent with a mitral valve prolapse. You order an abdominal CT to confirm the diagnosis.

Adult and Infantile Polycystic Kidney Disease

Etiology	**APKD: Autosomal dominant;** 90% resulting from mutation of **APKD1 gene** on chr 16 **IPKD: Autosomal recessive**
Pathology	**APKD:** Replacement of renal parenchyma bilaterally with multiple, large, variably sized cysts **IPKD: Closed, small, homogenous cysts** that are not in continuity with the collecting system
Clinical Manifestations	**APKD: Hypertension, hematuria, and palpable renal masses;** CT shows multiple cysts in both kidneys; associated with secondary polycythemia, polycystic liver disease, **berry aneurysms,** and mitral valve prolapse **IPKD:** CT shows multiple cysts at birth
Treatment and Prognosis	**APKD:** No therapy can prevent renal failure, although HTN treatment with ACE inhibitors and low-protein diet may slow progression of ESRD **IPKD:** Results in death shortly after birth
Notes	

A 40-year-old woman presents to the emergency room complaining of colicky abdominal pain and flank pain radiating toward her groin. After taking a complete history, you learn that she has seen large amounts of blood in her urine in recent weeks and that she has a history of recurrent UTIs. You order a plain abdominal film and find that there is a large staghorn calculus. As you prepare to admit the patient to the hospital, you call the urology service to schedule a percutaneous nephrolithotomy.

Urolithiasis (Kidney Stones)

Etiology	**Calcium oxalate and/or calcium phosphate** stones (80%–85%): Hypercalcemic conditions (eg, hyperparathyroidism, vitamin D intoxication, sarcoidosis) **Ammonium magnesium phosphate (struvite)** stones (10%): Urease-positive bacteria (eg, *Proteus vulgaris*) **Uric acid** stones (5%): Diseases with increased cell proliferation and turnover (eg, leukemia, myeloproliferative disorders) or hyperuricemia **Cystine** stones (< 5%): Cystinuria (hereditary impaired reabsorption of cystine)
Pathology	*Kidney:* Presence of stone within renal calyces, pelvis, or bladder Urolithiasis can also result in other pathologic conditions such as **renal colic** (painful ureter distention), **hydronephrosis,** and **pyelonephritis**
Clinical Manifestations	**Flank pain** radiating toward the groin and **hematuria** *Imaging:* Calcium stones and ammonium magnesium phosphate (struvite) stones are **radiopaque,** uric acid and cystine stones are **radiolucent** Complications include recurrence of stones (calcium) and increased incidence of UTIs (struvite)
Treatment	Hydrochlorothiazide (recurrent calcium stones) Allopurinol and brisk alkaline diuresis (uric acid stones) Increased fluid intake or surgical removal
Notes	**Hydronephrosis** refers to the dilation of the renal pelvis and calyces. It is caused by urinary outflow obstruction and is associated with progressive atrophy of the kidney.

A 40-year-old insulin-dependent diabetic patient has not been taking his daily insulin injections for 1 week. He presents to the emergency room with deep, regular, sighing respirations, abdominal pain, vomiting, and signs of severe dehydration. You conduct serum studies, which are significant for a low blood pH, low HCO_3^-, decreased P_{CO_2}, extreme hyperglycemia, and increased blood ketones. You immediately treat the patient with fluids and insulin to try and reverse this metabolic disturbance.

Metabolic Acidosis

Etiology	**Anion gap metabolic acidosis:** Causes include renal failure (azotemia), **lactic acidosis, diabetic ketoacidosis,** certain toxins (**methanol,** paraldehyde, phenformin, cyanide, carbon monoxide, **ethanol, ethylene glycol, salicylate**), and INH **Normal anion gap metabolic acidosis:** Causes include **traveler's diarrhea,** acetazolamide overdose, glue sniffing, renal tubular acidosis, and **hyperchloremic metabolic acidosis**
Pathophysiology	*Primary disturbance:* **Decrease in HCO_3^- concentration** *Compensatory response:* **Decrease in P_{CO_2}** results in vascular bed dilatation and decreased cardiac contractility (resistant to catecholamines) and can lead to shock
Clinical Manifestations	**Hyperventilation** or Kussmaul breathing (deep, sighing respirations); other specific signs and symptoms depend on cause of metabolic acidosis *Lab findings:* **Decreased pH, decreased P_{CO_2}, decreased HCO_3^-**
Treatment	Treat with bicarbonate if pH < 7.1 and treat underlying condition
Notes	*Anion gap calculation:* Anion gap = $Na^+ - (Cl^- + HCO_3^-)$. Anion gap is normally 6–12 mEq/L and is increased if unmeasured anion replaces HCO_3^-. *Compensation calculation (Winter's formula):* Decrease in $P_{CO_2} = 1.5\ (HCO_3^-) + 8 \pm 2$

A 50-year-old man presents to the emergency department with increased dizziness and weakness. After taking a history, you learn that he has been accidentally taking twice the amount of a prescribed diuretic. On physical examination, you notice that he has sunken eyes, poor skin turgor, hyporeflexia in all reflexes, and orthostatic hypotension. Laboratory studies show an arterial pH of 7.56 and an arterial P_{CO_2} of 45. Serum potassium and chloride are decreased. No other abnormalities are noted. You immediately begin to administer IV fluids and you suspect that this will reverse his metabolic abnormality.

Metabolic Alkalosis

Etiology	**Saline-responsive metabolic alkalosis:** Caused by extracellular volume contraction caused by vomiting, **diuretics**, or posthypercapnia alkalosis **Saline-resistant metabolic alkalosis:** Caused by **mineralocorticoid excess (Conn syndrome, renovascular disease, Cushing disease)** or alkali administration with decreased GFR (eg, **antacid** administration) or severe hypokalemia
Pathophysiology	*Primary disturbance:* **Increase in HCO_3^- concentration** *Compensatory response:* **Increase in P_{CO_2}**; hypoventilation causes P_{CO_2} to increase in order to increase bicarbonate concentration Metabolic alkalosis is generally associated with hypokalemia that acts to worsen the metabolic alkalosis by increasing bicarbonate absorption in the proximal tubule and hydrogen ion secretion in the distal tubule
Clinical Manifestations	May present with signs of **dehydration** (sunken eyes, poor skin turgor, lethargy, hypotension) and muscle weakness (because of hypokalemia); can also cause decreased cerebral blood flow and cardiac arrhythmias *Lab findings:* **Increased pH, increased P_{CO_2}, increased HCO_3^-, hypokalemia**
Treatment	**Saline-responsive:** Fluid replacement **Saline-resistant:** Treat underlying cause of mineralocorticoid excess; replete potassium
Notes	*Compensation:* P_{CO_2} increases 0.7 mm Hg for every 1 mEq/L HCO_3^- increase

A 30-year-old male heroin addict presents to the emergency room with shallow, deep breathing as well as nausea, vomiting, and constipation. On physical examination, the patient is confused and somnolent. Myoclonus with asterixis is apparent, as are pinpoint pupils. Track marks are found on both arms. Laboratory studies indicate an arterial pH of 7.30 and an arterial P_{CO_2} of 55. To reverse the drug overdose and thereby relieve the metabolic disturbance, you decide to administer 0.4 mg of naloxone IV.

Respiratory Acidosis

Etiology	Caused by acute lung disease (ARDS, airway obstruction), chronic lung disease (COPD), CNS depression (**opioids**, sedatives, narcotics), or weak respiratory muscles (ALS, kyphoscoliosis, MS, polio)
Pathophysiology	*Primary disturbance:* **Increase in P_{CO_2} (hypercapnia)** owing to decreased alveolar ventilation *Compensatory response:* **Increase in HCO_3^-** caused by increased renal HCO_3^- reabsorption as stimulated by low pH and high P_{CO_2}
Clinical Manifestations	**Hypoventilation; somnolence;** confusion; myoclonus with asterixis; signs of increased intracranial pressure (eg, papilledema, pseudotumor cerebri) *Lab findings:* **Decreased pH, increased P_{CO_2}, increased HCO_3^-**
Treatment	Treat underlying condition of acute respiratory acidosis No treatment necessary for chronic respiratory acidosis
Notes	*Acute compensation:* 1 mEq/L HCO_3^- increase for every 10 mm Hg P_{CO_2} increase *Chronic compensation:* 3.5 mEq/L HCO_3^- increase for every 10 mm Hg P_{CO_2} increase

A 30-year-old woman just learns that her brother was in a serious car accident, but is currently in stable condition. She begins to hyperventilate and starts complaining of feeling light-headed and having tingling in her hands and feet. Realizing that she is in danger of experiencing a metabolic disturbance, you hand her a paper bag and ask her to breathe into it.

Respiratory Alkalosis

Etiology	**Acute respiratory alkalosis:** Caused by **hyperventilation,** early phase of salicylate overdose, pneumonia, sepsis, pregnancy, pulmonary edema, pulmonary embolism, or cirrhosis **Chronic respiratory alkalosis:** Caused by **high altitude** or pregnancy
Pathophysiology	*Primary disturbance:* **Decrease in P_{CO_2}** *Compensatory response:* **Decrease in HCO_3^-** because of increased renal HCO_3^- secretion
Clinical Manifestations	Symptoms in acute respiratory alkalosis are related to decreased cerebral blood flow (light-headedness, anxiety, **paresthesias,** numbness about the mouth, tingling in distal extremities, **hyperventilation**); may also cause cardiac arrhythmias *Lab findings:* **Increased pH, decreased P_{CO_2}, decreased HCO_3^-**
Treatment	Acute hyperventilation syndrome from anxiety can be treated by breathing into paper bag to increase P_{CO_2}; otherwise, treat underlying cause (ie, sepsis or pneumonia)
Notes	*Acute compensation:* 2 mEq/L HCO_3^- decrease for every 1 mm Hg P_{CO_2} decrease *Chronic compensation:* 5 mEq/L HCO_3^- decrease for every 10 mm Hg P_{CO_2} decrease

A 70-year-old man presents to the emergency room because he is unable to urinate. After taking a detailed history, you learn that he has had increasing urinary hesitancy and decreased force of his urine stream for several months. He also complains of a sensation of incomplete bladder emptying. On rectal examination, you find a smooth, firm, elastic enlargement of the prostate. Examination of the lower abdomen reveals signs of a distended bladder. You order laboratory studies that show increased urinary sodium excretion and an elevated BUN and creatinine. You determine that the patient requires prompt urethral catheterization to help reverse his renal failure.

Acute Renal Failure (Prerenal, Intrarenal, and Postrenal Azotemia)

Etiology	**Prerenal:** Caused by decreased effective arterial volume (ie, CHF, hypovolemia, systemic vasodilation [sepsis]), or renal vasoconstriction (NSAIDs, ACE inhibitors, RAS) **Intrarenal:** Caused by acute tubular necrosis, acute interstitial nephritis, glomerulonephritis, and thrombotic microangiopathy **Postrenal:** Caused by kidney stones, BPH, neurogenic bladder, and neoplasia
Pathology and Pathophysiology	**Prerenal:** Renal hypoperfusion leads to decreased GFR, resulting in sodium and water retention **Intrarenal:** Characterized by patchy tubular necrosis, which leads to tubule obstruction and fluid backflow across the necrotic tubule and a resulting decrease in GFR **Postrenal:** Only develops with bilateral outflow obstruction
Clinical Manifestations	Oliguria; azotemia; hyperkalemia *Lab findings:* **(1) Prerenal:** urinary $Na^+ < 10$, urine osmolality > 500, Fe $Na^+ < 1\%$, **BUN/Cr > 20; (2) Intrarenal:** urine osmolality < 350, Fe $Na^+ > 2\%$, urinary **epithelial/granular casts; (3) Postrenal:** urinary $Na^+ > 40$, Fe $Na^+ > 4\%$; BUN/Cr > 20
Treatment	**Prerenal and intrarenal:** Fluid and electrolyte management; dialysis if necessary **Postrenal:** Treatment of obstruction
Notes	**Chronic renal failure** develops gradually and shows compensation that results in normal urine osmolality and volume until ESRD occurs. Common causes include hypertension and diabetes and clinical manifestations include azotemia, anemia, and renal osteodystrophy.

A 60-year-old man presents to the clinic with cola-colored urine and flank pain. After taking a careful history, you find that the man has had a low-grade fever and has lost 10 pounds over the past month. He is a chronic smoker (a pack of cigarettes a day for the last 30 years). On physical examination, you feel a large mass in the left kidney. Laboratory findings demonstrate secondary polycythemia. You suspect that an abdominal CT scan will show a solid renal mass and possible metastasis to regional lymph nodes.

Renal Cell Carcinoma

Etiology and Epidemiology	Associated with **von Hippel-Lindau disease,** deletion on chr 3 and cigarette **smoking** Most common among **men** (2:1 male:female ratio) in sixth decade of life (usually age 50–70)
Pathology	*Kidney:* Characterized by **polygonal clear cells** (demarcated only by cell membranes, nuclei pushed to the sides), which are derived from the tubular epithelium **Invades IVC and spreads hematogenously** to the lungs, bones, and other sites
Clinical Manifestations	Manifests with **hematuria, palpable mass, flank pain, long-standing fever,** and weight loss; associated with **paraneoplastic syndromes** (ectopic EPO, ACTH, PTHrP, prolactin, gonadotropins, renin) *Imaging:* Solid renal mass evident on CT *Lab findings:* Secondary polycythemia owing to increased erythropoietin production
Treatment	Radical nephrectomy; chemotherapy/radiation if invasive/distant disease
Notes	Renal cell carcinoma is the most common renal malignancy.

A 60-year-old man presents to the clinic with painless hematuria. A full history reveals that he worked in a factory that used aniline dyes for 20 years before retiring 10 years ago and that he also has smoked a pack of cigarettes per day for the last 30 years. You order serum and urine studies that demonstrate hematuria, exfoliated normal and abnormal urothelial cells in the urine, and anemia. You fear that this patient may be suffering from a neoplastic condition.

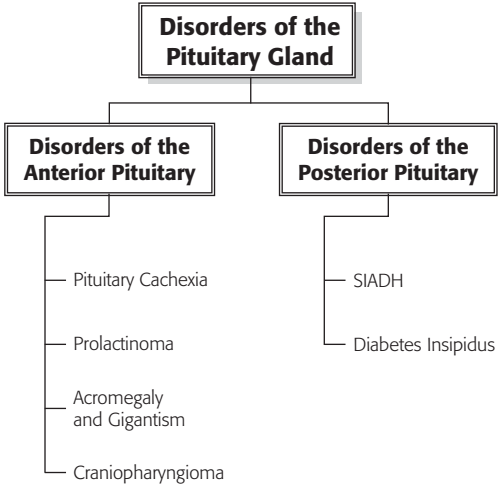
Transitional Cell Carcinoma

Etiology	Associated with **smoking,** exposure to **aniline dyes, cyclophosphamide** treatment, and phenacetin abuse
Pathology	*Gross:* Varies from flat to papillary and from noninvasive to invasive; can occur anywhere in urinary tract system (renal calyces, renal pelvis, ureters, bladder) and may spread by local extension to adjacent tissue *Microscopic:* **Multiple grades of carcinoma;** histopathology varies from well-differentiated tumor cells resembling normal transitional cells to anaplastic tumor cells with giant cells and multiple mitoses
Clinical Manifestations	Presents with **painless hematuria;** bladder transitional cell carcinoma may also present with **irritative voiding symptoms,** palpable mass on bimanual examination, hepatomegaly, or supraclavicular lymphadenopathy (if metastasized)
Treatment and Prognosis	Chemotherapy, radiotherapy, and transurethral resection for bladder cancer (often recurs after removal) Prognosis is dependent on stage and grade
Notes	**Squamous cell carcinoma** of the bladder accounts for 3%–7% of bladder cancers in the United States and is associated with schistosomiasis and other causes of chronic bladder infection.

A 3-year-old boy is brought to the emergency room by his mother because he is experiencing abdominal pain after accidentally falling onto a toy truck that hit his abdomen. On physical examination, you can feel a huge, palpable flank mass on his left side. Urinalysis reveals microscopic hematuria. When a CT scan reveals a large mass originating from the kidney, you begin to suspect that this child's condition is related to a gene deletion on chromosome 11.

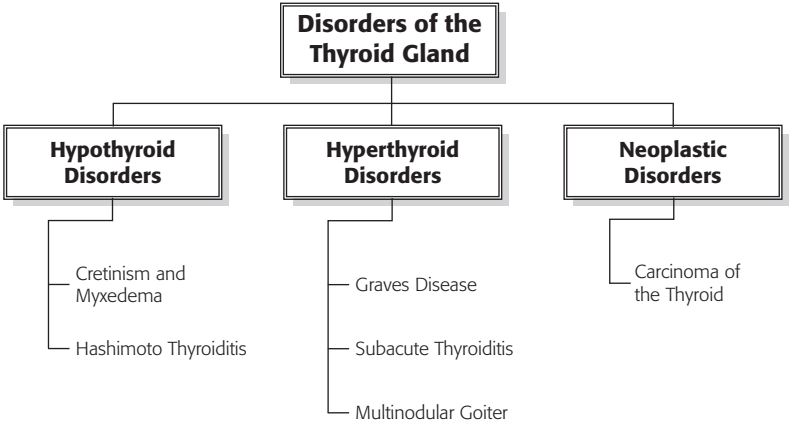
Wilms Tumor

Etiology and Epidemiology	Caused by deletion of **WT-1 gene** (tumor suppressor) on short arm of **chr 11** Most commonly seen in **early childhood** (ages 2–4)
Pathology	*Gross:* Large, solitary, **well-circumscribed renal mass;** originates from primitive metanephric tissue *Microscopic:* Immature stroma with primitive tubules and glomeruli; presence of mesenchymal elements (eg, bone, cartilage, connective tissue)
Clinical Manifestations	Presents as a huge, **palpable flank mass** in a **young child;** may also initially present as pain in abdomen after some traumatic incident, intestinal obstruction, or hypertension; can be associated with unilateral muscular hypertrophy (hemihypertrophy) *Lab findings:* **Microscopic hematuria**
Treatment and Prognosis	Surgery to remove tumor; radiotherapy and chemotherapy with actinomycin D and vincristine There is an excellent survival rate
Notes	Wilms tumor can be associated with the **WAGR complex** (*W*ilms tumor, *a*niridia [absence of iris], *g*enitourinary malformation, mental-motor *r*etardation).


Disorders of the Pituitary Gland
Disorders of the Anterior Pituitary
Disorders of the Posterior Pituitary
Pituitary Cachexia
Prolactinoma
Acromegaly and Gigantism
Craniopharyngioma
SIADH
Diabetes Insipidus

Hormones of the Pituitary Gland

Hormone	Site of Release	Action	Stimulators	Inhibitors
TSH	Anterior lobe	Stimulates release of TH from thyroid	TRH	TH
LH	Anterior lobe	Promotes testosterone and estrogen synthesis; stimulates ovulation and luteal development	GnRH; estrogen	Testosterone; progesterone; estrogen
FSH	Anterior lobe	Maintains spermatogenesis; stimulates estrogen synthesis & follicle development	GnRH; estrogen	Inhibin; progesterone; estrogen
ACTH	Anterior lobe	Stimulates steroid hormone synthesis in adrenal cortex	CRF	Cortisol
MSH	Anterior lobe	Stimulates melanin production in melanocytes	CRF	Cortisol
GH	Anterior lobe	Stimulates somatomedin production, which increases organ size	GHRH	Somatostatin; somatomedins; GH
Prolactin	Anterior lobe	Stimulates milk production and breast development; inhibits ovulation	TRH	Dopamine; prolactin
Oxytocin	Posterior lobe	Causes milk ejection from breast; causes contraction of uterus	Suckling; dilation of cervix; orgasm	N/A
ADH	Posterior lobe	Increases water uptake in collecting duct of nephron; vasoconstrictor	Hyperosmolarity; volume contraction	Hypo-osmolarity; ethanol


Disorders of the Thyroid Gland
Hypothyroid Disorders
Hyperthyroid Disorders
Neoplastic Disorders
Cretinism and Myxedema
Hashimoto Thyroiditis
Graves Disease
Subacute Thyroiditis
Multinodular Goiter
Carcinoma of the Thyroid

THYROID HORMONES : T_3 AND T_4

Biosynthesis

- Thyroglobulin (TG) is synthesized by the thyroid follicular cell and secreted into the colloid space
- Iodine is added to tyrosine residues on TG to form MIT and DIT
- T_3 is formed by oxidative coupling of MIT and DIT; T_4 = DIT + DIT

Thyroid Hormones in Circulation

- T_3 and T_4 circulate bound to thyroxine-binding globulin; only free T_3 and T_4 are biologically active
- T_3 is more active than T_4, thus T_4 is largely converted into T_3 in peripheral tissues

Regulation

- TRH release (hypothalamus) → TSH release (ant pituitary) → T_3 and T_4 release and glandular hyperplasia
- *Negative feedback system:* High levels of thyroid hormones suppress TSH and TRH release

Functions of Thyroid Hormones

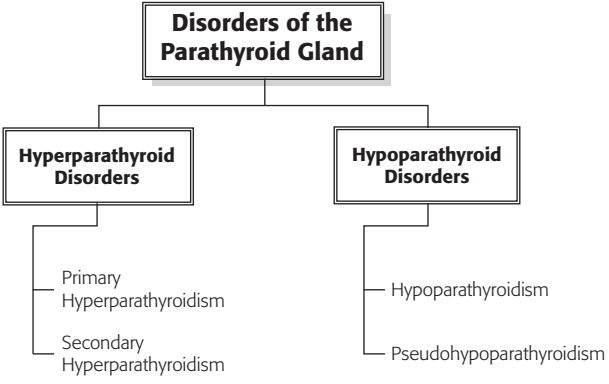
- Regulates metabolic rate; required for normal functioning of growth, immune system, CNS, and heart

HYPERTHYROIDISM

Symptoms: Weight loss, tachycardia, tremor, sweating, irritability, menstrual abnormalities
Lab Findings: Increased T_3 and T_4, decreased TSH (pituitary hyperfunction: increased TSH)

HYPOTHYROIDISM

Symptoms: Weight gain, hair loss, delayed deep tendon reflexes, cold intolerance, menorrhagia
Lab Findings: Decreased T_3 and T_4, increased TSH (pituitary hypofunction: decreased TSH)


Disorders of the Parathyroid Gland
Hyperparathyroid Disorders
Hypoparathyroid Disorders
Primary Hyperparathyroidism
Secondary Hyperparathyroidism
Hypoparathyroidism
Pseudohypoparathyroidism

PARATHYROID HORMONE (PTH)

Biosynthesis

- Secreted by the chief cells of the parathyroid gland

Mode of Action

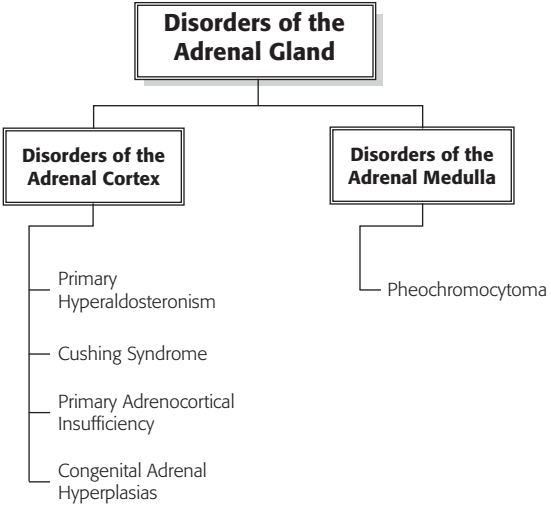
- PTH binds PTH receptor → activation of guanyl nucleotide regulatory protein → activation of adenylate cyclase → increased cAMP production

Regulation

- Increased serum calcium and increased 1,25-$(OH)_2D_3$ levels → decreased PTH secretion
- Decreased serum calcium → increased PTH secretion

Function: Overall effect is to increase serum calcium and decrease serum phosphate levels

- Effects on bone:
  → Promotes osteoclastic activity
  → Increases rate of skeletal remodeling
- Effects on kidney:
  → Promotes calcium reabsorption in the distal tubule of the nephron
  → Increases phosphate excretion
  → Increases the formation of 1,25-$(OH)_2D_3$ (activated vitamin D)
- Effects on intestine:
  → Increased 1,25-$(OH)_2D_3$ results in increased intestinal calcium and phosphate absorption.


Disorders of the Adrenal Gland
Disorders of the Adrenal Cortex
Disorders of the Adrenal Medulla
Primary Hyperaldosteronism
Cushing Syndrome
Primary Adrenocortical Insufficiency
Congenital Adrenal Hyperplasias
Pheochromocytoma

Adrenal Cortex Histology (3 layers)

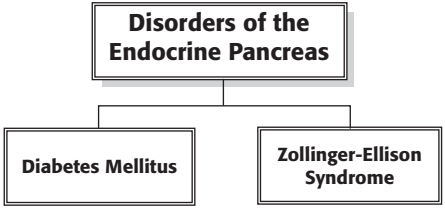
- *Zona glomerulosa:* Outermost layer; oval clusters of cells with bright nuclei
- *Zona fasciculata:* Middle layer; radially arranged cords of cells with pale cytoplasm
- *Zona reticularis:* Innermost layer; branching cords of cells with darker cytoplasm

Adrenal Medulla Histology

- Clusters of chromaffin cells (cells with large nuclei and basophilic cytoplasm)

Hormones of the Adrenal Gland

Hormone	Site of Release	Action	Regulation
Aldosterone	Zona glomerulosa	Increases renal Na^+ reabsorption; increases renal K^+ and H^+ secretion	*Stimulators:* Angiotensin II, hyperkalemia, ACTH
Cortisol	Zona fasciculata	Stimulates gluconeogenesis; immunosuppressant; anti-inflammatory; increases GFR; inhibits bone formation	*Stimulator:* ACTH *Inhibitor:* Cortisol
Androgens	Zona reticularis	Women: Pubic and axillary hair growth Men: Same as testosterone	*Stimulator:* ACTH *Inhibitor:* Cortisol
Catecholamines	Medulla	Relaxation of vascular smooth muscle in skeletal muscle, smooth muscle in GI tract and bladder, and of bronchioles	*Stimulator:* Acetylcholine from SNS


Disorders of the Endocrine Pancreas
Diabetes Mellitus
Zollinger-Ellison Syndrome

Endocrine Pancreas Histology

- *Islets of Langerhans:* Small, pale cells arranged in clusters among exocrine cells; composed of α, β, and γ cells

Exocrine Pancreas Histology

- *Acinar cells:* Triangular-shaped cells with apical secretory granules that surround central duct lumen
- *Ductal cells:* Line pancreatic ductal system

Secretions of the Pancreas

Substance	Site of Synthesis	Action	Stimulators of Secretion	Inhibitors of Secretion
Insulin	Islet β cells	Decreases blood glucose levels	High blood glucose; cortisol; glucagon; GH	Somatostatin; low-blood glucose; fasting
Glucagon	Islet α cells	Increases blood glucose levels	Decreased blood glucose; CCK; fasting	Insulin; somatostatin
Somatostatin	Islet γ cells	Inhibits gastrin, insulin, and glucagon secretion	Glucose; amino acids; fatty acids	Insulin;
α-Amylase	Acinar cells	Starch digestion	CCK; acetylcholine	Somatostatin
Lipase; colipase	Acinar cells	Fat digestion	CCK; acetylcholine	Somatostatin
Trypsin; chymotrypsin	Acinar cells	Protein digestion	CCK; acetylcholine	Somatostatin
Bicarbonate	Ductal cells	Neutralizes acidic chyme	Secretin	Somatostatin

A 28-year-old woman presents to your clinic complaining of amenorrhea and fatigue over the past year. A pregnancy test is negative; however, she tells you that she has an 8-month-old child, whose birth was complicated by severe hemorrhage. Further evaluation reveals loss of pubic hair, delayed deep tendon reflexes, and a blood pressure of 90/50. When blood tests reveal decreased levels of FSH, LH, TSH, ACTH, and GH, you inform her that she will have to be on hormone replacement therapy for the rest of her life.

Pituitary Cachexia

Etiology	Caused by **pituitary adenomas, Sheehan syndrome** (ischemic necrosis of anterior pituitary following postpartum hemorrhage), pituitary surgery, pituitary radiation, or pituitary injury
Pathology	**Adenoma:** Circumscribed lesion composed of similar, polygonal cells **Sheehan syndrome:** Early hemorrhagic lesion in anterior pituitary that resolves into small fibrous band later
Clinical Manifestations	**Generalized panhypopituitarism** manifesting as hypothyroidism (decreased TSH), hypogonadism and infertility (decreased LH and FSH), hypocortisolism (decreased ACTH), decreased prolactin, and decreased GH. If caused by adenoma, may have **bitemporal hemianopsia** (loss of lateral fields of vision) owing to compression of optic chiasm. *Lab findings:* Hypoglycemia; hyponatremia; decreased estrogen, testosterone, and progesterones; decreased cortisol; decreased TH
Treatment	Hormone replacement; surgical removal of adenoma
Notes	Pituitary adenomas can also cause hyperpituitarism and may be associated with MEN type 1 syndrome.

A 32-year-old woman presents to your office complaining of a milky discharge from both her nipples. Upon further questioning, you discover that her menstrual period has become extremely irregular and that her last menstruation was over 7 months ago. The laboratory reports a negative pregnancy test; however, this patient does have increased prolactin levels and decreased LH and FSH levels. You decide to send this patient for an MRI of her brain.

Prolactinoma

Etiology	Caused by **pituitary lactotroph adenoma** (most common pituitary tumor)
Pathology and Pathophysiology	**Pituitary adenoma:** Multiple **chromophobic cells** with secretory granules containing prolactin *Pathophysiology:* Hyperprolactinemia results in decreased LH and FSH levels via feedback inhibition
Clinical Manifestations	**Amenorrhea** (women) or **impotence** (men); infertility; **galactorrhea** **Bitemporal hemianopsia** or other visual disturbances owing to possible compression of optic chiasm *Lab findings:* **Decreased LH and FSH, increased prolactin levels**
Treatment	Bromocriptine (dopamine analog to suppress prolactin secretion) Surgery or radiation to remove adenoma
Notes	Hyperprolactinemia can also be caused by estrogen therapy, pharmacologic agents that interfere with dopamine secretion (methyl-dopa, reserpine), hypothalamic lesions, or renal insufficiency.

A 47-year-old man presents to your office complaining of occasional loss of vision in his lateral visual fields. Upon directed history, you learn that he has had to buy larger gloves and shoes and that he has gained 25 pounds over the past 3 months. Laboratory tests reveal hyperglycemia and increased GH levels. You tell the patient that he may need surgery to correct his condition and you refer him to an endocrinologist.

Acromegaly and Gigantism

Etiology	Caused by **pituitary somatotropic adenoma**
Pathology and Pathophysiology	**Pituitary adenoma**: Multiple **acidophilic cells** with secretory granules containing GH *Pathophysiology:* Increased GH results in increased insulin-like growth factor secretion from liver
Clinical Manifestations	**Gigantism**: Manifests in children as **tall stature** (adenoma appears before epiphyseal closure) **Acromegaly**: Manifests in adults (adenoma appears after epiphyseal closure) as **enlargement of hands, feet**, skull, and mandible with **weight gain; insulin resistance** resulting in hyperglycemia; hypertension; **cardiomegaly** and cardiac failure May also see **bitemporal hemianopsia** or other visual disturbances owing to possible compression of optic chiasm by adenoma
Treatment	Octreotide (somatostatin analog serves to decrease GH release by feedback inhibition); surgical removal of adenoma
Notes	

An 8-year-old girl presents to your office complaining of “eye troubles.” Physical examination reveals deficits in her lateral visual fields and you also note that she is small in stature for her age. Head radiographs reveal a calcified lesion in the sella turcica. You inform the girl and her parents that she will need surgery to treat this condition, which is caused by the remnants of an embryologic precursor structure.

Craniopharyngioma

Etiology and Epidemiology	Derived from **remnants of Rathke pouch** (embryologic precursor of anterior pituitary) Occurs most commonly during **childhood**
Pathology	**Pituitary craniopharyngioma:** Often **cystic** with **calcification;** cords of stratified squamous or columnar epithelium with keratin formation
Clinical Manifestations	**Bitemporal hemianopsia** or other visual disturbances owing to possible compression of optic chiasm; can result in growth retardation, diabetes insipidus, or other **pituitary deficiencies** *Imaging:* Radiographs can detect **calcified lesion** in brain
Treatment	Surgical removal of adenoma
Notes	

A 65-year-old man is brought to the emergency department by his daughter because of confusion. He was recently diagnosed with small-cell bronchogenic carcinoma and will be beginning chemotherapy shortly. Laboratory tests reveal significantly decreased serum sodium levels, decreased serum osmolality, and increased urine osmolality. As you admit him to the hospital, you suspect that this patient's condition is directly related to his lung cancer.

Syndrome of Inappropriate ADH (SIADH)

Etiology	Causes include pulmonary disorders (COPD, pneumonia), intracranial pathology (trauma, hemorrhage, stroke), pharmacologic agents (antipsychotics, chemotherapy), or pain; may also be caused by **ectopic ADH production by small-cell bronchogenic carcinoma** and other tumors
Pathophysiology	Increased ADH secretion results in **water retention** in the collecting duct of the nephron. Water retention leads to dilution of serum electrolytes, especially sodium, and subsequently decreased serum levels of electrolytes and serum osmolality.
Clinical Manifestations	**Fatigue and confusion** caused by decreased serum sodium; euvolemia *Lab findings:* **Hyponatremia, decreased serum osmolality,** increased urine osmolality
Treatment	Fluid restriction; demeclocycline; hypertonic saline if hyponatremia severe
Notes	

A 42-year-old woman presents to your office complaining of headaches. After taking a full history, you learn that she has been extremely thirsty lately and that she has been urinating frequently. A neurologic examination is unremarkable, but laboratory tests reveal increased serum osmolality and hypernatremia. You decide that further endocrinologic evaluation will be necessary to determine the etiology of her disorder.

Diabetes Insipidus

Etiology	**Central diabetes insipidus: Deficiency of ADH secretion** from the posterior pituitary; causes include hypothalamus damage (neoplastic or traumatic), histiocytosis, and idiopathic **Nephrogenic diabetes insipidus: Defective ADH receptors in the kidney;** causes include familial deficiency, drugs (lithium, demeclocycline), hypercalcemia, or tubulointerstitial kidney disease
Pathophysiology	A deficiency in ADH or the inability of the kidney to sense ADH results in the **inability to retain water** and, thus, increased urine output. Lack of water retention leads to an **increase in serum osmolality,** which stimulates thirst receptors in the brain and the posterior pituitary to release more ADH.
Clinical Manifestations	**Polydipsia and polyuria;** seizures; headaches; signs of dehydration *Lab findings:* **Increased serum osmolality, hypernatremia,** decreased urinary specific gravity
Treatment	Synthetic vasopressin for central diabetes insipidus Low-sodium diet and thiazide diuretic for nephrogenic diabetes insipidus
Notes	

A 37-year-old woman presents to your office complaining of fatigue and thinning of her hair. While discussing her health further, you find that she has gained 20 pounds over the past 6 months with no change in diet or exercise. During physical examination, you note that she has a mildly enlarged thyroid gland and dry skin. You decide to send her for a blood draw to check her thyroid function tests.

Cretinism and Myxedema

Etiology and Epidemiology	**Cretinism:** Hypothyroidism occurring during infancy; causes of cretinism include iodine deficiency, congenital deformity of the thyroid, and deficiency of enzymes that synthesize thyroid hormones **Myxedema:** Hypothyroidism in adults; most commonly seen in middle-aged women; causes of myxedema include **idiopathic,** iodine deficiency, and surgical or radiation destruction of the thyroid
Pathology	*Thyroid:* Moderate enlargement of the gland *Soft tissues:* Accumulation of glycosaminoglycans and hyaluronic acid
Clinical Manifestations	**Cretinism: Hypothyroidism;** impaired musculoskeletal and nervous system development manifested as **short stature**, distended abdomen, and mental retardation; goiter; edematous face; large tongue **Myxedema: Hypothyroidism;** goiter; **thickening of facial features;** periorbital edema; pale skin
Treatment	Synthetic levothyroxine
Notes	Although common in the past, cretinism has become less frequent owing to widespread addition of iodine to foods and screening of newborns for hypothyroidism.

A 42-year-old woman presents to your office complaining of fatigue, thinning hair, and a weight gain of 15 pounds over the last month despite no change in eating habits. During her physical examination, you note that she has a pulse of 52, delayed deep tendon reflexes, a puffy face and eyelids, and an enlarged thyroid gland. Laboratory tests revealing antibodies against thyroglobulin and TSH receptors confirm your suspected diagnosis.

Hashimoto Thyroiditis

Etiology and Epidemiology	**Autoimmune** disorder Incidence is more common among **middle-aged women,** in patients with a family history of Hashimoto or other autoimmune diseases, and in HLA-DR5- and HLA-B5-positive individuals
Pathology	*Gross:* Symmetrical enlargement of the thyroid forming a **goiter** *Microscopic:* **Lymphocytic and plasma cell infiltrate** of the thyroid gland with germinal center formation; atrophic thyroid follicles; Hurthle cells (epithelial cells with eosinophilic cytoplasm)
Clinical Manifestations	Transient hyperthyroidism, followed by **hypothyroidism** *Lab findings:* **Autoantibodies against thyroglobulin, thyroid peroxidase**, TSH receptors, and/or iodine receptors
Treatment	Synthetic levothyroxine
Notes	

A 35-year-old woman presents to your office complaining of palpitations and intolerance to heat. Upon further questioning, you learn that she has developed an increased appetite and that her husband has told her that she is quite irritable lately. During her physical examination, you note that she has exophthalmos, moist skin, a pulse of 110, and a diffusely enlarged thyroid gland. You immediately order a panel of thyroid function tests to confirm your suspected diagnosis.

Graves Disease

Etiology and Epidemiology	Caused by formation of **thyroid-stimulating immunoglobulin and thyroid growth immunoglobulin** Seen most commonly in women between the ages of 20 and 40 and in patients who are HLA-DR3 and HLA-B8 positive
Pathology and Pathophysiology	*Pathophysiology:* **Thyroid-stimulating immunoglobulin** binds thyroid follicle TSH receptors and stimulates TH production. **Thyroid growth immunoglobulin** also stimulates glandular hyperplasia and enlargement. *Gross:* Symmetrical enlargement of the thyroid gland *Microscopic:* Hypercellularity; follicles are small and wedged together with little colloid; interstitium may have a lymphocytic infiltrate
Clinical Manifestations	**Hyperthyroidism** symptoms; **exophthalmos** (protrusion of the eyes); thickened edematous nodules on lower extremities
Treatment	Radioactive iodine or antithyroid drugs (**propylthiouracil** blocks TH synthesis); thyroidectomy; β-blockers (**propranolol**) as needed to control tachycardia
Notes	

A 28-year-old woman presents to your office complaining of fever and anterior neck pain. She tells you that she has been suffering from a flu-like illness for the past week and a half. During her physical examination, you note that she has lid lag, a pulse of 100, and an extremely tender thyroid gland. You order serum studies looking specifically at thyroid hormone levels, which show marked elevation. Based on these results and your physical examination, you suspect that she will recover spontaneously within the next few weeks and do not recommend any further treatment.

Subacute (DeQuervain, Granulomatous) Thyroiditis

Etiology and Epidemiology	Associated with **viral infection** (especially mumps or *Coxsackievirus*) Most common in women between the ages of 30 and 50
Pathology	*Gross:* Mild enlargement of the thyroid *Microscopic:* Granulomatous inflammation; destruction of thyroid follicles
Clinical Manifestations	Flu-like illness associated with **transient hyperthyroidism,** fever, and a tender thyroid
Treatment and Prognosis	NSAIDs; prednisone if severe Self-limited illness
Notes	

A 58-year-old woman presents to your office complaining of several little lumps in her neck. She has a history of long-standing diffuse goiters, but her history is otherwise unremarkable. Her physical examination is significant for irregular enlargement of her thyroid. You note no cervical lymphadenopathy. You decide to check her thyroid hormone and TSH levels and you order an ultrasound of the thyroid as well as a fine needle aspiration biopsy to rule out carcinoma of the thyroid.

Multinodular Goiter

Etiology	Usually develops from **long-standing simple goiters,** which can arise from iodine deficiency, goitrogens (eg, calcium or fluorides), or TH biosynthetic enzyme deficiency
Pathology	*Gross:* **Asymmetrical, nodular** enlargement of the thyroid *Microscopic:* Individual nodules may show **colloid-rich follicles;** follicular epithelial hyperplasia; areas of hemorrhage, calcification, and fibrosis
Clinical Manifestations	**Goiter;** patients are usually **euthyroid,** but a few patients may present with hyperthyroidism; may see dysphagia or hoarseness owing to local compression of surrounding structures
Treatment	Synthetic levothyroxine (suppresses TSH levels → decreased hyperplasia) if patient is euthyroid
Notes	A goiter can be **toxic** (produces TH, thus leading to hyperthyroidism) or **nontoxic** (does not produce TH). Biopsy (FNA) should be performed for any large irregular nodules to rule out carcinoma.

A 52-year-old man presents to your office after noticing a lump in his neck that has been slowly enlarging. He denies any symptoms of hyper- or hypothyroidism, although he does tell you that he had radiation treatment for acne when he was a child. During his physical examination, you note that he has a nontender nodule in the anterior neck as well as some cervical lymphadenopathy. You become concerned and you order a blood test to check his thyroid hormone and TSH levels, a radioactive thyroid scan, and a fine needle aspiration biopsy of both the lump in his neck as well as his enlarged cervical lymph nodes.

Carcinoma of the Thyroid

Etiology	Associated with radiation to the head/neck, or genetic predisposition to thyroid carcinoma
Pathology	*Gross:* Firm nodule(s) on the thyroid *Microscopic:* Four histologic types: **(1) Follicular:** small uniform **follicles** filled with colloid; **(2) Papillary:** comprises 75%–80% of cases, papillae of cuboidal cells, **Orphan Annie nuclei, psammoma bodies; (3) Medullary:** derived from **C cells,** nests of cells within **amyloid** deposits; **(4) Anaplastic:** pleomorphic giant cells, spindle cells, small **anaplastic cells**
Clinical Manifestations	Nodule or **mass in neck;** dysphagia or hoarseness owing to local compression **Papillary:** Metastasizes to **local lymph nodes** **Follicular:** Metastasizes to lung and bone via **hematogenous spread** **Medullary:** Secretes **calcitonin;** associated with MEN IIa and IIb
Treatment and Prognosis	**Thyroidectomy** or lobectomy; radioactive iodine treatment Papillary has a good prognosis; anaplastic has a particularly poor prognosis
Notes	**Thyroid adenomas** are common. Microscopically, they contain uniform, colloid-filled follicles, although there are various histologic types. They are not considered premalignant and are usually nonfunctional.

A 63-year-old woman presents to your office complaining of generalized bone pain. While discussing her health further, you discover that she is also suffering from polyuria, constipation, and muscular weakness. A bone densitometry study reveals a significant loss of cortical bone. You order laboratory studies, which reveal increased calcium levels, increased PTH levels, increased alkaline phosphatase, and decreased phosphate levels. You believe that a parathyroid biopsy will reveal polygonal chief cells and larger oxyphil cells and that a bone biopsy would reveal brown tumors.

Primary Hyperparathyroidism

Etiology	Caused by **PTH adenoma,** PTH hyperplasia, PTH carcinoma, or production of PTH-like hormone by tumors (especially squamous cell bronchogenic carcinoma) Associated with MEN I and MEN IIa
Pathology	*Parathyroid Gland:* **Parathyroid adenoma:** circumscribed nodule composed of uniform, polygonal chief cells along with a few larger oxyphil cells *Bone:* **Osteitis fibrosa cystica:** cystic spaces filled with fibrous tissue **(brown tumors)**, owing to increased osteoclast activity
Clinical Manifestations	**Bone pain** owing to osteitis fibrosa cystica; **nephrocalcinosis;** peptic ulcers and other GI disturbances; weakness *Lab findings:* **Hypercalcemia, increased PTH levels,** increased serum alkaline phosphatase, decreased serum phosphate
Treatment	Surgical removal of the abnormal glands if disorder is caused by adenoma
Notes	Other causes of hypercalcemia include cancer originating in or metastatic to the bone, multiple myeloma, sarcoidosis, milk alkali syndrome, Paget disease of the bone, hyperthyroidism, and vitamin D intoxication.

A 58-year-old man presents to your office for a follow-up visit regarding his chronic renal insufficiency. When he mentions that he has been having some generalized bone pain, you become concerned and send him for a blood draw. His serum studies reveal decreased calcium and increased serum phosphate levels. You decide to check his PTH levels, which you believe will be elevated, and you recommend that he take calcium and vitamin D supplements.

Secondary Hyperparathyroidism

Etiology	Most commonly caused by chronic renal failure
Pathology and Pathophysiology	*Parathyroid:* Diffuse enlargement of gland caused by glandular **hyperplasia** of chief cells *Pathophysiology:* Decreased 1,25-$(OH)_2D_3$ production owing to failing kidney → decreased intestinal calcium absorption → hypocalcemia (also caused by increased calcium excretion by damaged kidney) → increased PTH
Clinical Manifestations	**Diffuse osteoclastic bone disease; metastatic calcification** in soft tissues *Lab findings:* **Hypocalcemia, increased PTH,** increased serum alkaline phosphatase, increased serum phosphate
Treatment	Surgical removal of the abnormal glands if disorder is severe Phosphate binders and vitamin D supplementation
Notes	

A 45-year-old woman presents to your office for a follow-up visit regarding her thyroidectomy. She tells you that she has been suffering from wrist spasms. During physical examination, you notice that she has carpal spasm 2 minutes after you inflate the blood pressure cuff and that she has facial twitching when you tap her facial nerve. You decide to check her calcium, phosphate, and PTH levels, but you fear that her previous surgery may have removed more than just her thyroid.

Hypoparathyroidism

Etiology	Caused by **surgical removal of the parathyroid glands,** congenital absence of the parathyroid glands (as seen in DiGeorge syndrome), radioactive iodine therapy, or idiopathic autoimmune atrophy of the parathyroids
Pathology	*Gross:* Mild shrinkage of gland *Microscopic:* Replacement of chief cells by fibrotic tissue
Clinical Manifestations	**Symptoms of hypocalcemia: Tetany** or other signs of neuromuscular irritability, **prolonged QT interval** on ECG, **Trousseau sign** (carpal spasm 2 minutes after inflation of blood pressure cuff above systolic blood pressure), **Chvostek sign** (twitching of the facial muscles upon superficial tapping of the facial nerve) *Lab findings:* **Hypocalcemia, decreased PTH levels,** increased serum phosphate levels
Treatment	Calcium and vitamin D supplementation
Notes	

A 19-year-old mentally retarded woman presents to your office as a new patient. You immediately notice that she is extremely short and has very short metacarpals on her fourth and fifth fingers of both hands. She tells you that she has been previously diagnosed with a genetic illness. On physical examination, you notice that she has carpal spasm after you inflate the blood pressure cuff above her systolic pressure. You suspect that it will be necessary to monitor her calcium, phosphate, and PTH levels on a regular basis.

Pseudohypoparathyroidism

Etiology	Autosomal recessive disorder resulting in a **defective PTH receptor**
Pathophysiology	**Type 1a:** Deficiency in $G_{s\text{-}\alpha}$ leads to decreased coupling of PTH receptor to adenylate cyclase, such that activation of PTH receptor does not activate target cell **Type 1b:** Regulation of $G_{s\text{-}\alpha}$ is altered such that the target cell is not activated by stimulation of the PTH receptor
Clinical Manifestations	**Symptoms of hypocalcemia: Tetany** or other signs of neuromuscular irritability, **prolonged QT interval** on ECG, **Trousseau sign** and **Chvostek sign** *Albright hereditary osteodystrophy:* Short stature, mental retardation, shortened fourth and fifth metacarpal and metatarsal bones, obesity *Lab findings:* **Hypocalcemia, decreased PTH levels,** increased serum phosphate levels
Treatment	Calcium and vitamin D supplementation
Notes	

A 37-year-old woman presents to your office for her annual checkup. Physical examination reveals a blood pressure of 160/100. Upon further questioning, she tells you that she has felt weak lately and that she seems to be urinating more frequently. Her past medical history is insignificant. Laboratory tests reveal low serum potassium levels, an increased serum bicarbonate level, an increased blood pH, and increased CO_2 levels. After checking several hormone levels, you decide to send her for an abdominal/pelvic CT scan because you suspect that her condition may originate from a small neoplasm in her abdomen.

Primary Hyperaldosteronism (Conn Syndrome)

Etiology	Caused by **aldosterone-secreting adrenocortical adenoma** or hyperplasia
Pathology	*Adrenal cortex:* **Adenoma:** solitary encapsulated lesion composed of uniform cortical cells filled with lipid-containing vesicles. **Hyperplasia:** hyperplasia of cells of zona glomerulosa.
Clinical Manifestations	**Hypertension;** muscular weakness sometimes with tetany; headache; polyuria and polydipsia *Lab findings:* **Metabolic alkalosis, decreased serum potassium, decreased renin levels, increased aldosterone levels**
Treatment	Adrenalectomy or spironolactone (potassium-sparing diuretic)
Notes	**Secondary hyperaldosteronism** is associated with any condition that results in the kidney sensing a low effective circulating volume (eg, renal ischemia, chronic renal failure, hepatic cirrhosis, CHF, or nephrotic syndrome). It is associated with increased aldosterone levels because of **increased renin levels.**

A 45-year-old woman presents to your office complaining of increased urination over the past several months. Upon questioning her further, you learn that she has gained 35 pounds over the past year, bruises easily, and has grown hair on her chin. While speaking with her, you note that she has moon facies and increased fat pads on the back of her neck. Blood tests reveal hyperglycemia, increased cortisol levels, and increased serum ACTH levels. To determine the etiology of her disorder, you decide to perform a dexamethasone suppression test.

Cushing Syndrome

Etiology	Caused by **hypercortisolism,** which can result from iatrogenic cortisol administration, increased ACTH production by pituitary adenoma/hyperplasia (Cushing disease), adrenal cortical adenoma/carcinoma, or ectopic ACTH-secreting tumors (usually small cell bronchogenic carcinoma)
Pathology	Adrenal gland pathology depends on etiology: **(1) Iatrogenic:** adrenocortical atrophy; **(2) ACTH overproduction:** bilateral adrenocortical nodular hyperplasia of lipid-rich cells in zona fasciculata; **(3) Adrenal adenoma:** small encapsulated lesion composed of uniform zona fasciculata cells; **(4) Pituitary hyperplasia or adenoma** (seen in Cushing disease): collection of basophilic cells
Clinical Manifestations	**Truncal obesity; hypertension; moon facies; buffalo hump** (fat on posterior neck); muscle wasting; hyperglycemia owing to **insulin resistance; skin changes** (purple abdominal striae, bruising); **osteoporosis;** hirsutism; mental changes; **immune suppression** *Lab findings:* **Increased cortisol levels, abnormal ACTH levels** (decreased in iatrogenic and adrenal adenoma, increased in pituitary adenoma and ectopic secretion of ACTH), **hyperglycemia**
Treatment	Surgical resection of pituitary/adrenal adenoma or ectopic ACTH-secreting tumors
Notes	The dexamethasone suppression test is used to determine the etiology of Cushing disease. Cortisol levels are decreased following high doses of dexamethasone in Cushing disease caused by pituitary adenomas, but are unchanged when caused by ectopic ACTH-secreting tumors.

A 47-year-old woman presents to your clinic complaining of nausea and fatigue. While speaking with her, you notice that she has hyperpigmented skin over her knuckles, knees, and elbows. Her blood pressure is 90/60 on physical examination and laboratory tests reveal hypoglycemia, hyperkalemia, and hyponatremia. You suspect that her condition may be caused by an autoimmune process and you prescribe replacement therapy of specific hormones to treat her symptoms.

Primary Adrenocortical Insufficiency (Addison Disease)

Etiology	Causes include **autoimmune destruction of the adrenal gland** (autoimmune adrenalitis), infection (TB), bilateral adrenal hemorrhage (owing to trauma, surgery, or anticoagulant therapy), amyloidosis, and neoplasms metastatic to the adrenal gland
Pathology	*Gross:* Shrunken, atrophied adrenal gland *Microscopic:* Few cortical cells; lymphoid infiltrate (seen in autoimmune adrenalitis)
Clinical Manifestations	**Signs of decreased glucocorticoids: Weakness** and fatigue; nausea and vomiting; **hyperpigmentation** of skin (owing to increased secretion of MSH, an ACTH precursor molecule) **Signs of decreased mineralocorticoids: Hypotension;** hypoglycemia; **hyperkalemia;** hyponatremia
Treatment	Glucocorticoid and mineralocorticoid replacement
Notes	**Secondary adrenocortical insufficiency** can be caused by any disorder of the pituitary or hypothalamus that reduces ACTH production such as **chronic glucocorticoid therapy**, cancer, infection, or trauma. This disorder presents similarly to primary adrenocortical insufficiency but there is no hyperpigmentation owing to decreased MSH levels. **Waterhouse-Friderichsen syndrome** refers to acute bilateral adrenal insufficiency usually owing to hemorrhagic necrosis of the adrenal glands, caused by DIC or meningococcemia.

A 16-year-old girl is brought to your office complaining of delayed menarche. She denies sexual activity and states that a home pregnancy test was negative. Physical examination reveals the absence of breasts, hair on her upper lip, chin, and axillary region, and hypertension. When laboratory results reveal decreased cortisol and aldosterone levels, you suspect that this girl may have a rare autosomal recessive enzyme deficiency.

Congenital Adrenal Hyperplasias

Etiology	Autosomal recessive **deficiency in enzymes involved in biosynthesis of cortical steroids**
Pathology and Pathophysiology	*Adrenal gland:* Bilateral nodular hyperplasia of gland with lipid-depleted cortical cells **21β-Hydroxylase deficiency**: Interferes with aldosterone and cortisol production; results in shunting of precursor molecules to form sex hormones **11β-Hydroxylase deficiency**: Interferes with aldosterone and cortisol production; results in shunting of precursor molecules to form sex hormones **17α-Hydroxylase deficiency**: Interferes with cortisol and sex hormone production; results in shunting of precursor molecules to form aldosterone
Clinical Manifestations	**21β-Hydroxylase deficiency: Masculinization; hypotension;** hyperkalemia; hyponatremia (**salt wasting** can lead to hypovolemia) **11β-Hydroxylase deficiency**: Masculinization; hypertension (weak mineralocorticoid precursor activity); no salt wasting **17α-Hydroxylase deficiency**: Hypertension; hypokalemia; no sexual maturation
Treatment	Replacement of deficiency hormones; symptomatic treatment
Notes	

A 29-year-old man presents to the emergency department complaining of a crushing headache and heart palpitations. He tells you that he has had similar episodes in the past. Physical examination reveals a pulse of 140 and a BP of 200/110. A 24-hour urine collection reveals increased VMA and metanephrine levels and blood tests demonstrate increased plasma catecholamine levels. You immediately prescribe phenoxybenzamine for the patient and tell him that it is likely that he will need surgery to definitively treat his condition.

Pheochromocytoma

Etiology	Most (90%) cases occur sporadically. Other cases are associated with MEN IIa, MEN IIb, neurofibromatosis, or von Hippel-Lindau disease.
Pathology	*Gross:* Variable changes in adrenal medulla; range from small, circumscribed lesions to large, hemorrhagic lesions with lobular pattern *Microscopic:* Tumor composed of **nests of polygonal chromaffin cells** containing catecholamine-rich granules; giant, pleomorphic cells are sometimes seen
Clinical Manifestations	Release of epinephrine and norepinephrine from tumors results in **intermittent** attacks of **hypertension, headache, palpitations,** and diaphoresis *Lab findings:* **Increased 24-hour urinary catecholamine and metanephrine levels, increased plasma metanephrine levels**
Treatment	Initial treatment with α-adrenergic blocking agents (phenoxybenzamine) followed by surgical resection of mass
Notes	Pheochromocytomas are associated with the **rule of 10s:** 10% are malignant, 10% bilateral, 10% familial, 10% extra-adrenal, and 10% occur in children. Pheochromocytomas can occur outside the adrenal gland and are then called paragangliomas.

A 10-year-old girl is brought to the emergency department by her parents. She is confused, hypotensive, and breathing rapidly and deeply. As you examine her, you notice that her breath has a fruity odor. Her parents tell you that their daughter has lost some weight recently, even though her appetite has increased. She also has appeared to be drinking and urinating more than usual. When laboratory tests reveal hyperglycemia, ketonemia, and an anion-gap metabolic acidosis, you immediately begin to administer insulin along with fluid and electrolyte replacement therapy.

Diabetes Mellitus (Part 1)

Etiology and Epidemiology

Type I: Insulin deficiency arising from pancreatic **β-cell destruction;** caused by genetic susceptibility (HLA-DR3 or -DR4), autoimmune reactions, and/or environmental factors (Coxsackie and other viruses); occurs in **patients < 20 years old**

Type II: Peripheral tissue insulin resistance mediated by decreased insulin receptors and decreased response of β-cells to glucose; of type II DM patients, 90% have a positive family history for DM; occurs in **obese middle-aged patients**

Pathophysiology

Hyperglycemia → increased glucose excretion in urine → osmotic diuresis, leading to large volumes of urine with loss of water and electrolytes **(polyuria)** → plasma hyperosmolarity → trigger thirst receptors → **polydipsia**

Insulin deficiency → protein/fat catabolism → **weight loss** with **increasing appetite**

Increased fat catabolism → increased levels of free fatty acids → production of ketone bodies → **ketoacidosis** (most commonly in type I DM)

Acute Clinical Manifestations

Type I: Hyperglycemia; glycosuria; **polyuria; polydipsia; weight loss** with increased appetite; **ketoacidosis** (manifested by dehydration, deep and rapid [Kussmaul] breathing, fruity breath, anion-gap metabolic acidosis, ketonemia, and ketonuria)

Type II: Hyperglycemia; glycosuria; polyuria; skin or vaginal infections; **nonketotic hyperosmolar coma**

Notes

Maturity-onset diabetes of the young (MODY): Another form of diabetes caused by autosomal dominant genetic defects in pancreatic β-cell function

A 48-year-old obese man presents to your office complaining of generalized weakness. Upon further questioning, you learn that he has lost 7 pounds over the last 6 months despite an increased appetite. Physical examination reveals decreased sensation over his hands and feet, diminished dorsalis pedis pulses, and proliferative retinopathy. When laboratory tests reveal fasting hyperglycemia and glycosuria, you inform the patient that his condition can be effectively managed, but that he could have serious chronic complications if his condition is not tightly controlled.

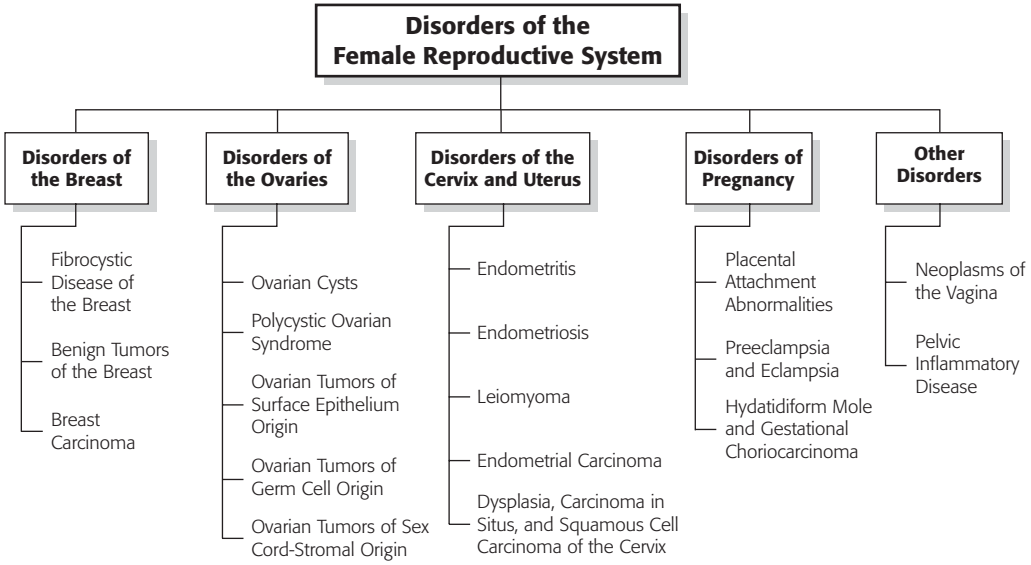
Diabetes Mellitus (Part 2)

Pathology of Pancreas	**Type I: Atrophy of islets;** T-lymphocytic infiltration **Type II: Amyloid replacement of islets** with minor reduction of islet size
Pathology and Pathophysiology of Chronic Complications	*Pathophysiology:* **Nonenzymatic glycosylation (NEG)** of proteins in vessel walls and tissues lead to trapping of molecules (eg, **LDL,** plasma proteins) causing complications; hyperglycemia can cause an **increase in intracellular sorbitol,** thereby causing osmotic cell damage (especially in the lens) **Ocular complications:** Cataracts; glaucoma; **proliferative retinopathy** (can cause blindness) **Accelerated atherosclerosis:** Can lead to MI, gangrene, and stroke **Diabetic microangiopathy:** NEG causes thickening of basement membranes in the retina, kidney, skin, and skeletal muscle; can lead to delayed wound healing with increased risk of infection **Diabetic nephropathy:** Owing to NEG damage to basement membranes **Peripheral and autonomic neuropathy:** Stocking-glove distribution of loss of sensation; can also have delayed motor movements, pain, and autonomic instability
Treatment	Diet restriction; insulin replacement for type I; hypoglycemic drugs (eg, sulfonylureas) or insulin for type II; treatment of atherosclerosis with statins; ACE-inhibitors for diabetic nephropathy
Notes	Long-term glucose control can be assessed by the levels of glycosylated hemoglobin **(HbA1C).**

A 38-year-old man presents to your office complaining of recurrent aching epigastric pain and diarrhea. The pain is generally relieved with food and antacids. Diagnostic tests confirm your suspicions that this man is suffering from peptic ulcer disease. Before you begin the patient on proton pump inhibitors to decrease gastric acid secretion, you decide to order a serum gastrin level. When laboratory tests reveal an elevated serum gastrin, you send the patient for radiologic studies to try and locate the cause of the increased serum gastrin levels.

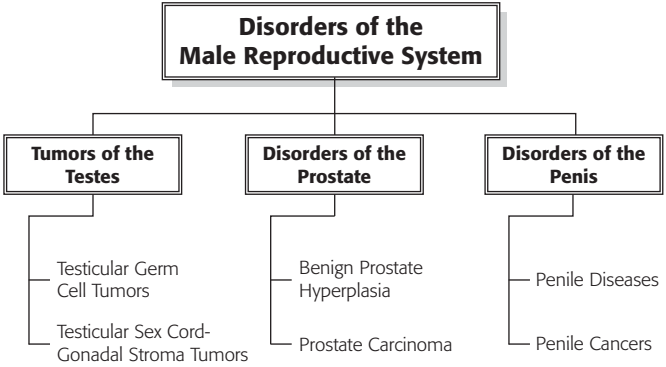
Zollinger-Ellison Syndrome

Etiology	Caused by **gastrinoma** (pancreatic islet cell tumor); most gastrinomas are sporadic, but 25% are associated with MEN I
Pathology and Pathophysiology	*Gastrinoma:* May arise in the pancreas or duodenum or in tissues surrounding pancreas; often malignant and metastasize to the liver but, histologically, they rarely show anaplasia *Pathophysiology:* **Gastrinomas secrete gastrin** causing **acid hypersecretion,** leading to peptic ulcers and pancreatic enzyme inactivation
Clinical Manifestations	**Peptic ulcer disease** (usually in duodenum) often complicated by ulcer perforation**; diarrhea,** steatorrhea, and weight loss (caused by pancreatic enzyme inactivation) *Lab findings:* **Increased gastrin levels, decreased gastric pH**
Treatment	Surgical removal of gastrinoma; control of gastric acid secretion with proton pump inhibitors
Notes	**Insulinoma** is a tumor of the islet cells of the pancreas that is characterized by increased secretion of insulin and increased C-peptide (molecule that is cleaved from proinsulin during insulin synthesis) levels. It is associated with the **Whipple triad** (episodic hyperinsulinemia and hypoglycemia, hypoglycemic CNS dysfunction, reversal of CNS dysfunction upon resolution of hypoglycemia).


Disorders of the Female Reproductive System
Disorders of the Breast
Fibrocystic Disease of the Breast
Benign Tumors of the Breast
Breast Carcinoma
Disorders of the Ovaries
Ovarian Cysts
Polycystic Ovarian Syndrome
Ovarian Tumors of Surface Epithelium Origin
Ovarian Tumors of Germ Cell Origin
Ovarian Tumors of Sex Cord-Stromal Origin
Disorders of the Cervix and Uterus
Endometritis
Endometriosis
Leiomyoma
Endometrial Carcinoma
Dysplasia, Carcinoma in Situs, and Squamous Cell Carcinoma of the Cervix
Disorders of Pregnancy
Placental Attachment Abnormalities
Preeclampsia and Eclampsia
Hydatidiform Mole and Gestational Choriocarcinoma
Other Disorders
Neoplasms of the Vagina
Pelvic Inflammatory Disease

Differential Features of Ovarian Masses

Ovarian Mass	Years Affected	Menstrual Irregularity	Malignancy
Follicular cysts	Menstrual years	Anovulation	No
Corpus luteum cysts	Menstrual years	Delayed period	No
Theca-lutein cysts	Menstrual years	Amenorrhea, hCG elevation	No
Dysgerminoma	Kids, young adults	None	Yes
Yolk sac tumor	Kids, young adults	None	Yes
Choriocarcinoma	Premenstrual	None, hCG elevation	Yes
Benign teratoma	All years	None	No
Malignant teratoma	Kids, young adults	None, hCG elevation	Yes
Cystadenocarcinoma	Menstrual years	None	Yes
Endometrioid tumor	Postmenopausal	None	Yes
Granulosa cell tumor	Premenarche or postmenopausal	Irregular/excessive bleeding	Sometimes
Ovarian thecoma	All years	Irregular	Rarely
Sertoli-Leydig cell tumor	All years	Amenorrhea	No


Disorders of the Male Reproductive System
Tumors of the Testes
Disorders of the Prostate
Disorders of the Penis
Testicular Germ Cell Tumors
Testicular Sex Cord-Gonadal Stroma Tumors
Benign Prostate Hyperplasia
Prostate Carcinoma
Penile Diseases
Penile Cancers

Ovarian and Testicular Tumor Analogues

Ovarian Tumors	Testicular Tumor Analogs
Dysgerminoma	Seminoma
Yolk sac tumor	Endodermal sinus tumor
Ovarian choriocarcinoma	Testicular choriocarcinoma
Ovarian teratoma (benign)	Testicular teratoma (malignant)
Sertoli-Leydig ovarian tumor	Leydig cell (interstitial) tumor, Sertoli cell tumor (androblastoma)

A 30-year-old woman presents to your clinic complaining of bilateral, diffuse breast pain. Her last menstrual period was 2 weeks ago and she says that she has felt several painful masses in both breasts during her self-examination in the shower. She is very concerned because she has a sister-in-law, who was recently diagnosed with breast cancer. On physical examination, you notice multiple, palpable masses on both breasts but no changes to the overlying skin. After taking a detailed history, you learn that the patient does not drink or smoke, has no immediate family members with a history of breast cancer, and there has been no nipple discharge. You order a fine needle aspiration cytology, which reveals an aspirate suggestive of a cyst. You reassure the patient that the lesion is benign and recommend that she avoid trauma to the affected regions and wear a brassiere that gives good support and protection.

Fibrocystic Disease of the Breast

Etiology and Epidemiology	Caused by **hormonal imbalance** (increased estrogens and/or decreased progesterones) Peak incidence is between 25 and 50 years old
Pathology	Several histologic types: **(1) Cystic:** multiple fluid-filled cysts appear blue **(blue-dome cyst),** cysts lined by polygonal cells with eosinophilic granular cytoplasm that are similar to apocrine epithelium **(apocrine metaplasia),** may see papillary projections of cystic epithelium; **(2) Epithelial hyperplasia of breast duct:** increase in number of epithelial layers in terminal duct lobules resulting in irregular lumens; **(3) Stromal fibrosis:** hyperplasia and fibrosis of breast stroma; **(4) Sclerosing adenosis:** increased number of acini, stromal fibrosis
Clinical Manifestations	Presents with **diffuse breast pain (midcycle tenderness)** and multiple, palpable lesions, often **bilateral;** no changes in overlying skin or nipple; rapid fluctuation in size of masses is common
Treatment	Symptom management with pain control
Notes	Fibrocystic disease is the most common breast disorder. Cystic and stromal fibrosis represent no increased risk for carcinoma, but epithelial hyperplasia and sclerosing adenosis do carry a mildly increased risk.

A 21-year-old African American woman presents to the clinic complaining of a large mass in her left breast. She has no immediate family members with breast cancer. On physical examination, you notice that the mass is round, rubbery, mobile, and nontender. It is approximately 4 cm in diameter. You order a needle biopsy that shows a combination of connective tissue and cystic spaces taking on a leaflike appearance. You inform the patient that this lesion is most often benign, but nevertheless you suggest that she be treated with a local excision to remove the growth.

Benign Tumors of the Breast

Epidemiology	**Fibroadenoma (FA):** Occurs in **women < 40;** tends to occur more frequently and at a younger age in African American women **Phyllodes tumor (PT):** Occurs most commonly **after the age of 50** **Intraductal papilloma (IP):** Occurs in middle-aged women
Pathology	**FA:** *Gross:* small, **mobile, rubbery, firm mass** with sharp, well-circumscribed edges. *Microscopic:* fibroblastic stroma surrounding cystic and glandular spaces; may regress after menopause and demonstrate calcifications. **PT:** *Gross:* **large, bulky mass** of connective tissue and cysts. *Microscopic:* cystic spaces on cut section of stroma contains **leaflike projections** from cyst walls; leaflike appearance on breast surface; 5%–10% undergoes malignant change with atypia (cystosarcoma phyllodes). **IP:** *Gross:* arising from major lactiferous ducts. *Microscopic:* proliferation of ductal epithelial tissue in **papillary growth** manner; apocrine metaplasia.
Clinical Manifestations	**FA and PT: Increased size and tenderness** of mass with pregnancy or menstrual cycle; no overlying skin changes; no lymphadenopathy; no nipple retraction **IP:** Presents with **nipple discharge**
Treatment	**FA:** No treatment or simple excision **PT:** Local excision with wide margin; can recur after resection **IP:** Simple excision
Notes	Phyllodes tumor and intraductal papilloma carry a mildly increased risk of breast carcinoma.

A 50-year-old woman presents to your clinic after finding a mass on the upper outer quadrant of her left breast. After taking a thorough history, you learn that her mother died from breast cancer and her maternal aunt was also diagnosed with breast cancer at an early age. The patient started her period at age 11, did not bear any children, and has not been through menopause. On physical examination, she is markedly obese and you notice retraction of the skin and the nipple on her left breast. You locate the mass in question during your breast examination and find that it is fixed, hard, and nontender. The mass was not present on her last mammogram dating back 2 years. You also feel palpable axillary lymph nodes. You schedule the patient for an immediate mammography and needle biopsy to confirm your suspicions.

Breast Carcinoma (Part I)

Etiology and Epidemiology

Risk factors include **family history** of first-degree relative with breast cancer at young age (highest risk), autosomal dominant inheritance of mutations in ***BRCA1*** or ***BRCA2*** gene, female gender, **increased age,** early first menarche, delayed first pregnancy, nulliparity, late menopause, radiation, and exogenous estrogen use

Incidence increases with age

Pathology

Infiltrating ductal carcinoma: Tumor cells arranged in cords, islands, or glands embedded in dense fibrous stroma; may arise from **ductal carcinoma in situ (DCIS)**

Intraductal comedocarcinoma: Sheet of tumor cells confined within duct; central necrosis; periductal fibrosis with inflammation

Inflammatory: Lymphatic involvement of overlying skin

Paget disease: Paget cells (large cells with clear halo of pale cytoplasm) extend from ducts and invade epidermis of nipple; underlying ductal adenocarcinoma within subareolar excretory ducts always present

Infiltrating lobular: Often multiple and **bilateral;** cells line up **(Indian file)** with tumor cells surrounding lobule in target fashion; signet ring cells; may arise from **lobular carcinoma in situ (LCIS)** after many years

Medullary: Solid sheets of cells with large nucleoli in scant stroma; lymphocytic infiltrate

Mucinous (colloid): Pools of extracellular mucin surrounding tumor cell clusters; gelatinous consistency

Notes

Breast carcinoma is the second most common cause of cancer death among women.

A 49-year-old woman presents to your office concerned about a rash on her left nipple that has developed over the past month. The rash is itchy, but painless. On physical examination, you find a large eczematous-like patch over the left nipple as well as a fixed mass in the left breast. You perform both a skin biopsy as well as a needle biopsy of the mass. When the skin biopsy reveals large cells with a clear halo of pale cytoplasm invading the epidermis, you become certain that the biopsy of the mass will reveal carcinoma of the breast.

Breast Carcinoma (Part II)

Clinical Manifestations	**Painless,** usually **fixed,** hard, nontender mass often found in **upper outer quadrant** of breast; retraction of overlying skin and nipple; palpable axillary lymph nodes
	Infiltrating ductal carcinoma: Firm, fixed, fibrous mass
	Inflammatory: Red, swollen, hot, painful to touch, **orange-peel** appearance of skin
	Paget disease: Itchy, scaly, painless, eczematous **patches on the nipple**
	Medullary: Soft, fleshy-consistency mass
	Lab findings: Paraneoplastic syndrome with secretion of PTH-related peptide may lead to hypercalcemia
	Imaging: Mammogram with microcalcifications, spiculated or enlarging mass
Treatment	**Surgery and radiation therapy;** chemotherapy; hormonal therapy (**tamoxifen or aromatase inhibitors**) for patients with cancer cells expressing estrogen receptor in their nuclei (ER/PR+); biologic therapy (**herceptin**) for patients with *HER2/neu* expression
Notes	Metastasis occurs to lymph nodes, lung, liver, and bone.

A 45-year-old woman presents to the clinic complaining of vague abdominal pain for the past 4 days. She describes her pain as more of a pelvic pressure that is generalized bilaterally. Her last menstrual period was 2 weeks ago and she states that she has regular menstrual cycles. She denies the possibility of pregnancy and is currently not taking oral contraceptives. She has not had any changes in digestive functions and denies any nausea, vomiting, constipation, or diarrhea. She has no family history of ovarian cancer. When an ultrasound confirms your suspicions, you place the patient on oral contraceptive pills, believing that her symptoms will disappear in 2 months, and you schedule her for a follow-up ultrasound.

Ovarian Cysts

Etiology and Epidemiology	**Follicular (F) cyst:** Associated with hyperestrinism and endometrial hyperplasia; most common cause of ovarian enlargement; mostly found during menstrual years **Corpus luteum (CL) cyst:** Found during menstrual years **Theca-lutein (TL) cyst:** Associated with choriocarcinoma, hydatidiform moles, and clomiphene (synthetic gonadotropin) therapy
Pathology	**F:** Often bilateral; distention of unruptured Graafian follicle; lined by granulosa cells **CL:** Often unilateral; contains clear fluid; lined by yellowish luteal cells with cytoplasmic lipid droplets; may hemorrhage into persistent mature corpus luteum **TL:** Often bilateral and multiple; lined by luteinized theca cells
Clinical Manifestations	All may be **asymptomatic** or present with pelvic pressure/pain or vague GI discomfort **F:** Pain not associated with menstruation **CL:** Delayed menstruation **TL:** Amenorrhea. *Lab findings:* hCG elevated as a result of trophoblastic proliferation.
Treatment	**F:** Often disappears with 2-month regimen of oral contraceptives; follow with serial ultrasounds; laparoscopic removal if persistent **CL and TL:** Cyst removal or unilateral oophorectomy
Notes	

A 30-year-old white woman presents to the fertility clinic with her husband, complaining of the inability to conceive. The couple has already checked the husband's sperm motility and count, which are within the normal range. The patient informs you that she has not menstruated for the last 4 months and that she has had a very irregular and sporadic menstrual cycle all of her life. You perform a physical examination, finding that the patient is obese with an inordinate amount of facial hair. She denies any abnormal uterine bleeding. You order serum studies that show elevated plasma LH and testosterone and decreased FSH levels. Based on these findings, you inform the patient that weight reduction will be the most effective treatment for restoring ovulation and that adjunct therapy with clomiphene can aid in ovulation.

Polycystic Ovarian Syndrome (Stein-Leventhal Syndrome)

Etiology and Epidemiology	Etiology unclear, but it is believed that a dysregulation of enzymes involved in androgen biosynthesis may be caused by **increased LH secretion,** thereby resulting in **excessive production of androgens;** associated with obesity, Cushing syndrome, congenital adrenal hyperplasia, genetic predisposition, and androgen-secreting adrenal tumors Common endocrine disorder affecting 2%–5% of women during **reproductive age**
Pathology and Pathophysiology	*Pathophysiology:* **Increased androgen production** causes anovulation, multiple follicular cysts, and theca cell hyperplasia *Gross:* Ovaries enlarged; pearly white thickened ovarian capsule; multiple cysts *Microscopic:* Cysts have granulosa cell layer and luteinized theca cells; cortical stromal fibrosis
Clinical Manifestations	**Amenorrhea;** infertility; **obesity; hirsutism** (in 70%); **insulin resistance** with increased risk of diabetes; virilism; increased risk of breast and endometrial carcinoma *Lab findings:* **Increased LH,** decreased FSH, **increased testosterone,** evidence of insulin resistance
Treatment	**Weight loss;** oral contraceptives; **metformin** for insulin resistance; gonadotropin analogs; ovulation induction with clomiphene
Notes	

A 40-year-old woman presents to the emergency room with generalized abdominal pain and pelvic pressure. After taking a more complete history, you learn that she has not passed stool for the last 3 days and vomited this morning. She tells you that the pain has been steady over the last week. You order an abdominal/pelvic CT scan, which is inconclusive, but does demonstrate bilateral enlargement of the ovaries. The patient is taken to the operating room for an exploratory laparotomy that shows extensive mucinous ascites, cystic epithelial implants on the peritoneal surfaces, and several adhesions. You believe that the patient's mucinous peritoneal involvement is caused by her ovarian condition.

Ovarian Tumors of Surface Epithelium Origin

Epidemiology	Usually occurs in women **> 20 years of age**
Pathology	**Serous cystadenoma:** Bilateral, benign cyst with **fallopian tube-like epithelium** **Papillary serous cystadenocarcinoma:** Bilateral, malignant cysts lined by stratified atypical epithelium; papillary growth; **psammoma bodies** **Mucinous cystadenoma:** Multilocular, benign cysts with columnar cells filled with mucin **Mucinous cystadenocarcinoma:** Malignant tumor with mucus-secreting atypical columnar epithelium; loss of gland architecture; necrosis **Brenner tumor:** Benign tumor with nests of cells **resembling bladder transitional epithelium** interspersed in fibrous stroma **Endometrioid tumor:** Malignant tumor resembling endometrium **Clear cell tumor:** Rare, malignant tumor composed of sheets of clear cells
Clinical Manifestations	Mild, nonspecific **abdominal discomfort**; malignant forms may present with weakness, weight loss, and anorexia; pseudomyxoma peritonei (intraperitoneal accumulation of mucinous material) is associated with mucinous cystadenocarcinoma *Lab finding:* Elevated **CA-125** in ovarian carcinomas
Treatment	Tumor removal; oophorectomy or hysterectomy; chemotherapy
Notes	Ovarian epithelial tumors make up 75% of ovarian tumors.

An 18-year-old white woman is admitted to your gynecologic service with a 1-month history of increasing abdominal pain and a rapidly enlarging pelvic mass. While admitting the patient, you perform a bimanual pelvic examination that reveals a left ovarian mass. This finding is consistent with the admitting note and was confirmed by abdominal/pelvic CT, which showed that the left ovary was twice as large as the right ovary. Serum studies demonstrate an elevated AFP level. There is no inguinal lymph node involvement and no signs of metastasis on imaging studies. Based on your findings, you perform a unilateral oophorectomy and send the diseased ovary for pathologic analysis. Histology shows glomerulus-like structures composed of a central blood vessel enveloped by germ cells within a space similarly lined by germ cells. These histologic bodies confirm your suspected diagnosis and you start the patient on combination chemotherapy.

Ovarian Tumors of Germ Cell Origin

Etiology and Epidemiology	Risk factors include **nulliparity,** positive **family history** of ovarian cancer, mutations in *BRCA1* and *BRCA2* genes and high expression of the *HER2/neu* oncogene Occurs most commonly in children and young adults (except for teratomas, which can occur at all ages)
Pathology	**Dysgerminoma:** Malignant unilateral tumor comprised of large vesicular cells with clear cytoplasm and central nuclei; analogous to male testicular seminoma **Yolk sac tumor:** Malignant tumor with **Schiller-Duval bodies** (glomerulus-like structure composed of central blood vessel enveloped by germ cells) **Choriocarcinoma:** Aggressive and malignant tumor with areas of necrosis and hemorrhage composed of neoplastic syncytiotrophoblasts and cytotrophoblasts **Teratoma:** 90% of germ cell tumors; **mature** teratomas **(dermoid cysts)** are **benign;** immature are malignant. *Histology:* structures from all germ layers. **Struma ovarii:** Unilateral ovarian teratoma composed of **thyroid tissue**
Clinical Manifestations	Mild, nonspecific **abdominal discomfort**; struma ovarii may lead to hyperthyroidism *Lab findings:* Increased **AFP** (yolk sac), increased **hCG** (choriocarcinoma)
Treatment	Tumor removal; oophorectomy or hysterectomy; chemotherapy
Notes	Germ cell tumors make up 25% of ovarian tumors.

A 12-year-old girl is brought into the emergency room because of heavy vaginal bleeding. The child is also complaining of GI discomfort and pelvic pressure. She states that she had her last menstruation 2 weeks earlier and she is not sexually active. Her first menstruation was at the age of 10. On physical examination, the child appears to have undergone precocious puberty. A pelvic examination reveals a palpable right ovarian mass, which is confirmed by a CT scan. Serum studies show a significantly increased level of circulating estrogen. When a biopsy reveals distinctive, gland-like structures filled with an acidophilic material, you worry that this patient may have an increased risk of developing endometrial carcinoma later in life if this mass is not removed.

Ovarian Tumors of Sex Cord–Stromal Origin

Etiology and Epidemiology	Risk factors include **nulliparity,** positive **family history** of ovarian cancer, mutations in *BRCA1* and *BRCA2* genes, and high expression of the *HER2/neu* oncogene Affects all age groups
Pathology and Pathophysiology	**Ovarian fibroma-thecoma (OFT):** Secretes **estrogen;** tumor composed of round lipid-containing cells in addition to well-differentiated fibroblasts **Granulosa cell tumor (GCT):** Secretes **estrogen,** causing endometrial hyperplasia/carcinoma in adults; characterized by **Call-Exner bodies** (small follicles filled with eosinophilic secretions) and small cuboidal, deeply stained granulosa cells arranged in anastomotic cords **Sertoli-Leydig cell tumor (SLCT):** Secretes androgens; tumor composed of Sertoli or Leydig cells interspersed with stroma
Clinical Manifestations	Mild, nonspecific abdominal discomfort **OFT**: Presents with Meig syndrome (triad of ovarian tumor, ascites, and hydrothorax) **GCT**: Vaginal bleeding from endometrial hyperplasia; cystic disease of breast; endometrial carcinoma **SLCT**: Virilism *Lab findings:* Increased estrogen levels (OFT and GCT)
Treatment	Tumor removal; oophorectomy or hysterectomy; chemotherapy
Notes	Ovarian sex cord–stromal tumors are rare.

A 31-year-old woman presents to the clinic complaining of abnormal vaginal bleeding. She states that her last menstrual period was 1 week ago and that she has not experienced abnormal bleeding before. Her past medical history is notable for two prior episodes of pelvic inflammatory disease in the last year. She has also been trying to conceive for the last year without success. On pelvic examination, redness and inflammation of the cervix is visible, but no discharge is apparent. You obtain an endometrial biopsy, which you suspect will show plasma cells along with macrophages and leukocytes in the glandular lumen. You begin empiric antibiotic therapy to prevent possible sequelae from the suspected diagnosis.

Endometritis

Etiology	**Acute endometritis:** Caused by trauma, *Staphylococcus aureus* and *Streptococcus* species; usually occurs after delivery or miscarriage **Chronic endometritis:** Caused by granulomatous disease, chronic PID, postpartal or postabortal states, and TB
Pathology	*Endometrium:* Plasma cells seen with macrophages and lymphocytes
Clinical Manifestations	**Acute:** Presents with inflammation after delivery or miscarriage **Chronic:** Presents with **abnormal vaginal bleeding,** pain, discharge, and infertility
Treatment	Antibiotic therapy (helps to prevent other sequelae, such as salpingitis)
Notes	**Endometrial polyps** are masses composed of endometrial tissue within the endometrial cavity. They tend to occur in women older than 40 years of age and may result in uterine bleeding, but are usually benign.

A 24-year-old woman presents to the clinic complaining of increased pain and bleeding during menstruation. Her last three menstruations have been accompanied by increasing intensity of cramping and larger amounts of blood. She tells you that her menstrual cycle has been irregular for the last 6 months. After taking a complete history, you learn that she has been having increased pelvic pain with intercourse. On pelvic examination, you palpate fixed, bilateral ovarian masses and an MRI reveals chocolate cysts on the ovary. You begin the patient on oral contraceptives and you suggest surgical removal of the masses if the pain persists.

Endometriosis

Etiology and Epidemiology	Etiology unknown, but thought to be caused by a combination of genetic, hormonal, and immune factors Afflicts 10% of women, usually between the ages of 20 and 30
Pathology	*Gross:* Non-neoplastic nodules, composed of **endometrial tissue** in abnormal locations **outside the uterus,** including **ovary** (most common), uterine ligaments, rectovaginal septum, and pelvic peritoneum; presence of **chocolate cysts** on ovaries that have resulted from cyclic bleeding (menstrual type) of ectopic endometrial tissue *Microscopic:* Endometrial glands; endometrial stroma; presence of hemosiderin pigment
Clinical Manifestations	Presents with fixed, palpable, bilateral ovarian masses, pain during menses **(dysmenorrhea),** and pain during intercourse **(dyspareunia);** menstrual irregularities may lead to infertility, which is the presenting complaint of 30%–40% of patients
Treatment	Oral contraceptives; progesterone; danazol; GnRH; surgical removal/coagulation of lesion
Notes	**Adenomyosis** is endometriosis within the myometrium and usually presents with uterine enlargement and irregular bleeding.

A 35-year-old African American woman presents to the clinic complaining of more frequent menstrual periods and profuse menstruation. She also complains of increased weakness and fatigue during her menstruations. On physical examination, you find a firm abdominal mass in the pelvic region. When questioned, she states that she was aware of the mass, but she notes that the mass often only appears during menstrual periods. When a biopsy of the mass reveals whorled bundles of smooth muscle cells, you reassure this patient that her condition is unlikely to proceed to malignancy.

Leiomyoma

Etiology and Epidemiology	Etiology unknown, but chromosomal abnormalities have been found in tumor cells Most common benign neoplasm of female genital tract Most commonly seen in women of **reproductive age** with an increased incidence in African Americans
Pathology	*Gross:* Multiple, enlarged, irregular, heterogenous tumors in the myometrium (intramural), beneath the endometrium (submucosal), or beneath the serosa (subserosal); tumor is **estrogen-sensitive** with its size increasing during pregnancy and decreasing with menopause *Microscopic:* Whorled pattern of smooth muscle bundles; rare mitoses in muscle cells, although cellular atypia and giant cells may be present
Clinical Manifestations	**Profuse menstruation; frequent menstrual periods;** acute or recurrent pelvic pain; urinary frequency (owing to compression of bladder); infertility *Lab findings:* Iron deficiency anemia (owing to blood loss)
Treatment	Myomectomy or hysterectomy; uterine artery embolization
Notes	Also called **uterine fibroids,** leiomyomas do not progress to leiomyosarcomas. **Leiomyosarcomas** are fleshy, irregular tumors with areas of necrosis and hemorrhage that arise de novo and may protrude from the cervix. Leiomyosarcomas are more prevalent among African Americans, are malignant, and can be treated with combination chemotherapy.

A 60-year-old woman presents to the clinic with postmenopausal vaginal bleeding. After taking a complete history, you learn that she is nulliparous and suffers from type 2 diabetes, which is well-controlled with diet and insulin. On physical examination, the woman is obese and has a blood pressure reading of 150/96. You decide to perform a PAP smear as well as an endometrial biopsy. Based on the patient's presenting signs and medical history, you are worried that you might find well-defined gland patterns lined by malignant stratified columnar epithelial cells on endometrial biopsy.

Endometrial Carcinoma

Etiology and Epidemiology	Risk factors include **unopposed estrogen use,** obesity, diabetes, HTN, nulliparity, and late menopause Peak incidence is between 55 and 65 years of age. Endometrial carcinoma is the most common gynecologic malignancy
Pathology	Typically preceded by **endometrial hyperplasia** *Gross:* Localized polypoid tumor or diffuse tumor involving entire endometrial surface *Microscopic:* **Adenocarcinoma** characterized by well-defined gland patterns lined by malignant stratified columnar epithelial cells; may see some squamous cells
Clinical Manifestations	Presents with **postmenopausal vaginal bleeding,** leading to early diagnosis; may cause obstruction of the cervix with collection of pus (pyometra) or blood (hematometra) presenting with lower abdominal pain
Treatment	Total hysterectomy and bilateral salpingo-oophorectomy; radiation therapy
Notes	**Endometrial hyperplasia** is abnormal endometrial gland proliferation caused by excess estrogen (eg, polycystic ovarian syndrome, estrogen-secreting ovarian tumor, estrogen replacement therapy). It manifests clinically with postmenopausal vaginal bleeding and may lead to endometrial cancer depending on degree of atypia.

A 42-year-old woman presents to the clinic complaining of postcoital bleeding and vaginal discharge. She complains of a 3-month history of spotting in her underwear after intercourse and an odorous vaginal discharge that is not purulent. Her social history is significant for past practice of prostitution and her past medical history is significant for several STDs that were appropriately treated. She has not had a routine PAP smear in over 10 years. After a PAP smear reveals abnormal cells, you perform a cervical biopsy, worrying that you may find invasive malignant cells in the cervix and adjacent koilocytosis. You fear that the patient will need to undergo a hysterectomy with possible adjunct radiation therapy if your suspected diagnosis is confirmed.

Dysplasia, Carcinoma in Situ, and Squamous Cell Carcinoma of the Cervix

Etiology and Epidemiology	Associated with **human papilloma virus (HPV)** types 16, 18, 31, and 33, early age of first intercourse and multiple sexual partners Occurs most commonly between the **ages of 30 and 45**
Pathology	**Cervical dysplasia:** Involves **squamocolumnar junction;** characterized by cells with hyperchromatic nuclei, irregular nuclear contours, and scant cytoplasm; epithelial growth begins at basal layer extending outward; classified as cervical intraepithelial neoplasia (CIN) subtypes grades I-III; CIN I is characterized by atypical undifferentiated cells only in lower third of epithelium, whereas CIN III has atypia through > 2/3 thickness of epithelium **Cervical carcinoma in situ (CIS):** Dysplastic cells extending through entire epithelium, but without invasion of basement membrane **Invasive cervical carcinoma (ICC):** *Gross:* can be exophytic, ulcerating, or infiltrating mass. *Microscopic:* usually **squamous cell carcinoma** with large cells and **keratinization;** can be adenocarcinoma or undifferentiated carcinoma; arises from preexisting CIN at squamocolumnar junction; non-neoplastic epithelial cells often demonstrate **koilocytosis** (associated with HPV infection).
Clinical Manifestations	**ICC: Irregular vaginal bleeding; postcoital spotting;** cervical ulceration; nonpurulent discharge; dysuria; invasive disease can obstruct ureters and lead to renal failure
Treatment	**ICC:** Hysterectomy; radiation therapy; prevention with HPV vaccine
Notes	**Screening for cervical cancer with PAP smears** should begin 3 years after intercourse and no later than age 21 and continue every 1–3 years until age 70.

A 20-year-old woman presents to you, her obstetrician-gynecologist, for her annual checkup. She has a family history significant for a mother, who was diabetic and treated with DES for threatened abortion during her pregnancy. Thus, the patient has been aggressively screened for vaginal histologic changes since the age of 15. On pelvic examination, you note a new abnormal growth on the upper third of the vaginal anterior wall about 5 cm in diameter. You biopsy the growth and send it for histologic analysis, expecting to find vacuolated, glycogen-containing cells in the sample.

Neoplasms of the Vagina (Clear Cell Carcinoma, Squamous Cell Carcinoma)

Etiology and Epidemiology	**Clear cell adenocarcinoma (CCA):** Rare; seen in daughters of women receiving **DES** therapy during pregnancy; usually diagnosed between ages of 15 and 20 **Squamous cell carcinoma (SCC):** Extremely rare; associated with **HPV infection**
Pathology	**CCA:** *Gross:* red granular lesion located on upper anterior vagina. *Microscopic:* **vacuolated, glycogen-containing cells;** preceded by **vaginal adenosis** (mucosal columnar epithelial-lined glands in areas normally lined by stratified squamous epithelium). **SCC:** *Gross:* invasive **plaque-like mass** in upper posterior vagina. *Microscopic:* begins as focus of **epithelial thickening** associated with dysplastic changes and transforms into invasive SCC with keratinization.
Clinical Manifestations	**CCA:** May be clinically silent; insidious onset with vaginal bleeding **SCC:** May be clinically silent; irregular spotting; vaginal discharge
Treatment	Surgery and irradiation; careful monitoring and screening in high-risk patients
Notes	**Sarcoma botryoides** is a rare, polypoidal embryonal rhabdomyosarcoma and is the most common sarcoma of children < 5 years old. It presents as a mass resembling a bunch of grapes projecting into the vagina and requires surgical resection and chemotherapy.

A 27-year-old woman presents to the emergency room with lower abdominal pain, chills, fever, and a purulent vaginal discharge. After taking a history, you learn that she has had multiple sexual partners over the last year and has not practiced safe sex. She states that the pain started 3 days ago with subsequent fevers, chills, and night sweats. On physical examination, she is febrile with a temperature of 102.4°F. Pelvic examination is significant for cervical motion tenderness with foul-smelling, purulent, cervical discharge. Her pregnancy test is negative. You admit the patient to the hospital and you begin her on IV cefoxitin plus doxycycline while awaiting the results of her endocervical culture.

Pelvic Inflammatory Disease

Etiology and Epidemiology	Common causes include **Chlamydia trachomatis (subacute), Neisseria gonorrhoeae (acute),** Gardnerella vaginalis, and Trichomonas vaginalis Usually occurs in young, nulliparous, **sexually active women** with multiple partners
Pathology	*Fallopian tubes:* **Edematous tubal serosa** with fibrin covering; purulent exudate in lumen; collections of pus may form a **pyosalpinx** or degrading pus may form a hydrosalpinx (water-filled fallopian tubes) Infection can also involve the ovaries and other pelvic structures
Clinical Manifestations	High **fever; lower abdominal pain; cervical motion tenderness** (chandelier sign); purulent cervical discharge; RUQ pain indicates perihepatitis **(Fitz-Hugh-Curtis syndrome)** Salpingitis is a risk factor for ectopic pregnancy, infertility, chronic pelvic pain, and adhesions
Treatment	Antibiotics effective against causative organism
Notes	**Ectopic pregnancy** occurs most often in fallopian tubes, but may also occur in ovary, abdominal cavity, or cervix. Risk factors include salpingitis, endometriosis, and tubal ligation. Clinical manifestations include severe abdominal pain 6 weeks after last menstruation and elevated hCG, which is lower than normal for pregnancy stage.

After vaginally delivering a newborn from a 32-year-old woman, you find the mother to be hemorrhaging an abnormally large amount of blood. You recall that she has had one previous C-section and extensive scarring. Given the amount of blood after delivery and the abnormal gross appearance of the placental remnants, you believe that the patient's pregnancy was complicated by a defective decidual layer that allowed the placenta to attach directly to the myometrium. You call the operating room to set up for an emergency hysterectomy, which you believe may be necessary to control the patient's massive hemorrhage.

Placental Attachment Abnormalities (Abruptio Placentae, Placenta Previa, Placenta Accreta)

Etiology	**Abruptio placentae:** May be associated with DIC; increased risk with smoking, cocaine, and hypertension **Placenta accreta:** Predisposed by prior C-section scars or endometrial inflammation **Placenta previa**: Predisposed by prior C-section scars
Pathophysiology	**Abruptio placentae: Premature separation of placenta** **Placenta accreta: Defective decidual layer** allows placenta to attach directly to myometrium **Placenta previa: Attachment of placenta to lower uterine segment** or cervix; may occlude cervical os; may coexist with placenta accreta
Clinical Manifestations	**Abruptio placentae: Painful uterine bleeding** usually during third trimester; can result in fetal death **Placenta accreta**: **Massive hemorrhage** after delivery **Placenta previa: Painless bleeding** in any trimester; premature labor
Treatment	**Abruptio placentae:** Immediate fetal delivery; control of maternal bleeding **Placenta accreta:** Hysterectomy may be necessary to stop bleeding **Placenta previa:** Bed rest; possible hospitalization
Notes	

A 31-year-old pregnant woman is brought to the emergency room complaining of headaches and blurred vision of 1-week duration. She is currently 32 weeks into her first pregnancy. On physical examination, you find edema of the face and lower extremities. Her blood pressure is 160/100, but she has no prior history of hypertension. Laboratory studies show a mild thrombocytopenia, elevated AST and ALT, and significant proteinuria. Based on these findings, you admit the patient for immediate bed rest, close monitoring, and blood pressure control. You tell the patient that it is possible that you may need to deliver her baby early in order to treat the patient's current condition.

Preeclampsia and Eclampsia

Etiology and Epidemiology	Risk factors include preexisting **hypertension, diabetes, chronic renal disease,** autoimmune disorders, or twin gestation Affects 7% of pregnant women usually during the **third trimester** of a woman's first pregnancy
Pathology and Pathophysiology	*Placenta:* Evidence of infarct; presence of retroplacental hematomas; decreased vascularity; fibrinoid necrosis *Pathophysiology:* Intrinsic defect in invading cytotrophoblast leads to remodeling of uterine vasculature and resulting **placental ischemia;** decreased placental perfusion induces vasoconstrictive effects leading to **toxemic hypertension** in susceptible women
Clinical Manifestations	**Preeclampsia:** Triad of **hypertension, proteinuria,** and **edema;** associated symptoms include headache, blurry vision, and abdominal pain **Eclampsia:** Preeclampsia triad plus **seizures,** altered mentation, hyperreflexia, and possibly DIC *Lab findings:* Thrombocytopenia, elevated LFTs, hyperuricemia, hemolytic anemia
Treatment	**Preeclampsia:** Delivery of fetus as soon as possible; bed rest; salt restriction; treatment of hypertension **Eclampsia:** Medical emergency; treat with IV magnesium sulfate and diazepam; delivery of fetus
Notes	**HELLP** syndrome refers to *h*emolysis, *e*levated *L*FTs, and *l*ow *p*latelets and is a severe form of preeclampsia.

An 18-year-old woman in her sixteenth week of pregnancy presents to the emergency room complaining of excessive nausea and vomiting as well as vaginal bleeding. She states that she has been vomiting 10 times each day for the last 3 days and is constantly nauseous. She has experienced spotting for the past 4 days with frank vaginal bleeding on the morning of presentation. You decide to obtain an ultrasound and you order serum studies including a serum hCG level. The ultrasound shows a classic snow storm appearance with multiple echoes, indicating edematous villi within an enlarged uterus and the absence of a fetus or placenta. Serum studies show hCG levels in excess of 50,000 mIU/mL. You admit the patient to the hospital and you schedule her for an immediate emptying of the uterus, preferably by suction.

Hydatidiform Mole and Gestational Choriocarcinoma

Etiology and Epidemiology	**Hydatidiform mole (HM):** Arises because of fetal chromosomal abnormalities; **complete mole is 46, XX** with chromosomes all derived from sperm and **partial mole is triploid (69, XXY)** or tetraploid and is usually owing to fertilization of ovum by multiple sperm **Gestational choriocarcinoma (GC):** Preceded by **complete hydatidiform mole,** abortions, and ectopic or normal pregnancy; increased incidence in Asia and Africa
Pathology	**HM:** *Complete:* edematous chorionic villi with cystic swelling **(grape-like clusters);** hyperplasia of trophoblastic cells; **honeycombed uterus** appearance; absence of fetal parts. *Partial:* edematous changes of some villi; presence of fetal parts. **GC:** Tumor with areas of necrosis and hemorrhage composed of cells resembling syncytiotrophoblasts and cytotrophoblasts; may see endometrial penetration
Clinical Manifestations	**HM:** Nausea and vomiting; **painless vaginal bleeding;** uterus is large for gestational age; may present with hypertension during first trimester. *Imaging:* **snowstorm appearance** with no fetal or placental parts seen on ultrasound. **GC:** Excessive vaginal bleeding after evacuation of mole or after delivery of fetus/abortant; hemoptysis owing to early hematogenous spread to lungs *Lab findings:* **Increased serum hCG** (HM and GC)
Treatment	**HM:** Immediate emptying of uterus by suction **GC:** Surgical removal; chemotherapy
Notes	

A 27-year-old white man presents to the clinic complaining of right testicular enlargement over the past 3 months. On taking a complete history, you find that he had no trauma to the area prior to the enlargement, experiences no pain, and denies any problems urinating. He does admit to having low-grade fevers, night sweats, fatigue, malaise, and a 15-pound weight loss over the last 3 months. On physical examination, the right testicle is twice the size of the left testicle, and the mass does not transilluminate with a flashlight shined through it. Serum studies are ordered and elevated hCG levels are found. AFP levels are normal. You obtain a biopsy and send it for histologic examination, expecting the results to show sheets of uniform cells with distinct cell membranes, clear cytoplasm, large nuclei, and prominent nucleoli divided into poorly demarcated lobules.

Testicular Germ Cell Tumors

Etiology and Epidemiology	Risk factors include **cryptorchidism,** genetic factors, and testicular dysgenesis **Seminoma (S): Most common form;** analogous to ovarian dysgerminoma **Embryonal carcinoma (EC):** Second most common form **Endodermal sinus (yolk sac) tumor (EST):** More common in **infants and children** **Teratoma (T):** 30% of all testicular tumors **Choriocarcinoma (CC)**: Most malignant form
Pathology	**S:** Sheets of uniform cells with distinct cell membranes, clear cytoplasm, and large nucleus **EC:** Glandular or tubular cell patterns with papillary convolutions **EST:** Mesodermal core with layers resembling those of primitive glomeruli **T:** Derived from two or more embryonic layers; mature teratomas are always malignant in contrast with ovarian dermoid cysts **CC:** Sheets/cords of cells similar to syncytiotrophoblasts and cytotrophoblasts with clear cytoplasm
Clinical Manifestations	**S: Painless testicular enlargement** **EC: Painful mass** in testes often with metastasis **EST:** Testicular mass presents at < 3 years of age **T:** Painful lump in testes; gynecomastia **CC:** Painless, nodular testicular swelling; gynecomastia; supraclavicular lymphadenopathy (if metastasized) *Lab findings:* Elevated hCG (S, EC, T, CC), elevated AFP (EST, T)
Treatment	Radiotherapy; chemotherapy; radical inguinal orchectomy
Notes	Most testicular tumors of all types occur in white boys and men between the **ages of 15 and 34.**

A 30-year-old man presents to the clinic complaining of enlarged breasts and a swollen left testicle. On physical examination, you find that the left testicle does not illuminate and is not associated with pain. You order serum studies that show no increase in hCG or AFP, but a marked increase of circulating estrogens is noted. You obtain a testicular biopsy, which demonstrates characteristic rod-shaped crystalloids in the cytoplasm of the testicular cells, thereby confirming your suspected diagnosis.

Testicular Sex Cord–Gonadal Stroma Tumors

Etiology and Epidemiology	Mostly benign tumors arising from sex cord stroma Analogous to Sertoli-Leydig cell ovarian tumors Seen most commonly between ages of 20 and 60
Pathology	**Leydig cell tumor:** Small yellowish-brown nodules composed of polygonal cells with eosinophilic cytoplasm and round nucleus; characteristic intracytoplasmic **Reinke crystals** (rod-shaped crystalloids); tend to produce **androgens** and **estrogens** **Sertoli cell tumor:** Firm nodule composed of tumor cells arranged in trabeculae and forming cord structures similar to seminiferous tubules
Clinical Manifestations	**Testicular swelling** **Precocious puberty** in children and **gynecomastia** in adults more commonly seen with Leydig cell tumors
Treatment	Radiotherapy; chemotherapy; radical inguinal orchectomy
Notes	**Testicular lymphomas** account for 5% of testicular neoplasms and are the most common testicular cancer in men older than 60.

A 72-year-old man presents to the clinic complaining that he feels that he cannot completely empty his bladder while urinating. He states that he has been experiencing increased frequency of urination as well as nocturia and that he has had difficulty starting and stopping the stream of urine. Laboratory results reveal an increased total PSA with a proportionate increase in the fraction of free PSA. You begin the patient on finasteride and advise him that his condition predisposes him to urinary tract infections.

Benign Prostatic Hyperplasia (BPH)

Etiology and Epidemiology	Caused by age-related **increase in estradiol levels** Very common in men **over the age of 50** (affects 90% of men by age 70)
Pathology and Pathophysiology	*Pathophysiology:* **Increase of estradiol** promotes expression of receptors for DHT leading to prostatic growth *Gross:* Rubbery, nodular enlargement of the periurethral and transurethral zones (middle and lateral lobes) of the prostate *Microscopic:* Hyperplasia of both glandular and fibromuscular stromal elements
Clinical Manifestations	Presents with increased **frequency** of urination, **nocturia, dysuria,** and difficulty starting and stopping the stream of urine (owing to compression of urethra by nodules). Complications include **urinary obstruction**, bladder distention and hypertrophy, hydronephrosis, hydroureter, and **UTIs** *Lab findings:* **Increased total PSA with proportionate increase in fraction of free PSA**
Treatment	**Finasteride** (5α-reductase inhibitor); transurethral resection of prostate (TURP)
Notes	BPH is **not considered a premalignant condition** and is the most frequent cause of urinary tract obstruction in men.

An 81-year-old man presents to the clinic complaining of pain with urination. On taking a complete history, you learn that he has had difficulty in starting and stopping the stream of urine for the last 4 months and has recently been suffering from severe back pain. On physical examination, you perform a digital rectal examination and find a large palpable prostate nodule, which is firm and irregularly shaped. You fear that laboratory tests will demonstrate an increased total PSA with a decreased fraction of free PSA and may also demonstrate an increase in serum alkaline phosphatase. You immediately refer the patient to a urologist for prostatic biopsy.

Prostate Carcinoma

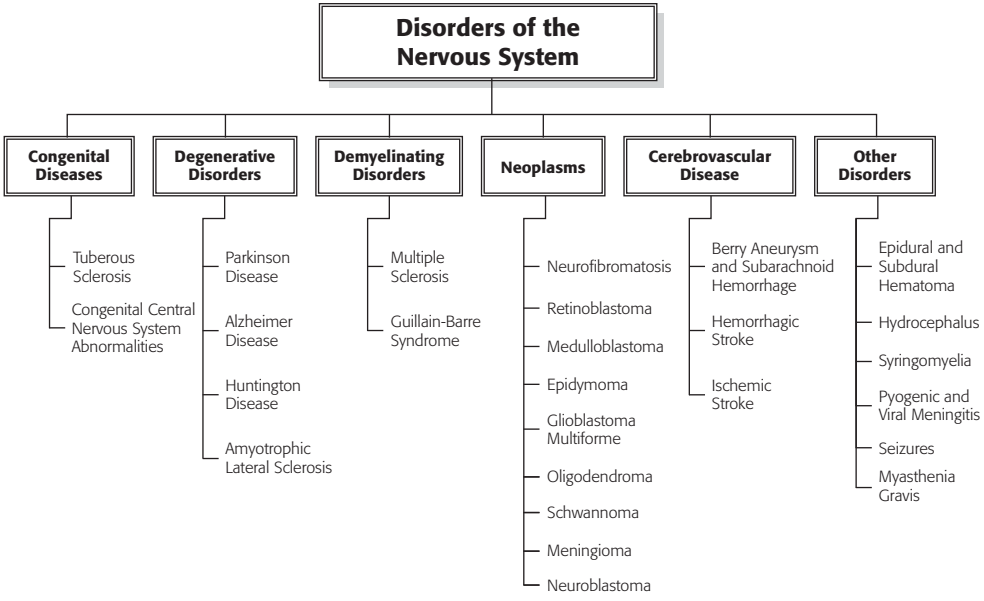
Epidemiology	**Most common cancer among men** and second leading cause of cancer death in men Occurs in men > 50 years of age
Pathology	*Gross:* Irregular nodules arising from peripheral group of glands (peripheral zone of **posterior lobe** is most common) *Microscopic:* **Adenocarcinoma** with well-defined glands lined by cuboidal cells with large nuclei and **prominent, large nucleoli;** may also be undifferentiated with cells growing in cords or sheets; often see invasion of vascular or lymphatic vessels of prostatic capsule In later stages, may progress to **bony osteoblastic metastasis** via hematogenous spread
Clinical Manifestations	Frequently **asymptomatic,** but may present with **dysuria,** increased urinary frequency or **back pain** (if metastasis to bone); most often diagnosed on digital rectal examination with palpation of **irregular, enlarged, firm nodule** with confirmation of diagnosis via prostatic biopsy *Lab findings:* **Increased serum PSA** and **prostatic acid phosphatase** (useful tumor markers for disease progression), increased total PSA with decreased fraction of free PSA, **increased serum alkaline phosphatase** (if osteoblastic metastasis)
Treatment and Prognosis	Prostatectomy; radiotherapy; GnRH analogues (leuprolide); antiandrogens (eg, flutamide); chemotherapy Can have an indolent or aggressive course as predicted by Gleason system of grading, which is based on differentiation of tumor
Notes	PSA testing and digital rectal examination should be offered annually for screening purposes beginning at age 50.

While on a humanitarian medical mission to South Africa as a urologist, you encounter a 4-year-old boy who is brought to your makeshift clinic because of the inability to pass urine. His mother is concerned that he has not been able to void for the last 2 days and that he has always struggled with the voiding of urine since birth. On physical examination, you find an abnormal urethral opening on the ventral surface of the penis. On further examination, you find that the testes are not palpable in the child's scrotum. You recognize the urethral defect as a common congenital abnormality and believe that your surgical skills can help relieve the urinary tract obstruction and prevent future risks of ascending urinary tract infections in this patient.

Hypospadias and Epispadias	*Definition:* Congenital malformation resulting in the abnormal urethral opening on the ventral (hypospadias) or dorsal (epispadias) surface of the penis; associated with failure of testicular descent and malformations of urinary tract (exstrophy of bladder) *Clinical manifestations:* Urinary tract obstruction and irregular ejaculation
Phimosis	*Definition:* Abnormally tight foreskin that cannot be retracted over glans penis; usually because of a congenital condition or can be the result of inflammation or trauma *Clinical manifestations:* Presents as penile pain or as acute urinary retention
Peyronie Disease	*Definition:* Subcutaneous fibrosis of the dorsum of the penis of unknown etiology *Clinical manifestations:* Abnormal curvature of the shaft or urethral constriction occurring in older men
Balanitis	*Definition:* Inflammation of the glans penis; caused by infection (syphilis, gonorrhea, herpes, chancroid, *Candida,* and *Gardnerella*) *Clinical manifestations:* Signs of penile infection occurring more often in uncircumcised men with poor hygiene

A 45-year-old Kenyan man, who has just immigrated to the United States, comes to your clinic complaining of a long-standing lesion on his penis that has started to bleed. He says that the growth has been there for over a year and that it just began to ulcerate. On physical examination, the penile lesion appears on the inner surface of the prepuce near the coronal sulcus. Macroscopically, the papillary lesions look like condylomata acuminata, producing a cauliflower-like fungating mass. There is a bleeding ulceration forming on the lesion. The patient denies any pain, fever, or urinary symptoms associated with the lesion. You biopsy the lesion in question and send it off for histologic examination to confirm your suspected diagnosis. You also work up the patient for possible venereal disease, which may be underlying his present condition.

Etiology and Epidemiology	**Bowen disease (BD):** Affects uncircumcised men > age 50 **Erythroplasia of Queyrat (EQ):** Median incidence in fifth decade; variant of Bowen disease **Bowenoid papulosis (BP):** Affects younger age group **Penile SCC:** Increased incidence in Asia and Africa; peak age 40–70; predisposed by uncircumcision, poor hygiene, and HPV types 16, 18, 31, and 33
Pathology	**BD:** Proliferating dysplastic epidermal cells with atypical mitoses; epidermal-dermal basement membrane intact **EQ and BP:** Histologically similar to Bowen disease **SCC:** Evolves from Bowen disease and EQ; papillary lesions simulate condyloma acuminata and produce a cauliflower-like fungating mass; flat lesions appear as areas of epithelial thickening accompanied by mucosal fissuring
Clinical Manifestations	**BD:** Single erythematous plaque on shaft of penis or scrotum; less than 10% evolve to invasive carcinoma; associated with an increased risk of visceral malignancy **EQ:** Single erythematous plaque on glans penis or prepuce; 10% evolve into invasive carcinoma **BP:** Multiple wart-like lesions resembling condylomata acuminatum; does not progress to invasive carcinoma **SCC:** Nonpainful lesion that may bleed or undergo secondary ulceration and infection
Treatment	Surgical removal of SCC
Notes	


Disorders of the Nervous System
Congenital Diseases
Tuberous Sclerosis
Congenital Central Nervous System Abnormalities
Degenerative Disorders
Parkinson Disease
Alzheimer Disease
Huntington Disease
Amyotrophic Lateral Sclerosis
Demyelinating Disorders
Multiple Sclerosis
Guillain-Barre Syndrome
Neoplasms
Neurofibromatosis
Retinoblastoma
Medulloblastoma
Epidymoma
Glioblastoma Multiforme
Oligodendroma
Schwannoma
Meningioma
Neuroblastoma
Cerebrovascular Disease
Berry Aneurysm and Subarachnoid Hemorrhage
Hemorrhagic Stroke
Ischemic Stroke
Other Disorders
Epidural and Subdural Hematoma
Hydrocephalus
Syringomyelia
Pyogenic and Viral Meningitis
Seizures
Myasthenia Gravis

Functional Areas of the Brain

Lobe	Functional Area
Frontal	Motor and premotor cortex, frontal eye fields, Broca speech area, executive functioning (concentration, judgment, and problem solving)
Temporal	Primary auditory cortex, memory, Wernicke area
Parietal	Sensory cortex, spatial orientation
Occipital	Primary visual cortex

Blood Supply to the Cerebrum

Artery	Origin and Region Supplied
Anterior cerebral artery	Branches from internal carotid; supplies medial surface of brain, anterior limb of internal capsule, basal ganglia, and frontal pole
Middle cerebral artery	Branches from internal carotid; supplies lateral surface of brain, posterior limb of internal capsule, and basal ganglia
Posterior cerebral artery	Branches from basilar artery; supplies occipital pole, inferomedial temporal lobes, and the thalamus
Lateral striate arteries	Branches from middle cerebral artery; supplies internal capsule and basal ganglia

A baby boy is born via an uncomplicated vaginal delivery. You notice a large birthmark, associated with dimples and hairy tufts, at the base of his back. Upon questioning his mother, you learn that she did not take any prenatal vitamins or receive prenatal care during her pregnancy. Although the child initially appears normal, you suggest that the child be evaluated for a disorder caused by a neural tube defect and you fear that he may develop autonomic and motor deficits later in life.

Neural Tube Defects

Etiology: Associated with **folate deficiency** during initial gestation and **elevated α-fetoprotein**

Spina bifida: Failure of posterior end of neural tube to close; results in vertebral bony defect through which meninges can herniate **(meningocele)** or meninges and spinal cord can herniate **(meningomyelocele)** resulting in neurologic symptoms; bony defect may also be asymptomatic until later in life, when neurologic symptoms appear **(spina bifida occulta)**

Encephalocele: Defect in the cranium allows for out-pouching of brain through skull

Anencephaly: Failure of anterior end of neural tube to close; results in absence of fetal brain and often absence of overlying skull

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Holoprosencephaly

Pathology: Failure of embryo's forebrain to divide into bilateral cerebral hemispheres, leading to **incomplete separation of cerebral hemispheres**

Clinical Manifestations: Facial and neurological defects

Arnold-Chiari Malformation

Pathology: Characterized by a small posterior fossa, resulting in **displacement of cerebellum** and medulla **through foramen magnum**

Clinical manifestations: Hydrocephalus; associated strongly with **thoracolumbar meningomyelocele** and **syringomyelia**

Dandy-Walker Malformation

Pathology: Characterized by large posterior fossa with **replacement of cerebellar vermis with large cyst;** associated with brainstem nuclei dysplasias

Clinical Manifestations: Seizures and cerebellar dysfunction

A 6-year-old boy presents to your office complaining of red nodules that have appeared on his face. He is mentally retarded and has a seizure disorder. His mother suffers from similar symptoms and has recently been diagnosed with a rhabdomyoma of the heart and renal angiomyolipomas. You begin to suspect that this boy is suffering from an autosomal dominant genetic disorder.

Tuberous Sclerosis

Etiology	**Autosomal dominant** disorder resulting from a mutation in one of several different genes
Pathology	**Brain hamartoma (cortical tuber):** Firm nodule **located in cerebral cortex** composed of **disorganized array of neurons** with large vesicular nuclei and eosinophilic cytoplasm Also associated with neoplasms occurring outside the CNS, including **cardiac rhabdomyomas, adenoma sebaceum of the face** (lesion consisting of malformed blood vessels), **renal angiomyolipomas** (lesion consisting of malformed blood vessels, adipocytes, and smooth muscle), and cysts of the bone and lung
Clinical Manifestations	**Seizures** and **mental retardation** in infancy; **red nodules** on face (adenoma sebaceum), which appear between the ages of 5 and 10; symptoms related to cardiac rhabdomyoma and renal angiomyolipoma
Treatment	Symptomatic (control seizures); genetic counseling
Notes	

A 27-year-old Caucasian woman presents to your office complaining of visual disturbances. During physical examination, you note that on lateral gaze, one eye does not adduct and the other eye has nystagmus on abduction. Testing of cerebellar function reveals an intention tremor and you also note decreased sensation on both legs. You obtain CSF fluid via a lumbar puncture and find multiple oligoclonal bands of IgG on electrophoresis. You order an MRI of the brain and refer the patient to a neurologist for further care of her condition.

Multiple Sclerosis

Etiology and Epidemiology	Etiology unknown, although **autoimmune,** genetic, and environmental factors have been implicated Incidence increases proportionally with distance from equator and incidence is more common in **HLA-DR2** individuals Most often presents in Caucasian **women** between the **ages of 20 and 30**
Pathology	*CNS:* **Multiple firm plaques** representing **demyelination** within the white matter of the **CNS,** especially in optic nerve, brainstem, and periventricular areas *Microscopic plaque:* **Depletion of oligodendrocytes;** monocytes, lymphocytes, and lipid-laden macrophages around vessels; **gliosis** and astrocyte proliferation
Clinical Manifestations	**Relapsing and remitting course,** but eventually remissions become incomplete; classic **Charcot triad:** nystagmus, scanning speech, and intention tremor; **motor and sensory impairment** of trunk and extremities (hemiparesis, ataxia); **visual impairment** (optic neuritis, retrobulbar neuritis, **internuclear ophthalmoplegia** [on lateral gaze, one eye does not adduct and the abducting eye has nystagmus caused by demyelination of MLF]); urinary/bowel incontinence owing to loss of sphincter control. *Lab findings:* Lumbar puncture shows mild lymphocytosis and elevated IgG, manifested as **multiple oligoclonal bands** on electrophoresis
Treatment	Corticosteroids and other immunosuppressants
Notes	

A 29-year-old man presents to the emergency room complaining of muscle weakness. He tells you that the weakness began in his calves and has now ascended to involve his thighs, hips, torso, and arms. Upon directed history, you learn that he recently recovered from a flu-like illness. Physical examination reveals symmetrical muscle weakness in all limbs and absent deep tendon reflexes. A lumbar puncture demonstrates an albumino-cytologic dissociation of the CSF. You admit this patient to the intensive care unit for observation as you fear that he may need mechanical respiratory support for his condition.

Guillain-Barre Syndrome

Etiology	Usually occurs after a flu-like **viral illness (**eg, EBV, HSV, CMV), but has also been associated with surgical procedures and bacterial infections (mycoplasma, campylobacter)
Pathology and Pathophysiology	*Pathophysiology:* Viral illness causes a T-cell-mediated immune reaction that results in **demyelination** of **peripheral nerves** *Peripheral nerves:* Endoneurial and perivenular **infiltration by lymphocytes and macrophages;** segmental demyelination
Clinical Manifestations	**Ascending muscle weakness and paralysis** beginning in distal lower limbs; absent deep tendon reflexes; sometimes sensory loss in extremities; **facial diplegia;** abnormal autonomic function (dysrhythmias, labile blood pressure) Can progress to respiratory failure or become chronic (chronic inflammatory demyelinating polyradiculoneuropathy) *Lab findings:* Lumbar puncture shows **albumino cytologic dissociation** of CSF (large protein content increase accompanied by only a mild cell count increase)
Treatment and Prognosis	**Plasmapheresis; IV immunoglobulin;** supportive care (respiratory support until recovery) Most patients recover after weeks to months, but 10%–20% are left with permanent disability
Notes	**Postinfectious encephalitis** can follow viral illnesses (eg, chicken pox, rubella, measles, mumps) and is characterized by transient, widespread demyelination.

A 78-year-old woman is brought to your clinic by her son and daughter. They tell you that she has been very forgetful lately and has twice wandered out of her house and gotten lost, requiring the police to bring her back. Upon speaking with the woman, you note that her short-term memory is compromised and that she has trouble finding the words to express what she wants to say. An MRI of the brain does not reveal any evidence of a stroke. You suspect that a biopsy of this woman's brain would reveal neuritic plaques and neurofibrillary tangles.

Alzheimer Disease

Etiology and Epidemiology	Etiology unknown, but theories involve abnormal expression of amyloid gene resulting in increased Aβ protein, deficiency of choline acetyltransferase leading to decreased acetylcholine levels, or atrophy of the nucleus basalis of Meynert. Familial Alzheimer disease involves mutations in amyloid precursor protein *(APP)* gene on chr 21, mutations in presenilin genes (chr 1,14), and the ε4 allele of apolipoprotein E (chr 19). Affects 50% of people > **85 years old**
Pathology	*Gross:* **Cortical atrophy of brain** with widening of sulci and ventricles *Microscopic:* **Neurofibrillary tangles** composed of tau protein within cytoplasm that displace nucleus; **neuritic plaques** (spherical cluster with Aβ protein core and peripheral astrocytes); **amyloid angiopathy;** Hirano bodies (eosinophilic bodies in hippocampal cells); granulovacuolar degeneration (cytoplasmic vacuoles in hippocampal cells)
Clinical Manifestations	**Dementia** presenting with progressive memory disturbances, disorientation, aphasias, visuospatial deficits, loss of motor skills or incontinence
Treatment and Prognosis	Donepezil (acetylcholinesterase inhibitor) to slow progression Progressive disease with **no cure**
Notes	**Pick disease** also causes dementia, but tends to affect women more than men. Histopathologically, it is characterized by cortical atrophy of the frontotemporal lobes and Pick bodies (cytoplasmic inclusion bodies made of neurofilaments).

A 48-year-old man presents to your clinic complaining of involuntary movements of his arms and legs. He tells you that his mother had similar symptoms, which eventually progressed to dementia. Physical examination and history reveal involuntary jerky movements, flattened affect, and poor concentration. When an MRI of the brain demonstrates atrophy of the caudate nucleus and putamen as well as dilatation of the ventricles, you fear that this patient will eventually succumb to the same dementia as his mother.

Huntington Disease

Etiology	**Autosomal dominant** disorder associated with **increased number of CAG repeats** in Huntington disease gene on chr 4
Pathology	*Gross:* **Atrophy of caudate nucleus and putamen;** may also see atrophy of globus pallidus and frontal lobe; dilation of lateral and third ventricles *Microscopic:* Loss of striatal neurons (GABAergic neurons); fibrillary gliosis
Clinical Manifestations	Progressive disorder that initially manifests between the **ages of 40 and 50; chorea** (involuntary jerky movements); cognitive impairment; mood disturbances Eventually progresses to **severe dementia**
Treatment and Prognosis	Symptomatic treatment for dyskinesia and mood disturbances Usually fatal within 15–20 years of diagnosis
Notes	Huntington disease, as well as fragile X syndrome and myotonic dystrophy, demonstrates **anticipation,** a phenomenon in which the number of repeats increases with each generation and results in more severe disease manifestations.

A 64-year-old man presents to your neurology clinic complaining of unsteadiness. As you obtain a history from this patient, you notice that he has expressionless facies and a pill-rolling tremor at rest. Physical examination reveals a shuffling gait, rigidity in response to passive movement, and bradykinesia. You suspect that the neurons of his substantia nigra may contain Lewy bodies and you prescribe levodopa to treat his symptoms.

Parkinson Disease

Etiology and Epidemiology	Etiology unknown Usually presents in people over the age of 50
Pathology and Pathophysiology	*Gross:* **Pale substantia nigra** and locus ceruleus *Microscopic:* **Loss of pigmented dopaminergic neurons** in substantia nigra with gliosis; **Lewy bodies** (eosinophilic, intracytoplasmic inclusion bodies) in substantia nigra neurons *Pathophysiology:* Loss of dopaminergic input to the striatum results in **loss of stimulation of the basal ganglia motor circuit**
Clinical Manifestations	Symptom constellation of **pill-rolling tremor, bradykinesia,** shuffling gait, **rigidity,** postural instability, and expressionless facies (all together known as *parkinsonism*) Of patients with Parkinson disease, 10%–15% develop dementia
Treatment	Pharmacologic therapy (amantidine, anticholinergics, levodopa, dopamine agonists, MAO-B inhibitors)
Notes	Other causes for **parkinsonism** include repeated trauma (as with boxers), drugs (especially MPTP), postencephalitic parkinsonism (observed after the influenza pandemic in the early 1900s), and Shy-Drager syndrome (parkinsonism with orthostatic hypotension and autonomic dysfunction).

A 47-year-old man presents to your clinic complaining of weakness in his hands. He states that he has been frequently dropping objects and is unable to perform fine motor tasks. Physical examination reveals a positive Babinski sign, hyperreflexia, atrophy, diminished strength in the muscles of the hands and calves, and fasciculations. You fear that this patient has a progressive condition, which will ultimately result in his death from respiratory failure in the near future.

Amyotrophic Lateral Sclerosis

Etiology and Epidemiology	Etiology of sporadic ALS unknown; 5%–10% of cases are familial with autosomal dominant inheritance of a defect on chr 21 or with a defect in SOD-1 (gene product involved in scavenging free radicals) Most commonly affects **men over the age of 40**
Pathology	Progressive disease associated with **loss of both upper and lower motor neurons** *Spinal cord:* **Reduced number of anterior horn neurons with reactive gliosis; degeneration of corticospinal tract neurons** *Muscle:* **Neurogenic atrophy** with target fibers (fibers with dark center area on cross-section)
Clinical Manifestations	**Lower motor neuron signs:** Atrophy of muscles; fasciculations **Upper motor neuron signs:** Hyperreflexia; positive Babinski sign; spasticity Lower and upper motor neuron degeneration tends to present initially with weakness of hands or cramping and spasticity of arms and legs. Involvement of respiratory muscles leads to lung infections and eventually death.
Treatment and Prognosis	Supportive care. **Death** from respiratory failure usually occurs **within 5 years of diagnosis**
Notes	**Werdnig-Hoffmann syndrome** is an autosomal recessive disease that affects the lower motor neurons and is associated with degeneration of anterior horns. It presents at infancy with tongue fasciculations and "floppy baby".

A 74-year-old woman is brought to the emergency department after developing left-sided paralysis 1 hour ago. Further evaluation reveals left-sided sensory and motor paralysis, left-sided hyperreflexia, left-sided Babinski reflex, and bilateral symmetric loss of vision in half of her visual fields. When you hear that she has a history of atherosclerosis, you become even more certain of your diagnosis. After obtaining a CT scan of the head to confirm that she does not have a head bleed, you immediately begin to administer thrombolytic therapy.

Ischemic Stroke

Etiology	Causes include **thrombosis**, **embolism**, dissection, vasculitis, or **hypotension**
Pathology	**Cerebral infarction:** Associated with **thrombosis or embolism;** ischemic neuronal change (nuclear pyknosis, eosinophilic cytoplasm) within 12 hours; microglia and monocyte infiltration within 2 days; **liquefactive necrosis** leading to fluid-filled cavity and reactive astrocytes by 1–3 weeks; gliosis (scar formation) after several months; may convert to **hemorrhagic infarction**, in which blood seeps into infarction and is reabsorbed **Watershed infarction:** Associated with **hypotension;** see **wedge-shaped infarction** occurring at the edge of area supplied by artery; usually occurs in area between ACA and MCA distribution **Lacunar infarcts:** Associated with hypertension and thrombotic obstruction of small vessels; see small cavitations with surrounding gliosis
Clinical Manifestations	**Depends on site of ischemia and extent of collateral circulation** **ACA:** Sensory loss and weakness in contralateral leg **MCA:** Contralateral paralysis and sensory loss; homonymous hemianopia (bilateral symmetric loss of vision in half of visual field); aphasias **PCA:** Contralateral sensory disturbance; macular-sparing homonymous hemianopia **Lateral striate arteries:** Contralateral paralysis
Treatment	**Thrombolytic therapy** within 3 hours of onset; antiplatelet therapy (aspirin, dipyridamole); physical therapy; statins for cholesterol-lowering effects
Notes	**Transient Ischemic Attack** refers to neurologic deficits caused by cerebral ischemia that resolves within 24 hours and suggests that the patient is at high risk for having a stroke in the near future.

A 67-year-old man presents to the emergency department after passing out on the sidewalk. When he is revived, he complains of a severe headache and nausea. Past medical history is significant for long-standing hypertension. Physical examination reveals right-sided hemiparesis. You think that this man's condition may be related to his high blood pressure, which may have caused the formation of Charcot-Bouchard microaneurysms. A CT scan of the head confirms your suspicions.

Hemorrhagic Stroke

Etiology	Most commonly caused by **hypertension;** other causes include bleeding disorders, arteriovenous malformations, brain tumors, or amyloid angiopathy
Pathology and Pathophysiology	*Pathophysiology:* Chronic hypertension is associated with **Charcot-Bouchard microaneurysms**, which are usually located within the basal ganglia. Rupture of these aneurysms may be the proximal cause of hemorrhage. *Brain:* Hemorrhage usually located in **basal ganglia or thalamus;** central area of blood surrounded by edematous brain tissue → edema resolves and reactive astrocytes and macrophages appear at the edge of the injury → gliosis
Clinical Manifestations	**Impairment of consciousness;** nausea and vomiting; headache; **neurologic deficits** (especially hemiparesis and sometimes hemisensory disturbance)
Treatment	Reverse any coagulopathies; strict blood pressure control; surgical decompression if necessary for large intracranial hemorrhage
Notes	

A 44-year-old woman presents to the emergency department complaining of nausea and the worst headache of her life. Upon further questioning, you learn that she is a heavy smoker and she has a history of poorly controlled hypertension. You decide to perform a lumbar puncture, which reveals blood in the CSF. A CT scan of the head demonstrates blood in the basal cisterns. You immediately admit her to the hospital for a cerebral angiography in order to evaluate for the best treatment of her condition.

Berry Aneurysm and Subarachnoid Hemorrhage

Etiology and Epidemiology

Causes of subarachnoid hemorrhage include **rupture of berry aneurysm, trauma,** and arteriovenous malformation. Most **berry aneurysms** occur sporadically, but risk factors include **hypertension, cigarette smoking,** coarctation of the aorta, APKD, connective tissue disorders, and neurofibromatosis type 1.

Rupture of berry aneurysms occurs more frequently in **women** and in those **over the age of 40**

Pathology

Subarachnoid hemorrhage: Blood in subarachnoid space; fibrosis, occurring after resolution, may lead to **CSF obstruction**

Berry aneurysm: Often occur at **arterial bifurcations of circle of Willis;** outpouching of arterial wall with intimal thickening and media thinning at neck of aneurysm; media is absent in sac wall

Clinical Manifestations

Subarachnoid hemorrhage: "Worst headache of my life;" nausea and vomiting; loss of consciousness, may have fever or nuchal rigidity, can be fatal

Lab findings: Lumbar puncture reveals **blood in CSF**

Imaging: CT scan demonstrates blood in basal cisterns

Treatment

Surgical repair; supportive care; therapeutic approach depends on cerebral angiography

Notes

Arteriovenous malformations are congenital vascular malformations usually localized to the subarachnoid space, but may extend into brain tissue. They manifest clinically in young adults as seizures or hemorrhage.

A 78-year-old woman is brought to the emergency department by her son because of headaches and altered mental status. He tells you that the patient fell down the stairs 2 weeks ago, but that she appeared fine immediately after the fall. Physical examination reveals bilateral papilledema. When a CT scan of the head reveals a 3-cm crescent-shaped collection of fluid on the right side of the head that crosses suture lines with a 7-mm midline shift, you suspect that her current condition is related to tearing of the bridging veins between the cerebrum and venous sinuses in the dura and you schedule her for immediate surgical drainage of the blood.

Epidural and Subdural Hematoma

Etiology	**Epidural hematoma:** Caused by **tearing of middle meningeal artery,** middle meningeal vein, or dural sinus, which is often caused by **skull fracture** **Subdural hematoma:** Caused by **tearing of bridging** veins located between the cerebrum and venous sinuses in the dura, often owing to **head injury**
Pathology	**Epidural:** Accumulation of **blood between dura and skull** leading to cerebral compression **Subdural:** Accumulation of **blood between the dura and arachnoid;** bleeding is self-limited, but hematoma can grow owing to osmotic movement of water; resolution with granulation tissue can occur as well leading to a **chronic subdural hematoma**
Clinical Manifestations	**Epidural:** Loss of consciousness, followed by **lucid period,** followed by headache, altered mental status, seizures, focal neurologic deficits, and eventually coma. *Imaging:* Head CT shows **biconcave disk** that does not cross suture lines. **Subdural: Headache;** altered mental status; other signs of cerebral compression; **clinical signs occur gradually,** appearing hours to weeks after injury. *Imaging:* Head CT shows **crescent-shaped** disk that crosses suture lines.
Treatment	Surgical drainage of blood; reversal of coagulopathy
Notes	

A 43-year-old woman presents to the emergency room complaining of episodic loss of vision. She also reports having had severe headaches associated with nausea and vomiting over the past month. Physical examination reveals bilateral papilledema and a CT scan of the head demonstrates dilation of the ventricular system of the brain. You suspect that she may need placement of a ventriculoperitoneal shunt to treat her condition and you admit her to the hospital to obtain neurosurgical consultation.

Hydrocephalus

Etiology	Caused by accumulation of **increased volume of CSF within the cranium,** which can either result from obstruction to the CSF circulation (attributed to tumors or inflammation) or from overproduction of CSF by tumors of the choroid plexus
Pathology	*Gross:* **Dilation of ventricles** **Four variants** of hydrocephalus: **(1) Internal:** excessive CSF is present only in ventricular system; **(2) External:** excessive CSF is present only in subarachnoid space; **(3) Communicating:** CSF flows freely between ventricles and subarachnoid space; **(4) Noncommunicating:** CSF flow between ventricles and subarachnoid space is obstructed
Clinical Manifestations	May present with **enlargement of the skull** in adults, seizures, **headaches, visual disturbances,** nausea and vomiting, and other signs of **increased intracranial pressure**
Treatment	Insertion of ventriculoperitoneal shunt; removal of obstruction or choroid plexus tumor
Notes	**Hydrocephalus ex vacuo** refers to the dilation of the ventricles with an increase in CSF volume resulting from a loss of brain tissue (often by infarction or Alzheimer disease).

A 25-year-old woman presents to your office complaining of diminished sensation in both arms. Further neurologic evaluation of her arms reveals that she has diminished pain and temperature sensation, but that her touch sensation and proprioception are intact. She demonstrates no other neurologic deficits. When an MRI reveals cystic dilation in the center of the cervical spinal cord, you refer her to a neurosurgeon for treatment of her condition.

Syringomyelia

Etiology	Often associated with **Arnold-Chiari malformation;** also caused by intraspinal neoplasms or trauma
Pathology	*Spinal cord:* Formation of **fluid-filled cavity often extending from central canal** usually in **cervical region** of cord (most commonly C7-T1); results in destruction of adjacent gray and white matter (the crossing fibers of spinothalamic tract) with resultant reactive gliosis
Clinical Manifestations	**Loss of pain and temperature sensation of upper extremities** usually with preservation of touch and proprioception; may eventually progress to involve motor and other sensory tracts
Treatment	Surgical drainage of cavity
Notes	

A 32-year-old woman presents to your office complaining of intermittent double vision. She tells you that this tends to occur in the afternoons and evenings. Physical examination reveals ptosis of both eyes that worsens when the patient is asked to actively keep her eyelids elevated. When her symptoms markedly improve after edrophonium administration, you wonder if she may also have a thymoma.

Myasthenia Gravis

Etiology and Epidemiology	Caused by **antibodies directed against the acetylcholine receptors at the neuromuscular junction** Presents most frequently in **women** under the age of 40
Pathology and Pathophysiology	*Neuromuscular junction:* Loss of acetylcholine receptors; infiltration of immune complexes and complement factors *Pathophysiology:* Antibodies lead to acetylcholine receptor degradation, thereby causing a virtual **block of synaptic transmission**
Clinical Manifestations	**Muscle weakness that worsens with fatigue**; common initial presentation is **ptosis** or **diplopia** owing to extraocular muscle involvement, but also involves muscles of the extremities and facial muscles. Diagnosis confirmed by improvement after administration of a short-acting anticholinesterase (edrophonium). Associated with **thymoma** or thymic hyperplasia. *Lab findings:* Antibodies to acetylcholine receptors
Treatment	**Anticholinesterase drugs (ie, pyridostigmine);** thymectomy; immunosuppression; plasmapheresis if severe flare
Notes	

A 10-year-old boy is brought to your pediatric neurology clinic by his parents who have noticed that he has self-limited periods of unresponsiveness, even though his eyes are open. When questioned, the patient states that he sees flashes or blinking lights at times and has momentary lapses of "forgetfulness." The parents report that their other child had similar episodes, but the episodes subsided after puberty. You inform the parents that you believe their child may have a mild form of epilepsy. You order an EEG, which you expect will demonstrate a classic 3-Hz spike-and-wave EEG pattern.

Seizures

Etiology	Causes for seizures include toxins (ie, **drugs,** alcohol withdrawal), **intracranial pathology** (stroke, bleed, tumor, infection, degenerative disorders), metabolic abnormalities (hyponatremia, hypoglycemia) or **epilepsy** (syndrome of recurrent seizures)
Pathophysiology	Abnormal discharge of CNS neurons results in neurological symptoms
Clinical Manifestations	Usually preceded by **aura (**odd smell/vision), then followed by seizure (see types below); seizure often followed by **postictal period** (minutes to hours of resolving confusion and lethargy) Seizures may be either partial (involving discrete area of brain) or generalized and include (1) **Simple partial**: no impairment of consciousness; involves motor, sensory, or autonomic brain; (2) **Complex partial:** similar to simple partial except that consciousness impaired; (3) **Tonic-clonic (grand mal)**: contraction of muscles alternating with relaxation; (4) **Absence**: lapse of consciousness without loss of postural tone; (5) **Myoclonic**: sudden, brief contractions
Treatment	Antiepileptic drugs; treat underlying causes
Notes	**Status epilepticus** refers to a continuous tonic-clonic seizure for over 30 minutes. Complications include anoxic brain injury and lactic acidosis.

A 21-year-old man presents to the emergency department complaining of a severe headache. Physical examination reveals a fever to 102°F, nuchal rigidity, and photophobia. You perform a lumbar puncture, which initially reveals purulent CSF infiltrated with neutrophils, increased protein content, and decreased glucose content. While you await culture results, you admit the patient to the hospital and begin empiric broad spectrum antibiotics to treat his condition.

Pyogenic and Viral Meningitis

Etiology	**Pyogenic meningitis:** Causes include group B streptococci, *E coli, Listeria* in neonates and infants; *H influenzae and N meningitidis* in children and young adults; pneumococcus, *Listeria,* and gram-negative rods in older adults **Viral meningitis:** Causes include HSV virus, coxsackie virus, echoviruses, and arboviruses
Pathology	**Pyogenic meningitis: Purulent exudate** within leptomeninges; **engorged meningeal vessels;** neutrophils within the subarachnoid space **Viral meningitis:** There may be no abnormality or a mild lymphocytic infiltrate in subarachnoid space; mild edema may be present
Clinical Manifestations	**Pyogenic meningitis: Headache; photophobia; neck stiffness;** fever; irritability. *Lab findings:* Lumbar puncture shows **cloudy CSF with neutrophils, increased protein, decreased glucose** and increased opening pressure. **Viral meningitis: Headache; photophobia; neck stiffness;** fever; irritability. *Lab findings:* Lumbar puncture shows **lymphocytosis, mildly elevated protein, and normal glucose.**
Treatment	**Pyogenic meningitis:** Antibiotics and supportive care **Viral meningitis:** Self-limiting illness; acyclovir for HSV meningitis
Notes	**Viral encephalitis** refers to infection of the brain and/or meninges **(meningoencephalitis).** It can be caused by many organisms, including arboviruses, herpes, cytomegalovirus, rabies, and poliovirus. Histopathologically, **glial nodules,** inclusion bodies in neurons, and **perivascular mononuclear cell infiltrates** are seen.

A 5-year-old boy presents to your office complaining of diminished vision and eye pain in his left eye. Physical examination reveals strabismus and a cat's eye pupillary reflex. Funduscopic examination suggests an intraocular mass. When you hear that the boy's father has had eye neoplasms, you order an MRI of the orbits and also refer this patient to both an oncologist and a medical genetics clinic. You fear that this boy may develop other cancers later in life.

Retinoblastoma

Etiology	Caused by **homozygous deletion** in both alleles of **RB gene,** a tumor-suppressor gene located on **chr 13,** which results in a tumor arising from neuroepithelial cells in retina. Can be either **familial or sporadic.** Familial form is transmitted as **autosomal dominant trait** even though homozygosity is necessary for disease. Over 90% of heterozygous carriers end up developing disease.
Pathology	*Retina:* Round cells with hyperchromatic nuclei and little cytoplasm arranged in **Flexner-Wintersteiner rosettes** (cuboidal cells positioned around central lumen) May metastasize to the brain, spinal cord, bone, or lymph nodes
Clinical Manifestations	Classically occurs in **young children** (familial form) who present with **diminished visual acuity, eye pain,** strabismus, intraocular mass on funduscopic examination, and **white cat's eye pupillary reflex** Patients with familial disease develop bilateral retinoblastoma and are at an increased risk for developing other cancers (eg, osteosarcoma)
Treatment and Prognosis	Surgery (removal of tumor or eye if necessary) and radiation Tumor is fatal once it has spread beyond eye
Notes	Prototype of **Knudson two-hit hypothesis:** Two mutations are required for disease. One deletion is either inherited (familial) or occurs sporadically. The second mutation results from a sporadic mutation in both familial and sporadic cases.

A 59-year-old man presents to your office complaining of severe headaches for the last week. He tells you that his headaches are often associated with projectile vomiting. Physical examination reveals bilateral papilledema and a CT scan of the head demonstrates an irregular mass in the left cerebral hemisphere. When a CT-guided brain biopsy demonstrates pseudopalisading malignant cells around areas of necrosis, you realize that this patient's prognosis is very poor.

Glioblastoma Multiforme

Etiology and Epidemiology	Associated with genetic mutations in several oncogenes and tumor-suppressor genes, including p53 and the *RB* gene **Most common primary brain neoplasm** Occurs most frequently in people between the ages of 40 and 60
Pathology	*Gross:* Variable, noncircumscribed lesion found in cerebral hemisphere *Microscopic:* High-grade astrocytoma (arises from astrocytes); **central areas of necrosis** and hemorrhage surrounded by multiple tumor cells, arranged in a **pseudopalisading** fashion; high degree of **anaplasia**
Clinical Manifestations	**Seizures; headaches;** nausea and vomiting; other signs of increased intracranial pressure *Imaging:* Mass effect, cerebral edema
Treatment and Prognosis	Surgical resection with chemotherapy and radiation **Prognosis is very poor** with most patients dying within a year of diagnosis
Notes	Low-grade astrocytomas, especially **pilocytic astrocytomas,** are benign, slow-growing tumors occurring in the cerebellum of children. On histology, Rosenthal fibers (eosinophilic, corkscrew fibers) are present.

A 42-year-old woman presents to your office complaining of headaches and vomiting over the past 4 months. Upon further questioning, you learn that she also feels as if she trips more than usual when she is walking and she has recently had more trouble remembering things. A physical examination reveals bilateral papilledema and reduced strength and hyperreflexia in both of her legs. A CT scan reveals a parasagittal mass compressing the brain and a CT-guided brain biopsy demonstrates a whorled pattern of tumor cells with psammoma bodies. You tell the patient that she will most likely need surgery to remove the tumor.

Meningioma

Etiology and Epidemiology	**Benign, slow-growing tumor** arising from meningothelial cells of the **arachnoid;** therefore, it is external to the brain Multiple meningiomas can be present in patients with neurofibromatosis type 2 Occurs most often in **women** after the age of 30
Pathology	*Gross:* Usually round **encapsulated mass** with dural base; usually occurs in the convexities of the cerebral hemispheres or the parasagittal region; usually **does not infiltrate brain** *Microscopic:* **Whorled pattern** of tightly packed tumor cells; **psammoma bodies** (laminated calcifications)
Clinical Manifestations	Symptoms associated with **compression of underlying brain,** including **seizures, headaches,** nausea, vomiting, and other signs of increased intracranial pressure
Treatment and Prognosis	Surgical removal of tumor Prognosis is good
Notes	Meningiomas are the second most common primary brain tumors.

A 49-year-old man presents to the emergency department with a seizure. When he has been stabilized, he tells you that he has had several severe headaches over the past couple of months. A CT scan of his head reveals a large mass in the frontal lobe of his brain that demonstrates areas of calcification. You admit him to the neurology service and you suspect that he will need surgery to treat his condition.

Oligodendroglioma

Etiology and Epidemiology	Relatively rare benign tumor derived from oligodendrocytes Commonly affects middle-aged people
Pathology	*Gross:* Circumscribed, **slow-growing gray mass** often with cysts; usually occurs in white matter of cerebral hemispheres (especially **frontal lobe**) *Microscopic:* Sheets of uniform cells with round nuclei with clear cytoplasm (**fried egg** appearance); often **calcification** is present**;** increased vascularity
Clinical Manifestations	**Seizures;** headaches; papilledema; other signs of increased intracranial pressure *Imaging:* **Calcification** of tumor is detected on CT scan
Treatment and Prognosis	Surgical resection, followed by radiotherapy and chemotherapy Average survival time is 5–10 years after diagnosis
Notes	

A 58-year-old woman presents to your clinic complaining of hearing loss and a ringing in her left ear. The Weber and Rinne hearing tests help you to determine that the hearing loss is caused by a sensory disturbance and not a conduction deficit. You send the patient for an MRI of her head, which reveals a mass at the left cerebellopontine angle, impinging on cranial nerve VIII. You refer this patient to a neurosurgeon for a biopsy and likely removal of the mass.

Schwannoma

Etiology	Usually benign tumors arising from **Schwann cells** Bilateral acoustic schwannomas are associated with neurofibromatosis type 2
Pathology	*Gross:* **Encapsulated masses,** often with cystic areas; usually occur in the **cerebellopontine angle,** where it can compress **cranial nerve VIII (acoustic schwannoma)** *Microscopic:* Two growth patterns: **(1) Antoni A:** tightly packed elongated cells with palisading nuclei; **(2) Antoni B:** loose arrangement of cells with microcysts
Clinical Manifestations	Presents with symptoms associated with **compression of involved nerve** (cranial nerve VIII compression leads to patients presenting with **ipsilateral hearing loss,** tinnitus, and vertigo)**, seizures, headaches,** nausea and vomiting, and other signs of increased intracranial pressure
Treatment and Prognosis	Surgical resection of tumor Prognosis is good
Notes	**Pineal tumors** usually occur in young men between the ages of 10 and 40. They present with **Parinaud syndrome** (*paralysis of upward gaze* caused by pretectal and superior colliculus damage, *obstructive hydrocephalus* [owing to compression of aqueduct of Sylvius], and *endocrine abnormalities* [owing to compression of hypothalamus]).

A 6-year-old boy presents to his pediatrician's office complaining of frequent falls. Upon further questioning, you learn that the boy has also been suffering from nausea and vomiting, which is usually associated with headaches. During physical examination, you note that the boy has an ataxic gait and bilateral papilledema. You send the boy for a CT scan, which reveals a mass in the cerebellum and dilated third and lateral ventricles. You immediately refer the patient to a neurosurgeon.

Medulloblastoma

Etiology and Epidemiology	Highly **malignant tumor** arising in **cerebellum;** associated with deletion on short arm of chr 17 (17p-) Occurs mostly in **children** and accounts for **20% of all brain tumors in children**
Pathology	*Gross:* Gray, well-circumscribed tumor located at midline of cerebellum *Microscopic:* Hypercellular sheets of **anaplastic cells,** demonstrating many mitoses, scant cytoplasm, and hyperchromatic nuclei; cells are often arranged in a **rosette or perivascular pseudorosette formation**
Clinical Manifestations	Unsteady gait; obstructive hydrocephalus (tumor may obstruct flow of CSF by compressing fourth ventricle); **seizures, headaches;** nausea and vomiting; other signs of increased intracranial pressure
Treatment and Prognosis	Surgery with radiation and chemotherapy With total excision and radiation, 5-year survival rate is 75%
Notes	

An 8-year-old girl presents to your clinic complaining of blurry vision. During physical examination, you note bilateral papilledema. A CT scan of the head demonstrates a mass extending from the floor of the fourth ventricle and dilated lateral and third ventricles. You suspect that a biopsy of the mass would demonstrate cells with blepharoplasts in a perivascular pseudorosette arrangement.

Ependymoma

Etiology and Epidemiology	Tumor arising from ependyma of the ventricular system Most commonly occur in **children** (usually in the **fourth ventricle**), but can occur in the spinal cord of adults
Pathology	*Gross:* Solid, papillary masses extending from floor of fourth ventricle *Microscopic:* Uniform cells with round nuclei set in a fibrillary stroma and arranged in a **perivascular pseudorosette formation;** tumor cells often have **blepharoplasts** (rod near nucleus, which represents basal ciliary bodies)
Clinical Manifestations	**Obstructive hydrocephalus** (tumor may obstruct flow of CSF **through compression of fourth ventricle); seizures; headaches;** nausea and vomiting; other signs of increased intracranial pressure
Treatment and Prognosis	Surgical excision (difficult owing to proximity of brainstem nuclei) Prognosis is poor with average survival time of 4 years
Notes	

A 2-year-old boy is brought to your office after his parents noticed a large abdominal mass while dressing him. They also remark that he seems to have lost weight over the past month. During physical examination, you note ecchymoses over his trunk, a large palpable abdominal mass, and a blood pressure of 160/100. Laboratory tests reveal an elevation of urinary VMA and catecholamines and a CT scan of the abdomen demonstrates a large mass arising from the right adrenal gland. When a biopsy of the mass reveals Homer-Wright pseudorosettes, you suspect that the amplification of a specific oncogene may be responsible for his condition.

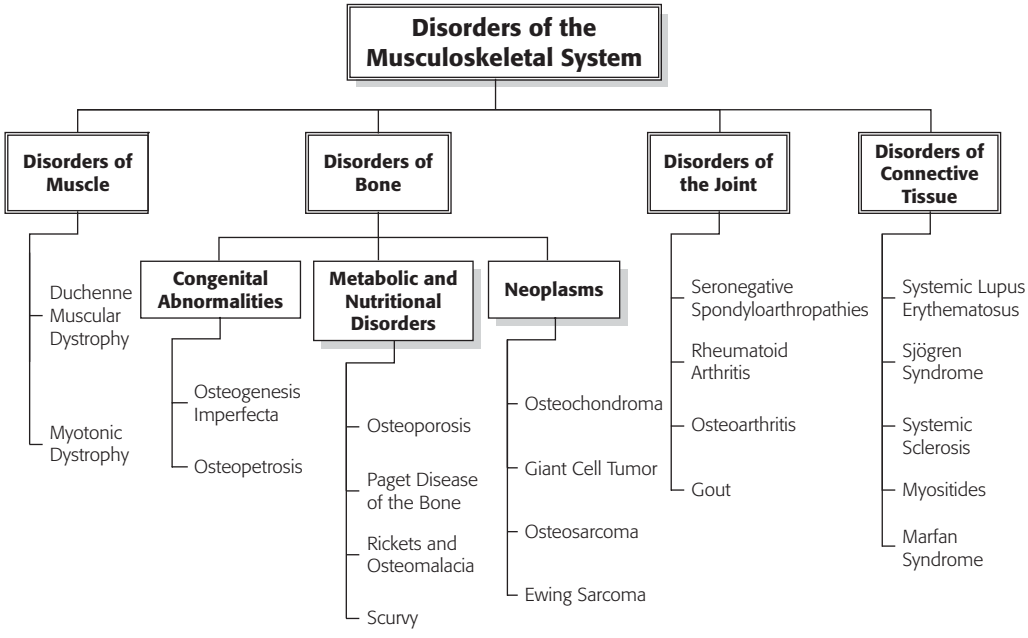
Neuroblastoma

Etiology and Epidemiology	Tumor arising **from neural precursor cells;** associated with **amplification of the *N-myc* oncogene and deletions in short arm of chr 1 (1p-)** Most commonly seen in **young children,** but does rarely occur in adults
Pathology	*Gross:* Classically arises in the **adrenal medulla,** but can arise in the sympathetic chain, pelvis, neck, or brain; variable in size; may be circumscribed; may show cyst formation or necrosis *Microscopic:* Sheets of small cells with dark nuclei and scant cytoplasm often arranged in **Homer-Wright pseudorosettes;** neurosecretory granules containing catecholamines
Clinical Manifestations	Classic presentation is **young child** (< 2 years old) with **large abdominal mass, hypertension,** and **weight loss.** Other symptoms include ecchymosis and proptosis (protrusion of eyes) Older children may present with symptoms of metastases to bone, liver, or lungs (manifesting as bone pain, respiratory, or GI symptoms) *Lab findings:* **Increased 24-hour urinary VMA** and metanephrine levels, **increased** plasma and urinary **catecholamine levels**
Treatment and Prognosis	Surgical resection with chemotherapy Prognosis is variable; younger age of patient and lower stage of cancer at diagnosis has a better prognosis
Notes	

A 14-year-old girl presents to your clinic complaining of multiple nodules on her skin. She tells you that her mother suffers from a similar condition. Upon further examination, you find multiple coffee-colored macules on her torso and limbs and pigmented nodules on her irises. You suspect that her condition is caused by an autosomal dominant genetic disorder and you refer her to a medical genetics clinic.

Neurofibromatosis Type 1

Etiology	**Autosomal dominant** disorder that is caused by a mutation in the neurofibromatosis type 1 ***(NF1)*** **gene**, a tumor suppressor gene located on **chr 17**
Pathology	*Neurofibroma:* Unencapsulated, well-circumscribed **masses of spindle cells,** which occur in the dermis (cutaneous), in the peripheral nerve (solitary), or in a large nerve trunk (plexiform); cutaneous neurofibromas are visible as skin nodules and may cause hyperpigmentation of overlying skin
Clinical Manifestations	**Neurofibromas** may cause neurologic symptoms (eg, gliomas of the optic nerve may lead to visual disturbances) **Lisch nodules:** Pigmented nodules of the iris **Café-au-lait spots:** Cutaneous pigmented macules
Treatment	Surgery to remove neurofibromas if disfiguring or causing neurologic abnormalities
Notes	**Neurofibromatosis type 2** is an autosomal dominant disorder that is caused by a mutation in the neurofibromatosis type 2 *(NF2)* gene, located on chr 22. It is rarer than neurofibromatosis type 1 and presents with bilateral acoustic schwannomas, multiple meningioma, and other neoplasms.


Disorders of the Musculoskeletal System
Disorders of Muscle
Disorders of Bone
Disorders of the Joint
Disorders of Connective Tissue
Duchenne Muscular Dystrophy
Myotonic Dystrophy
Congenital Abnormalities
Osteogenesis Imperfecta
Osteopetrosis
Metabolic and Nutritional Disorders
Osteoporosis
Paget Disease of the Bone
Rickets and Osteomalacia
Scurvy
Neoplasms
Osteochondroma
Giant Cell Tumor
Osteosarcoma
Ewing Sarcoma
Seronegative Spondyloarthropathies
Rheumatoid Arthritis
Osteoarthritis
Gout
Systemic Lupus Erythematosus
Sjögren Syndrome
Systemic Sclerosis
Myositides
Marfan Syndrome

COMPONENTS OF A SYNOVIAL JOINT

- *Articular Cartilage:* covers and protects articular surface of long bones
- *Fibrous Capsule and Ligaments:* maintains position of long bones in joint
- *Synovial Membrane:* forms the boundary of the joint space; attached to fibrous capsule
- *Synovium:* inner surface of synovial joint capsule
- *Synovial Fluid:* formed by synovium; serves to lubricate movement of articular surfaces

STRUCTURE OF BONE

- **Composition of Bone**
  - → Cellular component
    - → *Osteoblasts:* Large cells with basophilic cytoplasm; lay down osteoid
    - → *Osteocytes:* Inactive osteoblasts trapped within formed bone; small cells with dark nuclei
    - → *Osteoclasts:* Multinucleated cell with "ruffled border;" resorbs bone
  - → Osteoid (type I collagen matrix) which becomes mineralized by deposition of calcium hydroxyapatite
- **Arrangment of Bone**
  - → Rigid outer shell of compact bone (cortex) surrounding central medullary area filled with thin bone trabeculae and hematopoietic marrow

A 2-month-old baby boy is brought to the emergency department by his adoptive parents, who tell you that their baby has been fussy and seems to cry whenever his left arm is touched. On physical examination, you notice hypoactivity of the baby's left arm. You order an x-ray of the baby's arm, which reveals multiple fractures. You decide to order multiple radiographs of the skull, chest, and all extremities looking for evidence of other fractures. On closer physical examination, you do not see any abnormal bruising of the trunk, back, or buttocks, making child abuse less likely, but you do observe that the child has blue sclerae. You begin to suspect that his condition may be related to a deficiency in type 1 collagen.

Osteogenesis Imperfecta

Etiology	Caused by inherited mutations resulting in **deficient synthesis of type 1 collagen,** which comprises bone, teeth, ears, eyes, and skin. Inheritance is mostly **autosomal dominant,** but some forms are autosomal recessive. There are four variants with type II being most severe, and usually resulting in perinatal death.
Pathology	*Bone:* Marked cortical thinning; **thinning of trabeculae** similar to osteoporosis
Clinical Manifestations	**Multiple fractures** occurring from minimal trauma; **blue sclerae (**owing to translucency of connective tissue over choroids); hearing loss (owing to abnormal middle ear bones); dental imperfections
Treatment and Prognosis	Pneumatic bracing; avoidance of trauma Prognosis depends on form of disease and ranges from death in infancy to normal life span
Notes	**Achondroplasia** is caused by an autosomal dominant mutation in the fibroblast growth factor receptor 3 *(FGFR3)* gene located on chr 4, resulting in abnormalities in cartilage calcification and remodeling. It is clinically manifest as **dwarfism** (short limbs with normal trunk) and is characterized by narrow epiphyseal plates with short, thick bones.

A 15-year-old boy presents to the emergency department with suspected fractures of the left tibia and fibula following a fall. He tells you that he has broken several bones in the past and that his mother has a bone disease. Physical examination reveals slight hearing loss, facial asymmetry, and hepatosplenomegaly. Laboratory tests demonstrate anemia and an x-ray of his left leg shows fractures of both the tibia and fibula as well as an Erlenmeyer flask deformity. As you set this patient's leg in a cast, you suspect that his condition is associated with defective osteoclasts.

Osteopetrosis

Etiology	**Dysfunction of osteoclast activity,** which results in **defective bone resorption** There are multiple variants, including a fatal autosomal recessive type and a less severe autosomal dominant type
Pathology	*Gross:* Widened ends of bones **(Erlenmeyer flask);** thick, dense bones *Microscopic:* **Persistence of primary spongiosa,** which is calcified cartilage formed during endochondral bone development; **lack of trabeculae or hematopoietic marrow**
Clinical Manifestations	**Multiple fractures; anemia** (owing to lack of bone marrow); infections; hepatosplenomegaly (owing to extramedullary hematopoiesis); **cranial nerve palsies** (blindness, deafness, facial paralysis), and other neuropathies (owing to narrowed neural foramina, which cause nerve compression)
Treatment	Corticosteroids; bone marrow transplant
Notes	**McCune-Albright syndrome** is a disorder that occurs in young girls. It manifests with café-au-lait spots, precocious puberty, short stature, and polyostotic fibrous dysplasia (fibrous replacement of medullary bone in multiple locations).

A 68-year-old woman presents to your office complaining of aching lower back pain. Upon directed history, she tells you that she feels that she is getting shorter and you note that she is slightly hunched forward. An x-ray of her spine reveals a compression fracture of the L4 vertebra. When a bone density scan reveals decreased bone mass, you prescribe her a bisphosphonate as well as calcium and vitamin D supplements to treat her condition.

Osteoporosis

Etiology and Epidemiology	Defective bone synthesis or increased bone reabsorption, resulting in a **decrease in bone mass;** associated with **endocrine abnormalities** (**estrogen deficiency** in menopause, **Cushing**, hyperthyroidism, **calcium deficiency**), **physical inactivity,** genetic bone disorders, anorexia, and liver disease Most commonly seen in Caucasian elderly **women**
Pathology	*Bone:* Qualitatively normal but with **thinner and fewer trabeculae;** thin cortex; widened Haversian systems
Clinical Manifestations	**Back pain; fractures,** especially in thoracolumbar spine, hip, or femur; loss of height with kyphosis (owing to vertebral compression fractures) *Imaging:* Diffuse radiolucency on radiograph; bone density studies (DEXA) show **decreased bone mass**
Treatment	**Bisphosphonates** (inhibit osteoclast bone resorption); estrogen replacement (controversial); exercise; **calcium and vitamin D supplements**
Notes	

A 74-year-old man presents to your clinic complaining of bone pain in his left thigh. He also states that his hearing has deteriorated significantly over the last 6 months. Direct questioning reveals that he has noticed an increase in his hat size. Laboratory results demonstrate an increased serum alkaline phosphate with normal calcium, phosphorus, and PTH levels. An x-ray of his left thigh shows mixed thickening and lucency of the bone. You worry that this patient's condition may put him at risk for osteosarcoma and high-output cardiac failure.

Paget Disease of Bone

Etiology	Caused by an **increase of both osteoblastic and osteoclastic activity,** which is probably caused by a **viral infection** (perhaps paramyxovirus)
Pathology	*Gross:* Can occur in one bone (**monostotic**) or multiple (**polyostotic**) and tends to involve the skull, pelvis, femur, tibia, and spine *Microscopic:* Several morphologic stages in bone: *(1) Osteolytic:* large osteoclasts with multiple resorption pits; *(2) Osteoclastic osteoblastic:* **mosaic pattern** of lamellar bone demonstrating both bone destruction and bone formation, both osteoclasts and osteoblasts seen; *(3) Late osteosclerotic:* sclerotic bone with predominance of thick trabeculae, dark mosaic lines evident
Clinical Manifestations	Bone pain and **bone growth** (increase in hat size) Complications include **high-output cardiac failure** (increased vascularity results in numerous arteriovenous shunts), **osteosarcoma, hearing loss** (owing to narrowing of auditory foramen), and **long bone fractures** *Imaging:* Mixed thickening and lucency of bone *Lab findings:* **Increased serum ALP,** normal serum calcium and phosphorus, normal PTH levels
Treatment	Bisphosphonates (inhibit osteoclastic activity) for symptomatic disease
Notes	

A 5-year-old boy is brought to your office by his parents, who are concerned about skeletal deformities. Physical examination reveals a short boy with protrusion of the sternum, thinning of the occipital and parietal bones resulting in a squared appearance of the head, and the rachitic rosary. His parents tell you that he is well nourished, plays outside a lot, and has had no prior medical problems. You advise that the boy begin taking vitamin supplements and you schedule further tests to try and determine the etiology of this boy's condition.

Rickets and Osteomalacia

Etiology	Caused by **vitamin D deficiency,** which can be caused by malnutrition, inadequate sunlight exposure, malabsorption (owing to pancreatic insufficiency, liver disease, inflammatory bowel disease), or renal disease (owing to defect in renal synthesis of $1,25(OH_2)$ D) Other causes include dietary calcium deficiency, phosphate deficiency, or aluminum toxicity **Rickets** refers to the disease in childhood; **osteomalacia** refers to the disease in adulthood
Pathology and Pathophysiology	*Pathophysiology:* Vitamin D deficiency → decreased Ca^{2+} absorption → **decreased calcification of osteoid matrix** *Bone:* Increased unmineralized bone matrix; trabeculae have core of calcified bone, but are surrounded by coat of unmineralized osteoid
Clinical Manifestations	**Rickets: Skeletal deformities** (disruption of mineralization at epiphyses); **shortened stature;** pigeon breast (sternum protrusion); **rachitic rosary** (costochondral junction thickening); late closing of fontanelles; **craniotabes** (thinned occipital and parietal bones) **Osteomalacia: Diffuse bone pain;** muscle weakness. *Imaging:* Diffuse radiolucency with thinning of cortical bone on radiograph *Lab findings for both Rickets and Osteomalacia:* Decreased calcium and phosphate levels
Treatment	Vitamin D supplements; treatment of underlying cause
Notes	When osteomalacia occurs because of vitamin D deficiency and secondary hyperparathyroidism owing to renal disease, it is called **renal osteodystrophy.**

A 6-year-old homeless girl is brought to your clinic complaining of left knee pain. Further inspection reveals a thin, malnourished girl with a swollen left knee consistent with hemarthrosis, multiple purpura, and gingival swelling. Her mother tells you that the girl has not been eating a well-balanced diet because of their financial situation. When laboratory tests demonstrate anemia, you suspect that this patient's condition may be related to a nutritional deficiency and you recommend vitamin supplements.

Scurvy

Etiology	Caused by **vitamin C deficiency,** usually owing to inadequate intake
Pathology and Pathophysiology	*Pathophysiology:* Vitamin C deficiency → **impaired collagen synthesis → decreased osteoid matrix formation** by osteoblasts *Bone:* **Decreased osteoid matrix; cartilaginous overgrowth** with epiphyseal cartilage not being replaced by osteoid
Clinical Manifestations	**Subperiosteal hemorrhage; bleeding into joint spaces;** purpura and petechiae; **bleeding from gums;** gingival swelling; fatigue; weakness; **anemia; impaired wound healing** *Lab findings:* **Decreased plasma ascorbic acid,** decreased Hct
Treatment	Vitamin C supplements
Notes	

A 19-year-old boy presents to the emergency department complaining of right lower thigh pain following a fall. An x-ray of his right thigh reveals a fracture in a stalk of bone growth protruding from the end of his femur. Although you believe the growth to be benign and caused by an autosomal dominant trait, you order a bone biopsy to rule out malignancy. You expect that the histology examination of the biopsy will reveal endochondral ossification over the medullary cavity with no atypia.

Osteochondroma

Etiology and Epidemiology	Results from **displacement of lateral part of growth plate,** causing proliferation of bone away from long axis Multiple lesions occur in *multiple hereditary exostosis,* an autosomal dominant disease Most common in **men < 25 years old**
Pathology	*Gross:* Usually develops in metaphysis of **femur or tibia; stalk of bone growth covered by cartilage cap projecting from bone** *Microscopic:* **Endochondral ossification** leads to newly synthesized bone covering medullary cavity that forms core of stalk; **hyaline cartilage over new bone**
Clinical Manifestations	**Bone pain** caused by fracture of stalk or nerve impingement; rarely, it may transform to chondrosarcoma *Imaging:* Radiographs demonstrate stalk of bone growth
Treatment	Surgery if necessary
Notes	Osteochondroma is the most common benign tumor of bone. **Osteoid osteoma** and **Osteoblastoma** are benign tumors derived from osteoblasts. Osteoid osteomas tend to arise in the femur or tibia, while osteoblastomas tend to arise in the spine. These lesions most commonly present as bone pain in men under the age of 25.

A 32-year-old woman presents to your office complaining of pain in her right knee joint. Physical examination does not reveal any evidence of infection. Radiographs of the knee demonstrate a mass with a characteristic soap bubble appearance. You reassure the patient that this mass is probably benign, but you suspect that there is a good chance of recurrence even after surgical excision.

Giant Cell Tumor

Etiology and Epidemiology	Benign tumor derived from monocytes Most commonly affects **women** between the **ages of 20 and 40**
Pathology	*Gross:* Most commonly arises from **epiphyses of long bones especially around the knee (distal femur, proximal tibia);** large and red brown; often see cystic degeneration or necrosis and hemorrhage *Microscopic:* **Uniform oval mononuclear cells** demonstrating many mitoses; spindle-shaped **osteoclast-type giant cells** with up to 100 nuclei; fibrous stroma
Clinical Manifestations	**Joint pain** and other arthritic symptoms; fractures *Imaging:* **Soap bubble or double bubble** appearance on radiograph
Treatment and Prognosis	Surgical excision Very rarely becomes malignant, but is still aggressive and **recurs after treatment 40%–60% of the time**
Notes	**Enchondroma** is a benign cartilaginous neoplasm arising from the intramedullary bone and is most commonly seen in the hands and feet. Enchondromas are often asymptomatic and found incidentally on radiograph (characteristic "*O ring sign*" on x-ray), but they may be painful and cause a fracture.

A 13-year-old boy presents to your office complaining of pain and swelling in his left knee. He denies any trauma to the knee and has no fever to suggest an infectious process. Laboratory tests reveal an increased serum alkaline phosphate and an x-ray of the knee shows a mass with a sunburst growth pattern and a periosteal elevation by the mass, commonly called *Codman triangle.* You suspect he will need chemotherapy and possible surgical resection and you immediately refer the patient to an oncologist.

Osteosarcoma

Etiology and Epidemiology

Tumor derived from **malignant osteoblasts,** which synthesize bone

Risk factors include Paget disease of the bone, fibrous dysplasia, ionizing radiation, familial retinoblastoma, bone infarcts, and *p53* mutations

Most frequently occurs in **men** between the **ages of 10 and 20,** although there is a smaller peak of occurrence among the elderly

Pathology

Gross: Arises in **metaphysis** of long bones, especially **around knee** (distal femur, proximal tibia); large, bulky mass containing areas of hemorrhage and cystic degeneration; often destroys overlying cortex and spreads into medullary canal

Microscopic: Multinucleated giant cells; **anaplastic cells; neoplastic osteoid formation**

Clinical Manifestations

Pain and swelling around site; fracture; often metastasizes to the lung, brain, or liver and may present with symptoms of metastasis

Lab findings: **Increased serum ALP**

Imaging: **Codman triangle** (lifting of periosteum), **sunburst growth pattern** on radiograph

Treatment and Prognosis

Chemotherapy; surgical resection or limb amputation

5-year survival rate is 60%

Notes

Osteosarcoma is the **most common primary malignant tumor** of bone.

Chondrosarcoma is a **malignant cartilaginous tumor** that occurs most in **men,** aged 30–60. It most commonly occurs in pelvis, spine, ribs, tibia, and femur.

An 11-year-old boy presents to the emergency department complaining of a painful, swollen mass in his right leg. He denies any history of trauma to the leg. Laboratory tests reveal anemia, leukocytosis, and an elevated ESR. An x-ray of the mass demonstrates a lytic tumor with an onion-skin appearance in the medullary cavity of his right femur. You admit this patient to the oncology service and you fear that his prognosis is grim if the mass has metastasized.

Ewing Sarcoma

Etiology and Epidemiology	Associated with chromosomal translocation **t (11;22)** Categorized as a **small round blue cell tumor,** but tumor cell origin is unknown Occurs most frequently in **boys < 15 years old**
Pathology	*Gross:* Arises most often in the medullary cavity of **long bones, pelvis, ribs, and scapula** *Microscopic:* Sheets of small, round, blue, **uniform cells** with little cytoplasm; tumor cells may be arranged in **pseudorosette** fashion; necrosis may be apparent
Clinical Manifestations	**Painful, swollen, enlarging mass;** systemic signs including fever and anemia **(may mimic symptoms of osteomyelitis)** *Imaging:* Lytic tumor with **onion-skin** appearance on radiograph *Lab findings:* Leukocytosis, elevated ESR
Treatment and Prognosis	Surgical resection; chemotherapy; radiation Extremely **aggressive tumor** that is prone to metastasize early; 5-year survival is 70% if localized disease and 30% if metastatic disease
Notes	

A 44-year-old woman presents to your office complaining of chronically swollen finger joints over the past 6 months. She tells you that the swelling and pain are usually most severe in the morning, but do resolve within a couple of hours. Physical examination reveals swelling of the PIP and MCP joints of both hands and subcutaneous nodules over both of her elbows. When laboratory results reveal the presence of a specific IgM antibody directed against the Fc fragment of IgG, you begin the patient on NSAIDs and low dose steroids.

Rheumatoid Arthritis

Etiology and Epidemiology	Etiology unknown; it is theorized that an acute arthritis is triggered in genetically susceptible people **(HLA-DR4),** which causes a chronic **autoimmune reaction** Most common in **women** between 30 and 50 years old
Pathology	*Joint:* Initially, **lymphocytic infiltration** and edema in synovium with formation of villi composed of synovial lining cells; neutrophils in synovial fluid; later, the **cartilage is destroyed** and replaced with a **pannus** (fibrocellular granulation tissue). Scarring after inflammation leads to **joint deformity.** **Rheumatoid nodule:** Firm, nontender, subcutaneous nodule; core of **fibrinoid necrosis** surrounded by **palisade of macrophages,** lymphocytes, and fibroblasts
Clinical Manifestations	**Symmetric joint swelling** with stiffness and pain most commonly involving **PIP and MCP joints** of the fingers, wrists, knees, and ankles that is most **severe in morning** and improves with activity; **rheumatoid nodules** usually over bony prominences; characteristic **swan-neck deformity** (flexion of DIP with extension of PIP joint); **boutonniere deformity** (extension of DIP with flexion of PIP joint); **ulnar deviation of fingers;** joint deformities; fatigue; fever Complications include anemia, pericarditis, pulmonary fibrosis, pleuritis, vasculitis, and secondary amyloidosis *Lab findings:* Positive **Rheumatoid factor** (IgM antibody against IgG Fc fragment), positive anti-CCP antibody, increased ESR
Treatment	Glucocorticoids; NSAIDs; immunosuppressants
Notes	

A 67-year-old woman presents to your clinic complaining of stiffness and pain in both of her knees. Upon further questioning, she tells you that the pain becomes worse later in the day after she has been walking around. Physical examination reveals bilateral, swollen knees with mild joint effusion and crepitus with flexion. You also notice bony nodules on her DIP and PIP joints. You suspect that her condition is caused by the wear and tear of everyday life.

Osteoarthritis

Etiology and Epidemiology	Destruction of articular cartilage resulting from mechanical trauma to the joints that accumulates over time **(wear-and-tear arthritis)** Affects **women** more often than men; **age of onset is usually > 50;** associated with obesity
Pathology	*Joint:* **Joint cartilage flakes off** and is eroded, exposing underlying bone; **eburnation of bone** (polishing of bone due to rubbing of bone with bone); **cystic degeneration** beneath eburnated bone (subchondral cysts); **osteophyte formation** (growth of new bone at articular edges); **joint mice** (fractured osteophytes floating in synovial fluid)
Clinical Manifestations	**Joint pain** and stiffness that **worsens with use** most commonly occurring in the hip joint, knee joint, lumbosacral spine, MTP joint of the toe, and **DIP and PIP joints of the fingers;** may see **Heberden nodes** and **Bouchard nodes** (osteophytes at the DIP and PIP joints, respectively)
Treatment	NSAIDs; surgical replacement of joint
Notes	Osteoarthritis can be distinguished from rheumatoid arthritis on the basis of location of joint involvement, laboratory tests (normal in osteoarthritis), and description of joint pain (effect of movement on pain).

A 22-year-old man presents to your office complaining of lower back pain and stiffness. Upon further questioning, you discover that he occasionally has sharp pain and burning in his eyes. He denies any recent GI symptoms or illnesses and he is not sexually active. Physical examination reveals pain and limited range of motion of the lower back. When an x-ray of the spine demonstrates sacroiliac joint disease, you begin to suspect that this patient is probably an HLA-B27-positive individual. You prescribe NSAIDs and suggest physical therapy to relieve the stiffness and pain.

Seronegative Spondyloarthropathies

Ankylosing Spondylitis	*Epidemiology:* Most common in **young men** who are **HLA-B27 positive** *Clinical manifestations:* **Lower back pain and stiffness** (especially in morning) owing to fusing of vertebrae; uveitis; peripheral **arthritis** of spine and large joints; increased ESR; **bamboo spine** on radiograph
Reactive Arthritis	*Etiology and epidemiology:* Autoimmune reaction to prior GI or GU infection; most common in **young men** who are **HLA-B27 positive** *Clinical manifestations:* Triad of **arthritis, nongonococcal urethritis, and conjunctivitis;** presents as joint stiffness in large, weight-bearing joints and lower back pain; sausage fingers (synovitis of tendon sheath of fingers)
Enteropathic Arthritis	*Etiology and epidemiology:* Associated with **inflammatory bowel disease** or GI infections; most common in **HLA-B27-positive** individuals *Clinical manifestations:* **Oligoarthritis of the large joints** (knees, spine); erythema nodosum; generally resolves after several months
Psoriatic Arthritis	*Etiology and epidemiology:* Associated with **more than 10% of patients with psoriasis;** manifests between age 30 and 50 *Clinical manifestations:* Arthritis of the hands, feet, and large joints; sausage fingers; pitting of fingernails; eye inflammation; **"pencil-in-cup"** deformity of DIP joints on radiograph
Treatment	*For all spondyloarthropathies:* NSAIDs; physical therapy; intra-articular steroid injections

A 45-year-old obese man presents to the emergency department with a swollen, tender big toe on his right foot. He denies any trauma to the toe. Further questioning reveals that he had consumed a large amount of alcohol the night before. An aspirate of synovial fluid from the metatarsophalangeal joint of the right big toe demonstrates neutrophils along with needle-shaped, negatively birefringent crystals. You prescribe colchicine to treat his condition.

Gout

Etiology and Epidemiology	Caused by **joint deposition of urate crystals** owing to hyperuricemia *Primary:* Caused by idiopathic hyperuricemia; risk factors include obesity, alcohol use, and genetic susceptibility; most common in middle-aged men *Secondary:* Owing to hyperuricemia caused by myeloproliferative disorders, decreased urate excretion (renal disease), drugs (ie, diuretics), or Lesch-Nyhan syndrome (HGPRT deficiency)
Pathology	*Joint:* Neutrophils and **urate crystals (needle-shaped, negatively birefringent crystals)** in synovial fluid; edematous synovium with inflammatory infiltrate; later, urate deposits can lead to cartilage erosion *Tophi:* Cluster of urate crystals surrounded by fibroblasts, lymphocytes, and giant cells located in cartilage or soft tissues
Clinical Manifestations	**Swollen, tender joint** with sudden onset, often in **MTP joint** of big toe (podagra), ankles, or knees; chronic arthritis may develop; **tophi** on ears, hands, or feet (appear several months after acute arthritis); **urate nephropathy** with interstitial deposit of urate crystals and obstruction by uric acid stones *Lab findings:* **Hyperuricemia,** increased ESR, leukocytosis
Treatment	Colchicine, **NSAIDs** and/or steroids for acute flare; **allopurinol** or probenecid for chronic treatment
Notes	**Pseudogout** is caused by joint deposition of calcium pyrophosphate crystals (weakly positive, birefringent, rhomboid crystals). It is more common in elderly and usually affects large joints (eg, knee).

A 6-year-old boy presents to your office complaining of severe muscle weakness, especially of his thighs. The boy's parents tell you that his maternal uncle died of a muscle disease during adolescence. Physical examination reveals enlarged calves and decreased strength in the proximal muscles of the lower extremities. When you ask the boy to rise from a crouching position, you notice that he uses his arms to assist himself. Laboratory tests demonstrate increased serum creatine kinase levels. As you send the boy for a muscle biopsy, you begin to suspect that his prognosis is very poor.

Duchenne Muscular Dystrophy

Etiology and Epidemiology	**X-linked recessive** disorder resulting in **absence of dystrophin synthesis** usually caused by gene deletion Affects **males** with **onset by age 5**
Pathology and Pathophysiology	*Pathophysiology:* Dystrophin is involved in maintaining myocyte membrane integrity; absence leads to muscle fiber destruction *Muscle:* Variation in muscle fiber size; degeneration and necrosis of muscle fibers; replacement of necrotic fibers with fat and connective tissue
Clinical Manifestations	**Weakness in proximal muscles of extremities** (usually **pelvis**) that progresses superiorly and eventually leads to immobilization; **pseudohypertrophy of calves** (owing to replacement of muscle with fibrous and fatty tissue); presence of **Gowers maneuver** (use of arms to rise from crouching position) *Lab findings:* **Increased serum CK**
Treatment and Prognosis	No treatment **Death via respiratory failure in adolescence** caused by involvement of respiratory muscles
Notes	**Becker muscular dystrophy** is characterized by a **mutation** in the dystrophin gene that leads to reduced synthesis of dystrophin. It presents in a similar fashion to Duchenne muscular dystrophy, but is clinically less severe.

A 28-year-old man presents to your office complaining of generalized muscle stiffness. He mentions that his mother suffers from a disease causing similar symptoms. Physical examination demonstrates delayed relaxation of the hand muscles following prolonged grip and weakness of the distal muscles in the limb. You also notice the formation of bilateral cataracts, testicular atrophy, and frontal baldness. You prescribe phenytoin to treat his symptoms and you refer this patient to a medical genetics clinic.

Myotonic Dystrophy

Etiology and Epidemiology	**Autosomal dominant disorder** resulting in **increased CTG repeats** in the **myotonin protein kinase gene** on chr 19 Often presents between the ages of 20 and 30, but may manifest in childhood
Pathology	*Muscle:* Increased number of internal nuclei in muscle; ring fiber (cytoplasmic band within the center of the fiber); fiber splitting and necrosis of intrafusal fibers of muscle spindles
Clinical Manifestations	**Myotonia** (inability to relax contracted muscles), often presenting as muscle stiffness; wasting and **weakness of facial muscles** and distal limb Associated with **cataracts, testicular atrophy, baldness,** and decreased glucose tolerance
Treatment	Phenytoin to treat myotonia
Notes	Myotonic dystrophy, as well as fragile X syndrome and Huntington disease, demonstrates **anticipation,** which is a phenomenon in which the number of repeats increases with each generation and results in more severe disease manifestations.

A 32-year-old African American woman presents to your clinic complaining of fever and malaise. She has suffered bouts of fever and malaise off and on for the past year. After taking a complete history, you learn that she has gradually lost hair from her scalp over the past year, has lost 20 pounds over the same time period, and is experiencing increasing joint pain. She denies any change in bowel or urinary function. On physical examination, you notice a butterfly rash over her nose and cheeks, tender elbows and knees, and a friction rub. You order serum studies specifically looking for positive readings of ANA and anti-ds DNA antibodies to confirm your suspected diagnosis.

Systemic Lupus Erythematosus (SLE)

Etiology and Epidemiology	Autoimmune disorder; associated with HLA-DR2 and -DR3; certain drugs (hydralazine, INH, phenytoin, procainamide) can produce reversible SLE-like syndrome Most commonly affects African American **women between ages 20 and 40**
Pathology and Pathophysiology	*Pathophysiology:* Disease results from a **type III hypersensitivity reaction** with the deposition of **antigen-antibody complexes** in capillaries of visceral structures or results from **autoantibody-mediated destruction** of host cells *Heart:* **Mitral valve disease;** pericarditis; evidence of coronary artery disease *Kidney:* **Wire-loop lesions** and immune complex deposition (See card on Lupus Nephritis in chapter 6) *Skin:* Destruction of epidermal basal layer with dermal edema; necrotizing **vasculitis** *Joint:* Synovitis with neutrophils in synovial fluid and mononuclear infiltrate in subsynovial tissue *Lung:* Pleuritis; pleural effusions; interstitial fibrosis
Clinical Manifestations	Fever; fatigue; **malar butterfly rash;** hair loss; mucosal ulcers; **arthritis;** photosensitivity; seizures or psychosis; pleuritis; Libman-Sacks endocarditis; Raynaud phenomenon; renal disease with **proteinuria** *Lab findings:* **ANA, anti-ds DNA antibodies**, **anti-Smith antibodies; antihistone antibodies** (drug-induced SLE); false positive on syphilis test (RPR/VDRL); **hemolytic anemia; pancytopenia**
Treatment	NSAIDs; corticosteroids; immunosuppression
Notes	

A 50-year-old white woman presents to the clinic complaining of a gritty feeling in her eyes and a dry throat for the last 3 weeks. She further describes her ocular discomfort as burning and itching and she reports that she has not been able to produce many tears when crying. She finds that her mouth is excessively dry and that she has problems swallowing and speaking. Her past medical history is significant for rheumatoid arthritis. On physical examination, you also notice bilateral parotid enlargement. You order serum studies looking for the presence of autoantibodies, including anti-SS-A and anti-SS-B antibodies.

Sjögren Syndrome

Etiology and Epidemiology	Caused by **autoimmune destruction of lacrimal and salivary glands;** associated with HLA-DR2 and -DR3, **RA,** SLE and other autoimmune diseases Predominantly affects **women** between 40 and 60 years of age
Pathology	*Lacrimal and salivary glands:* Perivascular and periductal **lymphocytic infiltrate;** may see lymphoid follicles; hyperplasia of ductal epithelial cells; eventual fibrosis and atrophy of tissue May involve other exocrine glands or even extraglandular tissues
Clinical Manifestations	Presents with triad of **dry eyes** (xerophthalmia), **dry mouth** (xerostomia), and arthritis **(usually RA);** conjunctivitis and **parotid enlargement** may be noticeable; **increased risk for B-cell lymphoma** *Lab findings:* Rheumatoid factor and other autoantibodies common, **anti-SS-A (Ro) and anti-SS-B (La) antibodies**
Treatment	Artificial tears; immunosuppression; steroids
Notes	**Sicca syndrome** is a variant of Sjögren syndrome, consisting only of dry eyes and dry mouth. It may also be associated with nasal dryness, chronic bronchitis, reflux esophagitis, and vaginal dryness. **Juvenile rheumatoid arthritis** is a variant of rheumatoid arthritis occurring in children. It often has an acute onset with fever, rash, and hepatosplenomegaly. Extra-articular manifestations include pericarditis, pulmonary fibrosis, and glomerulonephritis.

A 55-year-old woman presents to your clinic complaining of muscle weakness and a rash. She states that she has had increased difficulty rising from chairs and climbing stairs over the last 3 months, even though she used to be an avid athlete. On physical examination, you see a malar rash across the patient's face that is dusky red. There is marked erythema over her neck and shoulders and she has frank periorbital edema as well as a purplish discoloration over her eyelids. Her hands are remarkable for scaly patches over the dorsum of the proximal interphalangeal and metacarpophalangeal joints bilaterally. You order serum studies, measuring levels of muscle enzymes including creatine phosphokinase and aldolase, and you order a muscle biopsy expecting to find lymphoid inflammatory infiltrates, which will confirm your suspected diagnosis.

Myositides (Polymyositis and Dermatomyositis)

Etiology and Epidemiology	Systemic disorders of unknown cause, although immunologic mechanisms are suspected Most commonly occur in **women** between ages 40 and 60
Pathology and Pathophysiology	**Polymyositis (P):** Associated with CD8+ T-cell injury to myofibers; presence of lymphocytic cells in endomysium; no vascular injury; necrotic muscle cells **Dermatomyositis (D):** Immune complex deposition in blood vessels with complement activation leading to inflammatory infiltrate in perivascular regions and in perimysial connective tissue of muscle fibers; atrophic and necrotic muscle fibers; vascular endothelial fibrosis
Clinical Manifestations	**P:** Gradual, progressive, symmetric **proximal muscle weakness;** late muscle atrophy and contracture; interstitial lung disease; myocarditis **D:** Characteristic dusky red **rash in malar distribution** mimicking SLE; **shawl sign** (erythema over face, neck, shoulders, and upper chest and back); periorbital edema; purplish suffusion over eyelids **(heliotrope rash);** scaly patches over interphalangeal and MCP joints **(Gottron papules); proximal muscle weakness;** interstitial lung disease; myocarditis; **increased risk of underlying malignancy** *Lab findings for all myositides:* **Elevated creatine kinase**, positive ANA, positive anti-Jo-1 antibodies, positive anti-Mi-2 antibodies
Treatment	High-dose corticosteroids; immunosuppression
Notes	

A 35-year-old African American woman presents to the clinic complaining of migrating polyarthralgia and skin tightness. She says she feels that her skin has tightened in both her face and hands over the past 6 months. On physical examination, you notice that the skin on her hands and face has become thick and hidebound with a loss of normal folds. She has several telangiectasias and areas of hyper- and hypopigmentation in the affected areas. You see ulcerations about the fingertips and subcutaneous calcifications bilaterally. On further questioning, she reports difficulty swallowing, episodes of chest pain, and feels that her hands and feet become painfully pale in cold temperatures. You order serum studies for ANA, anti-Scl antibodies, and anticentromere antibodies to confirm a diagnosis.

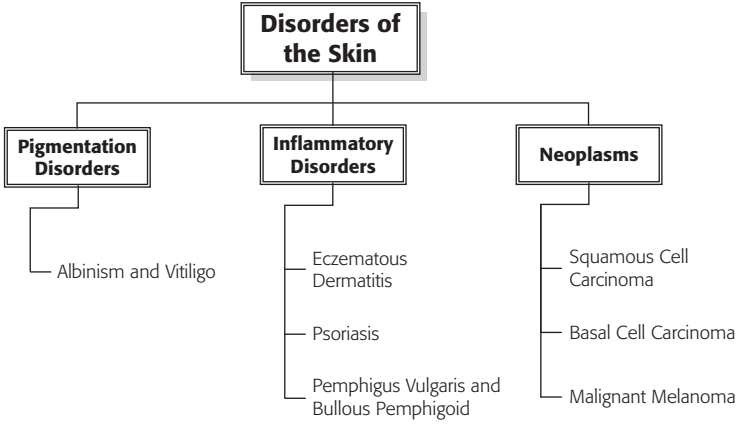
Systemic Sclerosis

Etiology and Epidemiology	Etiology unknown, but abnormality in immune system activation has been suggested Occurs most commonly in **women** between the **ages of 30 and 50**
Pathology	*General pathology:* **Fibrosis and collagen deposition** most commonly affecting the skin, heart, lungs, joints, GI tract (especially the esophagus), and kidneys *Skin:* Perivascular lymphocytic infiltrate with edema; eventual dermal fibrosis; may see subcutaneous calcifications *GI tract:* Fibrosis and atrophy of muscularis; loss of villi and microvilli in small bowel *Joints:* Inflammation of synovium with hypertrophy of synovial tissues *Kidneys:* Intimal thickening with collagenous deposition in vessel walls; vascular fibrinoid necrosis *Lungs:* Interstitial fibrosis; pulmonary HTN owing to vasospasm *Heart:* Pericarditis; myocardial fibrosis
Clinical Manifestations	**Dysphagia** and esophagitis; **pulmonary fibrosis;** pulmonary hypertension; **Raynaud phenomenon**; nephritic syndrome; arrhythmias; widespread **skin thickening (scleroderma)** with areas of increased and decreased pigmentation; tendon friction rubs over the wrists, ankles, and knees *Lab findings:* Positive anti-Scl-70 antibody, positive ANA
Treatment	**Steroids;** immunosuppression; NSAIDs
Notes	**CREST syndrome** refers to systemic sclerosis with limited cutaneous involvement (usually just face and hands) and classically includes Calcinosis, Raynaud phenomenon, Esophageal dysmotility (dysphagia), **S**clerodactyly (claw-like hands), and Telangiectasia. CREST syndrome is commonly associated with a positive anticentromere antibody.

A 25-year-old white man presents to his primary care clinic for follow-up after experiencing a detached retina the week before. His past medical history is significant for multiple shoulder dislocations as a teenager. On physical examination, the patient is very tall, with long arms, legs, and digits. He confesses that he is double jointed and proudly displays his flexibility. He explains that his father also had the same build and flexibility. Although his father was never diagnosed with any condition, he too had suffered from retinal detachments and joint dislocations. The patient informs you that his father passed away because of some type of cardiovascular accident. The rest of his physical examination is normal except for a heart murmur consistent with a mitral valve prolapse. You inform that patient of your suspected diagnosis and tell him that he is at risk for developing aortic dissection in the future.

Marfan Syndrome

Etiology	Caused by **mutation in fibrillin gene** on chr 15; most mutations are hereditary (autosomal dominant), but 20% of mutations are sporadic
Pathology and Pathophysiology	*Pathophysiology:* Fibrillin is a glycoprotein constituent of microfibrils and mutation of its gene leads to a defective extracellular matrix *Cardiovascular:* **Cystic medial necrosis of aorta** (leads to dilation of aortic valve and weakening of media with increased risk of intimal tear); **mitral valve prolapse** (owing to loss of connective tissue support of valvular leaflet) *Eye:* Bilateral subluxation or dislocation of lens *Skeletal:* Spinal deformities (kyphosis, scoliosis); pigeon-breast deformity
Clinical Manifestations	**Tall stature** with **long extremities; hyperextensible joints; long tapering digits (arachnodactyly); ectopia lentis** (dislocation of lenses); aortic valve incompetence; **increased risk for developing dissecting aortic aneurysm**
Treatment and Prognosis	Spine brace; aortic valve replacement if needed; β-blockers, frequent eye examinations; angiotensin receptor blockers Death is common between ages 30 and 40 from aortic dissection or CHF secondary to aortic regurgitation
Notes	**Ehlers-Danlos syndrome** presents with a constellation of hyperextensible skin, hypermobile joints, and the tendency to bleed owing to faulty collagen synthesis. The syndrome comes in 10 varieties with variable inheritance including autosomal dominant (type IV), autosomal recessive (type VI), and X-linked recessive (type IX).


Disorders of the Skin
Pigmentation Disorders
Albinism and Vitiligo
Inflammatory Disorders
Eczematous Dermatitis
Psoriasis
Pemphigus Vulgaris and Bullous Pemphigoid
Neoplasms
Squamous Cell Carcinoma
Basal Cell Carcinoma
Malignant Melanoma

Epidermal Layers from Superficial to Deep

Epidermal Layer	Contents
Stratum corneum	Flattened, dying cells containing keratin
Stratum granulosum	Cells involved in process of keratinization
Stratum spinosum	Cells involved in keratin synthesis; cells connected by desmosomes
Stratum basale	Germinal layer of epidermis; often see mitoses; can see melanocytes

Skin Disorder Terms

Term	Definition
Macule	Small, flat, discolored lesion
Plaque	Elevated skin lesion > 1 cm in diameter
Bullae	Large blister containing fluid
Acantholysis	Separation of epidermal cells from each other
Hyperkeratosis	Stratum corneum thickening
Parakeratosis	Hyperkeratosis associated with nuclei retention in keratinocytes

A 24-year-old African American man presents to your office complaining of irregular depigmented patches on his hands and around his mouth. He has recently been diagnosed with Hashimoto thyroiditis. A skin biopsy reveals no melanin pigment as well as an absence of melanocytes. You recommend that he use copious sunscreen because his condition puts him at a greater risk for skin cancers.

Albinism and Vitiligo

Etiology	**Albinism: Inherited inability of melanocytes to synthesize melanin,** either owing to tyrosinase deficiency or deficiency in uptake of tyrosine into the melanocyte; may be related to defective migration of neural crest cells (melanocytes are derived from neural crest ectoderm) **Vitiligo: Acquired loss of melanocytes,** possibly caused by an **autoimmune** reaction or to melanocyte damage by toxic intermediates of melanin synthesis; associated with autoimmune diseases (Addison disease, Hashimoto thyroiditis, Grave disease, pernicious anemia)
Pathology	**Albinism:** Can involve the eyes (ocular albinism) or the skin and hair (oculocutaneous albinism); **melanocytes present** in skin **Vitiligo: Absence of melanocytes** in skin
Clinical Manifestations	**Albinism: Hypopigmentation involving the eyes, skin, and hair;** may lead to loss of vision **Vitiligo:** Flat, **irregular lesions of pigment loss;** usually involving **hands,** axillae, or skin around eyes and mouth. *Lab findings:* Variable presence of antimelanocyte antibodies.
Treatment	**Albinism:** No cure; sun protection is necessary **Vitiligo:** Topical corticosteroids; sun protection
Notes	Patients with albinism or vitiligo are at a **greater risk for actinic keratoses and skin cancers.**

A 10-year-old boy presents to your office with a pruritic, vesicular rash. His mother tells you that he spent the previous day playing in the woods during a supervised summer camp outing. After ruling out any sort of infectious process, you prescribe topical corticosteroid creams and suggest that the boy avoid contact with certain plants to avoid recurrence.

Eczematous Dermatitis

Etiology	Chemicals **(contact dermatitis);** drugs or UV light; repeated trauma (irritant dermatitis); type IV hypersensitivity reaction **(atopic dermatitis)**
Pathology	May demonstrate **several histopathologic appearances of skin** depending on phase of disorder **Acute stage:** Edema fluid within epidermis **(spongiosis); vesicles;** perivascular lymphocytic infiltrate in epidermis; eosinophils when caused by drug reaction **Subacute stage:** Combination of acute and chronic features **Chronic stage: Acanthosis; hyperkeratosis;** lymphocytic infiltrate in dermis
Clinical Manifestations	Acutely, may present with red, oozing, pruritic, and crusted lesions Chronically, may develop into raised, poorly defined, scaling plaques
Treatment	Corticosteroids; removal of aggravating agent; antihistamines
Notes	**Erythema multiforme** is a skin disorder that results from hypersensitivity to microbes (herpes, mycoplasma) or drugs (penicillin, NSAIDs, sulfonamides). It presents with macules, papules, vesicles, and the characteristic **target lesion.** As a clinical syndrome, it can vary in severity, with the most severe form marked by systemic toxicity and mucosal involvement **(Stevens-Johnson syndrome).**

A 34-year-old woman presents to your office complaining of a chronic skin rash. The rash appears to consist of well-demarcated coral-colored plaques with silvery scales over the scalp, elbows, and knees. You discover that removing the scales results in pinpoint areas of bleeding. The patient also tells you that she suffers from some arthritic symptoms. You suspect that a skin biopsy would demonstrate acanthosis with Munro microabscesses, parakeratosis, and elongation of the rete ridges.

Psoriasis

Etiology	Etiology unknown; **autoimmunity** and **genetic predisposition** postulated
Pathology	*Skin:* **Thin stratum granulosum** with **parakeratosis;** epidermal thickening **(acanthosis)** leads to **lengthening of rete ridges;** thinning of surface epidermis over dermal papillae, leading to proximity of dermal blood vessels to surface; neutrophil clusters in epidermis (spongiform pustules) or in stratum corneum **(Munro microabscesses)**
Clinical Manifestations	**Defined coral-colored plaque covered with silver scales,** usually located on scalp, elbows, and knees; **positive Auspitz sign** (removal of scale results in tiny areas of bleeding); nail discoloration with separation of nail plate from nail bed Associated with **psoriatic arthritis,** enteropathy, or myopathy
Treatment	Topical corticosteroids; UVB light exposure; methotrexate
Notes	

A 51-year-old man presents to your clinic complaining of painful blisters over his entire body. He notes that he currently has several ulcers in his mouth as well. Physical examination reveals severe bullae. You note that a blister appears when you rub his skin with your finger. When a skin biopsy demonstrates acantholysis, you tell the patient that his symptoms are due to an autoimmune disorder and you prescribe steroids to treat his condition.

Bullous Pemphigoid and Pemphigus Vulgaris

Etiology and Epidemiology	**Bullous pemphigoid (BP):** Autoimmune disease characterized by **IgG antibodies against hemidesmosomes of the epidermal basement membrane;** most commonly **affects men > 60 years old** **Pemphigus vulgaris (PV):** Autoimmune disease characterized **by IgG antibodies against intercellular junctions between epidermal keratinocytes;** most commonly seen in patients, ages 30–60
Pathology	**BP: Subepidermal bullae** in skin; perivascular infiltrate of eosinophils and lymphocytes; immunofluorescence demonstrates **linear band of complement and IgG deposition** along basement membrane **PV:** Acantholysis of cells directly above basal cell layer of skin, resulting in suprabasal acantholytic blister; immunofluorescence demonstrates **IgG and complement encircling epidermal cells**
Clinical Manifestations	**BP:** Chronic relapsing and remitting course, characterized by **pruritic, fluid-filled blisters;** clinically **less severe than pemphigus vulgaris.** *Lab findings:* antibasement membrane antibodies. **PV: Severe, intraepidermal bullae** initially occurring in the **mouth,** but eventually involving whole body; ruptured bullae may lead to secondary infection; **positive Nikolsky sign** (development of blister after rubbing skin with finger). *Lab findings:* presence of antiadhesion molecule immunoglobulins.
Treatment	**BP:** Corticosteroids **PV:** Systemic corticosteroids and immunosuppressive drugs
Notes	**Paraneoplastic pemphigus** is distinct from PV and is associated with mucosal lesions, similar to erythema multiforme. Survival rates are low owing to the underlying malignancy.

A 67-year-old man presents to your office after noticing a hard, red, ulcerated nodule on the back of his left hand. A skin biopsy of the nodule reveals cellular atypia and anaplasia throughout the epidermis and extending into the dermis, as well as hyperkeratosis with keratin pearls. You tell him that he has cancer, but reassure him that a simple excision surgery will likely cure his condition.

Squamous Cell Carcinoma of the Skin

Etiology	Risk factors include **excessive exposure to sunlight** (UV light), tobacco, arsenic, immunosuppression, defective DNA repair mechanisms (eg, xeroderma pigmentosum), and exposure to tars and ionizing radiation
Pathology	**Actinic keratosis: Precursor lesion;** poorly defined, red, scaling lesion sometimes forming a cutaneous horn; **cellular atypia and hyperplasia of basal cells;** parakeratosis; intercellular bridges are present **In situ carcinoma:** Well-defined, red, scaling plaque or ulcerated nodule; ***not*** **invaded through basement membrane; cellular atypia** at all levels of epidermis; **hyperkeratosis** with keratin pearls **Invasive carcinoma: Invaded through basement membrane;** marked **anaplasia** of sheets of neoplastic epidermal cells; **keratinization** with keratin pearls
Clinical Manifestations	**Small, red, ulcerating nodule** occurring on sun-exposed areas (hands and face)
Treatment and Prognosis	Surgical excision Less than 5% of cases metastasize; surgery is usually curative
Notes	

A 62-year-old woman presents to your clinic complaining of a raised, ulcerated lesion on her right cheek. She tells you that she used to work as a gardener and enjoys working in her own garden several hours a day now that she is retired. Examination of the lesion reveals a pearly, ulcerated papule with overlying telangiectasias. When a skin biopsy demonstrates clusters of cells with dark blue nuclei surrounded by palisading basal cells, you reassure this patient that her condition, although serious, will likely be cured by surgery.

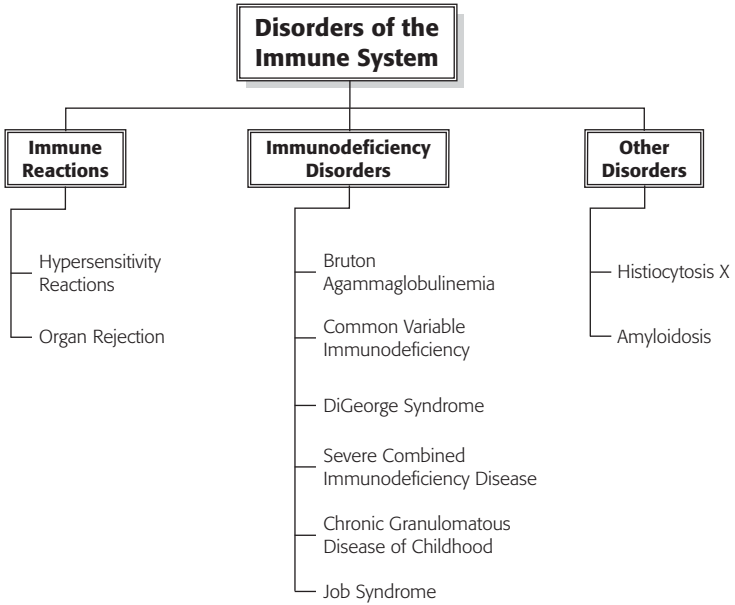
Basal Cell Carcinoma

Etiology and Epidemiology	Most common of all skin neoplasms Risk factors include **chronic exposure to sunlight** (UV light), fair skin, immunosuppression, and defective DNA repair mechanisms (eg, xeroderma pigmentosum)
Pathology	*Skin:* Clusters of **atypical tumor cells with dark blue nuclei** arising from basal cells of epidermis; tumor clumps surrounded by cells at periphery with palisading arrangement of nuclei; multiple growth patterns including nodular, cystic, and trabecular; **invades dermis**
Clinical Manifestations	**Pearly, telangiectatic papule,** which may ulcerate or bleed, usually occurring on sun-exposed areas (especially face)
Treatment and Prognosis	Surgical excision Rarely metastasizes, so surgery is usually curative
Notes	**Xeroderma pigmentosum** is an autosomal recessive disorder. It is characterized by defects in genes involved in nucleotide excision repair, which are necessary for the repair of pyrimidine dimers formed by UV light exposure. Clinical manifestations include increased incidence of all skin cancers.

A 48-year-old man presents to your office after noticing an irregularly shaped lesion on the extensor surface of his left forearm. He mentions that he had noticed the spot before, but it has recently changed color from a light brown to a dark reddish purple and it now seems to be more raised than it used to be. Examination of the lesion reveals a poorly defined, hyperpigmented, and multicolored nodule. You also note left axillary lymphadenopathy. When a biopsy of the lesion demonstrates nests of atypical pigmented cells invading the dermis, you suspect that there is a high probability that this lesion has metastasized and you refer the patient to an oncologist.

Malignant Melanoma

Etiology	Associated with **excessive exposure to sunlight,** genetic predisposition (10% of cases are familial), immunosuppression, and fair skin
Pathology	**Dysplastic nevus: Precursor lesion;** nests of nevus cells within epidermis demonstrating cellular atypia and anaplasia; mild lymphocytic infiltrate and linear fibrosis in dermis **Melanoma:** Arises from melanocytes or nevus cells; exhibits **two growth phases** in skin: *(1) Radial growth:* discolored **macule, horizontal growth** of nests of atypical cells within epidermis, **lymphocytic infiltrate** and melanin-containing macrophages in dermis, **does not metastasize;** *(2) Vertical growth:* **nodular** appearance, **growth into underlying dermis, does metastasize** and metastatic probability is directly proportional to depth of invasion
Clinical Manifestations	**Variation in pigmentation, size, and border in pigmented lesion;** may be pruritic **Clinical variants:** *(1) Superficial spreading:* most common form, irregularly bordered lesion, radial phase predominates with no invasion of dermis; *(2) Nodular:* vertical growth phase predominates; *(3) Lentigo maligna:* arises from precursor lesion (Hutchinson freckle); can give rise to spindle-cell melanoma or desmoplastic melanoma *Lab finding:* **Presence of S-100 tumor marker**
Treatment and Prognosis	Surgical excision along with regional lymph node dissection; chemotherapy; consider IL-2 treatment for metastatic disease Metastasis occurs frequently, especially to intestinal serosa, esophagus, eye, and meninges Metastatic disease and nodular variant have a particularly poor prognosis
Notes	


Disorders of the Immune System
Immune Reactions
Immunodeficiency Disorders
Other Disorders
Hypersensitivity Reactions
Organ Rejection
Bruton Agammaglobulinemia
Common Variable Immunodeficiency
DiGeorge Syndrome
Severe Combined Immunodeficiency Disease
Chronic Granulomatous Disease of Childhood
Job Syndrome
Histiocytosis X
Amyloidosis

Immunoglobulin Types and Function

Isotype	Structure	Location	Function(s)
IgM	Monomer or pentamer	Antigen receptor on B-cell surface	1° response to antigen; fixes complement
IgG	Monomer	Most abundant immunoglobulin	2° response to antigen; fixes complement; crosses placenta; opsonizes and neutralizes bacteria, viruses
IgA	Monomer or dimer	Secretions	Neutralizes bacteria & viruses by preventing adherence to mucous membranes
IgD	Monomer	B-cell surface, serum	Unknown function
IgE	Monomer	Low concentration in serum	Mediates type I hypersensitivity

A fellow medical student suddenly complains that he cannot breathe and within seconds is frantically gasping for air. You were about to help him examine a patient and both of you had just put on some latex gloves. You immediately take your and his gloves off and ask the nurse to draw up 1 mg of epinephrine and to bring an intubation box. You do a quick survey of your colleague and find, along with his acute dyspnea, he has marked edema of his upper extremities and face. You inject the epinephrine SQ and start an IV so that you can begin to administer a rapid IV infusion of large volumes of saline solution to combat any hypotension and shock. Your fellow medical student has markedly improved within minutes, however he is admitted to the hospital for further observation.

Hypersensitivity Reactions

Etiology	**Type I:** IgE-mediated immediate hypersensitivity **Type II:** Antibody-mediated cytotoxic hypersensitivity **Type III:** Immune complex–mediated hypersensitivity **Type IV:** T-cell-mediated delayed hypersensitivity
Pathophysiology	**Type I:** Antigen cross-links **cell-bound IgE** on presensitized mast cells and basophils, causing release of vasoactive amines that cause vasodilation, visceral smooth muscle contraction, vascular permeability, and tissue inflammation **Type II:** IgG or IgM antibody reacts to **cell-bound antigens** resulting in activation of the complement cascade and destruction of antigen-bound cell **Type III:** IgG or IgM antibody **complexes** with allergen and **deposits in tissue,** thereby activating complement cascade **Type IV:** Allergen binds endogenous protein, and is presented to T cells. If reexposed to allergen, **memory T cells** stimulate inflammatory reaction.
Clinical Manifestations	**Type I: Atopy; anaphylaxis;** asthma; allergic rhinitis; local wheal and flare **Type II:** Immune hemolytic anemia; **erythroblastosis fetalis;** ARF; Goodpasture syndrome **Type III: Arthus reaction** (localized cutaneous and subcutaneous inflammatory response to injected allergen); **serum sickness** (systemic disease fever, arthralgias, proteinuria, lymphadenopathy, and dermatitis); polyarteritis nodosa; SLE; RA **Type IV:** Allergic dermatitis; hypersensitivity pneumonitis
Treatment	Antihistamines; corticosteroids; treatment of specific disease
Notes	

Within 10 minutes of anastomosing a kidney from a living donor into your patient, you see that the kidney graft is rapidly becoming cyanotic, mottled, and flaccid in appearance. After several more minutes, a mere few drops of bloody urine are produced. You fear that the kidney will not be functional, likely because the recipient may have had preformed antidonor antibodies, and you decide to remove the nonfunctioning allograft. Subsequent histologic study of the rejected tissue demonstrates a neutrophilic infiltrate within the arterioles, glomeruli, and peritubular capillaries.

Organ Rejection

Etiology	**Hyperacute rejection:** Caused by **preformed antidonor antibodies** (eg, antiblood-type antibodies) present in recipient's circulation **Acute rejection:** Caused by **cytotoxic T-cell reaction** with class I MHC **Chronic rejection:** Decreased effectiveness of long-term immunosuppressive therapies allows for vascular changes within graft **Graft-versus-host disease (GVHD):** Grafted T cells proliferate in immunocompromised recipient and attack recipient host cells
Pathology	**Hyperacute:** Cyanosis of graft with necrosis; neutrophilic infiltration; fibrin-platelet thrombi **Acute:** Interstitial **mononuclear infiltrate** with edema and hemorrhage; necrotizing vasculitis with swollen endothelial cells and thrombosis **Chronic: Intimal fibrosis** of arteries leading to ischemic damage and atrophy to graft **GVHD:** Inflammatory damage to immune system, skin, liver, and GI tract
Clinical Manifestations	**Hyperacute:** Occurs within **minutes** after transplant **Acute:** Occurs **weeks** after transplant **Chronic:** Occurs **months to years** after transplant **GVHD:** Symptoms include maculopapular rash, jaundice, diarrhea, and hepatosplenomegaly
Treatment	**Hyperacute and chronic:** Irreversible **Acute:** Reversible with immunosuppression (eg, cyclosporine) **GVHD:** Treat donor tissue with antithymocyte globulin or monoclonal antibodies before graft; immunosuppression (eg, cyclosporine)
Notes	

A 9-month-old male infant is brought to the pediatric clinic for the fourth time in 8 weeks. The infant had been previously seen for pneumonia, sinusitis, and otitis media infections. He presents with what appears to be another otitis media infection. Suspicious of an immunologic disorder, you order serum studies to look at B-cell, T-cell, and immunoglobulin levels. The studies show an absence of B cells in the blood, normal T-cell levels, and low levels of all classes of immunoglobulins. You suspect that a lymph node biopsy would reveal poorly defined germinal centers and you refer this patient to an immunology clinic.

Bruton Agammaglobulinemia

Etiology and Epidemiology	**X-linked recessive** defect in tyrosine kinase gene, resulting in **failure of B-cell precursors to mature into B cells** Most commonly seen in **male** infants
Pathology	*Lymphoid tissue:* Absent or **poorly defined germinal centers**
Clinical Manifestations	Presents as **recurrent pyogenic bacterial infections** (otitis media, sinusitis, pneumonia) in boys **after 6 months of age** (when levels of maternal IgG begin to decline); cell-mediated immunity function is normal *Lab findings:* **Low levels of all classes of immunoglobulins, absence of serum B cells**
Treatment	Pooled gamma globulin
Notes	**Wiskott-Aldrich syndrome** is an X-linked recessive defect in the ability to mount an IgM response to encapsulated bacteria (eg, *Pneumococcus*). It is characterized by elevated IgA levels, low IgM levels, and normal IgE and total immunoglobulin levels. Patients present with the triad of recurrent pyogenic **infections, eczema,** and petechiae and bleeding owing to **thrombocytopenia.** Treatment is supportive with bone marrow transplant and splenectomy as alternative options.

An 18-year-old woman presents to the clinic with a recurrent sinus infection. She has also suffered from bronchitis, otitis media complicated by meningitis, steatorrhea, and pneumonia over the last year. Physical examination reveals hepatosplenomegaly. You order serum studies, which demonstrate a markedly depressed IgG level and subnormal serum IgA and IgM levels. Further testing reveals that the patient has absent functional antibody responses to protein antigen immunizations. You treat the sinusitis with antibiotics and you suggest IV gamma globulin therapy for treatment of her underlying condition.

Common Variable Immunodeficiency

Etiology and Epidemiology	Caused by an intrinsic **B-cell defect** preventing terminal maturation into antibody-secreting plasma cells with deficient synthesis of secreted antibody Onset is usually during adolescence or early adulthood
Pathology	*Spleen, liver, lungs, and skin:* **Noncaseating granulomas**
Clinical Manifestations	Increased incidence of **recurrent pyogenic infections,** sprue-like GI syndrome, and autoimmune phenomena Complications include an increased propensity for development of **B-cell neoplasms,** gastric carcinomas, and skin cancers *Lab findings:* **Depressed IgG levels** with all antibody classes eventually affected; decreased or absent functional antibody responses to protein antigen immunizations; absolute B-cell count in peripheral blood is normal
Treatment	Antibiotics; IV gamma globulin therapy
Notes	**Selective IgA deficiency** is the most common primary immunodeficiency disorder and is characterized by absence of serum IgA, possibly owing to an isotype switching defect. It presents with sinus and lung infections, milk allergies, and anaphylaxis to blood transfusions.

You are emergently called to see a newborn infant boy, who appears cyanotic in the nursery. Indeed, on physical examination, the infant appears agitated, cyanotic, and signs of tetany are apparent. The appearance of the mouth, ears, and facies is abnormal. You order serum studies that show normal immunoglobulin levels, but an absence of T cells in the peripheral blood. You believe that the cyanosis is caused by a congenital defect of the heart and great vessels and you order imaging studies to confirm your suspected diagnosis. When the infant's parents ask for a possible cause for their son's condition, you inform them that you believe that there was a developmental failure of the thymus and parathyroids owing to a chromosomal microdeletion.

DiGeorge Syndrome

Etiology	Caused by **microdeletion on chr 22q11,** which results in the **failure of development of third and fourth pharyngeal pouches**
Pathology and Pathophysiology	*Thyroid and parathyroid:* Hypoplasia of tissue *Pathophysiology:* Thymic hypoplasia results in **T-cell deficiency;** parathyroid hypoplasia results in hypocalcemia
Clinical Manifestations	**Recurrent** viral, fungal, and protozoal **infections;** tetany (owing to hypocalcemia); congenital **cardiovascular defects;** facial abnormalities including cleft palate
Treatment	Fetal thymus transplanted to restore T-cell immunity
Notes	**Chronic mucocutaneous candidiasis** is a T-cell dysfunction specifically against *Candida albicans* that presents with *Candida* skin and mucous membrane infections.

A male neonate presents to the hospital with prominent thrush consistent with oral candidiasis, extensive diaper rash, and failure to thrive. The infant has also developed a morbilliform rash. You begin to treat the infant empirically with antibiotics to combat his possible infections. When serum studies demonstrate markedly low levels of both B and T cells in the peripheral blood, you suspect that the patient may have a serious inherited immune disorder and you request an immunology consultation.

Severe Combined Immunodeficiency Disease (SCID)

Etiology	Fifty-five percent of cases caused by **X-linked recessive** disorder resulting in **defective IL-2 receptors on T cells;** remaining cases caused by **autosomal recessive** disorders, which result in other mutations including ***adenosine deaminase*** **deficiency,** tyrosine kinase deficiency, failure to synthesize class II MHC antigens, or a defective recombinase-activating gene mutation
Pathology and Pathophysiology	*Lymphoid tissues:* Small, undifferentiated thymus with reduced numbers of lymphocytes; other lymphoid tissues are hypoplastic with depletion of T-cell areas *Pathophysiology:* Mutations cause faulty stem cell differentiation, resulting in a **defect in both humoral and cell-mediated immune responses**
Clinical Manifestations	**Severe, recurrent viral, bacterial, fungal, and protozoal infections** (especially prone to infections by *C albicans, Pneumocystis carinii, Pseudomonas,* CMV, and VZV); may present with prominent thrush, extensive diaper rash, and **failure to thrive** *Lab findings:* Profound lymphopenia
Treatment	*Adenosine deaminase* gene transplantation; bone marrow transplantation; stem cell transplantation
Notes	

An 8-month-old male infant is brought to the clinic with a fever and noticeable difficulty breathing. The child had previously been hospitalized with newborn meningitis caused by *Escherichia coli* and a urinary tract infection caused by *Serratia*. A chest x-ray is suspicious for infiltrates consistent with pneumonia. You start the child on ventilatory support and broad spectrum antibiotics to treat his pneumonia. As his treatment is being initiated, you begin to suspect that this patient may have an immunodeficiency syndrome and you order a nitroblue tetrazolium dye reduction test to confirm your diagnosis.

Chronic Granulomatous Disease of Childhood

Etiology

Caused by inherited X-linked or autosomal recessive **defects in genes encoding components of *NADPH oxidase,*** an enzyme that generates superoxide

Pathophysiology

Neutrophils use the myeloperoxidase-halide system to combat bacteria. The myeloperoxidase-halide system requires H_2O_2 to function. H_2O_2 is produced by bacterial metabolism and by *NADPH oxidase*. Catalase-positive organisms (like *Staphylococcus*) can destroy the H_2O_2 produced by bacterial metabolism. **Without *NADPH oxidase* activity,** there is no source of H_2O_2 and the **myeloperoxidase-halide system is unable to kill catalase-positive bacteria.**

Clinical Manifestations

Presents with marked susceptibility to **opportunistic catalase-positive bacterial infections,** including *E coli,* ***Staphylococcus aureus,*** *Serratia,* and *Aspergillus*

Lab findings: **Negative nitroblue tetrazolium dye reduction test** because of absence of reactive O_2 intermediates

Treatment

Gamma interferon; prophylactic antibiotics; gene therapy

Notes

Chediak-Higashi syndrome is an autosomal recessive defect of leukocyte function affecting microtubules and lysosomal emptying of phagocytes. It presents with recurrent *Staphylococcus* and *Streptococcus* infections, neutropenia, albinism, bleeding, and neuropathy.

Leukocyte adhesion deficiency syndrome is caused by a defect in LFA-1 adhesion proteins on the surface of phagocytes that presents early in life with severe pyogenic infections and impaired wound healing.

A 1-year-old boy presents to the pediatric clinic with what appears to be an abscess on his left forearm. This is the second time the child has presented with such an abscess. On physical examination, you see a focal skin infection on the left forearm with no real sign of inflammation. You also note that the child has coarse facies and extensive eczema on his back and legs. You decide to order serum studies examining immunoglobulin levels, expecting to see an elevated IgE level, which would confirm your preliminary diagnosis.

Job Syndrome

Etiology	Failure of γ-interferon production by helper T cells
Pathophysiology	**Lack of γ-interferon** leads to an increase in helper T-cell type 2 production and subsequent increase in IgE levels. The **increase in IgE** levels leads to increased histamine release and **lack of inflammation.**
Clinical Manifestations	Presents with noninflamed, **cold** recurrent *Staphylococcal* **abscesses,** eczema, and **elevated IgE levels**; patients may also have coarse facies and retained primary teeth
Treatment	Antibiotics to treat infections
Notes	**Hyper-IgM syndrome** results from a defect in CD40 ligand on CD4 T helper cells leading to an inability to class switch from IgM to other classes. It presents with severe pyogenic infections early in life.

An 18-month-old girl presents to the pediatric clinic with a recurring otitis media and a widespread skin rash. On physical examination, you find cutaneous lesions resembling a seborrheic eruption over her trunk and the scalp. In addition to otitis media of her left ear, hepatosplenomegaly and cervical lymphadenopathy are present. Serum studies show marked anemia and thrombocytopenia. A series of radiographs demonstrates multiple bone lesions consistent with destructive osteolysis. You suspect that electron microscopy of a skin lesion would reveal the presence of tennis-racket shaped structures in the cytoplasm.

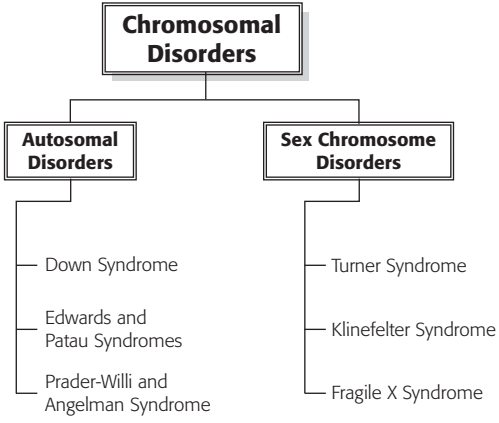
Histiocytosis X Syndromes

Etiology	Caused by a proliferation of dendritic tumor cells, which express HLA-DR and CD1a Three subtypes include **Letterer-Siwe (L-S)** disease, **Hand-Schüller-Christian (H-S-C)** disease, and **eosinophilic granuloma (EG)**
Pathology	*Gross:* Lesions involve multiple organ systems, including skin, bone, lung, and stomach *Microscopic:* Proliferation of **neoplastic histiocytic cells resembling epidermal Langerhans cells; Birbeck granules** (tennis-racket shaped cytoplasmic structures) within neoplastic cells; presence of eosinophils in lesions seen in eosinophilic granuloma
Clinical Manifestations	**L-S:** Presents **< 3 years** of age; **fever** followed by diffuse maculopapular eczematous **purpuric skin rash** over trunk and scalp; concurrent **hepatosplenomegaly;** lymphadenopathy; pulmonary involvement; bone involvement; recurrent **otitis media.** *Lab finding:* **pancytopenia.** **H-S-C:** Presents **< 5 years** of age; classic triad of cystic bony **skull lesions, diabetes insipidus** (hypothalamic involvement), and **exophthalmos** (orbit involvement) **EG: Solitary bone lesion** (skull, mandible, spine); possible lung involvement
Treatment and Prognosis	**L-S:** Corticosteroids; chemotherapy; very aggressive and often fatal disease **H-S-C:** Combination chemotherapy; curettage of bone lesions **EG:** Lesions resolve spontaneously; good prognosis
Notes	

A 56-year-old man with a past medical history significant for multiple myeloma develops flank pain and oliguria. Upon further history, you learn that he has also developed progressive shortness of breath on exertion over the past month. He is admitted to the hospital and serum and urine studies are ordered upon admission, showing the presence of monoclonal immunoglobulins and free light chains. When a fat pad biopsy, in which the Congo red dye is employed, shows apple-green birefringence under polarized light, you begin to suspect that this patient's current condition is related to his multiple myeloma.

Amyloidosis

Etiology	**Primary:** Associated with plasma cell dyscrasias **Secondary:** Occurs as a complication to underlying chronic infections (ie, TB, osteomyelitis) or chronic inflammatory diseases (ie, RA, IBD)
Pathology and Pathophysiology	**Primary:** Deposition of monoclonal immunoglobulin light chains (**AL protein**), usually in **heart, GI tract,** muscle**,** nervous system, and **kidneys** **Secondary:** Deposition of **AA protein,** which is derived from apolipoprotein precursors; usually involves **kidneys, GI tract**, and skin *Histopathology:* **Apple-green birefringence** of amyloid protein on Congo red stain *Pathophysiology:* Impaired organ function caused by **infiltration of tissues with insoluble protein fibrils**
Clinical Manifestations	Symptoms are related to malfunction of organ involved (eg, nephrotic syndrome, renal failure, restrictive cardiomyopathy, arthritis, neuropathy, intestinal malabsorption, respiratory failure)
Treatment	**Primary:** Melphalan and prednisone **Secondary:** Aggressive treatment of predisposing disease
Notes	Other diseases with amyloid deposition include Alzheimer disease (amyloid β-protein), Portuguese type of polyneuropathy (transthyretin), nephropathic hereditary amyloidosis (AA protein), diabetes (islet amyloid polypeptide), senile amyloidosis (transthyretin), medullary carcinoma of the thyroid (amyloid formed from calcitonin precursors), and dialysis amyloidosis (β-microglobulin).


Chromosomal Disorders
Autosomal Disorders
Sex Chromosome Disorders
Down Syndrome
Edwards and Patau Syndromes
Prader-Willi and Angelman Syndrome
Turner Syndrome
Klinefelter Syndrome
Fragile X Syndrome

DISRUPTIONS IN CHROMOSOMAL STRUCTURE OR NUMBER

- *Aneuploidy:* Chromosome number that is not a multiple of 23
  → Caused by addition/loss of chromosomes during meiosis through **nondisjunction** (failure of chromosomes to separate during cell division) or **anaphase lag** (loss of chromosome during cell division)
- *Polyploidy:* Chromosome number that is 3 or 4 times the haploid number of 23
- *Deletion:* Loss of part of chromosome
- *Translocation:* Exchange of chromosome parts between nonhomologous chromosomes
  → *Balanced translocation:* No genetic material lost; clinically asymptomatic
  → *Robertsonian translocation:* Joining of long arms of two acrocentric chromosomes with loss of short arms
- *Inversion:* Reunion of separated portion of chromosome back into an inverted position

A newborn boy born to a 48-year-old woman is referred to your medical genetics clinic. He has a flat face, wide-set eyes, epicanthal folds, white spots on the periphery of his irises, and a single palmar crease across both of his hands. Upon reading his medical chart, you discover that he also suffers from an ostium primum ASD, a VSD, and duodenal atresia. You suspect that this patient's karyotype will be markedly abnormal.

Down Syndrome

Etiology

Trisomy 21 accounts for **95% of cases** (usually because of meiotic nondisjunction). The incidence of trisomy 21 **increases with maternal age** so that Down syndrome occurs in 1 in 25 births to mothers over the age of 45.

Robertsonian translocation accounts for **4% of cases.** The long arm of chr 21 is translocated to another chromosome (usually chr 14 or 22).

Mosaicism accounts for **1% of cases,** resulting from mitotic nondisjunction of chr 21 during embryogenesis

Characteristics

Severe mental retardation; duodenal and esophageal atresia; short hands with **simian crease** (single palmar crease); specific facial features—flat face, **epicanthal folds, wide-set eyes,** and Brushfield spots (white spots on periphery of iris)

Congenital heart defects: Endocardial cushion defects leading to ostium primum ASD, VSDs, and AV valve malformations

Complications

Patients with Down syndrome have an increased chance of developing acute leukemias, increased susceptibility to infections, and degenerative changes in the brain, similar to **Alzheimer disease,** which occur in middle age

Treatment and Prognosis

Surgical treatment for duodenal atresia and congenital heart defects

More than 80% of patients survive past age 30, but life expectancy is shortened

Notes

A baby girl is born to a 46-year-old woman. The baby has multiple abnormalities, including polydactyly, a cleft lip and palate, and microcephaly, causing you to suspect that the baby most probably also has congenital heart and renal defects. You decide to send a sample of the baby's blood for chromosomal analysis, but you inform the mother that you suspect that her baby's prognosis is not good.

Edwards Syndrome and Patau Syndrome

Etiology

Edwards syndrome: Most cases are caused by **trisomy 18** (usually owing to meiotic nondisjunction). Incidence **increases with maternal age.** A few cases are caused by **mosaicism,** resulting from mitotic nondisjunction of chr 18 during embryogenesis.

Patau syndrome: Most cases are caused by **trisomy 13** (usually owing to meiotic nondisjunction). Incidence **increases with maternal age.** A few cases are caused by **mosaicism,** resulting from mitotic nondisjunction of chr 13 during embryogenesis or **translocation** between chr 13 and 14.

Characteristics

Edwards syndrome: Severe mental retardation; rocker-bottom feet; specific facial features—prominent occiput, micrognathia (small jaw), low-set ears; **congenital heart and renal defects;** overlapping third and fourth fingers

Patau syndrome: Severe mental retardation; microcephaly and holoprosencephaly; **cleft lip and palate;** microphthalmia (small eyes); **polydactyly;** congenital heart and renal defects; umbilical hernia; rocker-bottom feet

Prognosis

Edwards and Patau syndromes: Fatal within 1 year of birth

Notes

A 5-year-old girl presents to the emergency department with seizures. The girl's parents tell you that the child is mentally retarded. They also mention that the child has an off-balance gait and laughs at inappropriate times. You treat the seizures and you refer the patient and her family to a medical genetics clinic, while suspecting that the same mutation on the paternally derived chromosome would have resulted in a completely different phenotype.

Prader-Willi and Angelman Syndromes

Etiology	Both diseases are caused by an identical **deletion on chr 15q** Demonstrates **imprinting,** which is the phenomenon in which the same mutation results in different phenotypes depending on whether the mutated chromosome was of maternal or paternal origin
Characteristics	**Prader-Willi syndrome:** Deletion is on **paternally derived** chromosome; **mental retardation; hypogonadism;** hypotonia; **obesity** often leading to diabetes **Angelman syndrome:** Deletion is on **maternally derived** chromosome; **"happy puppet"** with ataxic gait and inappropriate laughter; **mental retardation;** seizures
Treatment	Treatment of symptoms with lifelong supervision
Notes	**Cri-du-chat syndrome** is a genetic disorder that results from a deletion of the short arm of chr 5 **(5p-).** It is characterized by **mental retardation,** wide-set eyes (hypertelorism), cardiac defects, **microcephaly,** and a **cat-like high-pitched cry.**

A 28-year-old man presents to an infertility clinic with his wife. They have been trying to conceive unsuccessfully for the last 3 years. Upon physical examination, you find that he has small atrophic testes and gynecomastia. Laboratory results reveal decreased testosterone levels and increased pituitary gonadotropins. You begin to suspect that this couple may be unable to have children naturally and you refer the patient to a medical genetics clinic.

Klinefelter Syndrome

Etiology	Caused by two or more X chromosomes with one or more Y chromosome (most commonly **47, XXY** karyotype with a **single Barr body**). This genetic disorder is most commonly caused by **maternal meiotic nondisjunction** and incidence rises with maternal age, but can also be caused by mosaicism or paternal meiotic nondisjunction.
Characteristics	Small, **atrophic testes; tall stature;** lack of secondary male characteristics and **gynecomastia; male infertility,** often caused by reduced spermatogenesis; occasionally associated with mild mental retardation *Lab findings:* **Decreased testosterone** levels; **increased FSH and LH** levels
Treatment	Testosterone replacement after puberty (does not treat infertility)
Notes	**XYY syndrome** results in tall men with severe acne. There is an increased frequency of XYY syndrome among criminals.

A 15-year-old girl presents to your office complaining of amenorrhea. Physical examination reveals a short girl with hypertension in the upper extremities, decreased femoral pulses, a webbed neck, and poor breast development. Laboratory tests reveal decreased estrogen levels and increased FSH and LH levels. You begin to suspect that the patient may be at increased risk for developing diabetes mellitus, osteoporosis, and Hashimoto thyroiditis later in life because of an underlying chromosomal disorder.

Turner Syndrome

Etiology	Caused by partial or complete monosomy of the X chromosome (**XO karyotype** with **no Barr body**)
Characteristics	**Short stature** with a **broad chest** and widely spread nipples; cystic hygroma of neck leading to **webbed neck** appearance; lymphedema of extremities; **primary amenorrhea** with replacement of ovaries with fibrous strands (no ova or follicles); infantile genitalia and breasts; **coarctation of the aorta** and other congenital heart defects Patients are at an increased risk for developing DM, hypertension, Hashimoto thyroiditis, and osteoporosis *Lab findings:* **Decreased estrogen** production; **increased FSH and LH** levels
Treatment and Prognosis	Estrogen replacement; growth hormone (to treat short stature) Decreased life expectancy owing to cardiovascular abnormalities
Notes	

A 4-year-old boy is brought to your office by his parents, who report that their son appears to have developmental delays. As you observe the child, you note that he has a long face with large ears and a large jaw. Neuropsychological testing reveals that the child is mentally retarded. You wonder if the child may have a chromosomal abnormality and you refer the family to a medical genetics clinic.

Fragile X Syndrome

Etiology and Epidemiology	Caused by increased number of **CGG repeats** in the familial mental retardation ***(FMR-1)*** **gene** on the **X chromosome** Affects both males and females (1:2000), although females generally have less severe clinical manifestations
Characteristics	Severe **mental retardation** with autistic characteristics; long face with large jaw and ears; **macroorchidism** (large testicles); connective tissue defect manifesting with hyperextensible joints and mitral valve prolapse
Prognosis	Lifespan is not affected, but lifelong supervision is required
Notes	Fragile X syndrome, along with Huntington disease and myotonic dystrophy, demonstrates **anticipation,** a phenomenon in which the number of repeats increases with each generation and results in more severe disease manifestations.

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