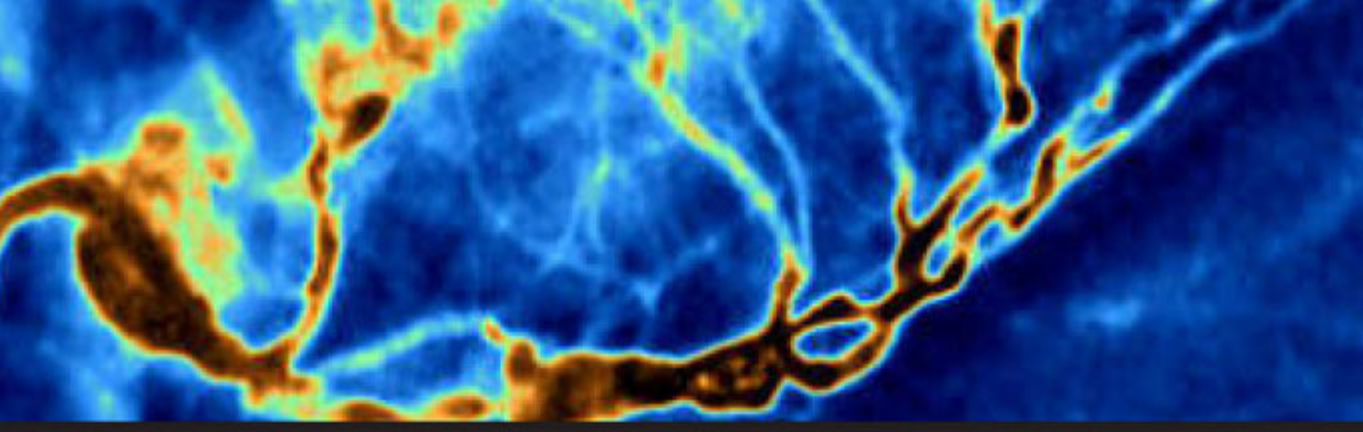
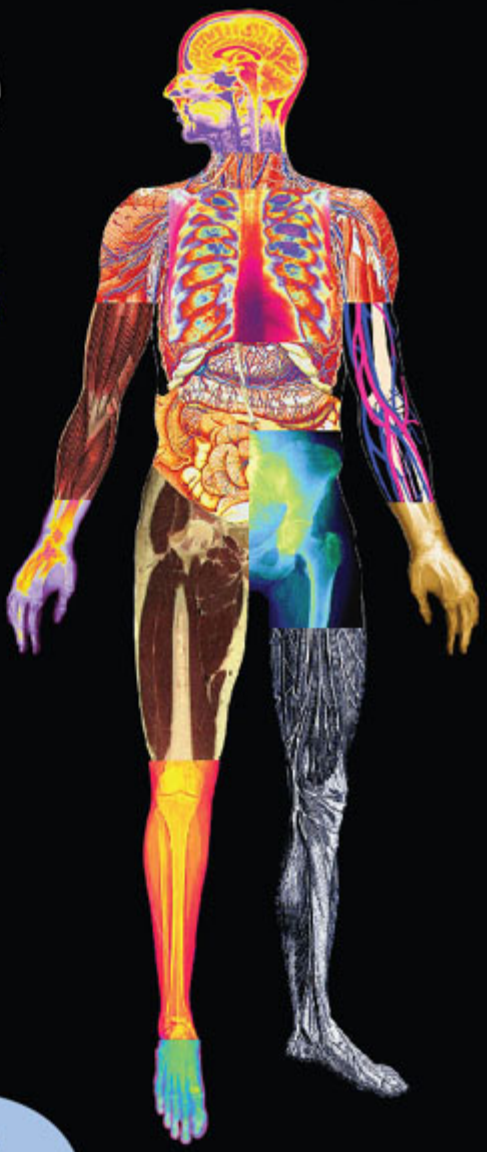


Pathophysiology of Disease Flashcards



120 Case-based cards with Q&A

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Pathophysiology of Disease Flashcards

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Preface

Pathophysiology of Disease: An Introduction to Clinical Medicine is the leading pathophysiology textbook, providing comprehensive coverage of the pathophysiologic basis of disease. These *Pathophysiology of Disease Flashcards* provide study aids for 120 of the most common topics germane to medical practice. The *Flashcards* provide key questions regarding the topics for a quick review and study aid for a variety of standardized examinations. As such, they will be very useful to medical, nursing, and pharmacy students. Each of the *Flashcards* begins with a clinical case and then presents key questions to help the reader think in a step-wise fashion through the various pathophysiologic aspects of the case.

Outstanding Features

- 120 common pathophysiology topics useful to learners in their preparation for a variety of course and certifying examinations
- Material drawn from the expert source, *Pathophysiology of Disease: An Introduction to Clinical Medicine*, now in its new 7th edition
- Concise, consistent, and readable format, organized in a way that allows for quick study
- Medical, nursing and pharmacy students, physician's assistants (PAs) and nurse practitioners (NPs) in training will find their clear organization and brevity useful

Organization

The 120 topics in the *Flashcards* were selected as core topics because of their relevance to both clinical practitioners and learners in order to enable understanding of the pathophysiologic basis of common diseases. There is one *Flashcard* for each topic. At the top of the front side, a **CASE** is presented. On the bottom of the front side and on the back side, 3 key ***Questions*** are listed in reference to the pathophysiology of the clinical entity illustrated by the case. To allow the user to think through their responses, the ***Answers*** to the 3 questions are printed upside down.

The questions asked on these *Flashcards* help develop the learner's knowledge of the pathophysiology associated with the disorder and thus support their clinical problem-solving skills regarding such cases. These *Flashcards* follow the

organization of *Pathophysiology of Disease: An Introduction to Clinical Medicine*, 7th edition which is organized by 23 disease categories:

- **GENETIC**
- **INFECTIONS**
- **BLOOD**
- **SKIN**
- **HEART DISEASE**
- **ADRENAL MEDULLA**
- **LIVER**
- **RENAL**
- **HYPOTHALAMUS & PITUITARY**
- **ADRENAL CORTEX**
- **FEMALE REPRODUCTIVE TRACT**
- **PARATHYROID, CALCIUM & PHOSPHORUS**
- **IMMUNE SYSTEM**
- **NEOPLASMS**
- **NERVOUS SYSTEM**
- **PULMONARY DISEASE**
- **VASCULAR DISEASE**
- **GASTROINTESTINAL TRACT**
- **EXOCRINE PANCREAS**
- **ENDOCRINE PANCREAS**
- **THYROID**
- **MALE REPRODUCTIVE TRACT**
- **INFLAMMATORY RHEUMATIC DISEASES**

Intended Audience

Medical students will find these *Flashcards* to be useful as they prepare for their Pathophysiology or Introduction to Clinical Medicine course examinations, and the USMLE Part 1 examination. Nursing and pharmacy students, NPs and PAs taking their internal medicine rotations can review core topics as they prepare for their standardized examinations.

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March 2014

1 Osteogenesis Imperfecta, A

A 4-week-old boy is brought in with pain and swelling of the right thigh. An x-ray film reveals an acute fracture of the right femur. Questioning of the mother reveals that the boy was born with two other known fractures—left humerus and right clavicle—which had been attributed to birth trauma. The family history is notable for bone problems in several family members. A diagnosis of type II osteogenesis imperfecta is entertained.

1. When and how does type II osteogenesis imperfecta present? To what do these individuals succumb?

- Of the four types of osteogenesis imperfecta, type II presents at or even before birth (diagnosed by prenatal ultrasound)
- There are multiple fractures, bony deformities, and increased fragility of nonbony connective tissue
- Death usually results during infancy due to respiratory difficulties

2. What are two typical radiologic findings in type II osteogenesis imperfecta?

- Presence of isolated "islands" of mineralization in the skull (wormian bones)
- Beaded appearance of the ribs

1 Osteogenesis Imperfecta, B

3. Explain how nonsense-mediated decay can help protect individuals affected by a genetic disease.

- Nonsense-mediated decay results when a mutation codes for a premature stop codon
- This results in partially synthesized mRNA precursors that carry the nonsense codon
- The cell recognizes these mRNA strands and degrades them before protein synthesis takes place
- This prevents the buildup of protein fragments that can accumulate and damage the cell

2 Phenylketonuria, A

A newborn girl tests positive for phenylketonuria (PKU) on a newborn screening examination. The results of a confirmatory serum test done at 2 weeks of age are also positive, establishing the diagnosis of PKU.

1. What are the primary defects in phenylketonuria?

- The primary defect in PKU is hyperphenylalaninemia
- Most people with PKU have a defect in phenylalanine hydroxylase, an essential enzyme in converting phenylalanine to tyrosine
- As a consequence, excessive phenylalanine and phenylalanine metabolites build up, leading to neurologic and other damage

2. Why is dietary modification a less than satisfactory treatment of this condition?

- Phenylalanine is an essential amino acid, meaning that some consumption of it is necessary for life
- However, in PKU, the levels of phenylalanine in the diet must be strictly limited to maintain a plasma concentration at or below 1 mmol/L
- This limitation must be maintained throughout the affected person's lifetime since even mild elevations during adulthood can lead to neuropsychological and cognitive defects

2 Phenylketonuria, B

3. Explain the phenomenon of maternal phenylketonuria.

- As an increasing number of treated females with PKU reach childbearing age and become pregnant, their developing fetuses are at risk of *in utero* exposure to phenylalanine
- The safe level of plasma phenylalanine for a developing fetus is 0.12–0.36 mmol/L, much lower than that for children or adults

- Newborn infants exposed to higher levels during pregnancy exhibit microcephaly, growth retardation, congenital heart disease, and growth retardation
- Strict control of maternal phenylalanine concentration before conception and during pregnancy can reduce the incidence of fetal abnormalities

3 Fragile X–Associated Mental Retardation, A

A young woman is referred for genetic counseling. She has a 3-year-old boy with developmental delay and small joint hyperextensibility. The pediatrician has diagnosed fragile X–associated mental retardation. She is currently pregnant with her second child at 14 weeks of gestation. The family history is unremarkable.

1. Explain why fragile X–associated mental retardation syndrome exhibits an unusual pattern of inheritance.

- The clinical syndrome is caused by an unusually large number of repeats of a triplet sequence (CGG) on the X chromosome between bands Xq27 and Xq28
- The number of repeats of this triplet sequence is highly variable and can become amplified (if there are >50–55 copies of the CGG triplet) during maternal transmission but not during paternal transmission
- Each subsequent maternal transmission can amplify the number of copies further
- Clinical disease occurs when there are >200 copies of the CGG triplet
- Thus, a transmitting male can pass on an X chromosome to a daughter who herself will not be affected with the disease since the CGG triplet will not have become amplified
- However, the daughter can pass on the X chromosome to her offspring who may be affected with disease since the number of CGG triplets can undergo amplification

3 Fragile X–Associated Mental Retardation, B

2. What is genetic anticipation? What are two explanations for it?

- Genetic anticipation refers to the phenomenon where penetrance or expressivity of a genetic disease seems to increase in each successive generation

- Fragile X–associated mental retardation and Huntington disease are two examples
- In both cases, a triple repeat nucleic acid sequence is amplified in each subsequent generation

3. What is an epigenetic change?

- Epigenetic change is an inheritable phenotypic change that is not determined by the DNA sequence
- Alterations to chromatin structure that include modification of DNA by methylation and modification of histones by methylation and/or acetylation are examples of epigenetic changes

4 Mitochondrial Disorders: Leber Hereditary Optic Neuropathy/Mitochondrial Encephalopathy with Ragged Red Fibers (LHON/MERRF), A

A 16-year-old boy presents with worsening vision for the past 2 months. He first noticed that he was having trouble with central vision in his right eye, seeing a dark spot in the center of his visual field. The dark spot had become larger over time, and he had also developed loss of central vision in his left eye. Two of his maternal uncles had loss of vision, but his mother and another maternal uncle and two maternal aunts had no visual difficulties. No one on his father's side was affected. Physical examination reveals microangiopathy and vascular tortuosity of the retina. Genetic testing confirms the diagnosis of Leber hereditary optic neuropathy (LHON).

1. What is the central defect in LHON?

- LHON arises from a mutation on mitochondrial DNA (mtDNA)
- mtDNA encodes the components of the electron transport chain involved in the generation of adenosine triphosphate (ATP)
- Mutations in the mtDNA impair the ability to generate ATP
- Tissues requiring intensive ATP use, such as skeletal muscle and the central nervous system, are especially affected

4 Mitochondrial Disorders: Leber Hereditary Optic Neuropathy/Mitochondrial Encephalopathy with Ragged Red Fibers (LHON/MERRF), B

2. How is this disorder inherited?

- LHON is inherited through mutations in mtDNA (as above)
- All of the mtDNA in our bodies comes exclusively from the egg
- As a consequence, LHON is inherited only from the mother

3. What is the principle of heteroplasmy?

- A typical cell carries 10–100 separate mtDNA molecules, only a fraction of which carry the mutation
- These mtDNA molecules can assort differently during meiosis
- Furthermore, within any given offspring, the level of mtDNA will vary from tissue to tissue and from cell to cell due to differential assortment during mitosis
- Thus, within any given egg in an affected woman, the level of mutant DNA may vary from 10% to 90%

5 Down Syndrome, A

A 40-year-old woman undergoes prenatal screening with amniocentesis during her 16th week of pregnancy. The results of the amniocentesis show trisomy 21 or Down syndrome. She has several questions about what she might expect.

1. What are the common features of the various different karyotypic abnormalities resulting in Down syndrome?

- Down syndrome may be caused by a variety of different karyotypic abnormalities that have in common a 50% increase in gene dosage of the genes on chromosome 21
- Most often, affected individuals have an extra chromosome 21, having three copies rather than the usual two
- This is due to nondisjunction of chromosome 21 during the anaphase of meiosis
- Occasionally, Down syndrome can be caused by the inheritance of an abnormal chromosome 21, which has additional translocated genetic material on it
- This abnormal chromosome is described as a robertsonian translocation

2. What are the major categories of abnormalities in Down syndrome, and what is their natural history?

- Congenital heart disease is the most significant abnormality associated with Down syndrome, and the major determinant of longevity in affected individuals

(continued on reverse side)

5 Down Syndrome, B

- Down syndrome is caused by an increased genetic load, leading to increased expression of specific genes
- Those individuals with Down syndrome due to robertsonian translocations can have less than a full double copy of chromosome 21
- This results in less of an increase in the gene dose, which can affect phenotype
- In addition, some individuals with translocations show mosaicism in which some cells are normal and some are abnormal
- This further can decrease the severity of phenotypic expression

3. Explain why trisomy 21 is associated with such a wide range of phenotypes from mild mental retardation to that of "typical" Down syndrome.

- There is also growth retardation
- There are characteristic changes in appearance such as brachycephaly, epicanthal folds, small ears, and transverse palmar creases
- The neurologic effects are developmental delay and premature onset of Alzheimer disease, with senile plaques present in almost all individuals by age 35 years
- There is also decreased immune function with an increased susceptibility to infections and leukemia

6 Allergic Rhinitis, A

A 40-year-old woman comes to the clinic with a history of worsening nasal congestion and recurrent sinus infections. She had been healthy until about 1 year ago when she first noticed persistent rhinorrhea, sneezing, and stuffiness. She noted that when she went on a 2-week vacation to Mexico, her rhinorrhea disappeared, only to return when she came home again. She has lived in the same house for the past 5 years along with her husband and one child. They have had a dog for 4 years and a cat for 1 year. On physical examination, she has boggy, swollen nasal turbinates and a cobblestone appearance of her posterior pharynx.

1. What are the major clinical manifestations of allergic rhinitis?

- Common symptoms are sneezing, nasal itching, clear rhinorrhea, and nasal congestion
- Common signs are pale, bluish nasal mucosa, serous otitis media, transverse nasal crease, and infraorbital cyanosis
- Sinusitis, hearing loss, and otitis media are possible complications of otitis media

6 Allergic Rhinitis, B

2. What are the major etiologic factors in allergic rhinitis?

- Allergic rhinitis is caused by a type I (IgE-mediated) immediate hypersensitivity to environmental allergens
- Nasal mucosa filters out particles larger than 5 μm
- These particles can be deposited on the nasal mucosa and generate an inflammatory response
- Common antigens include seasonal pollens, house dust mite antigen, cockroach antigen, mold, and animal (such as cat) dander

3. What are the pathogenic mechanisms in allergic rhinitis?

- Surface-bound IgE on nasal mucosa is bound by the inciting antigen
- Mast cells and basophils, which trigger the inflammation, become activated
- Mediators of the immediate inflammatory response such as histamine are released, triggering the early phase response of sneezing, nasal secretions, and nasal constriction
- The last phase of the immune response involves the influx of eosinophils and mononuclear cells, peaking at 6–12 hours after exposure
- The main symptoms of this response are erythema, itching, burning, and heat

7 Severe Combined Immunodeficiency Disease, A

A 2-month-old child is admitted to the ICU with fever, hypotension, tachycardia, and lethargy. The medical history is notable for a similar hospitalization at 2 weeks of age. Physical examination is notable for a temperature of 39°C, oral thrush, and rales in the right lung fields. Chest x-ray film reveals multilobar pneumonia. Given the history of recurrent severe infection, the pediatrician suspects an immunodeficiency disorder.

1. What are the major clinical manifestations of severe combined immunodeficiency disease (SCID)?

- SCID, like many other primary immunodeficiency disorders, presents early in the neonatal period
- In patients with SCID, there is an absence of normal thymic tissue, and the lymph nodes, spleen, and other peripheral lymphoid tissues are devoid of lymphocytes
- In these patients, the complete or near-complete lack of both the cellular and the humoral components of the immune system results in severe infections
- The spectrum of infections is broad because these patients may also suffer from overwhelming infection by opportunistic pathogens, disseminated viruses, and intracellular organisms
- Failure to thrive may be the initial presenting symptom, but mucocutaneous candidiasis, chronic diarrhea, and pneumonitis are common
- Vaccination with live viral vaccines or bacillus Calmette-Guérin (BCG) may lead to disseminated disease
- Without immune reconstitution by bone marrow transplantation, SCID is inevitably fatal within 1–2 years

7 Severe Combined Immunodeficiency Disease, B

2. What are the major pathogenetic mechanisms in SCID?

- SCID is a heterogeneous group of disorders characterized by a failure in the cellular maturation of lymphoid stem cells, resulting in reduced numbers and function of both B and T lymphocytes and hypogammaglobulinemia
- Defective cytokine signaling: X-linked SCID (XSCID) is the most prevalent form, resulting from a genetic mutation in the common γ chain of the trimeric (αβγ) IL-2 receptor, which is shared by the receptors for IL-4, IL-7, IL-9, and IL-15, leading to dysfunction of all of these cytokine receptors
  - These defects inhibit normal maturation of T lymphocytes and proliferation of T, B, and natural killer (NK) cells
- Defective T-cell receptor: The genetic defects for several other forms of the autosomal recessive SCID have also been identified, all involving T-cell signaling and maturation
- Defective gene recombination: Defective recombination-activating gene (*RAG1* and *RAG2*) products lead to a quantitative and functional deficiency of T and B lymphocytes
- Defective nucleotide salvage pathway: Approximately 20% of SCID cases are caused by a deficiency of adenosine deaminase (ADA), an enzyme in the purine salvage pathway, responsible for the metabolism of adenosine
  - Absence of the ADA enzyme results in an accumulation of toxic adenosine metabolites within the cells
  - These metabolites inhibit normal lymphocyte proliferation and lead to extreme cytopenia of both B and T lymphocytes
  - Similarly, purine nucleoside phosphorylase deficiency causes a buildup of toxic deoxyguanosine metabolites and inhibits T-cell development

8 X-Linked Agammaglobulinemia, A

An 18-month-old boy is brought to the emergency department by his parents with a high fever, shortness of breath, and cough. The boy was well until he was 6 months old. Since then, he has had four bouts of otitis media, and because of their severity and recurrence, he was placed for several months on prophylactic antibiotics. He was recently taken off the antibiotics to see how he would do. The day before presentation, he developed a cough that has quickly progressed into an illness with high fevers and lethargy. Both of his parents are healthy, and he has a healthy older sister. His father's family history is unremarkable, but his maternal uncle died of pneumonia in infancy. Examination is remarkable for a normally developed toddler who is lethargic and tachypneic. His temperature is 39°C, and he has decreased breath sounds at both lung bases. Chest x-ray film shows consolidation of the right and left lower lobes. He is admitted to the hospital, and the boy's blood cultures grow out *Streptococcus pneumoniae* the next day. Immunologic testing shows very low levels of IgG, IgM, and IgA antibodies in the serum, and flow cytometry shows the absence of circulating B lymphocytes.

1. What are the major clinical manifestations of X-linked agammaglobulinemia (XLA)?

- Presents within the first 2 years of life with recurrent sinopulmonary infections from mostly encapsulated bacteria such as *S pneumoniae*, other streptococci, and *Haemophilus influenzae* and, to a much lesser extent, viruses
- Fungal and opportunistic pathogens are rare
- Unique susceptibility to a rare but deadly enterovirus meningoencephalitis

8 X-Linked Agammaglobulinemia, B

2. What are the major pathogenetic mechanisms in XLA?

- Patients with XLA have pan-hypogammaglobulinemia, with decreased levels of IgG, IgM, and IgA
- They exhibit poor to absent responses to antigen challenge even though virtually all demonstrate normal functional T-lymphocyte responses to *in vitro* as well as *in vivo* tests (eg, delayed hypersensitivity skin reactions)
- The basic defect is arrested cellular maturation at the pre-B-lymphocyte stage
- Normal numbers of pre-B lymphocytes are in the bone marrow with absent circulating B lymphocytes
- Lymphoid tissues lack fully differentiated B lymphocytes (antibody-secreting plasma cells), and lymph nodes lack developed germinal centers
- The defective gene product, BTK (Bruton tyrosine kinase), is a B-cell–specific signaling protein belonging to the cytoplasmic tyrosine kinase family of intracellular proteins
- Gene deletions and point mutations in the catalytic domain of the *BTK* gene block normal BTK function, necessary for B-cell maturation

9 Common Variable Immunodeficiency, A

An 18-year-old man presents with complaints of fever, facial pain, and nasal congestion consistent with a diagnosis of acute sinusitis. His medical history is notable for multiple sinus infections, two episodes of pneumonia, and chronic diarrhea, all suggestive of a primary immunodeficiency syndrome. Workup establishes a diagnosis of common variable immunodeficiency.

1. What are the major clinical manifestations of common variable immunodeficiency?

- Common variable immunodeficiency is the most common serious primary immune deficiency disorder in adults
- Patients usually present within the first 2 decades of life with recurrent sinopulmonary infections, including sinusitis, otitis, bronchitis, and pneumonia
- Common pathogens are encapsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*
- Bronchiectasis can be the result of recurrent serious respiratory infections, leading to infection with more virulent pathogens, including *Staphylococcus aureus* and *Pseudomonas aeruginosa*, which in turn, can worsen the long-term prognosis
- Associated noninfectious disorders include gastrointestinal malabsorption, autoimmune disorders, and neoplasms (lymphoreticular, gastric, and skin)
- Autoimmune disorders occur in 20–30% of patients and may precede the recurrent infections
- Monthly infusions of intravenous immunoglobulin can reconstitute humoral immunity, decrease infections, and improve quality of life

9 Common Variable Immunodeficiency, B

2. What are the major pathogenetic mechanisms in common variable immunodeficiency?

- Common variable immunodeficiency is heterogeneous: marked reduction in antibody production is the primary disorder
  - The vast majority of patients demonstrate an *in vitro* defect in terminal differentiation of B cells
  - Antibody-secreting plasma cells are conspicuously sparse in lymphoid tissues
  - No single gene defect can be held accountable for the multitude of defects known to cause common variable immunodeficiency
  - In many patients, the defect is intrinsic to the B-lymphocyte population
    - Approximately 15% of patients with common variable immunodeficiency disease demonstrate defective B-cell surface expression of the transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), a member of the TNF receptor family, which keeps affected patients from responding to B-cell–activating factors
    - Decreased expression of the B-cell surface marker CD19, which normally complexes with CD21 and CD81 to facilitate cellular activation through B-cell receptors, leads to deficient humoral function
  - A variety of T-cell abnormalities may also lead to immune defects, with subsequent impairment of B-cell differentiation
    - Mutation of the inducible T-cell costimulator (ICOS) gene, expressed by activated T cells and responsible for B-cell activation/antibody production, is responsible in some cases
    - More than 50% of patients also have some T-lymphocyte dysfunction as determined by absent or diminished cutaneous responses to recall antigens

10 Acquired Immunodeficiency Syndrome (AIDS), A

A 31-year-old male injection drug user presents to the emergency department with shortness of breath. He describes a 1-month history of intermittent fevers and night sweats and a nonproductive cough. He has become progressively more short of breath, and now he feels dyspneic at rest. He appears to be in moderate respiratory distress. His vital signs show a temperature of 39°C, heart rate of 112 bpm, respiratory rate of 20/minute, and oxygen saturation of 88% on room air. Physical examination is otherwise unremarkable, including a normal lung exam. Chest x-ray film reveals a diffuse interstitial infiltrate characteristic of pneumocystis pneumonia, an opportunistic infection.

1. What are the major clinical manifestations of AIDS?

- Candidiasis of the esophagus, bronchi, trachea, or lungs
- Cryptococcosis, coccidioidomycosis, or histoplasmosis, extrapulmonary
- Cryptosporidiosis or isosporiasis, chronic intestinal (>1-month duration)
- Cytomegalovirus (CMV) disease (other than liver, spleen, or nodes), eg, retinitis
- HIV-related encephalopathy or progressive multifocal leukoencephalopathy
- Herpes simplex: chronic ulcers, or bronchitis, pneumonitis, or esophagitis
- Cancers: Kaposi sarcoma, invasive cervical cancer, lymphoma (Burkitt, immunoblastic, primary brain)
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, or extrapulmonary *Mycobacterium tuberculosis*, other extrapulmonary *Mycobacterium* infection
- *Pneumocystis jirovecii* pneumonia or toxoplasmosis of brain
- Recurrent pneumonia or *Salmonella* septicemia
- HIV-related wasting syndrome

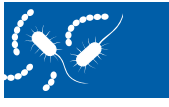
10 Acquired Immunodeficiency Syndrome (AIDS), B

2. What are the major steps in development of AIDS after infection with HIV?

- HIV reverse transcriptase converts uncoated viral RNA into double-stranded viral DNA, which integrates into the host chromosome
- Once integrated, the HIV provirus may remain latent or become transcriptionally active, depending on the activation state of the host cell
- Although only 2% of mononuclear cells are found peripherally, lymph nodes from HIV-infected individuals can contain large amounts of virus sequestered among infected follicular dendritic cells in the germinal centers
- For patients infected through vaginal or rectal mucosa, gut-associated lymphoid tissue is a major site of viral replication and persistence
- The persistence of virus in these secondary lymphoid structures triggers cellular activation and massive, irrevocable depletion of CD4 T-lymphocyte reservoirs, as well as disease latency due to several mechanisms:
  - Direct HIV-mediated infection and destruction of CD4 T lymphocytes during viral replication
  - Depletion by fusion and formation of multinucleated giant cells (syncytium formation)
  - Toxicity of viral proteins to CD4 T lymphocytes and hematopoietic precursors
  - Loss of T-lymphocyte costimulatory factors, such as CD28
  - Induction of apoptosis (programmed cell death) of uninfected T cells
- CD8 cytotoxic T-lymphocyte activity is initially brisk and effective at controlling viremia but later induces the generation of viral escape mutations
- Ultimately, viral proliferation outstrips host responses, and HIV-induced immunosuppression leads to disease progression

11 Infective Endocarditis, A

A 55-year-old man who recently emigrated from China presents to the emergency department with fever. He states that he has had recurring fevers over the past 3 weeks, associated with chills, night sweats, and malaise. Today, he developed new painful lesions on the pads of his fingers, prompting him to come to the emergency department. His medical history is remarkable for "being very sick as a child after a sore throat." He has recently had several teeth extracted for severe dental caries. He is taking no medications. On physical examination, he is febrile to 38.5°C, and his blood pressure is 120/80 mm Hg, heart rate 108 bpm, and respiratory rate 16/min, with an oxygen saturation of 97% on room air. Skin examination is remarkable for painful nodules on the pads of several fingers and toes. He has multiple splinter hemorrhages in the nailbeds and painless hemorrhagic macules on the palms of the hands. Ophthalmoscopic examination is remarkable for retinal hemorrhages. Chest examination is clear to auscultation and percussion. Cardiac examination is notable for a grade 3/6 holosystolic murmur heard loudest at the left lower sternal border, with radiation to the axilla. Abdominal and back examinations are unremarkable.



1. Which patients are at highest risk for infective endocarditis?

- The most common predisposing factor is the presence of structurally abnormal cardiac valves related to rheumatic heart disease, congenital heart disease, prosthetic valve, or prior endocarditis
- Injection drug use is also an important risk factor for endocarditis
- The patient's history of significant illness as a child after a sore throat suggests the possibility of rheumatic heart disease

11 Infective Endocarditis, B

2. What are the leading bacterial agents of infective endocarditis?

- The most common infectious agents causing native valve endocarditis are gram-positive bacteria, including viridans group streptococci, *Staphylococcus aureus*, and enterococci
- Given the history of recent dental work, the most likely pathogen in this patient would be viridans group streptococci, which are normal mouth flora that can become transiently bloodborne after dental manipulation
- Certain pathogens are more common in certain groups such as *S aureus* in injection drug users and *Listeria monocytogenes* in the elderly

3. What hemodynamic features predispose to infective endocarditis?

- The hemodynamic factors that predispose patients to the development of endocarditis include (1) a high-velocity jet stream causing turbulent flow, (2) flow from a high- to a low-pressure chamber, and (3) a comparatively narrow orifice separating two chambers that creates a pressure gradient
- The lesions of endocarditis tend to form on the surface of the valve in the lower pressure cardiac chamber. The predisposed, damaged endothelium of an abnormal valve—or jet stream–damaged endothelium—promotes the deposition of fibrin and platelets, forming sterile vegetations
- When bacteremia occurs, such as after dental work, microorganisms can be deposited on these sterile vegetations

12 Meningitis, A

A 25-year-old man presents to the emergency department with fever and in a confused, irrational state. He is accompanied by his wife, who provides the history. She states that he had been well until approximately 1 week ago, when he developed symptoms of upper respiratory tract infection that were slow to improve. On the morning of admission, he complained of progressive severe headache and nausea. He vomited once. He became progressively lethargic as the day progressed, and she brought him to the hospital. He has no other medical problems and takes no medications.

On examination, he is febrile to 39°C, with a blood pressure of 95/60 mm Hg, heart rate of 100 bpm, and respiratory rate of 18/min. He is lethargic and confused, lying with his hand over his eyes. Funduscopic examination shows no papilledema. The neck is stiff, with a positive Brudzinski sign. Heart, lung, and abdominal examinations are unremarkable. Neurologic examination is limited by the patient's inability to cooperate but appears to be nonfocal. Kernig sign (resistance to passive extension of the flexed leg with the patient lying supine) is negative.

1. What is the typical presentation of bacterial meningitis?

- Symptoms commonly associated with both bacterial and viral meningitis include acute onset of fever, headache, neck stiffness (meningismus), photophobia, and confusion

2. What are the major etiologic agents of meningitis, and how do they vary with age or other characteristics of the host?

(continued on reverse side)

12 Meningitis, B

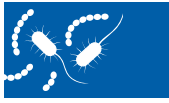
- In adults, the most likely bacterial pathogens are *Neisseria meningitidis* and *Streptococcus pneumoniae*
- In newborns younger than 3 months, the most common pathogens are those to which the infant is exposed in the maternal genitourinary canal, including *Escherichia coli* and other gram-negative bacilli, group B and other streptococci, and *Listeria monocytogenes*
- Between the ages of 3 months and 15 years, *N meningitidis* and *S pneumoniae* are the most common pathogens. *Haemophilus influenzae*, previously the most common cause of meningitis in this age group, is now primarily a concern in the unimmunized child

3. What is the sequence of events in development of bacterial meningitis?

- Most cases of bacterial meningitis begin with colonization of the host's nasopharynx
- This is followed by local invasion of the mucosal epithelium and subsequent bacteremia
- Cerebral endothelial cell injury follows and results in increased blood-brain barrier permeability, facilitating meningeal invasion
- The resultant inflammatory response in the subarachnoid space causes cerebral edema, vasculitis, and infarction, ultimately leading to decreased cerebrospinal fluid flow, hydrocephalus, worsening cerebral edema, increased intracranial pressure, and decreased cerebral blood flow

13 Pneumonia, A

A 68-year-old man presents to the hospital emergency department with acute fever and cough. He has had cough productive of green sputum for 3 days, with shortness of breath, left-sided pleuritic chest pain, fever, chills, and night sweats. His medical history is notable for chronic obstructive pulmonary disease. His medications include albuterol, ipratropium bromide, and corticosteroid inhalers. The patient lives at home and is active. On examination, he is febrile to 38°C, with a blood pressure of 110/50 mm Hg, heart rate of 98 bpm, and respiratory rate of 20/min. Oxygen saturation is 92% on room air. He is a thin man in moderate respiratory distress. Examination is notable for rales in the left lung base and left axilla and diffuse expiratory wheezes. Chest x-ray film reveals left lower lobe and lingular infiltrates. A diagnosis of pneumonia is made, and the patient is admitted to the hospital for administration of intravenous antibiotics.



1. What are the important pathogens for patients with community-acquired pneumonia based on severity of illness and site of care?

- The most likely pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*
- Other potential pathogens include *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Legionella pneumophila*, and respiratory viruses
- Tuberculosis, anaerobes, and fungi should also be considered, although these are less likely in this patient with such an acute presentation
- *Staphylococcus aureus* and *Pseudomonas aeruginosa* should be added to the differential diagnosis, particularly if the patient had been recently hospitalized and the patient were ill enough to require ICU admission

13 Pneumonia, B

2. What host features influence the likelihood of particular causes of pneumonia?

- An immunocompromised state, resulting in immune dysfunction and increased risk of infection
- Chronic lung disease, resulting in decreased mucociliary clearance
- Alcoholism or other reduction of the level of consciousness, which increases the risk of aspiration
- Injection drug abuse, which increases the risk of hematogenous spread of pathogens
- Environmental or animal exposure, resulting in inhalation of specific pathogens
- Residence in an institution, with its associated risk of microaspirations, and exposure via instrumentation (catheters and intubation)
- Recent influenza infection, leading to disruption of respiratory epithelium, ciliary dysfunction, and inhibition of polymorphonuclear neutrophils (PMNs)

3. What are the four mechanisms by which pathogens reach the lungs?

- Inhalation of infectious droplets into the lower airways
- Aspiration of oropharyngeal contents
- Spread along the mucosal membrane surface
- Hematogenous spread

14 Diarrhea, Infectious, A

A 21-year-old woman presents with the complaint of diarrhea. She returned from Mexico the day before her visit. The day before that, she had an acute onset of profuse watery diarrhea. She denies blood or mucus in the stools. She has had no associated fever, chills, nausea, or vomiting. She has no other medical problems and is taking no medications. Examination is remarkable for diffuse, mild abdominal tenderness to palpation without guarding or rebound tenderness. Stool is guaiac negative. Infectious diarrhea is suspected.

1. How many individuals in the world die yearly of infectious diarrhea?

- Each year throughout the world, more than 5 million people—most of them children younger than 1 year—die of acute infectious diarrhea

2. What are different modes of spread of infectious diarrhea? Give an example of each.

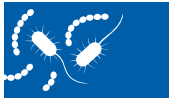
- Pathogens such as *Vibrio cholerae* are water-borne and transmitted via a contaminated water supply
- Several pathogens, including *Staphylococcus aureus* and *Bacillus cereus*, are transmitted by contaminated food
- Some pathogens, such as *Shigella* and *Rotavirus*, are transmitted by person-to-person spread and are, therefore, commonly seen in institutional settings such as child care centers

14 Diarrhea, Infectious, B

3. What are the different mechanisms by which infectious organisms cause diarrhea?

- **Secretory** (watery) **diarrhea** is caused by a number of bacteria (eg, *V cholerae*, enterotoxigenic *Escherichia coli* [ETEC], enteroaggregative *E coli* [EAEC]), viruses (rotavirus, norovirus), and protozoa (*Giardia*, *Cryptosporidium*)
- These organisms attach superficially to enterocytes in the lumen of the small bowel where some, such as cholera and ETEC, elaborate **enterotoxins**, proteins that increase intestinal cyclic adenosine monophosphate (cAMP) production, leading to net fluid loss
- **Inflammatory diarrhea** is a result of bacterial invasion of the mucosal lumen, with resultant cell death
- Pathogens associated with inflammatory diarrhea include enteroinvasive *E coli* (EIEC), *Shigella*, *Salmonella*, *Campylobacter*, and *Entamoeba histolytica*. *Shigella*, the prototypical cause of bacillary dysentery, invades the enterocyte through formation of an endoplasmic vacuole, which is lysed intracellularly
- Bacteria then proliferate in the cytoplasm and invade adjacent epithelial cells. Production of a **cytotoxin**, such as the Shiga toxin, leads to local cell destruction and death
- **Hemorrhagic diarrhea**, a variant of inflammatory diarrhea, is primarily caused by enterohemorrhagic *E coli* (EHEC), *E coli* O157:H7
- EHEC does not invade enterocytes; however, it does produce two Shiga-like toxins (Stx1 and Stx2) that resemble the Shiga toxin in structure and function
- After binding of EHEC to the cell surface receptor, the A subunit of the Shiga toxin catalyzes the destructive cleavage of ribosomal RNA and halts protein synthesis, leading to cell death

15 Sepsis, Sepsis Syndrome, Septic Shock, A



A 65-year-old woman is admitted to the hospital with community-acquired pneumonia. She is treated with intravenous antibiotics and is given oxygen by nasal cannula. A Foley catheter is placed in her bladder. On the third hospital day, she is switched to oral antibiotics in anticipation of discharge. On the evening of hospital day 3, she develops fever and tachycardia. Blood and urine cultures are ordered. The following morning, she is lethargic and difficult to arouse. Her temperature is 35°C, blood pressure 85/40 mm Hg, heart rate 110 bpm, and respiratory rate 20/min. Oxygen saturation is 94% on room air. Head and neck examinations are unremarkable. Lung examination is unchanged from admission, with rales in the left base. Cardiac examination is notable for a rapid but regular rhythm, without murmurs, gallops, or rubs. Abdominal examination is normal. Extremities are warm. Neurologic examination is nonfocal. The patient is transferred to the ICU for management of presumed sepsis and given intravenous fluids and antibiotics. Blood and urine cultures are positive for gram-negative rods.

1. What factors contribute to hospital-related sepsis?

- Factors that contribute to hospital-related sepsis are:
  - Invasive monitoring devices
  - Indwelling catheters
  - Extensive surgical procedures
  - Increased numbers of immunocompromised patients

15 Sepsis, Sepsis Syndrome, Septic Shock, B

2. Which organisms are most commonly associated with sepsis?

- Gram-negative bacteria, *Enterobacteriaceae* such as *Escherichia coli* and *Pseudomonas aeruginosa*, are common causes of sepsis
- Staphylococci are now the most common bacteria cultured from the bloodstream, presumably because of an increase in the prevalence of chronic indwelling venous access devices and implanted prosthetic material
- For similar reasons, the incidence of fungal sepsis due to *Candida* species has risen dramatically in the last decade
- Sepsis associated with *P aeruginosa*, *Candida*, or mixed (polymicrobial) organisms is an independent predictor of mortality

3. What is the role of the host immune system in the pathogenesis of sepsis?

- Specific stimuli such as organism, inoculum, and site of infection stimulate **CD4 T cells** to secrete cytokines with either inflammatory (type 1 helper T-cell) or anti-inflammatory (type 2 helper T-cell) properties
- Among patients who die of sepsis, there is significant loss of cells essential for the adaptive immune response (B lymphocytes, CD4 T cells, dendritic cells)
- Genetically programmed cell death, termed **apoptosis**, is thought to play a key role in the decrease in these cell lines and downregulates the surviving immune cells

16 Carcinoid Syndrome from Neuroendocrine Tumor (NET), A

A 54-year-old man presents with several weeks of facial flushing and diarrhea. His symptoms began intermittently but are becoming more constant. A 24-hour urine collection reveals an elevated level of 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin. An abdominal CT scan shows a 2-cm mesenteric mass in the ileum and likely metastatic tumors in the liver.

1. What products produced by NETs reflect their embryonic origin?

- Neuroendocrine tumors arise from neuroendocrine cells, specifically the enterochromaffin cells, which migrate during embryogenesis to the submucosal layer of the intestines and the pulmonary bronchi
- Carcinoid tumors are most commonly found in the intestines and lungs
- Since carcinoid tumors are derived from neuroendocrine tissue, they can secrete many peptides that have systemic effects
- This secretion is due to the inappropriate activation of latent synthetic ability that all neuroendocrine cells possess
- Production of serotonin (metabolized to 5-hydroxyindoleacetic acid [5-HIAA]) is characteristic of gut carcinoid tumors
- Bronchial carcinoids rarely produce 5-HIAA but instead often produce ectopic adrenocorticotropic hormone (ACTH), resulting in Cushing syndrome
- Many other peptides can be produced, including: calcitonin, gastrin, glicentin, glucagon, growth hormone, insulin, melanocyte-stimulating hormone (MSH), motilin, neuropeptide K, neurotensin, somatostatin, pancreatic polypeptide, substance K, substance, P, and vasoactive intestinal peptide

16 Carcinoid Syndrome from Neuroendocrine Tumor (NET), B

2. What are some short-term symptoms precipitated by release of excessive amounts of these products?

- Since many of these peptides are vasoactive, they can cause intermittent flushing as a result of vasodilation
- Other symptoms often observed include secretory diarrhea, wheezing, and excessive salivation or lacrimation

3. What are some long-term complications resulting from release of excessive amounts of these products?

- Long-term tissue damage from exposure to these substances and their metabolites includes:
  - Fibrosis of the pulmonary and tricuspid heart valves
  - Mesenteric fibrosis
  - Hyperkeratosis of the skin

17 Colon Carcinoma, A

A 54-year-old man presents to the clinic for a routine checkup. He is well, with no physical complaints. The history is remarkable only for a father with colon cancer at age 55 years. Physical examination is normal. Cancer screening is discussed, and the patient is sent home with fecal occult blood testing supplies and is scheduled for a colonoscopy. The fecal occult blood test results are positive. The colonoscopy reveals a villous adenoma as well as a 2-cm carcinoma.

1. What are the two principal lines of evidence in favor of the model of stepwise genetic alterations in colon cancer?

- It is believed that stepwise genetic alterations, including both oncogene activation and tumor suppressor gene inactivation, result in phenotypic changes that progress from adenoma to neoplasia
- The first line of evidence that supports the model of stepwise genetic alterations in colon cancer is the familial colon cancer syndromes that result from germline mutations, implicating a genomic cause
  - Familial adenomatous polyposis is the result of a mutation in the *APC* gene, whereas hereditary nonpolyposis colorectal carcinoma is associated with mutations in the DNA repair genes, *hMSH2* and *hMLH1*
- The second line of evidence comes from studies of carcinogenic substances derived from bacterial colonic flora, foods, or endogenous metabolites that are known to be mutagenic
  - Epidemiologic studies suggest that a diet low in these substances might reduce the risk of colon cancer

17 Colon Carcinoma, B

2. What is an explanation for the frequent appearance of occult blood in stools of patients with even early colon carcinoma?

- Early in the progression of dysplasia, disrupted architecture results in the formation of fragile new blood vessels and destruction of existing blood vessels
- These changes often occur before invasion of the basement membrane and, therefore, before progression to true cancer formation
- These friable vessels can cause microscopic bleeding
- This microscopic bleeding can be detected by fecal occult blood testing, an important tool in the early diagnosis of precancerous and cancerous colonic lesions

3. What are two genes whose products contribute to the classic phenotype of colon carcinomas?

- Familial adenomatous polyposis is the result of a mutation in the ***APC*** gene, which encodes a cell adhesion protein that has also been implicated in the control of β-catenin, a potent transcriptional activator
- Similarly, hereditary nonpolyposis colorectal cancer is associated with germline mutations in DNA repair genes such as ***hMSH2*** and ***hMLH1***
- Mutations in these genes can also occur in sporadic cancers

18 Breast Cancer, A

A 40-year-old woman presents for the evaluation of a left-sided breast lump. She has a strongly positive family history, with both her mother and one older sister having had breast cancer. Physical examination is notable for a 2-cm lump in the left breast. A biopsy shows invasive ductal carcinoma. The tumor is positive for estrogen receptor expression and *HER2* gene amplification.

1. What are some factors associated with increased risk of breast cancer?

- Linkage analysis has identified genetic markers that are known to confer a high risk of developing breast cancer
- In particular, two genes, *BRCA1* and *BRCA2*, have been implicated. Both are involved in repair of DNA
- Inherited mutations of *BRCA1* or *BRCA2* are associated with a lifetime risk of developing breast cancer of up to 80%
- Mutations in these genes are also associated with a high incidence of ovarian cancer in women and increased incidences of prostate cancer, melanoma, and breast cancer in men

18 Breast Cancer, B

2. What are the two main subtypes of breast cancer?

- **Ductal carcinomas** arise from the collecting ducts in the breast glandular tissue
- **Lobular carcinomas** arise from the terminal lobules of the glands

3. How often, how rapidly, where, and why do breast cancers tend to metastasize?

- Some breast cancers metastasize with high frequency, whereas others rarely do so
- Some breast cancers metastasize rapidly, whereas others do so only after a long latent period
- Some breast cancers preferentially metastasize to bone, whereas others metastasize to the liver or the lung and yet others to the brain
- Breast cancer is likely a compilation of many different disease subsets
- Specific molecular features must underlie its diverse phenotypes
- At least four overall molecular subtypes of breast cancer are now widely recognized, consisting of (1) the basal subtype, (2) the *HER2* overexpressing subtype, (3) the luminal A subtype, and (4) the luminal B subtype

19 Testicular Carcinoma, A

A 25-year-old man presents with a complaint of testicular enlargement. Examination reveals a hard nodule on the left testicle, 2 cm in diameter. Orchiectomy is diagnostic of testicular cancer.

1. From what cellular elements of the testes does testicular cancer generally arise?

- Testicular cancer arises from germinal elements within the testes
- Germ cells give rise to spermatozoa and thus can theoretically retain the ability to differentiate into any cell type
- The pluripotent nature of these cells is witnessed in the production of mature teratomas
  - These benign tumors often contain mature elements of all three germ cell layers, including hair and teeth, in lesions termed dermoid cysts
  - Malignant testicular cancers may coexist with benign mature teratomas

2. What are some characteristic markers that may be monitored in testicular tumor progression?

- One can measure the serum concentrations of proteins expressed during embryonic or trophoblastic development to monitor tumor progression and response to therapy, eg, alpha-fetoprotein and human chorionic gonadotropin

19 Testicular Carcinoma, B

3. How and where do testicular cancers metastasize?

- Malignant testicular carcinoma follows a lymphatic and hematogenous pattern of spread to regional retroperitoneal lymph nodes and distant organs such as liver, lung, bone, and brain

20 Osteosarcoma, A

A 16-year-old previously healthy teenager presents with a 2-month history of pain and swelling of his knee. He thought it began after a soccer game, but it just has not gotten better. Physical examination shows marked swelling of the knee and the distal thigh. Radiographs show a 3-cm partially calcified mass in the distal femur, just above the knee joint. A biopsy reveals an osteosarcoma.

1. What kinds of sarcomas are more common in children?

- Several of the less differentiated sarcomas that contain more embryonic cells are more common in children, because these precursor cells are more actively involved in growth and development during childhood
- These sarcomas include rhabdomyosarcomas and osteosarcomas

2. Compared with epithelial malignancies, are sarcomas more or less likely to directly invade adjacent tissues?

- There is less of a propensity for direct tissue invasion by sarcomas than by epithelial malignancies
- However, even if it does not invade, tissue destruction can result when a sarcoma compresses adjacent tissue, leading to the formation of a pseudocapsule

20 Osteosarcoma, B

3. To what sites do sarcomas commonly metastasize?

- Sarcomas most frequently metastasize to regional lymph nodes and to more distant organs, especially the lungs

4. What is the most common genetic lesion in sarcomas?

- Although various genetic abnormalities have been detected in sarcomas, mutations in the *p53* tumor suppressor gene are the most commonly detected lesion
- Such mutations are also found in epithelial neoplasms

5. What are the characteristics of type 1 neurofibromatosis, and what is a likely molecular basis for the development of sarcomas in this syndrome?

- Type 1 neurofibromatosis is an inherited syndrome characterized by café-au-lait hyperpigmented skin spots and multiple benign neurofibromas (benign tumors of Schwann cells) under the skin and throughout the body
- These can degenerate into malignant **neurofibrosarcomas** (**malignant schwannomas**)
- A germline mutation of the ***NF1* tumor suppressor gene** has been identified in patients with type 1 neurofibromatosis

21 Lymphoma, A

A 28-year-old woman presents to her primary care physician with complaints of fatigue, intermittent fevers, and 5 pounds of weight loss over a 6-week period. Her medical history is remarkable for a renal transplantation at age 15 years performed for end-stage renal disease as a result of poststreptococcal glomerulonephritis. Physical examination reveals two enlarged, matted, nontender lymph nodes in the left anterior cervical chain; a firm, nontender 1.5-cm lymph node in the right groin; and an enlarged liver. Biopsy of the lymph nodes in the cervical region reveals follicular, cleaved-cell lymphoma.

1. What are the hallmarks of hematologic malignancies?

- Hematologic neoplasms are malignancies of cells derived from hematopoietic precursors
- Distinct hematologic neoplasms can arise from each of the mature cell types
- Many of these arise in the bone marrow, circulate in the bloodstream, and can infiltrate certain organs and tissues
- Lymphomas, which arise from lymphoblasts, may form tumors in lymphoid tissue

2. What are some characteristics of low-grade lymphomas?

- Low-grade lymphomas, such as follicular lymphoma, retain the morphology and patterns of gene expression of mature lymphocytes, including cell surface markers such as immunoglobulin in the case of B lymphocytes
- Their clinical course is generally more favorable, being characterized by a slow growth rate
- Paradoxically, however, these lymphomas tend to present at a more advanced stage

21 Lymphoma, B

3. What are some characteristics of high-grade lymphomas?

- High-grade lymphomas such as mantle cell lymphoma, diffuse large-cell lymphoma, and Burkitt lymphoma are more aggressive
- Mantle cell lymphomas are significantly more resistant to treatment with combination chemotherapy than follicular lymphomas and often present with adenopathy and hepatosplenomegaly
- Diffuse large-cell lymphoma is the most prevalent subtype of non-Hodgkin lymphoma; one-third present with involvement of extranodal sites, particularly the head and neck, stomach, skin, bone, testis, and nervous system
- Virtually all cases of Burkitt lymphoma are associated with alterations of chromosome 8q24, resulting in overexpression of *c-myc*, an oncogene that encodes a transcriptional regulator of cell proliferation, differentiation, and apoptosis
- Most cases of Burkitt lymphoma that occur in Africa (endemic form) are associated with Epstein-Barr virus (EBV), whereas Burkitt lymphoma occurring in temperate zones is associated with EBV in only 30% of cases

22 Leukemia, A

A 22-year-old woman presents with a 2-week history of fatigue, bleeding from her gums, and very heavy menstrual bleeding. Physical examination reveals a pale woman with an enlarged spleen and petechiae on her legs. A complete blood cell count shows a markedly elevated white cell count (WBC 178,000) with severe anemia (hemoglobin 7.8) and thrombocytopenia (platelet count 25,000). Blast cells (abnormally immature leukemic cells) comprise 30% of the total white cell count. A bone marrow biopsy is positive for AML of the M1 type.

1. How are leukemias classified in general, and more specifically how are AMLs classified?

- Like all neoplasms, leukemias are classified by their cell of origin
- The first branch point is whether the malignant cell is of myeloid or lymphoid lineage, resulting in either a myeloid or lymphocytic leukemia
- All types can be acute, presenting with more than 20% blasts on bone marrow biopsy, or chronic
- Lymphocytic leukemias are further divided into T-cell or B-cell leukemias, depending on the type of lymphoid cell of origin
- This type can be distinguished by the cluster of differentiation (CD) antigens found on the surface of the tumor cells
- Myeloid leukemias are also divided into subtypes depending on the type of myeloid cell from which the leukemia arises
- AML types M1–M3 arise from myeloblasts, M4 and M5 from monocytes, M6 from normoblasts, M7 from megakaryoblasts

22 Leukemia, B

2. What accounts for the patient's symptoms and physical findings? What other major symptoms or signs may be present?

- Acute leukemias usually have pancytopenia, a decrease in the counts of all of the normal blood cells, including the normal white cells (the leukemic cells accounting for almost all of the high total WBCs), red blood cells, and platelets
- The fatigue and pallor are due to the anemia and the resulting reduced oxygen-carrying capacity
- The petechiae and bleeding are from the low platelets and reduced clotting ability
- Patients with leukemia are susceptible to serious infections due to the lack of normal WBCs
- Also, the markedly elevated numbers of leukemic cells can clog small blood vessels and result in strokes, retinal vein occlusion, and pulmonary infarction

3. What types of genetic abnormalities are responsible for the development of leukemias? How can this knowledge be used to treat some leukemias?

- Chromosomal deletions, duplications, and translocations have been identified in leukemias
- One such genetic abnormality is the so-called Philadelphia chromosome, a balanced translocation of chromosomes 9 and 22, that is commonly found in chronic myelogenous leukemia (CML)
- This translocation results in a fusion gene, *bcr-abl*, which is blocked by the therapeutic agent, imatinib mesylate, inducing remissions in patients with CML

23 Iron Deficiency Anemia, A

A 65-year-old previously well man presents to the clinic with complaints of fatigue of 3-months' duration. Questioning reveals diffuse weakness and feeling "winded" when walking uphill or climbing more than one flight of stairs. All of the symptoms have slowly worsened over time. There are no other complaints, and the review of systems is otherwise negative. The patient has no significant medical history, social history, or family history. On physical examination, he appears somewhat pale, with normal vital signs. The physical examination is unremarkable except for his rectal examination, which reveals brown, guaiac-positive stool (suggests the presence of blood in the stool). A complete blood cell (CBC) count reveals anemia, and 3/3 fecal occult blood test cards return positive.

1. What is the most common form of anemia? What is its most likely cause in premenopausal women? In men? In postmenopausal women?

- Iron deficiency anemia is the most common form of anemia
- In developed nations, it is primarily the result of iron loss, almost always through blood loss
- In premenopausal women, menstrual blood loss is the major cause of iron deficiency
- In men and in postmenopausal women, blood loss most commonly occurs in the gastrointestinal (GI) tract, as in this case

23 Iron Deficiency Anemia, B

2. Why is the serum ferritin level often not a good indicator of whether anemia is due to iron deficiency?

- The most commonly ordered test is serum ferritin, which, if low, is diagnostic of iron deficiency
- Results may be misleading, however, in acute or chronic inflammation and in severe illness
- Because ferritin is an acute-phase reactant, it can rise in these conditions, resulting in a normal ferritin level in someone with iron deficiency

3. What are the physiologic adaptations to slowly developing iron deficiency anemia?

- Superficial skin blood vessels may constrict, diverting blood to more vital structures
- Tachycardia may develop, which increases cardiac output and oxygen delivery to the tissues
- Elevation of **2,3-biphosphoglycerate** (2,3-BPG) concentrations in erythrocytes increases their ability to unload oxygen more efficiently in the body's tissues

24 Vitamin B_{12} Deficiency/Pernicious Anemia, A

A 58-year-old black woman presents to the emergency department with complaints of progressive fatigue and weakness for the past 6 months. She is short of breath after walking several blocks. On review of systems, she mentions mild diarrhea. She has noted intermittent numbness and tingling of her lower extremities and a loss of balance while walking. She denies other neurologic or cardiac symptoms and has no history of black or bloody stools or other blood loss. On physical examination, she is tachycardic to 110 bpm; other vital signs are within normal limits. Head and neck examination reveals pale conjunctivas and a beefy red tongue with loss of papillae. Cardiac examination shows a rapid regular rhythm with a grade 2/6 systolic murmur at the left sternal border. Lung, abdominal, and rectal examination findings are normal. Neurologic examination reveals decreased sensation to light touch and vibration in the lower extremities. The hematology consultant is asked to see this patient because of a low hematocrit level.

1. Name two crucial cofactors in DNA synthesis whose deficiency results in pernicious anemia. In what specific biochemical pathways do they participate?

- In DNA synthesis, cobalamin (vitamin B_{12}), along with folic acid, is crucial as a cofactor in the synthesis of deoxythymidine from deoxyuridine
- Cobalamin accepts a methyl group from methyltetrahydrofolate, which leads to the formation of two important intracellular compounds, **methylcobalamin**, which is required for the production of the amino acid methionine from homocysteine and **reduced tetrahydrofolate**, which is required as the single-carbon donor in purine and hence DNA synthesis

24 Vitamin B_{12} Deficiency/Pernicious Anemia, B

2. Why are neurologic defects observed in prolonged vitamin B_{12} deficiency?

- The neurologic manifestations, paresthesias and impaired proprioception, are caused by demyelination of the peripheral nerves and posterolateral spinal columns, respectively
- The lack of methionine caused by vitamin B_{12} deficiency appears to be at least partly responsible for this demyelination, but the exact mechanism is unknown
- Demyelination eventually results in neuronal cell death and may not be improved by treatment of the vitamin B_{12} deficiency

3. Why are symptoms of pernicious anemia usually relatively mild?

- Symptoms may be mild because the anemia develops slowly as a result of the extensive liver storage of vitamin B_{12}
- Patients with anemia usually adapt over time to slow changes in oxygen-carrying capacity
- Increases in 2,3-BPG that encourage oxygen delivery to the tissues from the hemoglobin in red cells occur to mitigate the reduced oxygen-carrying capacity from the anemia (decreased red cell number)

25 Cyclic Neutropenia, A

A 6-year-old boy presents to the pediatric emergency department. His mother states that he has had 3 days of general malaise and fevers to 38.5°C. He has no other localizing symptoms. Medical history is remarkable for multiple febrile illnesses. His mother says, "It seems like he gets sick every month." Physical examination is notable for cervical lymphadenopathy and oral ulcers. Blood tests reveal a neutrophil count of 200/μL. The patient is admitted to the hospital. Blood, urine, and cerebrospinal fluid cultures are negative, and over 48 hours, his neutrophil counts return to normal. He is then discharged.

1. How long does it take for a neutrophil to develop from a stem cell in the bone marrow? Once fully mature, what is its life span?

- It takes nearly 2 weeks for the full development of a neutrophil from an early stem cell within the bone marrow
- The average life span of a mature neutrophil in the blood is less than 12 hours

2. At what level of neutropenia does the incidence of infection dramatically increase?

- Absolute neutropenia is characterized by counts less than 1500–2000/μL
- The risk of severe infection dramatically increases when the neutrophil count is less than about 250/μL

25 Cyclic Neutropenia, B

3. What are the most common sites and types of infections observed in neutropenic patients?

- Skin infections, specifically small superficial pyogenic abscesses (**furunculosis**) or bacterial invasion of the dermis or epidermis (**cellulitis**), are the most common
- The next most common infection site is usually the gums, and chronic gingivitis is evident in about half of patients
- Cervical lymphadenopathy and oral ulcers are common
- Life-threatening bacterial and fungal infections are uncommon but can occur, particularly as a result of infection from endogenous gut flora

4. What is the probable underlying abnormality in cyclic neutropenia?

- Classic, childhood-onset cyclic neutropenia results from heterozygous germ-line mutations in the gene, *ELANE (ELAstase - Neutrophil Expressed)*, formerly known as *ELA2*, which encodes for a single enzyme, neutrophil elastase (NE)
- NE is found in the primary azurophilic granules of neutrophils and monocytes
- Studies of neutrophil kinetics in affected patients reveal that the gene defect results in abnormal production—rather than abnormal disposition—of neutrophils
- This production defect affects other cell lines, resulting in cyclic depletion but the deficiency in neutrophils is most apparent due to their very short life span
- In cyclic neutropenia, it is hypothesized that the mutant neutrophil elastase may have an overly inhibitory effect, causing prolonged trough periods and inadequate storage pools to maintain a normal peripheral neutrophil count

26 Immune Thrombocytopenic Purpura, A

A 36-year-old man was admitted to the hospital after sustaining multiple fractures to the lower extremities by jumping from a three-story building in a suicide attempt. His fractures required surgical repair. He has no significant medical history. Current medications include morphine for pain and subcutaneous heparin for prophylaxis against deep venous thrombosis. Consultation with a hematologist is requested because of a dropping platelet count. On physical examination, the patient has multiple bruises, and his lower extremities are casted bilaterally. Examination is otherwise normal. Laboratory tests from the last several days reveal a platelet count that has dropped from 170,000/μL on admission to 30,000/μL 5 days later.

1. What is the most common category of causes of thrombocytopenia?

- Drug-induced immune thrombocytopenia is the most common cause
- Many drugs have been associated with this phenomenon
- In practice, the association between a given drug and thrombocytopenia is usually made clinically rather than with specific tests
- Thrombocytopenia usually occurs at least 5–7 days after exposure to the drug, if given for the first time
- The suspect drug is stopped and platelet counts rebound within a few days

26 Immune Thrombocytopenic Purpura, B

2. Antibodies to which platelet protein are implicated in the pathogenesis of heparin-induced thrombocytopenia?

- Heparin can bind to a platelet-produced protein, platelet factor 4 (PF4), which is released by platelets in response to activation
- The heparin-PF4 complex acts as an antigenic stimulus, provoking the production of IgG
- IgG can then bind to the complex, forming IgG-heparin-PF4
- The new complex can bind to platelets via the Fc receptor of the IgG molecule or via the PF4 receptor leading to direct platelet destruction as well as activation

3. Why is major bleeding unusual in drug-induced thrombocytopenia?

- With platelet counts of less than about 5000/μL, pinpoint hemorrhages (**petechiae**) may spontaneously occur in the skin or mucous membranes
- These are self-limited because the plasma coagulation factors are still intact, and only a small number of aggregated platelets are needed to provide adequate phospholipid for clotting
- Spontaneous bleeding is unlikely until platelet counts are less than 20,000/μL but is still uncommon until counts are less than about 5000/μL, assuming that patients do not have other abnormalities of hemostasis
- When bleeding from thrombocytopenia does occur, it is most often mucosal or superficial in the skin. This is most commonly seen as a nosebleed (**epistaxis**)

27 Hypercoagulable States, A

A 23-year-old woman presents to the emergency department with a chief complaint of acute onset of shortness of breath. It is associated with right-sided chest pain, which increases with inspiration. She denies fever, chills, cough, or other respiratory symptoms. She has had no lower extremity swelling. She has not been ill, bedridden, or immobile for prolonged periods. Her medical history is notable for an episode about 2 years ago of deep venous thrombosis (DVT) in the right lower extremity while taking oral contraceptives. She has been otherwise healthy and is currently taking no medications. The family history is notable for a father who died of a pulmonary embolism. On physical examination, she appears anxious and in mild respiratory distress. She is tachycardic to 110 bpm, with a respiratory rate of 20/min. She has no fever, and blood pressure is stable. The remainder of the physical examination is normal. Chest x-ray film is normal. Ventilation-perfusion scan reveals a high probability of pulmonary embolus. Given her history of DVT, a hypercoagulable state is suspected.

1. What are the risk factors for pulmonary thromboemboli?

- As first noted by the pathologist Virchow, there are three possible contributors to formation of an abnormal clot (thrombus): decreased blood flow, vessel injury or inflammation, and changes in the intrinsic properties of the blood
- The deep leg veins are low-flow, high capacity veins and are at risk for clot formation, especially during periods of immobilization
- Vessel injury is common after surgery or trauma
- Changes in the intrinsic clotting ability can be due to inherited disorders or medications

27 Hypercoagulable States, B

2. What hemodynamic changes are brought about by significant pulmonary thromboemboli?

- The presence of the clot blocks blood flow from the heart to a portion of lung, leading to hypoxemia through areas of mismatched ventilation and perfusion
- Large pulmonary emboli can impair circulation directly by suddenly increasing the pulmonary artery pressure, leading to right ventricular failure

3. What are the clinical manifestations of pulmonary thromboembolism?

- Pulmonary emboli are the major source of morbidity and mortality after DVT of the lower extremity
- They typically present with acute-onset shortness of breath and hypoxemia, suggesting that lower extremity thrombus has now broken off and migrated through the right side of the heart into the pulmonary arterial system
- Signs of DVT are pain, swelling, and redness below the level of the thrombus, with normal arterial pulses and distal extremity perfusion
- Superficial collateral veins just under the skin may be prominent and engorged
- The swelling is mechanical, because normal arterial blood flow continues to the extremity while venous return is compromised, leading to engorgement
- Pain occurs primarily as a result of the swelling alone but can also occur from lactic acid buildup in the muscles of the legs if the pressure in the legs increases to the point that it compromises arterial blood flow and adequate oxygen delivery

28 Amyotrophic Lateral Sclerosis (Motor Neuron Disease), A

A 43-year-old right-handed man presents to the clinic with gradual onset of right-hand and arm weakness. He had been in good health and an avid golfer until a few weeks ago when he noted that he was having trouble keeping his club steady during his swing. His driving distance has markedly decreased, and he began to drop things that he was holding with his right hand. There is no numbness or other sensory symptoms. On physical examination, he appears well and has normal vital signs. He has mild muscle wasting and fasciculations along his right brachioradialis muscle. His grip strength is 4 out of 5 on the right and 5 out of 5 on the left. He has absent reflexes in his right arm and 1+ reflexes on the left. An electromyogram (EMG) shows features of denervation, including increased numbers of spontaneous discharges in resting muscle and a reduction in the number of motor units detected during voluntary contraction. A diagnosis of amyotrophic lateral sclerosis (ALS) is entertained.

1. What are the major clinical manifestations of ALS?

- In 80% of patients, the initial symptoms are due to weakness of limb muscles
- Symptoms are often bilateral but asymmetric
- Involvement of bulbar muscles causes difficulty with swallowing, chewing, speaking, breathing, and coughing
- Neurologic examination reveals a mixture of upper and lower motor neuron signs
- There is usually no involvement of extraocular muscles or sphincters
- The disease is progressive and generally fatal within 3–5 years, with death usually resulting from pulmonary infection and respiratory failure

28 Amyotrophic Lateral Sclerosis (Motor Neuron Disease), B

2. What are some factors in the pathogenesis of ALS?

- Selective degeneration of motor neurons in the primary motor cortex and the anterolateral horns of the spinal cord
- Many affected neurons show cytoskeletal defects with accumulations of intermediate filaments in the neuronal cell body and in the axons
- A subtle glial cell response is sometimes observed with minimal inflammation
- Possible causes include:
  - Glutamate, an excitatory neurotransmitter that leads to raised intracellular calcium; breakdown of normal mechanisms for terminating the excitatory signal leads to sustained elevations of intracellular calcium that cause cell death
  - About 10% of ALS cases are familial, with 20% of these familial cases due to missense mutations in the cytosolic copper-zinc superoxide dismutase (*SOD1*) gene, which catalyzes the formation of hydrogen peroxide from superoxide anion
  - Neurofilamentous inclusions in neuronal cell bodies and proximal axons are an early feature of ALS pathology; mutations in the heavy chain neurofilament subunit (NF-H) have been detected in some patients with sporadic ALS, suggesting that NF-H variants may be a risk factor. Transactive response DNA-binding protein 43 (TDP 43) plays a role in some familial cases of ALS (as well as Alzheimer and Parkinson disease)
  - Hexanucleotide repeats in an intron of C9ORF72 on chromosome 9 have been found in 34% of familial ALS cases and 6% of sporadic ALS cases (as well as 26% of familial frontotemporal dementia [FTD] cases and 5% of sporadic FTD cases); the resulting dysfunction is unknown

29 Parkinson Disease, A

A 63-year-old man comes to the clinic with a several-month history of difficulty with his gait and coordination. He finds walking difficult and has almost fallen on a number of occasions, especially when trying to change directions. He has also found that using his hands is difficult, and other people have noticed that his hands shake. Physical examination is notable for a resting tremor in the hands that disappears with intentional movement. He has a shuffling gait with difficulty turning. There is so-called cogwheeling rigidity in his arms, a jerky sensation with passive flexion and extension of the arms.

1. What are the clinical features of parkinsonism?

- Parkinsonism is a clinical syndrome characterized by rigidity, bradykinesia, tremor, and postural instability
- Most cases are due to Parkinson disease, an idiopathic disorder with a prevalence of about 1–2 per 1000
- Other causes include:
  - Von Economo encephalitis
  - Exposure to certain toxins such as manganese, carbon disulfide, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and carbon monoxide
  - Drugs, particularly butyrophenones, phenothiazines, metoclopramide, reserpine, and tetrabenazine
  - Repeated head trauma
  - Several basal ganglia diseases, including Wilson disease, some cases of early onset Huntington disease, Shy-Drager syndrome, striatonigral degeneration, and progressive supranuclear palsy

29 Parkinson Disease, B

2. What are two major mechanisms proposed to explain the pathophysiology of Parkinson disease?

- Alterations in mitochondrial complex I are observed in laboratory animals, following treatment with several drugs and toxins that produce parkinsonism in humans
- Functional changes in proteins coded by several neural genes also cause parkinsonism:
  - α-synuclein (*PARK1*)
  - Parkin (*PARK2*)
  - DJ-1 (*PARK7*)
  - Ubiquitin-C-hydrolase-L1 (*PARK5*)
  - PTEN (phosphatase and tensin homolog deleted on chromosome 10)—induced kinase 1 (*PINK1*)
  - Leucine-rich repeat kinase 2 (*LRRK2*), and
  - Glucocerebrosidase (GCase)

30 Myasthenia Gravis, A

A 35-year-old woman presents to the clinic with a chief complaint of double vision. She reports intermittent and progressively worsening double vision for approximately 2 months, occurring rarely at first but now daily. She works as a computer programmer, and the symptoms increase the longer she stares at the computer screen. She has also noted a drooping of her eyelids, which seems to worsen with prolonged looking at the screen. Both symptoms subside with rest. She is generally fatigued but has noted no other weakness or neurologic symptoms. Her medical history is unremarkable. Physical examination is notable only for the neurologic findings. Cranial nerve examination discloses impaired lateral movement of the right eye and bilateral ptosis, which worsen with repetitive eye movements. Motor, sensory, and reflex examinations are otherwise unremarkable.

1. What is the clinical presentation of myasthenia gravis?

- Fluctuating fatigue and weakness that improve after a period of rest and after administration of acetylcholinesterase inhibitors
- Muscles with small motor units, such as ocular muscles, are most often affected
- In severe cases, all muscle groups can be affected, including the diaphragm and intercostal muscles, and death may result from respiratory failure
- Oropharyngeal muscles, flexors and extensors of the neck, proximal limb muscles, and the erector spinae muscles are less often involved

30 Myasthenia Gravis, B

2. What causes myasthenia gravis?

- The major structural abnormality in myasthenia gravis is a simplification of the postsynaptic region of the neuromuscular synapse
- The number and size of the presynaptic vesicles are normal
- Electrophysiologic studies indicate that the postsynaptic membrane has a decreased response to applied acetylcholine with a 70–90% decrease in the number of receptors per end plate in affected muscles
- Circulating antibodies to the receptor are present in 90% of patients, and the disorder may be passively transferred to animals by administration of IgG from affected patients
- The antibodies block acetylcholine binding and receptor activation and cross-link receptor molecules, increasing receptor internalization, degradation, and complement-mediated destruction of the postsynaptic region
- Many patients who lack antibodies to the AChR have autoantibodies instead against the muscle-specific receptor tyrosine kinase (MuSK), which is an important mediator of acetylcholine receptor clustering at the end plate
- During repetitive stimulation of a motor nerve, in myasthenia gravis the number of quanta released from the nerve terminal declines with successive stimuli; this occurs because there is a deficiency in the number of functional receptors and neuromuscular transmission fails at lower levels of quantal release
- Electrophysiologically, this is measured as a decremental decline in the compound muscle action potential during repetitive stimulation of a motor nerve
- Clinically, this is manifested by muscle fatigue with sustained or repeated activity

31 Dementia, A

A 73-year-old man is brought in by his wife with concerns about his worsening memory. He is a retired engineer who has recently been getting lost in the neighborhood where he has lived for 30 years. He has been found wandering and has often been brought home by neighbors. When asked about this, he becomes upset and defensive and states that he was just trying to get some exercise. He has also had trouble dressing himself and balancing his checkbook. A physical examination is unremarkable, except that he scores 12 points out of 30 on the Mini-Mental State Examination, a test of cognitive function. A metabolic workup is normal. A computed tomography scan of the head shows generalized brain atrophy, though perhaps only what would be expected for his age. He is diagnosed with dementia, likely from Alzheimer disease.

1. What are the treatable causes of dementia?

- Treatable causes include: hypothyroidism, vitamin B_{12} deficiency, neurosyphilis, brain tumor, normal pressure (communicating) hydrocephalus, and chronic subdural hematoma
- In addition, although not curable, dementia associated with HIV infection may be slowed by antiretroviral treatment
- About 10–15% of patients referred for evaluation of dementia suffer from depression ("pseudodementia"), which may also respond to antidepressant treatment

31 Dementia, B

2. What are the clinical features of Alzheimer disease?

- Alzheimer disease is the most common cause of dementia and accounts for more than 50% of cases
- Slowly progressive, it runs a course of 5–10 years and typically begins with impairment of learning and recent memory
- Anomia, aphasia, and acalculia eventually develop, causing loss of employment and inability to manage finances
- Spatial disorientation causes patients to become lost easily, and apraxias lead to difficulty with cooking, cleaning, and self-care
- A frontal lobe gait disorder may appear, with short, shuffling steps, flexed posture, difficulty turning, and a tendency to fall backward (retropulsion) similar to that seen in Parkinson disease
- In later stages, social graces are lost, and psychiatric symptoms such as paranoia, hallucinations, and delusions may appear
- End-stage Alzheimer disease patients are bedridden, mute, and incontinent

3. What is the association between apolipoprotein E and Alzheimer disease?

- About 50% of Alzheimer patients have the ε4 isoform of apolipoprotein E (apoE4)
- ApoE is a 34-kDa protein that mediates the binding of lipoproteins to the low-density lipoprotein (LDL) receptor and the LDL receptor–related protein (LRP)
- The ε4 allele is associated with an increased risk and earlier onset of this disease

32 Epilepsy, A

A middle-aged man is transported to the emergency department unconscious. A witness states that the patient was in line in front of her in the hospital cafeteria when he suddenly fell to the floor. He then had a "generalized tonic-clonic seizure." She called for assistance and accompanied him to the emergency department. No other historical information is available. On physical examination, the patient is confused and unresponsive to commands. He is breathing adequately and has oxygen in place via nasal prongs. His vital signs are as follows: temperature, 38°C; blood pressure, 170/90 mm Hg; heart rate, 105 bpm; respiratory rate, 18/min. Oxygen saturation is 99% on 2 L of oxygen. Neurologic examination is notable for reactive pupils of 3 mm, intact gag reflex, decreased movement of the left side of the body, and Babinski reflexes bilaterally. Examination is otherwise unremarkable.

1. What is the clinical presentation of the major types of seizures?

- Generalized tonic-clonic seizures: Sudden loss of consciousness, followed rapidly by tonic contraction of muscles, causing limb extension and arching of the back
  - Afterward, the patient remains unconscious for several minutes with postictal confusion and focal neurologic abnormalities for several minutes
- Absence seizures: Brief lapses in consciousness lasting several seconds without loss of posture, with eyelid blinking, head movement, or brief muscle jerks
  - Fully alert soon after but may occur several times through the day
  - Begin in childhood and usually remit by adulthood
  - Electroencephalogram (EEG) shows characteristic runs of spikes and waves at a rate of three per second, particularly after hyperventilation

(continued on reverse side)

32 Epilepsy, B

- Idiopathic epilepsy accounts for more than 75% of all seizure disorders
- However, known secondary causes include: brain injury from stroke or trauma, mass lesion, infection, fever, or metabolic causes

2. What are some disorders that lead to secondary epilepsy and what changes in brain structure lead to it?

- In secondary epilepsy, loss of inhibitory circuits and sprouting of fibers from excitatory neurons appear to be important for the generation of a seizure focus

- Simple focal seizures: Begin with motor, sensory, visual, psychic, or autonomic phenomena, depending on the location of the seizure focus, with preserved consciousness unless the seizure discharge spreads, producing a tonic-clonic seizure (secondary generalization)
- Focal dyscognitive seizures: Sudden onset of impaired consciousness with stereotyped, coordinated, involuntary movements (automatisms), often preceded by an aura consisting of unusual abdominal sensations, olfactory or sensory hallucinations, unexplained fear, or illusions of familiarity (déjà vu)
  - The seizure focus usually lies in the temporal or frontal lobe

33 Stroke, A

A 72-year-old man presents to the emergency department with acute onset of right-sided weakness. The patient was eating breakfast when he suddenly lost strength in the right side of his body such that he was unable to move his right arm or leg. He also noted a loss of sensation in the right arm and leg and difficulty speaking. His wife called 911, and he was brought to the emergency department. His medical history is remarkable for long-standing hypertension, hypercholesterolemia, and recently diagnosed coronary artery disease. On physical examination, his blood pressure is 190/100 mm Hg. Neurologic examination is notable for right facial droop and a dense right hemiparesis. The Babinski reflex is present on the right. CT scan of the brain shows no evidence of hemorrhage. He is admitted to the neurologic ICU.

1. What are the differences between the clinical presentation of stroke resulting from ischemia and stroke caused by spontaneous hemorrhage?

- The focal symptoms and signs that result from stroke correlate with the area of brain supplied by the affected blood vessel
- Ischemic stroke, due to loss of blood flow to a specific brain region, produces a fairly characteristic pattern of neurologic deficits resulting from loss of functions controlled by that region
- Hemorrhage results in less predictable symptoms and more global symptoms, such as headache, because it not only depends on the location of the bleed but also on factors that affect the function of brain in other areas (eg, increased intracranial pressure, brain edema, compression of neighboring brain tissue, and rupture of blood into ventricles or subarachnoid space)

33 Stroke, B

2. What are the most common causes of stroke?

- Vascular: Atherosclerosis, fibromuscular dysplasia, vasculitis (inflammatory, infectious, or drug-induced), arterial dissection, lacunar infarction, migraine, venous or sinus thrombosis, multiple progressive intracranial occlusions (moyamoya syndrome), arteriovenous and other malformations, aneurysms, hypertension, trauma (leading to subdural or epidural hematoma)
- Cardiac: Emboli due to valvular disease, arrhythmias, endocarditis, myopathy, or septal defect
- Hematologic: Thrombocytosis, polycythemia, sickle cell, leukocytosis, hypercoagulable state

3. What role does glutamate play in neuronal injury during ischemia?

- CNS glutamate homeostasis is markedly altered during ischemia, leading to increased and toxic levels of extracellular glutamate
- Neurons deep within an ischemic focus die from energy deprivation, but at the edge of the ischemic region, neurons appear to die because of excessive stimulation of glutamate receptors
- Extracellular glutamate accumulates due to loss of normal ion regulation in ischemic areas
- This stimulates glutamate receptors on surrounding neurons, causing entry of calcium and sodium into those neurons
- The pathologic increase in intracellular calcium leads to cell death

34 Psoriasis, A

A 25-year-old woman presents with a complaint of rash that has developed over the past several weeks and seems to be progressing. On examination, she is noted to have several plaque-like lesions over the extensor surfaces of both upper and lower extremities as well as similar lesions on her scalp. The plaques are erythematous, with silvery scales, and are sharply marginated.

1. What evidence supports a genetic role in the development of psoriasis? An environmental role?

- There is a high rate of concordance for psoriasis in monozygotic twins and an increased incidence of psoriasis in the relatives of affected individuals
- Overexpression of gene products of class I alleles of the major histocompatibility complex (MHC) is often found in patients with psoriasis
- However, psoriasis is not likely to be completely genetic in nature since individuals with a genetic predisposition to psoriasis usually also require environmental triggers, such as trauma, cold weather, infections, stress, and drugs

34 Psoriasis, B

2. Which cell types hyperproliferate in psoriasis?

- There is shortening of the usual duration of the keratinocyte cell cycle and doubling of the proliferative cell population
- This excessive epidermatopoiesis results in skin thickening, plaque formation, and an accumulation of cells within the cornified layer with retained nuclei

3. What immunologic defects have been identified in psoriasis?

- Antigenic stimuli are thought to activate the innate immune response, leading to the production of cytokines, such as interferon, tumor necrosis factor, interleukin-23, and interleukin-12, by macrophages, dendritic cells and neutrophils
- This leads to attraction, activation, and differentiation of T cells. These T cells, most importantly T helper 1 and T helper 17 cells, produce cytokines that lead to epidermal hyperplasia, recruitment of inflammatory cells, and ultimately a positive feedback loop that perpetuates the pathologic process

35 Lichen Planus, A

A 35-year-old woman who recently returned from Africa presents to the clinic complaining of a rash. During her trip, she developed an itchy rash on both arms. She has an unremarkable medical history. Medications recently taken include only chloroquine for malaria prophylaxis.

Examination discloses multiple small violaceous papules on the flexor surfaces of the arms. The lesions have angular borders and flat tops. Some of the lesions have minute white streaks on the surface, barely visible to the naked eye.

1. What skin cells are damaged by cell-mediated immune reactions in lichen planus?

- Some form of antigenic stimulation leads to infiltration and activation of CD4 T lymphocytes
- These stimulated CD4 cells elaborate cytokines, leading to the recruitment of cytotoxic T lymphocytes
- Cell-mediated cytotoxicity, cytokines, interferon-γ, and tumor necrosis factor combine to injure keratinocytes and contribute to vacuolization and necrosis of these cells
- Injured, enucleated keratinocytes coalesce to form colloid bodies
- Melanocytes are destroyed as "innocent bystanders"

35 Lichen Planus, B

2. Which drugs have been most commonly implicated in licheniform eruptions?

- Antimalarial agents (such as chloroquine) and therapeutic gold are the drugs most closely linked to this phenomenon

3. What synchronous alterations in the skin are reflected in the clinical appearance of lichen planus?

- The appearance of the lichen planus papules is a direct reflection of the underlying histopathologic features
- The dense array of lymphocytes in the superficial dermis yields the elevated, flat-topped appearance of the papule
- The whitish coloration—Wickham striae—results from chronic inflammation and hyperkeratosis of the cornified layer of the epidermis
- The purple hue of the lesions is caused by the macrophage phagocytosis of the released melanin from melanocytes
- Although the melanin is brown-black, the melanophages are embedded in a colloid matrix
- This causes extensive scattering of light by an effect known as the Tyndall effect, resulting in interpretation of the lesion as dusky and violaceous

36 Erythema Multiforme, A

A 27-year-old woman presents to the urgent care clinic complaining of a red, itchy rash developing suddenly the day before on her arms and legs and spreading to the trunk. She denies ulcers in the mouth or genital area. Her medical history is significant for occasional outbreaks of genital herpes, most recently 2 weeks ago. She usually takes oral acyclovir for such outbreaks, but her prescription had lapsed, so she did not take it with her last bout. On physical examination, she has multiple erythematous papules over the arms, legs, and trunk. Many of the papules have a central area of duskiness or clearing, such that the lesions resemble targets. There are no mucosal lesions.

1. What are the prototypical lesions in erythema multiforme?

- Target-like lesions are the hallmark of **erythema multiforme minor**
- They reflect zonal differences in the inflammatory response and its deleterious effects
- At the periphery of the lesion, inflammation and vacuolization are sparse, resulting in the erythematous halo
- The dusky bull's eye in the center, on the other hand, is an area of dense epidermal vacuolization and necrosis
- Diagnosis of **erythema multiforme major** is based on involvement of at least two of three mucosal areas: oral, anogenital, or conjunctival sites
- Erythema multiforme major can also display severe, widespread cutaneous involvement, including **Stevens-Johnson syndrome**, with profound mucosal involvement, and **toxic epidermal necrolysis**, with necrosis of vast areas of skin and mucosa with secondary vesiculation

36 Erythema Multiforme, B

2. In what ways is erythema multiforme similar to and different from lichen planus?

- Erythema multiforme is similar to lichen planus in that both are interface dermatitides and both are caused by some inciting agent that results in lymphocyte migration to the epidermis and papillary dermis
- Cytotoxic T cells then combine with elaborated cytokines, interferon-γ, and tumor necrosis factor to kill keratinocytes, resulting in enucleation, vacuolization, and coalescence to form colloid bodies
- Unlike lichen planus, with its dense dermal inflammatory infiltrate, the dermal infiltrate of lymphocytes in erythema multiforme is sparse
- Thus, the vacuolated keratinocytes widely distributed in the epidermal basal layer are more conspicuous

3. What are some complications of toxic epidermal necrolysis?

- Toxic epidermal necrolysis is most often a reaction to a medication
- Pathologically, the findings are similar to a severe burn in that the integrity of a patient's skin fails, resulting in an increased risk of infections and metabolic sequelae

37 Bullous Pemphigoid, A

A 65-year-old man presents to the dermatology clinic complaining of blisters developing on his abdomen and extremities over the past week. The lesions consisted initially of red patches followed by blister formation. They are pruritic but not painful. The patient has no other complaints and denies lesions on any mucous membranes. Examination shows only multiple large, tense blisters with an erythematous base over the lower trunk and extremities. The clinical picture is felt to be most consistent with bullous pemphigoid.

1. How do pemphigus and pemphigoid differ and why is the distinction important?

- Bullous pemphigoid is characterized by subepidermal vesiculation and pemphigus by intraepidermal vesiculation
- The distinction is important because bullous pemphigoid has a more favorable prognosis

37 Bullous Pemphigoid, B

2. How does immunoglobulin (Ig) binding to the bullous pemphigoid antigen cause blistering in lesions of bullous pemphigoid?

- Blister formation is believed to begin with the binding of IgG to the bullous pemphigoid antigen, activating the complement cascade
- Complement fragments then induce mast cell degranulation and attract neutrophils and eosinophils
- The granulocytes and mast cells release multiple enzymes, resulting in enzymatic digestion of the epidermal-dermal junction and separation of the layers
- It is also possible that the bullous pemphigoid antigen plays a vital structural role that is compromised when the autoantibodies bind, leading to cleavage of the epidermal-dermal junction

3. Is there a connection between bullous pemphigoid and cancer?

- Some patients with bullous pemphigoid have developed skin lesions synchronously with a diagnosis of malignancy, but careful studies with age-matched controls have not demonstrated an increased incidence of bullous pemphigoid in cancer patients

- Bullous pemphigoid is a disease of the skin and mucous membranes only, and systemic involvement has never been documented

38 Leukocytoclastic Vasculitis, A

A 60-year-old man presents to the clinic with complaints of a recurring rash. He states that for the last 2–3 months, he has had several episodes of a painless, nonpruritic rash over his distal lower extremities. The lesions are described as purple and raised. His medical history is remarkable for hepatitis C—with no history of cirrhosis—and peripheral neuropathy. The patient has recently been treated for otitis media with amoxicillin. He has taken no other medications. Physical examination is notable only for multiple reddish-purple papules over the distal lower extremities (palpable purpura). The underlying skin is hyperpigmented. Biopsy reveals neutrophils, neutrophilic debris, and amorphous protein deposits involving the small blood vessels, consistent with fibrinoid necrosis.

1. Why are leukocytoclastic vasculitis lesions papular?

- Leukocytoclastic vasculitis lesions are raised and papular because lesional skin is altered and expanded by an intense vasocentric infiltrate containing numerous neutrophils
- The lesions are purpuric or erythematous because of the extravasated red blood cells that accumulate in the dermis

38 Leukocytoclastic Vasculitis, B

2. What are the most common precipitants of leukocytoclastic vasculitis?

- Common precipitants include infections and medications
- Bacterial, mycobacterial, and viral infections can all trigger leukocytoclastic vasculitis; *Streptococcus* and *Staphylococcus* are the most common infectious precipitants
- Hepatitis C is also associated with leukocytoclastic vasculitis
- Many drugs have been associated with this disorder, including antibiotics, thiazides, and nonsteroidal anti-inflammatory drugs (NSAIDs)
- Of the antibiotics, penicillins, such as the amoxicillin given to this man, are the most common offenders

3. When leukocytoclastic vasculitis is part of a systemic vasculitis, what additional symptoms are typically observed?

- Leukocytoclastic vasculitis may also involve small vessels in other portions of the body, including the joint capsules, soft tissues, kidneys, liver, and gastrointestinal (GI) tract
- The most common systemic symptoms include arthralgias, myalgias, and abdominal pain

39 Poison Ivy/Oak, A

A 30-year-old woman presents to the clinic complaining that she has an "itchy rash all over the place." She noticed that her legs became red, itchy, and blistered about 2 days after she had been hiking in a heavily wooded area. She says that scratching broke the blisters, and afterward the rash became much worse and spread all over. She is convinced that the rash could not be poison ivy because once before she was exposed to that plant and did not develop a rash. On examination, there are erythematous vesicles and bullae in linear streaks on both of her legs. Some areas are weepy, with a yellowish crust. There are ill-defined erythematous plaques studded with papulovesicles on the trunk and arms.

1. What is spongiosis and how does it relate to allergic contact dermatitis?

- Spongiosis is the pathologic hallmark of allergic contact dermatitis
- Spongiosis refers to edema of the epidermis, which separates keratinocytes from one another
- Edema makes the normally indiscernible "spines," or desmosomes, which interconnect the keratinocytes, visible under the microscope
- The inflammatory cellular infiltrate in spongiotic dermatitis is typically composed of lymphocytes with additional eosinophils often concurrently present in significant numbers
- Spongiotic dermatitis is accompanied by a variable amount of perivascular inflammation that may be around the superficial vascular plexus or deep vascular plexuses or both

39 Poison Ivy/Oak, B

2. What are the two phases of development of allergic contact dermatitis? What steps are involved in each?

- This rash is a delayed-type (type IV) hypersensitivity reaction that consists of two phases: induction (sensitization/afferent) and elicitation (efferent)
- In the induction phase, the allergen coming into contact with the individual who is naive to it binds to an endogenous protein that alters it to make it appear foreign
- This protein-allergen complex is then intercepted by the skins immunosurveillance cells, the Langerhans cells, bone marrow–derived dendritic cells that reside in the epidermis at the interface of the immune system with the environment
- These cells engulf the complex, partially degrade it, migrate to lymph nodes, and present antigenic fragments on their surface along with an MHC-II molecule
- At the node, these cells then contact naive T cells possessing T-cell receptors that specifically recognize the MHC-II–allergen complex
- Binding of the T-cell receptors to the MHC-II–allergen complex occurs in the context of important costimulatory molecules on the surface of the Langerhans cells and stimulates clonal expansion of the reactive T cells

3. What is the role of patch testing in patients with suspected allergic contact dermatitis?

- Patch testing is a useful technique for finding the cause when an unknown contactant is suspected to be the origin of a persistent or recurrent eruption

40 Erythema Nodosum, A

A 45-year-old-woman presents to the clinic with a rash on her legs for 2 months. She notes that the rash started soon after babysitting her niece, who had "strep throat." She initially had a sore throat herself, but it stopped hurting after she took 2 days of antibiotics she had left from a previous prescription. On examination, on the anterior lower legs, she has several scattered ill-defined erythematous nodules, which are tender to palpation.

1. What are the two general categories of panniculitis?

- Panniculitis can be separated into two broad categories based on the distribution of inflammation: mostly septal panniculitis and mostly lobular panniculitis
- The septa are the fibrous divisions between fat compartments and contain the neurovascular bundles
- The lobules are the conglomerations of adipocytes demarcated by septa
- The modifier "mostly" is meant to convey that the inflammatory process is not strictly confined to a single compartment but, in fact, will frequently spill over from one to the other

40 Erythema Nodosum, B

2. Which category of panniculitis does erythema nodosum fit into? What are the features of erythema nodosum histopathologically? Clinically?

- In erythema nodosum, the inflammatory response occurs in the subcutaneous septal compartment and consists of lymphocytes, histiocytes, neutrophils, and eosinophils
- The septa are thickened and may become fibrotic depending on the density of the infiltrate and the duration of the reaction
- There is commonly an element of fat necrosis in the form of an infiltrate of foamy (lipid-laden) macrophages at the periphery of subcutaneous lobules or in the form of small stellate clefts within multinucleate macrophages
- Clinically, erythema nodosum presents most often with tender red nodules on the anterior lower leg, typically a dozen or more lesions at onset
- Fever and other constitutional symptoms and arthralgias may occur at the onset of erythema nodosum
- The duration of the eruption is typically a few weeks to a few months

3. What are some common precipitators of erythema nodosum?

- Erythema nodosum may develop in response to infection (eg, streptococcal pharyngitis, as likely here), medication (eg, sulfonamides), hormones (eg, oral contraceptives, pregnancy), and inflammatory disease (eg, inflammatory bowel disease)

41 Sarcoidosis, A

A 52-year-old African American man presents to the clinic with a rash that has been worsening for several months. Review of systems is notable for a chronic cough. Examination reveals multiple red-brown dermis-based papules on the trunk, arms, and face. Several lesions are clustered near the nares. The exam is otherwise unremarkable.

1. Who gets sarcoidosis? How common is it?

- Sarcoidosis can affect patients of any age or ethnic background but occurs more frequently in young adults and, in the United States, is more common in people of black African descent
- In this population, estimates of disease incidence range from 35.5 to 64 cases per 100,000 compared with 10–14 cases per 100,000 in whites
- In Europe, Irish and Scandinavian populations are at increased risk

2. What pattern of inflammatory skin disease does sarcoidosis exhibit?

- Sarcoidosis is a nodular dermatitis with histiocytic granulomas situated within the dermis
- There are usually a few lymphocytes present in and around the granulomas
- Multinucleated histiocytes are frequently present

41 Sarcoidosis, B

3. How does the pathology of skin lesions of sarcoidosis correspond to clinical lesions?

- Sarcoidosis is manifest microscopically as collections of tissue macrophages (ie, histiocytes), known as granulomas, situated within the dermis
- Unlike the tuberculoid granulomas of tuberculosis, sarcoidal granulomas are noncaseating and do not show central coagulation necrosis
- Multinucleated histiocytes formed by the fusion of individual cells are a common finding
- The characteristic microscopic appearance of sarcoidal granulomas is of small numbers of lymphocytes around the granulomas ("naked granulomas")
- This appearance contrasts with the dense lymphocytic infiltrate that blankets the granulomas in many other granulomatous disorders, including tuberculosis
- Sarcoidal granulomas can occupy almost the entire dermis in affected skin or may occur only in relatively small foci that are widely spaced
- Lesions are often red-brown dermal papules or nodules that may occur anywhere on the cutaneous surface but have a special predilection for the face

42 Acne, A

A 15-year-old girl presents to the clinic complaining of "pimples" for 6 months. She has been using an over-the-counter face wash four times a day to keep the oil and dirt off, but it has not helped. Examination reveals several dozen erythematous papules and pustules over the forehead and central face with scattered open and closed comedones. A diagnosis of moderate inflammatory acne is made.

1. Why do some infants develop acne? Why does it spontaneously resolve?

- In the neonate, maternal androgens stimulate enlargement of sebaceous glands and concomitant sebum overproduction
- The presence of sebum promotes overgrowth of *Propionibacterium acnes*
- As the maternal androgens wane in the infant's circulation postpartum, the sebaceous glands atrophy and the acne resolves

2. What is the pathophysiology of lesion development in acne?

- Keratinocytes fail to slough from the follicles as they should producing a plugged follicle (a comedo)
- The buildup of sebum behind the plug expands the follicle
- *P acnes* overgrowth in the follicle breaks down sebum
- Bacterial factors and sebum breakdown products attract neutrophils to the follicle, thus forming a pustule

42 Acne, B

3. What are some broad categories of treatment for acne, and which aspect of acne pathogenesis does each address?

- Restoring normal keratinization and desquamation to follicular keratinocytes may be achieved with retinoids (vitamin A analogs) either topically or, if the condition is severe enough, orally
- *P acnes* and the inflammation it induces are controlled with topical or oral antibiotics
- Some common topical antibiotic agents include benzoyl peroxide and clindamycin

- Oral antibiotics such as erythromycin or tetracycline are frequently used in addition to topical antibiotics because of their anti-inflammatory properties independent of their antibacterial action
- Sebum production may be decreased through the use of retinoids, again topically or orally (oral therapy is much more effective for this purpose), or with antiandrogen medications such as spironolactone and oral contraceptives

43 Obstructive Lung Disease: Asthma, A

A 25-year-old previously well woman presents to your office with complaints of episodic shortness of breath and chest tightness. She has had the symptoms on and off for about 2 years but states that they have worsened lately, occurring two or three times a month. Her symptoms are worse during the spring months. She has no exercise-induced or nocturnal symptoms. Her father had asthma. She is single and works as a secretary in a high-tech firm. She lives with a roommate, who moved in approximately 2 months ago with her cat. The patient smokes occasionally when out with friends, drinks socially, and has no history of drug use. Examination is notable for mild end-expiratory wheezing.

1. What is the fundamental physiologic problem in obstructive lung disease?

- The fundamental physiologic problem in obstructive diseases is increased resistance to expiratory airflow as a result of reduction of caliber of airways
- This increased resistance can be caused by processes (1) within the lumen, (2) in the airway wall, or (3) in the supporting structures surrounding the airway

2. What are the three categories of provocative agents that can trigger asthma?

- Physiologic or pharmacologic mediators of asthmatic airway responses
- Allergens that can induce airway inflammation and reactivity in sensitized individuals
- Exogenous physicochemical agents or stimuli that produce airway hyperreactivity

43 Obstructive Lung Disease: Asthma, B

3. What are some of the common symptoms and signs of acute asthma, and what are their pathophysiologic causes?

- Dyspnea and chest tightness result from the greater muscular effort required to overcome increased airway resistance, hyperinflation from airway obstruction resulting in thoracic distention, and increased respiratory drive in the setting of respiratory muscle fatigue
- Wheezing comes from airway caliber reduction and prolonged turbulent airflow
- Cough results from the combination of airway narrowing, mucus hypersecretion, and stimulation of bronchial irritant receptors and peptide neurotransmitters
- Tachypnea and tachycardia may be absent in mild disease but are virtually universal in acute exacerbations
- Pulsus paradoxus is a fall of more than 10 mm Hg in systolic arterial pressure during inspiration, which occurs as a consequence of lung hyperinflation and compromise of left ventricular filling together with augmented venous return to the right ventricle during vigorous inspiration in severe obstruction
- Hypoxemia is caused by airway narrowing, which reduces ventilation to affected lung units, causing $\dot{V}/\dot{Q}$ mismatching with a shift toward low $\dot{V}/\dot{Q}$ ratios, resulting in an increase in the A-a gradient
- Other abnormalities include hypercapnia in severe attacks, obstructive defects on pulmonary function testing, and bronchial hyperresponsiveness on provocative (eg, methacholine or histamine) testing

44 Obstructive Lung Disease: Chronic Obstructive Pulmonary Disease (COPD), A

A 67-year-old man presents to your office with worsening cough, sputum production, and shortness of breath. He has been a cigarette smoker for the past 50 years, smoking about one pack a day. He has a chronic morning cough productive of some yellow sputum but generally feels okay during the day. He was in his usual state of health until 2 weeks ago when he developed a cold. Since then, he has had a hacking cough and increased thick sputum production. He also has had difficulty walking more than a block without stopping due to shortness of breath. Physical examination reveals prolonged expiration, audible wheezing, and diffuse rhonchi throughout both lung fields. Chest x-ray film shows hyperinflation of both lungs with a flattened diaphragm.

1. What is the leading cause of chronic bronchitis?

- Cigarette smoking is by far the leading cause, although other inhaled irritants may produce chronic bronchitis
- Chronic bronchitis is defined by a clinical history of productive cough for 3 months of the year for 2 consecutive years
- Dyspnea and airway obstruction, often with an element of reversibility, are intermittently to continuously present

44 Obstructive Lung Disease: Chronic Obstructive Pulmonary Disease (COPD), B

2. What are the pathophysiologic changes in emphysema vs chronic bronchitis?

- Chronic bronchitis is characterized by chronic airway injury and narrowing with inflammation, particularly of small airways, and by hypertrophy of large airway mucous glands, increased mucus secretion, and mucus obstruction of airways
- Emphysema is a disease of the surrounding lung parenchyma and not the airways
- Emphysema results from (1) destruction of terminal respiratory units, (2) loss of alveolar capillary bed, and (3) loss of the supporting structures of the lung, including elastic connective tissue
- Loss of elastic connective tissue reduces normal support of noncartilaginous airways, leading to diminished elastic recoil and increased compliance and premature collapse of the airways during expiration

3. Deficiency of which protein increases the risk of early onset emphysema?

- α_1-Protease (α_1-antitrypsin) inhibitor deficiency leads to early onset emphysema
- α_1-Protease inhibits several types of proteases, including neutrophil elastase, which is implicated in the genesis of emphysema
- Autosomal dominant mutations, especially in northern Europeans, produce abnormally low serum and tissue levels of this inhibitor, altering the balance of connective tissue synthesis and proteolysis
- A homozygous mutation (the ZZ genotype) results in inhibitor levels 10–15% of normal, leading to a very high risk of emphysema, particularly in smokers

45 Restrictive Lung Disease: Idiopathic Pulmonary Fibrosis, A

A 68-year-old man presents to the clinic with a complaint of shortness of breath. He states that he has become progressively more short of breath for the last 2 months, such that he is now short of breath after walking one block. In addition, he has noted a nonproductive cough. He denies fever, chills, night sweats, chest pain, orthopnea, or paroxysmal nocturnal dyspnea. He has noted no lower extremity edema. His medical history is unremarkable. Physical examination is remarkable for a respiratory rate of 19/min and fine dry inspiratory crackles heard throughout both lung fields. Digital clubbing is present. A diagnosis of idiopathic pulmonary fibrosis is made.

1. Name six mechanisms by which interstitial lung disease affects lung function.

- Decreased lung compliance (lungs that are stiffer and more resistant to expansion) increases static recoil pressure and increases the work of breathing
- Proportional reductions of lung volumes
- Alveolar ventilation is maintained by an increased respiratory rate
- Decreased pulmonary diffusing capacity (DL_{CO}) due to loss of pulmonary capillaries, reduction in pulmonary capillary surface area, and sometimes an increase in diffusion path length due to fibrosis
- Patchy nature of fibrosis leads to severe inhomogeneity in ventilation and mismatching of ventilation and perfusion including areas of absent ventilation
- Pulmonary hypertension from decreased pulmonary capillary surface area, increased pulmonary vascular resistance, and regional alveolar hypoxia

45 Restrictive Lung Disease: Idiopathic Pulmonary Fibrosis, B

2. What are five events in the pathophysiology of idiopathic pulmonary fibrosis?

- Initial tissue injury
- Vascular injury and endothelial cell activation, with increased permeability, exudation of plasma proteins into the extravascular space, and variable thrombosis and thrombolysis
- Alveolar epithelial cell injury and activation, with loss of barrier integrity and release of proinflammatory mediators
- Increased leukocyte adherence to activated endothelium, with transit of activated leukocytes into the interstitium
- Continued injury and repair processes characterized by alterations in cell populations and increased matrix production

3. What are the symptoms and signs of idiopathic pulmonary fibrosis?

- An intermittent, irritating, non-productive cough is often the first symptom
- Dyspnea often results from decreased lung compliance and the increased work of breathing
- Tachypnea results from the attempt to maintain a normal alveolar minute ventilation (and hence normal $PaCO_2$) as lung volumes decrease
- Diffuse fine, dry inspiratory crackles are common and reflect the successive opening on inspiration of respiratory units that are collapsed due to the fibrosis and the loss of normal surfactant

46 Pulmonary Edema, A

A 72-year-old man presents to the emergency department complaining of severe shortness of breath. He has a history of coronary artery disease and two prior myocardial infarctions. About 1 week before admission, he had an episode of substernal chest pain lasting approximately 30 minutes. Since then, he has noted progressive shortness of breath to the point that he is now dyspneic on minimal exertion. When he lies down, he is only comfortable when propped up by three pillows. On examination, he is afebrile, with a blood pressure of 160/100 mm Hg, heart rate of 108/min, respiratory rate of 22/min, and oxygen saturation of 88% on room air. He is pale, cool, and diaphoretic. Jugular venous pressure is 10 cm H_2O. Chest auscultation reveals rales in both lungs to the mid lung fields. Cardiac examination is tachycardic, with an audible S_3 and S_4. No murmurs or rubs are heard. Extremities are without edema. The ECG shows left ventricular hypertrophy and Q waves in the anterior and lateral leads. Chest x-ray film reveals bilateral fluffy infiltrates consistent with pulmonary edema. He is admitted to the ICU with a diagnosis of heart failure and possible recent myocardial infarction.

1. What four factors can be involved in the production of pulmonary edema?

- An increase in the hydrostatic pressure gradient (cardiogenic pulmonary edema)
- An increase in vascular endothelial cell and/or alveolar epithelial cell permeability (noncardiogenic pulmonary edema)
- A decrease in the oncotic pressure gradient (due to low protein in the plasma)
- An impaired lymphatic drainage either from physical lymphatic obstruction or from lymphatic obliteration that can occur following radiation treatment

46 Pulmonary Edema, B

2. How does poor cardiac function cause pulmonary edema?

- Cardiogenic pulmonary edema results from elevated pulmonary venous and left atrial pressures due to left ventricular systolic or diastolic failure, mitral stenosis, or mitral regurgitation
  - This is primarily a mechanical process resulting in an ultrafiltrate of plasma
- Usually, pulmonary capillary pressure (ie, pulmonary capillary wedge pressure) must exceed ~20 mm Hg before the fluid leaving the vascular space exceeds the rate of resorption leading to accumulation of interstitial and alveolar fluid that is termed pulmonary edema

3. What is acute respiratory distress syndrome (ARDS)? What are its common causes?

- ARDS is the final common pathway of a number of different serious medical conditions, all of which lead to increased pulmonary capillary leak (noncardiogenic pulmonary edema)
- Many conditions, including sepsis, pneumonia, pancreatitis, aspiration of gastric contents, shock, lung contusion, non-thoracic trauma, toxic inhalation, near-drowning, and multiple blood transfusions, can lead to ARDS
  - Sepsis is the most common responsible condition, accounting for one third of all ARDS cases

47 Pulmonary Embolism, A

A 57-year-old man undergoes total knee replacement for severe degenerative joint disease. Four days after surgery, he develops an acute onset of shortness of breath and right-sided pleuritic chest pain. He is now in moderate respiratory distress with a respiratory rate of 28/min, heart rate of 120 bpm, and blood pressure of 110/70 mm Hg. Oxygen saturation is 90% on room air. Lung examination is normal. Cardiac examination reveals tachycardia but is otherwise unremarkable. The right lower extremity is postsurgical, healing well, with 2+ pitting edema, calf tenderness, erythema, and warmth; the left leg is normal. He has a positive Homan sign on the right. Acute pulmonary embolism is suspected.

1. From where do almost all pulmonary thromboemboli originate? What are the risk factors for pulmonary thromboemboli?

- More than 95% of pulmonary thromboemboli arise from the deep veins of the lower extremity: the popliteal, femoral, and iliac veins
- Risk factors include:
  - Venous stasis: bed rest, immobilization of the limb, obesity, incompetent venous valves, low cardiac output, pregnancy, hypervisicosity, central venous catheters, increasing age
  - Increased coagulability: tissue injury from surgery or trauma, malignancy, nephrotic syndrome, a lupus anticoagulant, oral contraceptives, genetic coagulation disorders

47 Pulmonary Embolism, B

2. What hemodynamic changes are brought about by significant pulmonary thromboemboli?

- Pulmonary embolism decreases perfusion distal to the site of the occlusion
- This increases $\dot{V}/\dot{Q}$ mismatching, with a shift in the proportion of lung segments with high $\dot{V}/\dot{Q}$ ratios (alveolar dead space or wasted ventilation)
- A shift toward high $\dot{V}/\dot{Q}$ ratios impairs the excretion of carbon dioxide with minimal effect on oxygenation initially
- The patient initially compensates for this wasted ventilation by increasing total minute ventilation
- Eventually, local hypoperfusion reduces surfactant production, causing edema, alveolar collapse, and atelectasis, creating lung units with little or no ventilation
- Depending on the level of perfusion to these segments, there will be an increased number of lung units with low $\dot{V}/\dot{Q}$ ratios, including some areas of true shunting. These, in turn, contribute to an increased A-a APO_2 and arterial hypoxemia

3. What changes in ventilation/perfusion relationships are brought about by significant pulmonary thromboemboli?

- Pulmonary emboli cause mechanical obstruction of the pulmonary circulation
- As the obstruction of pulmonary circulation increases, pulmonary artery pressures rise, ultimately leading to right ventricular strain
- In severe pulmonary embolism, occlusion of the pulmonary outflow tract may occur, severely reducing cardiac output and even causing death

48 Acute Respiratory Distress Syndrome (ARDS), A

A 46-year-old man presents to the hospital with a 5-day history of worsening cough, high fever, and shortness of breath. On physical examination, he is noted to be tachypneic (respiratory rate of 30 breaths/min), hypoxic with a low oxygen saturation (89%), and febrile (39°C). Chest x-ray film reveals infiltrates in both lower lobes. A complete blood count reveals a high white blood cell count. He is admitted to the hospital. Despite treatment with oxygen and antibiotics, he becomes more hypoxic and requires endotracheal intubation and mechanical ventilation. Blood cultures grow *Streptococcus pneumoniae*. Despite mechanical ventilation using high oxygen concentrations, his arterial blood oxygen level remains low. His chest x-ray film shows progression of infiltrates throughout both lung fields. He is diagnosed with ARDS.

1. What are the main pathophysiologic factors in ARDS that cause accumulation of extravascular fluid in the lungs?

- Alveolar fluid accumulates due to loss of integrity of the alveolar epithelial barrier, allowing molecules such as albumin to enter the alveolar space
- The presence of high-protein fluid in the alveolus, particularly the presence of fibrinogen and fibrin degradation products, inactivates pulmonary surfactant, causing large increases in surface tension
- This results in a fall in pulmonary compliance and alveolar instability, leading to areas of atelectasis
- Increased surface tension decreases the interstitial hydrostatic pressure and favors further fluid movement into the alveolus

48 Acute Respiratory Distress Syndrome (ARDS), B

2. What accounts for the severe hypoxia often found in ARDS, despite the use of mechanical ventilation and high concentrations of oxygen?

- Damage to endothelial and epithelial cells causes increased vascular permeability and reduced surfactant production and activity
- These abnormalities lead to interstitial and alveolar pulmonary edema, alveolar collapse, a significant increase in surface forces, markedly reduced pulmonary compliance, and hypoxemia
- As the process worsens, there may be a further fall in compliance and disruption of pulmonary capillaries, leading to areas of true shunting and refractory hypoxemia
- Since the underlying process is heterogeneous, with normal-appearing lung adjacent to atelectatic or consolidated lung, ventilating patients at typical tidal volumes may overdistend normal alveoli, reduce blood flow to areas of adequate ventilation, and precipitate further lung injury ("volu-trauma")
- Hypoxemia can be profound, typically followed days later by hypercapnia due to increasing dead space ventilation, for one third of all ARDS cases

3. What are the two major reasons that mechanical ventilation is often required in ARDS?

- The combination of increased work of breathing (from decreased compliance of the lungs and atelectasis) plus progressive hypoxemia usually requires mechanical ventilation

49 Arrhythmia, A

A 25-year-old man presents to the hospital with lightheadedness and palpitations for the past 2 hours. He had four or five previous episodes of palpitations in the past, but they had lasted only a few minutes and went away on their own. These episodes were not associated with any specific activity or diet. He denies any chest pain. On physical examination, he is noted to be tachycardic with a heart rate of 180 bpm and a blood pressure of 105/70 mm Hg. An ECG shows a wide complex tachycardia at 180 bpm. The tachycardia terminates suddenly, and the patient's heart rate drops to 90 bpm. A repeat ECG shows sinus rhythm with a short PR interval and a wide QRS with a slurred upstroke (delta wave). The patient is diagnosed as having the Wolff-Parkinson-White syndrome.

1. What class of tachycardia occurs in the Wolff-Parkinson-White syndrome, and how common is it?

- The Wolff-Parkinson-White syndrome is probably the best studied example of a **reentrant tachyarrhythmia**
- Such tachyarrhythmias arise from a reentrant circuit (see below)
- The Wolff-Parkinson-White syndrome occurs in approximately 1 in 1000 persons

49 Arrhythmia, B

2. What is the main pathophysiologic abnormality that allows the tachycardia in the Wolff-Parkinson-White syndrome to develop?

- In the Wolff-Parkinson-White syndrome, an accessory pathway is present that is usually composed of normal atrial or ventricular tissue
- Because part of the ventricle is "pre-excited" over the accessory pathway rather than via the atrioventricular (AV) node, the surface ECG shows a short PR interval and a relatively wide QRS with a slurred upstroke, termed a **delta wave**
- Because the atria and ventricles are linked by two parallel connections (the AV node and the accessory pathway), reentrant tachycardias are readily initiated

3. What is a common sequence of events that can initiate a reentrant circuit in the Wolff-Parkinson-White syndrome?

- A premature atrial contraction takes place when the AV nodes are ready to conduct, but the accessory pathway is still refractory
- The impulse conducts to the ventricles via the AV node
- By the time the impulse reaches the accessory pathway, enough time has elapsed so that the accessory pathway has recovered excitability
- The cardiac impulse can travel in retrograde fashion to the atria over the accessory pathway and initiate a reentrant tachycardia

50 Heart Failure, A

A 66-year-old woman presents to the clinic with shortness of breath, leg swelling, and fatigue. She has a long history of type 2 diabetes and hypertension but until recently had been able to go for daily walks with her friends. In the past month, the walks have become more difficult due to shortness of breath and fatigue. She also sometimes awakens in the middle of the night due to shortness of breath and has to prop herself up on three pillows. On physical examination, she is noted to be tachycardic with a heart rate of 110 bpm and a blood pressure of 105/70 mm Hg. Her lung examination is notable for fine crackles on inspiration at both bases. Her cardiac examination is notable for the presence of a third and fourth heart sound and jugular venous distension. She has 2+ pitting edema to the knees bilaterally. An ECG shows sinus rhythm at 110 bpm with Q waves in the anterior leads. An echocardiogram shows decreased wall motion of the anterior wall of the heart and an estimated ejection fraction of 25%. She is diagnosed with systolic heart failure, likely secondary to a silent myocardial infarction.

1. What are the four general categories that account for almost all causes of heart failure (HF)?

- Inappropriate workloads placed on the heart, such as volume overload (eg, from aortic regurgitation) or pressure overload (eg, from long-standing hypertension or from aortic stenosis)
- Restricted filling of the heart (eg, from constrictive pericarditis)
- Myocyte loss (eg, myocardial infarction, as in this case)
- Decreased myocyte contractility (eg, from hypocalcemia)

2. What are the differences between the pathophysiology of HF resulting from systolic versus diastolic dysfunction?

- In **systolic dysfunction**, the isovolumic systolic pressure curve of the pressure-volume relationship is shifted downward
- This reduces the stroke volume of the heart with a concomitant decrease in cardiac output
- The heart can respond with three compensatory mechanisms: first, increased return of blood to the heart (preload) can lead to increased contraction of sarcomeres; second, increased release of catecholamines can increase cardiac output by both increasing the heart rate and shifting the systolic isovolumetric curve to the left; and third, cardiac myocytes can hypertrophy and ventricular volume can increase, which shifts the diastolic curve to the right
- Although each of these compensatory mechanisms can temporarily maintain cardiac output, each is limited in its ability to do so, and if the underlying reason for systolic dysfunction remains untreated, HF ultimately supervenes
- In **diastolic dysfunction**, the position of the systolic isovolumic curve remains unchanged (contractility of the myocytes is preserved), but the diastolic pressure-volume curve is shifted to the left, with an accompanying increase in left ventricular end-diastolic pressure and symptoms of HF
- Diastolic dysfunction can be present in any disease that causes decreased relaxation, decreased elastic recoil, or increased stiffness of the ventricle such as hypertension or ischemia
- In most patients, a combination of systolic and diastolic dysfunction is responsible for the symptoms of HF

51 Valvular Heart Disease: Aortic Stenosis, A

A 59-year-old man is brought to the emergency department by ambulance after experiencing a syncopal episode. He states that he was running in the park when he suddenly lost consciousness. He denies any symptoms preceding the event, and he had no deficits or symptoms upon arousing. On review of systems, he does say that he has had substernal chest pressure associated with exercise for the past several weeks. Each episode was relieved with rest. He denies shortness of breath, dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea. His medical history is notable for multiple episodes of pharyngitis as a child. On examination, his blood pressure is 110/90 mm Hg, heart rate 95 bpm, respiratory rate 15/min, and oxygen saturation 98%. Neck examination reveals both pulsus parvus and pulsus tardus. Cardiac examination reveals a laterally displaced and sustained apical impulse. He has a grade 3/6 midsystolic murmur, loudest at the base of the heart, radiating to the neck, and a grade 1/6 high-pitched, blowing, early diastolic murmur along the left sternal border. An S_4 is audible. Lungs are clear to auscultation. Abdominal examination is benign. He has no lower extremity edema. Aortic stenosis is suspected.

1. What are the most common causes of aortic stenosis?

- Congenital abnormalities (unicuspid, bicuspid, or fused leaflets)
- Rheumatic heart disease resulting from streptococcal pharyngitis
- Degenerative valve disease resulting from calcium deposition

51 Valvular Heart Disease: Aortic Stenosis, B

2. How does aortic stenosis cause syncope?

- The fixed obstruction in aortic stenosis causes decreased cerebral perfusion
- Transient atrial arrhythmias with loss of effective atrial contribution to ventricular filling can cause syncope
- Ventricular arrhythmias are more common in patients with aortic stenosis and can result in syncope.

3. What is the pathophysiologic mechanism by which aortic stenosis causes angina pectoris?

- Approximately half of all patients have comorbid significant coronary artery disease, which can lead to angina
- Even without coronary artery disease, aortic stenosis causes compensatory ventricular hypertrophy with an increase in oxygen demand as well as compression of the vessels traversing the cardiac muscle, resulting in decreased oxygen supply to the myocytes
- Finally, in the case of calcified aortic valves, calcium emboli can cause coronary artery obstruction, although this is rare

52 Valvular Heart Disease: Aortic Regurgitation, A

A 64-year-old man presents to the clinic with a 3-month history of worsening shortness of breath. He finds that he becomes short of breath after walking one block or up one flight of stairs. He awakens at night, gasping for breath, and has to prop himself up with pillows in order to sleep. On physical examination, his blood pressure is 190/60 mm Hg and his pulses are hyperdynamic. His apical impulse is displaced to the left and downward. On physical examination, there are rales over both lower lung fields. On cardiac examination, there are three distinct murmurs: a high-pitched, early diastolic murmur loudest at the left lower sternal border, a diastolic rumble heard at the apex, and a crescendo-decrescendo systolic murmur heard at the left upper sternal border. Chest x-ray film shows cardiomegaly and pulmonary edema, and an echocardiogram shows severe aortic regurgitation with a dilated and hypertrophied left ventricle.

1. What are the most common causes of aortic regurgitation?

- The pathogenesis of aortic regurgitation can be divided into valvular and aortic causes
- Valvular causes: congenital abnormalities, rheumatic heart disease, ankylosing spondylitis, and infective endocarditis
- Aortic causes: aortic aneurysm, connective tissue disorders (eg, Marfan syndrome), aortic inflammation (eg, syphilis and Takayasu arteritis), and dissection (eg, trauma or hypertension)

52 Valvular Heart Disease: Aortic Regurgitation, B

2. What are the pathophysiologic consequences of aortic regurgitation?

- In aortic regurgitation, blood enters the ventricle both from the left atrium and from the aorta during diastole, placing an abnormally high volume load on the left ventricle
- When regurgitation develops gradually, the heart can respond with "eccentric hypertrophy" or enlargement and displacement of the ventricle
- Chronic aortic regurgitation leads to huge ventricular volumes
- Aortic pulse pressure is widened with: (1) decreased diastolic pressure from the regurgitant flow back into the left ventricle; (2) increased compliance of the large central vessels; and (3) increased systolic pressures from elevated stroke volume

3. What are the major clinical manifestations of aortic regurgitation?

- The most common symptom is shortness of breath, resulting from heart failure, and development of pulmonary edema
- Physical examination findings include hyperdynamic pulses, a widened pulse pressure, three distinct murmurs (two diastolic and one systolic), a third heart sound, and a laterally displaced apical impulse

53 Valvular Heart Disease: Mitral Stenosis, A

A 45-year-old man presents with a history of shortness of breath, irregular heartbeat, and hemoptysis. He notes that over the past 2 weeks, he has become easily "winded" with minor activities. Also, he has coughed up some flecks of blood on a few occasions. He has noted a fast heartbeat and, on occasion, a pounding sensation in his chest. He gives a history of being ill for several weeks after a severe sore throat in childhood. On physical examination, his pulse rate is noted to be 120–130 bpm and his rhythm, irregularly irregular. He has distended jugular venous pulses and rales at the bases of both lung fields. On cardiac examination, there is an irregular heartbeat as well as a soft diastolic decrescendo murmur, loudest at the apex. An ECG shows atrial fibrillation as well as evidence of left atrial enlargement. An echocardiogram shows severe mitral stenosis.

1. What are the most common causes of mitral stenosis?

- Rheumatic heart disease is the most common cause, with symptoms developing up to 20 years after acute rheumatic fever
- Calcific mitral valve usually causes mitral regurgitation but can cause mitral stenosis
- Congenital mitral stenosis
- Collagen vascular disease such as systemic lupus erythematosus (rarely)

53 Valvular Heart Disease: Mitral Stenosis, B

2. What is the pathophysiology of mitral stenosis?

- The most common symptom is shortness of breath and hemoptysis resulting from elevated left atrial, pulmonary venous, and pulmonary capillary pressures
- Increased left atrial size predisposes patients with mitral stenosis to atrial arrhythmias such as atrial fibrillation
- Dilation of the left atrium and stasis of blood flow lead to thrombus formation in the left atrium in approximately 20% of patients with mitral stenosis
- The mitral valve is normally bicuspid, with the anterior cusp approximately twice the area of the posterior cusp
- The mitral valve area is usually 5–6 cm^2; clinically relevant mitral stenosis usually occurs when the valve area decreases to less than 1 cm^2
- Obstruction of flow causes elevation in left atrial pressures, elevated pulmonary venous pressure, and elevated right-sided pressures (pulmonary artery, right ventricle, and right atrium)
- Dilation and reduced systolic function of the right ventricle are commonly observed in patients with advanced mitral stenosis

3. What are the major clinical manifestations of mitral stenosis?

- This can lead to an embolic event and subsequent neurologic symptoms in 8% of patients with sinus rhythm and in 32% of patients with atrial fibrillation
- During auscultation, one can hear a diastolic rumble because of turbulent flow across the narrowed mitral valve orifice along with an opening snap

54 Valvular Heart Disease: Mitral Regurgitation, A

A 59-year-old man presents to the emergency department with a 4-hour history of "crushing" chest pain. His cardiac examination is normal with no murmurs and normal heart sounds. An ECG reveals ST segment elevation in the lateral precordial leads and cardiac enzymes show evidence of myocardial injury. He undergoes emergent cardiac catheterization that shows a thrombus in the left circumflex coronary artery. He undergoes successful angioplasty, and a stent is placed. He is monitored in the cardiac intensive care unit. He does well until the next day, when he develops sudden shortness of breath and decreasing oxygen saturations. Physical examination now reveals jugular venous distention, rales at both lung bases, and a blowing holosystolic murmur loudest at the apex, radiating into the axilla.

1. What are the most common causes of mitral regurgitation?

- Ruptured chordae tendineae from infective endocarditis, trauma, or acute rheumatic fever
- Ruptured or dysfunctional papillary muscles from ischemia, myocardial infarction, trauma, or abscess
- Perforated leaflet from endocarditis or trauma
- Inflammatory causes such as rheumatic heart disease or collagen vascular disease
- Destruction from myxomatous degeneration (due to underlying mitral valve prolapse) or calcification of the mitral annulus
- Congenital valvular abnormalities
- Many of the above conditions can be acute or chronic

54 Valvular Heart Disease: Mitral Regurgitation, B

2. What is the pathophysiology of mitral regurgitation?

- Regurgitation of blood into the left atrium from the ventricle during systole leads to dilation of the left ventricle and atrium
- Concomitant hypertrophy of the ventricular wall
- Diastolic filling of the ventricle increases with the sum of right ventricular output and the regurgitant volume from the previous beat

- In acute mitral regurgitation, chamber enlargement and/or hypertrophy cannot compensate for the sudden volume load on the atrium and ventricle
- The sudden increase in atrial volume leads to prominent atrial v waves with transmission of this elevated pressure to the pulmonary capillaries and the subsequent development of pulmonary edema

3. What are the major clinical symptoms of mitral regurgitation?

- In chronic mitral regurgitation, the most common symptom is shortness of breath, resulting from heart failure, whereas in acute mitral regurgitation, pulmonary edema can develop suddenly

- Fatigue can develop due to lack of forward blood flow to the peripheral tissues
- Left atrial enlargement may lead to the development of atrial fibrillation and accompanying palpitations with a 20% incidence of cardioembolic events

55 Coronary Artery Disease, A

A 55-year-old man presents to the clinic complaining of chest discomfort. He states that for the past 5 months he has noted intermittent substernal chest "pressure" radiating to the left arm. The discomfort occurs primarily when exercising vigorously and is relieved with rest. He denies associated shortness of breath, nausea, vomiting, or diaphoresis. He has a medical history significant for hypertension and hyperlipidemia. He is taking atenolol for his high blood pressure and is eating a low-cholesterol diet. His father died of myocardial infarction at age 56 years. He has a 50-pack-year smoking history and is currently trying to quit. His physical examination is within normal limits with the exception of his blood pressure, which is 145/95 mm Hg, with a heart rate of 75 bpm.

1. What is the clinical presentation of coronary artery disease along the continuum from stable angina to unstable angina to myocardial infarction?

- Angina, the chest pain associated with coronary artery disease, is classified according to the precipitant and the duration of symptoms
  - Stable angina is present if the pain occurs only with exertion and has been stable over a long period of time
  - Unstable angina is pain that occurs at rest but comes and goes
  - When angina continues uninterruptedly for a prolonged period, myocyte damage results and is referred to as a myocardial infarction

55 Coronary Artery Disease, B

2. How do the pathophysiologies of stable angina, unstable angina, and myocardial infarction differ?

- Stable angina results from a fixed narrowing of one or more coronary arteries
- The arterial lumen must be decreased by 90% to produce cellular ischemia when the patient is at rest, but during exercise, a 50% reduction in lumen size can lead to symptoms since cardiac demand rises greatly
- In unstable angina, fissuring of the atherosclerotic plaque can lead to platelet accumulation and transient episodes of thrombotic occlusion (usually 10–20 minutes)
- Platelet release of vasoconstrictive factors such as thromboxane A_2 or serotonin and endothelial dysfunction may cause vasoconstriction and further decrease coronary blood flow
- In myocardial infarction, deep arterial injury from plaque rupture may cause formation of a relatively fixed and persistent thrombus, which leads to myocyte damage and death

3. What are the major clinical manifestations of coronary artery disease?

- The most common symptoms are:
  - Chest pain (although up to 70–80% of ischemic episodes can be silent)
  - Shortness of breath and a fourth heart sound from systolic and diastolic dysfunction
  - Shock, bradycardia or tachycardia, and nausea and vomiting

56 Pericarditis, A

A 35-year-old man presents to the emergency department complaining of chest pain. The pain is reported as an "8" on a scale ranging from 1 to 10. It is retrosternal in location and sharp in nature. It radiates to the back, is worse with taking a deep breath, and is improved by leaning forward. On review of systems, he has noted a "flu-like illness" over the past several days, including fever, rhinorrhea, and cough. He has no medical history and is taking no medications. He denies tobacco, alcohol, or drug use. On physical examination, he is in moderate distress from pain and has a blood pressure of 125/85 mm Hg, heart rate of 105 bpm, respiratory rate of 18/min, and oxygen saturation of 98% on room air. He is afebrile. His head and neck examination is notable for clear mucus in the nasal passages and a mildly erythematous oropharynx. The neck is supple, with shotty anterior cervical lymphadenopathy. The chest is clear to auscultation. Jugular veins are not distended. Cardiac examination reveals tachycardia with a three-component high-pitched squeaking sound. Abdominal and extremity examinations are normal.

1. What is the clinical presentation of pericarditis?

- The main symptoms are severe chest pain that is sharp and retrosternal, radiates to the back, is worse with lying flat or deep breathing, and improves by leaning forward
- The pericardial rub is a high-pitched musical sound, often with two or more components. It is pathognomonic of pericarditis
- Prolonged inflammation of the pericardium can lead to fibrosis and constrictive pericarditis with elevated jugular venous pressure and an inappropriate increase in the jugular venous pulsation level with inspiration (Kussmaul sign)

2. What are the most common causes of pericarditis?

- Infection: coxsackievirus, tuberculosis, staphylococcus, pneumococcus, amebiasis, actinomycosis, and coccidioidomycosis
- Inflammation from a collagen vascular disease: systemic lupus erythematosus, scleroderma, and rheumatoid arthritis
- Neoplasm: metastatic disease is most common
- Metabolic: chronic kidney disease
- Injury: myocardial infarction, postinfarction, post-thoracotomy, trauma, and radiation
- Idiopathic

3. What are the sounds heard on cardiac examination and what are the causes?

- The squeaking sound described here is a pericardial rub originating from friction between the visceral and parietal pericardial surfaces
- The rub is traditionally described as having three components, each associated with rapid movement of a cardiac chamber
- The systolic component, which is probably related to ventricular contraction, is most common and most easily heard
- The early diastolic component results from rapid filling of the ventricle, and the late diastolic (quieter) component is thought to be due to atrial contraction
- The diastolic components often merge so that a two-component or "to-and-fro" rub is most commonly heard

57 Pericardial Effusion with Tamponade, A

A 65 year-old woman is hospitalized with a large anterior myocardial infarction. After 4 days in the hospital, she is doing well and plans are being made for discharge to a rehabilitation facility to help her regain her strength and recover her cardiac function. While going to the bathroom, she passes out suddenly. On examination, her blood pressure is 60/40 mm Hg, her heart rate is 120, and she has distant heart sounds. An emergent echocardiogram shows rupture of the anterior wall and pericardial tamponade.

1. What are the signs of pericardial tamponade?

- Three classic signs of pericardial tamponade (Beck triad) are hypotension, elevated jugular venous pressure, and muffled heart sounds
- The patient may have a decrease in systemic pressure with inspiration (paradoxic pulse)

2. What is the pathophysiology of the paradoxic pulse in tamponade?

- Marked inspiratory decline in left ventricular stroke volume occurs because of decreased left ventricular end-diastolic volume
- With inspiration, increased blood return augments filling of the right ventricle, which causes the interventricular septum to bow to the left and reduce left ventricular end-diastolic volume
- Also, flow into the left atrium from the pulmonary veins is reduced

57 Pericardial Effusion with Tamponade, B

3. What are the most common causes of pericardial effusion and tamponade?

- The causes are similar to the causes of pericarditis
- Infection: coxsackievirus, tuberculosis, staphylococcus, pneumococcus, amebiasis, actinomycosis, and coccidioidomycosis
- Inflammation from a collagen vascular disease: systemic lupus erythematosus, scleroderma, and rheumatoid arthritis
- Neoplasm: metastatic disease is most common
- Metabolic: chronic kidney disease
- Injury: myocardial infarction, postinfarction, post-thoracotomy, trauma, radiation, and aortic dissection
- Idiopathic

58 Atherosclerosis, A

A 65-year-old woman presents to the clinic to establish care. Her past medical history is notable for type 2 diabetes and hypertension. She has a 45-pack-year smoking history. A few weeks ago, she was shoveling her driveway when she had to stop due to tightness in her chest. She does not get any regular exercise due to the fact that her calves become very painful after walking one block.

1. What is the hypothesized mechanism of atherosclerotic plaque formation?

- The initial event in atherosclerosis is infiltration of low-density lipoproteins (LDLs) into the subendothelial region, especially at arterial branch points
- The LDLs are oxidized or altered and activate macrophages, natural antibodies, and proteins such as C-reactive protein and complement
- This stimulates uptake of the oxidized LDL into macrophages and the formation of foam cells, which turn into fatty streaks
- Vascular smooth muscle cells in the vicinity of foam cells are stimulated and move from the media to the intima where they proliferate, lay down collagen and other matrix molecules, and contribute to the bulk of the lesion
- In addition, the "loading" of macrophages with cholesterol can be lipotoxic to the endoplasmic reticulum, resulting in macrophage apoptosis and plaque necrosis
- Cholesterol crystals associated with necrotized macrophages further stimulate inflammation and lead to the recruitment of neutrophils, T cells, and monocytes, creating a vicious cycle of necrosis and inflammation
- As plaques mature, a fibrous cap forms over them, which can block flow directly or rupture and cause an acute thrombosis

58 Atherosclerosis, B

2. What are some ways in which atherosclerotic plaques can cause cardiovascular disease?

- In coronary arteries, atherosclerotic narrowing that reduces the lumen of a coronary artery more than 75% can cause angina pectoris, the chest pain that results when pain-producing substances accumulate in the myocardium during exertion
- Typically, the pain comes on during exertion and disappears with rest as the substances are washed out by the blood
- When atherosclerotic lesions cause clotting and occlusion of a coronary artery, the myocardium supplied by the artery dies (myocardial infarction)

3. Name five treatable risk factors that accelerate the progression of atherosclerosis.

- Hypertipidemia, which is treatable with cholesterol-lowering medications and diet
- Cigarette smoking, which is treatable with smoking cessation
- Hypertension, which is treatable with medications and lifestyle changes
- Diabetes mellitus, which is treatable with diet and medications to achieve better glycemic control
- Obesity, particularly abdominal obesity, which is treatable with weight loss from decreased caloric intake and increased exercise

59 Hypertension, A

A 56-year-old African American man presents to the clinic for a routine physical examination. He has not seen a physician for 10 years. On arrival, he is noted to have a blood pressure of 160/90 mm Hg.

1. Describe five physical findings in long-standing or severe hypertension.

- Hypertensive retinopathy, which is observed as narrowed arterioles seen on fundoscopic examination
- Retinal hemorrhages and exudates along with swelling of the optic nerve head (papilledema)
- Left ventricular hypertrophy, which can be detected by echocardiography or ECG, and cardiac enlargement, which can be detected on physical examination
- Renal bruits from narrowing of the renal arteries
- A blood pressure rise on standing sometimes occurs in essential hypertension presumably because of a hyperactive sympathetic response to the erect posture. This rise is usually absent in other forms of hypertension

59 Hypertension, B

2. Name the known causes of hypertension.

- Essential hypertension is the most common
- Renal: renovascular (atherosclerosis or fibromuscular dysplasia) or parenchymal (chronic kidney disease, obstructive uropathy)
- Endocrine: primary aldosteronism, Cushing syndrome, pheochromocytoma, adrenal enzyme deficiencies, hyperthyroidism, hyperparathyroidism, and acromegaly
- Obesity and metabolic syndrome
- Drug related: estrogen, androgens, corticosteroids, nonsteroidal anti-inflammatory drugs, cocaine, amphetamine, alcohol, decongestants, appetite suppressants, antidepressants, cyclosporine, and tacrolimus
- Other: pre-eclampsia, coarctation of the aorta, sleep apnea, polycythemia, and increased intracranial pressure

3. What is the effect on blood pressure of disrupting the gene for the endothelial cell form of nitric oxide synthase (NOS) in mice?

- In experimental animals, there is an increase in blood pressure following the administration of drugs that inhibit the production of NO and a sustained elevation in blood pressure in mice with genetic ablation of the endothelial form of NOS
- Thus, there may be a chronic blood pressure–lowering effect of NO. Inhibition of the production or effects of NO may thus be a cause of hypertension in humans

60 Shock, A

A young woman is brought to the emergency department by ambulance after a severe motor vehicle accident. She is unconscious. Her blood pressure is 64/40 mm Hg; heart rate is 150 bpm. She is intubated and is being hand-ventilated. There is no evidence of head trauma. The pupils are 2 mm and reactive. She withdraws to pain. Cardiac examination reveals no murmurs, gallops, or rubs. The lungs are clear to auscultation. The abdomen is tense, with decreased bowel sounds. The extremities are cool and clammy, with thready pulses. Despite aggressive blood and fluid resuscitation, the patient dies.

1. What are the four major pathophysiologic forms of shock?

- The four major pathophysiologic types of shock are hypovolemic (loss of blood or fluid), distributive (dilation of blood vessels), cardiogenic (decreased cardiac output), and obstructive (blockage such as from a massive pulmonary embolism)

2. Describe five specific forms of hypovolemic shock.

- Hemorrhagic: due to loss of blood from the body
- Traumatic: damage to muscle and bone with bleeding into the damaged areas
- Surgical: combination of loss of blood, bleeding into tissues, and dehydration
- Burns: loss of plasma from burn surfaces
- Fluid losses: vomiting, diarrhea, or sweating

60 Shock, B

3. Name three specific forms of distributive shock and distinguish them from hypovolemic shock.

- In distributive shock, vasodilation causes the skin to be warm, whereas in hypovolemic shock, the skin is cold and clammy
- In anaphylactic shock, an accelerated allergic reaction releases large amounts of histamine, producing marked vasodilation
  - Blood pressure falls because the size of the vascular system exceeds the amount of blood in it even though blood volume is normal
- In neurogenic shock, a sudden loss of sympathetic autonomic activity (as seen in head and spinal cord injuries) results in vasodilation and pooling of blood in the veins
  - The resulting decrease in venous return reduces cardiac output and frequently produces fainting, or syncope, a sudden transient loss of consciousness
- In septic shock, loss of plasma into the tissues ("third spacing") results in hypotension
  - In addition to the loss of plasma, cardiogenic shock results from toxins that depress the myocardium

61 Pheochromocytoma, A

A 39-year-old woman comes to the office complaining of episodic anxiety, headache, and palpitations. Without dieting, she has lost 15 pounds over the past 6 months. Physical examination is normal except for a blood pressure of 200/100 mm Hg and a resting pulse rate of 110 bpm. Chart review shows that prior blood pressures have always been normal, including one 6 months ago. A pheochromocytoma diagnosis is entertained.

1. Which catecholamines are secreted by the human adrenal medulla? Of these, which is the major product?

- The adrenal medulla secretes epinephrine, norepinephrine, and dopamine
- Most (80%) of the catecholamine output of the adrenal medulla is epinephrine

2. What genetic mutations are found in patients with pheochromocytoma?

- 10 known susceptibility genes are associated with familial pheochromocytoma and/or paraganglioma. Examples include:
  - Neurofibromatosis type 1 (Recklinghausen disease): *NF1* gene mutations
  - Von Hippel–Lindau syndrome: *VHL* tumor suppressor gene mutation
  - Multiple endocrine neoplasia type 2 (MEN-2): missense point mutations in the *RET* proto-oncogene
- 10–20% of sporadic cases and most familial cases of familial pheochromocytoma and/or paraganglioma carry germline mutations in *VHL, RET, NF1, SDHA, SDHB, SDHC, SDHD, SDHAF2, TMEM127*, or *MAX*. Somatic mutations in *VHL* and *RET* occur in 10–15% of tumors

61 Pheochromocytoma, B

3. What are some complications of untreated pheochromocytoma?

- Hypertensive retinopathy (retinal hemorrhages or papilledema)
- Nephropathy
- Myocardial infarction resulting from either catecholamine-induced myocarditis and/or dilated cardiomyopathy or coronary artery vasospasm and cardiovascular collapse (sometimes fatal)
- Pulmonary edema, secondary either to left-sided heart failure or noncardiogenic causes
- Stroke from cerebral infarction, intracranial hemorrhage, or embolism from mural thrombi in dilated cardiomyopathy
- Ileus, obstipation, and abdominal discomfort resulting from a large adrenal mass
- Maternal morbidity and fetal demise in pregnancy
- Increased blood sugar levels, even diabetes mellitus
- Increased blood lactate concentrations
- Weight loss (or, in children, lack of weight gain) from an increase in metabolic rate
- Mild basal body temperature elevation, heat intolerance, flushing, or sweating
- Marked anxiety, visual disturbances, paresthesias, or seizures and psychosis or confusion during paroxysms
- Paraneoplastic syndromes: hypercalcemia (excessive production of PTH-related peptide [PTHrP] or PTH itself in MEN-2a); or Cushing syndrome (ectopic production of ACTH)

62 Achalasia, A

A 60-year-old man presents to the clinic with a 3-month history of gradually worsening dysphagia (difficulty swallowing). At first, he noticed the problem when eating solid food such as steak, but now it happens even with drinking water. He has a sensation that whatever he swallows becomes stuck in his chest and does not go into the stomach. He has also developed worsening heartburn, especially upon lying down, and has had to prop himself up at night to lessen the heartburn. He has lost 10 kg as a result of his swallowing difficulties. His physical examination is unremarkable. A barium swallow x-ray reveals a decrease in peristalsis of the body of the esophagus along with dilatation of the lower esophagus and tight closure of the lower esophageal sphincter. There is a beaked appearance of the distal esophagus involving the lower esophageal sphincter. There is very little passage of barium into the stomach.

1. What is the role of the lower esophageal sphincter structure in achalasia?

- Achalasia is a condition where the lower esophageal sphincter fails to relax
- The lower esophageal sphincter is a 3–4 cm ring of smooth muscle that is usually contracted, under stimulation by vagal cholinergic inputs
- When a swallow is initiated, vagal inhibitory fibers allow the sphincter to relax so that the bolus of food can pass into the stomach
- In achalasia, there is degeneration of the myenteric plexus and loss of the inhibitory neurons that allow this relaxation
- Therefore, the sphincter remains tightly closed
- The neural dysfunction can also extend further up the esophagus as well, and effective esophageal peristalsis is also often lost

62 Achalasia, B

2. What are possible causes of achalasia?

- In most cases, the underlying cause of esophageal achalasia is unknown
- Degeneration of the myenteric plexus and loss of inhibitory neurons that release vasointestinal peptide (VIP) and nitric oxide, which dilate the lower esophageal sphincter, may contribute
- Esophageal involvement in Chagas disease, resulting from damage to the neural plexuses of the esophagus by the parasite *Trypanosoma cruzi*, bears a striking resemblance to esophageal achalasia
- A number of other disorders, including malignancies, may present with manometric pressure characteristics or radiographic features similar to those observed in idiopathic esophageal achalasia

63 Reflux Esophagitis, A

A 32-year-old woman presents to her primary care provider complaining of a persistent burning sensation in her chest and upper abdomen. The symptoms are worse at night while she is lying down and after meals. She has tried drinking hot cocoa to help her sleep. She is a smoker and frequently relies on benzodiazepines for insomnia. She notes a sour taste in her mouth every morning. Physical examination is normal.

1. What is the role of the lower esophageal sphincter structure in reflux esophagitis?

- Normally, the lower esophageal sphincter is tonically contracted, preventing the reflux of acid from the stomach back into the esophagus
- This is reinforced by secondary esophageal peristaltic waves in response to transient lower esophageal sphincter relaxations
- Effectiveness of that barrier can be altered by loss of lower esophageal sphincter tone (ie, the opposite of achalasia), increased frequency of transient relaxations, loss of secondary peristalsis after transient relaxations, increased stomach volume or pressure, or increased production of acid, all of which can make more likely reflux of acidic stomach contents sufficient to cause pain or erosion
- Recurrent reflux can damage the mucosa, resulting in inflammation, hence the term "reflux esophagitis"
- Recurrent reflux itself predisposes to further reflux because the scarring that occurs with healing of the inflamed epithelium renders the lower esophageal sphincter progressively less competent as a barrier

63 Reflux Esophagitis, B

2. What is the relationship of esophageal reflux to Barrett esophagus and cancer?

- Chronic recurrent reflux can also result in a change in the esophageal epithelium from a squamous to columnar histology (resembling that of the stomach and/or intestine)
- Termed Barrett esophagus, the disorder is more common in men and in smokers, and it leads to a greatly increased risk of adenocarcinoma
- Adenocarcinomas in the distal esophagus and proximal (cardiac) stomach related to Barrett esophagus are among the most rapidly increasing types of cancer in young, male patients in the United States

3. What are some other possible causes of reflux esophagitis?

- Occasionally, reflux esophagitis is caused by alkaline injury (eg, pancreatic juice refluxing through both an incompetent pyloric sphincter and a relaxed lower esophageal sphincter)
- Hiatal hernia, a disorder in which a portion of the proximal stomach slides into the chest cavity with upward displacement of the lower esophageal sphincter, can contribute to the development of reflux

64 Acid-Peptic Disease, A

A 74-year-old man with severe osteoarthritis presents to the emergency department reporting two episodes of melena (black stools) without hematochezia (bright red blood in the stools) or hematemesis (bloody vomitus). He takes 600 mg of ibuprofen three times a day to control his arthritis pain. He denies alcohol use. On examination, his blood pressure is 150/70 mm Hg and his resting pulse is 96/min. His epigastrium is minimally tender to palpation. Rectal examination reveals black tarry stool in the vault, grossly positive for occult blood. Endoscopy demonstrates a 3 cm gastric ulcer. *Helicobacter pylori* is identified on biopsies of the ulcer site.

1. How might motility defects contribute to gastric ulcer?

- Motility defects have been proposed to contribute to development of gastric ulcer in at least three ways:
  - A tendency of duodenal contents to reflux back through an incompetent pyloric sphincter (bile acids in the duodenal reflux material act as an irritant and may be an important contributor to a diminished stomach mucosal barrier)
  - Delayed emptying of gastric contents, including reflux material, into the duodenum
  - Delayed gastric emptying and hence food retention, resulting in increased gastrin secretion and gastric acid production
- It is not known whether these motility defects are a cause or a consequence of gastric ulcer formation

64 Acid-Peptic Disease, B

2. How do NSAIDs contribute to acid-peptic disease?

- NSAIDs may predispose to ulcer formation by attenuating the barrier created by the epithelial cells and the bicarbonate or mucus they secrete
- NSAIDs also reduce the quantity of prostaglandins the epithelial cells produce that might otherwise diminish acid secretion

3. What evidence indicates the importance of *H pylori* infection in acid-peptic disease?

- Of patients who do develop acid-peptic disease, especially among those with duodenal ulcers, the vast majority have *H pylori* infection
- Treatment that does not eradicate *H pylori* is associated with rapid recurrence of acid-peptic disease in most patients
- There are numerous strains of *H pylori* that vary in their production of toxins such as CagA and VacA that directly alter cellular signaling pathways
- As many as 90% of infected individuals show signs of inflammation (gastritis or duodenitis) on endoscopy, although many of these individuals are clinically asymptomatic
- Despite this high rate of association of inflammation with *H pylori* infection, the important role of other factors is indicated by the fact that only about 15% of infected individuals ever develop a clinically significant ulcer

65 Gastroparesis, A

A 67-year-old man with type 2 diabetes mellitus is seen by his primary care provider for frequent nausea, bloating, and intermittent diarrhea over the preceding 2 weeks. The vomiting typically occurs approximately 1–2 hours after eating. He states that over the past year, he has become increasingly depressed after the death of his wife and has been less adherent to his oral hypoglycemic regimen and evening insulin. He also reports 6 months of worsening neuropathic pain in his feet. His fasting fingerstick blood glucose level is 253 mg/dL, and his hemoglobin A_{1C} is 10.5%.

1. What are the symptoms of delayed versus rapid gastric emptying?

- Delayed gastric emptying causes symptoms of stomach distension, nausea, early satiety, and vomiting
- However, in some cases, delayed emptying can result in symptoms expected from excessively rapid emptying
  - An excessively contracted pylorus that can open completely but that does so infrequently can result in entry into the duodenum of too large a bolus of chyme from the excessively distended stomach
  - Such a bolus may not be efficiently handled by the small intestine, resulting in poor absorption and diarrheal symptoms characteristic of the dumping syndrome

65 Gastroparesis, B

2. What are the complications of gastroparesis?

- Development of bezoars from retained gastric contents
- Bacterial overgrowth from stasis of food
- Erratic blood glucose control
- Weight loss when nausea and vomiting are profound

- Elevated blood glucose can be either a cause or a consequence of delayed gastric emptying
- Bacterial overgrowth itself can result in both malabsorption and diarrhea

3. Why might erythromycin improve diabetic gastroparesis?

- Hormones play an ill-defined but important role in regulation of GI motility in health and disease
- Erythromycin binds to and inhibits the activation of the receptor for the GI hormone motilin, affecting GI motility

- Some patients with gastroparesis are observed to have substantial clinical improvement with erythromycin and its analogs, especially when complaints related to partial gastric outlet obstruction, such as bloating, nausea, and constipation, are prominent

66 Cholelithiasis and Cholecystitis, A

A 40-year-old woman presents to the emergency department with 2 days of worsening right upper quadrant pain. The pain started after she had pizza for dinner 2 nights before and is described as a sharp, stabbing sensation under her right ribs. She has also felt ill, developed slight nausea, and had a low-grade fever. There has been no vomiting or diarrhea. Physical examination reveals an obese woman with a low-grade fever and tenderness to palpation of the right upper quadrant of her abdomen. An abdominal ultrasound reveals a 2 cm gallstone lodged in the cystic duct with swelling of the gallbladder and edema and thickening of the gallbladder wall.

1. What are the mechanisms involved in gallstone formation?

- Factors affecting the lithogenicity of bile:
  - Cholesterol content
  - Nucleating factors
  - Prostaglandins and estrogen
- Gallbladder motility is also important since bile usually does not stay in the gallbladder long enough to form a gallstone; stasis allows stone formation
  - Rate of bile formation
  - Rate of water and electrolyte absorption

66 Cholelithiasis and Cholecystitis, B

2. What factors in the pathogenesis of gallstones may be responsible for the fact that it is more common in premenopausal women?

- High levels of serum estrogens increase cholesterol concentration of bile
- High estrogen levels also decrease gallbladder motility, leading to stasis

3. What local complications can ensue from gallstone disease?

- A gallstone may become lodged in the cystic duct, obstructing the emptying of the gallbladder
- This can lead to inflammation (cholecystitis) and infection of the static contents (empyema) of the gallbladder
- If untreated, such inflammation and infection can lead to necrosis of the gallbladder and sepsis
- If a gallstone becomes lodged in the common bile duct, it can cause obstructive jaundice with elevation in serum bilirubin levels and cholangitis, infection of the biliary tree behind the obstruction
- If lodged at the distal common bile duct blocking the pancreatic duct near the sphincter of Oddi, a gallstone can cause acute pancreatitis, perhaps because the pancreatic digestive enzymes are trapped in the pancreatic duct and cause pancreatic autodigestion and inflammation

67 Diarrhea, Non-Infectious, A

A 45-year-old man comes to the clinic with a history of excessive bloating, foul smelling flatus, and loose stools for the past several months. He notes that about 30–60 minutes after breakfast each morning, he feels cramping, bloating, passage of smelly flatus, and a very loose, watery bowel movement. He has not seen any blood or mucus in the stool and also denies any weight loss. This does not happen with lunch or dinner. Every day for breakfast, he eats a big bowl of cereal with milk and a yogurt smoothie. Physical examination is unremarkable with normal bowel sounds, no organomegaly, and no abdominal tenderness. He was advised to do a dietary trial of stopping dairy intake for 1 week. All his symptoms resolve, and he is diagnosed with lactose intolerance.

1. Name three ways in which an excessive osmotic load can occur in the GI tract.

- Direct oral ingestion of excessive osmoles such as sorbitol
- By ingestion of a substrate that may be converted into excessive osmoles (ie, bacterial action on the non-digestible carbohydrate lactulose generates a diarrhea-causing osmotic load in the colon)
- As a manifestation of a genetic disease such as an enzyme deficiency in the setting of a particular diet (ie, milk consumption by a lactase-deficient individual)

67 Diarrhea, Non-Infectious, B

2. What are the major causes of osmotic/malabsorptive diarrhea?

- Disaccharidase deficiencies (ie, lactase deficiency)
- Glucose-galactose or fructose malabsorption
- Mannitol, sorbitol ingestion
- Lactulose therapy
- Some salts (ie, magnesium sulfate)
- Some antacids (ie, calcium carbonate)
- Generalized malabsorption

- Pancreatic enzyme inactivation (ie, by excess acid) or deficiency
- Defective fat solubilization (disrupted enterohepatic circulation or defective bile formation)
- Ingestion of nutrient-binding substances
- Bacterial overgrowth
- Loss of enterocytes (ie, radiation, infection, ischemia)
- Lymphatic obstruction (ie, lymphoma, tuberculosis)

68 Inflammatory Bowel Disease: Crohn Disease, A

A 42-year-old man with long-standing Crohn disease presents to the emergency department with a 1-day history of increasing abdominal distention, pain, and obstipation. He is nauseated and has vomited bilious material. He has no history of abdominal surgery and has had two exacerbations of his disease this year. He is febrile with a temperature of 38.5°C. Examination reveals multiple oral aphthous ulcers, hyperactive bowel sounds, and a grossly distended, diffusely tender abdomen without an appreciable mass. Abdominal radiographs reveal multiple air-fluid levels in the small bowel with minimal colonic gas consistent with a small bowel obstruction.

1. How is inflammatory bowel disease distinguished from infectious diarrhea?

- Inflammatory bowel disease is distinguished from infectious entities by exclusion and by the following characteristics:
  - Recurrent episodes of mucopurulent bloody diarrhea (ie, containing mucus and white cells)
  - Lack of positive cultures for known microbial pathogens
  - Failure to respond to antibiotics alone

68 Inflammatory Bowel Disease: Crohn Disease, B

2. What are the differences between ulcerative colitis and Crohn disease?

- Crohn disease: transmural and granulomatous lesions that occur anywhere along the GI tract, most commonly in the distal ileum with discontinuous areas of ulceration and inflammation involving the entire thickness of the bowel wall
- Ulcerative colitis: superficial disease limited to the colonic and rectal mucosa, with nearly 100% involvement of the rectum

3. What are the complications of inflammatory bowel disease?

- Perforation, fistula formation, abscess formation, and small intestinal obstruction
- Frank bleeding from the mucosal ulcerations can be either insidious or massive
- Protein-losing enteropathy
- Increased incidence of intestinal cancer
- Extra-intestinal manifestations: inflammatory disorders of the joints (arthritis), skin (erythema nodosum), eye (uveitis, iritis), mucous membranes (aphthous ulcers of the buccal mucosa), bile ducts (sclerosing cholangitis), and liver (autoimmune chronic active hepatitis)
- Associated diseases: nephrolithiasis, amyloidosis, thromboembolic disease, and malnutrition

69 Diverticular Disease (Diverticulosis), A

A 76-year-old woman with chronic constipation reports a 4-day history of "achy" left lower quadrant abdominal pain, graded 7/10, accompanied by low-grade fever and nausea. A colonoscopy performed 2 years ago revealed sigmoid diverticular disease. On examination, she has a temperature of 38.6°C. Her abdomen has a tender 3 × 2 cm mass in the left lower quadrant. Bowel sounds are normal. Her stool is positive for occult blood. A CT scan with contrast of the abdomen and pelvis shows pericolonic fat stranding with no evidence of an abscess. She is started on antibiotics.

1. Where in the GI tract do most diverticulae occur?

- Most acquired diverticulae occur in the colon; the descending colon and sigmoid (left side) are involved in more than 90% of cases

2. What are the major complications of diverticular disease?

- Diverticulae are a source of bleeding in 3–5% of patients with diverticulosis, and diverticular bleeding is the most common cause of massive (painless) lower GI bleeding in the elderly
- Diverticulitis develops when a focal area of inflammation occurs in the wall of a diverticulum due to irritation by fecal material that causes abdominal pain and fever with a risk of progression to abscess with or without perforation
- Approximately 15–25% of patients who develop diverticulitis will require surgery

69 Diverticular Disease (Diverticulosis), B

3. What predisposing factors contribute to the development of diverticular disease?

- Diverticulosis results from an acquired deformity of the colon in which the mucosa and submucosa herniate through the underlying colonic wall
- 30% of adults in the U.S. population are affected, with an increased incidence with age starting from about 40 years
- Epidemiologic studies suggest that the consumption of more highly refined foods and less fiber is associated with a higher prevalence of chronic constipation. This consumption may be responsible for the increased prevalence of diverticular disease
- Constipation leads to a transmural pressure gradient from colonic lumen to peritoneal space as a result of vigorous muscle contraction of the colonic wall
- This functional abnormality is most likely related to the change in dietary habits; decreased dietary fiber makes forward propulsion of feces at normal transmural pressures more difficult

70 Irritable Bowel Syndrome, A

A 32-year-old woman comes to the clinic complaining of a 3-month history of abdominal bloating, crampy abdominal pain, and a change in her bowel habits. Previously, she had regular bowel movements, but 4 months ago, she developed gastroenteritis with nausea and vomiting after a cruise. The constant diarrhea and vomiting went away after a week, but since then she has had periods of constipation, lasting up to 3 days, alternating with periods of diarrhea. During the diarrheal episodes, she can have three to four loose bowel movements per day, without blood or mucus in the stool. She describes diffuse abdominal cramping and bloating that are somewhat relieved by bowel movements. Her symptoms worsen during periods of stress. There has been no weight loss or fever. There is no association with particular foods (eg, wheat or dairy products). Her physical examination is unremarkable except for mild abdominal tenderness with no rebound or guarding. Serologic tests for celiac sprue are negative. Stool cultures and examinations are negative for bacterial or parasitic infections. A colonoscopy is unremarkable.

1. List three characteristics of irritable bowel syndrome.

- A change in bowel habits, commonly alternating between diarrhea and constipation, is the principal characteristic of irritable bowel syndrome
- Abdominal pain, which may be caused by intestinal spasms, is also common to all patients with irritable bowel syndrome
- Bloating or perceived abdominal distention is another common feature

70 Irritable Bowel Syndrome, B

2. What are possible factors in the pathogenesis of the irritable bowel syndrome?

- Irritable bowel syndrome is a complex disorder, and its cause is poorly understood, but there are many theorized mechanisms
- Alterations in sensitivity of the extrinsic and intrinsic nervous systems of the intestine may contribute to exaggerated sensations of pain and to abnormal control of intestinal motility and secretion
- An alteration in the balance of secretion and absorption is also a potential cause
- Although there is no gross inflammation of the intestine, there are reports of increased influx of inflammatory cells (lymphocytes) into the colon as well as destruction of enteric neurons in affected individuals
- Intestinal microbes that normally inhabit the small intestine and colon may be altered as well, suggesting that antibiotics could have a role in treatment of this disorder
- Irritable bowel syndrome may develop as a result of an earlier and now resolved bout of interstitial inflammation
  - In experimental animals, induction of intestinal inflammation induces visceral hyperalgesia and altered intestinal motility and secretion that persists many months after the inflammation is resolved
  - A similar mechanism may occur in a subset of patients who develop irritable bowel syndrome after an infection causing intestinal inflammation

71 Acute Hepatitis, A

A 28-year-old man, recently emigrating from the Philippines, was noted to have a positive tuberculin skin test result in the clinic. His chest radiograph showed no active tuberculosis, and he denied any symptoms of this infection, including weight loss, cough, or night sweats. To prevent future disease, daily dosing with isoniazid was recommended for the next 9 months. Two weeks after initiating therapy, the patient reported progressive fatigue, intermittent bouts of nausea, and abdominal pain. He also noticed darkening of his urine and light-colored stools. His sister noted a gradual yellowing of his eyes and skin. Blood tests showed a marked increase in serum bilirubin and aminotransferases. The isoniazid was discontinued, and his symptoms subsided with normalizing of his liver enzymes.

1. Describe the range of clinical presentations of acute hepatitis.

- The severity of illness in acute hepatitis ranges from asymptomatic clinically inapparent disease to fulminant and potentially fatal liver failure
- Some patients are relatively asymptomatic, with abnormalities noted only by laboratory studies
- Symptoms and signs include anorexia, fatigue, weight loss, nausea, vomiting, right upper quadrant abdominal pain, jaundice, fever, splenomegaly, and ascites
- The extent of hepatic dysfunction can vary tremendously, correlating roughly with the severity of liver injury
- The relative extent of cholestasis versus hepatocyte necrosis is highly variable

71 Acute Hepatitis, B

2. How do drugs cause hepatitis?

- Many drugs have been implicated in hepatitis
- Acetaminophen is now the most common cause of acute liver failure in the United States and the United Kingdom
- Hepatic toxins can be further subdivided into those for which hepatic toxicity is predictable and dose dependent for most individuals (eg, acetaminophen) and those that cause unpredictable (idiosyncratic) reactions without relationship to dose (eg, nonsteroidal anti-inflammatory drugs such as diclofenac)
- Idiosyncratic reactions to drugs may be due to genetic predisposition in susceptible individuals to certain pathways of drug metabolism that generate toxic intermediates (eg, isoniazid)

3. Which viruses can cause hepatitis?

- Acute hepatitis is commonly caused by one of five major viruses: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV)
- Other viral agents that can result in acute hepatitis include: the Epstein-Barr virus (cause of infectious mononucleosis), cytomegalovirus, varicella virus, measles virus, herpes simplex virus, rubella virus, and yellow fever virus

72 Chronic Hepatitis B, A

A 44-year-old man is concerned about abnormal liver test results drawn for his pre-employment physical 6 months ago. His serum aminotransferase levels were more than two times the normal values. On further questioning, he has a distant history of heroin use. Currently, he reports some fatigue but says he feels well otherwise. His primary care physician orders serologic testing, which reveals: HBsAg positive, anti-HBs negative, and anti-HBc IgG positive. Anti-HDV and anti-HCV test results are both negative.

1. What are the categories of chronic hepatitis based on histologic findings on liver biopsy?

- All forms of chronic hepatitis exhibit inflammatory infiltration of hepatic portal areas with lymphocytes and plasma cells, and necrosis of hepatocytes within the parenchyma or immediately adjacent to portal areas
- In mild chronic hepatitis, the overall architecture of the liver is preserved with a lymphocyte and plasma cell infiltrate confined to the portal triad without evidence of active hepatocyte necrosis or fibrosis
- With progression, the portal areas expand with dense lymphocyte, histiocyte, and plasma cell infiltration, necrosis of hepatocytes at the lobule periphery, and erosion of the limiting plate around the portal triads (piecemeal necrosis)
- More severe cases also show evidence of necrosis and fibrosis between portal triads and bands of scar tissue and inflammatory cells link portal areas to one another and to central areas (bridging necrosis)
- Progression to cirrhosis is signaled by extensive fibrosis, loss of zonal architecture, and regenerating nodules

72 Chronic Hepatitis B, B

2. What are the causes of chronic hepatitis?

- Infection with several hepatitis viruses (B [with or without D] and C)
- Drugs and toxins (eg, ethanol, isoniazid, acetaminophen), often in amounts insufficient to cause symptomatic acute hepatitis
- Genetic and metabolic disorders (eg, α_1-antitrypsin deficiency, Wilson disease)
- Nonalcoholic fatty liver disease, a chronic liver disease associated with the metabolic syndrome and obesity
- Systemic diseases (eg, sarcoidosis or tuberculosis)
- Vascular injury (eg, ischemia or portal vein thrombosis)
- Mass lesions (eg, hepatic tumors)
- Cholestatic syndromes
- Immune-mediated injury of unknown origin

3. What are the consequences of chronic hepatitis?

- Insidious onset of nonspecific symptoms such as anorexia, malaise, and fatigue
- Hepatic symptoms such as right upper quadrant abdominal discomfort or pain
- Jaundice, if present, is usually mild
- There may be mild tender hepatomegaly and occasional splenomegaly
- Palmar erythema and spider telangiectasias in severe cases
- Possible progression to cirrhosis and portal hypertension (ie, ascites, collateral circulation, and encephalopathy)

73 Cirrhosis, A

A 63-year-old man with a long history of alcohol use presents to his new primary care physician with a 6-month history of increasing abdominal girth. He has also noted easy bruisability and worsening fatigue. He denies any history of GI bleeding. He continues to drink three or four cocktails a night but says he is trying to cut down. Physical examination reveals a cachectic man who appears older than his stated age. Blood pressure is 108/70 mm Hg. His scleras are anicteric. His neck veins are flat, and chest examination demonstrates gynecomastia and multiple spider angiomas. Abdominal examination is significant for a protuberant abdomen with a detectable fluid wave, shifting dullness, and an enlarged spleen. The liver edge is difficult to appreciate. He has trace pitting pedal edema. Laboratory evaluation shows anemia, mild thrombocytopenia, and an elevated prothrombin time. Abdominal ultrasonogram confirms a shrunken, heterogeneous liver consistent with cirrhosis, significant ascites, and splenomegaly.

1. What are the defining features of cirrhosis?

- All forms of cirrhosis are characterized by three findings:
  - Marked distortion of hepatic architecture
  - Scarring as a result of increased deposition of fibrous tissue and collagen
  - Regenerative nodules surrounded by scar tissue

73 Cirrhosis, B

2. What are some ways alcohol may injure the liver?

- Exact mechanism is unknown
- Chronic alcohol use has been associated with impaired protein synthesis, lipid peroxidation, and the formation of acetaldehyde, which may interfere with membrane lipid integrity and disrupt cellular function
- Local hypoxia, as well as cell-mediated and antibody-mediated cytotoxicity, have also been implicated

3. What are the major clinical manifestations of cirrhosis?

- Portal hypertension due to increased intrahepatic vascular resistance from scarring
- Ascites (excess fluid within the abdominal cavity)
- Hepatorenal syndrome (kidney injury resulting from renal vasoconstriction that develops in response to arterial vasodilation in advanced liver disease)
- Hypoalbuminemia, peripheral edema, and electrolyte abnormalities (eg, hyponatremia)
- Spontaneous bacterial peritonitis
- Gastroesophageal varices and bleeding
- Hepatic encephalopathy
- Coagulopathy (due to decreased hepatic production of clotting factors)
- Splenomegaly and hypersplenism (including thrombocytopenia)
- Hepatocellular carcinoma
- Hepatopulmonary syndrome and portopulmonary hypertension

74 Acute Pancreatitis, A

An admitting physician is called to the emergency department to evaluate a 58-year-old woman with a 2-day history of fever, anorexia, nausea, and abdominal pain. Suspecting pancreatitis, the physician inquires about a history of similar symptoms. She had been seen 2 months ago in the emergency department for an episode of unrelenting, achy right upper quadrant abdominal pain. At the time, an ultrasound imaging demonstrated multiple gallstones without evidence of cystic duct obstruction or gallbladder wall edema. Now, serum amylase and lipase levels are both grossly elevated. She is diagnosed with acute pancreatitis. On day 3 of her hospitalization, the physician is called urgently to evaluate her for hypotension, shortness of breath, and ensuing respiratory failure. She requires endotracheal intubation and mechanical ventilation. A chest radiograph and severe hypoxia support the diagnosis of acute respiratory distress syndrome.

1. What are the presenting symptoms and signs of acute pancreatitis?

- Two of the following three criteria help establish the diagnosis of acute pancreatitis: abdominal pain, elevation of serum amylase or lipase (more than three times the upper limit of normal), and characteristics findings on CT (or MRI or ultrasound)
- Signs and symptoms include:
  - Abdominal pain: intense, deep, searing pain with radiation to the back
  - Nausea and vomiting
  - Fever due to extensive tissue injury, inflammation, and release of interleukin (IL)-1 and other cytokines
  - Elevation of serum amylase and/or lipase

74 Acute Pancreatitis, B

2. What are the most common causes of acute pancreatitis?

- Biliary tract disease: gallstones, sludge
- Alcohol intake: binge, alcoholism
- Trauma: blunt abdominal trauma, postoperative, postprocedural, electric shock
- Infections: many viral, bacterial and parasitic causes
- Metabolic: hyperlipidemia, hypercalcemia, uremia, pregnancy, malnutrition, hemochromatosis, diabetic ketoacidosis
- Hereditary: familial pancreatitis, cystic fibrosis
- Poisons and toxins: venom, organophosphates, zinc, cobalt, mercuric chloride
- Drugs: numerous medications
- Vascular: vasculitis, shock, atheromatous embolism
- Mechanical: pancreas divisum, tumor, stenosis of the ampulla of Vater, penetrating duodenal ulcer

3. What are the complications of severe pancreatitis?

- Shock from retroperitoneal fluid loss/bleeding as well as release of kinins
- Disseminated intravascular coagulation (DIC)
- Acute respiratory distress syndrome (ARDS)
- Necrotizing pancreatitis with possible infection
- Pancreatic pseudocyst formation
- Pancreatic ascites and fistulas

75 Chronic Pancreatitis, A

A 52-year-old man with a 20-year history of alcohol abuse presents to his primary care provider complaining of recurrent episodes of epigastric and left upper quadrant abdominal pain. Over the past month, the pain has become almost continuous, and he has requested morphine for better pain control. He has a history of alcohol-related acute pancreatitis. Examination reveals a 10-pound weight loss over the past 6 months. He has some mild muscle guarding over the epigastrium with tenderness to palpation. Bowel sounds are somewhat decreased. Serum amylase and lipase are mildly elevated. A plain film of the abdomen demonstrates pancreatic calcifications.

1. What are causes of chronic pancreatitis?

- Chronic alcoholism accounts for about 70–80% of cases
- Cigarette smoking is a strong independent risk factor for the development of chronic pancreatitis; the combination of significant alcohol and cigarette use appears to be synergistic in augmenting the risk of chronic pancreatitis
- Chronic pancreatitis can also be caused by long-term obstruction of the pancreatic duct, eg, from neoplasm, papillary stenosis, cystic lesions (cystic tumors or pseudocysts), scarring or stricture, trauma, or pancreas divisum
- Tropical chronic pancreatitis is a juvenile form of chronic calcific pancreatitis, thought to be caused by protein and micronutrient deficiencies, or toxins
- Chronic hypercalcemia may cause pancreatitis, which is seen in 10–15% of patients with hyperparathyroidism
- Chronic hereditary pancreatitis accounts for about 1% of cases
- Other cases can be autoimmune or idiopathic or related to drugs (medications)

75 Chronic Pancreatitis, B

2. What are the symptoms and signs of chronic pancreatitis?

- Severe abdominal pain that can be constant or intermittent
- Nausea and vomiting
- Weight loss and malabsorption
- Hyperglycemia and diabetes mellitus
- Jaundice
- Pancreatic parenchymal and/or main duct calcifications on CT or x-ray films

3. How is alcohol thought to cause chronic pancreatitis?

- Lithostathines are pancreatic juice peptides that inhibit the formation of protein plugs and the aggregation of calcium carbonate crystals to form stones
  - Alcohol impairs secretion of lithostathines
  - Furthermore, when hydrolyzed by trypsin and cathepsin B, lithostathine H2/PSP-S1 is created and it polymerizes into the matrix of protein plugs
  - Also, there is hypersecretion of calcium into the pancreatic juice
- The formation of protein plugs in pancreatic juice that is thick, viscid, and protein-rich, coupled with a calcium carbonate concentration that is supersaturated leads to formation of calculi (stones)
- Lactoferrin, an iron-containing macromolecular protein, is elevated in the pancreatic secretions of alcoholic patients with pancreatitis
  - Lactoferrin can produce clumps of large proteins, such as albumin, and may thus contribute to the formation of protein plugs

76 Pancreatic Insufficiency, A

A 15-year-old boy with a history of cystic fibrosis comes to see you due to worsening diarrhea and weight loss. His lung disease has been relatively well controlled, but recently he has lost 5 kg unintentionally. His stools have also become loose and are very bulky, greasy, and foul smelling, especially after fatty meals. On examination, he is thin but otherwise normal appearing. His weight is 45 kg and his height is 160 cm (yielding a body mass index of 17.6 [underweight]). Lung exam is notable for scattered rhonchi and crackles, but the rest of the examination, including the abdominal examination, is normal. Stool collection verifies the presence of steatorrhea. He is started on pancreatic enzymes with resolution of his gastrointestinal symptoms.

1. What are the symptoms and signs of pancreatic insufficiency?

- Steatorrhea: voluminous or bulky, foul-smelling, greasy, frothy, pale yellow, and floating stools
  - Mild cases may require a 24-hour fecal fat collection for diagnosis
  - Severe cases may lead to fat-soluble vitamin deficiencies (vitamins A, D, E, and K)
- Diarrhea: unabsorbed hydroxylated fatty acids are cathartic
- Weight loss
- Hypocalcemia: deficiency of vitamin D coupled with the binding of dietary calcium to unabsorbed fatty acids contributes to hypocalcemia
- Nephrolithiasis: binding of dietary calcium to unabsorbed fatty acids results in excessive intestinal absorption of dietary oxalate and kidney stone formation
- Vitamin B_{12} deficiency

76 Pancreatic Insufficiency, B

2. What are the causes of pancreatic insufficiency?

- Chronic pancreatitis
- Neoplasm or resection of pancreas
- Severe protein-calorie malnutrition, hypoalbuminemia
- Cystic fibrosis, hemochromatosis, Shwachman syndrome, enzyme deficiencies
- Non-tropical sprue, gastrinoma
- Gastric surgery

3. Why is fat malabsorption the main symptom of pancreatic insufficiency?

- Pancreatic lipase is essential for fat digestion; its absence leads to fat malabsorption
- Although pancreatic amylase and trypsin are important for carbohydrate and protein digestion, the presence of these enzymes in gastric and intestinal juice can usually compensate for pancreatic deficiencies
- Thus, patients with pancreatic insufficiency seldom present with malabsorption of carbohydrate and protein

77 Carcinoma of the Pancreas, A

During a family reunion, a 62-year-old widower describes to his son a 1-month history of lethargy. He attributes it to the stress of a recent move from a large three-bedroom house into an apartment. His granddaughter comments that his eyes appear "yellow" and that he has lost a significant amount of weight since their last visit with him. Corroborating the finding of painless jaundice, his internist orders a contrast-enhanced spiral CT, revealing a 3-cm mass in the head of the pancreas.

1. What are the risk factors for pancreatic cancer?

- Cigarette smoking is thought to account for one quarter of diagnosed cases
  - N-nitroso compounds in cigarette smoke lead to pancreatic ductal hyperplasia, a possible precursor to adenocarcinoma
- Other risk factors include: a high dietary intake of saturated fat, and exposure to nonchlorinated solvents and the pesticide dichlorodiphenyl trichloroethane (DDT), although the overall contribution of these factors is likely small
- Diabetes mellitus has also recently been identified as a risk factor for the disease
- Chronic pancreatitis increases the risk of developing pancreatic adenocarcinoma by 10- to 20-fold
- Diets containing fresh fruits and vegetables are thought to be protective
- There is an increased incidence of pancreatic cancer among patients with hereditary pancreatitis, particularly among those with pancreatic calcifications
- Rarely, pancreatic carcinoma is inherited
- The majority of patients with pancreatic adenocarcinoma do not have risk factors

77 Carcinoma of the Pancreas, B

2. What are common symptoms and signs of pancreatic cancer?

- Pancreatic cancer may present like chronic pancreatitis
- Patients with carcinoma of the head of the pancreas usually present with painless, progressive jaundice, resulting from common bile duct obstruction and/or a dilated gallbladder palpable in the right upper quadrant (Courvoisier law)
- Patients with carcinoma of the body or tail of the pancreas usually present with epigastric abdominal pain, profound weight loss, abdominal mass, and anemia
  - These patients usually present at later stages and often have distant metastases, particularly in the liver
  - Splenic vein thrombosis may occur as a complication of cancers in the body or tail of the gland
- About 70% of patients with pancreatic cancer have impaired glucose tolerance or frank diabetes mellitus

3. How can you make the diagnosis of pancreatic cancer in a patient with suggestive symptoms and signs?

- A thin-cut helical CT scan or endoscopic ultrasound with fine needle aspiration may aid in diagnosis
- ERCP with brushings of the biliary or pancreatic duct also may be useful
- A variety of tumor markers can be found in the serum of patients with pancreatic cancer but have poor test sensitivity and specificity

78 Acute Kidney Injury: Acute Tubular Necrosis, A

A healthy 26-year-old woman sustained a significant crush injury to her right upper extremity while on the job at a local construction site. She was brought to the emergency department and subsequently underwent pinning and reconstructive surgery and received perioperative broad-spectrum antibiotics. Her blood pressure remained normal throughout her hospital course. On the second hospital day, a medical consultant noted an increase in her serum creatinine, from 0.8 to 1.9 mg/dL. Her urine output dropped markedly to 20 mL/h. Serum creatine kinase was ordered and reported as 3400 units/L.

1. What are the current theories for the development of acute tubular necrosis?

- Theories favoring either a tubular or vascular etiology have been proposed
- Tubular theory: occlusion of the tubular lumen with cellular debris forms a cast that increases intratubular pressure sufficiently to offset perfusion pressure and decrease or abolish net filtration pressure
- Vascular theory: decreased renal perfusion pressure from the combination of afferent arteriolar vasoconstriction and efferent arteriolar vasodilation reduces glomerular perfusion pressure and, therefore, glomerular filtration
- Both mechanisms may act to produce acute kidney injury, varying in relative importance in different individuals depending on the cause and time of presentation
- Renal damage, whether caused by tubular occlusion or vascular hypoperfusion, is potentiated by the hypoxic state of the renal medulla, which increases ischemia
- Cytokines and endogenous peptides such as endothelins and activation of complement and neutrophils increase vasoconstriction further and worsen injury

78 Acute Kidney Injury: Acute Tubular Necrosis, B

2. What is the natural history of acute kidney injury?

- The initial symptoms are typically fatigue and malaise, probably early consequences of loss of the ability to excrete water, salt, and wastes via the kidneys, often with decreased urine output
- Later, more profound symptoms and signs of loss of renal water and salt excretory capacity develop: dyspnea, orthopnea, rales, a prominent third heart sound (S_3), and peripheral edema
- If the cause is prerenal azotemia, this can often be rapidly reversed before progression to acute tubular necrosis takes place
- Altered mental status reflects the toxic effect of uremia on the brain, with elevated blood levels of nitrogenous wastes and fixed acids
- Recovery from acute tubular necrosis, if it occurs, follows a protracted course, often requiring supportive dialysis before adequate renal function is regained

3. What clues are helpful in determining whether newly diagnosed kidney disease is acute or chronic?

- Acute kidney injury: the most widely accepted definition is a rise in serum creatinine of ≥0.3 mg/dL within a 48-hour period or a fall in urine output to less than 0.5 mL/kg/h for at least 6 hours
- On the other hand, imaging of the kidneys in chronic kidney disease may show shrunken kidneys
- A previous creatinine value is helpful for differentiation between acute and chronic kidney disease

79 Chronic Kidney Disease, A

A 58-year-old obese woman with hypertension, type 2 diabetes, and chronic kidney disease is admitted to a hospital after a right femoral neck fracture sustained in a fall. Recently, she has been complaining of fatigue and was started on subcutaneous injections of epoetin alfa. Her other medications include an angiotensin-converting enzyme inhibitor, a β-blocker, a diuretic, calcium supplementation, and insulin. On review of systems, she reports mild tingling in her lower extremities. On examination, her blood pressure is 148/60 mm Hg. She is oriented and able to answer questions appropriately. There is no evidence of jugular venous distention or pericardial friction rub. Her lungs are clear, and her right lower extremity is in traction in preparation for surgery. Asterixis is absent. Her serum creatinine is 3.9 mg/dL.

1. What are the most common causes of chronic kidney disease (CKD)?

- In developed countries, the most common cause of CKD is diabetes mellitus
- Hypertension and glomerulonephritis are the second and third most frequent causes of CKD, respectively
- Less common causes are: polycystic kidney disease, interstitial nephritis, obstruction, and infection

79 Chronic Kidney Disease, B

2. What is uremia?

- Uremia is a syndrome characterized by a unique set of symptoms, physical examination findings, and laboratory abnormalities presumably caused by a accumulation of one or more uncharacterized toxins
- Symptoms: fatigue, confusion, lethargy, asterixis, peripheral neuropathy, seizures, coma, pruritus, anorexia, nausea, and vomiting
- Examination findings: pericardial rub, ecchymoses, pulmonary edema, hypotension, myoclonus, seizures, osteomalacia/osteoporosis, peripheral edema and ascites, and malnutrition
- Laboratory findings: hyponatremia, hyperkalemia, hyperphosphatemia, secondary hyperparathyroidism, anemia, leukopenia, and thrombocytopenia

3. What is the mechanism by which altered sodium, potassium, and volume status develop in chronic kidney disease?

- Patients with CKD typically have some degree of Na^+ and water excess, reflecting loss of the renal salt and water excretion in the face of ongoing intake
- These patients also have impaired renal salt and water conservation mechanisms, so they are more sensitive than normal to sudden extrarenal Na^+ and water losses (eg, vomiting, diarrhea, and increased cutaneous losses such as with fever)
- Hyperkalemia is a serious problem in CKD, especially for patients whose GFR has fallen below 5 mL/min when compensatory mechanisms for potassium excretion (such as aldosterone-mediated K^+ transport) fail

80 Poststreptococcal Glomerulonephritis, A

A 28-year-old nursery school teacher developed a marked change in the color of her urine ("cola-colored") 1 week after she contracted impetigo from one of her students. She also complained of new onset of global headaches and retention of fluid in her legs. Examination revealed a blood pressure of 158/92 mm Hg, resolving honey-crusted pustules over her right face and neck, and 1+ pitting edema of her ankles, with no cardiac murmur. Urinalysis revealed 2+ protein and numerous red cells and red cell casts. Her serum creatinine was elevated at 1.9 mg/dL. Serum complement levels (CH50, C3, and C4) were low. She was diagnosed with poststreptococcal glomerulonephritis.

1. What are common infectious causes of glomerulonephritis (GN)?

- Infections with certain "nephritogenic" strains of group A beta-hemolytic streptococci
  - In poststreptococcal GN, there is a lag (7–10 days) between clinical signs of infection and development of clinical signs of nephritis
- Subacute bacterial endocarditis (SBE) is another cause
- Poststreptococcal GN and SBE can produce acute GN or rapidly progressive GN (RPGN)
- Viral infections with hepatitis B virus and human immunodeficiency virus (HIV) can also produce RPGN

80 Poststreptococcal Glomerulonephritis, B

2. What is the pathophysiology of poststreptococcal GN?

- In postinfectious GN, there is cross-reactivity between an antigen of the infecting organism and a host antigen, resulting in deposition of immune complexes and complement in the kidney's glomerular capillaries and mesangium
- These are found as "humps" in the subepithelial space
- Resolution of glomerular disease typically occurs weeks after treatment of the original infection

3. What are the differences between acute GN and RPGN?

- Acute GN is an abrupt onset of hematuria and proteinuria with reduced GFR and renal salt and water retention
  - Complete recovery of renal function sometimes occurs
- RPGN is a subset of acute GN in which there is a progressive decline (weeks to months) in renal function, often leading to complete renal failure and oliguria
  - Early disease can be subtle but is marked by proteinuria and hematuria, followed by decreased GFR
  - This is often called "crescentic GN" since the characteristic finding on biopsy is cellular crescents in the Bowman space
  - Cellular crescents, visible on light microscopy, form in response to severe damage to the glomerular capillaries, a nonspecific final pathway in a variety of glomerular diseases
  - Recovery is rare without specific treatment

81 Nephrotic Syndrome: Minimal Change Disease, A

A 40-year-old man with Hodgkin lymphoma is admitted to the hospital because of anasarca. He has no known history of renal, liver, or cardiac disease. His serum creatinine level is 1.4 mg/dL. Serum albumin level is 2.8 g/dL. Liver function test results are normal. Urinalysis demonstrates no red or white blood cell casts, but 3+ protein and a 24-hour urine collection shows a protein excretion of 4 g/24 hours. He is diagnosed with nephrotic syndrome, and renal biopsy suggests minimal change disease. Corticosteroids and diuretics are instituted, with gradual improvement of edema. The hospital course is complicated by deep venous thrombosis of the left leg that requires anticoagulation.

1. What are the categories of glomerulonephritis, and what are their common and distinctive features?

- Acute glomerulonephritis (GN): abrupt onset of hematuria and proteinuria with reduced GFR resulting in renal salt and water retention; it often occurs in the setting of infectious diseases such as group A beta-hemolytic streptococci
- Rapidly progressive glomerulonephritis (RPGN) is a subset of acute GN in which there is a progressive and dramatic decline (weeks to months) in renal function, often leading to complete renal failure and oliguria
- Nephrotic syndrome: detailed below
- Chronic GN: characterized by persistent urinary abnormalities and slowly progressive (years) decline in renal function
  - RPGN appears to be a heterogeneous group of disorders, all of which display pathologic features of necrotizing vasculitis
  - Characteristic finding on biopsy is cellular crescents in the Bowman space

81 Nephrotic Syndrome: Minimal Change Disease, B

2. What are the pathophysiologic consequences of nephrotic syndrome?

- Nephrotic syndrome by definition requires albuminuria (24-hour urine protein excretion >3.5 g), hypoalbuminemia, hyperlipidemia, fat bodies in the urinary sediment, and edema
- Nephrotic syndrome may be either isolated (eg, minimal change disease) or part of some other glomerular syndrome (eg, with hematuria and casts)
- Patients with the nephrotic syndrome have profoundly decreased plasma oncotic pressure because of the loss of serum proteins in the urine, leading to intravascular volume depletion and activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system, as well as increased vasopressin secretion leading to edema or anasarca
- Despite volume overload, patients may develop signs of intravascular volume depletion, including syncope, shock, and acute kidney injury
- Hyperlipidemia associated with nephrotic syndrome appears to be a result of decreased plasma oncotic pressure that stimulates hepatic very-low-density lipoprotein synthesis and secretion. The fat bodies in the urinary sediment are a consequence of the hyperlipidemia
- Hypercoagulability often results from renal losses of proteins C and S together with antithrombin, as well as elevated serum fibrinogen and lipid levels
- Loss of other plasma proteins besides albumin may cause: (1) a defect in bacterial opsonization and thus increased susceptibility to infections (ie, as a result of loss of IgG); (2) vitamin D deficiency state and secondary hyperparathyroidism (ie, from loss of vitamin D–binding proteins); and (3) altered thyroid function tests without any true thyroid abnormality (ie, from reduced levels of thyroxine-binding globulin)

82 Renal Stone Disease, A

A 48-year-old white man presents to the emergency department with unremitting right flank pain. He denies dysuria or fever. He has significant nausea but no vomiting. He has never experienced anything like this before. On examination, he is afebrile, and his blood pressure is 160/80 mm Hg with a pulse rate of 110/min. He is writhing on the gurney, unable to find a comfortable position. His right flank is mildly tender to palpation, but abdominal examination is benign. Urinalysis is significant for 2+ blood, and microscopy reveals 10–20 red blood cells per high-power field. Nephrolithiasis is suspected, and the patient is intravenously hydrated and given pain medication with temporary relief.

1. How do patients with renal stones present?

- Patients with renal stones present with flank pain (which may radiate to the groin region) and hematuria (which may be macroscopic or microscopic)
- Depending on the level of the stone and the patient's anatomy (ie, if there is only a single functioning kidney or significant preexisting renal disease), the presentation may be complicated by obstruction with decreased or absent urine production

82 Renal Stone Disease, B

2. Why do renal stones form?

- Renal stones result from alterations in the solubility of various substances in the urine, such that there is nucleation and precipitation of crystals
- Dehydration favors stone formation
- A high-protein diet predisposes to stone formation due to transient metabolic acidosis and hypercalciuria due to increases in both calcium resorption (from bone) and glomerular calcium filtration and an inhibition of distal tubular calcium resorption
- A high-sodium diet predisposes to calcium excretion and calcium oxalate stone formation, whereas a low dietary sodium intake has the opposite effect
- A high urinary sodium excretion increases the urine saturation of monosodium urate, which can act as a nidus for calcium crystallization
- Citrate decreases the likelihood of stone formation by chelating calcium in solution and forming highly soluble complexes compared with calcium oxalate and calcium phosphate

3. What are the common categories of renal stones (by composition)?

- Calcium (calcium oxalate or calcium phosphate) stones (75–85% of all stones)
- Uric acid stones (5–10% of all stones)
- Struvite stones (from infection by urease-producing bacteria, such as *Proteus*) (5% of stones)
- Cystine stones (rare, hereditary)

83 Primary Hyperparathyroidism, A

A 56-year-old woman presents to her primary care physician complaining of progressive fatigue, weakness, and diffuse bony pain. She says that her symptoms have been getting worse over the past 2 months. Her medical history is notable for well-controlled hypertension and recurrent renal stones. Physical examination is unremarkable. A serum calcium level is elevated.

1. What is the most common cause of primary hyperparathyroidism?

- Primary hyperparathyroidism may be caused by a solitary parathyroid adenoma, parathyroid hyperplasia, or parathyroid carcinoma (rare)
- Parathyroid adenomas (chief cells) are most common, accounting for almost 85% of all cases
- The vast majority of parathyroid adenomas occur sporadically and are solitary

2. What is the occurrence of hyperparathyroidism in the multiple endocrine neoplasia syndromes?

- Parathyroid hyperplasia may be part of the autosomal dominant multiple endocrine neoplasia (MEN) syndromes
- In patients with MEN-1, caused by mutations in the *MENI* gene, there is high penetrance of hyperparathyroidism, affecting as many as 95% of patients
- Hyperparathyroidism also occurs in MEN-2A, though at a much lower frequency

83 Primary Hyperparathyroidism, B

3. What are the common symptoms and signs of primary hyperparathyroidism?

- Systemic: weakness, fatigue, weight loss, anemia, anorexia, pruritis
- Ocular: band keratopathy
- Cardiac: shortened QT interval, hypertension
- Skeletal: osteopenia, pathologic fractures, brown tumors of bone, bone pain, gout, pseudo-gout, chondrocalcinosis, osteitis fibrosa cystica
- Neurologic/psychiatric: depression, poor concentration, poor memory, neuropathy, muscle weakness
- Renal: stones, polyuria, polydipsia, metabolic acidosis, urine concentrating defects, nephrocalcinosis
- Gastrointestinal: peptic ulcer disease, pancreatitis, constipation, nausea, vomiting

84 Familial Hypocalciuric Hypercalcemia, A

A 40-year-old woman comes to the clinic to discuss some unexpected laboratory test abnormalities. She underwent these tests as part of a life insurance examination and was noted to have a mildly elevated serum calcium level. She has been healthy with no medical problems. She feels well and denies fatigue or pain. She does not take any medications or dietary supplements. There is no significant family history. Her physical examination is unremarkable. Repeated laboratory testing confirms a mildly elevated serum calcium level but also shows normal serum phosphorus level, intact parathyroid hormone (PTH), and 1,25-OH_2D levels. A 24-hour urinary calcium test returns low, at 60 mg/24 hr.

1. How can primary hyperparathyroidism be distinguished from familial hypocalciuric hypercalcemia?

- Familial hypocalciuric hypercalcemia is inherited in an autosomal dominant manner and is typically due to point mutations in one allele of the calcium-sensing receptor (CaSR) gene
- Individuals with this condition typically have a mildly elevated serum calcium and magnesium, normal or mildly elevated PTH levels, and hypocalciuria
- Urinary calcium levels are typically low and almost always less than 100 mg/24 hr
- Genetic testing for CaSR gene mutations is commercially available in several reference laboratories and is the best approach to achieving a definitive diagnosis

84 Familial Hypocalciuric Hypercalcemia, B

2. What is the mechanism for the abnormalities in familial hypocalciuric hypercalcemia?

- The CaSR, a member of the G protein–coupled receptor superfamily, is highly expressed in the parathyroid gland and kidney
- In the parathyroid, the CaSR molecule functions to detect changes in ambient serum calcium concentration and then adjust the rate of PTH synthesis and secretion
- In the kidney, the CaSR sets the level of urinary calcium excretion, based on its perception of the serum calcium concentration
- In familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism, the ability to detect serum calcium is faulty in both the kidney and parathyroid
- Familial hypocalciuric hypercalcemia is due to a partial reduction in the ability to sense extracellular calcium
- Parathyroid chief cells inappropriately sense the serum calcium as "low," and PTH secretion occurs when it should be suppressed
- This produces inappropriately normal (given the actual hypercalcemia) or slightly high PTH levels
- In the kidney, serum calcium concentrations are also detected (inappropriately) as low, and calcium is retained
- This produces the hypocalciuria typical of this condition
- In patients with homozygous mutations (both alleles affected), the clinical symptoms can be profound and life-threatening, as occurs in neonatal severe hyperparathyroidism

85 Hypercalcemia of Malignancy, A

A 69-year-old man presents to his primary care physician complaining of fatigue, nausea, weakness, and diffuse bony pain. He states his symptoms have been getting progressively worse over the last 2 months. In addition, he has noted a 15-pound weight loss over approximately the same time span. His wife, who has accompanied him, also noted that he seems increasingly confused. His medical history is notable for well-controlled hypertension and chronic obstructive pulmonary disease. He has a 100 pack-year smoking history. On physical examination, he is chronically ill appearing and thin. Vital signs are notable for a blood pressure of 120/85 mm Hg, a heart rate of 98 beats/min, and a respiratory rate of 16/min. Lungs have an increased expiratory phase, with mild expiratory wheeze. He has decreased breath sounds at the left base. The remainder of his examination is unremarkable. A serum calcium level is markedly elevated. Hypercalcemia of malignancy is suspected.

1. What tumors commonly result in hypercalcemia?

- Hypercalcemia occurs in approximately 10% of all malignancies
- Hypercalcemia is commonly seen with solid tumors, particularly squamous cell carcinomas (ie, lung, esophagus), renal carcinoma, and breast carcinoma
- Hypercalcemia occurs in more than one third of patients with multiple myeloma
- It is rarely seen in lymphomas and leukemias

85 Hypercalcemia of Malignancy, B

2. What are the mechanisms by which a tumor may cause hypercalcemia?

- Solid tumors usually produce hypercalcemia by secreting PTHrP, a 141-amino-acid peptide that is homologous with PTH at its amino terminal
- PTHrP has effects on bone and kidney similar to those of PTH; it increases bone resorption, increases phosphate excretion, and decreases renal calcium excretion, mimicking primary hyperparathyroidism
- Multiple myeloma produces hypercalcemia by a different mechanism: myeloma cells induce local bone resorption or osteolysis in the bone marrow, probably by releasing cytokines with bone-resorbing activity, such as interleukin-1 and tumor necrosis factor
- Rarely, lymphomas produce hypercalcemia by secreting $1,25\text{-}(OH)_2D$

3. What are the clinical symptoms and signs of hypercalcemia of malignancy?

- Patients with hypercalcemia of malignancy are typically very ill
- Hypercalcemia usually occurs in advanced malignancy—the average survival of hypercalcemic patients is usually several weeks to months—and the underlying cancer is often readily detectable on examination of the patient
- In addition, hypercalcemia is often severe and symptomatic, with nausea, vomiting, dehydration, confusion, or coma
- Biochemically, malignancy-associated hypercalcemia is characterized by a suppressed PTH and a decreased serum phosphate if it is PTHrP-dependent versus an increased serum phosphate if it is $1,25\text{-}(OH)_2D$-dependent

86 Hypoparathyroidism and Pseudohypoparathyroidism, A

A 32-year-old woman presents to the emergency department with complaints of involuntary hand spasms. She states that as she worked folding the laundry, she had a sudden severe spasm of her right hand such that her fingers flexed. The spasm was quite painful and lasted several minutes, resolving spontaneously. She is 6 months pregnant. Her medical history is otherwise notable for a thyroid tumor, status post-thyroidectomy 3 years ago. She is taking synthetic thyroid hormone and a prenatal multivitamin. Family history is unremarkable. On physical examination, she has positive Chvostek and Trousseau signs. Examination is otherwise unremarkable. Serum calcium level is low. Hypoparathyroidism as a complication of the thyroid surgery is suspected.

1. What are the causes of hypoparathyroidism?

- Complication of thyroid, parathyroid, or laryngeal surgery
- Autoimmune destruction of the parathyroid glands
  - Autoimmune polyendocrine failure syndrome type 1 (APS-1)
  - Isolated
- Secondary to magnesium depletion or excess
- Post-^{131}I therapy for Graves disease or thyroid cancer
- Accumulation of iron (thalassemia, hemochromatosis) or copper (Wilson disease)
- Genetic forms of hypoparathyroidism (several rare causes)
- Acquired activating mutations of the calcium-sensing receptor (CaSR)
- Autoimmune syndrome caused by autoantibodies to CaSR
- Tumor invasion (very rare)

86 Hypoparathyroidism and Pseudohypoparathyroidism, B

2. What is the mechanism of pseudohypoparathyroidism?

- PTH levels are usually elevated, but the ability of target tissues (particularly kidney) to respond to the hormone is subnormal
- In pseudohypoparathyroidism type 1, the ability of PTH to generate an increase in the second-messenger cAMP is reduced
  - Type 1a: deficiency of the α subunit of the stimulatory G protein ($G_{s\text{-}\alpha}$)
  - Type 1b, normal $G_{s\text{-}\alpha}$, but altered regulation of the $G_{s\text{-}\alpha}$ gene transcription
- In patients with pseudohypoparathyroidism type 2, urinary cAMP is normal but the phosphaturic response to infused PTH is reduced

3. What are the symptoms and signs of hypocalcemia?

- Tetany, spontaneous tonic muscular contractions, can result in painful carpal spasms and laryngeal stridor
- Latent tetany may be demonstrated by testing for Chvostek and Trousseau signs
  - **Chvostek sign** is elicited by tapping on the facial nerve anterior to the ear: twitching of the ipsilateral facial muscles indicates a positive test
  - A positive **Trousseau sign** is shown by painful carpal muscle contractions and spasms stimulated by an inflated blood pressure cuff
- If hypocalcemia is severe and unrecognized, airway compromise, altered mental status, generalized seizures, and even death may occur
- Chronic hypocalcemia can produce intracranial calcifications (with a predilection for the basal ganglia) and calcification of the lens and cataracts

87 Medullary Carcinoma of the Thyroid, A

A 23-year-old woman presents to her primary care physician complaining of diarrhea. The diarrhea is described as profuse and watery and has been getting progressively worse over the past 2 months. She has had no bloody or black bowel movements. The condition is not made worse by food and is not associated with fever, chills, sweats, nausea, or vomiting. On review of systems, she has had a 5-pound weight loss in the last 3 months. She also notes occasional flushing. She denies any significant family history. On physical examination, she is a thin white woman in no acute distress. She is afebrile, with a blood pressure of 100/60 mm Hg, heart rate of 100 bpm, and respiratory rate of 14/min. Head examination is unremarkable. Neck examination reveals bilateral hard nodules of the thyroid, a 2-cm nodule on the right upper pole, and a 1.5-cm nodule on the left upper pole. She has a firm 1-cm lymph node in the right anterior cervical chain. Lungs are clear. Cardiac examination shows mild tachycardia, with regular rhythm and no extra sounds. The abdomen has hyperactive bowel sounds and is soft, nontender, nondistended, and without masses.

1. How can you make the diagnosis of medullary carcinoma of the thyroid?

- A radionuclide thyroid scan may demonstrate one or more cold nodules
- Fine-needle aspiration biopsy may show the characteristic C-cell lesion with positive immunostaining for calcitonin (although almost half are nondiagnostic)
- The diagnosis of medullary thyroid carcinoma is often made from surgical pathology after thyroid resection
- Circulating calcitonin levels are typically elevated in most patients, and serum levels correlate with tumor burden

87 Medullary Carcinoma of the Thyroid, B

2. What is the treatment for medullary carcinoma?

- Surgery is the mainstay of therapy for patients with medullary thyroid carcinoma
- Total thyroidectomy is advocated because the tumors are often multicentric
- Patients with *RET* oncogene mutations are at high risk of medullary carcinoma
- More than 95% of patients with MEN-2 have been found to harbor *RET* mutations
- Sporadic cases of medullary carcinoma of the thyroid should also be tested to detect the occurrence of a new mutation for which other family members can then be screened
- Properly performed DNA testing is essentially unambiguous in predicting gene carrier status and can be used prospectively to recommend prophylactic thyroidectomy in young patients and children with MEN-2 before the development of C-cell hyperplasia or frank carcinoma
- Patients with MEN-2A or MEN-2B, even in the absence of symptoms, should undergo screening tests for the possibility of pheochromocytoma. With MEN-2A, it is also important to screen for hyperparathyroidism before any thyroid surgery since this disorder can be clinically silent
- Patients should be monitored indefinitely for recurrences because these tumors may be very indolent

3. Which patients are at high risk for medullary carcinoma?

88 Osteoporosis, A

A 72-year-old woman presents to the emergency room after falling in her home. She slipped on spilled water in her kitchen. She was unable to get up after her fall and was found on the floor in her kitchen by her son. She complains of severe right hip pain. On examination, she has bruising over her right hip. Range of motion in her right hip is markedly decreased, with pain on both internal and external rotation. X-ray film reveals a hip fracture and probable low bone mass. The situation raises concern about osteoporosis.

1. What is the relative importance of hereditary versus environmental or hormonal factors in contributing to osteoporosis?

- Peak bone mass depends on optimal nutrition, physical activity, general health, and hormonal exposure throughout childhood and adolescence
- After bone growth is completed, the bone mass is determined by the level of peak bone mass that was attained and the subsequent rate of loss
- Genetics are very important in determining bone mass; within the Caucasian population, more than half the variance in bone mass is genetically determined
- A number of hormonal and environmental factors can reduce the genetically determined peak bone mass or hasten the loss of bone mineral and thus represent important risk factors for osteoporosis

88 Osteoporosis, B

2. What are the risk factors for osteoporosis?

- Age, particularly post-menopausal state for women
- Female gender, Caucasian and Asian ethnicity
- Gonadal steroid deficiency, either estrogen (women) or androgens (men)
- Medications: corticosteroids or endogenous cortisol excess, excessive thyroid hormone, anticonvulsants, and chronic heparin therapy, alcohol abuse, smoking
- Immobilization
- Inadequate intake of calcium and vitamin D, high dietary protein and sodium chloride intake leading to urinary calcium losses
- Malabsorption
- Connective tissue diseases or certain malignancies such as multiple myeloma

3. What are the risk factors for a hip fracture in a patient with osteoporosis?

- Hip fractures typically occur in the elderly, with a sharply rising incidence in both sexes after age 80 years and a 6-month mortality of 20%
- About half of elderly people with a hip fracture will never walk freely again
- Diminished motor and visual function with aging that result in more frequent falls along with the decreased bone density are important risks
- An absolute 10-year fracture risk calculation algorithm (termed FRAX) has been developed by the WHO, which incorporates femoral neck bone mineral density values and several clinical risk factors to determine an individual's 10-year probability of a major osteoporotic or hip fracture

89 Osteomalacia, A

A 93-year-old woman is brought to the emergency department by ambulance for "failure to thrive." Today the woman's daughter was attempting to roll her to clean her, and the patient fell from the bed to the floor. They have been unable to pay for medications for several months. For many months, the patient has been eating only broth because of difficulty with chewing and swallowing. On examination, she is pale, with central obesity, wasting of her extremities, and flexion contractures of her right upper and lower extremities. On head and neck examination, she has temporal wasting, right facial droop, pale conjunctivas, and dry mucous membranes. Lungs are clear to auscultation. Cardiac examination is notable for an S_4 gallop. She moans when her extremities are palpated. Laboratory reports show hypocalcemia, hypophosphatemia, and elevated alkaline phosphatase. X-ray films of her pelvis reveal low bone mass and "pseudo-fracture" of the pubic rami. Osteomalacia is suspected.

1. What are the causes of osteomalacia?

- Vitamin D deficiency
- Deficiency of phosphate, due to renal wasting
- Deficient alkaline phosphatase: hereditary hypophosphatasia
- Drug toxicity
- Fluoride, aluminum excess
- Etidronate disodium
- Phosphate-binding antacids
- Chronic kidney disease

89 Osteomalacia, B

2. What are the two stages in which vitamin D deficiency produces osteomalacia?

- In early stages, reduced calcium absorption produces secondary hyperparathyroidism, preventing hypocalcemia at the cost of increased renal phosphate excretion and hypophosphatemia
- In later stages, hypocalcemia ensues, and hypophosphatemia progresses because of the combined effects of reduced absorption and the phosphaturic action of PTH

3. What are the symptoms and signs of osteomalacia?

- Patients with osteomalacia have bone pain, muscle weakness, and a waddling gait
- The hallmark is pseudo-fracture: local bone resorption that has the appearance of a nondisplaced fracture, classically in the pubic rami, clavicles, or scapulas
- In children with rickets, the leg bones are bowed (osteomalacia means "softening of bones"), the costochondral junctions are enlarged ("rachitic rosary"), and the growth plates are widened and irregular, reflecting the increase in unmineralized cartilage that bends under the child's weight, resulting in the bowing
- Biochemically, the hallmarks of vitamin D–deficient osteomalacia are hypophosphatemia, hyperparathyroidism, variable hypocalcemia, and marked reductions in urinary calcium to less than 50 mg/d
- The 25-(OH)D level is reduced, indicative of decreased body stores of vitamin D, and the alkaline phosphatase level is increased

90 Diabetes Mellitus: Diabetic Ketoacidosis, A

A 58-year-old homeless man with long-standing insulin-treated type 2 diabetes has been diagnosed with right lower extremity cellulitis. He has taken a prescribed oral antibiotic for the past week but has not noticed much improvement. For the last 2 days, he has complained of intermittent fevers and chills, nausea with poor oral intake, and proximally spreading erythema over his right leg. On the evening of admission, a friend notices that he is markedly confused and calls 911. In the emergency room, he is oriented only to his name. The patient is tachypneic, breathing deeply at a rate of 24/min. He is febrile at 38.8°C. He is normotensive, but his heart rate is elevated at 112 bpm. On examination, this patient is a delirious, unkempt man with a fruity breath odor. His right lower extremity is markedly erythematous and exquisitely tender to palpation. Serum chemistries reveal a glucose level of 488 mg/dL, potassium of 3.7 mEq/dL, and sodium of 132 mEq/L. Urine dipstick is grossly positive for ketones.

1. What are the pathophysiologic mechanisms at work in diabetic ketoacidosis?

- In the absence of insulin, lipolysis is stimulated, providing fatty acids that are preferentially converted to ketone bodies in the liver by unopposed glucagon
- Diabetic ketoacidosis (DKA) results in profound hyperglycemia and ketosis
- DKA is more common in type 1 diabetics but can occur in type 2 diabetics, particularly with infections, trauma, or other significant physiologic stressors
- Initially, elevated glucose levels result in an increase in osmolality, polyuria, glycosuria, and fluid loss
- If oral intake is unable to match losses, glycosuria is curtailed and osmolality increases, possibly leading to coma

2. Why do ketones appear to be increase during appropriate treatment of ketoacidosis?

- During treatment of diabetic ketoacidosis, measured serum ketones may transiently rise instead of showing a steady decrease
- This is an artifact because of the limitations of the nitroprusside test that is often used at the bedside to measure ketones in both serum and urine
- Nitroprusside only detects acetoacetate and not β-hydroxybutyrate
- During untreated diabetic ketoacidosis, accelerated fatty acid oxidation favors the formation of β-hydroxybutyrate over acetoacetate
- With insulin treatment, fatty acid oxidation decreases and the redox potential of the liver shifts back in favor of acetoacetate formation

3. Why is hyperosmolar coma without ketosis is a more common presentation than ketoacidosis in type 2 diabetes mellitus?

- The mechanisms underlying the development of hyperosmolality and hyperosmolar coma are the same as in diabetic ketoacidosis
- Only minimal levels of insulin activity are required to suppress lipolysis; most type 2 diabetics have sufficient insulin to prevent the ketogenesis that results from increased fatty acid flux
- Because of the absence of ketoacidosis and its symptoms, patients often present with more profound hyperglycemia and dehydration; glucose levels often range from 800 to 2400 mg/dL and the effective osmolality is more than 330 mOsm/L

91 Insulinoma, A

A 61-year-old man recently moved to San Francisco and is reestablishing primary care. During a comprehensive review of systems, he reports that he has experienced a 3-year history of "hypoglycemic attacks." These short periods of light-headedness, confusion, palpitations, and tremor occur more frequently in the late afternoon while jogging. His symptoms are relieved after drinking a sugared sports drink. He has no history of diabetes or cancer. His physical examination is unremarkable, and in the clinic, a fasting morning glucose level is 93 mg/dL. Suspecting that an insulinoma-induced hypoglycemic state may be responsible for his symptoms, his physician requests a diagnostic fast period during which glucose, insulin, and C-peptide levels are measured.

1. What is the clinical presentation of insulinoma?

- Insulinomas occur most frequently in the fourth to seventh decades, although they can occur earlier, particularly when associated with multiple endocrine neoplasia type 1 (MEN-1)
- The Whipple triad establishes the diagnosis of hypoglycemia: (1) symptoms and signs of hypoglycemia, (2) low plasma glucose level, and (3) reversibility of symptoms with glucose
- Symptoms are often present for years before diagnosis because patients unknowingly self-treat the hypoglycemia with frequent food intake
- Some patients (30%) have fasting hypoglycemia; others have late afternoon hypoglycemia, particularly when precipitated by exercise or alcohol intake
- Neurologic symptoms are common and include confusion (80%), loss of consciousness (50%), and seizures (10%)

91 Insulinoma, B

2. What is the pathogenesis of insulinoma?

- Fasting hypoglycemia in a healthy individual is usually due to an insulin-secreting tumor of the β cells of the islets of Langerhans or insulinoma
- Insulinoma is the most common islet cell tumor, but still a rare disorder
- Insulinomas are usually benign solitary adenomas composed of clusters of insulin-secreting β cells
- Multiple tumors (<10%), are seen most often in patients with MEN-1
- Fewer than 10% of the tumors are malignant

3. Why do insulinomas cause hypoglycemia?

- Normally, insulin levels decline during fasting, leading to an increase in glucagon-stimulated hepatic glucose output and a decrease in insulin-mediated glucose disposal in the periphery
- With exercise, low insulin levels allow: (1) glycogen to be utilized as a primary energy source in muscle; (2) glucagon and other counter-regulatory hormones to increase hepatic glucose output; and (3) counter-regulatory hormones to oxidize fatty acids for ketogenesis
- With an insulinoma, insulin levels remain high during fasting or exercise
- Glucagon-mediated hepatic glucose output and ketogenesis is suppressed while insulin-mediated peripheral glucose uptake continues
- The result is fasting or exercise-induced hypoglycemia in the absence of ketosis

92 Glucagonoma, A

A 52-year-old woman with a 3-year history of diet-controlled diabetes presents to her primary care provider complaining of a "stubborn poison ivy rash" over her legs, which she attributed to a possible exposure to the plant during a recent hike. She presented twice to the urgent care center and received high-potency topical steroid cream for this refractory erythematous rash with central blistering. A review of systems reveals intermittent diarrhea and constipation as well as weight loss. Her serum glucagon level is measured to be 20 times normal.

1. What are glucagonomas?

- Glucagonomas are solitary α-cell tumors of the pancreas
- Even though they are slow growing, they are usually large and have often metastasized by the time of diagnosis, making surgical resection difficult
- Octreotide, the synthetic somatostatin analogue, can be used to ameliorate symptoms via its suppression of glucagon secretion

2. What are the clinical manifestations of glucagonomas?

- Glucagonomas are usually diagnosed by the appearance of a characteristic rash in middle-aged individuals, particularly perimenopausal women, with mild diabetes mellitus
- Glucagon levels are usually increased 10-fold relative to normal values but can even be increased 100-fold
- Necrolytic migratory erythema, the characteristic rash in glucagonoma, begins as an erythematous rash on the face, abdomen, perineum, or lower extremities
  - After induration with central blistering develops, the lesions crust over and then resolve, leaving an area of hyperpigmentation
  - These lesions may be the result of nutritional deficiency, such as the hypoaminoacidemia that occurs from excessive glucagon stimulation of hepatic amino acid uptake and utilization as fuel for gluconeogenesis
  - Appearance of the rash is a late manifestation of the disease
- Diabetes mellitus or glucose intolerance is present in the vast majority of patients as a result of increased stimulation of hepatic glucose output by the inappropriately high glucagon levels
- Insulin levels are secondarily increased and the diabetes is mild and without ketosis
- Anemia and a variety of nonspecific gastrointestinal symptoms related to decreased intestinal motility also can accompany glucagonomas

93 Somatostatinoma, A

At the time of an elective laparoscopic cholecystectomy for gallstones, a 44-year-old woman with mild diabetes mellitus and chronic diarrhea is noted to have a 3–4 cm solitary mass on the surface of her duodenum. Omental lymphadenopathy is seen. Biopsy demonstrates a high-grade somatostatinoma with lymph node metastasis.

1. What is the clinical presentation of somatostatinomas?

- Somatostatinomas are very rare tumors, usually found incidentally during abdominal operations
- A classic triad of symptoms occur with excessive somatostatin secretion:
  - Diabetes mellitus secondary to the inhibition of insulin and glucagon secretion by somatostatin
  - Cholelithiasis secondary to somatostatin-mediated inhibition of gall-bladder motility; and
  - Steatorrhea induced by the inhibition of pancreatic exocrine function by somatostatin
- Hypochlorhydria, diarrhea, and anemia can also occur
- Documentation of elevated somatostatin levels confirms the diagnosis

93 Somatostatinoma, B

2. Where are these tumors found?

- Although the majority of somatostatinomas occur in the pancreas, a significant number are found in the duodenum or jejunum
- Like glucagonomas, somatostatinomas are often solitary and large and have frequently metastasized by the time of diagnosis

3. Why is the diabetes in this condition relatively mild?

- In type 1 and type 2 diabetes mellitus, the effects of insulin insufficiency are aggravated by the occurrence of elevated glucagon levels
- Somatostatinomas suppress both insulin and glucagon
- Therefore, the hyperglycemia resulting from insulinopenia is tempered by the absence of glucagon stimulation of hepatic glucose output
- Although low insulin levels are permissive for lipolysis, glucagon deficiency prevents hepatic ketogenesis
- The diabetes associated with somatostatinomas is, therefore, mild and not ketosis-prone

94 Obesity, A

A 53-year-old woman presents to the clinic to get help managing her weight. She has been overweight since childhood and has continued to gain weight throughout her adult life. She has tried numerous diets without lasting success. She initially loses weight but then regains it after a few months. She is otherwise healthy and is not taking any medications. Other family members are also overweight or obese. She does not do any regular exercise and has a sedentary office job. On examination, she is 5 feet 3 inches tall and 260 pounds, with a body mass index (BMI) of 46.2 (normal <25).

1. What is the definition of obesity?

- Body mass index (BMI) is the most commonly used index to define the terms overweight and obesity
- The BMI is calculated as the patient's body weight (in kilograms) divided by the height (in meters squared)
- The normal range is defined as a BMI of 18.5–25, overweight is defined as a BMI of 25.1–30, and obesity is defined as a BMI of more than 30

94 Obesity, B

2. What diseases are associated with obesity?

- Increased risk of several cancers
- Elevated uric acid levels can lead to gout
- Excess weight-bearing can leading to osteoarthritis
- Decreases in high-density lipoprotein and increases in low-density lipoprotein cholesterol, which can lead to coronary artery disease or stroke
- Increased vascular tone and sodium retention, leading to hypertension
- Increased insulin resistance and risk of type 2 diabetes
- Increases in serum estrogen (and cholesterol) increase the risk of gallstones
- Obstructive sleep apnea from increase soft tissue in the head and neck

3. How is body weight controlled?

- A complex interaction of hormones acts on the hypothalamus to maintain body weight over the short and the long term
- Neuroendocrine signals of the "gut-brain axis" communicate between the gastrointestinal tract and the brain
- The gut-brain crosstalk uses both neural components (afferent vagal fibers) and hormonal components (cholecystokinin [CCK], glucagon-like peptide-1 [GLP-1], and ghrelin)
- Long-term regulation is largely influenced by the degree of obesity
- Fat cells secrete the hormone leptin in proportion to the amount of triglyceride they have stored; leptin decreases appetite and increases metabolism

95 Pituitary Adenoma, A

A 30-year-old woman presents to the emergency department after sideswiping a parked car. She reports that she never saw the car until after she hit it. She denies any trauma to herself but does complain of headache. She states that she has had headaches every day for the past 3 months, and this one is similar to her other headaches. She describes the headache as a frontal throbbing pain that is worse when she lies down and occasionally it wakes her from sleep. She has no significant medical history, takes no medications, and denies alcohol, tobacco, or drug use. On review of systems, she notes irregular menses but denies other complaints. On examination, she appears to be well, with normal vital signs. Her neurologic examination is notable for bitemporal hemianopia. On breast examination, galactorrhea is present but no masses. The remainder of the examination is unremarkable.

1. What is a pituitary adenoma?

- An adenoma is a benign tumor of epithelial cell origin
- The pituitary is in an enclosed space with very limited capacity to accommodate an expanding mass
- A pituitary adenoma arises from one of several pituitary cell types that secrete hormones (eg, prolactin-secreting cells, also known as acidophil, lactotroph, or mammotroph cells), giving rise to pituitary hormone overproduction (eg, hyperprolactinemia) as well as to a mass effect from the tumor itself

95 Pituitary Adenoma, B

2. What brings patients with pituitary adenomas to medical attention?

- Many adenomas are nonfunctional
- Prolactinomas produce excess prolactin and can cause galactorrhea
- Growth hormone–secreting adenomas can cause gigantism or acromegaly
- ACTH-secreting adenomas can cause Cushing disease (hypercortisolism)
- Tumors secreting thyroid-stimulating hormone (TSH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) are extremely rare

3. What are the most common forms of pituitary adenoma?

- Pituitary adenomas are extremely common; most are clinically inapparent
- They can cause symptoms due to expanding intracranial mass (headaches, diabetes insipidus, vision changes due to pressure on the optic chiasm)
- They can cause symptoms of excess or deficiency of one or more pituitary hormones
- Hormone excess occurs when the adenoma secretes a particular hormone
- Hormone deficiency results from destruction of the normal pituitary by the expanding adenoma
- Microadenomas are less than 10 mm in diameter and usually are found incidentally on head CT scan or because of excessive hormone secretion
- Macroadenomas are more than 10 mm in diameter and are often found due to mass effect

96 Panhypopituitarism, A

A 31-year-old woman with a medical history significant for pituitary macroadenoma treated with radiation therapy 1 year ago presents to the clinic with a complaint of amenorrhea. She previously had irregular menses with menses lasting about 3 days and occurring about once every 1.5–2 months. However, for the past 4 months, she has had no menses. She denies sexual activity. On review of systems, she notes fatigue and a 10 pound weight gain. She is taking no medications. On examination, her blood pressure is 100/60 mm Hg and heart rate is 80 bpm. Neurologic examination is normal except for a slight delay in the relaxation phase of her deep tendon reflexes. On head-neck examination, she has somewhat coarse, brittle brown hair. Neck examination discloses no goiter or masses. Lung, cardiac, and abdominal examinations show no abnormalities. Pelvic examination reveals normal female genitalia without uterine or ovarian masses. Urine pregnancy test is negative.

1. What are the most common causes of panhypopituitarism?

- Ischemic: postpartum (Sheehan syndrome), head injury, and vascular disease
- Neoplasm: nonfunctioning adenoma, craniopharyngioma, and suprasellar chordoma, histiocytosis X (eosinophilic granuloma; Hand-Schüller-Christian disease)
- Pituitary: surgery, radiation
- Intrasellar cysts
- Inflammatory/infectious: tuberculosis, syphilis, and sarcoidosis
- Infiltrative: amyloidosis, hemochromatosis, and mucopolysaccharidoses
- Rare genetic mutations

96 Panhypopituitarism, B

2. How do patients with panhypopituitarism come to medical attention?

- Rapid pituitary destruction results in
  - Two potentially life-threatening situations, adrenal crisis and diabetes insipidus (due to loss of ACTH and vasopressin, respectively)
  - Absent stress response (due to lack of ACTH-stimulated glucocorticoid secretion)
  - Massive diuresis (from diabetes insipidus due to vasopressin deficiency)
- Slow pituitary destruction results in
  - Amenorrhea in women, and infertility or erectile dysfunction in men (due to lutenizing hormone [LH] and follicle-stimulating hormone [FSH] deficiency)
  - Lethargy, weight gain, or altered bowel habits (from hypothyroidism due to thyroid-stimulating hormone [TSH] deficiency)

3. Why might some hormone deficiencies in a patient with panhypopituitarism remain asymptomatic?

- Mineralocorticoid secretion is not controlled by ACTH
- Sufficient glucocorticoids to maintain basic biological function may be present despite low ACTH until a medical emergency occurs and the patient is unable to mount a normal stress response
- Vasopressin deficiency may go unnoticed as long as the patient is able to maintain adequate fluid intake to compensate for the inability to concentrate urine

97 Diabetes Insipidus, A

A 54-year-old man presents to his clinician complaining of polyuria. He states that he must get up three or four times each night to urinate. He also notes frequent thirst. He denies polyphagia, urinary urgency, difficulty initiating urination, or postvoid dribbling. His medical history is notable only for bipolar disease. He has a long-standing history of noncompliance with medications for this disease, with frequent hospitalizations for both mania and depression, but has been stable on lithium for the past 6 months. He denies any symptoms of mania or depression at this time. He takes no other medications. Family history is notable for depression and substance abuse. The patient has a history of polysubstance abuse but has been "clean and sober" for the past 6 months. On examination, the patient's vital signs are within normal limits. Head-neck examination reveals slightly dry mucous membranes. Rectal examination reveals a normal prostate without masses. The remainder of his examination is unremarkable. Urinalysis reveals dilute urine without glycosuria or other abnormality. Serum electrolytes reveal a mildly increased sodium level. A diagnosis of diabetes insipidus is entertained.

1. What clues would suggest diabetes insipidus in a new patient?

- Both central and nephrogenic diabetes insipidus result in the same symptoms and signs: polyuria, polydipsia, hypotonic urine, and hypernatremia
- Another clue would be the rapid onset of dehydration and hypernatremia progressing to coma if the patient is deprived of access to sufficient fluid intake

97 Diabetes Insipidus, B

2. How would you make a definitive diagnosis of diabetes insipidus?

- The hallmark of diabetes insipidus is dilute urine, even in the face of hypernatremia
- Dipstick testing of the urine for glucose can exclude diabetes mellitus
- Conditions in which osmotic diuresis is responsible for polyuria can be distinguished from diabetes insipidus by their normal or elevated urine osmolality
- Primary polydipsia is distinguished by low instead of normal or elevated serum sodium

3. What are the pathophysiologic differences between central and nephrogenic diabetes insipidus?

- Central diabetes insipidus results from lack of synthesis or secretion of antidiuretic hormone (ADH) or vasopressin
- It often results from acute injury (eg, post-infarction or post-trauma), leading to transient cessation of ADH secretion followed by gradual recovery
- Familial nephrogenic diabetes insipidus results from a generalized defect in either the V_2 class of vasopressin receptors or the aquaporin-2 water channel of the renal collecting ducts
- Drug-induced nephrogenic diabetes insipidus results from the effect of lithium, fluoride, and other salts on the activity of the vasopressin receptor. It occurs in 12–30% of patients treated with these drugs

98 Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), A

A 75-year-old man with small-cell carcinoma of the lung presents to the emergency department with altered mental status. The patient's wife, who is also his primary caregiver, has worked hard to keep him adequately hydrated by waking him every 2 hours to have him drink (an estimated 2–3 quarts of water daily). On examination, the patient is a cachectic white man in mild respiratory distress. He is lethargic but arousable. He is oriented to person only. Vital signs were temperature 38°C, blood pressure 110/60 mm Hg, heart rate 88 bpm, respiratory rate 18/min, and oxygen saturation 96% on 3 L of oxygen. Mucous membranes are moist. Neck is supple. There are decreased breath sounds in the left lower posterior lung field and rales in the upper half. Cardiac examination is normal. Abdomen is benign without masses. Extremities are without edema, cyanosis, or clubbing. Neurologic examination shows bilateral positive Babinski signs and asterixis. Laboratory studies reveal a serum sodium level of 118 mEq/L.

1. How would you distinguish SIADH from other causes of hyponatremia?

- Adrenal insufficiency is one cause of hypovolemic hyponatremia due to aldosterone deficiency, subsequent sodium loss, and ultimate volume depletion that triggers ADH secretion
- Chronic liver or heart failure or chronic kidney disease, while also dependent on ADH secretion for development of hyponatremia, presents with hypervolemia
- Hyponatremia accompanying CNS disorders can be caused by cerebral salt wasting with an increased release of natriuretic peptides (eg, BNP, ANP), which increase the total extracellular volume

98 Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), B

2. What conditions are associated with SIADH?

- Tumors: lung (especially small cell), duodenal, pancreatic, bladder, ureteral, prostate cancers, leukemia, lymphoma, thymoma, and sarcoma
- CNS disorders: mass lesions, infections, CVA, hydrocephalus, trauma, psychosis, demyelinating or degenerative disease, inflammation, and delirium tremens
- Confusion, asterixis, myoclonus, generalized seizures, and coma
- These occur as a result of osmotic fluid shifts and resulting brain edema and elevated intracranial pressures; brain swelling is limited by the size of the skull
- The more rapid the progression of hyponatremia, the more likely that the neurologic complications and herniation will lead to permanent damage
- Central pontine myelinolysis can cause permanent neurologic damage in patients whose hyponatremia is corrected too rapidly, so correction must be done slowly

- Lung disorders: infections (pneumonia, tuberculosis, abscess), respiratory failure, and positive pressure ventilation
- Drugs: vasopressin, clofibrate, chlorpropamide, carbamazepine, vincristine, vinblastine, tricyclic antidepressants, and phenothiazines
- Idiopathic

3. What are the neurologic consequences of SIADH, and how may they be prevented?

99 Hyperthyroidism, A

A 25-year-old African American woman presents with a complaint of rapid weight loss despite a voracious appetite. Physical examination reveals tachycardia (pulse rate 110 bpm at rest), fine moist skin, symmetrically enlarged thyroid, mild bilateral quadriceps muscle weakness, and fine tremor. These findings strongly suggest hyperthyroidism.

1. What are the various ways that hyperthyroidism can develop?

- Thyroid hormone overproduction
  - Graves disease (most common) due to thyroid-stimulating hormone receptor–stimulating antibody, TSH-R [stim] Ab (also known as thyroid-stimulating immunoglobulin [TSI])
  - Toxic multinodular goiter, follicular adenoma (note: thyroid cancer rarely results in hyperthyroidism)
  - Pituitary insensitivity to thyroid hormone negative feedback
  - Overproduction of TSH or thyrotropin-releasing hormone (TRH)
  - Germ cell tumors producing human chorionic gonadotropin
  - Ovarian teratoma with ectopic thyroid tissue (struma ovarii)
- Thyroid gland destruction with release of stored thyroid hormone (thyroiditis)
- Drug effects: ingestion of excessive exogenous thyroid hormone, or thyroiditis from drugs such as amiodarone or interferon alpha

99 Hyperthyroidism, B

2. What are the symptoms and signs of hyperthyroidism?

- Symptoms: alertness; emotional lability; nervousness; irritability; poor concentration; muscular weakness; fatigability; palpitations; voracious appetite; weight loss; hyperdefecation; heat intolerance
- Signs: hyperkinesia; rapid speech; proximal muscle (quadriceps) weakness; fine tremor; fine, moist skin; fine, abundant hair; onycholysis; lid lag; stare; chemosis; periorbital edema; proptosis; accentuated first heart sound; tachycardia; atrial fibrillation (resistant to digitalis); widened pulse pressure; dyspnea

3. What is the pathogenesis of Graves disease?

- More than 90% of patients with Graves disease have TSH-R [stim] Ab, an antibody directed to the thyroid follicular epithelial membrane TSH receptor
- TSH-R [stim] Ab stimulates TSH receptor–mediated hormone synthesis and secretion in an identical fashion to TSH
- The mechanism of TSH-R [stim] Ab production in Graves disease is uncertain
- A genetic contribution to the development of Graves disease is suggested by the finding of much higher concordance rates in monozygotic same-sex twin pairs (0.35) than in dizygotic pairs (0.03) and also from an increased risk of other autoimmune disorders in patients with Graves disease
- An immune response against a viral antigen that shares homology with TSH receptor or a defect of suppressor T lymphocytes may be responsible

100 Hypothyroidism, A

A 45-year-old woman presents complaining of fatigue, weight gain of 30 pounds despite dieting, constipation, and menorrhagia. On physical examination, the thyroid is not palpable; the skin is cool, dry, and rough; the heart sounds are quiet; and the pulse rate is 50 bpm. The rectal and pelvic examinations show no abnormalities, and the stool is negative for occult blood. A thyroid-stimulating hormone (TSH) level is 15 mIU/L.

1. What are some drugs that can cause hypothyroidism?

- Iodine, inorganic; iodine, organic (amiodarone)
- Thioamides (propylthiouracil, methimazole)
- Potassium perchlorate, thiocyanate, lithium, sunitinib

2. What are the most useful initial tests of thyroid function in hypothyroidism?

- TSH is the most sensitive test for early hypothyroidism (except in rare cases of pituitary or hypothalamic disease)
- Hypothyroidism is also characterized by abnormally low serum T_4 and T_3 levels
- Modest TSH elevations (5–20 mU/L) may be found in euthyroid individuals with normal serum T_4 and T_3 levels and indicate impaired thyroid reserve and incipient (often subclinical) hypothyroidism

100 Hypothyroidism, B

3. What are the key pathophysiologic findings in Hashimoto thyroiditis?

- Early on, the gland is diffusely enlarged, firm, rubbery, and nodular
- With progression, the gland becomes smaller leading to atrophy and fibrosis
- There is destruction of thyroid follicles and lymphocytic infiltration with lymphoid follicles
- The surviving thyroid follicular epithelial cells are large, with abundant pink cytoplasm (Hürthle cells)
- The most important thyroid autoantibodies in Hashimoto thyroiditis are thyroglobulin antibody (Tg Ab), thyroidal peroxidase antibody (TPO Ab) (formerly termed antimicrosomal antibody), and the TSH receptor blocking antibody (TSH-R [block] Ab)
- Serum levels of these antibodies do not correlate with the severity of the hypothyroidism, but their presence is helpful in diagnosis
- In general, high antibody titers are diagnostic of Hashimoto thyroiditis; moderate titers are seen in Graves disease, multinodular goiter, and thyroid neoplasm; and low titers are found in the elderly

101 Goiter, A

A 40-year-old woman who has recently emigrated from Afghanistan comes to an office practice to establish medical care. She complains only of mild fatigue and depression. Physical examination reveals a prominent, symmetrically enlarged thyroid about twice normal size. The remainder of the examination is unremarkable.

1. What are the causes and mechanisms of goiter formation?

- Diffuse thyroid enlargement most commonly results from prolonged stimulation by thyroid-stimulating hormone (TSH) (or a TSH-like agent)
- Stimulation can result in goiter in both hypothyroidism (ie, TSH in Hashimoto thyroiditis) or hyperthyroidism (ie, TSH-R [stim] Ab in Graves disease, chorionic gonadotropin [hCG] in a germ cell tumor or [rarely] TSH in a pituitary adenoma)
- Goiter may also occur in a clinically euthyroid patient
  - Iodine deficiency results from a diet that contains less than 10 µg/d of iodine; this hinders the synthesis of thyroid hormone, resulting in a compensatory increase in TSH and subsequent thyroid hypertrophy
  - Ingestion of goitrogens (factors that block thyroid hormone synthesis) either in food or in medication. Dietary goitrogens are found in vegetables of the *Brassicaceae* family (eg, rutabagas, cabbage, turnips, cassava). Goitrogenic hydrocarbons have been found in the water supply in some locations. Medications that act as goitrogens include thioamides and thiocyanates, sulfonylureas, and lithium
- A congenital goiter associated with hypothyroidism (sporadic cretinism) may occur due to a defect in any of the steps of thyroid hormone synthesis

101 Goiter, B

2. What is the basis for transition from nontoxic, TSH-dependent diffuse hyperplasia to a toxic or nontoxic TSH-independent multinodular goiter?

- In early goiters, the hyperplasia is TSH-dependent, but in later stages the nodules become TSH-independent autonomous nodules
- There may be a transition from a nontoxic, TSH-dependent, diffuse hyperplasia to a toxic or nontoxic, TSH-independent, multinodular goiter
- The exact mechanism underlying this transition is unknown
  - Mutations of the *gsp* oncogene have been found in nodules from many patients with multinodular goiter
  - Such mutations presumably occur during TSH-induced cell division
  - The *gsp* oncogene is responsible for activation of regulatory guanosine triphosphate (GTP)–binding (G_s) protein in the follicular cell membrane
  - Chronic activation of this protein and its effector, adenylyl cyclase, is postulated to result in thyroid cell proliferation, hyperfunction, and independence from TSH

3. How large can the thyroid gland become with decades of stimulation?

- With decades of TSH stimulation, enormous hypertrophy and enlargement of the gland can occur; the enlarged gland may weigh 1–5 kg and may produce respiratory difficulties secondary to obstruction of the trachea or dysphagia secondary to obstruction of the esophagus
- More modest enlargements pose cosmetic problems

102 Thyroid Nodule and Neoplasm, A

A 47-year-old man presents complaining of nervousness, difficulty concentrating, restlessness, and insomnia. He has lost 25 pounds over the past 6 weeks and complains of heat intolerance. Physical examination reveals a 1-cm nodule in the left lobe of the thyroid gland.

1. What is the most common type of thyroid nodule?

- Tumors of the thyroid usually present as a solitary mass in the neck
- Follicular adenoma is the most common neoplasm, accounting for 30% of all solitary thyroid nodules
  - It is a solitary, firm, gray or red nodule, up to 5 cm in diameter, completely surrounded by a fibrous capsule
  - Microscopically, the adenoma consists of normal-appearing follicles of varying size, sometimes associated with hemorrhage, fibrosis, calcification, and cystic degeneration
  - Malignant change probably occurs in less than 10% of follicular adenomas
  - While adenomas are often functional and autonomously produce excess thyroid hormone, thyroid cancer is usually not effective at hormone production and hence is nonfunctional

102 Thyroid Nodule and Neoplasm, B

2. What are the different types of thyroid cancers?

- Most thyroid cancers are derived from the follicular epithelium and, depending on their microscopic appearance, are classified as papillary or follicular carcinoma
- The major risk factor predisposing to epithelial thyroid carcinoma is exposure to radiation, but genetic factors have also been recognized
- Most papillary and follicular cancers pursue a prolonged clinical course (15–20 years)
  - Papillary carcinoma typically metastasizes to regional neck lymph nodes
  - Follicular cancer tends to spread via the bloodstream to distant sites such as bone or lung
- Medullary carcinoma is an uncommon neoplasm of the C cells (parafollicular cells) of the thyroid that produce calcitonin
  - Approximately 30% of all medullary thyroid carcinomas are a manifestation of multiple endocrine neoplasia type 2 (MEN-2), inherited in an autosomal dominant fashion

103 Familial Euthyroid Hyperthyroxinemia, A

A 28-year-old woman returns for follow-up after routine laboratory tests show a markedly elevated total T_4 level and a normal TSH level. The patient is totally asymptomatic, and the physical examination is unremarkable.

1. Why do individuals with sustained increases or decreases in thyroid-binding globulin (TBG) and other binding proteins remain clinically euthyroid?

- When a sustained increase in the concentration of thyroid-binding globulin (TBG) and other binding proteins occurs, the concentration of free thyroid hormones falls temporarily
  - This fall stimulates thyroid-stimulating hormone (TSH) secretion, which then results in an increase in the production of free hormone
  - Eventually, a new equilibrium is reached in which the levels of total plasma thyroxine (T_4) and triiodothyronine (T_3) are elevated, but the concentrations of free hormones, the rate of hormone degradation, and the rate of TSH secretion are normal
  - Therefore, individuals manifesting sustained increases in TBG and other binding proteins remain euthyroid
- A sustained decrease promotes changes in the opposite direction

103 Familial Euthyroid Hyperthyroxinemia, B

2. Describe unusual syndromes of familial euthyroid hyperthyroxinemia.

- There are several familial syndromes
  - Euthyroid dysalbuminemic hyperthyroxinemia: abnormal binding of T_4 (but not T_3) to albumin
  - Increased serum transthyretin level (transthyretin is a plasma protein that transports 15–20% of circulating T_4)
  - Mutations in transthyretin that markedly increase its affinity for T_4
- In all three of these syndromes, total T_4 is elevated, but free T_4 is normal and the patients are clinically euthyroid
- A fourth syndrome has also been described in which there is both pituitary and peripheral resistance to thyroid hormone; this condition may be due to point mutations in the human thyroid receptor (*hTR-β1*) gene, resulting in abnormal nuclear T_3 receptors

104 Cushing Syndrome, A

A 35-year-old woman has hypertension of recent onset. Review of systems reveals several months of weight gain and menstrual irregularity. On examination, she is obese with a plethoric appearance. Her blood pressure is 165/98 mm Hg. There are prominent purplish striae over the abdomen and multiple bruises over both lower legs. The patient's physician entertains a diagnosis of hypercortisolism (Cushing syndrome).

1. What are the major causes of Cushing syndrome?

- ACTH-dependent hypercortisolism, due to excessive ACTH production:
  - Cushing disease (ACTH-secreting pituitary adenoma) is the most common
  - Ectopic ACTH syndrome from tumors; small cell lung or bronchial carcinoid are most common, but many other tumors may produce ACTH
- ACTH-independent hypercortisolism: functioning adrenal tumor (usually adenoma, rarely carcinoma)
- Exogenous glucocorticoid administration

104 Cushing Syndrome, B

2. What are the symptoms and signs of glucocorticoid excess?

- Glucocorticoid excess has effects throughout the body
  - Hyperglycemia and diabetes with thirst and polyuria
  - Muscle wasting, especially proximal muscles (eg, difficulty rising from a chair)
  - Central obesity and body fat redistribution to face, neck, trunk, and abdomen
  - Thinning of the skin, abdominal striae, easy bruisability, poor wound healing, and frequent skin infections due to connective tissue loss
  - Perioral dermatitis, central facial erythema, acne, and acanthosis nigricans
  - Hirsutism in female patients
  - Osteoporosis and increased risk of bony fracture
  - Avascular (aseptic) necrosis of bone (usually of the femur or humerus) occurs sometimes with exogenous (iatrogenic) corticosteroids but is rare with endogenous hypercortisolemia
  - Cell-mediated immune response is impaired with increased risk of certain infections (eg, fungus or tuberculosis)
  - Hypertension occurs in 75–85% with spontaneous Cushing syndrome
  - Gonadal dysfunction: amenorrhea, impotence, loss of libido, and infertility
  - Mental symptoms: euphoria, increased appetite, irritability, emotional lability, impaired cognitive function, with poor concentration and poor memory, disordered sleep, depression, anxiety, psychosis with delusions or hallucinations, paranoia, or hyperkinetic (even manic) behavior
  - Elevation of intraocular pressure and glaucoma, posterior subcapsular cataracts

105 Adrenal "Incidentaloma", A

A 56-year-old man undergoes an abdominal computed tomography (CT) scan in the evaluation of abdominal pain. The scan is unremarkable except for the finding of a 3-cm mass in the right adrenal gland. The mass is homogeneous and smooth, and it has low density on the CT scan. The patient has a normal examination and feels well otherwise.

1. How common are adrenal masses and what is the risk of malignancy?

- Autopsy studies find an adrenal mass in ≥3% of persons older than 50 years
- Their occurrence varies from <1% for persons younger than 30 years to 7% for those 70 years or older
- Approximately 1 in 4000 adrenal tumors is malignant

2. What are the possible diagnoses of the adrenal masses?

- Benign: adrenocortical adenomas, some pheochromocytomas, myelolipomas, ganglioneuromas, adrenal cysts, hematomas
- Malignant: adrenocortical carcinomas, some pheochromocytomas, metastases
- 50% of adrenal incidentalomas are nonfunctioning tumors that do not secrete steroid hormone autonomously
- Up to 20% of patients have subclinical hormonal overproduction; such patients may be at risk for metabolic or cardiovascular disorders
- Most common is cortisol overproduction; less common are catecholamine excess and aldosterone excess

105 Adrenal “Incidentaloma”, B

3. What is the recommended management of adrenal incidentalomas?

- Testing to determine whether the lesion is hormonally active and whether it is likely to be malignant or benign
- Hormonal testing: 1-mg dexamethasone suppression test or a 24-hour urine collection for free cortisol; measurement of plasma aldosterone concentration and plasma renin activity; and measurement of plasma (or urinary) fractionated free metanephrines, for all patients
- Surgery for patients with unilateral incidentalomas with biochemical hormone excess
- The size and appearance of the mass on CT or MRI can help in distinguishing malignant from benign tumors
- Monitoring (if no surgery done): second imaging study 6–12 months later and, if symptomatic, repeat endocrinologic studies to exclude hormone hypersecretion
  - For patients with nonsecreting tumors that remain stable in size, no further monitoring is recommended
  - Vast majority of incidentalomas remain stable in size: about 5–25% increase in size by ≥1 cm, and 3–4% decrease in size
  - Overall, ≤20% of nonfunctioning tumors develop hormone overproduction (usually cortisol, rarely catecholamine or aldosterone, hypersecretion) when monitored for up to 10 years

106 Adrenocortical Insufficiency, A

A 38-year-old woman presents for annual follow-up of previously diagnosed Hashimoto thyroiditis, for which she has been receiving levothyroxine, 0.15 mg/d. She reports gradual onset of weakness, lethargy, and easy fatigability over the past 3 months. Review of systems reveals recent menstrual irregularity, with no menses in 2.5 months. Blood pressure is 90/50 mm Hg (compared with previous readings of 110/75 and 120/80 mm Hg), and her weight is down 13 pounds since her last visit 11 months ago. The skin appears to be tanned, but the patient denies sun exposure.

1. What are the major causes of adrenocortical insufficiency?

- **Primary adrenocortical insufficiency** (Addison disease), due to adrenal cortical dysfunction
  - Autoimmune destruction of the adrenal cortex, most common (80%)
  - Infections such as tuberculosis, histoplasmosis, other granulomatous diseases
  - Adrenal hemorrhage and infarction
  - Metastatic carcinoma and lymphoma (non-Hodgkin)
  - AIDS-related infections such as cytomegalovirus
  - Amyloidosis, hemochromatosis, sarcoidosis
  - Surgery, radiation, drugs (either toxic or inhibitory)
  - Congenital (such as congenital adrenal hyperplasia)
- **Secondary adrenocortical insufficiency**: chronic exogenous glucocorticoid therapy, pituitary or hypothalamic tumor or damage, acquired hypopituitarism

106 Adrenocortical Insufficiency, B

2. What are the clinical symptoms and signs of adrenocortical insufficiency?

- Symptoms (nonspecific): weakness, lethargy, easy fatigability, anorexia, nausea, joint and abdominal pain, diarrhea, dizziness
- Signs: weight loss, orthostatic hypotension, hyponatremia, hypoglycemia, anemia

- **Primary insufficiency:** only: hyperpigmentation of skin and mucous membranes, salt craving, hyperkalemia
- **Secondary insufficiency**: can present with amenorrhea, decreased libido, impotence, headache, visual symptoms if global pituitary dysfunction

3. How can one make the diagnosis of adrenocortical insufficiency?

- **Primary insufficiency:** adrenocorticotropic hormone (ACTH) stimulation test
  - After an 8 AM plasma cortisol level, 250 µg of synthetic ACTH (cosyntropin) is given and cortisol levels are checked at 30 and 60 minutes
  - Normal patients demonstrate a rise in plasma cortisol levels to >18 µg/dL
  - Patients with Addison disease have a low 8 AM plasma cortisol (and high ACTH) and virtually no increase in plasma cortisol at 30 and 60 minutes

- **Secondary insufficiency:** usually diagnosed by history or evidence of pituitary tumor (abnormalities of serum prolactin, thyroid-stimulating hormone [TSH], luteinizing hormone [LH], or follicle-stimulating hormone [FSH] tests)
- The "gold standard" test for diagnosis of secondary adrenal insufficiency is the insulin tolerance test, ie, an injection of insulin causes a rise of cortisol to >18 µg/dL as a response to symptomatic hypoglycemia rules out adrenal insufficiency

107 Hyperaldosteronism (Primary Aldosteronism), A

A 42-year-old man presents for evaluation of newly diagnosed hypertension. He is currently taking no medications and offers no complaints. A careful review of systems reveals symptoms of fatigue, loss of stamina, and frequent urination, particularly at night. Physical examination is normal except for a blood pressure of 168/100 mm Hg. Serum electrolytes are reported as follows: sodium, 152 mEq/L; potassium, 3.2 mEq/L; bicarbonate, 32 mEq/L; chloride, 112 mEq/L. The clinical picture is consistent with a diagnosis of primary aldosteronism.

1. What are the causes of hyperaldosteronism?

- **Primary aldosteronism:** Aldosterone-secreting adrenocortical adenoma, bilateral hyperplasia of zona glomerulosa, glucocorticoid-remediable hyperaldosteronism, aldosterone-secreting adrenocortical carcinoma (rare), idiopathic
- **Secondary hyperaldosteronism:**
  - Renal ischemia from renal artery stenosis or malignant hypertension
  - Low intravascular volume: heart failure, hypoproteinemic state, diuretics
  - Sodium-wasting: chronic kidney disease, renal tubular acidosis
  - Juxtaglomerular cell hyperplasia (Bartter syndrome)
  - Surreptitious vomiting or diuretic ingestion (pseudo-Bartter syndrome)
  - Oral contraceptives
  - Renin-secreting tumors (rare)

107 Hyperaldosteronism (Primary Aldosteronism), B

2. What are the presenting symptoms and signs of hyperaldosteronism?

- Potassium depletion with: fatigue, loss of stamina, weakness, thirst, and polyuria
  - Severely potassium-depleted patients may develop blunting of baroreceptor function, manifested by postural falls in blood pressure without reflex tachycardia, or even by malignant arrhythmias and sudden cardiac death
  - The alkalosis accompanying severe K^+ depletion may lower the plasma calcium to the point at which latent or frank tetany occurs
  - Mild glucose intolerance may result from K^+ depletion
  - The hypokalemia may cause severe muscle weakness, muscle cramps, and intestinal atony, or paresthesias
- Hypertension related to sodium retention and expansion of plasma volume
  - Retinopathy, renal damage, or left ventricular hypertrophy may result
- Laboratory findings in hyperaldosteronism include hypokalemia and alkalosis with:
  - An inappropriately large amount of potassium in the urine
  - A reduced hematocrit because of hemodilution by the expanded plasma volume
  - A failure to concentrate urine
  - An abnormal glucose tolerance test
  - A suppression of the plasma renin level in primary aldosteronism and an elevation of the plasma renin in secondary hyperaldosteronism

108 Type 4 Hyporeninemic Hypoaldosteronism, A

A 64-year-old man with a long history of gout and type 2 diabetes mellitus comes in for a routine checkup. Serum chemistries are as follows: sodium, 140 mEq/L; potassium, 6.3 mEq/L; bicarbonate, 18 mEq/L; BUN, 43 mg/dL; creatinine, 2.9 mg/dL; and glucose, 198 mg/dL. Chart review shows previous potassium values of 5.3 mEq/L and 5.7 mEq/L. The patient is currently taking only oral colchicine, 0.5 mg daily, and oral glyburide, 5 mg twice daily.

1. What are the causes of hypoaldosteronism?

- Primary mineralocorticoid deficiency (hypoaldosteronism) may result from destruction of adrenocortical tissue, which invariably results also in both androgen and glucocorticoid deficiency
- The disorder can be caused by defects in adrenal synthesis of aldosterone (eg, congenital adrenal hyperplasia due to mutations in the 21-hydroxylase gene) or inadequate stimulation of aldosterone secretion (hyporeninemic hypoaldosteronism)
- In pseudohypoaldosteronism, there is renal tubular resistance to mineralocorticoid hormones
- A secondary deficiency of endogenous mineralocorticoids may occur when renin production is suppressed or rendered deficient by the Na^+ retention and volume expansion resulting from exogenous mineralocorticoids (fludrocortisone acetate) or substances with mineralocorticoid-like effects due to activation of the mineralocorticoid receptor by cortisol (licorice or carbenoxolone inhibits the enzyme 11β-hydroxysteroid dehydrogenase that normally breaks down cortisol)

108 Type 4 Hyporeninemic Hypoaldosteronism, B

2. What are the clinical manifestations of hypoaldosteronism?

- Hypoaldosteronism is characterized by sodium loss, with hyponatremia, hypovolemia, and hypotension, and impaired secretion of both K^+ and H^+ ions in the renal tubules, resulting in hyperkalemia and metabolic acidosis
- The sodium and volume losses can be so profound as to lead to shock and death

3. What is the pathogenesis of type 4 hyporeninemic hypoaldosteronism?

- This disorder (also known as type IV renal tubular acidosis) is characterized by hyperkalemia and acidosis in association with chronic kidney disease
- Typically, affected individuals are men in the fifth to seventh decades of life who have underlying pyelonephritis, diabetes mellitus, gout, or nephrotic syndrome
- The chronic kidney disease is usually itself not severe enough to account for the hyperkalemia
- Plasma and urinary aldosterone levels and plasma renin activity are consistently low and unresponsive to stimulation by upright posture, dietary sodium restriction, or furosemide administration
- The syndrome is thought to be due to impairment in the synthesis or release of renin from the juxtaglomerular apparatus associated with the underlying renal disease

109 Congenital Adrenal Hyperplasia, A

A newborn full-term male infant is screened for 21-hydroxylase deficiency at birth and is noted to have a high 17-hydroxyprogesterone level on a heel stick blood sample. Both parents are healthy, and there is no history of hormonal problems in the family. The baby appears normal with normal vital signs and physical examination. He is brought back for a repeat examination at 2 weeks, and repeat blood tests show a still elevated 17-hydroxyprogesterone level, a sodium of 125 mEq/L, a potassium of 5.6 mEq/L, and a glucose of 60 mg/dL. He is suspected of having the salt-wasting form of congenital adrenal hyperplasia.

1. What are common defects in congenital adrenal hyperplasia?

- Congenital adrenal hyperplasia is a group of autosomal recessive disorders
- The primary disorder is an enzyme defect resulting in a shift of adrenal hormone production from corticosteroids primarily to androgens
- Congenital adrenal hyperplasia is caused by mutations in the *CYP21*, *CYP11B1*, *CYP17*, and *3βHSD* genes that encode steroidogenic enzymes and by mutations in the gene encoding the intracellular cholesterol transport protein, steroidogenic acute regulatory protein (StAR)
- By far, the most frequent cause of congenital adrenal hyperplasia is 21β-hydroxylase deficiency, followed by 11β-hydroxylase deficiency
- Each of these defects causes different biochemical and clinical consequences
- All of the biochemical defects lead to impaired cortisol secretion, resulting in compensatory hypersecretion of ACTH and consequent hyperplasia of the adrenal cortex; clinical severity varies and depends on the specific mutation

109 Congenital Adrenal Hyperplasia, B

2. Why are excess androgens produced in congenital adrenal hyperplasia?

- The low serum cortisol stimulates adrenocorticotropic hormone (ACTH) production; adrenal hyperplasia occurs, and precursor steroids—in particular 17-hydroxyprogesterone—accumulate
- These cannot enter the cortisol synthesis pathway and thus spill over into the androgen synthesis pathway, forming androstenedione and dehydroepiandrosterone/dehydroepiandrosterone sulfate (DHEA/DHEAS)
- Prenatal exposure to excessive androgens results in masculinization of the female fetus, leading to ambiguous genitalia at birth
- Newborn males have normal genitalia, but the excess androgens during childhood can produce pseudoprecocious puberty, premature growth acceleration, early epiphyseal fusion, and short stature

3. How does congenital adrenal hyperplasia classically present during the newborn period and childhood?

- Two classic presentations of congenital adrenal hyperplasia result from 21β-hydroxylase deficiency: salt wasting and non-salt wasting ("simple virilizing")
- Neonates with the salt-wasting form have severe cortisol and aldosterone deficiencies and, if undiagnosed and untreated, will develop potentially lethal adrenal crisis and salt wasting at 2–3 weeks of age
- In childhood, those with the non-salt-wasting form are usually diagnosed because of virilization between birth and 5 years of age

110 Menstrual Disorders: Dysmenorrhea, A

A 24-year-old woman presents to the clinic complaining of painful menses. She states that for the past several years she has had cramping pain in the days preceding her menses as well as during her menses. In addition, she notes bloating and weight gain in the week before her menses, with swelling of her hands and feet. She has irritability and severe mood swings during that time such that she cries easily and for no reason seems to become enraged at her family or boyfriend. On review of systems, she denies urinary symptoms, vaginal discharge, or gastrointestinal symptoms. She has no significant medical history. She has never been pregnant. She has never had a sexually transmitted disease. She is sexually active only with her long-standing boyfriend and says they always use condoms. She takes no medications. Her physical examination is unremarkable.

1. What are common causes of dysmenorrhea?

- Primary dysmenorrhea: no organic pelvic disease present
- Secondary dysmenorrhea has many causes:
  - Endometriosis: ectopic endometrium
  - Pelvic inflammatory disease: infection
  - Anatomic lesions: imperforate hymen, intrauterine adhesions, leiomyomas, polyps
  - Premenstrual syndrome (PMS)

110 Menstrual Disorders: Dysmenorrhea, B

2. What is the pathophysiology of primary dysmenorrhea?

- Painful menses and other symptoms including: sweating, weakness and fatigue, insomnia, nausea, vomiting, diarrhea, back pain, headache, dizziness, and syncope
- Prostaglandin synthesis inhibitors (nonsteroidal anti-inflammatory agents) often alleviate many of these symptoms if treatment is initiated prior to menses
- Primary dysmenorrhea is thought to be due to disordered prostaglandin production by the secretory endometrium
- Prostaglandin F2α (PGF2α) stimulates myometrial contractions of the nonpregnant uterus, whereas prostaglandins of the E series tend to inhibit its contraction
- Patients with severe dysmenorrhea generally have excessive production of PGF2α rather than increased sensitivity to this prostaglandin
- Unabated contractions of the myometrium result in ischemia of uterine muscle, which stimulates uterine pain fibers of the autonomic nervous system
- Anxiety, fear, and stress may lower the pain threshold and thereby exaggerate the prominence of these symptoms and averts the cascade of events that occur with production of prostaglandins
- If associated with PMS, other symptoms include a sensation of bloating, weight gain, edema of the hands and feet, breast tenderness, acne, anxiety, aggression, mood irritability, food cravings, and change in libido

3. How do patients with dysmenorrhea present?

111 Female Infertility, A

A 28-year-old woman presents to the clinic with a complaint of infertility. She states that she and her husband have been trying to get pregnant for approximately 1 year without success. She had menarche at age 14 years. Since that time, she has had regular menses lasting 5 days, without significant dysmenorrhea or abnormal bleeding. She has never been pregnant. Medical history is notable for gonorrhea and trichomoniasis at age 18. In addition, she has had an abnormal Pap smear consistent with human papillomavirus infection at age 20 years, with normal Pap smears since that time. She takes no medications. She has been married for 2 years and is sexually active only with her husband. Before her marriage, she had approximately 25 sexual partners, most during her college years. Her physical examination is unremarkable.

1. What are the most common causes of infertility in couples?

- Female factors account for about 30% of cases
  - Ovulatory dysfunction: amenorrhea, diminished ovarian reserve, polycystic ovarian syndrome (PCOS), hypothalamic amenorrhea
  - Tubal or pelvic pathology: endometriosis, scarring or adhesions from previous surgery, infections, tubal pregnancies
  - Miscellaneous: thyroid or prolactin abnormality
- Male factors (sperm defects) account for about 30% of cases
- About 30% of cases are caused by combined female and male factors
- About 10% of cases are unexplained

111 Female Infertility, B

2. What feature of the history suggests a tubal or uterine cause of infertility?

- History of previous sexually transmitted infections (such as gonorrhea)
- History of previous pelvic surgeries or ectopic pregnancies
- Painful menses, which could be an indication of endometriosis

3. How are ovulatory causes of infertility treated?

- In many cases, administration of exogenous gonadotropins will stimulate the ovaries to produce follicular growth
  - Oocytes can then be released in vivo and fertilized by intercourse or by artificial insemination
  - Alternatively, mature oocytes can be removed via transvaginal aspiration and subsequently fertilized utilizing in vitro fertilization (IVF) followed by return of the resultant embryos to the uterus transcervically
- Diminished ovarian reserve is age-related and can involve both the oocytes themselves and the secretory products of the ovary
  - Accelerated loss of follicles with the approach of menopause
  - Follicle-stimulating hormone (FSH) levels tend to rise, reflecting inadequate production of inhibin and anti-müllerian hormone
  - Treatment with clomiphene citrate, a weak estrogen antagonist, is a means of diminishing negative feedback and increasing endogenous gonadotropin stimulation of the ovary and restoring ovulation

112 Preeclampsia-Eclampsia, A

A 28-year-old woman presents to her obstetrician for her regularly scheduled prenatal examination. She is 30 weeks pregnant. She has noted some swelling of her hands and feet in the last 2 weeks that seems to be getting progressively worse. She is no longer able to wear her rings and can only wear open-heeled shoes. She is otherwise without complaints. She has no past medical problems. This is her first pregnancy. She has had regular prenatal care and, thus far, has had no pregnancy complications. She is taking only prenatal multivitamins. Family history is notable for maternal hypertension and diabetes mellitus. She is married and works as a schoolteacher. She denies alcohol, tobacco, and drug use. On examination, she appears to be well, with blood pressure of 152/95 mm Hg. Fundal height is consistent with gestational age. Fetal heart rate is 140 bpm. There is 1+ lower extremity edema to the knees and trace edema of the hands. Urine dipstick reveals 3+ protein.

1. What are the hallmarks of preeclampsia-eclampsia?

- Preeclampsia-eclampsia is characterized by hypertension, proteinuria, and edema
- Other associated findings may include:
  - Excessive weight gain along with ascites
  - Hyperuricemia and hypocalciuria
  - Increased liver enzymes
  - Thrombocytopenia and disseminated intravascular coagulopathy
  - Derangement in levels of clotting factors

112 Preeclampsia-Eclampsia, B

2. What are the risks to the fetus of untreated maternal hypertension?

- Placental deterioration and insufficiency can result in intrauterine growth restriction (IUGR) and fetal hypoxia
- This can lead to a small infant or even to intrauterine fetal asphyxia and death

3. What are some of the maternal sequelae of preeclampsia-eclampsia?

- Seizures
- Cerebral hemorrhage
- Cortical blindness
- Retinal detachment
- HELLP syndrome (hemolysis, elevated liver enzymes, low platelets)
- Hepatic rupture and necrosis
- Disseminated intravascular coagulation
- Pulmonary edema
- Laryngeal edema
- Acute renal cortical necrosis
- Acute renal tubular necrosis
- Abruptio placentae leading to fetal injury, death and/or maternal hemorrhage
- Delivery of the fetus and placenta is the only definitive cure for preeclampsia-eclampsia

113 Male Infertility, A

A married couple presents to their primary care clinician with a complaint of infertility. They have been trying to get pregnant for approximately 1 year. During that time, they have had intercourse approximately three or four times a week without birth control. The woman has a 3-year-old child from her prior marriage. The man has never had a child to his knowledge. He denies sexual dysfunction. He has had both gonorrhea and chlamydial infection in his early 20s, and one episode of prostatitis, all of which were treated. His medical history is otherwise unremarkable. He takes no medications. He denies tobacco or drug use and drinks only rarely. On examination, his testes are approximately 4.5 × 3 × 2.5 cm bilaterally. The epididymis is irregular to palpation bilaterally. There are no varicoceles or hernias. The vas deferens is present and without abnormality. The prostate is of normal size and without bogginess or tenderness. The penis is without fibrosis or angulation. The urethral meatus is appropriately situated.

1. From the perspective of the male reproductive system, what are the conditions that must be present for conception to occur?

- Spermatogenesis must be normal
- Seminal accessory glands must produce seminal fluids
- The ducts for sperm transport must be patent
- Ejaculation must occur so that sperm can be deposited near the female's cervix
- The spermatozoa must be able to travel to the uterine tubes
- The sperm must undergo functional changes which allows them to fuse with the oolemma (plasma membrane of oocyte)
- Any defect in these mechanisms can result in infertility

113 Male Infertility, B

2. What is the value of testing for a *CFTR* mutation or Y-chromosome microdeletion?

- Congenital bilateral absence of the vas deferens (CBAVD) occurs in cystic fibrosis (CF). More than 500 mutations of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene are responsible for CF
- CBAVD occurs in 1–2% of infertile men
- In addition, the long arm of the Y chromosome contains critical spermatogenesis genes
- Men with microdeletions in the AZFb or AZFa regions have no sperm; among those with microdeletions in the AZFc region, 70% have sufficient sperm production to allow sperm extraction via testis biopsy
  - Microdeletions most often causing defective spermatogenesis are found in the azoospermia factor region (AZF)
  - These are responsible for azoospermia or severe oligozoospermia and are estimated to account for about 7–10% of male infertility

3. What is the most common cause of obstructive azoospermia in the population?

- Vasectomy is the most common cause
- Other causes: congenital isolated ejaculatory duct obstruction associated with *CFTR* mutations, acquired ejaculatory duct obstruction
- Acquired cases: genitourinary infections, surgery, urethral trauma, chronic prostatitis, prostatic nodule, inspissated secretions in the ejaculatory ducts causing calculi, and calcifications and cysts in the prostate or seminal vesicles

114 Benign Prostatic Hyperplasia, A

A 68-year-old man presents to his physician with a complaint of urinary frequency. He has noted increased urgency and frequency for approximately 1 year, but his symptoms have become progressively worse. Currently, he seems to have to urinate "all the time" and often feels as if he has not completely emptied his bladder. He must get up to urinate three or four times each night. In addition, in the last month, he sometimes has had post-void dribbling. He denies fevers, weight loss, or bone pain. His medical history is notable only for hypertension. His medications include atenolol and aspirin. The family history is negative for malignancy. On examination, he appears healthy. His vital signs are notable for a blood pressure of 154/92 mm Hg. His prostate is diffusely enlarged without focal nodule or tenderness. Benign prostatic hyperplasia is suspected.

1. Which is the major androgen controlling prostate size?

- 80–90% of prostatic testosterone is converted to the more active metabolite, dihydrotestosterone (DHT), by the enzyme 5α-reductase
- In the prostate, once it is synthesized, the DHT acts in a paracrine fashion on androgen-dependent epithelial cells
- Interestingly, DHT levels are the same in hyperplastic and normal glands
- However, prostatic levels of DHT remain high with aging even though peripheral levels of testosterone decrease

114 Benign Prostatic Hyperplasia, B

2. What are some bladder changes that occur in patients with benign prostatic hyperplasia?

- Obstruction-induced changes in bladder function are of two basic types:
  - Detrusor overactivity (instability) causing frequency and urgency sometimes quite out of proportion to the degree of obstruction
  - Decreased detrusor contractility leading to decreased force of the urinary stream, hesitancy, intermittency, increased residual urine

3. What are some symptoms and signs of benign prostatic hyperplasia?

- There are two types of symptoms: irritative, which are related to bladder filling, and obstructive, which are related to bladder emptying
- Irritative symptoms occur as a consequence of bladder hypertrophy and dysfunction and include urinary frequency, nocturia, and urgency
- Obstructive symptoms result from distortion and narrowing of the bladder neck and prostatic urethra, leading to incomplete emptying and include difficulty initiating urination, decreased force and caliber of the urinary stream, intermittency of the urinary stream, urinary hesitancy, and dribbling
- To evaluate objectively the severity and complexity of symptoms in benign prostatic hyperplasia, a symptom index has been developed by the American Urologic Association

115 Gout, A

A 58-year-old man with a long history of treated essential hypertension and mild renal insufficiency presents to the urgent care clinic complaining of pain in the right knee. His primary care clinician had seen him 1 week ago and added a thiazide diuretic to improve his blood pressure control. He had been feeling well until the night before the urgent care clinic visit, when he noted some redness and slight swelling of his knee. He went to sleep and was awakened early by significant swelling and pain. He was able to walk only with assistance. He has no history of knee trauma. Physical examination confirmed the presence of a swollen right knee, which was erythematous and warm. Joint aspiration recovered copious dark yellow, cloudy synovial fluid. Microscopic analysis demonstrated 30,000 leukocytes/μL, a negative Gram stain, and many needle-like, negatively birefringent crystals consistent with urate crystals. He was diagnosed as having acute gout.

1. What physical factors other than uric acid concentration influence crystal formation in gout?

- Formation of crystals is markedly influenced by physical factors such as temperature and blood flow
- The propensity for gout to involve distal joints (eg, great toes and ankles), which are cooler than other body parts, probably reflects the presence of local physical conditions such as the lower temperature at these sites that favor crystal formation

115 Gout, B

2. Suggest five reasons why the intense acute inflammatory response in gout typically resolves spontaneously over the course of several days even in the absence of therapy.

- Efficient phagocytosis of crystals, preventing activation of newly recruited inflammatory cells
- Increased heat and fluid influx, altering local physical and chemical conditions to favor crystal solubilization
- Coating of crystals with serum proteins, rendering the surface of the crystals less inflammatory
- Secretion of a variety of anti-inflammatory cytokines (eg, TGF-β) by activated joint macrophages
- Phagocytosis of previously activated apoptotic neutrophils by macrophages in the joint, altering the balance of cytokines secreted by these macrophages in such a way that secretion of proinflammatory cytokines is inhibited while secretion of anti-inflammatory cytokines is enhanced

3. What are three metabolic conditions that can precipitate a gout flare?

- Gout attacks frequently occur in circumstances that increase serum uric acid levels, such as metabolic stressors leading to increased DNA or adenosine triphosphate (ATP) turnover (eg, sepsis, surgery, or dehydration)

116 Vasculitis, A

A 24-year-old man presents with a worsening rash. One week ago, he had been at an urgent care center with a sore throat and was diagnosed with "strep throat." He was prescribed penicillin and had been getting better. The day before presentation, he noted the development of a pink rash on his trunk, and on the day of his evaluation, it spread to his arms and legs. On examination, the patient has a symmetric maculopapular rash covering his extremities and trunk. Some of the lesions on his legs are palpable.

1. In what two immunologic settings does immune complex vasculitis occur, and which organs does it commonly affect?

- Immune complex vasculitis is an acute inflammatory disease of small blood vessels that occurs in the setting of ongoing antigen load and an established humoral (antibody) immune response
- Tissues primarily affected include:
  - Skin (leukocytoclastic vasculitis): rash, which appears as raised, red or violaceous papules (palpable purpura)
  - Joints: severe, rapid-onset and self-limited symmetric polyarthritis of medium and small joints
  - Kidney: immune complex–mediated glomerulonephritis

116 Vasculitis, B

2. What three physical properties determine whether immune complexes will be deposited in vessel walls?

- Immune complexes are efficiently cleared in most circumstances by the reticuloendothelial system and are only pathogenic when circulating immune complexes are deposited in the subendothelium, where they set in motion the complement cascade and activate myelomonocytic cells
- The propensity for immune complexes to deposit is a function of the relative amounts of antigen and antibody and of the intrinsic features of the immune complex: composition, size, and solubility
- The solubility of immune complexes is not a fixed property, because it is profoundly influenced by the relative concentrations of antigen and antibody, which generally change as an immune response evolves
- For physicochemical reasons, soluble immune complexes formed at slight antigen excess are not effectively cleared by the reticuloendothelial system and are of a size that allows them to gain access to and be deposited at subendothelial and extravascular sites
- When antibody is present in excess, immune complexes are rapidly cleared by the reticuloendothelial system and deposition does not occur

117 Systemic Lupus Erythematosus, A

A 22-year-old African American woman with a family history of systemic lupus erythematosus (SLE) is evaluated at a medical clinic for intermittent arthralgias in her knees. She denies any facial rash, photosensitivity, chest pain, or shortness of breath. She is convinced she has lupus and requests confirmatory blood tests.

1. What are the antigens against which antibodies are directed in SLE?

- Nuclear: nucleosomes (dsDNA and histone core) and ribonucleoprotein complexes (Sm, nRNP, La, Ro [60 kDa])
- Membrane-associated: anionic phospholipids or phospholipid-binding proteins
- Cytoplasmic: ribosomal protein P, Ro [52 kDa]

2. What are three stimuli that typically provoke SLE flares?

- Sunlight exposure (associated with both disease onset and flares)
- Viral infection (Epstein-Barr virus exposure is strongly associated with SLE in children)
- Certain drugs

117 Systemic Lupus Erythematosus, B

3. What organ systems are most prominently affected in SLE?

- Skin: ultraviolet light photosensitivity and a variety of SLE-specific skin rashes including a rash over the malar region, discoid pigmentary changes to the external ear, and erythema over the dorsum of fingers
- Joints: non-erosive symmetric polyarthritis
- Kidneys: a spectrum of glomerulonephritides are a frequent major cause of morbidity and mortality
- Blood: a variety of hematologic disturbances including hemolytic anemia, thrombocytopenia, and leukopenia
- Serosal surfaces: inflammation can result in pleuritis, pericarditis, and peritonitis
- Central nervous system: seizures, organic brain syndrome

118 Sjögren Syndrome, A

A 45-year-old woman presents to a medical clinic complaining of dry eyes and mouth, progressively worsening over the past year. At first, she thought it may have been worsening of her allergies, but her eyes feel irritated all of the time, as if she has sand in them. She gets mild relief with over the counter eye drops. Her mouth has also felt dry, and she has found it difficult to eat certain foods such as bread and crackers or carry on prolonged conversations due to her tongue sticking to the roof of her mouth. She recently saw her dentist and was found to have two cavities, the first since childhood. Physical examination is normal except for mild injection of her conjunctivae.

1. What are the steps in pathogenesis of Sjögren syndrome?

- Although a viral cause of Sjögren syndrome remains speculative, several pathways have been implicated in its pathogenesis
  - Autoimmunity to epithelial tissues: an immune response directed against several ubiquitously expressed antigens (eg, Fodrin, Ro, and La) as well as to some antigens expressed specifically in secretory epithelial cells (eg, type 3 muscarinic acetylcholine receptors [M3R])
  - Enrichment of HLA-DR3 in patients with Sjögren syndrome leads to possible enhanced ability to present peptides contained within the pathogenic autoantigens
  - The antibodies to M3R are believed to prevent stimulated secretion of saliva and tears and may be important in the hypersecretion that characterizes the disease
  - Exocrine tissue infiltration with activated cytotoxic lymphocytes induces death of duct and acinar epithelial cells, with resultant loss of functioning salivary tissue

118 Sjögren Syndrome, B

2. What are the clinical manifestations of Sjögren syndrome?

- The most prominent presenting symptoms in Sjögren syndrome are:
  - Xerophthalmia (ocular dryness): eye irritation, foreign body sensation or pain, and risk for corneal ulcer or perforation
  - Xerostomia (dry mouth): impaired production of saliva, difficulty in swallowing dry foods or in speaking at length, altered sensation of taste or of oral burning, new onset in mid-adult life of severe dental caries at the gum line
- Other epithelial surfaces may be similarly affected: skin, vaginal, and/or respiratory tract dryness with hoarseness and recurrent bronchitis
- Possible systemic symptoms: fatigue, arthralgias, myalgias, and low-grade fever
- Other potentially affected organ systems include the kidneys, lungs, joints, and liver (resulting in interstitial nephritis, interstitial pneumonitis, nonerosive polyarthritis, and intrahepatic bile duct inflammation)
- As many as half of affected individuals experience autoimmune thyroid disease
- Those with severe disease are at increased risk for cutaneous vasculitis (including palpable purpura and skin ulceration) and lymphoproliferative disorders (ie, mucosa-associated lymphoid tissue [MALT] lymphoma)

119 Myositis, A

A 55 year-old woman presents to a medical office with progressive weakness. She had been in good health until about six weeks ago when she began having trouble getting up from a low chair. Her muscle weakness has become more pronounced over time, and she now also has difficulty climbing stairs and brushing her hair. Her shoulders and thighs are mildly achy but not painful. She is well-appearing with normal vital signs and an essentially normal physical examination with the exception of mild tenderness of her shoulders and thighs. She does not have a rash. Laboratory tests are notable for a creatine phosphokinase level of 840 IU/L (normal female: 26–180 IU/L) and an aldolase value of 32 IU/L (normal: 1.0–7.0 IU/L). Her electromyogram shows that her muscles produce sharp waves and spontaneous discharges. She is diagnosed with polymyositis.

1. What are the clinical manifestations of polymyositis and dermatomyositis?

- Gradual and progressive motor weakness affecting the arms and legs, as well as the trunk, in association with histologic evidence of muscle inflammation
- Proximal muscles are most frequently affected, resulting in difficulty rising from a seat or bed, ascending a flight of stairs, reaching up, or brushing one's hair
- If very severe, patients can have impaired swallowing of solid foods and impaired full lung expansion due to esophageal and diaphragmatic muscle involvement
- Rarely, the disease can affect smooth muscle and even cardiac muscle
- Extramuscular involvement of the lung parenchyma (interstitial pulmonary fibrosis), peripheral joints (inflammatory polyarthritis), and skin (dermatomyositis) can also occur

119 Myositis, B

2. What is the pathophysiology of polymyositis and dermatomyositis?

- Polymyositis and dermatomyositis share several similar pathologic features but possess distinct ones as well
- Common traits: patchy muscle involvement, presence of inflammatory infiltrates, and areas of both muscle damage and regeneration
- In polymyositis, inflammation is located around individual muscle fibers ("perimyocyte"), and the infiltrate is T-cell (CD8+ > CD4+) and macrophage-predominant
- In dermatomyositis, the pathology is quite different with atrophy at the periphery of muscle bundles ("perifascicular atrophy"). The infiltrate is predominantly B cells and CD4+ T cells, localized to the perifascicular space and surrounding capillaries (which are reduced in number). Activation of the complement cascade results in major capillary involvement

3. What other disease is the adult patients with polymyositis or dermatomyositis at risk for, usually within 1–5 years after diagnosis?

- Cancer: several population-based studies link dermatomyositis and polymyositis with the development of cancer within the 1–5 years following diagnosis
  - For example, the diagnosis of dermatomyositis carries a 2-fold greater risk of incident malignancy, particularly of the stomach, lung, breast, colon, and ovary

120 Rheumatoid Arthritis, A

A 47-year-old woman presents to the clinic with a four-week history of fatigue, bilateral hand pain and stiffness, together with hand and wrist joint swelling. About a month before presentation, she noticed that her hands were stiffer in the morning, but thought that it was due to too much typing. However, the stiffness has worsened, and she now needs about an hour each morning to "loosen up" her hands. As the day goes on, the stiffness improves, although it does not go away entirely. She has also noticed that her knuckles and wrists are swollen and feel somewhat warm. Physical examination reveals warm, erythematous wrists and metacarpal joints bilaterally. Hand x-ray films show periarticular demineralization and erosions, and blood test results are significant for a mild anemia, elevated sedimentation rate, and a positive rheumatoid factor. The patient is diagnosed with rheumatoid arthritis.

1. What is the pathophysiology of rheumatoid arthritis?

- Much of the pathologic damage that characterizes rheumatoid arthritis is centered around the synovial linings of joints
- The synovium in rheumatoid arthritis is markedly abnormal, with a greatly expanded lining layer (8–10 cells thick) composed of activated cells and a highly inflammatory interstitium replete with B cells, T cells, and macrophages and vascular changes (including thrombosis and neovascularization)
- Rheumatoid arthritis synovial tissue (called pannus) invades and destroys adjacent cartilage and bone
- Genetic factors (twin concordance rate 15–35%) and nongenetic factors (several infectious agents, autoantibodies and elevated cytokines) are clearly involved

120 Rheumatoid Arthritis, B

2. What are the clinical manifestations of rheumatoid arthritis?

- Rheumatoid arthritis is most typically a persistent, progressive disease presenting in women in the middle years of life
- Fatigue and joint inflammation, characterized by pain, swelling, warmth, and morning stiffness, are hallmarks of the disease
- Multiple small and large synovial joints are affected on both sides of the body in a symmetric distribution
- Involvement of the small joints of the hands, wrists, and feet, as well as the larger peripheral joints, including the hips, knees, shoulders, and elbows, is typical
- Involved joints are demineralized, and joint cartilage and juxtaarticular bone are eroded by the synovial inflammation, inducing joint deformities
- Cervical involvement can also occur, potentially leading to spinal instability
- Extra-articular manifestations can include lung nodules, subcutaneous "rheumatoid" nodules (typically present over extensor surfaces), ocular inflammation (including scleritis), or small- to medium-sized arteritis

3. What characterizes the treatment for rheumatoid arthritis?

- Treatment should be prompt and aggressive to prevent permanent joint erosion and deformity
- Immune modifiers such as methotrexate and biologic modifiers of defined pathogenic pathways such as anti-tumor necrosis factor (TNF) therapy are the mainstays of treatment

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